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APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-580

Supporting document/s: SDN-57(N-056)
SDN-73(N-072)

Applicant's letter date 14 October, 2011 (10/17/11) – Complete Response
(CDER Stamp Date): 01/24/12 (01/25/12) – Nonclinical amendment

Product: Qnexa (phentermine HCl + topiramate FDC)

Indication: Obesity

Applicant: VIVUS, Inc.

Review Division: Metabolism and Endocrinology Products

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Review Completion Date: 22 March, 2012

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Review Notes and Abbreviations/Key

Some of the sponsor's tables and figures from the electronic NDA submission have been included and cited in this review. All drug-related trends are discussed in relation to concurrent vehicle control groups in each study unless otherwise noted. Vehicle for oral gavage administration was water for phentermine and 0.5% methylcellulose for topiramate unless otherwise noted. Common animal strains were used and abbreviated by common animal name, unless noted, as follows: Sprague-Dawley rat, CD-1 mouse, Beagle dog, Cynomolgus monkey, New Zealand White rabbit. Results from reviews of some studies previously reviewed under IND 68,651 and prior reviews under this NDA are used in support of the current NDA review.

Key: Phentermine HCl (PHEN, phentermine); topiramate (TPM); fixed-dose combination (FDC), once daily dosing (QD), twice daily dosing (BID); dosing groups – LD (low dose), MD (mid dose), HD (high dose); mg/kg (mg/kg/day); MRHD (maximum recommended human dose); NOAEL (no observed adverse effect level); LOAEL (lowest observed adverse effect level); statistically significant (ss); not statistically significant (nss); IR (immediate release), MR (modified release), DR (delayed release); PD (pharmacodynamic), PK (pharmacokinetic), TK (toxicokinetic); BW (body weight); GD (gestation day), LD (lactation day), PND (postnatal day); central nervous system (CNS), peripheral nervous system (PNS); CR (Complete Response, pertaining to regulatory action for NDA review).

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1 Executive Summary

1.1 Introduction

VIVUS submitted new information to support registration of phentermine (PHN) and topiramate (TPM) fixed-dose combination (FDC) capsules for treatment of obesity. Data address issues identified in a Complete Response (CR) letter from the Agency sent October 28, 2010. The Division's CR letter did not specifically require nonclinical studies, but the clinical requirements included a "comprehensive assessment" of teratogenic potential, including "nonclinical and clinical data".

In general, the nonclinical submissions were limited to data and review/discussion to assess nonclinical teratogenic potential of topiramate and combined PHEN/TPM. This review focused on the new information, including a pre- and postnatal rat development study with phentermine and topiramate coadministration. Rat PHEN/TPM treatment throughout fetal organogenesis and lactation included higher doses (5X/6X MRHD) than those tested in the embryofetal rat and rabbit studies ($\leq 2X$). Information from the original pharmacology/toxicology review is not recapitulated here in its entirety.

The proposed FDC capsule was designed to provide once daily oral dosing with immediate release (IR) phentermine and modified release (MR) topiramate. Phentermine was approved in 1959 for short term ("a few weeks") management of obesity and topiramate was approved in 1996 for chronic use to treat epilepsy and for prophylactic treatment of migraine.

1.2 Brief Discussion of Nonclinical Findings

The prior pharmacology/toxicology review recommended approval of phentermine plus topiramate FDC capsules for obesity treatment, contingent on a contraindication in pregnant women, at proposed maximum clinical doses of 15 mg PHEN and 92 mg TPM.^{1,2} Human exposure comparisons in this review were based on plasma exposure whenever possible based on estimated clinical exposures of $AUC_{0-24} = 2.5\mu\text{g}\cdot\text{h}/\text{ml}$ PHEN and $80\mu\text{g}\cdot\text{h}/\text{ml}$ TPM. When necessary, body surface area (BSA) exposure comparisons were based on 100 kg body weight estimate in the indicated obese population resulting in estimated $6\text{ mg}/\text{m}^2$ PHEN and $34\text{ mg}/\text{m}^2$ TPM exposures. Plasma and BSA exposure estimates are consistent with the original NDA review.

A single new pivotal toxicity study was reviewed. The pre- and postnatal rat study was designed to assess potential toxicity of combination phentermine and topiramate treatment during organogenesis and lactation. Maternal and fetal results were generally consistent with expected effects of individual and combination drug treatments. Dose-related reductions in maternal body weight and body weight gain led to slightly reduced weight and growth and development of pups which was considered consistent with the

¹ Carlson DB, NDA 22-580 Pharmacology/Toxicology Review #1, 10/1/10

² Listed maximum doses are 400 mg (200 mg BID) TPM for epilepsy, 100 mg (50 mg BID) TPM for migraine, and 37.5 mg PHEN HCl QD (30 mg PHEN free base)

expected pharmacodynamic effect and not toxicologically significant. A NOAEL was established for combination doses of 1.5 mg/kg phentermine and 10 mg/kg topiramate providing approximately 2- and 3-times MRHD plasma AUC exposure.

A high dose combination of 11.25/75 mg/kg PHEN/TPM provided plasma exposures approximately 5-fold higher (5X/6X MRHD) than previously investigated during rat embryofetal development. The high doses caused modest maternal toxicity including moderate, persistent reductions in body weight gain. F₁ pup survival was markedly reduced in the PHEN only group (-25%) and exacerbated when combined with HD topiramate (-46%). Pups that survived to lactation day 4 generally survived to adulthood but reduced birth weights persisted throughout development and resulted in biologically significant delayed growth, development, and sexual maturation. However, reduced body weights and delayed development did not affect learning, memory, fertility or reproductive success in the offspring.

Importantly, offspring in the pre- and postnatal rat study had external malformations consistent with known TPM teratogenicity. Pre- and postnatal development studies are not designed with comprehensive assessments of fetal malformations, but routine macroscopic observations of all offspring at various developmental time points identified limb (ectrodactyly and brachydactyly), tail (missing or portion missing) and eye (macrophthalmia) abnormalities. Similar malformations have been previously observed in various species treated with topiramate during development. In the study a single malformation was observed in a TPM only control animal, with all other malformations observed only in the high dose combination, suggesting phentermine coadministration exacerbated known topiramate drug-related teratogenesis.

Teratogenic findings listed in approved topiramate labels suggest rats are 5- to 10-fold less sensitive to topiramate-related teratogenicity. However, the malformations in the pre- and postnatal study suggest rat sensitivity to topiramate teratogenicity may be similar to rabbits. The new rat data, coupled with existing rabbit and mouse data, provide further support to the prior pharmacology/toxicology conclusion that topiramate is teratogenic in animals at approximate clinical exposure (ranging from 2- to 6-times MRHD estimates).

The Sponsor did submit a “comprehensive assessment” of nonclinical teratogenicity of topiramate, requested as part of the CR clinical requirements. The Sponsor essentially started with an assertion that clinical evidence shows topiramate is not teratogenic in humans. Individual species’ findings were then considered in isolation and dismissed for various reasons without significant discussion of how malformations across species may be related. It is possible that the wide variety of observed malformations (e.g., oral clefts, skeletal limb, digit, and tail malformations, and eye malformations) arise from similar embryologic tissues or similar, unexplained topiramate-induced toxicity common to different fetal tissues during organogenesis. The large variety of fetal malformations makes it difficult to explain a common teratogenic origin or mechanism(s), but also precludes discounting all observed fetal abnormalities with respect to hazard identification and potential risks to human fetal development. This reviewer concluded

the Sponsor's assessment was seriously flawed, particularly because of a failure to consider animal findings in the context of fetal effects across all species investigated, including humans.

New data provide further support to the prior pharmacology/toxicology conclusion that evidence in nonclinical species clearly identified fetal malformations as a potential hazard to humans. However, the mechanisms that contribute to topiramate-induced reproductive toxicity in non-clinical species remain incompletely defined. The Sponsor's conclusions that teratogenesis in mice administered topiramate is consistent with spontaneous background malformations and teratogenesis in the additional two species, rats and rabbits, is a consequence of reduced maternal body weight is not persuasive. The presence of teratogenesis in three species administered topiramate identifies a potential teratogenic hazard, but differences in species susceptibility and an incompletely defined mechanism precludes confidence in quantitatively assessing risk to human patients. In consideration of the existing animal and human data available for topiramate, it is unlikely that additional nonclinical studies would provide more than incremental information for human risk assessment.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended contingent on a Category X label to contraindicate use in pregnant women. Information submitted in the CR do not alter the original pharmacology/toxicology approval recommendation and contraindication during pregnancy.

As noted in the original NDA review, there are no apparent additional nonclinical studies that could be conducted to alleviate concerns about potential human teratogenic risk. In fact, results from a pre- and post-natal development study suggest rats may be more sensitive to limb, tail, and eye malformations than previously thought. Species sensitivity estimates in the original pharmacology/toxicology review suggested rats were as much as 5- to 30-times less sensitive to topiramate-induced teratogenicity than rabbits and mice, respectively. Phentermine and topiramate coadministration throughout fetal development and lactation/nursing showed malformations consistent with prior topiramate findings but at lower exposure (approximately 6-times MRHD exposures based on AUC estimates). The new data in rats suggests either a potentiation of topiramate-induced developmental toxicity with phentermine coadministration or simply a different estimate of rat sensitivity to topiramate.

1.3.2 Additional Non Clinical Recommendations

The proposed indication currently excludes pediatric use. Pediatric clinical trials are expected as part of a pediatric plan, including deferral for adolescents (aged 12-17) and younger children (aged 7-11) with a waiver for children up to 6 years old. Clinical trials have evaluated the safety of the proposed drug combination in adults but safety assessment in children has not been assessed. Topiramate has been studied in juvenile animals but neither phentermine nor combined phentermine and topiramate have been assessed in juvenile animals post-weaning. Phentermine and topiramate are active in

the central nervous system and cause neurological adverse events in some patients. Topiramate affects bone mineral density and growth plate density in juvenile animals and phentermine causes teeth toxicity in adult animals. Bone, teeth, brain and nervous system development continue throughout childhood and adolescence whereas toxicity in adults may be different. For example, nervous system toxicity in early life can lead to permanent behavioral, learning, and memory changes in animals and humans. Because both drugs act on nervous and bone systems, there are theoretical concerns that phentermine alone may cause irreversible toxicity and phentermine coadministration may potentiate topiramate induced toxicity. Behavioral, nervous system, and bone/teeth development should be assessed in juvenile animals prior to subjecting children to an unknown risk for permanent developmental toxicity. The severity of retinal degeneration and/or atrophy was also increased in rats with chronic phentermine treatment, so juvenile animal studies should also carefully assess ocular toxicity. Finally, reversibility should be assessed in juvenile animals to assess recovery from toxicity after stopping treatment.

Juvenile animal studies with phentermine and topiramate coadministration should be conducted prior to pediatric clinical trials to investigate reversibility of any toxicity, particularly drug-related effects on behavior, learning and memory, and general nervous system and bone/teeth development. However, if the available clinical data show an acceptable benefit to risk profile in adults, there is no reason to require juvenile animal studies prior to approval for the adult indication.

1.3.3 Labeling

Data submitted in the Complete Response do not alter previous pharmacology/toxicology conclusions about labeling requirements. VIVUS proposed a Pregnancy Category X label, consistent with the pharmacology/toxicology recommendation. The 'Highlights' and 'Warnings and Precautions' sections of the proposed label contraindicate Qnexa in pregnant women and that women should immediately stop taking the drug if they become pregnant. The contraindication and warnings/precautions are consistent with pharmacology/toxicology concerns based on teratogenic findings in three animal species.

Specific pharmacology/toxicology labeling recommendations are shown below. Recommendations are modified from the proposed label but no annotations or specific changes are shown from the proposed label because of major differences in the layout of the label. Additional minor editorial changes will be made directly to the draft label in the shared Division files ("eRoom").

Section 5 – Warnings and Precautions

5.X Fetal Toxicity

The sponsor included language from the current Topamax label, modified to reflect the pregnancy contraindication for Qnexa.

Section 8 – Use in Specific Populations

8.1 Pregnancy

Pregnancy Category X [see Warnings and Precautions]

Risk Summary

QNEXA is contraindicated in pregnant women. Infants exposed to QNEXA in utero may have an increased risk for cleft lip and/or cleft palate (oral clefts). Weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. No studies have been conducted using QNEXA in pregnant women.

Human Data (Reviewer's note – not included in pharmacology/toxicology review)

Animal Data

Phentermine/Topiramate

(b) (4)

Topiramate

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, (b) (4) at clinically relevant doses (b) (4)

Phentermine

Animal reproduction studies have not been conducted with phentermine. Limited data from studies conducted with the phentermine/topiramate combination indicate that phentermine alone was not teratogenic but resulted in lower body weight and reduced survival of offspring in rats at 5-fold the MRHD of Qnexa, based on AUC.

8.2 Labor and Delivery

The effect of Qnexa on labor and delivery in humans is unknown. The development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor. (Reviewer note: latter statement from Topamax label)

8.4 Pediatric Use

Reviewer's note – clinical data on human pediatric use is included in the topiramate monotherapy label and will likely need to be added to the QNEXA label

Juvenile Animal Studies

Juvenile animal studies have not been conducted with QNEXA. When topiramate (30, 90, or 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in males at the highest dose.

Section 13 – Nonclinical Toxicology

13.1 Carcinogenicity, mutagenesis and impairment of fertility

Phentermine/Topiramate

No animal studies have been conducted with the combined products in QNEXA to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies performed with phentermine or topiramate individually.

Topiramate

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 2 to 4 times steady-state exposures measured in patients receiving topiramate monotherapy at the maximum recommended human dose (MRHD) of 92 mg. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 4 to 10 times the MRHD based on AUC estimates).

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg or approximately 4 to 8 times male and female MRHD exposures based on AUC.

Phentermine

Phentermine was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in Chinese hamster lung (CHL-K1) cells, or an *in vivo* micronucleus assay.

Rats were administered oral doses of 3, 10, and 30 mg/kg/day phentermine for 2 years. There was no evidence of carcinogenicity at the highest dose of 30 mg/kg or approximately 11 to 15 times the maximum recommended clinical dose of 92 mg based on AUC exposure.

No animal studies have been conducted with phentermine to determine the potential for impairment of fertility.

13.2 Reproductive and Developmental Toxicology

Phentermine/Topiramate

Embryo-fetal development studies have been conducted in rats and rabbits with QNEXA. Phentermine and topiramate co-administered to rats during the period of organogenesis caused reduced fetal body weights but did not cause fetal malformations at the maximum dose of 3.75 mg/kg phentermine and 25 mg/kg topiramate (approximately 2 times the maximum recommended human dose based on AUC estimates for each component).

In a similar study in rabbits, no effects on embryo-fetal development were observed at approximately 0.1 times (phentermine) and 1 time (topiramate) clinical exposures at the MRHD based on AUC. Significantly lower maternal body weight gain was recorded at these doses in rats and rabbits.

A pre- and post-natal development study was conducted in rats with QNEXA. There were no adverse maternal or offspring effects in rats treated throughout organogenesis and lactation with 1.5 mg/kg/day phentermine and 10 mg/kg/day topiramate (approximately 2 and 3 times clinical exposures at the MRHD, respectively, based on AUC). Treatment with higher doses of 11.25 mg/kg/day phentermine and 75 mg/kg/day topiramate (approximately 5 and 6 times maximum clinical doses based on AUC, respectively) caused reduced maternal body weight gain and offspring toxicity. Offspring effects included lower pup survival after birth, increased limb and tail malformations, reduced pup body weight and delayed growth, development, and sexual maturation without affecting learning, memory, or fertility and reproduction.

Topiramate

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 2 times the recommended human dose (RHD) 92 mg/day on a mg/m² basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (34 times the RHD based on AUC estimates) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (2 times the RHD based on estimated AUC). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

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

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (16 times the RHD based on estimated AUC) and reductions in pre-and/or postweaning body weight gain at 2 mg/kg (2 times the RHD based on estimated AUC) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30, or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (34 times the RHD based on estimated AUC) and persistent reductions in body weight gain at 30 mg/kg (2 times the RHD based on estimated AUC) and higher.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

Phentermine Hydrochloride (HCl) – 1197-21-3 (HCl salt); 122-09-8 (free base)

Manufacturer's product code - 2610830

Topiramate – 97240-79-4

Manufacturer's product code – SPT1024

2.1.2 Generic Name

Phentermine HCl + topiramate FDC

2.1.3 Code Name

VI-0521

2.1.4 Chemical Name

Phentermine HCl

Benzeneethanamine- α,α -dimethyl-hydrochloride α,α -dimethylphenethylamine hydrochloride

Topiramate

2,3:4,5-Bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate; -or- β -D-fructopyranose, 2,3:4,5-bis-O-(1-methylethylidene)-sulfamate; -or- 2,3:4,5-di-O-isopropylidene- β -D-fructopyranose sulfamate

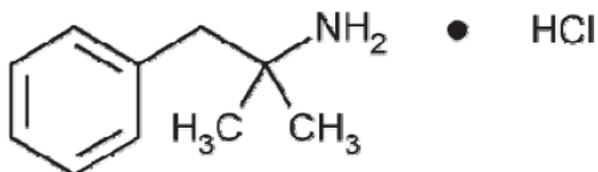
2.1.5 Molecular Formula/Molecular Weight

Phentermine HCl – $C_{10}H_{15}N \cdot HCl$ / 185.69 g/mol (free base 149.23 g/mol)

Topiramate – $C_{12}H_{21}NO_8S$ / 339.363 g/mol

2.1.6 Structure

Phentermine HCl



(b) (4)

2.1.7 Pharmacologic class

QNEXA® is a fixed-dose combination of phentermine, a sympathomimetic amine anorectic, and topiramate, an antiepileptic, indicated for treatment of obesity.

2.2 Relevant IND/s, NDA/s, and DMF/s

Phentermine – NDA 11-613 (Ionamin®) – Approved for short term treatment of obesity (i.e., weight loss), voluntarily withdrawn from market

NDA 88-023 (Adipex-P®) – Approved for short term treatment of obesity (i.e., weight loss) and currently marketed

NDA 85-128 (generic)

Topiramate – NDA 20-505 and NDA 20-844 (Topamax®) – Approved for treatment of epilepsy and prophylactic treatment of migraine

PHEN/TPM – IND 68,651 (obesity), (b) (4)

DMF – (b) (4)

2.3 Drug Formulation

No new drug product formulation information submitted.

2.6 Proposed Clinical Population and Dosing Regimen

The 'Complete Response' submission indicates the proposed PHEN/TPM FDC capsules (QNEXA®) for treatment of obese and overweight (with co-morbidities) males and women of non-childbearing potential. Discussions with the Division have led to changes in the indicated population and the drug label such that the indicated population will be the same as noted and discussed in the original NDA review.

2.7 Regulatory Background

Phentermine plus topiramate FDC capsules (Qnexa®) were originally submitted for review in NDA 22-580 on 28 December, 2009. A 'Complete Response' letter was issued 10/28/10. No specific nonclinical information request was included in the CR letter, but a "comprehensive assessment" of teratogenic potential that "should include nonclinical and clinical data" was required. The submission(s) reviewed here constitute the Sponsor's first CR to the Division's concerns about safety of the proposed uses.

3 Studies Submitted

3.1 Studies Reviewed

Pre- and post-natal development combination phentermine and topiramate assessment in rat.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Original NDA pharmacology/toxicology review by this reviewer (Carlson, Pharmacology/Toxicology Review #1, NDA 22-580, 10/1/10).

9 Reproductive and Developmental Toxicology

9.3 Prenatal and Postnatal Development

Pre- and postnatal rat combination phentermine + topiramate

GLP statement, 7/26/10 (Amended 8/25/10)

Topiramate and phentermine HCl: A study for effects on pre- and postnatal development, including maternal function in rats (Study No. 1060-042)

Doses	0/0 (vehicle control)	
(mg/kg/d)	1.5/10, 11.25/75 mg/kg (PHEN / TPM)	(2X/3X, 5X/6X MRHD) ³
	11.25/0 mg/kg (PHEN control)	(5X MRHD)
	0/75 mg/kg (TPM control)	(6X MRHD)

NOAEL (maternal) = 1.5/10 mg/kg (PHEN / TPM) (2X / 3X MRHD)

NOAEL (fetal) = 1.5/10 mg/kg (PHEN / TPM)

NOAEL determination – Dose-related reduced body weight and body weight gain were apparent in the parental generation, consistent with the intended pharmacodynamic effect of the drug. Reduced maternal BW gain led to reduced F₁ pup body weights and subsequent modest delays in growth and development. Slightly reduced growth and development did not affect sexual development, learning and memory, neurological development, or reproductive success in the LD combination. Maternal and F₁ effects were more pronounced in high dose combination 11.25/75 mg/kg PHEN/TPM (5X/6X MRHD) and individual high dose PHEN and TPM treatments. F₁ pup survival after birth was markedly reduced in HD combination and PHEN groups. F₁ animals that survived were smaller than controls and had delayed growth and development, including delayed sexual maturation. F₁ mating success, fertility, and reproductive success were generally comparable to controls with the exception of slightly smaller litter size in the HD combination. In addition, several F₁ animals from HD combination and TPM groups had external malformations consistent with known TPM teratogenicity.

Key study findings:

- Parental (P) body weight (↓8-13%) and body weight gain (↓ 29%) were reduced in HD combination dams throughout treatment during pregnancy. During lactation BW remained lower but BW gain recovered so BW reduction was stabilized.
- BW trends were similar in PHEN and TPM only P₀ controls but to a lower magnitude (approximately 5-8% reduced BW).

³ Drug exposures were not measured. Maternal exposure was estimated from female exposures measured in a 3-month rat combination toxicity not measured (Carlson, NDA Review #1, 10/1/10).

- Reduced BW gain was consistent with the expected PD effect of weight loss. BW reduction did not significantly effect most P pregnancy outcomes, but number of live pups/litter was reduced in HD combination (10 pups/litter) compared to controls (12.3 pups/litter).
- F₁ survival after delivery was markedly reduced in HD combination and PHEN treated dams. There was complete litter loss between LD 0 and LD 4 in 46% and 25% of HD combination and PHEN dams. Pup survival was virtually 100% in all other litters, with no treatment-related effect of survival in other groups or in any group after culling on LD 4.
- F₁ BW was reduced in all treatment groups. Pup weights were reduced only in HD combination at birth (↓5-6%), in all treatment groups by LD 7 and continued through weaning at LD 21 (↓6-24%) and post-weaning at PND 28 (↓5-19%).
- F₁ external macroscopic observations identified malformations in HD combination and TPM groups consistent with TPM-induced fetal malformations including limb (ectrodactyly and brachydactyly), tail (missing or portion missing) and eye (macrophthalmia) abnormalities.
- Developmental delays, consistent with delayed growth (i.e., reduced BW gain) were seen in treatment groups. LD combination effects were modest and limited to delayed eye opening. HD combination effects were most pronounced, consistent with greatest delayed growth, and included delayed pinna attachment and eye opening, delayed sexual maturation (vaginal opening or preputial separation), and slightly reduced activity at the earliest time points during behavioral assessments.
- Development delays did not affect learning and memory or neurological development.
- F₁ fertility and reproduction were largely unaffected by pre- and postnatal exposures and corresponding delayed growth and maturation. Number of corpora lutea were significantly reduced in HD combination F₁ pregnancies (15/dam) compared to controls (17/dam), which led to trends of reduced implantation and smaller litter size. The biological significance of approximately 1 fewer pup per dam is not clear but may be attributable to smaller maternal size as BW remained reduced by 7-9% in HD combination F₁ dams.

Study no:	1060-042
Study report location:	eCTD 4.2.3.5.2
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	3/15/09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phentermine HCl, Batch 0840775, 99.8% purity; Topiramate, Batch 70792AA010, 100.4% purity

Methods

Doses: 0, 1.5/10, 11.25/75, 11.25/0 (PHEN control), 0/75 (TPM control) mg/kg PHEN/TPM

Frequency of dosing: Daily

Dose volume: 10 ml/kg

Route of administration: Oral gavage

Formulation/Vehicle: PHEN – solution in distilled water
TPM – suspension in 0.5% methylcellulose (4000 cps) in deionized water

Species/Strain: Pregnant female SD rats / CrI:CD®(SD)

Number/Sex/Group: 25

Satellite groups: None

Study design: 8-10 wk old pregnant females (P) acclimatized from arrival (GD 0), dosed GD 6 to LD 20; pregnancy outcome documented, F₁ offspring culled to 4/sex/litter on LD 4, culled litters nursed through LD 21; F₁ neurobehavioral assessment LD 2 (static righting reflex, pinna detachment), LD 11 (cliff aversion), LD 13 (eye opening), LD 16 (air drop righting reflex), LD 21 (neuropharm, modified Irwin assay), PND 22 (auditory, Preyer's, response), PND 28 (♀ vaginal opening), PND 35 (♂ preputial separation; ♂,♀ motor activity), PND 70-80 (learning and memory 'step-through passive avoidance test); culled to 1/sex/litter PND 28, individually housed until mating at ≥80 days old (F₁ x F₁ cross by treatment); F₁ reproduction – pregnancy status, embryos, resorptions, implants, corpora lutea assessed GD 13, gross pathology (congenital anomalies) of F₁ dams & F₁ males at necropsy

Deviation from study protocol: Several minor deviations were documented and did not affect the outcome or conclusions.

Study Design Summary

Group Assignments			
Group Number	Dose Level (mg/kg/day)		Number of Time-mated Females
	PHEN	TPM	
1	0 (Distilled water)	0 (0.5% Methylcellulose)	25
2	1.5	10	25
3	11.25	75	25
4	11.25	NA	25
5	NA	75	25
NA – Not Applicable			

Observations and Results:P (F₀) Dams – Summary

- Survival: No apparent treatment-related findings. A single (1/25) PHEN control female (No. 297; 11.25 mg/kg/d PHEN) was euthanized *in extremis* on LD1 with a prolapsed vagina after delivery of 13 pups (4 stillborn, 9 alive).
- Clinical signs: NOAEL = LD combination. Increased activity attributable to PHEN was seen in both HD combination and HD PHEN dams. Increased salivation was also seen in HD combination. Other signs were seen at low incidence in HD combination and/or HD positive controls (aggressive behavior, discharge/ lacrimation, sparse hair certain regions > controls, rapid breathing, excessive licking (lactation phase)).
- Body weight: NOAEL = LD combination. BW and BW gain were decreased in HD combination and to a lesser extent in PHEN and TPM only groups. Details described below.
- Feed consumption: NOAEL = LD combination. Food consumption decreased with findings consistent with decreased BW effects. Details described below.
- Uterine content: Slight numeric (nss) decreases in mean pups/litter and liveborn pups/litter in LD and HD combination groups. Trend (nss) of increased stillborn index (mean %/litter) in all treatment groups, but overall number of stillborn pups was low. Details described below.
- Necropsy observation: NOAEL = HD combination. Macroscopic – generally unremarkable with exception of 1/25 HD PHEN dam with severe prolapsed vagina after delivery (animal & viable pups euthanized).
- Toxicokinetics: None.
- Dosing Formulation Analysis Homogeneity (99-108% nominal) and concentration (95-113% nominal) of dosing solutions were confirmed at the beginning of the study (homogeneity – wk 1) and throughout dosing (concentration – wks 1, 2, 3, 6). Test articles were not detected in vehicle control dosing solutions.

P (F₀) Dams (additional data and details)

Body Weight – NOAEL = LD combination. BW and BW gain were significantly lower in HD combination dams throughout treatment during pregnancy (BW ↓ 8-13%, ss; BW gain ↓ 29% GD 0-20, ss). During lactation BW remained lower than controls (↓ 8-14%), but BW gain was similar to controls even with continued treatment.

BW and BW gain were also lower in dams treated with PHEN and TPM alone, although to a lesser magnitude. BW was significantly lower in PHEN dams only at the end of gestation (↓ 5-7%, GD 17-20, ss) and continued during lactation (↓ 6-8%, ss), while BW gain was reduced significantly during pregnancy (↓ 17% GD 0-20, ss) but not during lactation. There was a trend of reduced BW in TPM only dams during pregnancy (BW ↓ ≤6%, nss), which was accompanied by significantly decreased BW gain (-11% GD 0-20, ss) and which persisted as significantly lower BW during lactation (BW ↓ ≤6%, ss). Consistent with HD combination animals, BW gain was comparable to controls during lactation for PHEN and TPM only groups.

Reduced BW gain in treatment groups was consistent with the intended pharmacodynamic effect and consistent with an expected increased effect of combined PHEN/TPM compared to effects of either drug alone.

Feed Consumption – NOAEL = LD combination. Food consumption trends were consistent with BW trends and consistent with the intended pharmacodynamic effect. That is, food consumption decreased in the HD combination group during treatment, with the effect more pronounced during pregnancy (↓ 21%) compared to during lactation (↓ 13%). Food consumption was decreased in PHEN and TPM only groups during pregnancy and in TPM only animals during lactation. The reduced food consumption contributed to decreased BW gain in the various treatment groups.

Necropsy (Implantation Sites, Pre- and Post-Implantation Loss, etc.) – There were no apparent drug-related effects and no statistical findings on gestation, delivery, or pregnancy. There were slight numeric decreases in mean pups/litter (11.8 and 11.4 vs. 12.5, nss) and liveborn pups/litter (11.7 and 11.3 vs. 12.4, nss) in LD and HD combination groups, respectively, compared to controls. Number of stillborn pups/litter was low in all groups (nss), but there was a trend (nss) of increased stillborn index (mean %/litter) in all treatment groups, 0.91, 0.89, 1.86, 1.32 compared to 0.59 in controls.

F₁ Generation

Survival/Mortality – NOAEL = LD combination. While there was no significant decrease in liveborn pups in treatment groups, pup survival to LD 4 prior to culling was significantly decreased in HD combination. The number of live pups/litter was reduced in the HD combination (10 vs. 12.3 in controls; ss) and there were numeric trends (nss) for decreased live pups/litter in LD combination (11.6, nss) and PHEN (11.4, nss) groups. Viability index (mean %/litter) was also decreased in HD combination (49.27%,

ss) and PHEN (74.26%, ss) compared to virtually complete survival in controls (98.89%), LD combination (99.28%) and TPM (98.69%).

The poor mean pup survival at LD 4 was attributed to complete litter loss in 11/24 (46%) dams in HD combination and 6/24 (25%) PHEN dams. There was evidence of maternal neglect, abuse, and/or cannibalization in the litters with complete pup loss. Pup survival was 100% in the remaining litters in HD combination and PHEN groups. That is, there was either complete litter loss or total litter survival in the affected HD combination and PHEN dams after delivery.

Clinical Signs (postnatal days 0 – 21) – NOAEL = LD combination. As noted above, there was evidence of maternal neglect, abuse (lacerations or puncture wounds), or cannibalization in HD combination and PHEN pups in a portion of the litters. Pups also had decreased activity and/or were cold to the touch in affected litters. Low incidences of transient breathing difficulty was seen in pups in all groups, with slight numeric increases in treatment groups (4/4, 7/7, 8/7, 9/9, 1/1 incidents/animals affected in respective groups).

Body Weight – Pup weights (F_1) were assessed at birth (LD 0) and throughout lactation. Trends were consistent across sexes and descriptions are for sexes combined unless noted. Mean pup weights were significantly lower than controls (6.77 g) at birth only in the HD combination group (6.42 g, ss), a reduction of approximately 5-7%. Slight numerical reduced mean pup weight was seen in TPM (6.55, nss). By LD 4 prior to culling, pup weights were lower in all treatment groups, slightly in LD combination (\downarrow 3%, nss) and reaching statistical significance in HD combination (\downarrow 17%, ss), PHEN (\downarrow 11%, ss), and TPM (\downarrow 8%, ss) groups. F_1 body weights remained lower throughout lactation in offspring reared to sexual maturity (4/sex/group post-culling on LD 4). Reduced F_1 BW was significant in all groups after LD 7, with approximate BW reductions at weaning (LD 21) of 6%, 24%, 10%, 12% and at post-weaning (PND 28) of 5%, 19%, 8%, and 10% in LD, HD combinations, PHEN, and TPM groups, respectively. Data showed slight recovery of BW after exposure through maternal milk ended at weaning.

The modest reduced pup BW in LD combination animals was within the historical control range. It was difficult to interpret pup BW in the context of historical control data because concurrent control mean BW (59.86 g) at weaning (LD 21) was outside the historical upper range (47.35 – 56.24 g) and LD combination BW (56.19 g) was at the top of the historical range. Trends were similar at post-weaning on PND 28. The modest reduction in LD combination BW (max. \downarrow 6%) is consistent with the expected pharmacologic effect of BW loss and in the absence of other adverse effects on development (e.g., physical or neurological development) would not necessarily be considered adverse for a weight loss drug.

Macroscopic observations – Overall there were low incidences of macroscopic effects in pups attributable to treatment. Of the pups in the HD combination and PHEN litters that did not survive until LD 4, there was evidence of maternal neglect (bite wounds and

cannibalization) which was considered treatment-related. There no treatment-related macroscopic findings in LD combination animals.

External malformations were observed in several pups that died on study, were culled on schedule at LD 4, or that survived to examination on PND 28 (see reviewer's Table 1, below). Most malformations were in HD females, including both forepaw and hindpaw limb malformations. Forepaw ectrodactyly (3 animals) and hindpaw brachydactyly (3 animals) are consistent with limb malformations described in the product label for topiramate. Additional malformations were also consistent with findings described for topiramate, including tail absent (2 HD combination females) or portion absent (1 LD combination male) and eye macrophthalmia (1 TPM male). No historical data was provided for macroscopic observations and the Sponsor's study report did not discuss the malformations. The abnormalities were considered treatment-related based on consistency with topiramate-mediated teratogenesis, dose-relationship and absence in concurrent controls, and low background incidence in embryofetal rat development studies.

Table 1 – External F₁ macroscopic abnormalities

		Macroscopic Observations (F ₁ pups) †									
Tissue	Finding	Male (#)					Female (#)				
		C	LD	HD	PHEN	TPM	C	LD	HD	PHEN	TPM
Forepaw	Ectrodactyly	0	0	0	0	0	0	0	3	0	0
Hindpaw	Brachydactyly	0	0	0	0	0	0	0	3	0	0
Tail	Absent, portion	0	0	1	0	0	0	0	0	0	0
	Absent	0	0	0	0	0	0	0	2	0	0
Eyes	Macrophthalmia	0	0	0	0	1	0	0	0	0	0

† Malformations or other findings, combined from animals that died on study, were culled as scheduled on LD 4, or at scheduled observation post-weaning on PND 28
 C = control, LD = 1.5/10 mg/kg PHEN/TPM, HD = 11.25/75 mg/kg PHEN/TPM, PHEN = 11.25 mg/kg PHEN, TPM = 75 mg/kg TPM

Physical Development – Several development endpoints in the F₁ generation were assessed at various times after birth, including neurobehavioral assessment LD 2 (static righting reflex, pinna detachment), LD 11 (cliff aversion), LD 13 (eye opening), LD 16 (air drop righting reflex), LD 21 (neuropharmacological, modified Irwin assay), PND 22 (auditory, Preyer's, response), PND 28 (♀ vaginal opening), PND 35 (♂ preputial separation; ♂,♀ motor activity), and, PND 70-80 (learning and memory 'step-through passive avoidance test).

Developmental delays, consistent with reduced pup body weights and delayed growth were observed and are shown in reviewer's Table 2, below. Trends included delayed static righting reflex (< 1 d, nss) and significantly delayed pinna detachment (0.7 d, ss) and eye opening (0.9 d, ss) in the HD combination. Slight delays were also seen in pinna detachment in TPM (0.4 d, ss), eye opening in the LD combination (0.4 d, ss) and air drop righting reflex in the PHEN (0.2 d, ss) groups. Sexual maturation, as evidenced by age at female vaginal opening or male preputial separation, was significantly delayed in HD combination females (approximately 1 d) and males (approximately 3 d). BW at respective sexual maturation endpoint remained lower consistent with reduced BW at post-weaning on PND 28.

Behavioral observations based on motor activity showed transiently, slightly reduced activity in HD combination males and females at the start of observations (0-5 min). Reduced activity was more pronounced in males, reaching statistical significance only in males and only for fine movement (-11%, ss) and rearing (-27%, ss). There were no differences from controls after the first 5 min period (i.e., from 5 min to 20 min during testing).

There were no treatment-related effects on auditory response.

Table 2 – F₁ Physical development

F ₁ physical development and sexual maturation †											
Endpoint	Units	Total (sexes combined) (\bar{x})									
		C	LD	HD	PHEN	TPM					
Static Righting Reflex	(Days)	2.5	2.5	2.8	2.4	2.6					
Pinna Detachment	(Days)	2.4	2.6	3.1**	2.7	2.8*					
Eye Opening	(Days)	14.5	14.9*	15.4**	14.7	14.8					
Air Drop Righting Reflex	(Days)	16.1	16.1	16.1	16.3**	16.1					
		Male (\bar{x})					Female (\bar{x})				
		C	LD	HD	PHEN	TPM	C	LD	HD	PHEN	TPM
Vaginal Opening	(Days)						32.0	31.8	32.9*	32.8	32.7
Body Weight on day passed vaginal opening	(g)						119.7	111.4*	105.1**	115.9	118.1

Preputial Separation (Days)	43.2	44.2	46.3**	44.9	44.4					
Body Weight on day passed vaginal opening (g)	257.2	256.2	242.2	244.3	233.5**					

† Sexes combined for endpoints other than sexual development

C = control, LD = 1.5/10 mg/kg PHEN/TPM, HD = 11.25/75 mg/kg PHEN/TPM, PHEN = 11.25 mg/kg PHEN, TPM = 75 mg/kg TPM

* p < 0.05, ** p < 0.01

Neurological Assessment – Learning and memory were assessed by ‘step-through’ passive avoidance in which the natural tendency to move from a bright area to a dark area is negatively reinforced. There were no significant learning and memory differences in treatment groups compared to controls. Neurologic development was also unaffected by treatment based on absence of effects in a modified Irwin assay (i.e., ‘neuropharmacologic assessment’).

F₁ Reproduction

Clinical observations of F₁ rats selected for reproductive assessment were generally unremarkable through mating (males weeks 1 to 13, females weeks 1 to 10 and gestation days 0 to 13). Sporadic observations were seen in low incidence in the HD combination, limited to aggressive behavior (2/25 ♂), hypersensitive to touch (2/25 ♂), and vocalization (4/25 ♂, 16 total observations) in males and tail bent (1/25 ♀) in females. During gestation, there single incidences of hypersensitive to touch and vocalization in 2/25 HD combination F₁ dams. One F₁ male that had successfully mated was found dead on day 67, with necropsy showing large intestines distended with gas.

Body weight generally remained significantly reduced in all treatment group males and females throughout the F₁ reproduction period. At study termination in males (F₁ week 13), BW remained statistically lower in LD combination (-6%), HD combination (-14%), PHEN (-7%), and TPM (-11%). Female pre-mating BW remained significantly lower in all treatment groups through F₁ week 5 and slightly lower at F₁ week 8 in LD combination (-5%, nss), HD combination (-9%, ss), PHEN (-5%, nss), and TPM (-3%, nss).

BW in F₁ dams during pregnancy were similar to controls in all groups except HD combination, which continued to have significantly reduced BW from GD 0 (-9%, ss) to GD 13 (-7%, ss). BW gain during pregnancy was similar across all groups.

Pregnancy success was similar across treatment groups. Nearly all F₁ females and males paired and mated with no treatment-related effect on time to copulation. Pregnancy parameters included mating index ≥92% ♀ and ≥96% ♂, fertility index ≥88% ♀ and ♂, and fecundity index ≥92% ♀.

Number of corpora lutea were significantly lower in HD combination dams (\bar{x} = 15.0) compared to controls (\bar{x} = 17.0), which corresponded to trends of reduced implantation sites (14.7 vs. 16.0, nss) and slightly smaller litter size (13.9 vs. 14.9, nss) compared to controls. No other pregnancy parameters were affected by treatment, including preimplantation or postimplantation loss and early or late resorptions.

Macroscopic findings of mature F₁ males and females were unremarkable.

10 Special Toxicology Studies

VIVUS was required to submit a comprehensive assessment of nonclinical teratogenic potential of topiramate and phentermine/topiramate combination exposure. Prior FDA determination of safety and effectiveness of topiramate concluded exposure during embryofetal development caused fetal malformations in three animal species. The teratogenic findings are described in the drug labels for indicated uses of topiramate. The CR requirement was not intended to facilitate a reevaluation of FDA's prior determination of topiramate's teratogenic potential; rather, the goal was for the Sponsor to critically evaluate the potential mechanisms of teratogenicity in the context of apparent differences in species sensitivity and the relationship of malformations across species (including humans).

Non-clinical assessment of teratogenic potential

Non-GLP (literature and data review), signed 9/29/11

Submission Title: Non-Clinical Review of Topiramate and PHEN/TPM Teratogenic Potential

A review of public data and published literature was submitted to address the Division's CR requirement for a comprehensive assessment of topiramate's teratogenic potential including "nonclinical and clinical data". The exact mechanism or mechanisms by which topiramate promotes weight loss is not completely understood but it is believed to affect multiple systems including voltage-gated ion channels, modulation of GABA receptors, and carbonic anhydrase inhibition. Similarly, the teratogenic mechanism(s) of topiramate have not been defined but may include multiple targets during embryofetal development. This pharmacology/toxicology review will identify several important points of disagreement or omission from the Sponsor's conclusions but it will not describe or critique every detail of the Sponsor's assessment.

The Sponsor's assessment of teratogenic potential primarily compared and contrasted findings from different animal species but did not directly address species differences with respect to topiramate mechanisms. The nonclinical discussion started with the assertion that topiramate is not teratogenic in humans, a conclusion that is not shared with the FDA based on a recent updated finding of safety and effectiveness that led to warnings of human fetal risk for listed topiramate drugs. The assertion is also in contrast to the current proposed label for phentermine and topiramate FDC contraindication in pregnancy based on concerns of cleft palate/lip. The discussion also seemed to compartmentalize each species effect as isolated from other species rather than consider potential common teratogenic relationships across species. As such, this reviewer considers the Sponsor's assessment seriously flawed because of a failure to consider animal findings in the context of fetal effects across all species investigated, including humans.

Public data and the FDA's prior conclusions about safety and effectiveness show topiramate caused fetal malformations in all animal species investigated (mouse, rat,

rabbit, and human). This reviewer does not consider it appropriate for the Sponsor to consider individual species' findings in isolation, which led to their assertion that none of the findings are relevant to human risk. A specific example relates to the role of carbonic anhydrase (CA) inhibition. Topiramate inhibits CA and it is thought that CA inhibition likely contributes to topiramate-induced pharmacology and toxicity; however, neither all of the weight loss effects nor all of the teratogenic effects can be attributed to CA inhibition. The sponsor noted there are species differences in CA expression and activity but data are not sufficient to account for all similarities and differences in teratogenic findings across species. For example, limb malformations due to specific CA inhibition in rodents are well studied but topiramate-induced limb malformations do not follow the exact same patterns. Levels of CA expression and sensitivity to CA inhibition also do not correspond directly to specific malformations or documented species susceptibility to topiramate-induced teratogenicity.

Rabbits seem to be more sensitive than mice or rats to topiramate-induced maternal toxicity. The sponsor noted fetal malformations occur at topiramate doses that cause maternal death and abortion, which could be attributed to drug-induced reduced body weight rather than drug-related toxicity.⁴ However, malformations in rabbits include skeletal malformations and cleft palate that may have similar topiramate-mediated mechanisms as limb malformations in rat and cleft palate in mouse and human. The sponsor did not investigate or discuss the potential biological significance of rabbit malformations that were previously considered drug-related.

Similarly, the sponsor dismissed some of the teratogenic findings in animals, particularly mouse, because of reduced maternal body weight gain and subsequently reduced fetal body weights. However, reduced maternal weight gain and even frank weight loss during pregnancy due to caloric restriction and not confounded by potential drug-induced maternal toxicity (i.e., absence of chemical treatments that cause reduced body gain) do not appear sufficient to cause fetal malformations in rat or rabbit.^{5,6} It is possible that small fetal size or strain sensitivity contributed to oral cleft malformations in mice, but clefts and other fetal malformations in mice increased with increased topiramate treatment compared to concurrent controls, supporting a drug-related effect (see Sponsor's summary in Table 3).

⁴ Matusuzawa T et al. (1981) *Toxicology* 22:255-259

⁵ Fleeman TL et al. (2005) *Birth Defects Research (Part B)* 74:442-449

⁶ Petrer JA et al. (1993) *Fundam Appl Toxicol* 21:517-522

Table 3 - Sponsor summary of mouse malformations (topiramate)

TPM Dose mg/kg	0	20	100	500	Historical Control CD-1 Upper limit*
No. litters	24	24	26	22	341–403
Relevant malformations in fetuses (# fetuses / # litters)					
Cleft palate	1/1	2/2	4/3	6/2	7/3
Folded retina	1/1	1/1	1/1	2/1	4/3
Ablepharon (open eyelid)	0	2/2	2/2	3/3	3/1
Exencephaly	0	0	1/1	1/1	1/1
Limb/digit abnormalities	0	1/1	1/1	0	9/9
Hydronephrosis	1/1	0	0	1/1	NR
(b) (4) Values are the highest incidence per study in 16– 19 studies conducted between 2004–2008. NR: Not Reported Source: Topamax SBA ⁸					

An additional limitation to the Sponsor's discussion of teratogenic findings in different species is the absence of a discussion of potential differences in pharmacokinetics/toxicokinetics or metabolism. While topiramate is not extensively metabolized in animals, several metabolites have been identified in animals and humans. Topiramate protein binding is also similar across species, with approximately 6 to 17% binding in rat, rabbit, and mice corresponding to 83-94% free drug in plasma. It is not clear if PK/TK or metabolism differences contribute to species differences (or similarities) in teratogenic effects of topiramate, but the possibility cannot be dismissed without further analysis.

Finally, as noted above, the Sponsor's nonclinical assessment of teratogenic risk lacks an adequate discussion of potential similarities between malformations across species. It is interesting and puzzling that topiramate causes several different types of malformations in different species. It is possible that the wide variety of malformations arise from similar embryologic tissues or similar, unexplained topiramate-induced toxicity common to different fetal tissues during organogenesis. The large variety of fetal malformations makes it difficult to explain any common origin or mechanisms, but also precludes discounting all observed fetal abnormalities with respect to hazard identification and potential risks to human fetal development.

11 Integrated Summary and Safety Evaluation

The proposed FDC capsule of PHEN/TPM was submitted in accordance with 21 USC 505(b)(2) for treatment of obesity. The individual drugs are both currently approved for use as monotherapy or adjunct therapy and the NDA relies in part on the FDA's previous findings of safety and effectiveness. The original application was recommended for approval by this pharmacology/toxicology reviewer, contingent on a pregnancy Category X label to contraindicate use in pregnant women.

One new pivotal GLP study, an evaluation of pre- and postnatal rat development when exposed to phentermine and topiramate during organogenesis and lactation, was submitted and reviewed for this review cycle. An assessment of Qnexa's teratogenic risks consisting of the Sponsor's review and discussion of public data and published literature was also submitted in accordance with 21 USC 505 (b)(2) regulations. This pharmacology/toxicology review focused on the new information submitted but was not intended to be a reevaluation of the FDA's prior determinations of safety and effectiveness for the listed drugs or the proposed FDC drug.

The pre- and postnatal rat study was appropriately designed to assess potential toxicity of combination phentermine and topiramate treatment during organogenesis and lactation compared to concurrent vehicle, phentermine only, and topiramate only treatments. Maternal and fetal results were generally consistent with expected effects of individual and combination drug treatments. Dose-related reductions in maternal body weight and body weight gain led to slightly reduced weight and growth and development of pups which was considered consistent with the expected pharmacodynamic effect and not considered toxicologically significant. The NOAEL combination dose of 1.5 mg/kg phentermine and 10 mg/kg topiramate resulted in approximately 2-times and 3-times plasma exposure by AUC compared to estimated maximum clinical doses for PHEN and TPM, respectively.

The pre- and postnatal rat high dose combination of 11.25/75 mg/kg PHEN/TPM provided plasma exposures approximately 5-times and 6-times estimated MRHD, respectively. Rat exposures were approximately 5-fold higher than combination doses previously investigated during rat embryofetal development and resulted in modest maternal toxicity including adverse clinical signs (aggressive behavior, discharge/lacrimation, alopecia, rapid breathing, excessive licking) and moderate, persistent reductions in body weight gain. F₁ pup survival was markedly reduced in the PHEN only group (-25%) and exacerbated when combined with HD topiramate (-46%). Pups that survived to LD 4 generally survived to adulthood but reduced birth weights persisted throughout development and resulted in biologically significant delayed growth, development, and sexual maturation. However, reduced body weights and delayed development did not affect learning, memory, fertility or reproductive success in the offspring.

Importantly, offspring in the pre- and postnatal rat study had external malformations consistent with known TPM teratogenicity. Pre- and postnatal development studies are not designed with comprehensive assessments of fetal malformations, but routine macroscopic observations of all offspring at various developmental time points identified limb (ectrodactyly and brachydactyly), tail (missing or portion missing) and eye (macrophthalmia) abnormalities. Similar malformations have previously been observed in various species treated with topiramate during development. In the study a single malformation was observed in a TPM only control animal, with all other malformations observed only in the HD combination, suggesting phentermine coadministration exacerbated known topiramate drug-related teratogenesis. No remarkable increase in toxicity was observed previously in phentermine and topiramate combination studies, but high doses in the pre- and postnatal study were about 5-fold higher than doses in prior developmental toxicity studies.

Teratogenic findings listed in approved topiramate labels suggest rats are 5- to 10-fold less sensitive to topiramate-related teratogenicity. However, the malformations in the pre- and postnatal study suggest rat sensitivity to topiramate teratogenicity may be similar to rabbits. The Sponsor's toxicity study report did not address the apparent fetal malformations, but the new data provide further evidence of topiramate teratogenicity relevant to human risks. The new rat data, coupled with rabbit and mouse data, further support a conclusion that topiramate is teratogenic in animals at approximate clinical exposure (ranging from 2- to 6-times estimated exposures for proposed obesity treatment).

The Sponsor did submit a "comprehensive assessment" of nonclinical teratogenicity of topiramate. A serious limitation of the discussion was the Sponsor's assertion that topiramate is not teratogenic in humans, as their nonclinical discussion focused on supporting their conclusion about limited human risk. However, the Sponsor did not indicate the recent update to the drug label for listed topiramate uses to pregnancy Category D. The new drug label confirms the FDA's finding of safety and effectiveness that there is adequate evidence of human fetal risk and topiramate "use during pregnancy can cause cleft lip and/or palate".⁷

This pharmacology/toxicology reviewer concludes evidence in nonclinical species has clearly identified a potential hazard to humans (i.e., fetal malformations). The mechanisms that contribute to topiramate-induced reproductive toxicity in non-clinical species remain incompletely defined. The Sponsor's conclusions that teratogenesis in mice administered topiramate is consistent with spontaneous background malformations and that teratogenesis in the additional two species, rats and rabbits, is a consequence of reduced maternal body weight are not persuasive. The presence of teratogenesis in three species administered topiramate identifies a potential teratogenic hazard, but differences in species susceptibility and an incompletely defined mechanism

⁷ NDA 020505/S-042 and NDA 020844/S-036, FDA Approved Labeling Text dated July 15, 2011 (Topamax® (topiramate) Tablets for oral use and Topamax® (topiramate) Sprinkle Capsules for oral use)

preclude confidence in quantitatively assessing risk to human patients. In consideration of the existing animal and human data available for topiramate, it is unlikely that additional nonclinical studies would provide more than incremental information for human risk assessment.

The proposed indication currently excludes pediatric use. Pediatric clinical trials are expected as part of a pediatric plan, including deferral for adolescents (aged 12-17) and younger children (aged 7-11) and a waiver for children up to 6 years old. Clinical trials have evaluated the safety of the proposed drug combination in adults but safety assessment in children has not been assessed. Topiramate has been studied in juvenile animals but neither phentermine nor combined phentermine and topiramate have been assessed in juvenile animals post-weaning. Phentermine and topiramate are active in the central nervous system and cause neurological adverse events in some patients. Topiramate affects bone mineral density and growth plate density in juvenile animals and phentermine causes teeth toxicity in adult animals. Bone, teeth, brain and nervous system development continue throughout childhood and adolescence whereas toxicity in adults may be different. For example, nervous system toxicity in early life can lead to permanent behavioral, learning, and memory changes in animals and humans. Because both drugs act on nervous and bone systems, there are theoretical concerns that phentermine alone may cause irreversible toxicity and phentermine coadministration may potentiate topiramate induced toxicity. Behavioral, nervous system, and bone/teeth development should be assessed in juvenile animals prior to subjecting children to an unknown risk for permanent developmental toxicity. The severity of retinal degeneration and/or atrophy was also increased in rats with chronic phentermine treatment, so juvenile animal studies should also carefully assess ocular toxicity. Finally, reversibility should be assessed in juvenile animals to assess recovery of toxicity after stopping treatment.

Juvenile animal studies with phentermine and topiramate coadministration should be conducted prior to pediatric clinical trials to investigate reversibility of any toxicity, particularly drug-related effects on behavior, learning and memory, and general nervous system and bone/teeth development. However, if the available clinical data show an acceptable benefit to risk profile in adults, there is no reason to require juvenile animal studies prior to approval for proposed use in adults.

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/s/

DAVID B CARLSON

03/22/2012

CR #1 - Pharmtox approval recommendation contingent on contraindication in pregnancy

TODD M BOURCIER

03/22/2012

pharm/tox supports AP

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-580

Supporting document/s: Original Submission (and updates)

Applicant's letter date
(CDER Stamp Date): 28 December, 2009 (12/28/09)

Product: Qnexa (phentermine HCl + topiramate FDC)

Indication: Obesity

Applicant: VIVUS, Inc.

Review Division: Metabolism and Endocrinology Products

Reviewer: David B. Carlson, Ph.D.

Supervisor/Team Leader: Todd Bourcier, Ph.D.

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Review Notes and Abbreviations/Key

Some of the sponsor's tables and figures from the electronic NDA submission have been included and cited in this review. All drug-related trends are discussed in relation to concurrent vehicle control groups in each study unless otherwise noted. Vehicle for oral gavage administration was water for phentermine and 0.5% methylcellulose for topiramate unless otherwise noted. Common animal strains were used and abbreviated by common animal name, unless noted, as follows: Sprague-Dawley rat, CD-1 mouse, Beagle dog, Cynomolgus monkey, New Zealand White rabbit. Reviews of some studies previously reviewed under IND 68,651 are cited and summarized in this NDA review.

Key: Phentermine HCl (PHEN); topiramate (TPM); fixed-dose combination (FDC), once daily dosing (QD), twice daily dosing (BID); dosing groups – LD (low dose), MD (mid dose), LMD (low mid dose), HMD (high mid dose), HD (high dose); mg/kg (mg/kg/day); MRHD (maximum recommended human dose); NOAEL (no observed adverse effect level); LOAEL (lowest observed adverse effect level); statistically significant (ss); not statistically significant (nss); IR (immediate release), MR (modified release), DR (delayed release); PD (pharmacodynamic), PK (pharmacokinetic), TK (toxicokinetic); BW (body weight); GD (gestation day); central nervous system (CNS), peripheral nervous system (PNS)

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1 Executive Summary

1.1 Introduction

The proposed drug is a FDC capsule of two drug substances listed for use in the United States. Phentermine (PHEN) was approved in 1959 for short term (“a few weeks”) management of obesity as an adjunct to diet and exercise. PHEN is indicated for use as an anorectic or appetite suppressant. Topiramate (TPM) was approved in 1996 for chronic use to treat epilepsy and for prophylactic treatment of migraine. The proposed formulation was designed to provide once daily oral dosing with immediate release (IR) of PHEN and modified release (MR) of TPM. The topiramate MR delayed T_{max} , decreased C_{max} , and provided similar total plasma (AUC). According to published information and the Sponsor’s data, PHEN and TPM are commonly prescribed for off-label combination use to treat obesity. The Sponsor claims the FDC capsule will improve safety and efficacy of the individual components by lowering daily dosing and improving the PK profile to maximize effectiveness throughout the day.

The new drug application was submitted in accordance with 21USC505(b)(2) and the Sponsor relied on primary data, publicly available information, and FDA’s previous findings of safety and efficacy to support the proposed use. The nonclinical submission contained literature reviews, PHEN and TPM pharmacokinetic studies, PHEN/TPM combination subchronic toxicity and embryofetal development studies, and a PHEN rat chronic toxicity and carcinogenicity study were submitted. Conclusions in this pharmacology/toxicology review are based on only original studies and public literature, including the FDA’s previous findings of safety and efficacy as reflected in the approved product labels for Adipex-P® (phentermine HCl) and Topamax® (topiramate).

Phentermine is not approved for chronic use and the label on the listed product(s) lacks information about nonclinical toxicology studies required to support chronic use. Topiramate is indicated for chronic use but a different benefit-to-risk determination is required based on a comparison of the listed indications (epilepsy and migraine) and the proposed obesity indication. The new nonclinical data, coupled with the history of approved uses and available public literature, are sufficient to make recommendations of safety and efficacy of the proposed drug combination for a chronic obesity indication.

1.2 Brief Discussion of Nonclinical Findings

All pivotal nonclinical studies were conducted using oral administration of drug, which is the clinical exposure route, and in accordance with US FDA GLP regulations (21CFR58) as stated by Sponsor and confirmed by this reviewer. Combination PHEN/TPM toxicity studies in rat and dog supported the expected pharmacodynamic effect of weight reduction and were sufficient to identify NOAEL exposures.

Safety margins to expected human exposure were estimated with the following conditions:

Maximum recommended human dose (MRHD) = 15 mg PHEN / 92 mg TPM¹

Body surface area (BSA) exposure in an obese population (i.e., 100 kg person) = 6 mg/m² PHEN and 34 mg/m² TPM

Human plasma exposure (AUC₀₋₂₄) = 2.5 µg*h/ml PHEN and 80 µg*h/ml TPM²

The Sponsor used nearly identical BSA and AUC estimates. The human exposures used throughout this review were estimated from single dose exposure in an obese population (Trial OB 103) and extrapolated to steady-state levels using accumulation ratios of 2.5x PHEN and 4x TPM (from multiple dose obesity Trial OB 102). No PK data were available from the pivotal chronic efficacy clinical trials. Any differences in exposure margins calculated in the pharmacology/toxicology review compared to the Sponsor (based on similar NOAELs) are due to the Sponsor's use of a "recommended" clinical dose, which they defined as the mid dose combination. This reviewer based safety margins on exposure at the maximum dose level proposed for marketing, which is the more appropriate analysis.

Overall NOAELs from three-month PHEN/TPM combination toxicity studies and the chronic PHEN toxicity study, with estimated margins to MRHD are:

Rat (3-month) – 1.5 / 15 mg/kg PHEN / TPM = 2X / 3X MRHD

Dog (3-month) – 4.5 / 30 mg/kg PHEN / TPM = 15X / 26X MRHD

Rat (2-year) – Female: 3 mg/kg PHEN = 1X MRHD
Male - 10 mg/kg PHEN = 2X MRHD

Pharmacology

Phentermine is a sympathomimetic amine in the β-phenethylamine family. It is a congener of amphetamine and stimulates norepinephrine (NE) release with approximately 6-fold lower potency than *d*-amphetamine. Compared to amphetamine, PHEN only slightly stimulates dopamine release due to approximately 7-fold selectivity for NE release compared to dopamine stimulation. PHEN seems to have a minor effect on pre-synaptic serotonin (5-HT), with IC₅₀ of approximately 3.5 µM for 5-HT release and 14 µM for 5-HT reuptake, which are approximately 90-fold lower than its effect on

¹ Listed maximum doses are 400 mg (200 mg BID) TPM for epilepsy, 100 mg (50 mg BID) TPM for migraine, and 37.5 mg PHEN HCl QD (30 mg PHEN free base)

² The FDA Clinical Pharmacology review noted exposures from a single dose trial of AUC₀₋₂₄ = 2.5 µg*h/ml PHEN / 62 µg*h/ml TPM and similar 2.5x and 4x accumulation ratios

NE stimulation. Despite the available information on neurotransmitter effects, it is not clear which mechanisms contribute directly to PHEN-induced weight loss. Weight loss seems to occur due to a combination of anorectic (decreased food consumption), thermogenic (increased metabolic activity), and drug-induced increased physical activity.

Topiramate is active in the central nervous system (CNS) where it is thought to exert anticonvulsant and migraine prophylactic effects for the approved indications. Several potential effects of the known CNS-modulating activity of TPM have been implicated in weight loss. Modulation of voltage-gated ion channels may affect resting metabolic rate, pancreatic hormone secretion, and modulate neurotransmitter and neuropeptide release, all of which may affect overall energy expenditure and homeostasis. Modulation of GABA receptors has been implicated in food intake and body weight regulation, including increased weight gain with clinical use of several GABAergic drugs (particularly those that increase GABA_A activity). Topiramate may exert a distinct effect on GABA modulation to result in weight loss rather than weight gain. Inhibition of carbonic anhydrase activity can inhibit hepatic lipogenesis and may contribute to TPM-induced effects on lipid metabolism and weight loss. NMDA receptors may also be inhibited indirectly by TPM inhibition of carbonic anhydrase, which may inhibit NMDA-modulated feed intake centers in the hypothalamus. The Sponsor also postulates that TPM effects in the gut, for example decreased gastrointestinal motility, may promote satiety and further improve the weight loss effects.

Potential for phentermine-induced primary pulmonary hypertension (PPH) and vascular heart disease (VHD) in lung and heart is a concern based on clinical toxicity with 'fen-phen' and 'dexfen-phen' combination use for weight loss. There was no evidence of pulmonary hypertension or heart disease in animal toxicity studies with phentermine or PHEN/TPM co-administration, although heart valves were not specifically examined in toxicity studies. The Sponsor, the FDA clinical reviewer, and this nonclinical reviewer conducted independent literature reviews of PPH and VHD and found no evidence to implicate phentermine in pulmonary hypertension or heart valve toxicity. Specifically, the 5-HT_{2b} receptor has been implicated in heart valvulopathy and several studies showed phentermine does not interact with the 5-HT_{2b} receptor and does not otherwise significantly increase lung or plasma serotonin levels.

Treatment-related decreased body weight (dog) and reduced body weight gain (rat) in combination toxicity studies was entirely attributable to PHEN, with no additive or synergistic effect of TPM co-administration. Drug exposure in rat was 2- to 3-fold higher in females than males for PHEN and TPM, respectively. There were no sex differences in exposure in dog.

Toxicology

During the nonclinical review, particular attention was given to assess potential nonclinical effects different from the known clinical side effects. Nonclinical findings similar to known clinical toxicity were also noted. General phentermine toxicity is

consistent with class related effects of sympathomimetics, particularly modest, transient cardiovascular/hemodynamic (palpitations, tachycardia, increased blood pressure) and CNS (overstimulation, restlessness, insomnia, euphoria) effects. The most common clinical side effects of topiramate are paresthesia, anorexia and weight decrease (consistent with the intended PD effect), behavioral effects (fatigue, somnolence, psychomotor slowing), and neurological signs (dizziness, nervousness, memory and concentration/attention difficulty, confusion).

Topiramate toxicity was extensively studied in nonclinical models to support approval of epilepsy and migraine indications but the Topamax® label does not describe general toxicity findings with TPM. The Sponsor's literature review showed TPM findings were generally consistent across species and included decreased body weight gain, clinical signs of decreased activity, ataxia, dyspnea, and convulsions, and liver, kidney, bladder, and stomach target organs. Additional findings included urinalysis and urinary tract effects, serum decreased K and increased Cl, decreased erythrocyte parameters (RBC, Hb, Hct), and altered lipid parameters (cholesterol, triglycerides). Warnings on the Topamax® label highlight known clinical toxicity and target organs, including eye (acute myopia and glaucoma); skin and temperature regulation (oligohidrosis, hyperthermia), neuropsychiatric (suicidal behavior/ideation, cognitive/neuropsychiatric dysfunction); kidney (stones), and metabolic acidosis, hyperammonemia, and encephalopathy.

When the Sponsor investigated PHEN/TPM combination toxicity in rat and dog subchronic studies, general trends showed minimal interactions between drugs and expected toxicity. Increased kidney weight with slightly increased BUN and bone marrow depletion were seen in high dose rat treatment (*PHEN/TPM 2X / 3X MRHD*). Findings in dogs were consistent with expected toxicity and the high dose was considered a NOAEL (*PHEN/TPM 15X / 26X MRHD*). Body weight gain decreased in both rat and dogs, consistent with the pharmacodynamic effect, but there was no apparent additive effect of drugs.

The PHEN chronic toxicity study in rats was designed to investigate carcinogenesis but provided insight into two apparent trends. PHEN treatment caused dose-dependent reduced body weight gain, consistent with the expected pharmacodynamic effect, and a dose-related decrease in background rate of chronic progressive nephropathy (CPN) and improved overall survival (likely due to a combination of reduced body weight and decreased CPN). Clinical signs also showed several treatment-related increases in tooth-related findings (broken, cut, missing, and malocclusion). Food consumption decreased slightly (3-10%) in HD rats, which may be partially attributable to tooth-related findings, however, the anorectic effect of PHEN contributed to body weight changes since food consumption differences alone did not account for dose-related reductions in body weight gain. Phentermine has stimulatory, amphetamine-like effects and tooth-related effects are consistent with literature reports of gum and tooth toxicity with methamphetamine abuse. The mechanism of phentermine-induced tooth toxicity has not been investigated and teeth were not examined histologically, but prevalence of clinical signs support a drug-related effect. In addition, 'palate hole' was noted in several animals, generally in relationship to dose, which was notable because of a possible

relationship to other drug-related findings in the oral cavity. There were no histological effects on bones examined histologically (femur, sternum), suggesting tooth findings may not share a common toxicity with other bone.

The major nonclinical toxicity concern is teratogenicity. Topiramate was found to be teratogenic in several species in reproductive toxicity studies conducted in support of approval for TOPAMAX. The TOPAMAX label lists fetal malformations related to bone growth and development in mouse (primarily craniofacial defects), rat (limb malformations including ectrodactyly, micromelia, and amelia), and rabbit (primarily rib and vertebral malformations). Fetal malformations occurred at clinically relevant doses for listed indications of epilepsy and migraine treatment, but sensitivity varied widely between mouse (most sensitive), rabbit (intermediate), and rat (least sensitive). Sensitivity to teratogenicity ranged from 2x to 34x the MRHD across species. It is notable that teratogenicity occurs in all three species tested and it is difficult to extrapolate where humans fall along this spectrum of sensitivity. The Topamax® label also notes TPM-induced reductions in bone growth plate thickness during male rat juvenile development. There was no apparent effect of topiramate treatment on male or female fertility at clinically relevant doses.

Topiramate teratogenic responses seem consistent with carbonic anhydrase (CA) inhibition and species differences may reflect differences in drug metabolism, CA activity, or biochemical and regulatory responses to acidosis. However, TPM has multiple physiologic effects and the contribution of CA inhibition and metabolic acidosis to development toxicity has not been shown definitively. Pharmacokinetic differences between species and humans may also account for differences in body surface area predictions and actual exposure multiples. For example, both PHEN and TPM significantly accumulate in plasma after repeated dosing, with 2.5- and 4-fold greater steady-state clinical exposure, respectively, compared to single dose exposures. In general subchronic toxicity studies, there was no evidence that phentermine co-administration increased the risk of topiramate-induced metabolic acidosis.

The Sponsor conducted embryofetal development studies in rat and rabbit with combination PHEN/TPM treatments, which were designed to investigate potential additive or synergistic effects on embryofetal development at a non-teratogenic dose of topiramate. Maximum tolerated doses of the combination were not evaluated in the rat and rabbit, but this is acceptable given the intent of the study. Results ruled out synergistic drug interactions at approximate human exposure levels, but they did not alleviate concerns about topiramate teratogenic potential already identified at higher doses. Combination reproductive toxicity study results should be considered in the context of the known teratogenic profile of topiramate in multiple species, the wide range of sensitivity to teratogenesis across species, the data from human pregnancy registries, and the patient population intended for Qnexa.

Neither phentermine nor topiramate showed evidence of genotoxic potential when tested individually. Genotoxicity was not assessed with the PHEN/TPM combination but there were no signals to raise concern about synergistic effects. Topiramate

carcinogenicity was assessed in mice and rats and the Topamax® label notes bladder tumors in mouse with questionable relevance to humans. Phentermine was not carcinogenic in rats (11- to 18-fold MRHD in males and females). Ordinarily, carcinogenic potential is assessed by lifetime treatment in two rodent species for obesity drugs intended for chronic use. However, the absence of a carcinogenic signal after five decades of clinical use and negative carcinogenicity findings in rats provide sufficient evidence that phentermine has limited carcinogenic risk to humans.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended contingent on a Category X label to contraindicate use in pregnant women.

The available nonclinical data clearly identify birth defects as a potential hazard of drug use during pregnancy at approximate human exposure. The topiramate component is teratogenic in all species tested and PHEN/TPM combination embryofetal development studies did not alleviate teratogenic concerns. In the opinion of the pharmacology/toxicology reviewer, this drug should not be used during pregnancy and it should be labeled pregnancy Category X. The final decision on pregnancy labeling will involve multiple disciplines but the pharmacology/toxicology recommendation is consistent with review team discussions and with the Maternal Health Team labeling recommendation.

It is important to highlight two additional concerns. First, there are no apparent additional nonclinical studies that could be conducted to alleviate concerns about potential human teratogenicity. Second, it may be difficult to mitigate risks of drug use in pregnant women due to several factors which were discussed in the public Advisory Committee meeting, including: a large number of women became pregnant while on drug during clinical trials (despite several mitigation steps); hormone and fertility irregularities in the indicated obese population may mask unplanned pregnancies; FDA experience that it is difficult to prevent pregnancies even with Category X labeling and strong Risk Evaluation and Mitigation Strategies (REMS); and, the proposed drug interacts with common estrogen-based hormonal contraceptives.

1.3.2 Additional Non Clinical Recommendations

- 1) Juvenile animal studies are recommended prior to clinical trials in a pediatric population
 - a. Phentermine and topiramate are both centrally acting drugs and no studies have been conducted with the combination to assess either pre- and post-natal development or neurodevelopment in juvenile animals
 - i. Neurotoxicity of both compounds is apparent based on neurological warnings and adverse events on approved drug labels

- b. Topiramate toxicity in developing bone was established in juvenile animal studies
 - i. It is not known whether co-administration of phentermine will exacerbate topiramate-induced toxicity
 - ii. Phentermine chronic administration in rat caused tooth-related toxicity and nothing is known about the mechanism and whether there will be any effects on developing teeth and bone

1.3.3 Labeling

- Nonclinical recommendations to be discussed for final labeling language
 - All labeling relevant to nonclinical data should be updated to include actual plasma exposure margins rather than BSA extrapolations
 - Data from reprotox. studies clearly show BSA extrapolations overestimate the safety margins to clinical exposure
 - 8.1 Pregnancy (8. USE IN SPECIFIC POPULATIONS)
 - Pharmacology/toxicology approval recommendation is predicated on contraindication in pregnant women
 - Pregnancy Category X label is recommended
 - Recommendation is consistent with chronic obesity indication and prior communications/recommendations to the Sponsor throughout drug development
 - Pregnancy Category (b) (4) label for current approved indications are not relevant to the risk:benefit calculation for obesity indication
 - Precedence exists for drugs with different Pregnancy Categories for different indications
 - Embryofetal development studies with PHEN/TPM combination treatment do not support safe use during pregnancy
 - Recommended label language will note:
 - Topiramate teratogenic findings in all species tested
 - Species sensitivity varies widely
 - Human sensitivity is unknown
 - Absence of synergistic response of combination treatment on teratogenesis in rat and rabbit
 - Exposure limited to human exposure
 - Remove language from proposed label
 - 13 Non-Clinical Toxicology
 - Carcinogenesis
 - Topiramate bladder tumors in mice

- Update language to remove reference to [REDACTED] (b) (4)

[REDACTED] doses
[REDACTED] (b) (4)

2 Drug Information

1.2 Drug

2.1.1 CAS Registry Number

Phentermine Hydrochloride (HCl) – 1197-21-3 (HCl salt); 122-09-8 (free base)
Manufacturer's product code - 2610830

Topiramate – 97240-79-4
Manufacturer's product code – SPT1024

2.1.2 Generic Name

Phentermine HCl + topiramate FDC

2.1.3 Code Name

VI-0521

2.1.4 Chemical Name

Phentermine HCl

Benzeneethanamine- α,α -dimethyl-hydrochloride α,α -dimethylphenethylamine hydrochloride

Topiramate

2,3:4,5-Bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate; -or- β -D-fructopyranose, 2,3:4,5-bis-O-(1-methylethylidene)-sulfamate; -or- 2,3:4,5-di-O-isopropylidene- β -D-fructopyranose sulfamate

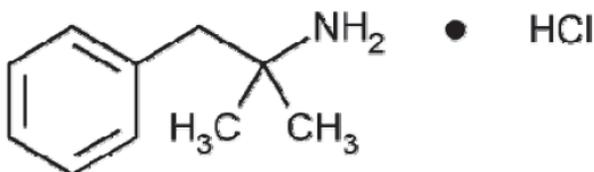
2.1.5 Molecular Formula/Molecular Weight

Phentermine HCl – $C_{10}H_{15}N \cdot HCl$ / 185.69 g/mol (free base 149.23 g/mol)

Topiramate – $C_{12}H_{21}NO_8S$ / 339.363 g/mol

2.1.6 Structure

Phentermine HCl



Topiramate

(b) (4)

2.1.7 Pharmacologic class

QNEXA® is a fixed-dose combination of phentermine, a sympathomimetic amine anorectic, and topiramate, an antiepileptic, indicated for treatment of obesity.

2.2 Relevant IND/s, NDA/s, and DMF/s

Phentermine – NDA 11-613 (Ionamin®) – Approved for short term treatment of obesity (i.e., weight loss), voluntarily withdrawn from market

NDA 88-023 (Adipex-P®) – Approved for short term treatment of obesity (i.e., weight loss) and currently marketed

NDA 85-128 (generic)

Topiramate – NDA 20-505 and NDA 20-844 (Topamax®) – Approved for treatment of epilepsy and prophylactic treatment of migraine

PHEN/TPM – IND 68 651 (obesity)

(b) (4)

DMF –

(b) (4)

2.3 Drug Formulation

Drug product VI-0521 is a FDC capsule (Catalent Pharma Solutions, LLC) containing immediate release (IR) phentermine HCl and modified release (MR) topiramate. Drug substances are formulated as PHEN Beads and TPM Beads and encapsulated in (b) (4) gelatin capsules, with phentermine dose as free base equivalents (Sponsor's Table 1 and Table 2). Composition of PHEN Beads and TPM Beads are shown in the Sponsor's table (Table 3). Composition of the capsule and capsule coating, including food grade inks, are shown in the Sponsor's table (Table 4). Drug substances phentermine HCl and

topiramate and all excipients, with the exception of (b) (4) gelatin capsule shells, are compendial (USP or NF) and specifications are more stringent than existing USP specifications for each drug. Letters of authorization to existing Drug Master Files (DMF) were provided to the NDA for the two drug substances and drug product components, including the (b) (4) gelatin capsules. No toxicity concerns were identified for (b) (4) (Sponsor's Table 5) or impurities. All excipients are within limits previously accepted for approved drug products, (b) (4)

Table 1 – FDC Capsule and Dose Summary

VI-0521 Capsule Dose Strength (PHEN/TPM)	Clinical Terms
3.75/23 mg	Low Dose
7.5/46 mg	Mid-Dose, Half Dose , ½ Dose
11.25/69 mg	Three Quarter Dose, ¾ Dose
15/92 mg	Full Dose

Reviewer's note – doses are equivalent to 2.3/14, 4.6/28, 7/43, 9/57 mg/m²

Table 2 – FDC Capsule Composition

Composition of PHEN/TPM Capsules

Component	PHEN/TPM 3.75/23 mg	PHEN/TPM 7.5/46 mg	PHEN/TPM 11.25/69 mg	PHEN/TPM 15/92 mg
PHEN	(b) (4)			
PHEN	(b) (4)			
	(b) (4)			
Printed (b) (4) Gelatin Capsule ^a	one	one	one	one

^a (b) (4) gelatin capsule colors are assigned by dosage strength (See Table 5).

Table 3 – Composition of PHEN and TPM Beads

Composition of PHEN Beads

Component	Function	PHEN Beads
Phentermine Hydrochloride, USP	Active ingredient	(b) (4)
(b) (4)	(b) (4)	Total (b) (4)
Total		(b) (4)

Composition of TPM Beads and TPM Bead (b) (4)

Component	Function	TPM Beads % (w/w)	TPM Bead % (w/w)
Topiramate, USP	Active ingredient	(b) (4)	(b) (4)
(b) (4)	(b) (4)	Total (b) (4)	(b) (4)
Total		(b) (4)	(b) (4)

Table 4 – Gelatin Capsule Composition

Composition of Printed (b)(4) Gelatin Capsules

Component	Function	% (w/w)	Regulatory References
Capsules for PHEN/TPM 3.75/23 mg- Purple Body, Purple Cap, White Print			
Body and Cap Composition			
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
Titanium Dioxide	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Gelatin	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Printing Ink	(b)(4)	(b)(4)	Food grade ^a
Capsules for PHEN/TPM 7.5/46 mg- Yellow Body (Black Print), Purple Cap (White Print)			
Body Composition (Yellow)			
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
Titanium Dioxide	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Gelatin	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Printing Ink	(b)(4)	(b)(4)	Food grade ^a
Cap Composition (Purple)			
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
Titanium Dioxide	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Gelatin	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Printing Ink	(b)(4)	(b)(4)	Food grade ^a
Capsules for PHEN/TPM 11.25/69 mg - Yellow Body, Yellow Cap, Black Print			
Body and Cap Composition (Yellow)			
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
Titanium Dioxide	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Gelatin	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Printing Ink	(b)(4)	(b)(4)	Food grade ^a
Capsules for PHEN/TPM 15/92 mg - White Body, Yellow Cap, Black Print			
Body Composition (White)			
Titanium Dioxide	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Gelatin	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Printing Ink	(b)(4)	(b)(4)	Food grade
Cap Composition (Yellow)			
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
(b)(4)	(b)(4)	(b)(4)	CFR21/95/45/EC
Titanium Dioxide	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Gelatin	(b)(4)	(b)(4)	USP/EU/FAO/WHO
Printing Ink	(b)(4)	(b)(4)	Food grade

(b)(4)

Reviewer's note – specifications for (b) (4) are consistent with ICHQ3C guidance

2.4 Comments on Novel Excipients

No novel excipients are listed in the drug product. Excipients and (b) (4) are discussed in Section 2.3 with respect to drug formulation. Various lots of drug substances were used in nonclinical and clinical studies.

2.5 Comments on Impurities/Degradants of Concern

Three potential phentermine impurities were identified, (b) (4) were identified as potential topiramate related impurities and specifications are within USP limits (b) (4). A topiramate (b) (4) impurity is the (b) (4) which has a specification limit of

(b) (4) (USP limit is 0.3% and manufacturer limit during drug development was (b) (4)
No other impurities above the (b) (4) identification threshold were identified.

All impurities (b) (4) were present in drug substances used in animal studies, (b) (4) tested in clinical trials and specified in the final drug product.

Eight lots of phentermine HCl from the manufacturer (b) (4) were used in preclinical and clinical trials. One batch purchased from (b) (4) was used for certain preclinical studies. Batch analysis data were provided and confirmed all batches, including the (b) (4) commercial batch, met specifications for impurities (b) (4). Phentermine lots in nonclinical and clinical studies and batch analyses from selected lots are shown in the Sponsor's tables (Table 6 and Table 8).

Several lots of topiramate from the manufacturer (b) (4) were used in preclinical and clinical trials (see Sponsor's Table 7). Batch analysis data were provided and confirmed all batches met specifications for impurities (b) (4) in the commercial product, although the manufacturer's limit was (b) (4) for the batches used during development.

Table 6 – Phentermine lots used during development**Lots Used for Preclinical Studies**

Lot number	Manufacturer (b) (4)	Study Number	Study Type
074K1059		1060-016	Dose Escalation Range Finding in Rats
		1060-017	13-week Repeat Dose Study in Rats
		1060-025	14-day Range Finding Study in Rats
		1060-026	13-week Repeat Dose Study in Rats
		1060-018	Dose Escalation Range Finding in Dogs
		1060-019	13-week Repeat Dose Study in Dogs
		AB29JU.503.BTL	Ames assay
		AB29JU.331.BTL	In vitro cytogenetics assay
		AB29JU.125.BTL	Rat micronucleus assay
0840775		1060-040	Pilot Study for Prenatal Development Toxicity in Rats
		1060-044	Pilot Study for Prenatal Development Toxicity in Rabbits
		1060-041	Study for Effects on Embryo-fetal Development in Rats
		1060-043	Study for Effect on Embryo-fetal Development in Rabbits
0640349		1060-020	2-year carcinogenicity study in rats
0740376			

Reviewer's note – clinical lots were characterized in nonclinical studies, including Lot No. 0640349 (Trials OB-102, OB-103, OB-107, OB-108, OB-109, OB-118, OB-202, OB-205, OB-301, OB-302, OB-303), Lot No. 0740376 (Trials OB-103, OB-107, OB-108, OB-109, OB-118, OB-205, OB-301, OB-302, OB-303)

Table 7 – Topiramate lots used during development

Lots Used for Preclinical Studies			Lots Used for Clinical Studies	
Lot Number	Study Number	Study Type	Lot Number	Study Number
70792AA003	1060-016	Dose-Escalation Range-Finding Study in Rats	70792AA004	OB-102
	1060-017	13-Week Repeat-Dose Study in Rats	70792AA005	OB-103
	1060-018	Dose-Escalation Range-Finding Study in Dogs	70792AA006	OB-105
	1060-019	13-Week Repeat-Dose Study in Dogs		OB-106
70792AA010	1060-040	Pilot Study for Prenatal Development Toxicity in Rats		OB-107
	1060-044	Pilot Study for Prenatal Development Toxicity in Rabbits		OB-108
	1060-041	Study for Effects on Embryo-fetal Development in Rats	70792AA006	OB-109
	1060-043	Study for Effect on Embryo-fetal Development in Rabbits	71199AA003	OB-110
			71199AA003	OB-118
			70792AA006	OB-202
			70792AA006	OB-205
			70792AA005	OB-301
			70792AA004	OB-302
			70792AA005	
			70792AA006	
			70792AA004	OB-303
			70792AA005	
			70792AA006	

Table 8 – Phentermine Batch Analysis (Selected)

Batch Analysis Results of (b) (4) Phentermine Hydrochloride USP

Test	Method	Acceptance criteria	Lot number				
			Manufacturing Date				
			0540682	0540618	0540596	0640349	0740376
Drug Product Manufacturer's Assigned Lot Number			N/A	N/A	N/A	526723	(b) (4)
Use			Manufacturer DMF only		Preclinical and Clinical Studies		Preclinical and Clinical Studies
Appearance	Visual	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder
Identity	IR Spectroscopy	conforms	conforms	conforms	conforms	conforms	conforms
	UV Spectroscopy	conforms	conforms	conforms	conforms	conforms	conforms
	(b) (4)	conforms	conforms	conforms	conforms	conforms	conforms
(b) (4)							

NM1 = not more than

2.6 Proposed Clinical Population and Dosing Regimen

The proposed PHEN/TPM FDC capsule is indicated for once daily oral dosing in obese and overweight (with co-morbidities) individuals. Capsules will be manufactured in four dosages: 3.75/23, 7.5/46, 11.25/69, and 15/92 mg PHEN/TPM (see Table 1, above). The “mid dose” (7.5/46) is listed as the intended maximum dose for most patients, whereas the maximum proposed dose (15/92), or “full dose”, is intended for use in patients with inadequate weight control on the “mid dose”. The “three quarter dose” is not indicated for use in a specific population, rather it is intended as an intermediate dose to be used in dose-escalation from the “mid dose” to the “full dose” in non-responders. The maximum listed dose, 15/92 mg PHEN/TPM is used throughout this review as the maximum recommended human dose (MRHD). The Sponsor’s proposed indication is as follows:

Sponsor’s 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 kg/m²), or overweight patients (BMI \geq 27 kg/m²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).”*

2.7 Regulatory Background

The proposed FDC capsule contains two drug substances listed for use in the United States. Phentermine was approved in 1959 for short term (“a few weeks”) management of obesity as an adjunct to diet and exercise. Phentermine is indicated for use as an anorectic or appetite suppressant. Topiramate was approved in 1996 for chronic use to treat epilepsy and later an indication for prophylactic treatment of migraine was added. Two separate INDs for obesity and type 2 diabetes mellitus indications with the Sponsor’s proposed drug substances are currently active. NDA and IND numbers for approved and investigational uses are noted above in Section 2.2.

Phentermine is not approved for chronic use and the label on the listed product(s) lacks information about nonclinical toxicology studies to support chronic use. Topiramate is indicated for chronic use but a different benefit-to-risk determination is required based on a comparison of the listed indications (epilepsy and migraine) and the proposed obesity indication. The new nonclinical data, coupled with the history of approved uses and available public literature, are sufficient to make recommendations of safety and efficacy of the proposed drug combination for a chronic obesity indication. The NDA was submitted in accordance with 21USC505(b)(2) and the Sponsor relied on primary data, publicly available information, and FDA’s previous findings of safety and efficacy to support the proposed use.

3 Studies Submitted

3.1 Studies Reviewed

Individual studies not previously reviewed under IND 68,651 are listed in the Table of Contents.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Some studies with VI-0521 were previously reviewed under IND 68,651 and summaries of reviews are included in this NDA review. Various written summaries, figures, and tables from IND reviews are reproduced and cited throughout the text.

4 Pharmacology

4.1 Primary Pharmacology

No original pharmacology studies were conducted or submitted in support of the proposed FDC drug. Pharmacology information provided by the Sponsor are based on a review of the published literature for the individual components phentermine and topiramate. No information is available on the pharmacology of combination PHEN and TPM treatment. Information on PHEN and TPM pharmacology are contained in the labels of the listed products and the sponsor discussed the pharmacology of the individual drug substances in reviews of publicly available literature. This reviewer's summary of available information on PHEN and TPM pharmacology are shown below and based on drug labels, published literature, and the Sponsor's literature reviews.

Pharmacology Report: Non-clinical pharmacology of phentermine – review of published literature (Report No. 09-PHEN-PHARM-01)

Phentermine

Phentermine is approved in the US for weight loss as an anorectic (or appetite suppressant) adjunct to diet and exercise. PHEN is a sympathomimetic amine in the β -phenethylamine family. It is a congener of amphetamine, lacking an α -hydrogen due to methylation at the α -carbon. PHEN stimulates norepinephrine (NE) release with approximately 6-fold lower potency than *d*-amphetamine. Compared to amphetamine, PHEN only slightly stimulates dopamine release due to approximately 7-fold selectivity for NE release compared to dopamine stimulation. PHEN seems to have a minor effect on pre-synaptic serotonin (5-HT), with IC_{50} of approximately 3.5 μ M for 5-HT release and 14 μ M for 5-HT reuptake, which are approximately 90-fold lower than its effect on NE stimulation.

Despite the available information on neurotransmitter effects, it is not clear which mechanisms contribute directly to weight loss. Weight loss seems to occur due to a combination of anorectic (decreased food consumption), thermogenic (increased metabolic activity), and drug-induced increased physical activity.

The Sponsor summarized the apparent pharmacologic effects of PHEN this way:

Phentermine hydrochloride, a synthetic sympathomimetic amine, is an anorectic agent. The primary mechanism of action, producing weight loss, is believed to be a pharmacologically induced reduction of caloric intake. Phentermine stimulates neurons to release or maintain high levels of catecholamines. It is postulated that increased circulating catecholamines may cause appetite suppression by increasing blood leptin levels; other studies have

demonstrated a correlation between blood leptin levels and body weight reduction. Increased catecholamine levels may also result in a decrease in neuropeptide Y production, which may result in increased satiety and decreased appetite.

Pharmacologic effects of amphetamine and sympathomimetics, coupled with mechanistic research on phentermine, provide insight into potential convergence of multiple pathways contributing to weight loss. Acute inhibition of food intake may be due to activation of hypothalamic β -adrenergic and dopamine receptors. Dopamine release in rodents *in vivo* seems to be involved in the anorectic response of phentermine (and amphetamine), however, the clinical relevance is unclear and no dopamine effect was seen in baboons by PET scan. Phentermine has no apparent effects on α -adrenergic, serotonergic, or cholinergic receptors. Modulation of various peptides involved in appetite and energy use has been postulated but no studies have been conducted with phentermine. For example, neuropeptide Y (NPY) is active in the perifornical hypothalamus and affects the amphetamine-mediated dopamine modulation and subsequent hypothalamic-mediated weight loss in rodents. The cocaine- and amphetamine-regulated transcript (CART) encodes secreted neurotransmitter peptides and is expressed in hypothalamic regions involved in energy regulation. Changes in leptin homeostasis may also play a role in weight loss because sympathetic nervous system activation and β -adrenergic stimulation decrease leptin expression, thereby decreasing the leptin-mediated control of food intake. There is also some evidence that amphetamine may increase cholecystokinin (CCK), which transiently inhibits food intake, by decreasing gastric emptying and intestinal motility.

Summary tables adapted from published literature and provided by the Sponsor compare the potency and efficacy of amphetamine and phentermine (see Table 9).

Table 9 – Sponsor’s Summary Tables (Adapted from published literature)***In Vitro* and *In Vivo* Pharmacological Profile of d-Amphetamine and Phentermine on Amphetamine Displacement and Behavioral Parameters**

	(+)-[³ H] amphetamine Displacement ^a	Anorectic activity ^b	Anorectic activity ^b	Behavior stimulation ^b	Behavior stimulation ^b
Drug	Ki (μM)	RD ₅₀ (mg/kg) ^c	Slope of response	RD ₅₀ (mg/kg) ^c	Slope of response
<i>d</i> -Amphetamine	1.6	1.9	-84	0.8	+232
Phentermine	7.5	4.7	-74	7.1	+126

^a Adapted from Paul *et al.* (Table 1).²³ Ki was determined by displacement of (+)-[³H] amphetamine radioligand binding from rat hypothalamic synaptosome membranes

^b Adapted from Cox and Maickel (Tables 1 and 2).¹⁵ Anorectic activity dose response was determined by inhibition of food intake in normal rats following single (i.p.) injection of d-amphetamine or phentermine. Behavior stimulation was measured using a continuous avoidance test in rats. Slope of response is compared to control rats.

^c RD₅₀ = dose required to produce 50% change in response

***In Vitro* and *In Vivo* Pharmacological Profile of d-Amphetamine and Phentermine on the Release and Re-Uptake of Biogenic Amines**

Drug	NE		5-HT		Dopamine		Selectivity for NE
	Release IC ₅₀ (nM)	Uptake Ki (nM)	Release IC ₅₀ (nM)	Uptake Ki (nM)	Release IC ₅₀ (nM)	Uptake Ki (nM)	NE vs. dopamine (ratio of release IC50s)
<i>d</i> -Amphetamine	7	39	1765	3830	25	34	3.5
Phentermine	39	244	3511	13900	262	1580	6.7

Adapted from Rothman *et al.* (Table V).²⁶

Pharmacology Report: Non-clinical pharmacology of topiramate – review of published literature (Report No. 09-TPM-PHARM-01)Topiramate

Topiramate is active in the central nervous system (CNS) where it is thought to exert anticonvulsant and migraine prophylactic effects for the approved indications. Known CNS effects of topiramate include: blockage of voltage-dependent sodium channels; increase activity of γ-aminobutyrate neurotransmitter as certain GABA-A receptors; antagonize glutamate receptor AMPA/kainate subtypes; and inhibit carbonic anhydrase isozymes II and IV. How and which combination of those effects of TPM contribute to weight loss is not clearly understood.

Several potential effects of the known CNS-modulating activity of TPM have been implicated in weight loss. Modulation of voltage-gated ion channels may affect resting metabolic rate, pancreatic hormone secretion, and modulate neurotransmitter and

neuropeptide release, all of which may affect overall energy expenditure and homeostasis. Modulation of GABA receptors has been implicated in food intake and body weight regulation, including increased weight gain with clinical use of several GABAergic drugs (particularly those that increase GABA_A activity). Topiramate may exert a distinct effect on GABA modulation to result in weight loss rather than weight gain. Inhibition of carbonic anhydrase activity can inhibit hepatic lipogenesis and may contribute to TPM-induced effects on lipid metabolism and weight loss. NMDA receptors may also be inhibited indirectly by TPM inhibition of carbonic anhydrase, which may inhibit NMDA-modulated feed intake centers in the hypothalamus. The Sponsor also postulates that TPM effects in the gut, for example decreased gastrointestinal motility, may promote satiety and further improve the weight loss effects.

The Sponsor summarized the apparent pharmacologic effects of PHEN this way:

Available pharmacological evidence suggests that topiramate-induced weight loss results from increased energy expenditure, decreased energy efficiency, and decreased caloric intake. While the glycemic benefit is primarily driven by weight reduction, data from nonclinical and clinical studies provide evidence for additional weight-independent effects of topiramate on glycemic parameters, blood pressure, and lipids. The precise mechanism for topiramate's effect on body weight is not completely understood; however, the topiramate inhibition of carbonic anhydrase may directly inhibit N-methyl-d-aspartate receptors, which have been implicated in feeding behavior.

4.2 Secondary Pharmacology

No secondary pharmacology or drug-drug interaction (DDI) studies were submitted. Secondary pharmacology and DDI information for the individual components phentermine and topiramate are based on a review of the published literature. Phentermine has been investigated for potential treatment of drug abuse and nonclinical effects showed attenuation of cocaine abuse in rhesus monkey and cocaine-induced dopamine release in rats. Phentermine has also been investigated for potential increased cognitive and motor function after sleep deprivation.

Topiramate is an approved therapy for epilepsy treatment and migraine prophylaxis. Additional potential secondary pharmacology effects of topiramate have been investigated clinically and in nonclinical models. Both clinical and nonclinical studies show potential for topiramate to improve blood glucose and improve diabetes, with some effects potentially independent of weight loss. Topiramate may also improve sleep apnea, hypertension, and hyperlipidemia in obese individuals with co-morbidities. Due to its multiple mechanisms of action in the CNS, topiramate has also been investigated for effects on a number of neurological conditions including neuropathic pain,

psychological disorders, treatment of drug and alcohol dependence, and general “neuroprotective” effects.

Additionally, topiramate monotherapy and combination therapy with phentermine has reportedly been widely prescribed for off-label use to treat obesity and induce weight loss.

4.3 Safety Pharmacology

No safety pharmacology studies were submitted. Safety pharmacology information for the individual components phentermine and topiramate are based on a review of the published literature.

Clinical adverse events and side effects for phentermine are listed on the label for approved drug(s) and are consistent with class related side effects of sympathomimetics, including: cardiovascular (palpitations, tachycardia, increased blood pressure); CNS (overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, and rare psychotic episodes); gastrointestinal (dry mouth, unpleasant taste, diarrhea, constipation, “other gastrointestinal disturbances”); allergic (urticaria); and endocrine (impotence, changes in libido). Primary pulmonary hypertension and/or regurgitant cardiac valvular disease are also listed on the phentermine label and will be discussed in more detail below.

Clinical adverse events and side effects for topiramate are listed on the label for approved drug(s). Warnings include: acute myopia and secondary angle closure glaucoma (i.e., elevated intraocular pressure); oligohidrosis and hyperthermia; suicidal behavior and ideation; metabolic acidosis; cognitive/neuropsychiatric dysfunction; hyperammonemia and encephalopathy; and, kidney stones. Common adverse reactions include: paresthesia (abnormal neurological sensations including numbness, tingling, burning, prickling, hyperesthesia/increased sensitivity); anorexia; weight decrease; fatigue; dizziness; somnolence; nervousness; psychomotor slowing; memory and concentration/attention difficulty; confusion; taste perversion; skin and appendages disorders (rash, alopecia); and, vision disorders (abnormal accommodation, eye pain).

The potential for phentermine abuse has been studied because amphetamine and derivatives are known drugs of abuse (e.g., ‘speed’ and ‘crystal meth’) and neural food reward center activation is thought to provoke a similar potential for abuse. There is some nonclinical evidence of self-administration of phentermine for stimulant effects but data from non-human primates showed a 5-fold lower “reinforcing potency” of phentermine as an anorectic compared to amphetamine (see Table 10). Dopamine activation in the nucleus accumbens is associated with drug abuse potential and amphetamine has a dopaminergic effect. As noted previously, phentermine has lower potency and efficacy compared to amphetamine for receptor activation (NE and dopamine release and reuptake) and anorectic and behavioral effects (see Table 9, above).

Table 10 – Sponsor’s Reinforcement Summary for Abuse Potential**Comparison of Anorectic:Reinforcement Ratio Phentermine and Amphetamine in Non-Human Primates**

Drug	Anorectic:Reinforcement Ratio^a
d-Amphetamine	1.0
Phentermine	0.21

^a Adapted from Griffiths *et al.*⁵³ Ratios were converted such that amphetamine had arbitrary ratio of 1.0.

Serious potential cardiovascular toxicity from phentermine use was identified in the 1990s based on adverse events from clinical use of combination fenfluramine and phentermine for weight loss. The Adipex-P® label lists warnings for primary pulmonary hypertension (PPH) and valvular heart disease (VHD) from phentermine use. While the Adipex-P® label notes that PPH and valvular heart disease have not been definitively linked to phentermine use, the warnings note the following (emphasis included in label):

Primary Pulmonary Hypertension (PPH) – a rare, frequently fatal disease of the lungs – has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out; there have been rare cases of PPH in patients who reportedly have taken phentermine alone....

Valvular Heart Disease: Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss...The possibility of an association between valvular heart disease and the use of phentermine alone cannot be ruled out; there have been rare cases of valvular heart disease in patients who reportedly have taken phentermine alone.

Nonclinical *in vitro* and animal studies do not support a role for phentermine in PPH or VHD. Mechanistic and clinical data implicate elevations in serotonin (5-HT) and activation of a specific serotonin receptor subtype, 5-HT_{2b}, in both PPH and VHD. Phentermine does not accumulate in lungs, there is minimal (or weak) serotonin release, and phentermine activity is short acting compared to PPH-inducing anorectics including the related chlorphentermine. Studies in rats have shown phentermine does not increase pulmonary pressure or lung toxicity (as evidenced by absence of histological lesions or macrophage infiltration), whereas the related chlorphentermine markedly increased pulmonary pressure and lead to gross and microscopic lung lesions including foam cells and macrophage infiltration.^{3,4} Recent clinical evidence also shows

³ Lüllmann H et al. (1972) *Arzneim-Forsch (Drug Res)* **22(12)**:2096-2099

no apparent effect of phentermine on PPH, while implicating fenfluramine and dexfenfluramine monotherapy or in combination with phentermine.^{5,6,7} General clinical cardiovascular effects of phentermine do include transient increases in blood pressure at doses 2- to 3-fold higher than necessary to produce intended pharmacologic CNS effects.

Extensive mechanistic and clinical data collected since the original cases surfaced implicate a serotonin (5-HT) effect on valve toxicity, typically by increasing availability of 5-HT for binding and activation, or by direct drug-mediated activation, of the 5-HT_{2b} receptor subtype (see reviews by Glazer⁸, Roth⁹, and Rothman and Baumann^{10,11}). The serotonin effect can be exacerbated by PPH, which may alter drug and 5-HT metabolism in the lung and increase 5-HT_{2b} active compounds in the heart.^{12,13} Reports in the literature showed minimal phentermine-induced plasma or brain 5-HT increases and no interactions with the 5-HT_{2b} receptor.^{5,14} In fact, phentermine interactions with 5-HT_{2b} receptor are so weak ($K_i > 10 \mu\text{M}$) that it has been used as a negative control for receptor interactions.¹⁵ The Sponsor's summary table, adapted from the literature, shows a comparison of phentermine to other anorectic drug effects on serotonin and monoamine transporters (Table 11, below). Similar to clinical investigations of PPH, clinical studies have shown phentermine monotherapy has not caused VHD and valvular toxicity seen with phentermine combination therapy has been linked to other agents (e.g., fenfluramine, dexfenfluramine, and chlorphentermine).^{16,17,7}

No pulmonary or cardiac toxicity consistent with PPH or VHD was seen in the nonclinical studies submitted in support of this NDA, either with phentermine alone or in combination treatments with topiramate. However, there were no toxicity studies with the proposed drug substances looking directly at cardiac valves and valves are not routinely examined in nonclinical toxicity studies.

⁴ Kacew S, Narbaitz R (1977) *Exp Mol Pathol* **27**:106-120

⁵ Rothman RB et al. (1999) *Circulation* **100**:869-875

⁶ Reeve HL et al. (1999) *Am J Physiol* **276** (*Lung Cell Mol Physiol* **20**):L213-L219

⁷ Rich S et al. (2000) *Chest* **117**:870-874

⁸ Glazer G (2001) *Arch Intern Med* **161**:1814-1824

⁹ Roth BL (2007) *NEJM* **356**:6-9

¹⁰ Rothman RB, Baumann MH (2009) *Am J Ther* **16**:354-364

¹¹ Rothman RB, Baumann MH (2009) *Expert Opin Drug Saf* **8(3)**:317-329

¹² Fishman AP (1999) *Circulation* **99**:156-161

¹³ Fitzgerald W et al. (2000) *Mol Pharmacol* **57**:75-81

¹⁴ Zolkowska D et al. (2006) *J Pharmacol Exp Ther* **318(2)**:604-610

¹⁵ Rothman RB et al. (2000) *Circulation* **102**:2836-2841

¹⁶ Jick H et al. (1998) *NEJM* **339**:719-724

¹⁷ Whigham LD et al. (2007) *Int J Obes* **31**:850-857

Table 11 – Sponsor’s Summary Table of Anorectic Drugs and Risk of PPH**Summary of the Relation between Transporter Activity, Monoamine Efflux, and Risk of PPH for Anorectic Medications**

Anorectic drug	Activity at DAT	Activity at SERT	Effect on DA Efflux	Effect on 5-HT Efflux	Linked to PPH
d-Amphetamine	Substrate	Substrate	Increase	Weak effect	No
Phentermine	Substrate	Weak substrate / uptake Inhibitor	Increase	Weak effect	No
Aminorex	Uptake Inhibitor	Substrate	Increase	Increase	Yes
Fenfluramine	Inactive	Substrate	No effect	Increase	Yes
d-Fenfluramine	Inactive	Substrate	No effect	Increase	Yes
Chlorphentermine	Uptake Inhibitor	Substrate	Weak effect	Increase	Possibly

SERT = 5-HT transporters; DAT = Dopamine transporters; DA = Dopamine;
 PPH = primary pulmonary hypertension

The classification of a drug as a substrate or uptake inhibitor is based on the binding-to-uptake ratio for that drug: Ratios ≥ 10 are considered to be indicative of substrate activity.

Adapted from Rothman *et al.* (Table 3).⁶⁸

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Individual study reports submitted with the NDA are reviewed here. The Sponsor submitted comprehensive reviews of publicly available literature which are briefly discussed below and considered in the overall NDA review. The Sponsor found no published nonclinical data on combination PHEN/TPM treatment. PK and TK data on combination PHEN/TPM treatment are contained in individual toxicology study reports. Overall PK, ADME, and TK data and trends are also discussed in the Integrated Summary (Section 11).

Analytical Methods and Validation

Bioanalytical methods were validated for extraction, quantification, and stability of phentermine and topiramate in plasma of all experimental animal species used in pivotal pharmacology and toxicology studies. Some of the methods were described as “partial” validation because the methods were based on methods validated in another species. The study reports also note the validation methods met all criteria specified in the US FDA Guidance for Industry for Bioanalytical Method Validation (May 2001). The methods were rigorous and adequate to quantify both drugs from rat, rabbit, and dog plasma. Study results and linear range for plasma analyses are briefly described below.

Validation of (b) (4) method V0003619 entitled “Method of analysis for the determination of phentermine in canine plasma by LC/MS/MS” (Report No. P0002967)

Signed GLP and QA statements, 4/17/09

Summary: Phentermine quantification in dog plasma was validated by LC/MS/MS over the range of 1 to 400 ng/ml. Stability in plasma was confirmed for long term storage of six months.

Partial validation in rat plasma of (b) (4) method V0003619 entitled “Method of analysis for the determination of phentermine in plasma by LC/MS/MS” (Report No. P0002977)

Signed GLP and QA statements, 4/17/09

Summary: Phentermine quantification in rat plasma was partially validated over the range of 1 to 400 ng/ml using the validated canine plasma LC/MS/MS method. Stability in plasma was confirmed for six months storage at -70°C.

Full validation of an LC-MS/MS assay for topiramate in rat plasma (Report No. 999-676)

Signed GLP and QA statements, 10/7/09

Summary: Topiramate quantification in rat plasma was validated by LC-MS/MS over the range of 0.05 to 50 µg/ml. Stability in plasma was confirmed for three months at -80°C.

Partial validation of an LC-MS/MS assay for phentermine in rabbit plasma (Report No. 999-684)

Signed GLP and QA statements, 10/29/09

Summary: Phentermine quantification in rabbit plasma was partially validated over the range of 1 to 400 ng/ml using the validated canine plasma LC/MS/MS method. Stability in plasma was confirmed for three months storage at -80°C.

Partial validation of an LC-MS/MS assay for topiramate in rabbit plasma (Report No. 999-685)

Signed GLP and QA statements, 10/29/09

Summary: Topiramate quantification in rabbit plasma was partially validated over the range of 0.05 to 50 µg/ml using the validated rat plasma LC/MS/MS method. Stability in plasma was confirmed for three months storage at -80°C.

Validation of ^{(b)(4)} research method V3416 entitled “Quantitation of topiramate in plasma by GC-MS” for canine plasma (Report No. P2710 and amendment 1)

Signed GLP and QA statements, 12/3/09 (Amendment 1, dated 12/22/09)

Summary: Topiramate quantification in dog plasma was fully validated by GC-MS over the range of 0.05 to 100 µg/ml. Stability in plasma was confirmed for six months at -80°C.

Partial validation in rat plasma of ^{(b)(4)} research method V3416 entitled “Quantitation of topiramate in plasma by GC-MS” (Report No. P2711)

Signed GLP and QA statements, 12/3/09

Summary: Topiramate quantification in rat plasma was partially validated over the range of 0.05 to 100 µg/ml using the validated dog plasma GC-MS method. Stability in plasma was confirmed for three months at -80°C. The laboratory considered the method valid for topiramate extraction and analysis. Method acceptance criteria was fulfilled for all endpoints with the exception of long-term stability being limited to three months.

Absorption

Absorption and bioavailability of the proposed phentermine and topiramate drug formulations were assessed in dogs and compared to currently marketed drug products.

Dogs were dosed with various capsule formulations and plasma drug concentrations were assessed for: (1) phentermine, comparing VIVUS's immediate release (IR) capsule and a marketed IR capsule when co-administered with topiramate; and, (2) topiramate, comparing various VIVUS modified (MR) or delayed release (DR) capsule formulations and the marketed IR Topamax® with and without phentermine co-administration. Individual comparative bioavailability studies are reviewed below.

Comparative bioavailability of VIVUS' immediate release phentermine versus marketed immediate release phentermine capsule in fasted male and female beagle dogs following a single 15 mg oral dose (Report No. 09-PHEN-PK-02; Appendix A – Study 1060-030)

Non-GLP, dated 9/14/09

Summary: Plasma phentermine concentration was determined in fasted beagle dogs after a single oral dose of 15 mg phentermine co-administered with 100 mg topiramate. The proposed VIVUS IR capsule was compared to a marketed IR capsule. In order to “acidify the pH of the dog stomach to a physiological level observed in humans”, each animal received a single *im* injection of 6 µg/kg pentagastrin 45 min prior to PHEN+TPM treatment. Pharmacokinetic parameters were assessed after administration to dogs (n=3/sex; 7.3 – 10.8 kg) in a crossover design (see Sponsor's study design/formulation summary, below). Various topiramate formulations were also assessed and TPM PK parameters were described separately (see study report 09-TPM-PK-02 review, below).

PK results showed the VIVUS phentermine IR formulation resulted in comparable absorption and bioavailability ($C_{max} = 191$ ng/ml, $t_{1/2} = 2.7$ h, $T_{max} = 1.2$ h, $AUC_{0-24} = 683$ ng*h/ml) as the currently marketed phentermine IR capsule ($C_{max} = 173$ ng/ml, $t_{1/2} = 2.2$ h, $T_{max} = 1.3$ h, $AUC_{0-24} = 672$ ng*h/ml). Relative oral bioavailability of the VIVUS formula was $105 \pm 11\%$ of the marketed capsule. There were no sex differences in exposure. Results are summarized in the Sponsor's summary table and figures, below (Table 12 and Figure 1).

Study Design (PHEN and TPM Formulations)

Day 1:	Phentermine 15 mg Capsule and Topamax 25 mg Sprinkle Capsule (Formulation D – Immediate Release Formulation)
Day 8:	Phentermine IR and Topiramate CR Prototype I Capsule (Formulation A)
Day 15:	Phentermine IR and Topiramate CR Prototype III Capsule (Formulation B)
Day 22:	Phentermine IR and Topiramate CR Prototype IV Capsule (Formulation C)
Day 29:	Topiramate CR Prototype V Capsule (Formulation E)
Day 36:	Topiramate IR Capsule (Formulation F)
Day 43:	Topiramate CR Prototype VI Capsule (Formulation G)
	Topiramate (Enteric Coated) Prototype VII Capsule (Formulation H)
Day 50:	Topiramate (IR) Prototype IX Capsule (Formulation I)
	Topiramate (Enteric Coated) Prototype VIII Capsule (Formulation J)
Day 57:	Topiramate (IR) Prototype X Capsule (Formulation K)
	Topiramate (API) Prototype XI Capsule (Formulation L)
Day 64:	Topamax (Topiramate) 100 mg (Formulation M)
	Topiramate CR Prototype V Capsule (Formulation N)

Table 12 – Sponsor’s Phentermine PK Summary

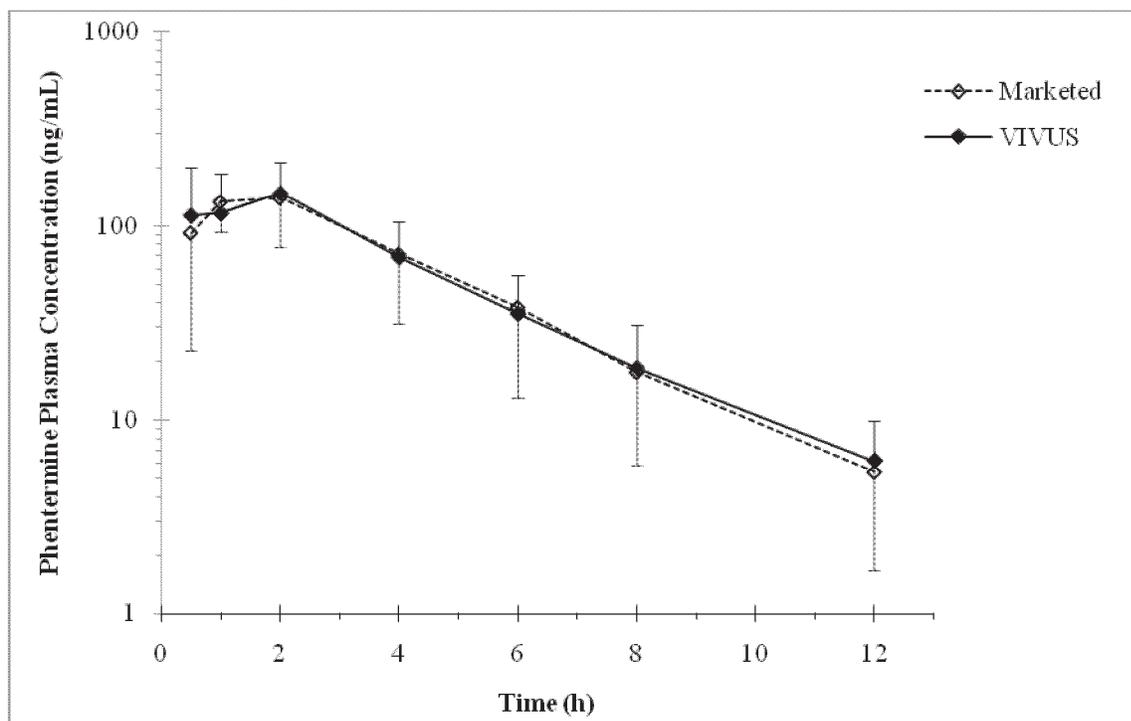
Comparative Pharmacokinetics of a Single Oral Dose of Phentermine 15 mg in Fasted Beagle Dogs (n=3/sex)

Batch	Value	C _{max} (ng/mL)	t _{max} (h)	AUC(0-24h) (ng.h/mL)	t _{1/2} (h)	F ^a (%)
Marketed capsule product	Mean	173	1.3	672	2.2	-
	(SD)	(47)	(0.6)	(268)	(0.2)	-
	CV (%)	27	49	40	9	-
VIVUS’ capsule	Mean	191	1.2	683	2.7	105
	(SD)	(37)	(0.7)	(208)	(0.6)	(11)
	CV (%)	19	59	30	23	10

^a: Oral bioavailability relative to the marketed product

Figure 1 – Sponsor’s Phentermine PK Time Course Summary

Gender Combined Mean (±SD) Plasma Concentration-Time Profiles of Phentermine in Beagle Dogs Following a Single Oral 15 mg Administration



Comparative bioavailability of VIVUS' modified or delayed release topiramate capsule formulations versus marketed immediate release topiramate capsule in fasted male and female beagle dogs following a single 100 mg oral dose (Report No. 09-TPM-PK-02; Appendix A – Study 1060-030; Appendix B – Study 1060-032)
Non-GLP, dated 12/8/09

Summary: Plasma topiramate concentration was determined in fasted beagle dogs after a single oral dose of 100 mg topiramate with and without co-administration of 15 mg phentermine. Seven different new VIVUS modified release (MR) and delayed release (DR) TPM formulations were compared to the marketed Topamax® IR Sprinkle capsule. In order to “acidify the pH of the dog stomach to a physiological level observed in humans”, each animal received a single *im* injection of 6 µg/kg pentagastrin 45 min prior to TPM+PHEN treatment. Pharmacokinetic parameters were assessed after administration to dogs (n=2-3/sex; 7.1 – 14.8 kg) in a crossover design (see Sponsor’s study design/formulation summary, below). Phentermine PK results were described separately and discussed above (see study report 09-PHEN-PK-02 review).

PK results showed varying topiramate bioavailability for the different VIVUS prototype formulations. Formulations V and VIII had the highest oral bioavailability (81% and 76%, respectively), lowered C_{max} by approximately 50%, and delayed T_{max} approximately 3-fold to 3.3-3.5 h. Prototype V was chosen for clinical and nonclinical development and two additional clinical batches used in Phase 1 and Phase 2 trials were also assessed for PK variability in dogs. The additional batch analyses showed similar topiramate PK characteristics with mean C_{max} ranging from 5510 – 5671 ng/ml at a T_{max} of 3.3-3.8 h. While C_{max} was lower and T_{max} was longer for the VIVUS formulation V, the estimated $t_{1/2}$ range of 3.2 – 3.6 h and mean relative oral bioavailability of 81-98% were similar to results with the listed Topamax® product. Total plasma topiramate exposure was slightly lower in all batches of the chosen VIVUS MR formulation, with an AUC_{0-24} range of approximately 81-90% of Topamax®. No gender differences were apparent. Overall, VIVUS concluded the different modified release clinical batches were bioequivalent. Summary PK results are shown in the Sponsor’s tables and figures, below (Table 13 and Figure 2).

Study Design (PHEN and TPM Formulations)**Test Article(s):**

Seven topiramate prototype formulations of VIVUS' topiramate modified release (MR) or delayed release (DR) formulations manufactured at dosage strengths of 25 or 100 mg capsules; 2 clinical batches of prototype V; 25 mg Topamax[®] capsule. The 100 mg dose was administered as four 25 mg capsule or one 100 mg capsule.

VIVUS' MR or DR Topiramate Capsule Formulations:

Prototype I, Lot No. VAB-J0013-BK1-P34

Prototype III, Lot No. VAB-J0013-BK1-P35

Prototype IV, Lot No. VAB-J0013-BK1-P36

Prototype V, Lot No. VAB-J0013-BK5-P6

Prototype VI, Lot No. VAB-J0013-BK5-PK9

Prototype VII, Lot No. VAB-J0013-BK5-PK10

Prototype VIII, Lot No. VAB-J0013-BK5-P14

Clinical Lot No. 07JM-215 (Prototype V)

Clinical Lot No. 0703309 (Prototype V)

Prototypes I, III, IV and V are modified release topiramate formulations and Prototypes VI, VII and VIII are delayed release topiramate formulations.

Day 1: Phentermine 15 mg Capsule and Topamax 25 mg Sprinkle Capsule
(Formulation D – Immediate Release Formulation)

Day 8: Phentermine IR and Topiramate CR Prototype I Capsule (Formulation A)

Day 15: Phentermine IR and Topiramate CR Prototype III Capsule (Formulation B)

Day 22: Phentermine IR and Topiramate CR Prototype IV Capsule (Formulation C)

Day 29: Topiramate CR Prototype V Capsule (Formulation E)

Day 36: Topiramate IR Capsule (Formulation F)

Day 43: Topiramate CR Prototype VI Capsule (Formulation G)

Topiramate (Enteric Coated) Prototype VII Capsule (Formulation H)

Day 50: Topiramate (IR) Prototype IX Capsule (Formulation I)

Topiramate (Enteric Coated) Prototype VIII Capsule (Formulation J)

Day 57: Topiramate (IR) Prototype X Capsule (Formulation K)

Topiramate (API) Prototype XI Capsule (Formulation L)

Day 64: Topamax (Topiramate) 100 mg (Formulation M)

Topiramate CR Prototype V Capsule (Formulation N)

Reviewer's footnote – Day 64 pre-treatment with pentagastrin was inadvertently missed prior to Formulation N dosing

Table 13 – Sponsor’s Topiramate PK Summary

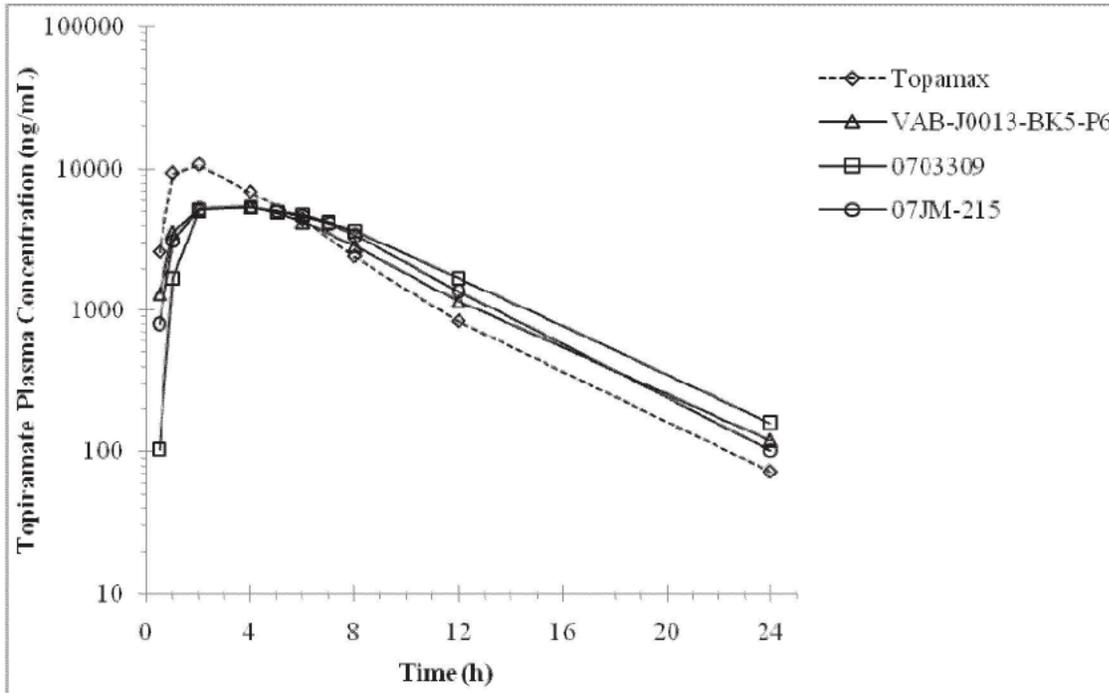
Pharmacokinetics of Topiramate in Fasted Beagle Dogs Following a 100 mg Oral Dose of Topamax[®] Capsule and Modified or Delayed Release Topiramate Capsule (n=2-3/sex)

Lot #	Value	C _{max} (ng/mL)	t _{max} (h)	AUC _(0-24h) (ng.h/mL)	t _{1/2} (h)	F ^a (%)
Topamax [®] (IR Sprinkle)	Mean	11333	1.3	61074	3.2	-
	(SD)	(1820)	(0.5)	(18149)	(0.6)	-
	CV(%)	16	38	30	19	-
Prototype V, Lot # VAB-J0013-BK5- P6	Mean	5661	3.3	49204	3.5	81
	(SD)	(1058)	(1.0)	(14998)	(0.6)	(5)
	CV(%)	19	30	30	17	6
Clinical Batch # 07JM-215 (same as Prototype V formulation)	Mean	5510	3.8	52582	3.2	94
	(SD)	(861)	(1.3)	(10231)	(0.2)	(14)
	CV(%)	16	34	19	6	15
Clinical Batch # 0703309 (same as Prototype V formulation)	Mean	5671	3.5	54837	3.6	98
	(SD)	(882)	(1.9)	(13354)	(0.3)	(14)
	CV(%)	16	54	24	8	14
Prototype I, Lot # VAB-J0013-BK1- P34	Mean	2830	3.7	31190	5.8	57
	(SD)	(740)	(0.8)	(8939)	(2.3)	(11)
	CV(%)	26	22	29	40	19
Prototype III, Lot # VAB-J0013-BK1- P35	Mean	1618	4.7	18297	5.0	32
	(SD)	(556)	(1.0)	(6091)	(1.0)	(5)
	CV(%)	34	21	33	20	16
Prototype IV, Lot # VAB-J0013-BK1- P36	Mean	1181	4.7	16831	7.1	27
	(SD)	(510)	(1.0)	(10391)	(4.0)	(2)
	CV(%)	43	21	62	56	7
Prototype VI, Lot # VAB-J0013-BK5- PK9	Mean	2780	4.0	27600	4.0	44
	(SD)	(393)	(0.0)	(5280)	(0.5)	(15)
	CV(%)	14	0	19	13	34
Prototype VII, Lot # VAB-J0013-BK5- PK10	Mean	4271	3.5	35800	3.3	68
	(SD)	(773)	(1.9)	(6420)	(0.6)	(15)
	CV(%)	18	54	18	18	22
Prototype VIII, Lot # VAB-J0013-BK5- P14	Mean	5198	3.5	39711	3.7	76
	(SD)	(629)	(1.0)	(5556)	(1.3)	(16)
	CV(%)	12	29	14	35	21

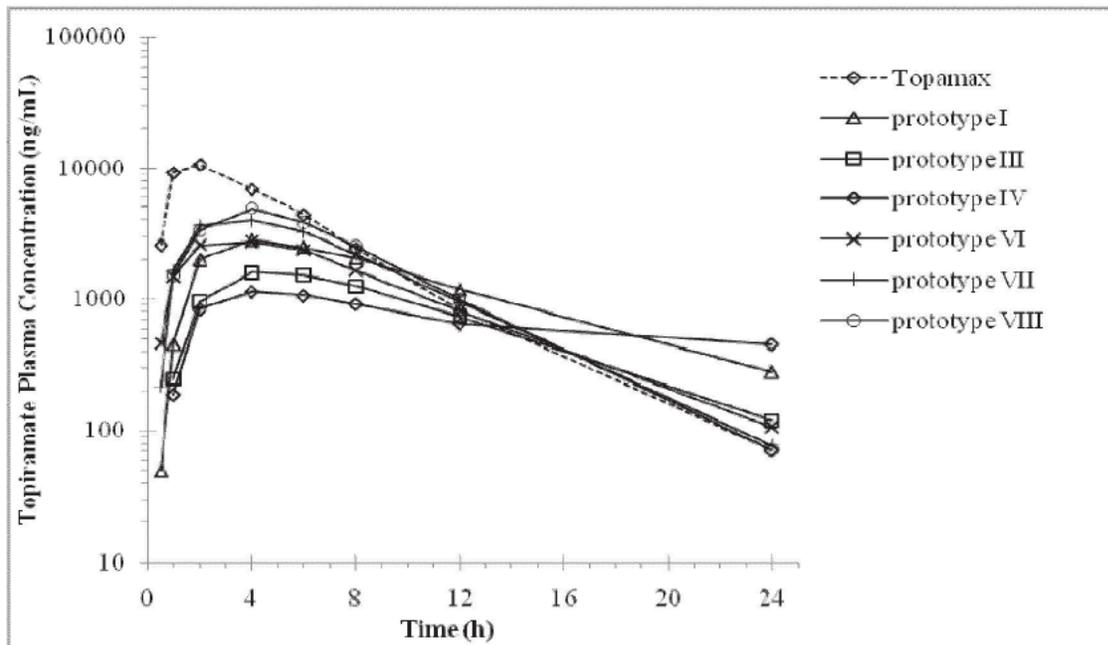
^a: Oral bioavailability relative to the marketed product Topamax[®]

Figure 2 – Sponsor’s Topiramate PK Time Course Summaries

Mean Plasma Concentration-Time Profiles of Topiramate in Beagle Dogs Following a 100 mg Oral Dose of Topamax® and Three Batches of VIVUS’ Modified Release Topiramate Capsule (Prototype V Formulation)



Mean Plasma Concentration-Time Profiles of Topiramate in Beagle Dogs Following a 100 mg Oral Dose of Topamax® and Six Prototypes of VIVUS’ Modified or Delayed Release Capsule



Distribution**Protein binding by equilibrium dialysis (Report No. 8VIVUP3R1)***Non-GLP, dated 7/15/09*

Summary: Plasma protein binding to phentermine was assessed by equilibrium dialysis in rat, dog, and human plasma. Phentermine binding was low in all species, with 11%, 18%, and 24% protein binding in rat, dog, and human, respectively. Thus, the majority of administered phentermine is expected to circulate unbound. Controls for low and high protein binding compounds confirmed the sensitivity of the assay. *In vitro* protein binding results are summarized in the reviewer's table (Table 14).

Table 14 – Plasma Protein Binding Summary

Plasma Protein Binding <i>In Vitro</i> †		
Species	Protein Binding	Free Phentermine
Rat	11%	89%
Dog	24%	76%
Human	18%	82%

† Equilibrium dialysis

Metabolism**Evaluation of the potential for induction of CYP1A2, CYP2B6, and CYP3A4 activities in cultured human hepatocytes by phentermine (Report No. 101-09-001)***Non-GLP, dated 6/26/09 (Phentermine HCl (USP), Lot No. 0640349, 98.7% purity)*

Summary: Primary human hepatocytes from three adult volunteer donors (2 female, 1 male) were cultured with phentermine for 48 h and CYP enzymatic activity and cytotoxicity were assessed. Metabolite formation by model substrates for CYP1A2, CYP2B6, and CYP3A4 were measured by LC/MS/MS after 1 to 4 h incubations after phentermine washout. Sensitivity of the assay system was confirmed with positive controls for enzyme induction and cytotoxicity. **Phentermine pre-treatment up to 10 µM did not induce CYP1A2, CYP2B6, or CYP3A4 activity. Phentermine was not cytotoxic to primary human hepatocytes (based on cellular ATP content).**

Metabolic stability of phentermine in pooled human liver microsomes (Report No. 8VIVUP2R3)*Non-GLP, dated 12/19/08 (Phentermine source/purity/lot not provided)*

Summary: Metabolism and stability of 1 µM phentermine were assessed in 1 h incubations ± NADPH energy generation system in pooled human liver microsomes.

Assay sensitivity was confirmed with positive control incubations. **Phentermine was stable under the assay conditions.** See Table 15, below.

Table 15 – Phentermine Metabolic Stability in Human Liver Microsomes

Metabolic Stability of Phentermine in Human Liver Microsomes

Remaining Phentermine (µM)				
Time (min)	Reaction Mixture	STD	Chemical Stability Control	STD
0	0.97	0.01	0.9	0.02
15	0.92	0.01	N/A	N/A
30	0.94	0.003	N/A	N/A
60	0.97	0.01	0.89	0.008
Remaining Phentermine (Avg. % to T=0)				
Time (min)	Reaction Mixture	STD	Chemical Stability Control	STD
0	100	1.39	100	2.28
15	95.2	1.49	N/A	N/A
30	97.2	0.31	N/A	N/A
60	100.5	1.19	98.7	0.89

% Remaining of Positive Control Compounds						
Compound	Time (min)				T _{1/2} (min)	ASLP Acceptance Criteria (min)
	0	15	30	60		
Testosterone	100	17.7	4.6	0.7	8.4	4.5 ≤ T _{1/2} ≤ 11.5
STD	7.98	0.39	0.11	0.24		
Propranolol	100	80.2	63.9	48.3	57.2	45 ≤ T _{1/2} ≤ 85
STD	1.68	0.89	4.68	3.17		

CYP and MAO reaction phenotyping of phentermine with cDNA expressed supersomes (Report No. 8VIVUP2R4)

Non-GLP, dated 12/19/08 (Phentermine source/purity/lot not provided)

Summary: Metabolism and degradation of 1 µM phentermine were assessed in 1 h incubations with various human cytochromes P450 (CYPs) and monoamine oxidases (MAOs) expressed in supersomes from cDNA-containing eukaryotic baculovirus expression systems. Positive control compounds confirmed the activity of MAOs in the supersomes but no positive controls for CYP-mediated metabolism were tested. **There was no significant metabolism or degradation of phentermine by expressed human CYPs (1A2, 2C8, 2C9, 2C19, 2D6, 3A4) or MAOs (MAO-A, MAO-B).** See Table 16, below.

Reviewer's note – literature reports suggest potential weak inhibition of MAOs by phentermine in vitro (K_is ≥ 85 µM; IC₅₀s ≥ 150 µM) and no significant inhibition of major CYPs (1A2, 2C9, 2D6, 2E1, 3A4). Estimated clinical plasma concentrations are ~0.7 µM, further supporting low in vivo risk of MAO inhibition.

Table 16 – Metabolic Stability of Phentermine with Expressed CYPs and MAOs

Percent Remaining of the Test Compound with CYP and MAO Supersomes

Supersomes	% Remaining of Initial after 60 Minutes Incubation				
	R1	R2	R3	Average	SD
CYP Negative Control	98.8	96.2	105	100	4.47
CYP1A2	99.9	104	103	103	2.31
CYP2C8	119	122	120	120	1.80
CYP2C9	114	105	112	110	4.83
CYP2C19	119	110	108	112	6.03
CYP2D6	102	105	99.1	102	2.95
CYP3A4	87.3	88.4	84.5	86.7	2.01
MAO Negative Control	104	89.9	106	100	8.78
MAO-A	94.0	112	106	104	9.17
MAO-B	110	109	117	112	4.36

Formation of 4-Hydroxyquinolinol with MAO Supersomes

Supersomes	Concentration (μM , mean \pm SD, n=3)	Formation Rate (pmol/min/mg protein)
MAO Negative Control	ND	ND
MAO-A	1.61 \pm 0.01	807
MAO-B	0.78 \pm 0.03	391

ND: not detected

Assessing the potential of phentermine to inhibit CYP2C19 under reversible conditions (Report No. 8VIVUP1R1)*Non-GLP, dated 12/19/08 (Phentermine source/purity/lot not provided)*

Summary: Inhibitory potential of 10 μM phentermine on CYP2C19 was assessed in pooled human liver microsome incubations. Positive controls confirmed the sensitivity of the assay system. **Phentermine showed essentially no inhibitory potential (maximum 5% inhibition) to human CYP2C19 in 30 min microsome incubations.** See Table 17, below.

Table 17 – Phentermine Inhibition of CYP2C19 in Human Liver Microsomes

Results of Quantification (n=3) of 4-hydroxymephenytoin in the Incubation Samples

Inhibitor	4-Hydroxy-mephenytoin (μM)	STD	Remaining activity, %	RSTD (%)
phentermine	0.221	0.011	94.8	4.5
(+)-N-benzylinivalol	0.022	0.009	9.6	4.1
omeprazole	0.050	0.002	21.6	0.7
ticlopidine	0.030	0.002	13.0	0.8
None	0.233	0.023	100	9.8

Excretion

No dedicated excretion studies or analyses were submitted for either phentermine or topiramate.

Other Pharmacokinetic Studies

Pharmacokinetic report: Non-clinical pharmacokinetics of phentermine – Review of published literature (Report No. 09-PHEN-PK-01)

The Sponsor reviewed literature reports and publicly available data on phentermine, which supplement primary data provided by the Sponsor. PHEN seems to be absorbed completely in rat after oral dosing. Single dose PHEN injection (inter-arterial) showed PHEN distributed to lungs, excretory organs, liver, and kidneys. Multiple dosing in rat (*ip* injection) showed tissue to blood ratios remained constant and drug did not continue to accumulate. PHEN distributes to brain with similar T_{max} (1 h) and $t_{1/2}$ (1.5 – 2 h) as blood distribution. PHEN undergoes limited metabolism in humans via *p*-hydroxylation and N-oxidation. Rat metabolism is more extensive, predominantly by the *p*-hydroxylation route and with limited N-oxidation similar to humans. Metabolism is different in rabbits, with more extensive metabolism by N-oxidation. *In vitro* studies confirmed P-450 mediated *p*-hydroxylation and N-oxidation in rat, rabbit, and guinea pig liver microsomes, with species differences in metabolic rate and activity. PHEN did not inhibit CYPs 1A2, 2C9, 2D6, 2E1, or 3A4 activity *in vitro* in human liver microsomes ($IC_{50} > 250 \mu M$). Urine is the major elimination route in both rat and human, but elimination is much more rapid in rat ($t_{1/2} \approx 1.5$ h) than human ($t_{1/2} \approx 21$ h). Renal tubular absorption of PHEN is decreased from acidic urine ($pK_a = 9.84$), thus PHEN excretion increases in acidic urine.

Structural differences on the α -carbon of phentermine (methylated) and amphetamine (non-methylated) lead to differences in metabolism, with amphetamine more highly metabolized to the active metabolite 4-hydroxynorephedrine. Amphetamine also inhibits monoamine oxidases (MAO) -A and -B, with 10-fold and 4-fold greater potency than PHEN in rats, respectively. PHEN showed limited *in vitro* inhibition of human MAOs, with K_i of 498 and 375 μM for MAO-A and MAO-B, respectively. In contrast, PHEN inhibits rat MAO-A ($K_i = 85-88 \mu M$) with approximately 6-fold greater potency than human, but with similarly weak inhibition of rat MAO-B ($K_i = 310-416 \mu M$).

Pharmacokinetic report: Non-clinical pharmacokinetics of topiramate – Review of published literature (Report No. 09-TPM-PK-01)

The Sponsor reviewed literature reports and publicly available data on topiramate, which supplement primary data provided by the Sponsor. TPM was rapidly absorbed and distributed after oral administration in rat and dog, with no apparent accumulation after multiple dosing. Protein binding was low in all species (approximately 85% or more unbound) *in vitro*, with apparent saturation of binding. Two erythrocyte binding sites were identified in dog and human (high-affinity, low capacity and low-affinity, high

capacity), with binding apparently due to interaction or binding with carbonic anhydrase isozymes in erythrocytes. Binding to low-affinity, high-capacity erythrocyte sites at high clinical doses effectively creates a circulating depot of TPM in the blood, contributing to longer blood half-life compared to plasma.

TPM undergoes limited metabolism in humans with no major metabolites identified (all metabolites < 5% of administered dose) and approximately 90% of drug remaining unchanged in plasma. TPM recovered in plasma in animals also showed limited metabolism but all human metabolites were present in nonclinical species. Human excretion is predominantly urinary, with approximately 80% administered dose recovered in urine and only 1% recovered in feces. Drug recovered by excretory routes in human remained predominantly unchanged in urine (82% unchanged) and feces (65% unchanged). Excreted TPM was more highly metabolized in rats, with only 5% and 47% unchanged in males and 32% and 86% unchanged in females in feces and urine, respectively.

Gender differences in rat exposure may be due to increased metabolism of TPM in males, likely mediated by sex-specific expression of CYPs (e.g., CYP2C11 and/or CYP3A2). TPM showed modest, concentration-dependent induction of CYP3A4 in primary human hepatocytes (particularly at $\geq 100 \mu\text{M}$ TPM), which was consistent with clinical drug-drug interactions of TPM-induced clearance of ethinyl estradiol. Similarly, modest (11-29%) inhibition of CYP2C19 by high concentrations of TPM *in vitro* (300-900 μM) are consistent with clinical reports of decreased phenytoin clearance with TPM introduction for anti-seizure treatment.

There is little evidence that TPM is affected by drug transporters. TPM had high membrane permeability in CACO-2 cells but was neither a substrate nor inhibitor of p-glycoprotein, and did not inhibit organic anion/cation transporters ($\text{IC}_{50} \geq 624 \mu\text{M}$ for OAT and OCT).

5.2 Toxicokinetics

No individual toxicokinetic studies were included in the NDA submission. Toxicokinetic analyses were included in single dose dog cross-over bioavailability studies for different drug formulations, 13-week combination PHEN/TPM rat and dog toxicity studies, 13-week PHEN rat toxicity study, and embryofetal development PHEN/TPM rabbit reproductive toxicity study.

6 General Toxicology

Toxicology studies used PHEN and TPM drug substances with phentermine doses based on weight of phentermine HCl. Exposure comparisons by body surface area (mg/m^2) extrapolated from animal mg/kg doses would overestimate nonclinical dosing by approximately 20% to clinical phentermine free base dosing. Corrections were not made in body surface area extrapolations throughout this review, but exposure comparisons by plasma exposure (AUC) are preferred, used when possible, and based on phentermine free base.

6.1 Single-Dose Toxicity

Single dose PHEN/TPM dose escalation studies in rat and dog

Signed GLP statements (Report Nos. 1060-016 (6/9/06) and 1060-018 (6/8/06))

Rat – 4.5/30, 15/100, 45/300, 150/1000 mg/kg PHEN/TPM (oral gavage, no TK)

Dog – 1.5/10, 4.5/30, 15/100, 9/60 mg/kg PHEN/TPM (oral gavage, no TK)

Summary: Single oral dose combination PHEN/TPM (VI-0521) rat (n=1/sex) and dog (n=1/sex) toxicity evaluations were conducted in conjunction with GLP-compliant, 14-day toxicity studies. No TK analyses were conducted.

Key Study Findings¹⁸:

- Mortality – 150/1000 mg/kg (rat), none in dog
- Decreased body weight – $\geq 150/100$ (rat), $\geq 1.5/10$ (dog, slight), $\geq 9/60$ (dog, moderate)
- Decreased food consumption (rat)
- Clinical signs – breathing abnormalities/difficulty (rat, dog), \uparrow activity (rat), \downarrow activity (dog), stereotypy and hypersensitivity to touch (rat), salivation and panting (dog), ataxia/impaired limb function & righting reflex/tremor (dog)

¹⁸ Summarized from original IND review (F. Alavi, Pharmacology/Toxicology Review #2, 6/7/07)

6.2 Repeat-Dose Toxicity

Dose-ranging 14-day rat combination PHEN/TPM toxicity study

GLP statement, 6/9/06 (Report No. 1060-016, Phase B)

0, 4.5/30, 15/100, 30/200 mg/kg PHEN/TPM (oral gavage)

NOAEL = 4.5/30 mg/kg PHEN/TPM (4X / 5X MRHD)

Summary: GLP-compliant repeat oral dose rat combination PHEN/TPM range-finding study (Phase B; 5/sex/dose) with single dose component (Phase A). Blood sampling for TK analyses were collected but no analyses were conducted. Tissue samples were collected but no histopathology analysis was performed.

Key Study Findings¹⁹:

- Abnormal clinical signs \geq 15/100 mg/kg (\uparrow activity, salivation, isolated rapid breathing and hunched back)
- Dose-related reduced BW gain (\geq 15/100 mg/kg) with concomitant, transient decreased food consumption (week 1 only)
- Dose-related organ weight changes (relative and absolute) at \geq 15/100 mg/kg – increased adrenal (+9-36%), kidney (+1-18%), ovarian (+13-40%) weight; decreased spleen (\downarrow 12-23%) and thymus weight (\downarrow 5-24%)

PHEN 14-day rat toxicity study (range-finding)

GLP statement, initiated 7/5/06 (Report No. 1060-025)

0, 10, 25, 50, 75, 100, 150 mg/kg PHEN (oral gavage)

MTD \approx 75 mg/kg PHEN (75X MRHD)

Summary: GLP-compliant repeat oral dose rat PHEN range-finding toxicity study (4/sex/dose). No organ weight or histopathology analyses were conducted.

Key Study Findings²⁰:

- Apparent drug-related mortality at \geq 100 mg/kg
- Clinical signs at \geq 50 mg/kg (e.g., nasal discharge, discolored material in eye-area, unkempt appearance, increased activity, rapid breathing, stereotypy/self-mutilation)
- Dose-related reduced food consumption and body weight

¹⁹ Summarized from original IND review (F. Alavi, Pharmacology/Toxicology Review #2, 6/7/07)

²⁰ *Ibid*

- Slightly increased BUN, ALT, AST at ≥ 100 mg/kg
- Female ≥ 75 mg/kg decreased lymphocytes (\downarrow 2- to 4-fold) and ≥ 100 mg/kg decreased leukocytes (\downarrow 1- to 2-fold)

Dose-ranging 14-day dog combination PHEN/TPM toxicity study

GLP statement, 6/8/06 (Report No. 1060-018, Phase B)

0, 1.5/10, 3/20, 6/40 mg/kg (PHEN/TPM) (oral gavage)

Summary: GLP-compliant repeat oral dose dog combination PHEN/TPM range-finding study (Phase B; 2/sex/dose) with single dose component (Phase A). No TK sampling or analyses were conducted. Tissue samples were collected but no histopathology analysis was performed.

Key Study Findings²¹:

- Clinical signs of salivation, pupil dilation, red discoloration of ears, ears warm to touch at all doses
- Moderate reduced BW gain (\downarrow 8-14%) in all treatment groups with no clear effect of dose
- Dose-related decreased food consumption during week one (but not week two), \downarrow 18-19% males, \downarrow 28-39% females
- Hematology changes at $\geq 3/20$ mg/kg, mainly in males (\downarrow RBC, Hb, Hct, reticulocytes)

²¹ *Ibid*

Three-month rat phentermine toxicity study*GLP statement, initiated 7/5/06***Phentermine hydrochloride: A 13-week oral toxicity study in rats (Study No. 1060-026)**

Male – 0, 10, 20, 30* mg/kg PHEN (* LD ♂ increased to 30 mg/kg week 4 to end)
5, 16, 27 µg*h/ml

Female – 0, 2.5, 10, 20 mg/kg PHEN
2, 12, 25 µg*h/ml

NOAEL = 20 mg/kg PHEN (♀) (20X MRHD)
30 mg/kg PHEN (♂) (30X MRHD)

Summary: Three-month repeat oral dose rat PHEN toxicity study conducted primarily to identify doses for a chronic, 2-year carcinogenicity study. Drug was well tolerated at all doses and LD male group (2.5 mg/kg) was increased to 30 mg/kg beginning week 4 in order to assess a higher maximum dose. Female doses continued unchanged (maximum 20 mg/kg). Toxicity was minimal up to the maximum doses tested, with the exception of the intended pharmacodynamic effects of decreased food consumption and decreased body weight gain. PHEN exposure was approximately 2-fold higher in females than males.

Key Study Findings²²:

- Dose-related reduced body weight in both males (↓ 17-29%) and females (↓ 4-38%) with concomitant decreased food consumption
- HD slightly increased reticulocytes (+30% ♀ only) and neutrophils (+45% ♂, +61% ♀)

²² *Ibid*

Three-month rat combination PHEN/TPM toxicity study*GLP statement, initiated 7/20/06***Topiramate and phentermine HCl: A 13-week oral toxicity study in rats with a 4-week recovery (Report No. 1060-017)**

Doses (mg/kg)	AUC ₀₋₂₄ (µg*h/ml)	
	Male	Female
0/0 (vehicle control)	--	--
15/0 (PHEN only)	9	18
0/100 (TPM only)	287	677
1.5/10 (PHEN/TPM)	--	--
15/100 (PHEN/TPM)	8 / 271	20 / 651

NOAEL = 15 mg/kg PHEN (15X MRHD)
 1.5/10 mg/kg PHEN/TPM (2X / 3X MRHD)

Key Study Findings²³:

- Dose-related reduced BW gain in PHEN groups, up to approximately 20-25%, with little apparent contribution of TPM in combination (consistent with the expected pharmacodynamic effect)
- Kidney and liver weights were slightly increased (15-28%) in combination PHEN/TPM groups, with no apparent additive effect of treatment or correlative histological lesions
- BUN was slightly increased in the HD PHEN/TPM group
- Minimal bone marrow depletion was seen in two HD PHEN/TPM males
- PHEN and TPM exposure was 2- to 3-fold higher in females than males (respectively)
- Overall, toxicity from PHEN/TPM combination treatment showed minimal interactions between the drugs in rats but potentially drug-related findings seen only in the PHEN/TPM HD (kidney (↑ BUN), bone marrow depletion) could not be ruled out

²³ *Ibid*

Three-month dog combination PHEN/TPM toxicity study*GLP statement, initiated 7/26/06***Topiramate and phentermine HCl: A 13-week oral toxicity study in beagle dogs with a 4-week recovery (Report No. 1060-019)**

Doses (mg/kg)	AUC ₀₋₂₄ (µg*h/ml)	
	Male	Female
0/0 (vehicle control)	--	--
4.5/0 (PHEN only)	2	2
0/30 (TPM only)	93	76
0.45/3 (PHEN/TPM)	0.2 / 11	0.1 / 6
4.5/30 (PHEN/TPM)	3 / 90	3 / 82

NOAEL = 4.5/30 mg/kg PHEN/TPM (15X / 26X MRHD)

Key Study Findings²⁴:

- Clinical signs in PHEN/TPM HD animals (↑ activity, stereotypy, rapid breathing, panting, warm skin)
- Mean body weight was decreased ~10% in PHEN only and PHEN/TPM HD groups, suggesting limited effect of administered TPM and no apparent synergistic effect of PHEN/TPM combination on body weight
- No drug-related effect on QT_c interval. Effects on hemodynamic and cardiovascular parameters were unremarkable but inter-individual ECG results were highly variable
- Slight, < 10% decreases in PHEN/TPM HD erythrocyte parameters (RBC, Hct)
- Modest, partially reversible, increased relative liver weight (+26-35%, ♂ and ♀) and increased absolute and relative adrenal weight (♂ only) in PHEN/TPM HD groups
- Minimal to mild hepatocellular vacuolation (fluid or glycogen accumulation) seen primarily in TPM treated animals (TPM alone and PHEN/TPM HD), but also seen in recovery group control animals and no changes in clinical chemistry biomarkers
- Histopathological skin lesions were seen in a 1/4 ♂ and 1/4 ♀ PHEN/TPM HD and 1/4 PHEN only ♀ animals (mild to moderate serocellular crust, mild necrosis and hyperplasia); findings consistent with dermatitis with listed PHEN clinical use

²⁴ *Ibid*

- HD combination PHEN/TPM was accepted as a NOAEL based on modest, predominantly reversible findings, absence of correlative biomarker effects, and absence of remarkable differences between PHEN/TPM groups and either PHEN or TPM treatment alone

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Genetic toxicity has not been assessed directly for the proposed PHEN/TPM combination drug substance.

Genetic toxicity was assessed for the original approval of topiramate. As described in the Topamax® label, TPM was not genotoxic in a battery of *in vitro* and *in vivo* studies, including mutagenicity assays (Ames, mouse lymphoma), unscheduled DNA synthesis in rat hepatocytes, and (b) (4) chromosomal aberration assays (*in vitro* human lymphocyte and *in vivo* rat bone marrow micronucleus).

Genetic toxicity assessment for the phentermine component of the proposed PHEN/TPM drug substance is discussed below.

PHEN bacterial reverse mutation assay

GLP-compliant, initiated 6/14/06

Bacterial reverse mutation assay (Report No. AB29JU.503.BTL)

Key Study Findings²⁵:

- PHEN was negative for mutagenic potential in the presence or absence of a metabolic activation system up to the limit dose of 5000 µg/plate

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

PHEN *in vitro* mammalian chromosome aberration test

GLP-compliant, initiated 6/15/06

***In vitro* mammalian chromosome aberration test (Report No. AB29JU.331.BTL)**

Key Study Findings²⁶:

- PHEN was negative for clastogenic potential in Chinese hamster lung (CHL-K1) cells in the presence or absence of a metabolic activation system up to concentrations that did not cause excessive cytotoxicity

²⁵ *Ibid*

²⁶ *Ibid*

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Mammalian erythrocyte micronucleus test

GLP-compliant, initiated 6/21/07

Mammalian erythrocyte micronucleus test (Report No. AB29JU.125.BTL)

0, 18/75, 37.5, 75 mg/kg PHEN

Key Study Findings²⁷:

- PHEN was negative for clastogenic potential *in vivo* in rats given a single oral gavage treatment up to an evaluable dose that also exceeded the MTD (based on deaths in 13% of males and 33% of females)

7.4 Other Genetic Toxicity Studies

None.

²⁷ *Ibid*

8 Carcinogenicity

Carcinogenicity in rodents or other species has not been assessed for the proposed PHEN/TPM combination drug substance.

Topiramate carcinogenicity has been assessed in oral lifetime exposure studies in mice and rats. The label for the listed product, Topamax®, notes there was no evidence of carcinogenicity in rats up to 120 mg/kg. The Topamax® label provides no rat plasma TPM exposure information, thus exposure estimates based on body surface area (mg/m^2) provide approximately 21X the MRHD for an obese individual. The Topamax® label states mice receiving 300 mg/kg dietary TPM had significantly increased numbers of urinary bladder tumors. Bladder tumors were predominantly in smooth muscle considered histomorphologically unique to mice. Mouse tumors occurred at steady-state plasma TPM levels approximately 2X to 4X exposure at the MRHD. The relevance of TPM-induced mouse bladder tumors to human cancer risk is uncertain.

Phentermine carcinogenicity was not assessed prior to approval for short term treatment of obesity. PHEN was first approved in 1959 and since then no evidence has emerged that PHEN is carcinogenic with common clinical use. Since PHEN is approved only for short term (“a few weeks”) use, the possibility of a carcinogenic effect from chronic use cannot be adequately addressed from clinical experience. VIVUS conducted a two-year oral carcinogenicity study in rat to assess potential for PHEN-induced carcinogenesis. Carcinogenicity of PHEN treatment was not assessed in mice. The rat PHEN carcinogenicity study is reviewed and discussed below.

Phentermine 2-year oral carcinogenicity in rats

0, 3, 10, 30, 0 (pair-fed) mg/kg PHEN (oral gavage)

NOAEL (neoplastic) = 30 mg/kg PHEN (♂ 11X / ♀ 18X MRHD)

NOAEL = Female - 3 mg/kg PHEN (1X MRHD)

(non-neoplastic) Male – 10 mg/kg PHEN (2X MRHD)

Key Study Findings: NOAEL = 30 mg/kg/day (neoplasms), 10 mg/kg/day (♂ non-neoplastic), 3 mg/kg/day (♀ non-neoplastic). There were no drug-induced tumors at the highest dose tested, providing MRHD exposure estimates of 11X for males and 18X for females. NOAELs for non-neoplastic toxicity were determined based on increased adverse tooth-related clinical signs in HD ♂ and MD and HD ♀.

Adequacy of Carcinogenicity Study – The final study report of a GLP-compliant, standard two year oral (gavage) carcinogenicity study in Sprague-Dawley rats was reviewed and results were discussed at a meeting of the Executive Carcinogenicity Assessment Committee (ECAC). The study was considered acceptable based on doses previously recommended by the ECAC and results showing the high dose at or near the MTD due to excessive reduced body weight compared to controls (consistent with the

intended pharmacodynamic effect). No satellite animals were included for toxicokinetic analyses but exposure could be estimated from previous chronic (6-month) studies in the same rat strain.

Appropriateness of Test Models – The Sponsor chose doses of 0, 3, 10, 30, 0 mg/kg/day phentermine based on previous recommendations of the ECAC. Two control groups were used, including vehicle treatment and a second vehicle treatment group with diet restricted to levels consumed in the high dose groups ('pair-fed' control). Results showed improved survival in treatment groups and pair-fed controls, consistent with a protective effect of reduced body weight on survival. Exposure at the high dose provided approximately 11X and 18X MRHD in males and females, respectively, based on total exposure (AUC₀₋₂₄).

Evaluation of Tumor Findings – There were no tumor increases in any phentermine treatment group that were considered treatment-related or biologically significant. Uterus benign granular cell tumors were significantly increased in HD females compared to vehicle only (but not pair-fed) controls but the tumor incidence was within the conducting laboratory's historical control range. Combined thoracic cavity benign and malignant hibernoma were positive for a dose-response increase but not for pair-wise comparison to vehicle or pair-fed controls. Neither benign nor malignant hibernomas were significantly different from vehicle or pair-fed controls when analyzed separately. Neither uterus granular cell tumors nor thoracic cavity hibernomas were considered drug-induced or biologically significant.

Title – Phentermine hydrochloride: A 2-year oral carcinogenicity study in rats

Study no.:	1060-020
Study report location:	eCTD (Section 4.2.3.4.1)
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	5/30/07
GLP compliance:	Yes (signed statement)
QA statement:	Yes (signed report)
Drug, lot #, and % purity:	Phentermine HCl, Batch Nos. 0640349 (100% purity) and 0740376 (100% purity)
CAC concurrence:	Yes

Methods

Doses:	0, 3, 10, 30 mg/kg/d phentermine HCl 0 (pair-fed control group)
Frequency of dosing:	Daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Distilled water
Basis of dose selection:	Range-finding (ECAC concurrence)
Species/Strain:	Sprague Dawley rat [CrI:CD (SD)]
Number/Sex/Group:	60 (+ 5 'sentinel'/group)
Age:	6 weeks
Animal housing:	Individual cages
Paradigm for dietary restriction:	Groups 1-4 <i>ad lib.</i> feeding Group 5 – pair-fed control (Week 3 onward; set to HD (group 4) mean food consumption from prior week)
Dual control employed:	Yes (based on ECAC recommendations, a pair-fed control group was added)
Interim sacrifice:	None; animals found dead or sacrificed <i>in extremis</i> subject to full clinical (“when possible”), gross, and histologic pathology examination.
Satellite groups:	None for TK sampling; an extra 5/sex/group ‘sentinel’ animals were included for general health and viral analyses
Deviation from study protocol:	Female group terminated week 98 due to excessive control group deaths (n=20 remaining). Additional minor deviations were documented but nothing affected interpretation of the study.

Study Design Summary

Group Assignments			
Group Number	Dose Level (mg/kg/day)	Number of Animals ^a	
		Male	Female
1	0 (Vehicle Control)	60	60
2	3	60	60
3	10	60	60
4	30	60	60
5	0 (Pair-fed)	60	60

^aFive additional animals/sex served as sentinel animals.

Observations and Results

Statistics – The conducting laboratory compared treatment groups to the vehicle control and separately compared the HD group to the pair-fed group (see Sponsor’s

summary table, below). The FDA statistical analyses included separate comparisons of treatment groups to vehicle control and pair-fed control groups. A standard set of combined tumors was also analyzed statistically by FDA.

Conducting Lab's Statistical Analysis Summary

Endpoints	Type of Analysis
Body Weights Food Consumption Hematology (except leukocyte counts)	Group Pair-wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)
Leukocyte Counts Total Leukocyte Counts Differential Leukocyte Counts	Log Transformation/Group Pair-wise Comparisons
Mortality Data	Survival Analysis
Tumor Data	Tumor Analysis

Mortality – Phentermine treatment did not adversely affect survival. In fact, survival trends (nss) showed vehicle control and LD survival was approximately 10-15% lower in both males and females compared to MD, HD, and pair-fed groups. The female study groups were terminated early at week 98 due to control group survival falling to 20 animals. Approximate **overall survival was 42%, 38%, 58%, 53%, 58% for males (Week 105) and 33%, 40%, 50%, 48%, and 48% for females (Week 98)** in vehicle control, LD, MD, HD, and pair-fed control groups, respectively (see reviewer's summary table, below).

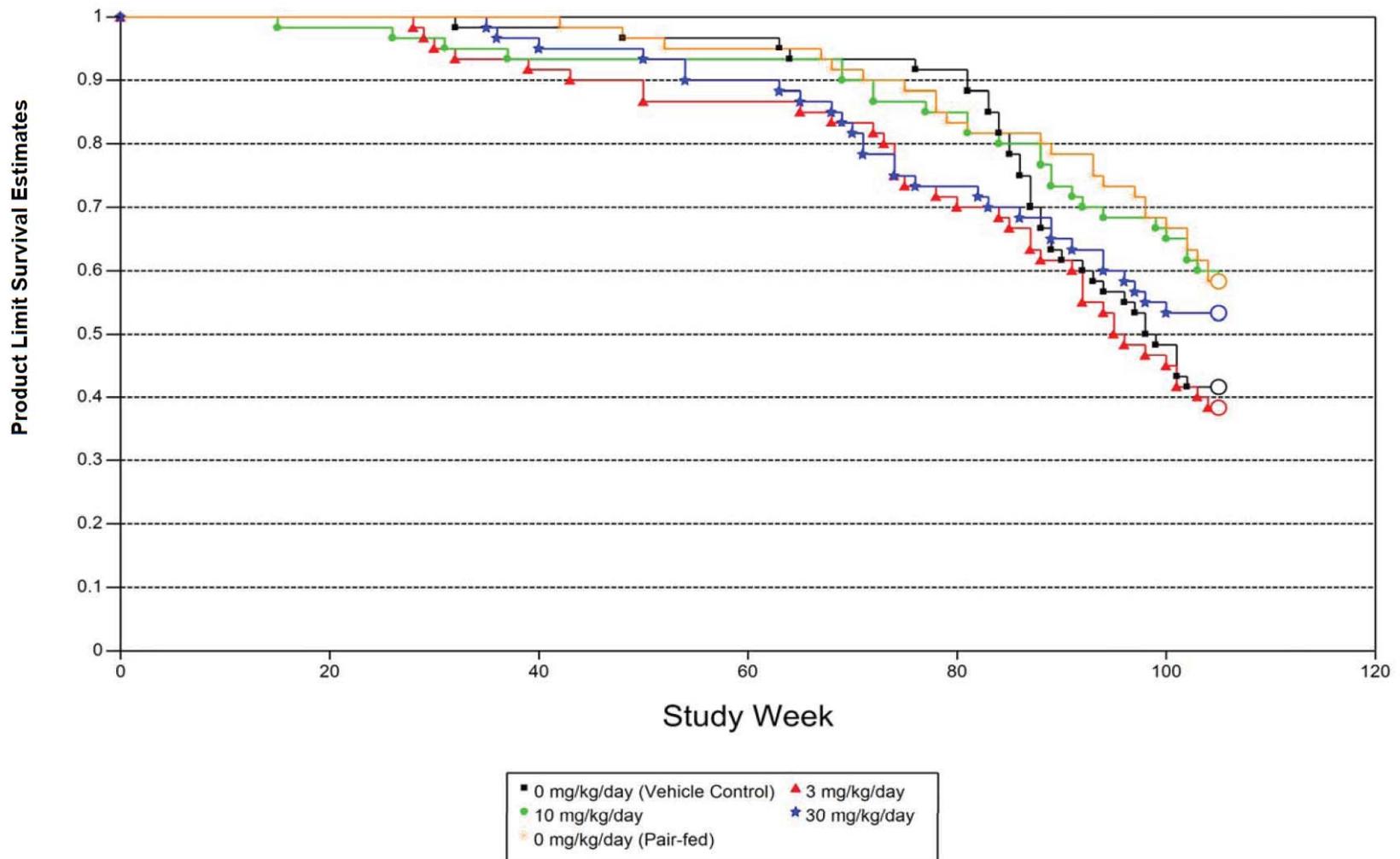
There were no apparent treatment-related differences in cause of death determined in animals found dead or euthanized *in extremis*.

Phentermine treatment (mg/kg/day)	Survival	
	Male (Week 105)	Female (Week 98)
0 (vehicle control)	42%	33%
3	38%	40%
10	58%	50%
30	53%	48%
0 (pair-fed control)	58%	48%

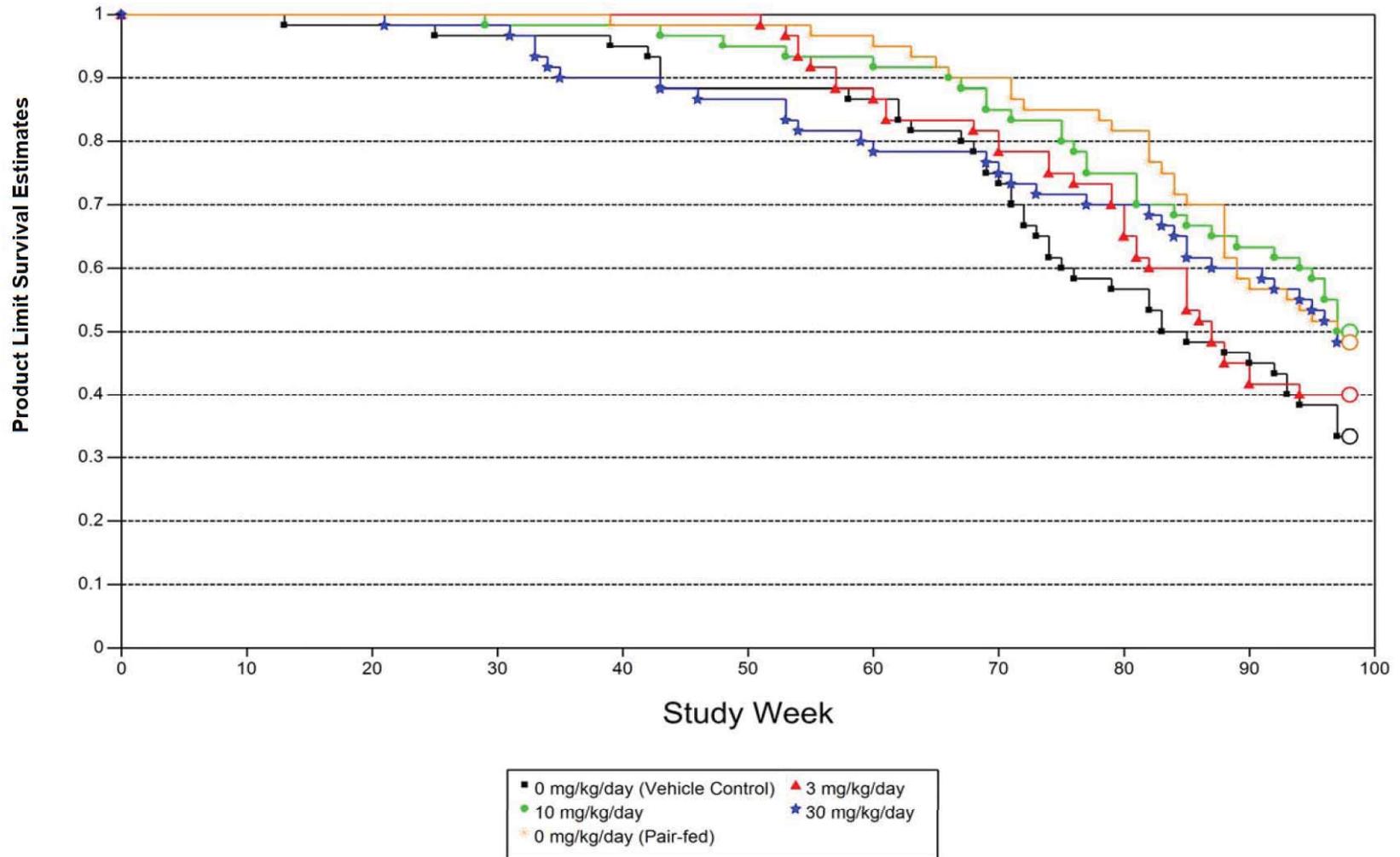
Apparent improved survival with increasing phentermine treatment was consistent with the expected pharmacodynamic effect of dose-related decreased body weight and positive effects of lower body weight on survival. The Sponsor's Kaplan-Meier plots of survival are shown below.

Figure 3 – Sponsor’s Kaplan Meier Survival Plots (Males and Females)

Summary of Survival Estimates - MALE



Summary of Survival Estimates - FEMALE



Clinical Signs – Several clinical signs were observed with increased incidence and/or frequency in HD males and females, including: **red discharge (external)** and **‘material around eyes’**; **abrasions, scabbed areas**, and **sparse hair**; **hunched posture** and **missing tail portion** (male only); and several **tooth-related findings (broken, cut, missing, and malocclusion)**. Tooth effects were also seen in MD females.

Phentermine has stimulatory, amphetamine-like effects and tooth-related effects are consistent with literature reports of gum and tooth toxicity with methamphetamine abuse. The mechanism of phentermine-induced tooth toxicity has not been investigated but prevalence of clinical signs support a drug-related effect.

‘Palate hole’ was observed in a few animals (0, 0, 0, 4, 2 males, 1, 0, 3, 1, 3 females, in vehicle, LD, MD, HD, pair-fed, respectively). Incidence was low but the finding is noted because of a possible relationship to other drug-related findings in the oral cavity. Note that this finding was also present in the pair-fed (non-dosed) group, so the relationship to drug treatment is tenuous.

Incidences of clinical signs are summarized in the reviewer’s summary table, below.

Detailed clinical observations included assessment of palpable masses. Individual animal data on palpable masses was not included but according to a statement and summary table provided, there was no drug-related increase in external palpable masses (see Sponsor’s table, below).

A separate analysis of subcutaneous masses was performed at necropsy. Many more masses of varying size were detected subcutaneously compared to external palpable masses but there was no apparent treatment-related effect.

Palpable Mass Incidence		
Dose Level	Number of Animals ^a	
	Males	Females
Vehicle Control	2/25	11/20
3 mg/kg/day	1/23	15/24
10 mg/kg/day	5/35	12/30
30 mg/kg/day	0/32	11/29
Pair-fed Control	2/35	15/29

^aNumber of times observed/Total number of animals

Clinical signs summary (# observations / # animals) †						
Organ/Tissue	Sex	Phentermine (mg/kg/day)				
		0 (vehicle)	3	10	30	0 (pair-fed)
Teeth broken	M	86/2	75/2	81/3	694/19	110/5
	F	120/3	197/7	413/15	219/10	92/4
Teeth cut	M	178/10	223/31	211/26	922/34	351/19
	F	175/15	336/29	717/25	595/30	177/12
Teeth missing	M	8/1	5/1	27/2	133/4	80/1
	F	0/0	0/0	72/6	67/5	0/0
Malocclusion	M	0/0	133/4	161/4	648/10	199/5
	F	72/2	43/3	332/14	203/6	185/5
Discharge, red	M	4/3	17/6	0/0	20/7	0/0
	F	1/1	0/0	3/2	12/4	6/3
Material around eyes, red	M	131/10	59/7	212/6	556/16	238/8
	F	186/18	258/19	480/25	391/14	124/15
Palate hole	M	0/0	0/0	0/0	18/4	3/2
	F	9/1	0/0	40/3	13/1	26/3
Posture hunched	M	20/4	8/6	52/5	185/17	22/5
	F	37/8	19/6	111/8	9/2	32/12
Tail missing, portion	M	76/1	49/1	34/1	135/8	0/0
	F	16/1	0/0	1/1	65/2	7/1
Pelage/skin abrasion	M	48/7	6/3	20/4	125/20	1/1
	F	6/4	32/7	21/8	52/11	13/4
Pelage/skin hair sparse	M	1091/22	879/19	2130/31	5018/40	496/19
	F	3953/39	4134/42	5275/45	7482/56	3236/38
Pelage/skin scabbed area	M	139/17	131/12	104/16	356/21	83/10
	F	53/11	107/14	63/10	189/22	41/14
Pelage/skin skin discolored, red	M	1/1	0/0	0/0	126/11	11/2
	F	0/0	9/2	4/2	2/2	2/1
Pelage/skin unkempt appearance	M	15/4	15/9	31/7	158/12	11/4
	F	9/4	5/2	23/7	4/2	24/5

† Incidence recorded as number of times observed / total number of animals affected
M = male, F = female

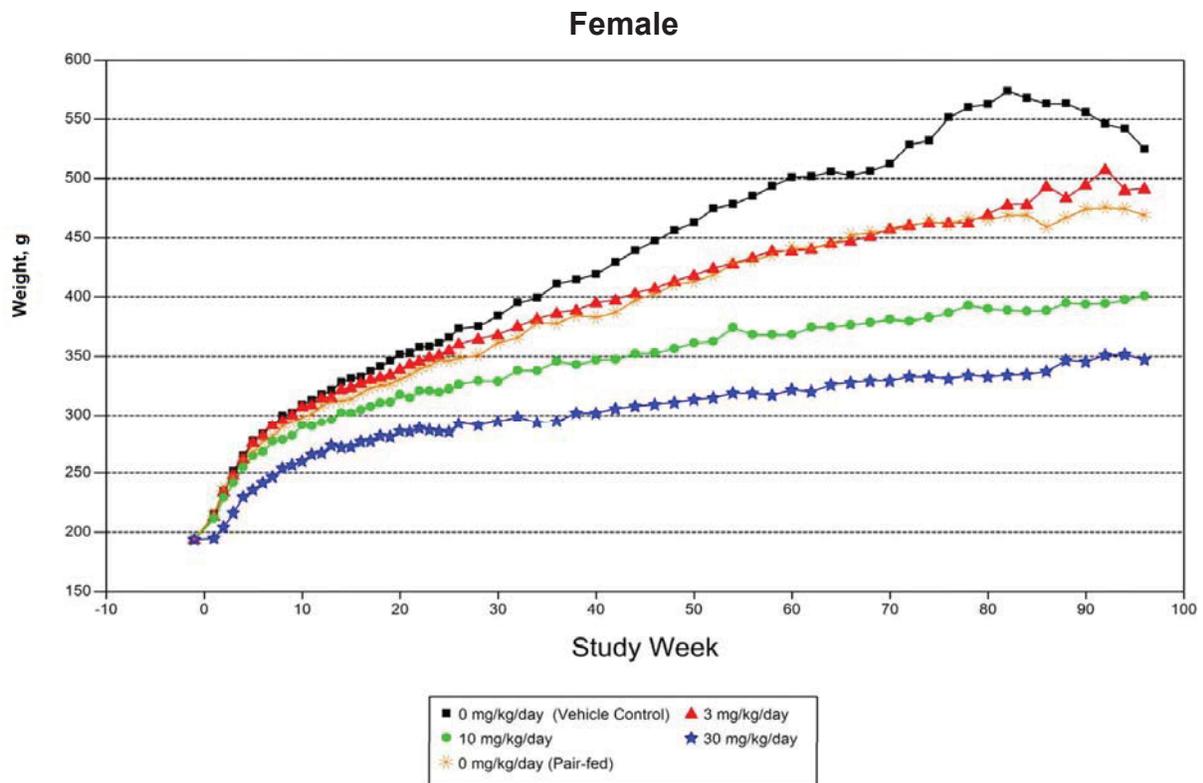
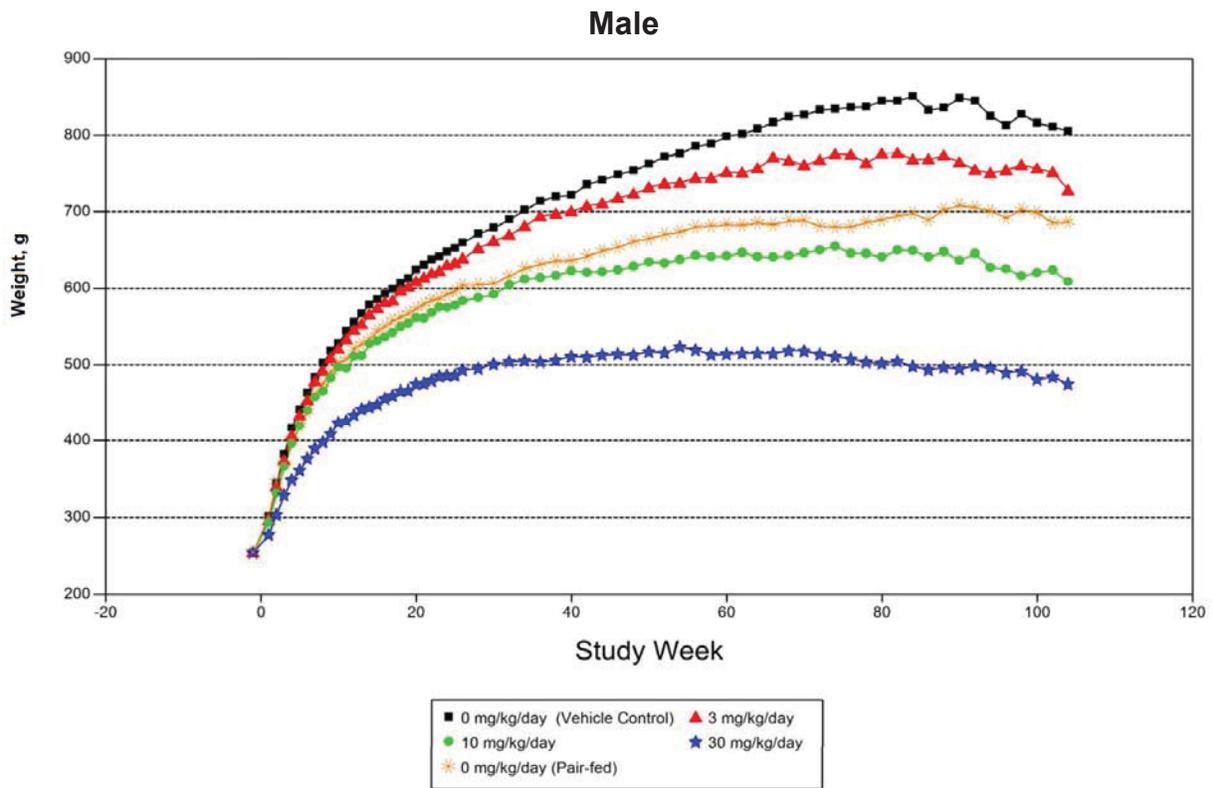
Body Weights – Body weights at termination were decreased in a dose-dependent manner compared to vehicle controls in males (↓ 10-41%) and females (↓ 6-34%). Pair-fed control body weights were also decreased compared to controls, but magnitude of weight differences (-15% ♂, -11% ♀) were lower than expected and statistically different than corresponding HD body weights (+31% vs. HD ♂ and +26% vs. HD ♀). Body weight differences between HD groups and corresponding pair-fed controls supports a

drug-related effect on weight loss independent of appetite suppression, which is consistent with the intended pharmacodynamic effect.

Body weight findings are shown in the Sponsor's summary table and figures, below.

Body Weights; g						
Dose Level Concentration	Males			Females		
	Pretest	Week 104	%	Pretest	Week 96	%
Vehicle Control	254.2	805.5	NA)	193.9	525.0	NA
3 mg/kg/day	254.3	728.0	(-9.6)	193.9	491.8	(-6.3)
10 mg/kg/day	254.2	608.1	(-24.5)	193.9	400.8	(-23.7)
30 mg/kg/day	254.2	475.2	(-41.0)	193.9	347.3	(-33.8)
Pair-fed Control	254.3	686.4	(-14.8)	194.0	468.8	(-10.7)
NA – Not applicable Week 96	(%) – Percent difference from vehicle control at Week 104 or Week 96					

Figure 4 – Body Weight Curves



Food Consumption – Food consumption decreased modestly with phentermine treatment, dose-dependently in males up to a maximum 10% reduction (HD) and only 3% (MD) and independent of dose in females. Food consumption was further reduced (1.5% ♂, 5.8% ♀) in pair-fed groups compared to HD groups used to set pair-fed diet. Clinical signs indicating tooth-related toxicity may have contributed to decreased food consumption, although as noted overall food consumption decreases were modest. Notably, the magnitude of reduced food consumption did not account for the magnitude of dose-related reductions in body weight. Food consumption data are shown in the Sponsor's summary table, below.

Mean Food Consumption; g				
Dose Level Concentration	Males		Females	
	Food Consumption	(%)	Food Consumption	(%)
Vehicle Control	27.16	NA	20.64	NA
3 mg/kg/day	26.75	(-1.5)	20.35	(-1.4)
10 mg/kg/day	25.10	(-7.6)	19.98	(-3.2)
30 mg/kg/day	24.48	(-9.9)	20.35	(-1.4)
Pair-fed Control	24.07	(-11.4)	19.15	(-7.2)
NA – Not applicable (%) – Percent difference from vehicle control				

Reviewer's note – differences from vehicle control were statistically significant for various individual weekly intervals in all treatment groups

Clinical Pathology – Blood (~1 ml, K₃EDTA anticoagulant) was collected from vena cava for hematology analyses prior to scheduled and unscheduled necropsy, when possible. Rats were not fasted prior to necropsy and blood collection.

Hematology findings were generally unremarkable. Erythrocyte counts were slightly elevated in HD males and females compared to vehicle controls (+10-11%, $p < 0.01$) and to a lesser extent pair-fed controls (+4-5%, $p < 0.05$). The biological significance of 5-10% increases in erythrocytes over the course of a two year treatment is likely negligible. Data are shown in the reviewer's summary table, below.

Hematology Findings		
Phentermine Treatment (mg/kg/day)	Erythrocyte Count ($10^6/\mu\text{l}$)	
	Male	Female
0 (vehicle control)	7.290 ± 0.89	6.809 ± 1.17
3	7.643 ± 1.03	6.705 ± 1.34
10	7.637 ± 0.66	7.106 ± 0.79
30	8.048 ± 0.58 ^{a, b}	7.575 ± 0.39 ^{a, b}
0 (pair-fed control)	7.655 ± 0.64	7.258 ± 0.65

^a $p < 0.01$ vs. vehicle control

^b $p < 0.05$ vs. pair-fed control

Gross Pathology – A comprehensive macroscopic examination was performed at necropsy. Palpable mass findings, which were unremarkable, were previously discussed. Gross pathology findings were generally unremarkable and consistent with clinical signs. Notably there were no bone-related findings, suggesting the drug-related effects on teeth were limited to localized effects in the oral cavity (potentially related to gum and salivary changes and/or behavioral changes such as teeth grinding). Macroscopic **tooth/teeth** findings were increased slightly in females only. **Lung focus/foci, white or tan**, and **small thymus gland** were observed in a few MD and HD males and females. Notable macroscopic findings are shown in the reviewer's summary table, below.

Gross pathology summary (incidence DOS / SNC) †						
Organ/Tissue	Sex	Phentermine (mg/kg/day)				
		0 (veh.)	3	10	30	0 (pair-fed)
Lung focus/foci, white	M	0/1	0/0	2/2	3/8	1/0
Lung focus/foci, tan	F	0/1	0/1	0/2	1/6	1/0
Tail, absent, portion (no grade)	M	0/0	0/0	0/1	1/5	0/0
Thymus gland, small	M	0/0	2/0	1/6	7/5	2/1
	F	3/2	1/3	5/4	5/7	4/7
Tooth/teeth (absent/broken/malocclusion/overgrown)	F	1/0	2/1	3/3	1/5	2/1

† Overall incidence in animals died or euthanized on study (DOS) or at scheduled necropsy (SNC)

Histopathology

Peer Review – None.

Neoplastic – There were no tumor increases in any phentermine treatment group that were statistically significant against both vehicle and pair-fed controls. Tumor incidence was independently assessed by FDA statistics staff using survival adjusted and unadjusted analyses. Notable tumor findings are discussed and summarized in the reviewer's summary table, below. See FDA statistics review for a list of combined tumors and a further discussion of tumor statistical analyses (M. Min, 7/7/10).

Uterus benign granular cell tumors (0, 0, 3, 5, 3 tumors in vehicle, LD, MD, HD, pair-fed, respectively) increased in HD females compared to vehicle controls, reaching statistical significance in the Sponsor's trend analysis (Cochran-Armitage trend test, $p = 0.0039$) and in FDA dose-response ($p=0.005$) and pair-wise comparison ($p=0.038$). However, the HD tumor incidence was not statistically different than pair-fed controls. In addition, HD female tumor incidence of 8% (5/60 animals) was within the historical control range of 0-10% in the conducting laboratory. The HD tumor increase was

considered incidental by the Sponsor and this reviewer concludes the finding was neither biologically significant nor drug-induced.

The incidence of brain astrocytoma was higher in the HD and pair-fed females compared to controls (5-7% vs. 2% in controls). This pattern was also seen with the uterine tumors described above. The similar tumor incidence in the non-dosed pair-fed control essentially excludes phentermine as the causative factor for either tumor type. Reasons for the higher incidence of these tumors is unclear, but may reflect spontaneous background or perhaps longer survival.

The FDA statistical analysis of combined tumor types identified female combined **thoracic cavity benign and malignant hibernoma** (1, 1, 1, 3, 0 tumors in vehicle, LD, MD, HD, pair-fed, respectively) positive for dose-response against pair-fed control ($p = 0.038$). Combined hibernomas were not significantly increased in the pair-wise analysis or against the vehicle control group. When analyzed individually neither the incidence of **benign hibernoma** (0, 0, 0, 2, 0, respectively) nor of **malignant hibernoma** (1, 1, 1, 1, 0, respectively) were significantly different from vehicle or pair-fed control groups. Hibernoma tumor findings were not considered biologically significant or drug-induced by this reviewer.

Tumors with marginal statistical significance are summarized in the reviewer's table, below.

Summary of tumors with any significant difference from controls †									
Tissue/Tumor	Sex	Phentermine (mg/kg/day)					Statistics (p-value)		
		0 (vehicle)	3	10	30	0 (pair-fed)	Trend		Pair-wise
							Control	Pair-fed	
Brain – astrocytoma, malignant	F	1	0	1	4	3	p=0.028	nss	nss
Uterus – granular cell tumor	F	0	0	3	5	3	p=0.005	p=0.05	p=0.038 ^a
Testes – adenoma (interstitial)	M	5	2	2	8	4	p=0.039	nss	nss
Thoracic cavity – hibernoma benign	F	0	0	0	2	0	nss	nss	nss
	M	0	0	0	0	0	nss	nss	nss
malignant	F	1	1	1	1	0	nss	nss	nss
	M	1	1	5	2	1	nss	nss	nss
combined	F	1	1	1	3	0	nss	p=0.038	nss
	M	1	1	5	2	1	nss	nss	nss

† Statistical analyses summarized from FDA statistics review (Min, 7/7/10)

F = female, M = male, nss = not statistically significant

^a High dose vs. vehicle control (not statistically different from pair-fed controls)

Non-Neoplastic

Phentermine treatment was generally well tolerated up to the maximum 30 mg/kg/day dose. Non-neoplastic histological findings were generally unremarkable in animals that died (or were euthanized) on study and at terminal necropsy. Noteworthy findings are discussed below and shown in the selected data from Sponsor's summary tables and reviewer's table, below.

Findings in males included a slight increase in incidence of ***subacute/acute inflammation in coagulating glands***, with 6/32 HD males (moderate to severe in 3 animals). Similar lesions were seen in rats that died or were euthanized on study, but only 1 other male (LD) had a similar lesion at scheduled necropsy.

Background incidence of ***chronic progressive nephropathy (CPN)*** was high in males with 100% incidence in control and 91% in LD at scheduled necropsy. Incidence and severity seemed to slightly decrease with increasing dose, with 69% incidence in MD and HD males and severity limited to 'minimal' in 21/22 (95%) HD males. Weight loss (the intended PD effect) may have been slightly protective since pair-fed male incidence was 80% overall, intermediate between vehicle controls and MD or HD males. Nevertheless, phentermine clearly did not increase background incidence of CPN in males and background incidence of CPN was low (and unaffected by treatment) in females.

Unilateral or bilateral ***retinal degeneration/atrophy*** in ***eyes*** was low (<10%) in all male and female groups, however, moderate to severe degeneration/atrophy was seen only in MD or HD treatments. The study pathologist considered findings consistent with common lesions in SD rats and unrelated to treatment. This reviewer did not consider retinal lesions to be biologically significant.

Lung findings included dose-related increased minimal to mild ***alveolar histiocytosis*** and minimal ***granulomatous inflammation*** in males and females (see Reviewer's table, below). Maximum alveolar histiocytosis incidences of 78% (males) and 38% (females) in HD were markedly higher than vehicle and pair-fed controls, which were near the high end of the contract laboratory's reported historical control incidence of 8-80% (male) and 9-55% (female). Maximum HD incidences of 22% (male) and 38% (female) granulomatous inflammation were approximately 4- to 5-fold higher than concurrent controls and above reported historical control incidences of 0-2% (male) and 0-10% (female). Concurrent vehicle and pair-fed controls were at the high end of the historical range and the study pathologist noted the lesions are often incorporated under the term 'chronic inflammation' which has maximal historical control incidence of 28% (male) and 22% (female). The study pathologist and Sponsor considered lung histiocytosis and inflammation unrelated to treatment. This reviewer concluded the relationship with dose suggests HD phentermine increased histiocytosis and inflammation, however, the biological significance is questionable because of high historical incidence of histiocytosis and the absence of any effect on survival or other

pathology biomarkers. The relationship of lung gross pathology findings of slightly increased HD focus/foci (white or tan) to histiocytosis or inflammatory lesions is not clear.

Lung microscopic lesion summary (incidence) †				
Phentermine Treatment (mg/kg/day)	Histiocytosis, alveolar		Inflammation, granulomatous	
	Male	Female	Male	Female
0 (vehicle control)	16%	5%	4%	10%
3	26%	21%	9%	8%
10	26%	30%	9%	17%
30	78%	41%	22%	38%
0 (pair-fed control)	17%	10%	3%	7%

† Incidence at scheduled necropsy, generally limited to minimal to mild severity (trends were generally similar in animals dead or euthanized on study)

With respect to clinical signs showing drug-related effects on teeth, it is worth noting that teeth were not examined histologically. There were no apparent drug-related effects on bone.

Summary of Microscopic Observations - MALE

Terminal

Tissue Observation	Severity	0 mg/kg/day (Vehicle Control)		3 mg/kg/day		10 mg/kg/day		30 mg/kg/day		0 mg/kg/day (Pair-fed)	
		DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		35	25	37	23	25	35	28	32	25	35
coagulating glands		(2)	(0)	(1)	(1)	(3)	(0)	(5)	(6)	(1)	(0)
inflammation, subacute/chronic		2	0	1	1	3	0	3	6	1	0
	- minimal	0	0	0	0	0	0	0	1	0	0
	- mild	1	0	0	1	1	0	0	2	0	0
	- moderate	0	0	1	0	1	0	3	2	1	0
	- severe	1	0	0	0	1	0	0	1	0	0
kidneys		(35)	(25)	(37)	(23)	(25)	(35)	(28)	(32)	(25)	(35)
nephropathy, chronic progressive		19	25	24	21	11	24	3	22	12	28
	- minimal	12	12	14	10	9	18	2	21	11	22
	- mild	5	11	4	8	1	4	1	1	1	3
	- moderate	1	1	3	3	1	1	0	0	0	3
	- severe	1	1	3	0	0	1	0	0	0	0
lung		(35)	(25)	(37)	(23)	(25)	(35)	(28)	(32)	(25)	(35)
adhesion/inflammation/fibrosis, pleural		0	0	0	0	0	0	2	5	2	0
	- minimal	0	0	0	0	0	0	2	5	1	0
	- mild	0	0	0	0	0	0	0	0	1	0
histiocytosis, alveolar		3	4	1	6	8	9	11	25	5	6
	- minimal	3	3	1	6	8	6	11	22	4	6
	- mild	0	1	0	0	0	2	0	3	1	0
	- moderate	0	0	0	0	0	1	0	0	0	0
inflammation, granulomatous	- minimal	1	1	0	2	3	3	1	7	0	1

DOS - Died or euthanized on study

SNC - Scheduled necropsy

() - Number observed

Summary of Microscopic Observations

Terminal

Tissue	Observation	Severity	0 mg/kg/day (Vehicle Control)		3 mg/kg/day		10 mg/kg/day		30 mg/kg/day		0 mg/kg/day (Pair-fed)	
			DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC
MALE												
Number of Animals Examined			35	25	37	23	25	35	28	32	25	35
eyes			(35)	(25)	(37)	(23)	(25)	(35)	(28)	(32)	(25)	(35)
degeneration/atrophy, retina, bilateral			0	1	0	2	0	2	0	2	0	0
- minimal			0	1	0	0	0	0	0	0	0	0
- mild			0	0	0	2	0	1	0	0	0	0
- moderate			0	0	0	0	0	1	0	2	0	0
degeneration/atrophy, retina, unilateral			0	1	0	1	1	1	0	1	0	0
- minimal			0	1	0	0	0	1	0	0	0	0
- mild			0	0	0	1	0	0	0	0	0	0
- severe			0	0	0	0	1	0	0	1	0	0
FEMALE												
Number of Animals Examined			40	20	36	24	30	30	31	29	31	29
eyes			(40)	(20)	(36)	(24)	(30)	(30)	(31)	(29)	(31)	(29)
degeneration/atrophy, retina, bilateral			0	0	0	0	0	4	1	1	0	0
- minimal			0	0	0	0	0	1	0	0	0	0
- mild			0	0	0	0	0	1	0	1	0	0
- moderate			0	0	0	0	0	2	1	0	0	0
degeneration/atrophy, retina, unilateral			0	1	0	0	0	2	0	1	0	1
- minimal			0	1	0	0	0	0	0	1	0	0
- mild			0	0	0	0	0	0	0	0	0	1
- moderate			0	0	0	0	0	1	0	0	0	0
- severe			0	0	0	0	0	1	0	0	0	0
lung												
histiocytosis, alveolar			9	1	7	5	10	9	8	12	7	3
- minimal			9	0	7	4	10	8	8	10	7	3
- mild			0	1	0	1	0	1	0	2	0	0
inflammation, granulomatous			1	2	2	2	6	5	5	11	0	2

DOS - Died or euthanized on study
 SNC - Scheduled necropsy
 () - Number observed

Toxicokinetics – No toxicokinetic sampling was performed. Rat plasma exposure (AUC_{0-24}) and human exposure multiple estimates, based on a prior 13-week study of 2.5, 10, and 20/30 mg/kg phentermine, are shown in the reviewer's table, below.

Estimates of rat exposure and human exposure multiples †			
Phentermine (mg/kg/day)	AUC_{0-24} (ng*h/ml)		MRHD ^a
	Male	Female	
3	700	2,200	0.3x ♂ 1x ♀
10	5,000	12,000	2x ♂ 5x ♀
30	27,000	44,000	11x ♂ 18x ♀

† Phentermine exposures estimated from steady state plasma levels from 13-week rat study (#1060-026)

^a Human exposure multiple based on maximum recommended human dose (MRHD) of 15 mg PHEN/92 mg TPM and $AUC_{0-24} = 2,500$ ng*h/ml in obese individuals treated with PHEN + TPM FDC clinical formulation

Stability and Homogeneity – Stock assay solutions were tested appropriately for stability, homogeneity, and drug concentration. All samples were within protocol acceptance criteria ($\pm 10\%$ relative error (RE) and $\leq 5\%$ relative standard deviation (RSD)). Control samples had positive responses for phentermine HCl in week 52 (confirmed contamination) and weeks 64, 72, 76 (sponsor considered insignificant because $\bar{x} < 1\%$ low dose concentrations). Low dose (0.3 mg/ml) solutions were outside the acceptance criteria for two samples (week 8 and 32). Overall, results met the protocol system suitability test (SST) parameters and minor deviations did not affect the integrity of the study or alter the study conclusions.

9 Reproductive and Developmental Toxicology

Information on reproductive and developmental toxicity and use during pregnancy are included on the labels for listed phentermine and topiramate monotherapy indications. PHEN for obesity is listed as Pregnancy Category $\text{(b)}_{(4)}$ for “use in pregnant women only if clearly needed” (Adipex-P®). No specific animal reproduction study data are listed in the PHEN label. Publicly available data, including the Summary Basis of Approval for lonamin®, provide no evidence that PHEN is teratogenic. TPM for epilepsy and migraine is also listed as Pregnancy Category $\text{(b)}_{(4)}$ with recommended use “during pregnancy only if the potential benefit outweighs the potential risk to the fetus” (Topamax®). The Topamax® label includes data that TPM is teratogenic in mouse, rat, and rabbit when administered to pregnant animals during the period of organogenesis.

Embryofetal development studies with co-administration of VIVUS’s PHEN and TPM drug substances were conducted in rat and rabbit. There was no evidence of teratogenicity in either species up to the maximum doses tested of 3.75/25 mg/kg PHEN/TPM in rat (1X / 2X MRHD by AUC) and rabbit (0.1X / 1X MRHD by AUC). Exposures in pregnant rat and rabbit in PHEN/TPM combination studies were expected to be below toxic levels based on range-finding studies.

9.1 Fertility and Early Embryonic Development

No new fertility or early embryonic development studies were conducted with the proposed PHEN/TPM combination. The drug label for Topamax® notes topiramate did not cause adverse effects on male or female rat fertility when treated with up to 100 mg/kg TPM (17X MRHD based on mg/m²). Plasma exposure cannot be estimated from the Topamax label, but extrapolation from TPM exposure (AUC) in other rat studies provides an exposure margin of approximately 4X MRHD. No fertility or early embryonic development studies with phentermine are noted in the Adipex-P® label.

9.2 Embryonic Fetal Development

Phentermine + topiramate embryofetal development (Seg II) in rats – Pilot

Phentermine HCl and topiramate: Pilot study for prenatal developmental toxicity in rats (b) (4) 1060-041; VIVUS No. 1060-040)

Doses 0/0 (vehicle control)
(mg/kg/d) 1.5/10, 3.75/25, 7.5/50, 15/100 (PHEN / TPM)

NOAEL (maternal) < 1.5/10 (PHEN/TPM mg/kg)
NOAEL (fetal) = 3.75 / 25 (PHEN/TPM mg/kg)

NOAEL determination – no maternal NOAEL was determined for dams based on 20% decreased body weight gain (consistent with the PD effect) during treatment at the lowest dose (1.5/10 mg/kg PHEN/TPM)

Key study findings: Major findings were limited to dose-dependent decreased maternal body weight (with corresponding decreased food consumption) and concomitant decreased fetal body weights at higher doses. There were no treatment-related effects on pregnancy parameters or fetal malformations or variations. Body weight decreases were consistent with the intended pharmacologic effect of weight loss and the absence of effects on pregnancy parameters or fetal viability suggest the MTD was not exceeded at the highest dose tested (3.75/25 mg/kg PHEN/TPM).

Study no:	(b) (4) 1060-040 (VIVUS Report No. 1060-040)
Study report location:	
Conducting laboratory and location:	(b) (4)
Date of study initiation:	
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phentermine HCl (USP), Lot No. 0840775, 99.8% Purity (Catalent Pharma Solutions, Winchester, KY USA) Topiramate, Lot No. 2091174, 100.2% Purity (Catalent Pharma Solutions)

Methods

Doses: PHEN / TPM (mg/kg/day)
 0/0 (control), 1.5/10, 3.75/25, 7.5/50, 15/100

Frequency of dosing: QD, Gestation days (GD) 6 – 17

Dose volume: 5 ml/kg/d

Route of administration: Oral gavage

Formulation/Vehicle: Distilled water (PHEN)
 0.5% methylcellulose (4000 cps) (TPM)

Species/Strain: Female (time-mated) SD rats /
 CD[CrI:CD(SD)]

Number/Sex/Group: 5 pregnant ♀

Satellite groups: None

Study design: Pilot/range-finding study for full embryofetal development study – PHEN & TPM were dosed consecutively, dams necropsied GD 20 for implantation, maternal pregnancy parameters, fetal viability, and fetal development and external malformations

Deviation from study protocol: Dosing formulations not analyzed for homogeneity and concentration

Study Design Summary

Group Assignments			
Group Number	Dose Level (mg/kg/day)		Number of Time-mated Females
	Phentermine HCl	Topiramate	
1	0 (Distilled Water)	0 (0.5% Methylcellulose)	5
2	1.5	10	5
3	3.75	25	5
4	7.5	50	5
5	15	100	5

Observations and Results:

Mortality – None.

Clinical Signs – Sporadic, transient incidences in control through HMD including material around mouth/nose (white, brown, or red). Sparse hair in forefoot and/or anogenital region was persistent in 2/5 HMD and 1/5 HD. HD dams also had incidences of increased activity (2/5) and salivation (4/5), and single incidences of red material in pan/bedding in 2/5 dams.

Body Weight – Dose-dependent decreased body weight and body weight gain in dams during treatment, which persisted in HMD and HD post-treatment from GD 18-20. Body weights were significantly decreased for LMD and higher groups (-9% to -18%, respectively). Body weight gain decreases were significant in all groups during

treatment (-20% to -59% from GD 6-18). See summary tables, below (modified from Sponsor's summary tables).

Summary of Gestation Body Weight Values

Study Interval (Day)	Vehicle		1.5/10 mg/kg/day		3.75/25 mg/kg/day		7.5/50 mg/kg/day		15/100 mg/kg/day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Body Weight Values g										
0	208.8	11.88	208.2	12.99	207.0	9.14	206.6	15.53	208.2	9.26
6	254.0	11.29	256.4	13.11	251.8	16.33	243.4	21.34	249.2	10.11
9	267.6	12.46	262.0	11.47	259.4	12.46	237.6 ^a	23.75	231.0 ^b	9.90
12	293.4	12.12	283.2	14.06	276.2	11.12	255.4 ^b	25.50	249.0 ^b	7.91
15	316.2	14.70	301.8	13.92	296.0	16.72	270.6 ^b	24.66	265.2 ^b	7.56
18	355.0	15.25	337.4	14.43	323.4 ^a	19.50	297.4 ^b	27.75	290.8 ^b	9.44
20	386.8	15.50	376.0	17.38	362.8	25.99	332.6 ^b	32.04	329.4 ^b	8.38

N - Number of measures used to calculate mean
SD - Standard Deviation

^a Significantly different from control; (p<0.05)
^b Significantly different from control; (p<0.01)

Summary of Gestation Body Weight Change Values

Study Interval (Day)	Vehicle		1.5/10 mg/kg/day		3.75/25 mg/kg/day		7.5/50 mg/kg/day		15/100 mg/kg/day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Body Weight Change Values g										
0-6	45.2	3.42	48.2	4.21	44.8	9.76	36.8	6.38	41.0	1.73
6-9	13.6	2.51	5.6	1.95	7.6	6.19	-5.8 ^b	5.17	-18.2 ^b	7.69
9-12	25.8	2.28	21.2	5.72	16.8 ^b	1.48	17.8 ^b	3.27	18.0 ^a	4.06
12-15	22.8	3.11	18.6	3.05	19.8	7.26	15.2	7.63	16.2	4.97
15-18	38.8	4.60	35.6	2.30	27.4 ^a	10.41	26.8 ^a	5.07	25.6 ^b	4.04
18-20	31.8	3.27	38.6	4.04	39.4	9.69	35.2	5.81	38.6	7.13
6-18	101.0	8.09	81.0 ^b	7.28	71.6 ^b	9.63	54.0 ^b	8.46	41.6 ^b	11.35
0-20	178.0	11.18	167.8	7.79	155.8	21.57	126.0 ^b	16.54	121.2 ^b	5.97

N - Number of measures used to calculate mean
SD - Standard Deviation

^a Significantly different from control; (p<0.05)
^b Significantly different from control; (p<0.01)

Feed Consumption – Dose-dependent decreased food consumption occurred during treatment (GD 6-18) for dams. Decreased consumption was modest in LD (-10%, nss) and statistically significant in LMD and higher groups (-15% to -30%, respectively). Food consumption decreases were most pronounced at the beginning of dosing from GD 6-12.

Toxicokinetics – None.

Necropsy – Macroscopic findings were unremarkable in all groups.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

All dams were pregnant at necropsy. There were no treatment-related effects on uterine implantation endpoints (e.g., implantation sites, viable fetuses, resorptions, pre- or post-implantation loss).

In HMD and HD dams, gravid uterine weights were slightly decreased (max. -15%, nss) and body weight parameters (body weight and weight gain adjusted for gravid uterine weight) were significantly lower than controls (consistent with overall body weight trends noted above).

Offspring (Malformations, Variations, etc.)

Fetal findings were limited to dose-dependent decreased fetal weights. LD and LMD fetal weights were slightly decreased (-4% to -10%, nss) and generally near the lower limit of historical fetal weight ranges. HMD (-9% to -11%) and HD (-16% to -19%) were significantly lower than controls and outside the historical control ranges.

Phentermine + topiramate embryofetal development (Segment II) in rats

Phentermine HCl and topiramate: Study for effects on embryo-fetal developmental in rats (Report No. 1060-040)

Doses 0/0 (vehicle control)
 (mg/kg/d) 0/3.75 (PHEN only)
 25/0 (TPM only)
 1.5/10, 3.75/25 (PHEN / TPM)

NOAEL (maternal)= 3.75 / 25 mg/kg PHEN / TPM (2X PHEN / 2X TPM MRHD)
 3.75 mg/kg PHEN (alone)
 25 mg/kg TPM (alone)

NOAEL (fetal) = 3.75 / 25 mg/kg PHEN / TPM (2X PHEN / 2X TPM MRHD)

NOAEL determination – high dose TPM (25 mg/kg) alone or in combination (3.75/25 mg/kg PHEN/TPM) caused modest reductions in maternal body weight gain. Maternal body weight changes were consistent with the expected PD effect of weight loss and were not considered evidence of drug-induced toxicity in the absence of other markers of toxicity. Similarly, modest decreases in fetal weight (compared to concurrent controls) that did not affect fetal survival or development were not considered evidence of drug-induced toxicity.

Key study findings:

- There was no evidence of a teratogenic effect of PHEN and TPM co-administration on embryofetal development in rats.
- Doses were below the MTD for maternal and fetal findings in a range-finding assay and limited to approximately 2-times expected human exposure (estimated AUC comparisons). The TPM dose was at least an order of magnitude lower than the expected teratogenic dose in rat. The study seemed to be designed to investigate a

potential additive or synergistic effect of combination treatment without directly addressing the teratogenicity of either compound alone.

- Total litter skeletal variations were slightly increased in treatment groups, but there was no effect of PHEN/TPM combination treatment and no clear teratogenic effect.
- Maternal body weight and body weight gain were reduced with increasing dose (consistent with the PD effect), concomitant with decreased food consumption. Body weight effects were most pronounced at the beginning of treatment, approximately additive for PHEN and TPM co-treatment, and persisted throughout the study.
- Maternal treatment-related pregnancy findings were limited to decreased body weight (-5%) and body weight gain (-16%) in the HD combination compared to vehicle controls and adjusted for gravid uterine weight.
- The major fetal finding was dose-related decreased fetal body weight in both sexes, up to a maximum ↓ 10% in HD combination.

Study no:	Report No. 1060-041
Study report location:	
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/11/09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phentermine HCl (USP), Lot No. 0840775, 99.8% Purity (Catalent Pharma Solutions, Winchester, KY USA) Topiramate, Lot No. 2091174, 100.2% Purity (Catalent Pharma Solutions)

Methods

Doses: 0/0 (vehicle control)
 (mg/kg/d) 1.5/10, 3.75/25 (PHEN / TPM)
 3.75/0 (PHEN only)
 0/25 (TPM only)

Frequency of dosing: QD, Gestation days (GD) 6 – 17

Dose volume: 5 ml/kg/d per compound (10 ml/kg/d total)

Route of administration: Oral gavage

Formulation/Vehicle: Distilled water (PHEN)
 0.5% methylcellulose (4000 cps) (TPM)

Species/Strain: Female (time-mated) SD rats /
 CD[CrI:CD(SD)]

Number/Sex/Group: 25 pregnant ♀

Satellite groups: None

Study design: PHEN & TPM were dosed consecutively, dams necropsied GD 20 for implantation, maternal pregnancy parameters and gross pathology, fetal viability (plus weight & sex), and fetal developmental variations and malformations (soft tissue, skeletal, and external)

Deviation from study protocol: Dosing on GD 17 was completed with formulations from ^{(b)(4)} Study 1060-043 (embryo-fetal rabbit study) and “several animals” were dosed beyond the specified dosing time-frame.

Study Design Summary

Group Assignments			
Group Number	Dose Level (mg/kg/day)		Number of Time-mated Females
	Phentermine HCl (PHEN)	Topiramate (TPM)	
1	0 (Distilled water)	0 (0.5% methylcellulose)	25
2	1.5	10	25
3	3.75	25	25
4	3.75	-	25
5	-	25	25

Reviewer's note – the high dose caused slightly decreased maternal body weight, body weight gain, and food consumption with a concomitant trend of slightly decreased fetal weights (-7% to 10%, nss) but no other apparent maternal or fetal toxicity in a pilot range-finding study

Observations and Results:

Mortality – No maternal mortality.

Clinical Signs – Detailed clinical exams daily GD 6 to 20 (not limited to cage-side observations). Notable treatment-related signs were limited to increased activity, excessive licking, and vocalization. The behaviors were most prominent in the PHEN only group, with similar numbers of animals affected in the HD combination group, consistent with a PHEN-mediated neurologic effect. The neurologic signs are consistent with the sympathomimetic effect of phentermine. Data are shown in the Sponsor's summary table, below.

Summary of Gestation Detailed Clinical Observations ⁺					
Days 6 to 20					
Observation	Vehicle	1.5/10 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
Number of Animals Alive at Start of Interval	25	25	25	25	25
Behavior/Activity					
Activity increased	0/0	0/0	7/3	10/8	2/2
Licking excessive	0/0	15/2	11/7	20/7	0/0
Vocalization	0/0	0/0	7/5	1/1	0/0

⁺ Number of times observed/Total number of animals affected

Body Weight / Food Consumption – Weighed/measured GD 0, 6, 9, 12, 15, 18, 20 and calculated for various time periods.

Dose-related trends in dams were consistent with the intended pharmacologic effects of PHEN/TPM during dosing, including decreased body weight and body weight gain concomitant with decreased food consumption. Body weight changes were statistically significant in the HD combination, with changes most pronounced during the first week of dosing. Trends in PHEN and TPM only groups were less pronounced than HD combination treatment, suggesting approximately additive effects. Food consumption increased during the post-treatment period in all groups, suggesting a compensatory response to decreased consumption and growth during treatment. Data are summarized in the reviewer's table, below.

Summary of Body Weight, Food Consumption, Body Weight Gain †															
Study Day (Interval)	Vehicle			LD (1.5/10)			HD (3.75/25)			PHEN (3.75)			TPM (25)		
	BW	FC	BWG	BW	FC	BWG	BW	FC	BWG	BW	FC	BWG	BW	FC	BWG
0	208			209			208			208			207		
6	251			252			251			254			253		
9	266			265			258			266			263		
6-9		20.8	14.8		19.6 ↓6%	12.5 ↓16%		16.1** ↓23%	6.8** ↓54%		19.2 ↓8%	12.8 ↓14%		19.1* ↓8%	10.6* ↓28%
12	285			280 ↓2%			270* ↓5%			280 ↓2%			277 ↓3%		
9-12		22.4	18.6		20.5* ↓8%	15.5 ↓17%		20.0** ↓11%	12.3** ↓44%		20.5* ↓8%	13.8** ↓26%		22.9 NC	14.0* ↓25%
15	310			304 ↓2%			295* ↓5%			307 NC			304 ↓2%		
12-15		24.2	25.4		21.2** ↓12%	23.5		21.1** ↓13%	24.8		22.2* ↓8%	27.2		22.5 ↓7%	27.0
18	338			332			322			335			331		
15-18		26.8	27.6		24.8** ↓8%	28.1		23.2** ↓13%	26.7		24.7** ↓8%	27.4		25.0* ↓7%	26.7
20	377			372 NC			359 ↓5%			377 NC			373 NC		
6-18		23.9	86.4		21.9** ↓8%	79.6 ↓8%		20.7** ↓13%	70.6** ↓18%		21.6** ↓10%	81.2 ↓6%		22.6* ↓5%	78.3 ↓9%
0-20		22.0	169		21.2 ↓4%	162 ↓4%		20.5** ↓7%	151** ↓11%		21.0 ↓5%	169 NC		21.5 ↓2%	166 ↓2%

† BW = body weight (g); FC = food consumption (mean g/animal/d); BWG = body weight gain (g); NC = no change (≤ 1% change compared to controls)

* p < 0.05, ** p < 0.01

Toxicokinetics – None.

Stability and Homogeneity – Dosing solutions tested within standard limits for stability and homogeneity.

Necropsy – No remarkable treatment-related macroscopic findings in dams.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Maternal pregnancy-related findings were limited to significantly decreased body weight (-5%) and body weight gain (-16%) compared to vehicle controls, adjusted for gravid uterine weights. There were no treatment-related effects on any other pregnancy parameters.

Offspring (Malformations, Variations, etc.)

Decreased fetal body weights were the major fetal finding. Male and female fetal weights were significantly decreased in combination LD (↓ 5-6%), HD (↓ 10%), and TPM alone (↓ 8-9%). With respect to historical control fetal weights, combination LD were within (near low end), combination HD were below, and TPM alone were equal to the lowest values of the historical control range. See Sponsor's summary table, below.

There were no apparent additive effects of combination PHEN + TPM treatment. Decreased fetal weights in the combination LD group were proportionally lower than HD group findings, which could be attributed entirely to effects of topiramate. There was no effect of phentermine alone on fetal weights or any other fetal parameter.

		Summary of Fetal Body Weight Values, g				
		Vehicle	1.5/10 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
Males	Mean	4.24 (4.24)	4.01 (4.01) ^a	3.83 (3.82) ^b	4.19 (4.19)	3.87 (3.88) ^b
	SD	0.299	0.254	0.286	0.324	0.208
	N	25	24	25	24	25
Females	Mean	4.03 (4.03)	3.80 (3.80) ^a	3.63 (3.63) ^b	3.98 (3.98)	3.69 (3.69) ^b
	SD	0.260	0.229	0.301	0.320	0.205
	N	25	24	25	24	25
Males + Females	Mean	4.14 (4.14)	3.90 (3.90) ^b	3.73 (3.73) ^b	4.07 (4.07)	3.78 (3.79) ^b
	SD	0.276	0.224	0.277	0.323	0.192
	N	25	24	25	24	25

N - Number of measures used to calculate mean

SD - Standard Deviation

() - Least Square Mean

^a Significantly different from control; (p<0.05)

^b Significantly different from control; (p<0.01)

Reviewer's note – historical control data

Males: $\bar{x} = 4.13 \text{ g (3.9 to 4.4 g)}$

Females: $\bar{x} = 3.93 \text{ g (3.7 to 4.3 g)}$

Combined: $\bar{x} = 4.03 \text{ g (3.8 o 4.3 g)}$

There were sporadic incidences of external or visceral variations and a few malformations in control and treatment groups, but there were no apparent drug-related effects. Total malformations are summarized in the Sponsor's table, below.

Summary of External, Visceral, and Skeletal Malformations					
Observation	Vehicle	1.5/10 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
No. Litters Evaluated	25	24	25	24	25
No. Fetuses Evaluated	283	286	291	287	311
Total Malformations					
No. Litters(%)	1 (4.0)	0 (0.0)	1 (4.0)	1 (4.2)	0 (0.0)
No. Fetuses(%) ¹	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
No. - Number		¹ Not statistically analyzed			

Individual skeletal malformations were unremarkable but there were slight differences in skeletal variations between treatment groups and controls. Overall incidence of skeletal variations was slightly higher in treatment groups compared to controls (76%, 88%, 88%, 88%, and 96% of litters, respectively), which suggested a possible treatment effect on skeletal variations (see Sponsor's summary table, below). The incidence of total skeletal variations in historical control groups was not provided, but the historical data were compared to individual skeletal variations by this reviewer. Skeletal variations that trended higher in treatment groups are shown in the Reviewer's summary table, below. The analysis showed most skeletal variations increased over concurrent vehicle controls were within the historical control range (e.g., cervical vertebrae, rib, and skull squamosal ossification). Of the other notable skeletal variations, there was no clear treatment-related effect since HD combination PHEN/TPM findings were typically less than additive of PHEN and TPM only findings.

Overall, doses were below the maternal MTD based on a range-finding study, but results in the PHEN/TPM combination treatment groups show there was no apparent synergistic effect and there was no evidence of drug-induced teratogenicity at doses that approximate human exposure

Summary of Skeletal Malformations and Developmental Variations					
Observation	Vehicle	1.5/10 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
No. Litters Evaluated	25	24	25	24	25
No. Fetuses Evaluated	144	144	143	144	157
Total Malformations					
No. Litters(%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. Fetuses(%) ¹	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Variations					
No. Litters(%)	19 (76.0)	21 (87.5)	22 (88.0)	21 (87.5)	24 (96.0)
No. Fetuses(%) ¹	46 (31.9)	48 (33.3)	56 (39.2)	57 (39.6)	77 (49.0)
No. - Number		¹ Not statistically analyzed			

Summary of individual skeletal variations

Site (Observation)	No. (%)	Vehicle	1.5 / 10 PHEN/TPM	3.75 / 25 PHEN/TPM	3.75 PHEN	25 TPM	Historical Control (Max. %)
Cervical vertebra(e)							
Neural arch, additional ossification center	Litter	0	1 (4%)	3 (12%)	1 (4%)	0	16.0%
	Fetus	0	1 (1%)	3 (2%)	1 (1%)	0	3.3%
Pelvic girdle							
Ischium, incompletely ossified	Litter	2 (8%)	0	1 (4%)	4 (17%)	0	4.2%
	Fetus	2 (1%)	0	1 (1%)	4 (3%)	0	0.8%
Ribs							
Ribs, rudimentary	Litter	8 (32%)	9 (38%)	12 (48%)	10 (42%)	13 (52%)	56.0%
	Fetus	8 (6%)	13 (9%)	18 (13%)	23 (16%)	28 (18%)	20.1%
Skull							
Interparietal bone, incompletely ossified	Litter	2 (8%)	2 (8%)	4 (16%)	1 (4%)	6 (24%)	8.3%
	Fetus	2 (1%)	2 (1%)	4 (3%)	1 (1%)	6 (4%)	2.8%
Parietal bone, incompletely ossified	Litter	2 (8%)	4 (17%)	4 (16%)	7 (29%)	5 (20%)	16.7%
	Fetus	2 (1%)	5 (4%)	5 (4%)	12 (8%)	5 (3%)	3.6%
Squamosal, incompletely ossified	Litter	0	2 (8%)	5 (20%)	3 (12%)	2 (8%)	21.7%
	Fetus	0	2 (1%)	5 (4%)	3 (2%)	2 (1%)	4.4%
Supra occipital bone, incompletely ossified	Litter	2 (8%)	2 (8%)	6 (24%)	4 (17%)	4 (16%)	10%
	Fetus	2 (1%)	2 (1%)	6 (4%)	8 (6%)	6 (4%)	4.2%
Sternum							
Sternebrae, not ossified	Litter	10 (40%)	10 (42%)	12 (48%)	6 (25%)	17 (68%)	58.3%
	Fetus	16 (11%)	17 (12%)	28 (20%)	9 (6%)	45 (29%)	19.7%

Notes – Trends outside the concurrent vehicle controls are shown in bold, shaded green if within the historical control range and shaded yellow if outside the historical range; maximum historical control litter and fetus incidences are shown in the far column, shaded green

Phentermine + topiramate embryofetal development (Seg II) in rabbits - Pilot**Phentermine HCl and topiramate: Pilot study for prenatal developmental toxicity in rabbits (Report No. 1060-044)**

Doses 0/0 (vehicle control)
 (mg/kg/d) 0.75/5, 1.9/12.5, 3.75/25, 7.5/50 (PHEN / TPM)

NOAEL (maternal)= 1.9 / 12.5 mg/kg PHEN / TPM

NOAEL (fetal) = 7.5 / 50 mg/kg PHEN / TPM

Key study findings:

- There was no evidence of fetal developmental toxicity at any dose (based on a limited fetal analysis in the range-finding design).
- Maternal toxicity was limited to weight loss during the first period of dosing (GD 6-10) in 3.75/25 and 7.5/50. Body weight gain recovered by GD 11 but overall body weight gain during treatment (GD 6-19) remained lower.
- Body weight effects were accompanied by decreased food consumption during treatment in the 3.75/25 and 7.5/50 groups.
- Dose-related effects on body weight and food consumption suggest a modest drug-related effect on does at those doses, but the absence of any pregnancy or fetal effects suggest the MTD was not exceeded at the highest dose tested (7.5/50 mg/kg PHEN/TPM).

Study no:	1060-44
Study report location:	eCTD Section 4.2.3.5.2
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	3/16/09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phentermine HCl (USP), Lot No. 0840775, 99.8% Purity (Catalent Pharma Solutions, Winchester, KY USA) Topiramate, Lot No. 2091174, 100.2% Purity (Catalent Pharma Solutions)

Methods

Doses:	PHEN / TPM (mg/kg/day) 0/0 (control), 0.75/5, 1.9/12.5, 3.75/25, 7.5/50
Frequency of dosing:	QD, Gestation days (GD) 6 – 18
Dose volume:	5 ml/kg/d total
Route of administration:	Oral gavage
Formulation/Vehicle:	Distilled water (PHEN) 0.5% methylcellulose (4000 cps) (TPM)
Species/Strain:	Female (time-mated) NZ White rabbits / [Hra:(NZW)SPF]
Number/Sex/Group:	6 pregnant ♀
Satellite groups:	None
Study design:	Pilot/range-finding study for full embryofetal development study – PHEN & TPM were dosed consecutively, does necropsied GD 29 for implantation, maternal pregnancy parameters, fetal viability, and fetal development and external malformations
Deviation from study protocol:	Dosing formulations not analyzed for homogeneity and concentration

Observations and Results:

Mortality – None.

Clinical Signs – Unremarkable. Sporadic incidences of hair discoloration and sparse hair in different regions were not considered drug-related and/or biologically significant.

Body Weight – Doe body weight gain over the course of treatment (GD 6-19) was lower in 3.75/25 (HMD) and 7.5/50 (HD) groups compared to controls. Body weight differences were attributable to does losing weight at the beginning of treatment (GD 6-10) in HMD (\bar{x} = 57 g) and HD (\bar{x} = 60 g) groups, while controls gained an average of 42 g over the same period. Body weight gain was similar to controls for all other time periods and terminal total body weight was not significantly different from controls in any treatment group.

Summary of Gestation Body Weight Change Values

Endpoint	Study	Vehicle			0.75/5 mg/kg/day			1.9/12.5 mg/kg/day			3.75/25 mg/kg/day			7.5/50 mg/kg/day		
	Interval (Day)	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight Change Values kg	0-6	0.153	0.0383	6	0.158	0.0492	5	0.173	0.0602	6	0.167	0.0535	6	0.177	0.0393	6
	6-10	0.042	0.0293	6	-0.002	0.0432	5	0.015	0.0647	6	-0.057 ^a	0.0885	6	-0.060 ^a	0.0642	6
	10-13	0.048	0.0172	6	0.032	0.0487	5	0.052	0.0172	6	0.033	0.0308	6	0.030	0.0502	6
	13-16	0.038	0.0534	6	0.038	0.0947	5	0.057	0.0575	6	0.050	0.0438	6	0.018	0.0343	6
	16-19	0.057	0.0314	6	0.062	0.0672	5	0.032	0.0147	6	0.040	0.0253	6	0.057	0.0427	6
	19-21	0.037	0.0137	6	0.066	0.0546	5	0.060	0.0276	6	0.042	0.0392	6	0.037	0.0308	6
	21-25	0.092	0.0256	6	0.102	0.0540	5	0.133	0.0413	6	0.117	0.0589	6	0.087	0.0441	6
	25-29	0.040	0.0775	6	0.032	0.0934	5	0.088	0.0325	6	0.087	0.0455	6	0.105	0.0288	6
	6-19	0.185	0.0647	6	0.130	0.0828	5	0.155	0.1247	6	0.067	0.0961	6	0.045	0.1193	6
	19-29	0.168	0.0880	6	0.200	0.1061	5	0.282	0.0966	6	0.245	0.0779	6	0.228	0.0574	6
	0-29	0.507	0.1244	6	0.488	0.1276	5	0.610	0.0817	6	0.478	0.1158	6	0.450	0.1699	6

N - Number of measures used to calculate mean
SD - Standard Deviation

^aSignificantly different from control; (p<0.05)

Feed Consumption – Trends (nss) were consistent with decreased body weight gain in HMD and HD groups. Food consumption was decreased 19-24% (HMD) and 23-19% (HD) at different intervals throughout the treatment period (GD 6-16). Total food consumption was 18% (HMD) and 22% (HD) lower than controls over the treatment period (GD 6-19).

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no treatment-related effects on pregnancy or maternal parameters. Maternal/pregnancy findings were limited to one doe in the LD group that was not pregnant. The non-pregnancy findings was considered unrelated to treatment because of the absence of abortion or implantation sites (i.e., the rabbit was apparently not pregnant upon arrival on study).

Offspring (Malformations, Variations, etc.)

There were no treatment-related effects on fetuses. Fetal findings were limited to malformations in one LD fetus (gastroschisis and malpositioned umbilicus). The malformations were considered spontaneous due to the absence of a dose-relationship. Gastroschisis, but not malpositioned umbilicus, was seen as a spontaneous malformation in the historical control database. Malpositioned umbilicus may have been secondary to the gastroschisis.

Phentermine + topiramate embryofetal development (Seg II) in rabbits**Phentermine HCl and topiramate: Study for effects on embryo-fetal development in rabbits (Report No. 1060-043)**

Doses 0/0 (vehicle control)
(mg/kg/d) 0.75/5, 3.75/25 (PHEN / TPM)
3.75/0 (PHEN)
0/25 (TPM)

NOAEL (maternal)= 3.75/25 mg/kg PHEN/TPM (combination)
3.75 mg/kg PHEN (alone)
25 mg/kg TPM (alone)

NOAEL (fetal) = 3.75 / 25 mg/kg PHEN / TPM (0.1X PHEN / 1X TPM MRHD)

NOAEL determination – high dose TPM (25 mg/kg) alone or in combination (3.75/25 mg/kg PHEN/TPM) caused maternal body weight loss at the beginning of treatment prior to stabilizing body weight gain. Maternal body weight changes were consistent with the expected PD effect of weight loss and were not considered evidence of drug-induced toxicity in the absence of other markers of toxicity.

Key study findings:

- There were no effects of PHEN/TPM co-administration or individual drugs alone on pregnancy or evidence of teratogenicity in rabbits
- There was no evidence of an additive or synergistic effect of PHEN / TPM co-treatment at doses that were not individually teratogenic
- TPM doses were limited to approximately 1X human exposure (AUC) and were several fold lower than doses that have previously been shown to be teratogenic in rabbits (and other species)
- Maternal toxicity was limited to transient body weight loss during the first few days of 3.75/25 mg/kg PHEN/TPM combination or 25 mg/kg TPM only treatment. Food consumption remained slightly lower throughout treatment which may have been caused maternal and fetal stress during pregnancy.
- High combination PHEN/TPM and TPM only doses were below the maternal and fetal MTD from a range-finding study. The study seemed to be designed to investigate a potential additive or synergistic effect of combination treatment without directly addressing the teratogenicity of either compound alone.

Study no: 1060-043
 Study report location: eCTD Section 4.2.3.5.2
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 5/13/09
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Phentermine HCl (USP), Lot No. 0840775, 99.8% Purity (Catalent Pharma Solutions, Winchester, KY USA)
 Topiramate, Lot No. 2091174, 100.2% Purity (Catalent Pharma Solutions)

Methods

Doses: 0/0 (vehicle control)
 (mg/kg/d) 0.75/5, 3.75/25 (PHEN / TPM)
 3.75/0 (PHEN)
 0/25 (TPM)
 Frequency of dosing: QD, Gestation days (GD) 6 – 18
 Dose volume: 5 ml/kg/d total
 Route of administration: Oral gavage
 Formulation/Vehicle: Distilled water (PHEN)
 0.5% methylcellulose (4000 cps) (TPM)
 Species/Strain: Female (time-mated) NZ White rabbits / [Hra:(NZW)SPF]
 Number/Sex/Group: 25 pregnant ♀
 Satellite groups: 4 pregnant ♀/treatment
 Study design: PHEN & TPM were dosed consecutively, detailed physical exam during dosing period, does necropsied GD 29 for implantation, maternal pregnancy parameters & gross pathology, fetal viability, and fetal development, external, visceral, and skeletal variations & malformations; blood pH determined GD 18, 1 h postdose (last 5 does/group)
Satellite TK – ~1 ml blood (K₃EDTA anticoagulant), GD 6 and 18, , 2, 4, 6, 12, 24 h postdose
 Deviation from study protocol: Several minor deviations noted in the study report but did not invalidate the results of the study

Observations and Results:

Mortality – One doe in the TPM only group aborted on GD 21 and was euthanized. All other females survived to scheduled termination.

Clinical Signs – Generally unremarkable. Various incidences of sparse and/or discolored hair in different regions were not considered drug-related and/or biologically

significant. Thin appearance was noted on several instances in HD combination and TPM only groups.

Body Weight – Treatment-related body weight findings were seen in HD combination and TPM only groups. Body weight gain during treatment (GD 6-19) was significantly reduced (-50% HD PHEN/TPM) compared to controls, which was attributable to transient BW loss (mean ↓ 42 g vs. control ↑ 15 g) at the beginning of treatment on GD 6-10. BW gain increased post-treatment and body weights at terminal necropsy were similar across all treatments. Trends were similar in the TPM only group (BW ↓ 42 g GD 6-10, BW gain ↓ 44% GD 6-19) with little apparent effect of PHEN on the body weight trends.

Food Consumption – Food consumption decreased during treatment in HD combination and TPM only groups, consistent with body weight findings. Food consumption significantly decreased 18-19% and 19-22% from GD 6-13 and 16% and 17% throughout treatment GD 6-19 in HD combination and TPM only groups, respectively. Trends in HD combination and TPM only groups were consistent with BW findings and suggest little effect of PHEN.

Blood pH – Blood pH was determined 1 h post-treatment on GD 6 and GD 19 to assess potential TPM-induced acidosis. There was no effect of any treatment on blood pH.

Toxicokinetics – Toxicokinetic parameters were assessed after initial treatment (GD 6) and after the final treatment (GD 18). No cross-contamination was apparent in control, PHEN only, or TPM only groups. Total PHEN exposure (AUC_{0-24}) was 142-268% higher with TPM co-treatment compared to PHEN only treatment (ss Day 6 only). PHEN exposure also increased greater than dose proportionally in combination PHEN/TPM groups. There was no apparent effect of PHEN co-treatment on TPM exposure. TPM exposure increased slightly greater than dose proportionally. There were no consistent trends for either PHEN or TPM after multiple dosing, thus there was no evidence of drug accumulation. TK data are summarized in the Sponsor's summary tables, below.

Sponsor's phentermine TK summary

Mean ± SD Pharmacokinetic Parameters for Phentermine						
Dose (mg/kg/day)	GD	C _{max} (ng/mL) Mean ± SD	T _{max} (hr) Mean ± SD	AUC _{0-t} (ng·hr/mL) Mean ± SD	AUC ₀₋₂₄ (ng·hr/mL) Mean ± SD	t _{1/2} (hr) Mean ± SD
0.75*	6	7.74 ± 5.59	1.00 ± 0	21.9 ± 15.9	26.0 ± 17.3	1.75 ± 0.46 ^a
	18	6.01 ± 5.18	1.00 ± 0	14.5 ± 15.7	17.5 ± 18.2	2.21 ^b
% Difference		-22%		-34%	-32%	
3.75*	6	55.5 ± 32.3	1.25 ± 0.50	227 ± 127	241 ± 130	2.40 ± 0.54
	18	43.2 ± 23.0	1.00 ± 0	130 ± 73	138 ± 73	3.29 ± 1.42
% Difference		-22%		-42%	-43%	
3.75 [#]	6	18.9 ± 14.0	3.75 ± 5.50	73.8 ± 49.6	90.9 ± 48.4	2.35 ± 0.46 ^a
	18	25.1 ± 24.3	3.75 ± 5.50	91.1 ± 66.1	97.4 ± 65.9	1.86 ± 0.46 ^a
% Difference		33%		23%	7%	

n = 4, except as noted.
^an = 3
^bn = 1
Note: Standard deviation not calculated when n < 3.
* Dosed in combination with topiramate.
[#] Dosed alone.

Sponsor's topiramate TK summary

Mean ± SD Pharmacokinetic Parameters for Topiramate						
Dose (mg/kg/day)	GD	C _{max} (ng/mL) Mean ± SD	T _{max} (hr) Mean ± SD	AUC _{0-t} (ng·hr/mL) Mean ± SD	AUC ₀₋₂₄ (ng·hr/mL) Mean ± SD	t _{1/2} (hr) Mean ± SD
5*	6	2,855 ± 594	1.25 ± 0.50	16,575 ± 3,783	17,950 ± 4,044	2.57 ± 0.05
	18	3,390 ± 292	1.00 ± 0	13,875 ± 2,068	14,725 ± 2,330	2.41 ± 0.11
% Difference		19%		-16%	-18%	
25*	6	14,225 ± 1,544	2.50 ± 1.00	122,500 ± 18,193	122,500 ± 18,193	2.96 ± 0.29
	18	15,350 ± 985	1.25 ± 0.50	80,950 ± 18,688	84,150 ± 16,787	2.46 ± 0.35
% Difference		8%		-34%	-31%	
25 [#]	6	11,705 ± 2,089	2.00 ± 1.41	86,825 ± 7,582	86,825 ± 7,582	2.88 ± 0.26
	18	16,125 ± 2,907	1.50 ± 0.58	102,475 ± 6,151	103,850 ± 5,211	2.59 ± 0.24
% Difference		38%		18%	20%	

n = 4 in all cases.
* Dosed in combination with phentermine hydrochloride.
[#] Dosed alone.

Stability and Homogeneity – Scheduled analyses confirmed the concentration and homogeneity of dosing solutions ($\pm 10\%$ PHEN solution, $\pm 15\%$ TPM suspension).

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no treatment-related effects on maternal gross pathology. One TPM only doe aborted on GD 21. The abortion was considered drug-related based on marked decreased food consumption and marked weight loss (-600 g during treatment) in the doe beginning with the initial treatment on GD 6. There were no other drug-related effects on maternal or pregnancy parameters or fetal trends (survival, BW, sex ratio).

Offspring (Malformations, Variations, etc.)

External fetal variations and malformations were limited to single fetal incidences that were generally seen in the historical control database. **Hind limb malrotation** was the only exception, observed in 1/225 LD and 1/207 HD combination treatment groups, which was not listed in the historical control database. Overall, the sporadic, single fetal incidences of external variations and malformations suggests they were not drug-induced birth defects. The Sponsor's summary of total external variations and malformations are shown in the table, below.

Summary of External Malformations and Developmental Variations					
Observation	Vehicle	0.75/5 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
No. Litters Evaluated	25	23	22	24	24
No. Fetuses Evaluated	225	225	207	215	228
Total Malformations					
No. Litters(%)	0 (0.0)	1 (4.3)	1 (4.5)	0 (0.0)	2 (8.3)
No. Fetuses(%) ¹	0 (0.0)	1 (0.4)	1 (0.5)	0 (0.0)	2 (0.9)
Total Variations					
No. Litters(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
No. Fetuses(%) ¹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

No. - Number

¹Not statistically analyzed

Fetal visceral variations and malformations were generally similar in control and treatment groups or isolated incidences in treatment groups that were within the historical control range. While there were no clear treatment-related findings overall, several notable findings occurred only in the HD combination group. **Malpositioned adrenal gland** was observed in a single fetus in the HD combination. The adrenal finding was not seen in historical control database but the relationship to drug is unclear since the finding was isolated to a single fetus in a single litter. **Eye(s) microphthalmia** was also observed in two fetuses (1% fetal incidence, separate litters (9.1% litter incidence)) in the HD combination group, which was slightly outside the historical control range (maximum 0.6% fetuses, 5.0% litters). **Hemorrhagic eye(s)** was observed in multiple fetuses in each treatment (maximum 6 fetuses, 15% of litters), including controls (4 fetuses, 16% of litters). Eye findings were not considered

remarkable and not likely to be drug-related by this reviewer. Two fetuses in the HD combination had multiple malformations. One fetus had **eye(s) microphthalmia**, **heart defects** of **small atrium**, **small ventricular**, and **interventricular septal defect**, with external malformation of **malrotated hind limb**. Another fetus from a separate litter had **heart defects** of **aortic arch defect** and **discontinuous interventricular septum**, plus **small pulmonary trunk**. All of the findings in the fetuses with multiple malformations occurred with similar incidence as historical background malformations. This reviewer considered the findings notable because they were only seen in the HD combination group and there were fetuses with multiple malformations, but there was no clear drug-related finding.

Other visceral findings occurred with similar incidence as historical controls or in individual fetuses with no apparent treatment-related trends. The Sponsor's summary of total visceral variations and malformations are shown in the table, below.

Summary of Visceral Malformations and Developmental Variations					
Observation	Vehicle	0.75/5 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
No. Litters Evaluated	25	23	22	24	24
No. Fetuses Evaluated	225	225	207	215	228
Total Malformations					
No. Litters(%)	2 (8.0)	0 (0.0)	4 (18.2)	0 (0.0)	3 (12.5)
No. Fetuses(%) ¹	3 (1.3)	0 (0.0)	4 (1.9)	0 (0.0)	3 (1.3)
Total Variations					
No. Litters(%)	11 (44.0)	6 (26.1)	9 (40.9)	13 (54.2)	11 (45.8)
No. Fetuses(%) ¹	21 (9.3)	8 (3.6)	14 (6.8)	23 (10.7)	23 (10.1)

No. - Number ¹Not statistically analyzed

Fetal skeletal variations and malformations were prevalent in controls and all treatment groups. Neither total variations nor total malformations were significantly elevated in any treatment group. Types of skeletal observations differed between groups but there were no clear treatment-related trends. In combination PHEN/TPM groups the common malformations (fused sternbrae, fused skull jugal bones) and variations (sternbrae not ossified) were similar to concurrent or historical controls. A single HD combination fetus had several malformations that were not seen in concurrent or historical controls (**hind limb**, **bent femur**, **bent tibiofibula**, and **misshapen tibiofibula** and **pectoral girdle bent scapula**). No similar malformations were seen in the TPM only group. Skeletal malformations are the hallmark of topiramate teratogenicity in rabbit, but the biological significance of uncommon malformations in a single fetus is not clear.

In the TPM only group, the variation **sternbrae not ossified** was significantly elevated over concurrent controls but fetal and litter incidences were similar to historical controls. Total malformations other than the most common types (fused sternbrae and skull jugal bones) were elevated in the TPM only group (9 fetuses, 5 litters (21%)) compared to concurrent controls (4 fetuses, 3 litters (12%)). The malformations were predominantly rib and vertebral, generally similar to historical controls, and not considered drug-related or biologically significant by this reviewer.

The absence of clear teratogenic trends in the HD combination or TPM only groups suggest the single fetus HD combination skeletal findings were not likely drug-related. The Sponsor's summary of total skeletal variations and malformations are shown in the table, below.

Summary of Skeletal Malformations and Developmental Variations					
Observation	Vehicle	0.75/5 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
No. Litters Evaluated	25	23	22	24	24
No. Fetuses Evaluated	225	225	207	215	228
Total Malformations					
No. Litters(%)	11 (44.0)	7 (30.4)	12 (54.5)	8 (33.3)	10 (41.7)
No. Fetuses(%) ¹	19 (8.4)	10 (4.4)	16 (7.7)	12 (5.6)	17 (7.5)
Total Variations					
No. Litters(%)	25 (100.0)	23 (100.0)	20 (90.9)	24 (100.0)	24 (100.0)
No. Fetuses(%) ¹	105 (46.7)	130 (57.8)	90 (43.5)	108 (50.2)	109 (47.8)
No. - Number		¹ Not statistically analyzed			

Overall, there were no clear drug-related effects on external, visceral, or skeletal malformations. The Sponsor's summary of total malformations shows the absence of a drug-related trend (see table, below). The individual variation and malformation differences between groups, in particular the combination LD or HD or TPM only groups, did not uncover any teratogenic signals or trends. The doses investigated were below the maternal MTD based on a range-finding study, but results show there was no apparent additive or synergistic effect of PHEN and TPM co-administration on rabbit embryofetal development at doses that approximate human exposure. The data also suggest the administered doses of TPM were below a threshold for TPM teratogenicity which has previously been demonstrated in rabbits and other species.

Summary of External, Visceral, and Skeletal Malformations					
Observation	Vehicle	0.75/5 mg/kg/day	3.75/25 mg/kg/day	3.75 mg/kg/day (PHEN)	25 mg/kg/day (TPM)
No. Litters Evaluated	25	23	22	24	24
No. Fetuses Evaluated	225	225	207	215	228
Total Malformations					
No. Litters(%)	12 (48.0)	8 (34.8)	12 (54.5)	8 (33.3)	13 (54.2)
No. Fetuses(%) ¹	21 (9.3)	11 (4.9)	17 (8.2)	12 (5.6)	21 (9.2)
No. - Number		¹ Not statistically analyzed			

9.3 Prenatal and Postnatal Development

No new pre- and postnatal development reproductive toxicity studies were conducted with the proposed PHEN/TPM combination. The drug label for Topamax® notes topiramate exposure *in utero* led to decreased viability and delayed physical development in rat pups exposed to ≥ 200 mg/kg [REDACTED] (b) (4) reductions in pre- and/or post-weaning body weight gain at ≥ 2 mg/kg [REDACTED] (b) (4) in rats exposed during late gestation and lactation, and persistent reduction in body weight gain in rat offspring exposed to ≥ 30 mg/kg TPM (2.5X MRHD) *in utero*. No pre- and postnatal development studies with phentermine are noted in the Adipex-P® label.

10 Special Toxicology Studies

None. The Sponsor noted their combination product doesn't absorb light in the UV or visible range (290-700 nm) and they did not conduct any phototoxicity studies. Neither individual drug label contains information or warnings about phototoxicity. Phototoxicity studies were not required based on the absence of any signal of potential phototoxicity.

No other safety signals were identified that required special toxicology studies.

11 Integrated Summary and Safety Evaluation

The proposed FDC capsule of PHEN/TPM was submitted in accordance with 21 USC 505(b)(2) for treatment of obesity. The individual drugs are both currently approved for use as monotherapy or adjunct therapy and the NDA relies in part on the FDA's previous findings of safety and efficacy. Topiramate is approved for chronic use to treat epilepsy and an extensive battery of nonclinical studies were conducted to support original approval. Phentermine is indicated only for short term treatment of obesity ("a few weeks") and it was originally approved in 1959 prior to the advent of current nonclinical regulatory guidelines and practices. Phentermine went through the 'DESI' process (Drug Efficacy Study Implementation) which in 1974 confirmed effectiveness for the indicated weight loss (39 FR 26459). Because of an observed side effect of weight loss with topiramate use for approved indications, topiramate monotherapy and combination therapy with phentermine have reportedly been widely prescribed for off-label obesity treatment.

Nonclinical studies to support phentermine for a chronic indication were not necessary for the original approval and the label for listed phentermine use lacks information about chronic toxicity. The Sponsor conducted *in vitro* and *in vivo* studies with phentermine and the proposed PHEN/TPM combination to support a chronic obesity indication. All pivotal studies were conducted in compliance with current GLP standards. In addition, the Sponsor submitted comprehensive reviews of available peer-reviewed literature and public data pertaining to phentermine and topiramate nonclinical pharmacology and toxicology. All supporting nonclinical information was reviewed for this NDA, including prior submissions under the IND (which are cited in this review as appropriate).

Pharmacology

Phentermine and topiramate are both centrally acting compounds that seem to provide complementary effects to control appetite and encourage weight loss. Phentermine effects seem to include a combination of anorectic (decreased food consumption), thermogenic (increased metabolic activity), and drug-induced increased physical activity. Topiramate seems to promote weight loss by increased energy expenditure, decreased energy efficiency, and decreased caloric intake by some combination of activity on voltage-gated ion channels, modulation of GABA receptors, and carbonic anhydrase inhibition.

PK/ADME

Limited new PK and ADME studies were conducted to support the proposed PHEN/TPM combination. Primary data provided by the Sponsor are noted where appropriate, otherwise, trends described here include publicly available information from the Sponsor's review and this reviewer's independent literature review.

Bioanalytical methods were validated for extraction, quantification, and stability of phentermine and topiramate in plasma of rat, rabbit, and dog used in pivotal pharmacology and toxicology studies.

Available data suggest phentermine is completely absorbed and readily bioavailable after oral dosing. Rat studies showed PHEN distributes to lungs, excretory organs, liver, and kidneys, with no accumulation in tissues or red blood cells. PHEN distributes to brain with similar T_{max} and $t_{1/2}$ as blood distribution, confirming distribution to the site of action and applicability of plasma drug concentrations to predict *in vivo* activity. Topiramate is also rapidly absorbed and distributed after oral administration in rat and dog, with no apparent accumulation after multiple dosing.

Studies submitted by the Sponsor showed plasma protein binding to phentermine is low in all species, with 11%, 18%, and 24% protein binding in rat, dog, and human, respectively. Topiramate protein binding is also reportedly low in all species (approximately 85% or more unbound *in vitro*) with an apparent saturation of binding. Thus, the majority of administered phentermine and topiramate is expected to circulate unbound. Literature on topiramate also identified two erythrocyte binding sites in dog and human (high-affinity, low capacity and low-affinity, high capacity), with binding apparently due to interaction or binding with carbonic anhydrase isozymes in erythrocytes. Topiramate binding to low-affinity, high-capacity erythrocyte sites at high clinical doses effectively creates a circulating depot of TPM in the blood, contributing to longer blood half-life compared to plasma.

The Sponsor directly assessed absorption and bioavailability of the proposed phentermine and topiramate drug formulations in dogs and compared them to currently marketed drug products. Dogs were dosed with various FDC capsule formulations and plasma drug concentrations were assessed for: (1) phentermine, comparing VIVUS's immediate release (IR) capsule and a marketed IR capsule when co-administered with topiramate; and, (2) topiramate, comparing various VIVUS modified (MR) or delayed release (DR) capsule formulations to the marketed IR Topamax®, with and without phentermine co-administration. PK results showed the proposed phentermine IR formulation resulted in comparable absorption and bioavailability as the currently marketed phentermine IR capsule. Topiramate results showed varying bioavailability for several different VIVUS modified release prototype formulations, with the 'to be marketed' MR formulation confirming a lower C_{max} and longer T_{max} but similar bioavailability (81-98%), mean $t_{1/2}$ (3.2 – 3.6 h) and AUC_{0-24} (81-90%) compared to the listed IR Topamax® product. There were no gender differences in dog exposure to phentermine or topiramate. The three month combination toxicity study in dog also showed no sex difference in dog exposures. In contrast, the three month rat combination toxicity study showed females had 2- to 3-fold higher PHEN and TPM exposures, respectively, than males.

Neither phentermine nor topiramate are extensively metabolized in humans or animals. PHEN undergoes limited metabolism in humans via *p*-hydroxylation and N-oxidation and there are no unique human metabolites. There are apparent species differences in

PHEN metabolism *in vivo* and *in vitro*, but major routes of metabolism are similar to humans. Urine is the major PHEN elimination route in both rat and human, but elimination is much more rapid in rat ($t_{1/2} \approx 1.5$ h) than human ($t_{1/2} \approx 21$ h). Structural differences on the α -carbon of phentermine (methylated) and amphetamine (non-methylated) lead to differences in metabolism, with amphetamine more highly metabolized to its active metabolite 4-hydroxynorephedrine, contributing to more potent sympathomimetic effects of amphetamine.

Inhibition of monoamine oxidases (MAO-1 and MAO-2) is a theoretical concern for phentermine, based on *in vitro* MAO inhibition by other amphetamine-like compounds. Similarly, potential for cytochrome P450 (CYP) induction or inhibition is important for potential drug-drug interactions. The Sponsor conducted *in vitro* assays to assess potential phentermine effects on MAOs and CYPs, particularly with respect to topiramate effects on CYP3A4 and CYP2C19. Metabolism and degradation of phentermine (1 μM) were assessed with various exogenously expressed human CYPs and MAOs and there was no significant phentermine metabolism or degradation by CYPs (1A2, 2C8, 2C9, 2C19, 2D6, 3A4) or MAOs (MAO-A, MAO-B). Data from published literature suggest potential weak inhibition of MAOs by phentermine in rats ($K_i \geq 85$ μM ; $\text{IC}_{50} \geq 150$ μM) and confirm no significant inhibition of major CYPs (1A2, 2C9, 2D6, 2E1, 3A4). Estimated phentermine clinical plasma concentrations are approximately 0.7 μM , further supporting a low risk of MAO inhibition *in vivo*. Phentermine pre-treatment up to 10 μM (a non-cytotoxic concentration) did not induce CYP1A2, CYP2B6, or CYP3A4 activity in primary human hepatocytes. Phentermine (10 μM) also showed essentially no inhibitory potential (maximum 5% inhibition) to human CYP2C19 in 30 min microsome incubations.

TPM undergoes limited metabolism in humans and animals with no major or unique human metabolites identified (all metabolites < 5% of administered dose) and approximately 90% of drug remaining unchanged in plasma. Human and animal excretion is predominantly urinary and topiramate is slightly more highly metabolized in excretory fractions (82% and 65% parent recovered in human urine and feces, respectively). Excreted TPM is more highly metabolized in rats than humans, with only 5-32% and 47-86% unchanged in male and female rat feces and urine, respectively. Rat gender differences may be due to increased metabolism by sex-specific CYPs (e.g., CYP2C11 and/or CYP3A2) in males.

Data in the literature show modest induction of CYP3A4 at high topiramate concentrations in primary human hepatocytes, which is consistent with reported clinical drug-drug interactions of TPM-induced clearance of ethinyl estradiol. Similarly, modest (11-29%) inhibition of CYP2C19 by very high concentrations of TPM *in vitro* (300-900 μM) are consistent with clinical reports of decreased phenytoin clearance with introduction of concomitant TPM anti-seizure treatment. In contrast, there is little evidence that topiramate is affected by drug transporters or that drug transporters play a role in TPM pharmacokinetics or drug-drug interactions.

Toxicology

The Sponsor relied predominantly on public literature and the FDA's prior safety determinations for listed phentermine and topiramate indications. Subchronic toxicity and embryofetal development were conducted with the Sponsor's PHEN/TPM drug substances and included individual drug control groups. Phentermine was assessed individually for chronic toxicity and carcinogenicity in a two-year rat bioassay. Neither individual study findings nor a complete review of public toxicity information will be recapitulated here. Rather, critical toxicity findings and trends will be discussed here, with particular attention given to potential clinical monitoring or new toxicity findings.

General phentermine toxicity is consistent with class related effects of sympathomimetics, particularly modest, transient cardiovascular/hemodynamic (palpitations, tachycardia, increased blood pressure) and CNS (overstimulation, restlessness, insomnia, euphoria) effects. The most common clinical side effects of topiramate are paresthesia, anorexia and weight decrease (consistent with the intended PD effect), behavioral effects (fatigue, somnolence, psychomotor slowing), and neurological signs (dizziness, nervousness, memory and concentration/attention difficulty, confusion).

Topiramate toxicity was extensively studied in nonclinical models to support approval of epilepsy and migraine indications but the Topamax® label does not describe general toxicity findings with TPM. The Sponsor's literature review showed TPM findings were generally consistent across species and included decreased body weight gain, clinical signs of decreased activity, ataxia, dyspnea, and convulsions, and liver, kidney, bladder, and stomach target organs. Additional findings included urinalysis and urinary tract effects, serum decreased K and increased Cl, decreased erythrocyte parameters (RBC, Hb, Hct), and altered lipid parameters (cholesterol, triglycerides). Toxicity is listed on the topiramate label for approved drug(s). Warnings include: acute myopia and secondary angle closure glaucoma (i.e., elevated intraocular pressure); oligohidrosis and hyperthermia; suicidal behavior and ideation; metabolic acidosis; cognitive/neuropsychiatric dysfunction; hyperammonemia and encephalopathy; and, kidney stones. Common adverse reactions include: paresthesia (abnormal neurological sensations including numbness, tingling, burning, prickling, hyperesthesia/increased sensitivity); anorexia; weight decrease; fatigue; dizziness; somnolence; nervousness; psychomotor slowing; memory and concentration/attention difficulty; confusion; taste perversion; skin and appendages disorders (rash, alopecia); and, vision disorders (abnormal accommodation, eye pain).

When the Sponsor investigated PHEN/TPM combination toxicity in rat and dog subchronic studies, general trends showed minimal interactions between drugs and expected toxicity. Increased kidney weight with slightly increased BUN and bone marrow depletion were seen in high dose rat treatment (*PHEN/TPM 2X / 3X MRHD*). Findings in dogs were consistent with expected toxicity and the high dose was considered a NOAEL (*PHEN/TPM 15X / 26X MRHD*). Body weight gain decreased in

both rat and dogs, consistent with the pharmacodynamic effect, but there was no apparent additive effect of drugs.

Genetic toxicity has not been assessed directly for the proposed PHEN/TPM combination drug substance. The drug label for topiramate notes it was not genotoxic in a battery of *in vitro* and *in vivo* studies. The Sponsor conducted a standard battery of genetic toxicity studies with the proposed phentermine drug substance and results showed no evidence of genotoxicity.

The Topamax® label notes topiramate caused bladder tumors in mice at approximate human exposures for epilepsy treatment (400 mg), which were approximately 4-fold than the maximum proposed obesity dose (92 mg TPM). Topiramate bladder cancer was attributed “primarily” to smooth muscle tumors histomorphologically unique to mice, thus the clinical relevance is unknown.

No evidence has emerged since initial marketing in 1959 that PHEN is carcinogenic with common clinical use. While phentermine monotherapy is indicated only for short term use, the absence of carcinogenic safety signal during five decades of use supported carcinogenicity assessment in a single species. A two-year oral carcinogenicity of the proposed phentermine drug substance in rats showed no evidence of drug-induced carcinogenicity at 11- to 18-fold MRHD in males and females, respectively. The Sponsor did not conduct a two-year carcinogenicity study in mouse. The history of clinical use and the absence of any apparent PHEN-induced carcinogenicity in the rat study, lead this reviewer to conclude that PHEN carcinogenic assessment in a second species is not necessary.

Oral cavity palate and tooth toxicity were the major new non-neoplastic findings uncovered in the lifetime rat carcinogenicity study. Tooth-related effects were consistent with literature reports of gum and tooth toxicity with methamphetamine abuse. The mechanism of phentermine-induced tooth toxicity has not been investigated but prevalence of clinical signs support a drug-related effect. NOAELs for chronic non-neoplastic toxicity were 3 and 10 mg/kg, or approximately 1X and 2X MRHD (based on estimated AUC exposure) for females and males, respectively.

Potential for phentermine-induced PPH and VHD in lung and heart is a concern based on clinical toxicity with ‘fen-phen’ and ‘dexfen-phen’ combination use for obesity treatment. There was no evidence of pulmonary hypertension or heart disease in animal toxicity studies with phentermine or PHEN/TPM co-administration, including rat chronic life-time exposure to phentermine. However, the Sponsor did not specifically examine heart valves in toxicity studies or independently investigate any mechanistic basis (or lack thereof) for phentermine in PPH or VHD. The FDA clinical reviewer and this nonclinical reviewer conducted independent literature reviews of PPH and VHD and found no evidence to implicate phentermine in pulmonary hypertension or heart valve toxicity. The Sponsor also conducted an independent literature review and similarly concluded phentermine was not implicated in the toxicities. Specifically, the 5-HT_{2b} receptor has been implicated in heart valvulopathy and several studies showed

phentermine does not interact with the 5-HT_{2b} receptor and does not otherwise significantly increase lung or plasma serotonin levels.

Topiramate was found to be teratogenic in several species in reproductive toxicity studies conducted in support of approval for TOPAMAX. The TOPAMAX label lists fetal malformations related to bone growth and development in mouse (primarily craniofacial defects), rat (limb malformations including ectrodactyly, micromelia, and amelia), and rabbit (primarily rib and vertebral malformations). Fetal malformations occurred at clinically relevant doses for listed indications of epilepsy and migraine treatment, but sensitivity varied widely between mouse (most sensitive), rabbit (intermediate), and rat (least sensitive). The Topamax® label also notes TPM-induced reductions in bone growth plate thickness during male rat juvenile development. There was no apparent effect of topiramate treatment on male or female fertility at clinically relevant doses.

Topiramate teratogenic responses seem consistent with carbonic anhydrase (CA) inhibition and species differences may reflect differences in drug metabolism, CA activity, or biochemical and regulatory responses to acidosis. However, TPM has multiple physiologic effects and the contribution of CA inhibition and metabolic acidosis to development toxicity has not been shown definitively. Pharmacokinetic differences between species and humans may also account for differences in body surface area predictions and actual exposure multiples. For example, both PHEN and TPM significantly accumulate in plasma after repeated dosing, with 2.5- and 4-fold greater steady-state clinical exposure, respectively, compared to single dose exposures. There was no evidence in subchronic rat or dog toxicity studies that phentermine co-administration increased the risk of topiramate-induced metabolic acidosis.

The Sponsor conducted embryofetal development studies in rat and rabbit with combination PHEN/TPM treatments, primarily to investigate any additive or synergistic effects of phentermine on topiramate effects. No information about fertility and early embryonic development (i.e., Segment 1) or prenatal and postnatal development (i.e., Segment 3) reproductive toxicity of phentermine is included on the Adipex-P® label. The Sponsor did not conduct Segment 1 or Segment 3 reproductive toxicity studies with their phentermine formulation, but the deficiencies are not critical because teratogenic effects of topiramate warrant a Pregnancy Category X label for the proposed PHEN/TPM combination therapy.

The teratogenic effect of topiramate alone in multiple animal species is directly relevant to risk assessment with the proposed PHEN/TPM combination. The proposed maximum topiramate dose for obesity (92 mg/day) is lower than the maximal daily dose approved for TOPAMAX (400 mg/day). Therefore, adjustment of exposure margins on the Topamax® label is necessary. Body surface area (BSA) exposure margins were estimated for Topamax®, apparently because actual plasma drug levels were unknown. Comparison of actual plasma drug levels (AUC) in animals and humans provides the most accurate estimate of exposure margin between nonclinical and clinical dose levels. There is now sufficient data to estimate total plasma drug exposure (AUC₀₋₂₄) in rats and rabbits, but not mice, for the proposed PHEN/TPM combination

based on toxicity studies conducted by VIVUS with the phentermine plus topiramate combination.

Table 18 summarizes the teratogenicity data for topiramate in animals with exposure margins adjusted for the maximum proposed dose of topiramate (92mg/day). Exposure margins, or 'human exposure multiples', were estimated based on both body surface area and estimated plasma drug levels (AUC_{0-24}) for comparison. Note that using body surface area results in much higher human exposure multiples than those based on estimated AUC. The body surface area comparisons tend to over-estimate human exposure multiples for topiramate since, as noted, AUC multiples are considered the most accurate exposure comparisons,. Based on an AUC comparison, topiramate is associated with teratogenicity in rabbits and rats at 6x and 34x the MRHD. Plasma drug levels are not available in mice, so based on body surface area, topiramate was teratogenic at 2x the MRHD (or essentially equivalent to clinical exposure). This represents a relatively wide range of sensitivity —2x to 34x the MRHD— across species, yet it is notable that teratogenicity occurs in all three species tested, and it is difficult to extrapolate where humans fall along this spectrum of sensitivity.

Table 18 – Topiramate Teratogenicity

Summary of Topiramate Teratogenicity †			
Topiramate Treatment ^a	Teratogenic or Reprotoxic Finding	Human Exposure Multiple	
		Body Surface Area (mg/m²)	AUC₀₋₂₄ ^b
Rat			
25 mg/kg	None ^c	4x	2x
100 mg/kg	None	17x	8x
200 mg/kg	Offspring effects	35x	16x
400 mg/kg	Teratogenic ^d	70x	34x
Rabbit			
25 mg/kg	None	9x	1x
35 mg/kg	Maternal/embryofetal death	12x	2x
120 mg/kg	Teratogenic	42x	6x
Mouse			
20 mg/kg	Teratogenic	2x	--

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

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

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

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

^d Teratogenic findings across species included rat limb malformations (ectrodactyly, micromelia, amelia), rabbit skeletal malformations (rib, vertebral), and mouse craniofacial defects

The data in Table 18 include NOAELs from embryofetal development studies with the phentermine plus topiramate combination in rats and rabbits, conducted by the Sponsor to support the proposed PHEN/TPM combination. The sponsor chose maximum doses of topiramate that are not associated with teratogenesis in either species. Indeed, the maximum doses of phentermine and topiramate tested provided drug exposure within 2-fold (and no higher) of the maximum observed human plasma exposure (15 mg PHEN/92 mg TPM). There were no drug-induced effects of combination phentermine plus topiramate treatment on embryofetal development or teratogenicity in either rats or rabbits. The combination phentermine plus topiramate embryofetal development studies were not designed to assess toxicity at teratogenic doses of topiramate. Rather, these studies were designed to investigate potential additive or synergistic effects on embryofetal development at a non-teratogenic dose of topiramate. This reviewer's conclusion that the combination of phentermine and topiramate did not result in teratogenesis indicate a lack of significant drug interaction on this toxicity endpoint.

While the Sponsor's embryofetal development studies were sufficient to rule out a synergistic effect of combination PHEN/TPM treatment, it is important to note limitations of the studies. Neither rat nor rabbit studies adequately assessed toxicity of combination PHEN/TPM up to maximum tolerated doses. Treatments were limited to doses that caused modest reduced body weight gain in pregnant females, but range-finding assays in both species showed treatments at higher doses did not affect pregnancy or fetal parameters. The maximum doses were limited on the assumption that body weight changes would cause maternal toxicity potentially confounding reproductive toxicity endpoints, however, the proposed drug is intended to lower body weight so reduced body weight or body weight gain is indicative of a pharmacologic, not a toxic, effect. Furthermore, recent data show marked decreased body weight gain (up to 50% reduction) and even frank body weight loss (as low as 0.85X baseline during treatment period) in rats do not cause fetal malformations²⁸. Body weight loss (but not marked reduced body weight gain) only reduced fetal body weight (without affecting fetal viability) and modest developmental delays manifest as skeletal variations.

In summary, rat and rabbit doses could have been increased to provide some margin of human exposure at which to assess teratogenicity of the PHEN/TPM combination. As conducted, the embryofetal development studies cannot rule out potential teratogenic effects of the proposed combination PHEN/TPM treatment but results do suggest an absence of synergistic drug interactions on embryofetal development. Based on topiramate teratogenicity in several species at or near predicted human exposures, there is a risk of fetal birth defects if used by pregnant women.

The nonclinical studies submitted in support of this NDA, coupled with the history of approved uses of the individual components and available public literature, are sufficient to make recommendations of safety and efficacy of the proposed drug combination for a chronic obesity indication. Nonclinical data support approval of the proposed phentermine/topiramate fixed dose combination capsule in males and non-pregnant

²⁸ Fleeman TL et al. (2005) Birth Defects Research (Part B) 74:442–449

females. The nonclinical do not support safe use of the drug in women who are pregnant or planning to become pregnant.

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/s/

DAVID B CARLSON

10/01/2010

PharmTox review -- Recommend approval contingent on contraindication in pregnant women

TODD M BOURCIER

10/01/2010

AP action recommended



Pharmacology/Toxicology
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Products

NDA SECONDARY REVIEW MEMO

Date:	29 September 2010
NDA #	22580
Sponsor:	Vivus Inc
Drug:	Phentermine + Topiramate FDC (Qnexa)
Primary Reviewer:	David Carlson, Ph.D.
Secondary Reviewer:	Todd Bourcier, Ph.D.

Vivus Inc is seeking marketing approval for a phentermine/topiramate fixed-dose combination drug product, proposed trade name Qnexa, as a treatment for obesity. Both pharmaceutical ingredients are FDA approved and currently marketed as Adipex and Topamax, respectively. Phentermine, as a sympathomimetic, increases thermogenesis and physical activity to effect weight loss. Topiramate's mechanism of weight loss is not clear, but may involve modulation of central targets to reduce food intake. Topiramate is currently approved as an anti-epileptic and for migraine prophylaxis. This NDA is regulated under 505(b)(2) provisions because the applicant is relying in part on preclinical information available in the literature and for the marketed components as described in the respective approved drug labels.

Dr. David Carlson, the primary pharm/tox reviewer, recommends that PHEN/TPM be approved on the condition that the label contraindicates use of PHEN/TPM in pregnancy (e.g., pregnancy category X). *I concur with Dr. Carlson's recommendation.* Dr. Carlson notes that general toxicology studies did not identify toxicities with the drug combination that differed from the anticipated and known toxicological profile of each drug component. The genotoxic and carcinogenic potential of each drug component is now known and the results do not raise substantial concern. The primary reason for recommending a contraindication for pregnancy is that topiramate is teratogenic in all animal species tested, included mice, rats, and rabbits, as described in the currently approved label of the reference listed drug, Topamax. I agree with Dr. Carlson's assessment that the embryofetal development studies conducted in rats and rabbits with the drug combination do not mitigate the known teratogenic findings with topiramate alone. Rather, the combination embryofetal study demonstrates that phentermine is unlikely to change the risk of teratogenicity presented by topiramate. While the Topamax label carries a 'Category (b) (4) pregnancy rating for indications of epilepsy and migraine prophylaxis, the differences in patient population, indication, and recent epidemiological information on teratogenic risk with topiramate are sufficiently compelling to support a contraindication for pregnancy with PHEN/TPM.

This recommendation is made cognizant of the difficulties in ensuring that exposure to PHEN/TPM during pregnancy is minimized. Yet, additional nonclinical studies conducted pre-approval are unlikely to either clarify or better quantitate the teratogenic risk of topiramate, a drug that is already marketed at higher doses than in PHEN/TPM. If avoidance of PHEN/TPM exposure in pregnancy is not a feasible goal in the post-market environment, then it appears the only step that would minimize risk while allowing approval of the NDA is to increase the safety margin by approving the lower dose of PHEN/TPM. Acceptability of the remaining risk would need to be considered in light of the clinical benefits afforded at the lower dose.

Whereas topiramate is approved for chronic use indications, phentermine is approved only for short term use for weight loss, defined as 'a few weeks' in the currently marketed label for Adipex. As such, the applicant was required to conduct additional studies to bridge the approved short term use with Adipex to long term use with PHEN/TPM. Prominent among these was a 2 year carcinogenicity study conducted in rats. Survival increased and body weight decreased over the 2 year period in drug-treated groups. Long-term toxicities considered related to phentermine included adverse dental findings (broken/cut/missing teeth in some individuals) and an increased incidence of minimal lung histiocytosis with granulomatous inflammation at the mid and high doses. No drug-related neoplasms were observed at exposures ~18-fold higher than the clinical dose, which will be described in the product label should PHEN/TPM be approved.

Dr. Carlson additionally recommends that a juvenile animal study be conducted with PHEN/TPM prior to initiating pediatric studies. This is a reasonable recommendation given the concerns of potential adverse bone effects of chronic carbonic anhydrase inhibition (topiramate) and adverse neurological development (topiramate and phentermine). The appropriate species and design for such a study will be determined in conjunction with the applicant's pediatric study plan.

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TODD M BOURCIER

10/01/2010

Pharm/tox recommends AP with pregnancy contraindication

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-580

Applicant: VIVUS, Inc.

Stamp Date: 12/28/10

Drug Name: QNEXA

NDA/BLA Type: NDA 505(b)2

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Literature reviews for listed drugs for toxicology, pharmacology, pharmacokinetics. Completed phen. carcinogenicity/chronic (rat) and combination toxicity studies for sub-chronic (rat, dog) and embryofetal development (rat & rabbit).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Review issue – formulations in tox. studies not clear (listed drugs purchased from chemical supply companies). CMC provided comments for 74-day letter that will address some formulation specifications and impurity questions. Administered orally in clinical and nonclinical studies.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		Oral dosing (animal gavage, clinical capsules).
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Rat carcinogenicity study with phentermine submitted, as requested.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A
NEW NDA/BLA**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Label notes Qnexa not recommended during pregnancy; but proposed label pregnancy Cat. ^(b) ₍₄₎ DMEP consistently cautioned that pregnancy Cat. X is expected. Preliminary review of Seg 2 combo. studies does not support changing prior recommendations for Cat. X labeling (although data show no clear additive or synergistic effects).
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No apparent impurity questions throughout development; any formulation/impurity issues will be a review issue since nothing was discussed during development.
11	Has the applicant addressed any abuse potential issues in the submission?	X		No pharmtox issues during development; clinical abuse potential issues with listed drug.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes__

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

DAVID B CARLSON
02/26/2010
Nonclinical -- recommend filing

TODD M BOURCIER
02/26/2010
Pharm/tox adequate for filing