

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201635Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW MEMORANDU: ADDENDUM

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<b>NDA</b>	NDA 201-635
<b>Brand Name:</b>	Trokendi XR™
<b>Generic Name:</b>	Topiramate Extended-Release Capsules
<b>Sponsor:</b>	Supernus Pharmaceuticals, Inc.
<b>Submission:</b>	505(b)(2), Standard
<b>Submission Date:</b>	01/14/2011 (original submission); 08/30/2011 (resubmission)
<b>OND Division:</b>	OND-1/Division of Neurology Drug Products
<b>OCP Divisions:</b>	Clinical Pharmacology DCP-1
<b>Primary Reviewer:</b>	Ta-Chen Wu, Ph.D.
<b>Team Leader:</b>	Angela Yuxin Men, M.D., Ph.D.

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In this 505(b)(2) application for Trokendi XR™, the applicant seeks approval by applying a NOVEL bioequivalence (BE)-based method in a PK study, demonstrating the BE at multiple time-points within the 24 hours at steady-state between the proposed Trokendi XR™ capsules given once-daily (QD) and the approved TOPAMAX® IR tablets given twice-daily (BID), without conducting a clinical efficacy trial.

The PK study evaluating the Trokendi XR™ capsules and the reference TOPAMAX® IR tablets (Study 538P103) showed that two formulations are BE with respect to AUC<sub>τ</sub>, C<sub>max</sub>, C<sub>min</sub>, and point-to-point comparison for topiramate partial AUC (AUC<sub>0-p</sub>; 'p' represents time points post-dose) at steady-state. Additional analyses showed that the point-to-point comparisons for topiramate plasma concentrations and the partial AUC between time-points (AUC<sub>t1-t2</sub>) are bioequivalent at steady-state for most of the time points throughout the day based on conventional BE criteria, except for the initial time points, mostly before 1.5 hour postdose. Please refer to the NDA201635 Clinical Pharmacology Review in DARRTS (dated 5/25/2012) for detailed information.

This addendum confirms that the applicant's BE approach is novel and has not been utilized in the past within Office of Clinical Pharmacology and Office of Generic Drugs for regulatory approval.

Ta-Chen Wu, Ph.D.  
Reviewer, Neurology Drug Products  
DCP-1, Office of Clinical Pharmacology

Angela Yuxin Men, M.D., Ph.D.  
Team Leader, Neurology Drug Products  
Office of Clinical Pharmacology

Concurrence: Mehul Mehta, Ph.D.  
Director, Division of Clinical Pharmacology-1  
Office of Clinical Pharmacology

cc: HFD-120 NDA 201-635  
CSO/J. Ware  
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/s/  
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TA-CHEN WU  
06/22/2012

YUXIN MEN  
06/22/2012

MEHUL U MEHTA  
06/22/2012

ONDQA Acting Deputy Office Director Memo  
NDA 201635, TROKENDI (topiramate)  
Extended Release Capsules, 25, 50, 100, and 200 mg  
Date: 13-JUN-2012

## Introduction

The purpose of this memo is to clarify and move forward the ONDQA-Biopharm recommendation regarding the approval of this NDA. Please see primary and secondary ONDQA-Biopharm reviews entered into the DARRTS record by Drs. Selen and Dorantes respectively. The drug product capsules contain coated beads which release the active drug in a controlled extended manner. There are several different types of beads comprising each strength of ER capsule drug product.

## Summary

In terms of in-vitro dissolution performance, the drug product exhibits low variability within a given batch. Between batches however, the variability is greater.

Specifically for the three hour time point, between batch variability resulted in a proposed dissolution range of approximately the mean (of multiple batches at this time point) (b) (4). Normally, a range of (b) (4) about the mean in situations such as this is considered a good quality product.

Although this is the first ER dosage form for this drug, topiramate is not new to the United States market. It has a known safety and efficacy history. Also, the three hour time point is near the inflection point of the dissolution profile curve. Greater dissolution variability is expected to be seen in the time range of the inflection point.

In a telephone discussion with the assigned OND Medical Officer (Dr. Martin Rusinowitz, 05-JUN-2012 at 11:41 a.m.), there was no obvious risk to safety or efficacy that he knew of which would preclude allowing the (b) (4) window for dissolution at the three hour time point. Thus, from the ONDQA-Biopharm primary review perspective, the (b) (4) window at the three hour dissolution time point was also a reasonable and acceptable risk in terms of safety and efficacy.

The applicant knew that the between batch variability was larger than the within batch variability and they addressed it. The source of the variability which the applicant was more recently learning to control, appears to involve the functional release coating (b) (4) as follows:

(b) (4)

The extended release technology and release controlling coating material used to make this drug product are not new. Furthermore, there is low dissolution variability seen over expiry within a batch at the three hour time point. Under normal circumstances the performance between batches (robustness) should be correspondingly similar to within batch performance. In this case a (b) (4) dissolution range at the three hour time point should be reasonably achievable.

In FTF discussions with Christine Moore (Acting Office Director for ONDQA), she expressed her concern over this lack of robustness of dissolution performance based on the NDA stability batch performance. The applicant is aware of this robustness issue, and they have addressed it and provided a reasonable approach to mitigate the variability between batches as described in item number 2 above. Unfortunately, this last control was not implemented in the NDA stability batches.

### **Conclusion**

While there is no known risk to safety or efficacy by allowing the (b) (4) dissolution limits at the three hour time point, data provided by the applicant indicate that recent improvements in the control of the excipient (b) (4) will reduce between batch variability to a level normally associated with a good quality drug product of this type (e.g., (b) (4)).

### **Recommendation.**

ONDQA-Biopharm recommends that the applicant's proposed dissolution criteria be accepted as amended via their recent agreement to the Q (b) (4) at six (6) hour condition. However, as part of this recommendation, the applicant will be asked to agree to provide appropriate data within fourteen (14) months of approval (via the appropriate submission pathway) which either support the current specification or provide the basis to tighten the 3 hour dissolution limit to (b) (4) about the mean.

### **Comments to be sent to the applicant. NOTE: An agreement is being sought.**

- 1. Your proposal of setting the dissolution acceptance criteria for your product on an interim basis for one year is acceptable. Please provide the updated specification Table for your product with the revised dissolution criteria.*
- 2. Additionally, we remained most concerned regarding the three (3) hour time point dissolution limits which appear to be set wide based on between batch variability. We*

*acknowledge that you have identified the root cause of the variability observed in the dissolution data between batches and that you have implemented a corrective action which is expected to minimize between batch variability in commercial manufacturing. Therefore, for the setting of the final dissolution acceptance criteria, we request that you agree to the following:*

- *To collect additional dissolution profile data for the commercial validation batches (each strength) manufactured during the first year after the action date, targeting more appropriate acceptance criteria in alignment with the FDA standards described in IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).*
- *To use the additional dissolution data generated from the commercial validation batches for the setting of the final acceptance criteria.*
- *To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches which are based on and reflective of the data discussed herein.*

Respectfully submitted,

Richard (Rik) Lostritto, Ph.D.  
Acting Deputy Office Director, ONDQA

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/s/  
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RICHARD T LOSTRITTO  
06/18/2012

## ONDQA BIOPHARMACEUTICS PRODUCT QUALITY REVIEW

<b>NDA Number</b>	<b>201-635 (Original NDA) resubmission (0006)</b>
<b>Product name, generic name of the active, and dosage strength and form</b>	<b>Topiramate, 25-, 50-, 100- and 200-mg Extended Release capsules (Trokendi® XR capsules)</b>
<b>Submission date</b>	<b>First submission:1/13/2011 RTF: March 2011 Second submission: 09/9/2011</b>
<b>Applicant</b>	<b>Supernus Pharmaceuticals, Inc. Rockville, MD</b>
<b>Medical Division</b>	<b>Division of Neurology Products</b>
<b>Type of Submission</b>	<b>505 b(2), Type 3 : New Dosage Form</b>
<b>Primary CMC/Quality Reviewer</b>	<b>Thomas M. Wong, Ph.D.</b>
<b>Biopharmaceutics Reviewer</b>	<b>Arzu Selen, Ph.D.</b>

### BACKGROUND

Topiramate is a sulfamate-substituted monosaccharide. Immediate release dosage forms, 25-, 50-, 100- and 200-mg topiramate tablets (TOPAMAX®, NDA 20-505) and 25-mg and 50-mg topiramate capsules, Sprinkle Capsules (TOPAMAX®, NDA 20-844) manufactured by Janssen were approved as an anti-epileptic in 1996 and 1998.

The first submission of this NDA was in January 2011 and it was refused to file. Subsequently, it was resubmitted by the Applicant in September of 2011.

The Applicant is seeking monotherapy and adjunctive therapy indications for epilepsy with once a day oral dosing of the topiramate extended-release capsules. The proposed Indications are:

- Monotherapy epilepsy: Initial monotherapy in patients ≥10 years of age with partial onset or primary generalized tonic-clonic seizures, and
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome.

### SUBMISSION

Initially, the Applicant identified the proposed product as TPM CR (topiramate controlled-release) and used the notation SPN-538T for the proposed drug product. Subsequently, Supernus has used a different identifier for this product such as TPM XR or TPM ER (topiramate extended-release) and more recently, the proposed product is identified as Trokendi XR. For purposes of this review, topiramate ER capsules are also referred to as Trokendi XR capsules.

Topiramate extended-release (Trokendi XR) capsules, 25mg, 50mg, 100mg, and 200mg, are intended for once-a-day administration and each strength contains three different types of mini-pellets (also called intermediate pellets) with different release characteristics (immediate release and two types of extended release mini-pellets).

The composite delivery profile is based on delivery from the immediate release (IR) mini-pellets (b) (4) of the label claim) and two extended-release pellet types contributing (b) (4) of the label claim.

The Applicant is submitting mainly clinical pharmacology studies to seek NDA approval via 505(b)(2) path for target patient population of (b) (4) for the proposed product. The Applicant is stating that except the difference in the age groups, the target indications are the same as TOPAMAX® tablet and sprinkle capsule formulations (approved for use in patients 2 years old and older).

The following table is a list of the early clinical studies (already completed) and the dosage strengths that were studied.

**Table 1**

**Table 1: Summary of Biopharmaceutical Studies**

Study	Objective	Dose	Crossover Treatment/ sequence/ period	Treatments				Subjects enrolled
				1	2	3	4	
583P103	Steady-state bioavailability	Multiple	2/2/2	200mg SPN-538T	200mg TOPAMAX®			39
538P104	Dose proportionality	Single	4/4/4	8 X 25mg SPN-538T	4 X 50mg SPN-538T	2 X 100mg SPN-538T	1 X 200mg SPN-538T	34
538P104.5	Dose linearity	Single	4/4/4	25mg SPN-538T	50mg SPN-538T	100mg SPN-538T	200mg SPN-538T	36
538P105	Food effect	Single	2/2/2	200mg SPN-538T Fed	200mg SPN-538T Fasted			32
538P106	Bridging, manufacturing sites	Single	2/2/2	100mg SPN-538T	100mg TPM ER*			28
538P106-50	Bridging, manufacturing sites	Single	2/2/2	50mg SPN-538T	50mg TPM ER*			32
538P106-200	Bridging, manufacturing sites	Single	2/2/2	200mg SPN-538T	200mg TPM ER*			32

\* For this table, TPM ER represents the product produced at the commercial manufacturing facility; SPN-538T represents the product produced at Supernus for clinical studies.

The Applicant refers to 4 additional clinical studies (2 completed and 2 ongoing at the time of this submission).

Of the two completed studies, Study 538P109 was conducted to compare pharmacokinetics of topiramate in healthy young (average age 33 years) and elderly (average age of 75) subjects. In the same study, topiramate relative bioavailability was evaluated following administration of contents of the topiramate ER 100-mg capsule mixed in one tablespoon of applesauce. Based on information submitted by the Applicant, topiramate bioavailability was similar when given as intact capsules or capsule contents mixed in one tablespoon of applesauce prior to administration. For the clinical pharmacology review of Study 538P109 and Study 538P108 (14-day repeated dose comparative study), please see Dr. Ta-Chen Wu’s clinical pharmacology review for his assessment of these studies.

**BIOPHARMACEUTICS SUMMARY**

This Biopharmaceutics findings and assessments section (starting on page 9 of this document) is specific for biopharmaceutics/product quality characterization of the proposed Trokendi XR (topiramate ER) capsules and also focuses on the evaluation of the proposed dissolution method and dissolution acceptance criteria for the proposed Trokendi XR capsules and the capsule contents (mini-pellets) and the dissolution acceptance criterion for the IR mini-pellets.

Please see Dr. Thomas Wong’s CMC/product quality review for his assessment of chemistry, manufacturing and controls of the Trokendi XR capsules.

In summary, this biopharmaceutics review addresses the following:

- 1) Biowaiver request for the 25-mg topiramate ER capsules
- 2) Dissolution method including the acceptance criteria for the capsules and the capsule contents (with ER characteristics) and the dissolution criterion for the mini-pellets with IR characteristics
- 3) Use of applesauce as a vehicle for administration of the capsule contents (not recommended by the Applicant)
- 4) Effect of alcohol on product integrity and potential of in vivo dose-dumping in the presence of alcohol

**Summary of the Biopharmaceutics Findings and Assessments:**

- 1) The requested biowaiver for the 25-mg capsules is acceptable for the following reasons:
  - a. The mini-pellets contained in the 25-mg and 50-mg capsules are of the same type and composition-proportional in the 25- mg and 50-mg Trokendi XR capsules (the 50-mg capsules contain twice the amount of the same type of mini-pellets contained in the 25-mg capsules).
  - b. In vitro dissolution profiles for release of topiramate from the ER capsules are similar for the two strengths when compared at pH 1, 4.5, 6.8, 7.5 and in de-ionized water. The f2 values were greater than 50 when in vitro dissolution profiles for the 25-mg and 50-mg Trokendi XR capsules were compared in pH 7.5 medium according to the proposed dissolution method.
  - c. In the clinical studies (538P104.5 and 538P104) assessing linearity in topiramate pharmacokinetics (over the 25-mg to 200-mg dose range) and in the unit-dose proportionality study comparing, 25-, 50-, 100- and 200-mg capsules at the 200-mg dose, in vivo exposure from the 25-mg capsules were dose-proportional and provide adequate in vivo bridging data for the 25-mg capsules to the other strengths. Please see Dr. Ta-Chen Wu's review for his assessment of these studies.

The dose-proportional in vivo exposures are consistent with the in vitro dissolution/performance results including dose-proportional composition of the 25-mg and 50-mg Trokendi XR capsules.

There is no IVIVC (in vitro in vivo correlation) established for predicting one-to-one in vitro to in vivo outcomes, however, based on the similarity of in vitro performance of the 25-, 50-, 100- and 200-mg Trokendi XR capsules and the mini-pellets in multiple pH media, similar in vivo performance is expected from the four strengths and was also observed in Study 538P104.

Based on in vitro and in vivo assessments, there is adequate information to support bioequivalence of the 25-mg capsules, at equimolar dose, to the higher strengths (also manufactured at commercial scale) and the biowaiver request for the 25-mg capsules is acceptable. This is also consistent with the FDA guidance- Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, March 2003, Revision 1.

- 2) Dissolution method and the proposed acceptance criteria for the proposed Trokendi XR capsules and the capsule contents (mini-pellets) are summarized under the recommendations section and are considered acceptable by this reviewer with minor revisions as indicated on page 7 of this review (and should be communicated to the Applicant).

The Applicant has provided extensive in vitro dissolution information for characterization of performance of the drug product over the pH range observed in vivo and during stability testing for the two presentations (100-count bottle and (b) (4)). In addition, the Applicant has provided the rationale and the data supporting the proposed dissolution method (USP Apparatus 2 (paddle), 50 rpm, 750 mL of pH 7.5 phosphate buffer at 37 °C ± 0.5 °C

In vitro dissolution testing was carried out at 1, 2, 4, 6, 8, and 10 hrs for the three stability batches with the proposed presentations (i.e. 100-count bottle and (b) (4)), at stability testing (25°C/60%RH) for 12 months, at the time of submission and under accelerated conditions. The provisional dissolution/release acceptance criteria are shown in Table 2:

**Table 2**

**Table 1: Provisional Dissolution Specifications Used for Release and Stability Testing of Registration Batches**

Capsule Strength	Provisional Dissolution Specifications <sup>a</sup>	
25mg and 50mg	Time (hours)	Percent Dissolved (b) (4)
	2	
	4 8	
100mg	Time (hours)	Percent Dissolved (b) (4)
	2	
	4 8	
200mg	Time (hours)	Percent Dissolved (b) (4)
	2	
	4 8	

<sup>a</sup> Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

The Applicant has provided the dissolution profiles (over a 10 hr period), and is proposing the following dissolution acceptance criterion for the Trokendi XR capsules (in Table 3).

**Table 3**

**Table 2: Proposed Commercial Dissolution Specifications**

Capsule Strength	Proposed Commercial Dissolution Specifications <sup>a</sup>	
25mg and 50mg	Time (hours)	Percent Dissolved (b) (4)
	1	
	3 8	
100mg	Time (hours)	Percent Dissolved (b) (4)
	1	
	3 8	
200mg	Time (hours)	Percent Dissolved (b) (4)
	1	
	3 8	

<sup>a</sup> Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

Review of the data sets support the Applicant's selection of 1 and 3 hr sampling times as more informative sampling times compared to the 2 and 4 hrs as the Applicant had initially planned. The purpose of collection of samples at these time points is to capture the early and mid point of dissolution of the topiramate ER capsules. The Applicant's proposal for selecting 1 and 3 hrs for sample collection times, is acceptable as it provides better characterization of the in vitro performance the product.

At the 1 hr sampling point, the major contributor to the dissolution results is the immediate release component and by 3 hrs, partial contribution from the extended release pellets become evident.

For the 25-, and 50-mg Trokendi XR capsules (b) (4) at release and for stability testing, the Applicant is proposing the topiramate dissolution acceptance range for the intact capsules as (b) (4) at 1 hr, (b) (4) at 3 hr and equal to (b) (4) of the label claim at 8 hrs. This proposed range is acceptable with dissolution of (b) (4) of the label claim at 6 hrs.

Similarly, for the 100-mg Trokendi XR capsules (b) (4) at release and for stability testing, the Applicant is proposing the topiramate dissolution acceptance range for the intact capsules as (b) (4) at 1 hr, (b) (4) at 3 hr and equal to (b) (4) of the label claim at 8 hrs. This proposed range is acceptable with dissolution of (b) (4) of the label claim at 6 hrs.

The 200-mg Trokendi XR capsules contain (b) (4). This may explain the (b) (4). The Applicant is proposing the topiramate dissolution acceptance range for the intact 200-mg Trokendi XR capsules as (b) (4) at 1 hr, (b) (4) at 3 hr and equal to (b) (4) of the label claim at 8 hrs. Based on review of individual dissolution data, including drug product performance in pH 1.1, 4.5 6.8, 7.5 and in de-ionized water, this reviewer agrees with the Applicant's recommendation for the 1 and 3 hr sample collection times and the dissolution acceptance range and instead of 8 hrs being the last sample, recommends 6 hrs sampling time as the third sample collection time for the 200-mg Tokendi XR capsules. The low boundary of the dissolution acceptance range at 6 hrs would be the same as proposed for the 8 hr sample- it would be equal to (b) (4) of the label claim.

With the recommended adjustment as listed on this page for the 25-, 50-, 100- and 200-mg capsules, this reviewer finds the Applicant's proposed dissolution method and acceptance criteria for the Trokendi XR capsules acceptable.

Based on extensive in vitro and biopharmaceutics characterization of the Trokendi XR capsules, this reviewer believes and supports the broader mean (b) (4) dissolution acceptance range proposed by the Applicant for the 3 hr samples. This reviewer also believes that there would be no discernable in vivo difference if the products with in vitro dissolution range of mean (b) (4) at 3 hrs and mean (b) (4) at 3 hrs were compared in a clinical bioavailability study. Furthermore, additional dissolution testing (L3) would not add to the product quality, hence, narrowing the range would not provide a direct impact on product quality. This reviewer supports the mean (b) (4) acceptance range at 3 hrs dissolution testing time point and believes that this approach (not requiring additional in vivo studies) is also consistent with the "good cause" regulations outlined in 21 CFR 320.22 (e).

- 3) Although the Applicant is recommending dosing Trokendi XR capsules intact, they have also included an in vivo relative bioavailability study (538P109) where capsule contents were mixed in a tablespoonful of applesauce and given to healthy volunteers.

This suggests the possibility of using applesauce as a vehicle for administering the capsule contents (mini-pellets) to patients who may not be able to swallow the capsules.

As a rationale for not recommending giving capsule contents in applesauce, in the submission, the Applicant is referring to patent issues. It is unclear whether these patent issues may be addressed in the future. At that time, data for assessment of product integrity and in vitro performance of the mini-pellets exposed to applesauce over extended periods would be needed.

In addition, the Applicant may need to be reminded to provide labeling information for soft food and drinks that are unsuitable for use as vehicles for administering contents of the Trokendi XR capsules.

- 4) Effect of alcohol (in vitro testing):

Topiramate release from Trokendi XR capsules was affected by the presence of alcohol in the dissolution medium when Trokendi XR capsules were evaluated using USP Apparatus 2 (paddle) at 50 rpm, in 750 ml of dissolution medium (0.1 HCl) containing varying amounts of ethanol. The effect of alcohol on the dosage form was more noticeable with 20% (v/v) and marked with 40% (v/v) alcohol in the dissolution medium (essentially, topiramate release was (b) (4)

The Applicant has not conducted a clinical in vivo study to evaluate the effect of alcohol on in vivo performance of this product.

The Applicant has conducted a comparative study in dogs with the IR topiramate and the topiramate ER capsules given with water or water containing 10% or 40% ethanol (total 10 mL dosing volume). This study is exploratory and may have provided some insight to the Applicant but it has no value for characterizing potential in vivo dose-dumping of the Trokendi XR capsules in the presence of alcohol which would be a very serious safety concern.

Furthermore, the dog was never shown to be a suitable in vivo predictive model for potential dosage form and alcohol interaction in humans. Although not considered part of this review, some information from the dog study is included in the Appendix 4 for ease of reference for future discussions for in vivo and in vitro studies.

As a side note, at the pre-NDA meeting and other meetings, a clinical alcohol dose-dumping study was requested from the Applicant due to the observed marked effect of alcohol on topiramate release from the Trokendi XR capsules. However, the Applicant has not responded to this request. This is documented in meeting minutes with the Applicant.

A strong labeling language for inclusion under sections 5 and 7 (Warnings and Precautions, and CNS depressants) and possibly under contraindications, highlighting the potential safety issue due to the effect of alcohol on drug release from this product was recommended to the review team.

**Other Considerations**

In addition, the Applicant states that topiramate is a BCS (Biopharmaceutics Classification) 1 drug; highly soluble and highly permeable although this classification determination has not been made by the Agency. There are some publications suggesting that absorption of topiramate may be complex and not as one might expect from a drug classified as BCS 1. Furthermore, for this extended release product, release of topiramate is significantly altered, such that median tmax values in the clinical trials are typically 20- 24 hrs and range from 10 to 48 hrs. Following administration of the topiramate IR dosage forms, topiramate tmax values are generally, 1-2 hrs under fasted conditions (References 1, 2).

In vitro results, mimicking to some extent in vivo conditions, exposure to acidic medium (pH 1.1) for 2 hrs, followed by in vitro exposure to pH 7.5 medium for 8 hrs show that approximately (b) (4) of the topiramate label claim is dissolved by 6 hrs and approximately (b) (4) of the label claim is dissolved/released by 10 hrs from the Trokendi XR capsules. As there is no in vivo data other than the tmax values that are greater than 10 hrs, indicating gradual drug release/absorption, it appears that in vivo topiramate dissolution/release represents a net effect of the dissolution/release from the pellets and continued dissolution/release from the precipitates that are formed following drug release from the pellets. This observation has led to the recommendation of the 6hr window for avoiding alcoholic beverages after the Trokendi XR dose is taken.

**RECOMMENDATION AND CONCLUSION ON APPROVABILITY**

Following review of the biopharmaceutics information in this NDA 201-635 for 25-, 50-, 100- and 200-mg Trokendi XR (topiramate ER) capsules, the provided information on biopharmaceutic characteristics of the product, the dissolution method and dissolution/release acceptance criteria for the intact capsules are adequate with the revision that for all strengths, release of topiramate is (b) (4) of the label claim at 6 hrs instead of 8 hrs.

The following proposed dissolution method and the dissolution acceptance criteria for the Trokendi XR capsules are acceptable. For the 25-mg, 50-mg, 100- mg and 200-mg Trokendi XR capsules, dissolution method including the acceptance criteria are as follows:

Method	Dissolution Acceptance Criteria for Trokendi XR capsules		
	25-mg, and 50-mg	100-mg	200-mg
<b>USP Apparatus:</b> 2 (paddle) <b>Spindle</b> <b>Rotation:</b> 50 rpm <b>Medium volume:</b> 750 mL <b>Temperature:</b> 37°C <b>Medium:</b> pH 7.5 phosphate buffer	1 hr: (b) (4)	1 hr: (b) (4)	1 hr: (b) (4)
	3 hr: (b) (4)	3 hr: (b) (4)	3 hr: (b) (4)
	6 hr (b) (4)	6 hr (b) (4)	6 hr (b) (4)

## Conclusion on Approvability

From the biopharmaceutics perspective, NDA 201-635 for the 25-, 50-, 100- and 200-mg Trokendi XR capsules is recommended for approval with the above dissolution method and acceptance range for the 25-, 50-, 100- and 200-mg Trokendi XR capsules.

## SIGNATURES

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**Arzu Selen, Ph.D.**  
**Biopharmaceutics Research Lead,**  
**Office of New Drug Quality Assessment**

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**Richard T. Lostritto, Ph.D.**  
**Acting Supervisory Biopharmaceutics Lead**  
**Office of New Drug Quality Assessment**

## References:

- 1) W. E. Rosenfeld, D. R. Doose, S. A. Walker et al. "A Study of Topiramate Pharmacokinetics and Tolerability in Children with Epilepsy", *Pediatric Neurology*, 20: 339- 344, 1999.
- 2) D. H. Doose, S. A. Walker, L. G. Gisclon, and H. K. Nayak, "Single-Dose Pharmacokinetics and Effect of Food on the Bioavailability of Topiramate, A Novel Antiepileptic Drug *J Clin Pharmacol* 1996 36: 884-891, 1996

**BIOPHARMACEUTICS FINDINGS AND ASSESSMENT**

**Drug substance**

Topiramate has a pKa of 8.61 at 25 °C and its solubility is approximately 11-12 mg/mL over the physiologic pH range as shown below (Table 4).

**Table 4**

**Table 1: Topiramate Aqueous Solubility at Various pH at 37°C**

pH	Aqueous Solution	Topiramate Solubility (mg/mL)
1.0	0.1N HCl	11.3
2.5	Acid Phthalate Buffer	12.9
4.7	Acetate Buffer	12.3
6.8	Phosphate Buffer	11.4
7.5	Phosphate Buffer	12.3

The Applicant has also determined that topiramate is sensitive to acidic pH (pH 1.1) and its degradation rate, depending on the temperature the sample is kept at, varies from (b)(4)% of label claim per hour. The results obtained from a 24 h study evaluating degradation of topiramate across the GI track pH range are provided in Table 5. Based on this, exposure to acidic media less than pH 4.5 should not be recommended.

**Table 5**

**Table 19: Topiramate Degradation Rates in Various pH Media**

Condition of Solution	Rate of Degradation (% label claim/hour)				
	pH 1.1	pH 4.5	pH 6.8	pH 7.5	DI Water
Kept at 5°C after sampling from dissolution bath @ 45 minutes	(b)(4)				
Kept at ambient conditions after sampling from dissolution bath @ 45 minutes					
Kept at 5°C after sampling from dissolution bath (37°C) at time point intervals from 1 to 10.67 hours					

(b)(4). The samples maintained at ambient conditions and re-analyzed after 8 days in each medium, showed adequate stability in pH 4.5 (b)(4) %LC, pH 6.8 (b)(4) %LC, pH 7.5 (b)(4) %LC, and DI water (b)(4) %LC. The degradation in pH 1.1 continued as described above.

Topiramate is (b)(4) by the manufacturer (ScinoPharm, Taiwan) and the particle size acceptance criteria is provided as follows:

(b)(4)

**Product Development**

Topiramate ER capsules are manufactured by Catalent Pharma Solutions in Winchester, Kentucky and packaged by (b) (4).

The Applicant initially developed single pellet formulations with various immediate release and extended release characteristics and these were studied in the 538P101 single-dose clinical study. In the Study 538P101 a corresponding rank order in *in vitro* dissolution rate and in mean topiramate plasma concentrations was observed. The results of the clinical study 538P101 led to development of three 50mg, multi-bead composite formulations of topiramate extended-release capsules which were studied in the 538P102 (a steady-state human clinical study). Dissolution profiles from these formulations are shown in Figure 1.

**Figure 1**  
**Figure 2: Dissolution Profiles of Multi-pellet Composite Research Scale Topiramate Controlled Release (Extended-Release) Capsules Studied in 538P102**



One of the three composite controlled-release formulations (Capsule C) studied in 538P102, a three-bead (three-pellet) formulation with one immediate release pellet (b) (4), and two different extended release mini-pellets (b) (4) was further developed into a development/laboratory scale formulation into four drug strengths of 25-, 50-, 100- and 200 mg topiramate extended-release capsules for once daily dosing. The immediate release (b) (4) pellet type and two extended release (b) (4) pellet types were contributing (b) (4) respectively, to the total topiramate dose. In order to develop the product with practical capsule sizes ranging from the 25 mg to 200 mg Trokendi XR capsules, the Applicant is stating that they further developed (b) (4)

(b) (4)

Composition of the topiramate ER capsule strengths and the composition of the capsule contents (mini-pellets) and the clinical trials they were studied in are provided in Table 6.

**Table 6**

**Table 12: Theoretical Formulation Compositions of Development Scale Topiramate Extended-Release Capsules Used in Human Clinical Studies**

Component	Reference to Quality Standard	Function	25mg Capsules (mg/capsule)	50mg Capsules (mg/capsule)	100mg Capsules (mg/capsule)	200mg Capsules (mg/capsule)
			538P104 538P104.5	538P103 538P104 538P104.5	538P103 538P104 538P104.5 538P106	538P103 538P104 538P104.5 538P105 538P106-200
(b) (4)						
[Redacted Content]						
(b) (4)						
[Redacted Content]						
(b) (4)						
[Redacted Content]						

## In Vitro Drug Product Characterization and Dissolution Testing

In this submission, the proposed dissolution method is USP Apparatus 2, using 750 mL of 50 mm phosphate buffer (pH 7.5) at 50 rpm. This is the same method as proposed in the first submission. However, the dissolution method development report is expanded and it is more informative compared to the first report submitted by the Applicant (TR-09-008.00) in the first submission. The focus of the first report was on determining the effect of using   (b) (4)

Additional descriptive information related to product composition, characterization of batches studied in clinical trials and in vitro comparison of the dissolution of the development scale product and commercial scale product are provided in Appendix 1. Comparison of the development scale and commercial scale pellets, also using the proposed dissolution method are also provided in Appendix 1.

Also in Appendix 1, for illustrative purposes, mean concentration-time profiles comparing multiples (as appropriate) of the 25-mg, 50-mg, 100-mg and 200-mg capsules, at 200-mg, dose are provided as well as comparison of topiramate pharmacokinetic parameters from 50-mg, 100-mg and 200-mg topiramate ER development and commercial scale capsules.

For all strengths, in vitro comparison of the products using USP Apparatus 2 (paddle) 50 rpm, in 750 mL of 50 mm phosphate buffer at pH 7.5 yielded acceptable f2 values (>50).

In the following Figures 2 and 3, in vitro comparison of the products studied in the clinical trials is provided. In Figure 2, the volume of the dissolution medium is   (b) (4) and in Figure 3, volume of the dissolution medium is 750 mL.

**Figure 2**

**Mean (n=6) in vitro dissolution of topiramate ER capsules studied in clinical trials**

Note: 25-, 50- and 100-mg capsules studied in 538P104, and 538P104.5 and 200-mg capsules studied in 538P103, 538P104, 538P104.5 and 538P105. Data in App. 2.7.1.4 Table3



Figure 3

**Mean (n=6) in vitro dissolution of topiramate ER capsules studied in clinical trials**

Note: 50-mg caps. studied in 538P106-50, 538P108, 100-mg caps. studied in 538P106, 538P108, 538P109 and 200-mg caps. Studied 538P108 and 538P106-200 (Data App. 2.7.1.4 Table 3)



In vitro dissolution test results of the topiramate ER capsules support similar in vitro dissolution characteristics for the 4 strengths except that [REDACTED] (b) (4) and the last sampling point for this strength [REDACTED] (b) (4) should be 6 hrs [REDACTED] (b) (4)

In response to our information request for assessment of the topiramate ER capsules and the mini-pellets in multiple pH media, as shown in the following figures, the Applicant provided results of dissolution testing of the intact capsules and the capsule contents (the mini-pellets) in pH 1, 4.5, 6.8 and 7.5 and de-ionized water.

The in vitro dissolution data for the intact capsules only in pH 7.5 medium are provided in Appendix 2.

As shown in Figures 4 A-D, pH 7.5 buffer medium is the most appropriate medium for dissolution testing of Trokendi XR capsules.

[REDACTED] (b) (4)  
The dissolution method is the same as the method used for intact capsules.

**Figure 4A**

**Figure 32: Mean % Dissolved for Topiramate Extended-Release Capsules, 25mg**



**Figure 4B**

**Figure 33: Mean % Dissolved for Topiramate Extended-Release Capsules, 50mg**



Figure 4C

Figure 34: Mean % Dissolved for Topiramate Extended-Release Capsules, 100mg



Figure 4D

Figure 34: Mean % Dissolved for Topiramate Extended-Release Capsules, 100mg



The Applicant has also provided dissolution testing of Trokendi XR capsules (b) (4)

Under these conditions as well, in vitro drug release from the four strengths is similar as previously shown in Figures 2 and 3 using a single dissolution medium of pH 7.5 phosphate buffer. The Applicant notes that

Figure 5



These results, albeit in vitro and in the absence of specific in vivo data, still seem to explain the gradual and continued drug release in vivo for extended periods, and the delay in topiramate t<sub>max</sub>.

Individual and mean in vitro dissolution data for topiramate dissolution/release (b) (4) are provided in Appendix 2 and shown in Figures 6 A-E.

Figure 6A



At this stage, a dissolution acceptance criterion for the IR and the criteria for the XR pellets are not under consideration for approvability of this product. Therefore, the following reviewer notes are for future internal reference and may be communicated to the Applicant in reference to this application.

Although the Applicant is not proposing in this application, if in the future, emptying capsule contents and mixing the pellets with soft foods for administration, is considered as a means of administration of Trokendi XR, dissolution acceptance criteria and criterion will be needed for the pellets. This reviewer recommends changing the timing of the Q value to (b) (4) min instead of (b) (4) for the (b) (4) and the (b) (4) pellets, and considers the Applicant's proposed dissolution method and acceptance range otherwise consistent with the in vitro performance of the product.



(b) (4)

#### **Biowaiver request for the 25-mg Trokendi XR capsules**

The 25-mg and 50-mg capsules are (b) (4) and the submitted clinical study data provide the necessary bridging for the 25- and 50-mg capsules, additional BE testing for the 25-mg capsules is not needed. Please also see Appendix 1. The following tables summarize the f2 values obtained from comparison of the developmental scale 25-mg and 50-mg topiramate ER capsules (Table 7) and the commercial scale 25-mg and 50-mg topiramate ER capsules (Table 8).

**Table 7**

Table 27: Dissolution Similarity Factor ( $f_2$ ) for Development Scale Topiramate Extended-Release Capsules, 25mg and 50mg

Timepoint:	Mean Percent Dissolved				
	1 hour	2 hours	4 hours	6 hours	8 hours
25mg (B08024B, n=6)	(b) (4)				
50mg (B08025E, n=6)					
Dissolution Similarity Factor ( $f_2$ )					

**Table 8**

Table 28: Dissolution Similarity Factor ( $f_2$ ) for Commercial Scale Topiramate Extended-Release Capsules, 25mg and 50mg

Timepoint:	Mean Percent Dissolved						
	1 hour	2 hours	3 hours	4 hours	6 hours	8 hours	10 hours
25mg capsules (batches 0912898, 0913728, 0914452, n=6 each batch)	(b) (4)						
50mg capsules (batches 0912372, 0913729, 0914453, n=6 each batch)							
Dissolution Similarity Factor ( $f_2$ )							

The rationale for accepting the Applicant’s biowaiver request is discussed earlier under the Biopharmaceutics summary section of this document (page 3).

#### **Effect of Exposure of Trokendi XR capsules to Apple-sauce**

The applicant carried out an in vitro study to determine whether there may be a possible dosage form interaction if apple sauce would be used to administer contents of topiramate ER capsules.

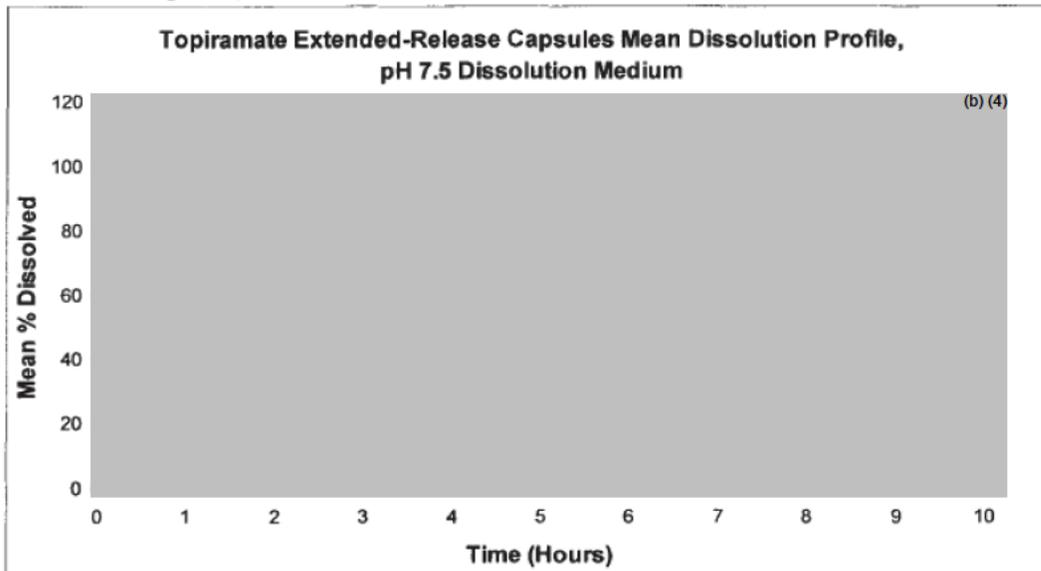
The capsule contents/pellets from a 100-mg Trokendi XR capsule (Lot B10001B from Bulk lot 0912373 used in clinical study 538P109 as lot B10001C) were emptied into an aluminum dish containing one tablespoonful of applesauce. After approximately a 5 min exposure to applesauce, the pellets were then transferred to the dissolution vessel containing the dissolution medium (pH 7.5 phosphate buffer at 37°C ± 0.5°C) and the aluminum dish was rinsed with dissolution medium.

Dissolution testing was carried out using n=12 capsules exposed to applesauce and n=12 capsules from the same lot of Trokendi XR capsules that were not exposed to applesauce.

The following figure (Figure 7) show mean in vitro dissolution profiles of topiramate from intact capsules of the same lot not exposed to applesauce and the pellets exposed to applesauce for 5 min.

Figure 7

**Figure 3: Comparison of Mean Dissolution Profiles for Topiramate Extended Release Capsules, 100mg Lot B10001B (Contents Exposed to Applesauce vs. Intact Capsules)**



This reviewer notes several limitations with this approach. However, the Applicant has not proposed recommending administration of capsule contents sprinkled onto applesauce or any other soft food. As a result, discussions about this approach with the Applicant have not taken place.

It is likely that applesauce may not have a dramatic effect, however, the exposure to applesauce should be studied for more than 5 min and furthermore, typical pH for applesauce, although variable, is between 3.5 to 4.5 and the in vitro performance of the intact capsules and the pellets at pH 4.5 is very different than the results provided here when the testing is carried out essentially in pH 7.5.

The applicant has also calculated f2 values for further comparison of similarity of the two profiles. The individual data and the values used for f2 calculation are in Appendix 3.

The Applicant appears to have used all of the data for f2 calculation although only one data point after 85% dissolution is reached can be incorporated into f2 calculations. Nevertheless, the similarity of the dissolution profiles, under the test conditions, is evident.

### Alcohol dose-dumping study

The Applicant evaluated dissolution profiles of 25-mg and 200-mg Trokendi XR capsules (n=12) in 750 mL of dissolution medium (0.1 N HCl, pH 1.1 ± 0.1) and also, in the same medium with varying amounts of ethanol (5%, 10%, 20% and 40%) using USP Apparatus 2 (paddle) at 50 rpm.

The samples collected from the dissolution medium were kept at 5 °C until HPLC/RI (Refractive Index) assay according to method TM-538-201-3

The following table summarizes the composition of the dissolution medium and the topiramate release as a percentage of the label claim for the 25-mg Trokendi XR capsules at 15 min and 120 min of dissolution testing. The dissolution/release results obtained for the 200-mg Trokendi XR capsules are also similar and provided in Appendix 4.

**Table 9: Composition Of Dissolution Medium and Topiramate Dissolved/Released from 25-mg Trokendi XR Capsules**

Vol. of 0.1 N HCl	Vol. of ethanol (% of total)	Mean % dissolved	
		30 min	120 min
750 mL	0%	(b) (4)	
712.5 mL	37.5 mL (5%)		
675 mL	75 mL (10%)		
600 mL	150 mL (20%)		
450 mL	300 mL (40%)		

In vitro dissolution of the 25-mg and 200-mg Trokendi XR capsules, in pH 1.1 medium without and with varying amounts of ethanol are illustrated in Figure 8 and 9, respectively.

**Figure 8**

**Figure 7: Dissolution Profiles for Registration Topiramate Extended-Release Capsules, 25mg with 0%, 5%, 10%, 20%, and 40% Ethanol in 0.1N Dilute HCl Medium**



**Figure 9**

**Figure 8: Dissolution Profiles for Registration Topiramate Extended-Release Capsules, 200mg with 0%, 5%, 10%, 20%, and 40% Ethanol in 0.1N Dilute HCl Medium**



These results show that release of topiramate from the Trokendi XR capsules is rapid under the in vitro test conditions and in the presence of 10% (v/v) and more ethanol in the dissolution medium.

Release/dissolution of topiramate is [REDACTED] <sup>(b) (4)</sup> with 40% (v/v) ethanol in the dissolution medium.

In the absence of in vivo data, it is difficult to use the in vitro information fully- however, in vitro results highlight the potential significant safety risk. This has been communicated to the review team.

## In Conclusion

- The Applicant has provided adequate information except for the potential alcohol dose-dumping study for biopharmaceutic characterization of the Trokendi XR capsules. Strong labeling recommendation for contraindication with alcohol is made for avoiding use of alcohol over a period of 6 hrs prior to and 6 hrs after Trokendi XR dose.
- In the Biopharmaceutic summary section of this review (pages 3 to 7) and in the Biopharmaceutics findings and assessment section of this document (page 9 to 23), key issues are discussed. The Applicant has addressed the concerns that were raised at the original submission which was refused to file when first submitted in 2011.
- The dissolution method with the small adjustments to the acceptance range and criteria described earlier for the 25-, 50-, 100- and the 200-mg Trokendi XR capsules is acceptable.
- Additional information derived from the stability studies used for the proposed dissolution criteria are provided in Appendix 5 for illustrative purposes.

Inspection of these results, along with the other biopharmaceutics information included in this submission support the Applicant's proposal for mean [REDACTED] <sup>(b) (4)</sup> range at the 3 hr sample for Trokendi XR capsules. This reviewer finds this range as acceptable and does not believe that a tighter acceptance range would result in product quality improvements for this product or additional bioavailability studies would provide additional information.

- The Applicant has also provided adequate data for their biowaiver request for the 25-mg Trokendi XR capsules.

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/s/  
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ARZU SELEN  
06/06/2012

RICHARD T LOSTRITTO  
06/14/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug  
Administration

OFFICE OF NEW DRUGS QUALITY  
ASSESSMENT

Biopharmaceutics Secondary Review

**Memorandum**

To: Richard Lostritto, Ph.D.  
Acting Biopharmaceutics Supervisor  
Office of New Drug Quality Assessment

From: Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

Subject: Biopharmaceutics Secondary Review  
NDA 201-635 for Trokendi XR™ (topiramate) Extended-Release  
Capsules, 25, 50, 100, and 200 mg

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## INTRODUCTION

This Memorandum relates to the suitability of the acceptance criteria for Topiramate Extended Release Capsules submitted under NDA 201-635. I have evaluated Dr. Arzu Selen draft review document and I have held meetings with the primary Biopharmaceutics Reviewer (Dr. Arzu Selen and the Acting Biopharmaceutics Supervisor (Dr. Rik Lostritto), as well as with the primary CMC Reviewer, Dr. Thomas Wong to discuss the issues related to the Applicant's dissolution data, the CMC manufacturing issues affecting the dissolution characteristics of the drug product, and the Applicant's proposed acceptance criteria for Topiramate Capsules and their acceptability based on the recommendations given in the ICH guideline Q6A (setting dissolution limits for extended release drug products in the absence of IVIVC) and in the FDA Guidance entitled "Extended Release Oral Dosage Forms: Development, Evaluation, And Application of In Vitro/In Vivo Correlations; Section B-1. Setting Dissolution Specifications without an IVIVC".

I have a very good understanding of the dissolution data available for topiramate capsules as well as knowledge of the FDA's regulatory requirements that should be followed to achieve consistency on the regulatory processes that should be used during the evaluation of dissolution data and during the regulatory

recommendations given to Applicants regarding the setting and approvability of the dissolution acceptance criteria.

## ASSESSMENT

**Background:** In NDA 201-635, the Applicant is seeking approval of Trokendi XR™ (topiramate) ER capsules as monotherapy and adjunctive therapy for epilepsy via 505(b)(2) application using the approved TOPAMAX® immediate-release (IR) tablets (NDA 20-505) as the reference listed drug (RLD). Trokendi XR™ capsules are multi-bead capsules (three-pellet composite formulations) in dosage strengths of 25, 50, 100, and 200 mg, administered one daily (QD).

**Schematic Representation of the Structures of Commercial Scale [REDACTED] (b) (4)**  
**[REDACTED] Pellets and Topiramate Extended-Release Capsules**



Topiramate Extended-Release Capsules

The following table presents the pellet types in the extended release formulation.

Pellet Type (containing % w/w of topiramate)	Amount of pellets, % (mg), in capsule of			
	25 mg Capsules	50 mg Capsules	100 mg Capsules	200 mg Capsules
(b) (4)				
Total	100% (144.6 mg)	100% (289.1 mg)	100% (423.7 mg)	100% (518.5 mg)
(b) (4)				

The proposed dissolution method and acceptance criteria are listed in the following tables.

Apparatus	USP apparatus 2, paddles
Spindle speed	50RPM
Dissolution medium	50mM phosphate buffer pH 7.5 ± 0.1
Temperature	37.0°C ± 0.5°C
Volume of medium (mL)	750mL
Filter	10µm
Vessel Covers	Low loss evaporation covers
Sampling times	1, 2, 3, 4, 6, 8, 10 hours

**Proposed Commercial Dissolution Acceptance Criteria**

Capsule Strength	Proposed Commercial Dissolution Specifications <sup>a</sup>	
25mg and 50mg	Time (hours)	Percent Dissolved
	1	(b) (4)
	3	(b) (4)
	8	(b) (4)
100mg	Time (hours)	Percent Dissolved
	1	(b) (4)
	3	(b) (4)
	8	(b) (4)
200mg	Time (hours)	Percent Dissolved
	1	(b) (4)
	3	(b) (4)
	8	(b) (4)

<sup>a</sup> Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

**Current Issue:** Acceptability of the proposed acceptance criteria for the dissolution test of Trokendi XR™ (topiramate) ER capsules.

The mean dissolution profile data for the 25, 50, 100, and 200 mg capsules from the PK and stability registration batches are presented in the following figures.

**Mean (n=6) in vitro dissolution of topiramate ER capsules studied in clinical trials**

Note: 25-, 50- and 100-mg capsules studied in 538P104, and 538P104.5 and 200-mg capsules studied in 538P103, 538P104, 538P104.5 and 538P105. Data in App. 2.7.1.4 Table3



**Mean (n=6) in vitro dissolution of topiramate ER capsules studied in clinical trials**

Note: 50-mg caps. studied in 538P106-50, 538P108, 100-mg caps. studied in 538P106, 538P108, 538P109 and 200-mg caps. Studied 538P108 and 538P106-200 (Data App. 2.7.1.4 Table 3)



Mean Dissolution Profiles (Release and Initial Stability Testing) of  
Topiramate Extended-Release Capsules, 25mg

(b) (4)



Mean Dissolution Profiles (Release and Initial Stability Testing) of  
Topiramate Extended-Release Capsules, 50mg

(b) (4)



Mean Dissolution Profiles (Release and Initial Stability Testing) of  
Topiramate Extended-Release Capsules, 100mg

(b) (4)



Mean Dissolution Profiles (Release and Initial Stability Testing) of  
Topiramate Extended-Release Capsules, 200mg

(b) (4)



**Comments**

1. Based on the dissolution information/data reviewed, I consider that the proposed (b) (4) range between the lower and higher values of the acceptance criteria for the 3 hour sampling time point is wide and should not be accepted

in absence of supportive IVIVC or bioequivalence data (as described the ICH guideline Q6A and/or the FDA IVIVC-guidance), or dissolution data from batches used in the pivotal clinical studies. Allowing wider dissolution acceptance criteria without any supportive data, promotes the lack of consistency in the regulatory decisions among reviewers and lack of consistency in the recommendations given to Sponsors/Applicants.

2. Also, in the absence of clinical data for the proposed topiramide product, it is not clear what criteria were applied to reach the conclusion that topiramide an antiepileptic drug can be classified as a low risk. Therefore, it is not known if the variability observed in the dissolution of the product will not translate into variability in plasma profiles, leading to variability in the efficacy and/or safety profiles of the product. Additionally, it should be noted that for the setting of the dissolution acceptance criteria, the recommendations given in the FDA's IVIVC-guidance or ICH guidelines do not differentiate between low and high risk drugs.
3. It should be noted that the dissolution data are showing low intra-batch variability, but high inter-batch variability, indicating some lack of robustness/reproducibility of the control release coating material. Therefore, in order to accommodate and pass the variable dissolution data for the 3 hour timepoint, the Applicant proposes a wider (b) (4) range for the acceptance criteria of this time point for the different strengths.
4. To better understand the root cause of the high inter-batch variability in the dissolution data, this issue was discussed with Dr. Tomas Wong, CMC Reviewer. Note that Dr. Wong also observed the variability in dissolution and he concluded that the age of the control release coating material will affect the release characteristics of the drug, and therefore dissolution. In order to address this issue, the following information for the (b) (4) of the pellets is reported in the CMC review authored by Dr. Thomas Wong, CMC Reviewer for this NDA.

(b) (4)



## RECOMMENDATION

After reviewing the available information and discussing the issues with Drs. Lostritto, Selen, and Wong, the provided dissolution data do not support an acceptance criteria range of (b) (4) for the 3 hrs time point. Also, the proposed (b) (4) for the last sampling time point was not supported by the dissolution data and it was revised to 6 hours. Note that the Applicant already accepted to implement (b) (4) at 6 hrs on an interim basis.

Taking into consideration that the Applicant has identified the root cause of the variability observed in the dissolution data for the 3 hour time point and that they are already have a corrective action\*, which is expected to minimize dissolution variability in commercial manufacturing, I am willing to align with the recommendation given by Drs. Selen and Lostritto and accept the proposed acceptance criteria on an interim basis, provided the Applicant commits to the following:

- To collect additional data from the commercial validation batches manufactured\* during the first year after the action date, targeting tighter acceptance criteria in alignment with the FDA standards described in their IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).
- The additional dissolution data generated for the commercial validation batches\* should be used for the setting of the final acceptance criteria.

- To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data from the commercial validation batches\*.

**\*NOTE:**

(b) (4)

**COMMENTS TO BE CONVEYED TO THE APPLICANT**

1. *Your proposal of setting the dissolution acceptance criteria for your product on an interim basis for one year is acceptable. Please provide the updated specifications table for your product with the revised dissolution criteria.*
2. *Additionally, we acknowledge that you have identified the root cause of the variability observed in the dissolution data and you already implemented a corrective action, which is expected to minimize variability in the commercial manufacturing. Therefore, for the setting of the final dissolution acceptance criteria, we request that you agree to the following:*
  - *To collect additional dissolution profile data for the commercial validation batches (each strength) manufactured during the first year after the action date, targeting tighter acceptance criteria in alignment with the FDA standards described in their IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).*
  - *To use the additional dissolution data generated from the commercial validation batches for the setting of the final acceptance criteria.*
  - *To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches.*

**Secondary Reviewer Signature**

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Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

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/s/  
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ANGELICA DORANTES  
06/13/2012

## CLINICAL PHARMACOLOGY REVIEW

<b>NDA:</b>	<b>201-635</b>
<b>Brand Name:</b>	Trokendi XR™
<b>Generic Name:</b>	Topiramate Extended-Release Capsules (SPN-538T)
<b>Sponsor:</b>	Supernus Pharmaceuticals, Inc.
<b>Dosage Form &amp; Strength:</b>	Extended Release (ER) Capsules (25 mg, 50 mg, 100 mg, and 200 mg)
<b>Indication:</b>	Monotherapy therapy for epilepsy for patients (b) (4) Adjunctive therapy for epilepsy for adult and pediatric patients (b) (4) and for patients (b) (4) with seizures associated with Lennox-Gastaut Syndrome (LGS)
<b>Submission:</b>	505(b)(2), Standard
<b>Submission Date:</b>	08/30/2011, 12/07/2011, 12/22/2011, 02/14/2012
<b>OND Division:</b>	OND-1/Division of Neurology Drug Products
<b>OCP Divisions:</b>	Clinical Pharmacology DCP-1
<b>Primary Reviewer:</b>	Ta-Chen Wu, Ph.D.
<b>Team Leader:</b>	Angela Yuxin Men, M.D., Ph.D.
<b>Pharmacometrics Reviewer:</b>	Joo-Yeon Lee, Ph.D.
<b>Pharmacometrics Team Leader:</b>	Yaning Wang, Ph.D.

The OCP office level briefing is held on May 18, 2012.

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## 1. Executive Summary

The applicant seeks approval of Trokendi XR™ (topiramate extended-release or ER capsules; SPN-538T) as monotherapy and adjunctive therapy for epilepsy via 505(b)(2) application using the approved TOPAMAX® immediate-release (IR) tablets (NDA 20-505) as the reference list drug (RLD). Since Trokendi XR™ is intended to be taken as an intact capsule, the Sponsor is seeking a monotherapy and adjunctive therapy indications for patients with epilepsy <sup>(b) (4)</sup> instead of  $\geq 2$  years old for the RLD. The Sponsor is not seeking indication for migraine. Trokendi XR™ capsules are multi-bead capsules (three-pellet composite formulations) in dosage strengths of 25, 50, 100, and 200 mg, administered one daily (QD). The current submission is a resubmission of the NDA 201-635 that was originally submitted to the Agency on January 14, 2011 but was subject of a refused to file on March 14, 2011 due to the Chemistry, Manufacturing, and Controls filing issues.

In this submission, the applicant presented a new clinical pharmacology-based method by demonstrating the bioequivalence (BE) at multiple time-points within the 24 hours at steady-state between the proposed Trokendi XR™ capsules given once-daily (QD) and approved TOPAMAX® IR tablets given twice-daily (BID), in addition to the conventional BE analyses for topiramate exposure. To demonstrate the similarity in topiramate plasma concentration-time curves between the proposed Trokendi XR™ capsules and the approved TOPAMAX® IR Tablets, the applicant proposed and performed additional time-point to time-point comparisons at steady-state with respect to ratios of topiramate plasma concentration, partial AUC (AUC<sub>0-p</sub>), and partial AUC (AUC<sub>t1-t2</sub>) between two time-points of XR relative to IR in the pivotal relative bioavailability study (538P103).

The clinical pharmacology program consists of eight Phase 1 studies in healthy adult volunteers assessing the steady-state relative bioavailability between Trokendi XR™ capsules and the reference TOPAMAX® IR Tablets, dose linearity/proportionality, food effect (200 mg), BE between the clinical and registration scale formulations (50, 100, and 200 mg), and the pharmacokinetic comparison between young and elderly adult subjects. Considering no clinical efficacy trial was conducted, the applicant conducted a Phase 2 conversion study to compare the relative bioavailability immediately after the switch from topiramate IR drug products (200, 250, 300, 350, or 400 mg/day, BID) to Trokendi XR™ (QD) and at steady-state in epilepsy patients support the formulation switch. In addition, the applicant performed a population pharmacokinetic analysis using data from six Phase 1 studies to examine the potential impact of food to support the use without regard to food intake. Biowaiver of in vivo relative BA study was requested for the 25 mg strength on the basis of formulation proportionality and dissolution similarity of 25mg and 50mg capsules. An in vivo study in dogs was conducted by the applicant, to evaluate the potential dose-dumping with alcohol (0%, 10%, and 40%).

### 1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-

1) has reviewed the submission and finds NDA 201-635 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

## 1.2 Phase IV Commitment

None

## 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

### Pharmacokinetics

- Linear pharmacokinetics (PK) of topiramate were observed following single oral doses of Trokendi XR™ over the range of 50 to 200 mg.
- The peak plasma concentrations (C<sub>max</sub>) of topiramate occurred at approximately 24 hours following a single 200 mg oral dose of Tokendi XR™, and at approximately 6 hours after repeat dosing.
- At steady-state, the AUC<sub>0-24hr</sub>, C<sub>max</sub>, and C<sub>min</sub> of topiramate from Tokendi XR™ administered once-daily and the immediate-release tablet administered twice-daily were shown to be bioequivalent.
- The topiramate PK profile from Trokendi XR™ capsules in epilepsy patients appear to be similar to that in healthy subjects.
- Fluctuation of topiramate plasma concentrations at steady-state for Trokendi XR™ administered once-daily was approximately 26% and 51% in healthy subjects and in epileptic patients, respectively, compared to approximately 40% for immediate-release topiramate.
- High-fat meal increased topiramate C<sub>max</sub> by approximately 37% following single dose of Tokendi XR™ and by 13% after the repeat dosing based on simulation. The overall topiramate plasma exposure (AUC) was not altered by a high-fat meal.
- Administration of contents of Tokendi XR™ capsule with applesauce in healthy young adult subjects did not have a significant effect on the bioavailability of topiramate, compared to Tokendi XR™ capsule.
- The mean elimination half-life of topiramate was approximately 38-50 hours following single oral doses and approximately 31 hours following repeat administration of Tokendi XR™.

### Dose/Exposure-Response relationships:

A similar exposure-response relationship for efficacy was established between steady-state C<sub>min</sub> and percent reduction in seizure frequency for the IR formulations between adults (16 years and above) and pediatrics (6-15 years) (refer to Dr. Anshu Marathe's review for NDA 20505/S042, 20844/S036, 7/11/2011 in DARRTS). There were reported "therapeutic window" regarding topiramate plasma levels for achieving more optimal clinical outcome that supports the applicant's topiramate extended-release drug product in reference to the approved Topamax IR tablets and the proposed dosing regimen (refer to Section 2.2.3.1 for details).

**Intrinsic factors:****Age:**

Following administration of a single 100 mg dose of Trokendi XR™ in elderly (71-84 years) and young (18-45 years) subjects, the elderly subjects had similar half-life (47-49 hours), shortened Tmax (16 vs. 24 hours), and 30~44% higher exposure (Cmax, AUC0-t, and AUC0-∞), compared to the young subjects. This is likely due to reduced renal function in the elderly. Dosage adjustment to half for Trokendi XR™ is indicated in the elderly patients when impaired renal function (creatinine clearance rate  $\leq 70$  mL/min/1.73 m<sup>2</sup>) is evident.

**PK Comparison of Trokendi XR™ Capsules vs. TOPAMAX® IR Tablets:**

Results from a comparative PK study evaluating the Trokendi XR™ capsules and the reference TOPAMAX® IR tablets (Study 538P103) showed that two formulations are bioequivalent with respect to the overall exposure (AUC $\tau$ , Cmax, and Cmin), point-to-point comparison for topiramate partial AUC (AUC0-p), and the point-to-point comparison for topiramate plasma concentrations at steady-state. Additional analyses showed that the point-to-point comparisons for topiramate plasma concentrations and the partial AUC between time-points (AUCt1-t2) are bioequivalent at steady-state for most of the time points throughout the day based on conventional BE criteria, except for the initial time points, mostly before 1.5 hour postdose. Smaller fluctuation (%FL) of topiramate plasma concentrations from Trokendi XR™ at steady-state was observed compared to that from TOPAMAX® IR (i.e., 26% vs. 40%).

**Formulation Conversion in Patients:**

The conversion study was conducted to compare the relative bioavailability immediately after the switch from TOPAMAX® IR (200, 250, 300, 350, or 400 mg/day, BID) to Trokendi XR™ (QD) and at steady-state in epilepsy patients.

- For all PK subjects (N=62), the exposure (AUC24h, Cmax, and Cmin) of topiramate at the steady-state was found to be bioequivalent for both formulations. Immediately after the switch, the Cmin from Trokendi XR™ was found to be approximately 10% lower, with 90% CI falling outside the BE range, which is not considered clinically significant.
- For Neutral subjects (N=47), BE was established for all exposure measures immediately after the switch and at the steady-state.
- For Induced subjects (N=13), BE was established for AUC for the switch. However, there were approximately 10% reductions in Cmin immediately after the switch and in both Cmax and Cmin at the steady-state, which is not considered clinically significant.

The overall results suggest that patients can be switched from IR to Trokendi XR™ formulation with the same total daily doses.

**Bridging between To-be-marketed (TBM) vs. Developmental Formulations**

Bioequivalence was established between TBM and the developmental formulations of 50 mg, 100 mg, and 200 mg strengths. The lowest 25 mg strength is compositionally similar

to the 50 mg strength and is subject to biowaiver for not needing additional in vivo bridging study.

Bioequivalence was established between contents from Trokendi XR™ in applesauce and the intact XR capsule.

**Food effect**

Food (high fat meal) increased topiramate C<sub>max</sub> from Trokendi XR™ by approximately 37% (90% CI: 124-155%) without having effect on topiramate AUC and half-life. The peak time (T<sub>max</sub>) was shortened from 24 hours to 8 hours postdose.

Simulation for repeat dosing showed that effect of food on C<sub>max</sub> would be reduced to approximately 13%, suggesting that Trokendi XR™ can be given without regard to meals.

**Potential Alcohol Interaction:**

In vitro dissolution study with 0~40% ethanol in dilute HCl media showed that there is a potential for dose-dumping for topiramate from the ER capsules. An in vivo study in dogs, conducted by the applicant, to evaluate the potential dose-dumping with alcohol (0%, 10%, and 40%) is not acceptable to OCP perspective. Concerning for the potentiation of CNS depression and the potential loss of seizure control prior to the next morning dose in the presence of alcohol, restriction for the alcohol consumption within 6 hours of Trokendi XR™ dosing is recommended by the Agency for the labeling.

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## 2. Question Based Review

### 2.1 General Attributes

#### 2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action of Trokendi™?

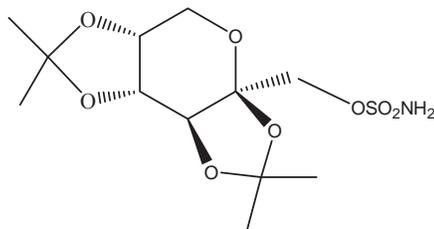
Trokendi XR™ (Topiramate extended-release (ER) capsule) is an antiepileptic (AED) agent indicated for:

1. Monotherapy epilepsy: Initial monotherapy in patients (b) (4) with partial onset or primary generalized tonic-clonic seizures.
2. Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS).

The precise mechanisms by which topiramate exerts its anticonvulsant effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

#### 2.1.2 What are the highlights of physico-chemical properties of the drug substance?

Topiramate, USP, is a sulfamate-substituted monosaccharide and is a white to off-white powder. Topiramate is freely soluble in polar organic solvents such as acetonitrile and acetone; and very slightly soluble to practically insoluble in non-polar organic solvents such as hexanes. Topiramate has the molecular formula  $C_{12}H_{21}NO_8S$  and a molecular weight of 339.4. Topiramate is designated chemically as 2,3:4,5 Di-*O*-isopropylidene- $\beta$ -D-fructopyranose sulfamate. The structure for carisbamate drug substance is provided in the Figure below. The available strengths of Trokendi XR™ extended-release capsules are 25mg, 50mg, 100mg and 200mg. The chemical structure of topiramate is shown below.



#### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes that the total daily dose of Trokendi XR™ should be administered orally regardless of food intake at the following proposed dosing regimens:

Indication	Initial Dose	Titration	Recommended Dose
(b) (4)			
Epilepsy monotherapy: adults and pediatric patients ≥ 10 years**	50 mg/day Once daily dose	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day Once daily dose
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day Once daily dose
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures	25-50mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50mg	400mg/day Once daily dose
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS	25 mg/day (based on a range of 1 to 3 mg/kg/day) nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3mg/kg/day  Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day Once daily dose

\* For adults and pediatric patients 10 Years and older, Trokendi XR™ should be titrated according to the following schedule:

- Week 1      50mg/day
- Week 2      100mg/day
- Week 3      150mg/day
- Week 4      200mg/day
- Week 5      300mg/day
- Week 6      400mg/day



(b) (4)

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant presented a new clinical pharmacology-based method by demonstrating the bioequivalence (BE) at multiple time-points within the 24 hours at steady-state between the proposed Trokendi XR™ capsules given once-daily (QD) and the approved TOPAMAX® tablets given twice-daily (BID) with respect to topiramate plasma concentration and partial AUC (AUC<sub>0-p</sub>) (Study 538P103).

The clinical program consists of eight Phase 1 studies in healthy adult volunteers, one Phase 2 conversion study in patients with epilepsy (538P109), and an ongoing study in pediatric patients (538P107), as presented in Table below. The Phase 1 program assessed the steady-state relative bioavailability (BA) between extended-release Trokendi XR™ capsules and the reference TOPAMAX® IR Tablets (538P103), dose linearity/proportionality (538P104, 538P104.5), food effect (538P105 with 200 mg), BE between the clinical and registration scale formulations (538P106 for 100mg, 538P106-50 for 50mg, 538P106-200 for 200 mg), and the pharmacokinetic (PK) comparison between young and elderly adult subjects (538P109). The conversion study compared the relative BA immediately after the switch from TOPAMAX® IR (200, 250, 300, 350, or 400 mg/day, BID) to Trokendi XR™ (QD) and at steady-state in epilepsy patients. In addition, the applicant performed a population PK analysis using data from six Phase 1 studies to examine the potential impact of food to support the use without regard to food intake.

Table. Tabular listing of the studies to support the NDA

Study ID	Primary Endpoint or Endpoints	Location of Study Report Synopsis	Study Objective	Study Design	Study & Control Drugs/ Dose/ Route/ Regimen	# Subjects by Arm Entered/ Completed	# Sites / Subject type	Duration
538P103	PK	Module 5, Section 5.3.3	Steady state PK	Comparative, randomized, multiple dose, 2-treatment, 2-sequence, 2-period crossover with active control	A: TPM CR 200mg x 10 days (after 3 weeks titration) B: Topamax 200mg x 10 days (after 3 weeks titration)	39 subjects enrolled, 33 subjects completed	Single center/ Healthy, normal	10 day maintenance with 21 day titration per treatment period
538P104	PK	Module 5, Section 5.3.3	Dose proportionality	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 8 x 25mg B: TPM CR 4 x 50mg C: TPM CR 2 x 100mg D: TPM CR 1 x 200mg	34 subjects enrolled 24 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P104.5	PK	Module 5, Section 5.3.3	Dose linearity	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 25mg B: TPM CR 50mg C: TPM CR 100mg D: TPM CR 200mg	36 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P105	PK	Module 5, Section 5.3.3	Food effect	Comparative, randomized, single dose, 2-treatment, 2-sequence, 2-period crossover study	A: TPM CR 200mg, fasted B: TPM CR 200mg, fed	32 subjects enrolled 28 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover	A: TPM CR 100mg, Clinical lot, fasted B: TPM CR 100mg, CMO lot, fasted	28 subjects enrolled, 27 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods

				study.				
538P106-50	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 50mg, Clinical lot, fasted B: TPM CR 50mg, CMO lot, fasted	32 subjects enrolled 31 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106-200	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 200mg, Clinical lot, fasted B: TPM CR 200mg, CMO lot, fasted	32 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P108	BA	Module 5, Section 5.3.1.2	PK of IR to ER Switch	Multi-center, open-label, two-treatment, single sequence conversion study	TPM ER – equivalent to current therapy TPM IR – equivalent to current therapy	62 patients with epilepsy (72 planned)	11 centers, adults with epilepsy on treatment with TPM	4 weeks.
538P109	PK	Module 5, Section 5.3.3	Young vs. Elderly	Comparative, single-dose, parallel group study	TPM CR 100mg, fasted	18 young adults enrolled and completed, 13 elderly enrolled and completed	Single center/ Healthy, normal young and elderly	Single dose, 1 treatment period
538P107	PK	Pending	Pediatric PK	Multi-center, open-label, switch to ER	TPM ER – equivalent to current therapy	Approximately 40 male and female pediatric subjects ages 4-17	Up to 15 centers, children with epilepsy on treatment with TPM	2 weeks

The applicant requested a biowaiver for in vivo relative BA study for the 25 mg strength on the basis of formulation proportionality and dissolution similarity of 25mg and 50mg capsules. Further, a study in dogs was conducted to assess the potential dose-dumping, instead of in humans as recommended by the Agency at the Pre-NDA meeting.

**2.2.2. What is the basis for selecting the clinical endpoints or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?**

Not applicable. The current submission is a 505(b)(2) submission without a clinical efficacy trial.

**2.2.3 Exposure-Response**

**2.2.3.1. Is there any significant exposure-response relationship? And does the relationship support the proposed dosing regimen?**

Yes. A similar exposure-response relationship for efficacy was established between steady-state topiramate trough concentration (C<sub>min</sub>) and percent reduction in seizure frequency for the IR formulations between adults (16 years and above) and pediatrics (6-15 years) (refer to Dr. Anshu Marathe’s review for NDA 20505/S042, 20844/S036, 7/11/2012 in DARRTS).

The proposed dosing regimen for Tokendi XR™ is the same as that for the reference drug TOPAMAX® IR tablets, which is supported by the similar relative BA (i.e., AUC<sub>τ</sub>, C<sub>max</sub>, and C<sub>min</sub>) at the steady-state as well as point-to-point comparisons for topiramate plasma concentrations and partial AUC (AUC<sub>0-p</sub>) throughout the day, based on conventional BE criteria.

In this submission, the applicant provided additional information, as summarized below, with regard to an existing therapeutic window for topiramate to support the approval and the same dosing regimen when compared to TOPAMAX<sup>®</sup> IR.

- Unbound topiramate plasma concentrations closely reflect the concentrations in the cerebrospinal fluid, and hence represent a reasonable surrogate for assessing topiramate concentrations in CNS (*Christensen et al. Ther Drug Monit. 2001 Oct;23(5):529-35*).
- The median percent reduction and percent responders were the greatest in the mid-range plasma topiramate concentrations from 3.2 to 5.4 µg/mL (TOPAMAX<sup>®</sup> sNDA, 1998).
- In a published concentration-controlled clinical study, the authors concluded that the “optimal treatment response is most likely found between 2 mg/L and 10.5 mg/L.” (*Christensen et al. Neurology. 2003 Nov 11;61(9):1210-8*)
- In pooled dose-response studies in adults with partial onset seizures (400, 600, 800, or 1000 mg/day, with doses ≥600 mg/day yielded C<sub>min</sub> proportionally higher than 10 mg/L), the author reported no significant improvement in efficacy at doses >400mg/day (*Peeters et al. Acta Neurol Scand. 2003;108:9-15*).
- In studies for the current application, 200 mg of SPN-538T QD or 100 mg TOPAMAX<sup>®</sup> BID doses resulted in C<sub>min</sub> ~5.3 mg/L (or 15-16 µM), whereas 400 mg/day doses corresponded to C<sub>min</sub> ~30-32 µM.

Given known efficacy and safety profiles for TOPAMAX<sup>®</sup>, as well as the reported clinical therapeutic range, the applicant’s approach is considered reasonable.

## **2.2.4 What are the PK characteristics of the drug and its major metabolite?**

### **2.2.4.1 What are the single and multiple dose PK parameters?**

Single and multiple dose PK characteristics of topiramate following administration of Trokendi XR<sup>™</sup> in healthy subjects and in epilepsy patients have been evaluated. In general, PK profiles of topiramate in epilepsy patients taking Trokendi XR<sup>™</sup> were similar to that in healthy subjects, except for a greater degree of fluctuation of topiramate levels. Detailed information is available in the following Sections.

### **2.2.4.2 What are the characteristics of drug absorption and Distribution?**

Linear PK of topiramate were observed following single oral doses of Trokendi XR<sup>™</sup> over the range of 50 to 200mg (Study 538P104-5). At the lowest 25mg dose, the PK of Trokendi XR<sup>™</sup> is not linear possibly due to the binding of topiramate to carbonic anhydrase in erythrocytes as reported in literature (see Section 2.2.4.4 for more details). Noted that the linearity and dose-proportionality were established for PK of topiramate from the reference TOPAMAX<sup>®</sup> IR over the dose range studied 200-800 mg/day.

The peak plasma concentrations (C<sub>max</sub>) of topiramate occurred at approximately 24 hours following a single 200 mg oral dose of Tokendi XR<sup>™</sup> (Study 538P103), and at approximately 6 hours after repeat dosing. At steady-state, the AUC<sub>0-24hr</sub>, C<sub>max</sub>, and

C<sub>min</sub> of topiramate from Tokendi XR™ administered once-daily and the immediate-release tablet administered twice-daily were shown to be bioequivalent. Fluctuation of topiramate plasma concentrations at steady-state for Tokendi XR™ administered once-daily was approximately 26% and 51% in healthy subjects and in epileptic patients, respectively, compared to approximately 40% for immediate-release topiramate. Steady-state was achieved by 14 days of repeat dosing.

High-fat meal increased topiramate C<sub>max</sub> by approximately 37% following single dose of Tokendi XR™ (Study 538P105) and by 13% after the repeat dosing based on simulation. However, the overall topiramate plasma exposure (AUC) was not altered by a high-fat meal (see Section 2.5.4 for more details).

Administration of contents of Tokendi XR™ capsule with applesauce in healthy young adult subjects did not have a significant effect on the bioavailability of topiramate, compared to Tokendi XR™ capsule, meeting BE criteria (Study 538P109).

Per communication with Dr. Lily Mulugeta working for Pediatrics group within Office of Clinical Pharmacology (OCP), the available data in literature (*Kearns GL et al. N Engl J Med 2003;349:1157-67; Tetelbaum M et al. Pediatrics in Review 2005;26:321*) indicates that gastric emptying, intestinal motility and the processes of both passive and active transport are fully mature in infants by approximately four months of age. Therefore, the absorption would not be different significantly in the age group (b) (4) for Tokendi XR™ comparing to the adults.

#### **2.2.4.3 What are the characteristics of drug metabolism and elimination?**

(Referred to TOPAMAX® and proposed Tokendi XR™ labels) Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in adults following oral administration. The mean elimination half-life of topiramate was approximately 38-50 hours following single oral doses and approximately 31 hours following repeat administration of Tokendi XR™.

#### **2.2.4.4 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?**

Dosage form proportionality and PK linearity of the development scale 25mg, 50mg, 100mg and 200mg topiramate ER development scale capsule strengths were evaluated in studies 538P104 and 538P104.5, respectively.

Study 538P104 was conducted to assess the dosage form proportionality with each subject received 200 mg SPN-538T as a single oral dose of 8 x 25 mg, 4 x 50 mg, 2 x 100 mg, or 1 x 200 mg capsule(s). Mean topiramate plasma concentration–time curves were similar from the four different treatments. Statistical analysis confirms the proportionality of the four strengths of topiramate ER capsules based on the point estimates and the 90% confidence intervals (CIs) for AUC0-t and AUC0-∞, and Cmax between treatments by BE acceptance criteria of 0.80-1.25.

Table. Summary of statistical analysis for dosage form proportionality

Parameter	Test TPM ER treatment (LS Mean)	Reference TPM ER (LS Mean)	Geometric Mean Ratio (T/R)	90% CI
Cmax (ng/mL)	8 x 25 mg	1 x 200 mg	1.109	(1.033, 1.191)
	4 x 50 mg	1 x 200 mg	1.051	(0.980, 1.128)
	2 x 100 mg	1 x 200 mg	1.036	(0.965, 1.112)
	8 x 25 mg	2 x 100 mg	1.070	(0.999, 1.147)
	4 x 50 mg	2 x 100 mg	1.014	(0.947, 1.086)
	8 x 25 mg	4 x 50 mg	1.055	(0.984, 1.131)
AUC0-t (ng•h/mL)	8 x 25 mg	1 x 200 mg	0.990	(0.948, 1.034)
	4 x 50 mg	1 x 200 mg	1.039	(0.995, 1.086)
	2 x 100 mg	1 x 200 mg	0.993	(0.951, 1.037)
	8 x 25 mg	2 x 100 mg	0.997	(0.955, 1.040)
	4 x 50 mg	2 x 100 mg	1.047	(1.004, 1.092)
	8 x 25 mg	4 x 50 mg	0.953	(0.913, 0.994)
AUC0-∞ (ng•h/mL)	8 x 25 mg	1 x 200 mg	0.996	(0.956, 1.038)
	4 x 50 mg	1 x 200 mg	1.038	(0.996, 1.082)
	2 x 100 mg	1 x 200 mg	0.993	(0.952, 1.035)
	8 x 25 mg	2 x 100 mg	1.004	(0.964, 1.045)
	4 x 50 mg	2 x 100 mg	1.046	(1.005, 1.089)
	8 x 25 mg	4 x 50 mg	0.959	(0.921, 0.999)

In Study 538P104.5 each subject received SPN-538T as a single oral dose of 25 mg, 50 mg, 100 mg, or 200 mg capsule. The linearity was assessed using conventional BE criteria and by Power Model.

The dosage form linearity of four different SPN-538T strengths was concluded for AUC0-t and AUC0-∞, but not for Cmax, based on the 90% CI's for the geometric mean ratios by BE acceptance criteria of 80-125%. The substantial and saturable binding of topiramate to carbonic anhydrase in erythrocytes may be attributable to the observed nonlinearity for Cmax and the prolonged t1/2 at low topiramate concentrations, especially at the lowest 25 mg dose. (*Epilepsy Res. 2005 Feb;63(2-3):103-12*).

Table . Summary of Power Model for dose linearity

PK Parameter	Point Estimate	Lower 95% CI	Upper 95% CI
AUC0-t (µg•h/mL)	1.079	1.055	1.102
AUC0-∞ (µg•h/mL)	0.987	0.966	1.007
Cmax (ng/mL)	1.202	1.154	1.250

The results confirm the proportionality and linearity of the four strengths of development scale topiramate ER capsules.

#### **2.2.4.5 How does the PK of the drug and its major metabolites in healthy subjects compare to that in patients?**

The topiramate PK profile from Trokendi XR™ capsules in epilepsy patients appear to be similar to that in healthy subjects. However, greater fluctuation (~51%) in topiramate plasma concentration-time curves was observed in patients, compared to that observed in healthy subjects (~26%) (refer to Section 2.5.2 for additional details).

#### **2.2.4.6 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?**

The mean inter-subject variability of PK parameters from Trokendi XR™ in single and multiple dose studies in healthy young or elderly subjects was approximately 20-35%. The mean estimate of inter-subject variability of CL/F and V/F in patients based on population PK analysis was 7.8% and 29.8%, respectively.

The intra-subject variability AUC, C<sub>max</sub>, and C<sub>min</sub> at steady-state after crossover between Trokendi XR™ capsule and TOPAMAX® tablet (Study 538P103) was relatively small at approximately 7.7%, 8.1% and 9.8%, respectively.

### **2.3 Intrinsic Factors**

#### **2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

The influence of various intrinsic factors, such as age, gender, race, hepatic impairment, and renal impairment, is referred to the approved TOPAMAX® label. The influence of age was further evaluated in young and elderly subjects with Trokendi XR™ for this application, as summarized below.

##### **2.3.1.1 Elderly**

Study 538P109 compared the PK of topiramate from Trokendi XR™ between young (18-45 years; N=18) and elderly (71-84 years; N=13) adult subjects. Following the administration of a single 100 mg dose of Trokendi XR™, the elderly subjects had similar elimination half-life (47-49 hours), shortened T<sub>max</sub> (16 vs. 24 hours), and 30% higher mean C<sub>max</sub>, 44% higher AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> values, compared to that in young subjects. This is likely due to reduced renal function in the elderly subjects.

As recommended in the proposed labeling for Trokendi XR™, the age-related changes are unlikely to have clinical significance in this target patient population to warrant dosage adjustment. However, as recommended for all patients, dosage adjustment for Trokendi XR™ may be indicated in the elderly patients when impaired renal function

(creatinine clearance  $\leq 70$  mL/min/1.73 m<sup>2</sup>) is evident. The renal function needs to be measured prior to the treatment (per the labeling).

## 2.4 Extrinsic Factors

The influence of various extrinsic factors leading to potential PK and/or PD interactions is available in the approved TOPAMAX<sup>®</sup> label. The evaluation for the potential alcohol-induced topiramate dose-dumping from Trokendi XR<sup>™</sup> for this application is summarized below.

**2.4.1 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?**

### 2.4.1.1 Effect of alcohol consumption on concomitant Trokendi XR<sup>™</sup>

As illustrated in the figure below, in vitro dissolution study with 0~40% ethanol in dilute HCl media showed that, in the presence of alcohol, the release of topiramate from Trokendi XR<sup>™</sup> capsules is markedly altered (referred to reviews by Office of New Drug Quality Assessment (ONDQA)). *In vitro* data suggest that an alcohol-induced dose-dumping for Trokendi XR<sup>™</sup> capsules in humans would likely alter the topiramate concentration-time curve as a result of greater amount of drug being released early.

**Dissolution Profiles for Topiramate Controlled Release Capsules, 25mg with 0% to 40% Ethanol in Dilute HCl**



The applicant conducted an *in vivo* study in dogs (538T-TOX2010-006) to evaluate the potential dose-dumping with alcohol (0%, 10%, and 40%), instead of a study in humans as recommended by the Agency at the IND stages. Although the results from the study in dogs showed a lack of dose-dumping potential from the ER capsules, such study and a lack of proper justification for its implication to humans were found not acceptable from an OCP perspective.

From a clinical pharmacology standpoint, we do not anticipate that a significant PK interaction with alcohol consumption is likely to occur at approximately 2~3 hours prior to or after the Trokendi XR™ dosing. The rationale for this conclusion is based on the available kinetic information on the gastrointestinal (GI) absorption and gastric emptying of ethanol (i.e., near complete disappearing from stomach by 30 min and 126 min under fasted and fed conditions, respectively) (*Levitt MD et al. Am J Physiol Gastrointest Liver Physiol. 1997; 273:G951-G957; Lennernäs H. Mol Pharm. 2009 Sep-Oct;6(5):1429-40*). In the absence of confirmatory human data, the concerns for efficacy and safety (i.e., CNS depression) taken into consideration for the recommended labeling languages are summarized below:

- The approved TOPAMAX® label recommends that “TOPAMAX® should be used with extreme caution if used in combination with alcohol.....” because of the potential for CNS depression.
- The potentially significant increase in systemic exposure of topiramate from the ER formulations at early time points as a result of alcohol-induced dose-dumping and the likelihood of potentiated PD interaction (i.e., CNS depression).
- The potential loss of efficacy for seizure control toward the later part of the day, prior to the next dose, as a result of insufficient drug substance available for continuous GI absorption and thus the sub-therapeutic topiramate levels.
- In vitro topiramate release profiles, i.e., 80% release in 6 hours, as reported by Dr. Arzu Selen of ONDQA.

Due to the potential PD interaction and the concerns delineated above, alcohol is contraindicated for 6 hours prior to or after the Trokendi XR™ dosing. The Agency’s recommended labeling languages for Contraindication, Warnings and Precautions (5.13) and Drug Interactions (7.3) sections are as follows:

#### CONTRAINDICATIONS

*Alcohol, when taken with Trokendi XR, can alter the release pattern of topiramate. Alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR administration (5.13).*

#### 5.13 Interaction with Alcohol

*In vitro data show that, in the presence of alcohol, the pattern of topiramate release from Trokendi XR capsules is markedly altered. As result, plasma levels of topiramate with Trokendi XR may be dangerously high soon after dosing and subtherapeutic later in the day. Therefore, alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR administration [see Drug Interactions (7.3)].*

#### 7.3 CNS Depressants or Alcohol

*Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressants drugs and alcohol can result in significant CNS depression. Alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR administration [see Warnings and Precautions (5.13)].*

## 2.5 General Biopharmaceutics

### 2.5.1 What are the compositions of the proposed Trokendi XR™ formulations?

Trokendi XR™ extended-release capsules contains the applicant's Microtrol® technology platform and topiramate, using a preset ratio of early, moderate, and late release beads within a capsule.

The applicant proposed 25 mg, 50 mg, 100 mg, and 200 mg strengths for Trokendi XR™, manufactured by Catalent Pharma Solutions, in Winchester, Kentucky. These four strengths were developed as a composite formulation of three intermediate pellets types: (b) (4)

The lowest 25 mg strength is compositionally similar (b) (4) to the 50 mg strength which is not compositionally similar to the 100 mg and 200 mg strengths. The 100 mg and 200 mg strengths are quantitatively and compositionally similar. The early development scale formulations of the same strengths are deemed similar to their respective TBM formulations, per ONDQA review team. The Trokendi XR™ formulations are provided in the tables below.

Table. Components and theoretical compositions of intermediate pellets in commercial scale topiramate extended-release capsules

Component	Reference to Quality Standard	Function	Amount per Capsule (mg/capsule)			
			25mg Capsules	50mg Capsules	100mg Capsules	200mg Capsules
(b) (4)						
			(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hard Gelatin Capsule <sup>a</sup>	(b) (4) DMF holder) in-house standard	Capsule shell	green opaque/ yellow opaque capsules)	green opaque/ orange opaque capsules)	green opaque/ blue opaque capsules)	pink opaque/ blue opaque capsules)
<b>Total (without hard gelatin capsule)</b>			(b) (4)			

Clinical Studies and Batch Numbers				
	538P107 (Batch B10021A)	538P106-50 (Batch B10024C) 538P106A (Batch B10024D and Batch B10026B) 538P107 (Batch B10024B) 538P108 (Batch B10024A)	538P106 (Batch B10001B) 538P106B (Batch B10001E and Batch B10028B) 538P107 (B10027A) 538P108 (Batch B10001A) 538P109 (Batch B10001C)	538P106- 200 (Batch B10002D) 538P106C (Batch B10002E and Batch B10030B) 538P107 (Batch B10002C) 538P108 (Batch B10002A)

Table. Components and theoretical compositions of (b) (4) pellets in commercial scale topiramate extended-release capsules

Component	Reference to Quality Standard	Function	Amount per Capsule (mg/capsule)			
			25mg Capsules	50mg Capsules	100mg Capsules	200mg Capsules
(b) (4)						

Table. Components and theoretical compositions of (b) (4) pellets in commercial scale topiramate extended-release capsules

Component	Reference to Quality Standard	Function	Amount per Capsule (mg/capsule)			
			25mg Capsules	50mg Capsules	100mg Capsules	200mg Capsules
(b) (4)						

Table. Components and theoretical compositions of (b) (4) in commercial scale topiramate extended-release capsules

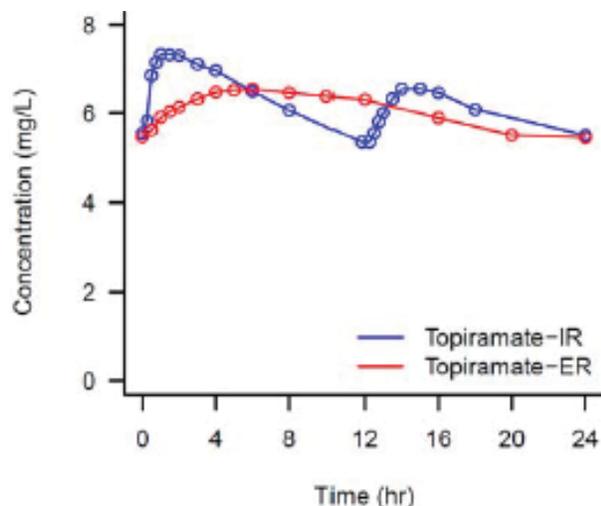
Component	Reference to Quality Standard	Function	Amount per Capsule (mg/capsule)			
			25mg Capsules	50mg Capsules	100mg Capsules	200mg Capsules
(b) (4)						

**2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference drug product?**

The applicant conducted two studies to evaluate the relative BA of a Trokendi XR™ vs. reference TOPAMAX® IR of the same total daily doses at steady-state in healthy subjects (538P103) and during the formulation conversion from TOPAMAX® IR to Trokendi XR™ in subjects with epilepsy (538P108).

Study 538P103 was a single-center, multiple-dose, single-blind, randomized, two-treatment, two-sequence, crossover study to evaluate the steady-state relative BA of 200-mg Trokendi XR™ (QD) compared to 100-mg TOPAMAX® tablet (BID, 12 hours apart). Subjects were titrated up for three weeks reach the 200 mg/day target dose, starting 50 mg and increasing in increments of 50 mg/week, and was maintained for a total of 10 days. The mean trough plasma concentrations were similar between the two formulations. The mean plasma concentration-time profiles are shown in the Figure below.

Figure. Mean plasma concentration-time curves at the steady-state (on Day 31)



As shown in the Table below, analysis demonstrated BE between Trokendi XR™ and TOPAMAX® with regard to AUC<sub>0-24</sub>, C<sub>max,ss 0-24</sub>, and C<sub>min,ss 0-24</sub>. Further, lower percent fluctuation (%FL) at steady-state were observed for Trokendi XR™ (26%) compared to TOPAMAX® Tablets (40%).

Table. Summary of statistical analysis for relative bioavailability of 200-mg dose of Trokendi XR™ vs. TOPAMAX® at steady-state

Parameter	N	Trokendi XR™ (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B, %)	90% CI
AUC <sub>0-24</sub> (ng·h/mL)	33	144000	149000	97.06	(94.01, 100.21)
C <sub>max,ss 0-24</sub> (ng/mL)	33	6690	7600	88.01	(85.10, 91.02)
C <sub>min,ss</sub> (ng/mL)	33	5120	5130	99.91	(95.87, 104.13)

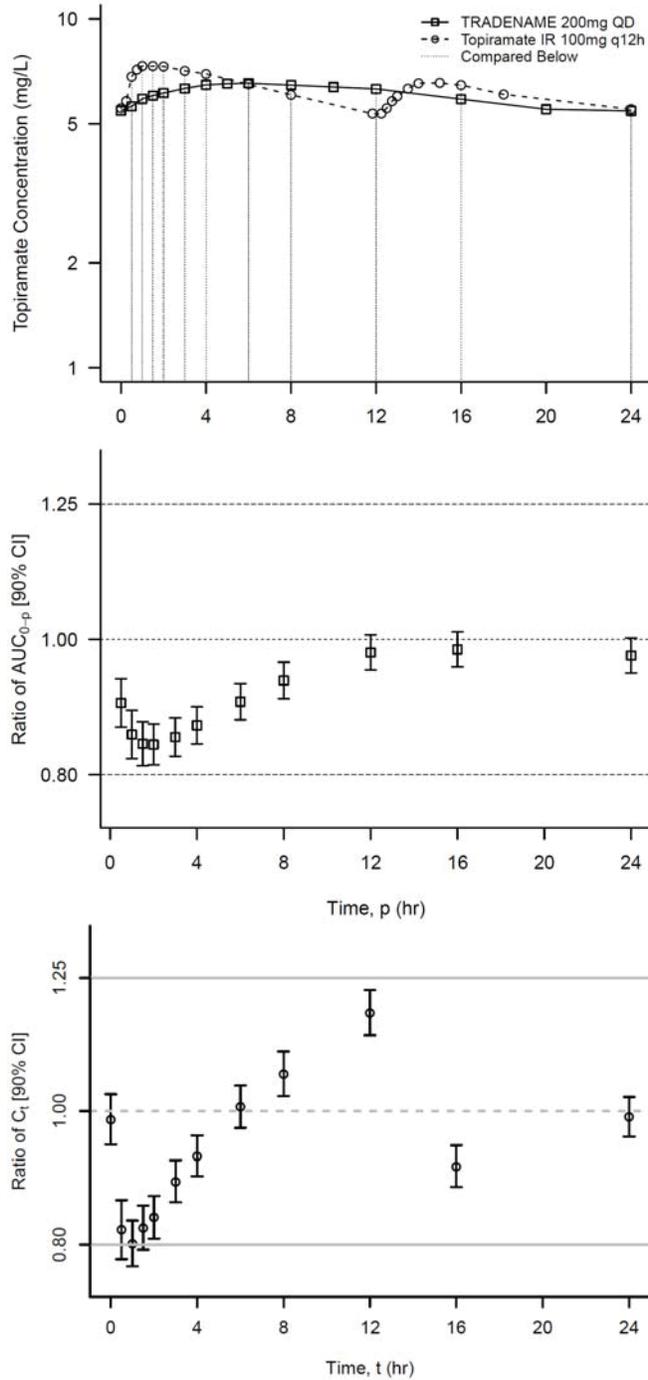
The intra-subject variability AUC, C<sub>max</sub>, and C<sub>min</sub> at steady-state after crossover between the two formulations was approximately 7.7%, 8.1% and 9.8%, respectively.

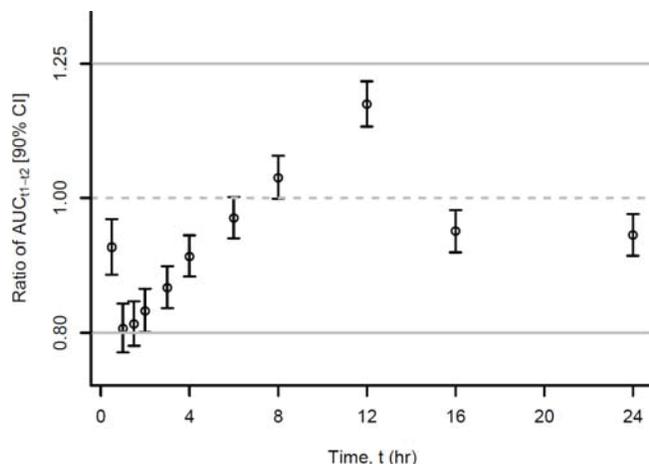
In addition to the BE analysis for partial AUC (AUC<sub>0-p</sub>) (i.e., “sustained bioavailability” per the applicant) in the original submission, the applicant submitted additional BE analysis results on February 14, 2012, per the OCP request, for comparing the point-to-point topiramate plasma concentrations and the partial AUC between two time-points (i.e., AUC<sub>t1-t2</sub>) to further examine and assure the plasma profile similarity.

As shown in the Figures below, point estimates and the 90% CIs for the ratios of steady-state partial AUC (AUC<sub>0-p</sub>) (i.e., “sustained bioavailability” per the applicant) and at each corresponding time point of the 24-hour plasma concentration-time curves for the two formulations were also within the 80-125% BE limits. In addition, the 90% CI for the ratios of point-to-point topiramate plasma concentration and partial AUC between two time points (i.e., AUC<sub>t1-t2</sub>) of the 24-hour curves for the two formulations were mostly within the 80-125% BE limits, except for the initial time points before

approximately 1.5 hour postdose where the 90% CIs fell slightly outside the lower BE limit.

Figures. Analysis of partial AUC ( $AUC_{0-p}$ ), point-to-point topiramate concentrations, and partial AUC between two time-points ( $AUC_{t1-t2}$ )

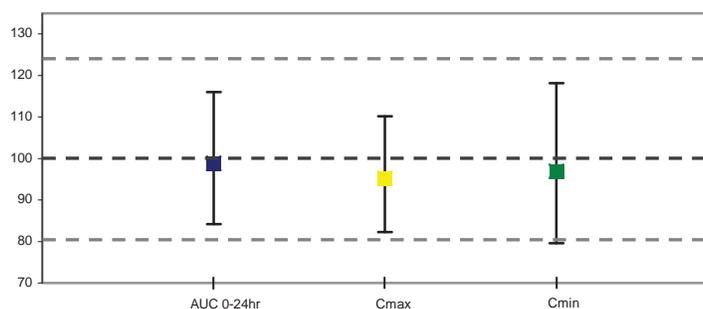


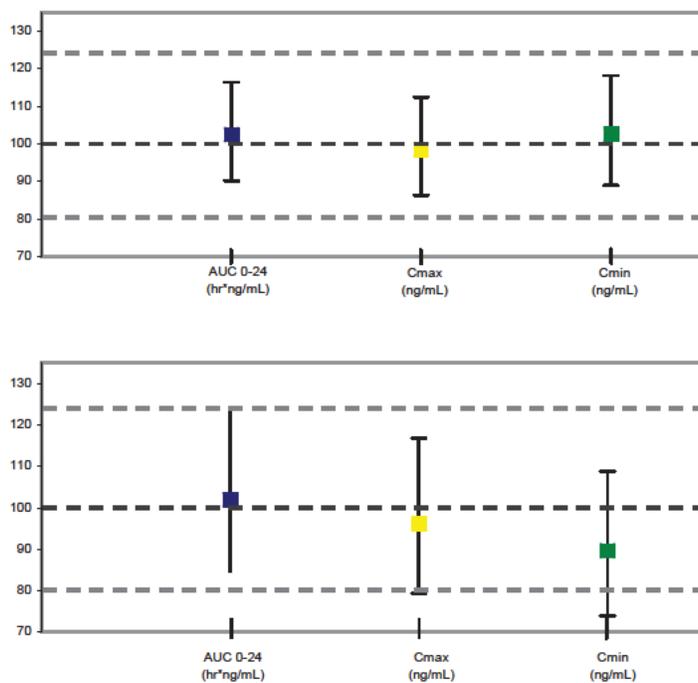


Study 538P108 compared the PK of topiramate in 69 enrolled epilepsy patients after 14 days of treatment with an IR formulation (TOPAMAX<sup>®</sup>) (200, 250, 300, 350, or 400 mg/day, BID), followed by 14 days of the same total daily dose of Trokendi XR<sup>™</sup> (QD). The relative BA of Trokendi XR<sup>™</sup> to topiramate IR at steady state (Day 14) was evaluated in terms of AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> after each treatment, and immediately after the switch from IR to ER formulation after Day 14. Point estimates and 90% CI for geometric mean ratios between two treatments were also assessed for the partial AUC (AUC<sub>0-p</sub>), assessed by BE acceptance criteria of 80-125%. In addition, an ad hoc analysis was performed on the PK data from subgroups of subjects taking enzyme-inducing AED (e.g., phenytoin or carbamazepine) for concomitant topiramate (Induced; N=13) vs. those who not taking any inducers (Neutral; N=47)).

As shown in the Figures below, in overall PK population and in neutral patients, the bioavailability of Trokendi XR<sup>™</sup> was equivalent to topiramate immediate-release product. In induced patients, there was an approximately 10% drop in C<sub>min</sub> for Trokendi XR<sup>™</sup> compared to topiramate immediate-release product, attributing to the potential drug-drug interaction. However, the 10% decrease observed for C<sub>min</sub> does not have clinical significance. No safety issues were reported for the formulation conversion.

Figures. Point estimates and the 90% CIs of AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> at steady-state for PK population (top), Neutral subjects (middle), and Induced subjects (bottom): Trokendi XR<sup>™</sup> (Day 28) vs. topiramate IR (Day 14)





In PK population immediately after the switching to Trokendi XR™, there was an approximately 10% drop in AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> for Trokendi XR™, compared to topiramate immediate-release product. In neutral patients, Trokendi XR™ was bioequivalent to topiramate immediate-release product. In Induced subjects, Trokendi XR™ had comparable AUC<sub>0-24</sub> but approximately 10% lower C<sub>max</sub> and C<sub>min</sub>, compared to topiramate immediate-release product. The AUC exposure in Induced subjects was approximately 23-33% lower within approximately 3 hours immediately after the switch.

The lower exposure immediately after the switch and at the steady-state could attribute to the various confounding factors, such as slower topiramate release and absorption from the XR capsules, relatively small number of subjects in the Induced group, effects of food intake, and the similar enzyme inducing effect for the approved IR formulation, Given results of the relative BA comparison from this study, patients may be switched from immediate-release topiramate products to Trokendi XR™ at the same daily dose.

### 2.5.3 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

Studies 538P106, 538P106-50, and 538P106-200 of similar study design compared the relative BA of the 100 mg, 50 mg and 200 mg dosage strengths, respectively, of SPN-538T lot used for the clinical studies, produced at Supernus (Treatment A), to a lot manufactured at Catalent Pharma Solutions intended for commercial use (Treatment B).

As presented in Tables below, analysis of the 90% CI for the geometric mean ratios of AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> for the two formulations in each study showed that they are

bioequivalent, meeting the acceptance BE criteria. The lowest 25mg dosage strength shares the identical composition and proportions of specific beads to that of the 50mg dose strength, no in vivo formulation bridging is necessary.

Table. BE analysis for 50 mg strength

Parameter	N	Treatment B LS Mean	Treatment A LS Mean	Geometric Mean Ratio (B/A, %)	90% CI
Cmax (ng/mL)	32	400	387	103.30	(95.18, 112.11)
AUC0-t (ng.h/mL)	32	24464	23893	102.39	(96.30, 108.86)
AUC0-∞ (ng.h/mL)	32	35804	35505	100.84	(95.20, 106.82)

Table. BE analysis for 100 mg strength

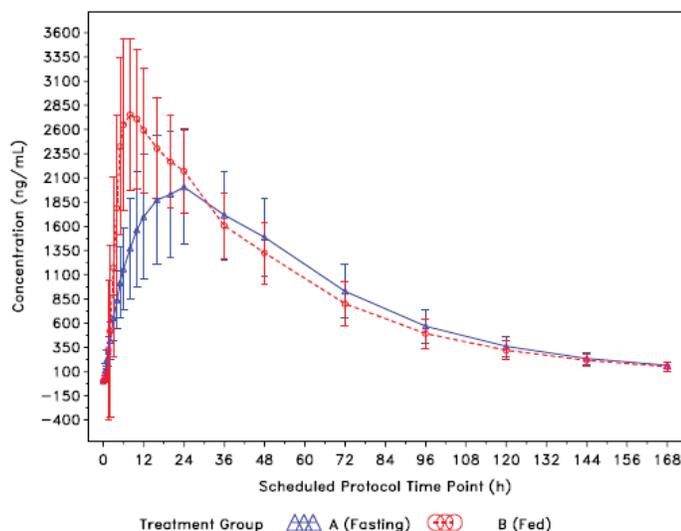
Parameter	N	Treatment B (LS Mean)	Treatment A (LS Mean)	Geometric Mean Ratio (B/A, %)	90% CI
Cmax (ng/mL)	27	1112	1199	92.75	(82.71,104.00)
AUC0-t (ng.h/mL)	27	76576	78483	97.57	(90.30, 105.43)
AUC0-∞ (ng h/mL)	27	84853	87281	97.22	(90.50, 104.43)

Table. BE analysis for 200 mg strength

Parameter	N	Treatment B LS Mean	Treatment A LS Mean	Geometric Mean Ratio (B/A, %)	90% CI
Cmax (ng/mL)	32	2298	2360	97.38	(89.36, 106.13)
AUC0-t (ng.h/mL)	32	125361	123385	101.60	(94.59, 109.13)
AUC0-∞ (ng.h/mL)	32	145761	143942	101.26	(94.51, 108.50)

**2.5.4. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Study 538P105 (N=28) was conducted to assess the potential effects of standard high-fat meal, per FDA Guidance, on PK profile of 200-mg Trokendi XR™ (the highest strength capsule), compared to fasted condition. With the formulation bridging achieved between TBM and developmental scale of the same strength, this food effect study on the 200-mg strength development scale capsule is considered acceptable. The Mean topiramate concentration-time profiles under fasted and fed conditions, as well as the statistical analysis, are presented in the figure and the table below.



Parameter	N	Fed (B) LS Mean	Fasted (A) LS Mean	Geometric Mean Ratio (B/A)	90% CI
C <sub>max</sub> (ng/mL)	28	2744.00	2004.72	136.9 *	(122.08, 153.47)
AUC <sub>0-t</sub> (ng•h/mL)	28	151777.99	142822.49	106.27	(99.80, 113.16)
AUC <sub>0-∞</sub> (ng•h/mL)	28	160762.28	152047.35	105.73	(99.54, 112.31)

\* Included only subjects who completed both treatment periods and had sufficient plasma concentration time data

Compared to the fasted state, high-fat meal increased the C<sub>max</sub> of topiramate by approximately 37% and shortened the T<sub>max</sub> to approximately 8 hours following a single dose of Trokendi XR™, while having no effect on the AUC.

At the IND stage, the Agency raised safety concern regarding the observed magnitude of increase in C<sub>max</sub> with food. The applicant provided an argument that single-dose design of study 538P105 exaggerated the effects of food that would be observed in clinical use of topiramate, which is administered chronically and accumulates substantially due to its long half-life. The applicant re-analyzed data from the same study using population PK approach to evaluate the impact of food on the rate and extent of topiramate absorption from once-daily 200-mg Trokendi XR™ following repeated administration for 3 weeks. Bioequivalence testing of the simulated data was performed. The food effect was re-assessed for AUC<sub>τ</sub>, C<sub>max</sub>, and C<sub>min</sub> at steady-state, as summarized in Table below.

Table. Statistical analysis for food effect from simulated data

PK Parameter	Comparison	Original Scale		CV%
		Ratio	90% CI	
AUC <sub>τ</sub>	Fed vs Fasted	102.45%	(95.38%, 110.04%)	17%
C <sub>max</sub>	Fed vs Fasted	113.28%	(105.32%, 121.85%)	18%
C <sub>min</sub>	Fed vs Fasted	91.84%	(85.30%, 98.88%)	18%

As shown in the above table, modeling of the observed single dose fed data with simulation to steady state showed that the effect on  $C_{max}$  is significantly reduced following repeat administrations. To further support the insignificant food effect, the applicant performed simulation to evaluate the impact of switching from TOPAMAX<sup>®</sup> to Trokendi XR<sup>™</sup> under four different states: Neutral subjects in the fasted state, Induced subjects in the fasted state, Neutral subjects in the fed state, Induced subjects in the fed state. Bioequivalence testing of the PK variables ( $C_{max}$ ,  $C_{min}$ , and  $C_{avg}$ ) derived from simulated topiramate concentration-time data was performed, and fluctuation was also computed. The results showed that BE criteria were met for most PK variables except for  $C_{max}$  for induced subjects in the fasted subjects (90% CI: (78, 80)). Overall fluctuation remained below 50% in all states on all days (refer to Pharmacometrics Review in Section 4.3 of Appendix for details). Therefore, Trokendi XR<sup>™</sup> can be taken without regard to meals.

Study 539P109 for effect of age also compared the relative BA of topiramate given as single 100-mg dose of intact Trokendi XR<sup>™</sup> capsules or as capsule contents in a tablespoon of applesauce to the young group (N=18). As shown in the table below, the 90% CIs of the ratio of geometric mean ratios between the two treatments with respect to  $C_{max}$  and AUCs were within acceptance BE limits.

Table. Statistical analysis for relative bioavailability following administration of capsule vs. capsule contents in applesauce

Parameter	Capsule (N=18)	Contents (N=18)	Geometric Mean Ratio (Contents/Capsule)	90% CI
$C_{max}$ (ng/mL)	1200	1034	86.16	(80.96 – 91.69)
AUC <sub>0-t</sub> (ng·h/mL)	77190	72420	93.82	(90.17 – 97.62)
AUC <sub>0-∞</sub> (ng·h/mL)	84310	79410	94.19	(90.58 – 97.93)

\* Exposure values expressed as geometric means

## 2.6 Analytical section

### 2.6.1 Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes. The parent compound topiramate is the active moiety and was measured in all studies.

### 2.6.2 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

Yes. A validated ultra-performance liquid chromatography with tandem mass spectrometer detection (LC/MS/MS) method was used to quantitate topiramate in human plasma over the range of 5.00 to 5000 ng/mL. The human plasma sample (100  $\mu$ L) is fortified with deuterated internal standard, extracted by supported liquid extraction and

analyzed by LC/MS/MS. Summary of bioanalytical method for topiramate is provided in the Tables below.

Validation	Experimental Details	Results
Linearity	8 Calibration Standards (5.00~5000 ng/mL), n ≥ 3 runs	Accuracy: 98-101% Precision: 1-2% R2: 0.9996
Intra-Run (within run) Precision and Accuracy	QC: (n=5; ≥ 3 runs) Low (15.0 ng/mL) Med (350 ng/mL) High (3500 ng/mL)	Accuracy: 95-103% Precision: 0-4%
Inter-Run (between run) Precision and Accuracy	QC: (n=15; ≥ 3 runs) Low (15.0 ng/mL) Med (350 ng/mL) High (3500 ng/mL)	Accuracy: 96-97% Precision: 2-4%
Sensitivity	LLOQ (5.00 ng/mL) (n ≥ 6 different lots)	Accuracy: 96-97% Precision: 2-4% Mean signal-to-noise ratio ≥ 10
Specificity	Blank plasma (n=1), (n ≥ 6 different lots)	Mean % interference: 0%
Dilution	Dilution QC (n ≥ 5) (QC level ~2xULOQ, DF~10)	Accuracy: 112-117% Precision: 2%
Recovery	Ratio of mean analyte peak area for Low, Med, High QCs (n=3) to mean analyte peak area for reference solutions prepared in 80:20 methanol:water at 7.5, 175 and 1750ng/mL TPR with TPR-d12 at 250ng/mL (n=3 injections)	Mean%: 57% (52-60%)
Carryover	Inject blank following ULOQ n ≥ 3	Mean%: 0-11%
Sample Analysis Batch Size	96-well plate (Blank, Blank+IS, Cal Curve, Low, Med, High QCs (n =5) and remainder blank+IS or other validation samples)	Accuracy: 96-98% Precision: 1-2%
TPR-d12 Spiking Solution Stability	Assess (n=3 injections) after ≥6 hours at room temperature	Accuracy: 98% Precision: 2%
TPR-d12 Spiking Solution Stability	Assess (n=3 injections) after ≥10 days in a refrigerator	Accuracy: 102% Precision: 0%
Extract Stability	TPR QC Concentrations stored at 6°C for 24~69 hours then reinjected	Accuracy: 98-100% Precision: 1-4%

### 3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for Trokendi XR™ extended-release oral capsules and found it acceptable provided that the recommended revisions are made to the labeling language.

Labeling recommendation to be sent to the Sponsor:

The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~Strikethrough text~~ is recommendation for deletion.

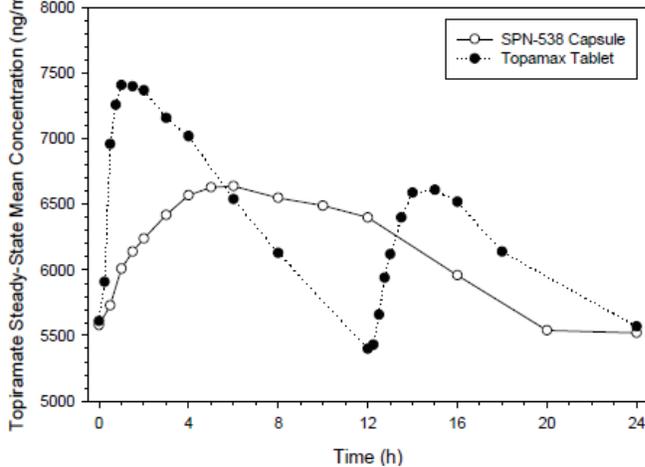
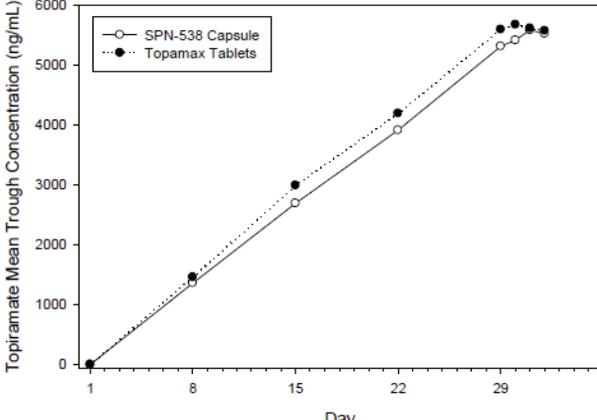
### 4. Appendices

#### 4.1 Proposed labeling

62 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

#### 4.2. Individual Study Review

Study Report #	<b>538P103</b>				
Title	A Single-Center, Multiple-Dose, Randomized, Single-Blind, Two-Treatment Crossover Study to Determine the Pharmacokinetic Profile of SPN-538 Capsules Relative to Topamax <sup>®</sup> Tablets in Healthy Adult Volunteers				
Investigator/Center	Philip Leese, MD, Quintiles Phase I Unit, Overland Park, KS				
Study Dates	March 31, 2009 ~ September 10, 2009				
Objectives	Comparison of Steady-state relative bioavailability				
Formulation	Treatment	TPM CR	Batch number		
	A	SPN-538T capsule, 200 mg	B08025E		
	B	Topamax IR tablet, 100 mg	B10024C		
Study Design	Phase 1, single-center, multiple-dose, single-blind, randomized, 2-treatment, 2-sequence, crossover study in healthy males and females, aged 18-55 years Screening period: 28 Days; washout period: 32 days; duration: 14.5 weeks Treatment Period for (A) SPN-538T QD and (B) Topamax IR BID: Days 1 - 7: 50mg/day Days 8 - 14: 100mg/day Days 15 - 21: 150mg/day Days 22 - 31: 200mg/day				
PK Assessment	<p>For SPN-538T:</p> <ul style="list-style-type: none"> <li>• Predose on the first day of each titration dose strength (Days 1, 8, 15, and 22) and Days 29 and 30.</li> <li>• Day 31 (last dose) time points: predose, postdose: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, and 168 hours.</li> <li>• AUC<sub>0-24</sub>, C<sub>avg,ss 0-24</sub>, C<sub>max,ss 0-24</sub>, C<sub>min,ss 0-24</sub>, C<sub>trough</sub>, FL%, k<sub>el</sub>, t<sub>1/2</sub>, and T<sub>max,ss 0-24</sub>.</li> </ul> <p>For Topamax IR:</p> <ul style="list-style-type: none"> <li>• Predose on the first day of each titration dose strength (Days 1, 8, 15, and 22) and Days 29 and 30.</li> <li>• Day 31 (last dose) time points: pre-first dose of the day, and postdose: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 11.83, 12.25, 12.5, 12.75, 13, 13.5, 14, 15, 16, 18, 24, 36, 48, 72, 96, 120, 144 and 168 hours.</li> <li>• AUC<sub>0-12</sub>, AUC<sub>0-24</sub>, AUC<sub>12-24</sub>, C<sub>avg,ss 0-24</sub>, C<sub>max,ss 0-12</sub>, C<sub>max,ss 0-24</sub>, C<sub>max,ss 12-24</sub>, C<sub>min,ss 0-12</sub>, C<sub>min,ss 0-24</sub>, C<sub>min,ss 12-24</sub>, C<sub>trough</sub>, FL%, k<sub>el</sub>, t<sub>1/2</sub>, T<sub>max,ss 0-12</sub>, and T<sub>max,ss 12-24</sub>.</li> </ul>				
Statistical Analysis	A mixed effect ANOVA model on log-transformed exposure measures and on untransformed FL%. Point estimates and 90% CI for geometric mean ratios of treatment differences (Treatment A/Treatment B) for the log-transformed AUC <sub>0-24</sub> , C <sub>max,ss 0-24</sub> , and C <sub>min,ss 0-24</sub> , judged by BE acceptance criteria of 80-125%.				
Bioanalytical Methods	<p><b>Table.</b> Assay performance</p> <hr/> <table> <tr> <td><b>Analyte</b></td> <td>Topiramate (plasma)</td> </tr> </table> <hr/> <p><b>Method:</b> HPLC/MS/MS</p>			<b>Analyte</b>	Topiramate (plasma)
<b>Analyte</b>	Topiramate (plasma)				

	<p><b>Standard Range:</b> 5.00 – 5000</p> <p><b>Curve:</b> ng/mL</p> <p>Precision: 1 - 3%</p> <p>Accuracy: 98 - 103 %</p> <hr/> <p><b>LOQ:</b> 5 ng/mL</p> <hr/> <p><b>QC:</b> 15.0 ng/mL      350 ng/mL      3500 ng/mL</p> <p>Precision: 4 %      3 %      3 %</p> <p>Accuracy: 108 %      98 %      105%</p> <hr/> <ul style="list-style-type: none"> <li>• Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>• Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><b>Comment:</b> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>
<p>Population/ Demographics</p>	<p>39 Randomized (6 subjects (subjects #119, 122, 110, 128, 118, 111) prematurely discontinued the study); 34 and 38 subjects received SPN-538 and Topamax IR, respectively; 33 completed for PK analysis, safety and PD analyses</p>
<p>PK Results</p>	<p><b>Figure 1.</b> Mean plasma concentration-time curves (Linear Scale) on Day 31</p>  <p><b>Figure 2.</b> Similar mean trough plasma concentrations</p>  <ul style="list-style-type: none"> <li>• Similar rate of accumulation after multiple dosing</li> </ul>

**Table 1.** Summary of pharmacokinetic parameters at steady-state

Pharmacokinetic Parameter	Topamax Tablets (BID) (N=33)	SPN-538 Capsule (QD) (N=33)
AUC <sub>0-24,ss</sub> (ng•h/mL)	151000 ± 26100	147000 ± 27600
C <sub>avg,ss 0-24</sub> (ng•h /mL)	6280 ± 1090	6120 ± 1150
C <sub>max,ss 0-24</sub> (ng/mL)	7680 ± 1250	6820 ± 1350
C <sub>min,ss 0-24</sub> (ng/mL)	5220 ± 989	5250 ± 1070
C <sub>trough,ss 0-24</sub> (ng/mL)	5610 ± 1070	5580 ± 1200
T <sub>max,ss 0-24</sub> (h)*	1.00 (0.25, 12.50)	6.00 (4.00, 24.00)
t <sub>1/2</sub> (h)	30.9 ± 3.10	31.4 ± 3.75
kel (1/h)	0.0226 ± 0.00222	0.0224 ± 0.00271
FL (%)	39.8 ± 8.4 (40.1)**	25.9 ± 6.4 (26.1)**

\* All data presented as arithmetic mean ± SD, except for T<sub>max,ss</sub> (median (range))

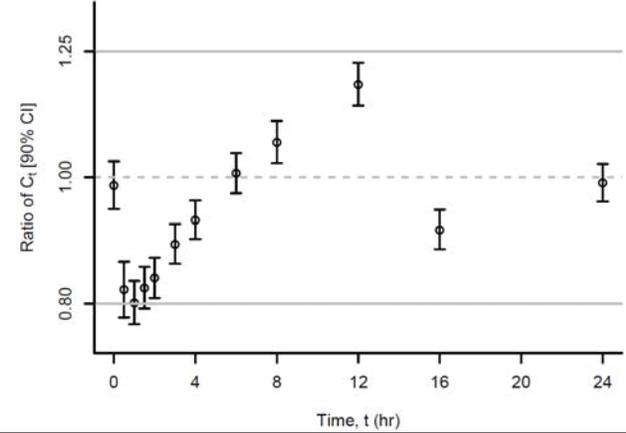
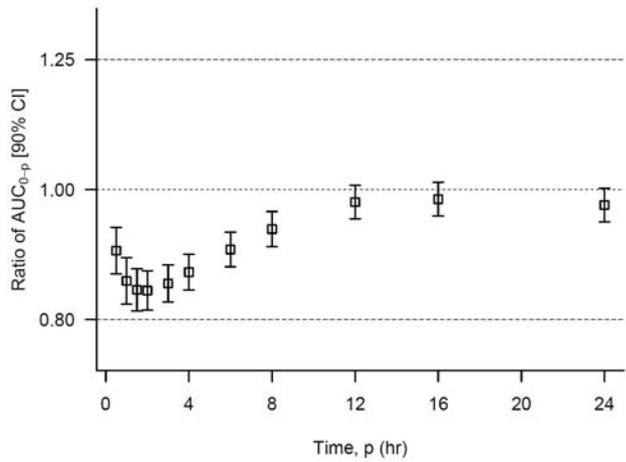
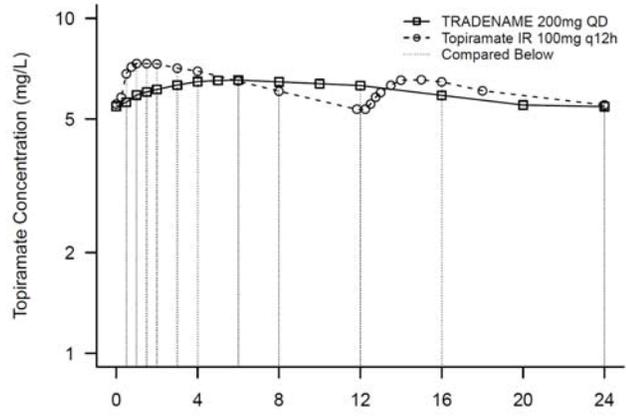
\*\* Based on geometric means

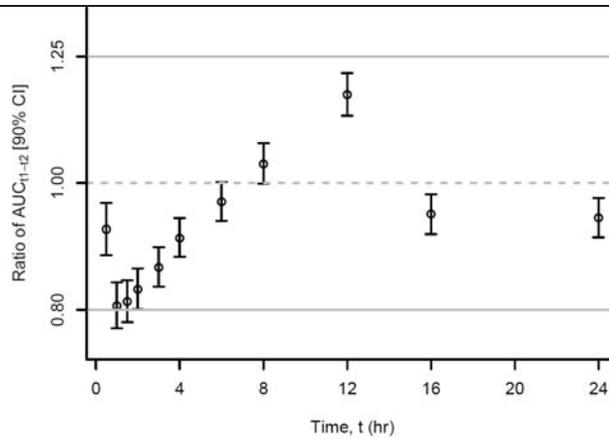
**Table 2.** Summary of statistical analysis for steady-state exposure

Parameter	N	Treatment B LS Mean	Treatment A LS Mean	Geometric Mean Ratio (A/B, %)	90% CI
AUC <sub>0-24</sub> (ng•h/mL)	33	149000	144000	97.06	(94.01, 100.21)
C <sub>max,ss 0-24</sub> (ng/mL)	33	7600	6690	88.01	(85.10, 91.02)
C <sub>min,ss</sub> (ng/mL)	33	5130	5120	99.91	(95.87, 104.13)

In addition to the BE analysis for partial AUC (AUC<sub>0-p</sub>), the applicant submitted additional BE analysis results for comparing the point-to-point topiramate plasma concentrations and the partial AUC between two time-points (i.e., AUC<sub>t1-t2</sub>) to further examine and assure the plasma profile similarity. Results of BE analyses are presented in Figures and Tables below.

**Figures 3~6.** Analysis of partial AUC (AUC<sub>0-p</sub>), point-to-point topiramate concentrations, and partial AUC between two time-points (AUC<sub>t1-t2</sub>)





**Tables 3~6.** Analysis of partial AUC (AUC<sub>0-p</sub>), point-to-point topiramate concentrations, and partial AUC between two time-points (AUC<sub>t1-t2</sub>)

Analysis of partial AUC (AUC<sub>0-p</sub>):

AUC <sub>0-t</sub> <sup>a</sup>	SPN-538T (n=33 <sup>b</sup> ) Geometric LSM (hr*mg/L)	TPM IR (n=33 <sup>b</sup> ) Geometric LSM (hr*mg/L)	Ratio (%) SPN-538T / TPM IR	90% CI (%)
AUC <sub>0-0.5</sub>	2.76	3.00	92.22	(88.09, 96.54)
AUC <sub>0-1</sub>	5.63	6.56	85.90	(82.36, 89.58)
AUC <sub>0-1.5</sub>	8.60	10.22	84.20	(80.95, 87.59)
AUC <sub>0-2</sub>	11.63	13.87	83.88	(80.76, 87.12)
AUC <sub>0-3</sub>	17.83	21.05	84.69	(81.67, 87.82)
AUC <sub>0-4</sub>	24.19	28.06	86.23	(83.24, 89.32)
AUC <sub>0-6</sub>	37.16	41.46	89.64	(86.60, 92.78)
AUC <sub>0-8</sub>	50.10	53.95	92.85	(89.71, 96.09)
AUC <sub>0-12</sub>	75.53	75.70	99.77	(96.39, 103.28)
AUC <sub>0-16</sub>	99.83	101.39	98.46	(95.25, 101.77)
AUC <sub>0-24</sub>	144.25	148.55	97.10	(94.02, 100.28)

<sup>a</sup> Nominal times were used to determine AUC<sub>0-t</sub>  
<sup>b</sup> PK Population; see clinical study report 538P103

Analysis of point-to-point topiramate concentrations:

C <sub>t</sub>	SPN-538T (n=33 <sup>b</sup> ) Geometric LSM (mg/L)	TPM IR (n=33 <sup>b</sup> ) Geometric LSM (mg/L)	Ratio (%) SPN-538T / TPM IR	90% CI (%)
C <sub>0</sub>	5.45	5.52	98.63	(94.57, 102.85)
C <sub>0.5</sub>	5.61	6.83	82.03	(78.07, 86.19)
C <sub>1</sub>	5.87	7.32	80.16	(77.14, 83.29)
C <sub>1.5</sub>	6.01	7.30	82.32	(79.33, 85.41)
C <sub>2</sub>	6.10	7.28	83.75	(80.81, 86.81)
C <sub>3</sub>	6.29	7.07	88.94	(85.89, 92.10)
C <sub>4</sub>	6.44	6.94	92.79	(89.68, 96.00)
C <sub>6</sub>	6.51	6.46	100.73	(97.23, 104.36)
C <sub>8</sub>	6.42	6.03	106.45	(102.54, 110.50)
C <sub>12</sub>	6.28	5.32	117.95	(113.56, 122.51)
C <sub>16</sub>	5.86	6.42	91.22	(88.12, 94.43)
C <sub>24</sub>	5.44	5.49	99.04	(95.81, 102.39)

<sup>b</sup> PK Population; see clinical study report 538P103

Analysis of partial AUC (AUC<sub>t1-t2</sub>):

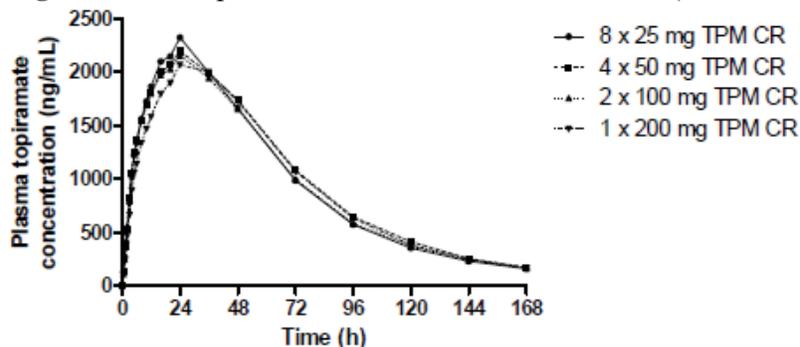
	SPN-538T (n=33 <sup>b</sup> )		TPM IR (n=33 <sup>b</sup> )		
	AUC <sub>t1-t2</sub> <sup>a</sup> Geometric LSM (hr*mg/L)	Geometric LSM (hr*mg/L)	Geometric LSM (hr*mg/L)	Ratio (%) SPN-538T / TPM IR	
				90% CI (%)	
	AUC <sub>0-0.5</sub>	2.76	3.00	92.22	(88.09, 96.54)
	AUC <sub>0.5-1</sub>	2.87	3.56	80.63	(77.43, 83.96)
	AUC <sub>1-1.5</sub>	2.97	3.66	81.23	(78.29, 84.27)
	AUC <sub>1.5-2</sub>	3.03	3.65	83.03	(80.10, 86.08)
	AUC <sub>2-3</sub>	6.19	7.18	86.30	(83.35, 89.35)
	AUC <sub>3-4</sub>	6.36	7.00	90.86	(87.85, 93.97)
	AUC <sub>4-6</sub>	12.97	13.40	96.78	(93.51, 100.16)
	AUC <sub>6-8</sub>	12.93	12.49	103.50	(99.85, 107.28)
	AUC <sub>8-12</sub>	25.42	21.74	116.93	(112.61, 121.41)
	AUC <sub>12-16</sub>	24.28	25.65	94.66	(91.44, 97.99)
	AUC <sub>16-24</sub>	44.36	47.15	94.09	(90.93, 97.36)
<sup>a</sup> Nominal times were used to determine AUC <sub>t1-t2</sub> <sup>b</sup> PK Population; see clinical study report 538P103					
Safety	<ul style="list-style-type: none"> <li>No deaths or SAEs</li> <li>Similar incidence and number of events related to treatment were similar after dosing with SPN-538 (N=33; 97.1%) and Topamax (N=30; 78.9%).</li> <li>Paresthesia, headache, disturbance in attention, somnolence, and dysgeusia were the most frequently reported AEs. Eight (21%) of subjects receiving Topamax experienced either dizziness or postural dizziness, compared to none of the 34 subjects receiving SPN-538.</li> <li>Two subjects discontinued due to AEs; one was considered related to the study drug (SPN-538).</li> <li>Incidence of moderate adverse events was similar between two treatment groups (26.5~28.9%).</li> <li>One post-traumatic headache severe in intensity was reported during Topamax treatment.</li> </ul>				
Conclusions	<ul style="list-style-type: none"> <li>The 90% CI's for the geometric mean ratios for the steady-state exposure measures (AUC<sub>0-24</sub>, C<sub>max,ss</sub> 0-24, and C<sub>min,ss</sub>) between treatments were within the BE acceptance criteria, 80-125%, indicating the bioequivalence between SPN-538 capsules and Topamax IR tablets.</li> <li>Lower percent fluctuation (FL%) at steady-state were observed for SPN-538T (26%) compared to Topamax Tablets (40%).</li> <li>Point estimates and the 90% CIs for the ratios of partial AUC (AUC<sub>0-p</sub>) (i.e., "sustained bioavailability") and at each corresponding time point of the 24-hour plasma concentration-time curves at steady-state for the two formulations were also within the 80-125% BE limits.</li> <li>Point estimates and the 90% CIs for the ratios of point-to-point topiramate plasma concentration and partial AUC (AUC<sub>t1-t2</sub>) of the 24-hour curves for the two formulations were mostly within the 80-125% BE limits, except for the initial time points before approximately 1.5 hour postdose where the 90% CIs fell slightly outside the lower BE limit but were deemed not clinically significant.</li> <li>Similar safety profiles between two formulations were reported, whereas SPN-538 may result in fewer episodes of dizziness compared to Topamax.</li> </ul>				
Comment	<p>In addition to the overall exposure parameters BE, three new PK parameters (AUC<sub>0-p</sub>, AUC<sub>t1-t2</sub>, and Ct) were also BE. The topiramate levels are within the reported therapeutic window. The applicant has provided a compelling</p>				

	evidence that two PK curves of the proposed ER and the reference IR formulations are sufficiently similar to warrant similar clinical outcome.
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Study Report #	<b>538P104</b>			
Title	A Randomized, Open-Label, 4-way Crossover Single Center Study Evaluating the Dosage Form Proportionality of Four Different Strengths of Topiramate Controlled Release Capsules (25, 50, 100 and 200 mg) Administered as a Single 200 mg Oral Dose to Healthy Subjects Under Fasting Conditions			
Investigator/Center	David Bell, MD, Bio-Kinetic Europe Limited, 14 Great Victoria Street, Belfast, BT2 7BA, Northern Ireland			
Study Dates	July 16, 2008 - Nov 18, 2008			
Objectives	Dosage form proportionality			
Formulation	TPM CR	Batch number		
	25 mg capsule	B08024B		
	50 mg capsule	B08025B		
	100 mg capsule	B08026B		
	200 mg capsule	B08027B		
Study Design	Phase 1, single-center, single-dose, randomized, 4-way crossover study in healthy males and females, aged 18-55 years <ul style="list-style-type: none"> <li>• Screening period: 28 Days; washout period <math>\geq 28</math> days; duration: 112 days</li> <li>• Topiramate CR: 1 x 200 mg, 2 x 100 mg, 4 x 50 mg, and 8 x 25 mg</li> </ul>			
PK Assessment	<ul style="list-style-type: none"> <li>• Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose</li> <li>• <math>AUC_{0-t}</math>, <math>AUC_{\infty}</math>, <math>C_{max}</math>, <math>T_{max}</math>, <math>k_{el}</math>, and <math>t_{1/2}</math>.</li> </ul>			
gStatistical Analysis	A mixed effect ANOVA model on log-transformed exposure measures among treatments. Point estimates and 90% CI for geometric mean ratios for the log-transformed $AUC_{0-t}$ , $AUC_{\infty}$ , and $C_{max}$ , judged by BE acceptance criteria of 80-125%.			
Bioanalytical Methods	<b>Table. Assay performance</b>			
	<b>Analyte</b>	Topiramate (plasma)		
	<b>Method:</b>	HPLC/MS/MS		
	<b>Standard</b> Range:	5.00 – 5000		
	<b>Curve:</b>	ng/mL		
	Precision:	1 - 2%		
	Accuracy:	99 - 101 %		
	<b>LOQ:</b>	5 ng/mL		
	<b>QC:</b>	15.0 ng/mL	350 ng/mL	3500 ng/mL
	Precision:	3 %	4 %	2 %
Accuracy:	101 %	99 %	99%	
	<ul style="list-style-type: none"> <li>• Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>• Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><b>Comment:</b> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <math>&lt;15\%</math>.</p>			
Population/	34 randomized; 24 completed; 23-25 PK analysis; 34 safety analysis			

Demographics \* Subject # 34 and 36 withdrew consent; # 06, 09, 13, 18, 20, and 22 excluded for PK analysis due to protocol violation

PK Results **Figure 1.** Mean plasma concentration - time curves (linear scale) by treatment



**Table 1.** Summary of pharmacokinetic parameters

Pharmacokinetic Parameter	TPM CR			
	8 x 25 mg (n=24)	8 x 25 mg (n=25)	2 x 100 mg (n=25)	1 x 200 mg (n=23)
AUC <sub>0-t</sub> (µg·h/mL)	160 (15.1)	165 (12.9)	157 (15.1)	159 (14.0)
AUC <sub>0-∞</sub> (µg·h/mL)	168 (16.1)	174 (13.7)	166 (16.5)	168 (14.4)
C <sub>max</sub> (ng/mL)	2340 (18.7)	2252 (16.1)	2222 (13.9)	2129 (18.4)
T <sub>max</sub> (h)	24.0 (16.0–36.0)	24.0 (16.0–48.0)	24.0 (12.0–36.0)	24.0 (16.0–48.0)
t <sub>1/2</sub> (h)	35.2 (3.9)	35.8 (4.3)	36.0 (5.1)	36.2 (3.8)
K <sub>el</sub> (1/h)	0.0199 (0.0022)	0.0196 (0.0022)	0.0196 (0.0025)	0.0194 (0.0021)

\* Exposure data presented as geometric mean (%CV), except for T<sub>max</sub> (median (range))

**Table 2.** Summary of statistical analysis

Parameter	Test TPM CR treatment (LS Mean)	Reference TPM CR (LS Mean)	Geometric Mean Ratio (T/R)	90% CI
C <sub>max</sub> (ng/mL)	8 x 25 mg	1 x 200 mg	1.109	(1.033, 1.191)
	4 x 50 mg	1 x 200 mg	1.051	(0.980, 1.128)
	2 x 100 mg	1 x 200 mg	1.036	(0.965, 1.112)
	8 x 25 mg	2 x 100 mg	1.070	(0.999, 1.147)
	4 x 50 mg	2 x 100 mg	1.014	(0.947, 1.086)
	8 x 25 mg	4 x 50 mg	1.055	(0.984, 1.131)
AUC <sub>0-t</sub> (ng·h/mL)	8 x 25 mg	1 x 200 mg	0.990	(0.948, 1.034)
	4 x 50 mg	1 x 200 mg	1.039	(0.995, 1.086)
	2 x 100 mg	1 x 200 mg	0.993	(0.951, 1.037)
	8 x 25 mg	2 x 100 mg	0.997	(0.955, 1.040)
	4 x 50 mg	2 x 100 mg	1.047	(1.004, 1.092)
	8 x 25 mg	4 x 50 mg	0.953	(0.913, 0.994)
AUC <sub>0-∞</sub> (ng·h/mL)	8 x 25 mg	1 x 200 mg	0.996	(0.956, 1.038)
	4 x 50 mg	1 x 200 mg	1.038	(0.996, 1.082)
	2 x 100 mg	1 x 200 mg	0.993	(0.952, 1.035)
	8 x 25 mg	2 x 100 mg	1.004	(0.964, 1.045)
	4 x 50 mg	2 x 100 mg	1.046	(1.005, 1.089)

		8 x 25 mg	4 x 50 mg	0.959	(0.921, 0.999)
	AUC <sub>0-t</sub> /AUC <sub>0-∞</sub> : 0.46~0.87 (median 0.70)				
Safety	<ul style="list-style-type: none"> <li>No death or SAEs</li> <li>The majority of AEs were mild and moderate.</li> <li>The most frequently reported AEs were headache, dizziness, and paraesthesia.</li> <li>1 subject withdrew due to 2 AEs of back pain and arthralgia, but not study drug related.</li> </ul>				
Conclusion	<ul style="list-style-type: none"> <li>The 90% CI's for the geometric mean ratios for the exposure measures (C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub>) between treatments were within the BE acceptance criteria of 0.80-1.25, indicating the dosage form proportionality for these 4 CR strengths.</li> <li>Mean topiramate plasma concentration–time curves were similar from the different TPM CR of different strengths.</li> </ul>				

Study Report #	<b>538P104.5</b>		
Title	A Randomized, Open-Label, 4-way Crossover Single Center Study Evaluating the Dosage Form Pharmacokinetic Linearity of Four Different Strengths of Topiramate Controlled-Release (TPM CR) Capsules (25, 50, 100, and 200 mg) Administered as a Single 25 mg, 50 mg, 100 mg, or 200 mg Oral Dose to Healthy Subjects Under Fasting Conditions		
Investigator/Center	David Bell, MD, Bio-Kinetic Europe Limited, 14 Great Victoria Street, Belfast, BT2 7BA, Northern Ireland		
Study Dates	July 16, 2008 - Nov 18, 2008		
Objectives	Dosage form proportionality		
Formulation	TPM CR	Batch number	
	25 mg capsule	B08024C	
	50 mg capsule	B08025C	
	100 mg capsule	B08026C	
	200 mg capsule	B08027C	
Study Design	<p>Phase 1, single-center, single-dose, randomized, 4-way crossover study in healthy males and females, aged 18-55 years</p> <ul style="list-style-type: none"> <li>Screening period: 28 Days; washout period ≥28 days; duration: 112 days</li> <li>Topiramate CR: (A) 1 x 25 mg, (B) 1 x 50 mg, (C) 1 x 100 mg, and (D) 1 x 200 mg</li> </ul>		
PK Assessment	<ul style="list-style-type: none"> <li>Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose</li> <li>AUC<sub>0-t</sub>, AUC<sub>∞</sub>, C<sub>max</sub>, T<sub>max</sub>, kel, and t<sub>1/2</sub>.</li> </ul>		
Statistical Analysis	<ul style="list-style-type: none"> <li>Dose-normalized C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> were compared using ANOVA model on log-transformed exposure measures among treatments. Point estimates and 90% CI for geometric mean ratios for the log-transformed AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub>, judged by BE acceptance criteria of 80-125%. Dosage form linearity would be concluded if all 90% CIs fall</li> </ul>		

	<p>within 80-125%.</p> <ul style="list-style-type: none"> <li>Power Model (<math>P=a \times \text{Dose}^b</math>) was also utilized to assess the linearity for each parameter (P). Linearity would be concluded if the 95% CI for b contained 1.</li> </ul>																																				
Bioanalytical Methods	<p><b>Table.</b> Assay performance</p> <table border="1"> <tr> <td><b>Analyte</b></td> <td colspan="3">Topiramate (plasma)</td> </tr> <tr> <td><b>Method:</b></td> <td colspan="3">HPLC/MS/MS</td> </tr> <tr> <td><b>Standard Range:</b></td> <td colspan="3">5.00 – 5000 ng/mL</td> </tr> <tr> <td><b>Curve:</b></td> <td colspan="3">Precision: 1.2 – 2.9%</td> </tr> <tr> <td></td> <td colspan="3">Accuracy: 98 - 101 %</td> </tr> <tr> <td><b>LOQ:</b></td> <td colspan="3">5 ng/mL</td> </tr> <tr> <td><b>QC:</b></td> <td>15.0 ng/mL</td> <td>350 ng/mL</td> <td>3500 ng/mL</td> </tr> <tr> <td></td> <td>Precision: 4.4 %</td> <td>3.6 %</td> <td>4.7 %</td> </tr> <tr> <td></td> <td>Accuracy: 101 %</td> <td>100 %</td> <td>98%</td> </tr> </table> <ul style="list-style-type: none"> <li>Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><b>Comment:</b> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>	<b>Analyte</b>	Topiramate (plasma)			<b>Method:</b>	HPLC/MS/MS			<b>Standard Range:</b>	5.00 – 5000 ng/mL			<b>Curve:</b>	Precision: 1.2 – 2.9%				Accuracy: 98 - 101 %			<b>LOQ:</b>	5 ng/mL			<b>QC:</b>	15.0 ng/mL	350 ng/mL	3500 ng/mL		Precision: 4.4 %	3.6 %	4.7 %		Accuracy: 101 %	100 %	98%
<b>Analyte</b>	Topiramate (plasma)																																				
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	Accuracy: 101 %	100 %	98%																																		
Population/ Demographics	<p>36 randomized; 32 completed; 33 PK analysis; 36 safety analysis  * 2 subjects withdrew consent; 1 subject had a protocol violation; 1 subject withdrew due to SAE.</p>																																				
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Kel (1/h)	0.0104 (0.0022)	0.0136 (0.0021)	0.0178 (0.0026)	0.020 (0.0029)
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\* Exposure data presented as geometric mean (%CV), except for Tmax (median (range))

**Table 2.** Summary of dose-normalized exposure parameters

Pharmacokinetic Parameter	TPM CR			
	1 x 25 mg (n=33)	1 x 50 mg (n=30)	1 x 100 mg (n=31)	1 x 200 mg (n=32)
AUC <sub>0-t</sub> (µg•h/mL)	0.651 (23.8)	0.729 (21.5)	0.776 (17.1)	0.766 (19.8)
AUC <sub>0-∞</sub> (µg•h/mL)	0.833 (22.3)	0.842 (19.6)	0.837 (17.9)	0.809 (19.6)
C <sub>max</sub> (ng/mL)	6.77 (32.6)	9.22 (36.9)	10.9 (24.1)	10.2 (26.1)

\* Data presented as geometric mean (%CV)

**Table 3.** Summary of statistical analysis

Parameter	Test TPM CR treatment (LS Mean)	Reference TPM CR (LS Mean)	Geometric Mean Ratio (T/R)	90% CI
C <sub>max</sub> (ng/mL)	1 x 50 mg	1 x 25 mg	1.35	(1.24, 1.46)
	1 x 100 mg	1 x 25 mg	1.59	(1.47, 1.72)
	1 x 200 mg	1 x 25 mg	1.5	(1.39, 1.63)
	1 x 100 mg	1 x 50 mg	1.18	(1.09, 1.28)
	1 x 200 mg	1 x 50 mg	1.12	(1.03, 1.21)
	1 x 200 mg	1 x 100 mg	0.945	(0.872, 1.02)
AUC <sub>0-t</sub> (ng•h/mL)	1 x 50 mg	1 x 25 mg	1.11	(1.07, 1.16)
	1 x 100 mg	1 x 25 mg	1.18	(1.13, 1.23)
	1 x 200 mg	1 x 25 mg	1.18	(1.13, 1.23)
	1 x 100 mg	1 x 50 mg	1.06	(1.01, 1.1)
	1 x 200 mg	1 x 50 mg	1.06	(1.01, 1.1)
	1 x 200 mg	1 x 100 mg	1.00	(0.957, 1.04)
AUC <sub>0-∞</sub> (ng•h/mL)	1 x 50 mg	1 x 25 mg	1.01	(0.969, 1.05)
	1 x 100 mg	1 x 25 mg	0.997	(0.96, 1.04)
	1 x 200 mg	1 x 25 mg	0.973	(0.937, 1.01)
	1 x 100 mg	1 x 50 mg	0.99	(0.952, 1.03)
	1 x 200 mg	1 x 50 mg	0.967	(0.93, 1.0)
	1 x 200 mg	1 x 100 mg	0.976	(0.94, 1.01)

**Table 4.** Summary of Power Model for dose linearity

PK Parameter	Point Estimate	Lower 95% CI	Upper 95% CI
AUC <sub>0-t</sub> (µg•h/mL)	1.079	1.055	1.102
AUC <sub>0-∞</sub> (µg•h/mL)	0.987	0.966	1.007
C <sub>max</sub> (ng/mL)	1.202	1.154	1.250

Safety

- No death or SAEs
- The majority of AEs were mild and moderate.
- The most frequently reported AEs were headache and paraesthesia (30% at 200mg dose).
- 1 subject (#009) withdrew due to SAE (diverticulitis) not related to study drug.

Conclusion

- Dosage form linearity for the TPM CR capsules of 4 different strengths was concluded for AUC<sub>0-t</sub> and AUC<sub>0-∞</sub>, but not for C<sub>max</sub>, based on the BE

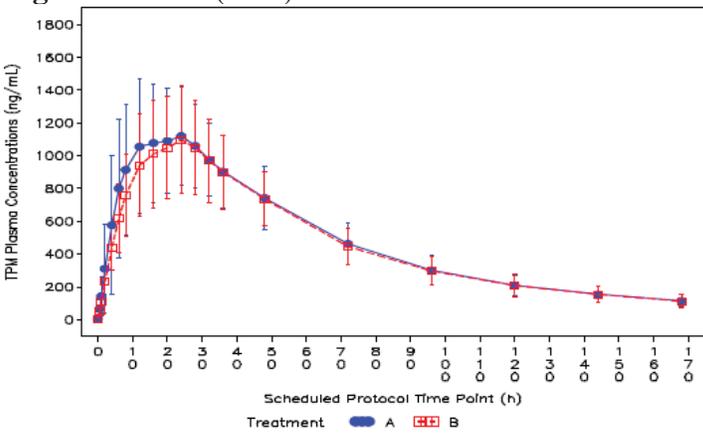
	<p>acceptance criteria of 0.80-1.25.</p> <ul style="list-style-type: none"> <li>• Results of the power model showed that only the 95% CI for the exponential coefficient for <math>AUC_{0-\infty}</math> includes 1. Although not being the case for <math>AUC_{0-t}</math>, the point estimate for the exponential coefficient for <math>AUC_{0-t}</math> is close to 1.</li> <li>• <math>T_{max}</math> was increased from 24 hours for the 25 mg, 50 mg and 100 mg strengths to 36 hours for the highest 200 mg strength.</li> <li>• Terminal <math>t_{1/2}</math> was prolonged as doses were decreased (Table 1), which can be attributed to the substantial and saturable binding of topiramate to erythrocytes.</li> <li>• Mean topiramate plasma concentration–time curves were similar from the different TPM CR of different strengths.</li> </ul>
Comment	The substantial and saturable binding of topiramate to carbonic anhydrase in erythrocytes may be attributable to the observed nonlinearity for $C_{max}$ and the prolonged $t_{1/2}$ at low topiramate concentrations, especially at the lowest 25 mg dose. ( <i>Epilepsy Res. 2005 Feb;63(2-3):103-12</i> )

Study Report #	<b>538P106-50</b>												
Title	Relative Bioavailability of Topiramate Controlled-Release Capsules in Healthy Adult Volunteers												
Investigator/Center	Azra Hussaini, MD, PAREXEL Early Phase Clinical Research - Baltimore 3001 South Hanover Street Baltimore, MD 21225, USA												
Study Dates	Sep 28, 2010 – Nov 05, 2010												
Objectives	Relative bioavailability of a single dose of two lots of TPM CR 50 mg capsules under fasting condition												
Formulation	Treatment	TPM CR	Batch number										
	A	SPN-538T capsule, 50 mg (Clinical)	B08025E										
	B	(b) (4) capsule, 50 mg (Catalent)	B10024C										
Study Design	Phase 1, single-center, single-dose, randomized, 2-period, 2-treatment, 2-sequence, crossover Screening period: 26 days; washout period 18 days; duration: 51 days												
PK Assessment	<p>For SPN-538:</p> <ul style="list-style-type: none"> <li>• Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, and 96 hours postdose</li> <li>• <math>AUC_{0-t}</math>, <math>AUC_{0-\infty}</math>, <math>C_{max}</math>, <math>T_{max}</math>, <math>k_{el}</math>, <math>t_{1/2}</math>, <math>AUC_{0-t}/AUC_{0-\infty}</math>.</li> </ul>												
Statistical Analysis	A mixed effect ANOVA model on log-transformed exposure measures. Point estimates and 90% CI for geometric mean ratios for the log-transformed $AUC_{0-t}$ , $AUC_{\infty}$ , and $C_{max}$ , judged by acceptance criteria of 80-125%.												
Bioanalytical Methods	<p><b>Table.</b> Assay performance</p> <hr/> <table> <tr> <td><b>Analyte</b></td> <td>Topiramate (plasma)</td> </tr> </table> <hr/> <table> <tr> <td><b>Method:</b></td> <td>HPLC/MS/MS</td> </tr> </table> <hr/> <table> <tr> <td><b>Standard</b></td> <td>Range: 5.00 – 5000</td> </tr> <tr> <td><b>Curve:</b></td> <td>ng/mL</td> </tr> <tr> <td></td> <td>Precision: 1 - 3%</td> </tr> </table>			<b>Analyte</b>	Topiramate (plasma)	<b>Method:</b>	HPLC/MS/MS	<b>Standard</b>	Range: 5.00 – 5000	<b>Curve:</b>	ng/mL		Precision: 1 - 3%
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	<p>Accuracy: 98 - 101 %</p> <hr/> <p><b>LOQ:</b> 5 ng/mL</p> <hr/> <p><b>QC:</b> 15.0 ng/mL      350 ng/mL      3500 ng/mL</p> <p>Precision: 9 %      3 %      2 %</p> <p>Accuracy: 97 %      96 %      94%</p> <hr/> <ul style="list-style-type: none"> <li>Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><u>Comment:</u> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>																																																																																																									
Population/ Demographics	<p>Randomized: 32; completed: 31; PK analysis: 32; safety analysis: 31</p> <p>Age: 18-55 years; males and females</p> <p>* One subject withdrew during period 2 due to non-treatment related fever and sore throat.</p>																																																																																																									
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	Parameter	N	Treatment B LS Mean	Treatment A LS Mean	Geometric Mean Ratio (B/A, %)	90% CI
	C <sub>max</sub> (ng/mL)	32	400	387	103.30	(95.18, 112.11)
	AUC <sub>0-t</sub> (ng.h/mL)	32	24464	23893	102.39	(96.30, 108.86)
	AUC <sub>0-∞</sub> (ng.h/mL)	32	35804	35505	100.84	(95.20, 106.82)
	AUC <sub>0-t</sub> /AUC <sub>0-∞</sub> : 0.46~0.87 (median 0.70)					
Safety	No deaths, SAEs, or AEs that led to premature study withdrawal					
Conclusion	<ul style="list-style-type: none"> <li>The 90% CI's for the geometric mean ratios for the exposure measures (C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>∞</sub>) between treatments were within the BE acceptance criteria of 80-125%, suggesting the BE between clinical and commercial (Catalent) formulations following single 1 x 50 mg capsule.</li> </ul>					
Comment	The PK sampling times were not considered sufficiently long and consequently resulted in ~30% of extrapolated AUC <sub>t-∞</sub> , based on ratio of AUC <sub>0-t</sub> / AUC <sub>0-∞</sub> ranging 0.46~0.87 (median 0.70). However, this study did show the highly similar PK profiles and the extrapolation for both clinical and commercial formulations is close to each other.					

Study Report #	<b>538P106</b>		
Title	Relative Bioavailability of Topiramate Controlled-Release (TPM CR) Capsules in Healthy Adult Volunteers		
Investigator/ Center	Azra Hussaini, MD, PAREXEL Early Phase Clinical Research - Baltimore 3001 South Hanover Street Baltimore, MD 21225, USA		
Study Dates	April 19, 2010 - May 31, 2010		
Objectives	Relative bioavailability of a single dose of two lots of TPM CR 100mg capsules under fasting condition		
Formulation	Treatment	TPM CR	Batch number
	A	SPN-538T capsule, 100 mg (Clinical)	B08026E
	B	(b) (4) capsule, 100 mg (Catalent)	B10001B
Study Design	Phase 1, single-center, single-dose, randomized, 2-period, 2-treatment, 2-sequence, crossover Screening period: 28 days; washout period 21 days; duration: 57 days		
PK Assessment	<u>For SPN-538:</u> <ul style="list-style-type: none"> <li>Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose</li> <li>AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, k<sub>el</sub>, t<sub>1/2</sub>, AUC<sub>0-t</sub>/AUC<sub>0-∞</sub>.</li> </ul>		
Statistical Analysis	A mixed effect ANOVA model on log-transformed exposure measures. Point estimates and 90% CI for geometric mean ratios for the log-transformed AUC <sub>0-t</sub> , AUC <sub>∞</sub> , and C <sub>max</sub> , judged by acceptance criteria of 80-125%.		
Bioanalytical Methods	<b>Table.</b> Assay performance		

	<p><b>Analyte</b> Topiramate (plasma)</p> <hr/> <p><b>Method:</b> HPLC/MS/MS</p> <hr/> <p><b>Standard Range:</b> 5.00 – 5000 ng/mL</p> <p><b>Curve:</b> Precision: 1 - 2% Accuracy: 98 - 101 %</p> <hr/> <p><b>LOQ:</b> 5 ng/mL</p> <hr/> <p><b>QC:</b> Precision: 15.0 ng/mL      350 ng/mL      3500 ng/mL Accuracy: 4 %                      2 %                      3 % 107 %                      106 %                      104%</p> <hr/> <ul style="list-style-type: none"> <li>Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><b>Comment:</b> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>																																																																																							
Population/ Demographics	<p>Randomized: 28; completed: 27; PK analysis: 27; safety analysis: 27 Age: 18-55 years; males and females * Subject #117, randomized to Sequence BA, withdrew consent.</p>																																																																																							
PK Results	<p><b>Figure 1.</b> Mean (<math>\pm</math>SD) Plasma Concentration - Time Curves (Linear Scale)</p>  <p><b>Table 1.</b> Summary of pharmacokinetic parameters</p> <table border="1" data-bbox="451 1371 1430 1875"> <thead> <tr> <th>Treatment</th> <th>Statistics</th> <th>C<sub>max</sub> (ng/mL)</th> <th>AUC<sub>0-t</sub> (ng h/mL)</th> <th>AUC<sub>∞</sub> (ng h/mL)</th> <th>T<sub>max</sub> (h)</th> <th>T<sub>1/2</sub> (h)</th> </tr> </thead> <tbody> <tr> <td rowspan="7"><b>A (Clinical)</b></td> <td>N</td> <td>27</td> <td>27</td> <td>27</td> <td>27</td> <td>27</td> </tr> <tr> <td>Mean</td> <td>1247</td> <td>80119</td> <td>88989</td> <td>21</td> <td>50</td> </tr> <tr> <td>SD</td> <td>394</td> <td>17594</td> <td>18858</td> <td>9</td> <td>8</td> </tr> <tr> <td>Median</td> <td>1210</td> <td>79259</td> <td>88628</td> <td>24</td> <td>50</td> </tr> <tr> <td>Minimum</td> <td>701</td> <td>54547</td> <td>61360</td> <td>4</td> <td>34</td> </tr> <tr> <td>Maximum</td> <td>2450</td> <td>129851</td> <td>139651</td> <td>36</td> <td>68</td> </tr> <tr> <td>CV (%)</td> <td>31.6</td> <td>22.0</td> <td>21.2</td> <td>43.1</td> <td>17.6</td> </tr> <tr> <td rowspan="6"><b>B (Catalent)</b></td> <td>N</td> <td>28</td> <td>28</td> <td>28</td> <td>28</td> <td>28</td> </tr> <tr> <td>Mean</td> <td>1157</td> <td>78063</td> <td>86542</td> <td>23</td> <td>51</td> </tr> <tr> <td>SD</td> <td>325</td> <td>17232</td> <td>19134</td> <td>8</td> <td>7</td> </tr> <tr> <td>Median</td> <td>1135</td> <td>74326</td> <td>84418</td> <td>24</td> <td>50</td> </tr> <tr> <td>Minimum</td> <td>603</td> <td>50582</td> <td>56075</td> <td>8</td> <td>40</td> </tr> <tr> <td>Maximum</td> <td>2010</td> <td>127665</td> <td>143331</td> <td>48</td> <td>66</td> </tr> </tbody> </table>	Treatment	Statistics	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng h/mL)	AUC <sub>∞</sub> (ng h/mL)	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	<b>A (Clinical)</b>	N	27	27	27	27	27	Mean	1247	80119	88989	21	50	SD	394	17594	18858	9	8	Median	1210	79259	88628	24	50	Minimum	701	54547	61360	4	34	Maximum	2450	129851	139651	36	68	CV (%)	31.6	22.0	21.2	43.1	17.6	<b>B (Catalent)</b>	N	28	28	28	28	28	Mean	1157	78063	86542	23	51	SD	325	17232	19134	8	7	Median	1135	74326	84418	24	50	Minimum	603	50582	56075	8	40	Maximum	2010	127665	143331	48	66
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	CV (%)	28.1	22.1	22.1	23.9	13.3
	Geo Mean	1113	76291	84625		
	* AUC <sub>0-t</sub> /AUC <sub>0-∞</sub> : 0.83-0.96 (median 0.90)					
	<b>Table 2.</b> Summary of statistical analysis					
	<b>Parameter</b>	<b>N</b>	<b>Treatment B (LS Mean)</b>	<b>Treatment A (LS Mean)</b>	<b>Geometric Mean Ratio (B/A, %)</b>	<b>90% CI</b>
	C <sub>max</sub> (ng/mL)	28 (27)	1113 (1112)	1200 (1199)	92.97 (92.75)	82.88, 103.89 (82.71, 104.00)
	AUC <sub>0-t</sub> (ng.h/mL)	28 (27)	76291 (76576)	78361 (78483)	97.36 (97.57)	90.17, 105.12 (90.30, 105.43)
	AUC <sub>0-∞</sub> (ng.h/mL)	28 (27)	84625 (84853)	87168 (87281)	97.08 (97.22)	90.43, 104.22 (90.50, 104.43)
	N=27: excluding subject #117.					
Safety	No deaths, SAEs, or AEs that led to premature study withdrawal					
Conclusions	The 90% CI's for the geometric mean ratios for the exposure measures (C <sub>max</sub> , AUC <sub>0-t</sub> , and AUC <sub>∞</sub> ) between treatments were within the BE acceptance criteria of 80-125%, indicating BE between clinical and commercial (Catalent) formulations following single 1 x 100 mg capsules.					

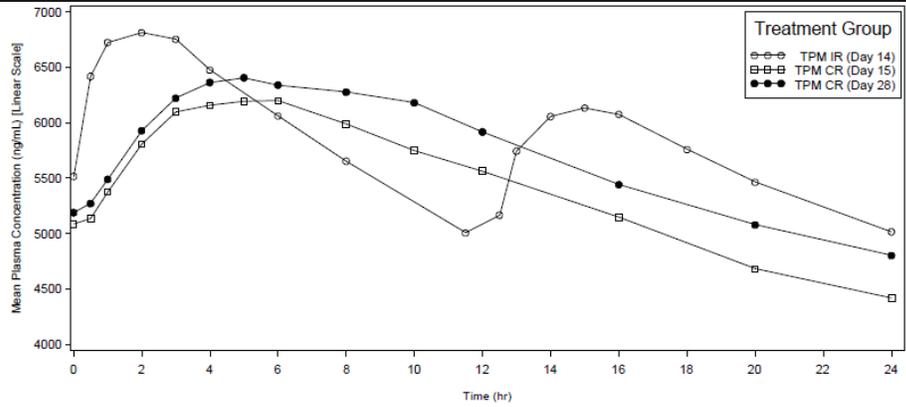
Study Report #	<b>538P106-200</b>		
Title	Relative Bioavailability of Topiramate Controlled-Release Capsules in Healthy Adult Volunteers		
Investigator/ Center	Kyle Patrick, DO, Dedicated Phase I, Inc., 734 W. Highland Ave., Phoenix, AZ 85013, USA		
Study Dates	Oct 01, 2010 – Dec 10, 2010		
Objectives	Relative bioavailability of a single dose of two lots of TPM CR 200 mg capsules under fasting condition		
Formulation	Treatment	TPM CR	Batch number
	A	SPN-538T capsule, 200 mg (Clinical)	B08027F
	B	(b) (4) capsule, 200 mg (Catalent)	B10002D
Study Design	Phase 1, single-center, single-dose, randomized, 2-period, 2-treatment, 2-sequence, crossover Screening period: 26 days; washout period 18 days; duration: 51 days		
PK Assessment	For SPN-538: <ul style="list-style-type: none"> <li>• Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, and 96 hours postdose</li> <li>• AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, k<sub>el</sub>, t<sub>1/2</sub>, AUC<sub>0-t</sub>/AUC<sub>0-∞</sub>.</li> </ul>		
Statistical Analysis	A mixed effect ANOVA model on log-transformed exposure measures. Point estimates and 90% CI for geometric mean ratios for the log-transformed AUC <sub>0-t</sub> , AUC <sub>∞</sub> , and C <sub>max</sub> , judged by acceptance criteria of 80-125%.		
Bioanalytical Methods	<b>Table.</b> Assay performance		
	<b>Analyte</b>	Topiramate (plasma)	

	<p><b>Method:</b> HPLC/MS/MS</p> <hr/> <p><b>Standard Curve:</b> Range: 5.00 – 5000 ng/mL Precision: 1 - 5% Accuracy: 99 - 104 %</p> <hr/> <p><b>LOQ:</b> 5 ng/mL</p> <hr/> <p><b>QC:</b> 15.0 ng/mL      350 ng/mL      3500 ng/mL Precision: 6 %      3 %      3 % Accuracy: 103 %      97 %      96%</p> <hr/> <ul style="list-style-type: none"> <li>• Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>• Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><b>Comment:</b> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>																																																																																																									
Population/ Demographics	32 Randomized (20 males and 12 females; aged 18-55 years); 32 completed; 32 for PK and safety analyses																																																																																																									
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<b>Table 2. Summary of statistical analysis</b>					
Parameter	N	Treatment B LS Mean	Treatment A LS Mean	Geometric Mean Ratio (B/A, %)	90% CI
C <sub>max</sub> (ng/mL)	32	2298	2360	97.38	(89.36, 106.13)
AUC <sub>0-t</sub> (ng.h/mL)	32	125361	123385	101.60	(94.59, 109.13)
AUC <sub>0-∞</sub> (ng.h/mL)	32	145761	143942	101.26	(94.51, 108.50)
AUC <sub>0-t</sub> /AUC <sub>0-∞</sub> : 0.75~0.97 (mean 0.86)					
Safety	No deaths, SAEs, or AEs that led to premature study withdrawal				
Conclusion	The 90% CI's for the geometric mean ratios for the exposure measures (C <sub>max</sub> , AUC <sub>0-t</sub> , and AUC <sub>∞</sub> ) between treatments were within the BE acceptance criteria of 80-125%, indicating the bioequivalence between clinical and commercial (Catalent) formulations following single 200 mg doses (1 x 200 mg capsules).				

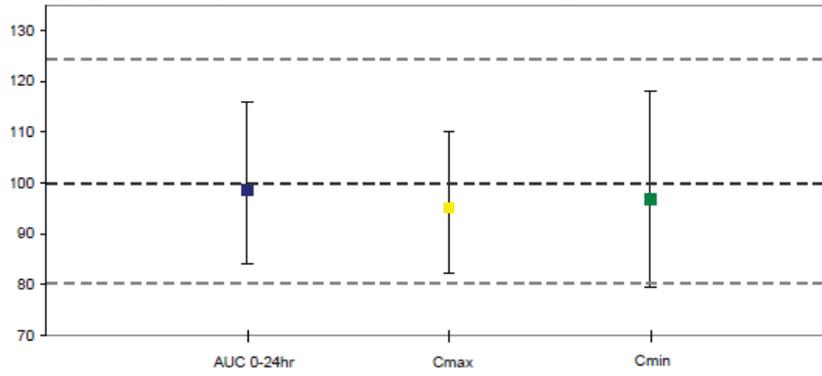
Study Report #	<b>538P108</b>	
Title	A Conversion Study to Determine the Relative Bioavailability of TPM ER vs. TPM IR in Subjects with Epilepsy	
Investigator/ Center	Multi-center (11 sites)	
Study Dates	July 11, 2010 – Jan 23, 2011	
Objectives	Relative bioavailability at steady-state; Relative bioavailability following the switch (TPM IR -> CR)	
Formulation	Treatment	TPM
	Period 1	Topamax IR Tablets
	Period 2	TPM CR capsules
Study Design	Phase 2, multi-center, open-label, 2-treatment conversion study for equivalent doses in male and female subjects, 18-65 years of age, inclusive, with partial onset seizures or primary generalized seizures currently under treatment with Topamax IR (200, 250, 300, 350, or 400 mg/day).  <u>Period 1:</u> Topamax IR (or TPM IR), BID, for 2 weeks; PK on Days 13, 14 <u>Period 2:</u> TPM CR, QD, for 2 weeks; PK on Days 15, 16, 28, 29	
PK Assessment	<u>For both CR and IR:</u> <ul style="list-style-type: none"> <li>• Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 (or 11.75), 16, 20, and 24 hours postdose</li> <li>• AUC<sub>0-24</sub>, C<sub>avg</sub>, C<sub>max</sub>, C<sub>min</sub>, C<sub>trough</sub>, T<sub>max</sub>, FL%, and partial AUC (AUC<sub>0-p</sub>).</li> <li>• For TPM IR only: T<sub>max,0-12</sub> and T<sub>max,12-24</sub>.</li> <li>• C<sub>trough</sub>: Days 13, 14, 27, and 18 for assessing attainment of steady-state</li> </ul>	
Statistical Analysis	<ul style="list-style-type: none"> <li>• A mixed effect ANOVA model on log-transformed exposure measures.</li> </ul>	

	<ul style="list-style-type: none"> <li>Point estimates and 90% CI for geometric mean ratios (CR/IR) for the In-transformed dose-normalized (1) AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> following the switch, and (2) partial AUC (AUC<sub>0-p</sub>) (i.e., “sustained bioavailability” per the applicant), assessed by BE acceptance criteria of 80-125%.</li> <li>Ad hoc analysis on the subgroup of subjects taking enzyme-inducing AED for concomitant topiramate (Induced) vs. those who not taking any inducers (Neutral).</li> </ul>																																											
Bioanalytical Methods	<p><b>Table.</b> Assay performance</p> <table border="1"> <tr> <td><b>Analyte</b></td> <td colspan="3">Topiramate (plasma)</td> </tr> <tr> <td><b>Method:</b></td> <td colspan="3">HPLC/MS/MS</td> </tr> <tr> <td><b>Standard</b></td> <td>Range:</td> <td colspan="2">5.00 – 5000</td> </tr> <tr> <td><b>Curve:</b></td> <td></td> <td colspan="2">ng/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td colspan="2">1 - 4%</td> </tr> <tr> <td></td> <td>Accuracy:</td> <td colspan="2">98 - 101 %</td> </tr> <tr> <td><b>LOQ:</b></td> <td colspan="3">5 ng/mL</td> </tr> <tr> <td><b>QC:</b></td> <td></td> <td>15.0 ng/mL</td> <td>350 ng/mL</td> <td>3500 ng/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td>5 %</td> <td>5 %</td> <td>4 %</td> </tr> <tr> <td></td> <td>Accuracy:</td> <td>99 %</td> <td>99 %</td> <td>98%</td> </tr> </table> <ul style="list-style-type: none"> <li>Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><b>Comment:</b> The bioanalytical methods (with or without the presence of specific AEDs in this study) were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>	<b>Analyte</b>	Topiramate (plasma)			<b>Method:</b>	HPLC/MS/MS			<b>Standard</b>	Range:	5.00 – 5000		<b>Curve:</b>		ng/mL			Precision:	1 - 4%			Accuracy:	98 - 101 %		<b>LOQ:</b>	5 ng/mL			<b>QC:</b>		15.0 ng/mL	350 ng/mL	3500 ng/mL		Precision:	5 %	5 %	4 %		Accuracy:	99 %	99 %	98%
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Population/ Demographics	<p>69 randomized; 61 completed; PK analysis: 62 (including Subject #03-005); safety analysis: 66</p> <ul style="list-style-type: none"> <li>Subject 03-005: discontinued on Day 15; PK data on Days 14 and 15 were included</li> <li>Subject 01-006: no Cp24h sample was collected for CR and was excluded for AUC calculation.</li> <li>8 subjects discontinued mostly due to withdrawal of subject consent/assent, followed by 1AE, 1 protocol violation, and 1 other.</li> <li>41 subjects (62.1%) were diagnosed with partial onset epilepsy, 24 subjects (36.4%) had primarily generalized epilepsy, and 1 subject (1.5%) had mixed type epilepsy.</li> <li>33 (48%) of the 69 enrolled subjects were on TPM monotherapy; one additional AED taken by 23 (33%) subjects; two additional AEDs taken by 10 (14%) subjects; 3 additional AEDs taken by 3 (4%) subjects.</li> <li>Induced (N=13): on carbamazepine and/or phenytoin (known to reduce concomitant topiramate levels of 30-40%)</li> <li>Similar baseline characteristics, though most were white or females.</li> </ul>																																											
PK Results	<p><b>I. Relative Bioavailability of TPM CR to TPM IR at Steady-State</b></p> <p><b>Figure 1.</b> Mean dose-normalized concentration-time profile (PK population)</p>																																											

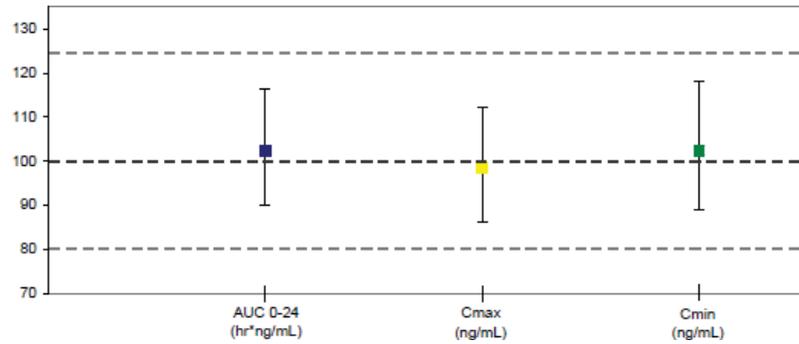


**Figure 2.** Geometric mean ratios and 90% CIs of the primary PK variables at steady-state: CR (Day 28) vs. IR (Day 14)

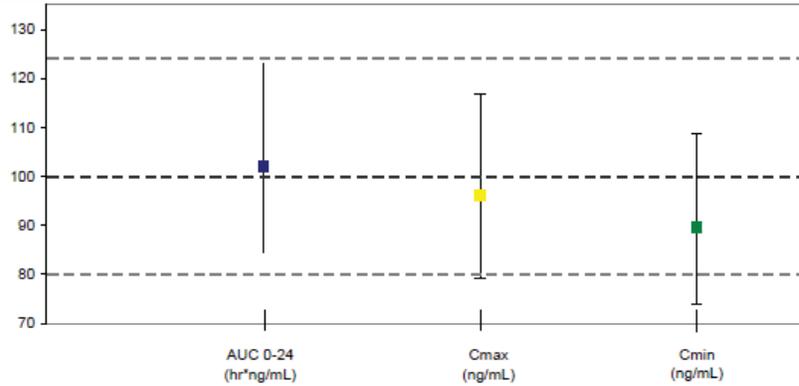
PK population: (N=59 for IR; N=60 for CR)



Neutral: (N=48 for IR; N=47 for CR)



Induced: (N=11 for IR; N=13 for CR)



**Table 1.** Summary of statistical analysis (PK population)

PK Parameter (Normalized to 200 mg Dose)	Geometric LSM TPM IR	Geometric LSM TPM ER	Geometric LSM Ratio TPM ER/TPM IR	90% Confidence Interval
AUC <sub>0-24</sub> (hr*ng/mL)	143475.74	141774.10	98.81	(84.17, 116.01)
C <sub>max</sub> (ng/mL)	7537.47	7175.41	95.20	(82.26, 110.17)
C <sub>min</sub> (ng/mL)	4815.29	4668.09	96.94	(79.58, 118.10)

**Table 2.** Summary of statistical analysis (Induced vs. Neutral)

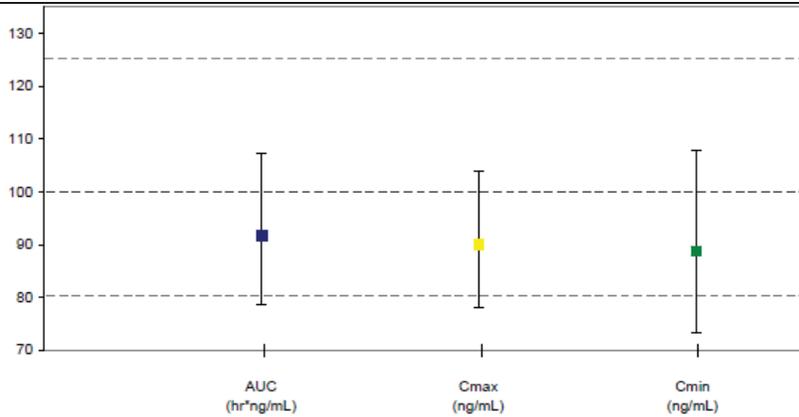
PK Parameter (Normalized to 200 mg Dose)	Geometric LSM TPM IR	Geometric LSM TPM ER	Geometric LSM Ratio TPM ER/TPM IR	90% Confidence Interval
<b>Induced Subjects</b>				
AUC <sub>0-24</sub> (hr*ng/mL)	83129.63	84810.58	102.02	(84.59, 123.05)
C <sub>max</sub> (ng/mL)	5184.17	4989.09	96.24	(79.33, 116.75)
C <sub>min</sub> (ng/mL)	2414.76	2164.01	89.62	(73.82, 108.80)
<b>Neutral Subjects</b>				
AUC <sub>0-24</sub> (hr*ng/mL)	150585.29	154320.97	102.48	(90.18, 116.46)
C <sub>max</sub> (ng/mL)	7784.71	7665.61	98.47	(86.31, 112.34)
C <sub>min</sub> (ng/mL)	5134.74	5264.04	102.52	(88.88, 118.26)

- An approximately 10% lower C<sub>min</sub> (toward the end of the 24-hour dosing interval) was observed for Induced subjects on CR prior to the next dose, compared to IR.

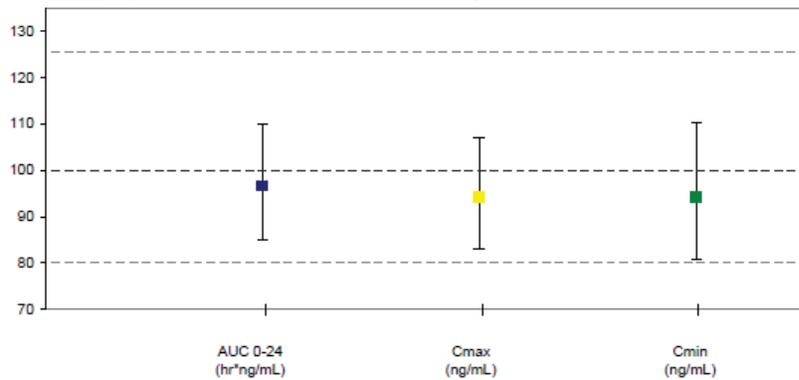
## II. Relative Bioavailability Immediately Following Switch

**Figure 3.** Geometric mean ratios and 90% CIs of the primary PK variables following the switch: TPM CR (Day 15) vs. TPM IR (Day 14)

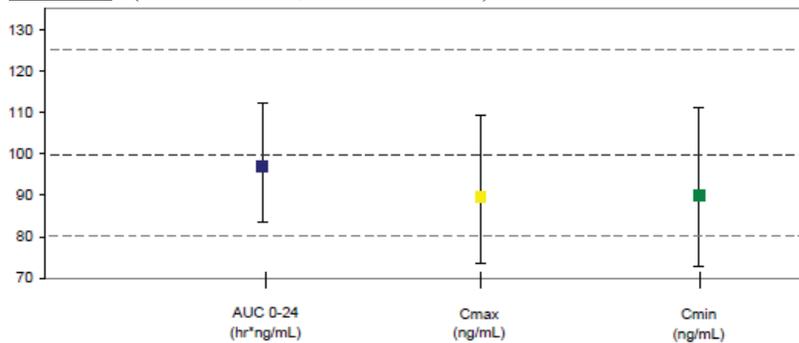
PK population: (N=59 for IR; N=59 for CR)



Neutral: (N=48 for IR; N=46 for CR)



Induced: (N=11 for IR; N=13 for CR)



**Table 3.** Summary of statistical analysis following IR to CR switch (Day 15 vs. Day 14) (PK population)

PK Parameter (Normalized to 200 mg dose)	Geometric LSM TPM IR	Geometric LSM TPM ER	Geometric LSM Ratio TPM ER/TPM IR	90% Confidence Interval
AUC <sub>0-24</sub> (hr*ng/mL)	144442.83	132599.36	91.80	(78.52, 107.33)
C <sub>max</sub> (ng/mL)	7554.83	6796.04	89.96	(77.99, 103.76)
C <sub>min</sub> (ng/mL)	4812.83	4273.22	88.79	(73.19, 107.72)

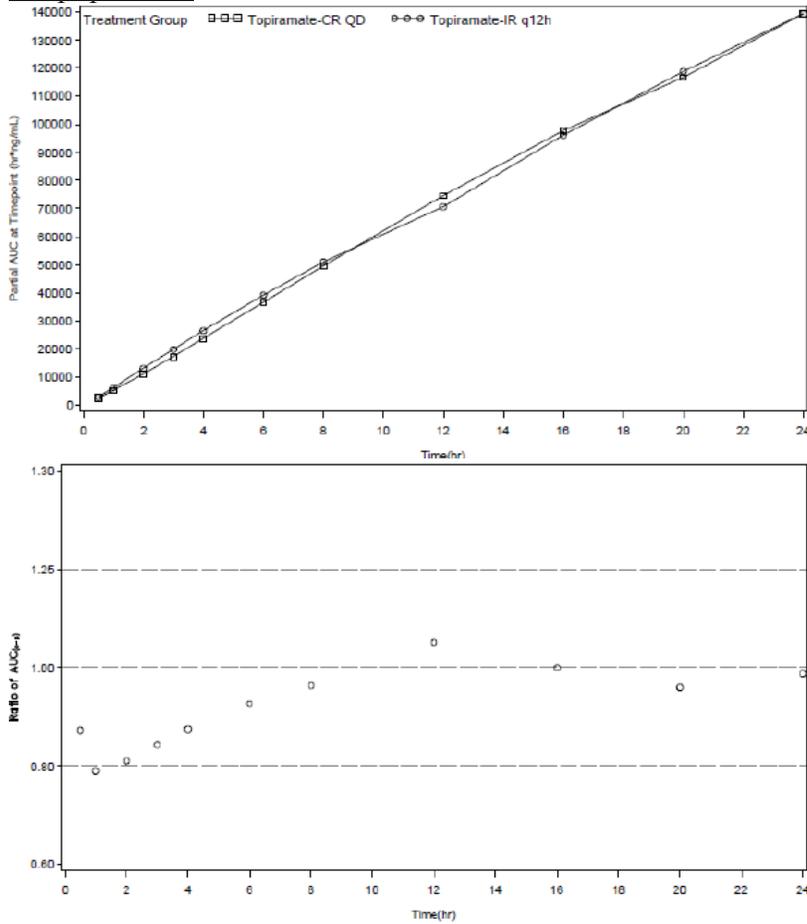
**Table 4.** Summary of statistical analysis following IR to CR switch (Day 15 vs. Day 14) (Induced vs. Neutral)

PK Parameter (Normalized to 200 mg Dose)	Geometric LSM TPM IR	Geometric LSM TPM ER	Geometric LSM Ratio TPM ER/TPM IR	90% Confidence Interval
<b>Induced Subjects</b>				
AUC <sub>0-24</sub> (hr*ng/mL)	83129.63	80583.99	96.94	(83.66, 112.33)
C <sub>max</sub> (ng/mL)	5184.17	4641.38	89.53	(73.39, 109.22)
C <sub>min</sub> (ng/mL)	2414.76	2172.19	89.95	(72.78, 111.18)
<b>Neutral Subjects</b>				
AUC <sub>0-24</sub> (hr*ng/mL)	152519.58	147587.76	96.77	(85.09, 110.05)
C <sub>max</sub> (ng/mL)	7834.18	7395.52	94.40	(83.18, 107.13)
C <sub>min</sub> (ng/mL)	5173.49	4879.25	94.31	(80.69, 110.24)

- Approximately 10% drop in topiramate levels (C<sub>max</sub> and C<sub>min</sub>) was observed for pooled or Induced subjects on CR prior to the next dose, compared to IR. This may be attributed to concomitant use of enzyme-inducing AEDs in Induced subgroup and other confounding factors (see comments)

### III. Partial AUC (AUC<sub>0-p</sub>) at Steady State

**Figure 4.** Partial AUC at steady state (Day 28-CR vs. Day 14-IR)  
PK population:

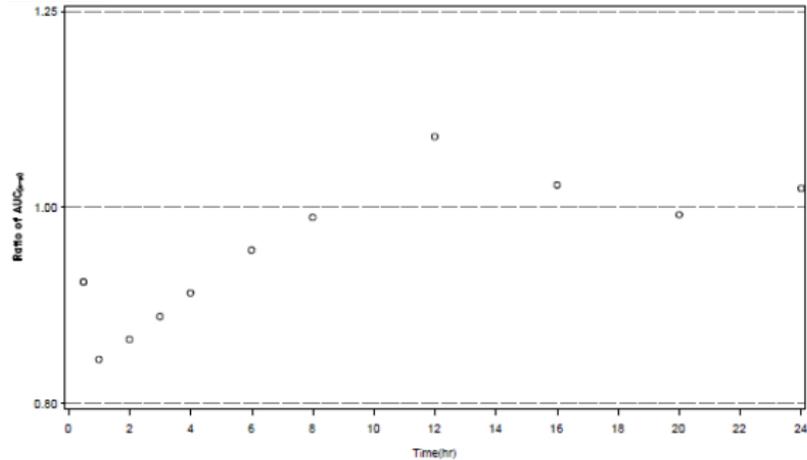


- The geometric mean ratios (CR/IR) for AUC<sub>0-p</sub> were between 79% and 106% throughout the dosing interval, with AUC<sub>0-6h</sub> of TPM CR being lower than that of TPM IR.

- The 90% CIs for AUC<sub>0-p</sub>, were contained within the BE limits (80-125%) for all time points  $\geq 8$  hours.

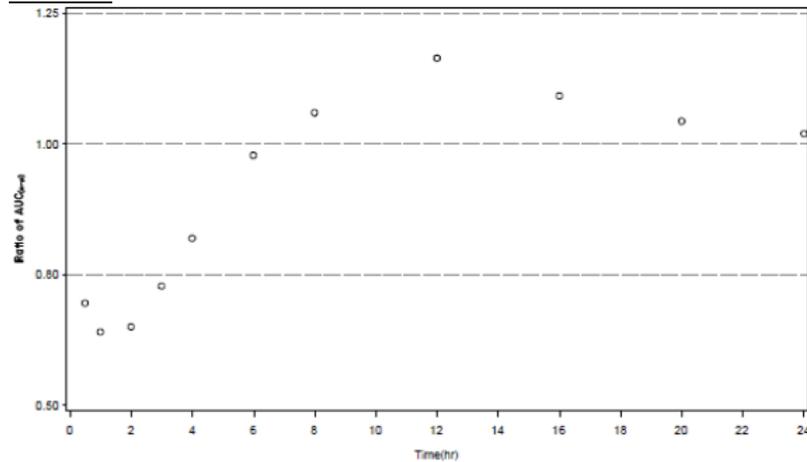
**Figure 5.** Partial AUC at steady state (Day 28-CR vs. Day 14-IR)

Neutral:



- Both geometric mean ratios (CR/IR) and corresponding 90% CIs were within the BE range (80-125%) for time points  $\geq 4$  hours postdose.

Induced:

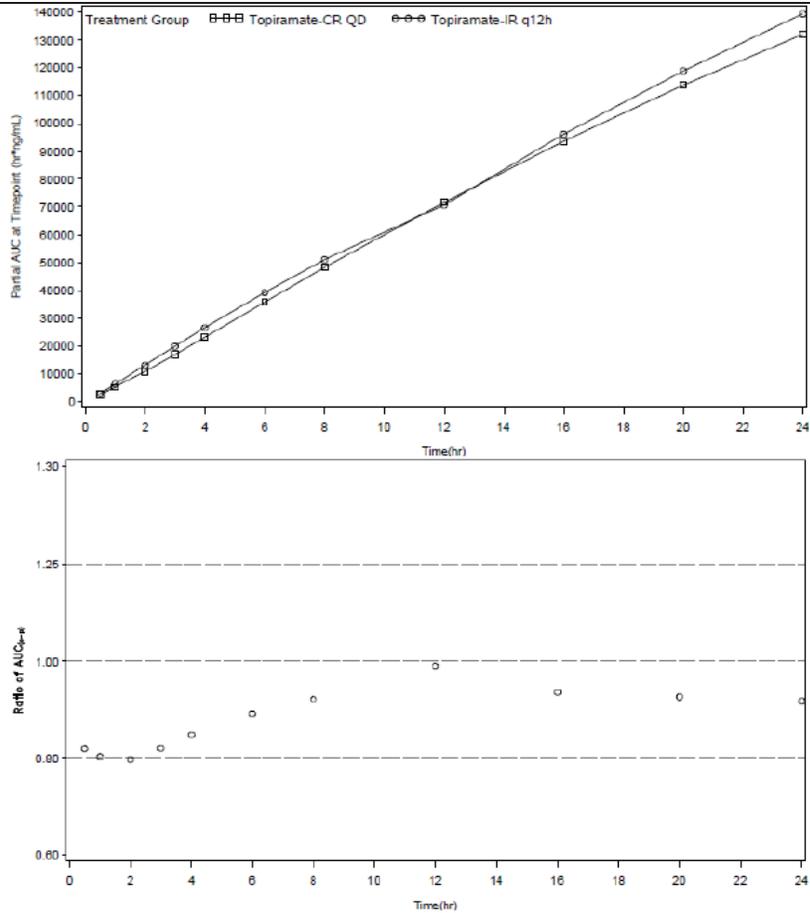


- Both geometric mean ratios (CR/IR) and corresponding 90% CIs were within the BE range (80-125%) for time points  $\geq 6$  hours postdose.
- The AUC exposure in Induced subjects was approximately 23~33% lower after the switch for time points up to 3 hours.

#### **IV. Partial AUC (AUC<sub>0-p</sub>) Immediately Following Switch**

**Figure 6.** Partial AUC at steady state (Day 15-CR vs. Day 14-IR)

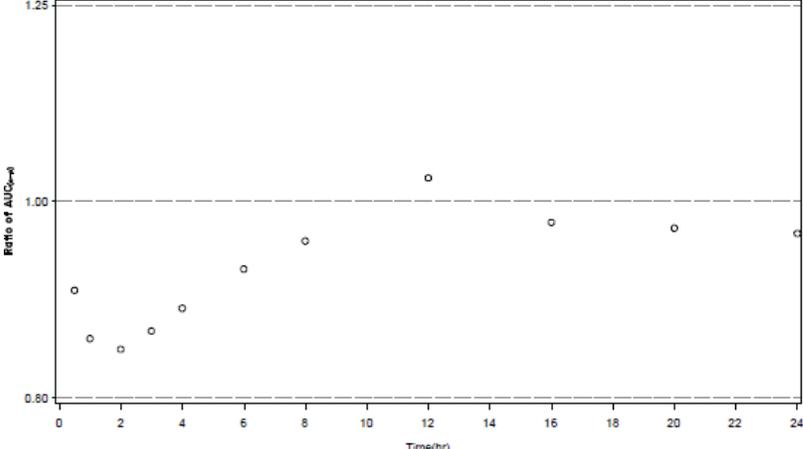
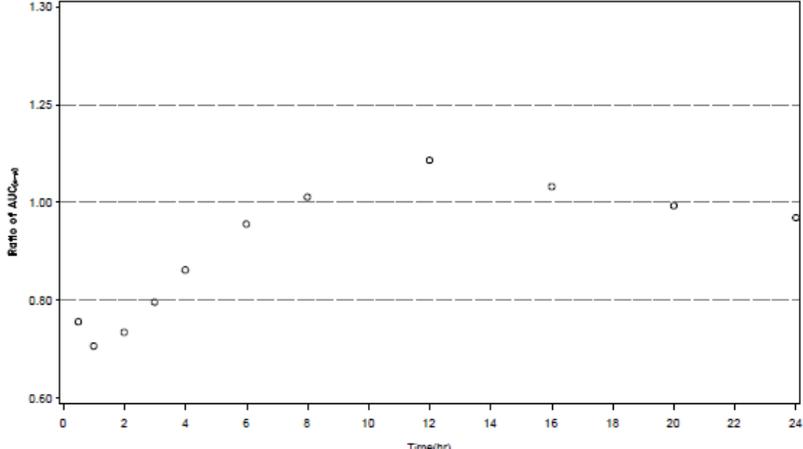
PK population:



- The geometric mean ratios (CR/IR) for AUC<sub>0-p</sub> were between 79% and 99% throughout the dosing interval, with AUC<sub>0-8h</sub> of TPM CR being lower than that of TPM IR.
- Both geometric mean ratios (CR/IR) and corresponding 90% CIs were within the BE range (80-125%) for 12 and 16 hours postdose. (Note: BE may be considered for time points  $\geq 4$  hours because of the lower bound of the 90% CIs being  $>78.5\%$ ).

**Figure 7.** Partial AUC at steady state (Day 15-CR vs. Day 14-IR)

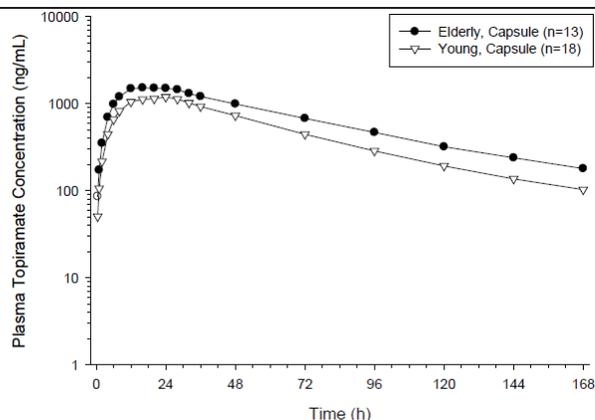
Neutral:

	 <ul style="list-style-type: none"> <li>• Both geometric mean ratios (CR/IR) and corresponding 90% CIs were within the BE range (80-125%) for time points <math>\geq 4</math> hours postdose.</li> </ul> <p><u>Induced:</u></p>  <ul style="list-style-type: none"> <li>• Both geometric mean ratios (CR/IR) and corresponding 90% CIs were within the BE range (80-125%) for time points <math>\geq 6</math> hours postdose.</li> <li>• The AUC exposure in Induced subjects was approximately 24~30% lower immediately after the switch for time points before 3 hours.</li> </ul>
Safety	<ul style="list-style-type: none"> <li>• No deaths or SAEs</li> <li>• More subjects treated with TPM CR (24 subjects, 38.7%) experienced at least one AE vs. subjects treated with TPM IR (7 subjects, 10.6%).</li> <li>• All AEs were of mild or moderate severity. The only AEs that occurred in more than one subject were headache and fatigue in subjects receiving TPM CR.</li> </ul>
Conclusion	<ul style="list-style-type: none"> <li>• The relative bioavailability of TPM CR and TPM IR at steady-state were equivalent for overall PK population, regardless the use of concomitant AEDs, based on systemic exposure (AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub>). However, the plasma TPM levels were lower in induced subjects than in Neutral subjects for both dosage forms.</li> <li>• Immediately following the switch from TPM IR to TPM CR in total PK population, the exposure was decreased by approximately 10%. The</li> </ul>

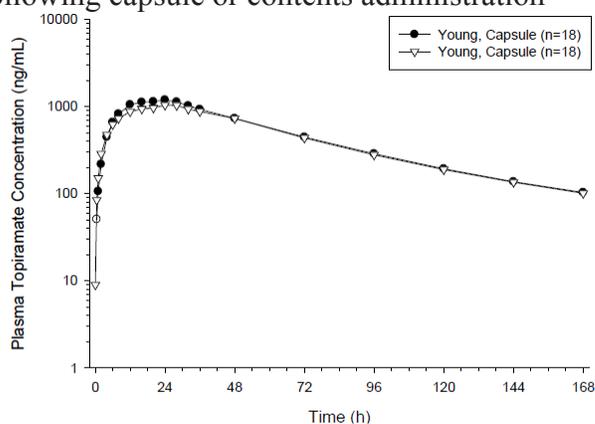
	<p>equivalent bioavailability was achieved only in Neutral subjects based on the acceptance BE criteria of 80-125% for point estimates and the 90% CIs.</p> <ul style="list-style-type: none"> <li>• Results of this study, based on overall PK population, seem to support a conversion from TPM IR (BID) to TPM CR (or SPN538T) (QD) for the same total daily dose for all patients, irrespective of the concomitant AEDs.</li> <li>• The immediate switch from IR to CR for ‘Induced’ patients on enzyme-inducing AEDs would likely result in up to 30% lower exposure within the first 2~3 hours, based on results of partial AUC (AUC0-p), and an approximately 10% lower drug levels or Cmin at steady-state prior to the next dose.</li> <li>• Results of Ctrough suggest that 14-day treatment period was sufficient for the steady state attainment following the switch from TPM IR to TPM CR.</li> <li>• The applicant reported that, of the 61 subjects who completed the study, once daily dosing was preferred by 57 (91.9%). Only 4 subjects (6.5%) preferred the twice a day dosing regimen.</li> <li>• No notable differences in seizure frequency were reported between subjects receiving TPM IR and TPM CR.</li> </ul> <p>Table. Summary of seizure frequency</p> <table border="1" data-bbox="500 856 1317 1003"> <thead> <tr> <th>Total # Seizures</th> <th>TPM IR (N=66), n (%)</th> <th>TPM CR (N=62), n (%)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>59 (89.4)</td> <td>57 (91.9)</td> </tr> <tr> <td>1</td> <td>3 (4.5)</td> <td>4 (6.5)</td> </tr> <tr> <td>2</td> <td>3 (4.5)</td> <td>0</td> </tr> <tr> <td>4</td> <td>0</td> <td>1 (1.6)</td> </tr> </tbody> </table>	Total # Seizures	TPM IR (N=66), n (%)	TPM CR (N=62), n (%)	0	59 (89.4)	57 (91.9)	1	3 (4.5)	4 (6.5)	2	3 (4.5)	0	4	0	1 (1.6)
Total # Seizures	TPM IR (N=66), n (%)	TPM CR (N=62), n (%)														
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1	3 (4.5)	4 (6.5)														
2	3 (4.5)	0														
4	0	1 (1.6)														
Comment	<ul style="list-style-type: none"> <li>• The lower exposure immediately after the switch and at the steady-state could attribute to the various confounding factors, such as slower topiramate release and absorption from the CR capsules, relatively small number of subjects in the Induced group, effects of food intake, and the similar enzyme inducing effect for the approved IR formulation. This ~10% decrease is not considered clinically meaningful. Given results of the relative BA comparison from this study, patients may be switched from immediate-release topiramate products to Trokendi XR™ at the same daily dose.</li> <li>• The study protocol did not specify dosing with respect to food intake and timing. Therefore, results of the study are supportive of a reduced food effect after multiple doses or at steady-state.</li> </ul>															

Study Report #	<b>538P109</b>
Title	Pharmacokinetics of Topiramate Controlled-Release in the Elderly and as Delivered in Food to Healthy Adults
Investigator/Center	Kelli Craven, MD, Quintiles Phase 1 Clinic, 6700 West 115 <sup>th</sup> Street, Overland Park, Kansas 66211, USA
Study Dates	June 03, 2010 – July 02, 2010
Objectives	<ul style="list-style-type: none"> <li>• Single-dose PK comparison in healthy young and elderly adult subjects</li> <li>• Single-dose PK comparison for TPM CR capsule vs. via applesauce in healthy young subjects</li> </ul>

Formulation	TPM CR capsule, 100 mg	Lot B10001C																																											
Study Design	<p><u>Phase 1</u>: single-center, single-dose, parallel-phase, open-label PK study of 100mg TPM CR administered to young adults (aged 18-45 years) and elderly subjects (aged &gt;69 years).</p> <p><u>Phase 2</u>: an open-label crossover following a washout of at least 21 days. All young subjects from Phase 1 received a single dose of the contents of a 100mg TPM CR capsule delivered in food (a tablespoon of applesauce).</p> <ul style="list-style-type: none"> <li>• Screening period: 28 days; duration: 57 days</li> </ul>																																												
PK Assessment	<p>For SPN-538:</p> <ul style="list-style-type: none"> <li>• Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose</li> <li>• AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, k<sub>el</sub>, t<sub>1/2</sub>, AUC<sub>0-t</sub>/AUC<sub>0-∞</sub>.</li> </ul>																																												
Statistical Analysis	<ul style="list-style-type: none"> <li>• Descriptive statistics were calculated for plasma concentrations and PK Parameters. A mixed effect ANOVA model on log-transformed exposure measures. Point estimates and 90% CI for geometric mean ratios for age groups (Elderly/Young) or for treatments (Contents/Capsule) for the log-transformed AUC<sub>0-t</sub>, AUC<sub>∞</sub>, and C<sub>max</sub>, judged by acceptance criteria of 80-125%.</li> </ul>																																												
Bioanalytical Methods	<p><b>Table.</b> Assay performance</p> <table border="1"> <tr> <td><b>Analyte</b></td> <td colspan="3">Topiramate (plasma)</td> </tr> <tr> <td><b>Method:</b></td> <td colspan="3">HPLC/MS/MS</td> </tr> <tr> <td><b>Standard</b></td> <td>Range:</td> <td colspan="2">5.00 – 5000</td> </tr> <tr> <td><b>Curve:</b></td> <td></td> <td colspan="2">ng/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td colspan="2">1 - 3%</td> </tr> <tr> <td></td> <td>Accuracy:</td> <td colspan="2">99 - 102 %</td> </tr> <tr> <td><b>LOQ:</b></td> <td></td> <td colspan="2">5 ng/mL</td> </tr> <tr> <td><b>QC:</b></td> <td></td> <td>15.0 ng/mL</td> <td>350 ng/mL</td> <td>3500 ng/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td>4%</td> <td>6 %</td> <td>5 %</td> </tr> <tr> <td></td> <td>Accuracy:</td> <td>106 %</td> <td>104 %</td> <td>103%</td> </tr> </table> <ul style="list-style-type: none"> <li>• Bioanalytical site: Supernus Pharmaceuticals, Inc., located at 1550 East Gude Drive, Rockville, MD 20850</li> <li>• Deuterated internal standard (topiramate-d12, TPR-d12)</li> </ul> <p><u>Comment:</u> The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being &lt;15%.</p>		<b>Analyte</b>	Topiramate (plasma)			<b>Method:</b>	HPLC/MS/MS			<b>Standard</b>	Range:	5.00 – 5000		<b>Curve:</b>		ng/mL			Precision:	1 - 3%			Accuracy:	99 - 102 %		<b>LOQ:</b>		5 ng/mL		<b>QC:</b>		15.0 ng/mL	350 ng/mL	3500 ng/mL		Precision:	4%	6 %	5 %		Accuracy:	106 %	104 %	103%
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	Precision:	4%	6 %	5 %																																									
	Accuracy:	106 %	104 %	103%																																									
Population/ Demographics	Randomized: 18 young and 13 elderly subjects (mean 75 and ranged 71-84 years); 31 completed; 31 for PK and safety analyses																																												
PK Results	<b>Figure 1.</b> Mean plasma concentration - time curves by age groups following capsule administration																																												



**Figure 2.** Mean plasma concentration - time curves in young subjects following capsule or contents administration



**Table 1.** Summary of pharmacokinetic parameters

PK Parameter	Elderly Subjects	Young Subjects	
	Capsule (N = 13)	Capsule (N = 18)	Contents (N = 18)
$C_{max}$ (ng/mL)	1640 ± 525	1230 ± 299	1080 ± 318
$T_{max}^a$ (h)	16.12 (12.00 - 28.00)	24.00 (12.00 - 28.00)	24.05 (12.02 - 28.00)
$AUC_{0-t}$ (ng·h/mL)	113000 ± 31800	79100 ± 18100	74600 ± 18500
$AUC_{inf}$ (ng·h /mL)	127000 ± 35800	86100 ± 18300	81400 ± 18700
$T_{1/2}$ (h)	49.0 ± 7.12	47.0 ± 6.58	47.0 ± 5.29

<sup>a</sup> Median (range)

- $AUC_{0-t}/AUC_{0-\infty}$ : mean 0.90~0.92 for all age groups and formulations

**Table 2.** Summary of statistical analysis (by age groups)

Parameter	Young (N=18)	Elderly (N=13)	Geometric Mean Ratio (Elderly/Young)	90% CI
$C_{max}$ (ng/mL)	1200	1559	130.01	(108.63, 155.59)
$AUC_{0-t}$ (ng·h/mL)	77190	109100	141.40	(120.30, 166.20)
$AUC_{0-\infty}$ (ng·h/mL)	84310	121800	144.47	(123.51, 168.99)

\* Exposure values expressed as geometric means

**Table 3.** Summary of statistical analysis (capsule vs. contents in applesauce)

	Parameter	Capsule (N=18)	Contents (N=18)	Geometric Mean Ratio (Contents/ Capsule)	90% CI
	Cmax (ng/mL)	1200	1034	86.16	(80.96 – 91.69)
	AUC0-t (ng•h/mL)	77190	72420	93.82	(90.17 – 97.62)
	AUC0-∞ (ng.h/mL)	84310	79410	94.19	(90.58 – 97.93)
	* Exposure values expressed as geometric means				
Safety	<ul style="list-style-type: none"> <li>No deaths, SAEs, or AEs that led to discontinuation</li> <li>AEs were more frequently reported in elderly (76.9%) compared with young subjects (44.4%) receiving capsules, and were least frequent (4.6%) in young subjects following treatment with the capsule contents on applesauce.</li> <li>Vessel puncture site hemorrhage (elderly only), headache, somnolence (young subjects only), and dysgeusia (young subjects only) were the most frequently reported AEs.</li> <li>All AEs were of mild severity and got resolved.</li> </ul>				
Conclusion	<ul style="list-style-type: none"> <li>Higher mean Cmax (by 30%) and AUC values (by 41-44%) were observed in elderly compared to young subjects.</li> <li>Elderly subjects had shorter median Tmax at 16 hours vs. 24 hours in young subjects.</li> <li>Elimination t1/2 was similar across age groups (49 vs. 47 hours).</li> <li>The topiramate exposures from 100mg capsule or as contents of a 100mg CR capsule emptied in applesauce were similar, as indicated by the 90% CIs for geometric mean ratios of Cmax, AUC0-t, and AUC∞ being contained within the BE range of 80-125%.</li> </ul>				
Comment	Considering the recommended dosage reduction to half for renally impaired patients with creatinine clearance $\leq 70$ mL/min/1.73 m <sup>2</sup> , dosage adjustment for Trokendi XR™ is recommended in the elderly patients when impaired renal function (creatinine clearance $\leq 70$ mL/min/1.73 m <sup>2</sup> ) is evident. The renal function needs to be measured prior to the treatment (per the labeling).				

Study Report #	<b>538T-TOX2010-006</b>		
Title	Evaluation of the Potential for Dose Dumping of SPN-538T with Co-Ingestion of Alcohol after Single Oral Doses to Dogs		
Investigator/ Center	Christie Scheurell, BS, Covance Laboratories Inc. 3301 Kinsman Boulevard Madison, WI 53704-2523		
Study Dates	June 24, 2010 – July 29, 2010		
Objectives	Pharmacokinetics and potential for alcohol-mediated dose dumping in dogs		
Formulation	Topiramate	Lot #	
	SPN-538T 100mg capsule	B10001B	
	TOPAMAX Tablet		
Study Design	SPN-538T (CR) or Topamax (IR) of 100 mg doses were administered to each of 2 fasted male dogs/group/phase (each of 5 Phases included Groups 1~5) with 10-mL of water, low ethanol (10%), or high ethanol (40%) in a Latin Square		

design with an approximately 7-day washout period between phases, as illustrated in the Table below.

Treatment	Dose Formulation	Dose Flush
A	Topamax (IR)	Water (control)
B	SPN-538T (CR)	Water (control)
C	Topamax (IR)	High EtOH (40% v/v in water)
D	SPN-538T (CR)	Low EtOH (10% v/v in water)
E	SPN-538T (CR)	High EtOH (40% v/v in water)

Gastric contents were sampled and the pH measured before each dosing.

- Dogs: weighed 10.2~11.9 kg, 6~8 months old
- During each phase predose and at 0.25, 0.5, 1, 2, 3, 4, 8, 12, and 24 hours postdose
- AUC<sub>0-24</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, λ<sub>Z</sub>, and t<sub>1/2</sub>.

Statistical Analysis: A mixed effect ANOVA model on log-transformed exposure measures among treatments. Point estimates and 90% CI for geometric mean ratios for the log-transformed AUC<sub>0-t</sub>, AUC<sub>∞</sub>, and C<sub>max</sub>, judged by BE acceptance criteria of 80-125%.

PK Results: Gastric pH: Pre-dose gastric pH measurements were **between pH 7 and 9** in all instances.

Figure 1. Mean plasma concentration - time curves after administration of TPM CR

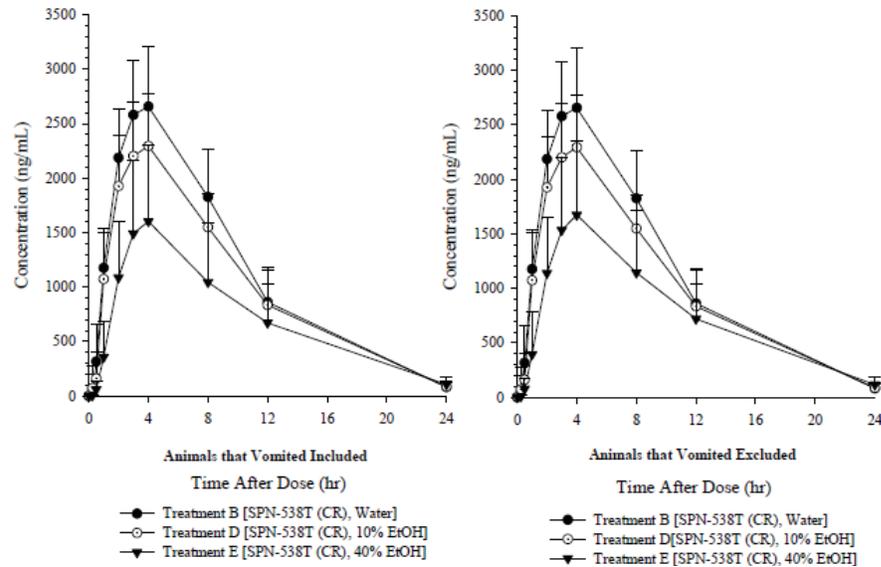


Figure 2. Mean plasma concentration - time curves after administration of TPM IR

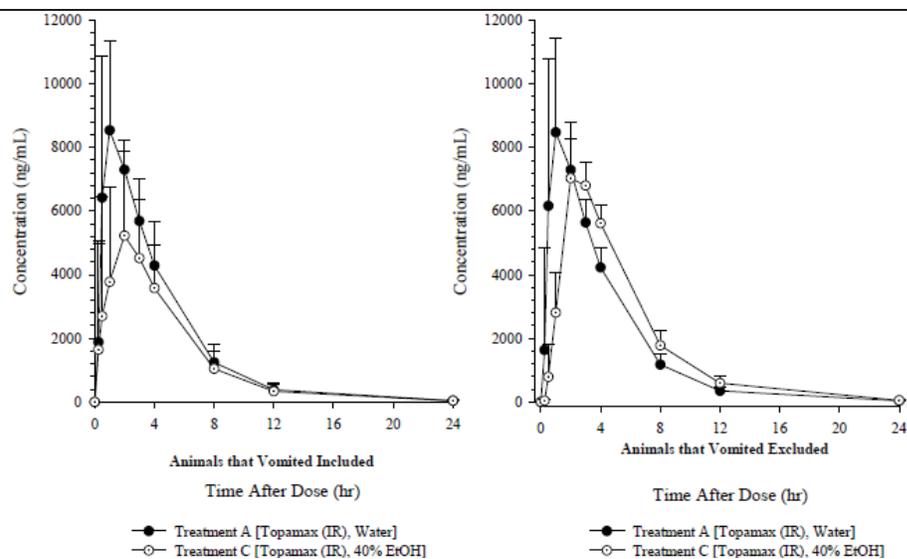


Table 1. Summary of pharmacokinetic parameters

Treatment	Dose Level (mg)		$C_{max}$ (ng/mL)	$T_{max}$ (hr)	$AUC_{0-24}$ (ng-hr/mL)	$AUC_{0-\infty}$ (ng-hr/mL)	$t_{1/2}$ (hr)
<u>All Animals</u>							
A [Topamax (IR) Water]	100	Mean	9654	0.850	41243	41432	3.30
		SD	1198	0.474	6306	6369	0.21
		N	10	10	10	10	10
B [SPN-538T (CR) Water]	100	Mean	2686	4.20	27102	27277	3.50
		SD	525	1.40	5404	5805	0.50
		N	10	10	10	9	9
C [Topamax (IR) 40% EtOH]	100	Mean	6309	1.70	29990	30179	3.90
		SD	3160	0.79	16016	16052	1.26
		N	10	10	10	10	10
D [SPN-538T (CR) 10% EtOH]	100	Mean	2308	3.70	24115	24601	3.65
		SD	482	0.48	5286	5542	0.63
		N	10	10	10	10	10
E [SPN-538T (CR) 40% EtOH]	100	Mean	1618	3.44	17035	17947	5.13
		SD	701	0.73	8046	8225	2.18
		N	9	9	9	9	9
<u>Excluding Animals With Emesis</u>							
A [Topamax (IR) Water]	100	Mean	9716	0.833	40334	40511	3.30
		SD	1253	0.500	5952	6009	0.22
		N	9	9	9	9	9
B [SPN-538T (CR) Water]	100	Mean	2686	4.20	27102	27277	3.50
		SD	525	1.40	5404	5805	0.50
		N	10	10	10	9	9
C [Topamax (IR) 40% EtOH]	100	Mean	7838	2.25	42475	42722	3.19
		SD	651	0.50	5174	5265	0.22
		N	4	4	4	4	4
D [SPN-538T (CR) 10% EtOH]	100	Mean	2308	3.70	24115	24601	3.65
		SD	482	0.48	5286	5542	0.63
		N	10	10	10	10	10
E [SPN-538T (CR) 40% EtOH]	100	Mean	1689	3.33	18193	19281	5.42
		SD	688	0.82	7618	7566	2.70
		N	6	6	6	6	6

Conclusion

- Although the alcohol dumping was observed in vitro, such effect after coadministration of Topamax (IR) or SPN-538T (CR) with 10% or 40% ethanol was not observed in dogs.

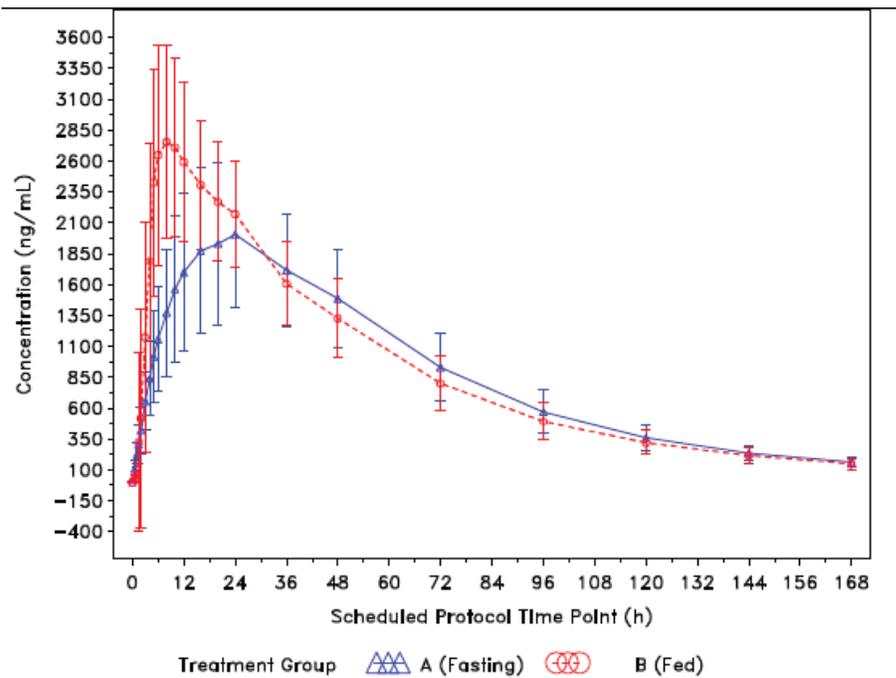
	<ul style="list-style-type: none"> <li>• The mean Tmax following the coadministration of SPN-538T (CR) with different strengths of ethanol or water was generally similar.</li> </ul>
Comment	<ul style="list-style-type: none"> <li>• Although the results from the study in dogs showed a lack of dose-dumping potential from the ER capsules, such study and a lack of proper justification for its implication to humans were found not acceptable from an OCP perspective.</li> <li>• The physiological difference in gastrointestinal between humans (more acidic gastric pH 1~3) and dogs (gastric pH 7~9) is noted. However, potential impact in gastric pH difference on topiramate release from the ER formulation in the presence of alcohol is unclear.</li> </ul>

### 4.3 Consult Review

## Office of Clinical Pharmacology Division of Pharmacometrics

**Background:** The sponsor has developed a once-daily formulation (hereafter SPN-538T) of the antiepileptic drug topiramate (hereafter TPM), and submitted six Phase I studies to evaluate the pharmacokinetics of SPN-538T. The study of 538P105 showed that  $C_{max}$  following a standard high-fat meal was 37% higher than that in the fasting state (**Figure 1, Table 1**).

Figure 1. Mean concentration-time profile at the dose of 200 mg from the study of 538P105 (N=28).



Source: the sponsor's report, p 18.

Table 1. Summary of food effect

Parameter	N	LS Means		Ratio of Geometric LS Means (Fed/Fasted, %)	90% CI for Ratio of Geometric LS Means
		Fed	Fasted		
$C_{max}$ (ng/mL)	28	2744.00	2004.72	136.88	(122.08, 153.47)
$AUC_{0-t}$ (ng*h/mL)	28	151777.99	142822.49	106.27	(99.80, 113.16)
$AUC_{inf}$ (ng*h/mL)	28	160762.28	152047.35	105.73	(99.54, 112.31)

Source: the sponsor's report, p 18.

FDA raised a concern that this marked difference in  $C_{max}$  might affect the safety of SPN-538T. The sponsor argued that single-dose design of study 538P105 exaggerated the effects of food that would be observed in clinical use of TPM, which is administered chronically and accumulates substantially due to its long half-life.

### Summary and Conclusion

The sponsor re-analyzed the data from 538P105 using population PK approach to understand better the impact of food on the rate and extent of absorption of SPN-538T upon repeated administration. Results obtained from the sponsor’s final model were used to simulate TPM concentrations under repeated dosing scenario in both the fasted and fed states.

Dosing was simulated separately for each state as 200mg QD for 3 weeks. PK time points were simulated daily (trough) for 3 weeks, then hourly on day 21.

The PK variables such as  $C_{max}$ ,  $C_{min}$ , and  $AUC_{\tau}$  from the simulated data were calculated using standard non-compartmental methods. Bioequivalence testing of the simulated data was performed. The food effect was re-assessed for  $AUC_{\tau}$ ,  $C_{max}$ , and  $C_{min}$  at steady state, and the results are summarized in **Table 2**.

Results of the analysis using simulated data obtained under repeated dosing scenario indicated that there was no food-effect as the 90% confidence intervals for  $AUC_{\tau}$ ,  $C_{max}$ , and  $C_{min}$  were within (80%, 125%).

Table 2. Summary of food effect from simulated data.

PK Parameter	Comparison	Original Scale		CV%
		Ratio	90% CI	
$AUC_{\tau}$	Fed vs Fasted	102.45%	(95.38%, 110.04%)	17%
$C_{max}$	Fed vs Fasted	113.28%	(105.32%, 121.85%)	18%
$C_{min}$	Fed vs Fasted	91.84%	(85.30%, 98.88%)	18%

Source: the sponsor’s report, p 53.

The simulation was also performed to evaluate the impact of switching from TOPAMAX® to SPN-538T under four different states: neutral subjects in the fasted state, induced subjects in the fasted state, neutral subjects in the fed state, induced subjects in the fed state. Bioequivalence testing of the PK variables ( $C_{max}$ ,  $C_{min}$ , and  $C_{avg}$ ) derived from simulated TPM concentration-time data was performed, and fluctuation was also computed. The results showed that bioequivalence criteria were met for most PK variables except for  $C_{max}$  for induced subjects in the fasted subjects (90% CI: (78, 80)). Overall fluctuation remained below 50% in all states on all days (see sponsor’s analyses section).

## Sponsor's analyses

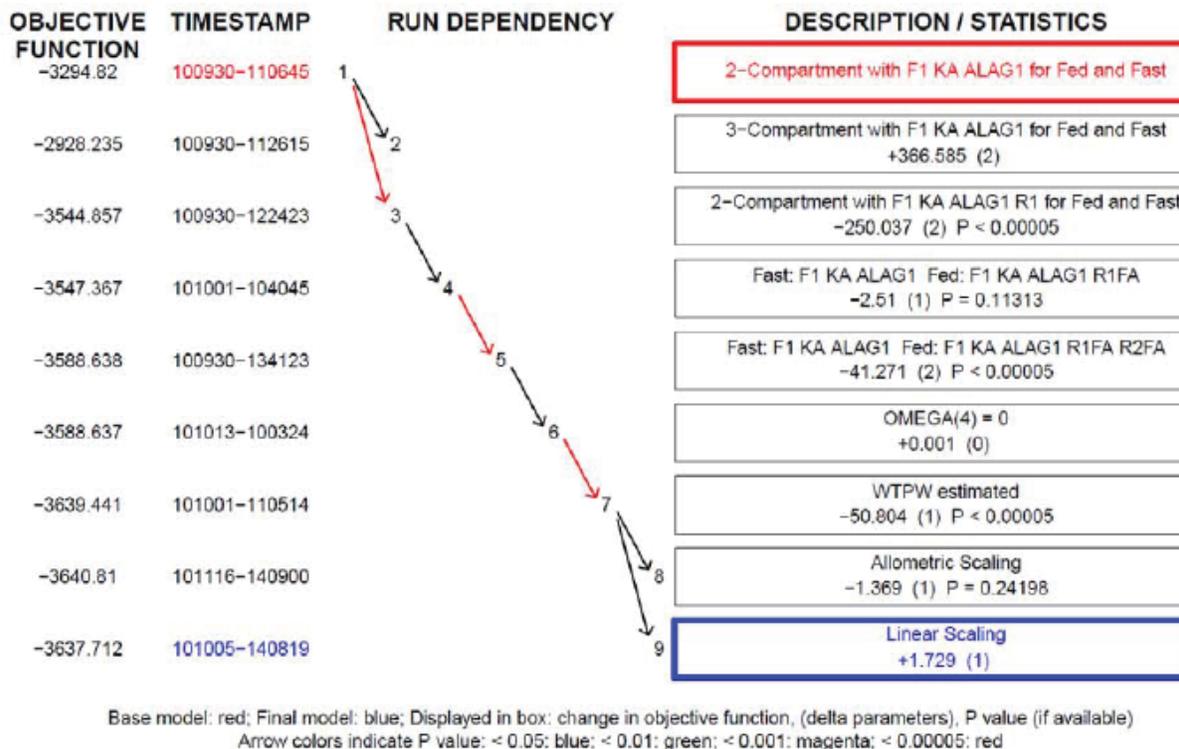
Data from about 30 subjects in the study of 538P105 were analyzed; 29 and 31 subjects received SPN-538T under fasting and fed conditions respectively.

The sponsor's analyses showed that a linear two-compartment model was found to fit the data reasonably well (see Appendix); the fasted absorption model for SPN-538T was described by first-order absorption from a depot; the fed absorption model for SPN-538T was a hybrid of zero-order release and first-order absorption. Both absorption models incorporated a lag time; bioavailability was similar in the fed and fasted states.

Covariates evaluated in the analyses were gender, weight, height, age, BMI and race. Among these, only weight is included in the final model.

The flow chart of the sponsor's model building strategy is summarized in Figure 2, and the parameter estimates from the sponsor's final model are presented in Table 3 along with absorption profiles for the fed and fasted states derived from the final model (**Figure 3**).

Figure 2. Flow chart of the sponsor's modeling building.



Source: the sponsor's report, p 29.

Table 3. Parameter estimates from the sponsor's final model.

Parameter	Typical Value	Between-subject Variability*	Standard Error %CV
CL/F (L/hr)	1.01	10.5%	7.8%
V <sub>1</sub> /F (L)	63.6	12.7%	4.1%
CL <sub>2</sub> /F (L/hr)	0.338	67.9%	31.4%
V <sub>2</sub> /F (L)	571	0†	29.8%
Fasted			
F§	1	0†	0††
k <sub>a</sub> (/hour)	0.0788	38.7%	7.8%
Absorption lag (hours)	0.140	73.8%	27.1%
Fed			
F§	1.02	0†	3.4%
k <sub>a</sub> (/hour)	0.596	99.5%	21.6%
Absorption lag (hours)	1.09	70.7%	11.8%
Release rate 1 (mg/hour)	417	0†	32.6%
Release rate 2 (mg/hour)	110	0†	9.8%
Time of rate switch (hour)	1.32	0†	4.6%

\* Calculated as  $\sqrt{\omega^2}$  where  $\omega^2$  is the variance of the corresponding  $\eta$  term; sixty-eight % of the population lies within this range of the typical value.

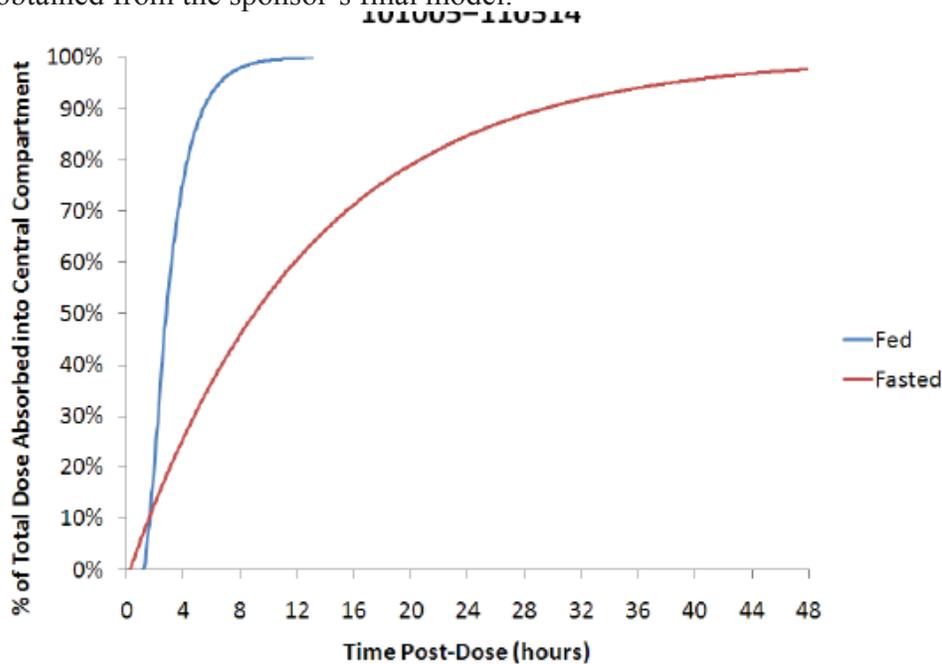
† Between-subject variability was not permitted for this parameter in the optimal model.

†† Parameter was fixed to 1 in the optimal model

§ Absolute bioavailability of TPM was not determined in this study. Bioavailability in the fed state was estimated relative to the fasted state. Bioavailability in the fasted state was set to 1.

Source: the sponsor's report, p 48.

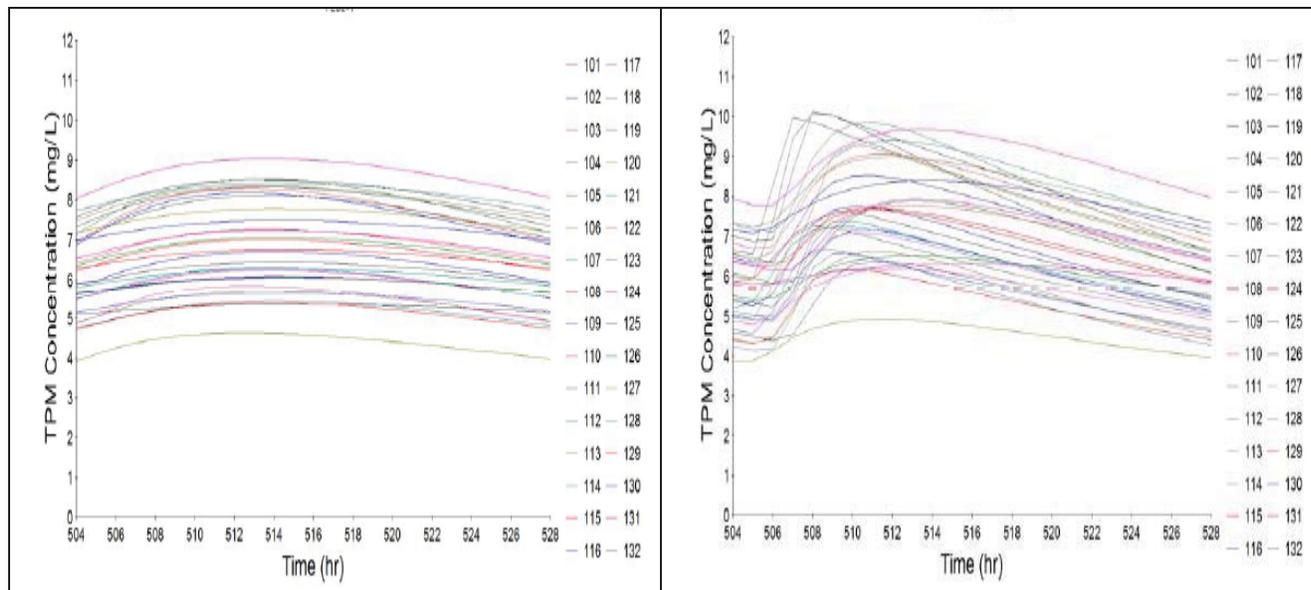
Figure 3. Percentage of the total TPM dose absorbed to the central compartment vs. time which was obtained from the sponsor's final model.



Source: the sponsor's report, p 49.

As a next step, concentration-time profiles upon repeated administration in the fasted and fed states were simulated for each subject in the study of 538P105. Dosing was simulated separately for each state as 200mg QD for 3 weeks. PK time points were simulated daily (trough) for 3 weeks, then hourly on day 21. Simulated concentration-time profiles for all 32 subjects in the study of 538P105 are displayed in Figure 4 under fasted and fed states over the 24-hour dosing interval on day 21.

Figure 4. Simulated TPM concentration time profile from repeated dosing on day 21. Left : under fasted condition, Right : under Fed condition.



Source: the sponsor's report, p 51.

The PK variables such as  $C_{max}$ ,  $C_{min}$ , and  $AUC_{\tau}$  from the simulated data were calculated using standard non-compartmental methods. Bioequivalence testing of the simulated data was performed. The food effect was re-assessed for  $AUC_{\tau}$ ,  $C_{max}$ , and  $C_{min}$ , and the results are summarized in Table 4.

Results of the analysis using simulated data obtained under repeated dosing scenario indicated that there was no food-effect as the 90% confidence intervals for  $AUC_{\tau}$ ,  $C_{max}$ , and  $C_{min}$  were within (80%, 125%).

**Table 4. Summary of food effect from simulated data.**

PK Parameter	Comparison	Original Scale		CV%
		Ratio	90% CI	
$AUC_{\tau}$	Fed vs Fasted	102.45%	(95.38%, 110.04%)	17%
$C_{max}$	Fed vs Fasted	113.28%	(105.32%, 121.85%)	18%
$C_{min}$	Fed vs Fasted	91.84%	(85.30%, 98.88%)	18%

Source: the sponsor's report, p 53.

### Switching Simulation:

It is expected that many patients will first experience SPN-538T upon switching from TOPAMAX® or a generically-equivalent formulation of immediate-release TPM. These patients may be taking TPM in either the fed or fasted state and may be taking concomitant medications including other AEDs. Of the common AEDs, carbamazepine (CBZ) and phenytoin have been shown to interact with TOPAMAX®. In order to better understand the behavior of SPN-538T following a switch from the immediate release, individual parameter estimates for subjects in study 538P105 from the sponsor's final model were used to simulate concentration-time profiles for subjects switching directly from a regimen of 100mg TOPAMAX® administered twice-daily to 200mg SPN-538T administered once-daily. Four states were considered:

- Neutral subjects in the fasted state
- Induced subjects in the fasted state
- Neutral subjects in the fed state
- Induced subjects in the fed state

where “neutral” denotes subjects receiving TPM alone or in combination with agents not considered to affect TPM metabolism, and “induced” denotes subjects receiving TPM in combination with CBZ or other agents known to increase TPM metabolism. The impact of enzymatic induction was simulated as a 2-fold increase in CL/F relative to the neutral state. The value of  $k_a$  for TOPAMAX® was set to  $6\text{hr}^{-1}$  for all subjects.

Dosing was simulated separately for each state as 100mg TOPAMAX® administered every 12 hours on days 1-120 followed by 200mg SPN-538T administered every 24 hours on days 121-240. For each state, PK time points were simulated over a 24-hour period on day 120 (the last day of TOPAMAX®), on day 121 (the first day of SPN-538T) and on day 240 (the last day of SPN-538T). As shown below, the exposure resulting from administration of SPN-538T in the four states evaluated was predicted to be similar to TOPAMAX® both immediately following the switch from TOPAMAX® to SPN-538T and after repeat administration of SPN-538T.

**Table 9: Bioequivalence testing of the simulation in neutral subjects in the fasted state**

Parameter	Geometric Mean			Geometric Mean Ratios*			
	Topamax	SPN-538T		Day 121 / Day 120		Day 240 / Day 120	
	Day 120	Day 121	Day 240	Ratio (%)	90% CI	Ratio (%)	90% CI
C <sub>max</sub> (mg/L)	9.4091	8.2422	8.5162	87.60	86.86 – 88.34	90.51	89.75 – 91.28
C <sub>min</sub> (mg/L)	7.7943	7.3245	7.7902	93.97	93.07 – 94.88	99.95	98.99 – 100.91
C <sub>avg</sub> (mg/L)	8.6078	7.9441	8.2584	92.29	91.53 – 93.05	95.94	95.16 – 96.73

**Table 10: Bioequivalence testing of the simulation in induced subjects in the fasted state**

Parameter	Geometric Mean			Geometric Mean Ratios*			
	Topamax	SPN-538T		Day 121 / Day 120		Day 240 / Day 120	
	Day 120	Day 121	Day 240	Ratio (%)	90% CI	Ratio (%)	90% CI
C <sub>max</sub> (mg/L)	5.2983	4.1700	4.4303	78.70	77.51 – 79.92	83.62	82.34 – 84.91
C <sub>min</sub> (mg/L)	3.6912	3.3765	3.7123	91.47	90.03 – 92.94	100.57	98.99 – 102.18
C <sub>avg</sub> (mg/L)	4.4774	3.9029	4.1716	87.17	85.95 – 88.40	93.17	91.87 – 94.49

**Table 11: Bioequivalence testing of the simulation in neutral subjects in the fed state**

Parameter	Geometric Mean			Geometric Mean Ratios*			
	Topamax	SPN-538T		Day 121 / Day 120		Day 240 / Day 120	
	Day 120	Day 121	Day 240	Ratio (%)	90% CI	Ratio (%)	90% CI
C <sub>max</sub> (mg/L)	9.4091	9.6896	9.4178	102.98	101.71 – 104.27	100.09	98.85 – 101.35
C <sub>min</sub> (mg/L)	7.7943	7.5103	7.2836	96.36	95.64 – 97.08	93.45	92.75 – 94.15
C <sub>avg</sub> (mg/L)	8.6078	8.6346	8.4173	100.31	99.66 – 100.96	97.79	97.16 – 98.42

**Table 12: Bioequivalence testing of the simulation in induced subjects in the fed state**

Parameter	Geometric Mean			Geometric Mean Ratios*			
	Topamax	SPN-538T		Day 121 / Day 120		Day 240 / Day 120	
	Day 120	Day 121	Day 240	Ratio (%)	90% CI	Ratio (%)	90% CI
C <sub>max</sub> (mg/L)	5.2983	5.5626	5.2791	104.99	102.76 – 107.26	99.64	97.52 – 101.80
C <sub>min</sub> (mg/L)	3.6912	3.4006	3.1693	92.13	90.87 – 93.40	85.86	84.69 – 87.05
C <sub>avg</sub> (mg/L)	4.4774	4.4852	4.2536	100.17	99.17 – 101.18	95.00	94.05 – 95.96

Source: the sponsor's report, p 61 (revised table).

**Fluctuation**

Fluctuation of TPM under the different states on different days is summarized in the Table 5.

**Table 5. Fluctuation of TPM in different subject states.**

Subject State	TOPAMAX® Day 120 Mean %FL	SPN-538T Day 121 Mean %FL	SPN-538T Day 240 Mean %FL
Neutral, Fasted	20%	12%	9%
Induced, Fasted	35%	20%	17%
Neutral, Fed	19%	25%	25%
Induced, Fed	35%	48%	50%

Source: the sponsor's report, p 66.

Fluctuation was higher for both TOPAMAX® and SPN-538T in induced subjects than in neutral subjects. This increased fluctuation was primarily due to the decreased  $C_{avg}$  in induced subjects, with absolute peak-to-trough differences ( $C_{max}-C_{min}$ ) being almost identical in the neutral and induced subjects. Overall fluctuation remained below 50% in all states on all days.

*Reviewer's comments:*

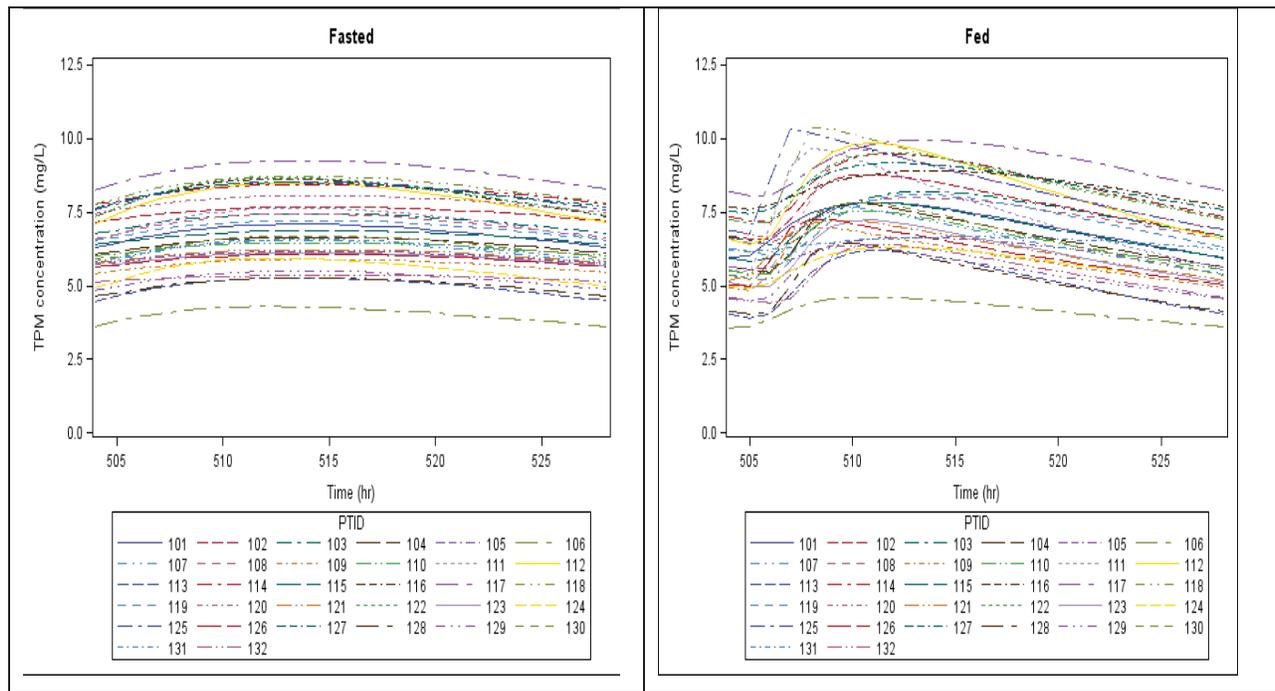
- *The sponsor's final model is acceptable based on the model diagnostics provided by the sponsor.*
  - o *However, the reviewer could not reproduce the sponsor's parameter estimates exactly, which could be due to different FORTRAN compiler or other factors related to the numerical stability of the computation systems.*
  - o *However, the difference is minor so it did not lead to noticeable difference in the simulation.*
  - o *The sponsor's simulation seems to be acceptable.*

## Appendix

1. The difference in the parameter estimates between the reviewer's and sponsor's.

Parameter	Sponsor	Reviewer
CL/F (L/h)	1.01	1.04
V1/F (L)	63.6	63.7
CL2/F(L/h)	0.34	0.31
V2/F (L)	571	481
Fasted		
F	1	1
Ka	0.0788	0.0785
Absorption lag (h)	0.140	0.135
Fed		
F	1.02	1.09
Ka	0.596	0.587
Absorption lag (h)	1.09	1.04
Release rate 1 (mg/h)	417	463
Release rate 2 (mg/h)	110	110
Time of rate switch (h)	1.32	1.30

2. Simulated TPM concentration - time profile using the reviewer's estimates.



3. Comparison of NonCompartmental Analysis (NCA) using simulated data between the sponsor's and reviewer's

**Cmax (mg/L)**

	Sponsor	Reviewer
Fasted		
Min, Max	(4.63, 9.04)	(4.67,9.07)
Median	6.75	6.76
Mean (sd)	6.9 (1.18)	6.9 (1.18)
Fed		
Min, Max	(4.93, 10.13)	(4.97,10.14)
Median	7.7	7.7
Mean (sd)	7.82 (1.36)	7.83 (1.35)

**Cmin (mg/L)**

	Sponsor	Reviewer
Fasted		
Min, Max	(3.93, 8.05)	(3.97,8.08)
Median	6.07	6.07
Mean (sd)	6.2 (1.03)	6.2 (1.02)
Fed		
Min, Max	(3.89, 7.79)	(3.93,7.82)
Median	5.7	5.7
Mean (sd)	5.66 (1.01)	5.67 (1.01)

**AUC<sub>0-τ</sub> (hr\*mg/L)**

	Sponsor	Reviewer
Fasted		
Min, Max	(105, 209)	(106,209)
Median	157	157
Mean (sd)	159 (27)	159 (27)
Fed		
Min, Max	(108, 214)	(109,215)
Median	160	161
Mean (sd)	163 (27)	163 (27)

#### 4.4 OCP Filing/Review Form

<b>Office of Clinical Pharmacology</b> <i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	Information		Information
<b>NDA/BLA Number</b>	201-635	<b>Brand Name</b>	Tradenam <sup>TM</sup>
<b>OCP Division (I, II, III, IV, V)</b>	DCP-1	<b>Generic Name</b>	Topiramate
<b>Medical Division</b>	HFD-120	<b>Drug Class</b>	Anticonvulsant
<b>OCP Reviewer</b>	Ta-Chen Wu, Ph.D.	<b>Indication(s)</b>	<ul style="list-style-type: none"> <li>• Monotherapy epilepsy: Initial monotherapy in patients (b) (4) with partial onset or primary generalized tonic-clonic seizures</li> <li>• Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS)</li> </ul>
<b>OCP Team Leader</b>	Angela Yuxin Men, M.D., Ph.D.	<b>Dosage Form</b>	Extended-release multi-bead capsules (SPN-538T: 25, 50, 100, and 200 mg strengths)
<b>Pharmacometrics Reviewer</b>	Joo-Yeon Lee, Ph.D.	<b>Dosing Regimen</b>	Once daily (See Appendix 1 under Clin Pharm & Biopharm Information section for details)
<b>PM Team Leader</b>	Yaning Wang, Ph.D.		
<b>Date of Submission</b>	08/30/2011	<b>Route of Administration</b>	Oral
<b>Estimated Due Date of OCP Review</b>	06/09/2012	<b>Sponsor</b>	Supernus Pharmaceuticals, Inc.
<b>Medical Division Due Date</b>	06/17/2012	<b>Priority Classification</b>	S
<b>PDUFA Due Date</b>	07/09/2012		
<b><i>Clin. Pharm. and Biopharm. Information</i></b>			
<b><u>Summary:</u></b>			
The sponsor seeks approval of topiramate extended-release capsules (SPN-538T) as monotherapy and adjunctive therapy for epilepsy via 505(b)(2) application and will reference the approved TOPAMAX <sup>®</sup> immediate-release			

(IR) tablets (NDA 20-505). Since SPN-538T is intended to be taken as an intact capsule, the Sponsor is seeking a monotherapy indication for patients with epilepsy (b) (4) instead of  $\geq 2$  years old for the RLD. The Sponsor is not seeking indication for migraine. The proposed dosing regimens are presented in Appendix 1. Topiramate extended-release capsules are multi-bead capsules (three-pellet composite formulations) in dosage strengths of 25, 50, 100, and 200 mg, administered one daily (QD).

The current submission is a resubmission of the NDA 201-635 that was originally submitted to the Agency on January 14, 2011 but was subject of a refused to file on March 14, 2011. In this submission, the Sponsor provided additional information in the following areas:

- (1) addressed the deficiencies outlined in the Refusal to File letter (including information request by OCP and an updated pediatric development program to address all pediatric age groups from birth through 17 years of age),
- (2) included update according to the update for the NDA 20505 for TOPAMAX<sup>®</sup> IR tablets, and
- (3) study report of a newly completed Study 538P108, a conversion study from TOPAMAX<sup>®</sup> to SPN-538T conducted in epilepsy patients.

With this submission, the Sponsor is presenting a clinical pharmacology-based new drug application by demonstrating the bioequivalent for time-point to time-point within the 24 hours at steady-state between the proposed CR capsules (QD) and approved IR tablets (BID). The clinical program, with current update, consists of 8 studies in healthy adult volunteers to support this NDA, as well as 2 ongoing studies in epilepsy patients, as summarized below. (also see Appendix 2)

1. Study 538P109: PK comparison between young and elderly adult patients; single 100mg dose
2. 7 Biopharm studies: establish steady-state BA/BE vs. IR, dose linearity/proportionality, food effect (200 mg), and BE between the clinical and registration scale formulations (50, 100, and 200 mg)
3. Study 538P108: a conversion study from TOPAMAX<sup>®</sup> IR (on either 200, 250, 300, 350, or 400 mg/day, BID) to SPN-538T (QD) in epilepsy patients (N=62); steady-state PK (day 14 of IR vs. 24 hour of SPN-538T)
4. Study 538P107: examines the PK profile of SPN-538T in pediatric epileptic population and is ongoing.

Note:

- “Development” formulations were studied for BA/BE vs. IR, dose linearity/proportionality, and food effect. At the Pre-NDA meeting, the Sponsor claimed that the commercial formulation of 200 mg strength was studied for food effect.
- “Registration” formulations were studied in formulation bridging.

Biowaiver of in vivo relative BA study was requested for the 25 mg strength on the basis of formulation proportionality and dissolution similarity of 25mg and 50mg capsules.

A study to assess the potential dose-dumping was conducted in dogs, instead of humans as recommended at the Pre-NDA meeting.

The plasma concentration of topiramax was determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

- Validation report TR-08-019: for Studies 538P103, 538P104, 538P104.5, 538P105, 538P109, and 538P106
- Validation report TM-538-902-1: for Studies 538P106-200, 538P106-50, and 538P108

**Appendix 1.** Proposed dosing regimens

	Initial Dose	Titration	Recommended Dose
(b) (4)			
Epilepsy monotherapy: adults and pediatric patients ≥ 10 years (2.1)	50 mg/day Once daily dose	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day Once daily dose
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day Once daily dose
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures (2.1)	25-50mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50mg	400mg/day Once daily dose
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS (2.1)	25 mg/day (based on a range of 1 to 3 mg/kg/day) nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3mg/kg/day  Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day Once daily dose

**Appendix 2. Tabular listing of studies to support the NDA:**

Study ID	Primary Endpoint or Endpoints	Location of Study Report Synopsis	Study Objective	Study Design	Study & Control Drugs/ Dose/ Route/ Regimen	# Subjects by Arm Entered/ Completed	# Sites / Subject type	Duration
538P103	PK	Module 5, Section 5.3.3	Steady state PK	Comparative, randomized, multiple dose, 2-treatment, 2-sequence, 2-period crossover with active control	A: TPM CR 200mg x 10 days (after 3 weeks titration) B: Topamax 200mg x 10 days (after 3 weeks titration)	39 subjects enrolled, 33 subjects completed	Single center/ Healthy, normal	10 day maintenance with 21 day titration per treatment period
538P104	PK	Module 5, Section 5.3.3	Dose proportionality	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 8 x 25mg B: TPM CR 4 x 50mg C: TPM CR 2 x 100mg D: TPM CR 1 x 200mg	34 subjects enrolled 24 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P104.5	PK	Module 5, Section 5.3.3	Dose linearity	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 25mg B: TPM CR 50mg C: TPM CR 100mg D: TPM CR 200mg	36 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P105	PK	Module 5, Section 5.3.3	Food effect	Comparative, randomized, single dose, 2-treatment, 2-sequence, 2-period crossover study	A: TPM CR 200mg, fasted B: TPM CR 200mg, fed	32 subjects enrolled 28 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover	A: TPM CR 100mg, Clinical lot, fasted B: TPM CR 100mg, CMO lot, fasted	28 subjects enrolled, 27 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods

538P106-50	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	study. Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 50mg, Clinical lot, fasted B: TPM CR 50mg, CMO lot, fasted	32 subjects enrolled 31 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106-200	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 200mg, Clinical lot, fasted B: TPM CR 200mg, CMO lot, fasted	32 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P108	BA	Module 5, Section 5.3.1.2	PK of IR to ER Switch	Multi-center, open-label, two-treatment, single sequence conversion study	TPM ER – equivalent to current therapy TPM IR – equivalent to current therapy	62 patients with epilepsy  (72 planned)	11 centers, adults with epilepsy on treatment with TPM	4 weeks.
538P109	PK	Module 5, Section 5.3.3	Young vs. Elderly	Comparative, single-dose, parallel group study	TPM CR 100mg, fasted	18 young adults enrolled and completed, 13 elderly enrolled and completed	Single center/ Healthy, normal young and elderly	Single dose, 1 treatment period
538P107	PK	Pending	Pediatric PK	Multi-center, open-label, switch to ER	TPM ER – equivalent to current therapy	Approximately 40 male and female pediatric subjects ages 4-17	Up to 15 centers, children with epilepsy on treatment with TPM	2 weeks

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			<ul style="list-style-type: none"> <li>Sponsor provided annotated PDF file, clean Word file and PDF file, and side-by-side comparison for labeling</li> </ul>
Reference Bioanalytical and Analytical Methods	X			<ul style="list-style-type: none"> <li>Validation reports for topiramate (LC/MS/MS)</li> <li>In-study validation and QC performance are provided.</li> </ul>
<b>I. Clinical Pharmacology</b>				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
<b>Healthy Volunteers-</b>				
single dose:	X			
multiple dose:	X			
<b>Patients-</b>				
single dose:	X			
multiple dose:	X			A new study (538P108) examines the conversion (IR -> ER) at steady-state; 5 doses
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
<b>Subpopulation studies -</b>				
ethnicity:	-			

gender:	-			
pediatrics:	-			
geriatrics:	X			
renal impairment:	-			
hepatic impairment:	-			
<b>PD -</b>				
Phase 2:	-			
Phase 3:	-			
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
<b>Population Analyses -</b>				1 report for PopPK
Data rich:	X			<ul style="list-style-type: none"> <li>Population PK analysis for steady-state food effect</li> <li>Rich data from Phase 1 studies</li> </ul>
Data sparse:	-			
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>	-			
<b>Relative bioavailability -</b>				
solution as reference:	-			
alternate formulation as reference:	X			• CR vs. IR (RLD)
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X			• Commercial formulation vs. clinical formulations; comparison of different manufacturing sites (See Appendix 2)
replicate design; single / multi dose:	-			
<b>Food-drug interaction studies</b>	X			• Study with highest 200mg strength of the “development” formulation
<b>Bio-waiver request based on BCS</b>	-			
<b>BCS class</b>	-			
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>	(X)			Study conducted in dogs (538T-TOX2010-006)
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>	-			
<b>Chronopharmacokinetics</b>	-			
<b>Pediatric development plan</b>	-			(b) (4)
<b>Literature References</b>	X			74 references
<b>Total Number of Studies</b>	<b>14</b>		<b>15</b>	9 PK + 1 Pop PK + 4 validation reports + 538T-TOX2010-006 (dog study)

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			50, 100, and 200mg strengths
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Cross-reference to approved Topamax label
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Cross-reference to approved Topamax label
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Generally acceptable but with some erroneous hyperlinks that requires reviewer's own effort
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Cross-reference to approved Topamax label
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Cross-reference to approved Topamax label
14	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			X	Cross-reference to approved Topamax label

	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Cross-reference to approved Topamax label
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			<ul style="list-style-type: none"> <li>• Food effect study on development formulation of 200mg</li> <li>• A review issue</li> </ul>
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_\_ Yes \_\_\_\_**

1. DSI inspection of the clinical and the analytical sites are needed for the following studies:

Study 538P103 (Pivotal BE study):

Clinical sites: Quintiles Phase I Services, Overland Park, Kansas, U.S.A.

Analytical site: Bioanalytical laboratory of Supernus Pharmaceuticals, Inc., located at 1550 East Gude Dr., Rockville, MD 20850.

Study 538P106-200 (formulation bridging study for the highest 200mg strength):

Clinical sites: Dedicated Phase I, Inc., 734 W. Highland Ave. Phoenix, AZ 85013, U.S.A.

Analytical site: Same as Study 538P103

Study 538P106 and Study 538P106-50 (formulation bridging study for 50mg and 100mg strengths):

Clinical sites: PAREXEL Early Phase Clinical Unit (EPCU) – Baltimore, 3001 South Hanover Street, Baltimore, MD 21225, USA

Analytical site: Same as Study 538P103

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Reviewing Clinical Pharmacologist

Date

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Team Leader/Supervisor

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TA-CHEN WU  
05/25/2012

JOO YEON LEE  
05/25/2012

YANING WANG  
05/25/2012

YUXIN MEN  
05/25/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
<b>NDA/BLA Number</b>	201-635	<b>Brand Name</b>	Tradename™
<b>OCP Division (I, II, III, IV, V)</b>	DCP-1	<b>Generic Name</b>	Topiramate
<b>Medical Division</b>	HFD-120	<b>Drug Class</b>	Anticonvulsant
<b>OCP Reviewer</b>	Ta-Chen Wu, Ph.D.	<b>Indication(s)</b>	<ul style="list-style-type: none"> <li>• Monotherapy epilepsy: Initial monotherapy in patients (b) (4) with partial onset or primary generalized tonic-clonic seizures</li> <li>• Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS)</li> </ul>
<b>OCP Team Leader</b>	Angela Yuxin Men, M.D., Ph.D.	<b>Dosage Form</b>	Extended-release multi-bead capsules (SPN-538T: 25, 50, 100, and 200 mg strengths)
<b>Pharmacometrics Reviewer</b>		<b>Dosing Regimen</b>	Once daily (See Appendix 1 under Clin Pharm & Biopharm Information section for details)
<b>Date of Submission</b>	08/30/2011	<b>Route of Administration</b>	Oral
<b>Estimated Due Date of OCP Review</b>	06/09/2012	<b>Sponsor</b>	Supernus Pharmaceuticals, Inc.
<b>Medical Division Due Date</b>	06/17/2012	<b>Priority Classification</b>	S
<b>PDUFA Due Date</b>	07/09/2012		

*Clin. Pharm. and Biopharm. Information*

Summary:

The sponsor seeks approval of topiramate extended-release capsules (SPN-538T) as monotherapy and adjunctive therapy for epilepsy via 505(b)(2) application and will reference the approved TOPAMAX® immediate-release

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

(IR) tablets (NDA 20-505). Since SPN-538T is intended to be taken as an intact capsule, the Sponsor is seeking a monotherapy indication for patients with epilepsy <sup>(b) (4)</sup> instead of  $\geq 2$  years old for the RLD. The Sponsor is not seeking indication for migraine. The proposed dosing regimens are presented in Appendix 1. Topiramate extended-release capsules are multi-bead capsules (three-pellet composite formulations) in dosage strengths of 25, 50, 100, and 200 mg, administered one daily (QD).

The current submission is a resubmission of the NDA 201-635 that was originally submitted to the Agency on January 14, 2011 but was subject of a refused to file on March 14, 2011. In this submission, the Sponsor provided additional information in the following areas:

- (1) addressed the deficiencies outlined in the Refusal to File letter (including information request by OCP and an updated pediatric development program to address all pediatric age groups from birth through 17 years of age),
- (2) included update according to the update for the NDA 20505 for TOPAMAX<sup>®</sup> IR tablets, and
- (3) study report of a newly completed Study 538P108, a conversion study from TOPAMAX<sup>®</sup> to SPN-538T conducted in epilepsy patients.

With this submission, the Sponsor is presenting a clinical pharmacology-based new drug application by demonstrating the bioequivalent for time-point to time-point within the 24 hours at steady-state between the proposed CR capsules (QD) and approved IR tablets (BID). The clinical program, with current update, consists of 8 studies in healthy adult volunteers to support this NDA, as well as 2 ongoing studies in epilepsy patients, as summarized below. (also see Appendix 2)

1. Study 538P109: PK comparison between young and elderly adult patients; single 100mg dose
2. 7 Biopharm studies: establish steady-state BA/BE vs. IR, dose linearity/proportionality, food effect (200 mg), and BE between the clinical and registration scale formulations (50, 100, and 200 mg)
3. Study 538P108: a conversion study from TOPAMAX<sup>®</sup> IR (on either 200, 250, 300, 350, or 400 mg/day, BID) to SPN-538T (QD) in epilepsy patients (N=62); steady-state PK (day 14 of IR vs. 24 hour of SPN-538T)
4. Study 538P107: examines the PK profile of SPN-538T in pediatric epileptic population and is ongoing.

Note:

- “Development” formulations were studied for BA/BE vs. IR, dose linearity/proportionality, and food effect. At the Pre-NDA meeting, the Sponsor claimed that the commercial formulation of 200 mg strength was studied for food effect.
- “Registration” formulations were studied in formulation bridging.

Biowaiver of in vivo relative BA study was requested for the 25 mg strength on the basis of formulation proportionality and dissolution similarity of 25mg and 50mg capsules.

A study to assess the potential dose-dumping was conducted in dogs, instead of humans as recommended at the Pre-NDA meeting.

The plasma concentration of topiramax was determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

- Validation report TR-08-019: for Studies 538P103, 538P104, 538P104.5, 538P105, 538P109, and 538P106
- Validation report TM-538-902-1: for Studies 538P106-200, 538P106-50, and 538P108

**Appendix 1.** Proposed dosing regimens

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Initial Dose	Titration	Recommended Dose
(b) (4)			
Epilepsy monotherapy: adults and pediatric patients $\geq 10$ years (2.1)	50 mg/day Once daily dose	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day Once daily dose
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day Once daily dose
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures (2.1)	25-50mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50mg	400mg/day Once daily dose
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS (2.1)	25 mg/day (based on a range of 1 to 3 mg/kg/day) nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3mg/kg/day  Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day Once daily dose

### Appendix 2. Tabular listing of studies to support the NDA:

Study ID	Primary Endpoint or Endpoints	Location of Study Report Synopsis	Study Objective	Study Design	Study & Control Drugs/ Dose/ Route/ Regimen	# Subjects by Arm Entered/ Completed	# Sites / Subject type	Duration
538P103	PK	Module 5, Section 5.3.3	Steady state PK	Comparative, randomized, multiple dose, 2-treatment, 2-sequence, 2-period crossover with active control	A: TPM CR 200mg x 10 days (after 3 weeks titration) B: Topamax 200mg x 10 days (after 3 weeks titration)	39 subjects enrolled, 33 subjects completed	Single center/ Healthy, normal	10 day maintenance with 21 day titration per treatment period
538P104	PK	Module 5, Section 5.3.3	Dose proportionality	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 8 x 25mg B: TPM CR 4 x 50mg C: TPM CR 2 x 100mg D: TPM CR 1 x 200mg	34 subjects enrolled 24 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P104.5	PK	Module 5, Section 5.3.3	Dose linearity	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 25mg B: TPM CR 50mg C: TPM CR 100mg D: TPM CR 200mg	36 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P105	PK	Module 5, Section 5.3.3	Food effect	Comparative, randomized, single dose, 2-treatment, 2-sequence, 2-period crossover study	A: TPM CR 200mg, fasted B: TPM CR 200mg, fed	32 subjects enrolled 28 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover	A: TPM CR 100mg, Clinical lot, fasted B: TPM CR 100mg, CMO lot, fasted	28 subjects enrolled, 27 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

538P106-50	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 50mg, Clinical lot, fasted B: TPM CR 50mg, CMO lot, fasted	32 subjects enrolled 31 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106-200	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 200mg, Clinical lot, fasted B: TPM CR 200mg, CMO lot, fasted	32 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P108	BA	Module 5, Section 5.3.1.2	PK of IR to ER Switch	Multi-center, open-label, two-treatment, single sequence conversion study	TPM ER – equivalent to current therapy TPM IR – equivalent to current therapy	62 patients with epilepsy  (72 planned)	11 centers, adults with epilepsy on treatment with TPM	4 weeks.
538P109	PK	Module 5, Section 5.3.3	Young vs. Elderly	Comparative, single-dose, parallel group study	TPM CR 100mg, fasted	18 young adults enrolled and completed, 13 elderly enrolled and completed	Single center/ Healthy, normal young and elderly	Single dose, 1 treatment period
538P107	PK	Pending	Pediatric PK	Multi-center, open-label, switch to ER	TPM ER – equivalent to current therapy	Approximately 40 male and female pediatric subjects ages 4-17	Up to 15 centers, children with epilepsy on treatment with TPM	2 weeks

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			<ul style="list-style-type: none"> <li>Sponsor provided annotated PDF file, clean Word file and PDF file, and side-by-side comparison for labeling</li> </ul>
Reference Bioanalytical and Analytical Methods	X			<ul style="list-style-type: none"> <li>Validation reports for topiramate (LC/MS/MS)</li> <li>In-study validation and QC performance are provided.</li> </ul>
<b>I. Clinical Pharmacology</b>				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
<b>Healthy Volunteers-</b>				
single dose:	X			
multiple dose:	X			
<b>Patients-</b>				
single dose:	X			
multiple dose:	X			A new study (538P108) examines the conversion (IR -> ER) at steady-state; 5 doses
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-			

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 201-635

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects of primary drug:	-			
In-vitro:	-			
<b>Subpopulation studies -</b>				
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	X			
renal impairment:	-			
hepatic impairment:	-			
<b>PD -</b>				
Phase 2:	-			
Phase 3:	-			
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
<b>Population Analyses -</b>				I report for PopPK
Data rich:	X			<ul style="list-style-type: none"> <li>• Population PK analysis for steady-state food effect</li> <li>• Rich data from Phase 1 studies</li> </ul>
Data sparse:	-			
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>	-			
<b>Relative bioavailability -</b>				
solution as reference:	-			
alternate formulation as reference:	X			• CR vs. IR (RLD)
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X			• Commercial formulation vs. clinical formulations; comparison of different manufacturing sites (See Appendix 2)
replicate design; single / multi dose:	-			
<b>Food-drug interaction studies</b>	X			• Study with highest 200mg strength of the “development” formulation
<b>Bio-waiver request based on BCS</b>	-			
<b>BCS class</b>	-			
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>	(X)			Study conducted in dogs
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>	-			
<b>Chronopharmacokinetics</b>	-			
<b>Pediatric development plan</b>	-			(b) (4)
<b>Literature References</b>	X			74 references
<b>Total Number of Studies</b>	<b>14</b>			9 PK + 1 Pop PK + 4 validation reports

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 201-635

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			50, 100, and 200mg strengths
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Cross-reference to approved Topamax label
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Cross-reference to approved Topamax label
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Generally acceptable but with some erroneous hyperlinks that requires reviewer's own effort
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Cross-reference to approved Topamax label
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Cross-reference to approved Topamax label
14	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			X	Cross-reference to approved Topamax label

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 201-635

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Cross-reference to approved Topamax label
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			<ul style="list-style-type: none"> <li>• Food effect study on development formulation of 200mg</li> <li>• A review issue</li> </ul>
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

\_\_\_ Yes \_\_\_

1. DSI inspection of the clinical and the analytical sites are needed for the following studies:

Study 538P103 (Pivotal BE study):

Clinical sites: Quintiles Phase I Services, Overland Park, Kansas, U.S.A.

Analytical site: Bioanalytical laboratory of Supernus Pharmaceuticals, Inc., located at 1550 East Gude Dr., Rockville, MD 20850.

Study 538P106-200 (formulation bridging study for the highest 200mg strength):

Clinical sites: Dedicated Phase I, Inc., 734 W. Highland Ave. Phoenix, AZ 85013, U.S.A.

Analytical site: Same as Study 538P103

Study 538P106 and Study 538P106-50 (formulation bridging study for 50mg and 100mg strengths):

Clinical sites: PAREXEL Early Phase Clinical Unit (EPCU) – Baltimore,  
3001 South Hanover Street, Baltimore, MD 21225, USA

Analytical site: Same as Study 538P103

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Reviewing Clinical Pharmacologist

Date

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Team Leader/Supervisor

Date

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for  
NDA\_BLA or Supplement 201-635

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/s/  
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TA-CHEN WU  
12/05/2011

YUXIN MEN  
12/13/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
<b>NDA/BLA Number</b>	201-635	<b>Brand Name</b>	Tradename™
<b>OCP Division (I, II, III, IV, V)</b>	DCP-1	<b>Generic Name</b>	Topiramate
<b>Medical Division</b>	HFD-120	<b>Drug Class</b>	Anticonvulsant
<b>OCP Reviewer</b>	Ta-Chen Wu, Ph.D.	<b>Indication(s)</b>	<ul style="list-style-type: none"> <li>• Monotherapy epilepsy: Initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures</li> <li>• Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS)</li> </ul>
<b>OCP Team Leader</b>	Angela Yuxin Men, M.D., Ph.D.	<b>Dosage Form</b>	Extended-release multi-bead capsules (SPN-538T: 25, 50, 100, and 200 mg strengths)
<b>Pharmacometrics Reviewer</b>	Satjit S. Brar, Pharm.D., Ph.D.	<b>Dosing Regimen</b>	Once daily (See Appendix 1 under Clin Pharm & Biopharm Information section for details)
<b>Date of Submission</b>	01/13/2011	<b>Route of Administration</b>	Oral
<b>Estimated Due Date of OCP Review</b>	09/14/2011	<b>Sponsor</b>	Supernus Pharmaceuticals, Inc.
<b>Medical Division Due Date</b>	10/07/2011	<b>Priority Classification</b>	S
<b>PDUFA Due Date</b>	11/14/2011		

*Clin. Pharm. and Biopharm. Information*

Summary:

The sponsor seeks approval of Topiramate extended-release capsules (SPN-538T) as monotherapy and adjunctive therapy for epilepsy via 505(b)(2) application and will reference the approved TOPAMAX® (NDA 20-505). The

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Sponsor is not seeking indication for migraine. Topiramate extended-release capsules are multi-bead capsules (three-pellet composite formulations) in dosage strengths of 25, 50, 100, and 200mg, administered one daily (QD).

With this submission, the Sponsor is presenting a clinical pharmacology-based new drug application by demonstrating the bioequivalent for time-point to time-point within the 24 hours at steady-state between the proposed CR capsules (QD) and approved IR tablets (BID).

The clinical program consists of 8 studies in healthy adult volunteers to support this NDA, as well as 2 ongoing studies in epilepsy patients, as summarized below. (also see Appendix 2)

1. 1 PK study: compared the PK profiles of young and elderly adult patients (Study 538P109)
2. 7 Biopharm studies: establish steady-state BA/BE vs. IR, dose linearity/proportionality, food effect (200mg), and BE between the clinical and registration scale formulations (50, 100, and 200mg)

Note:

- “Development” formulations were studied for BA/BE vs. IR, dose linearity/proportionality, and food effect. At the Pre-NDA meeting, the Sponsor claimed that the commercial formulation of 200 mg strength was studied for food effect.
- “Registration” formulations were studied in formulation bridging.

Biowaiver of in vivo relative BA study was requested for the 25 mg strength on the basis of formulation proportionality and dissolution similarity of 25mg and 50mg capsules.

A study to assess the potential dose-dumping was conducted in dogs, instead of humans as recommended at the Pre-NDA meeting.

The plasma concentration of topiramax was determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

**Appendix 1.** Proposed dosing regimen

Topamax IR:

	Initial Dose	Titration	Recommended Dose
Epilepsy monotherapy: adults and pediatric patients ≥10 years (2.1)	50 mg/day in two divided doses	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day in two divided doses

	Initial Dose	Titration	Recommended Dose
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day in two divided doses

Topiramate IR:

	Initial Dose	Titration	Recommended Dose
Epilepsy monotherapy: adults and pediatric patients ≥10 years (2.1)	50 mg/day Once daily dose	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6.	400 mg/day Once daily dose

	Initial Dose	Titration	Recommended Dose
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS (2.1)	25 to 50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200-400 mg/day Once daily dose

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Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS (2.1)	25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) (administered in two divided doses). Dose titration should be guided by clinical outcome.	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day in two divided doses	Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS (2.1)	25 mg/day ( based on a range of 1 to 3 mg/kg/day) (nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day Once daily dose
Migraine (2.3)	25 mg/day administered nightly for the first week	The dosage should be increased weekly by increments of 25 mg. Dose and titration should be guided by clinical outcome.	100 mg/day administered in two divided doses				

## Appendix 2. Tabular listing of studies to support the NDA:

Study ID	Primary Endpoint or Endpoints	Location of Study Report Synopsis	Study Objective	Study Design	Study & Control Drugs/ Dose/ Route/ Regimen	# Subjects by Arm Entered/ Completed	# Sites / Subject type	Duration
538P103	PK	Module 5, Section 5.3.3	Steady state PK	Comparative, randomized, multiple dose, 2-treatment, 2-sequence, 2-period crossover with active control	A: TPM CR 200mg x 10 days (after 3 weeks titration) B: Topamax 200mg x 10 days (after 3 weeks titration)	39 subjects enrolled, 33 subjects completed	Single center/ Healthy, normal	10 day maintenance with 21 day titration per treatment period
538P104	PK	Module 5, Section 5.3.3	Dose proportionality	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 8 x 25mg B: TPM CR 4 x 50mg C: TPM CR 2 x 100mg D: TPM CR 1 x 200mg	34 subjects enrolled 24 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P104.5	PK	Module 5, Section 5.3.3	Dose linearity	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 25mg B: TPM CR 50mg C: TPM CR 100mg D: TPM CR 200mg	36 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods
538P105	PK	Module 5, Section 5.3.3	Food effect	Comparative, randomized, single dose, 2-treatment, 2-sequence, 2-period crossover study	A: TPM CR 200mg, fasted B: TPM CR 200mg, fed	32 subjects enrolled 28 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover	A: TPM CR 100mg, Clinical lot, fasted B: TPM CR 100mg, CMO lot, fasted	28 subjects enrolled, 27 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

538P106-50	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	study. Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 50mg, Clinical lot, fasted B: TPM CR 50mg, CMO lot, fasted	32 subjects enrolled 31 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P106-200	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 200mg, Clinical lot, fasted B: TPM CR 200mg, CMO lot, fasted	32 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods
538P109	PK	Module 5, Section 5.3.3	Young vs. Elderly	Comparative, single-dose, parallel group study	TPM CR 100mg, fasted	18 young adults enrolled and completed, 13 elderly enrolled and completed	Single center/ Healthy, normal young and elderly	Single dose, 1 treatment period

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			<ul style="list-style-type: none"> <li>Sponsor provided annotated PDF file, clean Word file and PDF file, and side-by-side comparison for labeling</li> </ul>
Reference Bioanalytical and Analytical Methods	X			<ul style="list-style-type: none"> <li>Validation reports for topiramate (LC/MS/MS)</li> <li>In-study validation and QC performance are provided.</li> </ul>
<b>I. Clinical Pharmacology</b>				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
<b>Healthy Volunteers-</b>				
single dose:	X			
multiple dose:	X			
<b>Patients-</b>				
single dose:	X			
multiple dose:	X			
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
<b>Subpopulation studies -</b>				
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	X			
renal impairment:	-			
hepatic impairment:	-			
<b>PD -</b>				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 2:	-			
Phase 3:	-			
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
<b>Population Analyses -</b>				1 report for PopPK
Data rich:	X			<ul style="list-style-type: none"> <li>Population PK analysis for steady-state food effect</li> <li>Rich data from Phase 1 studies</li> </ul>
Data sparse:	-			
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>	-			
<b>Relative bioavailability -</b>				
solution as reference:	-			
alternate formulation as reference:	X			• CR vs. IR (RLD)
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X			• Commercial formulation vs. clinical formulations; comparison of different manufacturing sites (See Appendix 2)
replicate design; single / multi dose:	-			
<b>Food-drug interaction studies</b>	X			• Study with highest 200mg strength of the "development" formulation
<b>Bio-waiver request based on BCS</b>	-			
<b>BCS class</b>	-			
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>	(X)			Study conducted in dogs
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>	-			
<b>Chronopharmacokinetics</b>	-			
<b>Pediatric development plan</b>	-			(b) (4)
<b>Literature References</b>	X			72 references
<b>Total Number of Studies</b>	13			8 PK + 1 Pop PK + 4 validation reports

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			50, 100, and 200mg strengths
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Cross-reference to approved Topamax label

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Cross-reference to approved Topamax label
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	(X)			Except for the incomplete PK dataset in SAS .xpt files dataset for the each study
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Generally acceptable but with some erroneous hyperlinks that requires reviewer's own effort
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		<ul style="list-style-type: none"> <li>• Incomplete PK SAS dataset in SAS .xpt files for each study</li> <li>• Analysis datasets to support PopPK analysis</li> </ul>
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?		X		<ul style="list-style-type: none"> <li>• Incomplete PK dataset in SAS .xpt files for each study</li> <li>• Analysis datasets to support PopPK analysis</li> </ul>
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	Cross-reference to approved Topamax label
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	Cross-reference to approved Topamax label
14	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?			X	Cross-reference to approved Topamax label
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics	X			Cross-reference to

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	and exposure-response in the clinical pharmacology section of the label?				approved Topamax label
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			<ul style="list-style-type: none"> <li>• Food effect study on development formulation of 200mg</li> <li>• A review issue</li> </ul>
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

### IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

\_\_\_ Yes \_\_\_

1. Please provide the electronic datasets for PK parameters as SAS transport files (.XPT) for all studies.
2. Please submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:
  - a. All datasets and the final analysis dataset used for model development and validation should be submitted as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
  - b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
3. Please specify the content of high-fat food (i.e., standard FDA high fat food) for food-effect study, or direct the reviewer to where the information located.
4. DSI inspection of the clinical and the analytical sites are needed for the following studies:

Study 538P103 (Pivotal BE study):

Clinical sites: Quintiles Phase I Services, Overland Park, Kansas, U.S.A.

Analytical site: Bioanalytical laboratory of Supernus Pharmaceuticals, Inc., located at 1550 East Gude Dr., Rockville, MD 20850.

Study 538P106-200 (formulation bridging study for the highest 200mg strength):

Clinical sites: Dedicated Phase I, Inc., 734 W. Highland Ave. Phoenix, AZ 85013, U.S.A.

Analytical site: Same as Study 538P103

Study 538P106 and Study 538P106-50 (formulation bridging study for 50mg and 100mg strengths):

Clinical sites: PAREXEL Early Phase Clinical Unit (EPCU) – Baltimore,  
3001 South Hanover Street, Baltimore, MD 21225, USA

Analytical site: Same as Study 538P103

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

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Reviewing Clinical Pharmacologist

Date

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Team Leader/Supervisor

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TA-CHEN WU  
03/11/2011

YUXIN MEN  
03/11/2011

## ONDQA BIOPHARMACEUTICS FILING REVIEW

NDA Number	201-635 (Original NDA)
Product name, generic name of the active, and dosage strength and form	(b) (4) topiramate, 25-, 50-, 100- and 200-mg Extended Release capsules
Submission date	January 14, 2011
Sponsor	Supernus Pharmaceuticals, Inc. Rockville, MD
Medical Division	Division of Neurology Products
Type of Submission	Quality
Primary CMC/Quality Reviewer	Thomas M. Wong, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

### BACKGROUND

Topiramate is a sulfamate-substituted monosaccharide. Immediate release dosage forms, TOPAMAX<sup>®</sup> (topiramate) Tablets and TOPAMAX<sup>®</sup> (topiramate capsules) Sprinkle Capsules were approved as an anti-epileptic in 1996 and 1998.

In this submission, the Sponsor is seeking monotherapy and adjunctive therapy indications for epilepsy with once a day oral dosing of the topiramate extended-release capsules. The proposed Indications are:

- Monotherapy epilepsy: Initial monotherapy in patients  $\geq 10$  years of age with partial onset or primary generalized tonic-clonic seizures, and
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome.

### SUBMISSION

The Sponsor is submitting mainly clinical pharmacology studies to seek NDA approval via 505(b)(2) path and is claiming that there are adequate bridging studies to establish the link between the products studied in the clinical trials and the proposed commercial product.

The submission is poorly organized and the relevance of the submitted information with respect to the final proposed to be marketed product is not apparent. The Sponsor is referring to research scale, development scale and registration formulations, and is also stating that "The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches." Based on these statements, it is difficult to discern the extent that submitted information would apply to the final product. Similar concerns are also detailed in the IQA (dated 2/10/2011, prepared by Martha Heimann, Ph.D.).

Based on tables that are described as "Theoretical Formulation Composition of Development Scale Topiramate Extended Release Capsules Used In Human Clinical

Studies", the percentages of topiramate in the immediate release and extended release pellets are in the following table.

The proposed strengths are 25-mg, 50-mg, 100-mg, and 200-mg capsules containing immediate release (b) (4) and extended release pellets (b) (4)

<i>Topiramate controlled release capsules</i>	(b) (4)
<i>25-mg</i>	
<i>50-mg</i>	
<i>100-mg</i>	
<i>200-mg</i>	

## BIOPHARMACEUTICS

### In vitro characterization and dissolution testing

The information related to in vitro product characterization such as by dissolution testing is limited. Although it is an extended release product, a single dissolution test medium is provided and it is a very similar dissolution test method used for topiramate IR formulations with a difference being in the duration of the test method. Typically, there should be an assessment in acidic pH prior to testing dissolution at higher pH or a justification that such testing may not be needed.

The Sponsor is stating that topiramate is not stable in acidic pH. However, as in the following table, they are also providing solubility results over a physiologic pH range at 37°C. (Please see report TR-10-032.00). Based on this, the stated stability concerns are not readily apparent.

**Table 1: Topiramate Aqueous Solubility at Various pH at 37°C**

pH	Aqueous Solution	Topiramate Solubility (mg/mL)
1.0	0.1N HCl	11.3
2.5	Acid Phthalate Buffer	12.9
4.7	Acetate Buffer	12.3
6.8	Phosphate Buffer	11.4
7.5	Phosphate Buffer	12.3

Furthermore, there is limited information in the dissolution method development report. The dissolution method development report submitted by the Sponsor (TR-09-008.00) focus on determining the effect of (b) (4) on the capsules and the effect of agitation speed (b) (4) when dissolution test is carried out in 750 mL of 50 mm phosphate buffer (pH 7.5) using USP Apparatus 2. This approach is not a comprehensive presentation of method development efforts or method optimization efforts. It is not clear how the proposed in vitro dissolution method can be considered discriminating and should be discussed in the method development report. Questions related to the in vitro dissolution method development are included under the recommendations section of this review for questions to be communicated to the Sponsor.

The Sponsor has provided a validation report for the proposed dissolution method for the pellets and the capsules (TR-09-013.00). While it is a typical method validation report, due to uncertainties, leveraging information from this report may not be adequate and additional information may be needed during review.

In Section 2.7 of the submission, the Sponsor has provided the following in vitro dissolution test results for the topiramate ER capsules. It is not clear why the volume of the dissolution media (b) (4) Once in vitro dissolution method concerns are addressed, and additional in vitro dissolution data will be generated.

**Table 2: Summary of In Vitro Dissolution Studies**

STUDY REF. NO.	DISSOLUTION CONDITIONS	PRODUCT ID/BATCH NO.	DOSAGE FORM	NO. OF DOSAGE UNITS	COLLECTION TIMES MEAN AND RANGE OF % DISSOLVED										
					5 min	15 min	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	16 hrs	
538P103 538P104 538P104.5 538P105	(b) (4)	LIMS 11568, Lot B08024B [538P104 lot B08024B; 538P104.5 lot B08024C]	25mg capsules	6	(b) (4)										
		LIMS 11569, Lot B08025B [538P104 lot B08025B; 538P104.5 lot B08025C]	50mg capsules	6	(b) (4)										
		LIMS 11570, Lot B08026B [538P104 lot B08026B; 538P104.5 lot B08026C]	100mg capsules	6	(b) (4)										
		LIMS 11571, Lot B08027B [538P103 lot B08027E; 538P104 lot B08025B; 538P104.5 lot B08027C; 538P105 lot B08027D]	200mg capsules	6	5 min	15 min	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	16 hrs	(b) (4)

STUDY REF. NO.	DISSOLUTION CONDITIONS	PRODUCT ID/BATCH NO.	DOSAGE FORM	NO. OF DOSAGE UNITS	COLLECTION TIMES						
					MEAN AND RANGE OF % DISSOLVED						
538P106	(b) (4)	LIMS 15925, Lot B08026E [538P106 lot B08026E]	100mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs
		LIMS 15347, Lot 0912373 [538P106 lot B10001B]	100mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs
538P106-50	(b) (4)	LIMS 17276, Lot B08025E [538P106-50 lot B08025E]	50mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs
		LIMS 15345, Lot 0912372 [538P106-50 lot B10024C]	50mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs
538P106-200	(b) (4)	LIMS 17277, Lot B08027F [538P106-200 lot B08027F]	200mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs
		LIMS 15349, Lot 0912946 [538P106-200 lot B10002D]	200mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs
538P109	(b) (4)	LIMS 15347, Lot 0912373 [538P109 lot B10001C]	100mg capsules	6	1 hr	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	10 hrs

### Biowaiver request for the 25-mg capsules

A biowaiver issue raised by the Sponsor appears to be related to the discussions from earlier meetings between the Sponsor and the FDA when the Sponsor had ongoing clinical studies for the 50-, 100- and 200-mg strengths.

If the final product for the 25-mg and 50-mg capsules support that they are (b) (4) and the submitted clinical study data provide the necessary bridging for the 25- and 50-mg capsules, additional BE testing for the 25-mg capsules will not be needed.

The Sponsor needs to verify the actual compositions and how the products studied (listed in the following table) compare with the final product. If there are adequate in vivo links and the 25-mg and 50-mg capsules are composition proportional as claimed by the Sponsor in this submission, a BE study for further comparison of the 25-mg capsules to the 50-mg capsule, at an equivalent dose, is not needed.

Table 1: Summary of Biopharmaceutical Studies

Study	Objective	Dose	Crossover Treatment/sequence/period	Treatments				Subjects enrolled
				1	2	3	4	
538P103	Steady-state bioavailability	Multiple	2/2/2	200mg SPN-538T	200mg TOPAMAX®			39
538P104	Dose proportionality	Single	4/4/4	8 X 25mg SPN-538T	4 X 50mg SPN-538T	2 X 100mg SPN-538T	1 X 200mg SPN-538T	34
538P104.5	Dose linearity	Single	4/4/4	25mg SPN-538T	50mg SPN-538T	100mg SPN-538T	200mg SPN-538T	36
538P105	Food effect	Single	2/2/2	200mg SPN-538T Fed	200mg SPN-538T Fasted			32
538P106	Bridging, manufacturing sites	Single	2/2/2	100mg SPN-538T	100mg TPM ER*			28
538P106-50	Bridging, manufacturing sites	Single	2/2/2	50mg SPN-538T	50mg TPM ER*			32
538P106-200	Bridging, manufacturing sites	Single	2/2/2	200mg SPN-538T	200mg TPM ER*			32

\* TPM ER represents the product produced at the commercial manufacturing facility. SPN-538T represents the product produced at Supernus for clinical studies.

### Alcohol dose-dumping study

The in vitro dissolution method requires further work, however, even with that, it is evident that topiramate release from the topiramate ER capsules is faster with increasing alcohol concentrations in the dissolution media. The in vivo effect should be evaluated in a clinical pharmacology study.

## RECOMMENDATION

*It is recommended that the following comments are included under information request to support filing of this submission.*

1. The submission is poorly organized and the relevance of the submitted information with respect to the final proposed to be marketed product is not apparent.

The dissolution method development report that you have provided has limited information and does not provide *in vitro* product characterization with respect to drug release (dissolution testing) from the topiramate ER capsules in conditions mimicking GI environment. Typically, dissolution testing, carried out in several media as in the guidance documents, also provide information about in vitro drug release in various pH comparable to the pH of the GI tract.

Please provide in vitro dissolution test results of the pellets and the ER capsules (for all capsule strengths, n=12 units at each strength) in several media including

(b) (4)  
(Reference: Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997).

You indicate that the product is not stable under acidic conditions (pH 2). However, you have not indicated how the integrity of the topiramate ER capsules and the pellets are going to be protected when they are in gastric pH. Typically, for delayed release products dissolution test is performed in (b) (4)

Please provide justification for omitting the acid stage testing.

Furthermore, you have shown that topiramate solubility is approximately 12 mg/mL in physiologic pH (TR- TR-10-032.00). Based on this, the stated stability concerns are not readily apparent. Please provide stability information for the pellets and the CR capsules in acidic pH followed by dissolution testing in buffer (pH range as above).

2. You have submitted a dissolution method development report that is for determining the agitation speed (b) (4) and whether (b) (4)

To support product characterization and an assessment of quality of the topiramate ER capsules, you need to provide a comprehensive dissolution method development report which should also include the above information (in Item#1) such that all relevant information is integrated and an assessment of the following can be made:

- i. pH solubility profile for topiramate across the typical gastro-intestinal pH range  
(if topiramate stability is a concern, please provide the degradation profile.)
- ii. in vitro performance of the pellets and the ER capsules (as a dissolution profile) in several media (b) (4)
- iii. Dissolution testing with different dissolution apparatus and under different conditions, leading to justification of the selected apparatus and conditions.
- iv. Dissolution testing should be carried out with a minimum of n=12 units at each strength of the final proposed to-be marketed product. If there is a difference in formulation composition between the batches studied in the submitted clinical studies (as summarized in the following table) and the proposed to-be marketed ER capsules, the differences should be provided in comparative tables.

The dissolution data submitted should be identified with batch and formulation numbers, batch sizes, manufacturing dates along with in vitro dissolution method, and test results (individual, n=12, and mean data). The dissolution data should be labeled with clinical study numbers, if the specific batch was used in the clinical studies.

Study #	25-mg CR capsule	50-mg CR capsule	100-mg CR capsule	200-mg CR capsule
SPN-538T-538P104	B08024B	B08025B	B08026B	B08027B
Protocol 538P105				B08027B
SPN-538T-538P104.5	B08024C	B08025C	B08026C	B08027C
SPN-538T- 538P103		B08025D	B08026D	B08027E
Protocol 538P106			B08026E B10001B	
TPMT-538P109			B10001CP	
SPN-538T- 538P106-50		B08025E B10024C		
SPN-538T - 538P106-200				B08027F B10002D

Depending on the final proposed optimized dissolution method for product quality testing, a validation report on dissolution procedure and HPLC Analysis of topiramate in pellets and capsules may be needed.

In addition, based on the final proposed dissolution method, please provide proposed dissolution specification for the pellets and the topiramate ER capsules.

3. You have tested administering capsule contents in applesauce in a clinical study (TPMT-538109) and need to assess in vitro product performance (integrity:

stability and degradation profile, and release of topiramate from topiramate pellets after being kept in apple sauce).

In addition, for labeling purposes, stability of the pellets in other soft foods such as pudding, yogurt, etc. should be evaluated over a period not to exceed 2 hrs.

4. Please move in vitro dissolution testing report (effect of alcohol on dissolution rate) currently in module 4 to module 3 under product characterization.

## SIGNATURES

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**Biopharmaceutics Team Leader**  
**Office of New Drug**  
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| cc; NDA 201-635, Patrick Marroum Ph.D., Ramesh Sood Ph.D., Martha Heimann Ph.D,

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ARZU SELEN  
03/01/2011

ANGELICA DORANTES  
03/01/2011