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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	22-580: N-0084
Submission Date	April 5, 2012
Brand Name	QSYMIA®
Generic Name	Phentermine HCl and Topiramate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	VIVUS, Inc.
Formulation; Strength	Phentermine HCl immediate release and topiramate extended release fixed dose combination oral capsules; 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg
Relevant IND	68,651
Indication	As an adjunct to diet and exercise for chronic weight management in obese adults or overweight adults with comorbidities

Purpose

This memorandum documents the reasons for the recommended language in the proposed product label:

- P-glycoprotein substrate status for phentermine and topiramate
- Estimation of creatinine clearance without normalization to body surface area
- Exclusion of interacting drugs in Section 7 "Drugs Interactions"
- Order of Section 7 and the Drug Interactions list for the Highlights

P-glycoprotein substrate status for phentermine and topiramate

On July 11, 2011, the sponsor submitted 2 study reports to IND 68,651 and requested that the phentermine and topiramate in QNEXA (proposed brand name then) be classified as Biopharmaceutics Classification System Class 1 compounds. Per these 2 reports, this reviewer determined that:

- With phentermine hydrochloride's mean efflux ratio of 0.919, phentermine does not appear to be a P-gp substrate when compared to a known P-gp substrate such as digoxin with an efflux ratio of 3.9.
- With topiramate's mean efflux ratio of 1.125, topiramate does not seem to be a P-gp substrate when compared to a known P-gp substrate such as digoxin with an efflux ratio of 3.2.

See this reviewer's IND 68,651 review on March 2, 2012 for details.

The sponsor submitted these 2 reports on April 5, 2012 to NDA 22-580 for the substantiation that both phentermine and topiramate are not P-glycoprotein substrate. Thus, the Office of Clinical Pharmacology recommended the label to state "Phentermine is not a P-glycoprotein substrate." and "Topiramate is not a P-glycoprotein substrate."

Estimation of creatinine clearance without normalization to body surface area

Study OB-106 reported the participants' estimated creatinine clearance via Cockcroft-Gault equation with normalization per 1.73 m^2 of body surface area to classify participants' renal function statuses (see Attachment). Thus, the proposed label [redacted] (b) (4) However, this is inconsistent with the draft renal impairment guidance [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf] that the

Reference ID: 3150272

creatinine clearance estimate via the Cockcroft-Gault equation should be in "mL/min" (b) (4)

The original study protocol specified that the creatinine clearance estimate via the Cockcroft-Gault equation is body surface area-normalized (/1.73 m^2). However, the final classification of renal status via creatinine clearance estimate thru Cockcroft-Gault equation for Study OB-106 is not body surface area-normalized (/1.73 m^2). The sponsor noted this discrepancy as a protocol deviation (see Attachment). This reviewer also recalculated the creatinine clearance and confirmed that the reported creatinine clearance is not body surface area-normalized (/1.73 m^2). Thus, the sponsor's estimated creatinine clearance values are consistent with the recommendation of the draft renal impairment guidance. (b) (4) .

Exclusion of interacting drugs in Section 7 "Drugs Interactions"
The approved TOPAMAX label contains information on the drug-drug interactions (DDIs) between metformin and topiramate as well as between lithium and topiramate. The approved ADIPEX-P and SUPRENZA labels contain the information on the DDI between oral hypoglycemic medications and phentermine as well as between adrenergic neuron blocking drugs and phentermine. The Office of Prescription Drug Promotion commented that to be consistent among these approved labels, QSYMIA label should contain information of these DDIs. The following states the rationales for excluding such information:

- Metformin: In the presence of 15/92 mg/mg QSYMIA, metformin exposure increases 23%. In the presence of metformin, topiramate exposure decreases 5% upon administration of 15/92 mg/mg QSYMIA. Topiramate exposure does not increase in the presence of phentermine. Topiramate causes non-ion gap metabolic acidosis, whereas metformin causes lactic acidosis. The mechanism of acidosis that the 2 drugs cause is different. The highest QSYMIA's topiramate daily dose (92 mg) is less than ¼ that of TOPAMAX's (400 mg). Metformin-induced lactic acidosis is very rare.
- Lithium: Only for high topiramate dose per TOPAMAX label and may not apply to QSYMIA
- Oral hypoglycemic medications: Section 5.9 "Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-diabetic Therapy" has extensive coverage of this issue and thus will be redundant in Section 7 as there will be no addition of pharmacokinetic and dose information.
- Adrenergic Neuron Blocking Drugs: Seldom used clinically to treat hypertension

Order of Section 7 and the Drug Interactions list for the Highlights
The recommended Section 7 is the following (decreasing order of clinical significance):

  - Monoamine Oxidase Inhibitors (MAOI)
  - Oral Contraceptives
  - CNS Depressants Including Alcohol
  - Non-potassium Sparing Diuretics
  - Antiepileptic Drugs
  - Carbonic Anhydrase Inhibitors

- Although phentermine is not an MAOI in vitro, phentermine may cause other pharmacokinetic and pharmacodynamic effect in the presence of MAOI such as hypertensive crisis. Coadministration of QSYMIA with MAOI is contraindicated.
- The interaction between QSYMIA and oral contraceptive is important since topiramate can cause fetal harm and is contraindicated in pregnancy. However, the Division of Reproduction and Urology Products' consult shows that the increased norethindrone exposure in the presence of QSYMIA may not reduce contraceptive efficacy of the oral contraceptive.
- Receiving alcohol with either phentermine or topiramate will potentiate CNS depressant effects and such interaction is on both ADIPEX-P and TOPAMAX labels. Also, there is in vitro topiramate dumping in the presence of alcohol for QSYMIA.

- The interaction with hydrochlorothiazide is with topiramate and the TOPAMAX label does not mention it in Section 7 but in Section 12.
- The obese population is more likely to have hypertension and receive hydrochlorothiazide than antiepileptic drugs.
- There should be more coadministration with other antiepileptic drugs to treat seizures than coadministration with carbonic anhydrase inhibitors to treat open angle glaucoma and high altitude disease.
- Because of space, this reviewer recommends listing the top 4 drug interactions of Section 7 in the Highlights that are most relevant to the obese population.

Attachment starts here.

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Name of Sponsor/Company	Name of Finished Product	Name of Active Ingredient
VIVUS, Inc.	VI-0521 Capsule	Fixed dose combination of phentermine and topiramate

Diagnosis and Main Criteria for Inclusion: Subject was male or female; between 19 and 78 years of age (inclusive); with a weight of at least 50 kg and a body mass index (BMI) between 18 and 40 kg/m^2 (inclusive); and a non-smoker (for subjects with normal renal function).

Subjects with normal renal function in Group 1 had an estimated creatinine clearance (CLcr) of ≥80 mL/min/1.73 m^2 as determined at screening, and confirmed at admission via the Cockroft-Gault formula.

Subjects with renal impairment fulfilled the following additional criteria:

1. For eligibility in the renal impairment groups of the study:
   a. Group 2 subjects with mild renal impairment had a CLcr of ≥50 to <80 mL/min/1.73m^2
   b. Group 3 subjects with moderate renal impairment had a CLcr of ≥30 to <50 mL/min/1.73 m^2
   c. Group 4 subjects with severe renal impairment had a CLcr of <30 mL/min/1.73m^2. For women, the value was multiplied by 0.85.

   Even though the protocol called for a normalized BSA, the subjects were not categorized using a normalized BSA. This resulted in Subjects 2302 and 4301 being categorized to moderate renal impairment (instead of mild) and Subject 3201 being categorized to mild renal impairment (instead of moderate). All other subjects remained in the same renal impairment category even after BSA normalization.
2. Stable renal impairment (e.g., no clinically significant change in an estimated CLcr within 3 months or longer prior to screening, as determined by the Investigator).

Subject Disposition: 33 subjects were enrolled in this study and 32 completed the study.

Table S-1: Key Demographics

VI-0521 Demographic	Statistic	Normal n = 8	Mild n = 8	Moderate n = 8	Severe n = 9	Overall n = 33
Age (years)	mean (SD)	62 (8.8)	71 (3.9)	73 (7.4)	68 (7.1)	68 (7.9)
	min	50	66	55	55	50
	max	77	76	78	76	78
Weight (kg)	mean (SD)	81.3 (9.14)	72.5 (12.91)	67.2 (11.40)	75.1 (12.95)	74.0 (12.29)
	min	66.7	54.5	54.5	52.5	52.5
	max	91	92.4	84.3	93.7	93.7
Height (cm)	mean (SD)	166.2 (5.38)	164.0 (5.64)	157.6 (4.69)	167.1 (5.87)	163.8 (6.41)
	min	158	154.9	150	154.9	150
	max	173	174	165	176	176
BMI (kg/m^2)	mean (SD)	29.4 (3.14)	26.8 (3.85)	27.0 (3.67)	26.8 (3.99)	27.5 (3.68)
	min	25.2	22.7	22	19.1	19.1
	max	34.4	33.1	33.2	33.2	34.4

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Table 4 Cockroft-Gault Assessments by Subject

Subject Number	Age (years)	Weight (kg)	Gender	Serum Creatinine	CLcr*	Renal Impairment Category
1101	56	83.6	Female	0.8	103.63	Normal
1201	66	74.3	Female	0.9	72.12	Mild
1301	55	83.9	Female	1.7	49.52	Moderate
1401	76	74.5	Female	1.9	29.63	Severe
2101	65	83.6	Male	0.9	96.76	Normal
2102	52	91.0	Male	0.8	139.03	Normal
2103	77	86.0	Female	0.5	127.93	Normal
2104	50	66.7	Female	0.6	118.11	Normal
2201	70	75.3	Male	1.1	66.55	Mild
2202	73	92.4	Male	1.2	71.65	Mild
2203	76	54.5	Female	0.7	58.83	Mild
2204	76	58.0	Female	0.7	62.6	Mild
2301	71	84.3	Male	2.3	35.13	Moderate
2302	78	62.3	Male	1.1	48.77	Moderate
2303	77	56.0	Female	1.1	37.86	Moderate
2304	73	54.5	Female	1.1	39.19	Moderate
2401	61	81.2	Male	4.3	20.72	Severe
2402	68	76.8	Male	7.3	10.52	Severe
2403	66	56.5	Female	2.8	17.63	Severe
2404	55	52.5	Female	3.1	16.99	Severe
3101	62	83.3	Female	0.7	109.58	Normal
3201	68	81.7	Female	1.4	49.6	Mild
3401	70	81.5	Female	3.4	19.81	Severe
4101	66	67.7	Female	0.7	84.37	Normal
4102	64	88.6	Female	0.8	98.06	Normal
4201	71	63.4	Female	0.6	86.07	Mild
4202	67	80.1	Female	0.9	76.7	Mild
4301	77	62.0	Female	1.0	46.11	Moderate
4302	74	67.2	Female	1.4	37.4	Moderate
4303	75	67.0	Female	1.1	46.74	Moderate
4401	67	82.4	Male	7.3	11.44	Severe
4402	76	77.0	Female	2.0	29.09	Severe
4403	75	93.7	Female	2.5	28.76	Severe

Source: Listing 16.2.8-9.

* CLcr was not normalized for BSA, noted as a deviation

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06/26/2012

Reference ID: 3165102

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	22-580: N-0056
Submission Date	October 17, 2011
Brand Name	QNEXA®
Generic Name	Phentermine HCl and Topiramate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
Pharmacometric Reviewer	Justin Earp, Ph.D.
Pharmacometric Team Leader	Christine Garnett, Pharm.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	VIVUS, Inc.
Formulation; Strength	Phentermine HCl immediate release and topiramate extended release fixed dose combination oral capsules; 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg
Relevant IND	68,651
Indication	Treatment of obesity, including weight loss and maintenance of weight loss together with diet and exercise

Purpose

This memorandum concerns the rationales of recommendation for inclusion or exclusion of the following Clinical Pharmacology information on the proposed product label:

- Phentermine's potential as a monoamine oxidase inhibitor (MAOI)
- In vitro dose-dumping of topiramate in the presence of 40% alcohol
- Drug interaction results based on population pharmacokinetic analysis

Phentermine's Potential as an MAOI

Rothman stated in a commentary that there is no data to support the hypothesis that phentermine inhibits monoamine oxidase (MAO) at typical therapeutic doses [*Synapse* 1999;32:141-5].

Maher et al. observed the plasma dopamine concentrations increase and greater increase of blood platelet serotonin concentrations upon oral administration of 15 mg phentermine to 9 young, non-obese male volunteers (*Lancet* 1999;353:38). Maher's group later published the potential of phentermine as an MAOI in vitro based on rat lung, brain, and liver tissues [*Ulus et al. Biochem Pharmacol* 2000;59:1611-21].

Kilpatrick et al. published that phentermine is an unlikely MAOI based on in vitro rat brain tissue [*Int J Obes Relat Metab Disord* 2001;25:1454-8]. Nandigama et al. published that phentermine is an unlikely MAOI based on recombinant human purified liver MAO-A and MAO-B [*Biochem Pharmacol* 2002;63:865-9].

This reviewer used the reported Ki values (Table 1) and calculated the [I]/Ki values to assess the potential of phentermine as an MAOI in vitro. This approach is similar to the recommended approach to assess inhibition of cytochrome P450 enzymes per the draft drug interaction guidance.

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Table 1. Potential for phentermine as an MAOI in in vitro systems

	Phentermine's Ki for MAO	[I]/Ki	Tissue/Preparation	Reference
1	75 μM for MAO-A	0.022	Not specified	Rothman
2	85 – 88 μM for MAO-A	0.020	Rat lung, brain, and liver	Ulus
3	143 μM for MAO-A 285 μM for MAO-B	0.023 0.012	Rat brain	Kilpatrick
4	498 ± 60 μM for MAO-A 375 ± 42 μM for MAO-B	0.0034 0.0045	Recombinant human purified MAO-A and MAO-B	Nandigama

To be conservative, this reviewer (Lau) used the plasma phentermine concentration upon a mean daily dose of 36 mg phentermine as 1.6757 μM (250 ng/mL) [Douglas *Int J Obes* 7:591-5 (1983)]. The [I]/Ki values are all < 0.1 in the above estimations. If the [I]/Ki value is < 0.1, the potential of phentermine to inhibit MAO in vivo is remote.

If phentermine were not an MAOI, why would the plasma dopamine and blood platelet serotonin concentrations increase in Maher et al.'s study (*Lancet* 1999;353:38)? The answer to this question is unknown. At least, Maher et al. attributed the serotonin increase to the increased release of serotonin from the enterochromaffin cells. However, Maher et al. did not state the magnitude of increase and did not provide validation for the bioanalytical assays.

The MAO language appears in the "Contraindication" [redacted] (b) (4) sections of Qnexa's label. Per the in vitro data, phentermine is not an MAOI. This is a fact and should belong to Section 12.3's In Vitro Assessments of Drug Interactions. To be cautious that phentermine may cause other pharmacokinetic (Maher at al. *Lancet* 1999;353:38) and pharmacodynamic effect, this reviewer recommends retaining the MAO statement in the "Contraindication" section as in other approved phentermine products' label.

Dose-dumping of Topiramate

Per OND QA Biopharmaceutics Dr. Tien-Mien Chen's review (July 19, 2010), the results of the in vitro dose-dumping of topiramate in the dissolution medium showed that 40% alcohol accelerated the release of topiramate from Qnexa capsules and completed the release of topiramate in around 3 – 4 hours which is faster than that in water (around 8 hours).

If Qnexa's topiramate were to become immediate release in the presence of alcohol, Qnexa's maximum dose of 92 mg topiramate is still less than the approved maximum dose of 200 mg topiramate twice daily for the treatment of epilepsy. [redacted] (b) (4)

Drug Interaction Results Based On Population Pharmacokinetic Analysis

The proposed Qnexa product label has the following language in Section 121.3, Drug Interactions:

[redacted] (b) (4)

[redacted] (b) (4) Thus, we cannot support a label statement suggesting that [redacted] (b) (4)

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CLINICAL PHARMACOLOGY MEMORANDUM

NDA	22-580: N-0056; N-0077
Submission Date	October 17, 2011; February 21, 2012
Brand Name	QNEXA®
Generic Name	Phentermine HCl and Topiramate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
Division Director	Chandrahas Sahajwalla, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	VIVUS, Inc.
Formulation; Strength	Phentermine HCl immediate release and topiramate extended release fixed dose combination oral capsules; 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg
Relevant IND	68,651
Indication	Treatment of obesity, including weight loss and maintenance of weight loss together with diet and exercise

Background

The sponsor submitted a response on October 17, 2011 to address NDA 22-580's Complete Response letter. One of the safety issues is the dose-related increase in serum creatinine upon dosing the phentermine and topiramate fixed dose combination (FDC) capsules. Such increase may imply that phentermine and topiramate can affect the kidney function such as glomerular filtration to decrease creatinine elimination. The sponsor responded on February 21, 2012 that the serum creatinine increase is due to:

- fluid shift – acute weight loss by phentermine and topiramate and resulting body water loss
- topiramate's carbonic anhydrase activity
- topiramate's possible weak inhibition of human organic anion transporter 3 (hOAT3) and human organic cation transporter 1 (hOCT1) in the kidney

In an effort to understand the mechanism of the serum creatinine increase, this review concerns the inhibition potential of phentermine and topiramate on renal transporters such as hOATs and hOCTs.

Creatinine is a break-down product of creatine phosphate in muscle. The body produces creatinine at a fairly constant rate per muscle mass. Kidney chiefly eliminates creatinine from blood via glomerular filtration and proximal tubular secretion. Kidney tubular reabsorption of creatinine is little to none [Harrison's Principles of Internal Medicine, 18th ed., D.L. Longo et al. editors, 2011, Chapter 44. Azotemia and Urinary Abnormalities, J. Lin, B. M. Denker]. If the glomerular filtration and/or tubular secretion of kidney are deficient, serum creatinine concentration can rise.

Transporters in the kidney tubules remove creatinine from blood in the capillaries to urine in the lumen of kidney tubules. Figure 1 below shows the location of the different transporters and the direction of substrate movements in the proximal renal tubules.

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Figure 1. Kidney proximal tubules with different transporters [Giacomini et al. *Nat Rev Drug Discov* 2010;9:215-36].

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If inhibition for a renal transporter were to happen, this will affect the substrate movement of the particular transporter. For example, inhibition of OAT3 will prevent its substrate(s) to move effectively from the blood side to the urine side of the renal proximal tubule provided that no other basolateral (from blood to urine) transporters will transport the substrate. Thus, OAT3 substrate(s) will rise in the blood side of the renal proximal tubule.

Findings

In vitro data reported in the literature showed that the renal handling of creatinine is thru the following transporters:

- hOCT2 and not hOCT1 is responsible for the basolateral transport of creatinine in human kidneys [Urakami et al. *Pharm Res* 2004;21:976-81]
- Together with hOCT2, hMATE1 and hMATE2-K each at the brush border membrane of renal proximal tubule secrete creatinine into the lumen [Tanihara et al. *Biochem Pharmacol* 2007;74:359-71].
- hOCT2, hOAT3, hOAT4, and hOCT3 significantly uptake creatinine of which hOCT2 has the highest transport activity (see Figure 2) [Imamura et al. *Clin Pharmacol Ther* 2011;89:81-8].

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- hOCT2 plays a decisive role in renal secretion of creatinine [Ciarimboli et al. *Clin Cancer Res* 2012;18:1101-8]
- In summary, the above data show that hOCT2 is primarily responsible for creatinine renal secretion. If inhibition of these renal transporters were to happen, serum creatinine concentration can rise.

Metformin's elimination is primarily thru renal excretion without metabolism. Metformin does not bind to plasma proteins and the kidney readily filters metformin thru the glomerulus. Metformin is a substrate of

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hOCT2, multidrug and toxin extrusion protein 1 (hMATE1), and hMATE2-K in the kidney [Graham et al. *Clin Pharmacokinet* 2011;50:81-98].

Study OB-107 showed that phentermine and topiramate increased metformin C_{max} and AUC 16 and 23%, respectively, in obese otherwise healthy volunteers. Inferring such metformin exposure increase via hOCT2 inhibition by phentermine and topiramate has the following issues:

- Study OB-107 has the following dosing sequence:
  1) metformin
  2) sitagliptin
  3) phentermine and topiramate
  4) phentermine and topiramate plus probenecid
  5) phentermine and topiramate plus metformin
  6) phentermine and topiramate plus sitagliptin

  The Table below depicts the time frame of the dosing sequence.

Table. Study ON-107's dosing sequence (PHEN = phentermine, TPM = topiramate, and FDC = fixed dose combination):

	Metformin	Sitagliptin	PHEN/TPM FDC	PHEN/TPM FDC + Probenecid	PHEN/TPM FDC + Metformin	PHEN/TPM FDC + Sitagliptin
Screening	Days 1 – 5	Days 6 – 10	Days 11 – 28	Day 29	Days 30 – 34	Days 35 – 39

Assuming phentermine and topiramate were to cause the decrease in glomerular filtration. It would be difficult to attribute the metformin exposure increase to phentermine and topiramate's inhibition of renal transporters such as hOCT2 since the prior dosing of phentermine and topiramate in Periods 3 and 4 might have decreased glomerular filtration and caused the serum metformin increase instead.

- hOCT2 inhibitors may also be hMATE inhibitors. Metformin clinical inhibition interactions may involve hMATE1 or hMATE2-K in addition to, or even instead of, hOCT2. Thus, interpretation of in vivo inhibition of hOCT2 studies should be cautious [Giacomini et al. *Nat Rev Drug Discov* 2010;9:215-36].

The sponsor's claim that topiramate is a weak hOAT3 and hOCT1 inhibitor may be invalid since their substantiation is the English translation of the redacted Japanese Pharmaceuticals and Medical Devices Agency's Topina review page 42/82, which reported topiramate IC_{50} of 624.4 and 1063 μM, respectively, in hOAT3 and hOCT1 expressing cells. However, this reference did not provide details such as substrates, experimental conditions, and positive control. Thus, topiramate's inhibition statuses for hOAT3 and hOCT1 are inconclusive (see NDA 22-580's Clinical Pharmacology review).

Clinical Pharmacology Recommendations

To understand the mechanism of serum creatinine increase upon phentermine and topiramate administration, the sponsor should have a Post Marketing Requirement to conduct an in vitro study to determine the inhibition potential of both phentermine and topiramate individually and in combination on the following human transporters:

- organic cation transporter 2 and organic cation transporter 3
- organic anion transporter 3 and organic anion transporter 4
- multidrug and toxin extrusion protein 1 and multidrug and toxin extrusion protein 2-K

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CLINICAL PHARMACOLOGY REVIEW

NDA	22-580; N-000, N-012, N-041
Submission Dates	December 28, 2009, April 21, 2010 and August 27, 2010
Brand Name	QNEXA®
Generic Names	Phentermine HCl and Topiramate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
Pharmacometric Reviewer	Justin Earp, Ph.D.
Pharmacometric Team Leader (Acting)	Christine Garnett, Pharm.D.
OCP Division	Clinical Pharmacology II (HFD 870)
OND Division	Metabolism and Endocrinology Products (HFD 510)
Sponsor	VIVUS, Inc.
Formulation; Strength	Phentermine HCl immediate release and topiramate modified release fixed dose combination oral capsules; 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg
Relevant IND	68,651
Indication	Treatment of obesity, including weight loss and maintenance of weight loss together with diet and exercise

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1 Executive Summary

The sponsor is developing phentermine plus topiramate fixed-dose combination (PHEN/TPM FDC) capsules to treat obese patients. The proposed use of the PHEN/TPM FDC capsules together with diet

and exercise is for obese patients (BMI ≥ 30 kg/m^2) or overweight patients (BMI ≥ 27 kg/m^2) with weight related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity.

The PHEN/TPM FDC capsules have the following strengths and combinations for once daily oral administration:

- 15 mg phentermine immediate release (IR) beads plus 92 mg topiramate modified release (MR) beads – PHEN/TPM 15/92 mg "full dose"
- 11.25 mg phentermine IR beads plus 69 mg topiramate MR beads – PHEN/TPM 11.25/69 mg "¾ dose"
- 7.5 mg phentermine IR beads plus 46 mg topiramate MR beads – PHEN/TPM 7.5/46 mg "½ dose"
- 3.75 mg phentermine IR beads plus 23 mg topiramate MR beads – PHEN/TPM 3.75/23 mg "¼ dose"

The 3.75, 7.5, 11.25, and 15 mg are expressed as phentermine free base of phentermine HCl.

Phentermine HCl (ADIPEX-P®) has an indication to manage exogenous obesity. ADIPEX-P® is an oral 37.5 mg phentermine HCl (30 mg phentermine free base) IR tablet (ANDA 085128) and IR capsule (ANDA 088023). Patients may take a half tablet (18.75 mg phentermine HCl) once daily or a half tablet twice daily. Phentermine's original approval was on May 4, 1959 as Ionamin Resin® (NDA 11-613).

Topiramate (TOPAMAX®) has an indication to treat epilepsy as monotherapy and adjunctive therapy (both up to 400 mg daily) as well as prophylaxis of migraine (up to 100 mg daily) as oral 25, 50, 100, and 200 mg topiramate IR tablets (NDA 20-505 approved on December 24, 1996) and 15 and 25 mg topiramate IR sprinkle capsules (NDA 20-844 approved on October 26, 1998).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCPII) has reviewed NDA 22-580's Clinical Pharmacology data submitted under NDA 22-580, dated December 28, 2009, and finds it acceptable provided that a mutual agreement regarding the label language can be reached between the sponsor and the Food and Drug Administration.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

PHEN/TPM FDC Efficacy and Safety

Dose-Response Relationship for Efficacy

There is a dose-response for weight loss in the pivotal Phase 3 clinical trials. There is an increasing reduction in weight loss between placebo and the low (3.75/23 mg), middle (7.5/46 mg), and high (15/92 mg) PHEN/TPM FDC dose groups.

Weight loss was assessed by two efficacy criteria: mean drug-associated weight loss significantly exceeds mean placebo weight loss by at least 5% and proportion of subjects who lose greater than or equal to 5% of baseline body weight in the active-product group is at least 35% and approximately double the proportion in the placebo-treated group. Results of the Phase 3 trials show the 7.5/46 mg and 15/92 mg doses met the first criteria. All dose groups met the second criteria.

These observations support the efficacy of PHEN/TPM FDC for weight loss at the proposed dosing regimen. The recommended dose is PHEN/TPM 7.5/46 once daily with an increase to PHEN/TPM 15/92 mg once daily if weight loss goals are not achieved by 3 – 4 months.

Dose-Response Relationship for Safety

Topiramate has been associated with metabolic acidosis; psychiatric, cognitive and psychomotor adverse events; and teratogenetic effects in animal studies and in patients taking TOPAMAX®. The safety review of PHEN/TPM FDC is focused on determining if the proposed PHEN/TPM FDC doses are capable of producing similar safety events in a dose-dependent manner.

Metabolic acidosis has been reported with 400 mg topiramate daily doses during treatment of epilepsy and 2 cases were observed with PHEN/TPM FDC (one each at the 7.5/46 mg and 15/92 mg dose groups). Serum bicarbonate is generally reduced to < 21 mM in patients with acidic blood pH. There is a dose response for reduction in serum bicarbonate to < 21 mM. Dose adjustments or discontinuations are proposed for patients experiencing severe symptoms of metabolic acidosis.

Dose-response relationships were also identified for psychiatric (anxiety, depression, and insomnia), cognitive (memory impairment, cognitive disorders, and disturbance in attention), and psychomotor adverse events (asthenia, dizziness, dysgeusia, feeling jittery, hypoaesthesia, palpitations, paraesthesia, and blurred vision) in the Phase 3 clinical trials. These are expected adverse events from the use of topiramate or phentermine.

A thorough QT study does not detect the daily oral doses of PHEN/TPM 7.5/46 mg and PHEN/TPM 22.5/138 mg have QT prolongation effect.

Pharmacokinetics (PK)

Phentermine

Upon oral administration of a single PHEN/TPM 15/92 mg, the resulting mean phentermine t_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are 6 hr, 49.1 ng/mL, 1990 ng·hr/mL, and 2000 ng·hr/mL, respectively. Phentermine PK is best described via a linear 1-compartment population PK model with first-order absorption. The oral clearance (CL/F) and volume of distribution (V/F) are estimated to be 8.79 L/h and 348 L, respectively, upon PHEN/TPM FDC administration. Phentermine is 17.5% plasma protein bound and is not a P-glycoprotein substrate. Phentermine has two metabolic pathways, namely p-hydroxylation on the aromatic ring and N-oxidation on the alipthatic side chain. Cytochrome P450 (CYP) 3A4 primarily metabolizes phentermine but does not show extensive metabolism. Phentermine is neither an inhibitor nor an inducer of CYPs. Monoamine oxidase (MAO)-A and MAO-B do not metabolize phentermine. Seventy to 80% of a dose exists as unchanged phentermine in urine when administered alone. The mean phentermine terminal half-life is 20 hours. A high fat meal does not affect phentermine PK for PHEN/TPM 15/92 mg. The phentermine exposure increases approximately in dose-proportional manner from PHEN/TPM 3.75/23 mg to PHEN/TPM 15/100 mg. Upon dosing PHEN/TPM FDC to steady state, the mean phentermine accumulation ratios for AUC and C_{max} are both 2.5.

Topiramate

Upon oral administration of a single PHEN/TPM 15/92 mg, the resulting mean topiramate t_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, are 9 hr, 1020 ng/mL, 61600 ng·hr/mL, and 68000 ng·hr/mL, respectively. Topiramate PK is best described via a linear 2-compartment population PK model with first-order absorption. The CL/F, Vc/F (Vc is the volume of the central compartment), and Vp/F (Vp is the volume of the peripheral compartment) are estimated to be 1.17 L/h, 50.8 L, and 13.1 L, respectively, upon PHEN/TPM FDC administration. Topiramate is 15 – 41% plasma protein bound and does not show extensive metabolism. Six topiramate metabolites (via hydroxylation, hydrolysis, and glucuronidation) exist, none of which constitutes more than 5% of an administered dose. Topiramate does not inhibit CYPs 1A2, 2A6, 2B6, 2C9, 2D6, 2E1, and 3A4/5. However, topiramate is a mild inhibitor of CYP 2C19 and a mild inducer of CYP 3A4. About 70% of a dose exists as unchanged topiramate in urine when administered alone. The mean topiramate terminal half-life is 65 hours. A high fat meal does not affect topiramate PK for PHEN/TPM 15/92 mg. The topiramate exposure increases approximately in dose-

proportional manner from PHEN/TPM 3.75/23 mg to PHEN/TPM 15/100 mg. Upon dosing PHEN/TPM FDC to steady state, the mean topiramate accumulation ratios for AUC and C_{max} are both 4.0.

Intrinsic Factors

Moderate and mild hepatically impaired patients' phentermine $AUC_{0\text{-}inf}$s increased 60 and 37%, respectively, as compared to those of healthy volunteers, whereas topiramate $AUC_{0\text{-}inf}$ decreased 10% and increased 4%, respectively, as compared to those of healthy volunteers. Per the 60% increase in phentermine exposure, patients with moderate hepatic impairment should not exceed the PHEN/TPM 11.25/69 mg daily dose. However, the PHEN/TPM 11.25/69 mg strength capsule's proposed use is for dose titration rather than for maintenance and may not be marketed for maintenance therapy. Thus, patients with moderate hepatic impairment may not exceed the PHEN/TPM 7.5/46 mg daily dose for this purpose. The sponsor did not study the effect of severe hepatic impairment on PHEN/TPM FDC's PK.

Severe renally impaired patients' phentermine and topiramate exposure both increase about 100% as compared to those of healthy volunteers. Moderately renally impaired patients' phentermine and topiramate $AUC_{0\text{-}inf}$s increased 45 and 85%, respectively, as compared to those of healthy volunteers. Mildly renally impaired patients' phentermine and topiramate $AUC_{0\text{-}inf}$s increased 22 and 25%, respectively, as compared to those of healthy volunteers. Per the about 100% increase in phentermine and topiramate exposures, patients with moderate and severe renal impairment should not exceed the PHEN/TPM 7.5/46 mg daily dose.

While age, BMI, gender, and race do not significantly affect the PK of both phentermine and topiramate via population PK analysis, creatinine clearance and body weight are covariates for CL/F and V/F, respectively, for both phentermine and topiramate. Between subjects variation is 33% and 27% for phentermine and topiramate clearances, respectively. Thus, no PHEN/TPM FDC dose adjustment is necessary for age, BMI, gender, and race, whereas dose adjustments have been proposed for renally impaired patients. Diabetes does not affect the PK of phentermine and topiramate.

Extrinsic Factors

Topiramate exposure does not change in the presence of phentermine. However in the presence of topiramate, phentermine C_{max} and $AUC_{0\text{-}inf}$ increase 13 and 42%, respectively, and the population PK analysis noted that CL/F is 31% lower.

Phentermine has weak monoamine oxidase inhibition activity. However, phentermine is unlikely to be an MAO inhibitor at PHEN/TPM FDC capsule's dosing regimen.

In drug-drug interaction study, metformin, sitagliptin, and probenecid were found to affect neither the PK of phentermine nor the topiramate PK.

In population PK analysis, concurrent background therapies of metformin, statins, sulfonylureas, selective serotonin reuptake inhibitors or antihypertensives were found not to significantly alter phentermine or topiramate clearance. Concurrent PHEN/TPM FDC administration with thiazolidinediones, however, increased phentermine and topiramate clearances by 7 and 36%, respectively.

PHEN/TPM FDC did not affect sitagliptin PK but increased metformin C_{max} and $AUC_{0\text{-}\tau}$ of 16 and 23%, respectively.

PHEN/TPM 15/92 mg decreased ethinyl estradiol $AUC_{0\text{-}inf}$ of 16% as well as increased norethindrone C_{max} and $AUC_{0\text{-}inf}$ of 22 and 16%, respectively.

Biopharmaceutics

The sponsor proposed that the PHEN/TPM FDC belongs to Biopharmaceutics Classification System Class 1. Since the topiramate portion of the PHEN/TPM FDC is modified-release, the entire PHEN/TPM

FDC is a modified-release product. Hence, the Biopharmaceutics Classification System for immediate-release product is not applicable for the PHEN/TPM FDC.

The clinically-tested PHEN/TPM FDC [redacted] (b) (4) are bioequivalent to the to-be-marketed PHEN/TPM FDC [redacted] (b) (4)

_____
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The reviewers acknowledge Weili Hwang, Ph.D.'s help in the initial review for this NDA submission's 8 in vivo clinical pharmacology studies.

An Optional Inter-Division Clinical Pharmacology Briefing for NDA 22-580 was conducted on August 25, 2010; participants included D. Green, N. Hejazi, J. Leginus, N. Mehrotra, S, Doddapaneni, J. Vaidyanathan, T. Chen, K. Krudys, G. Burckart, A. Agrawal, X. Yang, M. Roberts, H. Zheng, L. Jain, J. Lazor, P. Madara, T. Wu, E. Shang, D. Lee, P. Dharia, M. Khurana, I. Zdrojewski, C. Garnett, J. Earp, S. Choe, and J. Lau.

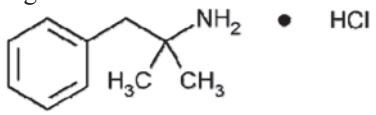
2 Question-Based Review

Since phentermine and topiramate are marketed drugs for decades, the sponsor performed limited number of clinical pharmacology studies for these drugs and heavily relied on published literature to support NDA 22-580. This reviewer also reviewed other published literature to support this review.

2.1 General Attributes

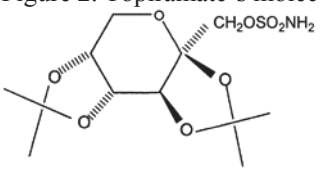
2.1.1 What are phentermine hydrochloride and topiramate's key physicochemical properties?

Figure 1. Phentermine HCl's molecular structure.



Phentermine hydrochloride has a molecular weight of 185.69, empirical formula of $C_{10}H_{15}N{\cdot}HCl$, and is soluble in water, methyl alcohol and ethyl alcohol, slightly soluble in chloroform, and insoluble in ether. Phentermine hydrochloride has a pK_a of 9.84. Phentermine's octanol:water partition coefficient (log P) is 1.9 [Jäger et al. *J Chem Inf Comput Sci* **43**:237-47 (2003)].

Figure 2. Topiramate's molecular structure.



Topiramate has a molecular weight of 339.363, empirical formula of $C_{12}H_{21}NO_8S$, and is soluble in methanol and acetone but slightly soluble in water. The topiramate molecule has 4 chiral centers. Topiramate has a pK_a of 9.7 and octanol:water partition coefficient (log P) of 0.51.

2.1.2 What is the formulation for the to-be-marketed oral PHEN/TPM FDC?

Tables 1 – 3 below show the to-be-marketed PHEN/TPM FDC formulation.

Table 1. Composition of the PHEN/TPM FDC

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 Beads				(b) (4)
PHEN Beads				
TPM Bead				(b) (4)
Printed (b) (4) Gelatin Capsule	one	one	one	one

Table 2. Composition of the PHEN Beads

Component	Function	PHEN Beads
		(b) (4)
Total		(b) (4) (b) (4)

Table 3. Composition of the TPM Beads and TPM Bead (b) (4)

Component	Function	TPM Beads % (w/w)	TPM Bead (b) (4) % (w/w)
Topiramate, USP	Active ingredient	(b) (4)	
Microcrystalline Cellulose, NF	(b) (4)		
Methylcellulose, USP			
Ethylcellulose, NF			
Povidone (b) (4) USP			
(b) (4) (b) (4)			
(b) (4)		Not applicable	
		Not applicable	
Total		(b) (4)	(b) (4)

How do phentermine and topiramate work to reduce body weight?
The exact mechanisms of action for phentermine and topiramate are unknown. Phentermine is a sympathomimetic amine and central appetite suppressant [Ioannides-Demos et al. *Drugs* **65**:1391-1418 (2006)]. Topiramate is a sulfamate-substituted monosaccharide antiepileptic and migraine prophylactic agent. Topiramate has carbonic anhydrase inhibition activity, which is related to the persistent weight loss of obese patients [Supuran et al. *Expert Opin Emerging Drugs* **13**:383-92 (2008)].

2.1.4 What are the sponsor's proposed indication and dosage regimen for PHEN/TPM FDC?

The proposed indication for the PHEN/TPM FDC is the treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise.

The proposed dose is PHEN/TPM 7.5/46 mg, taken once daily in the morning with or without food. If weight loss goals have not been achieved after 3 – 4 months of treatment, titration from the proposed dose of PHEN/TPM 7.5/46 mg to the PHEN/TPM 15/92 mg dose should be considered. The PHEN/TPM 3.75/23 mg dose may be considered for use as a treatment dose in some patients based on individual treatment goals.

Treatment should be initiated through dose titration starting with the PHEN/TPM 3.75/23 mg dose for 7 – 14 days followed by the daily dose of PHEN/TPM 7.5/46 mg. The PHEN/TPM 15/92 mg dose should be achieved by increasing the daily dose from PHEN/TPM 7.5/46 mg – PHEN/TPM 11.25/69 mg for 7 – 14 days prior to increasing the daily dose to PHEN/TPM 15/92 mg.

2.2 General Clinical Pharmacology

2.2.1 What are phentermine and topiramate's clinical pharmacokinetic (PK) characteristics?

Absorption

Study OB-110 showed that the mean phentermine t_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, and are 6 hr, 49.1 ng/mL, 1990 ng·hr/mL, and 2000 ng·hr/mL, respectively, upon oral administration of a single PHEN/TPM 15/92 mg. In the same study, the resulting topiramate t_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, are 9 hr, 1020 ng/mL, 61600 ng·hr/mL, and 68000 ng·hr/mL, respectively, upon oral administration of a single PHEN/TPM 15/92 mg. See Question 2.5.3 below for Study OB-110's details.

Distribution

Report 8V1VUP2R3 showed that at 5 µM (0.746 µg/mL) human plasma phentermine concentration, the protein bound fraction was 17.5% via equilibrium dialysis. The plasma phentermine concentration of 0.746 µg/mL is higher than the observed plasma phentermine concentrations. However, assessing plasma protein binding at higher concentration appears acceptable since phentermine may have low overall plasma protein binding. Topiramate is 15 – 41% bound to human plasma proteins over the blood concentration range of 0.5 – 250 µg/mL [TOPAMAX® label]. The fraction bound decreased as blood topiramate concentration increased.

Report 09-PHEN-BCS-01 showed that the average ± SD phentermine apical to basolateral membrane permeability is 77.2 ± 12.2 x 10^{-6} cm/sec and the basolateral to apical membrane permeability is 84.3 ± 8.0 x 10^{-6} cm/sec in in vitro Caco-2 experimental cell systems. The average ± SD digoxin apical to basolateral membrane permeability is 1.12 ± 1.3 x 10^{-6} cm/sec and the basolateral to apical membrane permeability is 13.3 ± 1.3 x 10^{-6} cm/sec. Digoxin is a P-gp substrate and these observations suggest that the Caco-2 system functions as expected (positive control). The bidirectional phentermine permeability is 1.09. Thus, phentermine is not likely a P-gp substrate. (b) (4)

Report TPM-BCS-01 only cited 2 references to support topiramate's P-gp status and did not present any experimental data. Crowe and Teoh [*J Drug Target* **14**:291-300 (2006)] showed that the following transport rates of 20 µM topiramate thru the Caco-2 subclone system (CLEFF9) at pH 7.4 in both the apical medium and the basolateral side of the monolayer:

Table 4. Transport rates of topiramate thru the Caco-2 subclone system (CLEFF9).

Modifier	Ap to Bas x 10^{-6} cm/sec	Bas to Ap x 10^{-6} cm/sec	Net transfer (Ap to Bas)
pH 7.4	14.6 ± 0.3	11.4 ± 1.1	1.28 X (uptake)*
pH 7.4 + PSC833	23.5 ± 2.2	12.7 ± 1.3	1.85 X (uptake)*
pH 7.4 + GF120918	13.0 ± 0.8	9.4 ± 1.7	1.37 X (no flux)

Ap = apical; Bas = basolateral; PSC833 and GF120918 are P-gp inhibitors. *Significant difference between Ap and Bas directions ($p<0.05$). All values are the mean ± SEM of triplicate samples.

Although Crowe and Teoh claimed no evidence exists that topiramate transport involves P-gp, their study lacks a positive control such as digoxin. P-gp, an efflux transporter, exists at the apical side of the Caco-2 cell and not the basolateral side. If topiramate were not a P-gp substrate, the net transfer should be 1 whereas the observed net transfer was 1.28 (uptake). If topiramate were not a P-gp substrate, the transfer rate from the apical side to the basolateral side should not change in the presence or absence of P-gp inhibitor. Yet, there is an increase in transfer rate (23.5 vs. 14.6) in the presence of PSC833. If topiramate were not a P-gp substrate, the transfer rate from the basolateral side to the apical side should not change in the presence or absence of P-gp inhibitor.

A study of membrane permeability via Caco-2 cells for 20 – 2000 µM topiramate showed that the apical to basolateral membrane permeability value and the basolateral to apical membrane permeability value were both 25 x 10^{-6} cm/sec; addition of 100 µM verapamil (P-gp inhibitor) did not inhibit the transport of

20 μM topiramate [English translation of the redacted Japanese Pharmaceuticals and Medical Devices Agency's Topina review (page 29/82)]. In addition, topiramate did not inhibit the transport of paclitaxel, a substrate of P-gp, at concentration of up to 100 μM (this reviewer is uncertain whether the 100 μM refers to topiramate, paclitaxel, or both which may be due to translation). This study lacks a positive control such as digoxin.

Marriott et al. reported that topiramate is a P-gp substrate [*Ann Int Med* **151**:143 (2009)].

Per these 3 references above, topiramate's substrate and inhibition statuses on P-gp are inconclusive.

The sponsor proposed labeling claim (b) (4) Since the Japanese review did not provide further experimental details such as substrates, experimental conditions, and positive control topiramate's inhibition statuses on hOAT and hOCT are inconclusive.

Metabolism and Excretion

Phentermine

Report 8VIVUP2R3 showed that phentermine was metabolically stable in in vitro human liver microsomes thru 60 minutes of incubation.

Report 8VIVUP2R4 showed that 1 μM phentermine was metabolically stable in in vitro cDNA expressed supersomes of human CYPs (cytochrome P450s) 1A2, 2C8, 2C9, 2C19, and 2D6 as well as MAO (monoamine oxidase) -A and –B. However, CYP 3A4 metabolized 13.3% of 1 μM phentermine for a 60-minute incubation.

Phentermine did not inhibit CYPs 1A2, 2C9, 2E1, 3A, and 2D6 in in vitro human liver microsomes with 100 μM phenacetin, 100 μM tolbutamide, 50 μM chlorzoxazone, 5 μM midazolam, and 25 μM dextromethorphan, respectively, as substrates [von Moltke et al. *J Clin Psychopharmacol* **18**:338-41 (1998)].

Report 8VIVUP1R1 showed that 10 μM phentermine did not inhibit 4 μM S-mephenytoin's 4' hydroxylation via CYP 2C19 (94.8% remaining activity) in in vitro human liver microsomes for a 30-minute incubation, whereas the positive controls (+)-N-benzylnirvalol, omeprazole, and ticlopidine inhibited CYP 2C19 activity.

Report 101-09-001 showed that 0.3, 1, or 10 μM phentermine did not induce CYPs 1A2, 2B6, and 3A4 in in vitro cultured human hepatocytes with 50 μM omeprazole, 1000 μM Phenobarbital, and 25 μM rifampin, respectively, as positive controls. Since phentermine did not induce CYP 3A4, phentermine may not be a CYPs 2C8, 2C9, or 2C19 inducer per the draft Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling Guidance.

Figure 3. Phentermine metabolic pathways in humans [Beckett & Belanger *J Pharm Pharmacol* **26**:205-6 (1974); Cho. *Res Comm Chem Path* **4**:67-78 (1974)]

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Phentermine has 2 metabolic pathways in humans. Hydroxylation at the para-position of the aromatic ring accounts for about 3 – 4% of the administered dose [Cho. *Res Comm Chem Path* **4**:67-78 (1974)]. N-oxidation to nitroso- and nitro-compounds accounts for less than 5% of the administered dose [Beckett & Belanger *J Pharm Pharmacol* **26**:205-6 (1974)]. About 70 – 80% of the dose is renally excreted under acidic urine condition [Beckett & Brooks. *J Pharm Pharmacol* **23**:288-94 (1971); Delbeke & Delbeke *Arzneim-Forsch* **36**:134-7 (1986)].

Topiramate

The sponsor conducted neither in vitro nor in vivo study to identify the metabolizing enzyme for topiramate as well as its inhibition and induction potentials on metabolizing enzymes.

The sponsor did not propose labeling claim of specific isozyme that metabolizes topiramate but cited the following:

- In a baculovirus expressed human CYP system, CYP 3A4+b5 generated 8.7 – 9.4% metabolites from 0.5 and 2 μM ^{14}C-topiramate, whereas those from CYPs 1A1, 2C8, 2C9, 2C19 were minimal [English translation of the redacted Japanese Pharmaceuticals and Medical Devices Agency's Topina review (page 41/82)]. This Japanese review did not provide further experimental conditions.
- Attempts to determine the CYP isoform catalyzing the formation of topiramate metabolite were unsuccessful. Topiramate metabolites were not detected after ^{14}C-topiramate was incubated with human liver microsomes [NDA 20-505's redacted Pharmacology and Toxicology review (page 23 of 77)].

Figure 4. Topiramate metabolic pathways in humans [Britzi et al. *Epilepsia* 46:378-84 (2005)].

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Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose) [TOPAMAX® label, Section 12.3]. Six topiramate metabolites (via hydroxylation, hydrolysis, and glucuronidation) exist in humans, none of which constitutes more than 5% of an administered dose.

In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes [TOPAMAX® label Section 7]. In vitro studies indicate that topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4 [TOPAMAX® label Section 7].

This reviewer found a published article that is not in the original submission but serves as a reference [Caldwell et al. *Eu J Drug Metab Pharmacokinet* **30**:151-64 (2005)]. In a mass balance study, 6 overnight-fasted men received a single oral dose of 100 mg ^{14}C-topiramate (0.97 μCi/mg). Serial plasma, urine, and fecal samples were collected predose and 120 hours postdose. Topiramate and metabolites were measured via HPLC-radioactivity detector or HPLC-mass spectrometry. Seventy-one and 1% of the total ^{14}C radioactive dose were recovered in urine and feces, respectively, as topiramate and its metabolites. Topiramate accounts for 82 and 65% of the recovered radioactivity in urine and feces, respectively. Four metabolites (2,3-diol-topiramate, 4,5-diol-topiramate, 10-OH-topiramate, and 9-OH-topiramate) exist in both plasma and urine samples with less than 5% recovery of total radioactivity each.

Metabolites' Pharmacological Activities

The sponsor did not conduct any study to assess the pharmacological activities of both phentermine and topiramate's metabolites. The sponsor asserts that both phentermine and topiramate are not extensively metabolized as well as no unexpected safety effects occurred in renally and hepatically impaired participants and the thorough QT study did not show unexpected ECG or other safety effects at a supratherapeutic dose.

The pharmacological activities of both phentermine metabolites and topiramate metabolites may not raise safety concerns since both drugs have been marketed for decades.

Topiramate's Chiral Inversion Potential

Topiramate has 4 chiral centers. For the chiral inversion potential of topiramate via metabolism, the sponsor asserted the following:

- Topiramate is not extensively metabolized and none of the metabolites exceed more than 5% of an administered dose.
- Characterizing this potential is challenging due to sensitivity to experimental conditions (such as pH) and low abundance of metabolites in plasma.
- Literature search showed neither such potential for topiramate nor its metabolites.

The potential for chiral inversion of topiramate via metabolism may not have safety concerns since topiramate has been marketed for more than a decade.

2.2.2 Are phentermine and topiramate PK dose-proportional upon oral administration?

Study OB-102 examined the single- and multiple-dose PK of the co-administered doses of phentermine and topiramate beads in the FDC to the coadministered single ingredient marketed products. The phentermine and topiramate beads used in this Study OB-102 were identical in composition and formulation to the beads used in the Phase 3 studies and the to-be-marketed formulation, however they were manufactured at a laboratory scale. The PHEN/TPM capsules do not contain (b) (4)
This was a parallel-design in a total of 45 men and women (30 kg/m^2 ≤ BMI ≤ 42 kg/m^2; 45 received at least 1 dose and 39 completed the study) with the following 3 treatments:

- Treatment 1: PHEN/TPM 7.5/50 mg
- Treatment 2: PHEN/TPM 15/100 mg
- Treatment 4: 15 mg phentermine (ADIPEX-P®) plus 100 mg topiramate (TOPAMAX®)

Serial plasma samples were collected predose and 96 hours post 1st dose (Period 1). Participants then continued treatments for 21 days with an accelerated dose titration (Period 2). Steady-state PK was assessed on Days 17, 18, 19, and 21 and the PK for the last dose was assessed 96 hours postdose. Phentermine and topiramate concentrations were determined in plasma samples via validated bioanalytical assays.

Per the power model to assess dose-proportionality (C_{max} or $AUC_{0\text{-}inf} = a \bullet [\text{Oral Dose}]^b$; "a" depends on the subject and error; "b" is the dose-proportionality factor; after transformation, ln C_{max} or ln $AUC_{0\text{-}inf}$ = ln a + b•ln Oral Dose; b = 1 when dose-proportional).

Table 5. Dose proportionality assessment of plasma phentermine for Study OB-102.

	PK Parameter	b (Slope)	Standard Error	95% CI
Period 1	C_{max}	1.091	0.09	(0.91, 1.27)
	$AUC_{0\text{-}t}$	1.197	0.11	(0.96, 1.43)
	$AUC_{0\text{-}inf}$	1.131	0.12	(0.89, 1.37)
Period 2	$C_{max,ss}$	1.005	0.11	(0.78, 1.23)
	$AUC_{0\text{-}tau}$	0.933	0.13	(0.67, 1.19)

Since the 95% CIs for the respective phentermine C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ for Treatments 1 and 2 at single-dose and multiple-dose included the value of 1, phentermine PK is dose-proportional from 7.5 mg/50 mg to 15 mg/100 mg.

Table 6. Dose proportionality assessment of plasma topiramate for Study OB-102.

	PK Parameter	b (Slope)	Standard Error	95% CI
Period 1	C_{max}	1.419	0.15	(1.12, 1.72)
	$AUC_{0\text{-}t}$	1.364	0.13	(1.10, 1.63)
	$AUC_{0\text{-}inf}$	0.941	0.12	(0.69, 1.19)
Period 2	$C_{max,ss}$	1.013	0.11	(0.78, 1.24)
	$AUC_{0\text{-}tau}$	1.040	0.11	(0.81, 1.27)

The 95% CIs for topiramate C_{max} and $AUC_{0\text{-}t}$ for Treatments 1 and 2 at single dose did not include the value of 1. However, the 95% CIs for topiramate $C_{max,ss}$ and $AUC_{0\text{-}tau}$ at multiple doses included the value of 1. Thus, topiramate PK is approximately dose-proportional between 7.5 mg/50 mg and 15 mg/100 mg.

Study OB-109 also examined phentermine and topiramate's PK dose-proportionality from 3.75/23 mg to 11.25/69 mg in single dose. See Question 2.5.2 below for the study details.

Table 7. Dose proportionality assessment of plasma phentermine for Study OB-109.

	PK Parameter	Slope (b)	Standard Error	95% CI
Formulation B (b) (4)	C_{max} (ng/mL)	1.08	0.0333	(1.02, 1.15)
	$AUC_{0\text{-}t}$ (ng*hr/mL)	1.16	0.0455	(1.07, 1.25)
	$AUC_{0\text{-}\infty}$ (ng*hr/mL)	1.14	0.0442	(1.05, 1.23)
Formulation A (b) (4)	C_{max} (ng/mL)	1.07	0.0366	(1.00, 1.15)
	$AUC_{0\text{-}t}$ (ng*hr/mL)	1.16	0.0382	(1.09, 1.24)
	$AUC_{0\text{-}\infty}$ (ng*hr/mL)	1.14	0.0377	(1.07, 1.22)

Per the power model, the 95% CIs for phentermine PK parameters of Formulations A and B at single dose ranged from 1.00 to 1.09 (lower bounds) and 1.15 to 1.25 (upper bounds), the phentermine PK is approximately dose-proportional from 3.75/23 mg to 11.25/69 mg at single dose.

Table 8. Dose proportionality assessment of plasma topiramate for Study OB-109.

	PK Parameter	Slope (b)	Standard Error	95% CI
Formulation B (b) (4)	C_{max} (ng/mL)	1.54	0.0593	(1.42, 1.66)
	AUC_{0-t} (ng*hr/mL)	1.21	0.0441	(1.13, 1.30)
	$AUC_{0-\infty}$ (ng*hr/mL)	1.07	0.0393	(0.99, 1.15)
Formulation A (b) (4)	C_{max} (ng/mL)	1.61	0.0666	(1.48, 1.75)
	AUC_{0-t} (ng*hr/mL)	1.28	0.0494	(1.19, 1.38)
	$AUC_{0-\infty}$ (ng*hr/mL)	1.14	0.0440	(1.05, 1.22)

Per the power model, the 95% CIs for topiramate AUC_{0-t} of Formulations A and B at single dose ranged from 1.13 to 1.19 (lower bounds) and 1.30 to 1.38 (upper bounds). The 95% CIs for topiramate $AUC_{0-\infty}$ of Formulations A and B at single dose ranged from 0.99 to 1.05 (lower bounds) and 1.15 to 1.22 (upper bounds). The 95% CIs for topiramate C_{max} of Formulations A and B at single dose ranged from 1.42 to 1.48 (lower bounds) and 1.66 to 1.75 (upper bounds). Thus, topiramate PK is approximately dose-proportional from 3.75/23 mg to 11.25/69 mg at single dose.

In sum, phentermine PK is approximately dose-proportional from 3.75/23 mg to 15/100 mg. Topiramate PK is approximately dose-proportional from 3.75/23 mg to 15/100 mg.

2.2.3 Does chronic oral dosing alter phentermine and topiramate PK?

Study OB-102 examined the accumulation of PHEN/TPM FDC upon multiple dosing. See Question 2.2.2 above for the study details. Upon dosing PHEN/TPM FDC to steady state, the mean phentermine accumulation ratios for AUC and C_{max} were both 2.5 as well as the mean topiramate accumulation ratios for AUC and C_{max} were both 4.0. The CL/F and V/F for phentermine and topiramate do not appear to change upon multiple-dosing of PHEN/TPM FDC.

2.2.4 How are the proposed daily oral phentermine and topiramate dosing regimens determined?

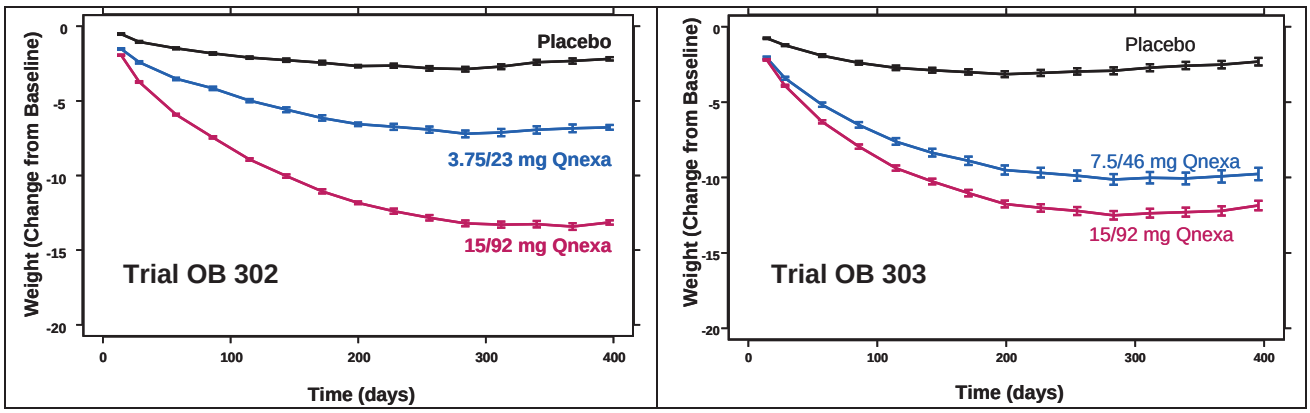
The lowest effective approved dose is 15 mg [ADIPEX-P® label]. The recommended adult total daily topiramate dose for seizure treatment is 25 – 400 mg in divided doses [TOPAMAX® label]. In studies involving topiramate as a weight loss agent, maximal weight loss was observed at 200 mg; however, this dose was associated with unacceptable tolerability. Topiramate doses of about 100 mg showed acceptable tolerability and significant weight loss when compared with placebo. Since phentermine and topiramate may have different mechanisms of action, the sponsor developed the PHEN/TPM FDC with lower doses of phentermine and topiramate to maximize the efficacy and minimize the safety of the obesity treatment. Thus, the sponsor evaluated the PHEN/TPM 15/92 mg, 7.5/46 mg, and 3.75/23 mg for efficacy and safety in treating obesity.

2.2.5 Exposure-Response

2.2.5.1 Is there evidence of dose-response for effectiveness?

There is a dose-response for weight loss in the pivotal Phase 3 clinical trials. Figure 5 shows an increasing reduction in weight loss between placebo and the low (3.75/23 mg), middle (7.5/46 mg), and high (15/92 mg) PHEN/TPM FDC dose groups. This observation supports the efficacy of PHEN/TPM FDC for weight loss at the proposed dosing regimen. The recommended dose is 7.5/46 mg daily with an increase to 15/92 mg daily if weight loss goals are not achieved by 3–4 months.

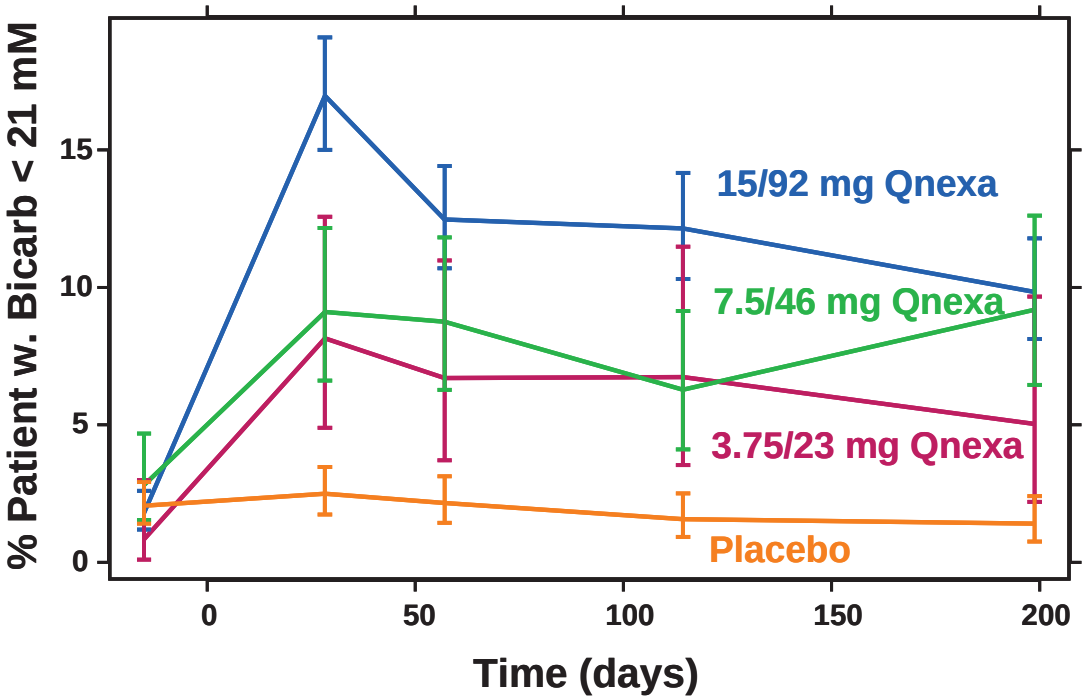
Figure 5. PHEN/TPM FDC exhibits a clear dose-response relationship for weight loss. Results are presented as mean±SEM for weight change from baseline from the intent-to-treat population excluding LOCF.



2.2.5.2 Is there evidence of a dose-response relationship for safety?

Yes, there is a dose-response for reduction in serum bicarbonate to <21 mM as shown in **Error! Reference source not found.** Serum bicarbonate is generally reduced to <21 mM in patients with acidic blood pH. Metabolic acidosis has been reported with high doses of topiramate (Topamax 400 mg/day) during treatment of epilepsy and two cases were observed with PHEN/TPM FDC (one each at the 7.5/46 mg and 15/92 mg dose). Dose adjustments or discontinuations are proposed for patients experiencing severe symptoms of metabolic acidosis.

Figure 6. There is dose-response for reduction in bicarbonate to <21 mM. The figure shows the time course for the percentage of patients with bicarbonate of <21 mM. Results are presented as percent of patients ± the 95% confidence interval for binomial probabilities.



Dose-response relationships were also identified for psychiatric (anxiety, depression, and insomnia), cognitive (memory impairment, cognitive disorders, and disturbance in attention), and psychomotor adverse events (asthenia, dizziness, dysgeusia, feeling jittery, hypoaesthesia, palpitations, paraesthesia, and blurred vision) in the phase 3 clinical trials. These adverse events are expected from this use of topiramate or phentermine.

See Pharamacometrics Review for more details on the dose-response for safety.

2.2.6 What would be the recommended optimal daily oral phentermine and topiramate FDC dose to reduce body weight?

The PHEN/TPM 7.5/46 dose is the recommended optimal daily dose for weight reduction. The PHEN/TPM 7.5/46 dose is the lowest dose that shows added benefit over monotherapy with either phentermine or topiramate. Also, the adverse event rates were generally higher for the PHEN/TPM FDC 15/92 mg dose than for the 7.5/46 mg dose (see Question 2.2.6). Further PHEN/TPM FDC's efficacy at the 7.5/46 mg dose is sufficient to satisfy both benchmarks for efficacy of weight loss products (1. The mean difference between placebo and treatment should be at least 5% and significantly different and 2. the proportion of subjects who lose greater than or equal to 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant) as outlined in the guidance document for weight loss products. Figure 5 in Section 2.2.5.1 shows that PHEN/TPM FDC meets the first benchmark for effectiveness of weight loss products for the 7.5/46-mg and 15/92-mg PHEN/TPM FDC doses since the response profiles for these treatment groups are greater than 5% lower than the placebo group. Table 9 shows that all PHEN/TPM FDC doses satisfy the second benchmark for efficacy.

Table 9. All PHEN/TPM FDC doses satisfy the second benchmark for effectiveness of weight loss products.

	OB-302			OB-303		
	Placebo	**Phen/Tpm 3.75/23 mg**	**Phen/Tpm 15/92 mg**	**Placebo**	**Phen/Tpm 7.5/46 mg**	**Phen/Tpm 15/92 mg**
ITT LOCF	*n=498*	*n=234*	*n=498*	*n=979*	*n=488*	*n=981*
≥ 5% Wt. Loss	**17.3%**	**44.9%**	**66.7%**	**20.8%**	**62.1%**	**70.0%**
Non-LOCF	*n=239*	*n=137*	*n=297*	*n=557*	*n=338*	*n=625*
≥ 5% Wt. Loss	**25.5%**	**59.1%**	**83.5%**	**26.2%**	**74.6%**	**85.1%**

On the other hand the 3.25/23 mg PHEN/TPM FDC dose does not meet the first benchmark for effectiveness. Therefore, the PHEN/TPM 7.5/46 dose is the recommended optimal daily dose for weight reduction.

2.2.7 Does PHEN/TPM FDC prolong the QT or QTc interval?

Study OB-118 examined PHEN/TPM 7.5/46 mg and PHEN/TPM 22.5/138 mg's QT prolongation potential in 108 healthy participants (mean BMI = 27 kg/m^2; range 24.1 – 29.8 kg/m^2). This was a randomized (1:1 female:male ratio), double-blind, placebo and active-controlled, parallel group/crossover design with the following 3 treatment groups:

- Group 1: PHEN/TPM was administered in a dose escalating fashion to allow assessment of the 7.5/46 mg dose at steady state on Day 10 and the 22.5/138 mg dose at steady state on Day 22. Moxifloxacin placebo was administered on Days 2 and 24 (56 subjects planned)
- Group 2: PHEN/TPM placebo was administered on Days 1-22, with a single oral dose of 400 mg moxifloxacin on Day 2 (28 subjects planned)
- Group 3: PHEN/TPM placebo was administered on Days 1-22, and a single oral dose of 400 mg moxifloxacin was administered on Day 24 (28 subjects planned)

The placebo capsule and PHEN/TPM FDC capsule had identical appearance and so were the placebo tablet and moxifloxacin tablet. Serial 12-lead ECGs were collected on Days 1 (baseline), 2, 10, 22, and 24. The ECG data were interpreted at a central cardiac laboratory. To maintain blinding, blood samples were obtained from all subjects for PK assessment; however, only samples from subjects receiving PHEN/TPM FDC were analyzed.

See the Interdisciplinary Review Team's review dated June 29, 2010 in DARRTS.

Study OB-118 does not detect the oral PHEN/TPM 7.5/46 mg and PHEN/TPM 22.5/138 mg doses have QT prolongation effect since:

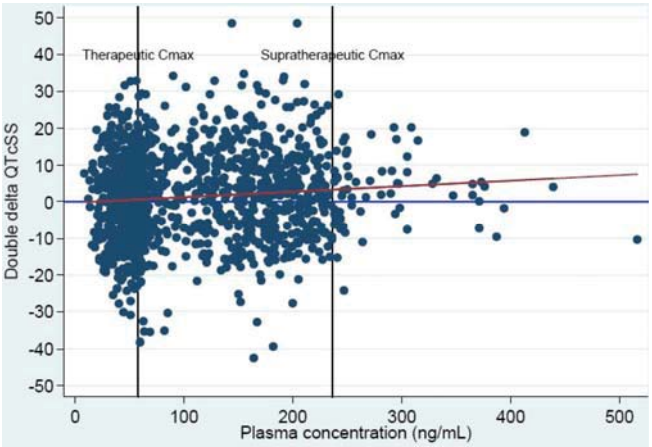
- The largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean difference between PHEN/TPM 7.5/46 mg and placebo as well as PHEN/TPM 22.5/138 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance.
- The largest lower bound of the 2-sided 90% CI for the placebo adjusted, study-specific corrected QTcN (ΔΔQTcN) for moxifloxacin was greater than 5 ms.

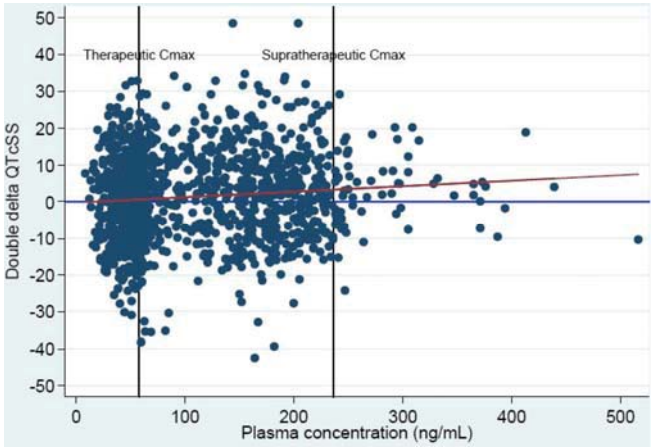
Table 10. Results of statistical analysis for the effect of PHEN/TPM FDC on QT prolongation

Treatment	Time (hour)	ΔΔQTcN (ms)	90% CI (ms)
PHEN/TPM 7.5/46	2	0.6	(-2.8, 4.0)
PHEN/TPM 22.5/138	12	3.0	(-0.2, 6.2)
Moxifloxacin 400 mg*	2	11.9	(9.3, 14.5)

* Multiple endpoint adjustment is not applied. The largest lower bounds after Bonferroni adjustment for 3 timepoints are 8.6 ms.

Figure 7 (left). ΔΔQTcF versus plasma phentermine concentration. Figure 8 (right). ΔΔQTcF versus plasma topiramate concentration.



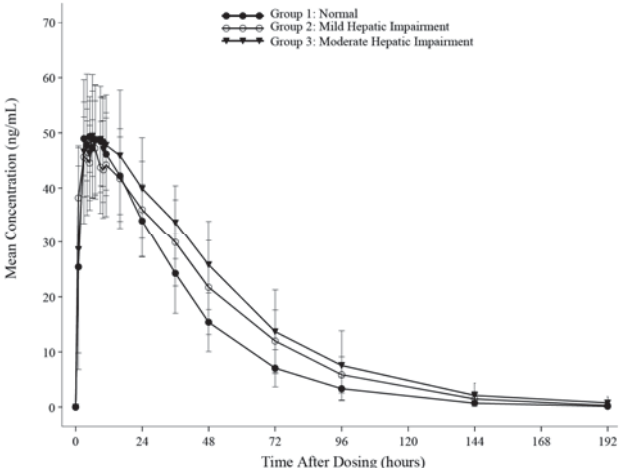


2.3 Intrinsic Factors

2.3.1 How does hepatic impairment affect phentermine and topiramate PK?

Study OB-105 examined the effect of liver impairment on phentermine and topiramate PK in 24 men and women with BMI ≥ 21 – ≤ 38 kg/m^2 (8 healthy, 8 mild impairment, and 8 moderate impairment per Child-Pugh Classification). Each overnight-fasted participant orally received a PHEN/TPM 15/92 mg dose. Serial plasma samples were collected predose and 192 hours postdose to determine phentermine and topiramate via validated HPLC/MS/MS bioanalytical assays.

Figure 9 (left). Mean plasma concentration-time profiles for phentermine. Figure 10 (right). Mean plasma concentration-time profiles for topiramate.



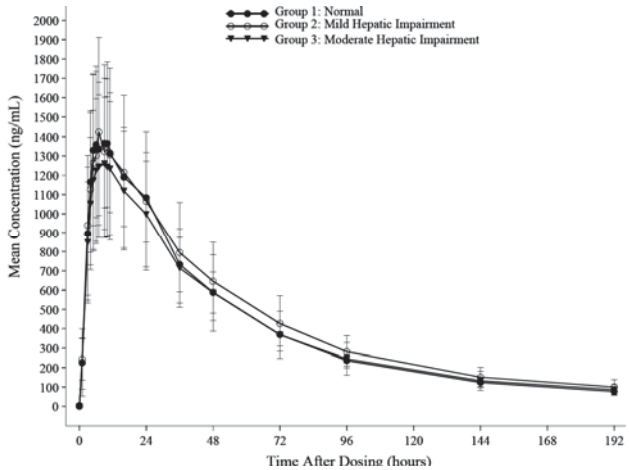


Table 11. Phentermine PK parameters for groups of varying hepatic function.

Parameter	Comparison	LS Means		Test/Reference	90%CI
		Test	Reference		
$AUC_{0\text{-}t}$ (ng*hr/mL)	Mild vs. Normal	2624	1936	136	(105.26 , 174.52)
$AUC_{0\text{-}t}$ (ng*hr/mL)	Moderate vs. Normal	3061	1936	158	(120.42 , 207.67)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	Mild vs. Normal	2685	1962	137	(106.46 , 175.96)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	Moderate vs. Normal	3146	1962	160	(122.33 , 210.24)
C_{max} (ng/mL)	Mild vs. Normal	52.3	51.1	102	(91.78 , 114.13)
C_{max} (ng/mL)	Moderate vs. Normal	53.5	51.1	105	(93.01 , 117.65)
$t_{½}$ (hr)	Mild vs. Normal	26.5	21.4	5.14	(-4.43 , 14.71)
$t_{½}$ (hr)	Moderate vs. Normal	29.3	21.4	7.92	(-2.40 , 18.23)

Table 12. Topiramate PK parameters for groups of varying hepatic function.

Parameter	Comparison	LS Means		Test/Reference	90% CI
		Test	Reference		
$AUC_{0\text{-}t}$ (ng*hr/mL)	Mild vs. Normal	84300	82549	102	(83.03 , 125.60)
$AUC_{0\text{-}t}$ (ng*hr/mL)	Moderate vs. Normal	72741	82549	88.1	(70.50 , 110.13)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	Mild vs. Normal	93236	89945	104	(83.62 , 128.50)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	Moderate vs. Normal	80970	89945	90.0	(71.42 , 113.48)
C_{max} (ng/mL)	Mild vs. Normal	1467	1444	102	(84.74 , 121.78)
C_{max} (ng/mL)	Moderate vs. Normal	1171	1444	81.1	(66.70 , 98.59)
$t_{½}$ (hr)	Mild vs. Normal	62.5	58.9	3.67	(-8.38 , 15.73)
$t_{½}$ (hr)	Moderate vs. Normal	65.6	58.9	6.80	(-6.19 , 19.79)

Moderate and mild hepatically impaired patients' phentermine $AUC_{0\text{-}int}$s increase 60 and 37%, respectively, as compared to those of healthy volunteers, whereas topiramate $AUC_{0\text{-}int}$s decrease 10% and increases 4%, respectively, as compared to those of healthy volunteers. Based on these data, we recommend that the dose for patients with moderate hepatic impairment should not exceed PHEN/TPM 11.25/69 mg. However, the PHEN/TPM 11.25/69 mg strength capsule's proposed use is for dose titration rather than for maintenance and may not be marketed for maintenance therapy. Thus, patients with moderate hepatic impairment may not exceed the PHEN/TPM 7.5/46 mg daily dose for this purpose.

2.3.2 How does renal impairment affect phentermine and topiramate PK?

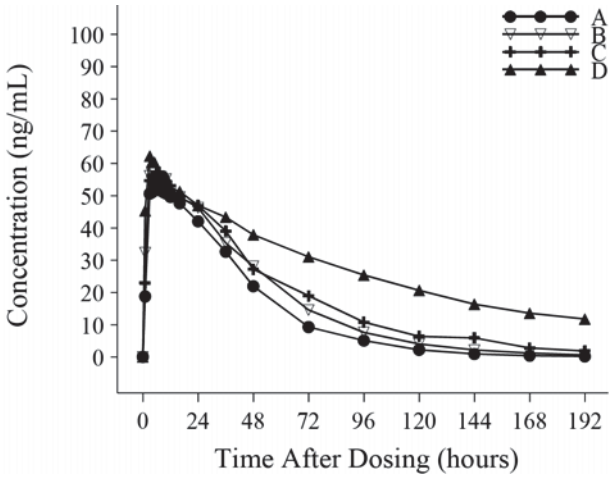
Study OB-106 examined the PK upon receiving an oral PHEN/TPM 15/92 mg dose after an overnight fast in 32 men and women (BMI ≥ 18 – ≤ 40 kg/m^2):

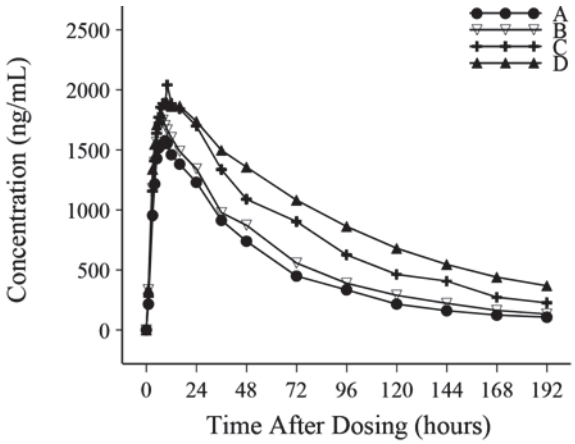
- Group 1 of healthy estimated creatinine clearance (CLcr) of ≥ 80 mL/min/1.73 m^2
- Group 2 of mild renal impairment with CLcr of ≥ 50 – < 80 mL/min/1.73 m^2

- Group 3 of moderate renal impairment with CLcr of ≥ 30 – < 50 mL/min/1.73 m^2
- Group 4 of severe renal impairment with CLcr of < 30 mL/min/1.73 m^2. For women, the CLcr value was multiplied by 0.85.

Classification of renal function groups was per the Renal Guidance via the Cockroft-Gault formula. For women, the value was multiplied by 0.85. Serial plasma samples were collected predose and 192 hours postdose to determine phentermine and topiramate via validated HPLC/MS/MS bioanalytical assays.

Figure 11 (left). Mean plasma concentration-time profiles for phentermine. Figure 12 (right). Mean plasma concentration-time profiles for topiramate.





A = Group 1, normal renal function; B = Group 2, mild renal impairment; C = Group 3, moderate renal impairment; D = Group 4, severe renal impairment

Table 13. Phentermine PK parameters for groups of varying renal function.

Parameter	Comparison	LS Means N	Test	N	Reference	Test/Reference	90% CI
AUC0-t (ng*hr/mL)	Severe vs. Normal	8	4946	8	2445	202	(160.39 , 255.03)
	Moderate vs. Normal	8	3521	8	2445	144	(109.43 , 189.49)
	Mild vs. Normal	8	3019	8	2445	123	(97.00 , 157.12)
AUC0-inf (ng*hr/mL)	Severe vs. Normal	6	4688	7	2449	191	(145.37 , 252.01)
	Moderate vs. Normal	7	3542	7	2449	145	(106.72 , 196.01)
	Mild vs. Normal	8	2976	7	2449	122	(93.43 , 158.01)
Cmax (ng/mL)	Severe vs. Normal	8	64.0	8	55.7	115	(102.86 , 128.24)
	Moderate vs. Normal	8	57.0	8	55.7	102	(89.84 , 116.64)
	Mild vs. Normal	8	58.2	8	55.7	104	(93.10 , 117.09)
t½ (hr)	Severe vs. Normal	6	51.0	7	19.6	31.4	(18.37 , 44.37)
	Moderate vs. Normal	7	38.5	7	19.6	18.8	(4.46 , 33.20)
	Mild vs. Normal	8	28.1	7	19.6	8.47	(-3.94 , 20.89)

Table 14. Topiramate PK parameters for groups of varying renal function.

Parameter	Comparison	LS Means				Test/Reference	90% CI
		N	Test	N	Reference		
AUC_{0-t} (ng*hr/mL)	Severe vs. Normal	8	174953	8	87320	200	(171.36 , 234.26)
	Moderate vs. Normal	8	146939	8	87320	168	(139.84 , 202.50)
	Mild vs. Normal	8	108171	8	87320	124	(105.29 , 145.75)
AUC_{0-inf} (ng*hr/mL)	Severe vs. Normal	8	215588	8	95240	226	(189.88 , 269.85)
	Moderate vs. Normal	7	176585	8	95240	185	(149.80 , 229.48)
	Mild vs. Normal	8	119205	8	95240	125	(104.26 , 150.25)
C_{max} (ng/mL)	Severe vs. Normal	8	1798	8	1590	113	(101.09 , 126.36)
	Moderate vs. Normal	8	1858	8	1590	117	(102.37 , 133.31)
	Mild vs. Normal	8	1681	8	1590	106	(94.13 , 118.70)
$t_{½}$ (hr)	Severe vs. Normal	8	77.5	8	64.8	12.7	(4.14 , 21.19)
	Moderate vs. Normal	7	71.9	8	64.8	7.08	(-3.26 , 17.42)
	Mild vs. Normal	8	56.6	8	64.8	-8.17	(-17.03 , 0.69)

Severe renally impaired patients' phentermine and topiramate exposure both increase about 100% as compared to those of healthy volunteers. Moderately renally impaired patients' phentermine and topiramate AUC_{0-int}s increase 45 and 85%, respectively, as compared to those of healthy volunteers. The sponsor proposed the dose for patients with moderate and severe renal impairment should not exceed 7.5/46 mg. This is acceptable.

A comparison of both phentermine and topiramate exposures (AUC values) in normal, mild, moderate, and severe patients were made using the population PK model (Table). Using the population PK model, mean AUC values in patients with mild impairment increased 33–35% and 21–22% for phentermine and topiramate, respectively. These increases do not exceed the degree of between subject variability for both phentermine (33%) and topiramate (27%) clearance. Based on these data, we recommend no change in the proposed dosing for patients with mild renal impairment.

Table 15. Phentermine and topiramate AUC values are shown for healthy volunteers and patients with reduced renal function at different PHEN/TPM FDC doses.

Degree of Renal Impairment	**Creatinine Clearance (mL/min)**	**Phentermine AUC (ug•hr/L) by Qnexa Dose**			
		3.75/23 mg	**7.5/46 mg**	**11.25/69 mg**	**15/92 mg**
Normal	80-125	0.42-0.55	0.83-1.11	1.25-1.66	1.66-2.22
Mild	50-80	0.55-0.75	1.11-1.50	1.66-2.25	2.22-3.00
Moderate	30-50	0.75-1.04	1.50-2.09	2.25-3.13	3.00-4.17
Severe	<30	>1.04	>2.09	>3.13	>4.17

Degree of Renal Impairment	**Creatinine Clearance (mL/min)**	**Topiramate AUC (ug•hr/L) by Qnexa Dose**			
		3.75/23 mg	**7.5/46 mg**	**11.25/69 mg**	**15/92 mg**
Normal	80-125	3.15-3.82	6.30-7.63	9.45-11.45	12.6-15.3
Mild	50-80	3.82-4.67	7.63-9.34	11.45-14.01	15.3-18.7
Moderate	30-50	4.67-5.82	9.34-11.63	14.01-17.45	18.7-23.3
Severe	<30	>5.82	>11.63	>17.45	>23.3

2.3.3 Do the intrinsic factors age, BMI, gender, race, and diabetes status affect phentermine and topiramate's PK?

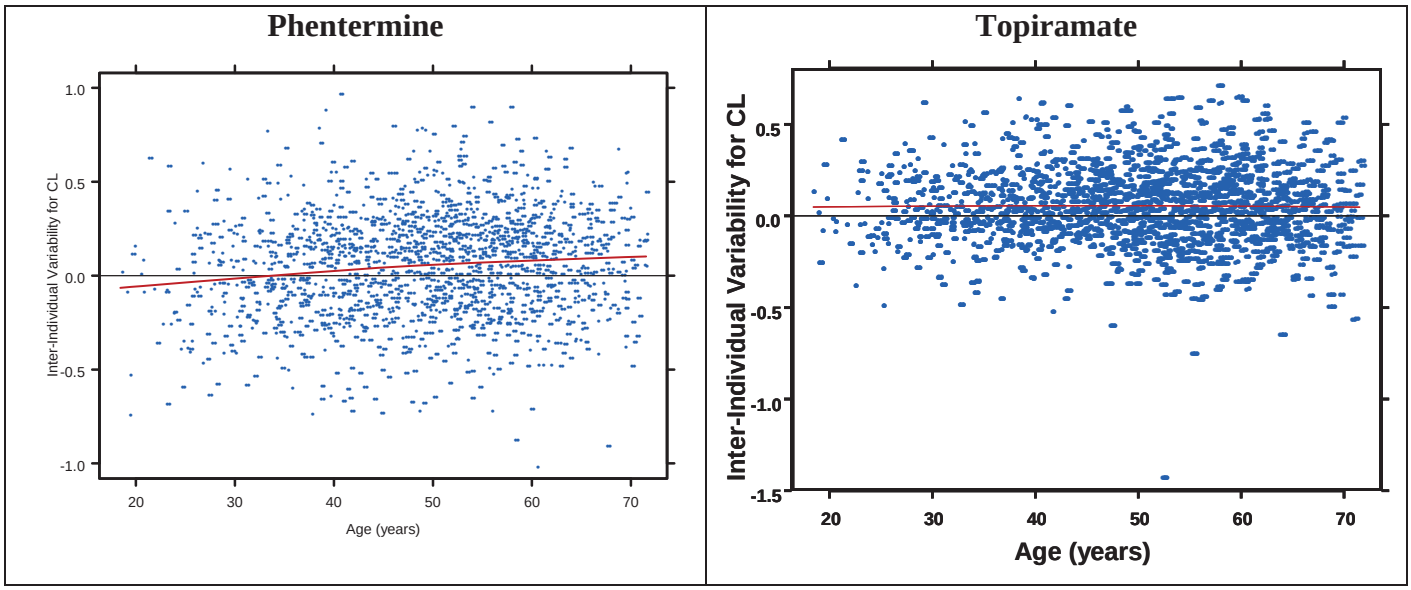
The effect of age, BMI, gender, race, and diabetes status on the pharmacokinetics of phentermine and topiramate were evaluated with the population PK analysis. There was no impact of these intrinsic factors

on the clearance of either phentermine or topiramate. No dose adjustment is recommended based on age, BMI, gender or race.

2.3.3.1 Age

In the population PK analysis, age (median = 48.8 yr, range = 18.1 – 71.0 yr) was not determined to have a significant effect on the population PK model estimate for CL or Vd. Figure 13 shows the individual estimates for CL are evenly distributed about the population mean across the range of ages.

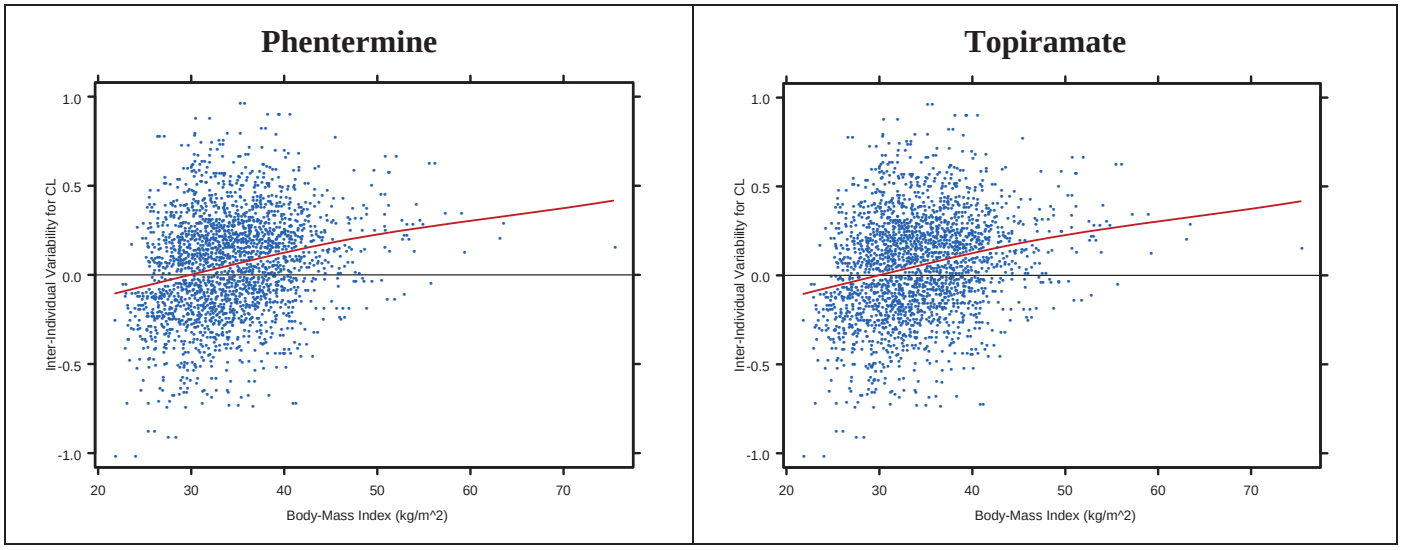
Figure 13. Age does not influence modeled phentermine and topiramate clearance. Scatter plots for phentermine and topiramate individual estimates of between-subject variability are shown with Loess smoothed lines to indicate potential trends in the data.



2.3.3.2 BMI

The PK of phentermine and topiramate are not influenced significantly by the patients' BMI. In the population PK analysis BMI was not considered a covariate with a statistically significant effect on either phentermine or topiramate CL or Vd. The loess trend line in Figure 14 shows a modest increase with BMI. However, BMI was not deemed statistically significant in the model for both phentermine and topiramate. Additionally, the magnitude of change in the trendline across the range of BMIs is not sufficient to warrant dose-adjustment.

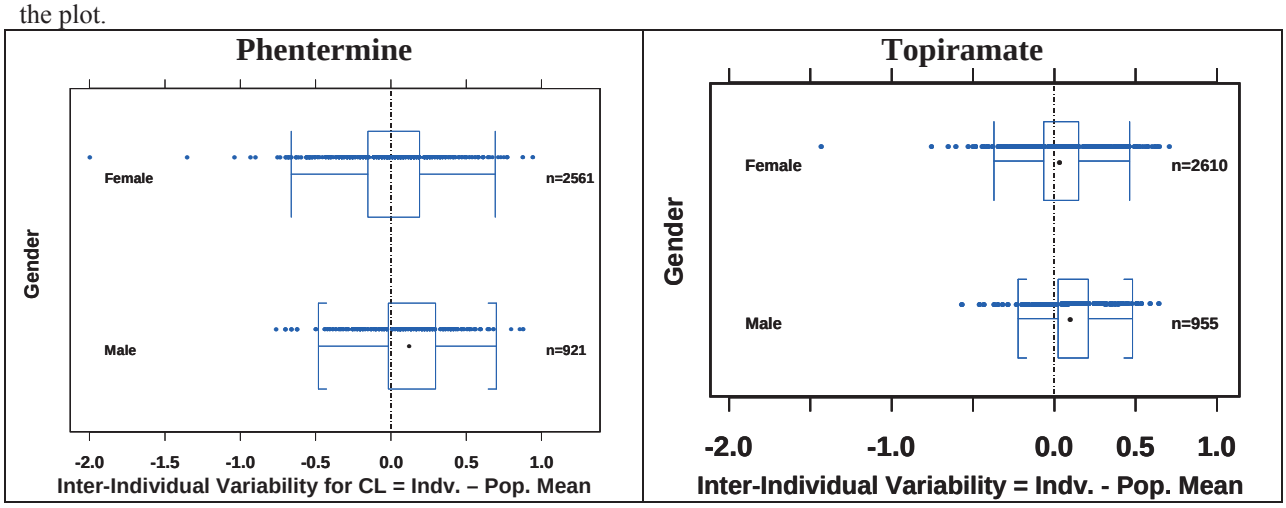
Figure 14. BMI does not influence modeled phentermine and topiramate clearance. Scatter plots for phentermine and topiramate individual estimates of between-subject variability are shown with Loess smoothed lines to indicate potential trends in the data.



2.3.3.3 Gender

Gender did not have an impact on the population PK analysis, for phentermine or topiramate. Figure 15 shows the individual estimates for CL are evenly distributed about the population mean for both males and females.

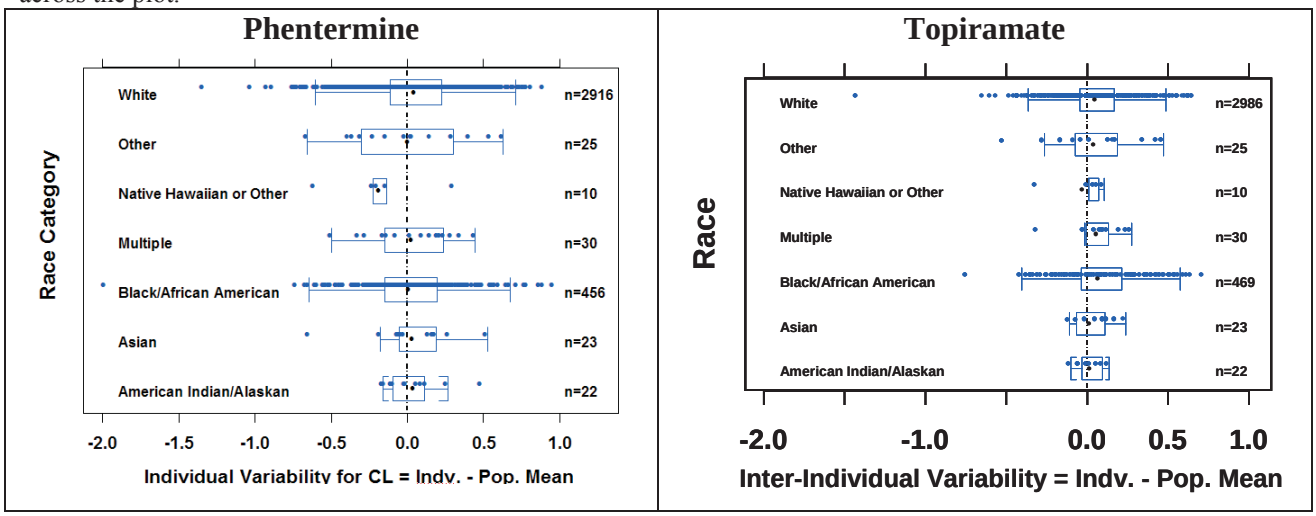
Figure 15. Gender does not Influence Modelled Phentermine Clearance. Boxplots are shown for each sex. The edge of the box represents the 25 and 75th percentiles. The end of the lines represents the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.



2.3.3.4 Race

Race did not have an impact on the population PK analysis, for phentermine or topiramate. Figure 16 shows the individual estimates for CL are evenly distributed about the population mean for each race category.

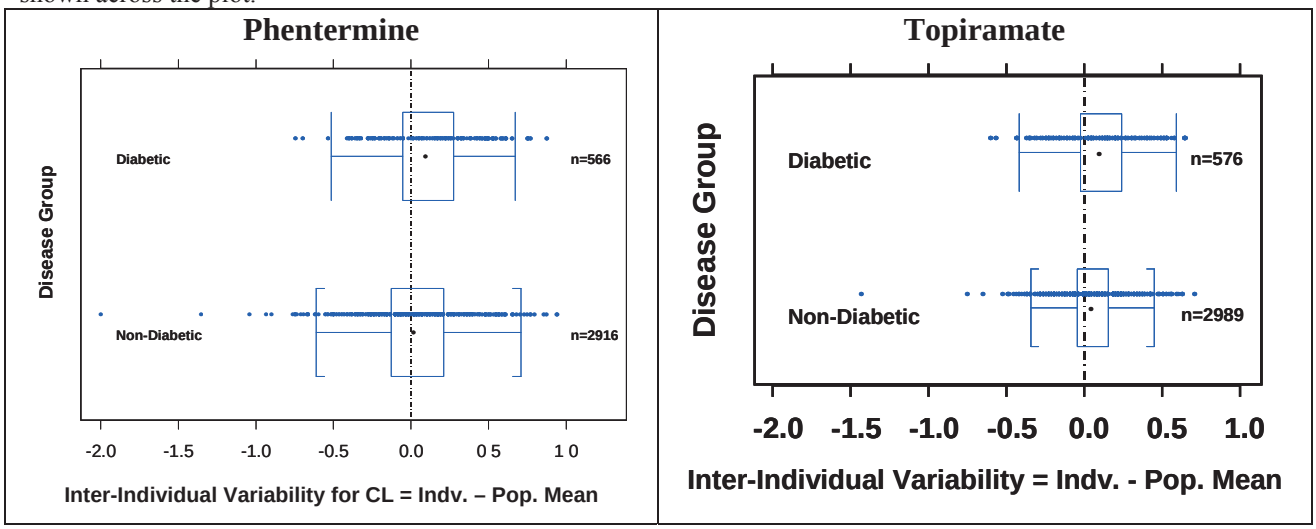
Figure 16. Race does not Influence Modelled Phentermine Clearance. Boxplots are shown for each race category. The edge of the box represents the 25 and 75th percentiles. The end of the lines represents the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.



2.3.3.5 Diabetes Status

The presence of diabetes did not have an impact on the population PK analysis, for phentermine or topiramate. Figure 17 shows the individual estimates for CL are evenly distributed about the population mean for each disease category.

Figure 17. Diabetes does not Influence Modelled Phentermine Clearance. Boxplots are shown for each disease state. The edge of the box represents the 25 and 75th percentiles. The end of the lines represents the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.



See the Pharmacometric Review for more details.

2.3.4 What pharmacogenomic information is in the application?

Pharmacogenomic information is not available in this submission.

2.4 Extrinsic Factors

2.4.1 How does food affect phentermine and topiramate's bioavailability (BA)?

Study OB-103 examined the effect of food on PHEN/TPM 15/92 mg capsule's bioavailability as well as the individual relative bioavailability of the phentermine alone capsule and topiramate alone capsule to

PHEN/TPM 15/92 mg capsule as a single-dose, 4-treatment, parallel design study. Sixty-five randomized healthy men and women of body mass index (BMI) ≥ 30 – ≤ 45 kg/m^2 participated in the study. Participants orally received the following 4 treatments in a 1:1:1:1 distribution of participants:

- Treatment A: a PHEN/TPM 15/92 after at least a 10 hours overnight fast
- Treatment B: a PHEN/TPM 15/92 thirty minutes after eating a high fat breakfast
- Treatment C: a 15 mg phentermine capsule after at least a 10 hours overnight fast
- Treatment D: a 92 mg topiramate capsule after at least a 10 hours overnight fast

The high fat breakfast's content is per the Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance. Serial plasma samples were collected predose and 168 hours postdose to determine phentermine and topiramate via validated LC/MS/MS assays.

Table 16. Comparison of PK parameters for phentermine and topiramate under fed and fasting conditions from PHEN/TPM FDC administration.

	PK Parameter	Fed (N = 16)	Fasting (N = 16)	90% CI	%GMR
Phentermine	C_{max} (ng/mL)	52.1	47.4	(100.7, 119.9)	109.9
	$AUC_{0\text{-}t}$ (ng*hr/mL)	2086.3	2057.6	(88.9, 115.7)	101.4
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	2119.4	2089.1	(88.8, 115.9)	101.4
Topiramate	C_{max} (ng/mL)	913.8	1008.0	(78.3, 104.9)	90.7
	$AUC_{0\text{-}t}$ (ng*hr/mL)	61821.2	65385.5	(84.0, 106.4)	94.5
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	68822.1	73927.7	(82.8, 104.7)	93.1

GMR = geometric mean ratio

Besides that of topiramate C_{max}, the ratio of the 90% confidence interval (CI) of the geometric mean ratios for all other phentermine and topiramate C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ between fed and fast conditions are within the 80 – 125% bioequivalence goalpost. The 10% lower topiramate C_{max} under fed condition will not raise safety (self-evident) and efficacy concerns since the lowest strength of PHEN/TPM FDC has weight reduction effect (see Question 2.2.5.1 above). Thus, food does not have significant effect on phentermine and topiramate's exposures. See Question 2.4.2.1 below for Study OB-103's other relative bioavailability results.

2.4.2 What are the potential drug-drug interactions for phentermine and topiramate?

Mutual interaction among:

2.4.2.1 Phentermine and topiramate

See Question 2.2.1 above for Study OB-103's details. Briefly, this question's treatments of interest are:

- Treatment A: a PHEN/TPM 15/92 mg capsule after at least a 10 hours overnight fast
- Treatment C: a 15 mg phentermine capsule after at least a 10 hours overnight fast
- Treatment D: a 92 mg topiramate capsule after at least a 10 hours overnight fast

The phentermine alone capsule and topiramate alone capsule used beads that were identical to the phentermine and topiramate beads used in the PHEN/TPM FDC.

Table 17. Comparisons of PK parameters for phentermine and topiramate for Treatment A versus Treatment C or Treatment D.

Phentermine	PK Parameters	Treatment A (N = 16)	Treatment C (N =17)	90% CI	%GMR
	C_{max} (ng/mL)	47.4	41.9	(103.9,123.4)	113.2
	$AUC_{0\text{-}t}$ (ng*hr/mL)	2057.6	1447.4	(124.9, 161.8)	142.2
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	2089.1	1472.8	(124.5, 161.7)	141.8
Topiramate	**PK Parameters**	**Treatment A (N = 16)**	**Treatment D (N = 16)**	**90% CI**	**%GMR**
	C_{max} (ng/mL)	1008.0	991.9	(87.8, 117.6)	101.6
	$AUC_{0\text{-}t}$ (ng*hr/mL))	65385.5	62373.3	(93.1, 118.0)	104.8
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	73927.7	70036.4	(93.9, 118.7)	105.6

In the presence of phentermine, no significant topiramate exposure change exists since the ratio of the 90% confidence interval for topiramate C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ in the presence of phentermine are within the 80 – 125% bioequivalence goalpost. However in the presence of topiramate, phentermine C_{max} and $AUC_{0\text{-}inf}$ increase 13 and 42%, respectively. This phentermine exposure increase may be due to topiramate's alkalinization of urine, thereby increase the reabsorption of phentermine from the renal tubules. Many case reports show topiramate-induced metabolic acidosis associates with an alkaline urine [Mirza et al. *Br J Clin Pharmacol* **68**:655–61 (2009)]. Beckett and Rowland show that the increased systemic amphetamine concentration is due to renal reabsorption of amphetamine from alkalinization of urine [*J Pharm Pharmacol* 17:628-39 (1965)]. Phentermine has an extra methyl group on the aliphatic side chain as compared to amphetamine's structure, thus a congener. The pKa's of phentermine and amphetamine are 10.1 and 10, respectively [Katsu et al. *Anal Sci* **17**:745-9 (2001); Sadeghtpour et al. *J Chromatogr* **761**:71-8 (1997)].

Coadministered drugs' effect on phentermine and topiramate PK:
2.4.2.2 Metformin, Sitagliptin, and Probenecid

Study OB-107 examined the effect of multiple twice daily 500 mg metformin dose, multiple once daily 100 mg sitagliptin dose, and a single 2 g probenecid dose, on multiple once daily PHEN/TPM 15/92 mg dose in 10 men and 10 women (mean BMI of 27.1 kg/m^2 and range of 22.2 – 32.7 kg/m^2). In addition, the study assessed the effect of multiple once daily PHEN/TPM 15/92 mg dose on multiple-dose 500 mg metformin twice daily dose and 100 mg sitagliptin once daily dose. Another objective of this study was to determine the semen topiramate concentrations upon multiple dosing of PHEN/TPM 15/92 mg. The study used the following open label and fixed-sequence design:

	Metformin	Sitagliptin	PHEN/TPM FDC	PHEN/TPM FDC + Probenecid	PHEN/TPM FDC + Metformin	PHEN/TPM FDC + Sitagliptin
Screening	Days 1 – 5	Days 6 – 10	Days 11 – 28	Day 29	Days 30 – 34	Days 35 – 39

Participants orally received the test medications after a 10 hour-overnight fast on Days 5, 10, 28, 29, 34, and 39. Serial plasma samples for measurement of phentermine and topiramate were collected predose and 24-hour postdose after the administration of the investigational drugs on Days 28, 29, 34, and 39. Serial plasma samples for measurement of sitagliptin were collected predose and 24-hour postdose after the administration of sitagliptin or sitagliptin plus phentermine/topiramate on Days 10 and 39. Serial plasma samples for measurement of metformin were collected predose and 12-hour postdose after the morning administration of metformin or metformin plus phentermine/topiramate on Days 5 and 34.

Predose plasma samples for determination of investigational drugs were collected in the morning on Days 4 and 33 for metformin; Days 9 and 38 for sitagliptin, and Days 27, 33, and 38 for phentermine and topiramate. Semen samples for determination of topiramate concentrations were collected on Day 28 between 5 and 7 hours after the phentermine/topiramate administration in 8 men.

Validated LC-MS/MS bioanalytical assays were used to measure plasma concentrations of phentermine, topiramate, metformin and sitagliptin as well as semen topiramate concentrations.

The $t_{½}$s for phentermine, topiramate, sitagliptin, and metformin are 20, 65, 12.4, and 6.2 hours, respectively. Thus, the dosing regimen is consistent with the time to reach steady state (3 – 5 $t_{½}$s). Probenecid's $t_{½}$ is 3 – 8 hours.

Table 18. Comparisons of phentermine and topiramate PK parameters for PHEN/TPM FDC plus sitagliptin versus PHEN/TPM FDC.

	PK parameter	Geometric L.S. Means		90% CI	% GMR
		PHEN/TPM + Sitagliptin	PHEN/TPM		
Phentermine	C_{max} (ng/mL)	144	131	105.15 - 114.61	109.78
	$AUC_{0-\tau}$ (ng*hr/mL)	2730	2490	105.01 - 114.04	109.43
Topiramate	C_{max} (ng/mL)	3930	4020	95.05 - 100.52	97.74
	$AUC_{0-\tau}$ (ng*hr/mL)	76500	77900	95.39 - 101.30	98.30

For phentermine and topiramate, the 90% CI for C_{max} and $AUC_{0-\tau}$ ratios (with/without sitagliptin) were within the bioequivalence goalpost of 80 – 125%.

Table 19. Comparisons of phentermine and topiramate PK parameters for PHEN/TPM FDC plus metformin versus PHEN/TPM FDC.

	PK parameter	Geometric L.S. Means		90% CI	% GMR
		PHEN/TPM + Metformin	PHEN/TPM		
Phentermine	C_{max} (ng/mL)	139	131	102.01–111.36	106.59
	$AUC_{0-\tau}$ (ng*hr/mL)	2610	2490	100.60–109.42	104.92
Topiramate	C_{max} (ng/mL)	3870	4020	93.46–98.94	96.16
	$AUC_{0-\tau}$ (ng*hr/mL)	73800	77900	92.02–97.61	94.78

For phentermine and topiramate, the 90% CI for C_{max} and $AUC_{0-\tau}$ ratios (with/without metformin) were within the bioequivalence goalpost of 80 – 125%.

Table 20. Comparisons of phentermine and topiramate PK parameters for PHEN/TPM FDC plus probenecid versus PHEN/TPM FDC.

	PK parameter	Geometric L.S. Means		90% CI	% GMR
		PHEN/TPM + Probenecid	PHEN/TPM		
Phentermine	C_{max} (ng/mL)	135	131	99.25–108.00	103.53
	$AUC_{0-\tau}$ (ng*hr/mL)	2490	2490	95.79–103.87	99.75
Topiramate	C_{max} (ng/mL)	4150	4020	100.43–106.10	103.23
	$AUC_{0-\tau}$ (ng*hr/mL)	78400	77900	97.79–103.59	100.65

For phentermine and topiramate, the 90% CI for C_{max} and $AUC_{0-\tau}$ ratios (with/without probenecid) were within the bioequivalence goalpost of 80 – 125%.

The recommended starting metformin dose is 500 mg BID and the recommended maximum daily dose is 2550 mg metformin. This study used the recommended daily dose of 100 mg sitagliptin. The recommended daily dose of probenecid is 2000 mg in divided doses. This study used a single 2000 mg probenecid dose to maximize its effect on the multiple-dose PK of phentermine and topiramate.

In vitro data showed that phentermine was metabolized by CYP3A4 (13.3% of 1 µM metabolized during a 60-minute incubation). Phentermine does not induce CYP enzymes, and it does not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. In addition, phentermine is neither a substrate nor potent inhibitor of MAOs. Phentermine is not a P-gp substrate.

Topiramate (up to 1 mM) does not inhibit CYPs 1A2, 2A6, 2B6, 2C9, 2D6, 2E1 and 3A4/5 isoenzymes. Topiramate inhibits CYP2C19 and induces CYP3A4 activity in primary human hepatocytes in a concentration-dependent manner.

Upon oral administration, about 90% of the absorbed metformin is eliminated via the renal route within the first 24 hours [GLUCOPHAGE® label]. Metformin is a substrate and inhibitor for human organic cation transporters (OCTs) [Fujita et al. *J Pharm Sci* **95**:25-36 (2006)].

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion [JANUVIA® label]. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin [JANUVIA® label]. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Sitagliptin and metformin do not mutually interact with each other pharmacokinetically [JANUVIA® label].

Probenecid undergoes hepatic metabolism resulting in active metabolites. Both parent drug and active metabolites are eliminated renally, mainly by tubular secretion. Small amounts of unchanged probenecid are filtered at the glomeruli. Parent drug is nearly completely reclaimed via tubular reabsorption; minor amounts of metabolites undergo tubular reabsorption [http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=509&sec=monphar]. Probenecid is an inhibitor for multidrug-resistance proteins (MRPs) and OATs [Giacomini & Sugiyama *Goodman & Gilman's the Pharmacological Basis of Therapeutics* 2005 ed. Ch 2].

Study OB-107 does not have the typical washout periods between treatments, which may be acceptable since each multiple-dose treatment is rather long and may serve as washout for the prior treatment. Competing metabolic interaction may not exist between PHEN/TPM FDC and metformin or sitagliptin since these drugs' primary elimination route is renal excretion of unchanged drug. There does not seem to be interactions for transporters as competing substrates or inhibitors. Thus, this multiple drug-drug interaction study appears to be acceptable with the caution that there may be not-yet-known enzyme(s) and transporter(s) that can interact as overlapping substrate, inducer and inhibitor, especially when not administered in the studied sequence and dosages.

The mean semen topiramate concentration upon multiple dosing of PHEN/TPM 15/92 mg between 5 to 7 hours postdose on Day 28 was 2490 ng/mL, which is bout 62% of the mean plasma topiramate concentration (4020 ng/mL) on Day 28. Based on the estimated total semen sample volumes, the mean estimated potential topiramate exposure through sexual conduct was 8.6 µg, which is less than 1/10,000th of the 92 mg topiramate in a single oral dose (assume intravaginal absorption).

Population PK analysis of drug-drug interactions with anti-hypertensives, metformin, SSRIs, statins, sulfonylureas, and thiazolidinediones.

In a population PK analysis of PHEN/TPM FDC, concurrent background therapies of metformin, statins, sulfonylureas, selective serotonin reuptake inhibitors or antihypertensives were shown not to alter phentermine or topiramate clearance significantly. In all cases the distributions of the residuals for the inter-individual variability of clearance were not statistically different from zero and not influenced by these concomitant medications. However, data from administration with thiazolinediones (TZDs) suggested there is an increase in phentermine and topiramate clearance. In a population PK fitting, concomitant administration with thiazolinediones increased phentermine and topiramate clearance 7% and 36%.

The magnitude of change of phentermine clearance does not appear to be clinically relevant when considering the effectiveness and safety profiles of PHEN/TPM FDC. No dose adjustment is recommended for PHEN/TPM FDC administration with concomitant TZD therapy.
See the Pharmacometrics Review for more details.

Phentermine and topiramate's effect on coadministered drugs' PK:
2.4.2.3 Sitagliptin and Metformin
See Question 2.4.2.2 above for Study OB-107's details.

Table 21. Comparisons of sitagliptin PK parameters for PHEN/TPM FDC plus sitagliptin versus sitagliptin.

PK parameter	Geometric L.S. Means		90% CI	% GMR
	PHEN/TPM + Sitagliptin	Sitagliptin		
C_{max} (ng/mL)	353	390	81.95–99.97	90.51
$AUC_{0-\tau}$ (ng*hr/mL)	3050	3150	93.05–100.34	96.62

For sitagliptin, the 90% CI for C_{max} and $AUC_{0-\tau}$ ratios (with/without PHEN/TMP FDC) were within the bioequivalence goalpost of 80 – 125%.

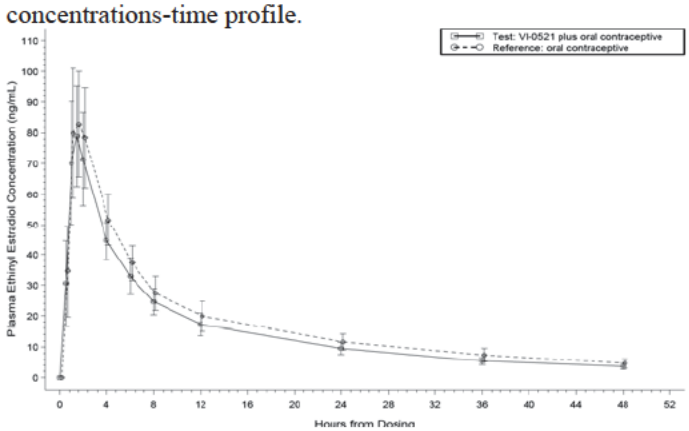
Table 22. Comparisons of metformin PK parameters for PHEN/TPM FDC plus metformin versus metformin.

PK parameter	Geometric L.S. Means		90% CI	% GMR
	PHEN/TPM + Metformin	Metformin		
C_{max} (ng/mL)	1080	932	104.87–127.57	115.67
$AUC_{0-\tau}$ (ng*hr/mL)	6620	5360	113.89–133.73	123.41

For metformin, the 90% CI for C_{max} and $AUC_{0-\tau}$ ratios (with/without PHEN/TPM FDC) were not within the bioequivalence goalpost of 80 – 125%. The mean metformin C_{max} and $AUC_{0-\tau}$ were about 16 and 23% higher in the presence of PHEN/TPM FDC to those in the absence of PHEN/TPM FDC.

2.4.2.4 Ethinyl Estradiol and Norethindrone
Study OB-108 examined the effect of multiple doses of PHEN/TPM FDC on the single dose PK of an oral contraceptive (NORTREL®; 35 µg ethinyl estradiol and 1 mg norethindrone) in 20 women (27 kg/m^2 ≤ BMI ≤ 35 kg/m^2). All participants received the oral contraceptive tablet on Days 1 and 29. From Days 3 to 30, all participants received a single PHEN/TPM FDC once daily each morning (Days 3 – 6: 3.75/23 mg, Days 7 – 10: 7.5/46 mg, Days 11 – 14, 11.25/69 mg, and Days 15 – 30: 15/92 mg). Serial plasma samples were collected on Days 1 and 29 predose and 48 hours postdose to determine ethinyl estradiol and norethindrone via validated LC-MS/MS bioanalytical assays.

Figure 18 (left). Mean plasma ethinyl estradiol concentrations-time profile. Figure 19 (right). Mean plasma norethindrone concentrations-time profile.



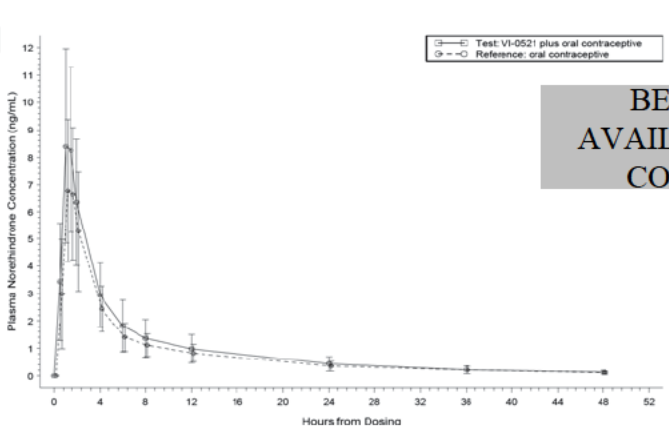


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Table 23. Comparison of oral contraceptive ethinyl estradiol PK parameters in the presence and absence of PHEN/TPM FDC.

	Geometric LS Means N = 20		Confidence Intervals	
Parameter	**PHEN/TPM + OC**	**OC**	**(90% Confidence)**	**% GMR**
C_{max} (pg/mL)	78.261	84.930	85.98 - 98.75	92.15
AUC_{0-t} (pg*hr/mL)	740.097	861.669	81.25 - 90.80	85.89
AUC_{0-inf} (pg*hr/mL)	825.639	981.074	79.23 - 89.39	84.16

The 90% CI of mean ratios (presence/absence of PHEN/TPM FDC) for ethinyl estradiol C_{max} and AUC_{0-t} were within the 80 – 125% bioequivalence goalpost, whereas the AUC_{0-inf} was not. The ethinyl estradiol AUC_{0-inf} was 16% lower with the coadministration of oral contraceptive and PHEN/TPM FDC.

Table 24. Comparison of oral contraceptive norethindrone PK parameters in the presence and absence of PHEN/TPM FDC.

	Geometric LS Means N = 20		Confidence Intervals	
Parameter	**PHEN/TPM + OC**	**OC**	**(90% Confidence)**	**% GMR**
C_{max} (ng/mL)	8.418	6.904	107.83 - 137.88	121.93
AUC_{0-t} (ng*hr/mL)	43.972	37.564	107.52 - 127.45	117.06
AUC_{0-inf} (ng*hr/mL)	45.724	39.305	106.75 - 126.76	116.33

The 90% CI of mean ratios (presence/absence of PHEN/TPM FDC) for norethindrone C_{max}, AUC_{0-t}, and AUC_{0-inf} were not within the 80 – 125% bioequivalence goalpost. The norethindrone C_{max}, AUC_{0-t}, and AUC_{0-inf} were 22, 17, and 16% higher with the coadministration of oral contraceptive and PHEN/TPM FDC.

Interpretation and Application of the Observation

No data exist for the interaction between phentermine and oral contraceptive. Thus this discussion focuses on the following:

- interaction between topiramate and oral contraceptive
- interaction between the disease state of obesity and oral contraceptive.

<u>Interaction between Topiramate and Oral Contraceptive</u>

Hepatic enzyme-inducing antiepileptic drugs such as topiramate can interact with oral contraceptives, thereby, reduce the efficacy of oral contraceptives. This may result from the induction of cytochrome P450 3A4 metabolism of estrogen/progestin and also from increased synthesis of sex hormone-binding globulin [D.S. Reddy. *Expert Rev Clin Pharmacol* **3**:183–92 (2010)]. Thus, women taking these drugs who also take oral contraceptives should use preparations containing at least 50 µg of ethinyl estradiol in order to reduce the chance of pregnancy. However, the contraceptive efficacy of higher-dose oral contraceptives is not well studied, and alternative methods such as barrier contraception should be discussed with the patients [J.A. French and T.A. Pedley. *N Engl J Med* **359**:166-76 (2008)].

Despite these changes in oral contraceptive regimens, the failure rate may still be higher than normal. It is unclear how much decrease in either the estrogenic or progestogenic concentrations by hepatic enzyme-inducing antiepileptic drugs will permit pregnancy to occur, making it difficult to estimate how the oral contraceptive regimen should be optimized to restore maximal efficacy. Hence, one must consider additional method of contraception [D.S. Reddy. *Expert Rev Clin Pharmacol* **3**:183–92 (2010)].

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species (rat and rabbit) at clinically relevant doses [TOPAMAX Labeling].

Counsel women to use an alternative method of contraception or a back-up method when moderate or weak enzyme inducers are used with combination oral contraceptives, and to continue back-up

contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability [NATAZIA Labeling].

The topiramate $t_{½}$ upon PHEN/TPM FDC administration ranges from 57 – 83 hours.

On the other hand, combination oral contraceptive's efficacy primarily results from the progestin (norethindrone) as evidenced via the progestin only product [ORTHO MICRONOR Labeling] and the estrogen is for the prevention of bleeding. With 16% increase in norethindrone AUC, this is in favor of the contraceptive efficacy of the coadministration of PHEN/TPM FDC and oral contraceptive.

A single-dose administration of LOESTRIN 24 Fe tablet with food decreased the maximum concentration of norethindrone by 11% and increased the extent of absorption by 27% and decreased the maximum concentration of ethinyl estradiol by 30% but not the extent of absorption. Despite these differences on norethindrone and ethinyl estradiol exposure, LOESTRIN 24 Fe tablets may be administered without regard to meals [LOESTRIN 24 Fe Labeling].

The rate of absorption of drospirenone and ethinyl estradiol following single administration of a formulation similar to YAZ was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of drospirenone, however, remained unchanged. In contrast, the extent of absorption of ethinyl estradiol was reduced by about 20% under fed conditions. Despite these differences on drospirenone and ethinyl estradiol exposure, YAZ can be taken without regard to meals [YAZ Labeling].

The above discussions do not take into consideration of the effect of obesity on oral contraceptive.

<u>Interaction between the Disease State of Obesity and Oral Contraceptive</u>
The use of oral contraceptives in obese women has at least the following issues [A. Edelman. *Contraception* **80**:583-90 (2009)]:

- Obese adult and adolescent women appear to be at increased risk for pregnancy as compared to normal body mass index counterparts due to higher rates of contraceptive nonuse.
- Oral contraceptive effectiveness (combined or progestin only) may be impaired in overweight and obese women [*Cochrane Database Syst Rev*. 2010 Jul 7;7:CD008452].
- Healthy obese women using combined oral contraceptive have moderately increased risk of venous thromboembolism as compared to nonobese users of combined oral contraceptive.
- Obesity is a risk factor for deep vein thrombosis. Among women with a body mass index greater than 25 kg/m^2 the synergistic effect with oral contraceptives should be considered when prescribing oral contraceptives [Abdollahi et al. *Thromb Haemost* **89**:493-8 (2003)].

Large, prospective studies that include overweight women are necessary to assess whether or not obesity alone plays a significant role in contraceptive efficacy. In the meantime, clinicians should not change prescribing practices based on patients' weight (except for the patch), but condom use should certainly be encouraged as a secondary contraceptive [S.A.B. Pitts and S.J. Emans. *Curr Opin Pediatr* **20**:383–389 (2008)].

Clinicians should take patients' clinical history to assess thrombotic risks prior to initiating an estrogen-containing contraceptive, explain the risks and benefits, and advise patients to avoid smoking [S.A.B. Pitts and S.J. Emans. *Curr Opin Pediatr* **20**:383–389 (2008)].

Conclusion
Clinical Pharmacology recommends the following for the coadministration of PHEN/TPM FDC and oral contraceptives in obese women:

- Patients should use additional contraception such as barrier method as back-up and continue back-up for 28 days after discontinuing PHEN/TPM FDC to ensure contraceptive reliability.
- Prescriber should use patient history to assess thrombotic risks.
- Prescriber should explain risks and benefits to the patients.
- Patients should avoid smoking.

Phentermine's own effect on coadministered drugs' PK:
2.4.2.9 Monoamine oxidase (MAO) substrates
2.4.2.9.1 Is phentermine an MAO inhibitor?
Amphetamine like drugs have MAO inhibitory activity [Scorza et al. *Biochem Pharmacol* **54**:1361-9 (1997)]. Since phentermine is a congener of amphetamine (1 more methyl group on the aliphatic chain as compared to amphetamine's structure), literature exists to postulate that phentermine has MAO inhibitory activity [Rothman. *Synapse* **32**:141-5 (1999)].
Table 25. Reported phentermine's Ki values for MAO and its prediction on interaction with MAO.

	Phentermine's Ki for MAO	[I]/Ki	Tissue/Preparation	Reference
1	75 μM for MAO-A	0.022	Not specified	Rothman
2	85 – 88 μM for MAO-A	0.020	Rat lung, brain, and liver	Ulus
3	143 μM for MAO-A¶	0.023	Rat brain	Kilpatrick
	285 μM for MAO-B¶	0.012		
4	498 ± 60 μM for MAO-A	0.0034	Recombinant human purified MAO-A	Nandigama
	375 ± 42 μM for MAO-B	0.0045	and MAO-B	

¶IC_{50} value instead. For competitive inhibition, Ki = ½ IC50. [Rothman. *Synapse* **32**:141-5 (1999); Ulus et al. *Biochem Pharmacol* **59**:1611-21 (2000); Kilpatrick et al. *Int J Obes Relat Metab Disord* **25**:1454-8 (2001); Nandigama et al. *Biochem Pharmacol* **63**:865-9 (2002)]

To be conservative, this reviewer used the plasma phentermine concentration upon a mean daily dose of 36 mg phentermine as 1.6757 μM (250 ng/mL) [Douglas *Int J Obes* **7**:591-5 (1983)]. The [I]/Ki values are all < 0.1 in the above estimations. If the [I]/Ki value is < 0.1, the inhibition potential is remote for the cytochrome P450 system per the draft Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling Guidance. Thus, phentermine is unlikely to be an MAO inhibitor at the dosing regimen of the PHEN/TPM FDC per the published in vitro Ki values.

Topiramate's own effect on coadministered drugs' PK:
See TOPAMAX® label's Sections 7 and 12.5, Bailer et al. *Clin Pharmacokinet* **43**:763-80 (2004), and D.S. Reddy. *Expert Rev Clin Pharmacol* **3**:183–92 (2010).

2.5 General Biopharmaceutics
2.5.1 What biopharmaceutics classification system (BCS) class does phentermine and topiramate in PHEN/TPM FDC belong?
Since the topiramate portion of the PHEN/TPM FDC is not immediate-release, OCP does not consider the entire PHEN/TPM FDC as an immediate-release product. Hence, the Biopharmaceutics Classification System does not apply for this PHEN/TPM FDC product.

2.5.2 Does difference exist between the to-be-marketed phentermine and topiramate formulations and the clinically-studied phentermine and topiramate formulations? If so, has the sponsor addressed it satisfactorily?

Yes. The PHEN/TPM FDC (3.75/23, 7.5/46, and 11.25/69 mg) clinically-tested formulations contain (b) (4) whereas the corresponding to-be-marketed formulations do not. The PHEN/TPM FDC 15/92 mg clinically-tested formulation (Formulation A) is identical to the PHEN/TPM FDC 15/92 to-be-marketed formulation (Formulation B).

Study OB-109 assessed the in vivo bioequivalence (BE) between the clinically tested and to-be-marketed PHEN/TPM FDC products in 120 male and 110 female obese participants (mean BMI: 34.0 kg/m^2; range: 30.0 – 41.6 kg/m^2) in a single-dose, 6-treatment, parallel study design. Each fasted (≥ 10 hours) participant orally received either 1 of the following treatments:

- Treatment A (n = 44): Formulation B (3.75/23 mg)
- Treatment B (n = 44): Formulation A (3.75/23 mg)
- Treatment C (n = 36): Formulation B (7.5/46 mg)
- Treatment D (n = 34): Formulation A (7.5/46 mg)
- Treatment E (n = 34): Formulation B (11.25/69 mg)
- Treatment F (n = 38): Formulation A (11.25/69 mg)

Serial plasma samples were collected predose and 168 hours postdose to determine phentermine and topiramate via a validated HPLC/MS/MS bioanalytical assays.

Table 26. Summary and statistical comparisons of phentermine and topiramate PK for PHEN/TPM 3.75/23 mg

		Formulation B	**Formulation A** (b) (4)	**Formulation B vs. Formulation A**	
		Treatment A (N=44)	**Treatment B (N=44)**	**90% CI**	**% Mean Ratio[e]**
PHEN	AUC_{0-t} (ng*hr/mL)	375 (1.03)	391 (1.03)	(89.01, 103.05)	95.78
	$AUC_{0-\infty}$ (ng*hr/mL)	388 (1.03)	403 (1.03)	(89.55, 103.36)	96.21
	C_{max} (ng/mL)	11.0 (1.03)	11.2 (1.03)	(92.35, 104.48)	98.23
	t_{max} (hr)	5.0 (2.0, 9.0)	5.0 (2.0, 16)	.	.
	$t_{1/2}$ (hr)	19 ± 5.0	20 ± 5.4	.	.
	CL/F (L/hr)	9.95 ± 2.44	9.47 ± 1.79	.	.
	Vd/F (L)	265 ± 75.4	264 ± 64.3	.	.
TPM	AUC_{0-t} (ng*hr/mL)	11200 (1.04)	10600 (1.04)	(97.81, 115.26)	106.17
	$AUC_{0-\infty}$ (ng*hr/mL)	14700 (1.03)	14000 (1.03)	(97.51, 112.84)	104.89
	C_{max} (ng/mL)	129 (1.05)	121 (1.05)	(95.16, 118.81)	106.33
	t_{max} (hr)	12 (7.0, 24)	12 (6.0, 24)	.	.
	$t_{1/2}$ (hr)	82 ± 17	83 ± 17	.	.
	CL/F (L/hr)	1.60 ± 0.316	1.69 ± 0.423	.	.
	Vd/F (L)	190 ± 62.5	204 ± 68.9	.	.

Table 27. Summary and statistical comparisons of phentermine and topiramate PK for PHEN/TPM 7.5/46 mg

		Formulation B (b) (4) Treatment C (N=36)	Formulation A (b) (4) Treatment D (N=34)[h]	Formulation B vs. Formulation A 90% CI	% Mean Ratio[f]
PHEN	AUC_{0-t} (ng*hr/mL)	855 (1.04)	940 (1.04)	(83.73, 98.68)	90.90
	$AUC_{0-\infty}$ (ng*hr/mL)	867 (1.03)	955 (1.04)	(83.75, 98.36)	90.76
	C_{max} (ng/mL)	23.5 (1.03)	24.3 (1.03)	(90.20, 103.58)	96.66
	t_{max} (hr)	6.0 (2.0, 10)	6.0 (2.1, 9.0)	.	.
	$t_{1/2}$ (hr)	20 ± 4.9	20 ± 3.7	.	.
	CL/F (L/hr)	8.89 ± 2.50	7.99 ± 1.46	.	.
	Vd/F (L)[d]	252 ± 69.1	230 ± 53.1	.	.
TPM	AUC_{0-t} (ng*hr/mL)	25600 (1.04)	27600 (1.04)	(84.46, 101.54)	92.61
	$AUC_{0-\infty}$ (ng*hr/mL)	30100 (1.04)	33200 (1.04)	(83.61, 98.60)	90.80
	C_{max} (ng/mL)	362 (1.05)	396 (1.06)	(80.60, 103.39)	91.29
	t_{max} (hr)	10 (7.0, 16)	9.6 (5.0, 16)	.	.
	$t_{1/2}$ (hr)	65 ± 12	65 ± 8.0	.	.
	CL/F (L/hr)	1.56 ± 0.325	1.42 ± 0.353	.	.
	Vd/F (L)	145 ± 40.5	133 ± 41.1	.	.

Table 28. Summary and statistical comparisons of phentermine and topiramate PK for PHEN/TPM 11.25/69 mg

		Formulation B (b) (4) Treatment E (N=34)	Formulation A (b) (4) Treatment F (N=38)	Formulation B vs. Formulation A 90% CI	% Mean Ratio[g]
PHEN	AUC_{0-t} (ng*hr/mL)	1340 (1.04)	1380 (1.03)	(89.24, 104.96)	96.78
	$AUC_{0-\infty}$ (ng*hr/mL)	1350 (1.04)	1390 (1.03)	(89.40, 104.78)	96.79
	C_{max} (ng/mL)	36.1 (1.03)	36.2 (1.03)	(93.33, 106.99)	99.93
	t_{max} (hr)	6.0 (2.0, 10)	6.0 (2.0, 9.0)	.	.
	$t_{1/2}$ (hr)	19 ± 4.7	19 ± 3.8	.	.
	CL/F (L/hr)	8.49 ± 1.59	8.20 ± 1.39	.	.
	Vd/F (L)	231 ± 64.9	216 ± 43.5	.	.
TPM	AUC_{0-t} (ng*hr/mL)	42800 (1.04)	42600 (1.04)	(91.73, 110.01)	100.45
	$AUC_{0-\infty}$ (ng*hr/mL)	48000 (1.04)	47900 (1.03)	(92.32, 108.52)	100.10
	C_{max} (ng/mL)	705 (1.06)	704 (1.05)	(88.63, 113.33)	100.22
	t_{max} (hr)	9.0 (7.0, 16)	8.1 (6.0, 16)	.	.
	$t_{1/2}$ (hr)	57 ± 8.0	58 ± 7.9	.	.
	CL/F (L/hr)	1.46 ± 0.237	1.47 ± 0.274	.	.
	Vd/F (L)	121 ± 29.5	124 ± 34.4	.	.

The 90% CI for the ratios of the respective phentermine C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ as well as the topiramate C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were all within the 80 – 125 goalpost for the 3.75/23, 7.5/46, and 11.25/69 mg. Thus, the clinically tested FDCs ere bioequivalent to the to-be-marketed PHEN/TPM FDCs.

Table 29. Batch size information for the formulations used in Study OB-109.

Strength	To-be-marketed Batch size (Lot number)	Clinically-tested Batch size (Lot number)
3.75/23	(b) (4) (0912479)	(b) (4) (07056-40)
7.5/46	0912485)	(0705641)
11.25/69	0912488)	(0703796)

The batch sizes for the 7.5/46 and 11.25/69 strengths of PHEN/TPM FDC used Study OB-109 are less than (b) (4), which is the recommended batch size for in vivo bioequivalence study. These batches of size less than (b) (4) may not be an issue, since the phentermine beads and topiramate beads make up the PHEN/TPM FDC. In many cases, the same batch was used to manufacture both the clinically-tested and

to-be-marketed (reference and test) formulations for each bead type. Batch sizes range from about (b) (4) (b) (4) for phentermine beads and (b) (4) for topiramate beads.

Upon inspection, the Division of Scientific Investigations (DSI) did not issue Form FDA-483 for the clinical portion of the study but have the following inspectional findings (See Dr. Xikui Chen's DSI review in DARRTS):

1. Although the run acceptance criteria for calibration standards and quality control samples were met, two analytical runs # 2 and 31 for Phentermine were re-assayed and rejected due to improbable contaminations.
2. 170 study samples identified Unacceptable Internal Standard Response (UISR) for Topiramate were re-assayed and the data for these UISR samples were rejected.
3. Failure to follow your SOP, Laboratory Documentation, SOP numer 03.01.009 version 19, dated 30-Apr-2009. Specifically, Sciclone Maintenance Logs, LH5 SIN 550450N4507, LH2, SIN 550235N4655, in review of these logs the "Disclosed To And Understood By" section should be signed and dated within 2 business days of signature date. The disclosed signature was not signed until 8 months later, and the "Verified By Date" was signed after the Disclosed Signature. In review of LC/MS# 19 SIN 5061020B, the "disclosed To And Unders tood By" section is again signed late. Some pages are marked "late Review" Some are not.

The DSI concluded the following:

1. Data from analytical runs # 2 and 31 for Phentermine should be accepted and utilized in the bioequivalence evaluation (see discussion in 483 Item 1).
2. Data of the 170 UISR samples prior to re-assay, coded as UISR in Table 6 "summary of reassay for analytical reasons" of the bioanalytical report, should be accepted and utilized in the bioequivalence evaluation for Topiramate (see discussion in 483 Item 2).

Subsequently, OCP/DCPII requested the sponsor to respond by August 20, 2010 for the following:

- Use analytical runs #2 and 31's plasma phentermine concentration data in evaluating phentermine bioequivalence for the phentermine/topiramate fixed dose combination capsules.
- Use the data for the 170 UISR samples prior to re-assay in evaluating topiramate bioequivalence for the phentermine/topiramate fixed dose combination capsules.
- Compare the phentermine and topiramate bioequivalence results between the two recommendations above to the reported phentermine and topiramate bioequivalence results.

The sponsor responded to the request above and sent a preliminary response on August 20, 2010 followed with the submission in the Electronic Data Room on August 27, 2010.

Table 30. Statistical Comparisons of Plasma Phentermine and Topiramate Pharmacokinetic Parameters at Three Dose Levels

Pharmacokinetic Parameters[a]		Formulation B (b) (4)	Formulation A (b) (4)	Formulation B Versus Formulation A	
PHEN/TPM 3.75/23		**Treatment A (N=44)**	**Treatment B (N=44)**	**90% CI[b]**	**% Mean Ratio[b]**
PHEN	C_{max} (ng/mL)	11.0 (1.03)	11.2 (1.03)	(92.48, 104.59)	98.35
	AUC_{0-t} (ng*hr/mL)	375 (1.03)	391 (1.03)	(89.08, 103.09)	95.83
	$AUC_{0-\infty}$ (ng*hr/mL)	388 (1.03)	403 (1.03)	(89.61, 103.39)	96.25
TPM	C_{max} (ng/mL)	129 (1.05)	122 (1.05)	(94.72, 118.18)	105.80
	AUC_{0-t} (ng*hr/mL)	11200 (1.04)	10600 (1.04)	(97.89, 115.27)	106.23
	$AUC_{0-\infty}$ (ng*hr/mL)	14700 (1.03)	14000 (1.03)	(98.02, 113.36)	105.41
PHEN/TPM 7.5/46		**Treatment C (N=36)**	**Treatment D (N=34)[e]**	**90% CI[c]**	**% Mean Ratio[c]**
PHEN	C_{max} (ng/mL)	23.5 (1.03)	24.3 (1.03)	(90.30, 103.66)	96.75
	AUC_{0-t} (ng*hr/mL)	855 (1.04)	939 (1.04)	(83.84, 98.78)	91.00
	$AUC_{0-\infty}$ (ng*hr/mL)	867 (1.03)	954 (1.04)	(83.86, 98.46)	90.87
TPM	C_{max} (ng/mL)	363 (1.05)	394 (1.06)	(81.56, 104.54)	92.34
	AUC_{0-t} (ng*hr/mL)	25700 (1.04)	27600 (1.04)	(84.84, 101.90)	92.98
	$AUC_{0-\infty}$ (ng*hr/mL)	30300 (1.04)	33200 (1.04)	(83.96, 98.96)	91.15
PHEN/TPM 11.25/69		**Treatment E (N=34)**	**Treatment F (N=38)**	**90% CI[d]**	**% Mean Ratio[d]**
PHEN	C_{max} (ng/mL)	36.1 (1.03)	36.2 (1.03)	(93.19, 106.80)	99.76
	AUC_{0-t} (ng*hr/mL)	1340 (1.04)	1380 (1.03)	(89.30, 104.99)	96.83
	$AUC_{0-\infty}$ (ng*hr/mL)	1350 (1.04)	1390 (1.03)	(89.46, 104.81)	96.83
TPM	C_{max} (ng/mL)	705 (1.06)	704 (1.05)	(88.67, 113.29)	100.22
	AUC_{0-t} (ng*hr/mL)	42800 (1.04)	42600 (1.04)	(91.74, 109.94)	100.43
	$AUC_{0-\infty}$ (ng*hr/mL)	48000 (1.04)	48000 (1.03)	(92.38, 108.52)	100.13

The results of the statistical comparisons of phentermine and topiramate PK parameters Cmax, AUC0-t, and AUC0-∞ for Formulation B versus Formulation A, via plasma phentermine concentration data from analytical Batches #2 and #31 and the topiramate concentration data from the 170 previously not reported samples coded with UISR, were consistent with the results reported in the clinical study report for OB-109. Hence, the inclusion of the original bioanalysis results for phentermine and topiramate did not significantly impact the conclusion of the report.

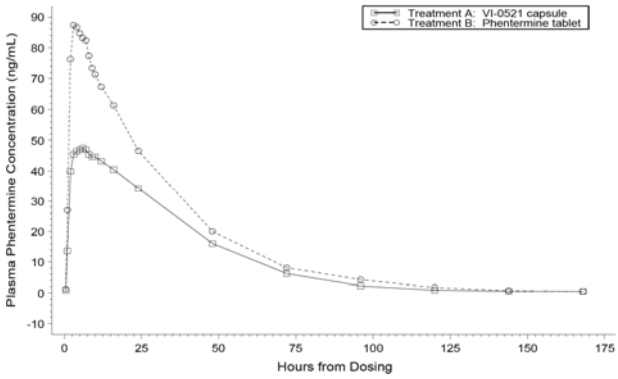
2.5.3 What is the relative bioavailability of the to-be-marketed phentermine and topiramate formulation to the marketed individual immediate release phentermine and topiramate tablets?

Study OB-110 is a randomized, open-label, parallel, single dose study to assess the relative bioavailability of to-be-marketed PHEN/TPM FDC compared to the marketed phentermine HCl tablet and topiramate tablet in 20 men and 21 women (mean BMI: 34.7 kg/m^2; range: 30.0-41.9 kg/m^2). Each fasted participant orally received the following treatments:

- Treatment A: a PHEN/TPM 15/92 mg capsule
- Treatment B: an ADIPEX-P® tablet (37.5 mg)
- Treatment C: a TOPAMAX® tablet (100 mg)

Serial plasma samples were collected predose and 168 hours postdose to determine phentermine and topiramate via validated HPLC/MS/MS bioanalytical assays.

Figure 20 (left). Mean plasma phentermine concentration-time profile. Figure 21 (right). Mean plasma topiramate concentration-time profile.



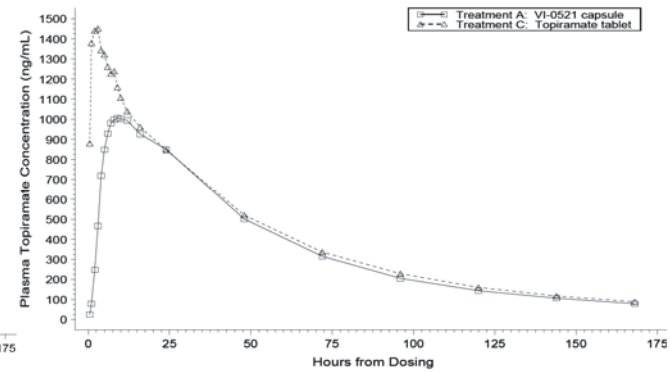


Table 31. Summary and statistical comparisons of phentermine PK.

Pharmacokinetic Parameters	PHEN/TPM 15/92 mg Treatment A (N=14)	37.5 mg ADIPEX-P® Treatment B (N=15)	Treatment A vs. Treatment B 90% CI	% Mean Ratio
C_{max} (ng/mL)	49.1 (1.04)	90.4 (1.04)	(49.21, 59.97)	54.32
AUC_{0-t} (ng*hr/mL)	1990 (1.06)	2990 (1.06)	(58.27, 76.18)	66.63
$AUC_{0-\infty}$ (ng*hr/mL)	2000 (1.06)	3000 (1.06)	(58.35, 76.28)	66.71
DN (C_{max}) (ng/mL)	98.3 (1.04)	90.4 (1.04)	98.41, 119.93)	108.64
DN (AUC_{0-t}) (ng*hr/mL)	3980 (1.06)	2990 (1.06)	116.54, 152.37)	133.25
DN ($AUC_{0-\infty}$) (ng*hr/mL)	4000 (1.06)	3000 (1.06)	116.71, 152.55)	133.43
t_{max} (hr)	6.0 (3.0, 7.0)	3.1 (3.0, 7.0)	.	.
$t_{1/2}$ (hr)	18 ± 3.7	19 ± 4.2	.	.

After dose normalization, the 90% CI of mean ratio for C_{max} was within 80% - 125%. But the 90% CIs of mean ratios for AUC_{0-t} and $AUC_{0-\infty}$ were not within 80% - 125%. The mean AUC_{0-t} and $AUC_{0-\infty}$ of phentermine for PHEN/TPM 15/92 were about 33% and 33% higher than those for ADIPEX-P® tablet (30 mg). This increase in phentermine in the presence of topiramate is consistent with that observed in Question 2.4.2.1 above. The phentermine median tmax values for PHEN/TPM 15/92 mg and ADIPEX-P® tablet were 6.0 hours and 3.1 hours.

Table 32. Summary and statistical comparisons of topiramate PK.

Pharmacokinetic Parameters	PHEN/TPM 15/92 mg Treatment A (N=14)	100 mg TOPAMAX® Treatment C (N=12)	Treatment A vs. Treatment C 90% CI	% Mean Ratio
C_{max} (ng/mL)	1020 (1.07)	1570 (1.08)	(55.06, 77.35)	65.26
AUC_{0-t} (ng*hr/mL)	61600 (1.04)	70900 (1.04)	(78.52, 96.34)	86.97
$AUC_{0-\infty}$ (ng*hr/mL)	68000 (1.04)	78900 (1.04)	(78.61, 94.46)	86.17
DN (C_{max}) (ng/mL)	1110 (1.07)	1570 (1.08)	(59.85, 84.08)	70.93
DN (AUC_{0-t}) (ng*hr/mL)	67000 (1.04)	70900 (1.04)	(85.34, 104.71)	94.53
DN ($AUC_{0-\infty}$) (ng*hr/mL)	73900 (1.04)	78900 (1.04)	(85.44, 102.68)	93.67
t_{max} (hr)	9.0 (7.0, 12)	2.0 (0.50, 3.0)	.	.
$t_{1/2}$ (hr)	54 ± 4.9	56 ± 13	.	.

The 90% CIs of mean ratios (treatment A/treatment B) for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were not within 80% - 125%. The mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of topiramate for PHEN/TPM 15/92 mg were about 65%, 87% and 86% of those for TOPAMAX® tablet (100 mg). After dose normalization, the 90% CIs of mean ratios for AUC_{0-t} and $AUC_{0-\infty}$ were within 80% - 125%. This topiramate exposure in the presence of phentermine is consistent with that observed in Question 2.4.2.1 above. But the 90% CIs of C_{max} mean ratio was not within 80% - 125%. The mean C_{max} of topiramate for phentermine/topiramate combination (15/92 mg) were about 71% of that for Topamax® tablet (100 mg). The topiramate median t_{max} values for PHEN/TPM 15/92 mg and TOPAMAX® tablet were 9.0 hours and 2.0 hours, respectively. The topiramate DN (AUC_{0-t}) and DN ($AUC_{0-\infty}$) showed that the topiramate exposure upon PHEN/TPM 15/92 mg administration is equivalent to that upon the 100 mg TOPAMAX® administration after dose adjustment.

2.5.4 How do the sponsor's phentermine alone capsule and topiramate alone capsule used in Study OB-301 compare to the marketed individual immediate release phentermine and topiramate tablets?

This question helps answer whether the sponsor formulated comparable phentermine alone capsule and topiramate alone capsule to the marketed products so as to show the superiority of their PHEN/TPM FDC products in the factorial design study (OB-301) since the sponsor did not use the marketed ADIPEX-P® and TOPAMAX® in Study OB-301. See Studies OB-110 and OB-103's details in Questions 2.5.3 and 2.2.1 above.

Table 33. Comparison of the marketed ADIPEX-P® and TOPAMAX® versus the sponsor's phentermine alone capsule and topiramate alone capsule.

	Study OB-110		Study OB-103	
¶	**ADIPEX-P® or TOPAMAX®***	15/92	15/92	**15 or 92**
Phentermine				
C_{max}, ng/mL	**45.2**	49.1	47.4	**41.9**
AUC_{0-t}, ng*hr/mL	**1495**	1990	2057.6	**1447.4**
$AUC_{0-\infty}$, ng*hr/mL	**1500**	2000	2089.1	**1472.8**
Topiramate				
C_{max}, ng/mL	**1444**	1020	1008.0	**991.9**
AUC_{0-t}, ng*hr/mL	**65228**	61600	65385.5	**62373.3**
$AUC_{0-\infty}$, ng*hr/mL	**72588**	68000	73927.7	**70036.4**

¶Least square means; *Dose normalized to 15 & 92. 30 mg phentermine and 100 mg topiramate

Although this is a cross-study comparison, both studies have the PHEN/TPM FDC 15/92 mg as the common reference. Besides phentermine C_{max}, phentermine exposure is comparable between ADIPEX-P® and the sponsor's phentermine alone capsule. Besides topiramate C_{max}, topiramate exposure is comparable between TOPAMAX® and the sponsor's topiramate alone capsule.

2.6 Bioanalytical

2.6.1 Are the bioanalytical methods properly validated?

Table 34. Validation for phentermine and topiramate's bioanalytical assays.

Study ID	Analyte	Analytical Parameter	Method (Validation Report ID#)
OB-101C OB-102 OB-103 OB-105 OB-106 OB-202 DM-230 OB-301 OB-302 OB-303	**Phentermine**	**Linear Range**: 0.500 ng/mL – 500 ng/mL **LLOQ**: 0.500 ng/mL **Intra-batch Precision** (C.V.%): 5.7 to 11.6% for 0.500 ng/mL (LLOQ); 2.6 to 9.4% for 1.50 ng/mL; 1.9 to 3.1% for 75.0 ng/mL; 1.6 to 3.1% for 375 ng/mL; **Intra-batch Accuracy** (% theoretical): -3.2 to 6.8% for 0.500 ng/mL (LLOQ); 2.0 to 6.0% for 1.50 ng/mL; -0.1 to 2.8% for 75.0 ng/mL; -2.7 to -1.1% for 375 ng/mL; **Inter-batch Precision** (C.V.%): 9.7% for 0.500 ng/mL; 6.2% for 1.50 ng/mL; 2.7% for 75.0 ng/mL; 2.4% for 375 ng/mL. **Inter-batch Accuracy** (% theoretical): 2.4% for 0.500 ng/mL; 4.0% for 1.50 ng/mL; 1.6% for 75.0 ng/mL; -1.9% for 375 ng/mL. **Recovery:** 60.6% for 1.50 ng/mL; 62.3% for 75.0 ng/mL; 61.7% for 375 ng/mL.	HPLC MS/MS (b) (4) Phentermine and the internal standard, phentermine-d_{13}, were extracted from human plasma by SPE. After elution followed by dilution, the sample was analyzed using HPLC with MS/MS detection. [**Ref:5.3.1.4.3**]
	Topiramate	**Linear Range**: 0.02 µg/mL – 20 µg/mL **LLOQ**: 0.0200 µg/mL **Intra-batch Precision** (C.V.%): 6.3 to 9.5% for 0.0200 µg/mL (LLOQ); 1.7 to 3.1% for 0.0600 µg/mL; 1.3 to 1.7% for 5.00 µg/mL; 1.5 to 2.0% for 16.0 µg/mL; **Intra-batch Accuracy** (% theoretical): -7.5 to -4.0% for 0.0200 µg/mL (LLOQ); -7.3 to -4.0% for 0.0600 µg/mL; -2.2 to 7.4% for 5.00 µg/mL; -3.7 to 3.1% for 16.0 µg/mL; **Inter-batch Precision** (C.V.%): 8.1% for 0.0200 µg/mL; 2.7% for 0.0600 µg/mL; 4.2% for 5.00 µg/mL; 3.5% for 16.0 µg/mL. **Inter-batch Accuracy** (% theoretical): -6.0% for 0.0200 µg/mL; -5.2% for 0.0600 µg/mL; 2.0% for 5.00 µg/mL; -1.2% for 16.0 µg/mL. **Recovery:** 83.7% for 0.0600 µg/mL; 86.5% for 5.00 µg/mL; 81.5% for 16.0 µg/mL.	HPLC MS/MS (b) (4) Topiramate and the internal standard, topiramate-d_{12}, were extracted from human plasma by protein precipitation. The supernatant was transferred, diluted, and then analyzed using HPLC with MS/MS detection. [**Ref:5.3.1.4.1**]

HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric detection; SPE = solid phase extraction.

Table 35. Validation for phentermine and topiramate's bioanalytical assays.

Study ID	Drug	Analytical Parameter	Method (Validation Report ID#)
OB-107 OB-108 OB-109 OB-110 OB-118	**Phentermine**	**Linear Range**: 0.250 ng/mL – 50 ng/mL **LLOQ**: 0.250 ng/mL **Intra-batch Precision** (C.V.%): 3.4 to 12.0% for 0.250 ng/mL (LLOQ); 3.2 to 6.8% for 0.750 ng/mL; 2.1 to 3.3% for 4.00 ng/mL; 1.2 to 3.1% for 37.5 ng/mL; **Intra-batch Accuracy** (% theoretical): 0.0 to 8.0% for 0.250 ng/mL (LLOQ); -0.9 to 0.0% for 0.750 ng/mL; -0.5 to 3.0% for 4.00 ng/mL; -1.9 to 1.1% for 37.5 ng/mL; **Inter-batch Precision** (C.V.%): 8.4% for 0.25 ng/mL; 5.3% for 0.75 ng/mL; 2.9% for 4.00 ng/mL; 2.5% for 37.5 ng/mL. **Inter-batch Accuracy** (% theoretical): 5.2% for 0.25 ng/mL; -0.4% for 0.75ng/mL; 1.3% for 4.00 ng/mL; -0.3% for 37.5ng/mL. **Recovery:** 92% for 0.750 ng/mL; 85% for 4.00 ng/mL; 88% for 37.5 ng/mL.	HPLC MS/MS (b) (4) Phentermine and the internal standard, phentermine-d_{13}, were extracted from human plasma by liquid-liquid extraction. The extracted samples were analyzed by an using HPLC with MS/MS detection **[Ref:5.3.1.4.4]**
	Topiramate	**Linear Range**: 10 ng/mL – 1000 ng/mL **LLOQ**: 10 ng/mL **Intra-batch Precision** (C.V.%): 8.9 to 14.2% for 10.0 ng/mL (LLOQ); 4.6 to 7.3% for 30 ng/mL; 1.9 to 4.2% for 350 ng/mL; 3.6 to 6.6% for 750 ng/mL; **Intra-batch Accuracy** (% theoretical): -0.7 to 2.0% for 10 ng/mL; -11.3 to -6.0% for 30ng/mL; -7.0 to -3.5% for 200 ng/mL; -8.7 to -4.8% for 750 ng/mL; **Inter-batch Precision** (C.V.%): 10.8% for 10 ng/mL; 6.1% for 30 ng/mL; 3.2% for 200 ng/mL; 5.2% for 750 ng/mL. **Inter-batch Accuracy** (% theoretical): 1% for 10 ng/mL; -8.3% for 30 ng/mL; -5.0% for 200 ng/mL; -7.3% for 750 ng/mL. **Recovery:** 88% over the range of 10.0 - 1000 ng/mL.	LC MS/MS (b) (4) Topiramate and the internal standard, topiramate-d_{12}, were extracted from human plasma by protein precipitation. The supernatant was transferred, diluted, and then analyzed using HPLC with MS/MS detection. ([**Ref:5.3.1.4.2**])

HPLC = high-performance liquid chromatography; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometric detection; SPE = solid phase extraction.

Both HPLC/MS/MS bioanalytical assays for phentermine and topiramate in plasma are acceptable with reasonable precision and accuracy.

Table 36. Summary of bioanalytical methods validations for drug interaction studies.

	Sitagliptin	Metformin	Topiramate	Ethinyl estradiol	Norethindrone
Study	OB-107	OB-107	OB-107	OB-108	OB-108
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix*	Plasma	Plasma	Semen	Plasma	Plasma
Sample size, mL	0.1	0.05		0.5	1
LOQ, ng/mL	2.5	30.0	10	0.002	0.05
Linear range, ng/mL	2.5 – 500	30.0 - 6000	10 – 1000	0.002 – 0.5	0.05 – 10
Accuracy, %					
Intrabatch	-5.6 – 4.9	-3.3 – 8.7		-2.2 – 10.5	-3.2 – 3.6
Interbatch	-2.4 – 3.1	-1.3 – 6.1	2.7 – 4.3	0.4 – 7	-1.7 – 0.9
Precision, %					
Intrabatch	2.2 – 6.0	1.2 – 5.3		1.1 – 6.1	0.5 – 3
Interbatch	2.9 – 5.5	3.1 – 4.8	≤ 3.6	3.6 – 5.6	2.6 – 3.4

LC/MS/MS = liquid chromatography and tandem mass spectrometry; *Plasma = EDTAed plasma

All of the bioanalytical methods validations for the in vivo drug interaction studies are acceptable with reasonable precision and accuracy.

Labeling Comments

This review will not discuss labeling comments yet since the approvability of NDA 22-580 is questionable after the public Advisory Committee Meeting on July 15, 2010 and internal Regulatory Briefing on August 20, 2010.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

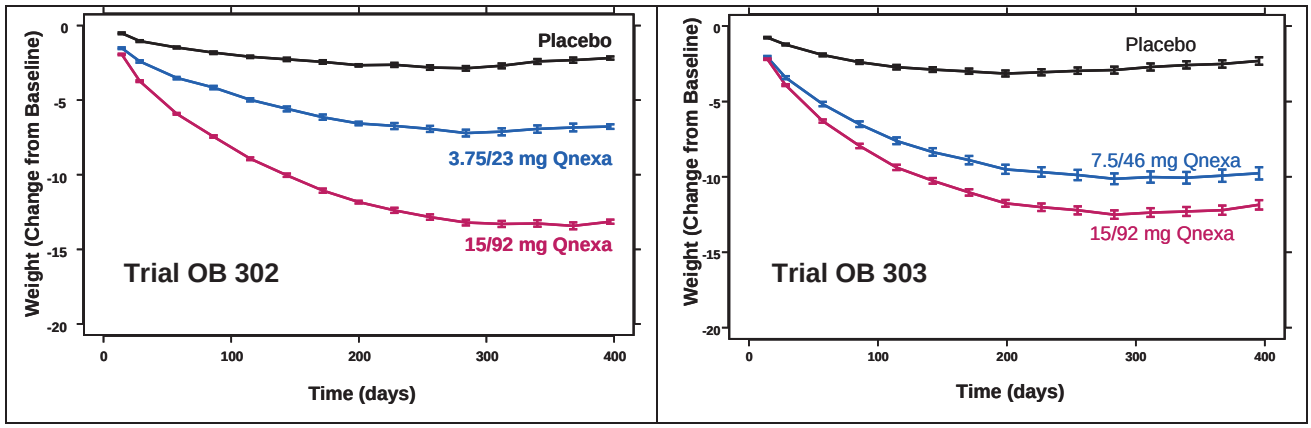
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there evidence of dose-response for effectiveness?

Yes, there is a dose-response for weight loss in the pivotal phase 3 clinical trials. Figure 1 shows an increasing reduction in weight loss between placebo and the low (3.75/23 mg), middle (7.5/46 mg), and high (15/92 mg) Qnexa dose groups. This observation supports the effectiveness of Qnexa for weight loss at the proposed dosing regimen. The recommended dose is 7.5/46 mg QD with an increase to 15/92 mg QD if weight loss goals are not achieved by 3–4 months.

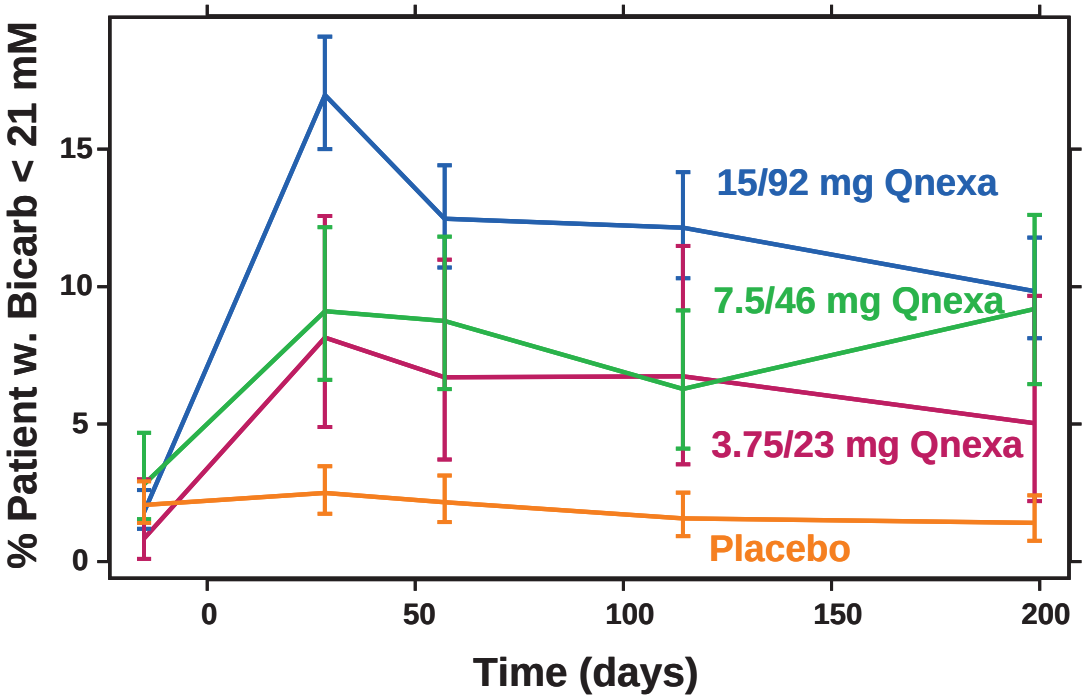
Figure 1. Qnexa exhibits a clear dose-response relationship for weight loss. Results are presented as mean±SEM for weight change from baseline from the intent-to-treat population excluding LOCF.



1.1.2 Is there evidence of a dose-response relationship for safety?

Yes, there is a dose-response for reduction in serum bicarbonate to <21 mM as shown in Figure 2. Serum bicarbonate is generally reduced to <21 mM in patients with acidic blood pH. Metabolic acidosis has been reported with high doses of topiramate (Topamax 400 mg/day) during treatment of epilepsy and two cases were observed with Qnexa (one each at the 7.5/46 mg and 15/92 mg dose). Dose adjustments or discontinuations are proposed for patients experiencing severe symptoms of metabolic acidosis.

Figure 2. There is dose-response for reduction in bicarbonate to <21 mM. The figure shows the time course for the percentage of patients with bicarbonate of <21 mM. Results are presented as percent of patients ± the 95% confidence interval for binomial probabilities.



Dose-response relationships were also identified for psychiatric (anxiety, depression, and insomnia), cognitive (memory impairment, cognitive disorders, and disturbance in attention), and psychomotor adverse events (asthenia, dizziness, dysgeusia, feeling jittery, hypoaesthesia, palpitations, paraesthesia, and blurred vision) in the phase 3 clinical trials. These adverse events are expected from this use of topiramate or phentermine.

1.1.3 Should patients with mild renal impairment receive high dose Qnexa (15/92 mg)?

Yes, patients with mild renal impairment may be titrated to the 15/92 mg dose. A comparison of both phentermine and topiramate exposures (AUC values) in normal, mild, moderate, and severe patients were made using the population PK model (Table 1). Using the population PK model, mean AUC values in patients with mild renal impairment increased 33–35% and 21–22% for phentermine and topiramate, respectively. These increases do not exceed the degree of between subject variability for both phentermine (33%) and topiramate (27%) clearance. Based on these data, we recommend no change in the proposed dosing for patients with mild renal impairment.

The sponsor has proposed the dose for patients with moderate and severe renal impairment not exceed 7.5/46 mg. This is acceptable.

Table 1. Phentermine and Topiramate AUC values are shown for healthy subjects and subjects with reduced renal function at different Qnexa doses.

Degree of Renal Impairment	Creatinine Clearance (mL/min)	Phentermine AUC (μg•hr/L) by Qnexa Dose			
		3.75/23 mg	7.5/46 mg	11.25/69 mg	15/92 mg
Normal	80-125	0.42-0.55	0.83-1.11	1.25-1.66	1.66-2.22
Mild	50-80	0.55-0.75	1.11-1.50	1.66-2.25	2.22-3.00
Moderate	30-50	0.75-1.04	1.50-2.09	2.25-3.13	3.00-4.17
Severe	<30	>1.04	>2.09	>3.13	>4.17

Degree of Renal Impairment	Creatinine Clearance (mL/min)	Topiramate AUC (μg•hr/L) by Qnexa Dose			
		3.75/23 mg	7.5/46 mg	11.25/69 mg	15/92 mg
Normal	80-125	3.15-3.82	6.30-7.63	9.45-11.45	12.6-15.3
Mild	50-80	3.82-4.67	7.63-9.34	11.45-14.01	15.3-18.7
Moderate	30-50	4.67-5.82	9.34-11.63	14.01-17.45	18.7-23.3
Severe	<30	>5.82	>11.63	>17.45	>23.3

1.1.4 Are the labeling statements derived from the population pharmacokinetics of Phentermine and Topiramate acceptable?

Yes, the conclusions made in the label based on the population PK model are acceptable. Only creatinine clearance and body weight were covariates for clearance (CL) and volume of distribution (Vd), respectively. Between subject variability for clearance was estimated to be 33% and 27% for phentermine and topiramate.

Drug interactions with concurrent background therapies of metformin, statins, sulfonylureas, SSRIs or antihypertensives were shown not to alter phentermine or topiramate clearance significantly. Concurrent Qnexa administration with thiazolidinediones (TZDs) increased phentermine and topiramate clearance by 7 and 36 percent. Diabetes status, race, and gender did not significantly affect clearance of either Qnexa component.

No dose-adjustments are needed for the studied concomitant background therapies, disease status, race, gender, body-mass index (BMI), or age.

1.2 Recommendations

The office of clinical pharmacology division of pharmacometrics has reviewed this application and found the Qnexa NDA acceptable.

1.3 Label Statements

No modifications to the sponsor's proposed label are required from a Pharmacometric perspective.

2 PERTINENT REGULATORY BACKGROUND

The active components of VI-0521 are phentermine hydrochloride and topiramate. Phentermine hydrochloride was approved by the FDA in 1959 as an appetite suppressant. Topiramate was approved in 1996 for the treatment of seizures in adults and in 2004 for the prevention of migraine headaches. Phentermine hydrochloride is available in the United States under the tradename Adipex-P® and the generic name of phentermine hydrochloride in oral capsule and tablet forms in multiple strengths. Topiramate is available in the United States under the tradename Topamax® and the generic name of topiramate in oral capsule and tablet forms in multiple strengths.

The NDA for Qnexa is submitted as a 505(b)(2) application and relies in part on the FDA's previous determination of safety for the approved phentermine and topiramate products. This NDA describes the clinical development program to support the efficacy and safety of Qnexa for the treatment of obesity.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Analysis 1: Identifying the Structural Model

3.1.1 Clinical Data

Study OB-102: This was an open-label, parallel-design, four-treatment study conducted in non-comorbid obese adults with a BMI between 30 and 42 kg/m^2. Each treatment included 16 subjects and consisted of a single-dose and multiple-dose period. For each treatment, the single and multiple-dose periods were separated by 5 days of washout. Each multiple dose treatment was initiated by co-administered daily doses of 25 mg of topiramate and of 7.5 mg of phentermine for three days, followed by increments of 25 mg topiramate and of 7.5 mg phentermine every 3 days until the final dose. Modified release formulations of topiramate and phentermine were also compared to commercial topiramate and phentermine formulations (Topamax® and Apidex-P®, respectively). Trough samples were collected on Days 17, 18, 19 of the multiple-dose period for the steady-state assessment. Serial blood samples were collected on Day 1 of the single-dose period and Day 21 of the multiple-dose period. On those days, subjects were fasted for at least 10 hours overnight prior to dose and for 4 hours after drug administrations.

Study OB-103: This was an open-label, single-dose, 4-treatment, parallel-design study. The primary objectives of Study OB-103 were to assess the effect of food on the bioavailability of a combination formulation of topiramate and phentermine (VI-0521) and to compare the relative bioavailability of each individual component (i.e., topiramate and phentermine) of the combination product versus the final formulation, VI-0521. This study was designed to investigate whether the synergistic effects on weight loss observed in a Phase II trial was due to a pharmacokinetic interaction between topiramate and phentermine in the combination product VI-0521.

3.1.2 Methodology

Population PK analysis of topiramate and phentermine was performed using non-linear mixed-effect modeling (NONMEM). In a first step, a population PK analysis assessing the PK of topiramate and phentermine following co-administration of both products was performed (Study OB-102). In a second step, the PK of topiramate and phentermine administered alone (Study OB-103) was evaluated using a similar structural model as for Study OB-102. Various structural models (1–2-compartment) and absorption processes (first-order or zero-order absorption rate, presence or absence of lag time) were evaluated to characterize the pharmacokinetics of phentermine and topiramate. Parameters were estimated using the first-order conditional estimation (FOCE) method with interaction. The model evaluation and selection were based on pertinent graphical representations of goodness-of-fit (e.g. fitted and observed plasma concentrations versus time, observations versus individual or population predictions, and residuals versus time) and based on the minimization of -2 x Log (Likelihood), which was presented as the minimum values of the objective functions (MOF).

The effect of covariates (e.g., age, sex, weight and renal function) on PK parameters of each model was assessed by a stepwise forward additive (p-value ≤ 0.05) and a backward elimination (p value ≤ 0.001) approach using NONMEM simulations. The inclusion of continuous covariates in the population PK model was tested using power function on the systemic PK parameters (i.e.,

CL/F and V/F). The contributions of creatinine clearance calculated by the Cockcroft-Gault equation for four different scenarios (Scenario 1: body weight and serum creatinine measured at baseline, Scenario 2: ideal body weight and serum creatinine measured at baseline, Scenario 3: body weight and serum creatinine measured at the end of study, and Scenario 4: ideal body weight and serum creatinine measured at the end of study), weight, age, and sex were evaluated on the ability of the model to describe the observed plasma concentration data of phentermine and of topiramate.

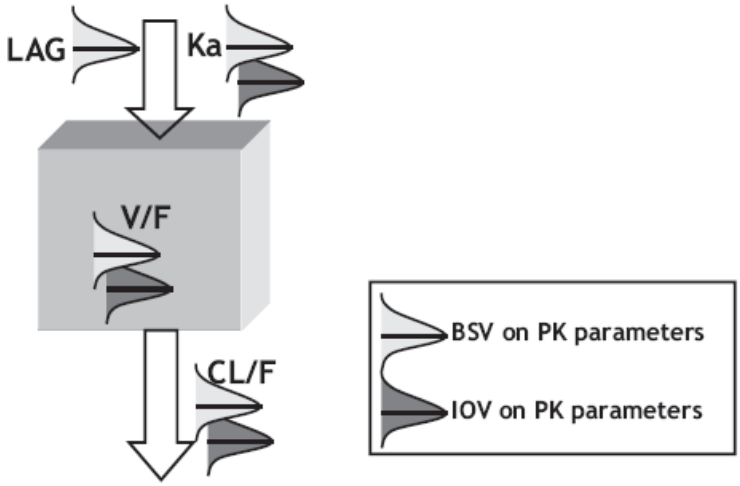
Population PK models of phentermine and topiramate were tested for stability by nonparametric bootstrap resampling technique. The bootstrap technique involved resampling from the original data and each individual subject as a sampling unit. A minimum of 1500 replicates of the data were generated by bootstrap for NONMEM analysis to obtain the median and 95% percentile of the fixed-effect and random-effect parameters.

3.1.3 Results

3.1.3.1 Population PK Analysis of Phentermine

PK Analysis of Phentermine Co-administered with Topiramate (Study OB-102): Following co-administration of phentermine and topiramate (either as a fixed-dose or as the separate formulations), plasma concentrations of phentermine were best modeled by a 1-compartment model with a first-order rate of absorption (Ka) and a lag-time (LAG). No formulation effect was captured during the model discrimination process suggesting that the various formulations of topiramate tested (modified-released capsules formulation and Topamax®) did not affect the absorption kinetics of phentermine. Inter-occasion variability (IOV) was then included for Ka, V/F and CL/F to explain differences between occasions (i.e., weeks). A schematic representation of the structural PK model for phentermine is presented in Figure 3.

Figure 3. Structural Schematic for Phentermine Population PK Model.

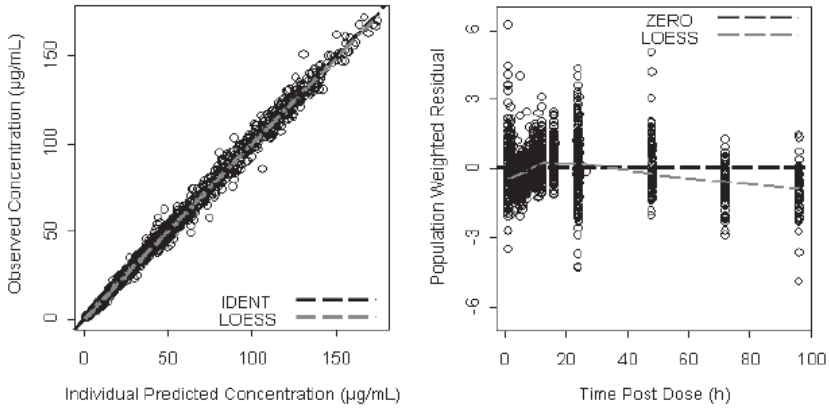


(Source: Sponsor's Population PK Report 1, Page 11)

Creatinine clearance (CrCL, calculated from the Cockcroft-Gault equation with body weight and serum creatinine measured at the end of study) and body weight (WT) were identified as statistically significant covariates explaining the variability of CL/F and V/F of phentermine,

respectively. The quality of fit of the final population PK model of phentermine is presented in Figure 4.

Figure 4. Phentermine Population PK Model Goodness of Fit Plots



(Source: Sponsor's Population PK Report 1, Page 11)

Overall, individual predicted concentrations of phentermine values were very well fitted with the final population PK model. High and low concentration values well distributed around the line of identity and weighted residuals were homogeneously distributed around zero.

Results of the final population PK analysis of phentermine from study OB-102 are presented in Table 2.

Table 2. Phentermine Population PK Parameter Estimates for Study OB-102

Population PK Parameters of Phentermine (Study OB-102)	Geometric Mean	BSV (%)	IOV (%)
Ka (1/h)	0.956	24.8%	45.3%
LAG (h)	0.508	34.1%	0, Fixed
CL/F (L/h)	$8.79 \times \left(\frac{CRCL}{120}\right)^{0.645}$	16.5%	17.6%
V/F (L)	$348 \times \left(\frac{WT}{105}\right)^{0.878}$	9.37%	16.5%

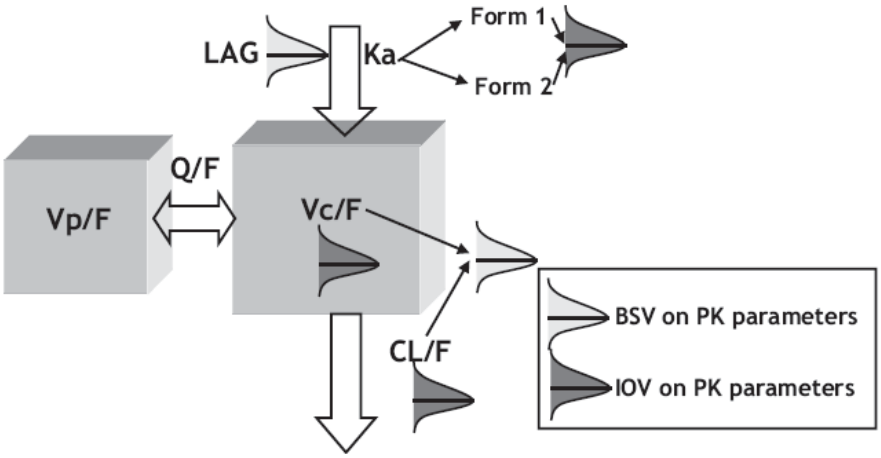
(Source: Sponsor's Population PK Report 1, page 12)

PK Analysis of Phentermine Administered Alone (Study OB-103): The oral clearance (CL/F) and volume of distribution (V/F) of phentermine administered alone were 12.8 L/h and 420 L, respectively. Overall, the CL/F of phentermine co-administered with topiramate was 31% lower than that observed when administered alone (*i.e.*, 8.79 vs. 12.8 L/h, respectively). As a result, the steady state AUC of phentermine in obese patients receiving concomitant treatments of phentermine and topiramate are expected to be approximately 31% higher than those receiving phentermine alone. The final PK models were used to predict peak concentrations under steady state conditions ($C_{max,ss}$) for a daily dose of 15 mg of phentermine. For phentermine alone, predicted $C_{max,ss}$ was 79.3 ng/mL whereas for phentermine co-administered with topiramate, the predicted $C_{max,ss}$ was 108 ng/mL.

3.1.3.2 Population PK Analysis of Topiramate

PK Analysis of Topiramate Co-administered with Phentermine (Study OB-102): Following co-administration of topiramate and phentermine, a 2-compartment model with a first-order rate of absorption and lag-time best fitted the concentration-time profiles of topiramate. A formulation-specific rate of absorption described the absorption processes of the modified-release capsules formulation versus Topamax® tablet adequately. A schematic representation of the structural PK model is presented in Figure 5.

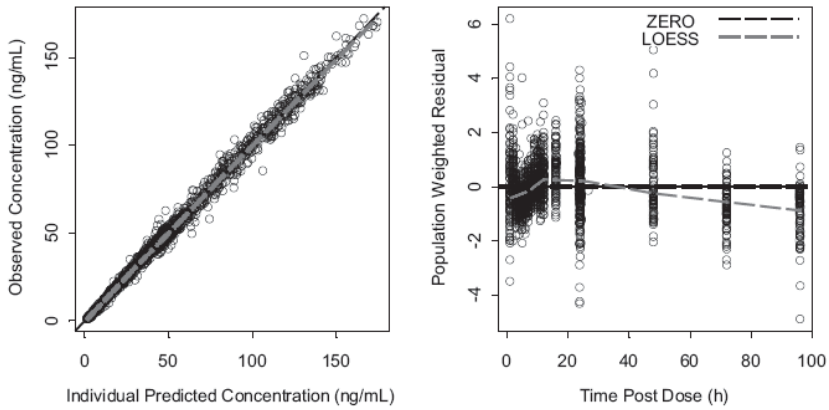
Figure 5 Structural Schematic of Topiramate Population PK Model



(Source: Sponsor's Population PK Report 1, Page 13)

Similar to phentermine, creatinine clearance (calculated from ideal body weight and serum creatinine at the end of the study) and body weight were identified as statistically significant covariates explaining the variability of CL/F and V/F of topiramate, respectively. The quality of fit of the final population PK model for topiramate is presented in Figure 6.

Figure 6. Topiramate Population PK Model Goodness of Fit Plots



(Source: Sponsor's Population PK Report 1, Page 13)

Individual predicted concentrations of topiramate were very well fitted with the final population PK model, with high and low concentration values well distributed around the line of identity, and an homogeneous distribution of weighted residuals around zero. Results of the final population PK analysis for topiramate from study OB-102 are presented in Table 3.

Table 3. Topiramate Population PK Parameter Estimates for Study OB-102

Population PK Parameters of Topiramate (Study OB-102)	Geometric Mean	BSV (%)	IOV (%)
Ka (1/h)	0.404 for Modified-Release 4.45 for Immediate-Release	0, Fixed	45.7%
LAG (h)	0.548	29.8%	0, Fixed
CL/F (L/h)	$1.17 \times \left(\frac{CRCL}{120}\right)^{0.43}$	16.2%	18.2%
Vc/F (L)	$50.8 \times \left(\frac{WT}{105}\right)^{1.17}$	13.3%	30.5%
Q/F (L/h)	2.72	0, Fixed	0, Fixed
Vp/F (L)	13.1	0, Fixed	0, Fixed

(Source: Sponsor's Population PK Report 1, Page 13)

PK Analysis of Topiramate Administered Alone (Study OB-103): The pharmacokinetics of topiramate administered alone under fasting condition was evaluated using the above population PK model. The apparent clearance (CL/F) of topiramate in men and women derived with the population PK model (1.48 and 1.26 L/h, respectively, corresponding to 24.7 and 21.0 mL/min) were within the range reported in literature (20-30 mL/min).

Overall, the mean population clearance of topiramate co-administered with phentermine in obese subjects was approximately 15% lower than the overall mean clearance (men and women combined) when topiramate was administered alone. As a result, the steady state AUC of topiramate in obese subjects receiving concomitant treatments of topiramate and phentermine is likely to be approximately 15% higher than those receiving topiramate alone, respectively. The final PK models were used to predict peak concentrations under steady state conditions ($C_{max,ss}$) for a daily dose of 92 mg of topiramate. For topiramate alone, the predicted $C_{max,ss}$ was 2.86 µg/L whereas for topiramate co-administered with phentermine, the predicted $C_{max,ss}$ was 3.63 µg/L (using a Ka of 0.404 h-1).

Concentration-time profiles of phentermine and topiramate following oral administration of Qnexa capsule under fasting conditions were used as an external dataset to validate the population PK model. A Bayesian analysis was performed on individual concentrations of phentermine and topiramate collected in study OB-103, and the resulting PK parameters were compared to those calculated using noncompartmental methods. Mean and individual plasma concentrations of phentermine and topiramate from study OB-103 were very well fitted with the structural PK model. Similarly, individual predicted $C_{max,ss}$ and AUC0-t values were very consistent with those derived with noncompartmental methods. These results suggest that the population PK model adequately described the concentration-time data of phentermine and topiramate for the final Qnexa capsule formulation used in OB-103. This provides sufficient evidence that the VIVUS phentermine and topiramate formulations used in OB-102 and OB-103 were equivalent. More importantly, this validates the use of the current population PK model to assess the exposure of phentermine and topiramate using Bayesian methods in phase 2 and 3 studies where the final Qnexa capsule formulation was used.

3.2 Population PK Analysis 2: Refining the Covariate Model

In the first part of the Population PK analysis covariate analyses were performed during the structural model development of topiramate and phentermine. During the second part of the population PK analysis, the effects of specific covariates on PK parameters were reevaluated due to the larger number of patients available. Covariate analyses were performed using visual inspection in order to identify relevant covariates. The following potential covariates were included: BMI, sex, race (Caucasian, Asian, Black or other), renal function (creatinine clearance as continuous covariates and renal impairment as categorical covariates), age, concomitant administration of drugs (statins, anti-hypertensives, anti-psychotics, SSRIs, metformin, SFU and TZD) and diabetic status. The sponsor's modeling effort is designed to determine exposure values in obese patients (diabetic and non-diabetic) based on sparse samples collected in patients from Phase III studies. Additionally the sponsor uses the modeling results to make claims regarding drug interaction of other agents on phentermine or topiramate PK in the Qnexa label.

3.2.1 Clinical Data

Data from the following Phase II and III studies were used for PK analyses:

- **Protocol OB-202:** *"A Phase II, Randomized, Double-Blind, Parallel-Design Study Comparing Efficacy and Safety of Qnexa to Placebo in the Glycemic Management of Obese Diabetic Adults"*
- **Protocol DM-230:** *"A Randomized, Double Blind Multicenter Study to Evaluate the Long- Term Safety and Efficacy of Qnexa Relative to Placebo in Providing and Maintaining Glycemic Control in Type 2 Diabetic Adults"*
- **Protocol OB-301:** *"A Phase III, Randomized, Double-Blind, Parallel-Design Study Comparing Multiple Doses of Qnexa to Placebo and their Single-Agent Phentermine and Topiramate Constituents for the Treatment of Obesity in Adults"*
- **Protocol OB-302:** *"A Phase III Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Determine the Safety and Efficacy of Qnexa in the Treatment of Obesity in an Adult Population with BMI > 35"*
- **Protocol OB-303:** *"A Phase III Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Determine the Safety and Efficacy of Qnexa in the Treatment of Obesity in Adults with Obesity-Related Co-Morbid Conditions"*

Descriptive statistics of demographic data of subjects used for the population PK analysis are summarized in Table 4.

Table 4. Descriptive Statistics for the Entire Population PK 2 Analysis Database

Descriptive Statistics	Age (years)	Baseline Weight (kg)	Height (cm)	Baseline BMI (kg/m^2)	Creatinine Clearance (mL/min)
N	4708	4708	4707	4707	4707
Mean	47.9	106	167	37.9	81.5
SD	11.6	19.5	9.36	5.56	20.5
Median	48.8	104	166	37.4	79.8
Min	18.1	57.5	127	21.3	32.1
Max	71.0	217	201	78.8	198
CV%	24.3	18.4	5.61	14.7	25.2

(Source: Sponsor's Population PK Report 2, Page 8)

Overall, demographic data of subjects randomized to active and placebo treatments were normally distributed. The quartiles of the baseline weight were similar for subjects in active and placebo treatments (i.e., $Q_1 \approx$ 92 kg, $Q_2 \approx$ 104 kg and $Q_3 \approx$ 117 kg). Approximately 5% of subjects had a baseline BMI lower than 30 kg/m^2, 63% between 32 and 40 kg/m^2, 32% higher than 40 kg/m^2. The majority of subjects were female (~75%) and were uniformly distributed throughout the placebo and active treatments. Caucasian subjects represented the most abundant race in the current population followed by Black. The proportion of diabetic subjects was slightly higher in the placebo group with a prevalence of 15.3% compared to 11.2% in the active treatment group.

3.2.2 Methodology

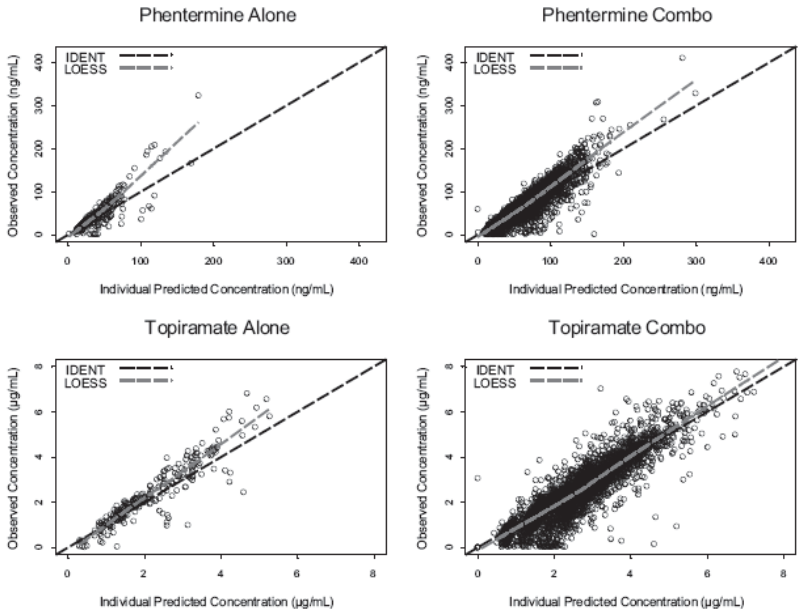
Data Handling: The final population PK analysis was performed using actual dosing information for almost all patients during the active treatment period.

Population PK Analysis-Bayesian Analysis: Population PK models previously described in 3.1 were used to perform a Bayesian analysis of sparse samples collected in Phase II and III studies. The robustness of population PK models to fit sparse samples was validated using clinical trial simulations. The current sparse sampling strategy in Phase II and III studies was expected to result in a precision within 10% of that observed for a rich sampling strategy. The population PK models previously developed were therefore used to derive individual PK parameters of phentermine and topiramate based on sparse sampling.

3.2.3 Results

PK parameters for each subject were derived by fitting nonlinear mixed-effects models on sparse concentration data of topiramate and phentermine. Individual predicted concentrations versus observed concentrations for each drug administered as monotherapy or combination therapies are presented in Figure 7.

Figure 7. Goodness of Fit Plots for Population PK Analyses of Phentermine and Topiramate.



(Source: Sponsor's Population PK Report 2, Page 10)

Overall, the population PK models adequately fitted the sparse concentrations collected for each subject and provided a good estimation of individual clearance values of phentermine and topiramate.

Descriptive statistics on PK parameters of phentermine and topiramate are presented in Table 5 and Table 6.

Table 5. Descriptive Statistics for Phentermine PK Parameters.

Dose Regimen	Descriptive Statistics	Phentermine Administered In Combination Product (Qnexa)		Phentermine Administered Alone	
		CL/F (L/h)	V/F (L)	CL/F (L/h)	V/F (L)
LOW PHEN/TPM 3.75/23 mg or PHEN 3.75 mg	N	288	288	100*	100*
	Geometric Mean	7.20	367	8.22	247
	Geometric CV (%)	34.9	18.7	64.1	159
MID PHEN/TPM 7.5/46 mg or PHEN 7.5 mg	N	815	815	72	72
	Geometric Mean	6.55	314	9.20	279
	Geometric CV (%)	30.7	20.5	38.7	47.6
FULL PHEN/TPM 15/92 mg or PHEN 15 mg	N	2379	2379	73	73
	Geometric Mean	6.58	316	7.46	215
	Geometric CV (%)	33.2	21.3	43.6	58.7

CL/F= Apparent clearance for phentermine; CV= Coefficient of variation; PHEN: immediate release phentermine beads; TPM: modified release topiramate beads; V/F= apparent volume of distribution for phentermine.
* Descriptive statistics for the low dose level of phentermine administered alone were derived from simulations using the Population PK model with 100 patients randomly selected in the PK/PD population.
(Source: Sponsor's Population PK Report 2, Page 11)

Table 6. Descriptive Statistics for Topiramate PK Parameters.

Dose Regimen	Descriptive Statistics	Topiramate Administered In Combination Product (Qnexa)		Topiramate Administered Alone	
		CL/F (L/h)	Vc/F (L)	CL/F (L/h)	Vc/F (L)
LOW PHEN/TPM 3.75/23 mg or TPM 23 mg	N	293	293	100*	100*
	Geometric Mean	1.00	54.2	1.29	26.1
	Geometric CV (%)	13.0	22.3	30.3	633
MID PHEN/TPM 7.5/46 mg or TPM 46 mg	N	839	839	68	68
	Geometric Mean	0.94	43.9	1.18	26.5
	Geometric CV (%)	20.7	26.9	25.2	81.8
FULL PHEN/TPM 15/92 mg or TPM 92 mg	N	2436	2436	66	66
	Geometric Mean	1.02	46.4	1.15	30.7
	Geometric CV (%)	25.0	29.3	23.5	77.1

CL/F= Apparent clearance for topiramate; CV= Coefficient of variation; PHEN: immediate release phentermine beads; TPM: modified release topiramate beads; Vc/F= apparent volume of distribution for topiramate.
* Descriptive statistics for the low dose level of topiramate administered alone were derived from simulations using the Population PK model with 100 patients randomly selected in the PK/PD population.
(Source: Sponsor's Population PK Report 2, Page 11)

PK parameters of phentermine and topiramate administered as the combination product (Qnexa) and separately were within 20% and 25% of those previously assessed in Phase I studies,

respectively. Clearance values were consistent and dose-independent for phentermine and topiramate, suggesting a dose-proportional increase in exposure**.**

Covariate Analysis - Effect of Intrinsic and Extrinsic Factors on PK: Population PK models for phentermine and topiramate (Qnexa) included creatinine clearance (calculated from ideal body weight and the last measured serum creatinine concentration) on CL/F and body weight on Vc/F. Following inclusion of creatinine clearance on CL/F and body weight on Vc/F, no residual effects were observed on the CL/F and Vc/F of phentermine and topiramate (Qnexa). Median CL/F values of phentermine and topiramate (Qnexa) in male subjects were higher than those observed in female subjects (28.1% and 16.3%, respectively). No relationship was observed between other covariates (BMI, race, age, diabetic status) and PK parameters of phentermine and topiramate (Qnexa). Overall, the above results suggest that creatinine clearance and body weight were the most important components describing the PK of phentermine and topiramate (Qnexa).

Covariate Analysis – Drug-Drug Interactions: Correlation analyses of PK parameters of phentermine or topiramate in patients with and without concomitant medications (i.e. statins, antihypertensives, SSRIs, and other medications) was performed. Overall, no correlation was observed between PK parameters of phentermine and topiramate in subjects receiving concomitant treatments with statins, anti-hypertensives and SSRIs. Likewise, no relationship was observed between PK parameters of phentermine and topiramate with and without concomitant administration with antidiabetic drugs such as metformin, sulfonylureas and thiazolidinedione.

3.3 Reviewer's Comments on Sponsor's Analysis:

The sponsor's population PK model of phentermine and topiramate administered as Qnexa is acceptable. The approach taken is simple and efficient, given the large amount of available data. The effort did not attempt to explain differences between monotherapy and concomitant administration of phentermine and phentermine with topiramate with the model. Rather phentermine, topiramate and both drugs in combination were modeled separately. The model development focused on identification of covariates that influence the clearance and volume of distribution of phentermine and topiramate.

The sponsor's covariate analysis using sparse data in obese patients is acceptable. It would have been ideal if the phase III sparse PK data was tested for covariate relationships with a NONMEM fitting of the PK model. However the data was too sparse and parameters would not be identifiable if one tried to fit more than one parameter. There was generally one trough concentration per dosing interval for 1-4 visits per individual. This limited evaluation of existing covariate correlations as only one covariate relationship could be evaluated. In fact no pharmacokinetic or covariate parameters were fitted with the sparse data, only the inter-individual variability on clearance was estimated. This data served as a validation of existing covariate relationships. Other covariate relationships were explored visually with graphics. No covariates beyond those identified in the model developed from the study 102 data were included to the model.

A further constraint was made to the model because of the limited phase III PK data (i.e. only trough concentrations were available). The between subject variability for Vd was made proportional to that of CL (i.e. eta_V=$theta_{BSVV}$*eta_{CL}). This essentially fixes the elimination slope for that individual since $theta_{BSVV}$ is a common parameter across the population. In their model Vd is a function of body weight whereas CL is a function of creatinine clearance which is calculated from ideal body weight. One artifact of this is that the estimated inter-individual

variability for clearance is correlated with actual body weight, since the different individual values of CL directly affect the value of Vd and vice versa when fitting the model to the trough concentrations of phentermine and topiramate. The sparse data was not used for further model refinement, but offered an opportunity to reevaluate existing covariates and explore other covariates because of the large population. Combining this large validation resource (data from studies 302 and 303) with the PK model that was developed on a population a population of 61 patients with richly sampled PK (Studies 102 & 103) provides a reasonable tool to make labeling conclusions from.

No additional population PK analyses were performed. Diagnostic plots and covariate relationships are presented in the reviewer's analysis (Section 4.6).

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor used their population PK model to make claims in the label regarding the covariate effects on the pharmacokinetics of phentermine and topiramate. The sponsor also proposes three different phentermine/topiramate fixed-dose amounts (3.75/23 mg, 7.5/46 mg, and 15/92 mg) for clinical use. It is the aim of this review to examine whether the label claims and proposed dose amounts are justified by the existing PK, efficacy, and safety data using both population PK and exposure-response analyses.

4.2 Objectives

Analysis objectives are:

1. Determine if the dose-response for efficacy supports the proposed doses
2. Determine if the dose-response for safety supports the proposed doses
3. Determine if the label claims regarding the impact of covariates on the pharmacokinetics of phentermine and topiramate are described accurately.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
Pop PK: OB 302 & 303	NMPheCom.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-02\analysis
Pop PK: OB 302 & 303	NMTopCom. xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-02\analysis
Pop PK: OB 102	NMPhe102. xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-01\analysis
Pop PK: OB 103	NMPhe103. xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-01\analysis
Pop PK: OB 102	NMTop102. xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-01\analysis
Pop PK: OB 103	NMTop103. xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-01\analysis
Pop PK: OB 302 & 303	PKPheCom. xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-02\analysis
Pop PK: OB 302 & 303	PKTopCom.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\09-vi0521-poppk-02\analysis
Other: NDA 20844	topiramate-all-pooled-ss-22jan07-csv.xpt	\\cdsesub1\EVSPROD\NDA020844\0007\m5\datasets\population-pharmacokinetics-analysis\analysis
OB 303	adae.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-

		crf-ipl\datasets\ob-303\analysis
OB 303	adexp.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\ob-303\analysis
OB 303	lb.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\ob-303\tabulations
OB 302	lb.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\ob-302\tabulations
OB 301	adeff.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\ob-301\analysis
OB 302	adeff.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\ob-302\analysis
OB 303	adeff.xpt	\\Cdsesub1\evsprod\NDA022580\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\ob-303\analysis

4.3.2 Software

NONMEM VI (Icon, Ellicott City, MD) was used to review the sponsor's pharmacokinetic and pharmacodynamic analysis. S-PLUS 8.0 (TIBCO Software Inc., Palo Alto, CA) was used to generate all plots and manage datasets. The statistical software R (www.r-project.org) was used in combination with the population PK tool library in order to generate diagnostic and pertinent covariate plots.

4.3.3 Models

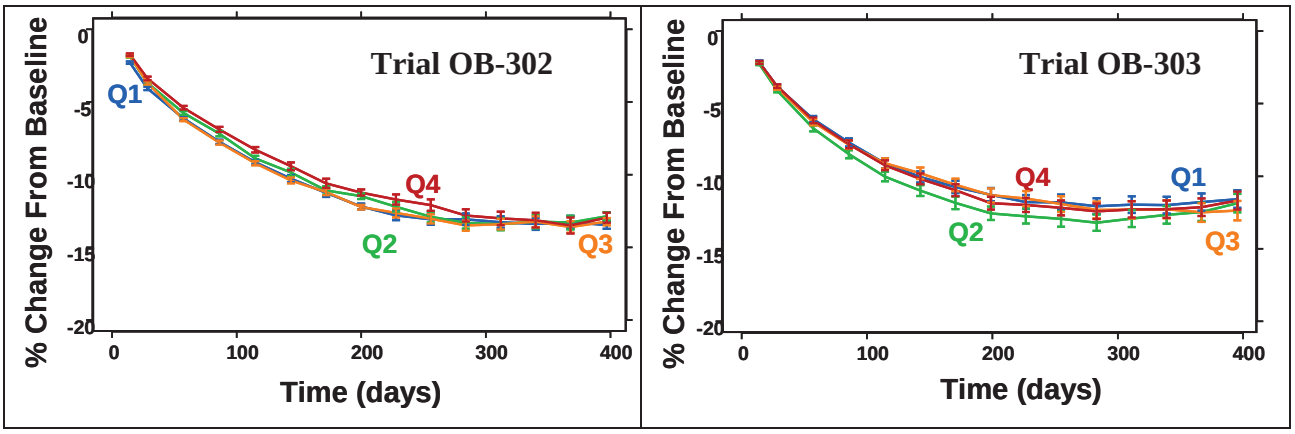
Based on the results, the sponsor's population PK model did not require further refinement. listed in the sponsor's analysis

4.4 Results: Dose-Response for Efficacy of Qnexa

Weight loss data from the registered trials OB-302 and OB-303 were plotted to identify if there was a dose-response for effectiveness following Qnexa administration. Figure 1 (shown previously) shows there is a dose-response relationship for weight loss. These plots show with increasing dose there is an increasing reduction in weight loss. This observation supports the effectiveness of Qnexa for weight loss at the proposed doses.

Figure 8 shows that baseline weight did not influence the amount of weight loss, *i.e*, the heaviest and lightest patients had similar % decrease in body weight from baseline.

Figure 8. Baseline Weight does not influence Qnexa effectiveness. Time courses of weight loss (expressed as percent change from baseline) for the 15/92-mg Qnexa doses are shown for four quartiles (Q1–Q4) of baseline weight. The left and right panels show the results for trials OB-302 and OB303. Data are presented as mean±SEM.



4.5 Results: Dose-Response for Safety of Qnexa

Topiramate has been associated with metabolic acidosis; psychiatric, cognitive and psychomotor adverse events; and teratogenetic effects in animal studies and in patients taking Topamax® (AERs database reporting, Topamax Label, Liamis 2010, Tatum 2001, Thompson 2000, Lee 2006, Mula 2003, Mula 2009, Hoffman 1977, Devan 1990, Lee 1998, Kanner 2003). The safety review of Qnexa is focused on determining if the proposed Qnexa doses are capable of producing similar safety events in a dose-dependent manner.

The first aim of the safety review was to compare the observed C_{max} values from the proposed Qnexa doses with the C_{max} values for approved Topamax doses. The second aim was to identify dose-response relationships for serum bicarbonate; psychiatric, cognitive and psychomotor adverse events; and other adverse events that occurred in >2% patients.

4.5.1 Comparison of Topiramate C_{max} Values between Qnexa and Topamax

Although the approved doses of Topamax for the treatment of epilepsy are up to 400 mg/day in two divided doses, the maximum recommended dose of topiramate in Qnexa is 92 mg. The question whether or not the 92 mg dose could produce exposures similar to that used for Topamax became of interest to the review team. Figure 9 shows topiramate Cmax values from various dose levels with Topamax administered to epileptic patients (doses >100 mg/day) and the Qnexa delayed release formulation (QD doses ≤ 100 mg) administered to obese patients. The Qnexa Cmax values were obtained from Trial OB-102 where PK samples were obtained at sufficient times to assess C_{max}.

It is evident from this comparison that the topiramate C_{max} values for Qnexa fall within the lower range of Cmax values for Topamax 200 mg BID. This is reassuring as the exposures are not expected to exceed the approved Topamax dose.

Figure 9. The C_{max} values from the 100 mg dose of Topiramate Qnexa (100 mg QD, delayed release formulation (DR)) do not exceed the median C_{max} value of the Topamax (200 mg BID, immediate release formulation) dose.

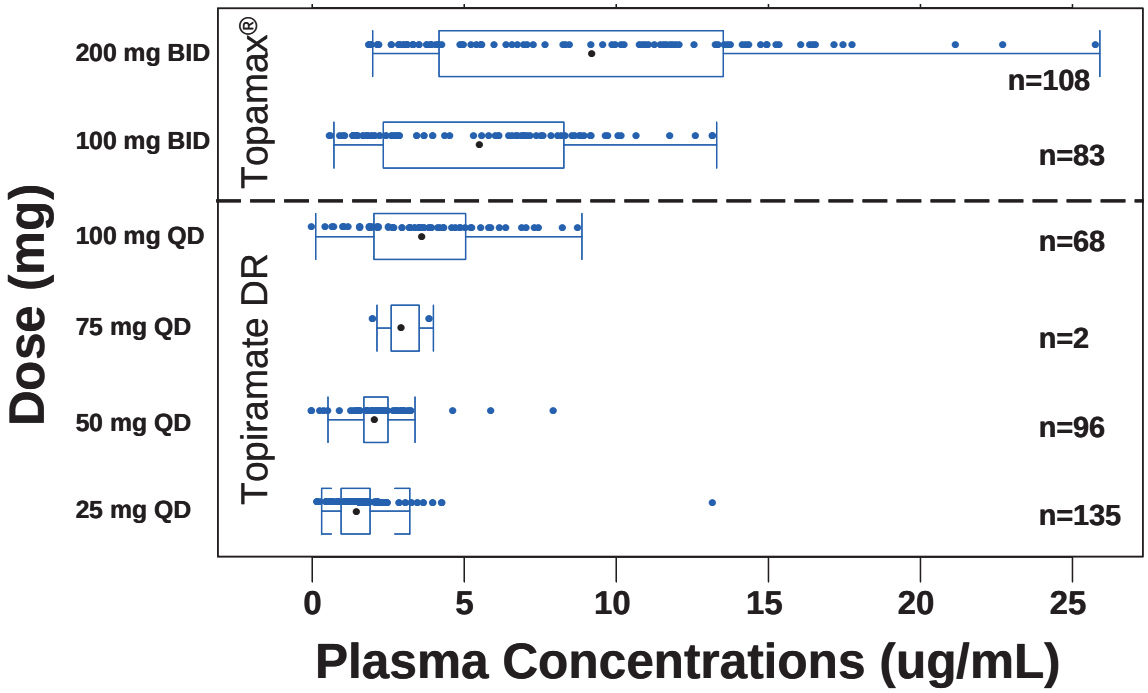


Table 8 provides the geometric mean and standard deviations for Cmax stratified by topiramate dose and formulation. Topiramate PK appear less than dose-proportional across the entire range of studied doses. This might be explained in part by co-administration of other anti-epileptic drugs that are inducers of the CYP3A4 isozyme (including phenytoin and carbamazepine which reduce topiramate exposures 40% and 48%), ultimately increasing topiramate clearance.

Table 8. Geometric Mean C_{max} and geometric standard deviations for Topiramate doses from Topamax (doses > 100 mg/day) and Qnexa (doses ≤ 100 mg QD) data.

Formulation	Dose (mg)	Geometric Mean Cmax (ug/L)	Geometric Std Dev
Topomax	200 BID	7.60	1.97
	100 BID	4.46	2.13
Topiramate Delayed Release (Qnexa)	100 QD	3.03	2.14
	75 QD	2.91	1.56
	50 QD	1.92	1.83
	25 QD	1.31	1.85

4.5.2 Dose-Response for Serum Bicarbonate

Treatment with high doses of topiramate (400 mg/day) has been associated with metabolic acidosis (Topamax Label, Liamis, 2010). Two cases were observed in the one-year safety cohort from trials OB-302 and OB-303. Serum bicarbonate is generally reduced in patients with acidic blood pH (Liamis, 2010). Therefore there was an interest in understanding if topiramate

concentrations from the Qnexa doses are sufficient to reduce serum bicarbonate to <21 mM (a value recognized as below the normal bicarbonate range).

Table 9 shows there is a dose response for reduction in bicarbonate to <21 mM. Data were taken from the registration trials OB-302 and OB-303. Bicarbonate concentrations were measured serially over the duration of the trial and reduction in bicarbonate was assessed by either one or two or more time points (pt) where bicarbonate was <21 mM.

Table 9. There is dose-response for reduction in bicarbonate to <21 mM. The table shows the incidence of patients with bicarbonate of <21 mM for one occurrence and more than one occurrence for trials OB-302 and OB-303.

Group	N	% w. 1 pt <21 mM	% w. 2+ pt <21 mM
Placebo	1505	6.64	0.930
3.75/23 mg	240	14.6	5.83
7.5/46 mg	498	21.5	6.02
15/92 mg	1505	28.4	10.2

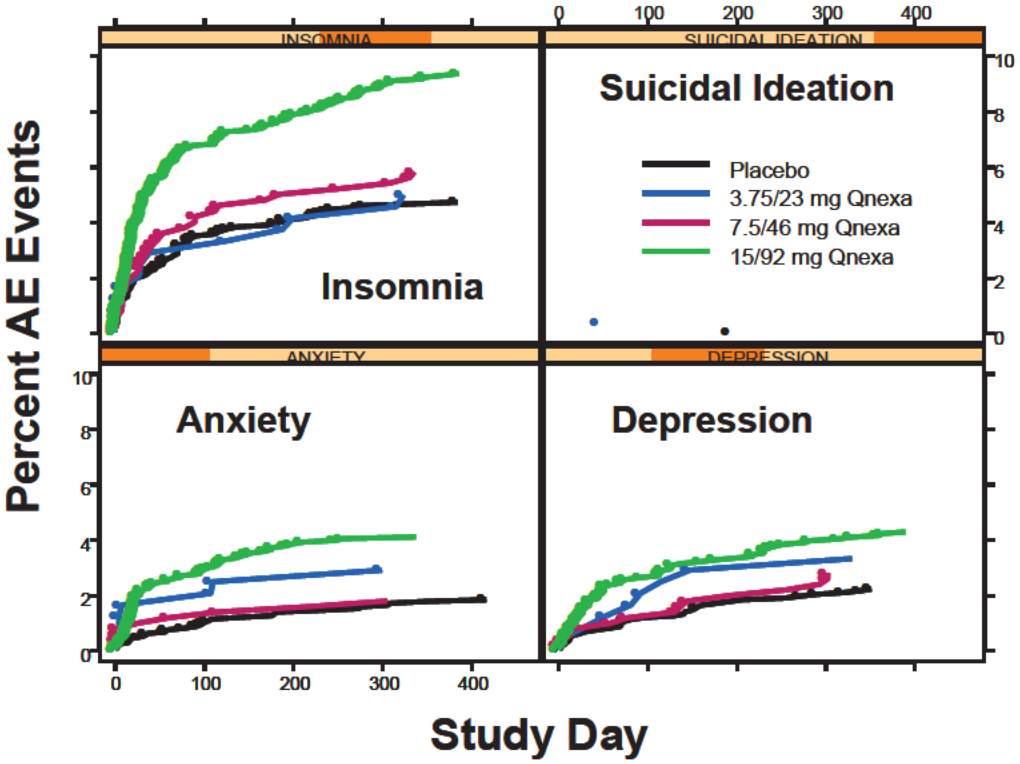
Figure 2 shows the time course for the percent of patients with bicarbonate of <21 mM for each dose group.

4.5.3 Dose-Response for Reported Psychiatric, Neurocognitive, and Psychomotor Adverse Events

The sponsor's data for adverse events from trials OB-302, OB-303, and OB-202/DM230 were analyzed to identify safety events that show a dose-response relationship. Only the first event of a particular adverse event type was counted for each subject.

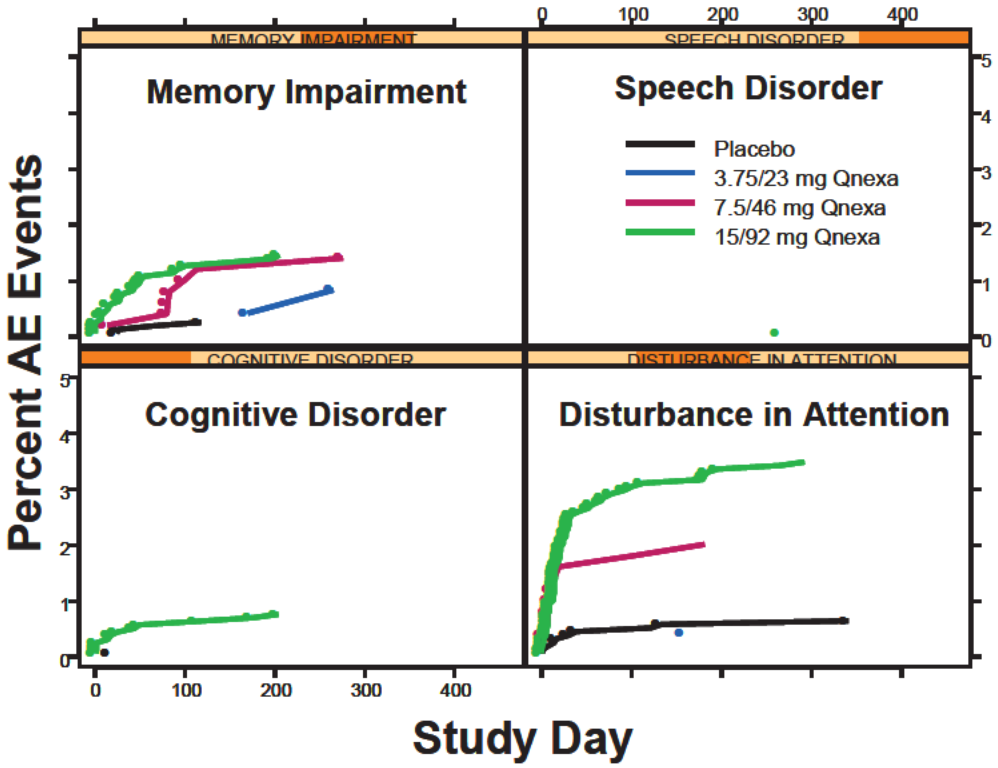
Topiramate has previously been associated with psychiatric adverse events with affective and psychotic disorders being the most frequent (See the Clinical Review by Mary D. Roberts, MD as well as Hoffman 1977, Devan 1990, Lee et al. 1998). Topiramate in patients with a previous history of depression has also been linked to depression (Kanner et al. 2003, Mula et al. 2009).

Figure 10. There are dose-response relationships for the psychiatric adverse events anxiety, depression, and insomnia. Results are presented as the cumulative adverse event rate in trials OB-302, OB-303, and OB-202/DM230. Green, red, and blue lines indicate the 15/92-mg, 7.5/46-mg, and 3.75/23-mg Qnexa dose groups. Black lines depict the placebo group.



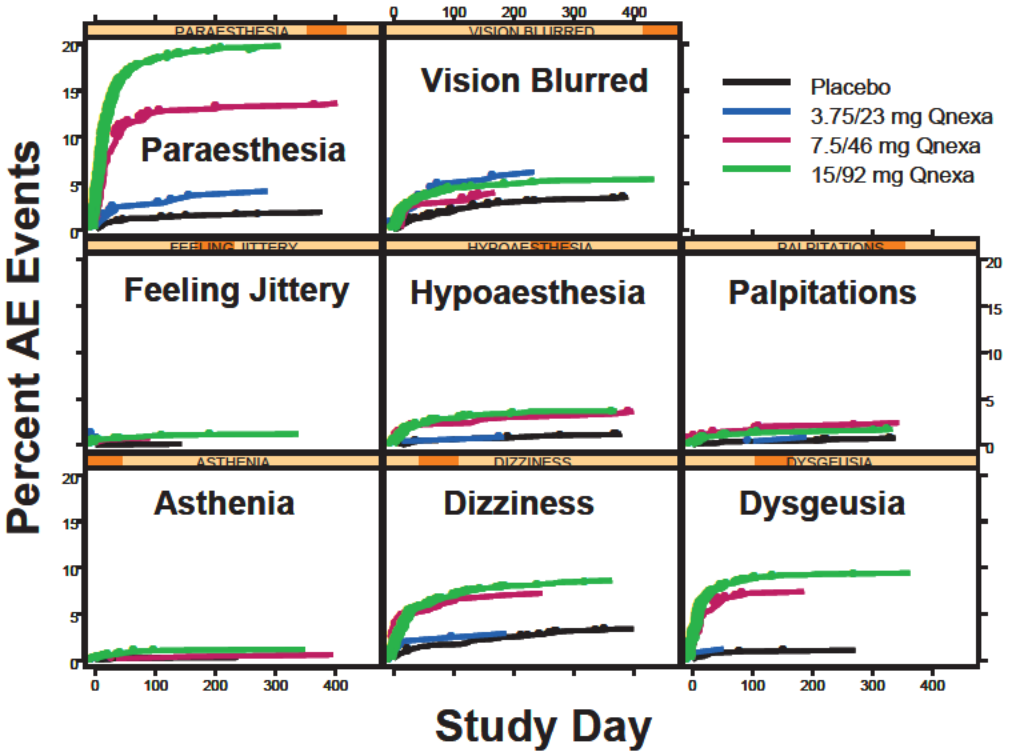
Topiramate has also been associated with disturbance in attention, memory impairment, slowed thinking, and language difficulties at high (≥200 mg/day) and low doses (<100 mg/day) (See the Clinical Review by Mary D. Roberts, MD as well as Tatum 2001, Thompson 2000, Lee 2006, Mula 2003). Therefore it was of interest to determine if a dose-response relationship existed for these events at the Qnexa dose levels. Figure 11 shows there are dose-relationships for disturbance in attention, memory impairment, and other cognitive disorders. Despite the only occurrence of speech disorder being in the high-dose group, there was insufficient data to conclude that a Qnexa dose-response relationship was present.

Figure 11. There are dose-response relationships for the cognitive adverse events cognitive disorder, disturbance in attention, and memory impairment. Results are presented as the cumulative adverse event rate in trials OB-302, OB-303, and OB-202/DM230. Green, red, and blue lines indicate the 15/92-mg, 7.5/46-mg, and 3.75/23-mg Qnexa dose groups. Black lines depict the placebo group.



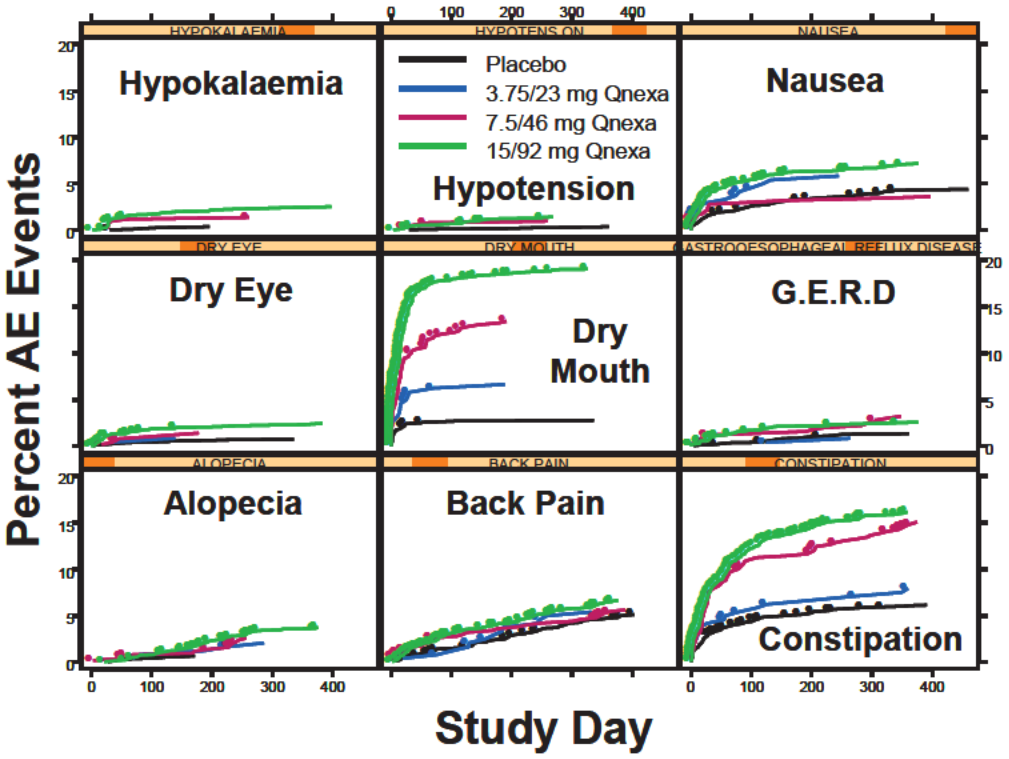
As Qnexa dose-response relationships were apparent for both psychiatric and neurocognitive adverse events, psychomotor events were also explored for dose-response relationships. Figure 12 shows the Qnexa dose response relationships for the relevant psychomotor events.

Figure 12. There are dose-response relationships for psychomotor adverse events. Results are presented as the cumulative adverse event rate in trials OB-302, OB-303, and OB-202/DM230. Green, red, and blue lines indicate the 15/92-mg, 7.5/46-mg, and 3.75/23-mg Qnexa dose groups. Black lines depict the placebo group.



Other adverse events that show dose-response with an incidence >2% are shown in Figure 13.

Figure 13. There are dose-response relationships for psychomotor adverse events. Results are presented as the cumulative adverse event rate in trials OB-302, OB-303, and OB-202/DM230. Green, red, and blue lines indicate the 15/92-mg, 7.5/46-mg, and 3.75/23-mg Qnexa dose groups. Black lines depict the placebo group.



One aspect of the time course plots for adverse event rates plots that remains clear is there is an apparent dose-response relationship for Qnexa and that the majority of the psychiatric, neurocognitive, and psychomotor adverse events occur within 3 months after initiating therapy.

Combining the fact there is overlap in C_{max} values between the 100 mg Qnexa dose and 200 mg BID Topamax dose combined with the type of adverse events that show dose-response indicates that the proposed doses of Qnexa are potentially capable of producing adverse events similar to those of Topamax.

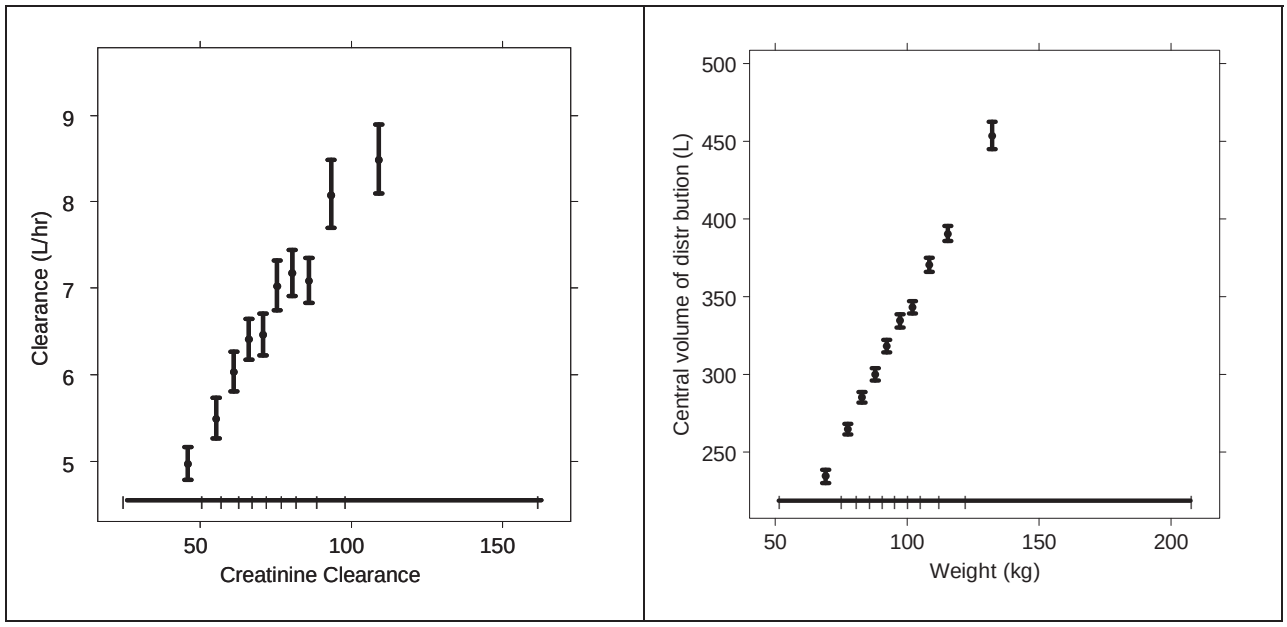
4.6 Population Pharmacokinetics

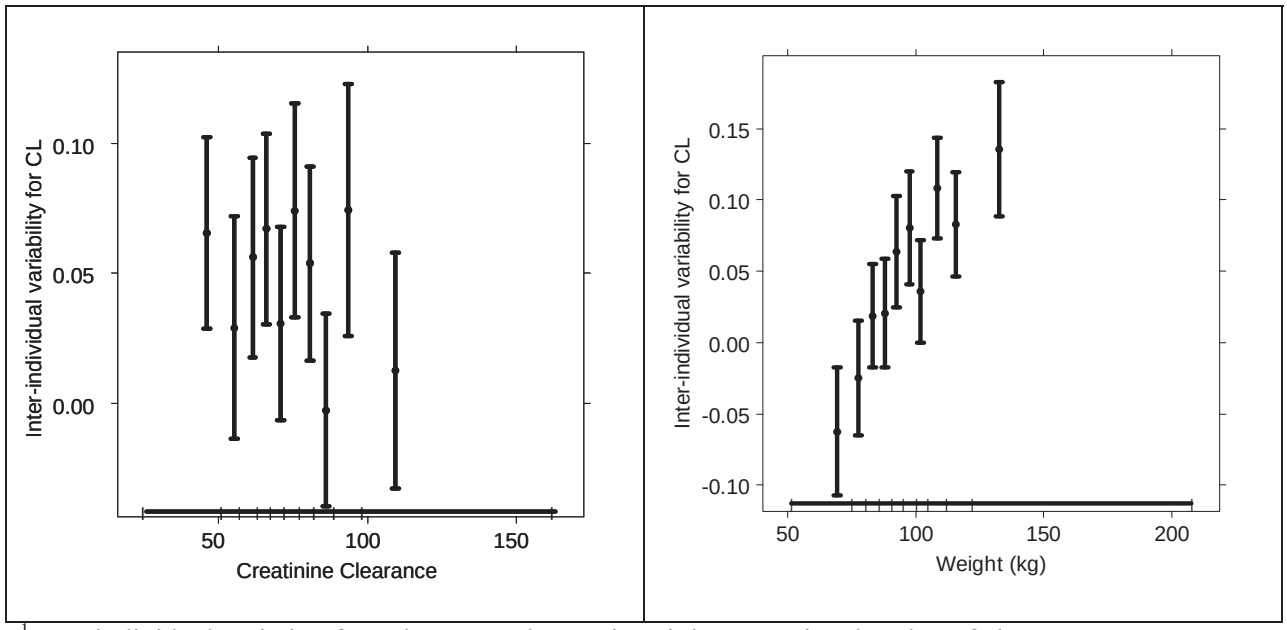
The pharmacokinetic models and concentration data for phentermine and topiramate were evaluated to determine if the label claims based on the population PK models were justified. Both drugs were modeled separately by the sponsor and the PK for each drug was modeled independently of the other drugs concentration. However, when given in combination the PK parameters of each drug were estimated differently than when given alone. This evaluation of the sponsor's models focuses on the PK model results where both drugs were administered in combination, as would be the case with Qnexa administration. For both phentermine and topiramate the main emphasis of the evaluation was placed on discerning whether the covariate relationships were identified correctly, were clinically meaningful, and if they were described accurately in the label.

4.6.1 Pharmacokinetic Analysis of Phentermine

Two aspects of the phentermine relevant covariate relationships are shown in Figure 14. The top row shows there is a relationship of clearance with creatinine clearance and volume of distribution with body weight. Clearance almost doubles between the lowest and highest creatinine clearance quantiles. This is consistent with the fact that phentermine is eliminated predominantly by the kidneys. The bottom row of Figure 14 shows the residuals from inter-subject variation in the estimates of CL or Vd after accounting for the correlation between CL and creatinine clearance or Vd and body weight. A covariate model would be considered to capture the central tendency of the data if the residuals in the plots on the bottom row were centered evenly about zero. Between subject variability for phentermine clearance was estimated to be 33%.

Figure 14. Continuous covariate relationships and corresponding eta plots show creatinine clearance and weight account for inter-patient variability in Phentermine PK. Points depict mean CL and Vd ± SEM for each of 10 quantiles of covariate values. The quantiles are plotted at the median of their respective values are bars at the bottom of the graph delineate the distribution of each quantile.





[1]Inter-individual variation for Vd was not shown since it is proportional to that of clearance.

Unexpectedly, this is not the case for the individual differences from the population mean for clearance versus body weight. This can be explained by a constraint that was made on the PK model regarding between-subject variation for volume.

In the PK model for phentermine the between subject variability for Vd was made proportional to that of CL (i.e. etaV=thetaBSVV*etaCL) since only trough concentrations were available in the phase III data. Volume is a function of actual body weight whereas clearance is a function of creatinine clearance, which is calculated from ideal body weight. One artifact of this is that the inter-individual variability for clearance is correlated with actual body weight, since the different individual values of CL directly affect the value of Vd and vice versa when fitting the model to the sparse data.

As the correlation between clearance and body weight is not presented in the label, this false relationship between clearance and body weight is not a concern. Regardless the sponsor visually evaluated whether the etas of clearance and volume of distribution were correlated with other parameters. Testing other covariates should not be influenced by the correlation between eta of clearance and body weight. The sponsor did not indicate why they were not tested with the model, but it is likely the data were too sparse to test subsequent covariate relationships while maintaining parameters be identifiable.

The PK of phentermine is not influenced significantly by the patients' age or BMI. In the population PK analysis, age and BMI were not found to be covariates with a statistically significant effect on phentermine CL or Vd. Figure 15 shows the individual estimates for CL are evenly distributed about the population mean across the range of ages. No dose adjustment is recommended based on the patient's age. The loess trend line in Figure 15 shows a modest increase with BMI. However, BMI was not found to be statistically significant in the model for phentermine. Additionally, the magnitude of change in the trendline across the range of BMIs is not sufficient to warrant dose-adjustment and is likely due to the model constraint that leaves clearance correlated with body weight.

Figure 15. Age and BMI do not Influence Modeled Phentermine Clearance. Scatter plots for phentermine individual estimates of between-subject variability for clearance are shown with Loess smoothed lines to indicate potential trends in the data.

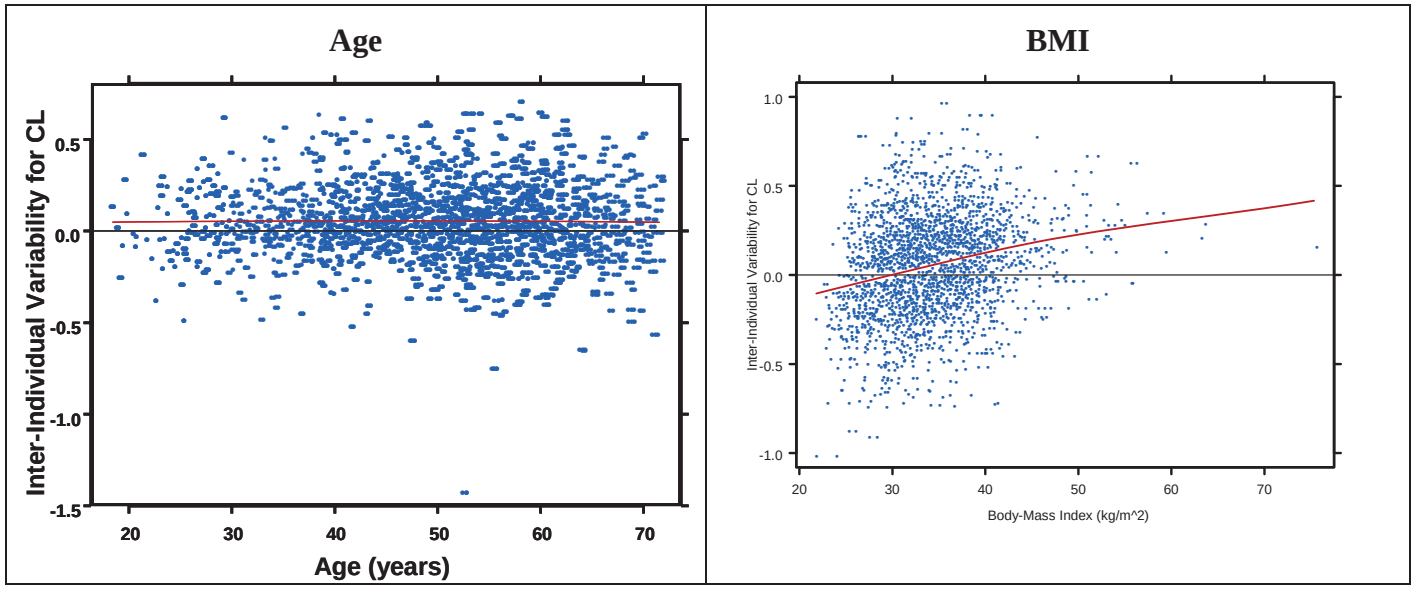
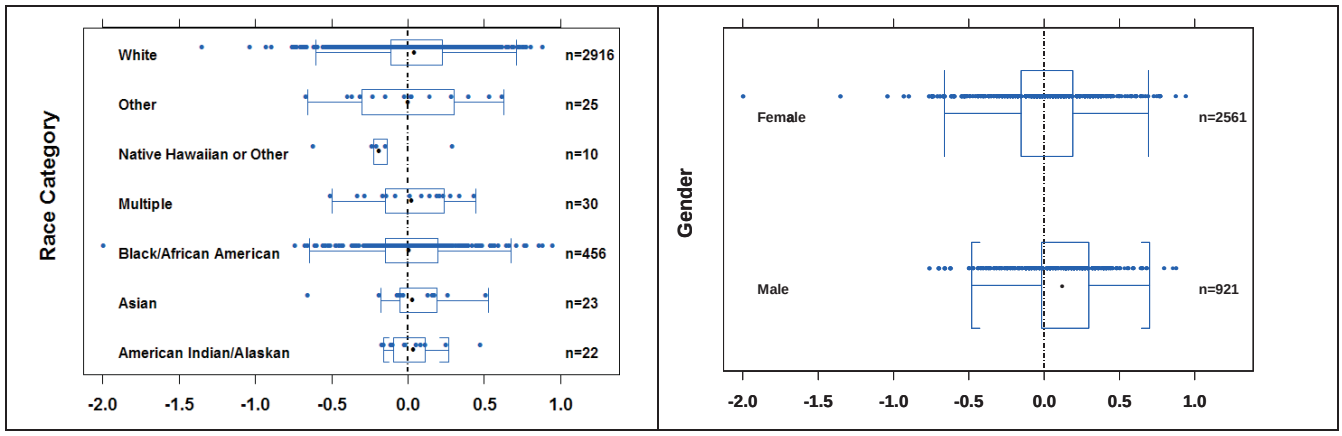


Figure 16 shows the relationship between the individual phentermine clearance residuals (after accounting for creatinine clearance) and the categorical covariates race, gender, presence of diabetes, and categorical creatinine clearance. In all cases the distributions of the residuals for the inter-individual variability of clearance were centered about zero and not influenced by these categorical covariates.

Figure 16. Categorical Covariates do not Influence Modeled Phentermine Clearance. Boxplots are shown for each category of covariate. The edge of the box represents the 25 and 75th percentiles. The end of the lines represent the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.



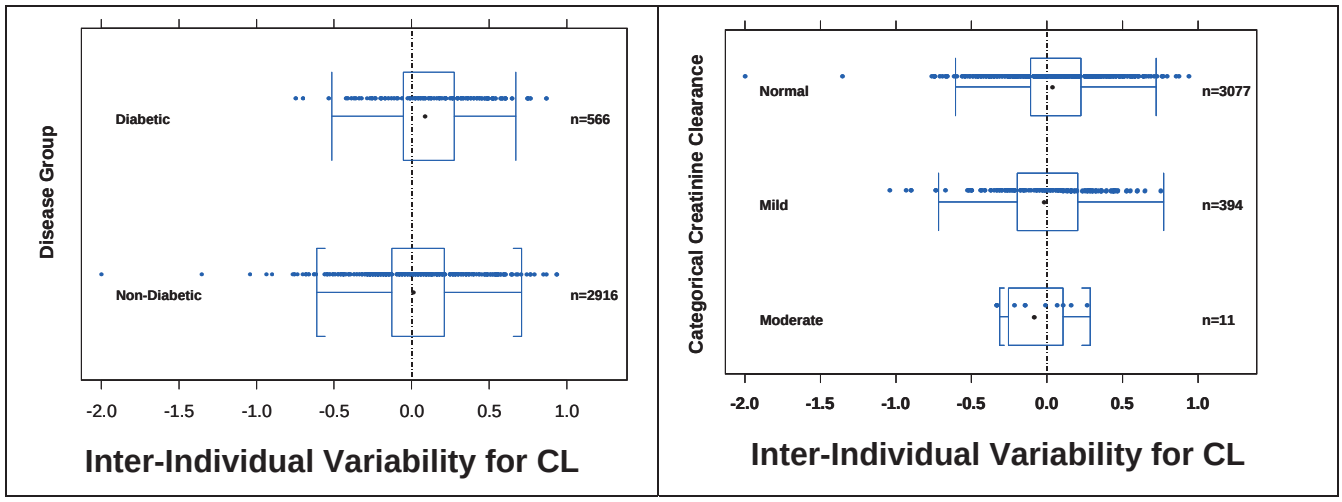
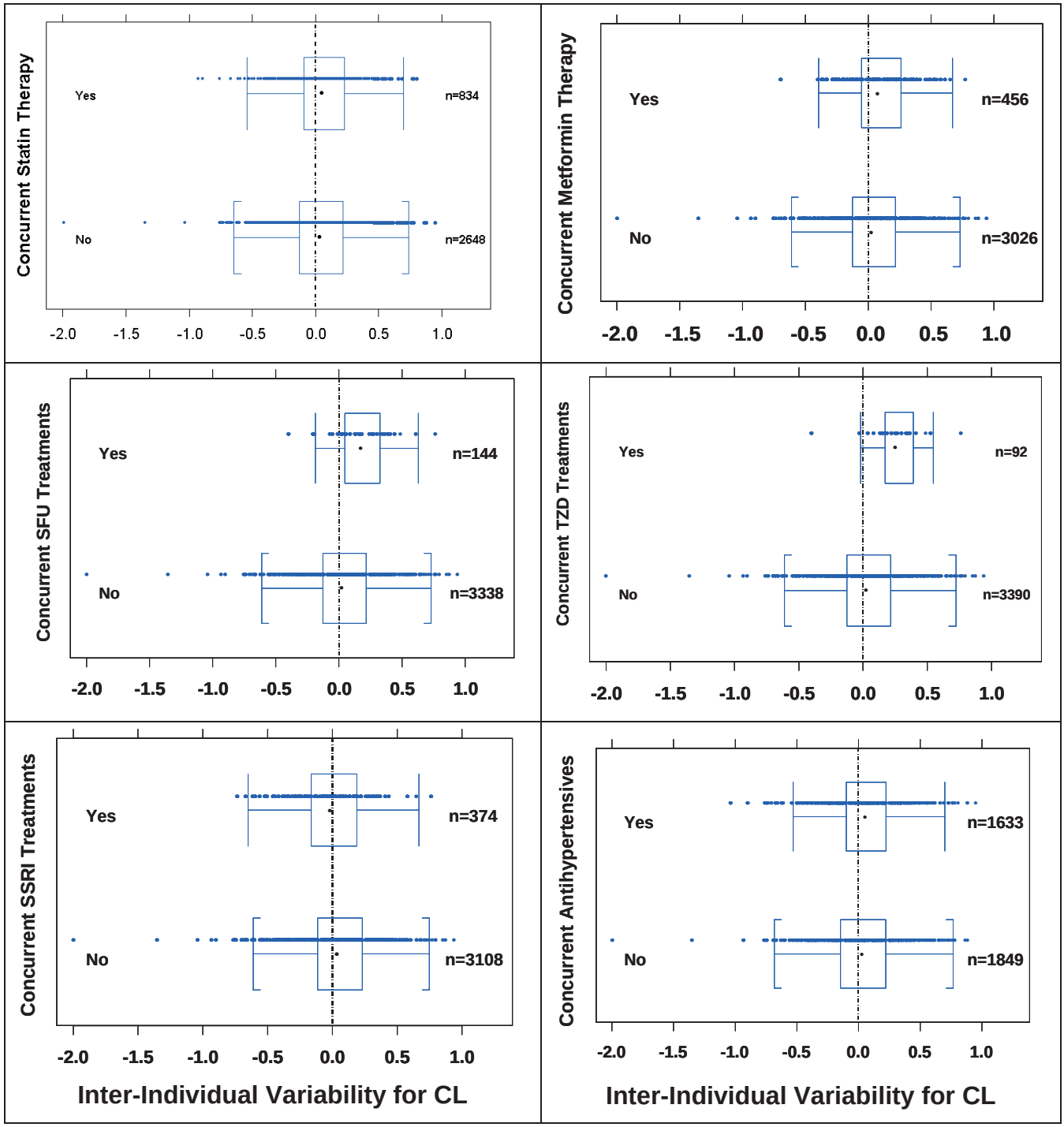


Figure 17 shows the relationship between the individual phentermine clearance residuals (after accounting for creatinine clearance) and the presence or absence of particular concomitant background therapy. Since the concomitant therapy was background medication, the assumption was made that any effect the concomitant medication was having on phentermine PK was at steady-state. This made the population PK assessment of the drug-drug interactions with sparse PK data feasible. In all cases the distributions of the residuals for the inter-individual variability of clearance were not statistically different from zero and not influenced by these concomitant medications. However, the plot for administration with thiazolinediones (TZDs) appeared to suggest an increase in phentermine clearance.

In a population PK fitting with NONMEM VI, concomitant administration with thiazolinediones increased phentermine clearance 7%, reduced the objective function value by 61 and reduced the between subject variation for clearance by 0.5%. Shrinkage of residuals for inter-individual variation was acceptable at 16.2% The magnitude of change of phentermine clearance does not appear to be clinically relevant when considering the effectiveness and safety profiles of Qnexa. No dose adjustment is recommend for Qnexa administration with concomitant TZD therapy. These findings support the sponsor's label statement with regards to phentermine.

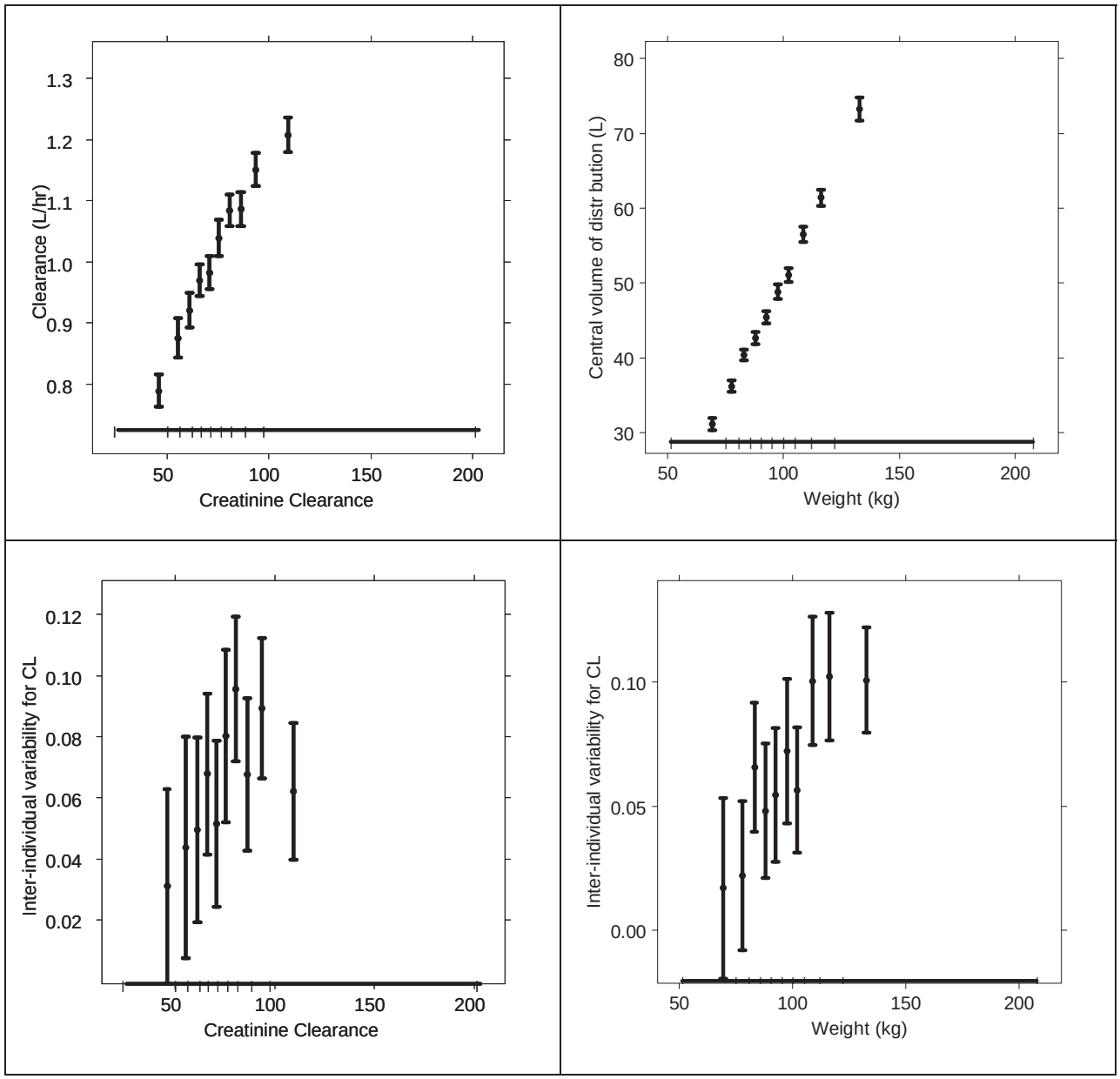
Figure 17. All concomitant therapies except TZDs do not influence phentermine clearance. Boxplots are shown for each category of covariate. The edge of the box represents the 25 and 75th percentiles. The end of the lines represent the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.



4.6.2 Pharmacokinetic Analysis of Topiramate

The top row of Figure 18 shows there is a relationship of topiramate clearance with creatinine clearance and volume of distribution with body weight. Clearance increases by about 50% between the lowest and highest creatinine clearance quantiles. This is consistent with the fact that topiramate is also eliminated predominantly by the kidneys. Between subject variability for topiramate clearance was estimated to be 27%.

Figure 18. Continuous covariate relationships and corresponding eta plots show creatinine clearance and weight account for inter-patient variability in Topiramate PK. Points depict mean CL and Vd ± SEM for each of 10 quantiles of covariate values. The quantiles are plotted at the median of their respective values are bars at the bottom of the graph delineate the distribution of each quantile.



The bottom row of Figure 18 shows the individual differences from the population mean for clearance plotted against the individual creatinine clearance and body weight values. As in Figure 14, the plots in the bottom row should be flat and consistently centered around zero to indicate that the value of clearance is not biased by the covariate after it has already been included in the model. Again, this is not the case for the individual differences from the population mean for topiramate clearance and body weight. This can be explained by the constraint that for topiramate between subject variability for volume was also made proportional to clearance to keep parameters identifiable. Testing other covariates with the phase III data should not be influenced by the correlation between inter-individual clearance residuals and body weight.

The PK of topiramate is not influenced significantly by the patients' age or BMI. In the population PK analysis, age and BMI were not found to be covariates with a statistically significant effect on topiramate CL or Vd. Figure 19 shows the individual estimates for CL are evenly distributed about the population mean across the range of ages. No dose adjustment is recommended based on the patient's age. The loess trend line in Figure 19 shows a modest increase with BMI. However, BMI was not found to be statistically significant in the model for topiramate. Additionally, the magnitude of change in the trendline across the range of BMIs is not sufficient to warrant dose-adjustment and is likely due to the model constraint that leaves clearance correlated with body weight.

Figure 19. Age and BMI do not Influence Modeled Topiramate Clearance. Scatter plots for topiramate individual estimates of between-subject variability for clearance are shown with Loess smoothed lines to indicate potential trends in the data.

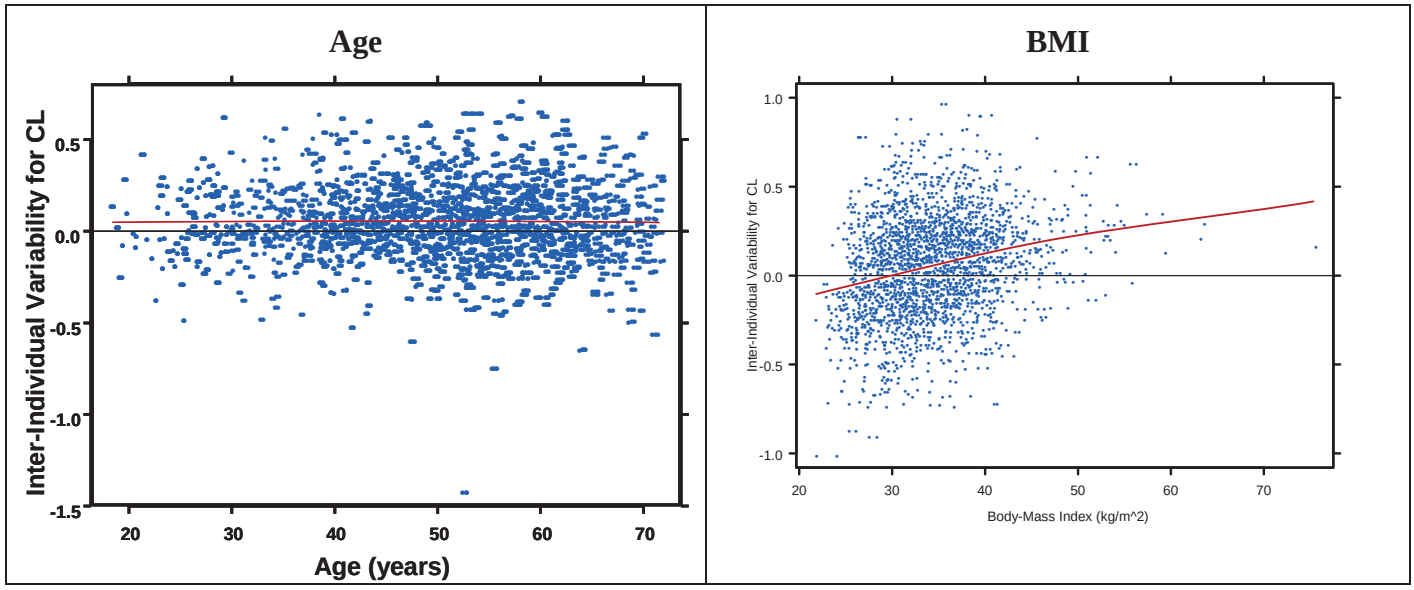


Figure 20 shows the relationship between the individual topiramate clearance residuals (after accounting for creatinine clearance) and the categorical covariates race, gender, presence of diabetes, and categorical creatinine clearance. In all cases the distributions of the residuals for the inter-individual variability of clearance were centered about zero and not influenced by these categorical covariates.

Figure 20. Individual Variation for Clearance for Categorical Covariates. Boxplots are shown for each category of covariate. The edge of the box represents the 25 and 75th

percentiles. The end of the lines represent the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.

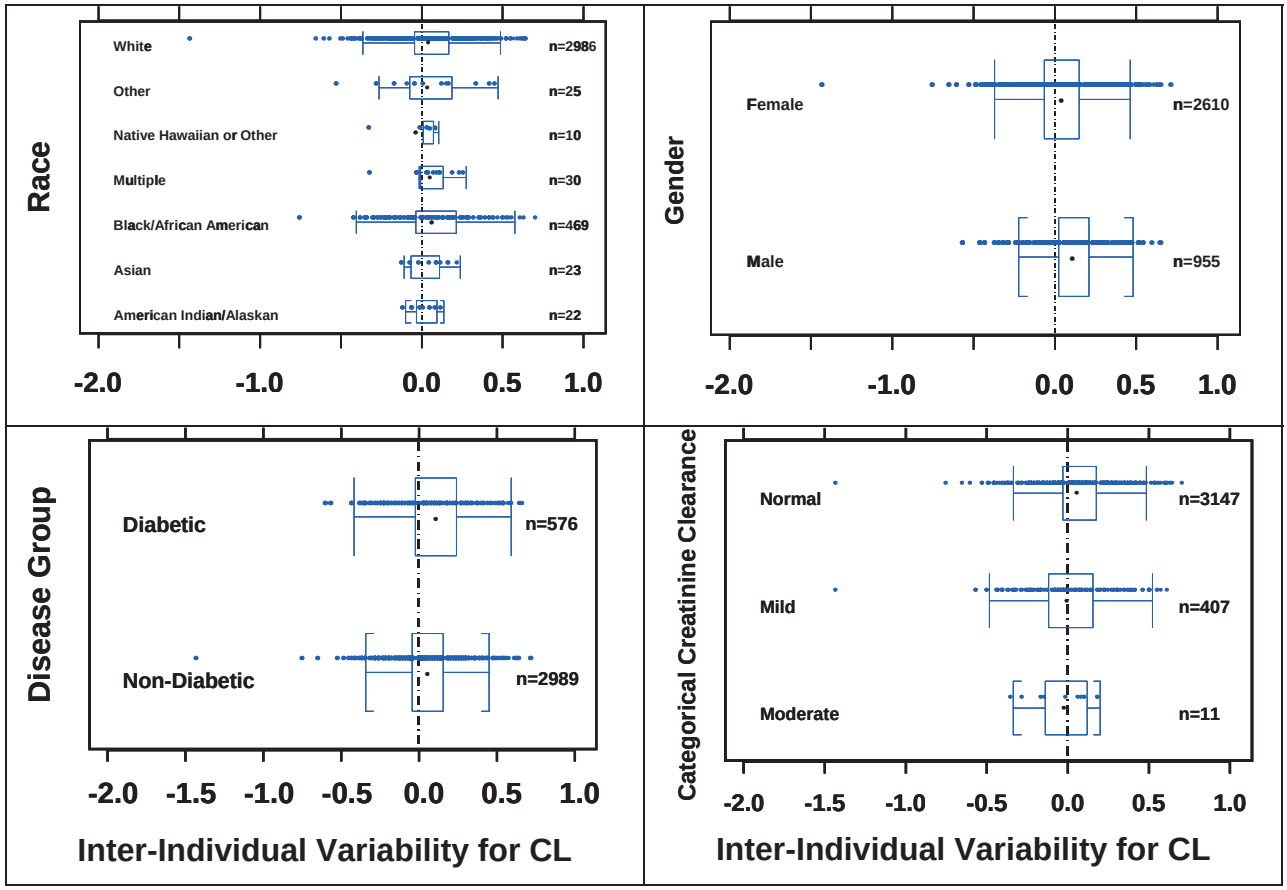
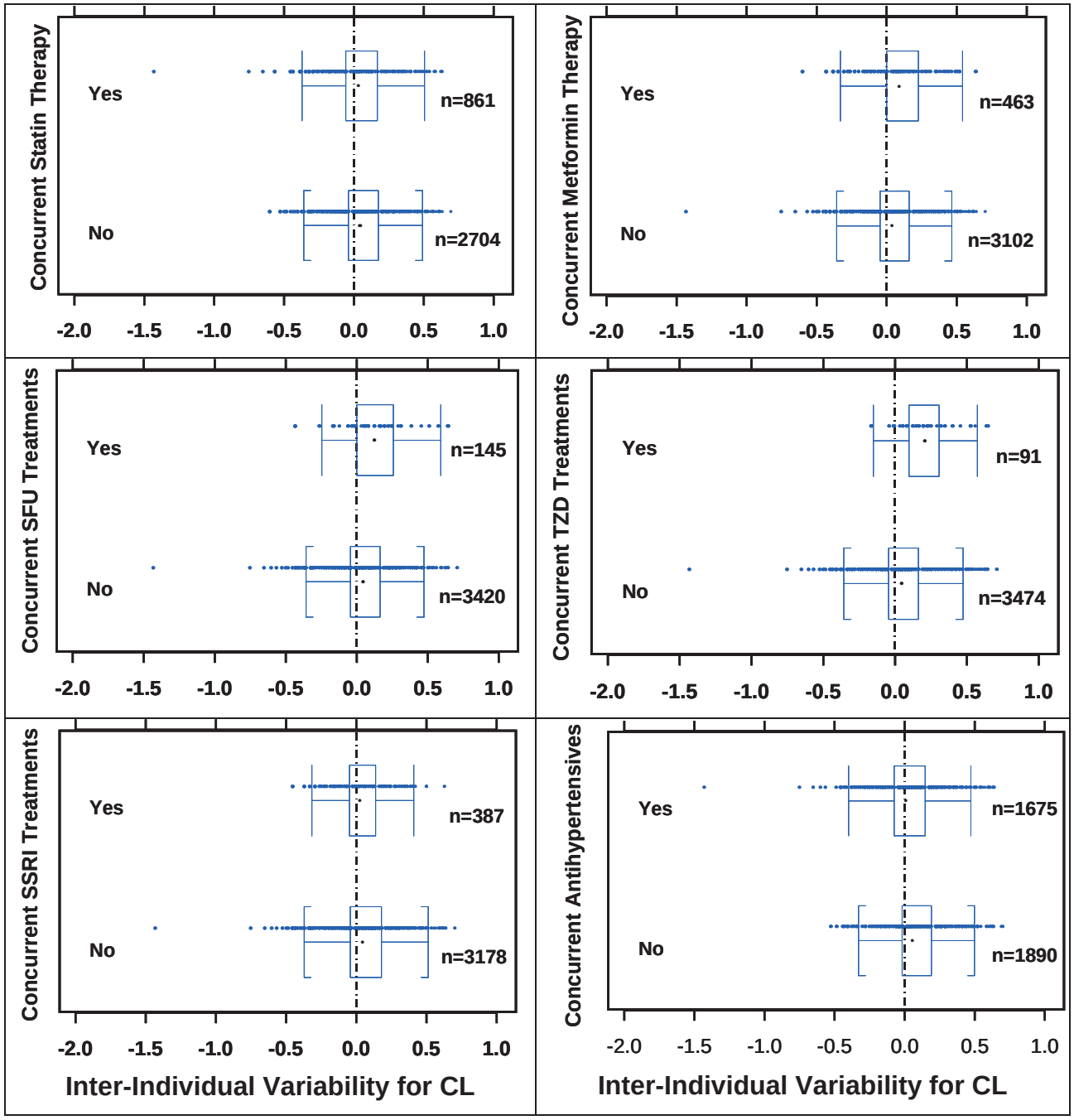


Figure 21 shows the relationship between the individual topiramate clearance residuals (after accounting for creatinine clearance) and the presence or absence of particular concomitant background therapy. Since the concomitant therapy was background medication, the assumption was made that any effect the concomitant medication was having on topiramate PK was at steady-state. This made the population PK assessment of the drug-drug interactions with sparse PK data feasible. In all cases the distributions of the residuals for the inter-individual variability of clearance were not statistically different from zero and not influenced by these concomitant medications. However, the plot for administration with TZDs appeared to suggest an increase in topiramate clearance.

In a population PK fitting with NONMEM VI, concomitant administration with TZDs increased topiramate clearance 36%, reduced the objective function value by 36 and reduced the between subject variation for clearance by 1.7%. Shrinkage of residuals for inter-individual variation was higher than that for phentermine at 28.6% but similar to the sponsor's value for their final population PK model, 28.8%. The magnitude of change in topiramate clearance does not require dose-adjustment during use with TZDs. There is a decrease in topiramate exposures which would suggest that dose-adjustment is not required for safety reasons. Also, the effectiveness of Qnexa on weight loss is sufficient to allow minor fluctuations in exposure, especially since the proposed regimen permits titration to higher doses. No dose adjustment is recommended for

Qnexa administration with concomitant TZD therapy. These findings support the sponsor's label statement with regards to topiramate.

Figure 21. Individual Variability for Topiramate Clearance with Different Concomitant Therapies. Boxplots are shown for each category of covariate. The edge of the box represents the 25 and 75th percentiles. The end of the lines represent the 5th and 95th percentiles. The solid black dot in each box depicts the mean. The number of subjects in each group is shown to the right and individual values are shown across the plot.



For both phentermine and topiramate PK, creatinine clearance influenced the plasma clearance of topiramate and volume of distribution was correlated with body weight. The results of the

population covariate modeling effort for topiramate PK were similar to the results for phentermine two reasons. Both drugs are primarily cleared by the same mechanism (kidneys) and both covariate relationships were defined from the same sampling regimen. Rich data was available for a set of patients where covariates with the most significant effects -- creatinine clearance and body weight, could be identified as covariates on clearance and volume of distribution. However, the data used to evaluate PK in the phase III patient population was 1) sufficiently sparse and 2) the magnitude of effects of the other tested covariates in the broader population was sufficiently small that further parameter evaluation did not yield significant covariate effects on the clearance or volume of phentermine or topiramate PK.

4.6.3 Exposure Matching for Renal Impairment

The sponsor proposed limiting the Qnexa dose for patients with renal impairment in the label, "In subjects with moderate (CLCr ≥ 30 – < 50 mL/min) and severe (CLCr < 30 mL/min) renal impairment to 7.5/46 mg. However, the sponsor did not recommend limiting the dose in patients with mild renal impairment.

A comparison of the exposures (AUC values, calculated with the 15/92 mg Qnexa dose) in normal, mild, moderate, and severe patients were made using both the population PK model and PK results from the renal impairment study (Table 10). It is apparent from Table 10 that the population PK model captures the phentermine exposures observed in the renal impairment study.

Table 10. The percent change in phentermine and topiramate AUC values with mild, moderate, and severe renal impairment is similar between the population PK model predictions and results from the renal impairment study. AUC values are presented as μg*hr/mL. Creatinine CL is presented as mL/min.

		POP PK		Renal Study	
Degree of Renal Impairment	Creatinine Clearance	Phen. AUC	Top. AUC	Phen. AUC	Top. AUC
Normal	80-125	1.66-2.22	12.6-15.3	2.45	9.52
Mild	50-80	2.22-3.00	15.3-18.7	2.98	11.9
Moderate	30-50	3.00-4.17	18.7-23.3	3.54	17.7
Severe	<30	>4.17	>23.3	4.69	21.6

Using the population PK model for the moderately impaired population suggests the AUC of phentermine nearly doubles and more than doubles for the severe renal impairment population. Based on the subset of patients studied in the renal impairment study with moderate impairment the AUC for phentermine and topiramate increased 44% and 86% compared to patients with normal renal function. For the subset of patients studied in the renal impairment study with severe impairment, the AUC for phentermine and topiramate increased 91% and 130% compared to patients with normal renal function. Based on the results of both the population PK model for both drugs and the renal impairment study, patients with moderate or severe should not exceed half the maximum dose for patients with normal renal function to maintain phentermine and topiramate exposures within the range found in patients with normal renal function.

The exposures for patients with mild renal impairment also increase. Using the population PK model, mean AUC values in patients with mild renal impairment increased 33–35% and 21–22% for phentermine and topiramate, respectively. These increases do not exceed the degree of between subject variability for both phentermine (33%) and topiramate (27%). Based on these data, we recommend no change in the proposed dosing for patients with mild renal impairment.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Qnexa_NDA22580_JCE
Adverse Events Rates Ti mecourses.ssc	Check Treatment adverse events for dose-response	\ER Analyses
Bicarbonate Timcourses 2 .ssc	generate timecourses of bicarbonate and data analysis	\ER Analyses
Covariate Trellis and Box plots.ssc	generates continuous and categorical covariate plots to verify results of pop PK analysis	\PK Analyses
PhenComShrinkage_CL.s sc	Determines shrinkage for the different NONMEM runs	\PK Analyses
WeightTimecourses.ssc	Displays efficacy in terms of weight loss over time, including and excluding LOCF.	\ER Analyses
ExposureOverlapDoseCm ax.ssc	Plots topiramate Qnexa exposures against Topamax topiramate exposures by dose	\PK Analyses
NMPhen102.ctl	NONMEM Code for Pop PK1: Phentermine In Combination, study 102	\PK Analyses\Qnexa Base Model Files
NMPhen103.ctl	NONMEM Code for Pop PK1: Phentermine Alone, study 103	\PK Analyses\Qnexa Base Model Files
NMTopi102.ctl	NONMEM Code for Pop PK1: Topiramate in Combination, study 102	\PK Analyses\Qnexa Base Model Files
NMTopi103.ctl	NONMEM Code for Pop PK1: Topiramate Alone, study 103	\PK Analyses\Qnexa Base Model Files
QnexaFin2.ctl	NONMEM Code for Pop PK2: Phentermine in Combination, studies 302 & 303	\PK Analyses\Qnexa PKPD Model Files
QnexaFin4.ctl	NONMEM Code for Pop PK2: Topiramate in Combination, studies 302 & 303	\ PK Analyses\Qnexa PKPD Model Files
QnexaPhen102.R	R code for population PK tool for phentermine in study 102	\PK Analyses\Qnexa Base Model Files
QnexaPhen103.R	R code for population PK tool for phentermine in study 103	\PK Analyses\Qnexa Base Model Files
QnexaPhenCom.R	R code for population PK tool for phentermine in studies 302 & 303	\ PK Analyses\Qnexa PKPD Model Files
QnexaTopi102.R	R code for population PK tool for Topiramate in study 102	\PK Analyses\Qnexa Base Model Files
QnexaTopi103.R	R code for population PK tool for Topiramate in study 103	\PK Analyses\Qnexa Base Model Files
QnexaTopCom.R	R code for population PK tool for Topiramate in studies 302 & 303	\ PK Analyses\Qnexa PKPD Model Files

6 REFERENCES

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Liamis,G., Milionis, H. J., and Elisaf, M. Pharmacologically-Induced Metabolic Acidosis: A Review. *Drug Saf* **33,** 371-391 (2010).

Mula, M., Trimble, M.R., Lhatoo, S.D., Sander, J.W. 2003 Topiramate and psychiatric adverse events in patients with epilepsy. *Epilepsia*. 2003 May;44(5):659-63.

Mula, M., Hesdorffer, D.C., Trimble, M., Sander, J.W. The role of titration schedule of topiramate for the development of depression in patients with epilepsy. *Epilepsia*. 2009 May;50(5):1072-6.

Tatum, W.O. 4th, French, J.A., Faught, E., Morris, G.L. 3rd, Liporace, J., Kanner, A., Goff, S.L., Winters, L., Fix, A.; PADS Investigators. Post-marketing antiepileptic drug survey. . Postmarketing experience with topiramate and cognition. *Epilepsia*. 2001 Sep;42(9):1134-40.

Thompson, P.J., Baxendale, S.A., Duncan, J.S., Sander, J.W. Effects of topiramate on cognitive function. *J Neurol Neurosurg Psychiatry*. 2000 Nov;69(5):636-41.

APPEARS THIS WAY ON ORIGINAL

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

S. W. JOHNNY W LAU
08/27/2010

JUSTIN C EARP
08/30/2010

CHRISTINE E GARNETT
08/30/2010

SALLY Y CHOE
08/30/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

NDA Number: 22-580 **Applicant: Vivus, Inc.** **Stamp Date: December 28, 2009**

Drug Name: phentermine + topiramate (QNEXA®) **NDA Type: Standard**

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

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	Yes		
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	Yes		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		Studies OB-301, OB-302, and OB-303
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			NA. The highest proposed dose is 15 mg phentermine + 92 mg topiramate and are ½ and < ¼ of the highest approved phentermine and topiramate dose, respectively.
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	Yes		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	Yes		Maximum of 7.5/46 mg/mg dose for patients with severe & moderate renal impairment
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA, the sponsor requested partial pediatric waiver of 0 (b) (4) years of age.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	NA, the sponsor submitted a Proposed Pediatric Study Request
11	Is the appropriate pharmacokinetic information	Yes		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

	submitted?			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?			NA

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology 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.
We recommend you to do the following:

- Conduct an in vitro release experiment to demonstrate whether alcohol will affect QNEXA®'s delayed release mechanism of topiramate for efficacy concern.
- Justify the absence or difference of certain drug interactions information in the proposed QNEXA® label (Section 12) from those in the approved TOPAMAX® label, such as the absence of the statement "Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated." and the difference of antiepileptic drugs interaction information.
- Justify the rationales for the confounded sequential design of the drug interactions study (OB-107) such as sensitivity to detect drug interactions via multiple doses, lack of washout period, potential confounding factors (drug metabolizing enzymes and transporters), and sequence of drug administration.
- Address the pharmacological activities of both phentermine and topiramate metabolites.
- Address the chiral inversion potential for topiramate via metabolism since it has 4 chiral centers.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist Date

Sally Y. Choe, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	22-580	Brand Name	QNEXA®
OCP Division	2	Generic Name	Phentermine HCl + topiramate
Medical Division	DMEP, HFD-510	Drug Class	Anorectic + antiepileptic
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat obesity
OCP Team Leader	Sally Y. Choe	Dosage Form	Fixed dose combination capsule (IR phentermine + DR topiramate beads)
Date of Submission	28-DEC-2009	Dosing Regimen	3.75/23, 7.5/46, 11.25/69, or 15/92 mg/mg daily
Estimated Due Date of OCP Review	1-JUN-2010	Route of Administration	Oral
PDUFA Due Date	28-OCT-2010	Sponsor	VIVUS, Inc.
Division Due Date	23-SEPT-2010	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	1		annotated
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
In vivo mass balance:				
In vitro isozyme characterization:	X	2		8VIVUP2R3; 8VIVUP2R4
In vitro metabolite Identity:				
In vitro metabolism inhibition:	X	1		8VIVUP1R1
In vitro metabolism induction:	X	1		101-09-001
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:	X	1		
Blood/plasma ratio:				8VIVUP3R1
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:	X	2		OB-101C; OB-102
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		OB-107
In-vivo effects of primary drug:	X	1		OB-108
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:	X	1		OB-106
hepatic impairment:	X	1		OB-105
PD:				
Phase 1:	X	1		OB-205
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:				
Phase 2	X	4		OB-201; OB-202; DM-230; DM231
Phase 3 clinical STUDIES (placebo controlled):	X	3		OB-301; OB-302; OB-303
Phase 3 clinical STUDIES (uncontrolled):	X	1		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

Population Analyses -				
Meta-analysis:				
NONMEM:	X	1		09-VI0521-POP-PK-01
Population PK/PD analysis	X	1		09-VI0521-POP-PK-02
II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence studies – traditional design	X	1		OB-109
Relative bioavailability	X	1		OB-110
alternate formulation as reference:				
Food-drug interaction studies:	X	1		OB-103
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment	X	1		OB-118
Total Number of Studies	26			

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	
Comments to be sent to firm?		See page 2's potential review issues to be forwarded to the Applicant for the 74-day letter.
QBR questions (key issues to be considered)		The reviewer shall focus on the following primary review issues: • The dose regimen and titration scheme for QNEXA®. • The 3 population pharmacokinetic claims in the label of "no effect on QNEXA® pharmacokinetics" due to: – age, gender, race, BMI – statins, anti-hypertensive, oral anti-diabetic, SSRIs – diabetes, hypertension, or hypertriglyceridemia • Specific populations and the need for dose adjustments • The 2 drug interaction studies, especially the confounded sequential design for 1 study and single dose oral contraceptive study for another • The thorough QT study's supratherapeutic dose is only 50% higher than the 15 mg phentermine/92 mg topiramate dose, yet severe renal impairment increases both phentermine and topiramate AUCs about 100%. The reviewer shall focus on the following as secondary review issues: • Proposed Pediatric Study request: – 1 single dose/multiple dose PK study in 12 - 17 years old – 1 safety & efficacy study in 12 – 17 years old for 1 year • Pharmacodynamic interaction between metformin and topiramate • Topiramate caused hyperthermia may lead to dehydration, which is a risk factor for metformin-induced lactic acidosis • Topiramate caused metabolic acidosis in study participants • Potential association of topiramate induced metabolic acidosis and arrhythmia • Potential decrease in serum potassium concentrations for coadministration of hydrochlorothiazide and topiramate • Lacks interaction between alcohol and modified topiramate release mechanism information, which may affect topiramate t_{max} and in turn affects efficacy • Topiramate release classification (immediate vs. modified release)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

Other comments or information not included above	**Study OB-109 links the Phase 3 clinically-tested formulation and the to-be-marketed formulation. Hence, a DSI inspection on this pivotal bioequivalence study is in order.** **Clinical Site (total of 230 enrolled and 229 completed participants):** **Scott Sharples, MD, Investigator** **MDS Pharma Services,** **2420 W. Baseline Road, Tempe, Arizona 85283** **Study OB-109 "A Randomized, Open Label, Parallel, Single Dose Study to Assess Bioequivalence of the Two Oral Capsule Formulations of the Combination Product VI-0521 in Healthy Subjects"** **Bioanalytical Site:** (b) (4) (b) (6) **Bioanalytical Principal Investigator** **Study: AA87817-01 "A Randomized, Open Label, Parallel, Single Dose Study to Assess Bioequivalence of the Two Oral Capsule Formulations of the Combination Product VI-0521 in Healthy Subjects: LC-MS/MS Determination of Topiramate in Human Plasma (EDTA)"** **Study: AA87817-02 "A Randomized, Open Label, Parallel, Single Dose Study to Assess Bioequivalence of the Two Oral Capsule Formulations of the Combination Product VI-0521 in Healthy Subjects: LC-MS/MS Determination of Phentermine in Human Plasma (EDTA)"**
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

Filing Memo

CLINICAL PHARMACOLOGY	
NDA:	**22-580**
Compound:	Phentermine + topiramate (QNEXA®; 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg)
Sponsor:	VIVUS, Inc.
Submission Date:	December 28, 2009
Relevant IND:	68,651
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

This document presents to the review team the fileability of NDA 22-580 in the clinical pharmacology perspective. The sponsor submitted NDA 22-580 to seek marketing approval for the 3.75/23, 7.5/46, 11.25/69, and 15/92 mg/mg phentermine/topiramate fixed dose combination (FDC) capsules (VI-0521; QNEXA®) to treat obesity, including weight loss and maintenance of weight loss in conjunction with diet and exercise. The sponsor submitted NDA 22-580 under the Federal Food, Drug, and Cosmetic Act's Section 505(b)(2) and relies partly on the FDA's previous determination of safety for the approved phentermine and topiramate products.

The VI-0521 FDC capsule has the following strengths and combinations for daily oral administration:

- 15 mg phentermine immediate release (IR) beads plus 92 mg topiramate modified release (MR) beads – PHEN/TPM 15/92 "full dose"
- 11.25 mg phentermine IR beads plus 69 mg topiramate MR beads – PHEN/TPM 11.25/69 "¾ dose"
- 7.5 mg phentermine IR beads plus 46 mg topiramate MR beads – PHEN/TPM 7.5/46 "½ dose"
- 3.75 mg phentermine IR beads plus 23 mg topiramate MR beads – PHEN/TPM 3.75/23 "¼ dose"

The 3.75, 7.5, 11.25, and 15 mg are expressed as phentermine free base of phentermine HCl.

Phentermine HCl (ADIPEX-P®) has an indication to manage exogenous obesity. ADIPEX-P® is an oral 37.5 mg phentermine HCl (30 mg phentermine free base) IR tablet (ANDA 085128) and IR capsule (ANDA 088023). Patients may take ½ tablet (18.75 mg phentermine HCl) daily or ½ tablet twice daily. Phentermine's original approval was on May 4, 1959 as Ionamin Resin® (NDA 11-613).

Topiramate (TOPAMAX®) has an indication to treat epilepsy as monotherapy and adjunctive therapy (both up to 400 mg daily) as well as prophylaxis of migraine (up to 100 mg daily) as oral 25, 50, 100, and 200 mg topiramate IR tablets (NDA 20-505) and 15 and 25 mg topiramate IR sprinkle capsules (NDA 20-844).

Findings

To support NDA 22-580's Clinical Pharmacology and Biopharmaceutics sections, the sponsor submitted studies' results as indicated in the table above or published literature. Findings' highlights follow:

- The sponsor submitted results for 3 placebo-controlled Phase 3 clinical studies (OB-301, OB-302, and OB-303).
- The sponsor submitted results for 4 Phase 2 clinical studies (OB-201, OB-202, DM-230, and DM-231).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

- The sponsor submitted results for 11 Phase 1 clinical studies (OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, and OB-205).
- The sponsor submitted results for 5 in vitro human material studies for phentermine (8VIVUP3R1, 101-09-001, 8VIVUP2R3, 8VIVU2R4, and 8VIVUP1R1).
- See Attachment for further details of the above studies.
- The sponsor conducted population pharmacokinetic analysis (Report 09-VI0521-POP-PK-01) and population pharmacokinetic/pharmacodynamic analysis (Report 09-VI0521-POP-PK-02) for phentermine and topiramate. The sponsor provided analysis dataset, analysis program, and analysis data definition for both analyses.
- The sponsor submitted proposed labeling with annotation. The submitted studies' results and associated information seem to support the proposed labeling statements but this will be a review issue.
- The sponsor submitted bioanalytical reports for phentermine, topiramate, sitagliptin, metformin, ethinyl estradiol, and norethindrone.
- The sponsor submitted electronic datasets for studies in ".jmp" files.
- The sponsor did not collect any samples for pharmacogenomic analysis.
- Formulation difference exists between [redacted] (b) (4) PHEN/TPM 15/92 capsule's clinically-tested formulation is identical to the PHEN/TPM 15/92 to-be-marketed formulation and does not contain [redacted] (b) (4) Thus the sponsor conducted Study OB-109 to show the human bioequivalence of phentermine and topiramate for the respective 3 lower strengths formulations.
- Per the July 22, 2010 pre-NDA meeting, Clinical Pharmacology commented on the need of pharmacokinetic bridge between Study OB-301's phentermine alone as well as topiramate alone formulations and the commercially available phentermine alone as well as topiramate alone products. Study OB-301 may satisfy the fixed-dose combination rule [CFR 21 Part 300.50 (a)] that the FDC capsule would show added safety/efficacy benefits beyond those of the single ingredient formulations. However, the relative bioavailability of Study OB-301's phentermine alone and topiramate alone formulations should be evaluated against the respective commercial single ingredient products to prevent inferior phentermine alone and topiramate alone formulations that result in lower phentermine and topiramate exposures so that the FDC capsule's added safety/efficacy benefits appear to be larger than those of the single ingredient formulations.
- The sponsor conducted Study OB-110 to assess the relative bioavailability between the to-be-marketed PHEN/TPM 15/92 FDC capsule and 37.5 mg phentermine HCl tablet (ADIPEX-P®) alone as well as 100 mg topiramate tablet (TOPAMAX®) alone. Study OB-103 (food-effect study) also assessed the relative bioavailability between PHEN/TPM 15/92 FDC capsule and PHEN 15 alone capsule as well as TPM 92 alone capsule. The lots of PHEN 15 (#07JM-304) and TPM 92 (#07JM-299) capsules as well as PHEN/TPM 15/92 FDC capsule (#0703834) used in Study OB-103 were also used in Study OB-301. Thus, Studies OB-110 and OB-103's results would address the pharmacokinetic bridge between Study OB-301's PHEN 15 alone and TPM 92 alone formulations and the commercially available phentermine alone and topiramate alone products.

- Study OB-107 has a confounded sequential design to assess the pharmacokinetic interaction between metformin, sitagliptin, or probenecid and the PHEN/TPM 15/92 FDC capsule.
- Safety of the PHEN/TPM FDC capsules such as metabolic acidosis [TOPAMAX® label; Mizra et al. *Br J Clin Pharmacol* **68**:655-61 (2009)] is of concern. Topiramate's approved labeling has this pharmacodynamic interaction statement "Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated."
- Per the annotated label, (b) (4)
- Topiramate tends to cause hyperthermia which may lead to dehydration. Dehydration is a risk factor for metformin-induced lactic acidosis. Obese diabetic patients will likely receive metformin.
- The sponsor conducted 2 specific population studies. Study OB-105 is for mild and moderate hepatic impairment patients. Study OB-106 is for mild, moderate, and severe renal impairment patients.
- The sponsor conducted a thorough QT study (OB-118) for doses of PHEN/TPM 7.5/46 and PHEN/TPM 22.5/138 FDC capsules.
- Study OB-108 assesses the effect of steady state PHEN/TPM 15/92 FDC capsule administration on the pharmacokinetics of single dose oral contraceptive (35 µg ethinyl estradiol/1 mg norethindrone).
- The sponsor did not address the pharmacological activities of metabolites for both phentermine and topiramate.
- The sponsor did not address whether there is chiral inversion via metabolism for topiramate since it has 2 chiral centers.
- The sponsor mentioned both phentermine and topiramate belong to BCS Class 1. However, the BCS Committee deemed neither phentermine nor topiramate is BCS Class 1 compound.

(b) (4)

- (b) (4)

(b) (4)

- The Chemistry, Manufacturing, and Control reviewer found that the in vitro dissolution profiles for topiramate do not match those for modified release mechanism.
- The sponsor seems to use Study OB-205 to address the interaction between alcohol and FDC's modified topiramate release mechanism via the psychomotor effects of alcohol versus those of VI-0521 FDC. However, Study OB-205 does not have the treatment arm of coadministration

of alcohol and VI-0521 in order to address the potential alcohol and modified topiramate release mechanism interaction.

Adequacy of Data for Review of the Proposed Labeling
As a cursory review for filing, the sponsor provided adequate study reports and published articles for substantive review of the proposed labeling. Briefly, the sponsor provided the following data for Section 12:
CLINICAL PHARMACOLOGY
12.1 Mechanism of Action: 09-VI0521-POP-PK-01 and 09-VI0521-POP-PK-02 plus ADIPEX-P® and TOPAMAX® labels
12.2 Pharmacodynamics: 09-VI0521-POP-PK-02 and Integrated Summary of Safety
12.3 Pharmacokinetics: Studies OB-103, 105, 106, OB-109, OB-110,
12.4 Age, Gender Race or BMI Effects on Pharmacokinetics: 09-VI0521-POP-PK-01
12.5 Drug Interactions: Studies OB-107 and OB-108

Attachment starts here.

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Table 1: List of Clinical Studies

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.1.2.1	OB-110	Phase 1 Study Complete Final Clinical Study Report November 2009	To assess the relative BA of PHEN and TPM in VI-0521 compared to the marketed, active, single constituent drug products in healthy subjects	Single-dose, randomized, open-label, 3-treatment, parallel study	VI-0521 (PHEN/TPM) 15/92 mg capsule Adipex-P (Phen) 37.5 mg tablet Topamax (Tpm) 100 mg tablet All doses administered with 240 mL of water Oral Single-dose	41 healthy male and female subjects 18 to 55 years of age, inclusive, with a BMI between 30 and 42 kg/m^2, inclusive, and a body weight of ≥50 kg
5.3.1.2.2	OB-109	Phase 1 Study Complete Final Clinical Study Report November 2009	To assess BE of 2 formulations of VI-0521 (Formulation A, (b) (4) (b) (4) and Formulation B, (b) (4) (b) (4) in healthy subjects	Single-dose, randomized, open-label, 6-treatment, parallel study	VI-0521 Formulation B (PHEN/TPM) 3.75/23 mg capsule VI-0521 Formulation A (PHEN/TPM) 3.75/23 mg capsule VI-0521 Formulation B (PHEN/TPM) 7.5/46 mg capsule VI-0521 Formulation A (PHEN/TPM) 7.5/46 mg capsule VI-0521 Formulation B (PHEN/TPM) 11.25/69 mg capsule VI-0521 Formulation A (PHEN/TPM) 11.25/69 mg capsule All doses administered with 240 mL of water Oral Single-dose	230 healthy male and female subjects 18 to 55 years of age, inclusive, with a BMI between 30 and 42 kg/m^2, inclusive, and a body weight of ≥50 kg

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

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Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.1.2.3	OB-103	Phase 1 Study Complete Final Clinical Study Report April 2009	To assess the effect of food on the BA of VI-0521 and to compare the relative BA of each individual component (phentermine or topiramate) vs. VI-0521	Single-dose, open-label, 4-treatment, parallel study	VI-0521 (PHEN/TPM) 15/92 mg capsule, fasted VI-0521 (PHEN/TPM) 15/92 mg capsule, fed PHEN 15 mg capsule, fasted TPM 92 mg capsule, fasted Oral All doses administered with 240 mL of water Single-dose	65 healthy males and females 19 to 70 years of age with a BMI between 30 and 45 kg/m^2, inclusive

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

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Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.1.2.4	OB-102	Phase 1b Study Complete Final Clinical Study Report July 2009	• To describe the single- and multiple-dose PK profiles of the VIVUS PHEN/TPM formulation the marketed formulations Adipex® and Topamax (only one formulation of PHEN/TPM tested) • To describe baseline adjusted assessments of topiramate formulations dosed with phentermine on body weight, waist circumference, blood pressure, lipid parameters, and VAS hunger and satiety scores	Single- and multiple-dose, open-label, 4-treatment, parallel study	*VIVUS' PHEN 7.5 mg capsule and TPM 25 mg capsule identical in* (b) (4) *and method of manufacturing to those proposed for commercial use* PHEN 7.5 mg capsule + TPM 50 mg capsule PHEN 15 mg capsule + TPM 100 mg capsule Adipex-P 15 mg tablet + Topamax 100 mg tablet Oral Single- and multiple dose with 240 mL water	45 healthy males and females 19 to 65 years of age with a BMI between 30 and 42 kg/m^2, inclusive

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

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Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.1.2.5	OB-101C	Phase 1 Study Complete Final Clinical Study Report June 2007	• To compare the PK of 3 co-administered doses of the marketed products (Topamax® [Tpm] and Phentermine) to split dosing to allow formulation optimization and dose selection for later phase trials • To evaluate safety and tolerability in healthy obese subjects	Single-dose, open-label, randomized, 4-period crossover study	*Commercially available phentermine and topiramate products were used* Topamax 25 mg and Phentermine 15 mg, co-administered Topamax 100 mg and Phentermine 15 mg, co-administered Topamax 125 mg and Phentermine 15 mg, co-administered Phentermine 15 mg at 08:00 a.m. and Topamax 100 mg at 12:00 p.m. Single oral dose with 240 mL water, with ≥7-day washout period between treatments	16 healthy male and female subjects 18 to 45 years of age with a BMI between 27 and 42 kg/m^2, inclusive
5.3.3.3.1	OB-105	Phase 1 Study Complete Final Clinical Study Report July 2009	To assess the single-dose PK of PHEN and TPM in VI-0521 capsules in subjects with mild and moderate hepatic impairment relative to healthy control subjects	Single-dose, non-randomized, open-label, 3-group, parallel study	VI-0521 (PHEN/TPM) 15/92 mg capsule with 240 mL water Oral Single-dose	24 male and female subjects with normal hepatic function and mild to moderate hepatic impairment, 18 to 65 years of age with a BMI between 21 and 38 kg/m^2, inclusive, and a body weight ≥50 kg

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.3.3.2	OB-106	Phase 1 Study Complete Final Clinical Study Report August 2009	To compare the PK of PHEN and TPM following a single dose of VI-0521 in subjects with mild, moderate, and severe renal impairment to subjects with normal renal function	Single-dose, non-randomized, open-label, parallel study	VI-0521 (PHEN/TPM) 15/92 mg capsule with 240 mL water Oral Single-dose	33 male and female subjects with normal renal function and mild to severe renal impairment, 19 to 78 years of age, inclusive, with a BMI between 18 and 40 kg/m^2, inclusive, and a body weight ≥50 kg

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.3.4.1	OB-107	Phase 1 Study Complete Final Clinical Study Report June 2009	• To compare the steady-state PK of TPM, PHEN, SIT, and MET following multiple oral doses of VI-0521 QD, SIT QD, and MET BID when administered alone or in combination in healthy subjects • To evaluate the effect of a single oral dose of PROB on the multiple-dose PK of PHEN and TPM • To determine the semen concentration of TPM following multiple oral doses of VI-0521 QD	Open-label, non-randomized, 1-sequence, crossover study	MET 500 mg tablet BID SIT 100 mg tablet QD VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD PROB 4 × 500 mg tablets (single-dose) Oral All doses administered with 240 mL of water Multiple-step titration of VI-0521 over 8 days, to maximum dose studied (PHEN/TPM 15/92 mg)	20 healthy males and females 19 to 45 years of age, inclusive, with a BMI between 19 and 35 kg/m^2, inclusive, and a body weight ≥50 kg

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.3.4.2	OB-108	Phase 1 Study Complete Final Clinical Study Report June 2009	• To determine whether concomitant administration of multiple oral doses of VI-0521 would alter the single-dose PK of an OC in healthy female subjects • To assess the safety and tolerability of multiple doses of VI-0521 with a single-dose of an OC in healthy female subjects	Open-label, fixed-sequence study	VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD Norethindrone 1.0 mg + ethinyl estradiol 0.035 mg tablets Oral All doses administered with 240 mL of water Multiple-step titration of VI-0521 over 12 days, to maximum dose studied (PHEN/TPM 15/92 mg)	20 healthy female subjects 19 to 45 years of age, inclusive, with a BMI between 27 and 35 kg/m^2, inclusive, and a body weight of ≥50 kg

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.4.1.1	OB-118	Phase 1 Study Complete Final Clinical Study Report August 2009	• To assess whether treatment with one of the possible therapeutic (PHEN/TPM 7.5/46 mg) doses or supra-therapeutic dose (PHEN/TPM 22.5/138 mg) of VI-0521 has the potential to cause QT/QTc prolongation in healthy volunteers • To demonstrate assay sensitivity by showing that MOX, corrected for placebo, produces a QTc change >5 msec	Randomized, double-blind, 3-arm, hybrid cross-over, parallel group Active- and placebo-controlled	Placebo MOX 400 mg tablet VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD VI-0521 (PHEN/TPM) 22.5/138 mg capsule QD All doses administered with 240 mL of water Oral Multiple-step titration of VI-0521 over 15 days, to maximum dose studied (PHEN/TPM 22.5/138 mg)	112 healthy male and female subjects with 1:1 female:male ratio, 19 to 50 years of age, inclusive, with a BMI between 24 and 30 kg/m^2, inclusive

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.4.1.2	OB-205	Phase 2 Study Complete Final Clinical Study Report August 2009	To evaluate the effects of VI-0521 compared to placebo on psychomotor performance with alcohol treatment as an active control	Randomized, double-blind, placebo-controlled, cross-over study	Placebo capsule QD VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD Oral During the titration period, doses were increased at weekly intervals for 4 weeks until VI-0521 (PHEN/TPM) 15/92 mg dose was reached.	80 male and female subjects between 21 and 45 years of age with a BMI between 27 and 35 kg/m^2, inclusive
5.3.5.1.1	OB-201	Phase 2 Study Complete Final Clinical Study Report May 2009	To compare and evaluate the safety and efficacy of topiramate100 mg QD and phentermine 15 mg QD with corresponding single agents and placebo in obese subjects prescribed a mildly hypocaloric diet	Randomized, double-blind, 2×2 factorial, parallel study Placebo-controlled	*Commercially available phentermine and topiramate products were used* Placebo Phen 15 mg capsule + placebo QD Tpm 100 mg capsule + placebo QD Phen 15 mg capsule (QD, a.m.) + Tpm 100 mg capsule (QD, p.m.) Oral 4-week titration period followed by a 24-week treatment period	200 healthy male and female subjects 18 to 60 years of age, inclusive, with a BMI between 30 and 50 kg/m^2, inclusive

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.5.1.2	OB-202	Phase 2 Study Complete Final Clinical Study Report July 2009	To demonstrate that the combination of Phen and Tpm is superior to placebo for improvement of glycemic control, in the presence of intensive background care, as measured by a reduction of glycosylated HbA_{1c} levels at 16 and 28 weeks	Randomized, double-blind, placebo-controlled, parallel, prospective study	*A dry powder blend of either Phen or Tpm drug substance was encapsulated and administered as separate capsules* Placebo capsule Phen 5 mg capsule (QD, a.m.) + Tpm 25 mg capsule (QD, p.m.) Phen 7.5 mg capsule (QD, a.m.) + Tpm 50 mg capsule (QD, p.m.) Phen 11.25 mg capsule (QD, a.m.) + Tpm 75 mg capsule (QD, p.m.) Phen 15 mg capsule (QD, a.m.) + Tpm 100 mg capsule (QD, p.m.) Oral 4-week titration period followed by a 24-week treatment period at the assigned dose level	210 male and female subjects between 18 and 70 years of age with a diagnosis of controlled T2DM and a BMI between 27 and 45 kg/m^2, inclusive

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.5.1.3	(b) (4)					
5.3.5.1.4	OB-301	Phase 3 Study Complete Final Clinical Study Report June 2009	• To demonstrate that 2 different dose levels of VI-0521 results in weight loss that is greater than placebo and the single-agent PHEN and TPM constituents that compromise each dose • To evaluate the safety of 2 different doses of VI-0521 compared to placebo and the single-agent constituents	Randomized, double-blind, placebo-controlled study	Placebo capsule QD PHEN 7.5 mg capsule QD PHEN 15 mg capsule QD TPM 46 mg capsule QD TPM 92 mg capsule QD VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD Oral 4-week titration period followed by a 24-week treatment period	756 male and female subjects ≤70 years of age with a BMI between 30 and 45 kg/m^2, inclusive

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.5.1.5	OB-302	Phase 3 Study Complete Final Clinical Study Report October 2009	To evaluate the safety and efficacy of 2 doses of VI-0521 for the treatment of obesity in adults with a BMI ≥35 kg/m^2	Randomized, double-blind, placebo-controlled study	Placebo QD VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD Oral 4-week titration period followed by a 52-week treatment period at the assigned dose level	1267 male and female subjects ≤70 years of age with a BMI ≥35 kg/m^2
5.3.5.1.6	OB-303	Phase 3 Study Complete Final Clinical Study Report November 2009	To evaluate the safety and efficacy of 2 doses of VI-0521 for the treatment of obesity in adults with ≥2 obesity-related, co-morbid conditions and to examine the effects of VI-0521 on obesity-related co-morbidities	Randomized, double-blind, placebo-controlled study	Placebo capsule QD VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD VI-0521 (PHEN/TPM) 15/92 mg capsule QD Oral 4-week titration period followed by a 52-week treatment period at the assigned dose level	2487 male and female subjects ≤70 years of age with a BMI between 27 and 45 kg/m^2, inclusive, with ≥2 obesity-related, co-morbid conditions

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

Table 1: List of Clinical Studies (Continued)

Location of the Study Report	Study Identifier	Type of Study Study Status Type of Report Date of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
5.3.5.2.1						(b) (4)

The 4-week titration schedule that was followed during studies was as follows: Week 1: VI-0521 (PHEN/TPM) 3.75/23 mg capsule QD; Week 2: VI-0521 (PHEN/TPM) 7.5/46 mg capsule QD; Week 3: VI-0521 (PHEN/TPM) 11.25/69 mg capsule QD; Week 4: VI-0521 (PHEN/TPM) 15/92 mg capsule QD.
BA = bioavailability; BE = bioequivalence; BMI = body mass index; CSR = Clinical Study Report; HbA_{1c} = hemoglobin A_{1c}; IR = immediate release; MET = metformin; MOX = moxifloxacin; MR = modified release; OC = oral contraceptive; Phen = phentermine; PHEN = IR phentermine beads; PK = pharmacokinetic; PROB = probenecid; QD = once-daily; SIT = sitagliptin; T2DM = type 2 diabetes mellitus; Tpm = topiramate; TPM = MR topiramate beads; VAS = visual analog scale; VI-0521 = fixed-dose combination of phentermine/topiramate.
Sources: OB-101C, OB-102, OB-103, OB-105, OB-106, OB-107, OB-108, OB-109, OB-110, OB-118, OB-201, OB-202, OB-205, DM-230, DM-231, OB-301, OB-302, and OB-303 CSRs

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/

S. W. JOHNNY W LAU
03/26/2010

SALLY Y CHOE
03/26/2010