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Lacosamide for uncontrolled primary generalized tonic-clonic seizures: An open-label pilot study with 59-week extension

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ABSTRACT

Objective: Assess the safety of adjunctive lacosamide for the treatment of uncontrolled primary generalized tonic-clonic seizures in patients (16–65 years) with primary generalized (genetic) epilepsy (PGE).
Methods: An open-label pilot safety study (SP0961; NCT01118949), comprising 12 weeks' historical baseline, 4 weeks' prospective baseline, 3 weeks' titration (target: 400 mg/day adjunctive lacosamide) and 6 weeks' maintenance. Patients who continued to the extension study (SP0962; NCT01118962) then received ≤59 weeks of flexible treatment (100–800 mg/day lacosamide with flexible dosing of concomitant antiepileptic drugs). The primary outcomes for SP0961 were the mean change (±standard deviation) in absence seizure or myoclonic seizure days per 28 days from prospective baseline to maintenance; for SP0962, the incidence of treatment-emergent adverse events (TEAEs) and withdrawals because of TEAEs.
Results: Of the 49 patients who enrolled, 40 (82%) completed the pilot study and 9 discontinued (5 because of adverse events). Of the 39 patients who continued to the extension study, 10 discontinued (2 owing to TEAEs) and 29 (74%) completed the study. During the pilot study, patients reported a reduction in mean (± standard deviation) absence and myoclonic seizure days per 28 days (−0.37 ± 4.80, −2.19 ± 5.80). Reductions were also observed during the extension study (−2.38 ± 5.54, −2.78 ± 6.43). Five patients in SP0961 and 2 patients in SP0962 experienced TEAEs of new or increased frequency of absence seizures or myoclonic seizures. The most common TEAEs during SP0961 were dizziness (39%) and nausea (27%), and during SP0962 were dizziness (26%) and upper respiratory tract infection (26%).
Conclusions: The safety profile of adjunctive lacosamide was similar to that previously published. Adjunctive lacosamide did not systematically worsen absence or myoclonic seizures, and appears to be well tolerated in patients with PGE.

1. Introduction

Epilepsy is broadly divided into focal and primary generalized types. Focal seizures originate in unilaterally distributed networks, whereas primary generalized seizures arise in bilaterally distributed networks. The precise nomenclature is periodically updated by the International League Against Epilepsy, who most recently introduced the terms 'genetic', 'structural-metabolic' and 'unknown', to replace the older terms 'idiopathic', 'symptomatic', and 'cryptogenic', respectively (Berg et al., 2010). From a practical clinical standpoint, correct syndromic diagnosis is important because the safety and efficacy of antiepileptic drugs (AEDs) can vary in different epilepsy types and certain AEDs can actually

Abbreviations: AE, adverse event; AED, antiepileptic drug; EEG, electroencephalogram; PGE, primary generalized (genetic) epilepsy; PGTCS, primary generalized tonic-clonic seizure; POS, partial-onset seizure; SD, standard deviation; SW, spike-wave; TEAE, treatment-emergent adverse event.

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worsen some primary generalized seizures (Perucca et al., 1998). Thus, the safety and efficacy of novel AEDs should be tested in patients with primary generalized (genetic) epilepsy (PGE) before they are used for the treatment of primary generalized tonic-clonic seizures (PGTCS).

PGE is characterized by the variable occurrence of absence, myoclonic or PGTCS, which may occur in combination or separately, associated with generalized, bisynchronous spike-wave (SW) discharges on electroencephalogram (EEG) (Benbadis, 2005; Beydoun and D'Souza, 2012). This type of epilepsy typically emerges in childhood, may resolve in adulthood and is often more responsive to AED treatment than focal epilepsy (Camfield and Camfield, 2005; Semah et al., 1998). Novel AEDs are often first evaluated in adult patients with focal seizures [previously termed partial-onset seizures (POS)] because focal epilepsy is more common in adults, and is associated with seizures that are more frequent and more easily documented than primary generalized seizures. Evaluation of new AEDs for the treatment of PGE is usually delayed until efficacy and safety have been first established in patients experiencing focal seizures. Of all of the AEDs that have demonstrated efficacy in the treatment of focal seizures, only valproate, lamotrigine, levetiracetam, topiramate and perampanel are currently approved for the treatment of seizures associated with PGE in the United States or European Union (Brown, 2016; French et al., 2015; Glauser et al., 2013), with some evidence also supporting the use of zonisamide (Rheims and Ryvlin, 2014). Lacosamide is approved for the treatment of focal seizures (POS) in several countries at doses up to 400 mg/day. In the United States, lacosamide is approved as monotherapy and adjunctive therapy for the treatment of focal (POS) seizures in patients 17 years or older (Vimpat (lacosamide) US Prescribing Information, 2015). In the European Union, adjunctive lacosamide is approved for the treatment of focal seizures (POS) in patients 16 years and older (Vimpat (lacosamide) Summary of Product Characteristics, 2014). The anticonvulsant activity of lacosamide is predominantly a consequence of selective enhancement of slow inactivation of voltage-gated sodium channels (Rogawski et al., 2015). This mechanism is fundamentally different from that of traditional sodium-channel blocking AEDs, which act through enhancement of voltage-gated sodium channel fast inactivation. Some AEDs that reduce focal seizures by enhancing fast inactivation of voltage-gated sodium channels have been shown to aggravate generalized seizures, particularly absence seizures and myoclonic seizures (Perucca et al., 1998; Talwar et al., 1994; Vendrame et al., 2007). Preclinical evaluation of lacosamide suggested increases in SW discharges in both WAG/Rij and genetic absence epilepsy rats (Unpublished results). We thus undertook this open-label pilot study with long-term extension in order to evaluate the safety of adjunctive lacosamide for the treatment of uncontrolled PGTCS in patients (16–65 years) with PGE. Specific focus was placed on the assessment of absence and myoclonic seizure frequency.

2. Methods

2.1. Study design

The initial pilot was a Phase II, multicenter, open-label study (SP0961; NCT01118949), comprising a 16-week combined baseline period (12-week historical baseline + 4-week prospective baseline), a 3-week titration period and a 6-week maintenance period. In the 12-week historical baseline, PGTCS frequency was verified from a documented source (i.e., seizure diary) prior to visit 1. This was immediately followed by a 4-week prospective baseline, when seizure activity was actively recorded (direct questioning and detailing of each seizure). During titration, patients were started on adjunctive lacosamide at a dose of 50 mg twice daily (100 mg/day, oral). The dose was increased by 100 mg/day per week towards a target (maximum) dose of 400 mg/day, if clinically warranted. One single dose reduction (by 100 mg/day) was allowed if required for tolerability, for *de novo* occurrence of absence or myoclonic seizures, or if a clinically significant seizure exacerbation occurred. Twenty-four–hour ambulatory EEG recordings were conducted on the final day of the prospective baseline period, before the patient received the first dose of lacosamide, and after the first week of maintenance treatment.

Nineteen sites in the US enrolled patients for the pilot study. Safety data were reviewed by the data-monitoring committee after 15, 30 and 49 patients had completed the maintenance period or withdrawn from the study. At the end of the maintenance period, patients could either enter a 3-week taper period or enroll directly into the extension study (SP0962; NCT01118962).

The extension study included a treatment period of up to 59 weeks (maximum of 56 weeks of flexible treatment followed by a taper period of up to 3 weeks). Patients entered the extension study taking the dose that they received at the end of the pilot study from all participating sites; however, the dose could be increased to a maximum of 800 mg/day or decreased to a minimum of 100 mg/day to optimize tolerability and seizure control. Reduction or elimination of concomitant AEDs, including to achieve lacosamide monotherapy, was allowed if clinically warranted. If patients did not have adequate response to the maximum tolerated lacosamide dose, then the addition of other AEDs approved for the treatment of PGTCS was allowed. Patients who experienced a clinically significant exacerbation or *de novo* emergence of myoclonic or absence seizures were evaluated for dose reduction or study withdrawal.

Both studies complied with local laws and were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and International Council for Harmonization guidelines. The protocols were approved by an Institutional Review Board.

2.2. Patient eligibility

The pilot study included male and female patients, 16–65 years of age, with PGE and uncontrolled PGTCS (International League Against Epilepsy, 1981, 1989). Diagnosis was established by clinical history and an EEG showing generalized SW discharges (performed within 5 years of visit 1). Enrollment criteria required patients to have had at least 1 PGTCS in the 12 weeks preceding the prospective baseline, despite use of 1–3 concomitant AEDs (stable use for ≥28 days before and during the prospective baseline). Concomitant vagal nerve stimulation was permitted and was not counted as a concomitant antiepileptic therapy if used for ≥6 months before study entry and on a constant setting for ≥28 days before the screening visit and during the prospective baseline.

Patients were excluded if they had a history of focal seizures or EEG findings consistent with focal seizures, a history of status epilepticus within the 5-year period before visit 1 (start of prospective baseline period), a current or previous diagnosis of other nonictal seizure-like events, a history of suicide attempt, counseling for suicidal ideation or current active suicidal ideation, sick sinus syndrome without a pacemaker, second- or third-degree atrioventricular block, a myocardial infarction in the previous 3 months or New York Heart Association Class III or Class IV heart failure. Disallowed antiepileptic treatments were ketogenic diet, current felbamate treatment or historic or current vigabatrin treatment with abnormal or missing visual field reports.

To enroll in the extension study, patients must have completed the pilot study and, in the opinion of the investigator, be expected to benefit from continued lacosamide therapy. Patients were excluded from the extension study if they were experiencing a serious ongo-