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Efficacy and safety of lacosamide as first add-on or later adjunctive treatment for uncontrolled partial-onset seizures: A multicentre open-label trial

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ABSTRACT

Purpose: To evaluate the efficacy and safety of lacosamide administered as either first add-on or later add-on antiepileptic drug (AED) therapy for patients with uncontrolled partial-onset seizures (POS).
Methods: In this open-label, multicentre trial, patients with POS initiated oral lacosamide (titrated to 400 mg/day) either as add-on to first AED monotherapy, or as later add-on to 1–3 concomitant AEDs after ≥2 previous AEDs. The primary efficacy variable was the proportion of patients achieving seizure freedom for the first 12 weeks of the 24-week Maintenance Phase.
Results: 456 patients received ≥1 dose of lacosamide (96 as first add-on, 360 as later add-on). In the first add-on cohort, 27/72 (37.5%) patients completed 12 weeks treatment and remained seizure-free; 18/68 (26.5%) remained seizure-free after 24 weeks. 64/91 (70.3%) patients achieved ≥50% reduction in seizure frequency during maintenance treatment. This was accompanied by a mean 7.1 ± 16.00 point improvement from Baseline in the Quality of Life Inventory in Epilepsy (QOLIE-31-P) total score for 24-week completers, with improvement reported in all subscales. Most common treatment-emergent adverse events (TEAEs) were dizziness (31.3%) and headache (13.5%). In the later add-on cohort, 39/261 (14.9%) and 29/249 (11.6%) patients remained seizure-free after completing 12 and 24 weeks' treatment, respectively. 178/353 (50.4%) patients achieved ≥50% reduction in seizure frequency during maintenance treatment. Mean change in QOLIE-31-P total score was 4.8 ± 14.74 points among 24-week completers. Common TEAEs were dizziness (33.6%), somnolence (15.0%) and headache (11.4%).
Conclusions: Lacosamide initiated as first add-on treatment was efficacious and well tolerated in patients with uncontrolled POS.

1. Introduction

More than 30% of patients with epilepsy have been reported to be unable to achieve remission despite appropriate antiepileptic drug (AED) therapy [1].

Lacosamide is a newer AED, approved at dosages up to 400 mg/day as monotherapy or adjunctive therapy in adults (≥17 years)

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with partial-onset seizures (POS) in the USA [2], and as adjunctive therapy in adults (≥16 years) with POS in the EU [3] and other countries. The efficacy and safety of adjunctive lacosamide have been demonstrated in three randomised placebo-controlled trials that recruited patients with uncontrolled POS [4–6]. Most patients (84.4%) were taking multiple (two or three) concomitant AEDs, with a lifetime use (started but previously discontinued) of >4 AEDs by 77.4% patients, and >7 AEDs by 45.2% patients [7].

Since the chance of seizure freedom declines significantly with subsequent AED regimens [8], it is of interest to assess the response to adjunctive lacosamide when used earlier in treatment than in the pivotal studies, such as first add-on therapy. In this study, we sought to evaluate the efficacy and safety of lacosamide in two populations of adults with POS using an evaluation schedule similar to the registration trials. The 'first add-on' cohort of patients received lacosamide as their first adjunctive treatment after a first monotherapy, while the 'later add-on' cohort had previously been treated with at least two prior AED treatment regimens before adding lacosamide.

2. Methods

This was a prospective open-label, non-randomised, Phase IIIb/IV study (SP0954; NCT00955357), conducted between August 2009 and August 2013 at sites in Austria, Bulgaria, Czech Republic, Denmark, Finland, France, Greece, Italy, Romania, Russia, Spain, Turkey, Mexico and the USA, according to ICH-GCP [9], the Declaration of Helsinki, and local laws of the countries involved. All patients provided written informed consent and the study was approved by an Ethics Committee or Institutional Review Board for each site.

2.1. Patients

2.1.1. Overall study population

The study enrolled male or female adults (aged ≥18 years in Mexico or Bulgaria, ≥17 years in the USA and ≥16 years in all other countries). Patient enrolment criteria required a diagnosis of epilepsy with simple partial seizures (SPS) and a motor component or complex partial seizures (CPS) with or without secondarily generalised seizures (sGS). The maximum permitted seizure frequency (motor and non-motor) during the 12 weeks prior to screening (Historical Baseline) was 40 POS per 28 days. Patients were required to be lacosamide-naïve and maintained on a stable AED regimen for at least 7 days prior to screening, with or without concurrent stable vagus nerve stimulation.

Patients were excluded if they had a seizure disorder characterised primarily by POS without motor signs, a history of primary generalised seizures or status epilepticus, uncountable seizures due to clustering or possible non-epileptic seizures/events. Patients were also excluded if they had any medical or psychiatric condition that might compromise their health, ability to participate in the trial or could interfere with lacosamide pharmacokinetics.

2.1.2. First add-on cohort

Patients included in the first add-on cohort were taking an appropriate first monotherapy, defined as a single AED taken for at least 28 days prior to screening, and had no history of AED polytherapy. Prior short-term intermittent rescue therapy was accepted. At screening, patients had ≤24 months since epilepsy diagnosis, and experienced ≥3 POS (SPS with motor signs, CPS or sGS) at any time during the 12-week Historical Baseline.

2.1.3. Later add-on cohort

The later add-on cohort included patients with more treatment-refractory epilepsy, who were taking 1–3 AEDs, had received ≥2 prior AED treatment regimens (concurrently or sequentially), and had been diagnosed with epilepsy at least 5 years before screening. They had a POS frequency (SPS with motor signs, CPS or sGS) of ≥1 per 28 days during the 12-week Historical Baseline.

2.2. Treatment

The study design is shown in Supplemental Figure 1. Eligible patients received open-label twice-daily oral treatment with lacosamide tablets. Scheduled clinic visits were at screening (1 week before treatment initiation), and at Weeks 0 (treatment initiation), 5, 6 (end of Titration Phase), 12, 18, 24 and 30 (End of Maintenance Phase), followed by a Taper/Safety Follow-Up Phase of up to 3 weeks.

During the 6-week Titration Phase, lacosamide was initiated at 100 mg/day (50 mg bid) and then increased by 100 mg/day/week for 4 weeks to a maximum of 400 mg/day (200 mg bid). Changes to concomitant AED treatment were not allowed until the end of Weeks 4 and 5, when existing doses could be adjusted (no new AED additions were permitted). A reduction in the lacosamide dosage to 300 mg/day was permitted (if required) at the end of Week 5.

One increase (to a maximum of 400 mg/day) or decrease (to a minimum of 300 mg/day) of the lacosamide dose was allowed at the end of Week 12 of the Maintenance Phase. No other change to the lacosamide dose was permitted thereafter. Changes to concomitant AEDs were not allowed at any time during the Maintenance Phase. Patients who completed the 24-week Maintenance Phase and chose not to continue receiving commercial lacosamide were gradually tapered off.

2.3. Patient analysis sets

The Safety Set (SS) included all patients who received at least one dose of lacosamide during the study. The full analysis set (FAS) included patients of the SS who had at least one post-Baseline seizure assessment. The Completer Set (CS) was defined as patients of the FAS who completed the first 12 weeks of the Maintenance Phase. Patients in the FAS who completed the 24-week Maintenance Phase were considered 24-week completers.

2.4. Outcome measures and statistical analysis

The primary efficacy outcome was the proportion of patients among the CS who achieved seizure freedom, i.e. reported no seizures, with no missing seizure data, during the first 12 weeks of the Maintenance Phase.

The proportion of patients who achieved seizure freedom throughout the 24-week Maintenance Phase was also analysed among 24-week completers. The percentage change in POS frequency per 28 days was evaluated from Baseline to the first 12 weeks of maintenance therapy among the CS, and at the end of the 24-week Maintenance Phase in the FAS, using the last observation carried forward (LOCF) method. Responder rates (proportions of patients with ≥50% or ≥75% decrease in POS frequency per 28 days from Baseline) were analysed after 12 weeks of maintenance therapy among the CS, and at the end of the 24-week Maintenance Phase in the FAS (LOCF).

Other efficacy measures analysed among the FAS population included the change in clinical status measured by the Clinical Global Impression of Change (CGIC) and the Patient's Global Impression of Change (PGIC) at the end of the Maintenance Phase/Early Discontinuation. The Quality of Life (QOL) Inventory in Epilepsy-31-P (QOLIE-31-P) was completed by all capable patients to assess the effects of treatment on activities of daily living and overall health-related QOL across seven domains. The QOLIE-31-P is an adaptation of the QOLIE-31, grouped into seven subscales and