CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205122Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Individual Study Reviews

(Question-Based Review for BRANDNAME XR™ is in DARRTS dated 02/07/2014)

NDA:	**205-122**
Brand Name:	BRANDNAME XR™
Generic Name:	Topiramate Extended-Release Capsules (USL255)
Sponsor:	Upsher-Smith Laboratories, Inc. (USL)
Dosage Form & Strength:	Extended Release (ER) Capsules (25mg, 50mg, 100mg, 150mg, and 200mg)
Indication:	Monotherapy for epilepsy for patients ≥10 years of age; Adjunctive therapy for epilepsy for adult and pediatric patients (b) (4) and for patients (b) (4) with seizures associated with Lennox-Gastaut Syndrome (LGS)
Submission:	505(b)(2), Standard
Submission Dates:	02/11/2013; 5/21/2013; 11/20/2013
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Ta-Chen Wu, Ph.D.
Team Leader:	Angela Yuxin Men, M.D., Ph.D.

Reference ID: 3464886

4. Appendices

4.3 Individual Study Reviews

<table>
<tr><td>Study Report #</td><td>P09-001</td></tr>
<tr><td>Title</td><td>Randomized, Single-Center, Open-Label, Five-Way Crossover Study to Evaluate the Dose-Proportionality of USL255 in Healthy Adult Subjects</td></tr>
<tr><td>Investigator/ Center</td><td>Aziz L. Laurent, MD, PPD Phase I Clinic, 7551 Metro Center Drive, Building 10, Suite 200, Austin TX 78744</td></tr>
<tr><td>Study Dates</td><td>September 02, 2009 - March 30, 2010</td></tr>
<tr><td>Objectives</td><td>To evaluate the PK, dose-proportionality, safety and tolerability of single dose of 25, 50, 100, 200, and 400 mg of USL255</td></tr>
<tr><td>Formulation</td><td>
<table>
<tr><td>TPM ER</td><td>Batch #</td></tr>
<tr><td>USL255-25-MD</td><td>268046</td></tr>
<tr><td>USL255-50-MD</td><td>268047</td></tr>
<tr><td>USL255-100-MD</td><td>268048</td></tr>
<tr><td>USL255-200-MD</td><td>268049</td></tr>
</table>
</td></tr>
<tr><td>Study Design</td><td>

Phase 1, randomized, single-center, open-label, single-dose, 5-way crossover (using A standard 5 × 5 Latin square) study in 30 eligible healthy males and females (N=6 per cohort), aged 18-65 years
Screening period: 4 weeks; washout period: at least 3 weeks between periods; duration: 18 weeks

</td></tr>
<tr><td>PK Assessment</td><td>

Plasma samples: predose and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 48, 72, 96, 120, 168, 216, 264, and 336h postdose
AUC0-t, AUC0-∞, Cmax, Tmax, kel, and t½.

</td></tr>
<tr><td>Statistical Analysis</td><td>

Descriptive statistics were used to summarize the PK parameteres
Power Model ($AUC_{ij} = \beta_{0i} \cdot Dose_{ij}^{\beta_{1i}} \cdot \exp(\varepsilon_{ij})$) was used to assess the dose-proportionality for 25-400mg dose range. The Rdnm was the model-predicted ratio of dose-normalized geometric means for highest dose relative to lowest dose, with 0.8 and 1.25 being lower and upper limits, respectively.
Dose linearity was tested by fitting the model: log(PK parameter) = a + b*log(dose) + Dose
Additional analysis using power model was performed to test dose-proportionality for 100-400mg doses
Additional analysis was performed to test dose-normalized Cmax and AUC using ANOVA model on log-transformed exposure measures between 400mg vs. 200mg, and between 200mg vs. 100mg. Point estimates and 90% CI for geometric mean ratios between treatments, judged by BE acceptance criteria of 80-125%. Dose proportionality would be concluded if all 90% CIs fall within 80-125%.

</td></tr>
<tr><td>Bioanalytical Methods</td><td>
Table. Assay performance
<table>
<tr><td>Analyte</td><td></td><td>Topiramate (plasma)</td></tr>
<tr><td>Method:</td><td></td><td>HPLC/MS/MS</td></tr>
<tr><td>Standard Curve:</td><td>Range:</td><td>10.00 – 10000 ng/mL</td></tr>
<tr><td></td><td>R:</td><td>0.9992</td></tr>
</table>
</td></tr>
</table>

Reference ID: 3464886

	Precision:	4.10 – 9.13%				
	Accuracy:	-1.82 – 2.42%				
LOQ:		10 ng/mL				
QC:		30 ng/mL	80 ng/mL	300 ng/mL	1200 ng/mL	7500 ng/mL
	Precision:	8.35%	6.70%	6.94%	6.57%	5.65%
	Accuracy:	-2.66%	-0.43%	-1.01%	-0.098%	1.57%

• Bioanalytical site: [redacted] (b) (4)

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

Population/ Demographics

- 30 subjects were enrolled, with 2 subjects (#112 and #101) being discontinued due to noncompliance with protocol.
- 83.3% of the subjects were white; mean age of 32.2 years (18-60 years).

PK Results

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

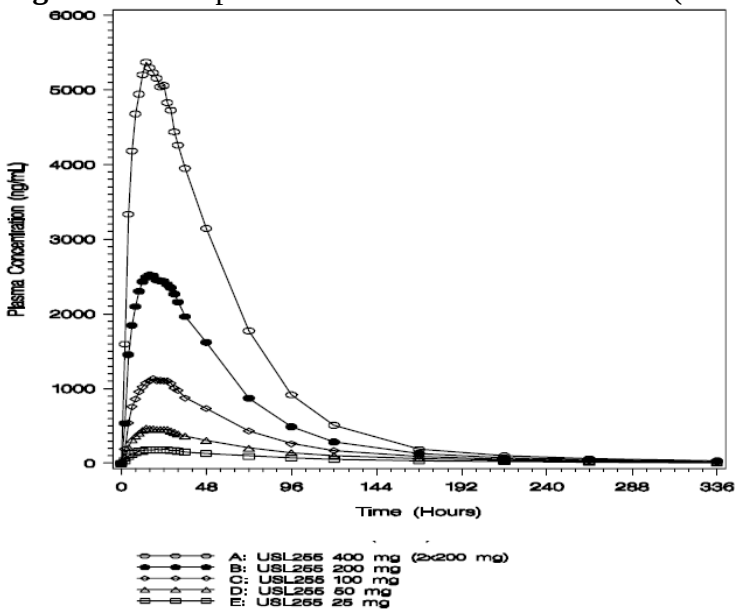

Table 1. Arithmetic means (SD) of topiramate pharmacokinetic parameters following a single doses of 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg of USL255

	25 mg USL255 (n = 22)		50 mg USL255 (n = 27)		100 mg USL255 (n = 28)		200 mg USL255 (n = 27)		400 mg USL255 (n = 26)	
Pharmacokinetic Parameter	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**
C_{max} (µg/mL)	0.203 (0.067)	32.9	0.512 (0.132)	25.8	1.23 (0.343)	27.8	2.78 (0.616)	22.2	5.79 (1.34)	23.1
AUC_{∞} (µg·h/mL)[a]	20.4 (5.58)	27.3	43.2 (9.12)	21.1	87.2 (19.6)	22.4	175 (40.2)	23.0	343 (69.4)	20.3
AUC_t (µg·h/mL)	18.6 (5.32)	28.6	40.6 (8.86)	21.8	84.3 (19.4)	23.1	174 (40.9)	23.5	340 (71.0)	20.9
k_{el} (h^{-1})[a]	0.0077 (0.0018)	23.4	0.0078 (0.0016)	20.8	0.0083 (0.0017)	20.4	0.0093 (0.0016)	17.7	0.0099 (0.0014)	14.1
$t_{½}$ (h)[a]	94.6 (23.0)	24.3	92.2 (19.5)	21.2	86.5 (18.2)	21.1	76.6 (13.1)	17.1	71.1 (9.8)	13.8
t_{max} (h)[b]	20 (8, 32)	26.5	18 (10, 36)	33.4	23 (12, 32)	29.3	18 (10, 30)	34.4	16 (8, 36)	36.7

a Four subjects (in 25mg, 200mg, and 400mg groups) were excluded from the summary statistics and statistical analyses related to this PK parameter because an elimination rate constant could not be calculated.
b Median (min, max) is reported for Tmax.

Table 2. Summary of statistical analysis for dose-proportionality for 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg of USL255

PK Parameter	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm* (90% CI)	Conclusion**
AUCt (µg•h/mL)	(18.6, 336)	1.04 (1.03, 1.06)	1.13 (1.08, 1.18)	Proportional
AUC∞ (µg•h/mL)	(20.4, 339)	1.01 (1.00, 1.03)	1.04 (1.00, 1.09)	Proportional
Cmax (µg/mL)	(0.203, 5.91)	1.22 (1.19, 1.24)	1.82 (1.69, 1.96)	Not Proportional
Cmax (µg/mL)[a]	(1.20, 5.65)	1.12 (1.07, 1.17)	1.18 (1.10, 1.27)	Approached Dose Proportionality

* Ratio of model-predicted geometric mean values for high and low dose, normalized for dose.
** Dose proportionality was concluded if the 90% CI for Rdnm was contained within 0.80-1.25 limits. If the 90% CI was completely outside of 0.80-1.25 limits, then not proportional was concluded. Otherwise inconclusive was concluded.
[a] Dose range: 100-400mg

Figure 2. Dose Proportionality of Cmax (25, 50, 100, 200, and 400 mg)

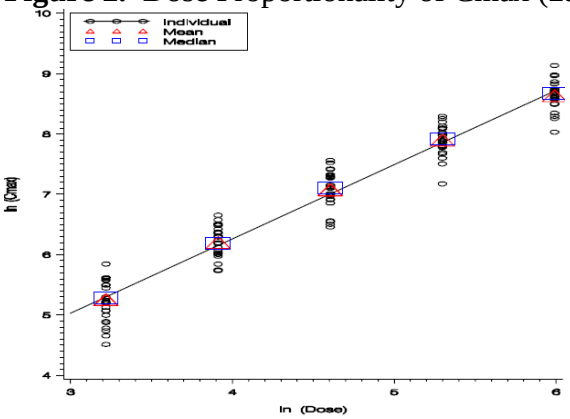

Figure 3. Dose Proportionality of AUC0-∞ (25, 50, 100, 200, and 400 mg)

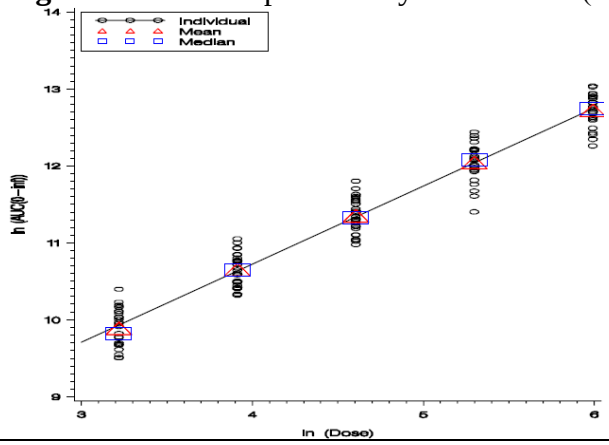

Figure for dose proportionality of AUC0-t is similar and thus is not presented.

	Table 3. Statistical Analysis of Linearity (25, 50, 100, 200, and 400 mg USL255) **Parameter** / **F-Statistic** / **P-value** AUC_{0-t} (ng•hr/mL) / 0.67 / 0.5731 $AUC_{0-\infty}$ (ng•hr/mL) / 0.37 / 0.7769 C_{max} (ng/mL) / 1.71 / 0.1688 Note: The p-values (not statistically significant) in Table 3 indicate that the statistical model was not able to detect any significant departures from linearity. ANOVA was performed on the dose-normalized AUC and Cmax for the 200mg vs.100mg and 400mg vs. 200mg doses showed that the 90% CIs are all contained within 0.80-1.25 limits (results now shown).
Safety	• The majority of TEAEs were mild. • The percentage of subjects who experienced a TEAE generally increased with increasing single doses of USL255. The percentage of subjects who experienced a TEAE after receiving single doses of were 11.1%, 18.5%, 14.3%, 25.9%, and 46.2% for 25, 50, 100, 200, and 400 mg, respectively.
Conclusion	• Statistical analysis confirms the proportionality for AUCt and AUC∞ over the entire 25-400mg dose range and for Cmax over 100-400mg dose range. [see Comment] • Median Tmax occurred at 16-23 h across the 25-400mg dose range. • Mean terminal t1/2 ranged 71.1-86.5 h for 100-400mg doses; however, it was prolonged as doses were decreased (Table 1), which can be attributed to the substantial and saturable binding of topiramate to erythrocytes.
Comment	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 lower 25-50 mg doses. (*Epilepsy Res. 2005 Feb;63(2-3):103-12*)

Study Report #	**P09-011**
Title	A Randomized, Placebo-controlled, Double-Blind Study to Evaluate the Safety and Pharmacokinetics of Single Ascending Doses of USL255
Investigator/ Center	Robert I. Cooper, MD, Cetero Research, 4801 Amber Valley Parkway, Fargo, ND 58104
Study Dates	January 04, 2010 - April 12, 2010
Objectives	To evaluate the PK, dose-proportionality, safety and tolerability of single ascending doses of 600mg ~1600 mg of USL255
Formulation	TPM ER / Batch # USL255-200-MD / 268049
Study Design	• Phase 1, randomized, single-center, placebo-controlled, double-blind, single-dose, study in planned 60 eligible healthy males and females (N=10 per cohort; 8:2 ratio for USL255:plaebo), aged 18-45 years • Screening period: 4 weeks; 4 days between cohorts; duration: 10 weeks

Reference ID: 3464886

<table>
<tr><td></td><td>

Planned doses for each cohort were as follows (fasted):

Cohort 1: 3 × 200 mg (600 mg) USL255 or matching placebo
Cohort 2: 4 × 200 mg (800 mg) USL255 or matching placebo
Cohort 3: 5 × 200 mg (1000 mg) USL255 or matching placebo
Cohort 4: 6 × 200 mg (1200 mg) USL255 or matching placebo
Cohort 5: 7 × 200 mg (1400 mg) USL255 or matching placebo
Cohort 6: 8 × 200 mg (1600 mg) USL255 or matching placebo

</td></tr>
<tr><td>PK Assessment</td><td>

Plasma samples: predose and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 48, 72, 96, 120, 168, 216, 264, and 336 h postdose
AUC0-t, AUC0-∞, f_{ext}(extrapolated fraction of AUC), Cmax, Tmax, kel, and t½.

</td></tr>
<tr><td>Statistical Analysis</td><td>

Descriptive statistics were used to summarize the PK parameteres
Dose-proportionality for 600-1400mg dose range was tested using Power Model (details are same as Study P09-001).
Dose linearity was tested by fitting the model: log(PK parameter) = a + b*log(dose) + Dose

</td></tr>
<tr><td>Bioanalytical Methods</td><td>
Table. Assay performance
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<tr><td>Analyte</td><td></td><td>Topiramate (plasma)</td><td></td><td></td><td></td><td></td></tr>
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<tr><td></td><td>R:</td><td>0.9992</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Precision:</td><td>4.43 – 9.04%</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Accuracy:</td><td>-1.76 – 2.57%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>LOQ:</td><td></td><td>10 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td>QC:</td><td></td><td>30 ng/mL</td><td>80 ng/mL</td><td>300 ng/mL</td><td>1200 ng/mL</td><td>7500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>8.01%</td><td>6.63%</td><td>6.62%</td><td>4.52%</td><td>4.74%</td></tr>
<tr><td></td><td>Accuracy:</td><td>-3.63%</td><td>-1.11%</td><td>-1.52%</td><td>1.72%</td><td>-0.238%</td></tr>
</table>
• Bioanalytical site: [redacted] (b) (4)
Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.
</td></tr>
<tr><td>Population/ Demographics</td><td>

50 subjects were enrolled and completed the study (i.e., safety population).
86.0% of the subjects were white; mean age of 25.7 years; equal numbers of males and females.
PK population (N=40): subjects received at least 1 dose and had sufficient PK samples for accurate PK estimates.

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<tr><td>PK Results</td><td>Figure 1. Mean plasma concentration - time curves (linear scale) by treatment</td></tr>
</table>

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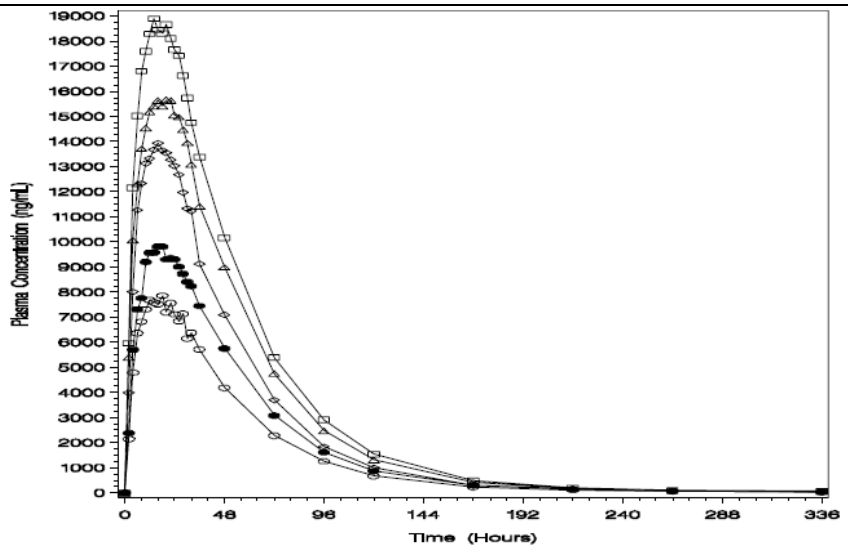


Table 1. Arithmetic means (SD) of topiramate pharmacokinetic parameters following a single doses of 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg of USL255

Pharmacokinetic Parameter	600 mg USL255 (n = 8)		800 mg USL255 (n = 8)		1000 mg USL255 (n = 8)		1200 mg USL255 (n = 8)		1400 mg USL255 (n = 8)	
	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%
C_{max} (µg/mL)	8.34 (1.62)	19.4	10.5 (1.56)	14.8	14.7 (2.13)	14.5	16.6 (3.33)	20.1	19.7 (4.52)	22.9
AUC_t (µg·h/mL)	479 (86.8)	18.1	608 (84.6)	13.9	789 (105)	13.3	965 (154)	15.9	1121 (257)	22.9
AUC_∞ (µg·h/mL)	465 (77.4)	16.7	613 (84.7)	13.8	805 (106)	13.2	970 (153)	15.8	1124 (257)	22.8
f_{ext} (%)	0.80 (0.40)	50.1	0.88 (0.46)	52.0	0.36 (0.17)	48.3	0.56 (0.28)	51.0	0.34 (0.15)	43.0
t_{max} (h)[a]	18.17 (10.16, 32.00)	36.5	17.08 (10.16, 36.00)	46.3	18.16 (10.16, 26.16)	31.4	18.00 (10.16, 24.00)	30.7	20.03 (14.16, 26.16)	24.5
k_{el} (h^{-1})	0.0099 (0.0020)	19.8	0.0089 (0.0014)	15.8	0.0125 (0.0012)	9.80	0.0102 (0.0018)	18.0	0.0126 (0.0022)	17.4
$t_{½}$ (h)	72.7 (14.5)	19.9	80.3 (16.3)	20.2	56.0 (5.63)	10.1	69.7 (11.6)	16.7	56.6 (9.93)	17.6

a Median (min, max) is reported for Tmax.

Table 2. Summary of statistical analysis for dose-proportionality for 600-1400mg of USL255

PK Parameter	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm* (90% CI)	Conclusion**
AUCt (µg•h/mL)	(464, 1100)	1.02 (0.87, 1.17)	1.02 (0.90, 1.15)	Proportional
AUC∞ (µg•h/mL)	(458, 1116)	1.05 (0.90, 1.20)	1.04 (0.92, 1.18)	Proportional
Cmax (µg/mL)	(8.11, 19.4)	1.03 (0.86, 1.20)	1.03 (0.89, 1.18)	Proportional

* Ratio of model-predicted geometric mean values for high and low dose, normalized for dose.

** Dose proportionality was concluded if the 90% CI for Rdnm was contained within 0.80-1.25 limits. If the 90% CI was completely outside of 0.80-1.25 limits, then not proportional was concluded. Otherwise inconclusive was concluded.

Figure 2. Dose Proportionality of Cmax (600-1400 mg)

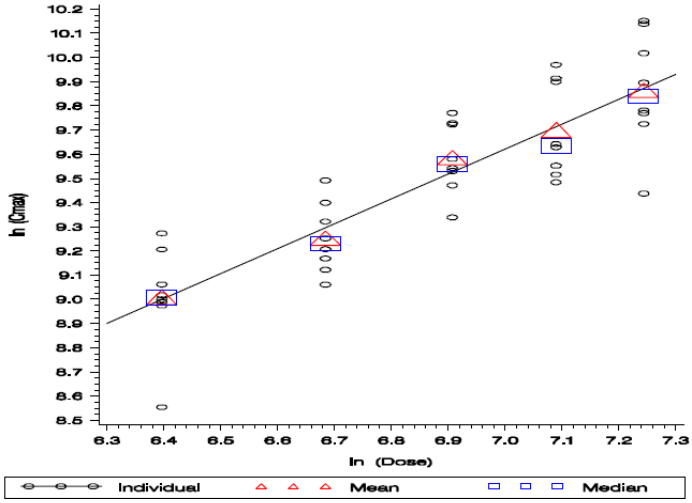


Figure 3. Dose Proportionality of AUC0-∞ (600-1400 mg)

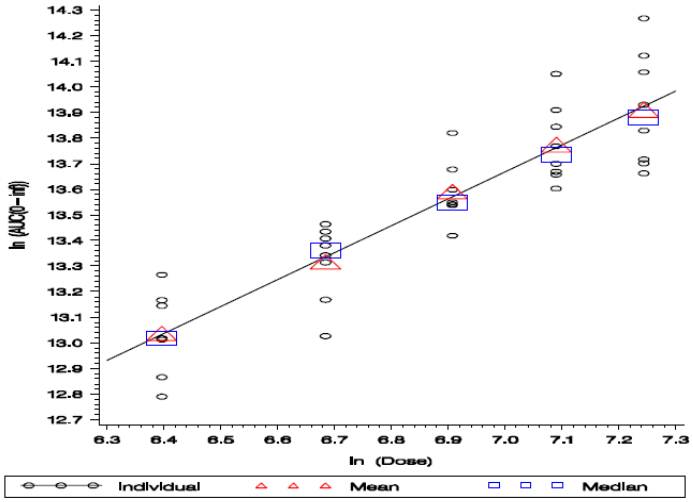


Figure for dose proportionality of AUC0-t is similar and thus is not presented.

Table 3. Statistical Analysis of Linearity (600-1400 mg USL255)

Parameter	F-statistic	P-value
AUC_{0-t} (ng•hr/mL)	0.15	0.9315
$AUC_{0-\infty}$ (ng•hr/mL)	0.10	0.9567
C_{max} (ng/mL)	0.42	0.7422

Note: The p-values (not statistically significant) in Table 3 indicate that the statistical model was not able to detect any significant departures from linearity.

Safety

- The study was stopped early after completion of Cohort 5 (1400 mg) based on review of safety and tolerability results. Within the first 24 hours of receiving a single oral dose of 1400 mg USL255, Subject 50 experienced the AEs of elevated blood pressure, facial numbness, difficulty concentrating, dysphasia, an unsteady gait, numbness in legs, and headache, each lasting between 1 and approximately 8 days.

	• There were no discontinuations due to an AE and no severe AEs, SAEs, or deaths, with 4 subjects experiencing TEAEs of moderate severity (3 related to study drug) and 35 subjects experiencing TEAEs of mild severity. • The data suggested that single doses of USL255 between 600 and 1400 mg resulted in no increase in QTc intervals, rather, a possible decrease in QTc intervals with increasing dose.
Conclusion	• Statistical analysis confirms the proportionality for AUCt, AUC∞ and Cmax over the entire 600-1400mg dose range. • Median Tmax occurred at 17-20 h across the 600-1400mg dose range. • Mean terminal t1/2 ranged 56-80 h for 600-1400mg doses. • The MTD in this study was determined to be 1200 mg USL255.

Study Report #	**P09-002**
Title	A Randomized, Single-Center, Open-Label, Three-Way Crossover Phase 1 Food-Effect Study to Evaluate the Relative Bioavailability of USL255 in Healthy Adult Subjects
Investigator/ Center	Aziz L. Laurent, MD, PPD Phase I Clinic, 7551 Metro Center Drive, Building 10, Suite 200, Austin TX 78744
Study Dates	December 21, 2009 - March 19, 2010
Objectives	Food effect; single-dose PK and relative BA
Formulation	Treatment / TPM / A: USL255 capsule, 200 mg; Batch # 268049; Lot #: 267879 / B: Topamax IR tablet, 100 mg; Lot # 9CG569
Study Design	• Phase 1, randomized, single-center, open-label, 3-way crossover study in 36 healthy males and females, aged 18-65 years, to compare the BA of USL255 200 mg administered in the fasted and fed conditions and to a single daily dosing of 100 mg Topamax® every 12 hours with the first dose administered in the fasted condition. • For fed condition, subjects received a standardized high-fat breakfast that was consumed within 30 min before dosing. • Duration of study: 12 weeks (4 weeks for Screening, 3 dosing periods, with ~3 weeks for washout between periods).
PK Assessment	Plasma PK samples: • USL255: predose, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 48, 72, 96, 120, 168, 216, 264, and 336 h postdose • Topamax: 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 24, 48, 72, 120, 168, 216, 264, and 336 h postdose • AUC0-t, AUC0-∞, f_{ext} (extrapolated fraction of AUC), Cmax, Tmax, kel, t1/2.
Statistical Analysis	Descriptive statistics were calculated for plasma concentrations and PK Parameters. A mixed effect ANOVA model was performed on log-transformed exposure measures. Point estimates and 90% CI for geometric mean ratios were computed for treatments (USL255 fed vs. USL255 fasted;

Reference ID: 3464886

<table>
<tr><td></td><td>fasted USL255 vs. Topamax®) for the log-transformed AUC0-t, AUC∞, and Cmax, judged by acceptance criteria of 80-125%.</td></tr>
<tr><td>Bioanalytical Methods</td><td>

Table. Assay performance

<table>
<tr><td>Analyte</td><td></td><td>Topiramate (plasma)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Method:</td><td></td><td>HPLC/MS/MS</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Standard Curve:</td><td>Range:</td><td>10.00 – 10000 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>R:</td><td>0.9989</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Precision:</td><td>9.50 - 4.27%</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Accuracy:</td><td>-1.28 - 1.87%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>LOQ:</td><td></td><td>10 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td>QC:</td><td></td><td>30 ng/mL</td><td>80 ng/mL</td><td>300 ng/mL</td><td>1200 ng/mL</td><td>7500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>10.4%</td><td>7.44 %</td><td>7.51 %</td><td>7.03 %</td><td>8.58 %</td></tr>
<tr><td></td><td>Accuracy:</td><td>-0.872 %</td><td>-0.178 %</td><td>-1.16%</td><td>-0.361 %</td><td>-1.63 %</td></tr>
</table>

- Bioanalytical site: (b) (4)

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

</td></tr>
<tr><td>Population/ Demographics</td><td>

- Similar demographics and baseline characteristics across treatment groups. Most subjects were white (88.9%) with a mean age of 37.5 years (20-62 years). There were the same numbers of male and female subjects.
- All subjects treated with at least 1 dose of either formulation and had sufficient PK samples for accurate estimation of PK parameters were included for PK analysis. Subject 123 was discontinued before receiving the Topamax® treatment
- The BE population included the subjects in the PK population who completed both the fed and fasted USL255 dosing periods, or both the fasted USL255 and Topamax® dosing periods.

</td></tr>
<tr><td>PK Results</td><td>

Figure 1. Mean plasma concentration - time curves by treatment

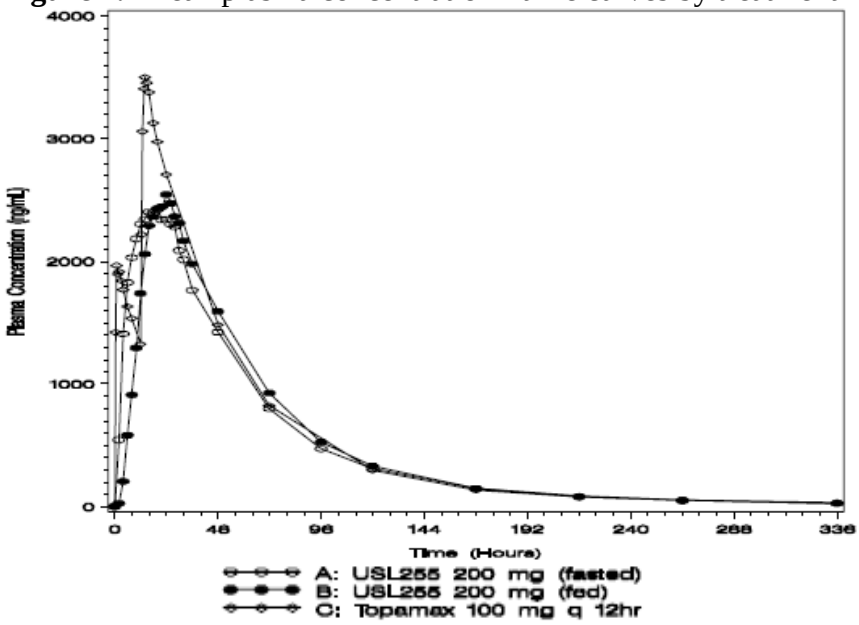


Table 1. Summary of pharmacokinetic parameters by treatment

</td></tr>
</table>

Pharmacokinetic Parameter	Treatment		
	200 mg USL255 Fasted (n=35)	200 mg USL255 Fed (n=36)	100 mg Topamax® (n=35)
C_{max} (ng/mL)	2,757 (840)	2,732 (848)	3,780 (650)
$AUC_{0-\infty}$ (ng•hr/mL)	173,784 (44,667)	169,611 (43,932)	186,926 (39,696)
AUC_{0-t} (ng•hr/mL)	170,068 (43,947)	166,061 (43,554)	183,105 (39,014)
k_{el} (hr^{-1})	0.0089 (0.0015)	0.0090 (0.0013)	0.0086 (0.0014)
$t_{1/2}$ (hr)	80.2 (14.2)	78.6 (10.9)	82.8 (14.4)
T_{max} (hr)[a]	20 (8, 36)	24 (14, 32)	14 (12.5, 18)

a Tmax: median (min, max)

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

Pharmacokinetic Parameter	Treatment	N	Geometric LSM	USL255-MD Fed/ USL255-MD Fasted Geometric LSM		
				Ratio	90% CI	
AUC_t (µg·h/mL)	USL255MD 200 mg SD, Fed	35	159	0.97	0.90	1.05
	USL255MD 200 mg SD, Fasted	35	165			
AUC_∞ (µg·h/mL)	USL255MD 200 mg SD, Fed	35	163	0.97	0.90	1.04
	USL255MD 200 mg SD, Fasted	35	168			
C_{max} (µg/mL)	USL255MD 200 mg SD, Fed	35	2.60	0.99	0.89	1.09
	USL255MD 200 mg SD, Fasted	35	2.64			

* Subjects 130 was excluded from the analysis due to insufficient concentration data for PK analysis.

Table 3. Summary of statistical analysis (USL255 vs. Topamax)

Parameter	Treatment	N	Geometric LSM	Ratio of Geometric LSM (USL 200 mg, fasted/Topamax® 100 mg Every 12 Hours Treatment)	90% CI of Ratio (USL 200 mg, fasted/Topamax® 100 mg Every 12 Hours Treatment)
AUC_{0-t} (ng•hr/mL)	USL255 Fasted	34	162,973.1		
	Topamax® [a]	34	178,968.7	0.91	0.87 - 0.95
$AUC_{0-\infty}$ (ng•hr/mL)	USL255 Fasted	34	166,687.9		
	Topamax® [a]	34	182,720.4	0.91	0.87 - 0.95
C_{max} (ng/mL)	USL255 Fasted	34	2,590.18		
	Topamax® [a]	34	3,721.00	0.70	0.65 - 0.74

* Subjects 123 (did not meet the Topamax BE Population criteria) and 130 were excluded from the analysis.
a Single day dosing, every 12 hours.

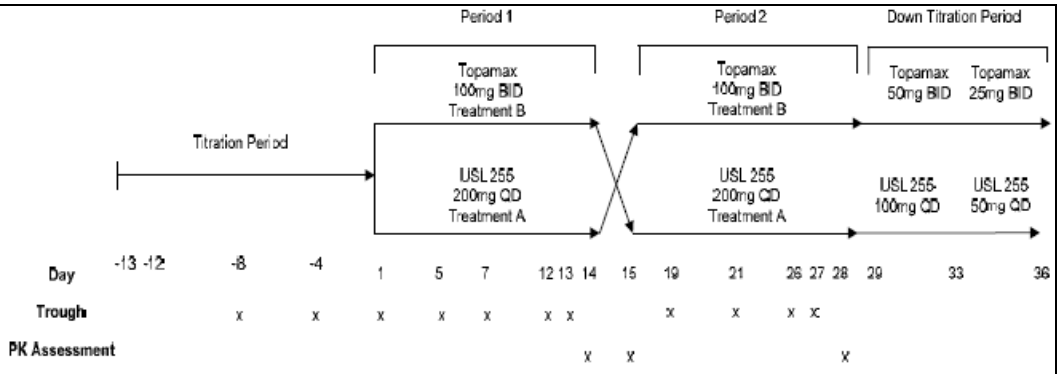
Median Tmax values were 20 h and 24 h under fasted and fed conditions, respectively.

Safety	• No deaths, SAEs, or AEs that led to discontinuation • Most common TEAEs: dizziness, paraesthesia, feeling drunk, nausea, headache, and thinking abnormal. • Most TEAEs were treatment-related and were mild in severity and were

	resolved. • Numbers of subjects who experienced TEAEs after USL255 under fasted and fed conditions were the similar.
Conclusion	• The point estimates and the corresponding 90% CI for the ratio of means for the single-dose AUC0–t, AUC∞, and Cmax were contained within the acceptance BE limits of 0.8-1.25, indicating that food had insignificant effect on topiramate plasma exposure after administration of USL255. • The Tmax for topiramate was delayed for approximately 4 hours (from 20 h) following single-dose administration of USL255 with food compared to fasted conditions, while t1/2 was not affected. • There was no significant differences in the plasma topiramate exposure (AUC0-t and AUC0-∞) when administered as a single oral dose of 200 mg USL255 compared with the 100 mg Topamax® every 12 hours treatment, supported by the BE results. However, the Cmax of topiramate from single-dose of 200 mg USL255 was approximately 30% lower than that from single-dose of 100 mg Topamax® every 12 hours treatment.
Comment	Food did not alter Tmax at steady-state compared to fasted conditions (Study P255-103). The totality of these results suggested that no dosage adjustment because of food is necessary.

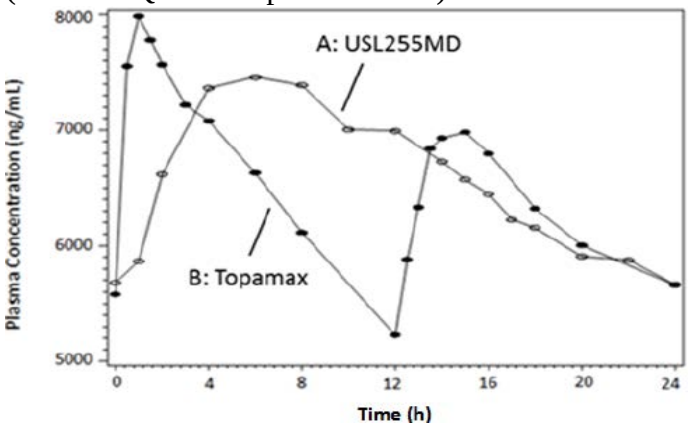
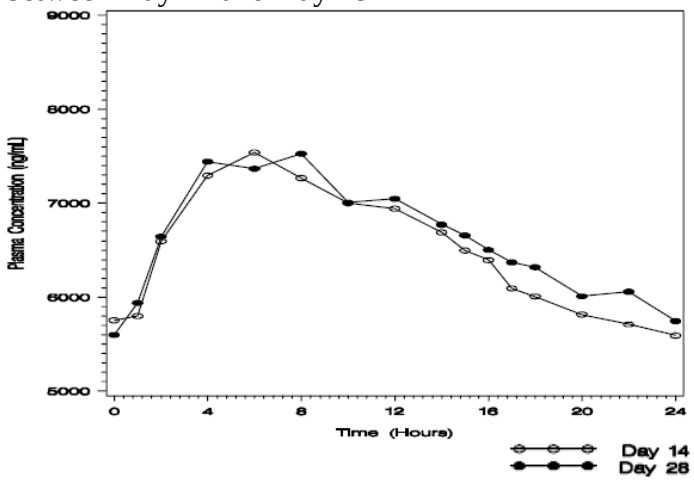
Study Report #	**P09-003**
Title	A Randomized, Single-Center, Open-Label, 2-way Crossover, Multi-Dose Pharmacokinetic Study of USL255 in Healthy Adult Subjects
Investigator/ Center	Ikenna Ogbaa, MD, PPD Phase I Clinic, 7551 Metro Center Drive, Building 10, Suite 200, Austin TX 78744
Study Dates	January 20, 2010 - April 20, 2010
Objectives	Comparison of Steady-state relative bioavailability
Formulation	TPM / Batch number USL255-50-MD capsule / 268047 USL255-200-MD capsule / 268049 Topamax IR tablet, 25 mg / 9CG506 (Lot#) Topamax IR tablet, 100 mg / 9CG566 (Lot#)
Study Design	• Phase 1, randomized (1:1 ratio), single-center, open-label, 2-way crossover study in 38 healthy males and females, aged 18-65 years, to assess the steady-state PK and relative BA between USL255 200 mg QD and daily dosing of 100 mg Topamax® BID under fasted condition. • Subjects were titrated up starting 50 mg/day and increasing in increments of 50 mg/day to reach the 200 mg/day target dose, and were maintained for a total of 14 days before the crossover. Steady-state PK samples were collected on Days 14, 15, and 28. Schematic of study design is as follows:

Reference ID: 3464886

<table>
<tr><td></td><td> 

Duration of study: 11 weeks (4 weeks for Screening, 2 week each for 2 dosing periods, with 2 weeks and 1 week for up- and down-titration periods, respectively).</td></tr>
<tr><td>PK Assessment</td><td>
USL255 QD: Predose, 1, 2, 4, 6, 8, 10, 12, 14, 15, 16, 17, 18, 20, 22, and 24h on Days 14, 15, and 28
Topamax BID: Predose, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, and 24h on Days 14, 15, and 28
Trough levels: during the up-titration period (Days -12, -8, and -4), Period 1 (Days 1, 5, 7, 12, and 13), and Period 2 (Days 19, 21, 26, and 27)
Steady-state PK: AUC0-τ, AUC0-24, Cmax, Tmax, Cmin, Cavg, FI (fluctuation index), Tss (time to steady-state), AUC0-p and AUCt1-t2
</td></tr>
<tr><td>Statistical Analysis</td><td>
A mixed effect ANOVA model was performed on log-transformed exposure measures and on untransformed FL%. Point estimates and 90% CI for geometric mean ratios were computed for treatment differences (USL255 vs. Topamax) for the ln-transformed steady-state AUC0-24, Cmax, and Cmin, judged by BE acceptance criteria of 80-125%.
Additional Point-to-point BE analyses were performed for ratios of partial AUC (AUCp) and partial AUC between two time-points (i.e., AUCt1-t2) over a 24-h period at steady-state, judged by BE acceptance criteria of 80-125%. Similar analysis was performed on topiramate concentrations, per request by the Agency on November 13, 2013.
The time to steady state was estimated by using the Helmert Contrast Transformation on the log-transformed trough concentrations.
Median Tmax was compared for each treatment using the nonparametric Wilcoxon rank sum test.
</td></tr>
<tr><td>Bioanalytical Methods</td><td>Table. Assay performance
<table>
<tr><td>Analyte</td><td></td><td>Topiramate (plasma)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Method:</td><td></td><td>HPLC/MS/MS</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Standard Curve:</td><td>Range:</td><td>10.00 – 10000 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>R:</td><td>0.9991</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Precision:</td><td>4.32 – 9.87%</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Accuracy:</td><td>-0.189 – 0.204%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>LOQ:</td><td></td><td>10 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td>QC:</td><td></td><td>30 ng/mL</td><td>80 ng/mL</td><td>300 ng/mL</td><td>1200 ng/mL</td><td>7500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>10.1%</td><td>10.2%</td><td>6.51%</td><td>6.20%</td><td>8.86%</td></tr>
</table></td></tr>
</table>

Reference ID: 3464886

	Accuracy: -1.82% 0.608% -0.253% -1.20% 0.06% • Bioanalytical site: (b) (4) Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.
Population/ Demographics	• Similar demographics and baseline characteristics across treatment groups. Most subjects were white (60.5%), followed by black or African American (36.8%), with a mean age of 35.6 years (20-62 years). There were the same numbers of male and female subjects. • 38 Randomized; 2 discontinued (Subjects 102 and 133) due to TEAEs after receiving Topamax; PK population = 36.
PK Results	**Figure 1.** Mean plasma topiramate concentration-time curves at steady-state (USL255 QD vs. Topamax ® BID)  **Figure 2.** Mean plasma topiramate concentration-time curves for USL255 QD between Day 14 and Day 28  **Table 1.** Summary of arithmetic mean (SD) of Topiramate Pharmacokinetic Parameters at steady-state

Pharmacokinetic Parameter	Day 14 and 28				Day 15			
	200 mg USL 255MD QD (n = 36)		100 mg Topamax® (Q12h) (n = 36)		200 mg USL 255MD QD (n = 17)		100 mg Topamax® (Q12h) (n = 19)	
	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV
$AUC_{0\text{-}24h}$ (µg·h/mL)	158 (31.6)	20.0	153 (33.2)	21.7	150 (23.9)	15.9	156 (39.3)	25.2
AUC_{tau} (µg·h/mL)	158 (31.6)	20.0	78.1 (16.8)	21.5	150 (23.9)	15.9	79.2 (19.6)	24.7
C_{max} (µg/mL)	7.88 (1.50)	19.1	8.43 (1.66)	19.7	7.51 (1.35)	18.0	8.36 (1.82)	21.8
t_{max} (h)[a]	6.00 (2.00, 17.00)	47.4	1.00 (0.50, 14.00)	157	6.00 (4.00, 10.18)	33.8	1.58 (0.50,14.07)	126
C_{min} (µg/mL)	5.31 (1.19)	22.4	5.03 (1.21)	24.1	5.02 (0.914)	18.2	5.14 (1.44)	28.0
C_{avg} (µg/mL)	6.60 (1.31)	20.0	6.51 (1.40)	21.5	6.25 (0.996)	16.0	6.60 (1.63)	24.7
FI	0.40 (0.11)	26.5	0.53 (0.12)	21.9	0.40 (0.11)	27.4	0.50 (0.12)	23.8

a. Tmax: median (range)

* FI: Ratio of geometric LSM (USL255/Topamax) and 90% CI: 0.74 (0.68-0.80)

Table 2. Statistical analysis for relative bioavailability of 200-mg dose of USL255 vs. Topamax ® at steady-state on Day 14 and Day 28

Parameter	N	USL255 (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B)	90% CI
AUC0–24h (µg·h/mL)	36	155	150	1.04	(1.02, 1.05)
Cmax,ss (µg/mL)	36	5.16	4.88	1.06	(1.03, 1.08)
Cmin,ss (µg/mL)	36	7.71	8.26	0.93	(0.90, 0.97)

Table 3. Statistical analysis for relative bioavailability of 200-mg dose of USL255 vs. Topamax ® on Day 14 and Day 15

Pharmacokinetic Parameter	USL255-MD to Topamax®			Topamax® to USL255-MD		
	Geometric LSM		Ratio of Geometric LSM[a] (90% CI)	Geometric LSM		Ratio of Geometric LSM[a] (90% CI)
	USL255-MD 200 mg QD Day 14 (n = 19)	Topamax® 100 mg Q12h Day 15 (n = 19)		Topamax® 100 mg Q12h Day 14 (n = 17)	USL255-MD 200 mg QD Day 15 (n = 17)	
$AUC_{0\text{-}24h}$ (µg·h/mL)	152	150	0.99 (0.97-1.02)	147	148	1.01 (0.98-1.04)
AUC_{tau} (µg·h/mL)	152	76.7	NA	75.0	148	NA
C_{min} (µg/mL)	5.05	4.95	0.98 (0.93-1.03)	4.89	4.95	1.01 (0.99-1.04)
C_{max} (µg/mL)	7.62	8.14	1.07 (1.02-1.12)	8.20	7.40	0.90 (0.86-0.95)
C_{avg} (µg/mL)	6.32	6.39	1.01 (0.98-1.04)	6.25	6.18	0.99 (0.96-1.02)

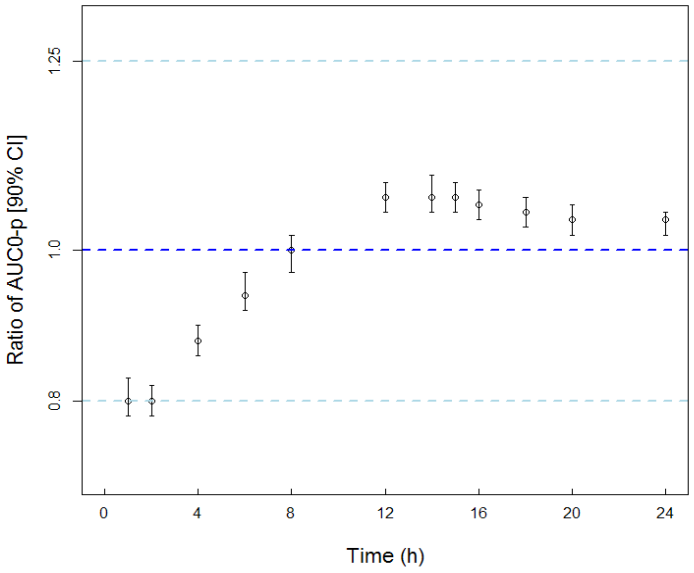
Steady-State Analysis: the 200mg USL255 QD reached steady-state on Day 5, whereas Topamax® 100 mg twice daily dosing reached steady-state on Day 7.

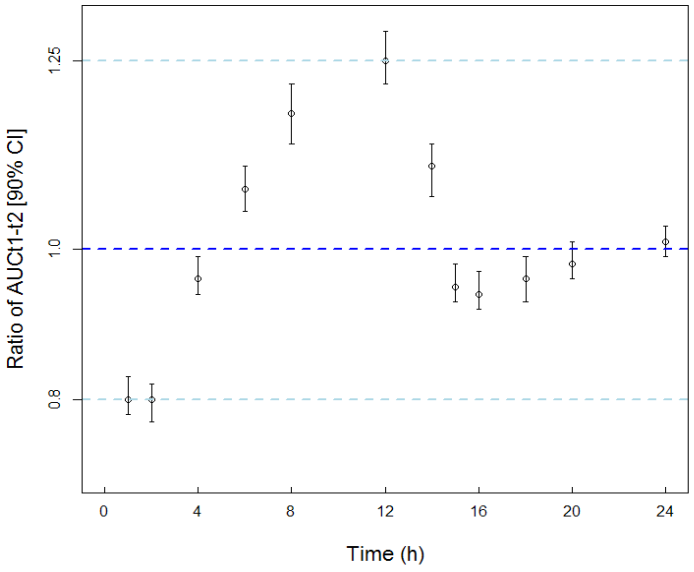
Point-to-Point Comparisons:

In addition to the BE analysis for partial AUC (AUC0-p), the applicant submitted additional BE analysis results for comparing the ratios of point-to-point partial AUC between two time-points (i.e., AUCt1-t2) to further examine and assure the plasma profile similarity. Similar analysis was performed on

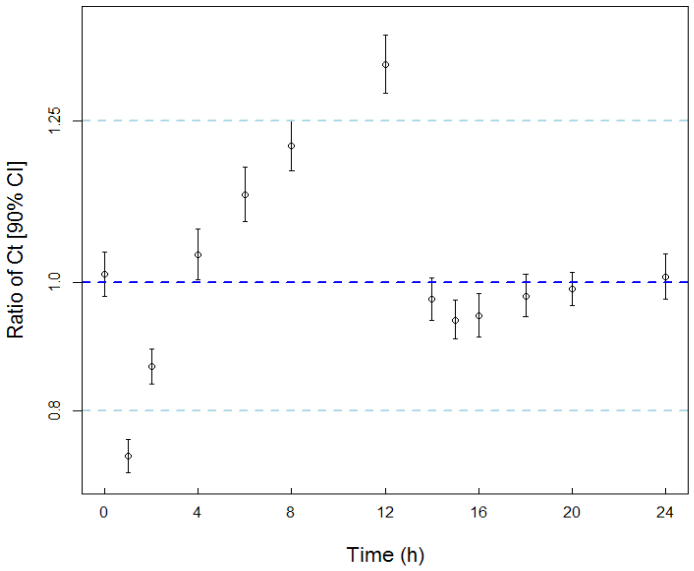
topiramate concentrations, per request by the Agency on November 13, 2013. Results of BE analyses are presented in Figures (created by this Reviewer) below.

Figures 3~5. Analysis of point-to-point partial AUC (AUC0-p), partial AUC between two time-points (AUCt1-t2), and topiramate concentrations





The 90% CIs of few time points (i.e., around 0-2h and 12h) fell outside the BE limits. Additional analysis for the partial AUCs (AUC1-12h, AUC6-12h, AUC12-18h, and AUC18-24h) showed the BE of drug exposure during these time periods from two formulations (data not presented here).

	 The time points (C1h and C12h) corresponding to the trough of TOPAMAX® BID profile where the 90% CIs fell outside the BE limits.
Safety	• No deaths or SAEs • Similar percentage of TEAEs: USL255 (61/1%) vs. Topamax (65.8%), all being mild in severity. • No clinical lab abnormality
Conclusions	• The 90% CI's for the geometric mean ratios for the steady-state exposure measures (AUC0-24, Cmax, and Cmin) between treatments were within the BE acceptance criteria (80-125%), indicating the bioequivalence between 200-mg USL255 QD and 100-mg Topamax BID. • Lower percent fluctuation (FI) at steady-state were observed for USL255 (0.4) compared to Topamax Tablets (0.53). • The 90% CI's for the geometric mean ratios for the topiramate exposure (AUC0-24, Cmax, and Cmin) between treatments on Day 14 and Day 15 (after the crossover) were within the BE acceptance criteria (80-125%). • USL255 BID reached steady state on Days 5. • Point estimates and the 90% CIs for the ratios of partial AUC (AUC0-p) and partial AUC (AUCt1-t2) at each corresponding time point of the 24-hour plasma concentration-time curves at steady-state for the two formulations were mostly within the 80-125% BE limits, with exception of the 90% CIs of few time points around 0-2h and 12h fell outside the BE limits but were deemed not clinically significant.. • Point estimates and the 90% CIs for the ratios of point-to-point topiramate plasma concentration of the 24-hour curves for the two formulations were mostly within the 80-125% BE limits, except for time points approximately 1 h and 12 h where the 90% CIs fell slightly outside the BE limits but were deemed not clinically significant.
Comment	In addition to the BE of overall exposure parameters, three new PK parameters

	(AUC0-p, AUCt1-t2, and Ct) were also BE. The few deviations outside the lower BE limit are not considered clinically significant based on the available information for topiramate. In addition, the topiramate levels are within the reported therapeutic window. The applicant has provided compelling evidence that two PK curves of the proposed USL ER capsule and the reference Topamax IR tablet are sufficiently similar to warrant similar clinical outcome.

Study Report #	**P255-102**
Title	A Randomized, Single-Center, Open-Label, Single Dose, Four-Way Crossover Study to Compare the Oral Relative Bioavailability of Three Formulations of USL255 and Sprinkles Administration in Healthy Adult Subjects Under Fasting Conditions
Investigator/ Center	Mark T. Leibowitz, MD, Worldwide Clinical Trials Early Phase Services, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, TX 78217
Study Dates	October 04, 2011 - January 12, 2012
Objectives	Single-dose relative BA of MK (b) (4) vs. MK-D capsule, MD vs. MK-D capsule, and MK-D capsule vs. sprinkled content onto soft food
Formulation	Treatment / TPM ER / Batch # A / USL255-200-MK (b) (4) ((b) (4) site; TBM) / 296805 B / USL255-200-MD (Phase 1) / 268049 C / USL255-200-MK-D (Denver site; TBM) / 296804 D / USL255-200-MK-D (Denver site; TBM) / 296804
Study Design	• Phase 1, randomized, single-center, open-label, single-dose, 4-way crossover study in 36 healthy males and females (9 per treatment sequence), aged 18-65 years, to compare the BA of three USL255 200 mg formulations (MD, MK (b) (4) and MK-D) under fasted conditions. In addition, content of USL255 200 mg (MK-D) sprinkled onto a tablespoon of applesauce and swallowed was compared to USL255 capsule swallowed intact after an overnight fast. • PK blood samples up to 336 h postdose were collected from all Treatment periods. • Duration of study: 15 weeks (4 weeks for Screening, 4 dosing periods, with ~3 weeks for washout between periods).
PK Assessment	• Plasma PK samples: predose, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 48, 72, 96, 120, 168, 216, 264, and 336 h postdose • AUC0-t, AUC0-∞, Cmax, f_{ext}, Tmax, kel, t1/2.
Statistical Analysis	• Descriptive statistics were calculated for plasma concentrations and PK Parameters. A mixed effect ANOVA model was performed on ln-transformed topiramate exposure measures. • Point estimates and 90% CI for geometric mean ratios were computed for treatments differences (B/D, C/D, and A/D) for the log-transformed AUC0-t, AUC∞, and Cmax, judged by acceptance BE criteria of 80-125%.
Bioanalytical Methods	**Table.** Assay performance

Reference ID: 3464886

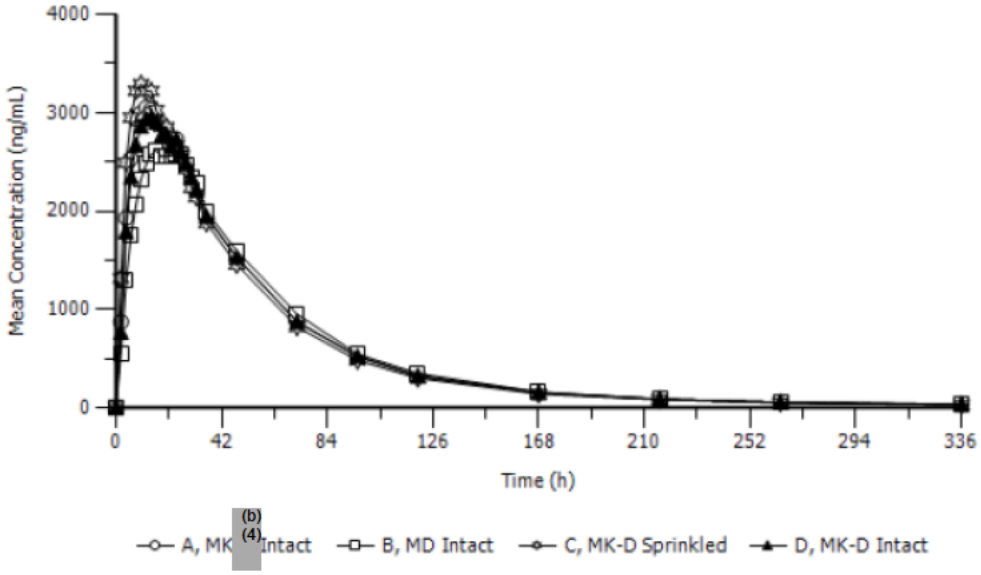
<table>
<tr><td></td><td>
<table>
<tr><td>Analyte</td><td colspan="2">Topiramate (plasma)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Method:</td><td colspan="2">HPLC/MS/MS</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Standard Curve:</td><td>Range:</td><td>10.00 – 10000 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>R:</td><td>0.9990</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Precision:</td><td>3.90 – 9.28%</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Accuracy:</td><td>-1.85 – 3.18%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>LOQ:</td><td colspan="2">10 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td>QC:</td><td></td><td>30 ng/mL</td><td>80 ng/mL</td><td>300 ng/mL</td><td>1200 ng/mL</td><td>7500 ng/mL</td></tr>
<tr><td></td><td>Precision:</td><td>9.31%</td><td>8.27%</td><td>6.51%</td><td>6.36%</td><td>5.81%</td></tr>
<tr><td></td><td>Accuracy:</td><td>-1.81%</td><td>-4.05%</td><td>-3.17%</td><td>-2.20%</td><td>-2.72%</td></tr>
</table>
• Bioanalytical site: (b) (4)
Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.
</td></tr>
<tr><td>Population/ Demographics</td><td>
• Similar demographics and baseline characteristics across treatment groups. Most subjects were white (80.6%) with a mean age of 41.3 years (18-64 years) and mean BMI of 26.2 kg/m^2 (19.1 to 29.7). Male: female=20:16
• 36 subjects completed at least one period of the study and were included in the PK statistical analyses. The BE population included the subjects in the PK population who completed both treatment periods being compared. Data from 33 subjects (dosed in Treatments A, C, and D) and 31 subjects (dose in Treatment B) were included in the PK analysis.
</td></tr>
<tr><td>PK Results</td><td>
Figure 1. Mean plasma concentration - time curves by treatment


Table 1. Summary of pharmacokinetic parameters by treatment
</td></tr>
</table>

Parameter	Treatment A: USL255 200 mg Formulation MK (b) (4) Intact				Treatment B: USL255 200 mg Formulation MD Intact			
	n	Arithmetic Mean	SD	CV%	n	Arithmetic Mean	SD	CV%
T_{max} (h)*	33	12.00	NA	NA	31	24.00	NA	NA
C_{max} (ng/mL)	33	3339.5	658.83	19.73	31	2896.9	736.52	25.42
AUC_{0-t} (h•ng/mL)	33	189590	33932	17.90	31	184190	35769	19.42
AUC_{0-inf} (h•ng/mL)	30	193930	35764	18.44	30	187260	35969	19.21
f_{ext} (%)	30	2.19	1.17	53.54	30	2.33	1.15	49.20
k_{el} (h^{-1})	30	0.0089	0.0017	18.77	30	0.0087	0.0016	18.28
$t_{1/2}$ (h)	30	80.65	18.52	22.96	30	82.28	16.47	20.02

Parameter	Treatment C: USL255 200 mg Formulation MK-D Sprinkled				Treatment D: USL255 200 mg Formulation MK-D Intact			
	n	Arithmetic Mean	SD	CV%	n	Arithmetic Mean	SD	CV%
T_{max} (h)*	33	10.00	NA	NA	33	14.00	NA	NA
C_{max} (ng/mL)	33	3425.9	606.61	17.71	33	3189.4	700.43	21.96
AUC_{0-t} (h•ng/mL)	33	187950	33225	17.68	33	187970	34059	18.12
AUC_{0-inf} (h•ng/mL)	32	192690	34166	17.73	32	191780	34836	18.16
f_{ext} (%)	32	2.07	0.89	43.02	32	2.23	1.14	51.16
k_{el} (h^{-1})	32	0.0086	0.0015	17.31	32	0.0090	0.0022	23.90
$t_{1/2}$ (h)	32	83.65	17.11	20.45	32	81.51	21.86	26.82

* Tmax: median (range)

Table 1. BE analysis for USL255-MD (B) vs. USL255-MK-D (D)

Parameter	N	Treatment B LS	Treatment D LS	Geometric Mean	90% CI
Cmax (µg/mL)	31	2.9	3.3	0.90	(0.857, 0.949)
AUC0-t (µg h/mL)	31	18	19	0.97	(0.944, 1.008)
AUC0-∞ (µg·h/mL)	29	19	19	0.98	(0.950, 1.016)

Table 2. BE analysis for USL255-MK-D Sprinkled (C) vs. USL255-MK-D intact (D)

Parameter	N	Treatment C (LS	Treatment D (LS	Geometric Mean	90% CI
Cmax (µg/mL)	31	3.5	3.3	1.08	(1.033,1.143)
AUC0-t (µg·h/mL)	31	19	19	1.00	(0.974, 1.040)
AUC0-∞ (µg h/mL)	29	20	19	1.01	(0.982, 1.049)

Table 3. BE analysis for USL255-MK (b) (4) (A) vs. USL255-MK-D (D)

Parameter	N	Treatment A LS	Treatment D LS	Geometric Mean	90% CI
Cmax (µg/mL)	30	3.4	3.3	1.05	(0.998, 1.105)
AUC0-t (µg h/mL)	30	19	19	1.01	(0.980, 1.047)
AUC0-∞ (µg·h/mL)	27	19	19	1.01	(0.979, 1.047)

Safety

- Similar percentages of subjects who experienced TEAEs after each formulation: ranging 36.4 ~ 48.5%
- Most common TEAEs: nausea, dizziness, headache, and paraesthesia.
- In general, no formulation-related differences were reported in AEs, clinical laboratory results, vital sign measurements, ECG results, assessments of suicidality, and physical examination findings.
- Subject 024 received MD formulation in Treatment B developed SAEs (hypotension) which were judged to be probably related to study medication.

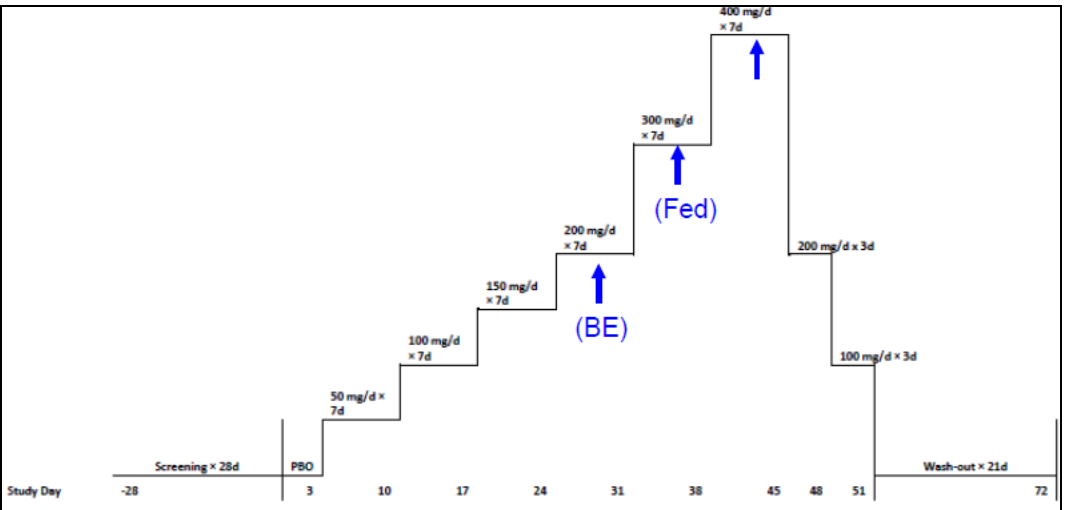
	• Subject 026 received the final dose of MD formulation in Treatment B developed SAE (hospitalization) which was judged to not related to study medication.
Conclusion	• The point estimates and 90% CIs showed that Phase 1 formulation (MD) is bioequivalent with the to-be-marketed formulation (MK), suggesting that results of PK characterization in Phase 1 studies are supportive of dosing regimen and labeling. • Results also showed that to-be-marketed formulation manufactured at (b) (4) (MK (b) (4)) and Denver (MK-D) sites are bioequivalent. • The USL255 200 mg MK-D capsule contents when sprinkled onto applesauce and swallowed under fasting conditions was bioequivalent to the same formulation administered intact under fasting conditions.

Study Report #	**P255-103**
Title	Crossover Study of USL255 and Immediate-release Topiramate Effects on Cognition and Steady-state Pharmacokinetics in Healthy Adult Subjects
Investigator/ Center	Terry E. O'Reilly, MD, Celerion, 2420 West Baseline Road, Tempe, Arizona 85283
Study Dates	May 12, 2012 - October, 13 2012
Objectives	Comparison of steady-state PK of USL255 QD and Topamax® BID; dose-proportionality; food effect at steady-state; safety and tolerability
Formulation	TPM / Lot # USL255-50-MJ capsule / 283256 USL255-100-MJ capsule / 283261 USL255-200-MJ capsule / 283269 Topamax 25 mg tablet / 1LG202 Topamax 50 mg tablet / LG215
Study Design	• Phase 1, randomized (1:1 ratio), single-center, open-label, 2-period crossover study in 48 healthy males and females, aged 18-55 years, to assess the steady-state PK comparison between USL255 200 mg every evening (QPM) and 100 mg Topamax® BID, as well as cognition, mood and alertness. Treatment sequences are as follows:

Treatment Sequence	Period 1	Period 2
AB	A (USL255 QPM dosing)	B (Topamax® Q12H)
BA	B (Topamax® Q12H)	A (USL255 QPM dosing)

• Study drug titration details are outlined in the schematic of study design below:

Reference ID: 3464886

	 • PK profiles for 24 h were obtained at 200 and 400 mg/day doses to assess steady-state PK parameters. PK equivalence was assessed at the 200 mg/day dose. • Duration of study: 144 days (72 days each for Periods 1 and 2, with a 21 days washout period between Periods).
PK Assessment	• USL255 QPM: Predose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 24 h post PM doses on Days 30 and 44 • Food effect: Predose, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, and 24 h post PM dose on Day 37 • Assessing steady-state: Cmin on Days 27, 28, 29, 34, 35, 36, 41, 42 and 43 • Dose proportionality: Days 10, 17 and 24. • PK parameters: AUC0-τ, AUC0-24, Cmax, Tmax, Cmin, Cavg, FI (fluctuation index), AUC0-p and AUCt1-t2
Statistical Analysis	• BE assessment: A mixed effect ANOVA model was performed on log-transformed exposure measures and on untransformed FL%. Point estimates and 90% CI for geometric mean ratios were computed for treatment differences (USL255 vs. Topamax) for the ln-transformed steady-state AUC0-24, Cmax, and Cmin, judged by BE acceptance criteria of 80-125%. • Additional Point-to-point BE analyses were performed for ratios of partial AUC (AUCp) and partial AUC between two time-points (i.e., AUCt1-t2) over a 24-h period at steady-state, judged by BE acceptance criteria of 80-125%. Similar analysis was performed on topiramate concentrations, per request by the Agency on November 13, 2013. • Attainment of steady state: estimated by using the Helmert Contrast Transformation on the log-transformed trough concentrations for 200~400 mg/day doses. • Dose-proportionality: for Cmin at 50, 100, 150, 200, 300, and 400 mg/day dose levels (dose proportionality on Cmin values was declared when the ratio of dose-normalized, predicted geometric mean values (Rdnm) and its 90% CI lay completely within 0.80~1.25); for Cmax and AUC0-24 for 200 and 400 mg/day doses. Dose

<table>
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- Food effect: for USL255 300 mg/day doses fed vs. 200 mg/day fasted, based on BE criteria.

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<tr><td>Bioanalytical Methods</td><td>

Table. Assay performance

Analyte		Topiramate (plasma)				
Method:		HPLC/MS/MS				
Standard Curve:	Range:	20.00 – 20000 ng/mL				
	R:	0.9974				
	Precision:	3.70 – 9.04%				
	Accuracy:	-3.73 – 2.79%				
LOQ:		20 ng/mL				
QC:		60 ng/mL	150 ng/mL	600 ng/mL	2500 ng/mL	15000 ng/mL
	Precision:	9.68%	6.10%	4.21%	4.02%	11.4%
	Accuracy:	0.472%	-0.173%	0.108%	0.472%	-1.98%

- Bioanalytical site: [redacted] (b) (4)

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

</td></tr>
<tr><td>Population/ Demographics</td><td>

- 48 subjects randomized, 40 subjects completed the study, 8 subjects discontinued (Subjects 01112, 01128, and 01139 due to AEs; Subjects 01105 and 01146 withdrew consent for personal reasons; Subjects 01136 and 01160 due to noncompliance; Subject 01143 lost to follow-up); PK population = 45 for either formulation

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<tr><td>PK Results</td><td>

Figure 1. Mean plasma topiramate concentration-time curves at steady-state (USL255 QD vs. Topamax ® BID)

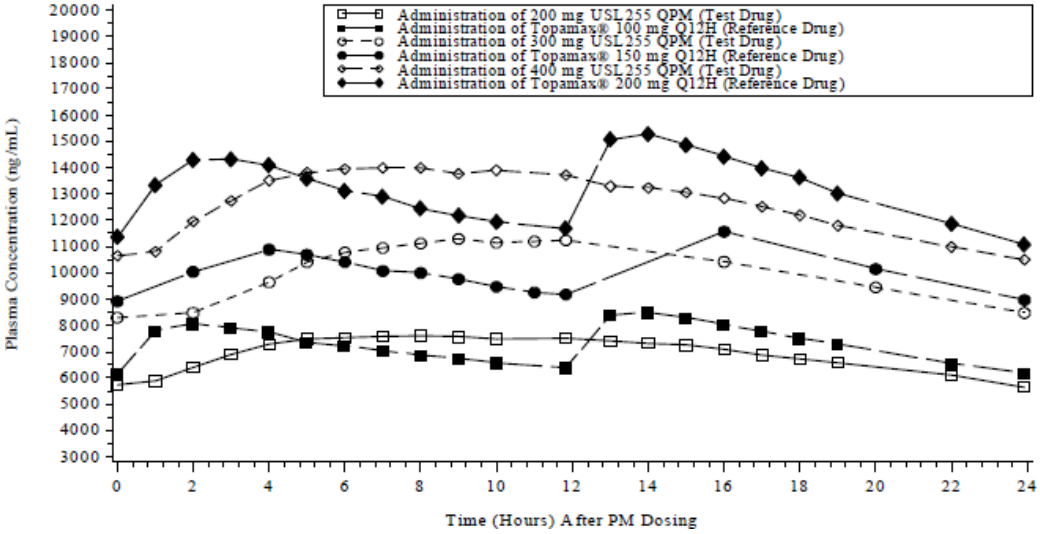

Table 1. Summary of arithmetic mean (SD) of Topiramate Pharmacokinetic Parameters at steady-state

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	Treatment					
	Day 30 and 31		Day 37 and 38		Day 44 and 45	
	USL255 200 mg QPM (n=44) Treatment A	Topamax® 100 mg Q12H (n=44) Treatment B	USL255 300 mg QPM (n=42) Treatment A	Topamax® 150 mg Q12H (n=43) Treatment B	USL255 400 mg QPM (n=42) Treatment A	Topamax® 200 mg Q12H (n=43) Treatment B
AUC_{0-24} (ng*hr/mL)	166000 ± 30300	175000 ± 29000	241000 ± 43100	242000 ± 35500	304000 ± 50800	316000 ± 46000
C_{max} (ng/mL)	7910 ± 1480	8890 ± 1500	11700 ± 2090	11700 ± 1630	14700 ± 2390	15900 ± 2380
C_{min} (ng/mL)	5440 ± 1130	5980 ± 1120	8030 ± 1660	8620 ± 1360	10100 ± 1860	10900 ± 1710
C_{avg} (ng/mL)	6930 ± 1260	7170 ± 1190	NC	NC	12700 ± 2120	13000 ± 1890
T_{max} (hr)	9.0 (4.0, 17)	13 (1.0, 4.0*)	9.0 (6.0, 12)	16 (2.0, 4.0*)	7.0 (2.0, 24)	13 (1.0, 6.0*)
AUC_{0-tau} (ng*hr/mL)	166000 ± 30300	86100 ± 14300	NC	NC	304000 ± 50800	156000 ± 22700
Fluctuation Index	0.360 ± 0.0834	0.410 ± 0.0842	NC	NC	0.371 ± 0.123	0.387 ± 0.0650

* No data were included for Subjects 01105 and 01139 (all TRTs), Subject 01112 (300 mg and 400 mg of TRTs B and all TRT A), Subject 01128 (300 mg and 400 mg of TRT B and all TRT A), Subject 01136 (300 mg and 400 mg of TRT A), Subject 01146 (all TRT A), and Subject 01160 (all TRT B).
** Tmax: median (range)

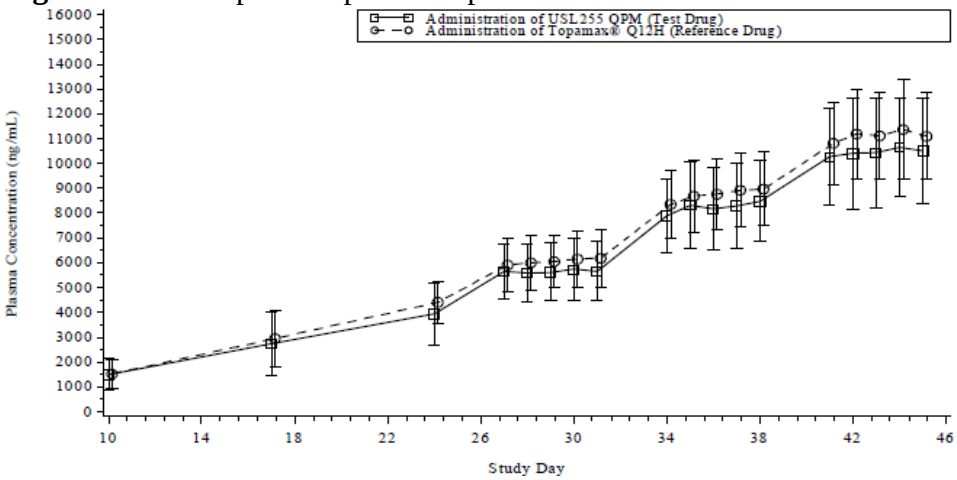
Table 2. Statistical analysis for relative bioavailability of USL255 200-mg QPM vs. Topamax ® BID at steady-state

Parameter	N	USL255 (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B)	90% CI
AUC0–24h (µg·h/mL)	36	163	174	0.942	(0.917, 0.967)
Cmax,ss (µg/mL)	36	7.77	8.81	0.882	(0.854, 0.911)
Cmin,ss (µg/mL)	36	5.31	5.92	0.970	(0.870, 0.925)

* FI: Ratio of geometric LSM (USL255/Topamax) and 90% CI: 0.879 (0.834-0.926)
** Subjects 01105, 01112, 01128, 01139, 01146, and 01160 were excluded from the analysis. Subjects 01105 and 01139 did not receive any of the treatments

Steady-State Analysis: Steady state under fasted conditions was attained 3 days after 200 and 400 mg/day QD doses, and 4 days after 300 mg/day QD dose under fed conditions for USL255.

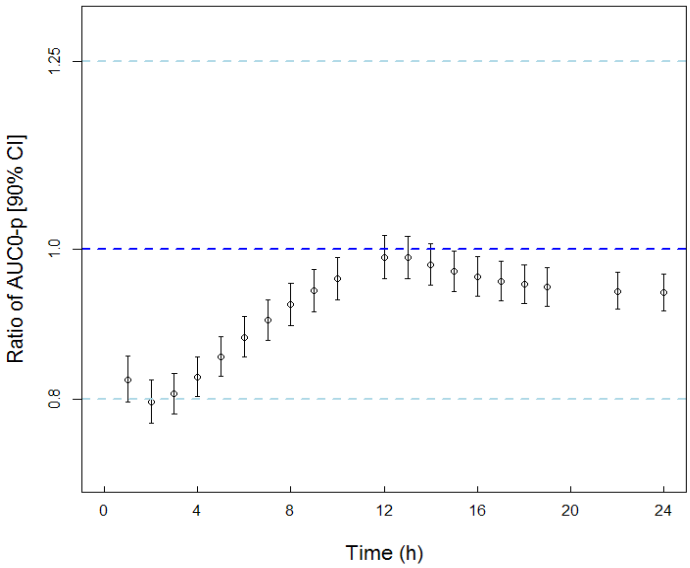
Figures 2. Mean predose plasma topiramate concentrations

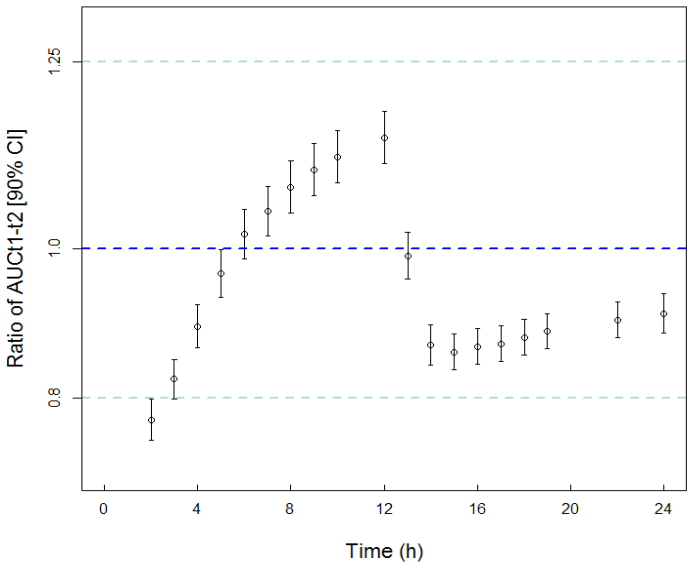


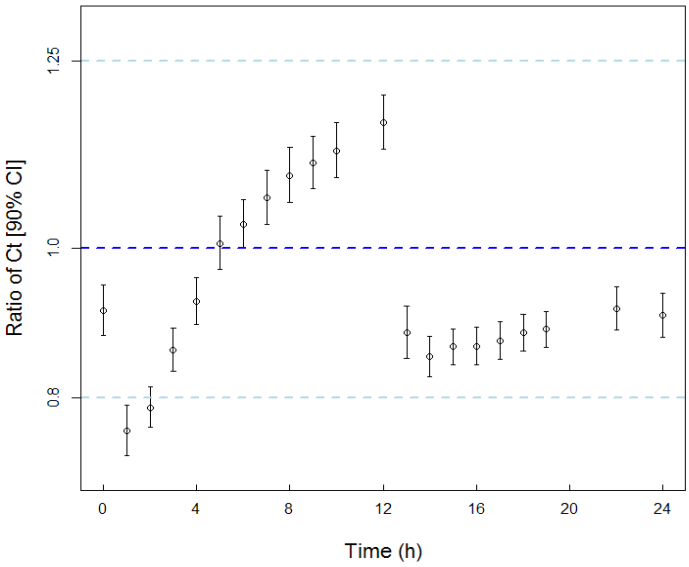
Point-to-Point Comparisons:
In addition to the BE analysis for partial AUC (AUC0-p), the applicant

submitted additional BE analysis results for comparing the ratios of point-to-point partial AUC between two time-points (i.e., AUCt1-t2) to further examine and assure the plasma profile similarity. Similar analysis was performed on topiramate concentrations, per request by the Agency on November 13, 2013. Results of BE analyses are presented in Figures (created by this Reviewer) below.

Figures 3~5. Analysis of point-to-point partial AUC (AUC0-p), partial AUC between two time-points (AUCt1-t2), and topiramate concentrations (normalized to 200 mg/day dose)







- Point estimates and the 90% CIs for the point-to-point comparisons of steady-state AUC0-p, AUCt1-t2, and topiramate plasma concentration over 24-h for the two formulations were mostly within the 80-125% BE limits. The 90% CIs of very few time points corresponding to the trough of TOPAMAX® BID profile (i.e., 0-3h) fell slightly outside the BE limits.

Dose-proportionality:
The dose-proportionality following multiple-dose administration of USL255 was concluded for predose Cmin over 100-400 mg dose range and for AUC0-24h and Cmax at steady-state over 200-400 mg dose range.

Figures 6. Assessment of Dose Proportionality at the USL255 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, and 400 mg QPM dose

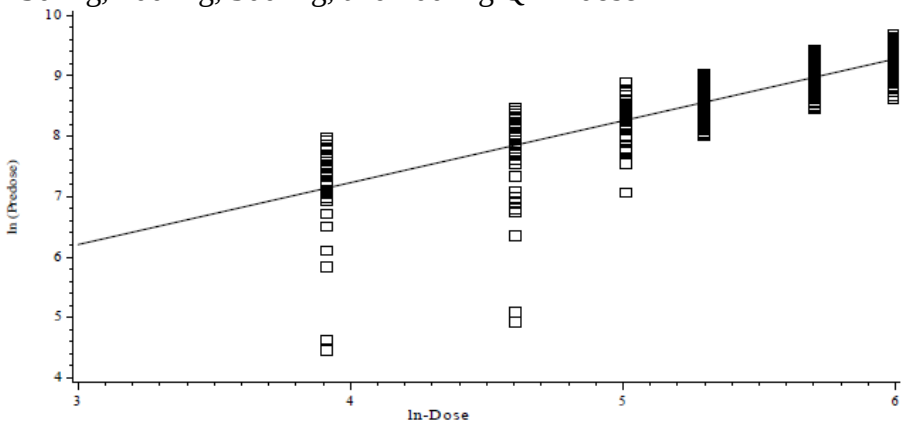


Table 3. Summary of statistical analysis for dose-proportionality

PK Parameter	Dose Range (mg)	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm (90% CI)	Conclusion

Predose Cmin (µg/mL)	50-400	(1.26, 10.6)	1.025 (0.938, 1.112)	1.05 (0.878, 1.263)	Proportional
Predose Cmin (µg/mL)	100-400	(2.56, 10.7)	1.029 (0.944, 1.114)	1.04 (0.925, 1.171)	Proportional

PK Parameter	Dose Range (mg)	Geometric Mean Ratio	90% CI
AUC0-24h (µg•h/mL)	200-400	1.09	(1.02, 1.16)
Cmax (µg/mL)	200-400	1.07	(1.00, 1.14)

Effect of food:

Table 4. Statistical analysis of the food effect on steady-state pharmacokinetic Parameters of Topiramate

Pharmacokinetic Parameter	USL255MJ 300 mg (Fed)	USL255MJ 200 mg (Fasted)	% Geometric Mean Ratio (Test/Reference)	90% Confidence Interval	
	Geometric LSM				
	Test	Reference		Lower	Upper
AUC_{0-24h} (µg·h/mL)	158	164	0.9686	0.9427	0.9953
C_{max} (µg/mL)	7.70	7.77	0.9911	0.9614	1.0218
C_{min} (µg/mL)	5.24	5.33	0.9835	0.9496	1.02

* Dose-normalized data at steady-state.
** Exposure values expressed as geometric means
*** Median Tmax values for fed and fasted were 9 h (6~12) and 9 h (5~17), respectively.

Safety	• No deaths or SAEs • 3 subjects were discontinued from the study due to AEs, 2 subjects with rash (one subject following each treatment) and one subject with increased heart rate (following Topamax®). • The most common drug-related AEs: headache, paresthesia and weight loss
Conclusions	• USL255 200 mg QPM capsules and reference Topamax® 100 mg Q12H tablets at the same daily dose were PK equivalent at steady-state under fasting conditions based on the BE acceptance criteria. • As shown in the Figures 3~5 above, point estimates and the 90% CIs for the ratios of steady-state partial AUC (AUC0-p), partial AUC between two time points (i.e., AUCt1-t2), and point-to-point topiramate plasma concentration at each corresponding time point of the 24-hour plasma concentration-time curves for the two formulations were mostly within the 80-125% BE limits. The 90% CIs of very few time points corresponding to the trough of TOPAMAX® BID profile (i.e., 0-3h) fell slightly outside the BE limits; however, the slight deviations are not considered clinically significant, considering the available information for topiramate (described in Section 2.2.3.1 of Question Based Review). • Steady-state was attained 3 days following USL255 200 mg and 400 mg QPM dosing and 4 days following USL255 300 mg QPM dosing. Steady-state was attained 6 days, 5 days, and 4 days following Topamax® 100, 150, and 200 mg Q12H dosing, respectively. • Predose concentrations increased proportionally with increasing USL255

	dose from 100 to 400 mg. In addition, total and peak exposures (AUC0-24 and Cmax, respectively) at steady-state increased proportionally with increasing USL255 dose, from 200 mg to 400 mg. • The ingestion of food had no effect on the bioavailability of USL255 300 mg dose at steady-state. Median Tmax values of 9 h of USL255 300 mg were similar between fed and fasted conditions.
Comment	In addition to the BE of overall exposure parameters, the additional analyses for point-to-point ratios of AUC0-p, AUCt1-t2, and Ct were also BE. Results supplemented the findings in Study P09-003 that two PK curves of the proposed USL ER capsule and the reference Topamax IR tablet are sufficiently similar to warrant similar clinical outcome.

Study Report	**Dose-Proportionality Report (Project No: 011063)**
Title	Dose Proportionality Assessment of Single-Doses of USL255 Based on Data From Two Pharmacokinetic Studies (P09-001 and P09-011)
Report Date	November 28, 2012
Objectives	Post-hoc analysis of USL255 clinical studies was to examine the dose-proportionality of single doses of 25-1400 mg.
Data Source	Data from 2 previously completed Phase 1 studies (P09-001 and P09-011) • Study P09-001: 25, 50, 100, 200 and 400 mg doses • Study P09-011: 600, 800, 1000, 1200 and 1400 mg doses
Population	Healthy men and women with BMI 18 kg/m2 to 30 kg/m2 who were 18-65 years of age in Study P09-001 and 18-45 years of age in Study P09-011
PK Parameters	• PK parameters: Cmax, AUC0-t, and AUC0-∞
Statistical Analysis	• Key assumption: the logarithm of the exposure parameter (area under the plasma concentration-time curve [AUC] or Cmax) is linearly related to the logarithm of the dose. • Power Model was used to assess the dose-proportionality: $AUC_{ij} = \beta_{0i} \times Dose_{ij}^{\beta 1i} \times exp(\varepsilon_{ij})$ $\beta_{0i} = \hat{\beta}_0 \times exp(\eta_{0i}),\ \beta_{1i} = \hat{\beta}_1 \times \exp(\eta_{1i})$ β_0: coefficient; β_1:exponent; η_{0i}: between-subject variability in the intercept; η_{1i}: slope; ε_{ij}: residual error • Dose proportionality is declared when the 90% CI for β1 lies completely within the critical region defined as: $1+\frac{ln(\theta_L)}{ln(r)}, 1+\frac{ln(\theta_H)}{ln(r)}$ R: ratio of the highest to lowest administered doses θ_L = 0.8, the lower critical limit of the ratio of dose-normalized mean values (Rdnm); and θ_H = 1.25, the upper critical limit of the Rdnm. • If dose proportionality is not declared for any of the PK parameters by the Smith criteria (θ_L=0.8, θ_H =1.25), the 90% CI for β_1 would be compared to a

Reference ID: 3464886

less stringent critical region based on θ_L=0.5 and θ_H=2.0 (Hummel criteria).

- The maximal dose ratio for which a conclusion of dose proportionality (ρ_1):

$$\rho_1 = \theta_H^{\left[\frac{1}{max(1-L,U-1)}\right]}$$

L = the lower 90% CI estimate for β_1
U = the upper 90% CI estimate for β_1

- Dose linearity was tested by fitting the following model:
  log(PK parameter) = a + b x *log(dose)* + Dose
- Additional ad-hoc analysis would be performed for 50-1400 mg or 100-1400 mg dose range if dose proportionality was not established for the entire range of 25-1400 mg.

Results

Table 1. Overall summary for mean (SD) of topiramate PK parameters following single dose of 25~1400mg USL255

	Treatment									
Pharmacokinetic Parameter	**25 mg USL255 (N=22)**	**50 mg USL255 (N=27)**	**100 mg USL255 (N=28)**	**200 mg USL255 (N=27)**	**400 mg USL255 (N=26)**	**600 mg USL255 (N=8)**	**800 mg USL255 (N=8)**	**1000 mg USL255 (N=8)**	**1200 mg USL255 (N=8)**	**1400 mg USL255 (N=8)**
AUC_{0-t} (ng×h/mL)	18,612 (5,317)	40,634 (8,856)	84,299 (19,437)	174,120 (40,922)	340,310 (70,955)	478,871 (86,762)	607,880 (84,641)	789,153 (104,944)	964,768 (153,644)	1,120,528 (256,765)
$AUC_{0-\infty}$ [a] (ng×h/mL)	20,424 (5,584)	43,175 (9,117)	87,188 (19,547)	174,735 (40,203)	342,655 (69,427)	465,112 (77,482)	613,144 (84,730)	805,068 (105,928)	970,048 (153,286)	1,124,174 (256,785)
C_{max} (ng/mL)	203 (67)	512 (132)	1,232 (343)	2,777 (616)	5,790 (1,335)	8,335 (1,618)	10,536 (1,559)	14,698 (2,134)	16,617 (3,333)	19,716 (4,518)
f_{ext} (%)	9.68 (4.55)	5.93 (2.94)	3.42 (1.83)	1.76 (0.86)	0.97 (0.37)	0.81 (0.41)	0.89 (0.47)	0.36 (0.17)	0.56 (0.29)	0.34 (0.15)
k_{el} (h^{-1})	0.0077 (0.0018)	0.0078 (0.0016)	0.0083 (0.0017)	0.0093 (0.0016)	0.0099 (0.0014)	0.0099 (0.0020)	0.0089 (0.0014)	0.0125 (0.0012)	0.0102 (0.0018)	0.0126 (0.0022)

Table 2. Summary of statistical analysis for dose-proportionality following single dose of 25~1400mg USL255

PK Parameter	Dose Range (mg)	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm (90% CI)	Conclusion
AUCt (µg•h/mL)	25-1400	(17.9, 1159)	1.04 (1.02, 1.05)	1.16 (1.09, 1.23)	Proportional*
AUC∞ (µg•h/mL)	25-1400	(19.7, 1142)	1.01 (0.995, 1.02)	1.03 (0.979, 1.09)	Proportional*
Cmax (µg/mL)	25-1400	(0.193, 22.7)	1.18 (1.16, 1.21)	2.10 (1.91, 2.30)	Not Proportional
Cmax (µg/mL)	50-1400	(0.493, 21.6)	1.13 (1.11, 1.16)	1.56 (1.43, 1.71)	Proportional**

* The 90% CI for slope was contained within the Smith limits (0.945, 1.055).
** Based on the Hummel limits (0.792, 1.208).

Table 3. Summary of statistical analysis of linearity following single dose of 50~1400mg USL255

PK Parameter	Dose Range (mg)	F-Statistic (p-value)	Conclusion
AUCt (µg•h/mL)	25-1400	0.86 (0.5627)	Linear
AUC∞ (µg•h/mL)	25-1400	0.51 (0.8678)	Linear
Cmax (µg/mL)	25-1400	2.54 (0.0095a)	Not Linear
Cmax (µg/mL)	50-1400	1.44 (0.1871)	Linear

a. Indicates deviation from linearity

Table 4. Summary of statistical analysis of log-transformed Cmax for

Reference ID: 3464886

100~1400 mg and 200~1400 mg doses

Dose Range	Predicted Geometric Mean		Slope Estimate (90% CI)			Rdnm (90% CI)[a]			Conclusion[b]
	Minimum	Maximum	Estimate	LCL	UCL	Estimate	LCL	UCL	
100 mg to 1400 mg	1185	20515	1.08	1.044	1.12	1.237	1.124	1.360	Proportional by Hummel limits criteria but not by Smith
200 mg to 1400 mg	2678	19754	1.03	0.978	1.08	1.073	0.944	1.221	Proportional by Smith and Hummel limits criteria

	Target Limits			
	Smith		Hummel	
100 mg to 1400 mg	0.915	1.085	0.737	1.263
200 mg to 1400 mg	0.885	1.115	0.644	1.356

a. Ratio of model-predicted geometric mean values for high and low dose, normalized for dose.
b. Dose proportionality was concluded if the 90% CI for slope was contained within the target limits for Smith or Hummel criteria.

Figure 1. Dose Proportionality of Cmax (25~1400 mg USL255)

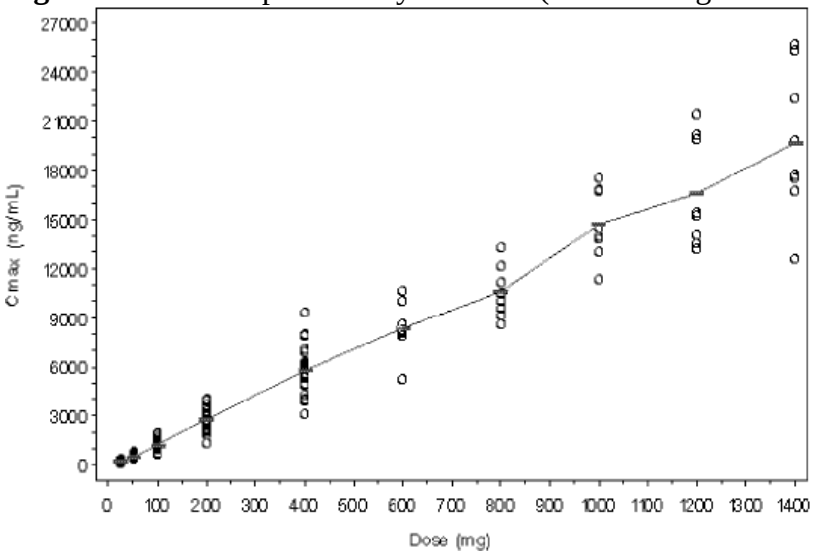


Figure 2. Dose Proportionality of AUC0-∞ (25~1400 mg USL255)

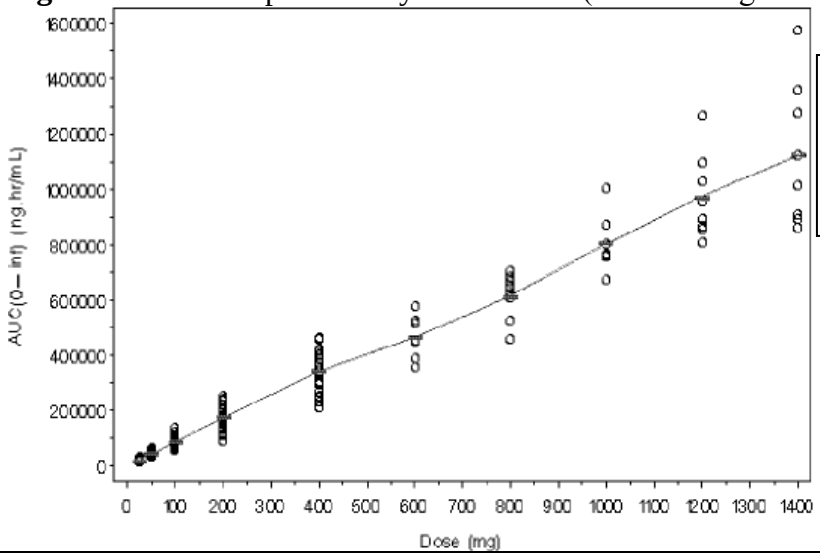


Figure for dose proportionality of AUC0-t is similar and thus is not presented.

Conclusion	Statistical analysis concluded the dose-proportionality and linearity for AUCs and Cmax values over a 25-1400mg (56-fold) and a 50-1400mg dose range, respectively.

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/s/

TA-CHEN WU
03/04/2014

YUXIN MEN
03/05/2014

CLINICAL PHARMACOLOGY REVIEW

NDA:	**205-122**
Brand Name:	BRANDNAME XR™
Generic Name:	Topiramate Extended-Release Capsules (USL255)
Sponsor:	Upsher-Smith Laboratories, Inc. (USL)
Dosage Form & Strength:	Extended Release (ER) Capsules (25mg, 50mg, 100mg, 150mg, and 200mg)
Indication:	Monotherapy for epilepsy for patients ≥10 years of age; Adjunctive therapy for epilepsy for adult and pediatric patients (b) (4) and for patients (b) (4) with seizures associated with Lennox-Gastaut Syndrome (LGS)
Submission:	505(b)(2), Standard
Submission Dates:	02/11/2013; 5/21/2013; 11/20/2013
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Ta-Chen Wu, Ph.D.
Team Leader:	Angela Yuxin Men, M.D., Ph.D.

Table of Contents

Reference ID: 3450667

1. Executive Summary

The applicant seeks approval of Brandname XR™ (topiramate extended-release or ER capsules; USL255) via 505(b)(2) application using the approved Topamax ® immediate-release (IR) tablets (NDA 20-505) as the reference list drug (RLD). The Sponsor is seeking a monotherapy and adjunctive therapy indications for patients with epilepsy ≥10 years old, instead of ≥2 years old for the RLD, due to marketing exclusivity for the Topamax® for "new patient population" (i.e., ≥2 to <10 years of age) listed in the FDA Orange Book. The Sponsor is not seeking indication for migraine. Brandname XR™ hypromellose capsules (25 mg, 50 mg, 100 mg, 150 mg, 150mg and 200 mg strengths) containing beads (b) (4) are developed for once-daily (QD) dosing.

In this submission, the applicant presented a clinical pharmacology-based method by demonstrating the bioequivalence (BE) of topiramate concentrations at multiple time-points within the 24 hours at steady-state between the proposed Brandname XR™ capsules given 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 Brandname 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 (AUC0-p), and partial AUC (AUCt1-t2) between two time-points of XR relative to IR in the pivotal relative bioavailability study (P09-003), as well as steady-state pharmacokinetics and cognition study (P255-103). This novel clinical pharmacology-based approach without an efficacy clinical trial has been utilized for gaining approval from the Agency for Trokendi XR® (NDA 201-635).

The clinical pharmacology program consists of nine Phase 1 studies in healthy adult volunteers assessing the steady-state relative bioavailability (BA) between Brandname XR™ capsules and the reference Topamax ® IR Tablets, dose linearity/proportionality following single doses across 25-1400 mg dose range, steady-state PK and cognition, food effect (200 mg and 300 mg), relative BA/BE between administration of intact Brandname XR™ and content sprinkled on applesauce, steady-state and BE between the clinical and proposed commercial formulations (200 mg) manufactured at different sites. Although the current submission is considered a clinical pharmacology-based application, the Sponsor did conduct one placebo-controlled efficacy clinical trial in epileptic patients (Study P09-004) and submitted the results to the Agency during review cycle to support the labeling. Biowaiver of in vivo relative BA study was requested for the 25 mg, 50 mg, 100 mg, and 150 mg strengths on the basis of formulation proportionality in active and inactive ingredients. The study for assessing the potential for alcohol-induced dose-dumping was not conducted in humans based on the in-vitro dissolution results and other supportive justifications.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 205-122 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) and dose-proportionality of topiramate were observed following single oral doses of Brandname XR™ over the dose range of 25 to 1400 mg for AUCs and 50 to 1400 mg for Cmax.
- The dose-proportionality following multiple-dose administration was demonstrated for Cmin over 100-400 mg and for Cmax and AUC0-24h over 200-400 mg dose range.
- The peak plasma concentrations (Cmax) of topiramate occurred at approximately 20 hours following single oral doses of Brandname XR™, and at approximately 6 hours at steady state.
- The mean terminal and effective half-life of topiramate was approximately 80 hours and 56 hours, respectively, following single oral doses of Brandname XR™.
- At steady-state, the AUC0-24hr, Cmax, and Cmin of topiramate from Brandname XR™ administered once-daily and the immediate-release tablet administered twice-daily were shown to be bioequivalent.
- Steady-state is reached in about 5 days after Brandname XR™ dosing.
- After multiple administrations of once-daily Brandname XR™, the mean peak-to-trough fluctuation (fluctuation index or FI) in plasma topiramate concentrations was approximately 26% lower than after immediate-release topiramate given twice daily.
- High-fat meal had no significant effect on topiramate plasma exposure after administration of Brandname XR™ following single or multiple doses.
- Administration of contents of Brandname XR™ capsule with applesauce in healthy young adult subjects did not have a significant effect on the bioavailability of topiramate, compared to Topamax® tablet.

Dose/Exposure-Response relationships:

Refer to OCP review for the approved topiramate ER drug product, Trokendi XR® (NDA 201-635). A similar exposure-response relationship for efficacy was established between steady-state Cmin 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). There

Reference ID: 3450667

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).

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

Results from a comparative PK study evaluating the Brandname XR™ capsules and the reference Topamax® IR tablets (Study P09-003 and P255-103) showed that two formulations are bioequivalent with respect to the overall exposure (AUCτ, Cmax, and Cmin) following repeat doses. Additional analyses showed that the point-to-point comparisons for topiramate partial AUC (AUC0-p), partial AUC between time-points (AUCt1-t2), and plasma concentrations are bioequivalent at steady-state for most of the time points throughout the day based on the conventional BE criteria, except for few initial time points (mostly before 3 hours) or time point at the trough of Topamax® IR (at 12 hours) postdose. Smaller fluctuation of topiramate plasma concentrations from Brandname XR™ at steady-state was observed compared to that from Topamax® IR. The overall results also suggest that patients can be switched from IR to Brandname XR™ formulation with the same total daily doses.

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

Bioequivalence was established between TBM and the clinical formulations (USL255-MD) of 200 mg strengths, and between the scaled-up TBM formulations manufactured at the (b) (4) facility (USL255-MK (b) (4)) and the USL Denver facility (USL255-MK-D). The lower 25~150 mg strengths are compositionally similar to the 200 mg strength and are subject to biowaiver for not needing additional in vivo bridging study.

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

Food effect

High-fact food had no significant effects on topiramate plasma exposure or elimination t1/2 after administration of Brandname XR™. The peak time (Tmax) was delayed for 4 hours following single-dose administration but was not altered at steady-state compared to fasted conditions. Brandname XR™ can be taken with regardless of food.

Potential Alcohol Interaction:

In vitro dissolution study with 0%, 5%, 20%, and 40% ethanol in media at pH 1.2, 4.5, and 7.2 showed that there is minimum potential for dose-dumping for topiramate from the Brandname XR™ capsules. An in vivo study to evaluate the potential dose-dumping with alcohol in humans was not necessary in view of the in-vitro results. However, concerning for the potentiation of CNS depression in the presence of alcohol,

concomitant use of alcohol should be avoided when taking Brandname XR™, as recommended by the Agency for the labeling.

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DCP-1, Office of Clinical Pharmacology

Concurrence: Angela Men, M.D., Ph.D.
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Office of Clinical Pharmacology

cc: HFD-120 NDA 205-122
CSO/T. Holmes
HFD-860 /DDD DCP-1/R. Uppoor
/DD DCP-1/M. Mehta

Reference ID: 3450667

2. Question Based Review

2.1 General Attributes

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

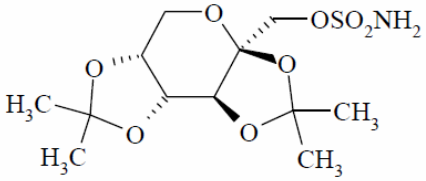
Brandname XR™ (Topiramate extended-release (ER) capsule) is an antiepileptic (AED) agent indicated for:

1. Monotherapy epilepsy: Initial monotherapy in patients ≥ 10 years of age 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 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-β-D-fructopyranose sulfamate. The structure for topiramate drug substance is provided in the Figure below.



Brandname XR™ capsules contain beads of topiramate in a hard capsule. The inactive ingredients are microcrystalline cellulose, hypromellose 2910, ethylcellulose, diethyl phthalate. The available strengths of BRANDNAME XR™ extended-release capsules are 25mg, 50mg, 100mg, 150mg and 200mg. The capsule shells for all strengths contain hypromellose 2910, titanium dioxide, black iron oxide, red iron oxide and/or yellow iron oxide, black pharmaceutical ink, and white pharmaceutical ink (200mg only).

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

The applicant proposes that the total daily dose of Brandname XR™ should be administered orally as whole capsules or opened and sprinkled onto a spoonful of soft food, regardless of food intake at the following proposed dosing regiments:

Indication	Initial Dose	Titration	Recommended Dose
Monotherapy:			
In adults and pediatric patients ≥ 10 years	50 mg once daily	Increase dosage weekly by 50 mg for the first 4 weeks then 100 mg for weeks 5 to 6	400 mg once daily
Adjunctive Therapy:			
In patients ≥17 years with partial onset seizures or LGS	25 to 50 mg once daily	Increase dosage weekly by 25 to 50 mg*	200-400 mg once daily
In patients ≥17 years with primary generalized tonic-clonic seizures	25 to 50mg once daily	Increase dosage weekly by 25 to 50 mg	400mg once daily
In patients ≥2 years with partial onset seizures, primary generalized tonic-clonic seizures or LGS	25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week	Increase dosage at 1- or 2-week intervals by 1 to 3 mg/kg once daily**	5 to 9 mg/kg once daily
* Titration schedule for the Brandname XR clinical trial in adults with partial onset seizures was 50 mg once daily initial dose, titration weekly by 50 mg for 3 weeks, and a final dosage of 200 mg once daily. ** Dose titration should be guided by clinical outcome.			

* For adults and pediatric patients 10 Years and older, Brandname 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

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 design of the multi-particulate formulation of USL255 and the basis of this submission is to demonstrate equivalence of the PK profiles of topiramate between Brandname XR™ capsules given once-daily (QD) and the approved Topamax ® tablets given twice-daily (BID). To support the application, the Sponsor presented a clinical pharmacology-based method by demonstrating the bioequivalence (BE) at multiple time-points within the 24 hours at steady-state between the proposed Brandname XR™

Reference ID: 3450667

capsules given QD and the approved Topamax® tablets given BID with respect to topiramate plasma concentration and partial AUC (Study P09-003). The similar approach was first proposed and performed to support the approval of another topiramate ER product Trokendi XR®.

The clinical pharmacology program consists of nine Phase 1 studies in healthy adult volunteers (including 2 pilot studies P08-003 and P08-008 for early formulation selection). Listing of the studies to support this clinical pharmacology-based NDA is presented in the Table below.

Table. Tabular listing of the studies to support the NDA

Study	Description	Population
Single-Dose Studies		
Formulation Selection		
P08-003	Randomized, single-center, open-label, 4-way crossover, relative bioavailability	24
P08-008	Randomized, single-center, open-label, 2-arm with crossover, relative bioavailability	42
Bioavailability Studies		
P09-002	Randomized, single-center, open-label, 3-way crossover, fed vs. fasted, relative bioavailability	36
P255-102	Randomized, single-center, open-label, 4- way crossover, bioequivalence	36
Dose-Proportionality Study		
P09-001	Randomized, single-center, open-label, 5-way crossover, dose proportionality	30
Ascending Dose Study		
P09-011	Randomized, single-center, double-blind, safety and pharmacokinetics of single ascending doses	50
Multiple-Dose Studies		
P09-003	Randomized, single-center, open-label, 2-way crossover, multi-dose, relative bioavailability	38
P255-101	Randomized, single-center, double- blind, 2-period crossover, relative bioavailability and pharmacodynamics effects on cognition	48
P255-103	Randomized, single-center, double-blind, 2-period crossover, relative bioavailability and effects on cognition	48

Although the current submission is considered a clinical pharmacology-based application, the Sponsor did conduct one placebo-controlled efficacy clinical trial in epileptic patients (Study P09-004, See Section 2.2.2) and submitted the results to the Agency during review cycle to support the labeling. However, the review and approvability of the application will hinge on the clinical pharmacology findings.

Reference ID: 3450667

The applicant requested a biowaiver of in vivo relative BA/BE studies for the 25 mg, 50 mg, 100 mg, and 150 mg strengths of USL255 capsules on the basis of BE between 200mg USL255 and Topamax IR (100mg BID) of 200mg strength, formulation proportionality in active and inactive ingredients, utilizing (b) (4) beads with (b) (4) extended-release coating (b) (4) No study in humans was conducted to assess the potential alcohol-induced dose-dumping based on the in vitro discussion results.

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?

Brandname XR™ was evaluated in a Phase 3 randomized, double-blind, placebo-controlled, multicenter, international clinical study for efficacy and safety in adult patients (18~75 years of age) with partial onset seizures and on stable 1~3 concomitant AEDs (e.g., carbamazepine, valproic acid, lamotrigine, and levetiracetam) prior to baseline. Patients who experienced at least 8 partial onset seizures, with or without secondary generalization, and no more than 21 consecutive seizure free days during the 8 week baseline phase were randomly assigned to placebo or Brandname XR™ administered once daily in addition to their other AEDs. Following randomization, 249 patients began the double-blind phase of treatment. During a 3 week titration period, patients received either Brandname XR™ or placebo beginning at 50 mg once daily; the dose was then increased weekly by 50 mg once daily. Following the 3 week titration, patients entered an 8 week maintenance period at the assigned 200 mg once daily maintenance dose. Positive efficacy outcome was demonstrated in this trial, as assessed by the significantly greater percent reduction in partial-onset seizure rate from baseline during the titration and maintenance periods and the responder rate (percentage of patients with at least a 50% reduction in seizures compared to baseline). Please refer to Medical Officer's review (DNP) and proposed labeling for additional detail and findings.

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 (Cmin) and percent reduction in seizure frequency for the IR formulations between adults (16 years and above) and pediatrics (6-15 years) (refer to the Agency's review for NDA 20505/S042, 20844/S036, 7/11/2012 in DARRTS).

The proposed dosing regimen for Brandname XR™ is the same as that for the reference drug Topamax ® IR tablets, which is supported by the similar relative BA (i.e., AUCτ, Cmax, and Cmin) at the steady-state as well as point-to-point comparisons for topiramate

plasma concentrations and partial AUC (AUC0-p) throughout the day, based on conventional BE criteria.

As summarized in the Office of Clinical Pharmacology review for the approved Trokendi XR® capsules (NDA 201-635), a therapeutic window for topiramate to support the approval and the same dosing regiment when compared to Topamax ® IR was reported:

- Unbound topirmate 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 ® 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 Cmin proportionally higher than 10 µg/mL), the author reported no significant improvement in efficacy at doses >400mg/day (*Peeters et al. Acta Neurol Scand. 2003;108:9-15*).

In studies (P09-003 and P255-103) for the current application for Brandname XR™, 200 mg QD doses resulted in Cmin ~5.31-5.44 µg/mL (or 15-16 µM), whereas 100 mg Topamax ® BID doses resulted in Cmin ~5.03-5.98 µg/mL. The 400 mg QD doses corresponded to Cmin ~10.1 µg/mL (30-32 µM). Given known efficacy and safety profiles for Topamax ®, 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 Brandname XR™ in healthy subjects have been evaluated. The PK profiles of topiramate in epilepsy patients taking Brandname XR™ are expected to be similar to that in healthy subjects, based on the available information in approved topiramate drug products. Detailed information is available in the following Sections.

2.2.4.2 What are the characteristics of drug absorption and Distribution?

Following a single 200 mg oral dose of Brandname XR™, peak plasma concentrations (Tmax) occurred approximately 20 hours after dosing. Multiple dose administration (200 mg QD) produced Tmax approximately 6 hours at steady state.

The pharmacokinetics of Brandname XR™ are linear with approximate dose-proportional increases in plasma concentration over the single-dose range 50 to 1400

mg/day. The dose-proportionality following single-dose administration was demonstrated for AUC over 25-1400 mg and for Cmax over 50-1400 mg dose range. At 25 mg, the pharmacokinetics of Brandname XR™ is nonlinear possibly due to the binding of topiramate to carbonic anhydrase in red blood cells. The dose-proportionality following multiple-dose administration was demonstrated for Cmin over 100-400 mg and for Cmax and AUC0-24h over 200-400 mg dose range.

Topiramate is 15 to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 µg/mL. The fraction bound decreases as blood concentration increases.

Taken once daily, Brandname XR™ provides steady-state plasma levels comparable to immediate-release topiramate tablets given every 12 hours when administered at the same total mg daily dose. Steady-state is reached in about 5 days after Brandname XR™ dosing in subjects with normal renal function. After administration of once-daily Brandname XR™ doses, the mean peak-to-trough fluctuation (fluctuation index) in plasma topiramate concentrations was approximately 36-40%, compared to 40-53% for immediate-release topiramate tablets given twice daily.

Food delayed Tmax by approximately 4 hours following a single dose of Brandname XR™, while having no effect on bioavailability (AUC and Cmax). Brandname XR™ sprinkled on a spoonful of soft food is bioequivalent to the intact capsule formulation.

As described in the Topamax® label, carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 mcg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate), decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

2.2.4.3 What are the characteristics of drug metabolism and elimination?

(Referred to TOPAMAX® label: 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.

The mean terminal half-life and effective half-life of topiramate following single-doses of Brandname XR™ is approximately 80 hours and 56 hours, respectively, with the latter being proposed by the Sponsor to reflect drug accumulation being a function of both elimination and absorption rates.

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

Single-Dose:

Dose-proportionality and PK linearity of single-doses of 25 mg, 50 mg, 100 mg, 150 mg and 200 mg USL255 capsules over a 25-1400 mg dose range were evaluated in Studies P09-001 and P09-011.

Study P09-001 was a Phase 1, randomized, single-center, single-dose, open-label, five-way crossover study to assess the dose proportionality of a single oral dose of 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg (200 mg x 2) USL255-MD in 30 healthy adult male and female subjects. The PK blood samples were collected over 336 hours after each dose for the determination of plasma topiramate concentrations. The PK parameters and dose-proportionality statistical analysis of the log-transformed PK parameters over the 25 mg to 400 mg dose range for USL255 are presented in the tables below. Statistical analysis confirms the proportionality for AUCt and AUC∞ over the entire 25-400mg dose range and for Cmax over 100-400mg dose range. The deviation from the dose proportionality of the observed Cmax at the lower doses (25-50mg) is likely due to the saturable, high-affinity binding of topiramate to carbonic anhydrase on red blood cells.

Table. Arithmetic means (SD) of topiramate pharmacokinetic parameters following a single doses of 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg of USL255

	25 mg USL255 (n = 22)		50 mg USL255 (n = 27)		100 mg USL255 (n = 28)		200 mg USL255 (n = 27)		400 mg USL255 (n = 26)	
Pharmacokinetic Parameter	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**
C_{max} (µg/mL)	0.203 (0.067)	32.9	0.512 (0.132)	25.8	1.23 (0.343)	27.8	2.78 (0.616)	22.2	5.79 (1.34)	23.1
AUC_{∞} (µg·h/mL)[a]	20.4 (5.58)	27.3	43.2 (9.12)	21.1	87.2 (19.6)	22.4	175 (40.2)	23.0	343 (69.4)	20.3
AUC_t (µg·h/mL)	18.6 (5.32)	28.6	40.6 (8.86)	21.8	84.3 (19.4)	23.1	174 (40.9)	23.5	340 (71.0)	20.9
k_{el} (h^{-1})[a]	0.0077 (0.0018)	23.4	0.0078 (0.0016)	20.8	0.0083 (0.0017)	20.4	0.0093 (0.0016)	17.7	0.0099 (0.0014)	14.1
$t_{½}$ (h)[a]	94.6 (23.0)	24.3	92.2 (19.5)	21.2	86.5 (18.2)	21.1	76.6 (13.1)	17.1	71.1 (9.8)	13.8
t_{max} (h)[b]	20 (8, 32)	26.5	18 (10, 36)	33.4	23 (12, 32)	29.3	18 (10, 30)	34.4	16 (8, 36)	36.7

a Four subjects (in 25mg, 200mg, and 400mg groups) were excluded from the summary statistics and statistical analyses related to this PK parameter because an elimination rate constant could not be calculated.

b Median (min, max) is reported for Tmax.

Table. Summary of statistical analysis for dose-proportionality

PK Parameter	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm* (90% CI)	Conclusion**
AUCt (µg•h/mL)	(18.6, 336)	1.04 (1.03, 1.06)	1.13 (1.08, 1.18)	Proportional
AUC∞ (µg•h/mL)	(20.4, 339)	1.01 (1.00, 1.03)	1.04 (1.00, 1.09)	Proportional

Reference ID: 3450667

Cmax (µg/mL)	(0.203, 5.91)	1.22 (1.19, 1.24)	1.82 (1.69, 1.96)	Not Proportional
Cmax (µg/mL)[a]	(1.20, 5.65)	1.12 (1.07, 1.17)	1.18 (1.10, 1.27)	Approached Dose Proportionality

* Ratio of model-predicted geometric mean values for high and low dose, normalized for dose.

** Dose proportionality was concluded if the 90% CI for Rdnm was contained within 0.80-1.25 limits. If the 90% CI was completely outside of 0.80-1.25 limits, then not proportional was concluded. Otherwise inconclusive was concluded.

[a] Dose range: 100-400mg

Study P09-011 was a Phase 1, randomized, placebo-controlled, double-blind, single-center study to assess the dose proportionality of a single ascending oral doses of 600 mg (200 mg x 3), 800 mg (200 mg x 4), 1000 mg (200 mg x 5), 1200 mg (200 mg x 6), or 1400 mg (200 mg x 7) USL255-MD in up to 60 healthy adult subjects. The PK blood samples were collected over 336 hours after each dose for the determination of plasma topiramate concentrations. The PK parameters and dose-proportionality statistical analysis of the log-transformed PK parameters over the 600-1400 mg dose range for USL255 are presented in the tables below. Statistical analysis confirms the proportionality for AUCt and AUC∞ over the entire 25-400mg dose range and for Cmax over 100-400mg dose range. 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. Arithmetic means (SD) of topiramate pharmacokinetic parameters following a single doses of 600 mg, 800 mg, 1000 mg, 1200 mg, and 1400 mg of USL255

Pharmacokinetic Parameter	600 mg USL255 (n = 8)		800 mg USL255 (n = 8)		1000 mg USL255 (n = 8)		1200 mg USL255 (n = 8)		1400 mg USL255 (n = 8)	
	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%
C_{max} (µg/mL)	8.34 (1.62)	19.4	10.5 (1.56)	14.8	14.7 (2.13)	14.5	16.6 (3.33)	20.1	19.7 (4.52)	22.9
AUC_t (µg·h/mL)	479 (86.8)	18.1	608 (84.6)	13.9	789 (105)	13.3	965 (154)	15.9	1121 (257)	22.9
AUC_∞ (µg·h/mL)	465 (77.4)	16.7	613 (84.7)	13.8	805 (106)	13.2	970 (153)	15.8	1124 (257)	22.8
f_{ext} (%)	0.80 (0.40)	50.1	0.88 (0.46)	52.0	0.36 (0.17)	48.3	0.56 (0.28)	51.0	0.34 (0.15)	43.0
t_{max} (h)[a]	18.17 (10.16, 32.00)	36.5	17.08 (10.16, 36.00)	46.3	18.16 (10.16, 26.16)	31.4	18.00 (10.16, 24.00)	30.7	20.03 (14.16, 26.16)	24.5
k_{el} (h^{-1})	0.0099 (0.0020)	19.8	0.0089 (0.0014)	15.8	0.0125 (0.0012)	9.80	0.0102 (0.0018)	18.0	0.0126 (0.0022)	17.4
$t_{½}$ (h)	72.7 (14.5)	19.9	80.3 (16.3)	20.2	56.0 (5.63)	10.1	69.7 (11.6)	16.7	56.6 (9.93)	17.6

a Median (min, max) is reported for Tmax.

Table. Summary of statistical analysis for dose-proportionality

PK Parameter	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm* (90% CI)	Conclusion**
AUCt (µg•h/mL)	(464, 1100)	1.02 (0.87, 1.17)	1.02 (0.90, 1.15)	Proportional

AUC∞ (µg•h/mL)	(458, 1116)	1.05 (0.90, 1.20)	1.04 (0.92, 1.18)	Proportional
Cmax (µg/mL)	(8.11, 19.4)	1.03 (0.86, 1.20)	1.03 (0.89, 1.18)	Proportional

* Ratio of model-predicted geometric mean values for high and low dose, normalized for dose.
** Dose proportionality was concluded if the 90% CI for Rdnm was contained within 0.80-1.25 limits. If the 90% CI was completely outside of 0.80-1.25 limits, then not proportional was concluded. Otherwise inconclusive was concluded.

The Sponsor performed an analysis for dose-proportionality and linearity using existing data from the above two Studies P09-001 and P09-011. Results confirmed the dose-proportionality and linearity for AUC and Cmax values over a 25-1400mg (56-fold) and a 50-1400mg dose range, respective.

Table. Summary of statistical analysis for dose-proportionality

PK Parameter	Dose Range (mg)	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm (90% CI)	Conclusion
AUCt (µg•h/mL)	25-1400	(17.9, 1159)	1.04 (1.02, 1.05)	1.16 (1.09, 1.23)	Proportional*
AUC∞ (µg•h/mL)	25-1400	(19.7, 1142)	1.01 (0.995, 1.02)	1.03 (0.979, 1.09)	Proportional*
Cmax (µg/mL)	25-1400	(0.193, 22.7)	1.18 (1.16, 1.21)	2.10 (1.91, 2.30)	Not Proportional
Cmax (µg/mL)	50-1400	(0.493, 21.6)	1.13 (1.11, 1.16)	1.56 (1.43, 1.71)	Proportional**

* The 90% CI for slope was contained within the Smith limits (0.945, 1.055).
** Based on the Hummel limits (0.792, 1.208).

Multiple-Dose:
Dose-proportionality of multiple-doses of 50 mg, 100 mg, 150 mg, 200 mg and 400 mg USL255 capsules were evaluated in Study P255-103 with 48 healthy subjects. Study P255-103 was a Phase 1, randomized, double-blind, two-period (USL255-MJ or Topamax®), crossover study to assess the effects of USL255 capsule every evening (QPM) on cognition, mood, alertness, and PK properties compared with Topamax® Q12h. As presented in the tables below, the dose-proportionality following multiple-dose administration of USL255 was concluded for predose Cmin over 100-400 mg dose range and for AUC0-24h and Cmax at steady-state over 200-400 mg dose range.

Table. Summary of statistical analysis for dose-proportionality

PK Parameter	Dose Range (mg)	Predicted Geometric Mean	Slope Estimate (90% CI)	Rdnm (90% CI)	Conclusion
Predose Cmin (µg/mL)	50-400	(1.26, 10.6)	1.025 (0.938, 1.112)	1.05 (0.878, 1.263)	Proportional
Predose Cmin (µg/mL)	100-400	(2.56, 10.7)	1.029 (0.944, 1.114)	1.04 (0.925, 1.171)	Proportional

PK Parameter	Dose Range (mg)	Geometric Mean Ratio	90% CI
AUC0-24h (µg•h/mL)	200-400	1.09	(1.02, 1.16)
Cmax (µg/mL)	200-400	1.07	(1.00, 1.14)

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

Reference ID: 3450667

The Sponsor's clinical development plan did not include PK characterization in target patient populations. However, gathering the available information pertaining to the topiramate in healthy subjects and patients, as seen in the labelings of the approved TOPAMAX® IR tablets and Trokendi XR® capsules, it is reasonable to anticipate that the topiramate PK profile from Brandname XR™ capsules in epilepsy patients will be similar to that in healthy subjects.

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 key PK parameters from Brandname XR™ in single and multiple dose studies in healthy subjects was approximately 15-35%, with or without food.

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.

2.3.1.1 Elderly

As recommended in the proposed labeling for Brandname 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 Brandname XR™ may be indicated in the elderly patients when impaired renal function (creatinine clearance $\leq$70 mL/min/1.73 m^2) 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® label. The evaluation for the potential alcohol-induced topiramate dose-dumping from Brandname XR™ for this application is summarized below.

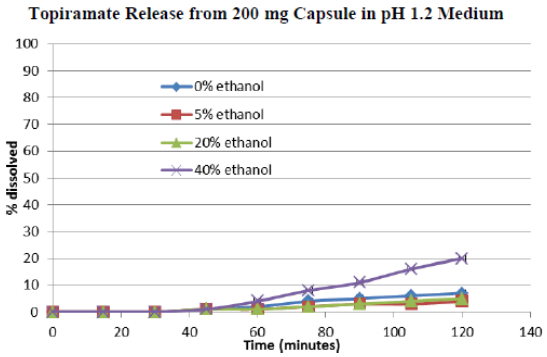
2.4.1 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

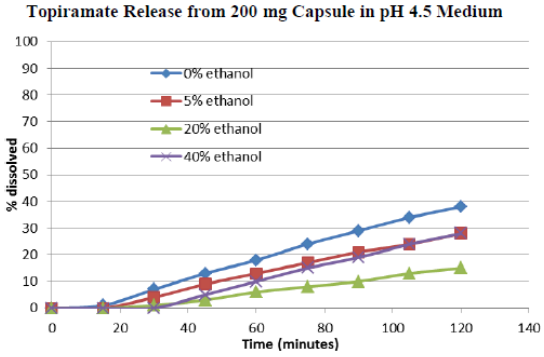
2.4.1.1 Effect of alcohol consumption on concomitant Brandname XR™

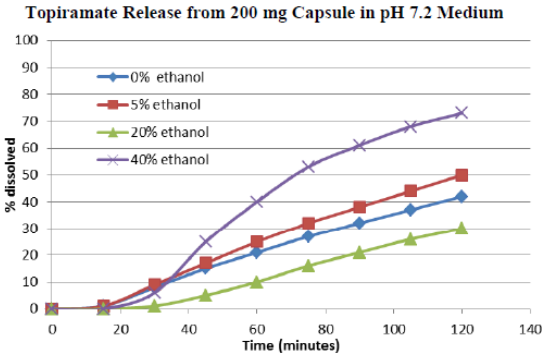
In vitro dissolution studies were conducted to evaluate the effects of ethanol at concentrations of 0%, 5%, 20%, and 40% (v/v) in media at pH 1.2, 4.5, and 7.2 on the dissolution of USL255. As illustrated in the figures below, at pH 1.2 with 40% alcohol approximately 20% of the topiramate was released by 2 hours and at pH 4.5, the addition of alcohol (5%-40%) was shown to slow drug release. At pH 7.2 and 40% alcohol there was evidence of 30% increase released compared to 0% alcohol. According to the Sponsor, *in vitro* data suggest that an alcohol-induced dose-dumping for Brandname XR™ capsules in humans would not likely alter the topiramate concentration-time curve as a result of greater amount of drug being released early, and therefore no in vivo study in humans was necessary.

From a clinical pharmacology standpoint, we agree and do not anticipate that a significant PK interaction with alcohol consumption is likely to occur early (e.g., approximately 2~3 hours) prior to or after the Brandname XR™ dosing. The conclusion is made based on the following considerations:

- Known 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; gastric emptying t1/2 approximately 21-26 min under fasted state and 36-200 min under fed conditions
- Rapid absorption of alcohol from the upper GI tract (the main site of alcohol absorption) and dilution of alcohol concentrations in GI tract
- Known human physiology (e.g., GI transit and regional pH distribution)
- Rapid absorption of topiramate
- The extents of drug release results in in-vitro testing (figures below).







However, as stated in approved labels for topiramate drug products, the PD-related safety concern (i.e., potentiation of CNS depression with concomitant alcohol consumption) exists, which is taken into consideration for the recommended labeling languages as follows:

7.3 CNS Depressants or Alcohol

Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressants drugs or alcohol can result in significant CNS depression. Concomitant used of alcohol should be avoided [see Clinical Pharmacology (12.3)].

2.5 General Biopharmaceutics

2.5.1 What are the compositions of the proposed Brandname XR™ formulations?

The applicant proposed 25 mg, 50 mg, 100 mg, 150 mg and 200 mg strengths for Brandname XR™ capsules. The ER formulations of USL255 utilized a multi-particulate bead technology. The differences between the formulations were (b) (4) The compositions of the USL255 formulations are provided in the tables below.

Both USL255-MD and USL255-MJ formulations were used in Phase 1 studies. USL255-MK is the proposed TBM formulation. Formulation MJ differs from MK in only capsule colors and size of the 200 mg capsule so no bridging study was necessary. USL255-200-MD was shown to be bioequivalent to the TBM formulation (USL255-MK). USL255-200-MK (b) (4) and USL255-200-MK-D represent the final to-be-marketed formulations manufactured at alternate manufacturing sites, (b) (4) and Upsher-Smith Laboratories, Inc., Denver, CO (USL Denver facility), respectively.

Table. Core bead and coating components of USL255 formulations used in clinical studies

Formulation Designation	MA	MB	MC	MD	ME	MH	MI	MJ and MK*
	Small Scale							Commercial Scale
Ingredient	Overall Coated Bead Formulation (% w/w)							
Core Bead Components	(b) (4)							
Topiramate, USP								
Microcrystalline Cellulose, NF (b) (4) (b) (4)								
Hypromellose 2910, USP (b) (4) (b) (4)								

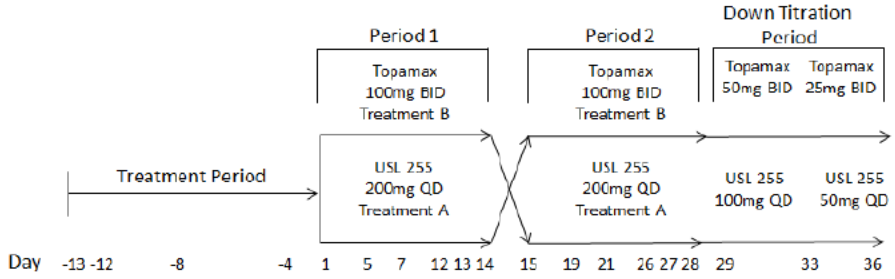
Coating Components	
	(b) (4)
Ethylcellulose, NF	(b) (4)
Hypromellose 2910, USP	(b) (4)
Diethyl Phthalate, NF	(b) (4

a The MK formulation is the to-be-marketed formulation. The MJ formulation is the same as the MK formulations differing only in capsule color and 200 mg capsule size.

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 Brandname XR™ (QD) vs. reference Topamax® IR (BID) of the same total daily doses at steady-state (P09-003). A second multiple-dose study was conducted in healthy subjects (P255-103) to provide additional supportive evidence.

Study P09-003 was a Phase 1, randomized, single-center, open-label, 2-way crossover study in 38 healthy subjects (1:1 ratio) to evaluate the steady-state PK and relative bioavailability (BA) of 200-mg USL255-MD (QD) compared to 100-mg Topamax® tablet (BID, 12 hours apart). Subjects were titrated up starting 50 mg/day and increasing in increments of 50 mg/day to reach the 200 mg/day target dose, and were maintained for a total of 14 days before the crossover. Schematic of study design is as follows:



The mean trough plasma concentrations were similar between the two formulations. Steady-state was generally reached on Day 5 for USL255 and on Day 7 for Topamax®. The key PK parameters, as well as mean topiramate plasma concentration-time profiles following multiple dosing of USL255MD and Topamax® after 14 days of dosing, are shown in the Table and Figure below.

Figure. Mean plasma concentration-time curves at the steady-state

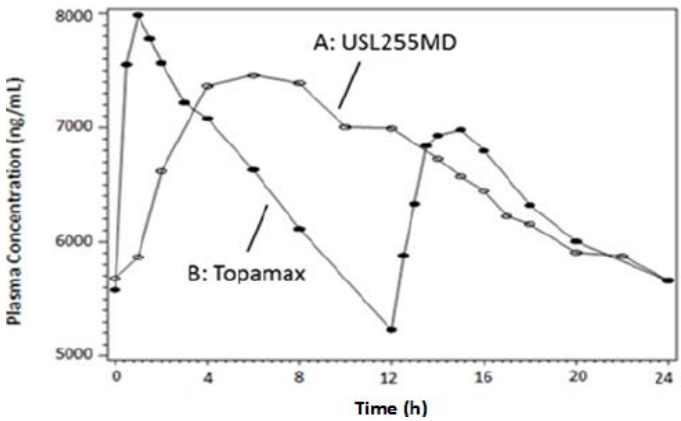


Table. Summary of arithmetic mean (SD) of Topiramate Pharmacokinetic Parameters

Pharmacokinetic Parameter	Day 14 and 28				Day 15			
	200 mg USL 255MD QD (n = 36)		100 mg Topamax® (Q12h) (n = 36)		200 mg USL 255MD QD (n = 17)		100 mg Topamax® (Q12h) (n = 19)	
	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV
$AUC_{0\text{-}24h}$ (µg·h/mL)	158 (31.6)	20.0	153 (33.2)	21.7	150 (23.9)	15.9	156 (39.3)	25.2
AUC_{tau} (µg·h/mL)	158 (31.6)	20.0	78.1 (16.8)	21.5	150 (23.9)	15.9	79.2 (19.6)	24.7
C_{max} (µg/mL)	7.88 (1.50)	19.1	8.43 (1.66)	19.7	7.51 (1.35)	18.0	8.36 (1.82)	21.8
t_{max} (h)[a]	6.00 (2.00, 17.00)	47.4	1.00 (0.50, 14.00)	157	6.00 (4.00, 10.18)	33.8	1.58 (0.50,14.07)	126
C_{min} (µg/mL)	5.31 (1.19)	22.4	5.03 (1.21)	24.1	5.02 (0.914)	18.2	5.14 (1.44)	28.0
C_{avg} (µg/mL)	6.60 (1.31)	20.0	6.51 (1.40)	21.5	6.25 (0.996)	16.0	6.60 (1.63)	24.7
FI	0.40 (0.11)	26.5	0.53 (0.12)	21.9	0.40 (0.11)	27.4	0.50 (0.12)	23.8

As shown in the Tables below, statistical analysis demonstrated (1) BE between Brandname XR™ and Topamax ® with regard to AUC0-24h, Cmax,ss, and Cmin,ss, and (2) BE between before and after the crossover between two formulations. Further, lower fluctuation (FI) at steady-state was observed for Brandname XR™ (~0.40) compared to Topamax ® Tablets (~0.50).

Table. Statistical analysis for relative bioavailability of 200-mg dose of Brandname XR™ vs. Topamax ® at steady-state

Parameter	N	USL255 (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B)	90% CI
AUC0–24h (µg·h/mL)	36	155	150	1.04	(1.02, 1.05)
Cmax,ss (µg/mL)	36	5.16	4.88	1.06	(1.03, 1.08)
Cmin,ss (µg/mL)	36	7.71	8.26	0.93	(0.90, 0.97)

Table. Statistical analysis for relative bioavailability of 200-mg dose of Brandname XR™ vs. Topamax ® on Day 14 and Day 15

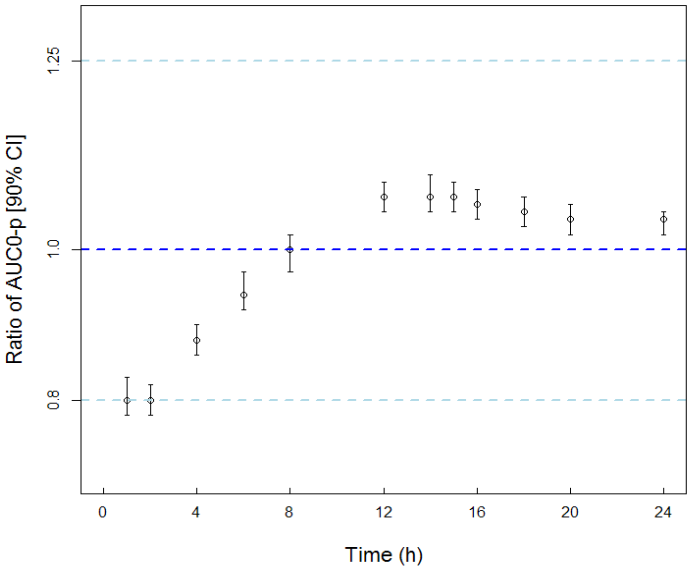
Pharmacokinetic Parameter	USL255-MD to Topamax®			Topamax® to USL255-MD		
	Geometric LSM		Ratio of Geometric LSM[a] (90% CI)	Geometric LSM		Ratio of Geometric LSM[a] (90% CI)
	USL255-MD 200 mg QD Day 14 (n = 19)	Topamax® 100 mg Q12h Day 15 (n = 19)		Topamax® 100 mg Q12h Day 14 (n = 17)	USL255-MD 200 mg QD Day 15 (n = 17)	
$AUC_{0\text{-}24h}$ (μg·h/mL)	152	150	0.99 (0.97-1.02)	147	148	1.01 (0.98-1.04)
AUC_{tau} (μg·h/mL)	152	76.7	NA	75.0	148	NA
C_{min} (μg/mL)	5.05	4.95	0.98 (0.93-1.03)	4.89	4.95	1.01 (0.99-1.04)
C_{max} (μg/mL)	7.62	8.14	1.07 (1.02-1.12)	8.20	7.40	0.90 (0.86-0.95)
C_{avg} (μg/mL)	6.32	6.39	1.01 (0.98-1.04)	6.25	6.18	0.99 (0.96-1.02)

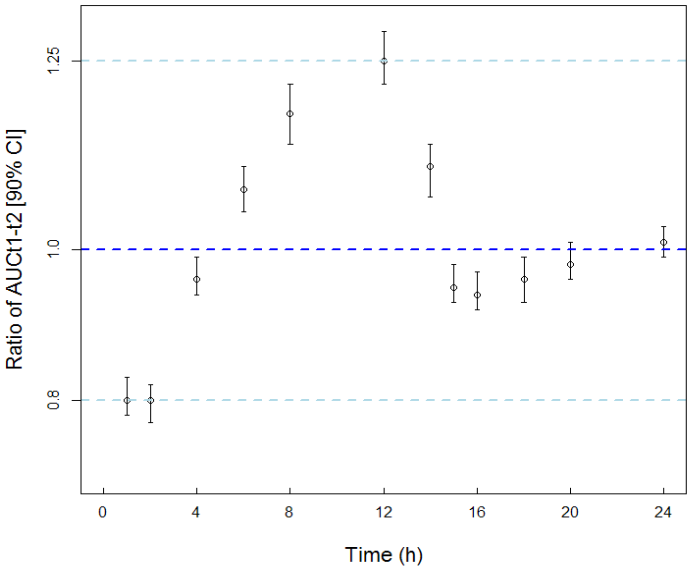
Analysis of partial AUC (AUCp and AUCt1-t2) and Cp at steady-state:

The Sponsor submitted results of point-to-point BE analysis for partial AUC (AUCp) and partial AUC between two time-points (i.e., AUCt1-t2) to demonstrate the PK profile similarity between Brandname XR™ QD and the reference drug Topamax ® BID during a 24-hour dosing interval at steady-state. Subsequently, upon the request by the OCP on November 13, 2013, the Sponsor submitted additional BE analysis results on November 20, 2013 for comparing the point-to-point topiramate plasma concentrations to further examine and assure the plasma profile similarity. This point-to-point BE analysis was first proposed to form the basis of approval of another topiramate ER drug product, Trokendi XR®.

As shown in the Figures below, point estimates and the 90% CIs for the ratios of steady-state partial AUC (AUC0-p) and partial AUC between two time points (i.e., AUCt1-t2) at each corresponding time point of the 24-hour plasma concentration-time curves for the two formulations were mostly within the 80-125% BE limits. The 90% CIs of few time points (i.e., around 0-2h and 12h) fell outside the BE limits. Additional analysis for the partial AUCs (AUC1-12h, AUC6-12h, AUC12-18h, and AUC18-24h) also showed the BE of drug exposure during these time periods from two formulations. In addition, the 90% CI for the ratios of point-to-point topiramate plasma concentration of the 24-hour curves for the two formulations were mostly within the 80-125% BE limits, except for the time points (C1h and C12h) corresponding to the trough of TOPAMAX® BID profile where the 90% CIs fell outside the BE limits. These deviations are not considered clinically significant.

Figures. Analysis of partial AUC (AUC0-p), partial AUC between two time-points (AUCt1-t2), and point-to-point topiramate concentrations (Study P09-003, 200 mg/day dose)





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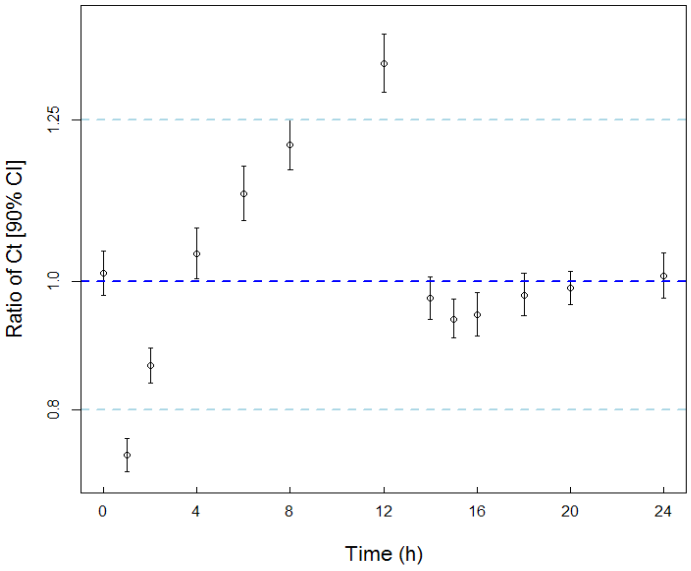


Study P255-103 was a Phase 1, randomized, double-blind, two-period, crossover study to compare the effects of USL255-MJ administered every evening (QPM) on cognition, mood, and alertness with Topamax® Q12h, as well as the steady-state PK in 48 healthy adult subjects. Subjects were randomized assigned to either treatment sequence (A or B; USL255 or Topamax ®, up-titrated starting 50 mg/day in weekly increments to reach the highest 400 mg/day for 7 days prior to the down-titration, minimum 21 days or washout period, and crossover. Topiramate PK was evaluated at 200 mg/day, 300 mg/day, and 400 mg/day doses, as presented in Figure below. The BE of USL255 200-mg QD to Topamax ® 100-mg BID was demonstrated in terms of AUC0-24, Cmax, and Cmin after each treatment, as presented in the Table below.

Figure. Mean plasma concentration-time curves at the steady-state

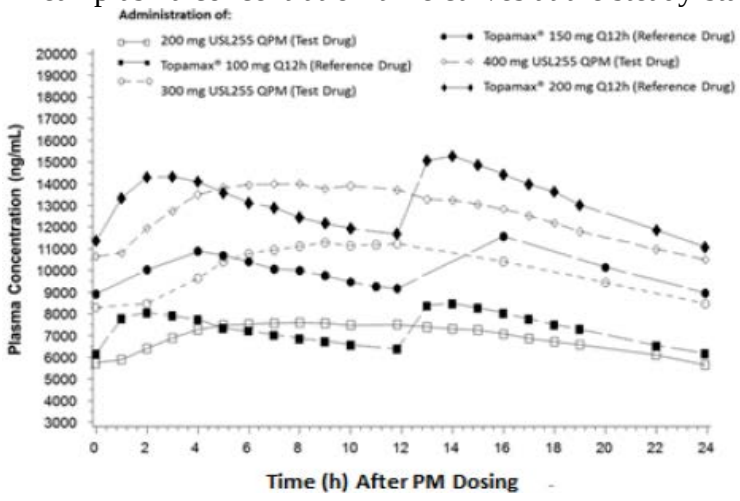
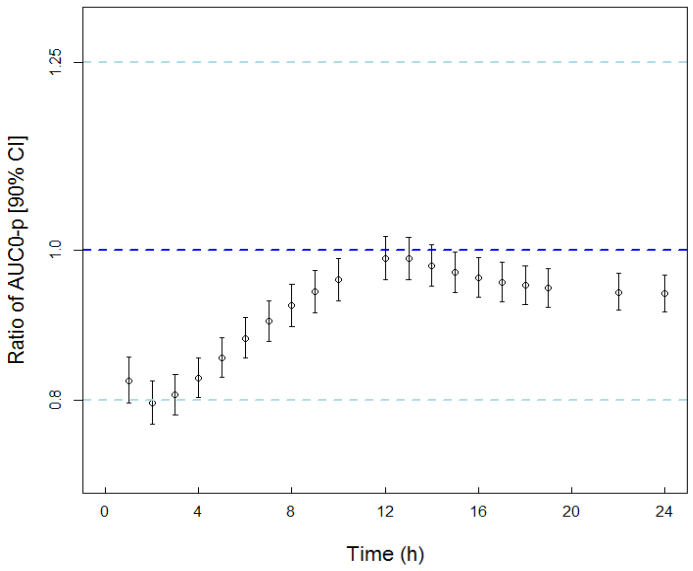


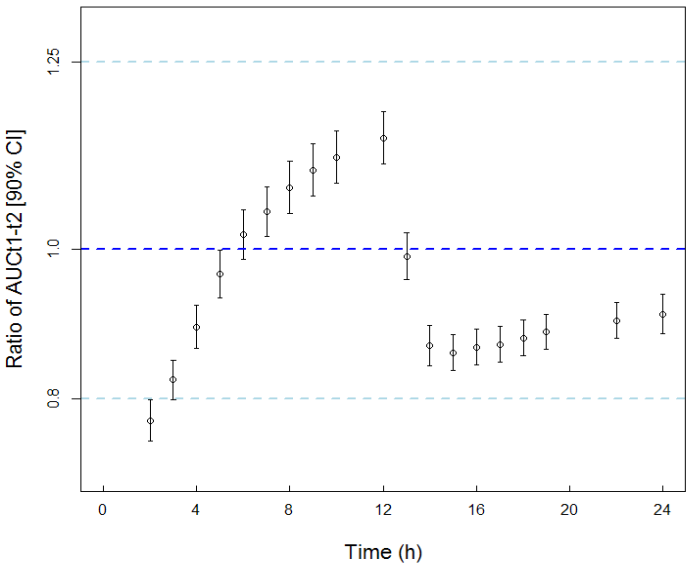
Table. Statistical analysis for relative bioavailability of USL255 200-mg QPM vs. Topamax ® BID at steady-state

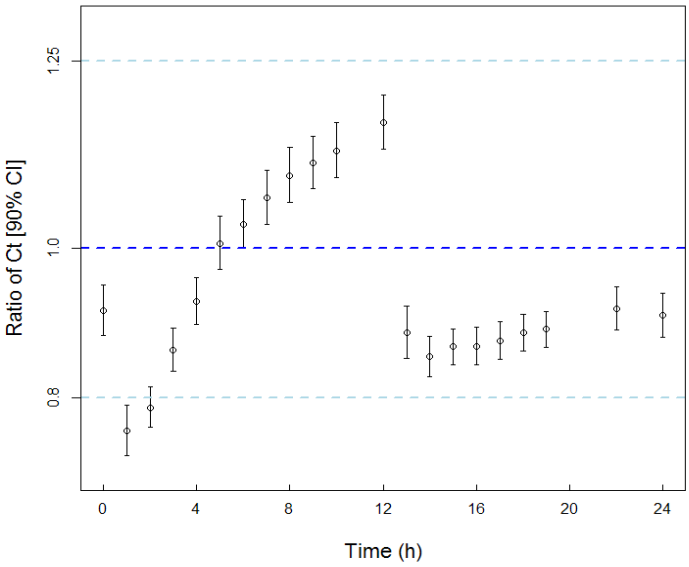
Parameter	N	USL255 (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B)	90% CI
AUC0–24h (µg·h/mL)	36	163	174	0.942	(0.917, 0.967)
Cmax,ss (µg/mL)	36	7.77	8.81	0.882	(0.854, 0.911)
Cmin,ss (µg/mL)	36	5.31	5.92	0.970	(0.870, 0.925)

Analysis of partial AUC (AUCp and AUCt1-t2) and Cp at steady-state:
As shown in the Figures below, point estimates and the 90% CIs for the ratios of steady-state partial AUC (AUC0-p), partial AUC between two time points (i.e., AUCt1-t2), and point-to-point topiramate plasma concentration at each corresponding time point of the 24-hour plasma concentration-time curves for the two formulations were mostly within the 80-125% BE limits. The 90% CIs of very few time points corresponding to the trough of TOPAMAX® BID profile (i.e., 0-3h) fell slightly outside the BE limits; however, the slight deviations are not considered clinically significant.

Figures. Analysis of partial AUC (AUC0-p), partial AUC between two time-points (AUCt1-t2), and point-to-point topiramate concentrations (Study P255-103, 200 mg/day dose)







Considering the exposure-response relationships of topiramate asdescribed in Section 2.2.3.1 with regards to Cmin,ss values and the reported therapeutic window, and the positive clinical outcome from a placebo-controlled Phase 3 trial (P09-004) (refer to review by the Medical officer), these deviations from BE limits are not considered clinically significant. Given results of the relative BA comparison from this study, patients may be switched from immediate-release topiramate products to Brandname 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?

Study P255-102 (a randomized, single-dose, 4-way crossover) was conducted with 36 subjects to assess the relative BA of various formulations of 200-mg strength that were manufactured at different sites (i.e., (b) (4) facility and USL Denver facility). The bioequivalence was determined based on the analysis of the 90% CIs of the geometric mean ratios (test/reference) for the exposure measures (AUC0-24h, Cmax, and Cmin) being within the BE acceptance limits of 0.80~1.25.

The USL255 formulation used in the Phase 1 studies (USL255-200-MD) was shown to be bioequivalent to the TBM formulation (USL255-MK). In addition, the scaled-up, TBM formulations manufactured at the (b) (4) facility (USL255-200-MK (b) (4)) and the USL Denver facility (USL255-200-MK-D) were shown to be bioequivalent. Further, results from the same study using the BE criteria demonstrated that USL255-200-MK-D capsules when opened and beads sprinkled on applesauce (test) and swallowed were bioequivalent to administration of the capsule intact (reference).

Table. BE analysis for USL255-MD (B) vs. USL255-MK-D (D)

Parameter	N	Treatment B LS Mean	Treatment D LS Mean	Geometric Mean Ratio (B/D)	90% CI
Cmax (µg/mL)	31	2.98	3.30	0.902	(0.857, 0.949)
AUC0-t (µg h/mL)	31	189	194	0.976	(0.944, 1.008)
AUC0-∞ (µg·h/mL)	29	193	197	0.983	(0.950, 1.016)

Table. BE analysis for USL255-MK-D Sprinkled (C) vs. USL255-MK-D intact (D)

Parameter	N	Treatment C (LS Mean)	Treatment D (LS Mean)	Geometric Mean Ratio (C/D)	90% CI
Cmax (µg/mL)	31	3.59	3.30	1.087	(1.033,1.143)
AUC0-t (µg·h/mL)	31	195	194	1.007	(0.974, 1.040)
AUC0-∞ (µg h/mL)	29	200	197	1.015	(0.982, 1.049)

Table. BE analysis for USL255-MK (b) (4) (A) vs. USL255-MK-D (D)

Parameter	N	Treatment A LS Mean	Treatment D LS Mean	Geometric Mean Ratio (A/D)	90% CI
Cmax (µg/mL)	30	3.47	3.30	1.051	(0.998, 1.105)
AUC0-t (µg h/mL)	30	197	194	1.013	(0.980, 1.047)
AUC0-∞ (µg·h/mL)	27	199	197	1.012	(0.979, 1.047)

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?

The effect of high-fat food on the single-dose (Cmax, AUCt, and AUC∞) and steady-state (Cmax, Cmin, AUC0-24h) PK parameters of USL255 were evaluated in Studies P09-002 and P255-103, respectively. The point estimates and the corresponding 90% CI for the ratio of means for the single-dose and steady-state AUCs and Cmax (see Tables below) were contained within the acceptance BE limits of 0.8-1.25, indicating that food had insignificant effect on topiramate plasma exposure after administration of USL255. The Tmax for topiramate was delayed for approximately 4 hours (from 20 h) following single-dose administration of USL255 with food compared to fasted conditions, while

Reference ID: 3450667

t1/2 was not affected. Food did not alter Tmax at steady-state compared to fasted conditions.

Table. Statistical analysis of the food effect on single-dose pharmacokinetic Parameters of Topiramate (Study P09-002)

Pharmacokinetic Parameter	Treatment	N	Geometric LSM	USL255-MD Fed/ USL255-MD Fasted Geometric LSM		
				Ratio	90% CI	
AUC_t (µg·h/mL)	USL255MD 200 mg SD, Fed	35	159	0.97	0.90	1.05
	USL255MD 200 mg SD, Fasted	35	165			
AUC_∞ (µg·h/mL)	USL255MD 200 mg SD, Fed	35	163	0.97	0.90	1.04
	USL255MD 200 mg SD, Fasted	35	168			
C_{max} (µg/mL)	USL255MD 200 mg SD, Fed	35	2.60	0.99	0.89	1.09
	USL255MD 200 mg SD, Fasted	35	2.64			

Table. Statistical analysis of the food effect on steady-state pharmacokinetic Parameters of Topiramate (Study P255-103)

Pharmacokinetic Parameter	USL255MJ 300 mg (Fed)	USL255MJ 200 mg (Fasted)	% Geometric Mean Ratio (Test/Reference)	90% Confidence Interval	
	Geometric LSM				
	Test	Reference		Lower	Upper
$AUC_{0\text{-}24h}$ (µg·h/mL)	158	164	0.9686	0.9427	0.9953
C_{max} (µg/mL)	7.70	7.77	0.9911	0.9614	1.0218
C_{min} (µg/mL)	5.24	5.33	0.9835	0.9496	1.02

* Dose-normalized data at steady-state.
** 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. Validated liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) method was used to quantitate topiramate in human plasma. Two assays developed and validated at [redacted] (b) (4) over ranges of 20-3000

Reference ID: 3450667

ng/mL and 20-6000 ng/mL, used for the pilot studies only. Two assays for the rest of the Phase 1 studies were developed and validated at [redacted] (b) (4) with linear ranges over 10-10000 ng/mL and 20-20000 ng/mL. The human plasma sample (100 µL containing K2 EDTA) 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.

Site (Report No.) [Method ID]		[redacted] (b) (4) **(V0805024.00)**	[redacted] (b) (4) **(V0908024.00)**	[redacted] (b) (4) **[LCMS470]**	[redacted] (b) (4) **[LCMS610]**
Method		LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Linear Range (ng/mL)		20.00 – 3000	20.00 – 6000	10.0 – 10000	20.0 – 20000
Quality Control (QC) (ng/mL)		60, 360, 2250	60, 500, 4500	10.0, 30.0, 80.0, 300, 1200, 7500	20.0, 60.0, 150, 600, 2500, 15000
Precision (%) Range for QC	Inter	3.9 – 6.1	2.9 – 3.9	6.1 – 13.2	1.9 – 10.5
	Intra	2.9 – 6.4	1.4 – 4.3	3.8 – 12.7	0.9 – 9.7
Accuracy (%) Range for QC	Inter	-5.3 – 1.3	1.6 – 2.8	-2.5 – 9.5	-0.76 – 2.1
	Intra	-7.2 – 1.3	-1.5 – 6.0	-6.4 – 19.1	-7.5 – 9.9
Stability of Analyte in Plasma Matrix	No. of Freeze/Thaw Cycles	6	6	3	5
	Room Temperature	24 h	24 h	24 h	24 h
	Long Term	11 days at -20°C ± 10°C	7 days at -20°C ± 10°C	28 days at -20°C	10 days at -20°C & -70°C 442 days at -20°C

Reference ID: 3450667

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for Brandname XR™ extended-release oral capsules and found it acceptable provided that an agreement is reached between the Sponsor and the Agency regarding the revised 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

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205-122	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	DCP-1	**Generic Name**	Topiramate extended-release (ER) capsules
Medical Division	HFD-120	**Drug Class**	Anticonvulsant
OCP Reviewer	Ta-Chen Wu, Ph.D.	**Indication(s)**	• Initial monotherapy in patients ≥10 years of age with partial onset seizures (POS) or primary generalized tonic clonic (PGTC) seizures • Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with POS or PGTC seizures, and in patients ≥2 years of age with seizures associated with Lennox Gastaut syndrome (LGS).
OCP Team Leader	Angela Men, M.D., Ph.D.	**Dosage Form**	Extended-release multi-bead capsules (25, 50, 100, 150 and 200 mg strengths)
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.	**Dosing Regimen**	Once daily (See Appendix 1 under Clin Pharm & Biopharm Information section for details)
Date of Submission	02/11/2013	**Route of Administration**	Oral
Estimated Due Date of OCP Review	10/01/2013	**Sponsor**	Upsher-Smith Laboratories, Inc. (USL)
Medical Division Due Date	10/11/2013	**Priority Classification**	S (Original 505(b)(2) NDA)
PDUFA Due Date	12/11/2013		

Clin. Pharm. and Biopharm. Information

Summary:

The sponsor seeks approval of (b) (4) (Topiramate extended-release capsules) via a clinical pharmacology-based 505(b)(2) NDA application for the same epilepsy indications as the reference product, Topamax®, with a modified monotherapy pediatric age range, due to marketing exclusivity for the Topamax® for "new patient population" (i.e., ≥2 to <10 years of age) listed in the FDA Orange Book. The Sponsor does not seek migraine indication. The proposed dosing regimens are presented in Appendix 1. The (b) (4) capsules (25 mg, 50 mg, 100 mg, 150 mg, and 200 mg strengths) for QD dosing consist of hypromellose capsules containing beads (b) (4)

(b) (4)

Formulations: USL255-MD and -MJ (used in Phase 1); USL255-MK (TBM); formulation MJ differs from MK in only capsule colors and size of the 200 mg capsule (no bridging was necessary).

Clinical Pharmacology Program:
This is a clinical pharmacology-based 505(b)(2) application which contains 9 human clinical studies in healthy adults (including 2 pilot studies P08-003 and -008) in the submission, as summarized below.

P08-003: Early development relative BA study [will not be reviewed]
P08-008: Formulation selection relative bioavailability study [will not be reviewed]

P09-001: Single-dose proportionality study
- 25-400 mg dose range; dose-proportionality

P09-002: Single-dose food-effect and relative BA study
- USL255 200 mg fasted vs. USL255 200 mg fed vs. Topamax® 100 mg Q12h (1st dose fasted)

P09-003: Steady-state PK equivalence study
- 50-400 mg once-daily in the evening (QPM); dose-proportionality at steady-state
- Multiple-dose PK equivalence (AUC0-24, Cmax, Cmin) between USL255 200 mg QD and Topamax® 100 mg Q12h at steady state and immediately after switching from IR BID to ER QD.
  - Post-hoc analysis for partial AUCp over a 24 hour dosing interval (USL255 200 mg QD vs. Topamax® 100 mg Q12h) => partial AUC (AUC0-t and AUCt1-t2)
  - Post-hoc equivalence analysis to support the switching between Topamax and USL255.

P09-011: Single ascending dose/maximum tolerated dose study
- 600-1400 mg dose range; dose-proportionality

P255-102: Single-dose bridging and sprinkle BE study
- 4-way crossover BE (bridging) between the 200-mg USL255 Phase 1 formulation (MD) and the TBM formulation (MK), between USL255 manufactured at (b) (4) site (MK (b) (4) and USL Denver site (MK-D), and between USL255 (MK-D) whole capsule and sprinkle (on soft food) administration.

P255-103: Steady-state PK and cognition study
- PK equivalence of USL255-MJ 200mg (fasted), 300mg (fed) and 400mg (fasted) once-daily in the evening (QPM) (50-400 mg studied) vs. Topamax IR of same doses (BID) => partial AUC (AUC0-t and AUCt1-t2)
- Assessing dose-proportionality at steady-state (Cmax, Cmin, AUC); food effect (300 mg/day dose); safety and tolerability

P255-101: Steady-state PK and cognition study [early termination; endpoints not analyzed; will not be reviewed]

Supportive analysis: [not in Tabular listing; no specific electronic datasets provided]
- Dose-proportionality pooling data from Studies P09-001 and P09-011 (25-1400 mg dose range)

Postmarketing Experience: [not in Tabular listing; no electronic datasets provided]
- PK/PD simulation for steepness of PK/PD curve (mono- and adjunctive therapy)
- Simulation for shape of curve between USL255 and Topamax IR (19 subjects)
- Delayed dose modeling and simulation report

Waiver requested:
1. Biowaiver of in vivo relative BA/BE studies for the 25 mg, 50 mg, 100 mg, and 150 mg strengths of USL255 capsules on the basis of BE between 200mg USL255 and Topamax IR (100mg BID) of 200mg strength, formulation proportionality in active and inactive ingredients, utilizing the (b) (4) beads with (b) (4) extended-release coating (b) (4)
2. (b) (4)
3. (b) (4)

Bioanalytical reports: The plasma concentration of topiramax was determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method:
- Validation report LCMS470 at (b) (4) for Studies P09-001, P09-002, P09-003, P09-011, P255-102

Reference ID: 3450667

- Validation report LCMS610 at (b) (4): for StudyP255-103
- Validation reports V0805024.00 and V0908024.00 at (b) (4) for Studies P08-003 and P08-008, respectively

Alcohol induced dose-dumping:
In vitro dissolution study using 200mg strength in pH 1.2, pH 4.5 and pH 7.2 media for 2 hours; ethanol levels were 0, 5, 20, and 40% at each pH. Results are presented in Appendix 2.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			• Annotated side-by-side comparative labeling in PDF • Word and PDF labelings.
Reference Bioanalytical and Analytical Methods	**X**			• Method validation (LC/MS/MS; 4 validation reports; 2 at (b) (4) supporting early (b) (4) development, 2 at support pivotal studies), in-study validation, QC performance are provided. • In-study validation and QC performance are provided.
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
Healthy Volunteers-				All studies were conducted in healthy subjects
single dose:	**X**			P08-003, P08-008, P09-002, P09-011 (MTD),
multiple dose:	**X**			P08-008, P09-003, P255-101
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting / non-fasting single dose:	**X**			P08-008, P09-001, P09-011
fasting / non-fasting multiple dose:	**X**			P255-103, P255-101, P255-103
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	-			
renal impairment:	-			
hepatic impairment:	-			
PD -				
Phase 2:	-			
Phase 3:	-			
PK/PD -	**X**			PK/PD curve simulation for Topamax IR

Reference ID: 3450667

Phase 1 and/or 2, proof of concept:	**X**			P255-101, P255-101 (steady-state PK and cognition)
Phase 3 clinical trial:	-			
Population Analyses -				Simulation reports based on established PopPK and PK/PD models for Topamax IR
Data rich:	-			
Data sparse:	-			
II. Biopharmaceutics				
Absolute bioavailability	-			
Relative bioavailability -				
solution as reference:	-			
alternate formulation as reference:	**X**			P09-002, P09-003 (ER vs. IR), P255-101, P255-103
Bioequivalence studies -				
traditional design; single / multi dose:	**X**			P255-102 (clinical formulation vs. TBM formulations of different manufacturing sites)
replicate design; single / multi dose:	-			
Food-drug interaction studies	**X**			P09-002 (highest 200mg strength), P255-103, P255-101, P255-103
Bio-waiver request based on BCS	-			
BCS class	-			
Dissolution study to evaluate alcohol induced dose-dumping	**X**			(b) (4) [redacted]
III. Other CPB Studies				
Genotype/phenotype studies	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			(b) (4) [redacted]
Literature References	**X**	**160**		
Total Number of Studies		**17**		9 Phase 1 (6 will be reviewed) + 4 validation reports + 4 supportive analyses

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
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

Reference ID: 3450667

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			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Datasets for the additional supportive analyses are not included (these analyses were not included during pre-submission discussions).
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
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 • PK/PD simulation for steepness of PK/PD curve for Topamax IR (mono- and adjunctive therapy)
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 and exposure-response in the clinical pharmacology section of the label?	X			Cross-reference to approved Topamax label with additional information for USL255
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design	X			

	and breadth of investigation to meet basic requirements for approvability of this product?				
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 P09-003: (Steady-State PK Equivalence Study)
   Clinical sites: PPD Phase I Clinic
   7551 Metro Center Drive
   Building 10, Suite 200
   Austin TX 78744
   Phone: 512-447-2985
   Analytical site: (b) (4) [redacted]

2. Please provide the electronic datasets that were used in (1) supportive meta-analysis for the dose-proportionality for 25-1400 mg dose range, and (2) supportive analyses (i.e., Topiramate IR Shape Simulation Report and Steepness of Concentration-Response Simulation Reports) in Module 5.3.6 Reports of Postmarketing Experience.

3. Please provide the Data Definition files for all the clinical pharmacology and biopharmaceutics studies in PDF format.

Ta-Chen Wu
Clinical Pharmacology Reviewer Date

Angela Men
Team Leader Date

Reference ID: 3450667

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

/s/

TA-CHEN WU
02/07/2014

YUXIN MEN
02/07/2014

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 205-122 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DNP		
Applicant:	Upsher-Smith	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	TBD	**Acting Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D.	
Generic Name:	Topiramate (USL255) Extended Release Capsules	**Date Assigned:**	April 18, 2013
Indication:	Antiepileptic drug	**Date of Review:**	Jan 13, 2014
Formulation/strength	ER Capsules, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	**Date of informal/Formal Consult**	**PDUFA DATE**
Feb 11, 2013 May 21, 2013 Aug 30, 2013. Oct 28, 2013	April 14, 2013	Feb 12, 2014

Type of Submission:	Original NDA
Key review points	1. Dissolution method and acceptance criteria 2. IVIVC 3. In vitro Alcohol Dose-Dumping 4. Biowaiver Request Supporting Approval of the Lower Strengths 5. Extended Release-Designation Claim 6. Bridging Across Phases of Drug Development 7. Role of dissolution in supporting several drug product specification limits

Reference ID: 3436609

TABLE OF CONTENTS

Reference ID: 3436609

criteria based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES **16**

13. What are the highlights of the drug product formulation development?

14. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

15. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

D) DISSOLUTION APPLICATIONS **19**

D.1 BIOWAIVERS

16. Is there a waiver request of in vivo BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

17. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data are provided to support the acceptability of the IVIVC model?

18. Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim of lack of dose-dumping in the presence of alcohol?

D.2 SURROGATES IN LIEU OF DISSOLUTION **24**

19. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

D.3 DISSOLUTION AND QBD **24**

20. Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

21. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

22. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

23. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

Reference ID: 3436609

1) SUMMARY OF BIOPHARMACEUTICS FINDINGS

USL255 is an oral extended-release capsule formulation of the antiepileptic drug (AED) topiramate designed for once-daily dosing for patients 10 year and older. The product consists of topiramate and excipients in multiparticulate beads with an extended release coating encapsulated in hypromellose capsules to provide the following strengths: 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg.

The reference drug for USL255 is the immediate-release product, Topamax® tablets (available as 25 mg, 50 mg, 100 mg, and 200 mg). Topamax® is approved in the United States for the treatment of epilepsy, in addition to an indication for the preventative treatment of migraine. Topamax® is approved as an initial monotherapy, or as adjunctive therapy, for adults and pediatric patients ≥ 2 years of age with POS or PGTC. Topamax® is also indicated as adjunctive therapy in patients ≥ 2 years of age with seizures associated with LGS. For the epilepsy indications, an initial dose of 25 mg or 50 mg/day is recommended, followed by up-titration to the maintenance dose.

The clinical program consisted of nine Phase 1 studies, six of which were BA/BE studies. Data regarding the dose proportionality of USL over the dose ranges of 25 mg to 400 mg (P01-001) and 600 mg to 1400 mg (P09-011) are reported after single dose and multiple doses of USL255. The product and process development of topiramate ER capsules was conducted under a Quality by Design (QbD) paradigm to ensure a desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the Critical Quality Attributes (CQAs) for the drug product.

This review focuses on the evaluation of: **1)** The acceptability of the dissolution method and acceptance criteria; **2)** The proposed IVIVC model; **3)** The in vitro alcohol-dose-dumping; **4)** The biowaiver request supporting approval of the lower strengths; **5)** The extended release-designation claim; **6)** The data supporting appropriate bridging across the phases of drug development; and **7)** The role of dissolution in supporting several drug product specification limits.

1) Dissolution Method and Acceptance Criteria:
The following dissolution method and dissolution acceptance criteria have been found acceptable (refer to submission dated Oct 28, 2013):

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criteria
I (basket)	100 rpm	900mL	37°C	50 mM TRIS Buffer, pH=7.2	**1 hr:** NMT (b) (4) **2 hrs:** (b) (4) **6 hrs:** NLT (b) (4)

The Applicant submitted sufficient information to support the discriminating ability of the dissolution method. The dissolution acceptance criteria was based on the mean dissolution profiles of pivotal clinical (BE batches) and stability batches.

2) Proposed IVIVC Model

The Applicant submitted an IVIVC correlation model [redacted] and it was not accepted. On a submission dated May 31, 2013, the Applicant acknowledged these deficiencies and stated that they do not plan to utilize the proposed IVIVC model for regulatory-decision making.

3) The In Vitro Alcohol-Dose-Dumping

The alcohol *in vitro* alcohol dose-dumping drug release studies were conducted using different media conditions (pH 1.2 HCl buffer, pH 4.5 sodium acetate buffer, and pH 7.2 TRIS buffer) and alcohol concentrations (0%, 5%, 20%, and 40% v/v ethanol).

The results of these studies showed that the integrity of the functional coating on the beads is compromised at the higher 20% and 40% ethanol concentrations. The loss of integrity of the functional coating leads to rapid *in vitro* drug release from the beads in the QC method in the presence of 40% ethanol and to a lesser extent in the presence of 20% ethanol. There was limited/no impact on *in vitro* drug release at the 5% ethanol level. No significant effect was observed at pH values of 1.2 (Figure 8) or pH 4.5.

During the NDA's Mid-Cycle meeting that took place on Oct 2013, this Reviewer presented the above in vitro-alcohol dose-dumping results and conveyed the following comment to the review team:

- *The clinical relevance of the in vitro alcohol dose-dumping results needs to be evaluated by the ClinPharm and Clinical teams.*

4) The Biowaiver Request Supporting Approval of the Lower Strengths

A waiver request for the requirement to submit in vivo BA/BE studies for the 25 mg, 50 mg, 100 mg, and 150 mg strengths of USL255 Topiramate ERR) Capsules versus the reference drug product, TOPAMAX® (topiramate) tablets was submitted. This biowaiver request is supported by the following data:

1. A relative BA and pharmacokinetic equivalence of the 200 mg USL255 Topiramate ER Capsules, with once daily dosing (QD) versus the 100 mg TOPAMAX® Tablets, with twice a day dosing (BID).
2. In vivo dose proportionality studies for overall exposure over the 25 mg – 1400 mg range of USL255 Topiramate ER Capsules (refer to the OCP review for details on the findings of these studies). The results from these studies indicate that the 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg strengths of USL255 Topiramate ER Capsules are proportionally similar in their active and inactive ingredients, utilizing [redacted] beads with [redacted] extended-release coating [redacted] filled into hard hypromellose capsules to produce each strength. The capsule strengths differ only in the color and size of the capsules [redacted].
3. Although not needed since an in vivo dose-proportionality study was conducted utilizing the proposed strengths (except the 150 mg strength), dissolution profiles comparisons with statistical testing (*f2* testing) were also included in different media to support the approval of the lower strengths. All the *f2* values comparing the lower strengths to the 200 mg capsules were higher than 50, indicating similarity.

Based on the above data the Biowaiver for the lower 25 mg, 50 mg, 100 mg, and 150 mg strengths is granted, provided OCP finds the pivotal BE study linking the proposed product to the reference drug acceptable.

5) The Extended Release-Designation Claim

The following data were provided to support the extended release designation claim:

- The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA;
- The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product;
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;

Data from multiple dose Study P03-03 demonstrated that the USL255MD plasma concentration-time curves following once daily administration have a smoother PK profile (e.g., lower Cmax and similar Cmin) with a decreased fluctuation index at steady-state plasma concentrations over 24 hours as compared with Topamax® given twice daily. In addition, the proposed product's %CV values for the relevant PK parameters are comparable and in some instances lower (e.g., for Tmax values) to those reported for the reference drug. In conclusion, the overall data support the extended-release claim for the proposed product and is acceptable.

6) Data Supporting Appropriate Bridging Across Phases of Drug Development

There were some major process and formulation changes implemented to the Phase 1 clinical trial formulation. These changes are supported by the result of two BA/BE studies linking the early formulations to the to-be-marketed formulation as described in the formulation development section. These studies are being reviewed by OCP. The definitive food effect study was conducted with the MD formulation. The MD formulation and the to-be-marketed formulation were bridged through PK Study P255-102. In addition, PK study P255-102 bridged the two proposed manufacturing sites, (b) (4) (b) (4) and Upsher-Smith Laboratories, Inc., Denver, CO (USL Denver facility).

Dissolution profile comparisons between the **MJ** and **MK** formulations were submitted in response to the FDA's information request to bridge these formulations. The USL255-200- **MK** (200 mg) product utilizes a slightly smaller capsule than the USL255-200-**MJ** product, in addition to having a different color. All **MJ** and **MK** batches were tested with the proposed QC method (TRIS buffer medium) at the time of release. All f2 values are above 50 indicating that for all strengths the **MJ** batches and **MK** batches are similar.

7) The Role of Dissolution in Supporting Several Drug Product Specification Limits

Several DoE studies were conducted to determine the effect product and process changes had on drug release. The following product characteristics and process changes which have an impact on drug release were identified:

(b) (4)

[redacted] (b) (4) Specifically, the dissolution method and recommended dissolution acceptance criteria will served as a QC tool to reject batches with release properties and manufactured under process parameters/material attributes other than those tested in the pivotal clinical trials (e.g. pivotal BE study).

II) RECOMMENDATION

From the Biopharmaceutics perspective, NDA 205-122 for Topiramate ER Capsules, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

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

Reference ID: 3436609

III) QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

1. ***What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?***

Drug Substance

Topiramate general physicochemical characteristics are summarized in Table 1.

Table 1. Topiramate General Properties

Appearance:	White to off-white powder	
Melting Range:	123 C to 127 C	
Specific Optical Rotation:[1]	Between –28.6 and –35.0 (0.4% in methanol at 20 C)	
Solubility:	Topiramate USP is freely soluble in dichloromethane. The solubility of topiramate USP is approximately 1:10 in acetone, chloroform, dimethylsulfoxide, ethanol, glacial acetic acid, and methanol. The solubility in water (unbuffered) is 9.8 mg/ml at 23□C. Aqueous solubility is a function of pH.	
	Solvent Media and pH	**Solubility (mg/mL) at 37°C**
	Aqueous buffer: pH 1.0	5.1 ± 0.2
	Aqueous buffer: pH 2.4	12.6 ± 0.0
	Aqueous buffer: pH 4.5	12.2 ± 0.0
	Aqueous buffer: pH 7.4	11.5 ± 0.2
	Aqueous buffer: pH 8.6	14.1 ± 0.1
	Aqueous buffer: pH 9.8	21.0 ± 0.2
Partition Coefficients:	Log P (octanol/water): 0.53	
Experimental Log P/Hydrophobicity:	-0.7 (Drug bank)	
Dissociation Constants:	pKa: 8.66	
Polymorphism:	Topiramate USP exists in a (b) (4) form.	
Chirality:	Topiramate USP has four chiral carbons. (b) (4) manufactures the levo form of Topiramate USP.	
UV Spectrum:	Topiramate USP is a carbohydrate derivative, which does not contain a good UV chromophore. It does not exhibit distinct UV spectra.	
Hygroscopicity:	Topiramate USP exhibits no pronounced hygroscopic behavior.	
Particle Size:	Topiramate USP is micronized to achieve a particle size of: (b) (4)	

Reference ID: 3436609

Drug Product

Topiramate Extended-Release (ER) Capsules, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg were developed as a treatment for initial monotherapy and adjunctive therapy for patients with partial onset or primary generalized tonic-clonic seizures and adjunctive therapy for patients with seizures associated with Lennox-Gastaut syndrome. Topiramate ER Capsules were developed for once daily dosing and consist of hypromellose capsules containing coated beads. The composition of the coated beads includes topiramate, microcrystalline cellulose and hypromellose, (b) (4) The components and composition of Topiramate ER Capsules, 200 mg are summarized in Table 2.

Table 2. Composition of Topiramate ER Capsules, 25 mg

Ingredient	Function	Base Formulation (% w/w)	mg/capsule	Overall Formulation (% w/w)	IIG Maximum (solid oral) mg/dose
Core Bead Components					
Topiramate, USP	Drug substance	(b) (4)			
Microcrystalline Cellulose, NF (b) (4)					
Hypromellose 2910, (b) (4)					
(b) (4)					
Coating Components					
Ethylcellulose, NF (b) (4)					
Hypromellose 2910, USP (b) (4)					
Diethyl Phthalate, NF					
(b) (4)					
Hypromellose 2910, USP					
Titanium Dioxide, USP (b) (4)					
Black Iron Oxide, NF					
Red Iron Oxide, NF					
		Theoretical Total	**99**	**100.0**	

Reviewer's Comments
All the strengths are proportionally similar in its active and inactive ingredients (formulas not shown here, refer to \\cdsesub1\evsprod\NDA205122\0000\m2\23-qos).

2. ***Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?***

According to the BCS system, topiramate is considered a highly soluble drug substance. The highest dosage strength (200 mg) is soluble in less than 250 mL across the relevant physiological pH range of 1 to 7.5. Given that the absorption of the drug substance from a topiramate ER product is primarily dependent upon drug dissolution which is in turn controlled by the ER attributes, this information is not critical for regulatory decision-making.

3. ***Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant's claim?***

The following information was included in the submission to support the extended release designation claim:

- The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
- The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;

The data from multiple dose Study P03-03, demonstrated that the USL255MD plasma concentration-time curves following once daily administration have a smoother PK profile (e.g.., lower C_{max} and similar C_{min}) with a decreased fluctuation index at steady-state plasma concentrations over 24 hours as compared with Topamax® given twice daily. In addition, the proposed product's %CV values for the relevant PK parameters are comparable and in some instances lower (e.g., for Tmax values) to those reported for the reference drug (Table 3).

Reference ID: 3436609

Table 3. Overall Summary of Arithmetic Mean (SD) of Topiramate ER Capsules and Topomax PK Parameters following multiple dose administration

Pharmacokinetic Parameter	Day 14 and 28				Day 15			
	200 mg USL 255MD QD (n =		100 mg Topamax® (Q12h) (n = 36)		200 mg USL 255MD QD (n = 17)		100 mg Topamax® (Q12h) (n = 19)	
	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV	Mean (SD)	% CV
AUC_{0-24h} (µg·h/mL)	158 (31.6)	20.0	153 (33.2)	21.7	150 (23.9)	15.9	156 (39.3)	25.2
AUC_{tau} (µg·h/mL)	158 (31.6)	20.0	78.1 (16.8)	21.5	150 (23.9)	15.9	79.2 (19.6)	24.7
C_{max} (µg/mL)	7.88 (1.50)	19.1	8.43 (1.66)	19.7	7.51 (1.35)	18.0	8.36 (1.82)	21.8
t_{max} (h)	6.00 (2.00, 17.00)	47.4	1.00 (0.50, 14.00)	157	6.00 (4.00, 10.18)	33.8	1.58 (0.50,14.07)	126
C_{min} (µg/mL)	5.31 (1.19)	22.4	5.03 (1.21)	24.1	5.02 (0.914)	18.2	5.14 (1.44)	28.0
C_{avg} (µg/mL)	6.60 (1.31)	20.0	6.51 (1.40)	21.5	6.25 (0.996)	16.0	6.60 (1.63)	24.7
FI	0.40 (0.11)	26.5	0.53 (0.12)	21.9	0.40 (0.11)	27.4	0.50 (0.12)	23.8

B) DISSOLUTION INFORMATION

4. What is the proposed dissolution method?

The dissolution method proposed as a quality control tool for all the strengths of Topiramate ER Capsules is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
I	100 rpm	900mL	37°C	50 mM TRIS Buffer, pH=7.2

5. What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

Dissolution Method Development

Following an IR letter submitted on May 21, 2013, the Applicant included data supporting the acceptability of the proposed dissolution method. Briefly, the dissolution method was evaluated to determine the effect that varying dissolution parameters would have on the *in vitro* drug release (for more detail refer to; \\cdsesub1\evsprod\NDA205122\0005\m1\us.

Reference ID: 3436609

The following method parameters were evaluated.
1. Dissolution media pH
2. Media concentration/ionic strength
3. Apparatus
4. Agitation Rate

From these series of studies, the TRIS buffer dissolution method was selected and further evaluated to determine the effect that varying dissolution parameters would have on the *in vitro* drug release. The influence of 1) apparatus, 2) rotation speed and 3) media ionic strength on *in vitro* drug release was evaluated. The results of these studies are shown in Figure 1.

Figure 1. Drug Release Profile Dependence on Dissolution Method Parameters.

Reviewer's Comments
The Applicant included a comprehensive dissolution method report. In summary, the in vitro drug release from the extended release beads was independent of most dissolution parameters. The TRIS buffer was selected for the dissolution media because it readily solubilizes the HPMC capsules and allows for a direct evaluation of the drug release from the coated beads. USP apparatus 1 was selected because of the possibility of greater variability in drug release with the other two commonly used USP apparatus. In addition, sufficient information demonstrating the discriminating ability of the method supports its acceptability (see data below).

6. ***What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?***

Dissolution Method Validation

The Applicant provided enough information to support the validity of the analytical method for dissolution testing of the Topiramate ER Capsules (refer to CMC review for more details; also see bionalytical report at: \\cdsesub1\evsprod\NDA205122\0000\m3\32-body-data\32p-drug-prod\topiramate-er-capsule\32p5-contr-drug-prod\32p52-analyt-proc/tm-00370).

7. ***What data are available to support the discriminating power of the method?***

In response to an IR letter submitted on May 21, 2013, the Applicant included data supporting the discriminating ability of the proposed dissolution method. The Applicant states that the drug release is related to (b) (4) The discriminating power of the dissolution method was tested against these tablet properties that could affect product performance as follows:

(b) (4)

(b) (4)

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8. Is the proposed dissolution method biorelavant? What data are available to support this claim?

There were no data in the submission to help in the assessment of the bio-relevancy of the method (e.g. the ability of the method to reject batches that are not bioequivalent). However, data for BE study P255-102 (a Phase 1 randomized, single-center, open-label, single-dose, four-way crossover study to assess the relative BA of three formulations of USL255 200 mg (USL255-MK (b) (4) and USL255-MK-D) showed that the dissolution method does not reject batches that are BE. Specifically, these tree batches met both the BE criteria (see table below) and the similarity testing (e.g., f2>50, Figure 3 comparing the MK (b) (4) batch 294278 vs. MK-D batch 289503).

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Topiramate MK (b) (4) Intact (Treatment A) Versus MK-D Intact (Treatment D) (n=36)

Parameter	Geometric LSM[a]		Ratio of Geometric LSM (%)[b]	90% CI of Ratio[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
C_{max} (ng/mL)	3466.2123	3299.4754	105.05	99.84	110.53
AUC_{0-t} (h•ng/mL)	196614.1926	194152.3713	101.27	97.95	104.70
AUC_{0-inf} (h•ng/mL)	199024.6124	196582.5150	101.24	97.87	104.73

[a]Geometric Mean for USL255 200 mg MK (b) (4) Intact (Test) and USL255 200 mg MK-D, Intact (Ref) based on Least Squares Means of log-transformed parameter values.

9. Is the proposed method acceptable? If not, what are the deficiencies?

The Applicant provided adequate information to support the acceptability and discriminating power of the proposed dissolution method.

B.2. ACCEPTANCE CRITERIA

10. What are the proposed dissolution acceptance criteria for this product?

The following dissolution acceptance criteria were proposed by the Applicant as a QC for the release of all strengths of Topiramate ER, Capsules:

Proposed Dissolution Acceptance criteria
1 hr: NMT (b) (4)
2 hrs: (b) (4)
6 hrs: NLT (b) (4)

11. What data are available to support these criteria?

According to the Applicant, the proposed criteria are based on release data from multiple formulations including the commercial scale batches tested in the pivotal BE study P255-102.

Reference ID: 3436609

12. ***Are the acceptance criteria acceptable? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?***

The originally proposed dissolution acceptance criteria were NOT acceptable. The proposed ranges (b) (4) did not follow the guidance recommendations and there were no in vivo data available to support the wider ranges. Based on data (Figure 5) submitted in response to the IR letter dated May 31, 2014, the dissolution acceptance criteria below were recommended on an IR letter dated Oct 08, 2013.

Figure 5. Mean dissolution profiles of batches used in Pivotal PK Studies and representative commercial batches (data constructed using data submitted on Aug 30, 2013)

Comments sent on IR letter dated Oct 08, 2013:

1. ***The provided dissolution data do not support the selection of your proposed acceptance criteria ranges for the 1 and 2 hour time points. Implement the following dissolution acceptance criteria for your proposed product and provide the updated specifications table for your product with the revised criteria.***

Acceptance criteria
1 hr: (b) (4)
2 hrs: (b) (4)
6 hrs: NLT (b) (4)

On the submission dated Oct 28, 2013, the Applicant submitted an updated sheet of specification reflecting the above recommended dissolution acceptance criteria.

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

13. What are the highlights of the drug product formulation development?

Two clinical studies were conducted to evaluate early USL255 ER formulations using the multi-particulate bead technology. (b) (4)

(b) (4) An ER formulation with the preferred release profile (USL255-MD) was selected from study P08-008 and was further studied in the pivotal clinical trials (P09-001, P09-002, P09-003, and P09-011).

(b) (4) In study P255-102, the to-be-marketed formulation (USL255-MK) was compared with the clinical trial formulation (USL255-MD).

(b) (4)

USL255-200-MK (b) (4) and USL255-200-MK represent the final to-be-marketed formulations manufactured at alternate manufacturing sites, (b) (4) and Upsher-Smith Laboratories, Inc., Denver, CO (USL Denver facility), respectively. Hereafter, these two sites will be referred to as (b) (4) facility and Denver facility. Study P255-102 also evaluated the effect of site change (e.g. Denver vs. (b) (4). A schematic Overview on the Topiramate Oral Formulation Development is shown in Figure 6. All BA/BE studies are being review by the OCP reviewer.

(b) (4)

Figure 6. Schematic overview of Topiramate ER Capsules formulation development

Reference ID: 3436609

A list of the formulations used in each clinical study can be found in Table 1, under Summary of Biopharmaceutics section (\\cdsesub1\evsprod\NDA205122\0000\m2\27-clin-sum). Table 4 contains a list of the core bead and coating components for each formulation.

Table 4. Core Bead and Coating Components of USL255 Formulations Used in Clinical Studies

Formulation Designation	(b) (4) MK*	
	Small Scale	Commercial Scale
Ingredient	Overall Coated Bead Formulation (% w/w)	
Core Bead Components		
Topiramate, USP		(b) (4)
Microcrystalline Cellulose, NF	(b) (4)	(b) (4)
Hypromellose 2910, USP	(b) (4)	(b) (4)
Coating Components		
	(b) (4)	(b) (4)
Ethylcellulose, NF	(b) (4)	
Hypromellose 2910, USP	(b) (4)	
Diethyl Phthalate, NF		(b) (4)

14. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

USL255 capsules are available at dosage strengths of 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. The range of capsule strengths is provided to support the proposed labeling including titration and maintenance doses.

Three clinical studies were conducted to establish the dose proportionality and PK profile of topiramate following administration of USL255. Therefore, the approval of the lower strengths (except the 150 mg strength) is based on the results of these dose-proportionality studies which are being review by OCP.

Specifically, the single dose PK of topiramate after administration of USL255 covering the dose range of 25 mg to 400 mg was evaluated in Study P09-001 and the dose range of 600 mg to 1400 mg in Study P09-011. A meta-analysis was also conducted combining the results of Studies P09-001 and P09-011 to assess the dose proportionality of USL255. According to the Applicant, the results of the meta-analysis confirmed the dose proportionality of C_{max} over a dose range of 50 mg to 1400 mg and AUC_{∞} and AUC_t over a dose range of 25 mg to 1400 mg. A third study (Study P255-103) investigated the dose proportionality of USL255 at steady state over the dose range of 50 mg QPM to 400 mg QPM. The Applicant stated that the results of this study established the dose proportionality of USL255 C_{min} over the dose range of 100 mg to 400 mg and C_{max} and $AUC_{0\text{-}24h}$ over the dose range of 200 mg to 400 mg.

Additionally, a biowaiver request and supporting information were included to support the approval of all the lower strengths (see section below on biowaivers).

15. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

There were some major process and formulation changes implemented to the Phase 1 clinical trial formulation. These changes are supported by the result of two BA/BE studies linking the early formulations to the to-be-marketed formulation as described in the formulation development section above. These studies are being reviewed by OCP. The definitive food effect study was conducted with the MD formulation. As stated above, the MD formulation and the to-be-marketed formulation were bridged through PK Study P255-102. In addition, PK study P255-102 bridged the two proposed manufacturing sites, (b) (4) and Upsher-Smith Laboratories, Inc., Denver, CO (USL Denver facility).

Dissolution profile comparison data bridging the MJ and MK formulations were submitted in response to the FDA's IR request dated Oct 08, 2013. Note that the USL255-200- MK (200 mg) formulation utilizes a slightly smaller capsule than the USL255-200-MJ formulation, in addition to having a different color. Table 5 summarizes the batches used in the comparison.

Table 5. Batches Selected for F2 Comparison

Strength	MJ Batch (Encapsulation)	MK Batch (Encapsulation)
200	283269[1]	294278[1]
100	283261[1]	294276
50	283256[1]	294272
25	284299	294270

1 PK Pivotal Clinical Batches

All MJ and MK batches were tested with the proposed QC method (TRIS buffer medium) at the time of release. All f2 values are above 50 indicating that for all strengths the MJ batches and MK batches are similar (refer to Figures 1-4 and Tables 4-11 on section \\cdsesub1\evsprod\NDA205122\0008\m1).

Reference ID: 3436609

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

16. Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

The Applicant included a biowaiver request for the requirement to submit data from in vivo BA/BE studies for the 25 mg, 50 mg, 100 mg, and 150 mg strengths of USL255 Topiramate Extended-Release (ER) Capsules versus the reference drug product, TOPAMAX® (topiramate) tablets approved under NDA 020505. This waiver request is based upon fulfillment of the following criteria:

1. A relative BA/BE and pharmacokinetic equivalence study of the 200 mg USL255 Topiramate ER Capsules, with once daily dosing (QD) versus the 100 mg TOPAMAX® Tablets, with twice a day dosing (BID). According the Applicant the BE between these products was demonstrated. Refer to OCP review for details on this study.
2. As mentioned previously, the in vivo dose proportionality for overall exposure was demonstrated over the 25 mg – 1400 mg range of USL255 Topiramate ER Capsules (refer to OCP review for details on the findings of this study).
3. The 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg strengths of USL255 Topiramate ER Capsules are proportionally similar in their active and inactive ingredients, utilizing (b) (4) beads with (b) (4) extended-release coating (b) (4) filled into hard hypromellose capsules to produce each strength. The capsule strengths differ only in the color and size of the capsules (b) (4)
4. Although not needed since an in vivo dose-proportionality study was conducted utilizing the proposed strengths (except the 150 mg strength), dissolution profiles comparisons (Figure 7) with statistical testing (*f2* testing) (Table 6) were also included to support the approval of the lower strengths.

Figure 7. Topiramate ER Capsules, 25, 50, 100, 150, and 200 mg In Vitro Drug Release in TRIS buffer.

Reference ID: 3436609

Table 6. Average results and f2 values in TRIS media with 200 mg Topiramate ER Capsule as Reference

T i	25 mg (MJ) (303232)	50 (MJ) (303231)	100 mg (MJ) (303230)	150 mg (MK) (303502)	200 mg (MK) (303501)
60	25	21	24	22	20
120	46	44	46	43	40
180	63	61	64	60	56
270	81	80	82	77	75
360	92	91	93	88	86
F2 value	61	69	59	77	reference

In addition, dissolution profiles comparison data in two different media, 0.01 HCl and acetate buffer pH 4.5 were also submitted. All the *f2* values comparing the 150 mg to the 200 mg capsules were higher than 50.

Reviewer's Comments

Statistical testing comparing all the strengths to each other was not included. However, since the f2 value comparing the 200 mg strength (b) (4) *to the 100 mg strengths* (b) (4) *was higher than 50, then it is highly likely that all the other strengths, which profiles are in between, also meet the similarity criteria.*

17. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data are provided to support the acceptability of the IVIVC?

An IVIVC correlation model was submitted. (b) (4) The following comments (deficiencies) were communicated to the Applicant as part of the 74-day letter:

(b) (4)

On a submission dated May 31, 2013, the Applicant acknowledged these deficiencies and stated that since they do not plan to utilize IVIVC further, no additional analyses in support of the IVIVC model and external validation of the IVIVC would be submitted.

18. Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim of lack of dose-dumping in the presence of alcohol?

The *in vitro* alcohol dose dumping studies were conducted consistent with FDA-requested methodology as outlined below:

Media: pH 1.2HCl buffer, pH 4.5 sodium acetate buffer, and pH 7.2 TRIS buffer
Alcohol levels: 0%, 5%, 20%, and 40% v/v ethanol
Samples: n= 12, 200 mg capsules (intended commercial formulation)
Apparatus: USP apparatus 1 (baskets) at 100 rpm
Pull points: Every 15 minutes out to 2 hours

The results of these studies showed that the integrity of the functional coating on the beads is compromised at high ethanol concentrations. The loss of integrity of the functional coating leads to rapid *in vitro* drug release from the beads in the QC method in the presence of 40% ethanol, and to a lesser extent in the presence of 20% ethanol. There was limited/no impact on *in vitro* drug release at the 5% ethanol level (Figure 8). No significant effect was observed at pH values of 1.2 (Figure 9) or pH 4.5 (Figure 10).

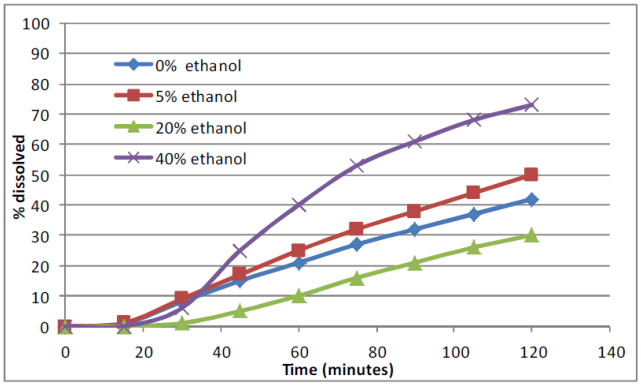

Figure 8. Drug Release from 200 mg Topiramate ER Capsule in pH 7.2 Medium Containing Varying Levels of Ethanol.

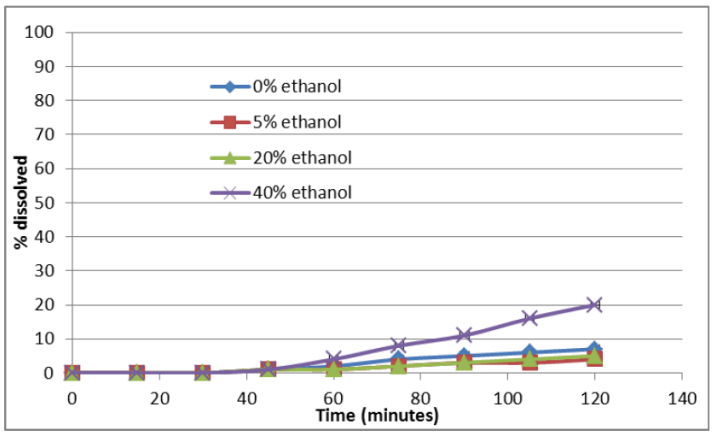

Figure 9. Drug Release from 200 mg Topiramate ER Capsule in pH 1.2 Medium Containing Varying Levels of Ethanol.

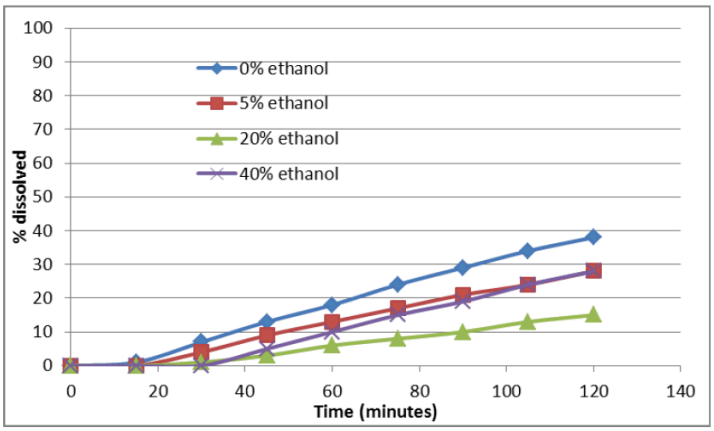

Figure 10. Drug Release from 200 mg Topiramate ER Capsule in pH 4.5 Medium Containing Varying Levels of Ethanol.

Reviewer's Comments

This reviewer presented the above in vitro-alcohol dose-dumping results during the mid-cycle meeting that took place on Oct 2013 and conveyed the following comment to the review team during:

- *The clinical relevance of the in vitro alcohol dose-dumping results needs to be evaluated by the ClinPharm and Clinical teams.*

D.2 SURROGATES IN LIEU OF DISSOLUTION

19. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?

No. In laboratory dissolution testing is being implemented.

D.3 DISSOLUTION AND QBD

20. If the application contains QbD elements, is dissolution identified as a CQA for defining design space?

Elements of Quality by Design and Quality Risk Management were applied to the development of these capsules. According to the Applicant, quality risk assessments and design of experiments (DoE) were performed to increase understanding of the robustness of the proposed commercial formulation and the parameters affecting the (b) (4) of the proposed commercial drug product process. Dissolution was identified as CQA.

From the QTPP, the critical quality attributes (CQAs) that could impact the safety and efficacy of topiramate ER capsules are the following:

1. Physical Attributes
2. Identity
3. Assay (potency)
4. Impurities/degradants
5. Content uniformity
6. Dissolution
7. Ethanol
8. Water Activity
9. Microbial Limits

21. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

As mentioned above, during the course of formulation development several DoE studies were conducted to determine the effect product and process changes had on drug release. (b) (4) did not influence the drug release. The following product characteristics and process changes which have an impact on drug release were identified:
(b) (4)

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Reference ID: 3436609

Average % Dissolution Data (n=3)

Batch number	1 hr. Disso (%)	2 hr. Disso (%)	3 hr. Disso (%)	4.5 hr. Disso (%)	6 hr. Disso (%)	9 hr. Disso (%)
PD334-142	(b) (4)					
PD334-134						
PD334-146						
PD334-126						
PD334-152						
PD334-150						
PD334-128						
PD334-130						
PD334-140						
PD334-154						
PD334-132						
PD334-156						
PD334-138						
PD334-144						
PD334-136B						
PD334-148						
PD342-029						
PD342-033						

Note results in bold red are outside the current proposed dissolution acceptance criteria

22. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

A design space is not being proposed.

23. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

No dissolution models were proposed.

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/s/

SANDRA SUAREZ
01/14/2014

ANGELICA DORANTES
01/14/2014

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
NDA/BLA Number	205-122	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	DCP-1	**Generic Name**	Topiramate extended-release (ER) capsules
Medical Division	HFD-120	**Drug Class**	Anticonvulsant
OCP Reviewer	Ta-Chen Wu, Ph.D.	**Indication(s)**	• Initial monotherapy in patients ≥10 years of age with partial onset seizures (POS) or primary generalized tonic clonic (PGTC) seizures • Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with POS or PGTC seizures, and in patients ≥2 years of age with seizures associated with Lennox Gastaut syndrome (LGS).
OCP Team Leader	Angela Men, M.D., Ph.D.	**Dosage Form**	Extended-release multi-bead capsules (25, 50, 100, 150 and 200 mg strengths)
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.	**Dosing Regimen**	Once daily (See Appendix 1 under Clin Pharm & Biopharm Information section for details)
Date of Submission	02/11/2013	**Route of Administration**	Oral
Estimated Due Date of OCP Review	10/01/2013	**Sponsor**	Upsher-Smith Laboratories, Inc. (USL)
Medical Division Due Date	10/11/2013	**Priority Classification**	S (Original 505(b)(2) NDA)
PDUFA Due Date	12/11/2013		

Clin. Pharm. and Biopharm. Information

Summary:

The sponsor seeks approval of (b) (4) (Topiramate extended-release capsules) via a clinical pharmacology-based 505(b)(2) NDA application for the same epilepsy indications as the reference product, Topamax®, with a modified monotherapy pediatric age range, due to marketing exclusivity for the Topamax® for "new patient population" (i.e., ≥2 to <10 years of age) listed in the FDA Orange Book. The Sponsor does not seek migraine indication. The proposed dosing regimens are presented in Appendix 1. The (b) (4) capsules (25 mg, 50 mg, 100 mg, 150 mg, and 200 mg strengths) for QD dosing consist of hypromellose capsules containing beads (b) (4)

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

(b) (4)

Formulations: USL255-MD and -MJ (used in Phase 1); USL255-MK (TBM); formulation MJ differs from MK in only capsule colors and size of the 200 mg capsule (no bridging was necessary).

Clinical Pharmacology Program:
This is a clinical pharmacology-based 505(b)(2) application which contains 9 human clinical studies in healthy adults (including 2 pilot studies P08-003 and -008) in the submission, as summarized below.

P08-003: Early development relative BA study [will not be reviewed]
P08-008: Formulation selection relative bioavailability study [will not be reviewed]

P09-001: Single-dose proportionality study
- 25-400 mg dose range; dose-proportionality

P09-002: Single-dose food-effect and relative BA study
- USL255 200 mg fasted vs. USL255 200 mg fed vs. Topamax® 100 mg Q12h (1st dose fasted)

P09-003: Steady-state PK equivalence study
- 50-400 mg once-daily in the evening (QPM); dose-proportionality at steady-state
- Multiple-dose PK equivalence (AUC0-24, Cmax, Cmin) between USL255 200 mg QD and Topamax® 100 mg Q12h at steady state and immediately after switching from IR BID to ER QD.
  - Post-hoc analysis for partial AUCp over a 24 hour dosing interval (USL255 200 mg QD vs. Topamax® 100 mg Q12h) => partial AUC (AUC0-t and AUCt1-t2)
  - Post-hoc equivalence analysis to support the switching between Topamax and USL255.

P09-011: Single ascending dose/maximum tolerated dose study
- 600-1400 mg dose range; dose-proportionality

P255-102: Single-dose bridging and sprinkle BE study
- 4-way crossover BE (bridging) between the 200-mg USL255 Phase 1 formulation (MD) and the TBM formulation (MK), between USL255 manufactured at (b) (4) site (MK (b) (4) and USL Denver site (MK-D), and between USL255 (MK-D) whole capsule and sprinkle (on soft food) administration.

P255-103: Steady-state PK and cognition study
- PK equivalence of USL255-MJ 200mg (fasted), 300mg (fed) and 400mg (fasted) once-daily in the evening (QPM) (50-400 mg studied) vs. Topamax IR of same doses (BID) => partial AUC (AUC0-t and AUCt1-t2)
- Assessing dose-proportionality at steady-state (Cmax, Cmin, AUC); food effect (300 mg/day dose); safety and tolerability

P255-101: Steady-state PK and cognition study [early termination; endpoints not analyzed; will not be reviewed]

Supportive analysis: [not in Tabular listing; no specific electronic datasets provided]
- Dose-proportionality pooling data from Studies P09-001 and P09-011 (25-1400 mg dose range)

Postmarketing Experience: [not in Tabular listing; no electronic datasets provided]
- PK/PD simulation for steepness of PK/PD curve (mono- and adjunctive therapy)
- Simulation for shape of curve between USL255 and Topamax IR (19 subjects)
- Delayed dose modeling and simulation report

Waiver requested:
1. Biowaiver of in vivo relative BA/BE studies for the 25 mg, 50 mg, 100 mg, and 150 mg strengths of USL255 capsules on the basis of BE between 200mg USL255 and Topamax IR (100mg BID) of 200mg strength, formulation proportionality in active and inactive ingredients, utilizing (b) (4) beads with (b) (4) extended-release coating (b) (4)
2. (b) (4)
3. (b) (4)

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

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

- Validation report LCMS470 at (b) (4) (b) (4) for Studies P09-001, P09-002, P09-003, P09-011, P255-102
- Validation report LCMS610 at (b) (4) for StudyP255-103
- Validation reports V0805024.00 and V0908024.00 at (b) (4) for Studies P08-003 and P08-008, respectively

Alcohol induced dose-dumping:
In vitro dissolution study using 200mg strength in pH 1.2, pH 4.5 and pH 7.2 media for 2 hours; ethanol levels were 0, 5, 20, and 40% at each pH. Results are presented in Appendix 2.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			• Annotated side-by-side comparative labeling in PDF • Word and PDF labelings.
Reference Bioanalytical and Analytical Methods	**X**			• Method validation (LC/MS/MS; 4 validation reports; 2 a (b) (4) supporting early development, 2 at (b) (4) support pivotal st , in-study validation, QC performance are provided. • In-study validation and QC performance are provided.
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
Healthy Volunteers-				All studies were conducted in healthy subjects
single dose:	**X**			P08-003, P08-008, P09-002, P09-011 (MTD),
multiple dose:	**X**			P08-008, P09-003, P255-101
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting / non-fasting single dose:	**X**			P08-008, P09-001, P09-011
fasting / non-fasting multiple dose:	**X**			P255-103, P255-101, P255-103
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	-			
renal impairment:	-			
hepatic impairment:	-			
PD -				
Phase 2:	-			
Phase 3:	-			

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

PK/PD -	**X**			PK/PD curve simulation for Topamax IR
Phase 1 and/or 2, proof of concept:	**X**			P255-101, P255-101 (steady-state PK and cognition)
Phase 3 clinical trial:	-			
Population Analyses -				Simulation reports based on established PopPK and PK/PD models for Topamax IR
Data rich:	-			
Data sparse:	-			
II. Biopharmaceutics				
Absolute bioavailability	-			
Relative bioavailability -				
solution as reference:	-			
alternate formulation as reference:	**X**			P09-002, P09-003 (ER vs. IR), P255-101, P255-103
Bioequivalence studies -				
traditional design; single / multi dose:	**X**			P255-102 (clinical formulation vs. TBM formulations of different manufacturing sites)
replicate design; single / multi dose:	-			
Food-drug interaction studies	**X**			P09-002 (highest 200mg strength), P255-103, P255-101, P255-103
Bio-waiver request based on BCS	-			
BCS class	-			
Dissolution study to evaluate alcohol induced dose-dumping	**X**			(b) (4) [redacted]
III. Other CPB Studies				
Genotype/phenotype studies	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			(b) (4) [redacted]
Literature References	**X**	**160**		
Total Number of Studies		**17**		9 Phase 1 (6 will be reviewed) + 4 validation reports + 4 supportive analyses

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
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			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 205-122

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

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			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Datasets for the additional supportive analyses are not included (these analyses were not included during pre-submission discussions).
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
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 • PK/PD simulation for steepness of PK/PD curve for Topamax IR (mono- and adjunctive therapy)
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 and exposure-response in the clinical pharmacology section of the label?	X			Cross-reference to approved Topamax label with additional information for USL255
	General				
18	Are the clinical pharmacology and biopharmaceutics	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 205-122

	studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
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 P09-003: (Steady-State PK Equivalence Study)
   Clinical sites: PPD Phase I Clinic
   7551 Metro Center Drive
   Building 10, Suite 200
   Austin TX 78744
   Phone: 512-447-2985
   Analytical site: (b) (4) [redacted]

2. Please provide the electronic datasets that were used in (1) supportive meta-analysis for the dose-proportionality for 25-1400 mg dose range, and (2) supportive analyses (i.e., Topiramate IR Shape Simulation Report and Steepness of Concentration-Response Simulation Reports) in Module 5.3.6 Reports of Postmarketing Experience.

3. Please provide the Data Definition files for all the clinical pharmacology and biopharmaceutics studies in PDF format.

Ta-Chen Wu
Clinical Pharmacology Reviewer — Date

Angela Men
Team Leader — Date

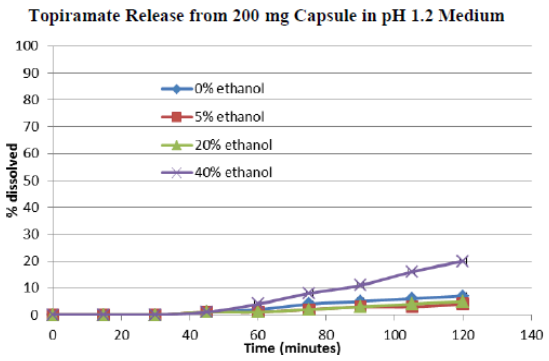
File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 205-122

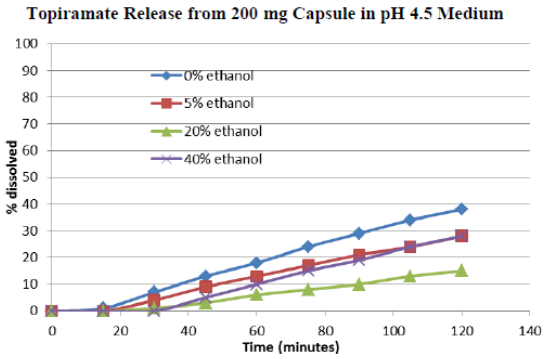
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

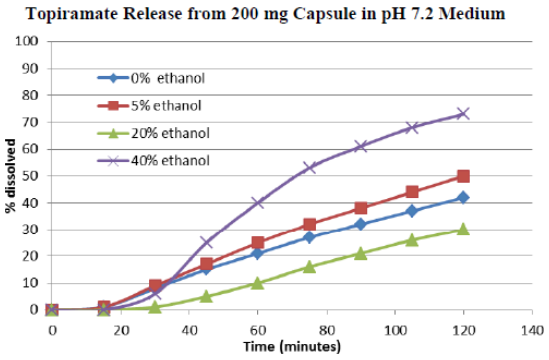
Appendix 1. Proposed dosing regimens

	Initial Dose	Titration	Recommended Dose
Epilepsy monotherapy: adults and pediatric patients ≥10 years	50 mg/day as single 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 as single dose
Epilepsy adjunctive therapy: adults with partial onset seizures or LGS	25 to 50 mg/day as single dose	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	200–400 mg/day as single dose
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures	25 to 50 mg/day as single dose	The dosage should be increased weekly to an effective dose by increments of 25 to 50 mg.	400 mg/day as single dose
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or LGS	25 mg/day as single dose (or less, 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 (administered in single dose). Dose titration should be guided by clinical outcome.	5 to 9 mg/kg/day as single dose

Appendix 2. Results of in-vitro discussion study in ethanol media







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/s/

TA-CHEN WU
05/01/2013

YUXIN MEN
05/03/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205-122
Product name, generic name of the active, and dosage form and strength	Topiramate Extended-Release Capsules (USL255) 25 mg, 50 mg, 100 mg, 150 mg and 200 mg
Submission date	Feb 11, 2013
Indication	Epilepsy
Applicant	Upsher-Smith Laboratories, Inc.
Medical Division	Division of Neurology Products
Type of Submission	505(b)(2)
Biopharmaceutics Reviewers	Deepika A. Lakhani, Ph.D. Sandra Suarez Sharp, Ph.D..
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

Background

USL255 is an oral extended-release capsule formulation of the antiepileptic drug (AED) topiramate designed for once-daily dosing. The product consists of topiramate and excipients in multiparticulate beads with an extended release coating encapsulated in hypromellose capsules to provide the following strengths: 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. The reference drug for USL255 is immediate-release product Topamax® tablets (available as 25 mg, 50 mg, 100 mg, and 200 mg).

The following parameters from the ONDQA Quality (Biopharmaceutics) filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A.	**BIOPHARMACEUTICS**			
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		The following dissolution method is proposed for routine testing: Medium: 900 mL 50 mM TRIS Buffer, pH=7.2@37ºC Apparatus: USP Apparatus I Speed: 100 rpm Temperature: 37°C Sampling Points: 1, 2, 3, 4.5, 6, 9 hours
2.	Is the dissolution test part of the DP specifications?	X		The proposed acceptance criteria is as follows: 1 hour: each unit NMT (b) (4) 2 hours: each unit (b) (4) 6 hours: each unit NLT (b) (4) Note: The acceptability of the proposed acceptance criteria will be a review issue.
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	The dissolution method development in the NDA is not sufficient and is being requested in the 74 day filing letter. The acceptability of this method will be a review issue.

Reference ID: 3296847

4.	Is there a validation package for the analytical method and dissolution methodology?	X		The analytical method (HPLC/Refractive Index) used for analysis of samples collected during dissolution testing is included.
5.	Does the application include a biowaiver request?	X		(b) (4)
6.	Is there information/data supporting the biowaiver request?	X		(b) (4)
7.	Is there enough information to assess the extended release designation claim?	X		The ER claim is: *"The mean effective half-life, or accumulation half-life, is approximately 56 hours after a single* (b) (4) *dose compared to 37 hours after a single topiramate immediate-release dose. Steady-state is thus reached in about 5 days after* (b) (4) *dosing in patients with normal renal function."* The Fluctuation Index has been provided and will be reviewed by the OCP. The claim will be a review issue.
8.	Does the application include an IVIVC model?	X		Data is provided to support a (b) (4) correlation (see Study Report 08-003). The review of the IVIVC will be a review issue.
9.	Does the application include information/data on in vitro alcohol dose-dumping potential?	X		The effect of various concentrations of alcohol (0%, 5%, 20%, and 40% v/v ethanol on the *in vitro* dissolution profile was studied. The medium selected for the alcohol dissolution study was pH 1.2HCl buffer, pH 4.5 sodium acetate buffer, and pH 7.2 TRIS buffer.
10.	Is there any in *vivo* BA or BE information in the submission?	X		See comment under No. 6.
11.	Is there any design space proposed using in vitro release as a response variable?	X		This submission has QbD elements. In vitro release has been identified as a CQA for particle sizing before coating, coating, sizing after coating, encapsulation, container closure system

Reference ID: 3296847

12.	Is the control strategy related to in vitro drug release?		X	
B.	**filing conclusion**			
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		• The NDA is fileable from Biopharmaceutics Perspective • The acceptability of the proposed dissolution method and acceptance criteria will be a review issue. • The adequacy of the data supporting the biowaiver request will be a review issue. • The claim of lack of dose-dumping in the presence of alcohol in vitro setting will be a review issue. • The acceptability of the proposed IVIVC will be a review issue. • The proposed design space using in vitro release as a response parameter will be a review issue.
14.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
16.	Are there any potential review issues identified?	X		• Complete dissolution method development has not been provided and will be requested in the 74-day letter.

Reference ID: 3296847

17.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		*The following comments need to be included in the 74-Day letter.* 1. Submit the dissolution method report supporting the proposed QC/IVIVC dissolution method. (b) (4)
18.	Are there any internal comment to other disciplines:		X	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

{See appended electronic signature page}

Deepika Arora Lakhani, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Sandra Surez Sharp, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

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

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

/s/

DEEPIKA LAKHANI
04/22/2013
NDA is fileable from Biopharmaceutics perspective. Comments to be sent in the 74 day filing letter.

SANDRA SUAREZ
04/22/2013

ANGELICA DORANTES
04/22/2013