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RESEARCH**

APPLICATION NUMBER:

205122Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205122
Priority or Standard	S
Submit Date(s)	2/11/13
Received Date(s)	2/11/13
PDUFA Goal Date	3/11/14
Division / Office	DNP/OND1
Reviewer Name(s)	Steven Dinsmore DO
Review Completion Date	
Established Name	Topiramate
Investigational Product Name	USL255
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Anti-Epilepsy Drug
Applicant	Upsher-Smith Laboratories
Formulation(s)	Extended release (b) (4)
Dosing Regimen	Oral, once daily
Indication(s)	Monotherapy for patients with partial onset or primary generalized tonic-clonic seizures. Adjunctive therapy for patients

	with partial onset seizures or primarily generalized tonic-clonic seizures and in patients with seizures associated with Lennox-Gastaut syndrome.
Intended Population(s)	Monotherapy: in patients 10 years of age and older. Adjunctive Therapy: adults and pediatric patients ages 2 to 16 years. Lennox-Gastaut patients 2 years of age and older.

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The review supports approval of topiramate XR (USL255) in the framework of a 505(b)(2) application where the reference listed drug is Topamax®. The sponsor has adequately bridged to the reference immediate release tablet formulation with one adequate and well controlled clinical study ([P09-004, section 6](#)) which demonstrates efficacy at a 200mg dose. The sponsor has also shown bioequivalence based on the pharmacokinetic parameters (AUC, C_{max}, and C_{min}) and the 90% confidence interval (CI) of the test/reference means ratio being between the 0.80 and 1.25 bioequivalence criteria. Additional evidence is included in the clinical pharmacology review which reveals acceptable congruence of the plasma concentration-time curves of USL255 and topiramate immediate release such that a difference in efficacy is not expected, [section 4.4](#). As a result of the data provided the indications of the RLD should be retained, with the exception of monotherapy in patients ≥ 10 years¹ of age.

1.2 Risk Benefit Assessment

Improved compliance with once daily treatment as well as some reduction of C_{max} associated common adverse events provides a reasonable argument for the benefit of this preparation. The risk of topiramate has been characterized over an interval of 19 years since the international birthday of the RLD topiramate IR on 7/18/1995. Topiramate was first registered in the UK and approved on 12/24/1996 in the United States. Currently, topiramate is licensed in 104 countries around the world. There is a benefit to this preparation due to the once daily dosing. This mode of delivery will likely enhance compliance and also attenuate adverse effects associated with C_{max}. This is not a groundbreaking advance in epilepsy treatment but is a benefit of acceptable magnitude when weighted against the well characterized risk profile of the active pharmaceutical ingredient, topiramate, which has been available on the world market for 19 years. Topiramate has been used with an acceptable safety profile during this time period. The topiramate extended release form, as stated, may attenuated some of the C_{max} associated adverse events but the more serious risks identified in the “Warnings and Precautions” section of the Trileptal label remain unchanged.

¹ Pediatric patient age changed from (b) (4) to “ ≥ 10 years” due to Topamax exclusivity for epilepsy monotherapy indication for pediatric population 2 to <10 years.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Medication Guide

1.4 Recommendations for Postmarket Requirements and Commitments

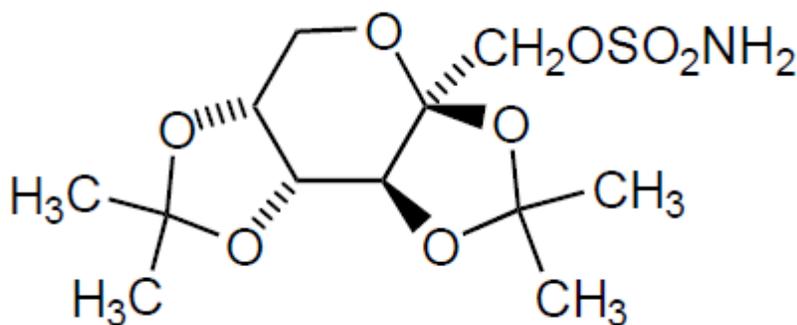
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2 Introduction and Regulatory Background

2.1 Product Information

The product under review is an extended-release formulation of topiramate for once daily dosing. The proposed trade name is (b) (4). The reference listed drug for this 505(b)(2) application is Topamax® an immediate release form of topiramate. The first approval of topiramate was in the United Kingdom on July 18, 1995 with US approval on December 24, 1996.

Topiramate has the molecular formula $C^{12}H^{21}NO^8S$ and a molecular weight of 339.36. Topiramate is a sulfamate-substituted monosaccharide designated chemically as 2,3:4,5Di-O-isopropylidene- β -D-fructopyranose sulfamate and has the following structural formula:



The sponsor is requesting the same epilepsy indications as Topamax® for use as adjunctive and monotherapy with the exception that unlike the reference listed drug the indication for monotherapy will begin at 10 years of age (b) (4) due to ongoing Topamax® exclusivity. These indications in full are as follows:

Monotherapy epilepsy: Initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures.

Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome.

This extended release dosage form is supplied as extended release capsules containing beads of topiramate in a hard capsule intended for once daily oral dosing. Initial dose and maintenance dose are stratified by age group and indication with a maximum starting dose of 50mg/day and maximum maintenance (target) dose of 400mg/day.

The full prescribing information is provided below:

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

2.2 Tables of Currently Available Treatments for Proposed Indications

Anticonvulsants in common clinical use for the treatment of partial epilepsy

Carbamazepine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital
Phenytoin

Potiga
Pregabalin
primidone
Tiagabine
Topiramate
Valproic acid
Zonisamide

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient topiramate has been available in the United States since the initial US approval of Topamax® in 1996.

2.4 Important Safety Issues With Consideration to Related Drugs

As an extended release form of an established API, topiramate, the important safety issues have been well characterized. The common adverse effects produced by topiramate were observed in study P09-004. Serious adverse effects noted for the reference product in warnings and precautions are acute myopia and secondary angle closure glaucoma, oligohidrosis and hyperthermia, metabolic acidosis, suicidal behavior and ideation, cognitive/neuropsychiatric adverse reactions, fetal toxicity, sudden unexplained death in epilepsy (SUDEP), hyperammonemia and encephalopathy with or without concomitant valproic acid use, kidney stones, hypothermia with concomitant valproic acid use, and decreased hepatic function. Some non-serious adverse effects are also well characterized for sodium channel active anticonvulsants. These are primarily CNS effects of sedation, fatigue.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

5/20/2008: IND Safety Review date response and comments on the clinical development plan which included recommendation for future development that indicated- multiple dose bioequivalence studies should be performed for comparison to the commercially available IR formulation. Comparison for bioequivalence should not only include C_{max} and AUC but C_{min} as well. In addition the division emphasized that the different shape of the PK curves between the ER and IR formulations could result in different pharmacodynamic properties. This difference may be due to differences in the rate of change in concentrations.

7/27/2011: Type C meeting between the sponsor and the office of Clinical Pharmacology and Office of New Drug Quality Assessment.

7/16/2012: Cardiac Safety and Alcohol interaction communication: in this correspondence the division was in agreement that no further QT assessment was needed for topiramate extended release. The division recommended in vitro alcohol interaction data to be followed by a judgment on whether an in vivo study is needed. The division agreed that the draft blinded data review plan for the efficacy trial was acceptable.

11/30/2012: Type A meeting, discussion of application based on PK data alone. The division indicated that the partial AUC argument was strong but with reservation about the possibility that an extended release topiramate product whose concentration time curve does not closely match that of the innovator product might differ in effect from the innovator product. The division urged consideration of additional data or arguments to address that concern. The division agreed that an application on this basis would be fillable but could not state that the proposal would support approval.

Pediatric study plan was also discussed. (b) (4)

(b) (4) A deferral will be needed pending development of an age appropriate formulation. There was also a post-meeting note indicating that (b) (4)

(b) (4) and patients age 2 to 6 years with primary generalized tonic-clonic seizures, if the Sponsor pursues approval for both seizures disorders based upon a PK/PD argument.

2.6 Other Relevant Background Information

At the Type A meeting of 11/30/12 the sponsor desired to submit a package for approval based on PK data alone. Since this was not a certainty the sponsor indicated a clinical trial (P09-004) was near completion. The sponsor questioned if a PK based application could be submitted followed by the clinical trial data. The division stated this is an unsatisfactory proposal because a clinical trial would not be a minor amendment. Submission of a clinical trial would extend the review clock an additional three months, so unless the amendment was submitted soon after the PK package this method would not advance the approval date. The events that followed were submission of a PK based submission on 2/11/13 followed by submission of the primary efficacy clinical trial data as the 120 day safety update, containing the full study p09-004 clinical trial data. This amendment was judged a major amendment and resulted in a goal date extension of three months to 3/11/2014.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was divided into two separate submissions. The initial submission of 12/11/2013 was an application for approval based upon demonstration of equivalence between the pharmacokinetic profiles of USL255 and immediate-release (IR) topiramate (Topamax®). Partial AUC (AUC_p) analyses were conducted to evaluate similarity of the systemic exposure of topiramate at various intervals in the steady-state concentration-time curve between USL255 and Topamax®. Subsequently on 5/21/13 the sponsor submitted results of a pivotal phase 3, randomized, double blind, multicenter clinical trial to support approval. This was submitted under the heading of a 120 day safety update. Due to the magnitude of this amendment the review clock was extended 3 months.

3.2 Compliance with Good Clinical Practices

A DSI audit was not requested for the pivotal clinical trial. Study integrity was assessed by identification of the largest patient recruitment sites, efficacy effect by site, screening failure due to protocol violations by site and serious adverse events by site. These data were then examined to determine if there was a single site with a disproportionate effect on the efficacy outcome. In addition sites were examined to determine if there was an excess of protocol deviations in sites with large patient recruitment. An assessment was also performed to determine if there was a disproportional occurrence of serious adverse events in a given site.

In concert with the statistical reviewer the examination revealed there was no single site with a disproportionate effect on the primary outcome. The two sites with the greatest number of patient screenings each had 15 subject screens, one of these had a 40% screening failure rate while the other had a 20% failure rate. These large screening and enrollment sites did not have a disproportionate effect on efficacy. Four study sites had 100% screening failure, with a maximum of 5 failures in one site, two at 2 sites and one patient failed screening and was the only patient screened at that site. Eight serious adverse events occurred during the pivotal trial, these were distributed among 7 patients (4 from ITT safety population) from seven different study sites. Exclusions from the per protocol population were examined for clustering of protocol violations or violations of special concern. There were 28 patient exclusions from the per protocol population, these were distributed among 24 study sites and occurred in 5 different categories where the most common was a violation of inclusion or exclusion criteria.

Reviewer Comment: there was no indication of deviation from good clinical practice based on the data available in the submission.

3.3 Financial Disclosures

The sponsor's initial financial disclosure certification form 3454 had only certification for a single investigator adjacent to each study site; presumably this is the primary

investigator of each site. All study sites were accounted for but without apparent subinvestigator certification and disclosure. Due to this anomaly a request for certification of disclosure of subinvestigators was sent to the sponsor on 7/11/13. This request directed the sponsor to "The Guidance for Clinical Investigators, Industry and FDA staff, Financial Disclosure by Clinical Investigators"

On 7/17/13 an updated financial disclosure certification form 3454 was received. This updated form contained the signature of the USL Chief Financial Officer & Executive Vice President followed by the names of 178 subinvestigators and one primary investigator from each study site. A confirmation that no USL2555 clinical investigators were full or a part-time employee was also provided.

Reviewer Comment: Financial disclosure requirements have been adequately completed.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review entered into DARRTS indicates an approval is still pending adequate responses regarding the acceptance of dissolution specification criteria by ONDQA Biopharmaceutics but there are no other quality deficiencies pending. The Office of Compliance has rendered an acceptable recommendation for the manufacturing and testing facilities (22-Jul-13).

4.2 Clinical Microbiology

none

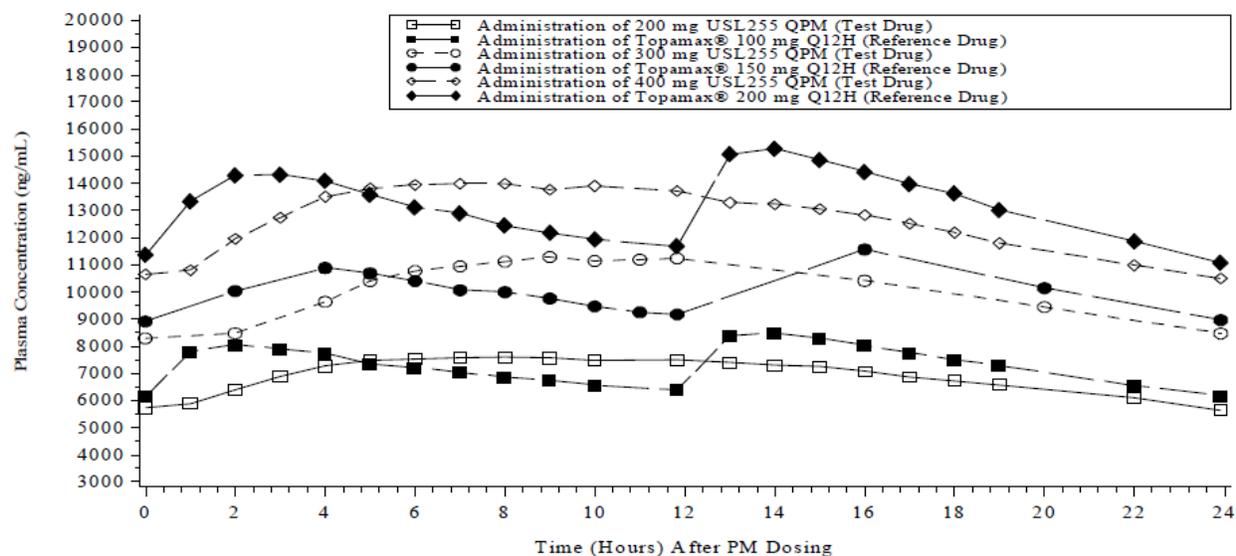
4.3 Preclinical Pharmacology/Toxicology

The sponsor posted questions to the division regarding the investigational plan in the initial IND submission of 3/5/2008 concerning the need for additional non-clinical data. The division indicated that provided there are no new excipients and no new impurities that would require qualification, then no additional non-clinical studies would be needed.

4.4 Clinical Pharmacology

The clinical pharmacology review team notes that In this submission, the applicant presented a clinical pharmacology-based method of demonstrating bioequivalence (BE) and acceptable congruence of the USL255 and topiramate concentration time curves (200mg, steady state). This was accomplished by examination of topiramate concentrations at multiple time points within the 24 hours at steady-state between the proposed USL255 capsules given QD and approved Topamax® IR tablets given twice-daily (BID), in addition to the conventional BE analyses for topiramate exposure. A graphic display of the mean plasma topiramate concentration time curves over time for 200mg, 300mg and 400mg doses is shown in Figure 1. To demonstrate the similarity in topiramate plasma concentration-time curves between the proposed USL255 capsules and the approved Topamax® IR Tablets, the applicant performed additional time-point to time-point comparisons at steady-state with respect to ratios of topiramate plasma concentration (Figure 4), partial AUC (AUC_{0-p}) (Figure 2), and partial AUC (AUC_{t1-t2}) between two time-points of XR relative to IR (Figure 3) 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 overall results also suggest that patients can be switched from IR to USL255 formulation with the same total daily doses.

Figure 1 Mean Plasma Topiramate Concentrations vs Time²



2 Clinical Pharmacology Review, NDA 205122, Primary Reviewer Ta-Chen Wu, Ph.D.

Figure 2 Point Estimate of Ratio and CI of Topiramate Plasma Concentration, Partial AUC (AUC_{0-P})²

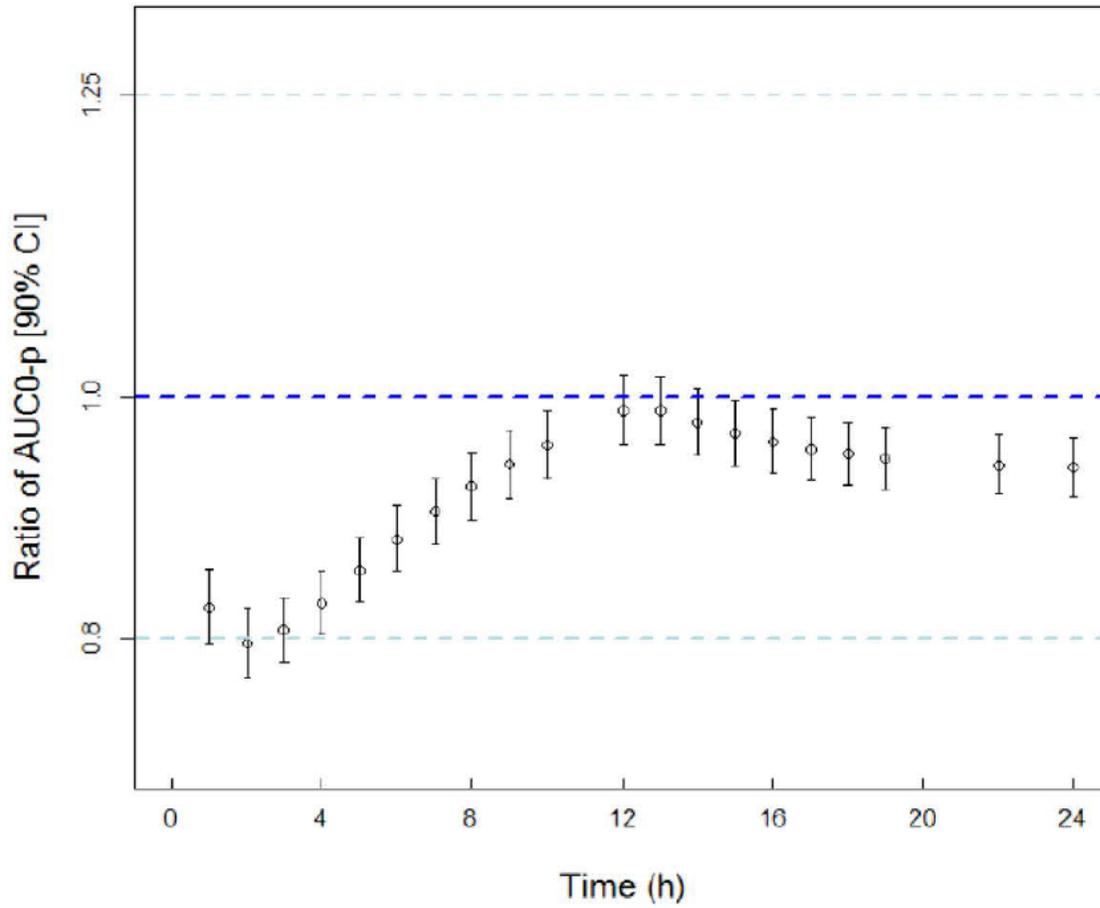


Figure 3 Point Estimate of Ratio and CI of Partial AUC (AUC_{t1-t2}) between two time-points of USL255 Relative to topiramate IR²

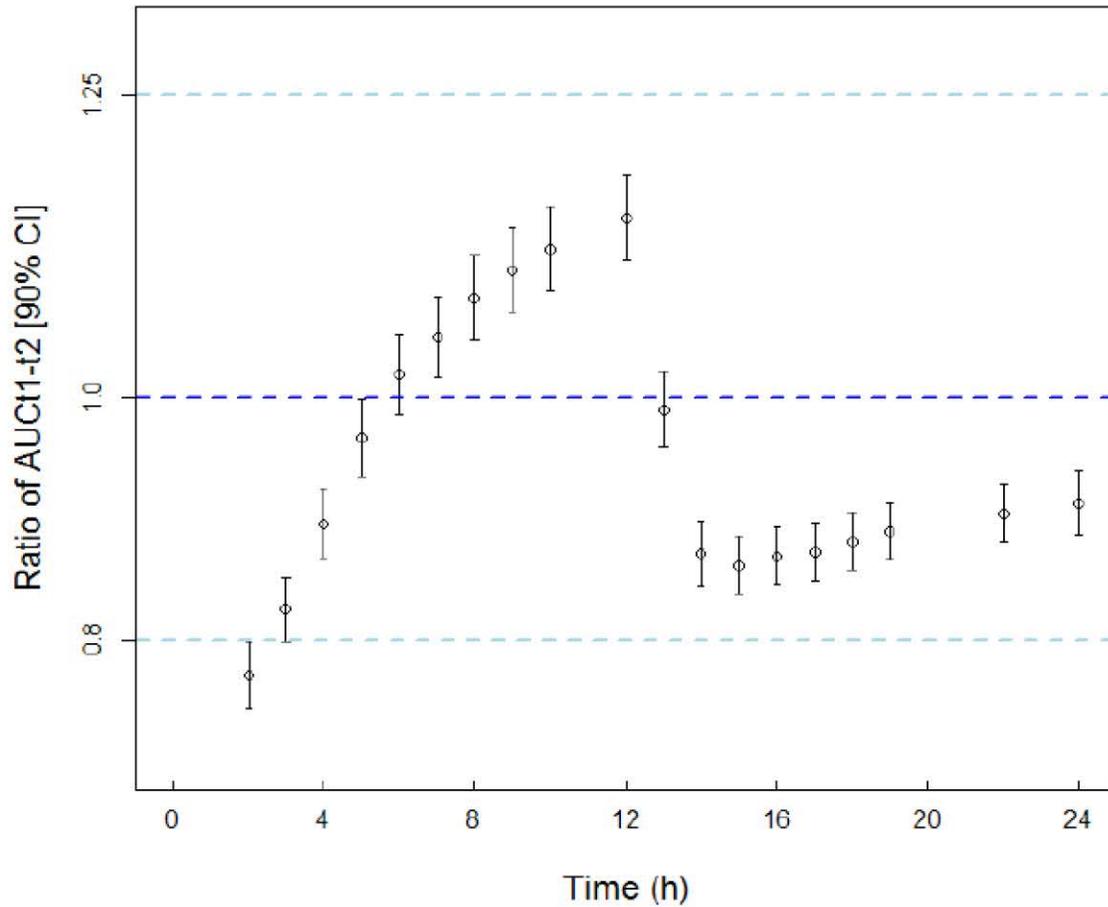
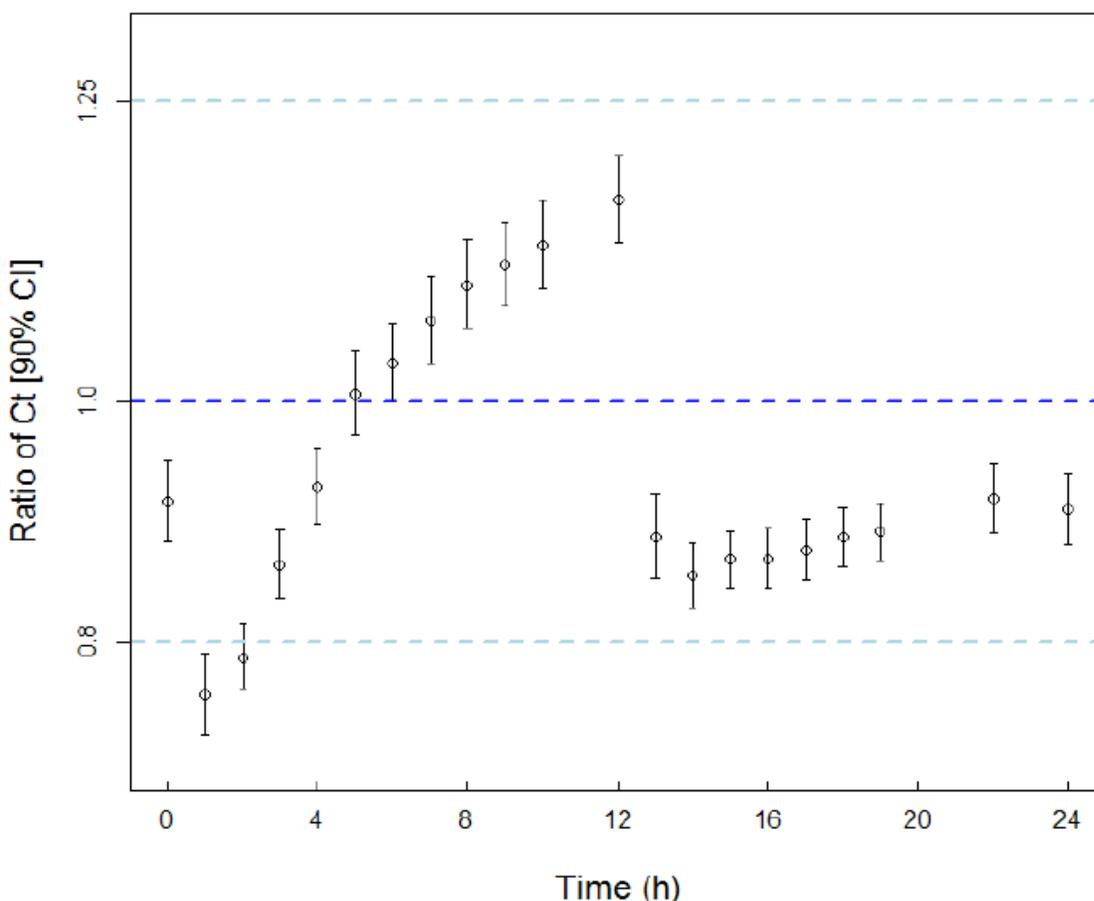


Figure 4 Point Estimate of Ratio and CI of Topiramate Plasma Concentration, 200mg, Steady State²



The final recommendation of the clinical pharmacology review team found NDA205122 acceptable from an OCP (Office of Clinical Pharmacology) perspective provided that an agreement is reached between the Sponsor and Agency regarding revised labeling language presented by OCP².

QT discussion in section [7.4.5](#)

4.4.1 Mechanism of Action

The precise mechanisms by which topiramate exerts its 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 IV³.

4.4.2 Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the GABAA receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia⁴.

4.4.3 Pharmacokinetics

Pharmacokinetics Summary, from OCP review²

- Linear pharmacokinetics (PK) and dose-proportionality of topiramate were observed following single oral doses of USL255 over the dose range of 25 to 1400mg 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 USL255 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 USL255.
- At steady-state, the AUC0-24hr, Cmax, and Cmin of topiramate from USL255 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 USL255 dosing.
- After multiple administrations of once-daily USL255 the mean peak-to trough fluctuation (fluctuation index or FI) in plasma topiramate concentrations was

³ Reference listed drug label, Topamax®, section 12.1 (Clinical Pharmacology)

⁴ Reference listed drug label, Topamax®, section 12.2 (Clinical Pharmacology)

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 USL255 following single or multiple doses.
- Administration of contents of USL255 capsule with applesauce in healthy young adult subjects did not have a significant effect on the bioavailability of topiramate, compared to Topamax ® tablet.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Clinical studies have come through two separate submissions. In the initial submission where the basis for the submission was to demonstrate equivalence between the pharmacokinetic profile of USL255 and immediate release topiramate (Topamax) there was included 9 studies from the development program. Eight studies were completed for this package with six providing bioavailability (BA)/ bioequivalence (BE) data and two providing dose proportionality data. A ninth study P255-101 was terminated due to the site's improper administration of the Controlled Oral Word Association Test (COWAT) baseline testing. The second submission, the 120 day safety update contained safety and efficacy information from a phase 3 safety and efficacy study in epilepsy patients, study P09-004.

Clinical Pharmacology subjects all healthy volunteers.

Table 1 Clinical Pharmacology Studies

Study ID	Date Completed	Number of subjects ⁵	Description
Single-Dose Studies			
Formulation Studies			
P08-003	21Nov2008	24	Randomized, single-center, open-label, 4-way crossover, relative bioavailability
P08-008	30Sep2009	42	Randomized, single-center, open-label, 2-arm with crossover, relative bioavailability
Bioavailability Studies			

⁵ Clinical Pharmacology subjects are all healthy volunteers

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P09-002	19Mar2010	36	Randomized, single-center, open-label, 3-way crossover, fed vs fasted, relative bioavailability
P255-102	01Feb2012	36	Randomized, single-center, open-label, 4- way crossover, bioequivalence
Dose-Proportionality Study			
P09-001	30Mar2010	30	Randomized, single-center, open-label, 5-way crossover, dose proportionality
Ascending Dose Study			
P09-011	04Mar2010	50	Randomized, single-center, double-blind, safety and pharmacokinetics of single ascending doses
Multiple-Dose Studies			
P09-003	20Apr2010	38	Randomized, single-center, open-label, 2-way crossover, multidose, relative bioavailability
P255-101	18Nov2011	48	Randomized, single-center, double-blind, 2-period crossover, relative bioavailability and pharmacodynamic effects on cognition (terminated by sponsor- improper administration of baseline)
P255-103	13Oct2012	48	Randomized, single-center, double-blind, 2-period crossover, relative bioavailability and effects on cognition

Table 2 Phase 3 Clinical Safety And Efficacy Trial, study P09-004

Study ID/ No. of Study Sites/ Location(s) Type of Study	First Subject Enrolled/ Last Subject Visit	Study Design	Study Objectives	No. of Subjects Planned/ Entered/ Completed	Gender/ Mean Age ± SD (y)/ Race/Diagnosis	Primary Endpoints
P09-004/66/in 16 countries (Argentina, Australia, Belgium, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, and United States) Phase 3 Efficacy and Safety Study	25May2010/ 18Dec2012	Phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel-group	(1) Assess the efficacy of USL255 compared to placebo in subjects with refractory partial-onset seizures (POS) with or without secondary generalization (2) Assess the safety of USL255 compared to placebo in subjects with refractory POS with or without secondary generalization	216 (236 after blinded data review)/ 249/217	132 men, 117 women/ 37.6 y ± 11.02/ 214 White, 16 Asian, 5 Black or African American, 2 Native Hawaiian or other Pacific Islander, 12 Other/ Subjects with refractory POS with or without secondary generalization diagnosed for at least 12 months prior to Visit 1	<i>Primary efficacy endpoint:</i> Percent reduction from Baseline in weekly (7-day) POS frequency during the Titration + Maintenance Phase.

5.2 Review Strategy

5.3 Discussion of Individual Studies/Clinical Trials

The objective of study P09-004 is to assess the efficacy of USL255 compared to placebo in subjects with refractory partial-onset seizures with or without secondary generalization. This was a multinational phase 3 randomized, multi-national, multicenter, double-blind, placebo controlled, parallel group study. The study was conducted at 60 centers in 16 countries. There were 270 patients enrolled with 216 randomly assigned to study drug or placebo.

6 Review of Efficacy

This NDA in the initial submission of 2/11/13 was directed at approval based on the demonstration of equivalence between the pharmacokinetic profiles of USL255 and immediate-release topiramate (Topamax). The sponsor at that time had a randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 clinical trial underway to evaluate the efficacy and safety of USL255 as adjunctive therapy in patients with refractory partial onset seizures. This study after completion was submitted in the 120 day safety update on 5/21/13. This study is the only phase 3 clinical trial in the NDA package which will be covered in the subsequent "Review of Efficacy"

Efficacy Summary

The sponsor seeks approval of an extended-release (ER) formulation of topiramate (USL255) for once-daily dosing. USL is substantially relying on FDA's findings of safety and effectiveness for Topamax® (topiramate) Tablets, NDA 020505, by Janssen Pharmaceuticals, Inc., for approval of this application for USL255 Topiramate Extended-Release (ER) Capsules, submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Although the approval of topiramate, the active pharmaceutical ingredient, supports efficacy of this anti-epilepsy drug the extended release formulation administered once daily will not have identical concentration time curve to the immediate formulation administered twice daily. Additional support for the efficacy of this extended release formulation USL255 is derived from a single adequate and well controlled trial P09-004. The details of this study are provided in the following sections of section 6, "Review of Efficacy".

The primary endpoint of the study, the median percent reduction from baseline of partial-onset seizure frequency during the titration plus maintenance phase in the ITT efficacy population revealed a significantly greater reduction in the USL255 treatment group compared to placebo treatment group. The USL255 had a 39.5% reduction

compared to a 21.65% reduction in the placebo treatment group. The p value for this difference was <0.001 using the Wilcoxon rank-sum test for the ITT efficacy population, see [Table 3](#).

Table 3 Primary Efficacy Results

Time point	Statistic	Weekly Partial-Onset Seizure Frequency ^a		
		USL255 (N = 124)	Placebo (N =125)	P Value
Baseline Phase	Mean (SD)	7.45 (27.620)	5.18 (6.212)	
	Median	2.29	2.66	
	Min, Max	1.0, 297.6	0.9, 37.4	
Titration + Maintenance Phase	Mean (SD)	5.98 (26.604)	4.96 (8.128)	
	Median	1.41	2.05	
	Min, Max	0, 287.0	0, 64.8	
Absolute Median Reduction		0.88	0.61	
Absolute Mean Reduction		1.5	0.22	
Percent Reduction from Baseline to Titration + Maintenance Phase	Mean (SD)	32.32 (47.326)	12.10 (65.413)	
	Median	39.5	21.65	< 0.001^b
	Min, Max	-227.3, 100.0	-531.2, 100.00	
	LS Mean (SE)	32.91 (5.092)	11.51 (5.071)	0.003 ^c
	95% CI	22.88, 42.95	1.52, 21.50	
^a Weekly seizure frequency = (total number of partial-onset seizures and partial-onset clusters during each phase/ number of days with seizure diary in each phase) × 7. Percent reduction from Baseline in weekly seizure frequency = [(B-T)/B] × 100, where T = weekly frequency during the Treatment Phase and B = weekly frequency during Baseline.				
^b Treatments were compared using the Wilcoxon rank-sum test; ranks for tied data were the mean of the corresponding ranks.				
^c Treatments were compared using an ANCOVA, controlling for geographic region, with Baseline partial-onset seizure frequency as covariate				

6.1 Indication

Upsher Smith Laboratories (USL) is seeking approval of an extended release formulation of topiramate (USL255) for once daily dosing. USL is substantially relying on FDA's finding of safety and effectiveness for Topamax tablets, NDA 020505 by Janssen Pharmaceuticals, Inc for approval and is submitted as a 505(b)(2) application.

The proposed indications based on data provided in the application are:

- Initial monotherapy for patients 10 years of age and older with partial-onset (POS) or primary generalized tonic-clonic (PGTC) seizures

- Adjunctive therapy for patients two years of age and older with POS or PGTC
- Adjunctive therapy for patients two years of age and older with seizures associated with Lennox-Gastaut syndrome (LGS)

6.1.1 Methods

The study was a phase 3, randomized, multicenter, double-blind, placebo controlled, parallel-group study designed to evaluate the efficacy and safety of USL255 compared with placebo as adjunctive therapy in subjects with refractory partial-onset seizure with or without secondary generalization.

The study design had a blinded data review plan to adjust sample size due to uncertainty of initial assumptions used to derive sample size. Initial sample size estimate was based on the mean difference between two treatment groups in the natural log-transformed seizure frequency per week. A sample size of 216 ITT efficacy subjects (108 per treatment arm) was expected to provide a power of 90% to detect a difference in mean log-transformed seizure frequency per week of 0.20 assuming that the common standard deviation is 0.45 in the log scale and using a 2 sample t test with a 0.05, 2 sided significance level.

Due to the uncertainty of the projected standard deviation of the seizure frequency the sponsor submitted a blinded data review plan on 10/31/2011. The plan proposed 1 blinded data review of the seizure frequency per week when up to 55% of patients completed the maintenance phase. At this specified point of review the assumption (SD 0.45) may be confirmed or amended with subsequent adjustment of the sample size not to exceed 172 subjects per treatment arm. The plan was reviewed by Biometrics. The biometrics reviewer indicated the sponsor planned to base the sample size re-estimation on the Wilcoxon Rank-sum Test (WRST) rather than the t-test of the original plan. The reviewer indicated that the blinded data review plan was acceptable. Based on the blinded data review, a sample size of 118 subjects per treatment group provided 91% power for this analysis. This value was used to adjust enrollment in the study.

P09-004 study design:

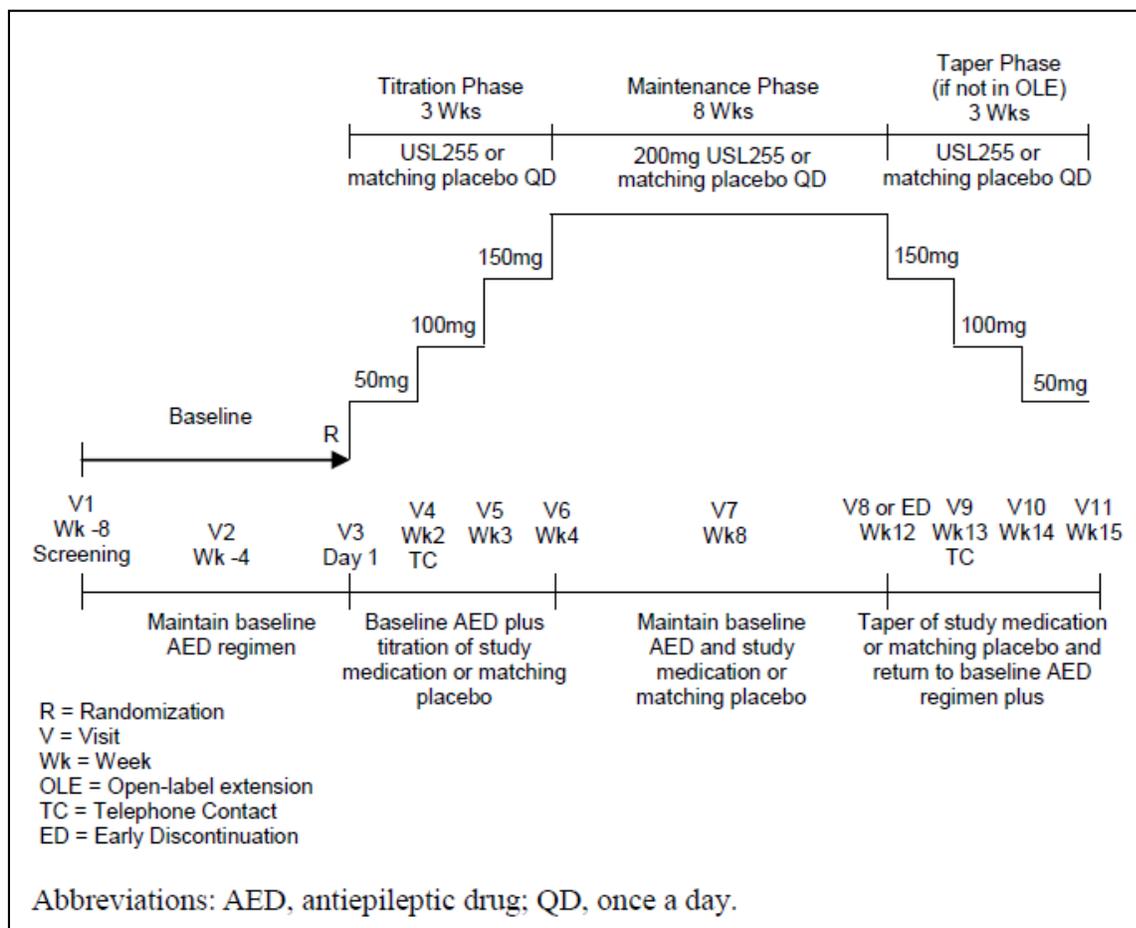
Based on the blinded data review, a sample size of 118 subjects per treatment group was used for the planned enrollment in the study. Subjects were 18 to 75 years of age, inclusive, and were diagnosed with partial-onset seizures, with or without secondary generalization, for greater than 12 months. Subjects, prior to the baseline phase were treated with a stable and optimal dosing regimen of 1 to 3 AEDs (except vigabatrin, felbamate, and topiramate) for at least 4 weeks (12 weeks for phenobarbital and primidone). Vagus nerve stimulators (VNSs) could be included as 1 AED, provided the VNS had been in place for at least 6 months and on a stable setting for at least 1 month prior to Visit 1. The VNS settings and concomitant AED regimen were to remain

unchanged throughout the course of the study (baseline, titration and maintenance phases).

The duration of the study was up to 22 weeks for each subject. Subjects underwent a screening visit (Visit 1) and an 8-week baseline phase (Visit 1 through Visit 3). During the 8-week baseline phase, subjects must have had at least 8 partial-onset seizures, with no more than 21 consecutive days without a seizure. At Visit 3/Day 1, subjects who met the study enrollment criteria were randomly assigned to receive USL255 or placebo in the double-blind treatment phase, which included a 3-week dose titration phase (Visit 3 through Visit 6) and an 8-week maintenance phase (Visit 6 through Visit 8). The maintenance phase was followed a 3-week taper phase to discontinue study drug for subjects who did not enter the open-label extension (OLE) study (Visit 8 through Visit 11.)

Starting at Visit 3/Day 1 of the titration phase, subjects were administered 50 mg QD of USL255 or matching placebo. Subsequently, the daily dose was titrated up in a blinded manner by 50 mg per week to 200 mg over a 3-week phase. If subjects were unable to tolerate 200 mg, they were discontinued from the study. Upon completion of the 3-week titration phase, subjects entered the 8-week maintenance phase of the study. Subjects were maintained on 200 mg QD for the remainder of the study. The titration plus maintenance phase was planned to be 11 weeks in duration. Following completion of the maintenance phase, at Visit 8, subjects could either enter into the OLE study (P09-005) or have their study drug daily dose tapered in a blinded manner by 50 mg per week.

Figure 5 P09-004 Study Design Schematic



Key Inclusion Criteria

- Subject has a confirmed diagnosis of partial-onset seizures with or without secondary generalization for at least 12 months prior to Visit 1. The diagnosis of partial-onset seizures with or without secondary generalized seizure is defined by the ILAE commission in 1981.
- Currently on a stable dosing regimen of 1 to 3 AEDs for at least 4-weeks prior to Visit 1 (12 weeks for phenobarbital and primidone).
 - Note: VNS was counted as one of the AEDs provided the VNS has been in place for at least 6 months and on a stable setting for at least 1 month prior to Visit 1. The VNS settings could not change throughout the course of the study (baseline, titration, and maintenance phases).
 - Note: Benzodiazepines (BZD) taken more than once per week, for any indication, were counted as one of the AEDs.
- Male or female, aged 18 to 75 years, inclusive.
- Can safely be treated, in the opinion of the investigator, with topiramate

- Have a minimum of 8 partial-onset seizures and no more than 21 consecutive seizure free days, during the 8-week baseline.
 - *Note:* Only simple partial seizures with motor signs, complex partial seizures, and partial seizures with secondary generalization are counted toward this inclusion.

Exclusions

- Have a predisposing condition or patient is on medication that may interfere with the absorption of USL255.
- Have a history of seizure episodes within 3 months prior to visit 1, lasting less than 30 minutes in which several seizures occur with such frequency that the initiation and completion of each individual seizure cannot be distinguished.
- Have a history of pseudoseizures or status epilepticus within three months prior to visit 1.
- Have a history of metabolic acidosis, nephrolithiasis, ureterolithiasis, or narrow angle glaucoma.
- Have a history of suicidal attempts, suicidal ideation, or uncontrolled psychiatric illness within 2 years of Visit 1.
- Have taken topiramate within the past 6 months.
- History of lack of efficacy to topiramate for epilepsy despite adequate exposure
- History of safety or tolerability issues to topiramate not related to dose titration.
- Currently taking or have taken felbamate within the past 18 months, or have taken vigabatrin in the past.

A total of 333 subjects were screened and 249 subjects were randomly assigned to treatment, including 124 in the USL255 treatment group and 125 in the placebo group.

6.1.2 Demographics

The treatment groups were comparable with respect to demographics and baseline characteristics ([Table 4](#)). Subjects in the ITT safety population were predominantly White (85.9%) and not Hispanic or Latino (69.5%). The mean age of subjects was 37.6 years (range: 19-71 years). The age distribution of subjects was similar between

treatment groups. A large portion of the subjects in both treatment groups were in the ranges of 18-39 years of age, and 40-64 years of age. Only 1 subject in each treatment group was 65 years of age or older. Mean height, weight, and BMI were 167.4 cm, 74.79 kg, and 26.57 kg/m², respectively. Slightly more than half (53.0%) of all subjects were males. Study drug was taken by similar numbers of subjects in the morning (50.6%) and in the evening (49.4%).

Table 4 Demographic Characteristics of Study Population

	USL255 (N=124)	Placebo (N=125)	Total (N=249)
Characteristics			
Age			
N	124	125	249
Mean (SD)	37.6 (10.97)	37.6 (11.11)	37.6 (11.02)
Age Range			
N	124	125	249
18 to <40	73 (58.9%)	77 (61.6%)	150 (60.2%)
40 to <65	50 (40.3%)	47 (37.6%)	97 (39.0%)
≥ 65	1 (0.8%)	1 (0.8%)	2 (0.8%)
Gender			
N	124	125	249
Male	66 (53.2%)	66 (52.8%)	132 (53.0%)
Female	58 (46.8%)	59 (47.2%)	117 (47.0%)
Ethnicity			
N	124	125	249
Hispanic or Latino	40 (32.3%)	36 (28.8%)	76 (30.5%)
Not Hispanic or Latino	84 (67.7%)	89 (71.2%)	173 (69.5%)
Race			
N	124	125	249
White	107 (86.3%)	107 (85.6%)	214 (85.9%)
Asian	9 (7.3%)	7 (5.6%)	16 (6.4%)
Black or African African American	1 (0.8%)	4 (3.2%)	5 (2.0%)
Native Hawaiian or other Pacific Islander	1 (0.8%)	1 (0.8%)	2 (0.8%)
other	6 (4.8%)	6 (4.8%)	12 (4.8%)
Height			
N	124	124	248
Mean (SD)	167.0 (10.35)	167.9 (10.58)	167.4 (10.46)
Weight			
N	124	125	249
Mean (SD)	75.57 (19.099)	74.01 (18.141)	74.79 (18.603)
BMI kg/m ²			
N	124	124	248

Mean (SD)	27.03 (6.190)	26.10 (5.803)	26.57 (6.006)
When Subject took Study Drug			
N	124	125	249
AM	65 (52.4%)	61 (48.8%)	126 (50.6%)
PM	59 (47.6%)	64 (51.2%)	123 (49.4%)

Table 5 presents the distribution of subjects randomly assigned to treatments by region and country. The largest percentage enrollment was from Eastern Europe at 29% followed by 28% from South America, 24% from Western Europe and 19% from North American and Similar (US, Canada, Australia, New Zealand).

Table 5 Distribution of Subjects by Region & Country

Geographic Region (Number of Subjects) Country	Number of Subjects Randomly Assigned to Study Drug
Western Europe, N= 57 (24%)	
Belgium	1
Germany	13
Spain	9
Greece	11
South Africa	10
Israel	13
Eastern Europe, N= 69 (29%)	
Poland	23
Hungary	6
Russia	40
South America, N= 65 (28%)	
Argentina	32
Chile	33
North America and Similar, N=44 (19%)	
United States	33
Canada	2
Australia	7
New Zealand	2

TOTAL	235
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[Table 6](#) summarizes the duration of epilepsy in the ITT safety population upon entering the study, their baseline frequency of partial-onset seizures, and their AED use. The mean duration of epilepsy was similar between treatment groups (USL255, 20.9 years; placebo, 20.0 years), but the mean (SD) baseline weekly seizure frequency was notably greater in the USL255 treatment group (7.45 [27.62]) compared with the placebo treatment group (5.18 [6.21]). These treatment group differences in mean and SD were largely due to 1 subject in the USL255 treatment group (102/159) who had a very high baseline weekly seizure frequency (297.63) which was almost 4 times the frequency of the subject with the next highest seizure frequency. In contrast, the maximum baseline weekly seizure frequency in the placebo treatment group was 37.4. The median baseline weekly seizure frequency in the 2 treatment groups (USL255, 2.29; placebo, 2.66) and minimum baseline weekly seizure frequency in the 2 treatment groups (USL255, 1.0; placebo, 0.9) were similar.

A subject with an exceptionally high baseline weekly seizure frequency was located in the North America and Similar geographic region, and consequently the mean baseline weekly seizure frequency was much higher in the USL255 treatment group (32.34) than in the placebo treatment group (6.05). The South America median weekly seizure frequencies were similar to the overall frequency (USL255, 2.13; placebo, 2.25). Western Europe had somewhat higher overall median weekly seizure frequencies due to moderately higher frequencies in the USL255 treatment group (3.41) compared with the placebo treatment group (2.50).

The types of seizures experienced by subjects during the baseline period were also similar between treatment groups. Complex partial seizures were most common (USL255: 85.5%; placebo, 82.4%). Partial seizures that became secondarily generalized were experienced by 41.1% of USL255 subjects and 40.0% of placebo subjects. Simple partial seizures (with and without motor signs) were experienced by 27.4% of USL255 subjects and 33.6% of placebo subjects.

All subjects used at least 1 other AED while in the study, and a large majority of subjects were receiving polytherapy at baseline. Some imbalance was noted between treatment groups in the number of AEDs being used, and the number of AEDs used during the subjects' lifetimes was somewhat different between treatment groups.

Table 6 Epilepsy History, ITT Safety Population

	USL255 (N=124)	Placebo (N=125)	Total (N=249)
Characteristics			
Duration of Epilepsy			
N	124	125	249

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Mean (SD)	20.9 (13.66)	20.0 (13.12)	20.4 (13.37)
Baseline weekly partial onset seizure frequency			
N	124	125	249
Median	2.29	2.66	2.52
Mean (SD)	7.45 (27.620)	5.18 (6.212)	6.31 (19.974)
Min, Max	1.0, 297.6	0.9, 37.4	0.9, 297.6
Baseline weekly partial-onset seizure frequency: By Region			
Western Europe			
N	32	25	57
Mean (SD)	5.53 (5.789)	7.33 (9.668)	6.32 (7.709)
Eastern Europe			
N	36	33	69
Mean (SD)	3.36 (3.187)	4.69 (4.013)	3.99 (3.641)
South America			
N	34	31	65
Mean (SD)	4.65 (5.329)	3.53 (3.470)	4.11 (4.539)
North America and Similar			
N	14	30	44
Mean (SD)	32.34 (79.215)	6.05 (6.725)	14.41 (45.618)
India			
N	8	6	14
Mean (SD)	1.96 (2.054)	3.12 (4.423)	2.46 (3.186)
Subjects with seizures during baseline period			
N	124	125	249
Simple partial with and without motor signs	34 (27.4%)	42 (33.6%)	76 (30.5%)
Complex partial	106 (85.5%)	103 (82.4%)	209 (83.9%)
Partial secondarily generalized	51 (41.1%)	50 (40.0%)	101 (40.6%)
Other	1 (0.8%)	0	1 (0.4%)
Number of Concurrent AEDs			
N	124	125	249
1 AED	23 (18.5%)	37 (29.6%)	60 (24.1%)
2 AEDs	68 (54.8%)	50 (40.0%)	118 (47.4%)
3 AEDs	33 (26.6%)	35 (28.0%)	68 (27.3%)
4 AEDs	0	3 (2.4%)	3 (1.2%)
Number of AEDs tried			

during lifetime			
N	124	125	249
≤3	65 (52.4%)	49 (39.2%)	114 (45.8%)
4-6	38 (30.6%)	48 (38.4%)	86 (34.5%)
7-9	15 (12.1%)	19 (15.2%)	34 (13.7%)
≥10	6 (4.8%)	9 (7.2%)	15 (6.0%)
Prior use of topiramate			
N	124	125	249
Yes	10 (8.1%)	8 (6.4%)	18 (7.2%)
No	114 (91.9%)	117 (93.6%)	231 (92.8%)

Reviewer Comment: The most notable difference between active and placebo treatment is seen in the North America and similar subgroup where the baseline partial seizure rate was 32.3/ week while the placebo rate was 6.05. This is explained by the sponsor as due to a single outlier subject with an exceptionally high baseline weekly seizure frequency located in the North America and similar group. Otherwise active treatment and placebo groups are comparable in duration of epilepsy, baseline seizure frequency, seizure type in baseline, number of concomitant AEDs, AED exposure during lifetime and prior use of topiramate. The treatment groups were otherwise comparable with respect to demographics and baseline characteristics.

Concomitant AEDs

The most frequently used AEDs (5% or greater of subjects in either treatment group) are summarized in [Table 7](#). Carbamazepine was the most commonly used AED in this population (USL255, 47.6%; placebo, 37.6%). This was followed by valproic acid and its derivatives (USL255, 32.3%; placebo 32.0%) and lamotrigine, (USL255, 22.6%; placebo 32.8%), levetiracetam (USL255, 25.0%; placebo, 20.8%), phenobarbital (USL255, 17.7%; placebo, 14.4%), oxcarbazepine USL255, 11.3%; placebo, 12.8%), lacosamide (USL255, 8.9%; placebo 11.2%), and others used by less than 10% in either treatment group.

Table 7 Concomitant Antiepileptic Medications Used by ≥5% of Subjects in Either Treatment Group, ITT Safety Population, N (%)

AED	USL255 N = 124	Placebo N = 125
Carbamazepine	59 (47.6%)	47 (37.6%)
Valproic acid	40 (32.3%)	40 (32.0%)
Lamotrigine	28 (22.6%)	41 (32.8%)
Levetiracetam	31 (25.0%)	26 (20.8%)
Phenobarbital	22 (17.7%)	18 (14.4%)
Oxcarbazepine	14 (11.3%)	16 (12.8%)

Lacosamide	11 (8.9%)	14 (11.2%)
Phenytoin	11 (8.9%)	11 (8.8%)
Clobazam	10 (8.1%)	7 (5.6%)
Clonazepam	8 (6.5%)	5 (4.0%)

6.1.3 Subject Disposition

Study completion was defined as a subject completing the maintenance phase of the study (Visit 8). Accordingly, subjects who completed the maintenance phase of the study but discontinued during the taper phase were not counted as early discontinuations. The majority of randomized subjects (87.1%, both treatment groups combined) completed the study. The early discontinuation rates were greater by 8.1% in the USL255 group (USL255: 21 [16.9%]; placebo: 11 [8.8%]), [Table 8](#).

The primary reason for early discontinuation was for an AE, with about three times as many discontinuations for an AE in the USL255 treatment group compared with the placebo treatment group (USL255: 12 [9.7%]; placebo 4 [3.2%]), [Table 8](#).

Table 8 Subject Disposition

	N(%) of Patients		
	USL255	Placebo	Total
Screened			333
Screen Failures			84 (25.2%)
Randomized	124	125	249
Completed Study	103 (83.1%)	114 (91.2%)	217 (87.1%)
Discontinued from the Study	21 (16.9%)	11 (8.8%)	32 (12.9%)
Adverse Event	12 (9.7%)	4 (3.2%)	16 (6.4%)
Lack of Efficacy	2 (1.6%)	1 (0.8%)	3 (1.2%)
Other	1 (0.8%)	2 (1.6%)	3 (1.2%)
Physician Decision	1 (0.8%)	1 (0.8%)	2 (0.8%)
Protocol Discontinuation Criteria met	1 (0.8%)	0	1 (0.4%)
Withdrawal by subject	4 (3.2%)	3 (2.4%)	7 (2.8%)

Reviewer Comment: The higher number of discontinuations in the USL255 treatment group is not of unusual magnitude for an AED study and is accounted for primarily by the larger number of discontinuations due to an adverse event in the USL255 treatment group.

Table 9 Efficacy Dataset Analyzed

	USL255	Placebo	Total
ITT Efficacy Population	124	125	249
PP Population	96	106	202
Excluded from PP population	28 (22.6%)	19 (15.2%)	47 (18.9%)
Inclusion/exclusion	9 (7.3%)	6 (4.8%)	15 (6.0%)
Drug compliance <70%	2 (1.6%)	2 (1.6%)	4 (1.6%)
Randomization error	0	0	0
Received the wrong drug	0	0	0
Investigational product overdose	0	0	0
Change in AED regimen	4 (3.2%)	4 (3.2%)	8 (3.2%)
Benzodiazepine as-needed use	1 (0.8%)	2 (1.6%)	3 (1.2%)
Did not complete maintenance phase	21 (16.9%)	11 (8.8%)	32 (12.9%)

Reviewer Comment: There is a 7.4% difference between the per protocol exclusions in the USL255 group compared to the placebo group. This does not suggest serious bias in the loss of patients between groups.

6.1.4 Analysis of Primary Endpoint(s)

Primary Endpoint: The primary endpoint comparing median percent reduction from baseline to DB treatment (titration + maintenance) phase has been an accepted endpoint for regulatory AED clinical trials. The choice of change in the weekly seizure frequency has also been accepted for a prior extended release for of an approved immediate release anti-epilepsy drug formulation.

Power analysis for sample size: The sponsor based the sample size on a standard deviation of the seizure frequency per week of 0.45. A one-time blinded data review was integrated into the protocol for sample size adjustment in the event this assumption was wrong, see [section 6.11](#). Based on the blinded data review, a sample size of 118 subjects per treatment group was used for the planned enrollment in the study. There was no multiplicity adjustment for the blinded interim analyses.

Efficacy population: The ITT efficacy population consisted of all subjects randomly assigned to study drug, who received at least 1 dose of study drug, and who had at least one post randomization seizure data point. Subjects in the ITT efficacy population (USL255: 124; placebo: 125) were grouped according to the treatment assigned at randomization.

Entry Criteria: inclusion criteria captured confirmed patients with a diagnosis of partial onset seizures with or without secondary generalization who were refractory to their current treatment. This was ensured by the requirement for 8 partial onset seizures and no more than 21 consecutive seizure free days during the 8 week baseline phase. Dosing regimen on 1 to 3 AEDs also captures the situation seen in refractory patients. The age range, 18 to 75 is a broad spectrum although in the completed study only 1 patient each in the placebo and USL255 group was greater than age 65. The criteria for entry into study P09-004 are characteristic of those with refractory partial seizures and represent the more severe spectrum of the epilepsy population.

Duration of Double Blind interval: The 11 week double blind treatment interval in this study is comparatively short compared to most AED clinical trials which utilize a double blind interval ranging from 16 to 19 weeks. The results show this short trial duration was adequate in light of the separation between placebo and treatment group.

Missing data: Days with missing seizure diary data were removed from the denominator when computing seizure frequency. If a subject had no diary data within a particular phase, the weekly seizure frequency of that phase was set to missing. The efficacy endpoints using seizure dairies were analyzed using the observed values without imputation. Mean seizure diary compliance rate during the titration + maintenance phase of study P09-004 was 99.97% for the USL255 treatment group and 99.58% for the Placebo group. All patients in the USL255 treatment group had ≥85% compliance with the seizure diary while 99.2% of patients in the placebo group had ≥85% compliance with seizure diary entry. One patient in the placebo group fell within the range of 50% to <70% compliance with seizure diary entry.

Differences between treatment groups: as noted in [Table 4](#) and [Table 6](#) above the treatment groups were otherwise comparable with respect to demographics and baseline epilepsy history characteristics. The mean duration of epilepsy was similar between treatment groups (USL255, 20.9 years; placebo, 20.0 years). There was a difference in the mean baseline weekly seizure frequency between the USL255 group and the placebo group, 7.45 and 5.18 respectively. The sponsor reports this is due largely to 1 subject in the USL255 treatment group who had a high baseline weekly seizure frequency. This same subject is discussed below in the section on geographic regional differences, located in North American and similar region, in the USL255 treatment group, seen in [Table 6](#) above. The median baseline weekly seizure frequency in the 2 treatment groups (USL255, 2.29; placebo, 2.66) and minimum baseline weekly seizure frequency in the 2 treatment groups (USL255, 1.0; placebo, 0.9) were similar.

Difference by geography: Geographical regions were categorized into five regions by the sponsor. These were Western Europe, Eastern Europe, South America, North America and similar, and India: The most notable difference between active and placebo treatment was seen in the North America and similar subgroup

where the baseline partial seizure rate was 32.3 per week while the placebo rate was 6.05. This is explained by the sponsor as due to a single outlier subject with an exceptionally high baseline weekly seizure frequency located in the North America and similar group. Among the remaining geographic categories the seizure frequencies were similar between the treatment and placebo groups. The maximum separation seen in these remaining geographical regions was 1.8 seizures per week in the Western European group. In the geographical regions not including North America and similar the separation between maximum and minimum weekly seizure frequency in USL255 treatment groups was 3.57 seizures/ week. In the geographical regions not including North America and similar the separation between maximum and minimum weekly seizure frequency in placebo treatment groups was 4.21 seizures/ week. The seizure frequency by geographical region can be seen in [Table 6](#). A test of treatment by geographic region interaction was computed using an ANCOVA, controlling for geographic region, with baseline partial-onset seizure frequency as covariate and the treatment by geographic region interaction with a resulting non-significant P value (0.751).

Concomitant AEDs: the large diversity of combinations of AEDs used by study patients does not allow a clear analysis of the influence of these combinations on differences in efficacy between treatment groups.

Discussion: The primary endpoint is consistent with the endpoint used in other AED development programs. The plan for a single blinded data review for sample size adjustment was accepted by biometrics. Absence of adjustment for multiplicity is acceptable due to the blinding of the evaluation. The short double blind treatment interval does not have a clear bias toward or against a positive outcome. The abbreviated interval would be impacted by subjects with longer interval between seizures creating a bias if there were an unequal distribution of patients with infrequent seizures between treatment arms. The baseline data reveals a mean frequency which is greater in the USL255 treatment group and only a small difference in median seizure frequency between treatment groups. This does not appear to favor the USL255 over the placebo group.

The single controlled trial is acceptable because the efficacy of the active pharmaceutical ingredient is supported by the clinical trial results of the approved and marketed immediate release formulation of topiramate. As in the trial endpoint, the placebo group on stable active therapy is an accepted form of control comparator in antiepilepsy drug trials. There was no notable divergence between placebo and treatment groups in demographic features. The study cohort represents the more difficult to control epilepsy population and thus will support labeling carried over from the reference listed drug.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoint, responder rate: The key secondary endpoint was percentage of subjects with 50% or greater reduction in weekly partial onset seizure frequency during the titration plus maintenance phase compared to baseline in the ITT population. This measure is the recommended efficacy metric in the EMA “Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders”.

The results of the responder rate analysis revealed the number of patients with 50% or greater reduction in the weekly partial onset seizure frequency was significantly greater in the USL255 treatment group (37.9%) compared with the placebo treatment group (23.2%). The treatment differences in this endpoint were assessed within the ITT efficacy population using a prespecified Cochran-Mantel-Haenszel (CMH) tests, controlling for one of geographic region, gender, race, or age group. All were significant. A post hoc Fisher exact test was also performed and found to have significance ($p=0.013$).

Additional Secondary Endpoint Analyses

Percent reductions from baseline in weekly (7-day) partial-onset seizure frequency during the titration and maintenance phases, separately: The median percent reduction in seizure frequency from baseline was significantly greater in the USL255 treatment group compared with the placebo treatment group in both the titration phase (USL255, 33.93%; placebo, 8.57%; P value <0.001) and in the maintenance phase (USL255, 45.70%; placebo, 22.09%; P value = 0.001) analyzed separately using the ITT efficacy population.

Percent reduction from baseline in weekly (7-day) all seizure frequency during the titration plus maintenance phase: The median percent reduction in seizure frequency from baseline was significantly greater in the USL255 treatment group compared with the placebo treatment group when all seizure types were combined (USL255, 39.50%; placebo, 21.65%; P value <0.001), although there were only 2 subjects (1 USL255 subject and 1 placebo subject) who experienced any seizures other than partial-onset seizures during the titration plus maintenance phase.

Proportions of subjects with 50% or greater reduction (responder rate) during the titration and maintenance phases, separately: The responder rate was significantly greater in the USL255 treatment group compared with the placebo treatment group in both the titration phase (USL255, 33.9%; placebo, 17.6%; P value = 0.007) and in the maintenance phase (USL255, 44.2%; placebo, 30.8%; P value = 0.048), analyzed separately using the ITT efficacy population.

Reviewer Comment: The findings of the secondary endpoints reveal greater reduction in seizure frequency in the USL255 treatment group compared to the placebo group with all showing significant separation.

6.1.6 Other Endpoints

Clinical Global Impression of Change Score

The CGIC score at end of the maintenance phase was compared between treatment groups by an ANOVA model where the score was the response variable and treatment and geographic region were fixed effects. The evaluation used a 7 category scale where 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

Mean (SD) scores were significantly lower (ie, improved) in the USL255 treatment group compared with the placebo treatment group (USL255, 2.9 [1.13]; placebo, 3.5 [1.07], P value <0.001); however, the Shapiro-Wilk test indicated a non-normal distribution of the results. For this reason, a Cochran-Mantel-Haenszel (CMH) test was performed controlling for geographic region, gender, age category, and race. By the CMH test, USL255 significantly improved the CGIC score compared with placebo, and the result was not sensitive to the variables of geographic region, gender, age category, or race (P value <0.001 for each controlled variable).

Quality of Life in Epilepsy Questionnaire

Quality of Life in Epilepsy-31-P questionnaire scores were summarized by domain and overall at Day 1 and end of maintenance/ED. Change from baseline values were summarized and compared between treatment groups by an ANCOVA, controlling for geographic region, with baseline score as the covariate.

No significant difference between treatment groups was observed in the QOLIE-31-P questionnaire change from baseline overall score or the distress score. Only for the seizure worry subscale change from baseline was a significant difference between treatment groups observed (Mean [SD]: USL255, 14.1 [25.74]; placebo, 4.1 [18.62], P value <0.001). No significant differences between treatment groups were observed for subscales overall quality of life, emotional well-being (Emotions), energy/fatigue (Energy), cognition (Mental Activity), medication effects, and social function (Daily Activities).

6.1.7 Subpopulations

Utilization of topiramate in subpopulations is carried by the RLD topiramate immediate release label. Notable differences among specific populations are not anticipated based

on an extended release formulation. Proposed text on “Use in Specific Populations” is referenced from the RLD labeling- TOPAMAX, approved on October 2012 with the exception of migraine prophylaxis which is not contained in proposed topiramate extended release labeling.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Proposed text on dosing information is referenced from the RLD labeling- TOPAMAX, approved on October 2012.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Because only the dosing form is changed but the active pharmaceutical ingredient, topiramate, is unchanged there is no anticipated alteration in the durability of the therapeutic effect.

6.1.10 Additional Efficacy Issues/Analyses

The single controlled trial is acceptable because the efficacy of the active pharmaceutical ingredient is supported by the clinical trial results of the approved and marketed immediate release formulation of topiramate.

7 Review of Safety

Safety Summary:

The application contains a single phase 3 placebo controlled efficacy study for safety evaluation with a control group, 124 patients in the USL255 treatment arm and 125 patients in the placebo treatment arm. The content and frequency of the clinical testing through the course of the phase 1 and phase 3 trials was appropriate for the known risks of topiramate.

One death has been reported in the Phase 3 (P09-005) study due to ischemic stroke in a 54 year old patient. This event occurred approximately 6 months into open label treatment with USL255. This death which occurred after a long interval of open label treatment on a background of cerebrovascular disease and a potentially sustained vasculopathy (rheumatic vasculitis) does not support a causal relationship to the study drug.

The frequency of SAEs in the controlled clinical trial P09-004 was equal in the placebo and study drug treatment groups with one of the two events in the drug treatment arm unrelated to study drug and the second of two events was pneumonia. Pneumonia is in the current topiramate IR label and this single case is not sufficient to promote this

event from the currently labeled position. The continuation study of P09-004 had unlabeled events of ischemic stroke (same as death above), cholelithiasis and cholecystitis. The high background rate of cholelithiasis and cholecystitis confounds the relationship to USL255. Overall no new safety signal is identified in study of this extended release topiramate.

Examination of adverse events leading to discontinuation revealed a profile of preferred terms commensurate with the known adverse event profile of topiramate and does not reveal a new safety signal. Common adverse events observed during the phase 1 and phase 3 trials also reveals a profile of preferred terms commensurate with the known adverse event profile of topiramate.

Clinical chemistry safety evaluation revealed signals for diminished serum bicarbonate and elevated serum chloride. The clinical hematology studies revealed an excess of shift from normal to high in USL255 treated patients compared to placebo for the RDW (red cell distribution width). However; due to the high baseline occurrence of elevated RDW and the non-specific nature of this RBC parameter the interpretation of the above observations is uncertain. A true signal for variation in the RBC population of treated patients is possible but there are no converging lines of evidence to support this conclusion based on the absence of treatment to placebo differences in hemoglobin and MCV values as well as no report of anemia seen in the AE dataset.

In conclusion the safety signals identified in labeling for immediate release topiramate remain unchanged following review of the safety data in this application. The observation of an excess shift of RDW in USL255 treated patients is of uncertain significance. The reviewer recommends pharmacovigilance for related AEs of iron, B-12, or folate deficiency, hemolytic anemias or myelodysplastic syndrome. This observation does not rise to the level where a formal post-marketing safety program is required.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data for this application are derived from two elements, the original submission and an amendment submitted at the time of the 120 day safety update which provides safety and efficacy data from a Phase 3 study, P09-004. The original submission presented safety data from short term Phase 1 studies. The basis of the original submission was the establishment of pharmacokinetic equivalence between the profiles of USL255 and immediate-release (IR) topiramate (Topamax®) in healthy volunteer studies. In the original submission safety data were summarized for all subjects who received at least one dose of study drug in each of 2 integrated Phase 1

study populations: the single dose study populations that were comprised of 6 single dose Phase 1 studies and 3 multiple dose Phase 1 studies.

Table 10 List of Studies Providing Safety Data

Study #	Date completed	Total Population	Description	Study Population
Phase 1 Studies				
Single Dose Studies				
Formulation Studies				
P08-003	21Nov2008	24	Randomized, single-center, open-label, 4-way crossover, relative bioavailability	Healthy male subjects
P08-008	30Sep2009	42	Randomized, single-center, open-label, 2-arm with crossover, relative bioavailability	healthy male subjects
Bioavailability Studies				
P09-002	19Mar2010	36	Randomized, single-center, open-label, 3-way crossover, fed vs fasted, relative bioavailability	36 healthy male and female subjects
P255-102	01Feb2012	36	Randomized, single-center, open-label, 4-way crossover, bioequivalence	36 healthy male and female subjects
Dose-Proportionality Study				
P09-001	30Mar2010	30	Randomized, single-center, open-label, 5-way crossover, dose proportionality	Healthy males and females
Ascending Dose Study				
P09-011	04Mar2010	50	Randomized, single-center, double-blind, safety and pharmacokinetics of single ascending doses	Healthy males and females
Multiple-Dose Studies				
P09-003	20Apr2010	38	Randomized, single-center, open-label, 2-way crossover, multidose, relative bioavailability	Healthy males and females
P255-101	18Nov2011	48	Randomized, single-center, double-blind, 2-period crossover, relative bioavailability and pharmacodynamic effects on cognition	48 Healthy males and females

P255-103	13Oct2012	48	Randomized, single-center, double-blind, 2-period crossover, relative bioavailability and effects on cognition	48 healthy subjects
Phase 3 Studies				
P09-004	18Dec2012	249	Randomized, multicenter, double-blind, safety and efficacy	249 Epilepsy patients
P09-005	Ongoing	210	Multicenter, open-label extension, safety and efficacy	Patients from P09-004

7.1.2 Categorization of Adverse Events

MedDRA dictionary: Phase 1 studies, SAP for the summary of clinical safety indicates MedDRA ver 11.0 is used for all phase 1 studies. The Adverse Event Analysis Dataset (ADAE) indicates MedDRA 14.1 as the source of dictionary derived term. Phase 3 study P09-004: MedDRA ver 11.0

Phase 1, Healthy Subject Studies

All adverse events were pooled into the adae.xpt dataset. The phase 1 pool contained 352 subjects. There were 1668 adverse event entries from 188 subjects. Within these entries there were 605 verbatim terms. These verbatim terms were coded to 236 preferred terms. The verbatim term listings were inspected and compared to the preferred terms to determine the coherence and consistency of the preferred term assignments.

Upon inspection of the verbatim to dictionary term coding the reviewer had concerns about the transcoding of three verbatim terms.

The first concern was lightheadedness coded to dizziness. From a medical prospective lightheadedness may be a near syncopal or presyncopal event which has more serious hemodynamic implications than dizziness. Examination of the 14.0 dictionary does not reveal an available preferred term to map from lightheadedness which has hemodynamic implications. Seventeen of 352 Phase 1 subjects experienced this adverse event. There are non-hemodynamic etiologies of lightheadedness such as transient vestibular dysfunction or a non-specific central nervous system effect which may be caused by centrally acting agents such as topiramate.

The categorization of concern in mapping verbatim to preferred term was numbness, whether of a limb or cephalic site. Numbness was mapped to hypoaesthesia but may

actually be a paresthesia symptom which is a known adverse effect of topiramate. Examination of the MedDRA 14.0 dictionary does not reveal available mapping of numbness to paresthesia. This does not represent a new safety concern for topiramate.

The third categorization concern was the mapping of “sensation of heavy breathing” to the preferred term “sensory disturbance”. This mapping represents a potential understatement of this verbatim term. A more appropriate term would be found in the HLT “respiratory signs and symptoms NEC”. Preferred terms within this HLT that may more accurately capture “sensation of heavy breathing” include the preferred terms “chest discomfort”, “respiratory fatigue” or “suffocation feeling”. These terms convey more physiologically meaningful content of the experience of “sensation of heavy breathing”. This adverse event occurred in one subject in study P255-103 a 7 day multiple dose crossover study.

The remainder of the examination did not reveal categorizations which would cause loss of physiologically important information and there was no evidence of split mapping to preferred terms that would result in loss of a safety signal.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events from the healthy subject Phase 1 trials were pooled in the initial NDA submission to establish pharmacokinetic equivalence between the profiles of USL255 and immediate release topiramate (Topamax) in healthy volunteer studies in order to rely on FDA finding of safety and effectiveness for the RLD Topamax. As noted in section 7.1.3 there were 352 subjects in this pool. One hundred eighty eight of these subjects experienced a total of 1668 adverse events.

The 120 day safety update contained safety data from a completed Phase 3 study (P09-004) and the available safety data from the open label extension of P09-004 entitled P09-005. The safety data from the initial PK trials and subsequent clinical trial are not pooled.

Discussion and analysis of the safety data from the initial submission and the 120 day safety update with the clinical trial data was combined in the revised “Summary of Clinical Safety” submitted in the 120 day safety update amendment. The adverse event datasets were not pooled, however the reviewer pooled the adae.xpt from the initial submission with the adae.xpt from study P09-004 provided in the 120 day safety update to allow examination of pooled adverse events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Topiramate is not a new molecular entity rather a new formulation of an established active pharmaceutical ingredient. Topiramate was first approved as Topamax® on December 24, 1996. The current submission is a 505(b)(2) referencing the Topamax New Drug Application 020505 [topiramate oral tablet (Janssen Pharmaceuticals)]. It is implicit that the ICH E1 population exposure guidelines were achieved in the reference application.

Safety exposure requirements for change in formulation / excepted: The bulk of risk is considered to be carried by the API. There are no clear guidelines for appropriate exposures of new formulations of an established API. The exposure for this extended release formulation of topiramate does not meet the ICH E1 thresholds of 300 patients exposed for six months and 100 exposed for 1 year. However sustained exposure to USL255 does reach approximately half those six month and 1 year ICH E1 targets as seen in [Table 13](#).

STUDIES: A single Phase 3 efficacy study (P09-004) as adjunctive treatment of seizures in adults in addition to exposure in all subjects who received at least 1 dose of study drug in each of 2 integrated Phase 1 study populations: (1) the single-dose studies population comprised 6 single-dose, Phase 1 studies; and (2) the multiple-dose studies population comprised 3 multiple-dose, Phase 1 studies.

Phase 1 Single Dose Studies

Table 11 USL255 Exposure by Dose and Overall—Single-Dose Safety Population*

Exposure	USL255								
	< 200 mg ^b	200 mg ^c	400 mg ^d	600 mg ^e	800 mg ^e	1000 mg ^e	1200 mg ^e	1400 mg ^e	Overall
No. of Subjects	30	163	46	8	8	8	8	8	206
No. of Doses, n (%) ^g									
1	4 (13.3)	30 (18.4)	46 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	—
2	0	83 (50.9)	0	0	0	0	0	0	—
3	26 (86.7)	21 (12.9)	0	0	0	0	0	0	—
4	0	29 (17.8)	0	0	0	0	0	0	—
Total No. of Dose	82	375	46	8	8	8	8	8	543

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^a Subjects may have received up to 5 single doses of USL255.
^b P09-001.
^c P08-003, P08-008, P09-002, P255-102, P09-001.
^d P08-008, P09-001.
^e P09-011.
^f Number of unique subjects dosed.
^g For percentages, numerator is number of subjects who received the specified number of doses; denominator is number of subjects receiving at least one dose.
^h From "Summary of Clinical Safety", page 33, table 3

Phase 1 Multiple Dose Studies

Table 12 USL255 Exposure by Dose and Overall—Phase 1 Multiple-Dose Safety Population*

Exposure	USL255						Overall
	50 mg ^b	100 mg QD ^c	150 mg QD ^d	200 mg QD ^e	300 mg QD ^f	400 mg ^g	
No. of Subjects Dosed ^h	10 5	104	7 5	80	4 4	4 2	105
No. of Dosing Days, n (%) ⁱ							
1	1 (1.0)	0	0	0	0	0	0
4	36 (34.3)	36 (34.6)	20 (26.7)	0	0	0	—
5	0	0	5 (6.7)	0	2 (4.5)	0	—
6	4 (3.8)	1 (1.0)	6 (8.0)	0	0	0	—
7	64 (61.0)	22 (21.2)	44 (58.7)	0	42 (95.5)	42 (100.0)	—
8	0	1 (1.0)	0	0	0	0	—
10	0	2 (1.9)	0	44 (55.0)	0	0	—
11	0	42 (40.4)	0	0	0	0	—
14	0	0	0	36 (45.0)	0	0	—
Total No. of Dosing Days	61 7	794	44 9	944	30 4	29 4	3402

^a Results are combined for up-titration, maximum dose, and down-titration periods.
^b Up-titration in Studies P09-003, P255-101, and P255-103; down-titration in Study P09-003.
^c Up-titration in Studies P09-003, P255-101, and P255-103; down-titration in Studies P09-003 and P255-103.
^d Up-titration in Studies P09-003, P255-101, and P255-103.
^e Maximum dose in Study P09-003; up-titration and down-titration in Study P255-103.
^f Up-titration in Study P255-103.
^g Maximum dose in Study P255-103.
^h Number of unique subjects dosed.
ⁱ For percentages, numerator is number of subjects who received the specified number of doses, denominator is number of subjects receiving at least one dose.
*From "Summary of Clinical Safety", page 34, table 4

Phase 3 Studies P09-004 and P09-005

Table 13 Overall USL255 Exposure—Phase 3 P09-004 and P09-005 ITT Subjects Combined*

Exposure	USL255 (N = 235)
Duration in days	
N	235
Mean (SD)	242.5 (150.21)
Median	232.0
Min, Max	1, 507
Total exposure time,	Patients n^{a,b}, %
≥ 30 days	217 (92.3)
≥ 60 days	207 (88.1)
≥ 90 days	182 (77.4)
≥ 120 days	169 (71.9)
≥ 180 days	133 (56.6)
≥ 270 days	112 (47.7)
≥ 360 days	71 (30.2)
Abbreviations: ITT = intent to treat a Exposure in P09-005 is based on an interim data cut of 25 January 2013. b Exposure: If a subject received USL255 in P09-004 and did not enroll in P09-005, exposure = last dose date in P09-004 – first dose date in P09-004 + 1. If a subject received USL255 in P09-004 and enrolled in P09-005, exposure = last visit date in P09-005 – first dose date in P09-004 + 1. If a subject received placebo in P09-004 and enrolled in P09-005, exposure = last visit date in P09-005 – first visit date P09-005 + 1. Subjects who received placebo in P09-004 and did not enroll in P09-005 are not included.	

Reviewer Comment: The notable feature of exposure from [Table 13](#) above is the sustained exposure of 133 patients for six months or greater and 71 patients for approximately 1 year. These exposures approach one half of the ICH E1 thresholds for a new API and appear adequate for the extended release form of a long established API. [Table 11](#) reveals 32 patients have had single dose exposures to USL255 of more than twice the therapeutic dose. Overall the exposure to USL255 is appropriate for a new formulation of a marketed, well characterized drug.

7.2.2 Explorations for Dose Response

Not applicable here for this 505b2 submission where immediate (Topamax) release topiramate is the reference listed drug and dose is established.

7.2.3 Special Animal and/or In Vitro Testing

The nonclinical safety of USL255 relies on the safety information for its active ingredient, topiramate, as assessed by the US Food and Drug Administration (FDA) and other regulatory bodies and described in the Topamax® labeling (p29, study report).

7.2.4 Routine Clinical Testing

Study P09-004 assessments included medical history, physical and brief neurological examination, vital signs, clinical laboratory procedures, 12 lead ECG at screening, maintenance phase and study completion, FSH (females), urine drug screen.

Table 14 Study P09-004 Clinical Laboratory Studies

Hematology	Serum Chemistry^a	Urinalysis^b
CBC with differential, Hgb, Hct Platelets MCV MCH MCHC RDW	BUN Creatinine ^d Total bilirubin Total protein Alkaline phosphatase AST (SGOT) ALT (SGPT) Glucose Albumin Potassium Sodium Chloride Bicarbonate	pH Specific Protein Glucose Ketone Bilirubin Blood Nitrites Urobilinogen Leukocytes Microscopic analysis
Urine Drug Screen	Additional Screening Test	Pregnancy Test^c
Ethyl alcohol Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine metabolites Opiates, Phencyclidine	FSH (females only)	β-hCG
<p>^aBlood draw n at Visits 6 w ill only have 7 serum chemistry parameters measured: sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose. ^bmicroscopic analysis performed if urine positive for red blood cells r leukocytes. ^cPregnancy tests at Visits 1 and 8 will be done via serum. Pregnancy tests at all over visits w ill be done via urine at the clinical site and if positive, w ill be confirmed w ith serum. ^dSerum creatinine w ill be used to calculate the estimated creatinine clearance Abbreviations: β -hCG=beta-human chorionic gonadotropin; ALT(also know n as SGPT)=alanine aminotransferase; AST(also know n as SGOT)=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; Hct=hematocrit; Hgb=hemoglobin; MCH=mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; pH=hydrogen ion concentration; RDW=red cell distribution w idth; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.</p>		

Phase 1 Studies

Subject in the phase 1 studies had medical history, vital signs, physical examination, clinical chemistry and hematology laboratory studies, FSH (females), Baseline ECG only in 3 studies, baseline and final visit ECG in 3 studies, and baseline ECG and Holter monitor, holter monitor during treatment and final visit ECG in 3 studies. A listing of clinical chemistry and hematology studies performed in the phase 1 studies is shown in [Table 15](#). The only difference between the single and multiple dose studies was a magnesium level was obtained in the single dose studies.

Table 15 Clinical Laboratory & Hematology Studies Obtained in Single Dose & Multiple Dose Phase 1 studies

Clinical Laboratory & Hematology Studies Obtained in <u>Single Dose</u> Phase 1 studies	Clinical Laboratory & Hematology Studies obtained in <u>Multiple dose</u> phase 1 studies
Alanine Aminotransferase	Alanine Aminotransferase
Albumin	Albumin
Alkaline Phosphatase	Alkaline Phosphatase
Aspartate Aminotransferase	Aspartate Aminotransferase
Basophils	Basophils
Basophils %	Basophils %
Bicarbonate	Bicarbonate
Blood Urea Nitrogen	Blood Urea Nitrogen
Chloride	Chloride
Creatinine	Creatinine
Eosinophils	Eosinophils
Eosinophils %	Eosinophils %
Ery. Mean Corpuscular Hemoglobin	Ery. Mean Corpuscular Hemoglobin
Ery. Mean Corpuscular HGB Concentration	Ery. Mean Corpuscular HGB Concentration
Ery. Mean Corpuscular Volume	Ery. Mean Corpuscular Volume
Erythrocytes Distribution Width	Erythrocytes Distribution Width
Glucose	Glucose
Hematocrit	Hematocrit
Hemoglobin	Hemoglobin
Lymphocytes	Lymphocytes
Lymphocytes %	Lymphocytes %
Mean Platelet Volume	Mean Platelet Volume
Monocytes	Monocytes
Monocytes %	Monocytes %
Neutrophils	Neutrophils
Neutrophils %	Neutrophils %
Platelets	Platelets
Potassium	Potassium

Clinical Laboratory & Hematology Studies Obtained in <u>Single Dose</u> Phase 1 studies	Clinical Laboratory & Hematology Studies obtained in <u>Multiple dose</u> phase 1 studies
Protein	Protein
Red Blood Cells	Red Blood Cells
Sodium	Sodium
Total Bilirubin	Total Bilirubin
Urine Bacteria	Urine Bacteria
Urine Bilirubin	Urine Bilirubin
Urine Blood	Urine Blood
Urine Casts	Urine Casts
Urine Crystals	Urine Crystals
Urine Glucose	Urine Glucose
Urine Ketones	Urine Ketones
Urine Leukocyte Esterase	Urine Leukocyte Esterase
Urine Nitrite	Urine Nitrite
Urine pH	Urine pH
Urine Protein	Urine Protein
Urine Red Blood Cells	Urine Red Blood Cells
Urine Specific Gravity	Urine Specific Gravity
Urine Urobilinogen	Urine Urobilinogen
Urine White Blood Cells	Urine White Blood Cells
White Blood Cells	White Blood Cells
magnesium	

Reviewer comment: The content and frequency of the clinical testing through the course of the phase 1 and phase 3 trials was appropriate for the known risks of topiramate.

7.2.5 Metabolic, Clearance, and Interaction Workup

This 505(b)(2) New Drug Application references the Topamax® (topiramate) Tablets, New Drug Application 020505. No new data is provided here, the sponsor is reliant on work from the reference listed drug.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No new data is provided here, this topiramate product is expected to have the same comparator “drugs in class” as the reference listed topiramate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the single-dose and multiple-dose Phase 1 studies; and no deaths were reported during the Phase 3 P09-004 study.

One death has been reported in the Phase 3 P09-005 study due to ischemic stroke in a 54 year old patient. This event occurred approximately 6 months into open label treatment with USL255. The narrative indicates the ischemic event occurred in the region of the right anterior and posterior cerebral artery. The patient had pre-existing cerebrovascular disease with a history of a middle cerebral artery stroke at approximately age 16 years, a posterior cerebral artery stroke 4 years prior to this event and a history of mitral insufficiency and rheumatic vasculitis

Reviewer Comment: This death which occurred after a long interval of open label treatment on a background of cerebrovascular disease and a potentially sustained vasculopathy (rheumatic vasculitis) does not support a causal relationship to the study drug.

7.3.2 Nonfatal Serious Adverse Events

Single Dose Phase 1 studies: In the single-dose study population, 3 subjects experienced an SAE: two of the subjects were receiving 200 mg of USL255 (reports of spontaneous abortion and anemia) and one subject was receiving 100 mg of Topamax® (report of forearm fracture). The subject who suffered the spontaneous abortion had a negative beta HcG upon entering the study. Inferred from the expected timeline of events the subject was exposed to only one 200 mg dose of an extended release topiramate formulation and then subsequently found to be pregnant. The subject was discontinued from the study. Later, at an estimated 9 weeks gestation, the subject presented to an emergency room with scant vaginal bleeding and cramping. A spontaneous abortion occurred 4 days later. The relationship of the event to the single dose of extended release topiramate formulation is uncertain. It is known that topiramate may cause fetal malformation and is categorized as a Pregnancy category D agent.

Multiple Dose Phase 1 Studies: No serious adverse events were reported during the Phase 1 multiple-dose studies.

Placebo controlled Clinical Trial, Study P09-004: Five SAEs were reported in 4 subjects (2 (1.6%) subjects, in the USL255 group and 2 (1.6%) subjects in the placebo group). Two SAEs (epileptic psychosis and suicidal ideation) were reported in a placebo treated patient, [Table 16](#).

Table 16 Serious Adverse events in Study P09-004

Subject No.	Treatment	Age (y)/Sex/Race	MedDRA Preferred Term	Severity	Relationship to Study Drug	Outcome
245/265	Placebo	24/F/White	Convulsion	Severe	Not related	Resolved
291/293	Placebo	56/M/Other	Epileptic psychosis	Severe	Probably related	Resolved
			Suicidal ideation	Severe	Probably related	Resolved
101/078	USL255	22/F/White	Physical assault (patient assaulted)	Severe	Not related	Resolved
231/164	USL255	68/M/White	Lobar pneumonia	Mild	Not related	Resolved

There were two serious adverse events experienced by patients on study drug treatment. The one event of physical assault is not related to study drug. Pneumonia is labeled in the reference listed drug (Topamax®). A summary of the patient narrative is presented below. The event appears to be a community acquired pneumonia but will not be considered a new safety signal based on this single event.

USL255 treatment patient 231/164: This 68 yo white Israeli male developed a right lower lobe pneumonia on study day (b) (4). He presented to the emergency room with weakness and urinary retention which had developed in the previous 24 hours. No fever or dyspnea was noted but a chest X-ray revealed right-sided abnormalities which included a blurry right diaphragm, blunting of the right costophrenic angle and a small infiltrate and atelectasis in the right base. The subject was hospitalized. Oxygen saturation was 94%. The following out-of-range laboratory values were noted during the hospitalization: white blood cell count, 30.10 (units not reported) with a reference range of 4 to 10 (units not reported); neutrophils, 91.2 (units not reported) with a reference range of 38 to 52 (units not reported). Throughout the course of treatment, the subject's white blood cell count decreased to 11 (units not reported). The patient was treated with ciprofloxacin and cefuroxime orally and the patient was discharged from the hospital after 4 days and continued outpatient antibiotic therapy for an additional 10 days. The patient remained in the study and completed study P04-009 on study day 78.

Open Label Phase 3 Extension trial P09-005 (extension of P09-004): In this ongoing trial 11 subjects experience 15 SAEs displayed in [Table 17](#). Among the 15 adverse events the intervertebral disc protrusion and appendicitis are unlikely to be study drug related. The remaining events deserve consideration as possibly study drug related. These are diarrhea, ischemic stroke, cholelithiasis (2 events), pneumonia (2 events), fractures (2) cholecystitis, headache, appendicitis, epilepsy related event (2) and acute psychosis. Review of the reference listed drug label (Topamax®) reveals that diarrhea, psychosis, infection and headache are present in the "Other Adverse Reactions Observed During Double-Blind Epilepsy Adjunctive Therapy Trials", section 6.4, while pneumonia is present both in the "Other" section 6.4 and in [table 9](#), "Incidence (%) of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Add-On Epilepsy Trials in Pediatric Patients (Ages 2 -16 Years)" of section 6.5. Fractures and osteoporosis are present in the label, noted to be a possible consequence of the metabolic effect of

topiramate. The relationship of fracture to the metabolic state of patient 182 is unknown. The signal for these events was evaluated in the original NDA for the RLD and will not be evaluated again here since the frequency of the events do not appear sufficient to change the position in current labeling. Convulsive events occur in epilepsy trials due to the nature of the underlying illness and their occurrence during a long extension trial is expected.

The remaining events in Table 17 to explore as a new safety signal are ischemic stroke, cholelithiasis and cholecystitis. These do not appear in current labeling. The ischemic stroke is unlikely to be study drug related and is discussed in section 7.3.1 Deaths. There are two reports of cholelithiasis, one with cholecystitis which are unlabeled events, however; the background incidence of cholelithiasis is high. Ten to 20% of Europeans and Americans carry gallstones and in the US there are 700,000 cholecystectomies performed each year. Due to this high background incidence of cholelithiasis it is unlikely that the two reports from study P09-005 represent a new safety signal for topiramate. In addition a PubMed using the search string “topiramate” and “cholelithiasis” did not yield any references^{6,7}.

Table 17 Serious Adverse events in P3 open label extension trial P09-005

Subject No.	Age (y)/ Sex/Race	MedDRA Preferred Term	Severity	Relationship to Study Drug	Outcome
107/063	43/M/Hispanic	Diarrhea infectious	Severe	Not related	Resolved
241/249	36/F/White	Convulsion	Moderate	Not related	Resolved
261/056	30/M/White	Intervertebral disc protrusion	Moderate	Not related	Resolved
265/041	58/M/White	Ischemic stroke	Severe	Not related	Death
266/022	46/F/White	Cholelithiasis ^a	Moderate	Possibly related	Resolved with sequelae
300/224	60/F/Asian	Lobar pneumonia	Severe	Not related	Resolved
301/182	38/M/White	Fibula fracture	Severe	Not related	Resolved with sequelae
		Tibia fracture	Severe	Not related	Resolved with sequelae
415/233	44/M/White	Cholecystitis acute	Severe	Not related	Resolved
		Cholelithiasis	Severe	Not related	Resolved

⁶ Krawczyk M, et al. Genetics and treatment of bile duct stones: new approaches. *Curr Opin Gastroenterol* 2013, 29:329–335

⁷ Lammert F and Miquel JF. Gallstone disease: From genes to evidence-based therapy. *Journal of Hepatology* 48 (2008) S124–S135

423/139	24/F/White	Headache	Moderate	Not related	Resolved
423/166	49/F/Other	Appendicitis	Mild	Not related	Resolved
423/169	50/F/White	Status epilepticus	Severe	Not related	Resolved
		Pneumonia aspiration	Moderate	Not related	Resolved
		Acute psychosis	Moderate	Not related	Resolved

Reviewer Comment: The frequency of SAEs in the controlled clinical trial P09-004 was equal in the placebo and study drug treatment groups with one of the two events in the drug treatment arm unrelated to study drug and the second of two events was pneumonia. Pneumonia is in the current topiramate IR label and this single case is not sufficient to promote this event from the currently labeled position. The continuation study of P09-004 had unlabeled events of ischemic stroke, cholelithiasis and cholecystitis. The stroke occurred in a patient who had a background of cerebrovascular disease. The high background rate of cholelithiasis and cholecystitis confounds the relationship to USL255. Overall no new safety signal is identified in study of this extended release topiramate.

7.3.3 Dropouts and/or Discontinuations

Single Dose Phase 1 studies: One subject after receiving 200 mg of USL255 was discontinued because of an SAE (report of spontaneous abortion), which was judged as not related to the study drug.

Multiple Dose Phase 1 Studies: Four subjects receiving Topamax® and 1 subject receiving USL255 were discontinued from the study due to a TEAE. In the USL255 group, a subject developed a mild macular rash that was assessed as possibly related to the study drug. In the Topamax® group, 4 subjects were discontinued from the study due to the following TEAEs: postural dizziness, diarrhea, papular rash, and heart rate increased. All of these TEAEs were assessed as possibly or probably related to the study drug.

Placebo controlled Clinical Trial, Study P09-004: Eleven (8.9%) subjects in the USL255 group and 5 (4.0%) subjects in the placebo group discontinued from the ITT safety population due to TEAEs, [Table 18](#).

Table 18 Treatment-Emergent Adverse Events That Led to Study Discontinuation, ITT Safety Population, N (%)

Preferred Term	USL255 N = 124	Placebo N= 125
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Subjects with at least 1 treatment-emergent adverse event that led to study discontinuation	11 (8.9%)	5 (4.0%)
Disturbance in attention	2 (1.6%)	1 (0.8%)
Somnolence	2 (1.6%)	0
Aphasia	1 (0.8%)	0
Depression suicidal	1 (0.8%)	0
Dizziness	1 (0.8%)	0
Drug intolerance	1 (0.8%)	0
Headache	1 (0.8%)	0
Irritability	1 (0.8%)	0
Mental impairment	1 (0.8%)	0
Psychomotor retardation	1 (0.8%)	0
Rash	1 (0.8%)	0
Tension headache	1 (0.8%)	0
Thinking abnormal	1 (0.8%)	0
Bradyphrenia	0	1 (0.8%)
Convulsion	0	1 (0.8%)
Epileptic psychosis	0	1 (0.8%)
Fatigue	0	1 (0.8%)
Memory impairment	0	1 (0.8%)
Suicidal ideation	0	1 (0.8%)

Open Label Phase 3 Extension trial P09-005 (extension of P09-004): Seventeen of 210 subjects have discontinued from the study due to a total of 19 TEAEs as of the cut-off date of 25 January 2013. The subjects were discontinued from the study due to the following TEAEs (in 1 subject each, except where noted): diarrhea, infectious diarrhea, gait disturbance, convulsion (in 2 subjects), disorientation, aphasia, suicidal thoughts, thrombocytopenia, ischemic stroke, asthma, cholelithiasis, dizziness, urinary tract infection, bradyphrenia, asthenia (in 2 subjects), depression, and acute psychosis.

The extension trial events of diarrhea, infectious diarrhea, convulsion, cholelithiasis, acute psychosis and ischemic stroke have been discussed in the section on the SAEs which occurred in study P09-005, [see above](#).

The event of gait abnormal is noted in labeling for other adverse events for add on trials in both adults and pediatric patients therefore it is reasonable to conclude that the term “gait disturbance” is captured within the “gait abnormal” term. Topiramate has well characterized adverse effects on cognitive functions. The adverse event of

disorientation although not specifically identified in the current topiramate label is very closely aligned with known cognitive adverse events and does not represent a new type of cognitive adverse event. Urinary tract infection is identified in the topiramate IR label as an event in add on trials which occurred in greater than 1% of topiramate treated patients and was at a frequency greater than placebo. It was also seen as an event with a frequency of greater than 2% in any topiramate treatment group and greater than the rate in placebo treated patients. Asthma is present in the listing of “other adverse reactions observed during migraine clinical trials”. Thrombocytopenia is listed as an infrequent event under the heading of “neoplasms” in “Other Adverse Reactions Observed During All Epilepsy Clinical Trials”.

Reviewer Comment: Examination of adverse events leading to discontinuation does not reveal a new safety signal.

7.3.4 Significant Adverse Events

The significant adverse events in the use of topiramate have been well characterized and are seen in the warnings and precautions section 5 of the reference listed drug Topamax®. New adverse events of a significant magnitude are not expected in the use of an extended release formulation.

7.3.5 Submission Specific Primary Safety Concerns

Healthy Adult subjects, phase 1 studies: no events of increased or unusual significance occurred in the phase 1 study subjects.

Study P09-004 : no events of increased or unusual significance occurred.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Single Dose Phase 1 studies:

TEAEs were reported in 61.7% (127 of 206) of subjects receiving USL255, 37.4% (37 of 99) of subjects receiving Topamax®, and 20.0% (2 of 10) of subjects receiving placebo. After treatment with < 200 mg, 200 mg, or 400 mg of USL255, TEAEs were reported in 36.7% (11 of 30), 47.2% (77 of 163), and 39.1% (18 of 46) of subjects, respectively while TEAEs were reported in 37.4% (37 of 99) of subjects receiving Topamax® 200mg to 400mg.

After all USL255 treatment doses were combined, the most commonly reported TEAEs that occurred in > 10.0% of subjects were dizziness (26.7%), headache (17.0%),

paresthesia (17.0%), and nausea (14.1%). After Topamax® treatment, only dizziness (18.2%) was reported in > 10% of subjects.

After USL255 (all doses <200mg to 400mg n= 239, 600mg to 1400mg, n=40) and Topamax® treatment (200mg to 400mg, n= 99), the most frequently reported TEAEs by SOC were Nervous System Disorders (47.1% and 29.3%), Gastrointestinal Disorders (23.8% and 9.1%), General Disorders and Administration Site Conditions (18.9% and 10.1%), and Psychiatric Disorders (10.2% and 6.1%), respectively. In comparison, after USL255 doses of < 200 mg, 200 mg, and 400 mg, TEAEs in the Nervous System Disorders SOC occurred in 16.7%, 34.4%, and 30.4% of subjects; Gastrointestinal Disorders occurred in 13.3%, 17.2%, and 10.9% of subjects; General Disorders and Administration Site Conditions occurred in 0, 14.7%, and 13.0% of subjects; and Psychiatric Disorders occurred in 3.3%, 9.8%, and 8.7% of subjects, respectively.

Multiple Dose Phase 1 Studies (P09-003, P255-101, P255-103):

Overall, a similar percentage of subjects reported TEAEs in the USL255 (75.2%) and Topamax® (78.9%) groups. In the USL255 group, the most commonly reported TEAEs that occurred in > 10.0% of subjects were paresthesia (24.8%), headache (18.1%), constipation (17.1%), somnolence (13.3%), diarrhea (12.4%), insomnia (12.4%), weight decreased (11.4%), and dry eye (10.5%). In the Topamax® group, the most commonly reported TEAEs that occurred in > 10% of subjects were paresthesia (29.4%), headache (24.8%), weight decreased (16.5%), constipation (11.9%), dyspepsia (11.9%), diarrhea (11.0%), dizziness (11.0%), insomnia (11.0%), and somnolence (10.1%). (P56 sum clin safety)

Reviewer Comment: the profile of common adverse events is similar in type and frequency between the subjects receiving USL255 and Topamax® in phase 1 studies.

Study P255-103

This was a phase 1, randomized, double blind, 2 period crossover study to assess the effects of USL255 400mg each evening (QPM) on cognition, mood, and alertness compared with Topamax 200mg twice a day Q12H. A report of the cognitive effects was not submitted with this NDA, the sponsor notes a follow up study report will summarize the cognitive findings. A complete report of adverse effects was, however, provided in the study report to this NDA. There were no deaths or serious adverse events in this study. The common adverse events that occurred are presented in [Table 19](#) and [Table 20](#).

Table 19 Study 255-103 Comparison of Adverse Events by System, Organ, Class (SOC), % of Patients*

SOC	USL255	Topamax
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Clinical Review
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	% patients	% patients
Nervous system disorders	55.6	72.3
Gastrointestinal Disorders	48.9	44.7
Investigations	31.1	42.6
Skin and Subcutaneous Tissue Disorders	26.7	42.6
Eye Disorders	33.3	38.3
General Disorders and Administration Site Conditions	33.3	34
Psychiatric Disorders (PT insomnia)	26.7	36.2
Respiratory, Thoracic and Mediastinal Disorders	22.2	19.1
Musculoskeletal and Connective Tissue Disorders	22.2	4.3
Injury , poisoning and Procedural Complications	15.6	10.6
Reproductive System and Breast disorders	17.8	17
*From sponsor narrative of AE by SOC, p76, P255-103 study report		

Table 20 Study 255-103, USL255 Compared to Topamax; Examination of Most Frequent Adverse Reactions in Adjunctive Therapy noted in Topamax Label*

Term from Topamax Label, section 6.2	PT: Most Closely related preferred term from study Adverse Event data	USL255		Topamax	
		N	%	N	%
Somnolence	Somnolence	12	27	11	23
Dizziness	Dizziness	7	16	1	15
Ataxia	No related terms coded	0	0	1	2
Speech disorders and related speech problems	No related terms coded				
Psychomotor slowing	No related terms coded				
Abnormal vision	Vision blurred	2	4	4	9

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	(PT)				
Abnormal Vision	Visual disturbance (LLT)	3	7	3	6
Difficulty with memory	Memory impairment	2	4	4	9
Paresthesia	Paresthesia	15	33	19	40
Diplopia	No related terms coded				

*"The most commonly observed adverse reactions associated with the use of TOPAMAX® at dosages of 200 to 400 mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in TOPAMAX®-treated patients and did not appear to be dose-related were somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia". FDA Approved Labeling Text dated October 2012

Reviewer Comment: Examination of the occurrence of adverse events by SOC reveals a modest reduction in those SOCs most representative of the common central nervous system effects of topiramate. USL255 has 16% fewer events in the Nervous system disorders SOC and 9% fewer events in the Psychiatric Disorders SOC than topiramate immediate release. The most frequent occurring adverse reactions terms from the Topamax label seen in adjunctive treatment trials were examined in study 255-103. Somnolence was seen to be 4% greater in the USL255 treatment than in Topamax treatment. Dizziness had the same frequency in both treatments. For terms closely related to the Topamax label term "abnormal vision" there were equal events for the PT "visual disturbance" and 5% more frequent occurrence of the PT "vision blurred". The frequency of "difficulty with memory" and "paresthesia" during Topamax treatment exceeded the frequency seen during USL255 treatment by 5% and 7% respectively. There were no terms identified in study 255-103 adequately close to the terms "ataxia", Speech disorders and related speech problems, psychomotor slowing, and diplopia for comparison between USL255 and Topamax treatment. Overall there is not a differentiation in the frequency of the common topiramate adverse reactions between the topiramate immediate release formulation and USL255.

Study P09-004:

Overall, a higher percentage of subjects reported TEAEs in the USL255 group (66.1%) compared with the placebo group (52.8%). In the USL255 group, only somnolence (12.1%) was reported in > 10.0% of subjects; in comparison, 2.4% of placebo-treated subjects reported somnolence. Except for somnolence, paresthesia (6.5% vs 2.4%, respectively), and weight decrease (6.5% vs 0%, respectively), the absolute difference in the percentage of subjects with TEAEs by PT in the USL255 and placebo groups was < 3%.

In the USL255 treatment group 82 patients reported 199 adverse events among 98 preferred terms. The same preferred term was reported twice in 8 of the 66 patients

resulting in 191 unique adverse event terms identified. The five most frequent adverse events were somnolence, dizziness, paresthesia, weight decreased and fatigue. The 20 most frequent adverse event preferred terms are shown in [Table 21](#) .

In the placebo treatment group 66 patients reported 157 adverse events among 91 preferred terms. There were repeat adverse event terms reported in 10 patients resulting in 142 unique adverse event terms identified. The five most frequent adverse events (frequency order) were headache, dizziness, fatigue, nausea, and disturbance in attention. The 20 most frequent adverse events are shown in [Table 22](#)

Table 21 Multiple comparison table showing frequency of top 20 common adverse events for USL255 treatment. Columns show comparison of USL255 percent of patients who experience AE, placebo to USL255 treatment delta, and reference label (Topamax®) adjunctive therapy, PBO to treatment delta. Note this is an exploratory cross trial comparison.

	Study P09-004				Topamax® Label
	USL255 Adverse Events by Preferred Term	USL255 Adverse Events by Preferred Term	Placebo Adverse Events by Preferred Term	Difference in percent of patients affected between USL255 and Placebo	Difference in percent of patients affected between Topamax and Placebo in adjunctive treatment trials
AEDECOD (preferred term)	Patients	% of n (n=124)	PBO %	Δ USL255 - PBO	Topamax® Add on Epilepsy trials in adults, 200-400mg treatment arm, Δ treatment - PBO %⁸
SOMNOLENCE	16	12.9	2.4	10.5	17
DIZZINESS	9	7.3	5.6	1.7	10
PARESTHESIA	8	6.5	2.4	4.1	7
WEIGHT DECREASED	8	6.5	0.8	5.7	6
FATIGUE	7	5.6	4.8	0.8	2
DECREASED APPETITE	5	4.0	1.6	2.4	*
HEADACHE	5	4.0	5.6	-1.6	*
NASOPHARYNGITIS	5	4.0	3.2	0.8	4 (pharyngitis)**
HYPERTENSION	4	3.2	0.8	2.4	*
ANOREXIA	3	2.4	0.8	1.6	6
APHASIA	3	2.4	0	2.4	11 (Speech disorders/Related speech problems)
ASTHENIA	3	2.4	0.8	1.6	5
DISTURBANCE IN ATTENTION	3	2.4	3.2	-0.8	*
DYSARTHRIA	3	2.4	0.8	1.6	11 (Speech disorders/Related speech problems)
INSOMNIA	3	2.4	1.6	0.8	*
IRRITABILITY	3	2.4	0.8	1.6	*
MEMORY IMPAIRMENT	3	2.4	0.8	1.6	*

⁸ Label for Topamax from “Drugs at FDA” 10/29/12. (Titration 100mg to 200mg weekly to target dose)

	Study P09-004				Topamax® Label
	USL255 Adverse Events by Preferred Term	USL255 Adverse Events by Preferred Term	Placebo Adverse Events by Preferred Term	Difference in percent of patients affected between USL255 and Placebo	Difference in percent of patients affected between Topamax and Placebo in adjunctive treatment trials
AEDECOD (preferred term)	Patients	% of n (n=124)	PBO %	Δ USL255 - PBO	Topamax® Add on Epilepsy trials in adults, 200-400mg treatment arm, Δ treatment - PBO %⁸
NAUSEA	3	2.4	4.8	-2.4	2
PSYCHOMOTOR RETARDATION	3	2.4	0	2.4	11 (psychomotor slowing)**
UPPER RESPIRATORY TRACT INFECTION	3	2.4	2.4	0.0	*
*note: asterisk indicates there is no comparison preferred term to the USL255 trial. **Comparable term in Topamax label.					

Table 22 Twenty most frequent TEAEs (common adverse events) in Placebo treatment patients.

AEDECOD (preferred term)	Placebo patients	Placebo % of n (n=125)
HEADACHE	7	5.6
DIZZINESS	7	5.6
FATIGUE	6	4.8
NAUSEA	6	4.8
DISTURBANCE IN ATTENTION	4	3.2
DYSPEPSIA	1	0.8
NASOPHARYNGITIS	4	3.2
ATAXIA	2	1.6
CONTUSION	3	2.4
DIARRHOEA	3	2.4
PARESTHESIA	3	2.4
SKIN LACERATION	3	2.4
SOMNOLENCE	3	2.4
UPPER RESPIRATORY TRACT INFECTION	3	2.4
URINARY TRACT INFECTION	3	2.4
VOMITING	3	2.4
CONVULSION	2	1.6
DECREASED APPETITE	2	1.6
EXCORIATION	2	1.6
FALL	2	1.6

Reviewer Comment: In study P09-004 the profile of common adverse events is very similar to the reference drug, Topamax®, while the difference in adverse event rate between treatment and placebo is less than a similar comparison between treatment and placebo in the 200 to 400mg dose range of the adjunctive therapy trials of the Topamax label. As noted in [Table 21](#) this difference may be accounted for by the higher (400mg) dose range in labeled adjunctive therapy trials. In addition this is a cross trial comparison.

7.4.2 Laboratory Findings (Study P09-004)

Based on a review of preferred terms, in the Phase 3 P09-004 study, 5 subjects after USL255 exposure and 3 subjects after placebo exposure had a clinical laboratory test result reported as a TEAE.

- neutropenia in 2 (1.6%) subjects in the USL255 group and 1 (0.8%) subject in the placebo group
- leukopenia in 1 (0.8%) subject in the placebo group
- glucose tolerance impaired in 1 (0.8%) subject in the USL255 group
- hyperglycemia in 1 subject each in the USL255 and placebo groups
- hyperkalemia in 1 (0.8%) subject in the USL255 group

Clinical Chemistry

Select Laboratory Values (those laboratory tests described in the Topamax® prescribing information that may require monitoring during topiramate treatment): bicarbonate, blood urea nitrogen [BUN], chloride, and creatinine.

Table 23 Priority Laboratory Parameters for known properties of topiramate*,**

Laboratory Parameter	Statistic	USL255 (n=124)			Placebo (n=125)		
		Baseline	Last Observation	Change	Baseline	Last observation	change
Bicarbonate (mEq/L)	n	119	119	119	121	121	121
	Mean (SD)	26.5 (2.93)	23.0 (2.94)	-3.5 (2.64)	26.5 (2.86)	26.5 (2.61)	0 (2.73)
	Median	27.0	23.0	-4.0	27.0	27.0	0
	Min, Max	18, 33	13, 32	-9, 3	16, 32	20, 33	-7, 8
BUN (mg/dL)	n	119	119	119	121	121	121
	Mean (SD)	12.9 (4.41)	13.3 (4.56)	0.5 (3.96)	12.6 (4.30)	12.4 (4.27)	-0.2 (3.42)
	Median	13.0	13.0	1.0	12.0	11.0	0
	Min, Max	4, 33	4, 27	-20, 11	5, 32	6, 27	-11, 7
Chloride (mEq/L)	n	119	119	119	121	121	121
	Mean (SD)	102.0 (3.37)	105.7 (3.51)	3.7 (3.00)	102.1 (3.38)	101.9 (3.84)	-0.2 (2.71)
	Median	102.0	107.0	4.0	103.0	103.0	0
	Min, Max	85, 109	94, 114	-4, 12	91, 108	87, 110	-7, 7
Creatinine (mg/dL)	n	119	119	119	121	121	121
	Mean (SD)	0.80 (0.156)	0.85 (0.177)	0.05 (0.104)	0.84 (0.197)	0.83 (0.164)	-0.02 (0.129)
	Median	0.80	0.80	0.10	0.80	0.80	0
	Min, Max	0.4, 1.3	0.5, 1.5	-0.2, 0.4	0.5, 1.8	0.5, 1.3	-0.9, 0.2

* Green shaded results have been check for reproducibility by reviewer
** Check of sponsor calculation derived from "Identified Last Obs. for Lab Test" and "Result/Finding Change from Baseline" column variables

Reviewer comment: the baseline to last observation means and medians for these select laboratory parameters do not reveal trends greater than expected compared to the know characteristics of topiramate. The decline in mean and median values for bicarbonate as well as the downward shift in minimum and maximum values are not unexpected.

Clinical Chemistry Change from Baseline to End of Study, means and medians.

During the interval from baseline measurement to final laboratory value there was no notable variation in the means and medians of the laboratory parameters shown in [Table 24](#).

Table 24 Change from Baseline to Last Observation for Chemistry Parameters, USL255 and Placebo Groups (ITT Safety Population)*,.**

Laboratory Parameter	Statistic	USL255 (n= 124)			Placebo (n=125)		
		Baseline	Last Observation	Change	Baseline	Last observation	change
ALT (U/L)	n	105	105	105	115	115	115
	Mean (SD)	20.6 (11.84)	18.5 (9.34)	-2.1 (8.72)	20.3 (12.99)	17.8 (9.92)	-2.4 (10.34)
	Median	17.0	16.0	-2.0	18.0	16.0	-1.0
	Min, Max	5, 69	6, 55	-46, 19	5, 89	6, 62	-79, 12
Albumin (g/dL)	n	105	105	105	115	115	115
	Mean (SD)	4.53 (0.311)	4.50 (0.299)	-0.02 (0.290)	4.61 (0.296)	4.55 (0.288)	-0.06 (0.286)
	Median	4.50	4.50	0	4.60	4.60	0
	Min, Max	3.5, 5.5	3.5, 5.4	-1.0, 0.8	4.0, 5.5	3.7, 5.4	-0.8, 0.4
Alkaline phosphatase (U/L)	n	105	105	105	115	115	115
	Mean (SD)	82.2 (32.06)	84.0 (31.85)	1.8 (11.51)	74.9 (24.50)	74.6 (25.25)	-0.3 (9.18)
	Median	76.0	77.0	1.0	70.0	71.0	0
	Min, Max	38, 182	34, 181	-24, 41	30, 139	30, 182	-20, 50
AST (U/L)	n	105	105	105	115	115	115
	Mean (SD)	20.5 (6.74)	18.7 (6.26)	-1.8 (7.17)	20.8 (6.79)	19.3 (6.19)	-1.5 (5.92)
	Median	19.0	17.0	-1.0	20.0	19.0	-2.0
	Min, Max	10, 47	9, 46	-26, 19	10, 43	8, 54	-20, 30
Glucose (mg/dL)	n	118	118	118	121	121	121
	Mean (SD)	92.5 (19.46)	92.4 (15.31)	-0.1 (21.72)	91.2 (20.16)	91.6 (17.88)	0.5 (16.21)
	Median	90.0	90.0	1.0	89.0	89.0	0
	Min, Max	64, 261	58, 158	-163, 52	38, 239	66, 163	-76, 53
Potassium (mEq/L)	n	119	119	119	121	121	121
	Mean (SD)	4.33 (0.435)	4.14 (0.404)	-0.19 (0.425)	4.33 (0.407)	4.30 (0.370)	-0.03 (0.433)
	Median	4.30	4.10	-0.20	4.20	4.30	0
	Min, Max	3.0, 5.6	2.8, 5.0	-1.2, 0.8	3.5, 5.8	3.1, 5.7	-1.6, 1.5
Protein (g/dL)	n	105	105	105	115	115	115
	Mean (SD)	7.32 (0.466)	7.25 (0.447)	-0.07 (0.385)	7.26 (0.425)	7.17 (0.420)	-0.10 (0.412)
	Median	7.30	7.20	-0.10	7.20	7.10	0
	Min, Max	6.2, 8.8	6.3, 8.6	-1.4, 1.0	6.4, 8.5	6.1, 8.6	-1.2, 1.0
Sodium (mEq/L)	n	119	119	119	121	121	121
	Mean (SD)	139.9 (3.36)	140.3 (3.10)	0.3 (2.90)	140.3 (3.41)	139.9 (3.76)	-0.4 (2.25)
	Median	140.0	141.0	1.0	141.0	141.0	0
	Min, Max	122, 148	127, 146	-11, 11	127, 147	125, 147	-8, 7
Total bilirubin (mg/dL)	n	105	105	105	113	113	113
	Mean (SD)	0.302 (0.1646)	0.306 (0.1667)	0.005 (0.1607)	0.319 (0.1427)	0.324 (0.1334)	0.005 (0.1119)
	Median	0.270	0.270	0.010	0.300	0.290	0.010
	Min, Max	0.10, 0.87	0.11, 1.36	-0.40, 1.03	0.12, 1.02	0.13, 0.89	-0.26, 0.32

* Green shaded results have been check for reproducibility by review er

Clinical Review
Steven T. Dinsmore
NDA 205122
Topiramate Extended Release

Laboratory Parameter	Statistic	USL255 (n= 124)			Placebo (n=125)		
		Baseline	Last Observation	Change	Baseline	Last observation	change
** Check of sponsor calculation derived from "Identified Last Obs. for Lab Test" and "Result/Finding Change from Baseline" column variables							

Clinical Chemistry Shift from Baseline to Last Observation, means and medians.

Table 25 Shifts from Baseline to Last Observation in Chemistry Parameters in Subjects Who Received USL255 or Placebo (ITT Safety Population)

Laboratory Parameter	Result at Last Observation ^a	Result at Baseline, n (%) ^a					
		USL255 (n= 124)			Placebo (n= 125)		
		Below Normal	Normal	Above Normal	Below Normal	Normal	Above Normal
ALT	Below normal	5 (4.8)	10 (9.5)	0	3 (2.6)	10 (8.7)	0
	Normal	5 (4.8)	76 (72.4)	6 (5.7)	7 (6.1)	84 (73.0)	6 (5.2)
	Above normal	0	0	3 (2.9)	0	1 (0.9)	4 (3.5)
Albumin	Below normal	0	0	0	0	0	0
	Normal	0	105 (100.0)	0	0	115 (100.0)	0
	Above normal	0	0	0	0	0	0
Alkaline phosphatase	Below normal	1 (1.0)	1 (1.0)	0	1 (0.9)	2 (1.7)	0
	Normal	0	84 (80.0)	4 (3.8)	0	101 (87.8)	4 (3.5)
	Above normal	0	4 (3.8)	11 (10.5)	0	1 (0.9)	6 (5.2)
AST	Below normal	0	4 (3.8)	0	0	2 (1.7)	0
	Normal	0	99 (94.3)	1 (1.0)	0	109 (94.8)	3 (2.6)
	Above normal	0	0	1 (1.0)	0	1 (0.9)	0
Bicarbonate	Below normal	5 (4.2)	18 (15.1)	0	0	1 (0.8)	0
	Normal	1 (0.8)	95 (79.8)	0	2 (1.7)	118 (97.5)	0
	Above normal	0	0	0	0	0	0
BUN	Below normal	0	2 (1.7)	0	0	0	0
	Normal	1 (0.8)	103 (86.6)	4 (3.4)	0	111 (91.7)	3 (2.5)
	Above normal	0	7 (5.9)	2 (1.7)	0	5 (4.1)	2 (1.7)
Chloride	Below normal	1 (0.8)	0	0	5 (4.1)	1 (0.8)	0
	Normal	4 (3.4)	108 (90.8)	0	1 (0.8)	114 (94.2)	0
	Above normal	0	6 (5.0)	0	0	0	0
Creatinine	Below normal	5 (4.2)	8 (6.7)	0	12 (9.9)	5 (4.1)	0
	Normal	13 (10.9)	92 (77.3)	0	7 (5.8)	96 (79.3)	1 (0.8)
	Above normal	0	1 (0.8)	0	0	0	0
Glucose	Below normal	0	0	1 (0.8)	0	0	0
	Normal	0	105 (89.0)	3 (2.5)	2 (1.7)	107 (88.4)	3 (2.5)
	Above normal	0	8 (6.8)	1 (0.8)	0	5 (4.1)	4 (3.3)
Potassium	Below normal	1 (0.8)	3 (2.5)	0	0	1 (0.8)	0
	Normal	1 (0.8)	108 (90.8)	6 (5.0)	0	110 (90.9)	6 (5.0)
	Above normal	0	0	0	0	3 (2.5)	1 (0.8)
Protein	Below normal	0	0	0	0	0	0
	Normal	0	96 (91.4)	5 (4.8)	0	107 (93.0)	4 (3.5)

Laboratory Parameter	Result at Last Observation ^a	Result at Baseline, n (%) ^a					
		USL255 (n= 124)			Placebo (n= 125)		
		Below Normal	Normal	Above Normal	Below Normal	Normal	Above Normal
	Above normal	0	2 (1.9)	2 (1.9)	0	1 (0.9)	3 (2.6)
Sodium	Below normal	2 (1.7)	3 (2.5)	0	7 (5.8)	0	0
	Normal	1 (0.8)	108 (90.8)	2 (1.7)	0	112 (92.6)	1 (0.8)
	Above normal	0	2 (1.7)	1 (0.8)	0	0	1 (0.8)
Total Bilirubin	Below normal	0	0	0	0	0	0
	Normal	0	104 (99.0)	0	2 (1.7)	113 (98.3)	0
	Above normal	0	1 (1.0)	0	0	0	0

^a Percentages are based on the number of subjects with both a Baseline and a post baseline result available for each laboratory test.

Clinical Chemistry Outliers

Albumin

Outliers: values from the entire study timeline are examined for both the USL255 and placebo treatment arms. In the USL255 treatment arm there is only one instance of an albumin value outside of reference range. This occurred at screening only. There were no placebo values out of reference ranges in the placebo treatment group.

Alkaline Phosphatase

Outliers: values from the entire study timeline are examined for both the USL255 and placebo treatment arms. In the USL255 treatment arm there were 5 instances of alkaline phosphatase values greater than 1.5 x ULN. All but one of these instances occurred at screening or baseline. In the single instance where there was a value greater than 1.5 x ULN at end of maintenance phase the patient also had a baseline value which was 1.6 x ULN which was also this patient's maximum alkaline phosphatase value observed during the study (182 U/L).

ALT

Outliers: values from the entire study timeline are examined for both the USL255 and placebo treatment arms. In the USL255 treatment arm there was one ALT value greater than 2 times upper limit of normal. This value occurred in screening phase of the study and declined to 1.7 x ULN by end of maintenance phase of the study. Four instances of ALT value > 2 X ULN occurred in the placebo treatment arm. These all occurred in screening or baseline phase of the study.

AST

Outliers: values from the entire study timeline are examined for both the USL255 and placebo treatment arms. No values greater than 2 x ULN were found in the USL255

treatment arm. In the placebo arm there was one instance of AST elevated greater than 2x ULN, this occurred during screening phase of the study.

Bicarbonate

Outliers: values below the lower limit of normal will be examined for bicarbonate because the known effect of topiramate on this parameter. Values from the entire study timeline are examined for both the USL255 and placebo treatment arms.

USL255 group: Forty (40) patients had bicarbonate below the normal reference range of 21meq/L. Six (6) of these patients had abnormal low values at baseline. Of the remaining 34 (27% of all USL255) patients with normal baseline values 16 were seen to be below normal during the titration phase only while 8 were low at end of maintenance phase only and 7 patients were seen to be below normal range at both titration and maintenance. One patient was below normal only during titration from USL255 at end of study and 2 patients were low at early termination from the study.

Six subjects had values below 18meq/L in the USL255 treatment group. Four of these values occurred in titration phase and 2 in maintenance phase as shown in [Table 26](#).

Table 26 USL255 treatment outliers with Bicarbonate less than 18meq/L

Visit	Bicarbonate meq/L
End of Maintenance Phase	13
End of Titration Phase	14
End of Titration Phase	16
End of Titration Phase	16
End of Titration Phase	16
End of Maintenance Phase	16

Placebo group: Seven patients in the placebo group were found to have bicarbonate values below normal at some point during the study. Five 5(5) of these events occurred during baseline or screening. Among the remaining two with normal baseline values one patient had a value below normal at end of maintenance and one patient during taper phase at the conclusion of the study.

BUN

Values in the upper range of the distribution will be examined for BUN values. Values from the entire study timeline are examined for both the USL255 and placebo treatment arms. The baseline values were available for 249 study

patients. Examination of these values revealed that a BUN of 22mg/dl was two standard deviations from the mean value of 12.7 mg/dl. Based on this observation, values greater than 22mg/dl were considered outliers for this analysis. The sponsor high normal reference range value is 20mg/dl.

USL255 group: There were 10 patients with BUN values greater than 22mg/dl. Five of these occurrences were in baseline or screening. Among the remaining five patients the high value occurred during the titration phase in one patient. In one patient a high value was present in both titration and maintenance. In one patient the high value occurred in titration and at early study discharge and in two patients a high value occurred at end of maintenance phase only. Within these five patients the maximum BUN value was 27mg/dl.

Placebo group: There were five patients in the placebo group with BUN values greater than 22mg/dl. In three patients the maximum value occurred at screening or baseline. In the remaining two patients the high value occurred during titration in one patient and at end of maintenance in the other. The maximum value noted in these two patients was 24mg/dl.

Chloride

Values in the upper range of the distribution will be examined based on the known properties of topiramate where section 5.15 of the reference listed drug labeling states that "Topiramate treatment causes non-anion gap, hyperchloremic metabolic acidosis manifested by a decrease in serum bicarbonate and an increase in serum chloride. Values from the entire study timeline are examined for both the USL255 and placebo treatment arms. The sponsor reference range upper limit of chloride is 110meq/L while the 109meq/L is found to be two standard deviations from the mean of the baseline chloride values for 249 study patients. All values above the reference range upper limit will be considered outliers.

USL255 group: There were 8 patients identified with chloride values greater than 110meq/L. The maximum value was 114meq/L. In one patient the high value occurred at the baseline measurement. In two patients the high chloride value occurred in titration phase while in the remaining five patients the high value occurred at the end of maintenance phase.

Placebo group: In the placebo group there were no chloride values greater than 110meq/L.

Creatinine

Values in the upper range of the creatinine distribution will be examined due to the known relationship between elevated creatinine and disturbance in renal function. Values from the entire study timeline are examined for both the USL255 and placebo treatment arms. There were two patients in the USL255 treatment group who had a creatinine value above the sponsor reference range value of 1.4mg/dl. Both of these values were 1.5mg/dl. One occurred at end of titration phase while the other occurred at end of maintenance phase. There were two patients in the placebo treatment group with creatinine values greater than the upper limit of reference range. One of these occurred at baseline and the other at end of titration phase.

Glucose

Glucose values from the entire study timeline are examined for both the USL255 and placebo treatment arms.

USL255 group: There were two patients with glucose values lower than the sponsor reference range lower limit of 60mg/dl, both of these low glucose measurements occurred at end of titration phase. There were 17 patients with glucose values greater than the sponsor reference range upper limit of 115mg/dl. In 7 patients an elevated glucose value was present at baseline/screening. In 4 patients the elevated value occurred at end of titration phase. In 3 patients the elevated value occurred at end of maintenance phase. In one patient an elevated value was identified at both end of titration and end of maintenance. In one patient an elevated value occurred at end of titration and at early study discharge and in the final patient an elevated value occurred during taper from the completed study.

Placebo group: There were 4 patients with glucose values below the sponsor reference range of 60mg/dl. These all occurred at screening or baseline measurements. There were 16 patients with glucose values greater than the sponsor reference range upper limit of 115mg/dl. In 8 patients there was an elevated glucose value at baseline or screening. In 3 patients the elevated glucose value occurred at the end of titration visit. In 2 patients the elevated value occurred at the end of maintenance visit. In one patient there was an elevated value at both the end of titration and end of maintenance visit. In one patient there was an elevated value at end of titration and end of study taper. In one patient there was an elevated value at end of study taper only. The maximum value which occurred during treatment interval was 162mg/dl which occurred at an end of titration visit.

Potassium (K⁺)

Potassium values from the entire study timeline are examined for both the USL255 and placebo treatment arms.

USL255 group: There were 12 patients identified with potassium values below the sponsor reference lower limit of 3.5meq/L. Two of these values occurred in baseline or screening, seven at end of titration and 3 at end of maintenance. The minimum value which occurred was 2.8meq/L in a patient who had a potassium value of 3.3 at screening and 3.0meq/L at baseline. The second in order of severity was a value of 3.2 seen at end of titration in a patient normal at baseline. There were 12 patients who experienced a potassium value > 5.0meq/L. Ten of these cases occurred at screening or baseline and 2 at end of titration. The maximum value seen was 5.6meq/L.

Placebo group: there were 3 patients in the placebo group with a potassium value below 3.5meq/L. Two of these occurred in baseline or screening and one at end of maintenance interval. There were 16 patients with a value greater than 5.0meq/L. Twelve of these occurred at baseline or screening, 2 at end of maintenance and one at end of the titration interval.

Sodium (Na⁺)

Sodium values from the entire study timeline are examined for both the USL255 and placebo treatment arms.

USL255 group: There were 10 patients identified with sodium values below the sponsor reference low of 133meq/L. Six of these events occurred in baseline or screening, one at end of titration phase, two at end of maintenance and one patient had a low value at both end of titration and end of maintenance. The minimum value observed in a patient during USL255 treatment was 127meq/L at end of maintenance phase. There were 6 patients identified with a sodium value greater than the sponsor reference upper limit of 145meq/L. Four of these occurred at baseline or screening and two occurred at end of maintenance. The maximum value seen in a patient while on USL255 treatment was 146meq/L.

Placebo group: There were 10 patients identified with a sodium value below the sponsor reference range lower limit of 133meq/L. Nine of these occurred at baseline or screening and one occurred at end of titration

phase. There were 4 patients identified with a sodium value greater than the sponsor reference upper normal limit of 145meq/L. Three of these measurements occurred in baseline or screening and one occurred at end of titration phase.

Total Serum Protein

Serum protein values from the entire study timeline are examined for both the USL255 and placebo treatment arms.

USL255 group: There were 17 patients with an occurrence of a total protein value greater than the sponsor reference upper limit of 8g/dl. Thirteen of these measurements occurred in baseline or screening. One of these measurements occurred at end of titration interval and 3 at end of maintenance phase. The maximum total protein value of a patient on USL255 treatment was 8.2g/dl. There were no occurrences of a value below the sponsor reference lower limit of normal value of 6.0g/dl.

Placebo group: There were 11 patients with an occurrence of a total protein values greater than the sponsor reference upper limit of 8g/dl. Nine of these measurements occurred in baseline or screening. One event occurred at end of maintenance phase and one at an unscheduled visit. There were no occurrences of a value below the sponsor reference lower limit of normal value of 6.0g/dl.

Total Bilirubin

Total bilirubin values from the entire study timeline are examined for both the USL255 and placebo treatment arms. Only values that exceed the upper boundary of the sponsor reference range of 1.1mg/dl are examined for this laboratory parameter.

USL255 group: One patient is observed to have a bilirubin value greater than the sponsor reference range upper limit of normal (1.1mg/dl). This value of 1.36mg/dl (1.2 x ULN) occurred at the end of maintenance phase and was in normal limits at baseline. The corresponding ALT was within normal limits.

Placebo group: There were no patients observed with a total bilirubin value greater than the upper limit of the sponsor reference range (1.1mg/dl).

Reviewer Comment: The clinical chemistry evaluation reveals notable alterations in bicarbonate, chloride and potassium. The evaluation of central tendency, analysis of

outlier values and baseline to end of maintenance shift for bicarbonate reveal a notable signal for a decline in serum bicarbonate. The evaluation of central tendency, analysis of outlier values and baseline to end of maintenance shift for chloride reveal a notable signal for an increase in serum chloride. Shift analysis reveals a minor excess of normal to low serum potassium shift compared to placebo with no notable signal for hypokalemia in the evaluation of central tendency or outlier values for potassium. Each of these clinical chemistry safety signals are present in the current labeling of Topamax, the reference listed drug for this application. There is no new safety signal identified. There was no notable trend to increase in ALT or bilirubin in the examination of central tendency, shift analysis or outliers and no patients in the study met Hy's law criteria for hepatic dysfunction.

Hematology

Note: in outlier analysis the baseline and EOM (end of maintenance) the numbers of patients differs due to study discontinuation after baseline and on some occasions absence of a specific laboratory measurement.

Combined tabular presentation of Laboratory Parameter Central tendency, Outliers and Shift from Baseline to last Observation

White Blood Cell Count (WBC)

Table 27 WBC, Means & Medians -Change from Baseline at End of Maintenance Phase (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population.

Change from Baseline at EOM, means and medians in (10³)/mm³, (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n= 103)	
Mean	0.06		-0.08	
median	-0.2		0	
range	-3.3 to 5.2 (x 10 ³)/mm ³		-4.7 to 5.5 (x 10 ³)/mm ³	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)
Patients: High	0	2 (2%)	3 (2.4%)	3 (2.9%)

Max Value	-	12.8 (x 10 ³)/mm ³	13.4	12.8 (x 10 ³)/mm ³
Patients: Low	7 (5.7%)	3 (3.1%)	3 (2.4%)	4 (3.8%)
Min Value	2.8	2.4 (x 10 ³)/mm ³	2.6	3.3 (x 10 ³)/mm ³
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
White blood cells (K/mm ³)	2 (2.1%) [†]	4 (3.8%) [†]	2 (2.0%) [†]	2 (1.9%) [†]
*Based on reference range 3.7 to 11 (x 10 ³)/mm ³				
† (% of last observations)				

Total Neutrophils

Table 28 Total Neutrophils, Means & Medians Change from Baseline at End of Maintenance Phase (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population.

Change from Baseline at EOM means and medians in (10 ³)/mm ³ , (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n= 102)	
Mean	-0.05		-0.07	
median	-0.05		-0.1	
range	-3.8 to 4.9 (x 10 ³)/mm ³		-4.1 to 4.4 (x 10 ³)/mm ³	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (123)	EOM (105)
Patients High	0	2 (2%)	3 (2.4%)	3 (2.9%)
Max Value	-	9.9	10.8	9.3
Patients Low	4 (3.3%)	7 (7.1%)	5 (4.1%)	6 (5.7%)
Min Value	1.3	0.5**	0.3	1.0
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Total neutrophils	5 (5.0%) [†]	5 (4.9%) [†]	2 (2.0%) [†]	1 (1.0%) [†]

(K/mm ³)				
* Based on reference range 1.7 to 7.9 (x 10 ³)/mm ³				
**Subject 133, Baseline low at 2.0 x 10 ³ /mm ³ , 1 AE- respiratory infection, resolved, non-SAE				
† (% of last observations)				

Lymphocytes

Table 29 Lymphocytes, Means & Medians, Change from Baseline at End of Maintenance Phase (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population.

Change from Baseline at EOM, means and medians in (10 ³)/mm ³ , (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n= 102)	
Mean	0.16		-0.01	
median	0.2		0	
range	-1.5 to 2.1 (x 10 ³)/mm ³		-1.4 to 1.2 (x 10 ³)/mm ³	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (123)	EOM (105)
Patients High	0	1 (1.0%)	3 (2.4%)	1 (0.95%)
Max Value	-	4.3	4.2	4.1
Patients Low	1 (0.8%)	1 (1.0%)	1 (0.8%)	2 (1.9%)
Min Value	0.8	0.8	0.8	0.8
Lymphocyte count, Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Lymphocytes (%)	1 (1.0%) [†]	1 (0.9%) [†]	1 (1.0%) [†]	1 (0.9%) [†]
*Based on reference range 0.9 to 3.6 (x 10 ³)/mm ³				
† (% of last observations)				

Platelet Count

Table 30 Platelet Count, Means & Medians Change from Baseline at End of Maintenance Phase (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population.

Change from Baseline at EOM, means and medians in (10³)/mm³, (n= # with change from baseline measurements)				
Statistic	USL255 (n=93)		Placebo (n= 96)	
Mean	9.0		-3.07	
median	2.0		-1.0	
range	-98 to 419 (x 10 ³)/mm ³		-125 to 82 (x 10 ³)/mm ³	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (121)	EOM (95)	Baseline (120)	EOM (100)
Patients High	3 (2.5%)	3 (3.2%)	2 (1.7%)	2 (2.0%)
Max Value	410	679**	411	381
Patients Low	0	1 (1.05%)	3 (2.5%)	1 (1.0%)
Min Value	-	124	55	40
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Platelet count (K/mm ³)	1 (1.0%) [†]	0	2 (2.0%) [†]	1 (1.0%) [†]
* Based on reference range 125 to 375 (x 10 ³)/mm ³				
**patient 164, baseline plt 260, had 4 AE entries (dizziness, fatigue, asthenia, wt decreased) and 1 SAE entry (lobar pneumonia- date 2012-02-03) Lab test date 2012-02-20.				
[†] (% of last observations)				

Eosinophils

Table 31 Eosinophils, Means & Medians Change from Baseline at End of Maintenance Phase (EOM) , Outliers, Shift from Baseline to Last Observation, ITT safety population.

Change from Baseline at EOM, means and medians in (10³)/mm³, (n= # with change from baseline measurements)		
Statistic	USL255 (n=96)	Placebo (n=102)
Mean	-0.001	0.012

median	0		0	
range	-0.3 to 0.4 (x 10 ³)/mm ³		-0.4 to 0.9 (x 10 ³)/mm ³	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (123)	EOM (105)
Patients High	1 (0.8%)	1 (1.0%)	0	2 (1.9%)
Max Value	1.3	1.5	-	1.1
Patients Low	-	-	-	-
Min Value	-	-	-	-
Eosinophil count, Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Eosinophils (%)	0	0	0	1 (1.0%) [†]
* Based on reference range 0.0 to 0.8 (x 10 ³)/mm ³				
† (% of last observations)				

Hemoglobin (HGB)

Table 32 Hemoglobin, Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

Change from Baseline at EOM, means and medians in g/dL. (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n=103)	
Mean	0.03		-0.09	
median	-0.1		-0.1	
range	-1.4 to 2.4 g/dL		-1.5 to 1.5 g/dL	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)
Patients High	0	3 (3.1%)	1 (0.8%)	2 (1.9%)

Max Value	-	16.6	16.1	17.1
Patients Low	4 (3.3%)	2 (2.0%)	0	2 (1.9%)
Min Value	10.7	11.5	-	10.7
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Hemoglobin (g/dL)	1 (1.0%) [†]	2 (1.9%) [†]	3 (2.9%) [†]	2 (1.9%) [†]
*two different reference ranges present in this dataset, 11 to 15.5 g/dl and 12.5 to 17 g/dl. High low assignments based on patient specific reference range.				
[†] (% of last observations)				

Hematocrit

Table 33 Hematocrit, Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

Change from Baseline at EOM, means and medians in Percent. (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n=103)	
Mean	-0.06		-0.26	
median	-0.35		0.1	
range	--4.8 to 8.9 %		-8.1 to 4.7 %	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)
Patients High	3 (2.5%)	3 (3.1%)	0	2 (1.9%)
Max Value	53.2	51.8	-	52.7
Patients Low	1 (0.8%)	1 (1.0%)	1 (0.8%)	1 (0.95%)
Min Value	32.9	34.3	36.8	32.5
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Hematocrit (%)	1 (1.0%) [†]	1 (1.0%) [†]	1 (1.0%) [†]	2 (1.9%) [†]

*two different reference ranges present in this hematocrit dataset, 33 to 47% and 37 to 51%, High / Low assignments will be based on the subject specific reference range
† (% of last observations)

Mean Corpuscular Hemoglobin (MCH)

Table 34 MCH, Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

Change from Baseline at EOM, means and medians in pictograms (pg). (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n=103)	
Mean	0.25		-0.015	
median	0.2		0.1	
range	--1.6 to 2.4 pg		-2.3 to 3.4 %	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)
Patients High	17 (14%)	15 (15.3%)	11 (8.9%)	8 (7.6%)
Max Value	36.7	37.7	36.6	35.1
Patients Low	4 (3.3%)	2 (2.0%)	1 (0.8%)	0
Min Value	21.7	22.2	25.9	-
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
MCH (pg)	0	0	4 (4.7%) [†]	4 (4.1%) [†]
* based on reference range 27 to 34 picograms (pg)				
† (% of last observations)				

Mean Corpuscular volume (MCV)

Table 35 MCV, Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

Change from Baseline at EOM, means and medians in femtoliters (fl). (n= # with change from baseline measurements)

Statistic	USL255 (n=96)		Placebo (n=103)	
Mean	0.46		-0.07	
median	0.4		0	
range	--9.1 to 7.5 fl		-11.9 to 7.9 fl	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)
Patients High	28 (23%)	25 (25.5%)	24 (19.3%)	21 (20%)
Max Value	112.5	112.7	114	113.6
Patients Low	3 (2.5%)	2 (2.0%)	1 (0.8%)	0
Min Value	66.8	71.3	81.2	-
Shifts From Baseline to Last Observation, ITT Safety Population, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
MCV	0	0	5 (4.8%) [†]	8 (7.5%) [†]
* two different reference ranges present in this MCV dataset, 78 to 100 fl and 82 to 102 fl, High / Low assignments will be based on the subject specific reference range.				
[†] (% of last observations)				

Red Blood Cells (RBC)

Table 36 RBC count, Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

RBC Count, Change from Baseline at EOM in 10 ⁶ /cu mm. (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n=103)	
Mean	-0.03		-0.024	
median	-0.06		-0.03	
range	-0.62 to 0.8 10 ⁶ /cu mm		-0.6 to 0.58 10 ⁶ /cu mm	
outliers*				
	USL255		PBO	
Time point of Measurement (available)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)

measurements at baseline / EOM				
Patients High	2 (1.6%)	2 (2.0%)	1 (0.8%)	0
Max Value	5.97	5.61	5.67	-
Patients Low	8 (6.6%)	8 (8.2%)	9 (7.3%)	6 (5.7%)
Min Value	3.38	3.47	3.41	3.25
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Red blood cells ($\times 10^6/\text{mm}^3$)	5 (5.3%) [†]	2 (2.0%) [†]	1 (1.0%) [†]	0
* two different reference ranges present in this RBC count dataset, 3.7 to 5.2 $\times 10^6/\text{mm}^3$ and 4 to 5.6 $\times 10^6/\text{mm}^3$ High / Low assignments will be based on the subject specific reference range.				
[†] (% of last observations)				

Red Cell Distribution Width (RDW)

Table 37 RDW , Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

Red Cell Distribution Width, Change from Baseline at EOM. Units of RDW = %. (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n=103)	
Mean	0.42		-0.13	
95% CI of mean	0.15, 0.69		-0.35, 0.10	
median	0.3		0	
range	-4 to 3.5 %		-4.4 to 3.1 %	
RDW Baseline and EOM (end of maintenance) Mean & Median Values				
RDW Baseline	USL255 (n=122)		Placebo (n= 124)	
Mean	14.9		14.8	
median	14.6		14.8	
RDW EOM	USL255 (n=98)		Placebo (n=105)	
Mean	15.2		14.7	
Median	15		14.6	
outliers*				
	USL255		PBO	
Time point of Measurement (available)	Baseline (122)	EOM (98)	Baseline (124)	EOM (105)

measurements at baseline / EOM				
Patients High	63 (52%)	67 (68%)	69 (56%)	57 (54%)
Max Value	20.3	20.1	20	18.7
Patients Low	0	0	0	0
Min Value	-	-	-	-
Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
RDW (%)	0	0	27 (26.0%) [†]	14 (13.2%) [†]
*based on reference range 11.5 to 14.5%				
[†] (% of last observations)				

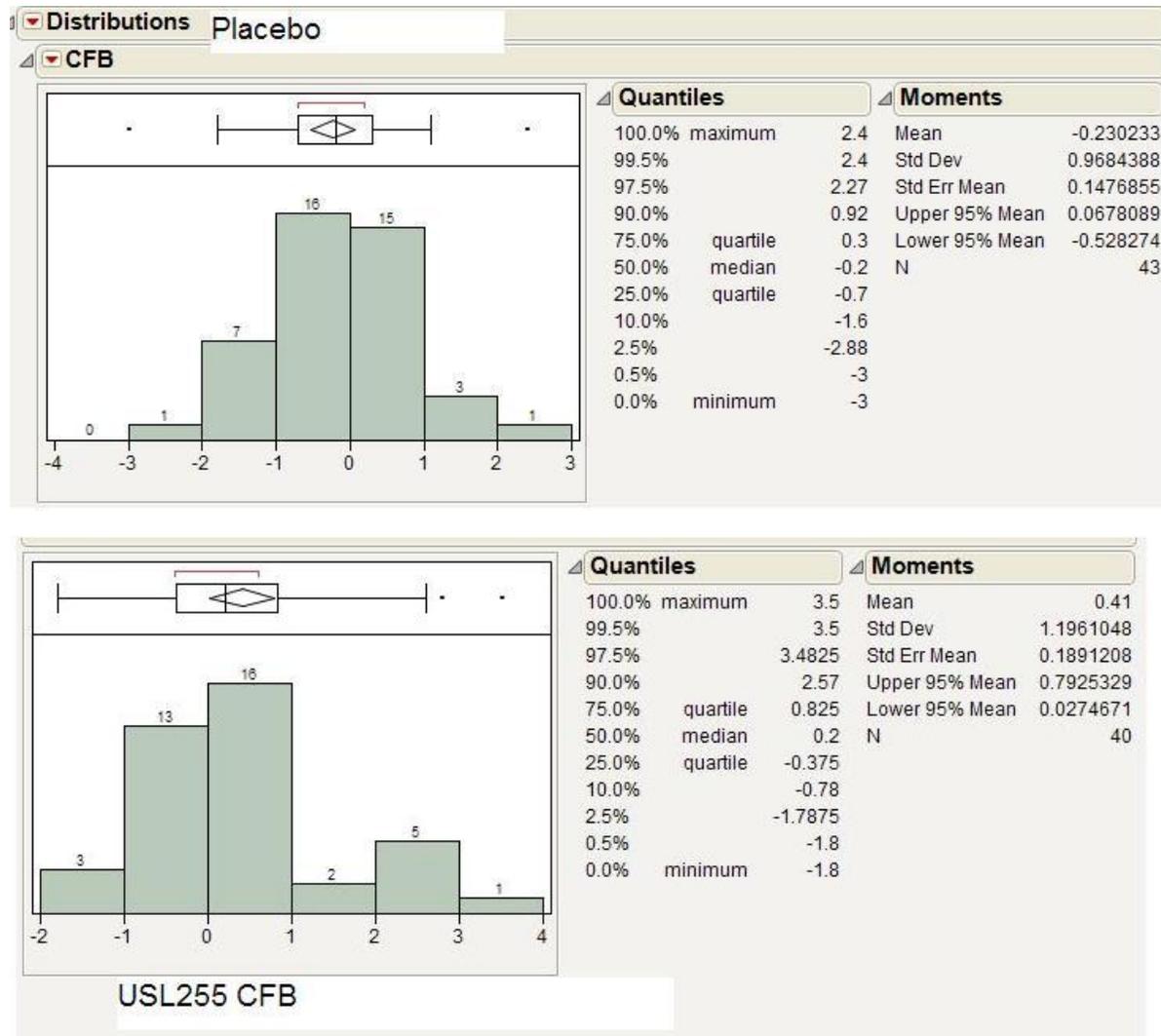
Table 38 Properties of patients with elevated RDW at baseline, USL255 and placebo groups.

RDW: USL255 and Placebo High at baseline groups		
Statistic	USL255 (n=63)	Placebo (n=69)
Mean	15.8	15.8
median	15.4	15.4
range	14.5 to 20.3	14.6 to 20%

Table 39 properties of patient with shift from normal to high RDW values in USL255 and placebo treatment groups.

RDW: USL255 & PBO High shift group properties		
Statistic	USL255 (n=27)	Placebo
Mean	15.5	15.1
median	15.1	14.9
range	14.6 to 17.8	14.6 to 16

Table 40 CFB in patients High at Baseline and EOM in USL255 & PBO



RDW analysis:

(Notable increase in RDW %, treatment over placebo in baseline to last observation and treatment over placebo outliers at EOM.

Table 37 reveals the frequency of shift from normal to abnormal- high Red Cell Distribution Width (RDW) in the USL255 treatment arm is double the rate seen in the placebo treatment group. In addition the outlier analysis reveals an excess of 14% high (above normal reference range) at EOM in the USL255 treatment arm compared to the placebo group. The findings of the group means and medians change from baseline to EOM also reveals a minor change toward overall increase in RDW values in the USL255 treatment arm compared to placebo.

The RDW is based on an automated measurement of red blood cell size and is a quantitative indicator of anisocytosis. The RDW can be used in the laboratory as a flag to select those samples that should have manual review of blood films for red cell morphology⁹. The reference range for RDW is 11.5 to 14% in this clinical trial. There are several possible etiologies of variation in RBC size. Variable size of the RBC population may be seen in iron deficiency anemia, sickle cell-b-thal, sickle cell anemia, vitamin B12 or folate deficiency, immune hemolytic anemia, cytotoxic chemotherapy, chronic liver disease, or myelodysplastic syndrome. Elevated RDW has been associated with risk of cardiovascular disease and also observed to be elevated in a variety of chronic disorders^{7,10}. The topiramate IR RLD (reference listed drug) label is examined and reveals: *Frequent*: anemia, *Rare*: marrow depression, pancytopenia in section 6.6, "Other Adverse Reactions Observed During All Epilepsy Clinical Trials."

RDW Dataset analysis

The outlier analysis reveals a high baseline frequency of elevated RDW value in both the USL255 treatment 63 (52%) and placebo 69 (56%) treatment arms of the study. At the EOM measurement the USL255 treatment group has 67 (68%) patients with an elevated RDW, including 27 new, shift high patients with the placebo group has 57 (54%) with elevated RDW including 14 new shift high patients, [Table 37](#). Among those patient with elevated RDW at baseline the mean, median and range of the baseline high USL255 group show a minor increase over the same values for the placebo group, [Table 38](#). Those in the USL255 group who had a shift from normal to high RDW value show a minor increase over the mean, medians and range of RDW values seen in the placebo normal to high shift group, [Table 39](#). The magnitude of the change from baseline in those patients with high baseline and EOM values are compared in order to determine if a further shift to high range continued. This analysis revealed a minor positive difference in the USL255 treatment group compared to the placebo group, [Table 40](#). There is no observed shift from normal to low in either the USL255 or placebo treatment group.

Outliers by study site and country are examined. All baseline measurements have a mean value of 14.8 with a standard deviation of 1.38. This standard deviation added to the mean yields a value of 15.88%. Based on this value of mean plus one standard deviation a value of 16% or greater is chosen as an outlier value. At the EOM period (end of maintenance) there were 35 values of 16 % or greater identified¹² in the placebo group and 23 in USL255 group. These are derived from 22 study sites in 11

9 Ryan DH. Examination of Blood Cells. Part 1, Chapter 2. In Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT (eds): Williams Hematology, 8e. Copyright ©2010, by The McGraw-Hill Companies, Inc.

10 Patel KV, et al. Red Cell Distribution Width and Mortality in Older Adults: A meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2010 Vol. 65A, No. 3, 258–265

countries, 3 in western hemisphere the remainder in Eastern hemisphere.. The laboratory analysis in this study were performed by (b) (4) with one site each in Europe and the United States.

The original topiramate NDA, Topamax, approved 12/24/1996 was examined to determine if an evaluation of RDW was performed. The medical reviews from 1994, 1995 and 1996 identified that the only RBC parameters evaluated were hemoglobin and hematocrit. RDW does not appear in the array of hematologic parameters present in these reviews.

Reviewer Comment: Examination of the RDW parameter reveals a notable excess in the number of normal to high shift patients in the USL255 treatment group compared to the placebo group. The frequency is double in the treatment group. Further examination of the means, medians and range of those patients with EOM high RDW values reveals a minor increase in mean, median and the observed range of values. This same treatment to placebo trend is seen in the patients who were high at baseline and at EOM. This shift occurs on a very high baseline frequency of high RDW values in both the treatment 63 (52%) and placebo 69 (56%) groups. This high baseline occurrence suggests that there may be a predisposition to elevated RDW in this study cohort which confounds interpretation of the observed shifts from baseline to EOM.

RDW is not a disease but a potential biomarker for several diseases of the red blood cell. As such the abnormality of RDW seen in topiramate XR treatment does not indicate a specific adverse effect but points to the potential for an AE which may be in a spectrum of disorders. Examination of the AE profile does not reveal any of these diseases to be present. The shortcoming is the have not been specific studies done to determine if specific diseases have occurred, for example Fe, folate and b-12 studies have not been performed. If the RDW biomarker is pointing to a disease or abnormality caused by USL255 treatment it would need to be an acquired phenomena rather than a hereditary disorder such a sickle cell, b-thal. There is no laboratory testing for the potential acquired disorders which could be a drug effect such as vitamin B12, folate or iron deficiency. The hemoglobin (Table 32) and MCV (Table 35) have been examined for evidence of depressed hemoglobin values in the treatment compared to placebo and alterations in RBC size between treatment and placebo but no notable difference is identified.

Additional sources of this laboratory anomaly are concentration of outliers at one or a few individual study sites or error associated with a specific laboratory. Examination of RDW outliers revealed a fairly broad distribution of outlier values from 22 sites in 11 countries. The laboratory examinations were done at two central laboratories, one in Europe and one in the United States. Three of the study sites with outliers were in the Western Hemisphere thus the trend to high RDW values does not appear to be localized exclusively to a single laboratory. The original topiramate IR NDA application was examined to determine if RDW was a hematologic analysis parameter that might

inform the observations in the current application. RDW does not appear in the array of hematologic parameters present in earlier reviews.

Conclusion: Due to the high baseline occurrence of elevated RDW and the non-specific nature of this RBC parameter the interpretation of the above observations is uncertain. A true signal for variation in the RBC population of treated patients is possible but there are no converging lines of evidence to support this conclusion based on the absence of treatment to placebo differences in hemoglobin and MCV values as well as no report of anemia seen in the AE dataset.

Monocytes

Table 41 Monocytes , Means & Medians Change from Baseline at End of Maintenance (EOM), Outliers, Shift from Baseline to Last Observation, ITT safety population

Change from Baseline at EOM in (10 ³)/mm ³ . (n= # with change from baseline measurements)				
Statistic	USL255 (n=96)		Placebo (n=102)	
Mean	-0.044		-.006	
median	0		0	
range	-0.6 to 0.6 (x 10 ³)/mm ³		-0.5 to 0.5 (x 10 ³)/mm ³	
outliers*				
	USL255		PBO	
Time point of Measurement (available measurements at baseline / EOM)	Baseline (122)	EOM (98)	Baseline (123)	EOM (105)
Patients High	0	0	0	0
Max Value	-	-	-	-
Patients Low	0	0	0	0
Min Value	-	-	-	-
Monocyte count, Shifts From Baseline to Last Observation, N (%)				
	Emergent Low		Emergent High	
	USL255 N = 124	Placebo N = 125	USL255 N = 124	Placebo N = 125
Monocytes (K/mm ³)	0	0	0	0
*based on reference range 0 to 1.2 (x 10 ³)/mm ³				

Reviewer Comment: Examination of the hematology central tendency, outlier and shift tables do not reveal a new safety signal. An anomaly of RDW is discussed in that section.

7.4.3 Vital Signs

Weight

Change from baseline: mean, median

Table 42 Weight at End of Maintenance, Change from Baseline in Kg (ITT safety population)

Statistic	USL255 (n=107)	Placebo (n= 117)
Mean	-2.0	0
median	-1.4	0
range	-17.5 to 5 kg	-6 to 4.7 kg

Outliers

An outlier threshold of $\pm 8\%$ change in body weight is chosen. 10 subjects were identified who had an 8% or greater loss of body weight at end of maintenance phase compared to baseline. No subjects were identified with an increase of body weight greater than or equal to 8%.

Among the 10 patients with weight loss at the outlier threshold 8 were in the USL255 treatment arm and 2 were in the placebo treatment arm. Three of the USL255 patients had an adverse event of weight loss and one USL255 patient had adverse events of both weight loss and anorexia. None of the patients discontinued the study. The maximum weight loss observed was 14% which occurred in a USL255 patient with a baseline weight of 128kg.

Reviewer comment: the results of the weight analysis are concordant with the known property of topiramate to produce weight loss in some patients and is identified in the adverse reactions section of the topiramate IR label.

Blood Pressure

Systolic blood pressure; mid maintenance measurement is examined to allow for drug effect but to avoid accommodation to any adverse effect.

Change from baseline: mean, median

Table 43 Systolic Blood pressure at End of week 7 (mid maintenance), Change from baseline in mmHg. (ITT safety population)

Statistic	USL255 (n= 112)	Placebo (n= 119)
Mean	0.34	0.8
median	0	0
Range	-19 to 32 mmHg	-41 to 30 mmHg

Systolic Outliers (defined as at least 20% change from baseline and a result that was either 150 mm Hg or higher or 90 mm Hg or lower):

Examination of the USL255 treatment arm at end of week 7 revealed 5 patients with an increase in systolic pressure greater than 20% over baseline. None of the resultant systolic blood pressures were greater than 150mmHg. The maximum increase over baseline was 32mmHg. No patients were observed with a 20% decrease in systolic blood pressure compared to baseline and no patient had a systolic blood pressure less than 90mmHg.

Examination of the placebo treatment arm at end of week 7 revealed 3 patients with an increase in systolic pressure greater than 20% over baseline. Two of the patients had a resultant blood pressure value greater than 150mmHg. In both patients the resultant systolic blood pressure was 160mmHg. The maximum increase over baseline among these three patients was 30mmHg. One patient had a decrease from baseline greater than 20%. This patient had a decline of 41mmHg. The resultant systolic blood pressure was 119mmHg.

Diastolic Blood Pressure

Change from baseline: mean, median

Table 44 Diastolic Blood pressure at End of week 7 (mid maintenance), Change from baseline in mmHg. (ITT safety population)

Statistic	USL255 (n= 112)	Placebo (n= 119)
Mean	-0.6	1.28
median	0	0
Range	-27 to 22 mmHg	-28 to 40 mmHg

Diastolic Outliers (defined as at least 20% change from baseline and a result that was either 100 mm Hg or higher or 60 mm Hg or lower)

Examination of the USL255 treatment arm at end of week 7 revealed 9 patients had a 20% or greater change from baseline measurement. In six patients there was a decline in the diastolic blood pressure while in 3 the change was in an increasing direction. In only one of the patients did the resultant diastolic blood pressure value cross the defined abnormal boundary. This occurred in a patient with a decline in diastolic blood pressure from 69mmHg at baseline to 53mmHg at visit 7.

Examination of the placebo treatment arm at end of week 7 revealed 16 patients had a 20% or greater change from baseline diastolic blood pressure measurement. In 5 of these patients there was a decline in the value compared to baseline. Among these 5 patients the resultant diastolic blood pressure value was 60mmHg or less. In 11 of the sixteen patients there was an increase in the diastolic blood pressure measurement. In one of these patients the resultant blood pressure value was greater than 100mmHg.

Heart rate (beats per minute)

Change from baseline: mean, median

Table 45 Heart rate at end of week 7 (mid maintenance), Change from baseline in beats per minute. (ITT safety population).

Statistic	USL255 (n= 112)	Placebo (n= 119)
Mean	0.06	0.4
median	0	0
Range	-28 to 20 BPM	-19 to 28 BPM

Heart Rate Outliers (at least 20% change from baseline and a result that was either 120 beats per minutes (BPM) or higher or 50 BPM or lower)

Examination of the USL255 treatment arm at end of week 7 revealed 3 patients had a 20% or greater change from baseline heart rate. In two of these patients there was an increase in heart rate compared to baseline; neither of these patients had a resultant heart rate greater than 120. In one patient there was a decline in heart rate from 92 to 64 beats per minute.

Examination of the placebo treatment arm at end of week 7 revealed 10 patients had a 20% or greater change from baseline heart rate. In 2 of these ten patients there was a decline in heart rate. In one of these patients the resultant heart rate was 60 BPM and 65 BPM in the second. In 8 of the 10 patients there was an increase in heart rate but none of the 8 patients had a resultant blood pressure greater than 120 BPM. The highest resultant heart rate was 96 BPM.

Reviewer Comment: Analysis of vital sign data reveals a signal for decline in weight in the USL255 treatment arm. This represents a known property of topiramate currently

contained in reference listed drug labeling. There is no signal identified for alteration in blood pressure or heart rate.

7.4.4 Electrocardiograms (ECGs)

The ECG dataset contains only investigators assessment of the study. All abnormal results are noted to be “not clinically significant”.

From among the USL255 treatment group (n=124) where patients had a baseline ECG, there were 36 patients with a normal baseline study and abnormal visit 8, early discharge or visit 11 ECG study.

The Placebo treatment group (n= 125) where patients had a baseline ECG, there were 38 patients with normal baseline ECG but an abnormal study at visit 8, visit 11 or early discharge.

Reviewer Comment: The ECG data is limited to an investigator assessment. Comparison of the frequency of an abnormal assessment between the USL255 and placebo treatment groups does not reveal a difference between groups. All abnormal assessments are noted to be “not clinically significant”. The available evidence does not indicate a safety signal for ECG findings.

7.4.5 Special Safety Studies/Clinical Trials

QT Waiver and Labeling

The sponsor presented a phase 1 protocol to support cardiac conduction safety. Notification of agreement was sent to the sponsor on 5/14/2010. Subsequently a request for waiver of QT study was submitted by the sponsor on 7/18/11. This waiver request included the following cardiac safety data and was reviewed by the QT-IRT:

- ECG assessment of 40 subjects receiving 600 mg to 1400 mg single doses of USL255 in the P09-011 Phase 1 Single Ascending Dose Study and 38 subjects at 200 mg steady state doses of USL255 in the P09-003 Phase 1 Steady-State PK Study;
- AERS database review;
- Literature database review;
- FDA Advisory Committee Meeting Sponsor Briefing Package, TQT study results for Vivus Inc. Qnexa.
- Cardiac safety assessments available from the Topamax NDA 020505 and NDA020844 Drug Approval Packages.

On 10/17/11 following review of the information package the QT-IRT concluded that no further QT assessment was needed for the topiramate XR formulation. This was further affirmed in an advise/information request to the sponsor on 7/16/12. In this document the sponsor queried "Does the Agency agree that the data package adequately establishes the cardiac conduction safety of topiramate and that no further cardiac safety data are required to support approval of USL255?" The division agreed that no further QT assessment is needed for topiramate extended release.

(b) (4)
The sponsor cites study P09-011, A randomized, placebo controlled, double blind study to evaluate the safety and pharmacokinetics of single ascending doses of USL255.

P09-011:

A Randomized, Placebo-controlled, Double-Blind Study to Evaluate the Safety and Pharmacokinetics of Single Ascending Doses of USL255

Objectives:

- To evaluate the safety and tolerability of single ascending doses of USL255.
- To evaluate the PK properties of single ascending doses of USL255.
- To determine the maximum tolerated dose (MTD) of USL255 when given as single ascending doses.
- To evaluate dose proportionality of single ascending doses of USL255.

Design and Sample Size:

A total of up to 60 subjects were planned for enrollment into 6 cohorts of 10 subjects each, with each cohort composed of 8 subjects randomly assigned to receive a single dose of USL255 and 2 subjects randomly assigned to receive matching placebo, and each cohort separated by at least 4 days. Each dose was administered with approximately 240 mL (8 fl oz) of room temperature water after an overnight fast of at least 10 hours.

Planned doses for each cohort were as follows:

- 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

Safety data were collected in a blinded fashion up to Study Day 4.

On Study Day 4, after AE causality had been determined, the blind was to be broken and safety and tolerability results (ie, vital sign measurements, ECG results, clinical laboratory test results, and AEs) reviewed by the sponsor and clinical research

organization (CRO). If safety and tolerability were demonstrated in the dose administered, the study would continue to the next sequential cohort until an MTD was defined or Cohort 6 was completed. If escalation to the next higher dose was prevented, then the previous dose would be named as the MTD.

Subjects were confined to the clinic for at least 12 hours before and at least 96 hours after dosing. Following the in-house portion of each treatment, subjects returned to the clinic at predetermined times for additional blood sampling for PK profiling.

Inclusion Criteria:

1. age 18 to 45 years
2. male or nonpregnant, non-breastfeeding female.
3. Normal admission medical history and physical exam
4. Normal 12 lead ECG meeting the following criteria:
 - a. QTcF (QT interval corrected using Fridericia's formula) interval ≤ 450 ms
 - b. for males and ≤ 470 ms for females
 - c. b. Consistent sinus rhythm
 - d. c. No clinically significant conduction disorders as determined by the investigator
 - f. d. PR interval between 120 and 220 ms
 - g. e. Resting HR between 40 and 100 bpm
 - h. f. QRS interval ≤ 110 ms
 - i. g. QT intervals that could be consistently analyzed
5. body mass index 18 to 30kg/m^2
6. must abstain from alcohol, caffeine and xanthine containing beverages for 24 hours prior to admission and through completion of the study.
7. Has not used tobacco products within 90 days prior to screening

Exclusion Criteria

1. Clinically relevant current illness
2. Condition that could interfere with the absorption, distribution, metabolism or excretion of drugs or any condition that could confound analysis.
3. Clinically significant cardiovascular, renal, hepatic, gastrointestinal, neurological, endocrine, hematological, dermatological, immunologic, psychiatric or metabolic disease as determined by medical history and physical examination
4. History of nephrolithiasis or ureterolithiasis
5. Had a systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of
6. ≥ 90 mm Hg
7. History of malignancy
8. Positive screen of drugs of abuse
9. Positive test for HIV, hepatitis B or hepatitis C.

10. Had a history of additional risk factors for torsade de pointes (eg, hypokalemia, history of drowning survival, family history of long QT syndrome, family history of short QT syndrome, or family history of unexplainable early sudden death).
11. Had taken a prescription medication within 14 days prior to beginning study on Day -1 or taken over-the-counter medications, including topical medications, vitamins, herbal or dietary supplements/remedies (eg, St John's wort or milk thistle) within 14 days of dosing.

Concomitant Medications: Subjects were prohibited from concomitant use of any medications during the course of the study, unless approved by the Investigator.

Study Assessments

Study Phase (each dosing cohort)	Screening	Check-in	Treatment				Final Study Visit (Day 15)
	(Day -28 to Day -1)	Day -1	Day 1	Days 2-4	Day 5	Days 6, 8, 10, 12, and 15 ^a	
Informed consent	X ^b	X ^b					
Eligibility (Inclusion/exclusion)	X	X ^c					
Prior medication assessment	X	X ^c					
Medical/surgical history	X	X ^c					
Demographics	X						
Vital sign measurements ^d	X ^e		X ^{f, g}	X ^{f, g}	X ^{f, g}	X ^{f, g}	X
Physical examination ^h	X						X
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X	X ^j		X ^{j, k}			X ^j
HIV antibody, hepatitis B surface antigen, and hepatitis C antibody screen	X						
Pregnancy screen (all females)	X	X		X ^k			X
FSH ^l	X						
Urine drug screen/creatinine	X	X					
Safety 12-lead ECG	X ^m	X					X
12-lead ECG from Holter monitor			X ⁿ	X ⁿ			
Study drug administration			X				
Pharmacokinetic sampling			X ^o	X ^o	X ^o	X ^o	
Adverse event monitoring	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X

Abbreviations: ECG=electrocardiogram; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus.
^a Nonconfinement days.
^b A general informed consent form was signed at the screening visit and a study-specific ICF was signed prior to beginning any study-specific assessments.
^c Updated and/or reviewed.
^d Vital signs were collected while subjects were at rest (at rest for a minimum of 5 minutes).

e Oral temperature was collected at Screening for each cohort.
f Blood pressure and heart rate were measured at Baseline (within 90 minutes prior to dosing) and at 10, 14, 18, 22, 26, 30, 32, 36, 48, 72, 96, 120, 168, 216, 264, and 336 hours after each dose.
g Respiratory rate was measured along with vital signs at 168, 216, 264, and 336 hours after dosing in Cohort 1, and at Baseline (within 90 minutes prior to dosing) and at 26, 48, 72, 96, 120, 168, 216, 264, and 336 hours after dosing in Cohorts 2 through 5.
h Physical examination included skin, head/ears/eyes/nose/throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, musculoskeletal/extremities.
i Fasting blood sample.
j Serum chemistry and hematology only.
k Performed on Day 3.
l If necessary to document postmenopausal status.
m Safety 12-lead ECG performed at Screening was sent to central laboratory for reading.
n Electrocardiograms were conducted in triplicate at Baseline (30 minutes before dosing) and 10, 14, 18, 22, 26, and 30 hours after dosing.
o Pharmacokinetic (PK) samples were collected at Baseline (within 90 minutes before dosing) and 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 hours after dosing (PK samples collected at study hours 10, 14, 18, 22, 26, and 30 hours were collected 10 minutes after the nominal ECG time point).

ECG collection and interpretation

All subjects had continuous 12-lead ECGs extracted in triplicate at Baseline (30 minutes before dosing) and at 10, 14, 18, 22, 26, and 30 hours after dosing. The 12-lead ECGs were collected while subjects were at rest (supine position), at least 10 minutes before each ECG sampling time point through at least 10 minutes after each scheduled time point. The time of Holter startup on Day -1 was approximately 30 minutes before the scheduled dose administration time.

The equipment was supplied and supported by the central ECG reading center. Electrocardiograms were acquired from 24-hour Holter recordings using high-resolution, digital 12-lead ECG devices (Mortara H-12+, Mortara Instruments, Milwaukee, WI). The 12-lead digital ECG data were stored onto high-density (ie, 1000 Hz) flashcards approximately every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed.

Central ECG over-read and intervals measurements were provided by experienced, qualified, and certified cardiac safety specialists (primary reader). The readers were blinded to treatment details and timing of ECGs and a single reader read all ECGs for a given subject. Final ECG assessments were performed by a single US board-certified cardiologist who evaluated the ECG from a morphological perspective and who confirmed the interval measurements performed by the primary reader.

RESULTS

PK:

There was dose proportionality of the total drug exposure ($AUC_{0-\infty}$) over the entire range of doses administered, from 600 mg to 1400 mg. Total exposure (AUC) and peak exposure (C_{max}) were dose proportional across the dose levels studied.

The ER formulation of topiramate used in this study, median T_{max} occurred much later, with median T_{max} varying from 17 to 20 hours after dosing. These results are consistent with the results described in the investigator's brochure for previous multiparticulate ER formulations of USL255. Mean half-lives for the treatment groups in this study ranged from 56.0 to 80.3 hours.

ECG results:

The ECG results of this study demonstrate that a single dose of USL255 between 600 and 1400 mg did not increase QT_c intervals. The data suggested a possible decrease in QT_c intervals with increasing dose. Data taken from the sponsor's safety report reveal that mean QT_cF reaches a maximum change from baseline at approximately 25 hours post dose. This nadir is approximately -19msec for the 1000mg and 1200mg dose, -16msec for the 1400mg dose group, -13 msec for the 600mg dose group and -10msec for the 800mg dose group. The mean QT_cF across dose groups by hour post dose can be seen in [Figure 7](#). The proportion of subjects within each dose group who had a change from baseline, at any hour post dose, was examined, [Figure 6](#). This analysis reveals that 38 percent of subjects in the placebo group were found to have at least one post dose recording of a change from baseline less than -15 msec. In the 600mg dose group 38% of subjects had at least one post dose recording less than -15 msec and 13% had one recording less than -20 msec. The 800mg dose group is similar to the 600mg group while the proportions with a data point less than -20 msec increase notably in the 1000mg and 1200mg dose groups.

Figure 6 QTcF Shortening, Proportion of Subjects in Each Dose Group with Select Change from Baseline (<-15, <-20 msec), Study P09-011

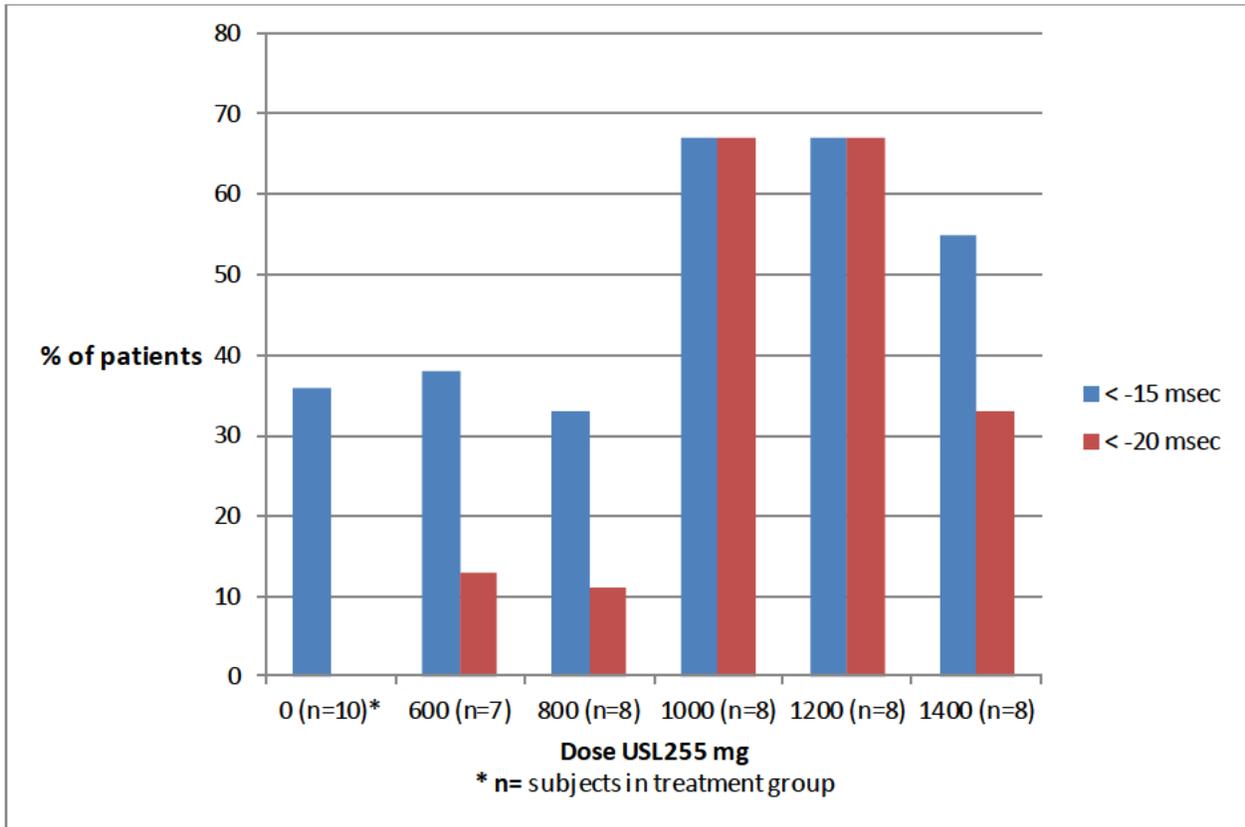
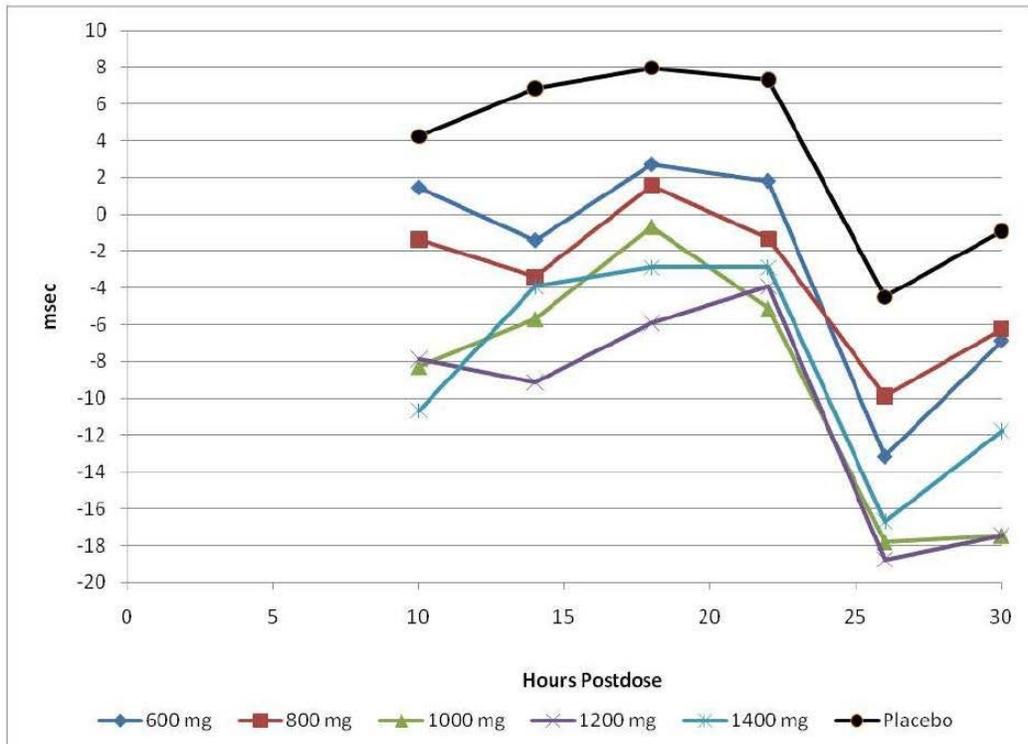
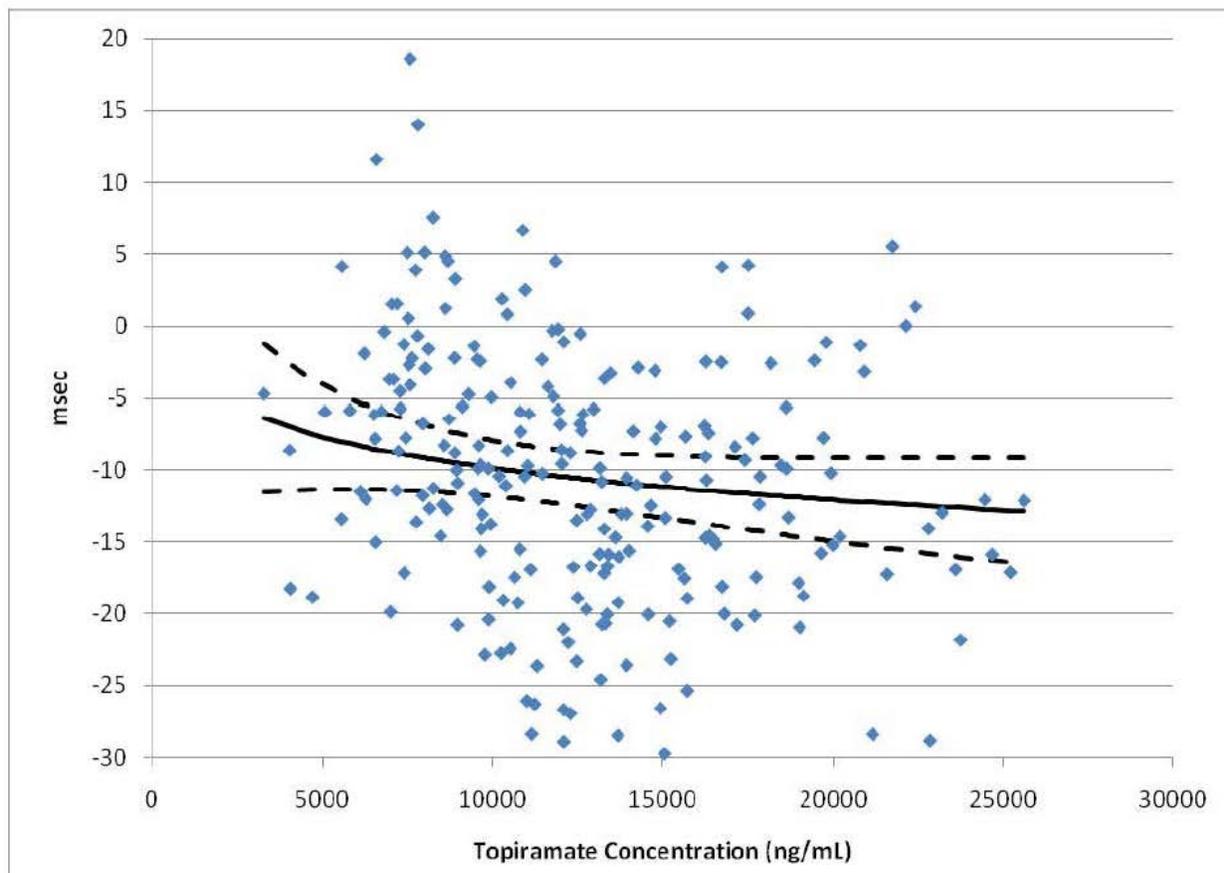


Figure 7 USL255 QTcF Mean Change from Baseline by Dose and Time after Administration. From P09-011 Cardiac Safety Report, Figure 10



All mean differences from placebo in QTcF were less than zero, and all but 1 mean difference from placebo in QTcB was less than zero. Moreover, all 1-sided upper 95% confidence bounds on mean differences from placebo were less than 10 ms. No subject had a QTcF interval greater than 450 ms following any USL255 dose, and only 2 subjects had a total of 3 QTcB intervals greater than 450 ms following USL255. No USL255 subject had any increase from Baseline in QTc greater than 30 ms. A regression relating placebo-subtracted differences in change from Baseline in QTcF and topiramate concentration produced a negative slope (Figure 8), indicating that there was no increase in mean differences from placebo in QTcF with increasing topiramate concentration.

Figure 8 Time-Matched Differences From Placebo in Changes From Baseline in QTcF vs. Topiramate Concentration and 90% CI on Estimated Values. From P09-011 Cardiac Safety Report, Figure 9.



Examination of all post dose measurement intervals of QTcF and QTcB for all dose groups reveals one measured QTc less than 365 msec. This value (364 msec) was found in subject 31 in the 800mg dose group at 14 hours post dose. This represented a 12 msec reduction from pre-dose baseline QTcB. The threshold of concern for shortening of the QT interval is not clearly established. Several studies which examined large healthy cohorts identify 365 msec as 2 standard deviations below the mean for females and 350 msec for males¹¹.

Reviewer Comment: Study P09-011 provides support that topiramate extended release does not prolong QT interval although there was no positive control in this study to qualify as a thorough QT study according to ICHE14 guidelines. There is a trend of

11 Maluli HA, Meshkov AB. A Short Story of the Short QT Syndrome. Cleve Clin J Med. 2013 Jan;80(1):41-7.

QTc reduction from pre-dose baseline more prominent in the high dose groups. The proportion of subjects in the 600mg and 800mg dose groups with a shortening less than -20 msec from baseline is approximately 13%. This increases to 67% in the 1000mg and 1200mg groups. These post dose reductions did not result in any QTc below 365 msec. In the only case of a measured QTcB below 365 msec the reduction from pre-dose baseline was 12 msec.

There is minimal evidence that the observed trend of QT shortening is of clinical concern. Foremost in the analysis is the absence of a clear QT value to be considered pathologically short. The threshold chosen for this discussion is derived from the range of QT intervals observed in healthy populations as noted in reference 11. Based on this threshold none of the subjects found to have QTc shorting more than 15 msec from baseline had a resultant QTc value below 365 msec. An additional factor for consideration of this shortening trend is the topiramate dose. All topiramate doses in this study are suprathapeutic. The most notable shortening trend occurs in the 1000mg and greater dose cohorts. One thousand milligrams is 2.5 times the labeled upper dose recommendation of 400mg. Finally, this API has been on the market since 1996. Examination of the AERS database using Empirica Signal reveals no entries for the drug- event combination “topiramate” and “Electrocardiogram QT shortened”. Overall the observed QT shortening trend does not rise to the threshold to be considered a new safety signal.

(b) (4)

7.4.6 Immunogenicity

Topiramate is a small molecule drug and thus less likely than a therapeutic protein to elicit an antibody response, immunogenic action has not been established. Current Topiramate IR (Topamax®) labeling has no warning for hypersensitivity. In section 6.4 “Other Adverse Reactions Observed During Double-Blind Epilepsy Adjunctive Therapy Trials”, table 6, a composite of topiramate add on trials in adults with epilepsy reveals 1 patient in the placebo group compared with 5 (n=597) in the topiramate treatment group had an adverse reaction of “allergy”. Overall topiramate does not have a strong signal for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The topiramate extended release pivotal trial was a single dose trial. This design does not allow examination of adverse event across dose arms.

The label of the reference listed drug (Topamax®) reveals that adverse reactions in the adult monotherapy trial were more frequent in the 400mg treatment arm than the 50mg treatment arm. These adverse reactions were paresthesia, weight decrease, anorexia, somnolence, and difficulty with memory. In the pediatric monotherapy trial the adverse reactions more common in the 400mg treatment arm were fever, weight decrease, mood problems, cognitive problems, infection, flushing, and paresthesia.

In adjunctive therapy trials the dose related adverse reactions were noted to be fatigue nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems and weight decrease¹².

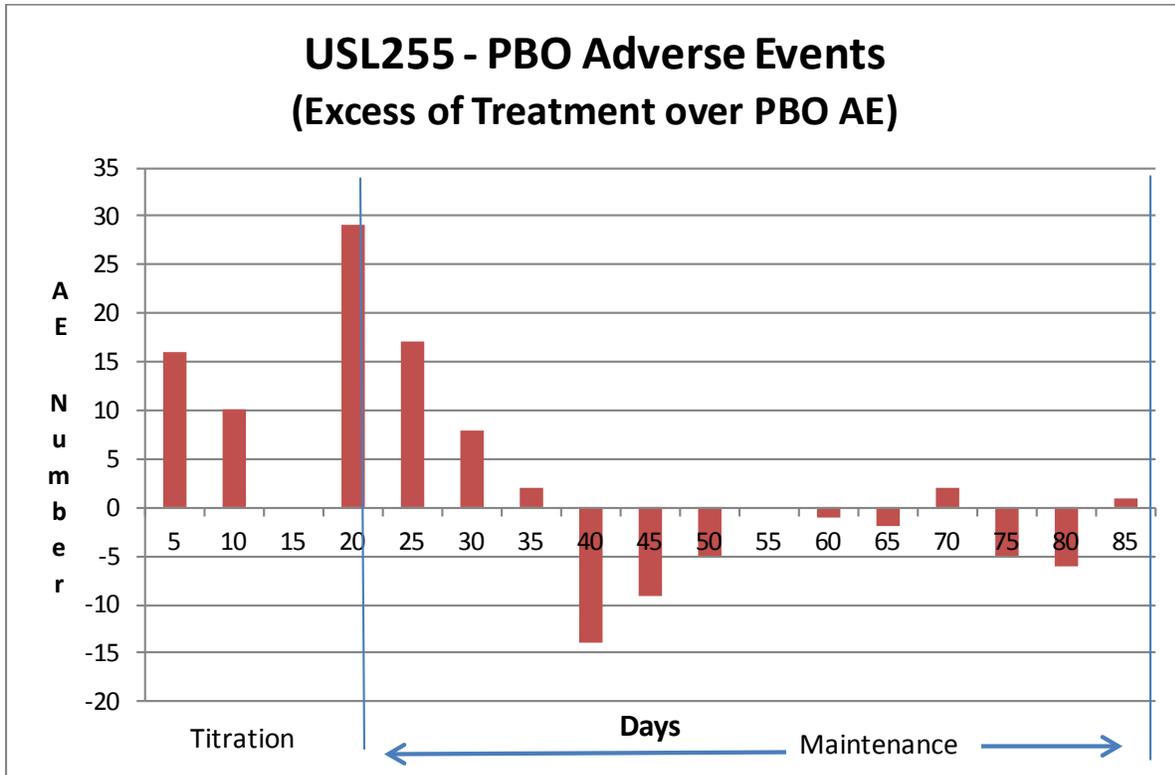
7.5.2 Time Dependency for Adverse Events

The topiramate label indicates in section 5.5 of “Warnings and Precautions” that Rapid titration rate and higher initial dose were associated with higher incidences of these reactions.

Adverse events in the topiramate extended release pivotal trial (study P09-004) were most frequent during late titration, approximately day 20, and early in the maintenance interval then declined by day 40. The titration-maintenance interval was complete on day 84. See [Figure 9](#)

12 Reference listed drug label, Topamax®, section 6.1 (Adverse Reactions)

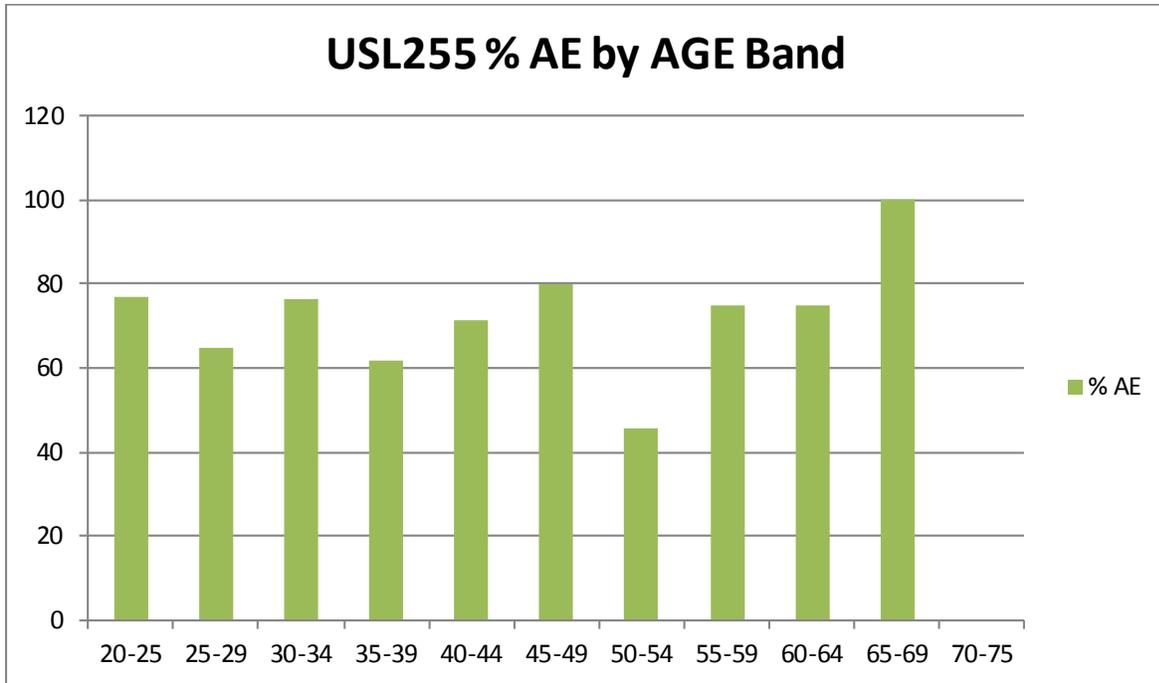
Figure 9 Difference between USL255 Adverse event frequency and Placebo frequency during the 11 week titration – maintenance interval



7.5.3 Drug-Demographic Interactions

Occurrence of adverse event by 5 year age bands in the USL255 treatment group is examined. The percent of patients experiencing an AE in each 5 year bin is shown in [Figure 10](#). This analysis does not reveal a clear difference among age groups. The 65 to 69 year old group had the highest percentage occurrence but this group was limited to 1 patient.

Figure 10 Percent of patients in 5 year age bands who experienced 1 or more adverse events in the USL255 treatment group.



The frequency of adverse events by sex is examined. It was found that 71% of females in the USL255 treatment group experienced 1 or more adverse events while 59% of female patients in the placebo group experienced 1 or more adverse events. Sixty seven percent of males in the USL255 treatment are experienced 1 or more adverse events while 58% of males in the placebo group experienced 1 or more adverse events, [Figure 11](#) . There was no notable difference between the occurrences of adverse events in the USL255 treatment group. The analysis does show a greater proportion of patients in the USL255 treatment group experienced adverse events compared to the placebo group, although this finding is expected.

Figure 11 Percent of Patients by Sex who experience 1 or more AEs in the USL255 and PBO treatment groups.

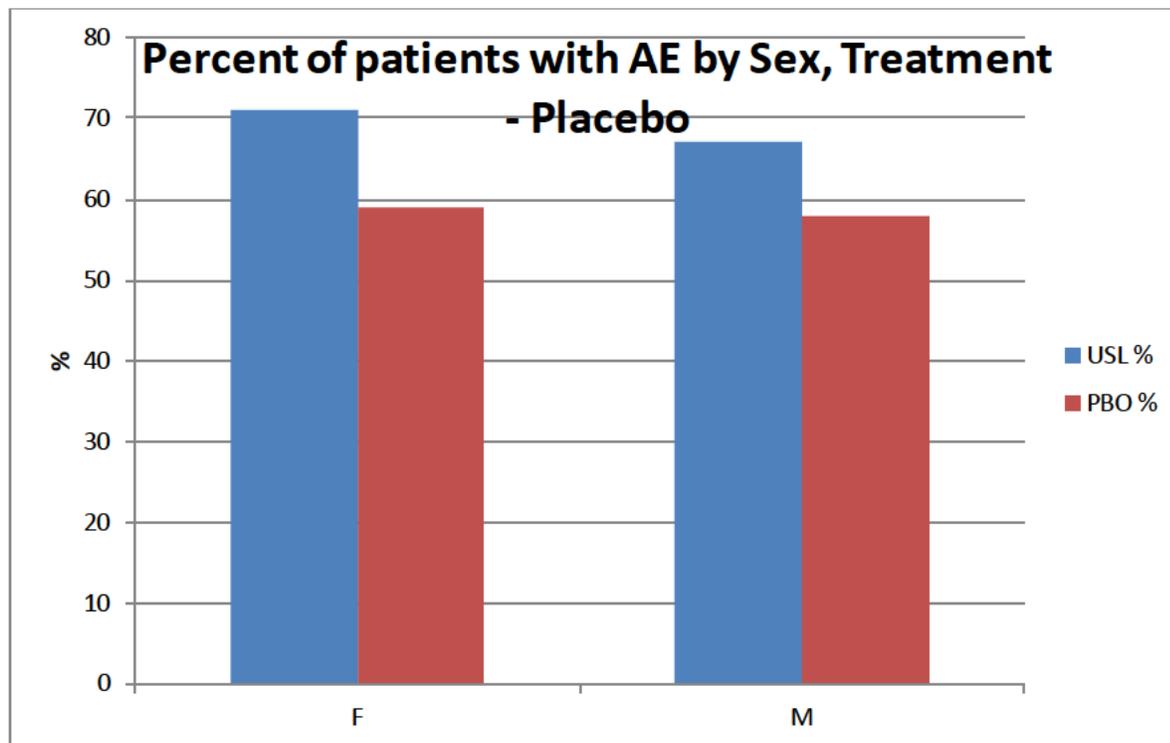


Table 46 All Cause Discontinuations, male / female distribution

All Cause Discontinuations	USL255	% USL255	PBO	% PBO
F	12	9.7	3	2.4
M	9	7.3	8	6.4

Reviewer Comment: Examination of adverse events does not reveal a notable differentiation by age, and sex. There is a 2.4% excess of all cause discontinuations among females over males in the USL255 treatment group and notable differentiation from the placebo group.

7.5.4 Drug-Disease Interactions

Dose adjustment is directed for patients with decreased hepatic function and patients with renal failure in section 2 “Dosage and Administration” of the RLD Topamax®.

7.5.5 Drug-Drug Interactions

Drug – Drug Interactions of topiramate XR is not expected to differ from the experience with presented in the RLD product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

New carcinogenicity studies are not performed for this 505(b)(2) application. The reader is directed to section 13 “Non-Clinical Toxicology” of the RLD product Topamax® for available information of carcinogenicity risk based on non-clinical data.

7.6.2 Human Reproduction and Pregnancy Data

Topamax® is classified as a pregnancy category D. See section 5.6 and 8.1 of the RLD product label.

7.6.3 Pediatrics and Assessment of Effects on Growth

The pivotal clinical trial P09-004 studied patients in the age range 18 to 75 years. No pediatric assessment is available in this application. There is adverse reaction data for pediatric patients age 6 to <16 years in section 6.1 of the RLD.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This submission does not contain an abuse potential study. The RLD label indicates that the abuse and dependence potential of Topamax® has not been evaluated in human studies nor has topiramate been systematically studied in animals or humans for its potential for tolerance or physical dependence.

Overdosage is covered in section 10 of the RLD product label.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

No postmarketing safety assessments have been conducted by OSE.

9 Appendices

9.1 Literature Review/References

References are presented as footnotes

9.2 Labeling Recommendations

The new clinical study P09-004 should be included in the label to add confirmation of the effectiveness of the 200mg dose. Where there is comparison of adverse events to the IR formulation a qualifying statement to indicate lower doses were studied than in the majority of the IR studies.

9.3 Advisory Committee Meeting

No Advisory committee is scheduled for this application. The product is an extended release formulation of an established immediate release (IR) product for use in an IR approved indication.

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/s/

STEVEN T DINSMORE
03/05/2014

NORMAN HERSHKOWITZ
03/06/2014