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R. Edward Hogan
Washington University School of Medicine in St. Louis

Ilan Blatt
Chaim Sheba Medical Center

Balduin Lawson
Hospital Dr. Sotero del Rio

Venkatesh Nagaraddi
Neurological Clinic of Texas

Toufic A. Fakhoury
Bluegrass Epilepsy Research

See next page for additional authors

Authors
R. Edward Hogan, Ilan Blatt, Balduin Lawson, Venkatesh Nagaraddi, Toufic A. Fakhoury, Bob Anders, Annie M. Clark, Dawn Laine, Mark B. Halvorsen, and Steve S. Chung

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Brief Communication

Efficacy of once-daily extended-release topiramate (USL255): A subgroup analysis based on the level of treatment resistance

R. Edward Hogan [a,*], Ilan Blatt [b], Balduin Lawson [c], Venkatesh Nagaraddi [d], Toufic A. Fakhoury [e], Bob Anders [f], Annie M. Clark [f], Dawn Laine [f], Mark B. Halvorsen [f], Steve S. Chung [g]

[a] Washington University in St. Louis, Washington University School of Medicine, Adult Epilepsy Center, 660 S Euclid Ave., Campus Box 811, St. Louis, MO, USA
[b] The Chaim Sheba Medical Center, Charles Clore Hospitalization Tower, East Wing, Tel Hashomer, Israel
[c] Hospital Dr. Sótero del Río, Oficina de Investigaciones Médicas, Puente Alto, Chile
[d] Neurological Clinic of Texas, 12221 Merit Dr., Suite 350, Dallas, TX, USA
[e] Bluegrass Epilepsy Research, 1401 Harrodsburg Rd B280, Lexington, KY, USA
[f] Upsher-Smith Laboratories, Inc., 6701 Evenstad Drive, Maple Grove, MN, USA
[g] Barrow Neurological Institute, 500 West Thomas Road, Suite 300, Phoenix, AZ, USA

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ABSTRACT

Results from a previously conducted global phase III study (PREVAIL; NCT01142193) demonstrate the safety and efficacy of once-daily USL255, Qudexy™ XR (topiramate) extended-release capsules, as adjunctive treatment of drug-resistant partial-onset seizures (POSs). In this study, we report a post hoc analysis of PREVAIL data according to patient level of treatment resistance (based upon the number of concomitant antiepileptic drugs [AEDs] and lifetime AEDs) at baseline, with patients defined as either having "highly" drug-resistant seizures (≥2 concurrent AEDs and ≥4 lifetime AEDs) or having "less" drug-resistant seizures (1 concurrent AED or <4 lifetime AEDs) at baseline. For each subgroup, median percent reduction in POS frequency (primary endpoint), responder rate, Clinical Global Impression of Change (CGI-C), and Quality of Life in Epilepsy — Problems (QOLIE-31-P) survey were assessed. Of 249 PREVAIL patients, 115 were classified as having highly drug-resistant seizures (USL255: n = 52, placebo: n = 63), and 134 were classified as having less drug-resistant seizures (USL255: n = 72, placebo: n = 62) at baseline. For the primary endpoint, USL255 resulted in significantly better seizure outcomes compared with placebo regardless of drug-resistant status ($P = .004$ and $P = .040$ for "highly" and "less", respectively). Responder rate was also significantly improved in patients with highly drug-resistant group ($P = .023$). The CGI-C scores indicated significant improvement in both subgroups ($P = .003$ and $P = .013$ for "highly" and "less", respectively). On the QOLIE-31-P, a significant improvement on the seizure worry subscale for the group with less drug-resistant seizures was noted in USL255-treated patients compared with placebo-treated patients ($P = .003$); the overall score and all other subscales were not significantly different for both subgroups. We conclude that USL255 led to significant improvements across multiple outcomes compared with placebo, including in those classified as having highly drug-resistant seizures to prior treatment, making it a valuable treatment option for patients with epilepsy.

1. Introduction

Up to 40% of patients with epilepsy still have ongoing seizures despite being on their initial antiepileptic drug (AED) treatment [1]. While some of these patients may ultimately achieve seizure control through other AED monotherapy regimens or upon initiation of adjunctive AED therapy, approximately 30% of patients remain resistant to currently available treatments currently available treatments [2].

The use of successive AEDs is associated with a reduced likelihood of achieving seizure freedom, yet the addition of a new AED has resulted in approximately one in six patients achieving long-term seizure remission, even when as many as five prior AEDs had proven ineffective [3]. Therefore, continued trials of different AEDs in patients with medically drug-resistant epileptic seizures may result in significant improvement in seizure control.

Immediate-release topiramate (TPM-IR) administered twice daily is a broad-spectrum, well-established AED with nearly 20 years of demonstrated efficacy in the adjunctive treatment of epilepsy [4]. USL255

* Corresponding author at: Washington University School of Medicine, Adult Epilepsy Center, 660 S Euclid Ave., Campus Box 811, St. Louis, MO 63110, USA. Tel.: +1 314 362 7845.
E-mail address: hogane@neuro.wustl.edu (R.E. Hogan).

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(Qudexy™ XR [topiramate] extended-release capsules, Upsher-Smith Laboratories, Inc., Maple Grove, MN) is a proprietary, once-daily formulation developed to deliver consistent release over a 24-hour dosing interval [5]. In 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) [6,7]. The recent PREVAIL phase III study demonstrated that USL255 significantly improved seizure control in adults with drug-resistant partial-onset seizures (POSs) taking one to three concomitant AEDs [8]. USL255 was recently approved by the FDA (March 11, 2014) as initial monotherapy in patients ≥10 years of age with POSs or primary generalized tonic–clonic (PGTC) seizures and adjunctive therapy in patients ≥2 years of age with POSs, PGTC seizures, or seizures associated with Lennox–Gastaut syndrome [9].

The objective of this post hoc analysis of the PREVAIL study data was to evaluate the efficacy of USL255 in patients with the most drug-resistant epilepsy. In addition, we report Clinical Global Impression of Change (CGI-C) and quality-of-life findings in PREVAIL subgroups also stratified by the level of AED treatment resistance.

2. Methods

2.1. Original PREVAIL study

Detailed methods of the original PREVAIL study (NCT01142193) have been described previously [8]. Briefly, PREVAIL was a randomized, multinational, multicenter, double-blind, placebo-controlled, parallel-group study of USL255. The study included an 8-week baseline phase, a 3-week titration phase, and an 8-week maintenance phase. The maintenance phase was followed by a 3-week down titration or entry into a one-year open-label extension (OLE) study (NCT01191086). Eligible patients were adults 18–75 years of age with a confirmed diagnosis of POSs (for ≥1 year) with a minimum of eight POSs (with or without secondary generalization) and no more than 21 consecutive seizure-free days during the 8-week baseline phase. Patients were required to be on a stable regimen of one to three AEDs. Prior to randomization, all patients provided written informed consent. Patients were randomized 1:1 to once-daily USL255 or placebo, and titration occurred in 50 mg/week increments over the 3-week titration phase to the maintenance dosage of 200 mg/day USL255 or matching placebo. Primary and key secondary efficacy endpoints were median percent reduction from baseline in weekly POS frequency and responder rate (proportion of patients with ≥50% reduction in seizure frequency) for the entire treatment period (titration and maintenance phases). Clinical status assessments included the CGI-C with assessments completed by investigators at the end of the maintenance phase or upon early discontinuation. The CGI-C is a clinician-reported 7-point scale with lower scores indicating greater improvement (scores range from 1 = very much improved to 7 = very much worse). The Quality of Life in Epilepsy — Problems (QOLIE-31-P) survey was completed at the end of baseline and at the end of maintenance by patients in countries where it was available and validated for the spoken language. The QOLIE-31-P is composed of 7 subscales including seizure worry, overall quality of life, emotions, energy, mental activity, medication effects, and daily activities. Higher QOLIE-31-P scores indicate greater well-being.

2.2. Methods for this post hoc analysis

In the post hoc analyses described here, subgroups were based upon the baseline level of AED resistance using the number of current concomitant AEDs and lifetime AEDs as a surrogate measure of drug resistance. Specifically, patients were defined as either having "highly" drug-resistant seizures (≥2 concurrent AEDs and ≥4 lifetime AEDs) or having "less" drug-resistant seizures (1 concurrent AED or <4 lifetime AEDs) based upon our clinical experience and a more stringent approach relative to a recent analysis defining "refractory" as those patients on 3 or more concomitant AEDs [10]. For each of these two subgroups, median percent reduction in POS frequency, responder rate, CGI-C, and QOLIE-31-P were assessed. Differences between USL255 and placebo treatment groups were compared using a Wilcoxon rank-sum test (median percent reduction in POS frequency) and Fisher's exact test (responder rate). Treatment effect on the overall mean CGI-C scores was assessed using an analysis of variance (ANOVA) model, where the CGI-C score was the response variable and treatment and geographic region were the fixed effects. Quality of Life in Epilepsy — Problems comparisons were based upon an analysis of covariance (ANCOVA) model with the baseline score as the covariate. Analyses were performed using the intent-to-treat (ITT) population (all patients who received at least one dose of study drug and had at least one evaluable postrandomization diary entry).

3. Results

Baseline demographics have been reported in detail for the full patient population [8]. Briefly, the overall population, on average, reflected a patient population with difficult-to-treat seizures. The median duration of epilepsy was approximately 20 years, and 20% of the patients had taken ≥7 lifetime AEDs. Most (76%) were on an AED regimen with at least two concomitant AEDs. Active treatment and placebo groups were well matched with respect to baseline demographics and clinical characteristics. Of the 249 patients included in the total ITT study population, 115 were classified in this post hoc analysis as having highly drug-resistant seizures (USL255: n = 52, placebo: n = 63), and 134 were classified as having less drug-resistant seizures (USL255: n = 72, placebo: n = 62) at baseline. Completion rates were high and were similar between the group with highly drug-resistant seizures and the group with less drug-resistant seizures (87.0% and 87.3%, respectively).

Seizure frequency (as assessed by median percent reduction in POS frequency) was significantly reduced in both the highly drug-resistant and less drug-resistant subgroups (USL255: 40.4% versus placebo: 18.1%, $P = .004$ and USL255: 37.7% versus placebo: 22.7%, $P = .040$, respectively; Fig. 1A). Responder rate was also significantly improved in patients with highly drug-resistant seizures (USL255: 38.5% versus placebo: 19.0%, $P = .023$; Fig. 1B). The responder rate observed in patients with less drug-resistant seizures was numerically greater in the USL255 group compared with the placebo group but did not reach the level of statistical significance (USL255: 37.5% versus placebo: 27.4%, $P = .269$). For both efficacy outcomes, improvements with USL255 in the group

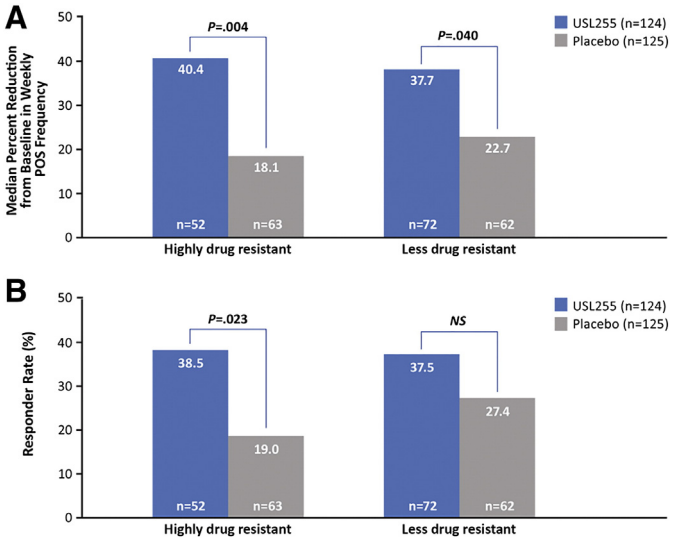

Fig. 1. Seizure reduction (A) and responder rate (B) by drug-resistant status.

with highly drug-resistant seizures were at least 2-fold those observed with placebo (Fig. 1).

For the CGI-C, patients in both subgroups were significantly improved with USL255 compared with placebo (mean CGI-C score at the end of maintenance = USL255: 3.1 versus placebo: 3.7, $P = .003$ and USL255: 2.8 versus placebo: 3.2, $P = .013$ in the group with highly drug-resistant seizures and in the group with less drug-resistant seizures, respectively; Fig. 2). Three times as many patients with highly drug-resistant seizures receiving USL255 (33.3%) had CGI-C scores that were 'very much improved' or 'much improved' compared with those receiving placebo (11.1%; $P = .005$). On the QOLIE-31-P, a significant improvement on the seizure worry subscale for the group with less drug-resistant seizures was noted in USL255-treated patients compared with placebo-treated patients ($P = .003$); the overall score and all other subscales were not significantly different for both subgroups.

4. Discussion

In this post hoc subgroup analysis of the PREVAIL study, USL255 was significantly more efficacious than placebo regardless of a patient's level of treatment resistance at baseline, defined based upon both the number of concomitant AEDs and the number of lifetime AEDs. This is notable given that prior history of failure of AEDs to achieve adequate seizure control is associated with a lower probability of response to a newly administered treatment [3]. The current results are consistent with the primary findings from the PREVAIL study, which demonstrated that USL255 significantly reduced median percent seizure frequency and significantly improved responder rate relative to placebo in the entire patient population [8]. The current findings also are in line with a post hoc analysis reported along with the primary PREVAIL findings in which efficacy was evaluated according to the number of baseline concomitant AEDs. In that analysis, patients taking the most concomitant AEDs (≥ 3) showed significantly greater seizure control with USL255 than with placebo as assessed by both median percent seizure reduction (52.8% [n = 33] versus 11.4% [n = 38], $P < .001$) and responder rate (57.6% versus 13.2%, $P < .001$) [8].

Optimal treatment of even the most drug-resistant patients is a priority, given the patient burden associated with inadequate seizure control both in terms of diminished quality of life and in terms of higher morbidity and mortality [11–13]. Annual total costs of drug-resistant epilepsy in the United States approach $4 billion, with average annual health-care costs for a patient with drug-resistant seizures (defined as those on ≥ 3 AEDs) at $33,613 [10]. Patient benefit in the current analyses was evident not only through traditional measures of seizure frequency but also on the CGI-C, which indicated that clinicians deemed patient status significantly improved with USL255 relative to placebo. On the QOLIE-31-P, only the seizure worry subscale for the group deemed having less drug-resistant seizures showed a significant difference compared with placebo, though a lack of significance on QOLIE-31-P subscales such as overall quality of life may not be surprising, given the relatively short duration of the study. Because commonly reported adverse events with AEDs such as TPM-IR include fatigue and cognitive effects [14], the lack of significance on subscales for energy, mental activities, and medication effects is notable in that USL255 was comparable with placebo.

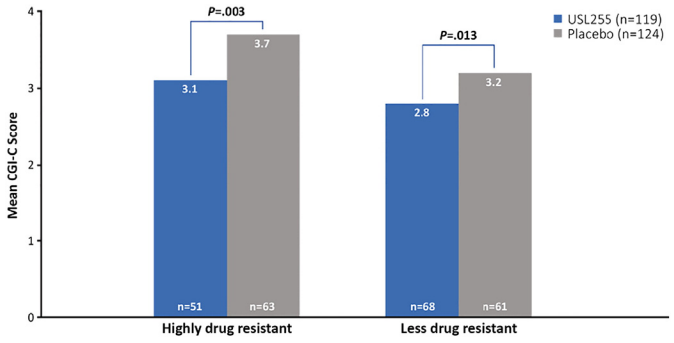

Fig. 2. Mean CGI-C score[a] at the end of the maintenance phase by drug-resistant status.
[a]Lower scores indicate greater improvement.

The authors acknowledge that the assumptions used in this post hoc analysis include a distinct and author-defined threshold for "highly" and "less" drug-resistant seizures. A task force appointed by the International League Against Epilepsy has proposed a definition of "refractory" or "drug-resistant" epilepsy as a failure of adequate trials of two, tolerated, appropriately chosen, and administered AEDs (as either monotherapy or adjunctive therapy) [15]. Our study design allows clear definition of seizure frequency among our study groups but does not allow definitive verification of adequate trials of past AEDs. Lack of definitive verification of adequate AED trials is a limitation of the study. In spite of this limitation, the goal of this analysis was to isolate patients with the most drug-resistant seizures from a group already established with a priori-defined criteria that existed within the strict parameters of a clinical study while still allowing for a comparison of similarly sized groups.

The specific definitions we chose for patients having "highly drug-resistant" seizures (≥ 2 concurrent AEDs and ≥ 4 lifetime AEDs) or patients having "less drug-resistant" seizures (1 concurrent AED or < 4 lifetime AEDs) were based on our clinical experience as well as a recent pharmacoeconomic study that classified 'refractory patients' as those on 3 or more AEDs [10]. Our analysis investigates an important group of patients with ILAE-defined "treatment failure." The importance of ongoing investigation of patients defined as having "treatment failure" includes past studies showing that their seizures patients can improve with further treatment even after their seizures fail to improve with two to five AEDs [3]. If complete seizure control is not achieved with trials of two appropriate AEDs, the likelihood of success with subsequent regimens is much reduced [16], necessitating a careful clinical reevaluation of the etiology of seizures and exploration of other treatment options, such as epilepsy surgery. However, drug resistance may "remit" over time (at a rate of 4% per year among adults and a higher rate among children), suggesting a fluctuating course in seizure response [16]. Additionally, other studies provide a quantitative estimate of the value of changing drug therapy in patients in whom seizures were uncontrolled by previous therapy [17]. Our results help to confirm the principle that intractable seizures may respond to ongoing treatment with different AEDs. It should be noted that the PREVAIL study was not powered to detect differences in the subgroups examined in this post hoc analysis. To our knowledge, this is the first analysis to define drug-resistant status based on both lifetime AED use and concomitant AED use.

5. Conclusion

USL255 resulted in significant improvement for the primary endpoint, compared with placebo, regardless of a patient's level of drug resistance at baseline. Responder rate was also significantly improved in patients with highly drug-resistant seizures. The CGI-C scores indicated significant improvement at study end in both subgroups, and USL255 was not associated with negative effects relative to placebo on QOLIE-31-P subscales for energy, mental activities, and medication effects. In this post hoc analysis, USL255 efficacy was significantly improved relative to placebo, even in those patients likely to be highly resistant to treatment making it a valuable treatment option for patients with epilepsy.

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Conflicts of interest

R.E. Hogan has served as a consultant for Upsher-Smith and had institution sponsorship of clinical trials through Upsher-Smith and Eisai Pharmaceuticals.

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 for Upsher-Smith and had institution sponsorship of clinical trials through Upsher-Smith.

V. 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.

T. 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.

B. Anders, A. Clark, D. Laine, and M. Halvorsen are employed by Upsher-Smith Laboratories, Inc.

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, Esai, Lundbeck, Medtronics, Upsher-Smith, and SK Life Science.

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