FULL-LENGTH ORIGINAL RESEARCH

USL255 extended-release topiramate: Dose-proportional pharmacokinetics and tolerability in healthy volunteers

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Summary

Objective: **Evaluate the pharmacokinetics (PK), safety, and tolerability of single doses of once-daily USL255, Qudexy XR (topiramate) extended-release capsules, over a wide dosing range.**

Methods: **Two single-dose, phase I studies in healthy adults were used to evaluate the PK profile and maximum tolerated dose (MTD) of USL255 from 25–1,400 mg. Standard PK parameters assessed included area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}). Dose proportionality, linearity, and intersubject and intrasubject variability (coefficient of variation [%CV]) of AUC and C_{max} were evaluated. Investigator-reported adverse events (AEs) were obtained throughout the studies.**

Results: **After the initial increase in plasma concentration levels immediately following administration of USL255 25–1,400 mg, plasma topiramate concentration-time profiles were flat up to 24 h after dosing. AUC was dose proportional from 25–1,400 mg, and C_{max} was dose proportional from 50–1,400 mg; both AUC and C_{max} were linear across the entire dose range. Low intersubject and intrasubject %CV values were observed for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} (intersubject %CV: 20.2, 19.6, and 22.4%, respectively; intrasubject %CV of dose-normalized mean values: 10.8, 8.2, and 13.2%, respectively). USL255 was generally safe and well tolerated with MTD established at 1,200 mg.**

Significance: **These results demonstrate that USL255 provides consistent plasma topiramate exposure across an extended-dosing interval and predictable plasma topiramate concentrations over a wide dosing range. Overall, the favorable safety profile and consistency of exposure suggest once-daily USL255 can be a useful treatment option for patients with epilepsy.**

KEY WORDS: **Epilepsy, Seizures, Once-daily, Antiepileptic drug, Antiepileptic.**

For patients with epilepsy, the goal of antiepileptic drug (AED) therapy is long-term seizure control with minimal or no side effects. However, fluctuations in plasma AED concentrations may increase the risk of breakthrough seizures at trough plasma concentrations and adverse events (AEs) at peak plasma concentrations.[1–3] Side effects, in particular, can lead to treatment nonadherence,[4,5] a significant problem in patients with epilepsy with a prevalence as high as 40%.[6] Periods of poor adherence to AED therapy can result in undesirable clinical consequences, such as increased seizure occurrence and higher incidences of emergency department visits, hospital admissions, motor vehicle injuries, fractures, and death, when compared with periods of compliant dosing.[6–8]

Maintenance of effective and stable target plasma AED concentrations over time, without major fluctuations in plasma levels, is important for long-term seizure control in patients with epilepsy.[1,2] Although immediate-release (IR) AEDs are effective, some require multiple daily doses (up to 4 times/day) and are associated with large fluctuations in plasma concentrations.[2] To reduce these fluctuations, extended-release (XR) formulations are designed to maintain

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relatively flat plasma drug concentrations over an extended period.[1,9] An optimal AED formulation would exhibit a predictable, linear pharmacokinetics (PK) profile[10] with low intersubject and intrasubject variability, thereby providing reliable exposure during titration and dosing adjustments and consistent exposures during maintenance therapy. Extended-release AEDs may also result in increased medication adherence compared with IR formulations, as compliance improves with reduced dosing frequency and increased tolerability.[4,5] Overall, the introduction of XR formulations of AEDs has improved the management of epilepsy by reducing dosing frequency and limiting fluctuations in plasma drug concentrations,[5] resulting in improved compliance, increased seizure control, and reduced occurrence of peak-related side effects.[11,12]

Immediate-release topiramate (TPM-IR, Topamax, Janssen Pharmaceuticals, Titusville, NJ, U.S.A.) is a well-established, broad-spectrum AED approved for use in the United States in 1996.[13] TPM-IR dosed twice daily is characterized by a plasma elimination half-life that ranges from 21 to 42 h and dose proportional pharmacokinetics from 200–800 mg.[13,14] The lack of dose proportionality at lower dose ranges, particularly for maximum plasma concentration (C_{max}), is a result of saturable binding of TPM to red blood cell (RBC) carbonic anhydrase.[15]

USL255, Qudexy XR (topiramate) extended-release capsules (Upsher-Smith Laboratories, Inc., Maple Grove, MN, U.S.A.), is a once-daily XR topiramate developed for the treatment of epilepsy. USL255 is a proprietary multiparticulate (beads in a capsule) formulation recently approved by the U.S. Food and Drug Administration (FDA; 11 March 2014) as initial monotherapy in patients ≥10 years of age with partial-onset seizures (POS) or primary generalized tonic–clonic (PGTC) seizures and adjunctive therapy in patients ≥2 years of age with POS, PGTC, or seizures associated with Lennox-Gastaut syndrome.[16] In previous phase I studies, USL255 displayed equivalent drug exposure to TPM-IR, with a smoother concentration-time curve and an improved steady-state PK profile (e.g., reduced fluctuation index, significantly decreased maximum plasma concentrations).[17,18] In addition, switching between topiramate formulations did not affect steady-state exposure, including minimum plasma topiramate concentrations, suggesting that at equivalent total daily doses, USL255 will maintain topiramate concentrations at or above the minimum concentrations provided by TPM-IR.[18] In a recently completed global phase III study of USL255 for the adjunctive treatment of refractory partial onset seizures (PREVAIL; NCT01142193), USL255 led to significant improvements in the reduction of seizure frequency compared with placebo.[19]

To further evaluate the PK of USL255 and consistency of topiramate exposure over a wide dosing range, additional post hoc analyses were performed using data obtained from two separate phase I clinical studies. Presented here are the single-dose PK, maximum tolerated dose (MTD), and safety/tolerability profiles of USL255 from 25 to 1,400 mg in healthy adult volunteers.

Methods

Study overview

Two phase I, single-center studies in healthy adult volunteers were conducted to evaluate single-dose PK, MTD, and safety/tolerability of USL255 at doses of 25–400 mg (study 1)[20] and 600–1,600 mg (study 2).[21] The institutional review boards of the participating U.S. clinical sites approved the study protocols, and participants provided written informed consent prior to conduct of study procedures.

Study design

Study 1 (N = 30) was a randomized, open-label, 5-way crossover study with five treatment sequences (n = 6/sequence) and five treatment periods.[20] Each treatment sequence consisted of five doses of USL255 (25, 50, 100, 200, and 400 mg) administered in different order per sequence. Participants randomized to each sequence received a single dose of USL255 per treatment period under fasting conditions. Treatment periods were separated with a 21-day minimum washout. Blood sampling and tolerability assessments were conducted for 14 days post-dose. For each treatment period, participants were confined to the clinic for at least 10 h before and 36 h after dosing.

Study 2 (N = 60 [planned], N = 50 [final]) was a randomized, placebo-controlled, double-blind, single ascending dose, MTD study with six separate dose cohorts (600, 800, 1,000, 1,200, 1,400, or 1,600 mg USL255, or matching placebo), where increasing USL255 doses were administered to the next cohort if tolerability was established for the previous dosing group.[21] Each dose cohort consisted of 10 participants, randomly assigned 8:2 to receive a single dose of USL255 or matching placebo in the fasted state. Blood samples were collected, and tolerability was evaluated for each cohort over a 14-day period after dosing. If tolerability was demonstrated over the first 4 days, the next sequential dose cohort commenced at post-dose day 7 until all six cohorts were completed. However, if USL255 did not meet a priori safety and tolerability criteria, the previous dose would be declared the MTD and dose escalation would cease. Dose-limiting criteria were defined as USL255-related effects that were considered a serious adverse event (SAE), were intolerable, or were deemed by the investigator and/or sponsor to pose a medical risk if a higher dose were to have been administered. Participants were confined to the clinic for at least 12 h before and at least 96 h after dosing.

Participants and study populations

Adult volunteers (18–65 years [study 1] or 18–45 years [study 2]) in generally good health, with a body mass index

of 18–30 kg/m^2 and weighing at least 110 pounds, were allowed to participate. Participants were required to have refrained from tobacco products within 90 days of screening and were willing to abstain from tobacco through the final study visit. In addition, participants were required to abstain from alcohol, caffeine, and xanthine-containing beverages for 24 h prior to admission through 72 h after each dose (study 1) or through completion of the study (study 2). Dosing of prescription medication was not allowed for 14 days prior to initiation of both studies, and over-the-counter drugs were not allowed 3 days before the PK period of study 1 and within 14 days of USL255 dosing in study 2. Participants with a known hypersensitivity to topiramate or any clinically relevant illness or history of alcohol or drug abuse were excluded from the study.

Patient demographics, baseline characteristics, and safety/tolerability analyses were based on the safety population, defined as all randomized participants who received at least one dose of study drug. The PK population was defined as all participants treated with at least one dose of study drug that had sufficient PK samples to enable an accurate estimation of PK parameters.

Pharmacokinetic assessments and analyses

Blood samples were collected at baseline (within 60 min [study 1] or 90 min [study 2] before dosing), every 2 h until 32 h postdose, and at hours 36, 48, 72, 96, 120, 168, 216, 264, and 336 postdose. Plasma samples were analyzed for topiramate as previously described using a validated method consisting of high-performance liquid chromatography with tandem mass spectrometry (HPLC MS/MS), with a lower limit of quantification of 10 ng/ml.[17] Briefly, a 100-µl matrix aliquot was fortified with 25 µl of 150 ng/ml internal standard (topiramate-$^{13}C_6$) working solution. Analytes were isolated through supported liquid extraction, and the final extract was analyzed via HPLC with MS/MS detection. The quantification range of the assay was 0.01–10 mg/L using 500 µl of plasma. The interassay precision (% coefficient of variation) throughout the quantification range was between 7.03 and 10.4%, and the interassay accuracy (% nominal) was in the range of −0.178 and −1.63% at the above quantification range.

For each study, PK parameters were calculated from the plasma concentration-time data using noncompartmental methods.[22] Pharmacokinetic parameters included area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{0-t}) calculated using the linear trapezoidal rule, AUC from time zero to infinity ($AUC_{0-\infty}$) calculated using the linear trapezoidal rule of summation and extrapolated to infinity, maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), and terminal elimination half-life ($t_{1/2}$).

Post hoc PK analyses included assessments of dose-proportionality and linearity, as well as evaluation of intersubject and intrasubject variability. Dose proportionality of AUC and C_{max} were assessed over the entire dose range of both studies (25–1,400 mg) using mixed-effects power model approach on combined data from study 1 and study 2 (Smith criteria).[23] Dose proportionality was declared when the 90% confidence interval (CI) of the model-predicted ratio of dose-normalized geometric means for highest dose relative to lowest dose (R_{dnm}) lay completely within the range of 0.80–1.25. If dose proportionality was not established for the PK parameters using the Smith criteria, the 90% CIs were compared using the Hummel criteria (0.50–2.0 range), which is recommended for evaluations involving a fourfold or greater dose range.[24] Deviation from dose linearity across the entire 25–1,400 mg dose range was assessed through statistical modeling, using the type I F test with dose as the categorical factor ($\alpha = 0.05$).[23]

Intersubject variability was calculated for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} and expressed as a percent coefficient of variation (%CV) using the equation: (standard deviation/mean values) ×100. For intrasubject variability, %CV was calculated in participants from study 1 who received at least three doses of USL255 using the equation: (standard deviation/mean dose-normalized AUC or C_{max} values) ×100, with standard deviation calculated from dose-normalized parameters. Intrasubject variability was calculated for the USL255 doses from study 1 in which AUC and C_{max} were dose proportional or neared proportionality when this study was analyzed independently. Intrasubject variability in AUC was evaluated from 25 to 400 mg, as it was previously shown to be dose proportional across this range.[20] However, due to a lack of dose proportionality of C_{max} at lower doses,[20] a modified range of 100–400 mg was selected for this parameter; this resulted in the inclusion of three USL255 doses (100, 200, 400 mg) in the calculation of intrasubject C_{max} %CV.

Safety and tolerability analyses

Safety and tolerability assessments were conducted at baseline and throughout the two studies. Spontaneously reported treatment-emergent adverse events (TEAEs) were classified by study investigator based on intensity (mild, moderate, or severe) and relationship to study drug. In addition, changes from baseline in vital signs, clinical laboratory evaluations (e.g., hematology, serum chemistry, and urinalysis), physical examinations, and 12-lead electrocardiography (ECG) were assessed. To allow for comparison of TEAEs across the two studies, a post hoc analysis was performed in which TEAEs were normalized by dividing the total number of TEAEs experienced in each USL255 dosing group by the number of participants per group.

Results

Participant demographics and disposition

Overall, no major differences in baseline demographics and characteristics were observed between dose groups in the safety population (Table 1). In study 1, a total of five

Table 1. Demographics and baseline characteristics (safety population of each study)

					Race, n (%)			
	USL255 Dose, mg	N	Age, mean (range), year	Male, n (%)	White	African American	Asian	American Indian/Alaska Native
Study 1 (N = 30)	25	27	32.2 (18–60)	14 (52)	22 (81)	4 (15)	1 (4)	–
	50	27	32.4 (18–60)	14 (52)	22 (81)	4 (15)	1 (4)	–
	100	28	32.3 (18–60)	14 (50)	23 (82)	4 (14)	1 (4)	–
	200	27	32.9 (18–60)	13 (48)	23 (85)	3 (11)	1 (4)	–
	400	26	33.0 (18–60)	13 (50)	22 (84)	3 (12)	1 (4)	–
Study 2 (N = 50)	600	8	29.5 (22–37)	4 (50)	8 (100)	–	–	–
	800	8	27.0 (18–42)	5 (62.5)	8 (100)	–	–	–
	1,000	8	22.0 (19–29)	4 (50)	5 (62.5)	–	2 (25)	1 (12.5)
	1,200	8	23.3 (20–26)	4 (50)	6 (75)	–	–	2 (25)
	1,400	8	29.4 (21–43)	3 (37.5)	6 (75)	1 (12.5)	1 (12.5)	–
	Placebo	10	23.7 (20–29)	5 (50)	10 (100)	–	–	–

(17%) of the 30 participants randomized to treatment discontinued the study; four discontinued due to protocol violations and one elected to withdraw from further participation in the study (not due to an adverse event). As a result of these discontinuations, a total 27 of 30 participants received at least three doses in study 1. All participants received a single dose of USL255 in study 2 and completed the study.

Pharmacokinetic profile and consistency of USL255 exposure

Mean plasma topiramate concentrations over 14 days following a single dose of USL255 from 25 to 1,400 mg are presented in Figure 1. The 1,600 mg dose cohort was not initiated due to decreased tolerability observed with the 1,400 mg USL255 dose. Table 2 shows mean PK parameters for USL255 over the entire dose range. Topiramate

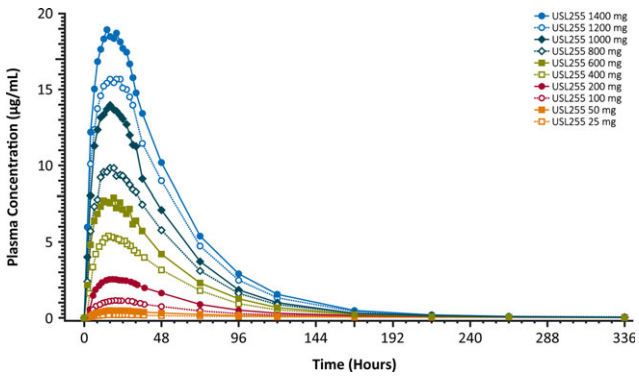

Figure 1.
Mean plasma topiramate concentrations after single-dose administration of USL255 25 to 1,400 mg. Pharmacokinetic data from five participants receiving 25 mg USL255 in study 1 were excluded from the summary statistics and statistical analyses due to predose topiramate concentrations >5% of C_{max}; all participants in study 2 had sufficient PK measurements for statistical analyses. See Table 2 for number of participants in each USL255 dosing group.

AUC and C_{max} increased with ascending doses of USL255. Mean $t_{1/2}$ generally decreased with increasing doses, ranging from 94.6 h (25 mg) to 56.6 h (1,400 mg). The median T_{max} for USL255 dosing groups ranged from 16 to 23 h.

After the initial increase in topiramate concentrations following dosing, USL255 displayed a consistent plasma concentration-time profile up to 24 h after each single dose, with plasma topiramate concentrations staying approximately constant between 10 and 24 h post dose (Fig. 2).

Dose proportionality and linearity of USL255

AUC was dose proportional over the entire dose range from 25 to 1400 mg, as the 90% CIs of the R_{dnm} values were contained within the range of 0.80–1.25 (AUC_{0-t} and $AUC_{0-\infty}$ R_{dnm} [90% CI] were 1.16 [1.09, 1.23] and 1.03 [0.98, 1.09], respectively). Linearity was observed for AUC_{0-t} and $AUC_{0-\infty}$ from 25 to 1,400 mg (F-statistic 0.86 and 0.51, respectively; $p > 0.05$ for both). Although not proportional over the entire 25–1,400 mg dose range, C_{max} was dose proportional from 50 to 1,400 mg by Hummel criteria (R_{dnm} [90% CI]: 1.56 [1.43, 1.71]) and linear from 50 to 1,400 mg (F-statistic 1.44; $p > 0.05$).

Intersubject and intrasubject variability

USL255 also demonstrated low intersubject and intrasubject variability in several PK parameters. Across both studies, intersubject %CV over the entire 25–1,400 mg dosing range was relatively low for AUC and C_{max} (overall mean [range] %CV: AUC_{0-t}, 20.2% [13.3–28.6%]; $AUC_{0-\infty}$, 19.6% [13.2–27.3%]; C_{max}, 22.4% [14.5–33%]). For participants who received at least three doses of USL255 in study 1, intrasubject %CV of dose-normalized mean AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} values were less than 14% (%CV: AUC_{0-t}, 10.8%; $AUC_{0-\infty}$, 8.2%; C_{max}, 13.2%).

Safety and tolerability

In study 1, 17 (56.7%) of 30 participants receiving at least one dose of USL255 experienced a TEAE. Generally, an

Table 2. Pharmacokinetic Parameters of USL255

	USL255 Dose, mg	n	AUC_{0-t}, mean (SD), μg h/ml	$AUC_{0-\infty}$, mean (SD), μg h/ml	C_{max}, mean (SD), μg/ml	T_{max}, median (range), hr	$t_{1/2}$ mean (SD), hr
Study 1 (N = 30)	25	22[a]	18.6 (5.3)	20.4 (5.58)	0.20 (0.07)	20 (8–32)	94.6 (23)
	50	27	40.6 (8.9)	43.2 (9.12)	0.51 (0.13)	18 (10–36)	92.2 (19.5)
	100	28	84.3 (19.4)	87.2 (19.5)	1.23 (0.34)	23 (12–32)	86.5 (18.2)
	200	27	174 (40.9)	175 (40.2)	2.78 (0.62)	18 (10–30)	76.6 (13.1)
	400	26	340 (71.0)	343 (69.4)	5.79 (1.34)	16 (8–36)	71.1 (9.8)
Study 2 (N = 50)	600	8	479 (86.8)	465 (77.5)	8.34 (1.62)	18 (10–32)	72.7 (14)
	800	8	608 (84.6)	613 (84.7)	10.6 (1.56)	17 (10–36)	80.3 (16.3)
	1,000	8	789 (105)	805 (106)	14.7 (2.13)	18 (10–26)	56 (5.6)
	1,200	8	965 (154)	970 (153)	16.6 (3.33)	18 (10–24)	69.7 (11.6)
	1,400	8	1,121 (257)	1,124 (257)	19.7 (4.52)	20 (14–26)	56.6 (9.9)

AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal elimination half-life.

[a]Pharmacokinetic data from five participants were excluded from the summary statistics and statistical analyses due to predose TPM concentrations >5% of C_{max}.

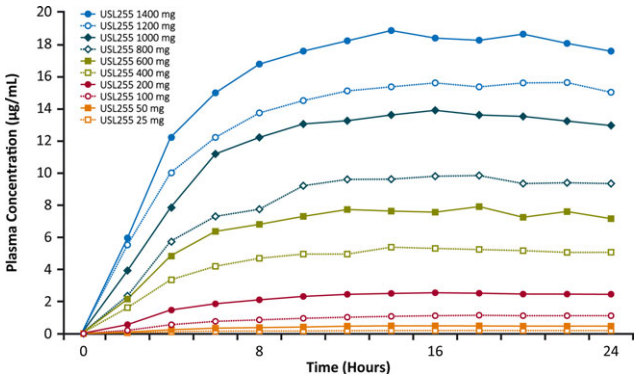

Figure 2.
Mean plasma topiramate concentrations from 0 to 24 h after single-dose administration of USL255 25–1,400 mg. Pharmacokinetic data from five participants receiving 25 mg USL255 in study 1 were excluded from the summary statistics and statistical analyses due to predose topiramate concentrations >5% of C_{max}; all participants in study 2 had sufficient PK measurements for statistical analyses. See Table 2 for number of participants in each USL255 dosing group.
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increasing number of participants reported TEAEs with each increasing dose (11% for 25 mg USL255 up to 46% for 400 mg USL255). In study 2, 39 (78%) of participants receiving USL255 or placebo experienced at least one TEAE. MTD was declared as 1,200 mg after a single individual reported 16 mild-to-moderate treatment-related AEs following a single dose of USL255 1,400 mg. Within 24 h after dosing, the participant experienced elevated blood pressure, facial numbness, difficulty concentrating, dysphasia, an unsteady gait, numbness in legs, and headache; each AE lasted from one to 8 days. For both studies, most TEAEs were deemed by the investigator as treatment related and mild in intensity, with no severe AEs, SAEs, or deaths reported in either study. Furthermore, no participants withdrew from either study due to AEs.

To compare the incidence of adverse events across the two studies, TEAEs were normalized to the number of participants in each dosing group. The mean number of TEAEs increased with ascending doses (Fig. 3). The most commonly reported TEAEs (>10% of overall participants in either study) were classified as nervous system and gastrointestinal disorders (Table 3).

There were no clinically significant vital signs or physical examination findings in either study. No significant changes from baseline in ECG recordings were observed at any dose of USL255, and no individual hematology, serum chemistry, or urinalysis abnormalities were considered clinically

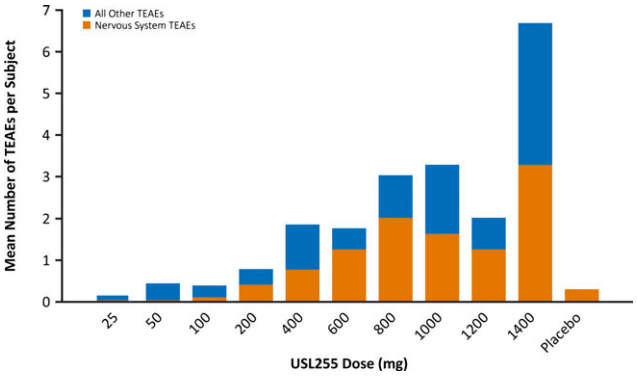

Figure 3.
Treatment-emergent adverse events after single-dose administration of USL255, normalized per dosing group. The large number of normalized TEAEs after dosing USL255 1,400 mg was due largely to multiple AEs in a single participant. See Table 1 for number of participants in each dosing group.
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Table 3. Summary of TEAEs with an incidence of >10% USL255 participants in either study

	Study 1[a] N = 30	Study 2[a] N = 50	
n (%)	25–400 mg USL255 (N = 30)	600–1400 mg USL255 (n = 40)	Placebo (n = 10)
Participants with ≥1 TEAE	17 (57)	37 (92)	2 (20)
Nervous system disorders			
Dizziness	6 (20)	23 (58)	0
Paresthesia	8 (27)	13 (32)	0
Headache	8 (27)	10 (25)	2 (20)
Disturbance in attention	3 (10)	8 (20)	0
Hypoesthesia	0	5 (12)	0
Gastrointestinal disorders			
Nausea	5 (17)	5 (12)	0
Paraesthesia oral	0	5 (12)	0

[a]Participants in study 1 received up to five single doses of USL255; participants in study 2 each received a single USL255 dose.

significant or reported as AEs in either study, other than increases in alanine and/or aspartate aminotransferase (ALT and AST) values in two study 1 participants, which were not accompanied by changes in bilirubin. One participant had prolonged elevation in AST levels (1.5–2× the upper limit of normal [ULN]) reported as an AE, but was not considered clinically significant by the investigator. Another participant in study 1, who discontinued due to noncompliance (positive opiate test), had increased ALT (1.4× ULN) and AST (1.1× ULN) values at early termination reported as mild AEs; 4 days after early termination, ALT and AST values were 4.5× and 2.6× ULN, respectively, which were deemed clinically significant.

Discussion

Presented here are two studies in which the PK, MTD, safety, and tolerability profiles of USL255, once-daily XR topiramate, were evaluated over a wide dose range. Consistent with trends observed following dosing of TPM-IR from 100 to 1,200 mg,[25] topiramate AUC and C_{max} increased with ascending doses of USL255 and were dose proportional from 25–400 mg and 50–1,400 mg, respectively. The establishment of dose proportionality aids in predicting the effects of dose titration and adjustment, which is important in determining optimal AED doses for patients with epilepsy. The T_{max} for USL255 following single-dose administration was increased compared with TPM-IR (16–23 h [this study] versus ~1 h[17]), as would be expected for an XR formulation. However, this difference in T_{max} is greatly reduced following dosing at steady state (6 h USL255 vs. 1 h TPM-IR[18]). Mean $t_{1/2}$ generally decreased with increasing doses, a trend also observed for TPM-IR, and is likely due to saturable high-affinity binding of topiramate to RBC carbonic anhydrase.[15] Topiramate binding to carbonic anhydrase may also explain the slight deviations from dose proportionality observed for C_{max} at the lowest doses, which have been observed in previous studies with TPM-IR doses below 200 mg.[25]

Extended-release formulations of AEDs, such as USL255, are designed to maintain relatively constant plasma drug concentrations over extended periods. In contrast to TPM-IR, which displays a rapid rise to C_{max} followed by a steep decrease in plasma concentrations 1–2 h after twice-daily dosing,[18] plasma topiramate concentrations after each single-dose administration of USL255 remained relatively constant over the 24-h dosing interval, with a slower rise to C_{max} following dosing. The smooth PK profile presented here is supported by steady-state data from a previous study in which USL255 displayed a 26% reduction in fluctuation index ($[C_{max} - C_{min}]/C_{avg} \times 100$) compared with TPM-IR.[18] Because adverse effects of AEDs are often concentration dependent,[9] the consistent plasma concentrations of USL255 may help minimize adverse effects. This has been observed with other XR AEDs, in which improved tolerability has been demonstrated after conversion from IR formulations.[11,26]

The consistency in USL255 exposure is further demonstrated by the relatively low values for intersubject and intrasubject variability. Intersubject variability, defined as the variability in exposure from one patient to another when administered the same dose, is an important indicator of how efficacy and safety may vary from patient to patient.[27] For USL255, mean intersubject variability %CV values for AUC (19.6% [$AUC_{0-\infty}$]; 20.2% [AUC_{0-t}]) and C_{max} (22.4%) were within values calculated for other XR AEDs, which range from 12 to 20% and 12.5 to 34%, respectively.[28–33]

In addition, it is important to evaluate intrasubject variability—the variation in plasma drug levels within the same individual—as these estimations are an important measure of how plasma concentrations may vary in the

same patient from day-to-day. Although no reports in the literature of comparable study design were found (e.g., evaluation of an AED in the same individual over ascending doses), values observed for USL255 intrasubject %CV of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were low at 10.8%, 8.2%, and 13.2%, respectively, which confirms the consistency and predictability of USL255 exposure over time. Due to the limitations of the study design, dose-normalization of AUC and C_{max} values were required for these analyses.

Taken together, the dose proportionality and low variability observed in these studies suggest that USL255 will provide consistent plasma topiramate levels over an extended-dosing interval, with the potential for improved treatment compliance, fewer peak-effect AEs, and possibly fewer break through seizures. This XR formulation should result in predictable changes in plasma drug levels when adjusting a patient's dosage. Overall, the favorable safety profile and consistent, predictable pharmacokinetics suggest that USL255 may be a useful treatment option for patients with epilepsy.

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Disclosure or Conflict of Interest

Drs. Clark, Braun, and Halvorsen are employees of Upsher-Smith Laboratories, Inc. Dr. Cloyd earns consulting income from Upsher-Smith Laboratories, Inc., the company sponsoring this research. This interest has been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policies. In addition, within the last 3 years, he has received speaker, grant, or consultancy support from Allergan, Neurelis, Lundbeck, CyDex, Xeris, Medtronic, Sunovion, Ikano, Glaxo, UCB, and Valeant. Ms. Johnson has no conflict of interest to disclose. We, the authors, confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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