Epilepsy & Behavior 41 (2014) 136–139

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

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

ARTICLE INFO

*Article history:*
Received 9 June 2014
Revised 15 August 2014
Accepted 22 September 2014
Available online 21 October 2014

*Keywords:*
Extended-release
Antiepileptic drugs
Partial seizures
Drug resistance
Topiramate

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).

http://dx.doi.org/10.1016/j.yebeh.2014.09.061
1525-5050/

(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

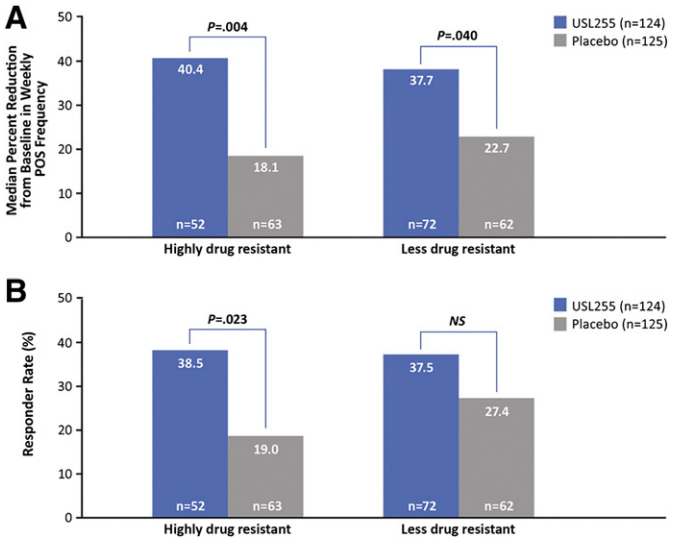


**Fig. 1.** Seizure reduction (A) and responder rate (B) by drug-resistant status.