






ARTICLE

The pharmacokinetic, safety, and tolerability profiles of eslicarbazepine acetate are comparable between Korean and White subjects

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Abstract

Eslicarbazepine acetate (ESL) is a prodrug antiepileptic medication for the treatment of focal seizures. ESL shows a well-established pharmacokinetic (PK)-pharmacodynamic relationship and has similar extrinsic epilepsy-related factors across ethnicities. This study evaluated and compared ESL safety, tolerability, and PK characteristics between Korean and White subjects. A randomized, double-blind, placebo-controlled, single- and multiple-dose escalation study was conducted in healthy Korean and White adults. Participants randomly received a single dose and multiple oral doses of ESL (400–1600 mg) or placebo once daily for 11 days at a ratio of 8:2. Serial blood samples were collected to determine the plasma concentration of ESL and its metabolites (eslicarbazepine, [R]-licarbazepine and oxcarbazepine). Safety and tolerability were assessed throughout the study. A total of 29 Korean and 20 White subjects completed the study. The PK profiles of the metabolites of ESL were similar between Korean and White subjects. The geometric mean ratio (90% confidence interval) of Korean to White subjects for the area under the concentration–time curve within a dosing interval of eslicarbazepine was 1.06 (0.97–1.17) and 0.96 (0.87–1.06) after multiple oral doses of 400 and 1600 mg ESL, respectively. Other PK parameters were also similar between the two ethnic groups. ESL was well-tolerated in healthy Korean and White subjects, and its PK characteristics were similar between the two ethnic groups. The results of this study support to use the same dosage regimen of ESL in both White and Korean patients with seizures.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Eslicarbazepine acetate (ESL) is an anti-epileptic drug for monotherapy or adjunctive therapy for partial-onset seizures. There are little clinical data of ESL for Koreans patients, although the sensitivity of ESL to ethnic factors is assessed to be low.

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WHAT QUESTION DID THIS STUDY ADDRESS?

This study investigated pharmacokinetics (PKs), safety, and tolerability of ESL after single and multiple dose administration in healthy Korean and White subjects.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The PKs of ESL and its active metabolites were similar between Korean and White subjects. In addition, ESL was well-tolerated in healthy Korean subjects. The efficacy and safety data from White patients with epilepsy can be extrapolated to Korean patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

This study demonstrated that there was no difference in ESL PKs between healthy Korean and White subjects. The dosage regimen of ESL can be extrapolated to Korean patients according to the results of this bridging accumulating data in respect of ethnic differences.

INTRODUCTION

Eslicarbazepine acetate (ESL) is an anti-epileptic drug (AED) for monotherapy or adjunctive therapy for partial-onset seizures that was approved by the European Medicines Agency (EMA) in 2009, the US Food and Drug Administration (FDA) in 2013, and the Ministry of Food and Safety (MFDS) in 2020.¹ ESL is structurally related to carbamazepine and oxcarbazepine (OXC), which contains the dibenzazepine carboxamide.² However, distinct from carbamazepine, ESL is not metabolized to carbamazepine-10,11-epoxide, which can lead to adverse events, including nausea and headache, and is not susceptible to metabolic autoinduction.^{2,3} ESL behaves as a prodrug and is extensively hydrolyzed to eslicarbazepine, which is the major active metabolite. Eslicarbazepine is subsequently converted to the minor active metabolite OXC (Figure 1).^{2,4,5} Furthermore, OXC can be reversibly converted to eslicarbazepine and (R)-licarbazepine (Figure 1).^{2,4} More than 90% of the ESL dose is excreted in urine as eslicarbazepine and its glucuronide metabolite.⁴ As ESL shows low affinity for sodium channels in the resting state, ESL has an enhanced inhibitory selectivity for rapidly firing neurons, and the systemic exposure of eslicarbazepine is more directly related to its efficacy.⁶ The sensitivity of ESL to ethnic factors is expected to be low based on the known pharmacokinetic (PK), pharmacodynamic (PD), and PK–PD relationships, which were evaluated according to the International Conference on Harmonization (ICH) E5 guideline.⁷ ESL showed a linear PK profile with a dose range of 400–1600 mg and a flat effect-concentration curve, showing that the efficacy was saturable over 800 mg once daily (q.d.).⁶ It has a wide therapeutic dose range of 400–1600 mg for a once-daily regimen and is generally well-tolerated.¹ Most of ESL is hydrolyzed to eslicarbazepine by first-pass metabolism, and there is no association between genetic polymorphism and

ESL-related enzymes.⁴ ESL exhibits high bioavailability (90%) and low protein binding (<40%).^{8,9} The PKs of ESL is not significantly affected by co-administration, including gabapentin, topiramate, and valproate, and dose adjustment of ESL is not required when ESL is co-administered with other AEDs.^{4,6,10} ESL has a systemic mode of action and little potential for inappropriate use. Therefore, ESL has been found to be safe and effective in White patients with refractory partial-onset seizures.¹¹

Because a small number of Korean patients were included in the clinical studies of ESL, a bridging clinical study was needed to accept foreign clinical data supporting the safe and efficacious use of ESL for Korean patients.¹¹ The PKs of eslicarbazepine are linear and dose proportional in healthy subjects and patients with partial-onset seizures.^{2,4} The exposure–response relationship of ESL between plasma concentration and a reduction in seizure frequency is well-established.¹² The population PK analysis suggested that ethnicity did not significantly affect the PKs of eslicarbazepine, whereas weight and renal function were identified as covariates of eslicarbazepine PKs.¹⁰ Considering these characteristics of ESL, a PK study design was considered an appropriate bridging study method for ESL.

Based on these findings, this study aimed to evaluate the PKs, safety, and tolerability of ESL after single and multiple dose administrations in healthy Korean and White subjects.

METHODS

Study population and study design

This study was a dose randomized, double-blind, placebo-controlled, single and multiple dosing, dose-escalation phase I study ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT04095182). This

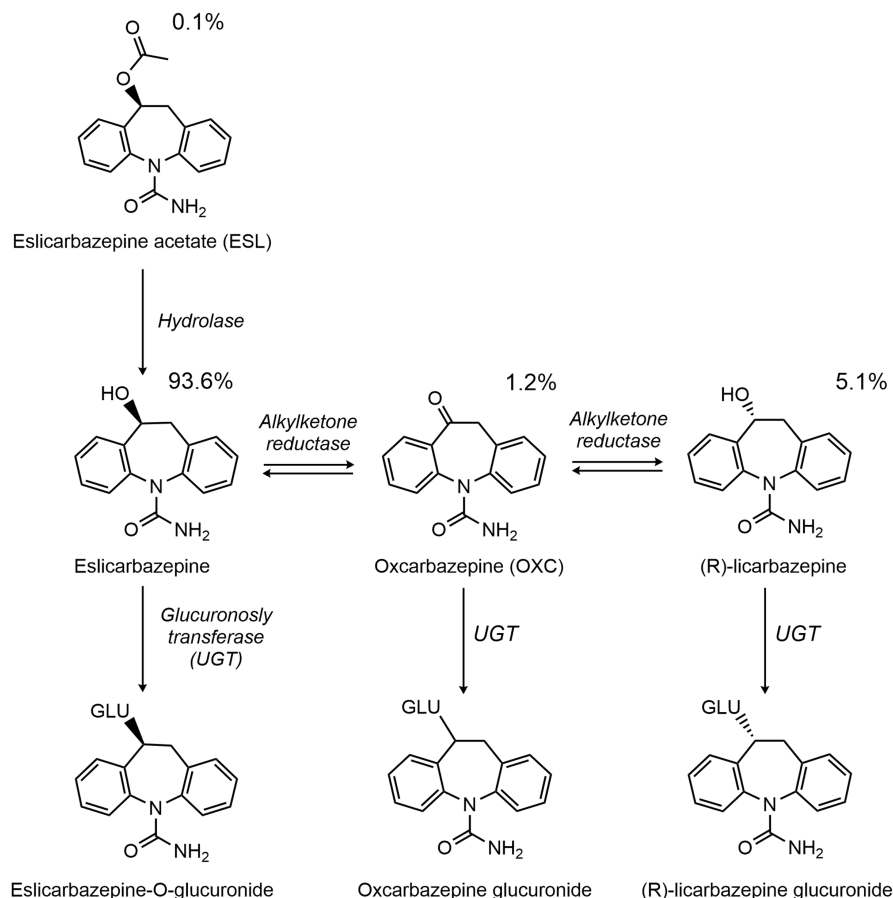


FIGURE 1 Clinical structures and the metabolic pathways of eslicarbazepine acetate and its metabolites (eslicarbazepine, (R)-licarbazepine, oxcarbazepine). Figure concept from Galiana et al.² and Perucca et al.¹⁹

study was reviewed and approved by the Institutional Review Board (IRB) at Seoul National University Hospital. The study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice (KGCP). Written informed consent was obtained from all subjects before enrollment.

Healthy Korean and White male subjects aged 19–45 years with a body mass index (BMI) between 18.0 and 28.0 were eligible for the study. Subjects were excluded if they had any history of severe trauma; current evidence or treatment history of psychiatric diseases, including mood disorders and obsessive-compulsive disorder; and any hypersensitivity to carbamazepine, carbamazepine-related drugs, and any other medications. Korean subjects were assigned to three dose groups of 400, 800, and 1600 mg, and White subjects were assigned to two dose groups of 400 and 1600 mg. The subjects were randomized to ESL (Zebinix; Whanin Pharmaceutical Company) or placebo in an 8:2 ratio in each dose group of 10 subjects. All subjects received ESL once daily according to each assigned treatment on day 1 and day 5 to day 11. Serial blood samples were collected to analyze the plasma concentration of ESL

and its active metabolites (eslicarbazepine, OXC, and (R)-licarbazepine). Blood samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 h postdose after the first dose (day 1); trough (predose) samples were collected from days 6 to 11 and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 h after the last dose (day 11) using heparinized tubes. The collected samples were centrifuged at 1900 g and 4°C for 10 min, and plasma samples were stored at –70°C until analysis.

Quantification of ESL, eslicarbazepine, OXC, and (R)-licarbazepine

The plasma concentrations of ESL and its metabolites were analyzed by a liquid chromatography–tandem mass spectrometry (LC-MS/MS) system with a valid method. To validate the determination of ESL, OXC, eslicarbazepine and (R)-licarbazepine in human plasma, their internal standards (ESL-d3, OXC-d4, eslicarbazepine-d3, and (R)-licarbazepine-d3, respectively) were diluted by using protein precipitation with 50% acetonitrile for ESL and OXC and 100% acetonitrile for eslicarbazepine

and (R)-licarbazepine. The results of validation showed that the analytical method was properly applied for the determination of ESL and OXC in the range of 5–1000 ng/ml and the determination of eslicarbazepine and (R)-licarbazepine in the range of 40–40,000 and 10 to 10,000 ng/ml, respectively.

For analysis of ESL and OXC, plasma samples (50 μ l) and internal standards (10 μ l of 1000 ng/ml ESL-d3 and OXC-d4) were prepared and added to a tube with 180 μ l of acetonitrile. The samples were mixed for 5 min and centrifuged for 5 min at 40,000 g approximately, and 100 μ l of the supernatant was diluted with 200 μ l of 0.1% formic acid. After mixing for 10 s, 5 μ l of the samples was injected into the LC–MS/MS system. The separation was performed with an analytical column (Gemini C18, 3 μ m, 50 \times 3 mm; Phenomenex) using acetonitrile with a 0.1% (v/v) formic acid mobile phase at a flow rate of 0.3 ml/min with 6 min of run time. The analytes were detected by electrospray ionization (ESI) performed in the positive ion mode. Ion detection was performed by monitoring the m/z transitions of 297.4 to 194.3 for ESL, 300.3 to 197.3 for ESL-d3, 253.3 to 208.2 for OXC, and 257.3 to 212.3 for OXC-d4.

To prepare the samples for the analysis of eslicarbazepine and (R)-licarbazepine, plasma samples (200 μ l) and internal standards (50 μ l of 200 ng/ml eslicarbazepine-d3 and (R)-licarbazepine-d3) were added to a tube with 1500 μ l of 100% acetonitrile. The samples were mixed for 5 min and centrifuged for 10 min at 40,000 g approximately. Two microliters of the supernatant samples were injected into the LC–MS/MS system. The separation was performed with a C18 column (CHIRALPAK IC, 3 μ m, 150 \times 4.6 mm; Daicel) using acetonitrile with a 0.1% (v/v) formic acid mobile phase at a flow rate of 0.65 ml/min with 6 min of run time. The analytes were detected by ESI performed in the positive ion mode. Ion detection was performed by monitoring the m/z transitions of 255.097 to 192.072 for eslicarbazepine, 258.059 to 197.076 for eslicarbazepine-d3, 255.084 to 194.053 for (R)-licarbazepine, and 258.068 to 197.077 for (R)-licarbazepine-d3.

PK analysis

The PK parameters were calculated by noncompartmental methods using WinNonlin software version 8.3 (Pharsight Co, Mountain View, CA). The maximum serum concentration (C_{\max}) after a single dose and at steady-state ($C_{\max,ss}$) and the time to reach C_{\max} (T_{\max}) after a single dose and at steady state ($T_{\max,ss}$) were obtained from the observed concentrations and times. The area under the

concentration–time curve (AUC) from 0 to the last measurable time point (AUC_{last}), the AUC from 0 to 24 h after a single dose (AUC_{0-24h}), and the AUC over a dosing interval at steady state ($AUC_{\tau,ss}$) were calculated by the linear-up/log-down trapezoidal method. The AUC from 0 to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{\text{last}} + C_{\text{last}}/\lambda_z$; C_{last} is the last measurable concentration, and λ_z is the terminal elimination rate constant. The terminal half-life ($t_{1/2} = \ln 2/\lambda_z$), apparent clearance ($CL/F = \text{dose}/AUC_{0-\infty}$), and apparent volume of distribution ($V_z/F = CL/F/\lambda_z$) were also analyzed.

Safety, tolerability, and other observations assessment

Safety and tolerability were evaluated by monitoring adverse events (AEs), physical examination, neurological examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests. For evaluation of mood change, the Columbia Suicide Severity Rating Scale (C-SSRS) was conducted for all subjects.

Statistical analysis

SAS software version 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis. The Kruskal–Wallis test was used to compare the demographic characteristics between the groups. PK parameters and AE results were summarized by descriptive statistics. The geometric mean ratio (GMR) and 90% confidence interval (90% CI) of ESL and its metabolites were calculated to compare the PK parameters, such as C_{\max} and AUC, between Korean and White subjects. The dose proportionality and linearity of ESL and its metabolites were evaluated in Korean subjects in the dose range of 400–1600 mg after single and multiple doses. The dose-normalized C_{\max} and AUC values between the dose groups were compared by the Kruskal–Wallis test. The dose proportionality of ESL and its metabolites was assessed by a power model and a linear regression between the log-transformed dose and log-transformed C_{\max} and AUC. Statistical significance was defined as a p value < 0.05 .

RESULTS

Study population

A total of 50 male subjects (30 Koreans and 20 Whites) were enrolled, and one Korean subject in the ELS 800 mg

dose group dropped out. This subject withdrew his consent after multiple dose administrations due to a personal reason. Therefore, the remaining 49 subjects completed the study as planned. The PK characteristics of ESL and its metabolites were evaluated in 49 subjects who completed the study. Safety and tolerability were assessed with 50 subjects who had received at least one dose of ESL. The demographic characteristics were similar between Korean and White subjects (Table 1).

PK analysis

The PK characteristics of eslicarbazepine, (R)-licarbazepine, and OXC after single and multiple oral doses of ESL were similar between Korean and White subjects. The mean plasma concentration–time profiles of eslicarbazepine, (R)-licarbazepine, and OXC were similar between Korean and White subjects after single and multiple oral doses of ESL (Figure 2). Because ~99.9% of

TABLE 1 Comparison of demographic characteristics between Korean and White subjects

Characteristics	Korean			White		p Value ^a
	400 mg (N = 8)	800 mg (N = 8)	1600 mg (N = 8)	400 mg (N = 8)	1600 mg (N = 8)	
Age, years	29 ± 5	31 ± 6	35 ± 5	34 ± 3	28 ± 3	0.1248
Height, m	1.75 ± 0.06	1.73 ± 0.06	1.74 ± 0.06	1.77 ± 0.09	1.75 ± 0.05	0.8353
Weight, kg	71.2 ± 10.8	69.7 ± 9.2	73.3 ± 11.4	72.7 ± 11.8	70.8 ± 6.9	0.7396
Body mass index, kg/m ²	23.1 ± 2.5	23.4 ± 3.3	24.2 ± 2.5	23.1 ± 2.6	23.1 ± 2.2	0.6344

Note: Data are presented as the mean ± SD.

^aThe p values were calculated by the Kruskal–Wallis test.

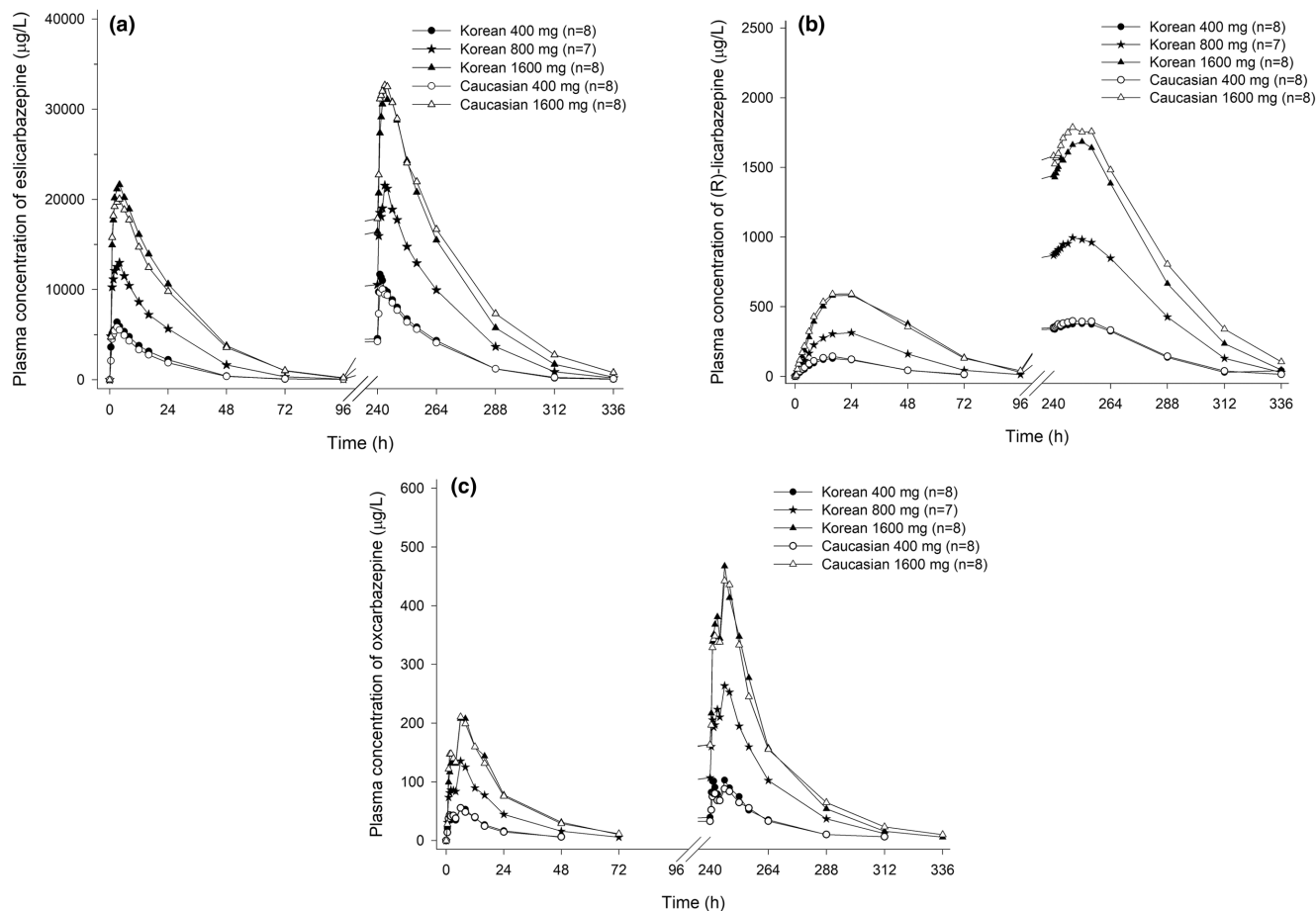


FIGURE 2 Mean plasma concentration–time profiles of (a) eslicarbazepine, (b) (R)-licarbazepine, and (c) oxcarbazepine after single and multiple oral doses of 400, 800, or 1600 mg eslicarbazepine acetate in Korean and White subjects.

ESL is rapidly hydrolyzed to metabolites, the plasma concentration of ESL was below the detection limit in most of the samples. Eslicarbazepine reached the maximum concentration with a median time of 1–3 and 1.5–3 h after the single or multiple oral doses of ESL in Korean and White subjects, respectively (Table 2). The mean $t_{1/2}$ values of eslicarbazepine were 9.32–11.05 and 10.05–15.12 h in Korean and White subjects, respectively (Table 2). The GMRs (90% CI) of Korean to White subjects for $AUC_{\tau,ss}$ of eslicarbazepine after multiple doses of ESL 400 and 1600 mg were 1.06 (0.97–1.17) and 0.96 (0.87–1.06), respectively (Table 3). Additionally, the 90% CI of the GMR for C_{max} and the AUC of (R)-licarbazepine and OXC included (Table 3).

The systemic exposure to eslicarbazepine was increased less than dose-proportionally after single and multiple dose administration of ESL (Figure 3, Figure S3). The slope and 95% CIs of C_{max} , $C_{max,ss}$, and $AUC_{\tau,ss}$ of ESL in the power model were 0.8334 (0.6685–0.9984), 0.7533 (0.6226–0.8840), and 0.7842 (0.7673–0.9811), respectively. Systemic exposure to (R)-licarbazepine and

OXC increased dose-proportionally. The slope and 95% CIs of C_{max} , $C_{max,ss}$, and $AUC_{\tau,ss}$ in the power model were 1.029 (0.9532–1.2526), 1.0733 (0.9023–1.2444), and 1.0612 (0.8855–1.2369) for (R)-licarbazepine, respectively, and 0.9730 (0.8005–1.1456), 1.0835 (0.8930–1.2739), and 1.1096 (0.9120–1.3073) for OXC, respectively.

Safety and tolerability

A total of 24 AEs were reported in 12 subjects (24%), and 23 AEs were related to the study drug and evaluated as adverse drug reactions, except one AE occurring in one subject who received the placebo (Table S3). Among those AEs, 19 occurred in eight Korean subjects, and five occurred in four White subjects (Table 4). The most frequently reported AE was headache and the incidence of AE increased as the dose of ESL increased in both Korean and White subjects (Table 4). All AEs were mild and resolved without sequelae. Serious AEs did not occur in this study. No clinically significant changes were observed in

TABLE 2 Pharmacokinetic parameters of eslicarbazepine after single and multiple oral doses of 400, 800, or 1600 mg eslicarbazepine acetate in Korean and White subjects

	Korean			White	
	400 mg (N = 8)	800 mg (N = 7)	1600 mg (N = 8)	400 mg (N = 8)	1600 mg (N = 8)
After a single dose					
T_{max} , h	1.0 (0.5–3.0)	2.0 (1.0–4.0)	1.8 (1.0–4.0)	2.5 (1.0–3.0)	3.0 (1.0–6.0)
C_{max} , mg/L	7.43 ± 1.16	16.94 ± 2.73	23.83 ± 4.98	6.39 ± 0.89	21.94 ± 5.33
AUC_{0-24h} , h·mg/L	93.61 ± 11.90	208.27 ± 20.09	373.84 ± 54.87	83.56 ± 7.81	345.96 ± 37.43
AUC_{last} , h·mg/L	122.59 ± 14.66	307.18 ± 42.71	592.57 ± 88.85	109.16 ± 15.32	554.27 ± 46.31
$AUC_{0-\infty}$, h·mg/L	124.1 ± 14.35	309.43 ± 43.54	595.34 ± 90.16	110.91 ± 15.12	558.93 ± 48.47
$t_{1/2}$, h	9.32 ± 0.73	10.29 ± 1.72	10.44 ± 2.51	10.05 ± 1.43	11.73 ± 3.66
CL/F, L/h	3.26 ± 0.37	2.64 ± 0.46	2.76 ± 0.52	3.67 ± 0.52	2.88 ± 0.23
V_z/F , L	43.91 ± 6.68	38.51 ± 4.10	40.68 ± 8.00	52.43 ± 4.50	48.03 ± 12.68
After multiple doses					
$T_{max,ss}$, h	1.0 (0.5–2.0)	2.0 (0.5–4.0)	3.0 (1.0–6.0)	1.5 (0.5–4.0)	3.0 (1.0–6.0)
$C_{max,ss}$, mg/L	12.15 ± 1.66	23.85 ± 3.68	34.66 ± 5.54	10.87 ± 1.16	34.29 ± 3.48
$AUC_{\tau,ss}$, h·mg/L	170.68 ± 17.46	362.73 ± 51.23	574.83 ± 68.18	160.70 ± 18.00	593.95 ± 53.76
$t_{1/2,ss}$, h	10.7 ± 1.85	11.05 ± 1.85	10.91 ± 3.28	10.47 ± 1.43	15.12 ± 4.17
CL _{ss} /F, L/h	2.36 ± 0.24	2.25 ± 0.37	2.82 ± 0.40	2.52 ± 0.29	2.87 ± 0.26
$V_{z,ss}/F$, L	36.54 ± 7.40	35.96 ± 9.01	44.33 ± 14.15	37.59 ± 2.83	58.6 ± 14.60
Accumulation ratio ^a	1.83 ± 0.70	1.55 ± 0.15	1.93 ± 0.17	1.74 ± 0.26	1.74 ± 0.13

Note: Data are presented as the mean ± SD except for T_{max} and $T_{max,ss}$, which are presented as the median (minimum–maximum).

Abbreviations: AUC_{0-24h} , area under the curve from 0 to 24 h; $AUC_{0-\infty}$, area under the concentration–time curve from 0 to infinity; AUC_{last} , area under the concentration–time curve from 0 to the last measurable concentration; $AUC_{\tau,ss}$, area under the concentration–time curve within a dosing interval at steady-state; C_{max} , maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady-state; CL/F, apparent clearance; CL_{ss}/F, apparent clearance at steady-state; $t_{1/2}$, terminal half-life; $t_{1/2,ss}$, terminal half-life at steady state, T_{max} , time to reach C_{max} ; $T_{max,ss}$, time to reach $C_{max,ss}$; V_z/F , apparent volume of distribution; $V_{z,ss}/F$, apparent volume of distribution at steady state.

^aRatio of $AUC_{\tau,ss}/AUC_{0-24h}$.

TABLE 3 Comparison of pharmacokinetic parameters of metabolites after single and multiple oral doses of 400 or 1600 mg eslicarbazepine acetate in Korean and White subjects

Parameters	400 mg			1600 mg			
	Korean (N = 8)	White (N = 8)	Geometric mean ratio ^a (90% CI)	Korean (N = 8)	White (N = 8)	Geometric mean ratio ^a (90% CI)	
Eslicarbazepine							
After a single dose	C _{max} (mg/L)	7.34	6.33	1.16 (1.01–1.34)	23.32	21.38	1.09 (0.88–1.34)
	AUC _{0–24h} (h·mg/L)	92.95	83.24	1.12 (1.01–1.23)	369.91	344.16	1.07 (0.95–1.21)
After multiple doses	C _{max,ss} (mg/L)	12.04	10.81	1.11 (1.00–1.24)	34.21	34.13	1.00 (0.88–1.14)
	AUC _{τ,ss} (h·mg/L)	169.91	159.81	1.06 (0.97–1.17)	570.88	591.77	0.96 (0.87–1.06)
(R)-licarbazepine							
After a single dose	C _{max} (mg/L)	0.13	0.14	0.89 (0.74–1.07)	0.58	0.6	0.97 (0.81–1.16)
	AUC _{0–24h} (h·mg/L)	2.26	2.54	0.89 (0.73–1.09)	9.99	10.32	0.97 (0.80–1.18)
After multiple doses	C _{max,ss} (mg/L)	0.38	0.4	0.95 (0.80–1.11)	1.68	1.79	0.94 (0.79–1.12)
	AUC _{τ,ss} (h·mg/L)	8.51	8.95	0.95 (0.80–1.13)	37.07	39.9	0.93 (0.78–1.11)
Oxcarbazepine							
After a single dose	C _{max} (mg/L)	0.06	0.06	0.99 (0.81–1.20)	0.21	0.21	1.02 (0.81–1.28)
	AUC _{0–24h} (h·mg/L)	0.78	0.78	1.00 (0.81–1.23)	3.27	3.25	1.01 (0.83–1.22)
After multiple doses	C _{max,ss} (mg/L)	0.11	0.09	1.2 (0.97–1.48)	0.49	0.46	1.06 (0.90–1.24)
	AUC _{τ,ss} (h·mg/L)	1.57	1.45	1.08 (0.89–1.31)	7.32	7.01	1.04 (0.87–1.26)

Abbreviations: AUC_{0–24h}, area under the curve from 0 to 24 h; AUC_{τ,ss}, area under the concentration–time curve within a dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; C_{max,ss}, maximum plasma concentration at steady state.

^aGeometric mean ratio of Korean to White subjects.

the physical examination, neurological examination, vital signs, 12-lead ECG, laboratory tests, or C-SSRS.

DISCUSSION

The present study showed that the PK characteristics of ESL and its active metabolites were similar between Korean and White subjects after single and multiple dose administration of ESL. The systemic exposure of eslicarbazepine increased less than dose-proportionally, whereas the systemic exposure of (R)-licarbazepine and OXC increased dose-proportionally in Korean subjects with the dose range of 400–1600 mg. No substantial difference in safety and tolerability was observed between Korean and White subjects, and the incidence of AEs increased as the dose of ESL increased.

Similar PK characteristics of ESL were expected between Korean and White subjects based on previous study results.^{10,12–16} In previous PK studies, including a population PK analysis, patient body weight and co-administered drugs (phenytoin, phenobarbital, and carbamazepine) significantly influenced the PK of eslicarbazepine.^{4,12} However, the exposure to eslicarbazepine was not significantly different between the various ethnic groups.^{10,12,15}

As ESL is highly converted to eslicarbazepine by hydrolyase in the intestine and liver, the hydrolyase activity was similar between the different ethnic groups.^{15–17} Renal excretion is the main elimination route of ESL metabolites, including eslicarbazepine, which is generally not affected by different ethnicities.^{2,4,18} As expected, the PK parameters were similar between Korean and White subjects in this study (Tables 2, 3, Figures 2, 3, Tables S1, S2, and Figure S1, S2).

In our study, the systemic exposure of eslicarbazepine increased in a less than dose-proportional manner in the range of 400–1600 mg ESL, and the systemic exposure of (R)-licarbazepine and OXC increased dose-proportionally. Overall, the PK of eslicarbazepine is dose proportional and linear in both White healthy subjects and patients over the dose range of 400–1200 mg q.d.^{2,5,15,19} Otherwise, the dose-normalized PK parameters were similar in the dose range of 400–800 mg q.d., but decreased at 1600 mg q.d. in this study (Figure S3). The absorption might be saturated when more than 1200 mg ESL is administered. Considering that the maintenance dose of ESL is 800 mg orally q.d.,¹⁸ and a flat PD curve was shown at ESL doses >800 mg, the effect of less than dose proportionality of eslicarbazepine would not be clinically significant.²⁰

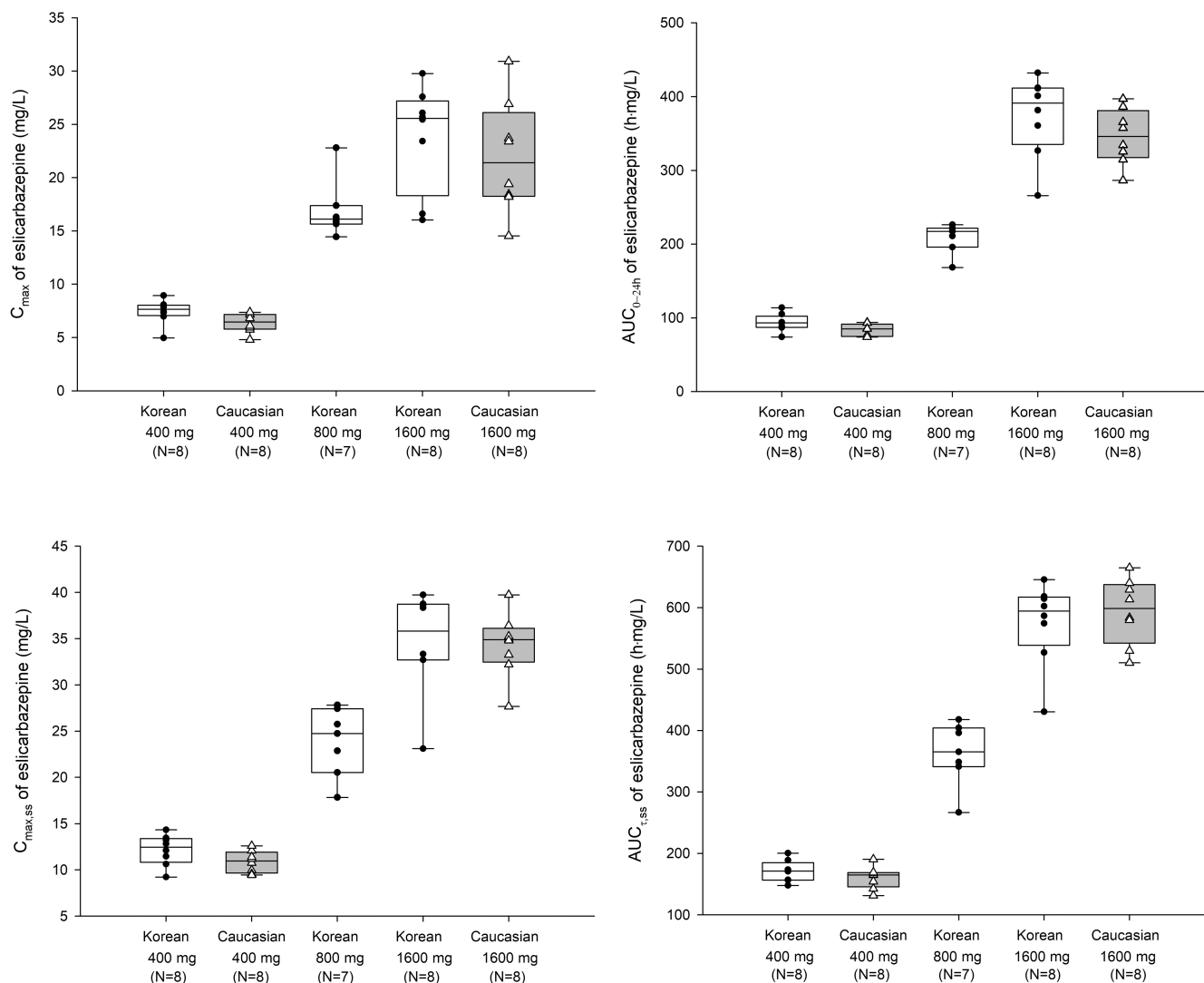


FIGURE 3 Comparison of the pharmacokinetic parameters of eslicarbazepine after single and multiple oral doses of 400, 800, or 1600 mg eslicarbazepine acetate in Korean and White subjects. AUC_{0-24h} , area under the curve from 0 to 24 h; $AUC_{\tau,ss}$, area under the concentration–time curve within a dosing interval; C_{max} , maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady state.

There are several limitations in this study. First, this study was planned to recruit healthy subjects regardless of sex, but only male subjects participated in the study. In this study, ESL PKs were not significantly different between Korean male and White male subjects. However, considering that the previous studies showed that the PK characteristics of ESL was not significantly affected by sex, the PK characteristics of ESL is expected to be similar between Korean female and White female subjects.^{13,18} Second, the present study was conducted in healthy subjects to minimize possible confounding factors. However, ESL PKs were not significantly different between the healthy subjects and the patients with partial-onset seizures.¹⁹ Based on the results of this study, similar ESL PK characteristics are expected between Korean and White patients with epilepsy.

Similar to the previous study results, single and multiple doses of ESL 400–1600 mg were well-tolerated in both Korean and White subjects in this study.² AEDs, including ESL, may increase the risk of suicidal thoughts or behavior, but no clinically meaningful changes were observed in the C-SSRS in this study.^{18,21} All AEs were mild, and no serious AEs occurred throughout the study. The previously reported common AEs of ESL were associated with the nervous system and gastrointestinal disorders, such as dizziness, somnolence, headache, nausea, and vomiting, and headache was also the most commonly observed AE in this study.^{2,20,22,23} The incidence of AEs increased as the dose of ESL increased, which was consistent with previous studies.^{21,22}

As the PK characteristics between Korean and White subjects were similar, the efficacy and safety data from

TABLE 4 Summary of treatment-emergent adverse events after single and multiple oral doses of 400, 800, or 1600 mg eslicarbazepine acetate or placebo in Korean and White subjects by system organ class and preferred term

	Korean				White		
	400 mg (N = 8)	800 mg (N = 8)	1600 mg (N = 8)	Placebo (N = 6)	400 mg (N = 8)	1600 mg (N = 8)	Placebo (N = 4)
Treatment-emergent adverse events	2 (25.0) [2]	2 (25.0) [2]	4 (50.0) [15]		3 (37.5) [4]		1 (25.0) [1]
Nervous system disorders	1 (12.5) [1]	1 (12.5) [1]	3 (37.5) [7]		1 (12.5) [1]		
Dizziness			3 (37.5) [3]				
Headache	1 (12.5) [1]	1 (12.5) [1]	2 (25.0) [3]				
Lethargy			1 (12.5) [1]				
Somnolence						1 (12.5) [1]	
Gastrointestinal disorders			4 (50.0) [5]			2 (25.0) [2]	
Abdominal discomfort			1 (12.5) [1]				
Aphthous ulcer			1 (12.5) [1]				
Constipation						1 (12.5) [1]	
Nausea			2 (25.0) [2]			1 (12.5) [1]	
Vomiting			1 (12.5) [1]				
Skin and subcutaneous tissue disorders			2 (25.0) [3]				1 (25.0) [1]
Dermatitis contact							1 (25.0) [1]
Pruritus			2 (25.0) [2]				
Rash			1 (12.5) [1]				
Musculoskeletal and connective tissue disorders		1 (12.5) [1]				1 (12.5) [1]	
Arthralgia		1 (12.5) [1]					
Musculoskeletal chest pain						1 (12.5) [1]	
General disorders and administration site conditions	1 (12.5) [1]						
Sensation of foreign body	1 (12.5) [1]						

Note: Data are presented as number of subjects (%) [number of events].

White patients can be reasonably extrapolated to Korean patients. The ICH E5 guideline (Ethnic Factors in the Acceptability of Foreign Clinical Data) provides guidance about regulatory and development strategies to evaluate the influence of ethnic factors on drug efficacy and safety.⁷ Appendix D suggests that the properties of drugs are less likely to be sensitive to ethnic factors, with such properties including linear PK, a flat effect-concentration curve for both efficacy and safety in the range of the recommended dosage, and a wide therapeutic dose range. Analysis of the ethnic sensitivity of ESL according to these factors revealed the following: first, in terms of linear PK, eslicarbazepine showed linear PK with a dose range of 400–1600 mg. Second, ESL has a flat effect-concentration curve.^{24,25} ESL showed a dose-response relationship between 400 and 800 mg q.d., and the rate of increase in efficacy decreased at doses over 800 mg q.d.⁶ The median relative reductions in seizure

frequency (standard seizure frequency) and efficacy over the 12-week period were 23.4%, 33.4%, and 37.8% for 400, 800, and 1200 mg, respectively.²⁵ Third, ESL has a wide therapeutic dose range in which the starting dose of ESL is 400 mg q.d., and the dose can be increased to the maximum dose of 1600 mg.¹⁸ Fourth, the bioavailability of ESL is more than 90%, and its absorption is not affected by food.^{8,9} Last, the protein binding fraction of ESL is lower than 40%.⁹ Overall, ESL appears to be less likely to be sensitive to ethnic factors.

In conclusion, the PKs between Korean and White subjects was similar after single and multiple doses of 400–1600 mg ESL, and the systemic exposure of eslicarbazepine increased dose linearly with the range of 400–1600 mg. It is expected that the efficacy and safety of ESL in Korean subjects would be similar to those in White subjects. Based on these study results, the currently approved dose regimens in White subjects can be applied to Korean subjects with no dose adjustments.

AUTHOR CONTRIBUTION

S.H., S.L., J.Y.C., and J.O. wrote the manuscript. I.H., J.Y.C., I.J.J., and J.O. designed the research. I.H., J.Y.C., I.J.J., and J.O. performed the research. S.H. and E.K. analyzed the data.

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CONFLICT OF INTEREST

The 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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