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ARTICLE

Long-term effects of adjunctive eslicarbazepine acetate in adult Asian patients with refractory focal seizures: *Post hoc* analysis of a phase III trial

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Abstract

A *post hoc* analysis of data from Asian patients included in the study BIA-2093-304 was conducted to evaluate the long-term safety/tolerability and efficacy of adjunctive eslicarbazepine acetate (ESL) in adult Asian patients with refractory focal seizures. Part I was a randomized controlled trial, in which patients received ESL (800 or 1200 mg once daily [QD]) or placebo, assessed over a 12-week maintenance period. Patients completing Part I could enter two open-label extension periods (Part II, 1 year; Part III, ≥2 years), during which all received ESL (400–1600 mg QD). Safety/tolerability was assessed by evaluating treatment-emergent adverse events (TEAEs). Efficacy assessments included responder and seizure freedom rates. The safety population included 125, 92, and 23 Asian patients in Parts I, II, and III, respectively. Incidence of ESL-related TEAEs was 61.3%, 45.7%, and 17.4% during Parts I, II, and III, respectively. ESL-related TEAEs (most commonly, dizziness, somnolence, and headache) were consistent with ESL's known safety profile. During Part I, responder rates were higher with ESL 800 (41.7%) and 1200 mg QD (44.4%) versus placebo (32.6%), although not statistically significant. Seizure freedom rates with ESL 800 (5.5%) and 1200 mg QD (11.1%) were also higher versus placebo (0%) ($p < 0.05$ for ESL 1200 mg QD versus placebo). At the end of Part II, responder and seizure freedom rates were 60.3% and 14.7%, respectively. In summary, adult Asian patients with refractory focal seizures were responsive to treatment with ESL as adjunctive therapy and generally showed treatment tolerance well for up to 3 years. No new/unexpected safety findings were observed.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Only one other study has investigated the use of eslicarbazepine acetate specifically in Asian subjects (healthy Korean adults).

WHAT QUESTION DID THIS STUDY ADDRESS?

This study addresses the question: what is the long-term safety profile of adjunctive eslicarbazepine acetate therapy when used to treat adult Asian patients with refractory focal seizures, and is it efficacious in this setting?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study is the first to specifically assess the use of eslicarbazepine acetate in Asian patients with epilepsy. It demonstrated that eslicarbazepine acetate was generally well tolerated when used as an adjunctive therapy in adult Asian patients with refractory focal seizures for up to 3 years. No new or unexpected safety findings were observed. Response to eslicarbazepine acetate treatment was sustained over the long term.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides valuable information on the use of adjunctive eslicarbazepine acetate therapy in adult Asian patients with refractory focal seizures.

INTRODUCTION

Epilepsy affects 50 million people worldwide, of whom approximately half live in Asia.[1,2] The incidence of epilepsy is higher in Asia than in Western countries, which may be due to a variety of factors, including comparatively high risks in Asia of endemic central nervous system infections (e.g., cerebral malaria), traumatic brain injury, perinatal injury, and stroke.[1] However, Asia encompasses over 40 countries that are heterogeneous in terms of population, socioeconomic status, culture, and healthcare provision, and the prevalence of epilepsy varies by region from 1.5/1000 (Hong Kong) to 14.0/1000 (Vietnam).[1] The incidence of epilepsy in Asia is highest during childhood and early adulthood, whereas, in Western countries, the highest incidence is during childhood and late adulthood, perhaps reflecting the relatively young age of the general population in Asia, in comparison with Western countries.[1]

Ethnicity can affect the pharmacokinetic and pharmacodynamic profiles of drugs, resulting in variability in safety/tolerability and efficacy.[2,3] Such variability may result from racial, genetic, and/or lifestyle factors.[3,4] For example, differences in the expression of genes for major histocompatibility complex class I B (HLA-B) and cytochrome P450 (CYP) enzymes may affect response to antiseizure medications (ASMs).[2] Frequencies of the *HLA-B*1502* allele vary among different ethnic populations, with a greater prevalence in some Asian populations, including individuals of Han Chinese and Thai origin, and this has been shown to increase the risk of developing severe cutaneous reactions following treatment with carbamazepine.[2,5–7] Some *CYP* polymorphisms observed in Asian populations are also known to affect the pharmacokinetic profile of other ASMs, including phenytoin and phenobarbital.[8–11] Consequently, ethnicity should be considered when evaluating the benefit–risk of using a particular ASM for an individual patient.[2]

Eslicarbazepine acetate (ESL) is a once-daily (QD) ASM that is approved in Europe and in the USA for the treatment of focal-onset seizures as monotherapy or adjunctive therapy.[12,13] The efficacy and safety/tolerability of ESL as adjunctive therapy for focal seizures were established in a series of phase III, randomized, double-blind (DB), placebo-controlled trials (Studies BIA-2093-301, -302, and -304).[14–17] A phase I, dose randomized, DB, placebo-controlled, single and multiple dosing, dose-escalation study was performed and demonstrated that the pharmacokinetic characteristics of ESL and its active metabolites were similar between Korean and White healthy subjects after single and multiple dosing, and that there were no substantial differences in safety and tolerability between the groups.[18] Since the study BIA-2093-304 recruited patients from sites in Asia and therefore included a substantial proportion of patients of Asian ethnicity, a *post hoc* analysis of the study was conducted to specifically evaluate the long-term safety, tolerability, and efficacy of adjunctive ESL therapy in adult Asian patients with refractory focal seizures.

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METHODS

Study design

Part I of the study BIA-2093-304 was a phase III, international, multicenter, randomized, DB, placebo-controlled, parallel-group trial, conducted in patients aged ≥16 years with uncontrolled focal-onset seizures despite treatment with one or two ASMs, the results of which have been published previously.[17] The trial was conducted at 173 centers in 19 countries (Argentina, Australia, Brazil, Belgium, Canada, Cyprus, France, Germany, Greece, Hungary, India, Italy, Poland, Turkey, South Korea, Romania, South Africa, Ukraine, and the USA) between December 2008 and January 2012.[17]

After an 8-week baseline period, patients were randomized in a ratio of 1:1:1 to receive ESL 800 mg QD, ESL 1200 mg QD, or placebo during a 2-week titration period and subsequent 12-week maintenance period (Figure 1).[17] Patients completing Part I were eligible to enter Part II. During Part II, all patients were initially treated with ESL 800 mg QD for 1 month, after which ESL dosing was adjusted in 400-mg increments within the dose range 400–1600 mg QD, according to clinical response and tolerability, and continued for 1 year (Figure 1). Patients completing Part II were eligible to enter Part III. During Part III, patients continued ESL at the dose at which they completed Part II, with treatment subsequently adjusted in 400-mg increments within the dose range 400–1600 mg QD, according to clinical response and tolerability, and continued for an additional 2 years (Figure 1). The duration of Part III was longer than 2 years in some countries and up to 4 years: Brazil (additional 1 year), USA and Canada (additional 2 years), Argentina and South Korea (additional 4 years).

Study BIA 2-093-304 was approved by the appropriate institutional review boards and was conducted in accordance with international and local regulations of the countries involved.[17] The full list of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) is provided in Table S2. Informed consent was obtained from all patients.[17]

Study population

To be included in the study BIA-2093-304, patients were required to be aged ≥16 years; have a documented diagnosis of epilepsy for ≥12 months; have at least eight documented focal seizures during the baseline period (with at least three seizures during each 4-week period and no seizure-free interval exceeding 28 consecutive days); and be receiving treatment with a stable dose of one or two ASMs (except oxcarbazepine) for ≥1 month prior to screening.[17] Patients were excluded if they had focal seizures with no motor symptoms; primary generalized seizures; hypersensitivity to carbamazepine/carbamazepine derivatives; a positive *HLA-B*1502* test (for patients of Asian ancestry); second- or third-degree atrioventricular blockade not corrected with a pacemaker; relevant clinical laboratory abnormalities; a history of schizophrenia or suicide attempts; and if they were currently being treated with oxcarbazepine.[17] The current *post hoc* analysis only included Asian patients aged ≥18 years.

Study assessments

Safety/tolerability

Safety/tolerability were assessed during the DB trial (Part I) and open-label extension (OLE) periods (Parts II and III). Assessments included evaluation of

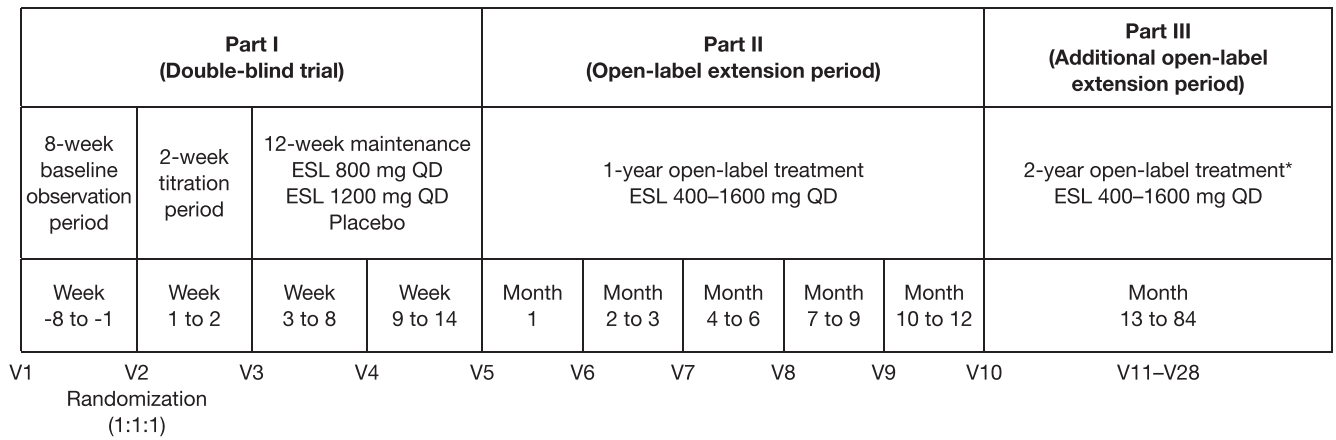

FIGURE 1 Study design. *Duration of Part III was longer than 2 years in some countries: Brazil (additional 1 year), USA and Canada (additional 2 years), Argentina and South Korea (additional 4 years). ESL, eslicarbazepine acetate; QD, once daily; V, visit.

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treatment-emergent adverse events (TEAEs), including any TEAEs, related TEAEs (defined as TEAEs considered to be definitely, probably or possibly related to ESL treatment, and those with "missing" information on relatedness), serious TEAEs, TEAEs leading to death, TEAEs by severity (mild, moderate, and severe) and TEAEs leading to discontinuation.

Retention and exposure

Retention was assessed during both OLE periods (Parts II and III). Exposure to ESL was assessed during the DB trial and OLE periods (Parts I, II, and III).

Efficacy

Efficacy was assessed during the DB trial (Part I) and first 1-year OLE period (Part II). Efficacy assessments comprised standardized seizure frequency (SSF; defined as the number of seizures per 4 weeks), responder rate (defined as ≥50% seizure frequency reduction from DB baseline) and seizure freedom rate (defined as 100% seizure frequency reduction from DB baseline). Efficacy was not assessed during the second OLE period (Part III) due to the number of patients during this period.

Statistical analyses

The Safety Population was defined as all randomized patients who received at least one dose of study drug. The Intention-To-Treat (ITT) population was defined as all randomized patients who received at least one dose of study drug and had at least one post-baseline seizure frequency assessment. The ITT population included patients who used event entry and daily entry diaries. During the DB trial (Part I), safety assessments were conducted for the safety population and all other assessments were conducted for the ITT population. During the OLE periods (Parts II and III), all assessments were conducted for the Safety Populations. All endpoints and outcomes were assessed for Asian patients only.

For Part I, SSF was compared for ESL 800 mg QD versus placebo and ESL 1200 mg QD versus placebo. Statistical analysis was based on an analysis of covariance (ANCOVA) model. Response was Napierian log-transformed SSF, with treatment group and diary version included as fixed effects and baseline ln SSF included as a covariate. No imputation of missing data were used. This was a *post hoc* exploratory analysis, no adjustment for multiplicity was conducted and results should be interpreted carefully. Forest plots of least squares (LS) mean differences between ESL versus placebo for change from baseline in SSF were plotted, with 95% confidence intervals (CIs), by ESL dose (800 mg QD, 1200 mg QD). Responder and seizure freedom rates were statistically evaluated using the Fisher's test to compare the ESL arms against placebo. All remaining assessments were analyzed using descriptive statistics. Quantitative variables were described as mean, standard deviation (SD), median and range. Qualitative variables were described as absolute frequencies and percentages.

RESULTS

Study population

A total of 936 patients were screened for participation in study BIA-2093-304, of whom 653 were randomized to receive treatment with placebo ($n = 226$), ESL 800 mg QD ($n = 216$), and ESL 1200 mg QD ($n = 211$).[17] Overall, 504/653 patients (77.2%) completed Part I and 496 entered Part II; 346/496 patients (69.8%) completed Part II and 240 entered Part III; and 55/240 patients (22.9%) completed Part III.

The Safety Population included 125 Asian patients in Part I, 92 Asian patients in Part II, and 23 Asian patients in Part III (Figure 2). Demographic and baseline characteristics were generally well balanced between treatment groups within the Asian cohort (Table 1; Table S1). At DB baseline (i.e., baseline of Part I), 60.8% of the overall Asian cohort were male, mean age was 33.5 years (69.4% aged <40 years), mean time since epilepsy diagnosis was 14.5 years, 70.4% had focal impaired awareness seizures, and 20.8% had focal to bilateral tonic–clonic seizures. Most patients (79.2%) were being treated with two concomitant ASMs at baseline; 44.0% were being treated with carbamazepine and 11.2% with phenytoin. The 125 Asian patients included in Part I came from India ($n = 59$), South Korea ($n = 57$), the USA ($n = 3$), Argentina ($n = 3$), Australia ($n = 1$), Brazil ($n = 1$), and Italy ($n = 1$).

Safety/tolerability (Safety Population)

During the DB trial (Part I), 64.0% of Asian patients experienced TEAEs, and 46.4% experienced TEAEs that were considered related to treatment (Table 2). The incidence of related TEAEs was higher in patients treated with ESL 1200 mg QD (76.9%) and ESL 800 mg QD (46.3%) than in those treated with placebo (20.0%). The most frequently reported ESL-related TEAEs were dizziness (22.5%) and

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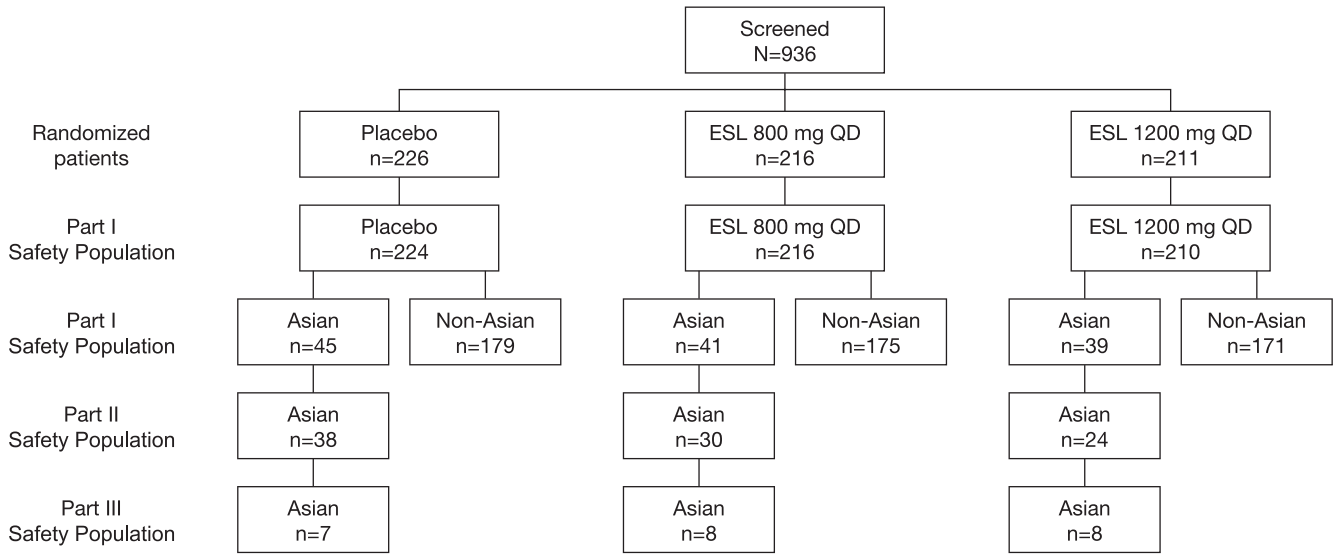

FIGURE 2 Flow chart of Safety Population during Parts I, II, and III. ESL, eslicarbazepine acetate; QD, once daily.

somnolence (15.0%), and the incidences of these were higher in patients treated with ESL 1200 mg QD versus ESL 800 mg QD (dizziness, 30.8% vs. 14.6%; somnolence, 23.1% vs. 7.3%). Only one patient experienced a serious ESL-related TEAE: a case of severe leukocytoclastic vasculitis in a patient treated with ESL 800 mg QD. The proportion of patients who discontinued due to ESL-related TEAEs was 20.0%, and the most common ESL-related TEAEs leading to discontinuation were dizziness (8.8%) and nausea (3.8%). The incidence of these were again higher in patients treated with ESL 1200 mg QD versus ESL 800 mg QD (dizziness, 10.2% vs. 7.3%; nausea, 5.1% vs. 2.4%). There were no deaths resulting from ESL-related TEAEs.

During the first 1-year OLE period (Part II), 71.7% of Asian patients experienced TEAEs, and 45.7% experienced TEAEs that were considered at least possibly related to treatment (Table 2). The incidence of related TEAEs was higher in patients who switched to ESL having been treated with placebo in the DB trial (55.3%) than in those who continued to receive ESL having been treated with ESL 800 mg QD or ESL 1200 mg QD in the DB trial (36.7% and 41.7%, respectively). The most frequently reported related TEAEs (≥5% of patients in the overall cohort) were dizziness (18.5%) and somnolence (12.0%). Only one patient experienced a serious-related TEAE: a case of severe somnolence in a patient who had previously been treated with ESL 1200 mg QD in the DB trial. The proportion of Asian patients who discontinued due to related TEAEs was 3.3% and no individual-related TEAE led to discontinuation of more than one patient. There were no deaths resulting from related TEAEs.

During the second OLE period (Part III), 87.0% of Asian patients experienced TEAEs, and 17.4% experienced TEAEs that were considered at least possibly related to treatment (Table 2). No individual-related TEAE was experienced by ≥5% of patients in the overall cohort. Two patients experienced serious-related TEAEs: one patient experienced a case of severe dizziness, and another experienced a case of severe vomiting; both had initially been treated with placebo in the DB trial. No patients experienced related TEAEs that led to discontinuation. As in the other study periods, there were no deaths resulting from related TEAEs.

Retention and exposure (Safety Population)

During the first 1-year OLE period (Part II), the retention rate in the Asian cohort was 73.9% (68/92) and during the second OLE period (Part III), it was 0% (0/23). During the DB trial (Part I), median (range) exposure to study drug was 97.0 (31–110) days in the placebo subgroup, 98.0 (2–104) days in the ESL 800 mg QD subgroup, and 98.0 (10–109) days in the ESL 1200 mg QD subgroup. During the first 1-year OLE period (Part II), the median (range) exposure to ESL was 358.0 (38–415) days in the overall cohort. During the second OLE period (Part III), the median (range) exposure to ESL was 657.0 (79–2019) days in the overall cohort.

Efficacy

SSF

During the maintenance period of the DB trial (Part I), the mean difference (95% CI) in LS mean change from

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TABLE 1 Patient demographic and baseline characteristics of Asian patients in Part I (Safety Population).

Characteristic	Placebo *n* = 45	ESL 800 mg QD *n* = 41	ESL 1200 mg QD *n* = 39
Sex			
n	45	41	39
Male, *n* (%)	27 (60.0)	26 (63.4)	23 (59.0)
Female, *n* (%)	18 (40.0)	15 (36.6)	16 (41.0)
Age, years			
n	44	41	39
Mean (SD)	33.8 (10.8)	33.1 (10.2)	34.4 (10.7)
Median (range)	33.0 (19–60)	31.0 (18–61)	33.0 (19–58)
Age category			
n	44	41	39
<40 years, *n* (%)	31 (70.5)	29 (70.7)	26 (66.7)
40–65 years, *n* (%)	13 (29.5)	12 (29.3)	13 (33.3)
>65 years, *n* (%)	0	0	0
Height, cm			
n	45	41	39
Mean (SD)	163.1 (9.0)	163.4 (7.6)	162.4 (8.9)
Weight, kg			
n	45	41	39
Mean (SD)	59.4 (10.0)	62.6 (11.5)	60.9 (13.4)
Body mass index, kg/m^2			
n	45	41	39
Mean (SD)	22.3 (3.4)	23.4 (3.8)	22.9 (3.6)
Time since epilepsy diagnosis, years			
n	45	40	39
Mean (SD)	13.2 (8.9)	16.3 (9.4)	14.2 (7.8)
Median (range)	11.1 (1.1–36.4)	16.4 (1.4–33.4)	13.1 (2.3–39.3)
Seizure type[a]			
n	45	41	39
Focal aware, *n* (%)	12 (26.7)	9 (22.0)	7 (17.9)
Focal impaired awareness, *n* (%)	29 (64.4)	30 (73.2)	29 (74.4)
Focal to bilateral tonic–clonic, *n* (%)	8 (17.8)	9 (22.0)	9 (23.1)
Unclassifiable, *n* (%)	0	0	1 (2.6)
Other, *n* (%)	0	0	0
Seizure frequency (total seizures)[a]			
n	45	41	39
Mean (SD)	10.9 (16.5)	20.0 (64.8)	21.0 (55.6)
Median (range)	7.0 (4–84)	6.0 (3–420)	7.0 (4–351)
Number of concomitant ASMs			
n	45	41	39
1, *n* (%)	12 (26.7)	6 (14.6)	8 (20.5)
2, *n* (%)	33 (73.3)	35 (85.4)	31 (79.5)
Carbamazepine use			
n	45	41	39
Yes, *n* (%)	19 (42.2)	16 (39.0)	20 (51.3)

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TABLE 1 (Continued)

Characteristic	Placebo $n=45$	ESL 800 mg QD $n=41$	ESL 1200 mg QD $n=39$
Phenytoin use			
n	45	41	39
Yes, *n* (%)	6 (13.3)	5 (12.2)	3 (7.7)

Abbreviations: ASM, antiseizure medication; ESL, eslicarbazepine acetate; QD, once daily; SD, standard deviation.

[a]During the 4 weeks prior to screening.

baseline in SSF in the Asian cohort was −0.32 (−0.77, 0.14) seizures/4 weeks for ESL 800 mg QD versus placebo ($p=0.17$) and −0.28 (−0.74, 0.18) seizures/4 weeks for ESL 1200 mg QD versus placebo ($p=0.23$) (Table 3; Figure 3).

During the first 1-year OLE period (Part II), further reductions in SSF were observed (Table 3). At the end of Part II, the mean (SD) reduction from DB baseline in SSF was −4.4 (12.3) seizures/4 weeks in the overall cohort.

Responder and seizure freedom rates

During the maintenance period of the DB trial (Part I), the responder rates in patients treated with ESL 800 mg QD (41.7%) and ESL 1200 mg QD (44.4%) were higher than the responder rate in patients treated with placebo (32.6%), although the differences versus placebo were not statistically significant (Figure 4a). The seizure freedom rates in patients treated with ESL 800 mg QD (5.5%) and ESL 1200 mg QD (11.1%) were also higher than the seizure freedom rate in patients treated with placebo (0%), and the difference was statistically significant for ESL 1200 mg QD versus placebo ($p<0.05$) (Figure 4a).

At the end of the first 1-year OLE period (Part II), the responder rates were higher in patients who had previously received ESL 800 mg QD and ESL 1200 mg QD during Part I (69.2% and 64.7%, respectively) than in those who had received placebo during Part I and switched to ESL during Part II (48.0%) (Figure 4b). Similarly, seizure freedom rates were higher in patients who had previously received ESL 800 mg QD and ESL 1200 mg QD during Part I (23.1% and 17.6%, respectively) than in those who had received placebo during Part I and switched to ESL during Part II (4.0%).

DISCUSSION

In this *post hoc* analysis of a phase III, randomized, DB, placebo-controlled trial, adult Asian patients with refractory focal seizures were responsive to treatment with ESL as adjunctive therapy and generally tolerated treatment well for up to 3 years. No new or unexpected safety signals emerged following long-term ESL treatment and TEAEs considered to be at least possibly related to ESL treatment (most commonly, dizziness, somnolence, and headache) were consistent with ESL's known safety profile.[12] The incidences of serious-related TEAEs and related TEAEs leading to discontinuation were comparatively low; during Part I, the proportion of Asian patients with ESL-related TEAEs (46.4%) was lower than that reported for the overall study BIA-2093-304 population (66.7%), as was the incidence of serious-related TEAEs (0.8% vs. 1.4%) and the incidence of related TEAEs leading to discontinuation (14.4% vs. 25.7%).[17]

There was no indication of an increased risk of adverse cutaneous reactions in Asian patients, although it should be noted that patients with hypersensitivity to carbamazepine/carbamazepine derivatives and/or a positive *HLA-B*1502* test were excluded from participation. Carbamazepine is known to cause cutaneous adverse drug reactions in up to 10% of patients, this risk being elevated in those carrying the *HLA-B*1502* allele.[19] ESL and oxcarbazepine belong to the same dibenzazepine family of ASMs as carbamazepine but are metabolized differently, having been developed to avoid the severe adverse reactions caused by carbamazepine.[19,20] Although the risk of cutaneous adverse drug reactions has been shown to be reduced in Asian patients treated with oxcarbazepine, in comparison with carbamazepine, current evidence for the use of ESL in Asian patients is lacking.[19] In clinical studies of ESL in epileptic patients, rash developed as an adverse reaction in 1.2% of the total treated population, and severe cutaneous adverse reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in the post-marketing setting.[12] It is therefore recommended that ESL be withdrawn immediately and an alternative treatment be considered, as appropriate, if a patient develops signs or symptoms that indicate such reactions.[12]

During Part I of the study, the responder rate in Asian patients treated with ESL 1200 mg QD was similar to that reported for the overall study BIA-2093-304 population (44.4% vs. 42.6%) but the responder rate in Asian patients treated with ESL 800 mg QD was higher than in the overall study BIA-2093-304 population (41.7% vs. 30.5%).[17]

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TABLE 2 Summary of TEAEs in Asian patients during Parts I, II, and III (Safety Population).

Part I	Placebo $n=45$	ESL 800 mg QD $n=41$	ESL 1200 mg QD $n=39$	ESL total $n=80$	Total $N=125$
Patients with any TEAEs,[a] *n* (%)	21 (46.7)	26 (63.4)	33 (84.6)	59 (73.8)	80 (64.0)
Most frequently reported[b] (any) TEAEs,[a] *n* (%)					
Dizziness	5 (11.1)	6 (14.6)	13 (33.3)	19 (23.8)	24 (19.2)
Headache	3 (6.7)	1 (2.4)	9 (23.1)	10 (12.5)	13 (10.4)
Somnolence	1 (2.2)	3 (7.3)	9 (23.1)	12 (15.0)	13 (10.4)
Balance disorder	0	3 (7.3)	9 (23.1)	12 (15.0)	12 (9.6)
Nausea	0	1 (2.4)	5 (12.8)	6 (7.5)	6 (4.8)
Vomiting	0	1 (2.4)	5 (12.8)	6 (7.5)	6 (4.8)
Vision blurred	0	3 (7.3)	2 (5.1)	5 (6.3)	5 (4.0)
Diplopia	0	0	4 (10.3)	4 (5.0)	4 (3.2)
Vertigo	0	1 (2.4)	3 (7.7)	4 (5.0)	4 (3.2)
Ataxia	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Dysarthria	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Nasopharyngitis	3 (6.7)	0	0	0	3 (2.4)
Sinus bradycardia	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Patients with related[c] TEAEs, *n* (%)	9 (20.0)	19 (46.3)	30 (76.9)	49 (61.3)	58 (46.4)
Most frequently reported[b] related[c] TEAEs, *n* (%)					
Dizziness	2 (4.4.)	6 (14.6)	12 (30.8)	18 (22.5)	20 (16.0)
Somnolence	1 (2.2)	3 (7.3)	9 (23.1)	12 (15.0)	13 (10.4)
Headache	1 (2.2)	0	6 (15.4)	6 (7.5)	7 (5.6)
Balance disorder	0	3 (7.3)	3 (7.7)	6 (7.5)	6 (4.8)
Nausea	0	1 (2.4)	5 (12.8)	6 (7.5)	6 (4.8)
Vomiting	0	1 (2.4)	5 (12.8)	6 (7.5)	6 (4.8)
Vision blurred	0	3 (7.3)	2 (5.1)	5 (6.3)	5 (4.0)
Diplopia	0	0	4 (10.2)	4 (5.0)	4 (3.2)
Ataxia	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Dysarthria	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Vertigo	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Patients with serious-related[c] TEAEs, *n* (%)	0	1 (2.4)	0	1 (1.3)	1 (0.8)
Types of serious-related[c] TEAEs, *n* (%)					
Leukocytoclastic vasculitis	0	1 (2.4)	0	1 (1.3)	1 (0.8)
Patients with related[c] TEAEs leading to discontinuation, *n* (%)	2 (4.4)	6 (14.6)	10 (25.6)	16 (20.0)	18 (14.4)
Types of related[c] TEAEs leading to discontinuation, *n* (%)					
Dizziness	1 (2.2)	3 (7.3)	4 (10.2)	7 (8.8)	8 (6.4)
Nausea	0	1 (2.4)	2 (5.1)	3 (3.8)	3 (2.4)
Headache	0	0	2 (5.1)	2 (2.5)	2 (1.6)
Somnolence	0	1 (2.4)	1 (2.6)	2 (2.5)	2 (1.6)
Vision blurred	0	1 (2.4)	1 (2.6)	2 (2.5)	2 (1.6)
Patients with any related[c] TEAE leading to death, *n* (%)	0	0	0	0	0

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TABLE 2 (Continued)

Part II	Placebo[d] $n=38$	ESL 800 mg QD[d] $n=30$	ESL 1200 mg QD[d] $n=24$	ESL total[d] $n=54$	Total $N=92$
Patients with any TEAEs,[a] *n* (%)	31 (81.6)	18 (60.0)	17 (70.8)	35 (64.8)	66 (71.7)
Most frequently reported[b] (any) TEAEs,[a] *n* (%)					
Dizziness	12 (31.6)	3 (10.0)	4 (16.7)	7 (12.9)	19 (20.7)
Somnolence	7 (18.4)	5 (16.7)	2 (8.3)	7 (12.9)	14 (15.2)
Headache	4 (10.5)	2 (6.7)	3 (12.5)	5 (9.3)	9 (9.8)
Vomiting	3 (7.9)	2 (6.7)	3 (12.5)	5 (9.3)	8 (8.7)
Nasopharyngitis	4 (10.5)	2 (6.7)	1 (4.2)	3 (5.6)	7 (7.6)
Decreased appetite	3 (7.9)	1 (3.3)	1 (4.2)	2 (3.7)	5 (5.4)
Nausea	3 (7.9)	2 (6.7)	0	2 (3.7)	5 (5.4)
Asthenia	1 (2.6)	1 (3.3)	2 (8.3)	3 (5.6)	4 (4.4)
Hyponatremia	3 (7.9)	1 (3.3)	0	1 (1.9)	4 (4.4)
Pyrexia	3 (7.9)	0	1 (4.2)	1 (1.9)	4 (4.4)
Vision blurred	3 (7.9)	0	1 (4.2)	1 (1.9)	4 (4.4)
Abdominal pain upper	3 (7.9)	0	0	0	3 (3.3)
Diplopia	1 (2.6)	2 (6.7)	0	2 (3.7)	3 (3.3)
Dyspepsia	2 (5.3)	0	1 (4.2)	1 (1.9)	3 (3.3)
Diarrhea	2 (5.3)	0	0	0	2 (2.2)
Fatigue	2 (5.3)	0	0	0	2 (2.2)
Injury	2 (5.3)	0	0	0	2 (2.2)
Myalgia	0	0	2 (8.3)	2 (3.7)	2 (2.2)
Periodontal disease	2 (5.3)	0	0	0	2 (2.2)
Patients with related[c] TEAEs, *n* (%)	21 (55.3)	11 (36.7)	10 (41.7)	21 (38.9)	42 (45.7)
Most frequently reported[b] related[c] TEAEs, *n* (%)					
Dizziness	10 (26.3)	3 (10.0)	4 (16.7)	7 (20.0)	17 (18.5)
Somnolence	6 (28.6)	3 (10.0)	2 (8.3)	5 (9.3)	11 (12.0)
Headache	3 (7.9)	0	1 (4.2)	1 (1.9)	4 (4.4)
Nausea	3 (7.9)	1 (3.3)	0	1 (1.9)	4 (4.4)
Vision blurred	3 (7.9)	0	1 (4.2)	1 (1.9)	4 (4.4)
Vomiting	2 (5.3)	0	2 (8.3)	2 (3.7)	4 (4.4)
Diplopia	1 (2.6)	2 (6.7)	0	2 (3.7)	3 (3.3)
Dyspepsia	2 (5.3)	0	1 (4.2)	1 (1.9)	3 (3.3)
Fatigue	2 (5.3)	0	0	0	2 (2.2)
Patients with serious-related[c] TEAEs, *n* (%)	0	0	1 (4.2)	1 (1.9)	1 (1.1)
Types of serious-related[c] TEAEs, *n* (%)					
Somnolence	0	0	1 (4.2)	1 (1.9)	1 (1.1)
Patients with related[c] TEAEs leading to discontinuation, *n* (%)	2 (5.3)	0	1 (4.2)	1 (1.9)	3 (3.3)
Types of related[c] TEAEs leading to discontinuation, *n* (%)					
Somnolence	0	0	1 (4.2)	1 (1.8)	1 (1.1)
Ataxia	1 (2.6)	0	0	0	1 (1.1)
Dizziness	1 (2.6)	0	0	0	1 (1.1)
Headache	1 (2.6)	0	0	0	1 (1.1)

(Continues)

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TABLE 2 (Continued)

Part II	Placebo[d] $n=38$	ESL 800 mg QD[d] $n=30$	ESL 1200 mg QD[d] $n=24$	ESL total[d] $n=54$	Total $N=92$
Patients with any related[c] TEAE leading to death, *n* (%)	0	0	0	0	0
Part III	**Placebo[d] $n=7$**	**ESL 800 mg QD[d] $n=8$**	**ESL 1200 mg QD[d] $n=8$**	**ESL total[d] $n=16$**	**Total $N=23$**
Patients with any TEAEs,[a] *n* (%)	6 (85.7)	8 (100.0)	6 (75.0)	14 (87.5)	20 (87.0)
Most frequently reported[b] (any) TEAEs,[a] *n* (%)					
Headache	2 (28.6)	3 (37.5)	2 (25.0)	5 (31.3)	7 (30.4)
Dizziness	3 (42.9)	2 (25.0)	1 (12.5)	3 (18.8)	6 (26.1)
Nasopharyngitis	3 (42.9)	0	1 (12.5)	1 (6.3)	4 (17.4)
Insomnia	0	2 (25.0)	1 (12.5)	3 (18.8)	3 (13.0)
Memory impairment	1 (14.3)	1 (12.5)	1 (12.5)	2 (12.5)	3 (13.0)
Tremor	2 (28.6)	1 (12.5)	0	1 (6.3)	3 (13.0)
Alopecia	0	1 (12.5)	1 (12.5)	2 (12.5)	2 (8.7)
Diplopia	1 (14.3)	1 (12.5)	0	1 (6.3)	2 (8.7)
Enteritis	2 (28.6)	0	0	0	2 (8.7)
Rib fracture	1 (14.3)	0	1 (12.5)	1 (6.3)	2 (8.7)
Toothache	0	1 (12.5)	1 (12.5)	2 (12.5)	2 (8.7)
Patients with related[c] TEAEs, *n* (%)	2 (28.6)	2 (25.0)	0	2 (12.5)	4 (17.4)
Most frequently reported[b] related[c] TEAEs, *n* (%)					
Diplopia	1 (14.3)	0	0	0	1 (4.3)
Dizziness	1 (14.3)	0	0	0	1 (4.3)
Insomnia	0	1 (12.5)	0	1 (6.3)	1 (4.3)
Irritability	0	1 (12.5)	0	1 (6.3)	1 (4.3)
Thyroxine-free decreased	0	1 (12.5)	0	1 (6.3)	1 (4.3)
Vomiting	1 (14.3)	0	0	0	1 (4.3)
Patients with serious-related[c] TEAEs, *n* (%)	1 (14.3)	0	0	0	1 (4.3)
Types of serious-related[c] TEAEs, *n* (%)					
Dizziness	1 (14.3)	0	0	0	1 (4.3)
Vomiting	1 (14.3)	0	0	0	1 (4.3)
Patients with related[c] TEAEs leading to discontinuation, *n* (%)	0	0	0	0	0
Patients with any related[c] TEAE leading to death, *n* (%)	0	0	0	0	0

Abbreviations: ESL, eslicarbazepine acetate; QD, once daily; TEAE, treatment-emergent adverse event.

[a]TEAEs with causality "Definite," "Probable," "Possible," "Unlikely," "Not related," "Unknown," and "Missing."

[b]≥5% of patients in any group.

[c]TEAEs with causality "Definite," "Probable," and "Possible."

[d]Assigned treatment group in Part I.

The lack of statistical significance for ESL versus placebo observed in Asian patients was likely to have been influenced by the relatively low sample size, since the original trial was not powered to detect treatment differences in the subgroup corresponding to the Asian cohort. However, it was also likely to have been affected by the high placebo response rate in Asian patients: during Part I, the responder rate in Asian patients treated with placebo was 32.6% (compared to 23.1% in the overall study BIA-2093-304 population[17]). The high placebo response

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TABLE 3 Summary of SSF (number of seizures per 4 weeks) during Part I (ITT Population) and Part II (Safety Population).

Part I (ITT Population)	Placebo	ESL 800 mg QD	ESL 1200 mg QD	ESL total	Total
n	43	36	36	72	115
SSF during maintenance period					
Mean (SD)	10.0 (15.2)	9.3 (15.9)	13.2 (21.9)	11.2 (19.1)	10.8 (17.7)
Median (range)	5.6 (1.0–72.0)	4.8 (0.3–90.3)	4.5 (0.3–101.1)	4.6 (0.3–101.1)	4.9 (0.3–101.1)
LS mean (SE)	5.5 (2.0)	3.9 (1.4)	4.0 (1.4)	4.0 (1.3)	–
95% CI for LS mean	2.6, 11.0	1.9, 7.8	2.0, 7.8	2.1, 7.4	–
Ln[a] mean difference (95% CI) in LS mean vs. placebo	–	−0.32 (−0.77, 0.14)	−0.28 (−0.74, 0.18)	−0.30 (−0.69, 0.09)	–
Unadjusted *p*-value for pairwise comparison vs. placebo	–	0.17	0.23	0.13	–
p-value for treatment-by-diary version interaction[b]	–	0.92			–
p-value for treatment-by-baseline SSF interaction[b]	–	0.21			–
Part II (Safety Population)	**Placebo[c]**	**ESL 800 mg QD[c]**	**ESL 1200 mg QD[c]**	**ESL total[c]**	**Total**
SSF at baseline of Part I (V2)					
n	38	30	24	54	92
Mean (SD)	11.9 (15.3)	12.4 (11.6)	11.4 (9.3)	12.0 (10.6)	12.0 (12.7)
Median (range)	6.7 (3.5–70.3)	7.6 (3.8–48.5)	8.1 (3.8–34.2)	7.9 (3.8–48.5)	7.4 (3.5–70.3)
SSF at end of Part II (V10)					
n	25	26	17	43	68
Mean (SD)	8.3 (16.4)	8.2 (18.3)	4.0 (5.5)	6.6 (14.6)	7.2 (15.2)
Median (range)	3.4 (0–79.3)	1.4 (0–84.3)	1.6 (0–18.8)	1.6 (0–84.3)	1.7 (0–84.3)
Change in SSF from V2 to V10					
n	25	26	17	43	68
Mean (SD)	−2.9 (15.8)	−5.3 (12.2)	−5.1 (4.3)	−5.2 (9.7)	−4.4 (12.3)
Median (range)	−2.5 (−69.0–22.6)	−4.5 (−30.6–35.8)	−3.9 (−15.3–1.0)	−4.4 (−30.6–35.8)	−3.8 (−69.0–35.8)

Note: Results are based on an ANCOVA model with ln baseline SSF and diary version (event entry, daily entry) as covariates and treatment as a fixed effect. The pairwise comparisons are each ESL dose versus placebo. LS means and CIs were back-transformed via the exponential function and subtracting 0.333. SEs for LS means were back-transformed via the Delta Method. Patients who discontinued from the study during the titration period were not included.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ESL, eslicarbazepine acetate; ITT, Intention-To-Treat; LS, least squares; QD, once daily; SD, standard deviation; SE, standard error; SSF, standardized seizure frequency (defined as number of seizures per 4 weeks); V, visit.

[a]Napierian log-transformed.

[b]From separate ANCOVA models (Type III ANCOVA) but including the respective interaction term as a fixed effect.

[c]Assigned randomized treatment group in Part I.

rate observed in the current study is consistent with previous evidence demonstrating significantly higher placebo response rates in East Asian versus Western patients treated with other ASMs, including topiramate, levetiracetam, zonisamide, gabapentin and pregabalin.[21] Potential reasons for this are unclear, but may include differences in patient characteristics, such as duration of epilepsy.[21] In the current study, the mean duration of epilepsy was approximately 14.5 years (compared with approximately 21.4 years in the overall study BIA-2093-304 population[17]).

During Part I of the study, the seizure freedom rates in Asian patients treated with ESL 800 and 1200 mg QD (5.5 and 11.1%, respectively) were higher than that in the overall study BIA-2093-304 population (2.0% and 2.2%, respectively), whereas the seizure freedom rate in Asian patients treated with placebo (0%) was lower than that in the placebo group of the overall study BIA-2093-304 population (0.9%).[17] Indeed, unlike in the overall study BIA-2093-304 population, the seizure freedom rate in Asian patients treated with ESL 1200 mg QD was statistically significantly higher than in those treated with placebo ($p < 0.05$). Response to ESL treatment continued to improve with long-term treatment: by the end of Part II (after over a year of ESL treatment),

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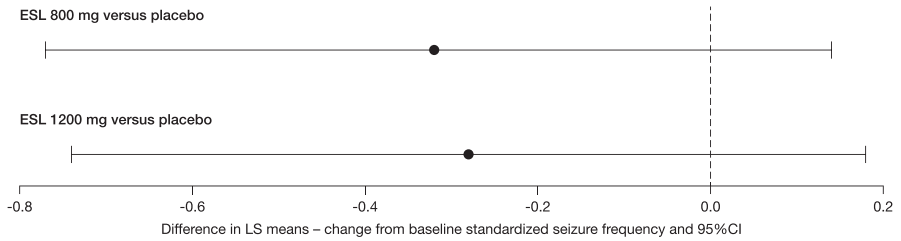

FIGURE 3 Forest plots of mean differences in SSF in Asian patients in Part I: (a) ESL 800 mg QD versus placebo and (b) ESL 1200 mg versus placebo (ITT Population). CI, confidence interval; ESL, eslicarbazepine acetate; LS, least square; QD, once daily; SSF, standardized seizure frequency.

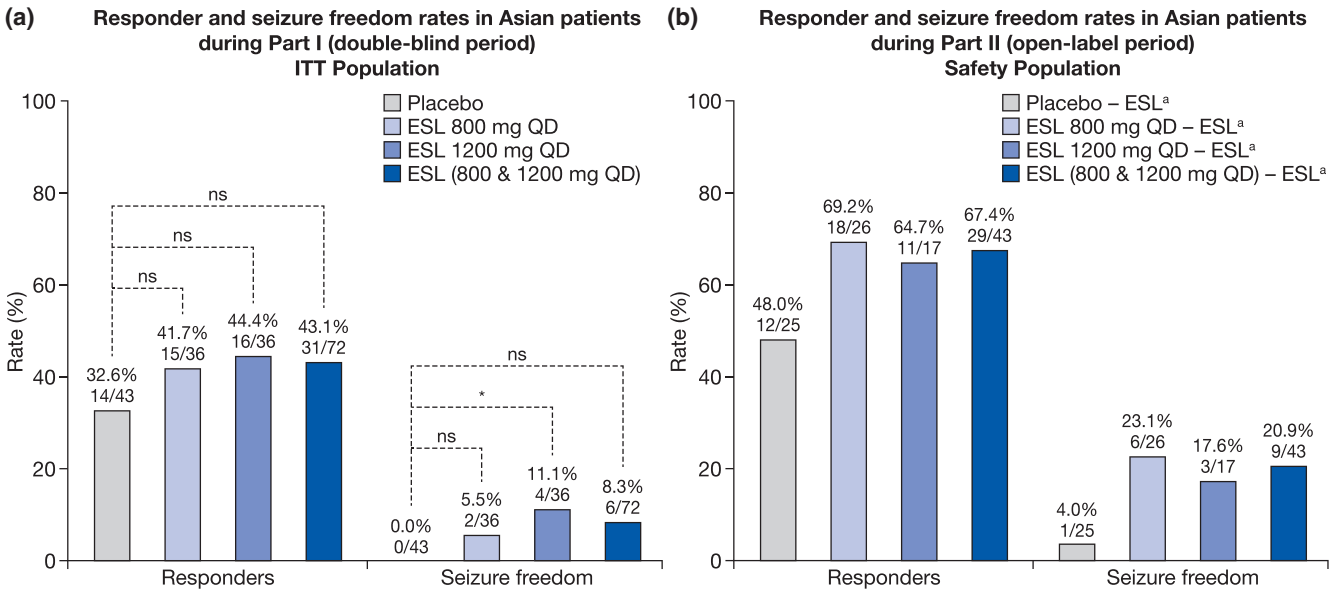

FIGURE 4 Responder and seizure freedom rates in Asian patients during (a) Part I (ITT Population) and (b) Part II (Safety Population). *$p < 0.05$; [a]First treatment corresponds to randomized treatment during Part I (DB period); during Part II (1-year OLE period), all patients received ESL 400–1600 mg QD, according to the Investigator. DB, double-blind; ESL, eslicarbazepine acetate; ITT, Intention-To-Treat; ns, not significant; QD, once daily; OLE, open-label extension.

60.3% of Asian patients had responded to treatment and 14.7% were seizure-free. Since this exploratory *post hoc* analysis was not powered to assess outcomes specifically in Asian patients, no conclusions can be drawn regarding the relative effectiveness of ESL in Asian patients in comparison with patients from other ethnic backgrounds. In a pooled analysis of Studies BIA-2093-301, -302, and -304, no significant interaction was observed between the effect of ESL treatment and race/ethnicity.[22] To the best of our knowledge, only one other study has investigated the use of ESL specifically in Asian subjects. This was a phase I, dose randomized, DB, placebo-controlled, single and multiple dosing, dose-escalation study that evaluated and compared the safety, tolerability, and pharmacokinetic characteristics of ESL when administered to 30 Korean and 20 White healthy adult individuals.[18] Pharmacokinetic parameters were similar between the groups and there were no notable between-group differences in safety and tolerability,[18] consistent with the lack of a significant interaction between the effect of ESL treatment and race/ethnicity reported in the aforementioned pooled analysis.[22] As in the current study, the most frequently reported TEAEs in the Korean subjects were headache and dizziness, the incidences of which were dose-related.[18] Pruritus and rash developed in two and one Korean subjects, respectively, both of whom were treated with highest ESL dose (1600 mg/day).[18]

This study was limited in being an exploratory *post hoc* subgroup analysis of a previous trial and was not prospectively powered to assess outcomes specifically in Asian patients. The study was also unable to provide a clear indication of the risk of adverse cutaneous reactions in Asian patients treated with ESL, since individuals with hypersensitivity to carbamazepine/carbamazepine derivatives and/or a positive *HLA-B*1502* test were excluded from

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participation. Although most patients included in the study came from India and South Korea, a range of countries was represented, and all patients identified themselves as "Asian."

In summary, this study is the first to specifically assess the use of ESL in Asian patients with epilepsy. It demonstrated that adult Asian patients with refractory focal seizures responded to treatment with ESL as adjunctive therapy and treatment was generally well tolerated for up to 3 years. Long-term safety/tolerability with adjunctive ESL treatment in an Asian adult population with refractory focal seizures was consistent with the known safety profile of ESL for other ethnicities, with no new or unexpected safety findings emerging in this setting.

Further research is required to assess the use of ESL in Asian patients treated in clinical practice, outside the protocol-defined restrictions of the clinical trial setting.

AUTHOR CONTRIBUTIONS

S.K.L., S.A.L., S.B.H., Y.W.C., G.C.-F., M.M.F., J.M., H,G., and J.H. wrote the manuscript; G.C.-F., M.M.F., J.M., and H.G. designed the research; G.C.-F., M.M.F., J.M., and H.G. performed the research; G.C.-F., M.M.F., J.M., and H.G. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

GCF, MMF, JM, HG and JH are all current employees of Bial. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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