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Psychiatric and cognitive adverse events: A pooled analysis of three phase III trials of adjunctive eslicarbazepine acetate for partial-onset seizures

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ABSTRACT

Objective: To evaluate the nature and incidence of psychiatric and cognitive adverse events (AEs) reported with eslicarbazepine acetate (ESL) used as adjunctive treatment for refractory partial-onset seizures (POS) in adults.
Methods: This was a post-hoc analysis of data pooled from three randomized double-blind, placebo-controlled trials (BIA-2093-301, -302, -304). After an 8-week baseline period, patients received placebo or adjunctive ESL 400 mg (studies 301 and 302 only), 800 mg, or 1200 mg once daily (QD) for 14 weeks (2-week titration period, 12-week maintenance period). Psychiatric and cognitive AEs were identified from individual patient data. Suicidality was also evaluated using the Columbia-Classification Algorithm of Suicide Assessment (C-CASA), or the Columbia-Suicide Severity Rating Scale (C-SSRS). P-values were obtained using the chi-square test of independence or Fisher's exact test, without correcting for multiplicity.
Results: The analysis population included 1447 patients (ESL, n = 1021; placebo, n = 426). Psychiatric treatment-emergent AEs (TEAEs) occurred in 10.8% of patients receiving ESL, and in a comparable proportion (10.3%) of patients receiving placebo (p = 0.802). The incidence of depression and suicidality-related TEAEs was higher for ESL (7.4%) vs. placebo (3.8%) (p = 0.009). The occurrence of these TEAEs differed between treatment groups (p = 0.010), but there was no notable trend between increasing ESL dose and increasing incidence of depression and suicidality-related TEAEs. Aggression/hostility-related TEAEs occurred in <0.1% of patients taking ESL vs. 0.9% taking placebo. The incidence of cognitive TEAEs was higher for ESL (7.1%) vs. placebo (4.0%) (p = 0.023); incidences of memory impairment, attention disturbance, apathy, and aphasia were higher for ESL 1200 mg than for other treatment groups. Incidences of psychiatric and cognitive serious AEs were (0.6% and 0.2% with ESL, and 0.5%

Abbreviations: ADHD, attention deficit hyperactivity disorder; AED, antiepileptic drug; AE, adverse event; CBZ, carbamazepine; C-CASA, Columbia-Classification Algorithm of Suicide Assessment; C-SSRS, Columbia-Suicide Severity Rating Scale; ESL, eslicarbazepine acetate; LEV, levetiracetam; LTG, lamotrigine; MedDRA, Medical Dictionary for Regulatory Activities; OXC, oxcarbazepine; POS, partial-onset seizures; QD, once daily; SAE, serious adverse event; SMQ, standardized MedDRA queries; TEAE, treatment-emergent adverse event; VPA, valproic acid.

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and 0% with placebo, respectively. Psychiatric and cognitive TEAEs leading to discontinuation occurred in 1.9% and 1.4% of patients taking ESL. and 0.7% and 0.5% taking placebo, respectively.
Conclusions: In phase III clinical trials of adjunctive ESL for treatment-refractory POS, psychiatric and cognitive TEAEs were reported infrequently with ESL and placebo. The incidences of depression and suicidality-related TEAEs and of cognitive TEAEs were higher for patients taking ESL vs. placebo. Incidences of psychiatric and cognitive SAEs, and TEAEs leading to discontinuation, were low with ESL and placebo.

1. Introduction

Psychiatric illness and cognitive abnormalities are common comorbidities in patients with epilepsy [1,2]. In addition, most antiepileptic drugs (AEDs) carry a risk of psychiatric adverse events (AEs; including hyperactivity, agitation, irritability, aggression, depression, and psychosis) and might also have the potential to induce suicidal ideation and behavior; the risk varies between AED classes [3–6]. AEDs can also have a detrimental effect on cognitive function, which can lead to impairments in learning, driving ability, and memory [6,7].

Eslicarbazepine acetate (ESL, Aptiom®, Sunovion Pharmaceuticals Inc., Marlborough, MA; Zebinix®, BIAL - Portela & C[a], S.A., S. Mamede do Coronado, Portugal) is a once-daily (QD) oral AED for the treatment of partial-onset seizures (POS).

Three randomized, double-blind, phase III, placebo-controlled studies (BIA-2093-301, 302, and 304) examined the efficacy and safety of ESL as adjunctive therapy in adult with treatment-refractory POS [8–10]. Treatment with ESL 800 mg QD resulted in a statistically significant reduction in seizure frequency in two of the three studies, while ESL 1200 mg QD significantly reduced seizure frequency in all three studies [8–10]. The overall incidences of treatment-emergent AEs (TEAEs) and TEAEs leading to discontinuation were higher at higher ESL doses; the overall incidence of serious TEAEs with ESL was 5.3% versus 2.8% with placebo, and TEAEs leading to discontinuation occurred in 17.5% of patients taking ESL versus 6.6% of patients taking placebo [11].

This post-hoc analysis of data pooled from these three studies examines the nature and incidence of psychiatric AEs, and of AEs potentially related to changes in cognitive function, reported during treatment with adjunctive ESL.

2. Methods

2.1. Standard protocol approvals, registration, and patient consents

The three studies (BIA-2093-301 [NCT00957684]; -302 [NCT00957047]; and -304 [NCT00988429]; registered at ClinicalTrials.gov) were undertaken at centers in 35 countries between 2004 and 2012, in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines and all national, state, and local laws of the pertinent regulatory authorities. Approval was received from the relevant independent ethics committees/institutional review boards; written informed consent was obtained from all patients.

2.2. Study design

The study designs (including sample size determination), standard protocol approvals, registrations, and patient consents for studies 301, 302, and 304 have been reported previously [8–10]. Following an 8-week baseline period, patients were randomized equally to receive placebo or ESL 400 mg (studies 301 and 302 only), 800 mg, or 1200 mg tablets orally QD for 14 weeks (2-week titration period followed by a 12-week maintenance period), followed by a 2-week tapering-off period (studies 301 and 304) or abrupt discontinuation of treatment (study 302). Study treatment was added to continued stable doses of baseline AEDs.

2.3. Patients

Patients aged 16–75 years with POS not adequately controlled by one to two (studies 301 and 304) or one to three (study 302) AEDs were eligible for inclusion. The use of oxcarbazepine (OXC) was not allowed due to similarities between OXC and ESL metabolites. Further details of the inclusion and exclusion criteria for these trials have been published previously [8–10]. Patients with a history of suicide attempts or major psychiatric disorders, including schizophrenia, were excluded from the studies.

2.4. Assessment of TEAEs

Individual patient data from studies 301, 302, and 304 were pooled and analyzed, and patients with psychiatric or cognitive TEAEs were identified; investigators recorded TEAEs and were asked to assess them in terms of severity (mild, moderate, severe) and seriousness (serious, nonserious). A serious AE (SAE) was classified as any TEAE that: resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a birth defect; or was another medically important condition. TEAEs were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) v13.1.

Psychiatric TEAEs were identified as those within the System Organ Class "Psychiatric Disorders". Psychiatric TEAEs (including signs and symptoms) from the three trials were evaluated. TEAEs were also identified by clinical audit of investigator records and case report forms, and by review of patient narratives and SAE reports (Council for International Organizations of Medical Sciences forms).

Depression and suicidality TEAEs were identified by standardized MedDRA queries (SMQs; validated sets of MedDRA TEAEs used to identify specific safety topics of interest) for "depression" (excluding "suicide" and "self-injury") and "suicide/self-injury" (TEAEs with the Preferred Terms "suicide", "suicidal", or "self-injury"). Suicidality was also evaluated retrospectively by blinded review using the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) (studies 301 and 302), and prospectively using the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal behavior after the baseline period (study 304) [12]. The number of patients with C-CASA scores of one to four (suicidal behavior/ideation) or seven (nonsuicidal self-injurious behavior) was determined for each treatment group, and the number of patients with C-SSRS ratings of "any suicidal behavior" or "worsening in suicidal ideation" was recorded separately.

Hostility/aggression-related TEAEs were identified by a narrow SMQ for "hostility/aggression".

The following searches were used to identify cognitive TEAEs: SMQs for "hostility/aggression" and "psychosis and psychotic disorders"; any investigator-reported TEAEs of "memory impairment", "amnesia", "bradyphrenia", "psychomotor retardation", "speech disorder", "aphasia", "disturbance in attention", or "change in sustained attention"; and any investigator-reported TEAE in the high level term of "mental impairment" (excluding dementia and memory loss) or "cognitive and attention disorders and disturbances not elsewhere classified". Searches used TEAEs from the clinical database, and additional potential TEAEs identified during reviews of subject records.

The safety population (patients who received ≥1 dose of study drug after randomization) was used for these analyses.