Epilepsy & Behavior 59 (2016) 13–20

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Long-term safety and sustained efficacy of USL255 (topiramate extended-release capsules) in patients with refractory partial-onset seizures

Steve S. Chung [a,*], R. Edward Hogan [b], Ilan Blatt [c], Balduin Lawson P. [d], Huy Nguyen [e], Annie M. Clark [e], Bob Anders [e], Mark B. Halvorsen [e], on behalf of the PREVAIL OLE Study Group [1]:

[a] Banner University Medical Center, Phoenix, AZ, USA
[b] Washington University in St. Louis, St. Louis, MO, USA
[c] The Chaim Sheba Medical Center, Tel Hashomer, Israel
[d] Hospital Dr. Sótero del Río, Oficina de Investigaciones Médicas, Puente Alto, Chile
[e] Upsher-Smith Laboratories, Inc., Maple Grove, MN, USA

ARTICLE INFO

Article history:
Received 15 December 2015
Revised 4 March 2016
Accepted 5 March 2016
Available online xxxx

Keywords:
Epilepsy
Antiepileptic drug
Qudexy® XR
Open-label extension (OLE)
PREVAIL
Topiramate
Extended release

ABSTRACT

Objective: The aim of this study was to evaluate long-term safety, efficacy, and quality of life (QOL) of ≤400-mg/day USL255, Qudexy® XR (topiramate) extended-release capsules, as adjunctive therapy for partial-onset seizures (POS) in adults.

Methods: Patients who completed the 11-week double-blind treatment phase of the phase 3 PREVAIL study were eligible to enroll in this 1-year open-label extension (OLE) study (PREVAIL OLE). The primary objective was to evaluate the safety and tolerability of USL255 (including treatment-emergent adverse events [TEAEs]). The secondary objective was to assess seizure frequency in patients (e.g., median percent reduction from baseline in weekly POS frequency, responder rate [proportion of patients with ≥25%, ≥50%, ≥75%, or 100% reduction from baseline in POS frequency], and seizure-free intervals [proportion of patients who were seizure-free for 4, 12, 24, 36, or 48 weeks]). Exploratory clinical-status endpoints included the Global Impression of Change (CGI-C) and Quality of Life in Epilepsy—Problems (QOLIE-31-P) questionnaires. Post hoc analyses evaluated neurocognitive TEAE incidences during the first 11 and entire 55 weeks of treatment and efficacy by patient age and drug-resistant status.

Results: Of the 217 patients who completed PREVAIL (USL255, n = 103; placebo, n = 114), 210 (97%) enrolled in PREVAIL OLE and were included in the ITT population. Across the entire 55-week treatment period, USL255 was generally safe and well tolerated, with low individual neurocognitive TEAE incidences. Seizure reduction was sustained across the year-long study and observed in patient subgroups, including those with highly drug-resistant seizures and those ≥50 years of age. Improvements in CGI-C and QOLIE-31-P were also observed.

Significance: The results of PREVAIL OLE are consistent with those from PREVAIL and demonstrate that adjunctive treatment with up to 400 mg/day of USL255 may be a safe and effective treatment option for a variety of adult patients with refractory POS.

1. Introduction

Up to 30% of patients with epilepsy still experience seizure activity despite antiepileptic drug (AED) treatment [1], and seizures in others remain completely resistant to currently available treatments [2]. Uncontrolled seizures occur at severe psychosocial cost to patients [3], who would benefit from any reduction in seizure activity. Extended-release formulations of AEDs are designed to reduce dosing frequency and maintain relatively consistent drug plasma concentrations, which may reduce breakthrough seizures, cognitive-related and other adverse events (AEs), and improve overall quality of life (QOL). USL255, Qudexy® XR (topiramate) extended-release capsules (Upsher-Smith, Maple Grove, MN, U.S.A. [4]), is an extended-release, once-daily formulation of the well-established AED topiramate. USL255 is a proprietary multiparticulate (beads in a capsule) formulation, which was developed to deliver consistent drug release over a 24-h dosing interval. USL255 provides an overall plasma topiramate exposure that is equivalent

* Corresponding author at: 1111 E. McDowell Rd., Phoenix, AZ 85006, USA. Tel.: +1 602 839 6533; fax: +1 602 839 2522.
E-mail address: steve.chung@bannerhealth.com (S.S. Chung).
[1] See Appendix for the list of coinvestigators for the PREVAIL OLE Study Group.

http://dx.doi.org/10.1016/j.yebeh.2016.03.005

to immediate-release topiramate but with a significantly lower maximum concentration (C_{max}) and higher minimum concentration (C_{min}), resulting in decreased fluctuations in drug plasma concentrations [5,6].

The efficacy and favorable tolerability of 200-mg/day USL255 as adjunctive therapy for partial-onset seizures (POS) were demonstrated in a randomized, double-blind, placebo-controlled, multicenter, 11-week phase 3 study (PREVAIL). A longer-term safety evaluation is important because certain TEAEs can be delayed, particularly when topiramate is used as add-on treatment [7]. Moreover, topiramate may be associated with neurocognitive-related treatment-emergent AEs (TEAEs) [8] that can continue over the long term [9,10]. Therefore, this year-long open-label extension (OLE) study (PREVAIL OLE) was conducted to evaluate the long-term safety and efficacy of ≤400-mg/day USL255 as adjunctive therapy for POS. In addition, post hoc analyses examining new onset (incidence) of neurocognitive TEAEs and seizure reduction in various patient subgroups were performed.

2. Methods

2.1. Trial conduct

The PREVAIL OLE study was conducted from October 2010 to March 2014 at 54 study centers in 15 countries (Argentina, Australia, 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 E6 Guideline for Good Clinical Practice and applicable regulatory requirements. The institutional review boards and the European Research Council supervised and safeguarded the rights, safety, and well-being of all study subjects. Prior to any screening procedures, all patients provided written informed consent. The PREVAIL OLE study is registered with ClinicalTrials.gov (NCT01191086).

2.2. Patients

Eligible patients were those who completed the 11-week double-blind treatment phase (three weeks titration + eight weeks maintenance) of the PREVAIL study (ClinicalTrails.gov identifier: NCT01142193). Detailed methods of PREVAIL have been described previously [11]. Briefly, adults (18–75 years of age at time of entry into PREVAIL) with a confirmed diagnosis of refractory POS for at least one year on a stable regimen of 1–3 concomitant AEDs were eligible to enroll in PREVAIL and continue into the OLE. Eligible patients had a minimum of eight POS and no more than 21 consecutive seizure-free days during the 8-week baseline period of PREVAIL. Seizures classified as simple partial with motor signs, complex partial, or partial with secondary generalization qualified patients to meet inclusion criteria. Patients could have had more than one seizure type.

2.3. Study design

Upon entry into PREVAIL OLE (following 11 weeks of USL255 or placebo treatment in PREVAIL), patients underwent a 3-week blinded-conversion phase followed by a 52-week open-label phase. During blinded conversion, patients previously randomized to placebo in PREVAIL were titrated in 50-mg/week increments to 200-mg/day USL255, and patients previously randomized to 200-mg/day USL255 in PREVAIL continued treatment. Following blinded conversion, open-label maintenance at 200-mg/day USL255 for eight weeks was required for all patients. After 11 weeks of the OLE (3-week blinded conversion + +8-week maintenance), USL255 dosages were allowed to be titrated up or down by 50 mg/week, up to a maximum daily dosage of 400 mg/day. Concomitant AEDs (except vigabatrin, felbamate, and topiramate) could be added, removed, or dose-adjusted (but not within 3 days of a change in USL255 dose) as long as patients remained on 1–3 concomitant AEDs. At the end of the 55-week OLE, patients were tapered off USL255 by 50 mg/week over the course of at least three weeks or, with physician approval, were converted directly to the equivalent daily dose of immediate-release topiramate without taper.

2.4. Assessments

The primary objective of the study was to evaluate the safety and tolerability of USL255 as adjunctive treatment in patients with POS. Primary endpoints examined included spontaneously reported TEAEs, clinical laboratory values, vital signs, physical/neurological examinations, and suicidality assessments via the Columbia Suicide Severity Rating Scale (C-SSRS). Treatment-emergent adverse events were summarized by frequency, treatment relatedness, and maximum severity. Post hoc safety analyses included incidence (new onset) of neurocognitive TEAEs for the first 11 weeks of USL255 treatment (for newly exposed patients [PBO-USL]) and for the duration of PREVAIL OLE.

The secondary objective of the study was to assess seizure frequency in patients with POS receiving open-label USL255. Secondary endpoints included various seizure frequency outcomes (documented through patient diaries), the median percent reduction from baseline in weekly POS frequency, and responder rate (proportion of patients with ≥25%, ≥50%, ≥75%, or 100% reduction from baseline in weekly POS frequency); analyses included all patient data regardless of trial completion. Baseline was defined as the 8-week baseline period prior to the start of PREVAIL. Patients were also evaluated for seizure-free intervals (defined as the percentage of patients who were seizure-free for an interval of 4, 12, 24, 36, or 48 weeks at any time during the study). For the efficacy analyses, treatment periods evaluated included the 3-week blinded conversion phase, the 52-week open-label phase, and the overall 55 weeks of PREVAIL OLE (blinded conversion + open-label). For the 52-week open-label phase, seizure rates also were calculated during each consecutive 12-week interval. Post hoc efficacy analyses included median percent reduction from baseline in weekly POS frequency and responder rate by patient age (18 to <35, 35 to <50, and ≥50 years of age) and by drug refractoriness. Based on a surrogate measure of drug refractoriness (the number of current and lifetime AEDs), patients were divided into two groups: patients with ≥2 concurrent AEDs and ≥4 lifetime AEDs were defined as having "highly" drug-resistant seizures, while the rest of the study population comprised the group of patients with "less" drug-resistant seizures (one concurrent AED and/or <4 lifetime AEDs) [12].

Exploratory clinical-status endpoints included the clinician-reported Global Impression of Change (CGI-C) and the patient-reported Quality of Life in Epilepsy—Problems (QOLIE-31-P) questionnaires, both performed at baseline and week 55 or early termination (ET, if applicable). The CGI-C was used to evaluate patient clinical status by assessing seizure frequency and severity, occurrence of adverse events, and overall functional status. The CGI-C is a 7-point scale with lower scores indicating greater improvement; scores range from 1 = very much improved to 7 = very much worse. The QOLIE-31-P was used to evaluate change from baseline in QOL and was completed by patients in countries where it was available and validated for the spoken language(s). The QOLIE-31-P is composed of seven subscales (seizure worry, overall quality of life, emotions, energy, mental activity, medication effects, and daily activities), and higher scores indicate greater well-being.

2.5. Data analyses

Safety and tolerability, efficacy, and QOL analyses were performed using the intent-to-treat (ITT) population, defined as all patients who received at least one dose of USL255 in PREVAIL OLE. Subgroup analyses included patients who were randomized to USL255 in PREVAIL (USL-USL) and patients who were randomized to placebo in PREVAIL (PBO-USL). The 8-week baseline period prior to the start of treatment in PREVAIL was used as baseline for all PREVAIL OLE endpoints. Descriptive statistics were calculated for all assessments, and endpoints were summarized using an observed cases analysis.