LONG-TERM EFFICACY 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]

ESL was approved by the European Medicines Agency as monotherapy treatment for newly diagnosed adults with focal seizures on the basis of a Phase III, randomized, double-blind (DB), active-controlled, non-inferiority study (Study 311).[3] This demonstrated that treatment with QD ESL was non-inferior to treatment with twice-daily (BID) controlled-release carbamazepine (CBZ-CR): overall, 71.1% of ESL-treated patients and 75.6% of those treated with CBZ-CR were seizure-free for ≥6 months at the last evaluated dose (average risk difference, -4.28%; 95% confidence interval, -10.30–1.74; predefined non-inferiority criterion, -12%).[3] Patients completing the DB Study 311 could continue into a 2-year, open-label extension (OLE) study, in which all patients received flexible dosing with ESL monotherapy. Presented here are the efficacy results from the OLE study.

PURPOSE

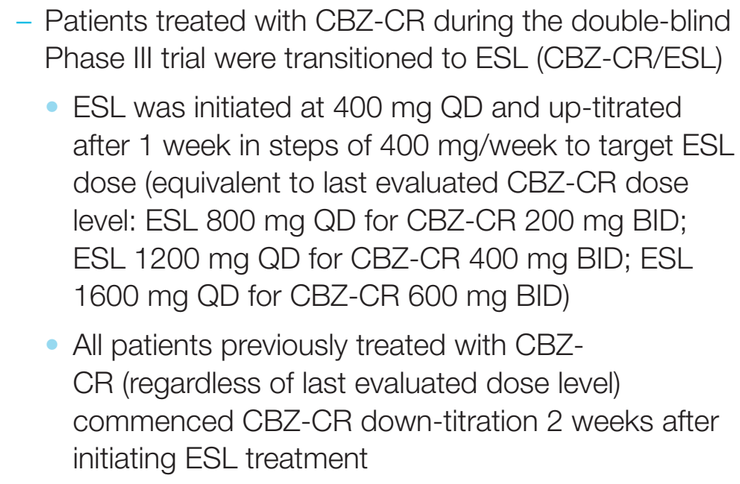
To confirm maintenance of efficacy of ESL monotherapy during long-term treatment and to investigate efficacy of ESL in patients switching from CBZ-CR treatment, in adults who have completed DB Study 311.

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 (311-EXT), in which all patients received open-label treatment with flexibly-dosed ESL monotherapy (**Figure 1**)
  - 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)

Figure 1. Study design of double-blind Phase III trial (311) and OLE study (311-EXT)



Adapted from Trinka et al, 2018.[3] BID, twice daily; CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; OLE, open-label extension; QD, once daily

*If seizures occurred during the evaluation period, patients were assigned to the next dose level using 1-week titration period (CBZ-CR required titration, ESL did not) and 1-week stabilization period, followed by 26-week evaluation period as before. †Patients who remained seizure free for 26 weeks at any dose during the evaluation period entered the 26-maintentance period. ¶Patients who received CBZ-CR during the double-blind Phase III trial transitioned to ESL at the start of the open-label extension study

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 double-blind Phase III trial that could impact compliance in OLE study; suicidal risk (based on investigator's opinion and Columbia Suicide-Severity Rating Scale); occurrence of an 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

Key efficacy assessments

- Seizure freedom rate
  - Seizure freedom was defined as no seizures during the entire OLE study
- Overall treatment satisfaction
  - Rated by patients and investigators using a four-point scale ('Very good', 'Good', 'Fair' or 'Poor')

Statistical analyses

- All assessments were conducted for the Full Analysis Set which included all randomized patients who took at least one dose of study drug and remained on ESL monotherapy treatment during OLE 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)
- The majority of patients, 184 out of 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 (**Table 1**)
  - Overall, 155/184 (84.2%) patients completed the study and completion rates were similar between groups (ESL/ESL, 83.3%; CBZ-CR/ESL, 85.2%)
  - Withdrawal due to treatment-emergent adverse events was low and similar between groups (ESL/ESL, 3.1%; CBZ-CR/ESL, 4.5%)

Table 1. Summary of demographic and epilepsy-related characteristics (Full Analysis Set)

	ESL/ESL (n=96)	CBZ-CR/ESL (n=88)	Total (n=184)
Demographic characteristics[a]			
Sex, n (%)			
Male	55 (57.3)	45 (51.1)	100 (54.3)
Female	41 (42.7)	43 (48.9)	84 (45.7)
Age, years			
Mean (SD)	42.5 (15.8)	41.6 (15.79)	42.1 (15.76)
Median (range)	40.0 (20–76)	39.0 (20–78)	40.0 (20–78)
Ethnicity			
Caucasian	90 (93.8)	81 (92.0)	171 (92.9)
Other	6 (6.3)	7 (8.0)	13 (7.1)
Body mass index, kg/m²			
Mean (SD)	25.673 (4.3606)	25.927 (4.6124)	25.794 (4.4723)
Median (range)	25.460 (17.84–36.14)	25.075 (16.38–45.20)	25.365 (16.38–45.20)
Epilepsy-related characteristics[b]			
Age at onset of epilepsy, years			
Mean (SD)	39.5 (15.83)	38.9 (15.77)	39.2 (15.76)
Median (range)	37.0 (18–74)	37.0 (18–75)	37.0 (18–75)
Time since last seizure, days			
Mean (SD)	19.3 (20.69)	20.6 (22.91)	19.9 (21.71)
Median (range)	11.0 (0–88)	10.0 (0–88)	11.0 (0–88)
Number of seizures[c] in previous 3 months, n			
Mean (SD)	6.7 (12.81)	10.7 (28.31)	8.6 (21.68)
Median (range)	2.0 (1–91)	3.0 (1–230)	2.0 (1–230)
Etiology, n (%)			
Idiopathic	2 (2.1)	0 (0.0)	2 (1.1)
Infection/diseases	2 (2.1)	1 (1.1)	3 (1.6)
Congenital/hereditary disorders	2 (2.1)	2 (2.3)	4 (2.2)
Brain tumor	2 (2.1)	0 (0.0)	2 (1.1)
Cranial tumor/injury	5 (5.2)	21 (23.9)	26 (14.1)
Cerebrovascular disease	17 (17.7)	7 (8.0)	24 (13.0)
Other	8 (8.3)	11 (12.5)	19 (10.3)
Unknown	58 (60.4)	46 (52.3)	104 (56.5)
Family history of epilepsy, n (%)			
Yes	7 (7.3)	4 (4.5)	11 (6.0)

[a]At baseline of OLE study; [b]At baseline of initial double-blind trial; [c]All seizure types. CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; OLE, open-label extension; SD, standard deviation

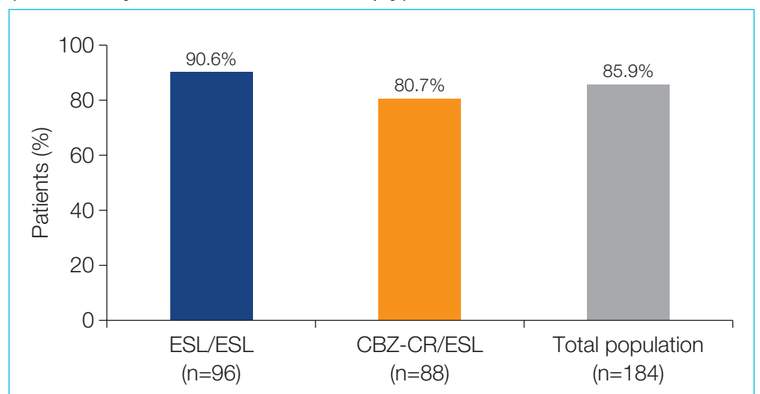
ESL dosing

- Mean (standard deviation) daily dose of ESL during the OLE study was 904.5 (210.51) mg QD overall (median, 800.0 mg QD; range, 756–1600 mg QD)
  - ESL/ESL group: 899.2 (205.03) mg QD (median, 800.0 mg QD; range, 756–1600 mg QD)
  - CBZ-CR/ESL group: 910.3 (217.36) mg QD (median, 796.2 mg QD; range, 773–1573 mg QD)
- The 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

Seizure freedom rate

- 158/184 (85.9%) of patients achieved seizure freedom during the 2-year OLE study (**Figure 2**)
- Seizure freedom rate was higher in the ESL/ESL group (90.6%) than the CBZ-CR/ESL group (80.7%)

Figure 2. Seizure freedom rate during 2-year OLE study (Full Analysis Set-Monotherapy)

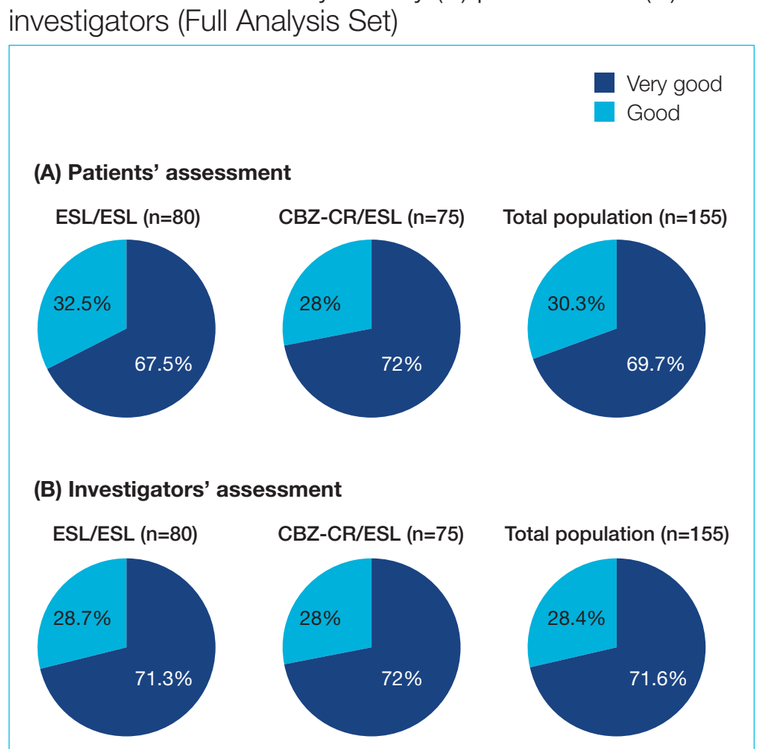


Seizure freedom was defined as no seizures during the entire OLE study. CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate

Overall treatment satisfaction

- At the end of study visit, overall treatment satisfaction was rated for 155 patients (ESL/ESL, n=80; CBZ-CR/ESL, n=75)
  - Overall treatment satisfaction was rated as 'very good' or 'good' by 100% of patients and investigators (**Figure 3**)
  - No patients or investigators rated overall treatment satisfaction as fair or poor

Figure 3. Assessment of overall satisfaction with treatment at end of study visit by (A) patients and (B) investigators (Full Analysis Set)



Overall satisfaction was rated on a four-point scale ('Very good', 'Good', 'Fair', 'Poor'). CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate

CONCLUSIONS

- The efficacy of ESL monotherapy observed in the double-blind Phase III trial was sustained during long-term treatment, in patients initially treated with ESL monotherapy and in those who transitioned from CBZ-CR monotherapy.
  - More than 80% of patients in each group were seizure free during the 2-year OLE study.
- These findings support the use of ESL as long-term monotherapy in patients with focal epilepsy.

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3. Trinka E, Ben-Menachem E, Kowacs PA, *et al*. Efficacy and safety of eslicarbazepine acetate versus controlled-release carbamazepine monotherapy in newly diagnosed epilepsy: A phase III double-blind, randomized, parallel-group, multicenter study. *Epilepsia* 2018;59:479–91.

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