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Effects of adjunctive eslicarbazepine acetate on neurocognitive functioning in children with refractory focal-onset seizures

Sergiusz Jóźwiak [a,b], P. Veggiotti [c,d], J. Moreira [e], H. Gama [e], F. Rocha [e], P. Soares-da-Silva [e,f,g,*]

[a] Department of Child Neurology, Warsaw Medical University, Warsaw, Poland
[b] Department of Neurology and Epileptology, The Children's Memorial Health Institute, Warsaw, Poland
[c] Child Neurology Department, V. Buzzi Hospital, Milan, Italy
[d] L. Sacco Department, University of Milan, Milan, Italy
[e] BIAL – Portela & Cª. S.A., Coronado (S. Romão e S. Mamede), Portugal
[f] Department of Biomedicine, Pharmacology and Therapeutics Unit, Faculty of Medicine, University Porto, Porto, Portugal
[g] MedInUP - Center for Drug Discovery and Innovative Medicines, University Porto, Porto, Portugal

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ABSTRACT

Purpose: This was a phase-II, randomized, double-blind (DB), placebo-controlled study aimed to evaluate neurocognitive effects of eslicarbazepine acetate (ESL) as adjunctive therapy in pediatric patients with refractory focal-onset seizures (FOS).

Methods: Children (6–16 years old) with FOS were randomized (2:1) to ESL or placebo. Treatment started at 10 mg/kg/day, was up-titrated up to 30 mg/kg/day (target dose), and maintained for 8 weeks, followed by one-year open-label follow-up. The primary endpoint was change from baseline to the end of maintenance period in the composite Power of Attention assessed with the Cognitive Drug Research (CDR) system. Behavioral and emotional functioning and quality of life (QOL), secondary endpoints, were assessed with Child Health Questionnaire-Parent Form 50 (CHQ-PF50), Child Behavior Checklist (CBCL), and Raven's Standard Progressive Matrices (SPM). Efficacy was evaluated through changes in standardized seizure frequency (SF), responder rate, and proportion of seizure-free patients. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs).

Results: One hundred and twenty-three patients were randomized. A noninferiority analysis failed to reject the null hypothesis that the change from baseline in the Power of Attention score in the ESL group was at least 121 ms inferior to the placebo group for all age groups. The CDR scores showed no differences between placebo and ESL in Power of Attention (1868.0 vs 1759.5), Continuity of Attention (1.136 vs −1.786), Quality of Working Memory (−0.023 vs −0.024), and Speed of Memory (−263.4 vs −249.6). Nonsignificant differences between placebo and ESL were seen for CHQ-PF50, CBCL scores, and Raven's SPM. Episodic Memory Index showed significant negative effect on ESL. Efficacy results favored the ESL group (SF least square [LS] means 1.98 vs 4.29). The TEAEs had a similar incidence between treatment groups (41.0% vs 47.5%).

Conclusions: Overall ESL did not produce statistically significant effects on neurocognitive and behavioral functioning in patients with epilepsy aged 6 to 16 years. Additionally, ESL was effective in reducing seizure frequency and was well-tolerated.

1. Introduction

Worldwide, epilepsy is estimated to affect over 50 million people [1], with children and adolescents being disproportionally impacted by this neurological condition [2–4]. Antiepileptic drugs (AEDs) can be used to successfully treat up to 70% of the affected children and adults [1]. Despite combination therapy, a large proportion of patients continue to have seizures, and among children, 25% remain refractory to treatment [5]. Adverse effects (AEs) caused by antiepileptic drugs are major contributors for treatment failure [6], leading to low treatment adherence [7,8] or discontinuation [8,9]. Epilepsy is often accompanied by impairment of cognitive functions [10], and in children, it is linked to attention, internalization, and thought difficulties that lead to poor psychosocial outcomes in adulthood [11]. The underlying causes of these problems are often challenging to precisely identify, but factors such as the etiology, developmental problems of the disease, and adverse effects of antiepileptic treatment may all play a role [12,13]. The most common cognitive effects associated with chronic use of

* Corresponding author at: Department of Research and Development, BIAL, A Av. da Siderurgia Nacional, 4745-457 S. Mamede do Coronado, Portugal.
E-mail address: psoares.silva@bial.com (P. Soares-da-Silva).

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AEDs include impaired mental and psychomotor development, vigilance, and attention [14]. Even though many pediatric studies reporting cognitive effects of AEDs have been reviewed as inconclusive [15], the therapeutic benefits of AEDs may largely outweigh the negative cognitive effects. This is of particular concern in children given the potential to negatively impact learning, social behavior, and school performance [15]. The risk of cognitive effects also highlights the need for appropriately designed prospective studies, based on thorough and well validated tools, to evaluate the effects of AEDs on cognitive function in children and to enable better comparisons across studies [16].

Eslicarbazepine acetate (ESL) is a once-daily antiepileptic drug (AED) [17,18] that has been approved by the European Medicines Agency (EMA), Food and Drug Administration (FDA), and Health Canada as adjunctive therapy in adults with focal-onset seizures (FOS), with or without secondary generalization. Later, both EMA- and FDA-approved ESL for monotherapy in the same population of patients; ESL has also been approved by EMA as adjunctive therapy in children aged above 6 years old with FOS. More recently, ESL received FDA approval for expanded indication to treat FOS in children and adolescents 4 years of age and older.

The current study was aimed at evaluating the effect of adjunctive therapy with ESL on cognitive function in children and adolescents aged 6 to 16 years old with refractory FOS. Efficacy and safety of ESL treatment in this age group are also addressed.

2. Patients and methods

This was a multicenter phase II, randomized, double-blind (DB), placebo-controlled, parallel study to evaluate the cognitive effects of ESL as adjunctive therapy in children with refractory FOS (NCT01527513). The study was conducted in 4 countries (Italy [18 patients], Poland [18 patients], Russia [47 patients], and Ukraine [40 patients]). Children (6–16 years old), diagnosed with epilepsy for ≥12 months prior to enrolment, with at least 2 epileptic FOS (≥4 in the month before enrolment), receiving 1–2 AEDs (except oxcarbazepine), and intelligence quotient (IQ) ≥70, were randomized (2:1) to ESL or placebo.

Part I consisted of an observational baseline period of 4 weeks, followed by a double-blind period of 12 weeks, comprising a 4-week up-titration period from 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks (to a maximum of 1200 mg/day). This was followed by an 8-week double-blind maintenance period at 30 mg/kg/day (or to a maximum of 1200 mg/day) if no intolerable AEs occurred at 20 mg/kg/day; if intolerable AEs occurred, the patient was down-titrated to the previous dose or discontinued. Patients down-titrated to 10 mg/kg/day during titration period received this dose for the 8-week maintenance period. There was a tapering-off period of up to 4 weeks where study treatment was tapered off in 10 mg/kg/day steps, and then, there was an additional 4-week observational follow-up period (Fig. 1). Treatment was given in 200-mg divisible tablets. The individual calculated dose was rounded to the nearest 100 mg. Study treatments were provided as 200-mg tablets, and doses were rounded to the nearest 100 mg (half tablet).

Part II consisted of a one-year, open-label, uncontrolled period which started after completion of the last 2 weeks, 10 mg/kg/day down-titration step in Part I (Fig. 1). All patients who entered this period initially received a dose of 10 mg/kg/day ESL, but this dose was titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg once daily (QD)). Doses were rounded to the nearest 100-mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored). Down-titration was allowed according to clinical response or in case of intolerable AEs, as often as needed. As much as possible, concomitant AED therapy (1 or 2 AEDs) was kept stable throughout Part II under the direction of the patient's physician. Patients entering the one-year open-label extension attended the study clinic for six scheduled visits during Part II for ongoing safety monitoring and performance of study assessments. At the end of Part II, patients either entered a tapering-off/follow-up period or a further period of open-label treatment with ESL (Part III). For patients who completed Part II and did not enter the additional two-year open-label extension, a poststudy visit (PSV) was performed approximately 4 weeks after study treatment was tapered off.

The Cognitive Drug Research (CDR) test battery [19,20] was used to assess changes in cognitive function. The test is designed to cover attention (focused and vigilant), working and episodic memory, and information processing/psychomotor speed, and has been validated in pediatric patients receiving AEDs [20]. An Episodic Memory Index (SI) was created, taking the Word Recognition Sensitivity Index (DRECSI) for children aged 9 to 16 years and the Picture Recognition Sensitivity Index (DPICSI) for children aged 6 to 8 years. Global cognitive skills were evaluated using the Raven's Standard Progressive Matrices (SPM) test [21–24] for children which consists in a series of short, non-verbal reasoning problems, based on visual spatial tasks that are used to assess intelligence in persons from age 6 to adulthood, independently of their cultural level. The test is composed of a total of 60 items presented in 5 sets (A–E), with 12 items per set. Social competence was assessed using the CBCL 6–18, which assesses child life function, and provides 2 major summary scores as follows: competence and problem behaviors. It is a parent-rated questionnaire for children aged 6–18 years old. In this study, only the competence score was evaluated as a measure of the child's social behavior and competence. Abnormal competence scores have been previously reported for children with epilepsy [25]. The quality of life (QOL) was evaluated using the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), a parent-rated questionnaire to assess the child's health, well-being, and the impact of illness on life function that was designed and normalized for children 5–18 years old. The CHQ-PF50 provides two weighted and standardized summary scores for physical and psychosocial health (CHQ summary scores). The physical health summary score measures the child's general health, pain, and limitations in physical and social activities due to health. The psychosocial health summary score measures the child's self-esteem, mental health, and the impact of the illness on physical and social activities. Efficacy was evaluated by relative reduction in standardized seizure frequency (SSF; seizure frequency per 4 weeks), proportion of responders (≥50% SSF reduction), and proportion of seizure-free patients (100% seizure reduction) from baseline. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs).

Sample size was calculated for a noninferiority study comparing the Power of Attention following treatment with ESL as add-on therapy with the Power of Attention in patients on placebo. Assuming a SD of 202.3 for the Power of Attention score, a noninferiority limit of 121 ms, and a one-tailed test at the 0.025 significance level, a total of 102 patients in the Cognitive per-protocol (PP) population would provide 80% power to reject the null hypothesis that the mean increase from baseline Power of Attention was at least 121 ms smaller in the placebo group than in the ESL group versus the alternative hypothesis that any advantage in the placebo group was less than in the inferiority limit [20]. Allowing for premature discontinuations and/or major protocol violations (and hence exclusion from the Cognitive PP population), a total of 117 patients were to be randomized (39 patients in the placebo group and 78 patients in the ESL group).

The study was approved by an ethics committee. Written informed consent was obtained from parent/legal representative and written assent was obtained from the patient.

2.1. Statistical analysis

The primary endpoint was change from baseline to the end of maintenance period in the composite Power of Attention (sum of the reaction time measures from the attentional tasks) measured with the CDR to assess information processing speed and attention/psychomotor