FULL-LENGTH ORIGINAL RESEARCH

Once-daily USL255 as adjunctive treatment of partial-onset seizures: Randomized phase III study

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Summary

Objective: **To evaluate the efficacy and safety of USL255, Qudexy™ XR (topiramate) extended-release capsules, as an adjunctive treatment for refractory partial-onset seizures (POS) in adults taking one to three concomitant antiepileptic drugs.**

Methods: **In this global phase III study (PREVAIL; NCT01142193), 249 adults with POS were randomized 1:1 to once-daily USL255 (200 mg/day) or placebo. The primary and key secondary efficacy endpoints were median percent reduction in weekly POS frequency and responder rate (proportion of patients with ≥50% reduction in seizure frequency). Seizure freedom was also assessed. Safety (adverse events, clinical and laboratory findings), as well as treatment effects on quality of life (QOLIE-31-P) and clinical global impression of change (CGI-C), were evaluated.**

Results: **Across the entire 11-week treatment phase, USL255 significantly reduced the median percent seizure frequency and significantly improved responder rate compared with placebo. Efficacy over placebo was observed early in treatment, in patients with highly refractory POS, and in those with the most debilitating seizure types (i.e., complex partial, partial secondarily generalized). USL255 was safe and generally well tolerated with a low incidence of neurocognitive adverse events. USL255 was associated with significant clinical improvement without adversely affecting quality of life.**

Significance: **The PREVAIL phase III clinical study demonstrated that once-daily USL255 (200 mg/day) significantly improved seizure control and was safe and generally well tolerated with few neurocognitive side effects.**

KEY WORDS: **Epilepsy, Topiramate, Antiepileptic drug, Extended release.**

Treatment nonadherence is common among patients with epilepsy[1] and can increase seizures, adversely affect quality of life (QoL),[2] and increase epilepsy-related health care costs.[3] A number of factors may contribute to nonadherence including side effects, frequent daily dosing, and cost. Compared with immediate-release (IR) antiepileptic drugs (AEDs), extended-release (XR) formulations reduce fluctuations in drug plasma concentrations, which may mitigate adverse events (AEs) caused by peak-dose toxicity or alleviate breakthrough seizures that can occur at trough concentrations.[4,5]

Immediate-release topiramate (TPM-IR) is a broad-spectrum, well-established AED with multiple mechanisms of action.[6] TPM-IR is approved in many countries as an adjunctive treatment for partial-onset seizures (POS) or primary generalized tonic–clonic (PGTC) seizures in adults

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and children. The maintenance TPM-IR dosage of 200–400 mg/day is administered as a divided dose. USL255, Qudexy XR (topiramate) extended-release capsules (Upsher-Smith, Maple Grove, MN, U.S.A.), is a proprietary once-daily XR topiramate formulation that was developed using a coated-bead technology to deliver consistent drug release over a 24 h dosing interval.[7] USL255 provides plasma topiramate exposure equivalent to TPM-IR with a significantly lower maximum concentration (C_{max}) and higher minimum concentration (C_{min}), leading to decreased fluctuations in drug plasma concentrations.[8,9] In addition, USL255 maintains the therapeutic minimum topiramate concentrations achieved by TPM-IR following a formulation switch.[9] USL255 was recently approved by the U.S. Food and Drug Administration (FDA; 11 March 2014) as initial monotherapy in patients ≥10 years of age with POS or PGTC seizures and adjunctive therapy in patients ≥2 years of age with POS, PGTC, or seizures associated with Lennox-Gastaut syndrome.[10] Presented here are the efficacy, safety, and tolerability results from the global phase III PREVAIL study of once-daily USL255 for the adjunctive treatment of refractory POS.

Methods

Trial conduct

PREVAIL was conducted between May 2010 and December 2012 at 66 centers in 16 countries (Argentina, Australia, Belgium, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, and the United States). This study was conducted in accordance with the International Conference on Harmonization (ICH) E6, Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. Institutional review boards and ethics committees supervised and safeguarded the rights, safety, and well-being of all study participants. Prior to randomization, all patients provided written informed consent.

Patients

Adults (18–75 years) diagnosed with refractory POS, with or without secondary generalization, for ≥1 year based on the International League Against Epilepsy (ILAE) classification[11] were eligible. They must have had ≤21 consecutive seizure-free days and ≥8 POS during the 8-week baseline period. Only seizures classified as simple partial with motor signs, complex partial, or partial with secondary generalization qualified patients to meet inclusion criteria; however, patients could have >1 seizure type. To ensure that seizures were classified correctly at study centers, a seizure-training and review program developed by The Epilepsy Study Consortium was utilized.[12] Investigators/study center coordinators were trained using a seizure identification video and required to pass an interactive quiz. Each site submitted a Seizure Identification Form (SIF) for all patients, which included patient and/or caregiver seizure descriptions and the investigator's classification(s) of seizure(s). SIFs were reviewed independently by The Epilepsy Study Consortium immediately after the screening visit and approved prior to patient randomization; misclassifications were communicated to the study team to allow for investigator/coordinator retraining, and correction of seizure classification prior to the first dose of study medication.

Patients must have been on a stable dosing regimen of one to three AEDs for ≥4 weeks (or ≥12 weeks for phenobarbital and primidone) prior to visit 1 (screening). Vagus nerve stimulation (VNS) was considered an AED and must have been in place for ≥6 months and on a stable setting for ≥1 month prior to visit 1. Benzodiazepine use was not allowed during the trial, except in the event of seizure emergency. Benzodiazepines taken more than once per week for any indication, or taken as rescue medication for a prolonged convulsive seizure, were counted as an AED.

Exclusion criteria included any predisposing condition or medication that might interfere with the absorption of USL255 (e.g., Crohn's disease, ileostomy, short bowel syndrome), psychogenic nonepileptic seizures, status epilepticus, or seizure episodes lasting <30 min (in which several seizures occurred with such frequency that the initiation and completion of each individual seizure could not be distinguished), within 3 months prior to visit 1, a history of metabolic acidosis, nephrolithiasis, ureterolithiasis, or narrow angle glaucoma, or a history of suicidal attempts, suicidal ideation, or uncontrolled psychiatric illness within 2 years of visit 1. In addition, patients currently or formerly taking felbamate (within 18 months) or vigabatrin were excluded, as were patients who had taken topiramate within 6 months, had a history of lack of efficacy to topiramate for epilepsy despite adequate exposure (200 mg/day), or had a history of safety or tolerability issues with topiramate not related to dosage titration.

Study design

PREVAIL was a phase III, randomized, double-blind, parallel-group study consisting of baseline (8 weeks), titration (3 weeks), and maintenance (8 weeks) phases. The 11-week treatment phase (titration + maintenance) was followed by downtitration or entry into a 1-year open-label extension (OLE) study (NCT01191086).

Eligible patients were randomized 1:1 to once-daily USL255 or matching placebo. Randomization by an independent statistician was generated using permuted blocks with a block size of 4 without stratification (SAS 9.1.3, SAS Institute Inc., Cary, NC, U.S.A.). The interactive voice response group programmed the randomization schedule for investigators to dispense study drug. Treatment remained blinded throughout the study. Titration occurred in 50 mg/week increments to maintenance dosage of 200 mg/day. Patients were discontinued if they were unable to tolerate any dosage of USL255. At the end of maintenance, patients not entering the OLE were downtitrated by

50 mg/week for 3 weeks. Dosing of study medication was permitted any time during the day, as long as dosing remained consistent throughout the study. VNS settings and concomitant AED dosing were to remain unchanged throughout the course of the study.

Assessments

The primary efficacy endpoint was median percent reduction from baseline in weekly POS frequency during the double-blind phase. The key secondary endpoint was responder rate (proportion of patients with ≥50% reduction from baseline in weekly POS frequency). A priori analyses of these endpoints by study phase (titration vs. maintenance) were also performed, as well as post hoc analyses evaluating the first and last 4 weeks of the maintenance phase. Additional post hoc analyses included efficacy by seizure type (seizure-type groups were not mutually exclusive), number of concomitant AEDs during the trial (1, 2, ≥3 AEDs), and trial week. Seizure freedom (exploratory endpoint) was determined by evaluating the proportion of patients with 100% reduction in seizure frequency during treatment (titration plus maintenance) and during maintenance alone, as well as by post hoc evaluation of the number of patients demonstrating ≥21 days with no seizures prior to the last dose of study drug. Clinical-status assessments included the clinician-reported Global Impression of Change (CGI-C) and the patient-reported Quality of Life in Epilepsy–Problems (QOLIE-31-P) survey. A post hoc analysis of the number of patients at end of maintenance with CGI-C scores corresponding to improvement (scores of 1 [very much improved], or 2 [much improved]) was performed.

Safety and tolerability were assessed by evaluating treatment-emergent adverse events (TEAEs), laboratory parameters, vital signs, physical and neurologic examinations, and 12-lead electrocardiography (ECG). TEAEs were analyzed over the treatment period (a priori) and by study phase (post hoc; titration, maintenance, first 4 weeks and last 4 weeks of maintenance). Suicidality was monitored using the Columbia-Suicide Severity Rating Scale (C-SSRS). Treatment adherence, defined as the ratio of number of doses taken to the number of doses that should have been taken based on duration of treatment (days), was calculated based on the number of unused capsules returned at each visit.

Statistical analyses

To detect an 18% treatment difference with 91% power using Wilcoxon rank-sum test (WRST), a sample size of 118 patients/treatment arm was estimated.

Safety and tolerability analyses were performed using all patients who received ≥1 dose of study drug. Efficacy analyses were performed using the intent-to-treat (ITT) population (all patients who received ≥1 dose of study drug and had ≥1 evaluable postrandomization diary entry). For the primary efficacy endpoint, WRST was used to evaluate the effects of treatment as nonnormal distribution of data was expected. The treatment difference and 95% confidence interval (CI) were calculated using asymptotic Hodges-Lehmann methods. Differences between treatment groups in the key secondary endpoint were assessed using the Fisher's exact test. The treatment difference and 95% CI for the responder rate were calculated using exact unconditional method. Subgroup analyses of the primary and key secondary endpoint were evaluated using WRST and Fisher's exact test, respectively. For the post hoc by-week analysis of the primary efficacy outcome, seizure rates were calculated during each consecutive 7-day interval within the titration and maintenance phases, and USL255 and placebo-treated patients were compared using the WRST. Differences between treatment groups in the number of patients achieving 100% reduction in seizure frequency were assessed using Fisher's exact test for the treatment phase (titration plus maintenance) and for the maintenance phase alone. Percentages of patients who were seizure-free for ≥21 days prior to the last dose of study drug were estimated using a Kaplan-Meier analysis, with differences between treatment groups assessed using the log-rank test.

Changes from baseline to the end of maintenance phase in QOLIE-31-P survey (each domain and overall) were evaluated using an analysis of covariance (ANCOVA) model controlling for geographic region with the baseline score as a covariate. Treatment effect on the CGI-C score was assessed using an analysis of variance (ANOVA) model, where the CGI-C score was the response variable and treatment and geographic region were fixed effects. For the post hoc analysis of CGI-C scores corresponding to improvement, treatment groups were compared with the Fisher's exact test.

For safety/tolerability assessments, TEAEs were summarized by frequency, treatment relatedness, and maximum severity, as well as by study phase (titration vs. maintenance); changes from baseline in vital signs, physical examinations, and ECG studies were summarized. Normal-range shift tables of laboratory data were generated using the Bowker test of symmetry.[13] Change from baseline to the last postbaseline weight measurement was summarized by treatment group, and the difference in the change from baseline in weight was analyzed using ANCOVA.

Results

Baseline demographics, patient disposition, and medication adherence

All 249 randomized patients were included in the safety and ITT populations (n = 124 USL255; n = 125 placebo). Most patients completed PREVAIL (87%) and less than 10% in either treatment group discontinued due to AEs (Fig. 1). Mean treatment adherence was high in both treatment groups (99% USL255; 100% placebo).

Baseline demographics and clinical characteristics were similar between the treatment groups (Table 1). The median

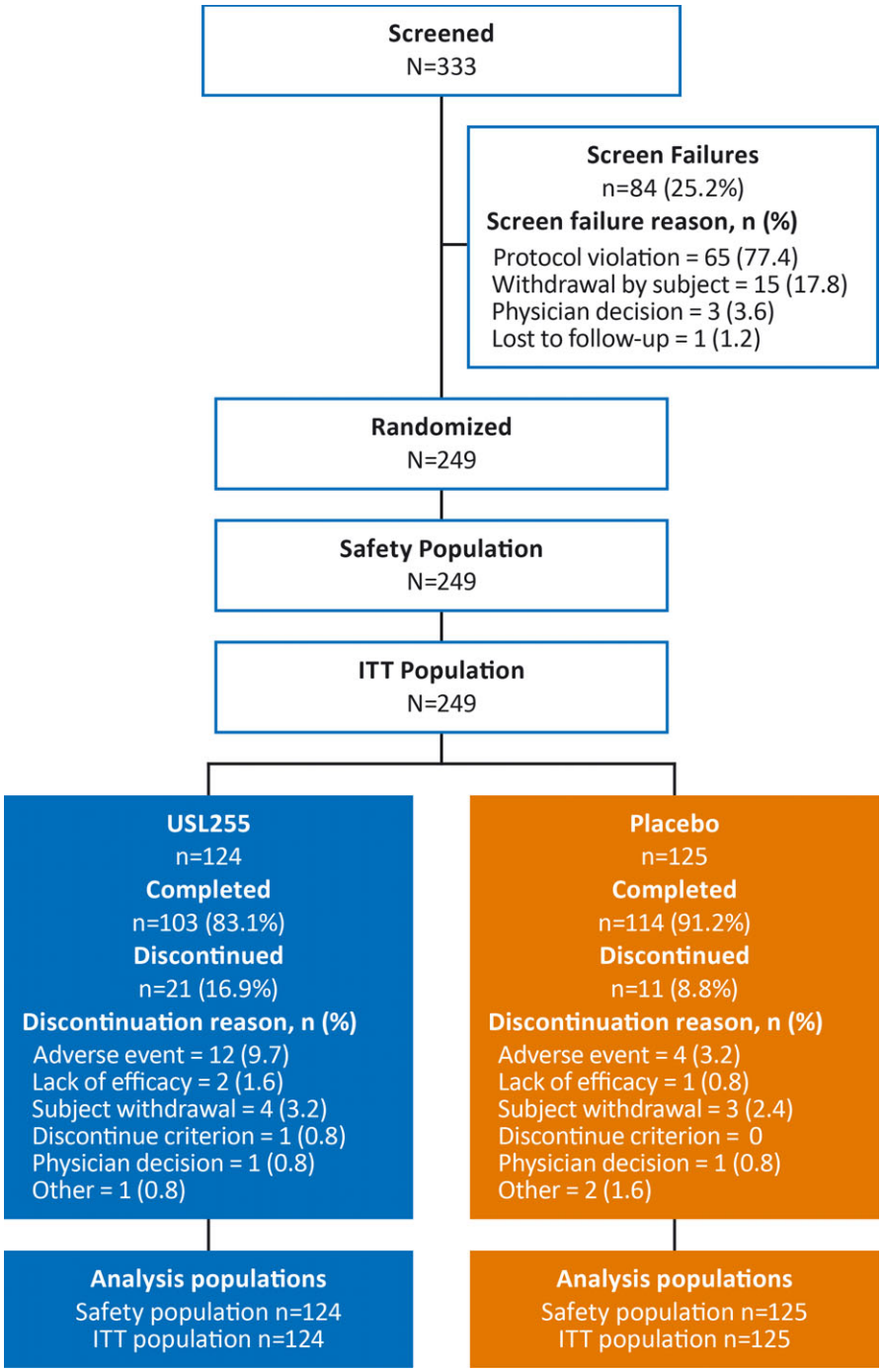

Figure 1.
Study flow.
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duration of epilepsy was approximately 20 years, and 20% of the overall population had taken ≥7 lifetime AEDs. At baseline, all patients were receiving three or fewer concomitant AEDs. During the trial, the use of benzodiazepines by three patients (2.4%) in the placebo group (who were already taking three concomitant AEDs) was counted as a fourth AED (Table 1). Seizure misclassifications in PREVAIL were low (3.6%), as only 11 of the 308 baseline SIFs reviewed by The Epilepsy Study Consortium had misclassified seizures that had to be corrected.[12]

Efficacy—primary and key secondary endpoints

During 11 weeks of double-blind treatment (3-week titration plus 8-week maintenance), the median percent

Table 1. Demographic and baseline characteristics (ITT population)

Characteristics	USL255 n = 124	Placebo n = 125	Total n = 249
Age, mean (SD), year	37.6 (11.0)	37.6 (11.1)	37.6 (11.0)
Age range, n (%), year			
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)
Male, n (%)	66 (53.2)	66 (52.8)	132 (53.0)
Race, n (%)			
White	107 (86.3)	107 (85.6)	214 (85.9)
Asian	9 (7.3)	7 (5.6)	16 (6.4)
Black or African American	1 (0.8)	4 (3.2)	5 (2.0)
Native Hawaiian/Pacific Islander	1 (0.8)	1 (0.8)	2 (0.8)
Other	6 (4.8)	6 (4.8)	12 (4.8)
Weight, mean (SD), kg	75.6 (19.1)	74 (18.1)	74.8 (18.6)
Duration of epilepsy,[a] mean (SD), year	20.9 (13.7)	20 (13.1)	20.4 (13.4)
Baseline weekly POS frequency, median (range)	2.3 (1 – 298)	2.7 (0.9–37)	2.5 (0.9–298)
Seizure types observed during baseline, n (%)[b]			
Complex partial	106 (85.5)	103 (82.4)	209 (83.9)
All secondarily generalized	51 (41.1)	50 (40.0)	101 (40.6)
Simple partial without motor signs	18 (14.5)	27 (21.6)	45 (18.1)
Simple partial with motor signs	22 (17.7)	20 (16.0)	42 (16.9)
Other	1 (0.8)	0	1 (0.4)
Number of concomitant AEDs during the trial, n (%)			
1 AED	23 (18.5)	37 (29.6)	60 (24.1)
2 AEDs	68 (54.8)	50 (40.0)	118 (47.4)
≥3 AEDs[c]	33 (26.6)	38 (30.4)	71 (28.5)
Number of lifetime AEDs, n (%)			
≤3	65 (52.4)	49 (39.2)	114 (45.8)
4–6	38 (30.6)	48 (38.4)	86 (34.5)
≥7	21 (16.9)	28 (22.4)	49 (19.7)

SD, standard deviation.
[a]Duration of epilepsy is computed as year of diagnosis to year of screening.
[b]In descending order; patients could report >1 seizure type.
[c]All patients were receiving three or fewer concomitant AEDs at baseline. During the trial, the use of benzodiazepines by 3 (2.4%) patients in the placebo group (who were already taking three concomitant AEDs) was considered a fourth AED.

reduction from baseline in weekly POS frequency was significantly greater in the USL255 group than the placebo group (39.5% vs. 21.6%; $p < 0.001$; Fig. 2A). Using asymptotic Hodges-Lehmann methods, this corresponds to a median treatment difference of 18.5% (95% CI 8.53–28.1). Similarly, a significantly greater proportion of USL255-treated patients had a ≥50% reduction in weekly POS seizure frequency compared with placebo-treated patients (37.9% vs. 23.2%; $p = 0.013$; Fig. 2B) during the treatment phase. Median treatment difference between USL255 and placebo responder rates was 14.7% (95% CI 2.05–26.5).

When evaluating efficacy by study phase, significant reductions in seizure frequency with USL255 compared with placebo were observed during the 3-week titration and 8-week maintenance phases separately, as well as within the first 4 weeks and last 4 weeks of maintenance (Table 2). Median POS frequency was reduced significantly as early as week 1 with USL255 (when patients were receiving 50 mg/day) compared with placebo (28.6% vs. 9.2%, $p = 0.02$; Fig. 3). Reductions in POS frequency continued to be observed with USL255 in subsequent weeks (Fig. 3). The responder rate was also significantly greater with USL255 treatment compared with placebo in the titration and maintenance phases, as well as within the first 4 weeks and last 4 weeks of maintenance (Table 2).

Efficacy by seizure type and concomitant AED use

In patients who experienced complex partial or partial seizures with secondary generalization, USL255 (n = 119) significantly reduced weekly seizure frequency (40.6% vs. 17.7%; $p < 0.001$) and was associated with a higher responder rate (42.0% vs. 20.9%; $p = 0.001$) compared with placebo (n = 115). USL255 demonstrated similar trends for patients experiencing simple partial seizures (SPS) with motor signs, although the sample size was small (Table 1). For patients with SPS with motor signs in USL255 (n = 22) and placebo (n = 20) groups, the median percent reductions were 45.6% versus 38.8% ($p = 0.496$) and responder rates were 45.5% versus 30.0% ($p = 0.497$). In the analysis of

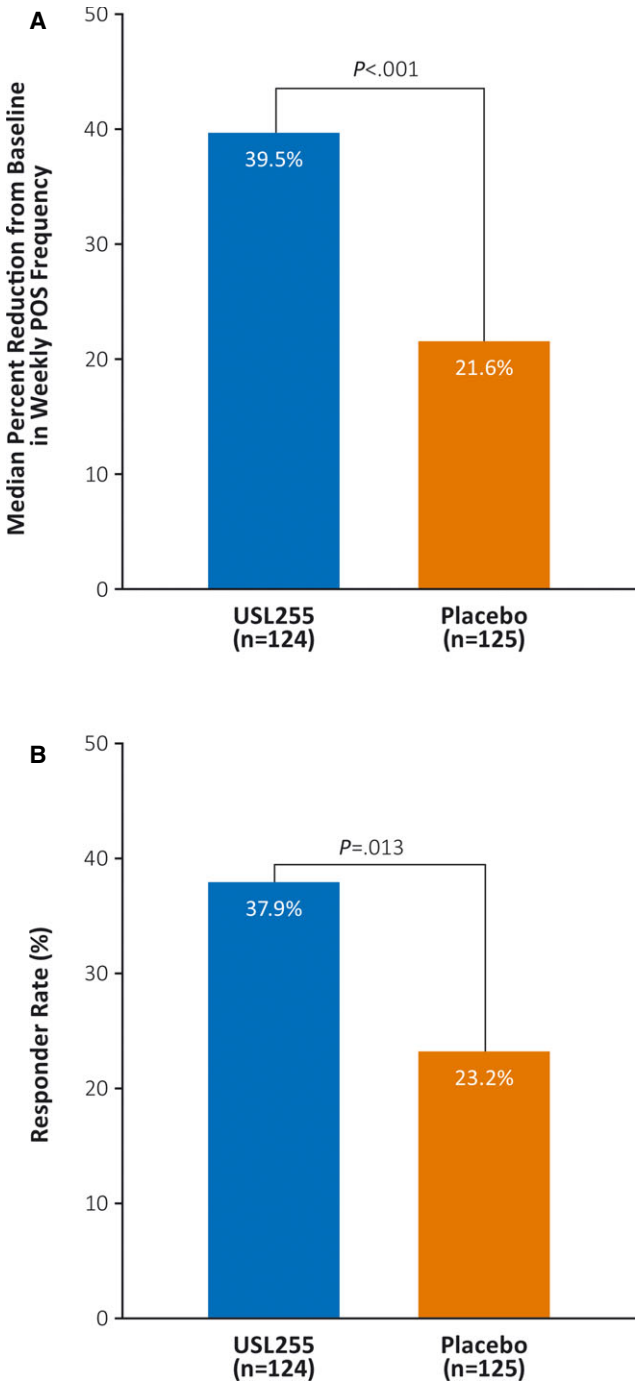

Figure 2.
Median percent reduction from baseline (**A**) and 50% responder rate (**B**) for weekly seizure frequency (ITT population).
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efficacy by number of concomitant AEDs (1, 2, ≥3), USL255 treatment resulted in greater median percent POS reduction versus placebo in all groups, and there was a significant difference in patients taking ≥3 AEDs (52.8% [n = 33] vs. 11.4% [n = 38], p < 0.001). Similarly, responder rate was significantly greater in USL255-treated patients taking ≥3 concomitant AEDs compared with placebo (57.6% vs. 13.2%, p < 0.001).

Efficacy—seizure freedom

In the ITT population, a greater percentage of USL255-treated patients were seizure-free (100% reduction in weekly seizure frequency) during treatment (titration plus maintenance) than placebo-treated patients (3.2% [4/124] vs. 1.6% [2/125]), although this difference was not significant. A similar trend was observed during the maintenance phase alone (7.1% [n = 8/124] USL255 vs. 3.3% [n = 4/125] placebo). In addition, the percentage of USL255-treated patients who were seizure-free for ≥21 days prior to the last dose of study drug was significantly increased compared with placebo (16.1% [n = 20/124] vs. 5.6% [n = 7/125], p = 0.006).

Efficacy—QOLIE-31-P and CGI-C scales

The overall mean score for patients who were administered the QOLIE-31-P (USL255, 5.2 [n = 100]; placebo, 4.5 [n = 108]) was not significantly different between treatment groups; however, significant improvements in one subscale (Seizure Worry) were observed in the USL255-treated group compared with placebo (14.1 vs. 4.1, p < 0.001). The remaining subscales (Energy, Emotions, Daily Activities, Mental Activities, Medical Effects, and Overall Quality of Life), many of which can be influenced by medication effects, showed no significant differences between USL255-treated and placebo-treated patients.

Of the 243 patients for whom CGI-C data were collected, improved clinical status was observed in USL255-treated patients (n = 119), as the overall mean CGI-C score was significantly lower (2.9 vs. 3.5; p < 0.001) compared with placebo (n = 124). Consistent with the overall score, the percentage of USL255-treated patients with CGI-C scores corresponding to improvement (scores of 1 [very much improved], or 2 [much improved]) was nearly double that of placebo-treated patients (37.8% vs. 19.4%; p = 0.002).

Safety and tolerability

Over the course of the study, <10% of patients in each treatment group discontinued due to a TEAE. In both treatment groups, the only TEAEs that led to discontinuation in >1 subject were somnolence (USL255 n = 2; placebo n = 0) and disturbance in attention (USL255 n = 2; placebo n = 1). Over the 11-week treatment period, a significantly greater number of USL255-treated patients (66%) reported ≥1 TEAE versus placebo (50%; p = 0.015). The majority of TEAEs were mild-to-moderate in intensity, with low occurrence of severe AEs (Table 3). The six TEAEs reported in ≥5% of patients in any treatment group are listed in Table 3. Of these TEAEs, somnolence, paraesthesia, and weight decrease were ≥2% higher with USL255 treatment versus placebo. Headache was the only TEAE reported more often in placebo-treated patients. During the 3-week titration

Table 2. Efficacy by treatment phase (ITT population)

	Seizure reduction,[a] %			Responder rate,[b] %		
	USL255 n = 124	Placebo n = 125	p Value	USL255 n = 124	Placebo n = 125	p Value
Titration	33.9	8.6	<0.001	33.9	17.6	0.007
Maintenance						
Overall	45.7	22.1	0.001	44.2	30.8	0.048
First 4 weeks	46.9	28.5	0.002	47.8	34.2	0.045
Last 4 weeks	48.5	26.7	0.002	46.2	29.3	0.012

[a]Median percent reduction from baseline in weekly partial-onset seizure frequency.
[b]Proportion of patients with ≥50% reduction from baseline in weekly partial-onset seizure frequency.

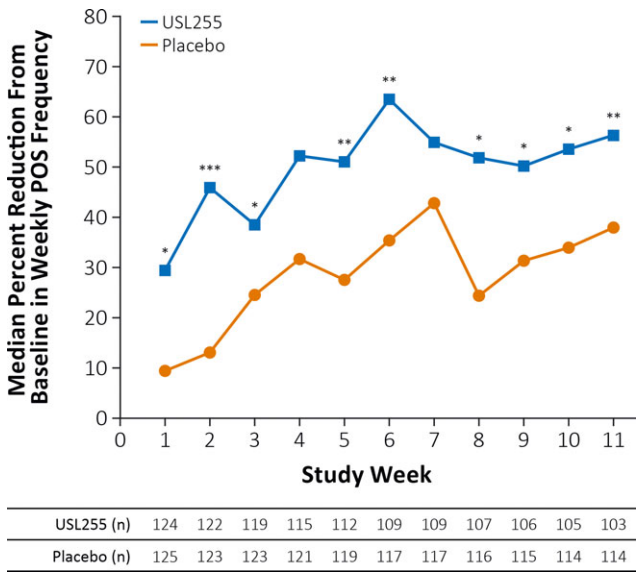

Figure 3.
Median percent reduction from baseline in seizure frequency by study week. *Indicates $p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
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phase, a greater proportion of USL255-treated patients experienced a TEAE compared with placebo (50.0% [n = 124] vs. 31.2% [n = 125]). During the 8-week maintenance phase, the incidence of TEAEs for USL255 (40.7% [n = 113]) was lower than in the titration phase, while remaining relatively unchanged for the placebo group (33.3% [n = 120]). When evaluating maintenance phase time intervals comparable to the length of the titration phase, the treatment difference between USL255 and placebo was greatly reduced; the incidence of TEAEs for USL255 approached that of placebo in the first 4 weeks (26% USL255 [n = 113] vs. 24% placebo [n = 120]) and last 4 weeks (21% USL255 [n = 107] vs. 17% placebo [n = 117]) of maintenance. The proportion of USL255-treated patients reporting ≥1 TEAE generally increased with increasing numbers of concomitant AEDs, a trend not observed with placebo.

Neurocognitive and neuropsychiatric TEAEs, such as memory impairment or psychomotor slowing, were reported in <3% of patients for each AE in both treatment groups, with the exception of disturbance in attention (2.4% USL255; 3.2% placebo). No deaths were reported during the study, and none of the serious AEs reported in the USL255-treatment group (lobar pneumonia and physical assault) were considered treatment related.

Although more USL255 patients experienced decreased serum bicarbonate and corresponding increases in serum chloride levels, shifts from baseline were generally within reference ranges and not unexpected, as variations in serum chemistry parameters can occur with topiramate use. Topiramate has been associated with secondary angle closure glaucoma within the first 2 weeks of treatment, which was not observed in this trial.[14] Additional safety concerns associated with long-term topiramate use include metabolic acidosis, kidney stones, decreased sweating, and increased body temperature,[6] none of which were observed in PREVAIL, although the length of this study may preclude their detection. Although there was a statistically significant decrease in mean body weight with USL255 compared with placebo at last observation (−1.87 kg vs. −0.04 kg; $p < 0.001$), this was commensurate with decreases reported for TPM-IR.[6] No significant changes were observed in physical or neurologic examinations, hematology or urinalysis; no effects on cardiac function (12-lead ECG studies) were observed for either USL255 or placebo.

Although no subject in the USL255 treatment group experienced suicidal behavior, one subject experienced a single event of suicidal ideation. In the placebo group, one subject reported two types of suicidal behavior (preparatory acts/behavior and suicidal behavior), and three patients experienced a total of six suicidal ideations.

Discussion

The results of this double-blind, randomized, placebo-controlled PREVAIL study demonstrate that once-daily USL255 200 mg/day is an effective adjunctive treatment for reducing the frequency of POS (with or without secondary generalization) in patients with refractory epilepsy. As an adjunctive treatment, USL255 reduced weekly median seizure frequency by approximately 40% during the

Table 3. Treatment-emergent adverse events reported in the 11-week treatment phase (ITT population)

	USL255 n = 124	Placebo n = 125
Patients with ≥1 TEAE	82 (66.1)	63 (50.4)[a]
Patients with ≥1 treatment-related TEAE[b]	64 (51.6)	39 (31.2)
TEAE leading to discontinuation	11 (8.9)[c]	5 (4.0)[d]
Patients reporting any SAE	2 (1.6)[e]	2 (1.6)
Intensity of TEAEs		
Mild	47 (37.9)	35 (28.0)
Moderate	27 (21.8)	22 (17.6)
Severe	8 (6.5)	6 (4.8)
TEAEs reported in ≥5% of patients in any treatment group		
Somnolence	15 (12.1)	3 (2.4)
Dizziness	9 (7.3)	7 (5.6)
Paraesthesia	8 (6.5)	3 (2.4)
Weight decreased	8 (6.5)	0
Fatigue	7 (5.6)	6 (4.8)
Headache	5 (4.0)	7 (5.6)

SAE, serious adverse event, TEAE, treatment-emergent adverse event.
Data reported as n (%). Adverse events with onset after start of study drug and up to 30 days after the last dose of study drug are considered TEAEs.
[a]p = 0.015 versus USL255 using Fisher's exact test.
[b]Adverse events with causality assessments of possibly, probably, definitely, or unknown were considered treatment related.
[c]Number is 1 lower than reported in Figure 1; adverse event that led to discontinuation was not treatment emergent and thus not counted in this table.
[d]Number is 1 higher from that reported in Figure 1; subject completed the study but had two adverse events, which were marked as causing study termination.
[e]Not related to USL255 treatment, as determined by the investigator.

11-week treatment (titration and maintenance phases), with more than one third of patients demonstrating a ≥50% reduction in seizure frequency. Trends of improved seizure control with USL255 were observed for all seizure types assessed, and were significant for the most disabling and potentially harmful seizure types (complex partial seizures and partial seizures with secondary generalization). Of note, the rate of seizure misclassification in PREVAIL (<4%) was lower than rates previously reported by The Epilepsy Study Consortium for other AED trials in patients with POS (14% and 10%).[15,16]

USL255 was efficacious even in patients receiving ≥3 concomitant AEDs, and about twice the number of USL255-treated patients achieved 100% seizure freedom during treatment compared to placebo, although the rate was low (3.2% [4/124] vs. 1.6% [2/125]). The rate of seizure freedom observed in other AED trials ranges from approximately 1–20% for treatment versus 0–5% for placebo.[17,18] The proportion of USL255-treated patients who were seizure-free for ≥21 days prior to the last dose of study drug was significantly higher than placebo.

Although people with epilepsy usually report a lower QoL than the general population,[19,20] meaningful changes/improvements in QoL can occur with appropriate treatment, and improved QoL has been recognized as a component of the management of patients with epilepsy.[21] Following treatment, QOLIE-31-P scores indicated that USL255 significantly reduced the effect of seizure worry and did not cause significant unwanted physical or mental medication side effects. Although overall QOLIE-31 scores were not significantly different from placebo, the duration of treatment during PREVAIL was relatively short, which may have precluded detection of differences in quality of life. In addition, significant improvements were observed by the investigators as measured by the CGI-C scale.

All AEDs can produce adverse effects, most notably AEs related to the CNS, which can be additive or synergistic with polytherapy.[22] In the PREVAIL study, USL255 demonstrated a favorable safety and tolerability profile when used in combination with other AEDs, although the proportion of patients reporting a new TEAE was greatest in those taking ≥3 AEDs, as would be expected. Consistent with a favorable safety profile, the most common AEs associated with either USL255 or placebo in this study (somnolence and dizziness) were each reported by <15% of patients. This is of particular interest as other AEDs have reported dose-dependent incidence from 15% to 50% for one or both of these CNS-related TEAEs; however, differences in design and dosing complicate direct comparisons between trials.[23–27] Rapid titration and higher initial dose of topiramate are associated with higher incidences of cognitive-related AEs,[6] and individual neurocognitive and neuropsychiatric AEs have been observed in up to 20% of patients with 200 mg topiramate using rapid titration.[6,28] Slower titration of topiramate improved the cognitive AE profile, with the only cognitive AE reported in ≥5% of patients being concentration/attention difficulty (5% topiramate, 0% placebo).[6,29] In PREVAIL, which used a similar slow titration, the proportion of USL255-treated patients who experienced individual neurocognitive or neuropsychiatric AEs was <2.5%. The

low rate of these AEs in the PREVAIL study may be due to the more uniform release of topiramate with USL255 as well as slow titration, but specific cognitive testing would be needed to fully address the potential difference between topiramate formulations.

The limitations of the PREVAIL study included fixed-dose treatment and a treatment population restricted to patients with highly treatment-resistant POS. In practice, AEDs are titrated for each patient to maximize efficacy and tolerability of the drug. The single dose used in the study is the lowest topiramate maintenance dosage approved for the adjunctive treatment of seizures (200 mg/day). Treatment with USL255 resulted in efficacy outcomes comparable to TPM-IR 200 mg/day[28,29] and other newly approved AEDs, such as perampanel,[30,31] lacosamide,[24,32] and ezogabine.[33,34] Of interest, USL255 50 mg/day demonstrated an almost 30% reduction in seizure frequency during the first week of the titration phase, suggesting that antiseizure effects may occur early in treatment. As significant antiseizure effects were achieved with USL255 <200 mg/day, consistent with other observations of low-dose topiramate efficacy,[29] it is possible that some patients may be effectively treated with doses lower than the maintenance dose studied here, thereby further reducing the potential for TEAEs.

USL255, once-daily XR topiramate, was designed to provide a simple dosing regimen and limited fluctuations in plasma concentrations, with the goal of achieving seizure control and improved adherence. Medication nonadherence contributes to undesirable social and clinical consequences (e.g., increased rates of hospitalization, emergency department visits, vehicle injuries, and death[35,36]). Similar to other chronic conditions, adherence rates in epilepsy have been shown to be higher among patients on once-daily treatment regimens.[35,37] Acknowledging that measurement of adherence in short-duration studies is not ideal and the accuracy of the method used in this study (return of unused capsules) is limited,[38] the high rate of adherence observed in PREVAIL suggests that treatment with once-daily USL255 may have a positive impact on adherence, although comparative study of immediate-release topiramate versus USL255 would be required to address this question.

The PREVAIL phase III clinical study demonstrated that, compared with placebo, USL255 can significantly reduce weekly seizure frequency, even in patients with debilitating seizure types. USL255 was generally well tolerated, with a favorable safety profile and a low incidence of neurocognitive side effects. These results, combined with convenient once-daily dosing, support the role of USL255 as a valuable treatment option for the management of epilepsy.

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Conflicts of Interest

S.S. Chung has served as a consultant for UCB Pharma, Lundbeck, SK Life Science, Upsher-Smith, and Neuronex; is a member of a speaker's bureau for GSK, UCB Pharma, Lundbeck, and Supernus; and has grant/research support through Valeant, Schwarz Pharma, UCB Pharma, Supernus, Eisai, Lundbeck, Medtronics, Upsher-Smith, and SK Life Science. T.A. Fakhoury has served as a consultant for GSK, Sunovion, UCB Pharma, and Upsher-Smith; is a member of a speaker's bureau for GSK, UCB Pharma, and Supernus; and has grant/research support through UCB Pharma, Sunovion, Upsher-Smith, SK Life Science, and West-Ward Pharmaceuticals. E. Hogan has served as a consultant for Upsher-Smith and had institution sponsorship of clinical trials through Upsher-Smith and Eisai Pharmaceuticals. V.N. Nagaraddi has served as a consultant for Upsher-Smith Laboratories, is a member of a speaker's bureau for UCB Pharma, and has sponsorship of clinical trials through Upsher-Smith Laboratories and UCB Pharma. I. Blatt has served as a consultant for GSK and Upsher-Smith and has had institution sponsorship of clinical trials through Cyberonics, GSK, Upsher-Smith, and Eisai Pharmaceuticals. B. Lawson has served as a consultant to Upsher-Smith and had institution sponsorship of clinical trials through Upsher-Smith. S. Arnold has served as a consultant for UCB, Eisai, Upsher Smith, and Desitin and received honoraria for conducting clinical trials for UCB, Eisai, and Upsher Smith. B. Anders, A.M. Clark, D. Laine, and M.B. Halvorsen are employed by Upsher-Smith Laboratories, Inc. R.S. Meadows is employed by PPD, a contract research organization paid by Upsher-Smith Laboratories, Inc. We 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.

Appendix
List of Co-Investigators for PREVAIL (NCT01142193)

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References

1. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav* 2002;3:338–342.
2. Hovinga CA, Asato MR, Manjunath R, et al. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: Survey of patients with epilepsy and physicians. *Epilepsy Behav* 2008;13:316–322.
3. Begley CE, Annegers JF, Lairson DR, et al. Estimating the cost of epilepsy. *Epilepsia* 1999;40(Suppl. 8):8–13.
4. Werz MA. Pharmacotherapeutics of epilepsy: use of lamotrigine and expectations for lamotrigine extended release. *Ther Clin Risk Manag* 2008;4:1035–1046.
5. Leppik IE, Hovinga CA. Extended-release antiepileptic drugs: a comparison of pharmacokinetic parameters relative to original immediate-release formulations. *Epilepsia* 2013;54:28–35.
6. Janssen Pharmaceuticals Inc. *Topamax prescribing information*. Titusville, NJ: Janssen Pharmaceuticals Inc.; 2012.
7. Halvorsen MB, Braun TL, Clark AM, et al. USL255, extended-release topiramate, demonstrates dose-proportional pharmacokinetics and

tolerability over a wide dosing range in healthy subjects. *Epilepsia* 2013;54:62.
8. Lambrecht LJ, Shekh-Ahmad T, Todd WM, et al. Comparative pharmacokinetic analysis of USL255, a new once-daily extended-release formulation of topiramate. *Epilepsia* 2011;52:1877–1883.
9. Bialer M, Shekh-Ahmad T, Braun TL, et al. Comparative steady-state pharmacokinetic evaluation of immediate-release topiramate and USL255, a once-daily extended-release topiramate formulation. *Epilepsia* 2013;54:1444–1452.
10. Food and Drug Administration (FDA). Qudexy XR NDA Approval, 2014. Available at:http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205122Orig1s000ltr.pdf. Accessed March 17, 2014.
11. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489–501.
12. DiVentura B, French J, Anders B, et al. Use of investigator training to improve seizure classification in PREVAIL – a phase 3, global study evaluating USL255, once-daily extended-release topiramate, in adults with partial-onset seizures. *Epilepsy Curr* 2014;14:397.
13. Bowker AH. A test for symmetry in contingency tables. *J Am Stat Assoc* 1948;43:572–574.
14. Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004;111:109–111.
15. French J, DiVentura B, Posner H, et al. Real-time central patient review improved quality in once-a-day trial of pregabalin forpartial epilepsy in adults. *15th Annual Meeting of the American Society for Experimental Neurotherapeutics (ASENT)*, Bethesda, MD, USA.
16. Vogelsong B, French J, Brodie M. Assessment of seizure classification in multinational, multicenter antiepileptic drug trials. *Epilepsy Curr* 2011;11(Suppl. 1):111.
17. Ben-Menachem E, Biton V, Jatuzis D, et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007;48:1308–1317.
18. Naritoku DK, Warnock CR, Messenheimer JA, et al. Lamotrigine extended-release as adjunctive therapy for partial seizures. *Neurology* 2007;69:1610–1618.
19. Sperling MR. The consequences of uncontrolled epilepsy. *CNS Spectr* 2004;9:98–101, 106–109.
20. Berto P. Quality of life in patients with epilepsy and impact of treatments. *Pharmacoeconomics* 2002;20:1039–1059.
21. Privitera M, Ficker DM. Assessment of adverse events and quality of life in epilepsy: design of a new community-based trial. *Epilepsy Behav* 2004;5:841–846.
22. Cramer JA, Mintzer S, Wheless J, et al. Adverse effects of antiepileptic drugs: a brief overview of important issues. *Expert Rev Neurother* 2010;10:885–891.
23. Gil-Nagel A, Lopes-Lima J, Almeida L, et al. Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures. *Acta Neurol Scand* 2009;120:281–287.
24. Chung S, Sperling MR, Biton V, et al. Lacosamide as adjunctive therapy for partial-onset seizures: A randomized controlled trial. *Epilepsia* 2010;51:958–967.
25. Beydoun A, D'Souza J, Hebert D, et al. Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. *Expert Rev Neurother* 2009;9:33–42.
26. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;55:236–242.
27. Messenheimer J, Ramsay RE, Willmore LJ, et al. Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. *Epilepsia* 1994;35:113–121.
28. Faught E, Wilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group. *Neurology* 1996;46:1684–1690.
29. Guberman A, Neto W, Gassmann-Mayer C. Low-dose topiramate in adults with treatment-resistant partial-onset seizures. *Acta Neurol Scand* 2002;106:183–189.
30. French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012;79:589–596.
31. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013;54:117–125.
32. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, et al. Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. *Epilepsia* 2009;50:443–453.
33. Brodie MJ, Lerche H, Gil-Nagel A, et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010;75:1817–1824.
34. French JA, Abou-Khalil BW, Leroy RF, et al. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology* 2011;76:1555–1563.
35. Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. *Epilepsia* 2008;49:446–454.
36. Faught E, Duh MS, Weiner JR, et al. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology* 2008;71:1572–1578.
37. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012;18:527–539.
38. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23:1296–1310.