LONG-TERM SAFETY AND TOLERABILITY OF ESLICARBAZEPINE ACETATE (ESL): RESULTS FROM BIA-2093-311/EXT STUDY – THE 2-YEAR OPEN-LABEL EXTENSION OF THE ESL MONOTHERAPY STUDY (BIA-2093-311)

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INTRODUCTION

Eslicarbazepine acetate (ESL) is a once-daily (QD) antiepileptic drug (AED) that is approved in Europe as monotherapy in the treatment of partial-onset seizures, with or without secondary generalization, in adults with newly diagnosed epilepsy, and as adjunctive therapy in adults, adolescents and children aged >6 years with partial-onset seizures, with or without secondary generalization.[1] In the USA, ESL is approved for the treatment of partial-onset seizures in patients aged ≥4 years.[2]

The safety/tolerability of ESL monotherapy was assessed in a Phase III, randomized, double-blind, active-controlled, non-inferiority study (Study 311), which demonstrated that the incidence of treatment-emergent adverse events (TEAEs) was generally similar for patients treated with QD ESL monotherapy (76.3%) and those treated with twice-daily (BID) controlled-release carbamazepine (CBZ-CR; 79.6%).[3] The incidence of TEAEs considered at least possibly related to treatment was lower for ESL than CBZ-CR (42.1% vs. 51.5%), as was the incidence of TEAEs leading to discontinuation (14.0% vs. 18.4%).[3] Overall, the safety/tolerability profile of ESL monotherapy was generally consistent with its profile in the adjunctive therapy setting.[1,3] However, data on the long-term safety/tolerability of ESL monotherapy, as well as the nature and frequency of TEAEs of ESL in patients switching from CBZ-CR treatment, are currently limited.

Patients completing the double-blind Phase III trial could continue into an open-label extension (OLE) study (311-EXT), where they received flexible dosing with ESL for a further 2 years. Presented here are the ESL monotherapy safety/tolerability results from the OLE study.

PURPOSE

To assess the long-term safety/tolerability of ESL monotherapy in patients initially treated in the double-blind Study 311 with ESL and those who switched from CBZ-CR monotherapy to ESL.

MATERIAL AND METHODS

Study design

- Study 311 was a randomized, double-blind, non-inferiority trial that employed a stepwise design with three dose levels (ESL, 800, 1200 and 1600 mg QD; CBZ-CR, 200, 400 and 600 mg BID), details of which have been published previously[3]
- Patients who completed the double-blind Phase III trial (i.e. who remained seizure free for ≥6 months at the last evaluated dose) were eligible to enter a 2-year extension study, in which all patients received open-label treatment with flexibly-dosed ESL monotherapy
  - Patients treated with ESL during the double-blind Phase III trial (ESL/ESL) continued at their last evaluated dose level
  - Patients treated with CBZ-CR during the double-blind Phase III trial were transitioned to ESL (CBZ-CR/ESL)
    - ESL was initiated at 400 mg QD and up-titrated after 1 week in steps of 400 mg/week to target ESL dose (equivalent to last evaluated CBZ-CR dose level: ESL 800 mg QD for CBZ-CR 200 mg BID; ESL 1200 mg QD for CBZ-CR 400 mg BID; ESL 1600 mg QD for CBZ-CR 600 mg BID)
    - All patients previously treated with CBZ-CR (regardless of last evaluated dose level) commenced CBZ-CR down-titration 2 weeks after initiating ESL treatment
  - Subsequently, ESL dosing was adjusted within the dose range 800–1600 mg QD, according to response and tolerability
    - Concomitant AED treatment could be added, if required (according to investigator's opinion)

Study population

- Initial double-blind Phase III trial included adult patients (≥18 years old) with newly diagnosed epilepsy, provided they had at least two focal-onset seizures (with or without secondary generalization) within 12 months of screening and at least one seizure during the previous 3 months[3]
  - Patients were also required to: have had an electroencephalogram and brain computerized axial tomography or magnetic resonance imaging (to exclude a progressive neurological lesion) in the previous 12 months; provide written informed consent; and demonstrate cooperation and willingness to complete the study[3]
- Patients who completed the double-blind Phase III trial (i.e. who remained seizure free for ≥6 months at the last evaluated dose) were eligible to enter the OLE study
  - Key exclusion criteria included: presence of any major protocol violation during initial trial that could impact compliance in OLE study; suicidal risk (based on investigator's opinion and Columbia Suicide-Severity Rating Scale [C-SSRS]); occurrence of an adverse event (AE) in initial trial indicating suspected presence of atrioventricular block (second degree or above) or contraindicative to further participation (investigator's judgement); events of alcohol/drug/medication abuse during initial trial; presence of clinically relevant laboratory abnormalities (e.g. sodium <125 mmol/L); pregnancy or lactation
- Patients with concomitant AED treatment (a total of 22/206 [10.7%]) were excluded from the analysis presented here

Study assessments

- Rate of study completion/discontinuation
  - Reasons for discontinuation were recorded
- Safety and tolerability
  - Evaluated by assessing the rate and types of:
    - TEAEs
    - Treatment-related TEAEs (defined as at least possibly related)
    - Serious TEAEs
    - Treatment-related serious TEAEs
    - TEAEs by severity
    - TEAEs leading to discontinuation

Statistical analyses

- All assessments were conducted for the Monotherapy Safety Set, defined as all patients who received at least one dose of ESL and remained on monotherapy treatment during the OLE study
- Kaplan-Meier analysis was used to assess withdrawal from the study
- Categorical and continuous variables were summarized using descriptive statistics

RESULTS

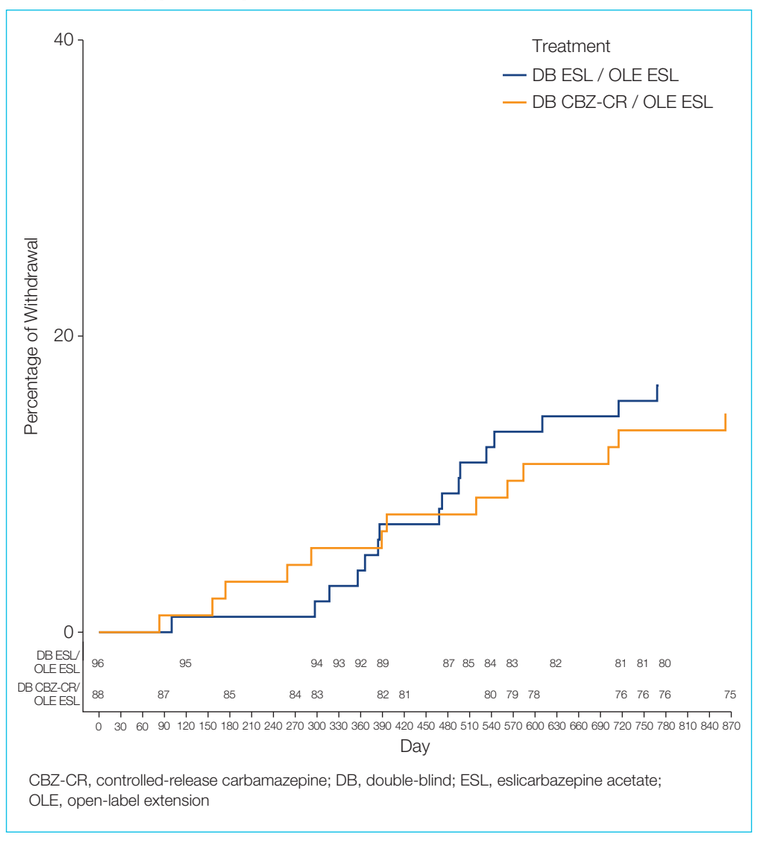
Study population

- A total of 206 patients entered the OLE study (ESL/ESL, n=109; CBZ-CR/ESL, n=97)
  - Majority of patients (184/206 [89.3%]) received ESL monotherapy throughout the OLE study (ESL/ESL, n=96; CBZ-CR/ESL, n=88)
  - Demographic and baseline characteristics of patients in the ESL/ESL and CBZ-CR/ESL groups were generally similar
  - For the monotherapy population, 57.3% of patients were male, mean age was 42.5 years, mean age at onset of epilepsy was 39.2 years, median time since last seizure was 11.0 days (interquartile range, 0–88), and median number of seizures in previous 3 months was 2.0 (interquartile range, 1–230)

Patient disposition

- Overall, 155/184 (84.2%) patients completed the study and completion rates were similar between groups (ESL/ESL, 83.3%; CBZ-CR, 85.2%) (**Figure 1**)

Figure 1. Withdrawal rate (any reason) during OLE study (Monotherapy Safety Set)



CBZ-CR, controlled-release carbamazepine; DB, double-blind; ESL, eslicarbazepine acetate; OLE, open-label extension

- Withdrawal due to TEAEs was low and similar between groups (ESL/ESL, 3.1%; CBZ-CR/ESL, 4.5%)
- No patients were discontinued due to protocol violations, to development of suicide-related thoughts and behaviors identified (based upon clinical interview and C-SSRS), and to development of hypersensitivity signs or symptoms, including rash

ESL exposure

- Mean (standard deviation [SD]) daily dose of ESL during the OLE study was 904.5 (210.5) mg QD overall (median, 800.0 mg QD; range, 756–1600 mg QD)
  - ESL/ESL group: 899.2 (205.0) mg QD (median, 800.0 mg QD; range, 756–1600 mg QD)
  - CBZ-CR/ESL group: 910.3 (217.4) mg QD (median, 796.2 mg QD; range, 773–1573 mg QD)
- Mean (SD) duration of treatment during the OLE study was 683.2 (144.4) days overall (median, 732.0 days; range, 39–769 days)
  - ESL/ESL group: 685.8 (129.2) days (median, 734.0; range 84–769 days)
  - CBZ-CR/ESL group: 680.5 (160.1) days (median, 730.5 days; range, 39–758 days)
- Majority of patients in the ESL/ESL and CBZ-CR/ESL groups maintained the same ESL dose during the OLE study (95.8% and 89.8%, respectively)
  - In the ESL/ESL group, four patients (4.2%) had a dose increase
  - In the CBZ-CR/ESL group, nine patients (10.2%) had a dose increase

Safety and tolerability

- Overall, 109/184 (59.2%) patients reported TEAEs (ESL/ESL, 53.1%; CBZ-CR/ESL, 65.9%) (**Table 1**)

Table 1. Summary of TEAEs (Monotherapy Safety Set)

	ESL/ESL (N=96)	CBZ-CR/ESL (N=88)	Total (N=184)
Patients with any TEAE, n (%)	51 (53.1)	58 (65.9)	109 (59.2)
Most frequently reported[a] TEAEs, n (%)			
Blood creatine phosphokinase increased	7 (7.3)	5 (5.7)	12 (6.5)
Nasopharyngitis	5 (5.2)	6 (6.8)	11 (6.0)
Hypertension	5 (5.2)	6 (6.8)	11 (6.0)
Influenza	6 (6.3)	4 (4.5)	10 (5.4)
Back pain	3 (3.1)	5 (5.7)	8 (4.3)
Dizziness	3 (3.1)	5 (5.7)	8 (4.3)
Headache	3 (3.1)	5 (5.7)	8 (4.3)
Somnolence	3 (3.1)	5 (5.7)	8 (4.3)
International normalized ratio increased	2 (2.1)	5 (5.7)	7 (3.8)
Gamma-glutamyltransferase increased	5 (5.2)	1 (1.1)	6 (3.3)
Bronchitis	0	5 (5.7)	5 (2.7)
Patients with any treatment-related[b] TEAE, n (%)	17 (17.7)	16 (18.2)	33 (17.9)
Most frequently reported[c] treatment-related[b] TEAEs, n (%)			
Blood creatine phosphokinase increased	3 (3.1)	1 (1.1)	4 (2.2)
Gamma-glutamyltransferase increased	4 (2.2)	0	4 (2.2)
Nausea	0	3 (3.4)	3 (1.6)
C-reactive protein increased	0	2 (2.3)	2 (1.1)
Obesity	2 (2.1)	0	2 (1.1)
Headache	0	2 (2.3)	2 (1.1)
Somnolence	2 (2.1)	0	2 (1.1)
Patients with any serious TEAE, n (%)	7 (7.3)	5 (5.7)	12 (6.5)
Patients with any treatment-related[b] serious TEAE, n (%)	0	1 (1.1)	1 (0.5)
Seizure	0	1 (1.1)	1 (0.5)
Patients with any TEAE leading to death, n (%)	3 (2.8)	0	3 (1.5)
Sudden death	1 (1.0)	0	1 (0.5)
Cerebral hemorrhage	1 (1.0)	0	1 (0.5)
Pulmonary embolism	1 (1.0)	0	1 (0.5)
TEAEs by severity, n (%)			
Mild	42 (43.8)	49 (55.7)	91 (49.5)
Moderate	25 (26.0)	27 (30.7)	52 (28.3)
Severe	8 (8.3)	4 (4.5)	12 (6.5)
Most frequently reported[d] severe TEAEs, n (%)			
Back pain	1 (1.0)	1 (1.1)	2 (1.1)
Blood creatine phosphokinase increased	1 (1.0)	1 (1.1)	2 (1.1)
Patients with any TEAE leading to discontinuation, n (%)	3 (3.1)	4 (4.5)	7 (3.8)

[a]≥5% patients in any group; [b]At least possibly related to study drug; [c]≥2% patients in any group; [d]≥2 patients in any group; TEAE, treatment-emergent adverse event

- TEAEs considered to be at least possibly related to treatment were reported for 33/184 (17.9%) patients overall, and rates were similar for the ESL/ESL (17.7%) and CBZ-CR/ESL (18.2%) groups
  - The most frequently reported treatment-related TEAEs (≥2% patients in any group) were blood creatine phosphokinase increased, gamma-glutamyltransferase increased, nausea, C-reactive protein increased, obesity, headache, and somnolence
    - Some of these TEAEs were only reported by patients in the ESL/ESL group (gamma-glutamyltransferase increased, somnolence, obesity) or CBZ-CR/ESL group (nausea, C-reactive protein increased, headache)
- Serious TEAEs were reported for 12/184 (6.5%) patients overall (ESL/ESL, 7.3%; CBZ-CR/ESL, 5.7%)
  - No serious TEAE was reported for more than one patient
  - Only one serious TEAE was considered to be at least possibly related to treatment (a case of seizure in the CBZ-CR/ESL group)
- A total of three patients died during the OLE study
  - All three deaths occurred in the ESL/ESL group but none were considered related to treatment (sudden death, n=1; cerebral hemorrhage, n=1; pulmonary embolism, n=1)
- The majority of TEAEs were of mild or moderate intensity (77.7% overall; ESL/ESL, 69.8%; CBZ-CR/ESL, 86.4%)
  - Severe TEAEs were reported for 12/184 (6.5%) patients overall (ESL/ESL, 8.3%; CBZ-CR/ESL, 4.5%)
  - The only severe TEAEs reported for more than one patient were back pain (ESL/ESL, n=1; CBZ-CR/ESL, n=1) and blood creatine phosphokinase increased (ESL/ESL, n=1; CBZ-CR, n=1)
- Overall, a total of 7/184 (3.8%) patients had TEAEs leading to discontinuation (ESL/ESL, 3.1%; CBZ-CR/ESL, 4.5%)

CONCLUSIONS

- ESL monotherapy was generally well tolerated during this 2-year OLE study, in patients initially treated with ESL monotherapy and those who transitioned from CBZ-CR monotherapy to ESL monotherapy.
  - Most TEAEs were of mild or moderate intensity, the rate of discontinuation due to TEAEs was low and only one patient experienced a serious TEAE that was considered at least possibly related to treatment.
- The long-term safety/tolerability profile of ESL monotherapy was consistent with what has been reported in previous clinical trials including OLE studies[1] and no new safety signals emerged.
- These findings support the use of ESL as long-term monotherapy, including in those patients previously treated with CBZ-CR.

References

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