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Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: Results of a 1-year open-label extension study☆

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Summary
Objective: To evaluate the long-term safety, tolerability and efficacy of once-daily eslicarbazepine acetate (ESL) as adjunctive therapy in adults with partial-onset seizures.
Methods: One-year open-label extension (OLE) study with ESL in patients who completed a randomised, double-blind placebo-controlled trial (study BIA-2093-302; *Epilepsy Res.* 89 (2010) 278—285). Starting dose was 800 mg once-daily, for 4 weeks; thereafter, dose could be individualised within the 400—1200 mg range. Doses of concomitant antiepileptic drugs were to be kept stable.

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Results: Overall, 325 patients were enrolled (intent-to-treat population); 223 (68.6%) patients completed 1-year of treatment. ESL median dose was 800 mg once-daily. Compared to the baseline period of the double-blind study completed prior to this OLE study, median seizure frequency decreased by 32% in weeks 1—4, and between 37% and 39% thereafter. The responder rate (seizure reduction $\geq$ 50%) was 37% during weeks 1—4 and thereafter ranged between 38% and 42% per 12-week interval. Proportion of seizure-free patients per 12-week interval ranged between 5% and 11%. Improvements from baseline in several Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and Montgomery Asberg Depression Rating Scale (MADRS) scores were observed. Adverse events (AEs) were reported by 83% of patients. AEs occurring in $\geq$10% of patients were dizziness, headache and somnolence. AEs were usually of mild to moderate intensity.

Conclusion: In this study, ESL demonstrated a sustained therapeutic effect and was well tolerated during 1-year add-on treatment of adults with partial-onset seizures. Additionally, significant improvements in quality of life domains and depressive symptoms were observed under long-term treatment with once-daily ESL.

Introduction

Eslicarbazepine acetate (ESL) is a once-daily voltage-gated sodium channel (VGSC) blocker (Benes et al., 1999; Almeida and Soares-da-Silva, 2007; Almeida et al., 2009) approved by the European Medicines Agency (EMA) in 2009 as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation, based on a clinical program that included an initial proof-of-concept phase II study (Elger et al., 2007, 2009; Gil-Nagel et al., 2009; Ben-Menachem et al., 2010; Halasz et al., 2010) and three subsequent phase III studies (Elger et al., 2007, 2009; Gil-Nagel et al., 2009).

Study BIA-2093-302 was a two-part multicentre study conducted in 45 sites in 13 countries (Argentina, Australia, Belgium, Brazil, Denmark, Germany, The Netherlands, Portugal, Romania, South Africa, Spain, Sweden and United Kingdom) (Ben-Menachem et al., 2010). Part I consisted of an 8-week observational baseline period, after which patients were randomised to once-daily placebo (n = 100) or ESL 400 mg (n = 96), 800 mg (n = 101), or 1200 mg (n = 98). Patients then entered a 14-week double-blind treatment phase. All patients started on their full maintenance dose except for those in the ESL 1200 mg group who received once-daily ESL 800 mg for 2 weeks before reaching their full maintenance dose. The results of Part I are reported elsewhere (Ben-Menachem et al., 2010). Patients who completed the double-blind maintenance period had the option to enter a 1-year open-label extension (OLE) study (Part II) with results reported here. The objectives of Part II were to evaluate the safety and tolerability, the maintenance of the therapeutic effect in terms of seizure control, and the health-related quality-of-life and depressive symptoms over a 1-year treatment period with ESL.

Methods

Patients who completed Part I of the study (n = 327), including those who had received placebo during Part I, and consented to participate in Part II (1-year OLE study) were enrolled (n = 325). Selection criteria for participation in the placebo-controlled part of the study (Part I) are described elsewhere (Ben-Menachem et al., 2010). Of note, patients concomitantly treated with oxcarbazepine or felbamate were excluded from participating in the study.

In Part II, the ESL starting dose was 800 mg once-daily. After 4 weeks, ESL doses could be titrated up or down at 400 mg intervals between 400 mg and 1200 mg once-daily to individualise therapy at the investigator's clinical judgement. The dosage of allowed concomitant AEDs (1—3) was to be kept stable throughout the entire study. Subjects were evaluated after the first 4 weeks of treatment, and every 12 weeks afterwards. Pre-dose blood sampling for the assay of AEDs administered, as well as clinical laboratory safety tests (haematology, coagulation, biochemistry, thyroid function, and urinalysis), vital signs, body weight and electrocardiogram (ECG) recordings, were performed at regular intervals.

The study was conducted in accordance with the ICH Good Clinical Practices and the laws of the countries where the study was performed. All patients gave written informed consent prior to enrollment.

The efficacy assessments were based on patient diaries, in which participants recorded seizures by date and time of occurrence, type and number. Efficacy variables included seizure frequency adjusted per 4 weeks, relative reduction in seizure frequency, reduction in frequency by seizure type, proportion of responders (patients with a reduction in seizure frequency $\geq$ 50%), proportion of seizure-free patients (100% seizure reduction) and number of days with seizures, compared to the baseline period of Part I.

Quality of life was evaluated using the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) (Cramer et al., 1998). The QOLIE-31 contains 7 multi-item scales (emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life). In accordance with the Scoring Manual, an overall QOLIE-31 score was calculated as a weighted average of the multi-item scale scores. The effect of ESL treatment on depressive symptoms was evaluated by using the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The MADRS consists of 10 items (apparent sadness, inner tension, reported sadness, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) measuring depressive symptoms on a scale of 0 (least severe or absent) to 6 (most severe). The overall MADRS score is the sum of all individual item scores combined.