Eslicarbazepine Acetate (BIA 2-093)

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Summary: Eslicarbazepine acetate (ESL) [(*S*)-(−)-10-acetoxy-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide], formerly known as BIA 2-093, is a novel central nervous system (CNS)-active compound with anticonvulsant activity. It behaves as a voltage-gated sodium channel (VGSC) blocker and is currently under clinical development for the treatment of epilepsy and bipolar disorder. ESL shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11-position. This molecular variation results in differences in metabolism, preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11 epoxide. In pharmacokinetic studies in humans, ESL was rapidly and extensively metabolized to eslicarbazepine (S-licarbazepine), which is responsible for pharmacological activity. ESL has been tested in patients with refractory partial-onset seizures and was found to be efficacious and well tolerated. Monotherapy studies in adult epileptic patients and add-on studies in epileptic children are in the planning process. The efficacy and safety data appear to be very promising considering the refractory nature of the epileptic population enrolled in studies to date. Results of ongoing phase III studies in adult epileptic patients are expected to be available in 2007 and are required to define the position of ESL in the therapy of patients with epilepsy. **Key Words:** Eslicarbazepine acetate, BIA 2-093, antiepileptic drugs, drug therapy, epilepsy.

INTRODUCTION

Eslicarbazepine acetate (ESL) [(*S*)-(−)-10-acetoxy-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide], formerly known as BIA 2-093, is a novel CNS-active compound currently completing phase III clinical trials as adjunctive therapy in partial epilepsy refractory to standard antiepileptic drugs (AEDs) and undergoing phase II clinical trials as monotherapy in partial epilepsy and in bipolar disorder.

ESL mechanism of action is to block the voltage-gated sodium channel (VGSC).[1,2] ESL shares with carbamazepine (CBZ) and oxcarbazepine (OXC) the basic chemical structure of a dibenzazepine nucleus with the 5-carboxamide substituent, but is structurally different at the 10,11-position.[1,2] (FIG. 1). This molecular variation results in differences in ESL metabolism: ESL is reduced by liver esterases to the major active metabolite eslicarbazepine (also known as S-licarbazepine or S-MHD), and, unlike CBZ, is not metabolized to CBZ-10,11-epoxide and is therefore not susceptible to enzyme induction or autoinduction.[3] ESL also originates R-licarbazepine and OXC as minor metabolites by non–cytochrome P450 mediated metabolism.[3] In humans, renal excretion appears to be the major route of elimination of the ESL metabolites.[4,5]

The method used for drug assays consists of solid phase extraction followed by high performance liquid chromatography with mass spectrometric detection (LC-MS) and has been reported elsewhere.[6]

PHARMACOLOGY

The precise antiseizure mechanism of action of ESL is unknown. However, *in vitro* electrophysiological studies indicate that both ESL and its metabolites competitively interact with site 2 of the inactivated state of VGSC. ESL stabilizes the inactive form of the sodium channel, preventing its return to the active state, and sustains repetitive neuronal firing. These actions are thought to be important in the prevention of seizure genesis and spread throughout the intact brain. ESL has a much higher affinity for the inactivated state of the channel compared with the resting state. The affinity of ESL for resting channels is about threefold lower than that of CBZ. This profile suggests that ESL has an enhanced inhibitory selectivity for rapidly firing neurons over those displaying normal activity.[7] ESL does not appear to interact

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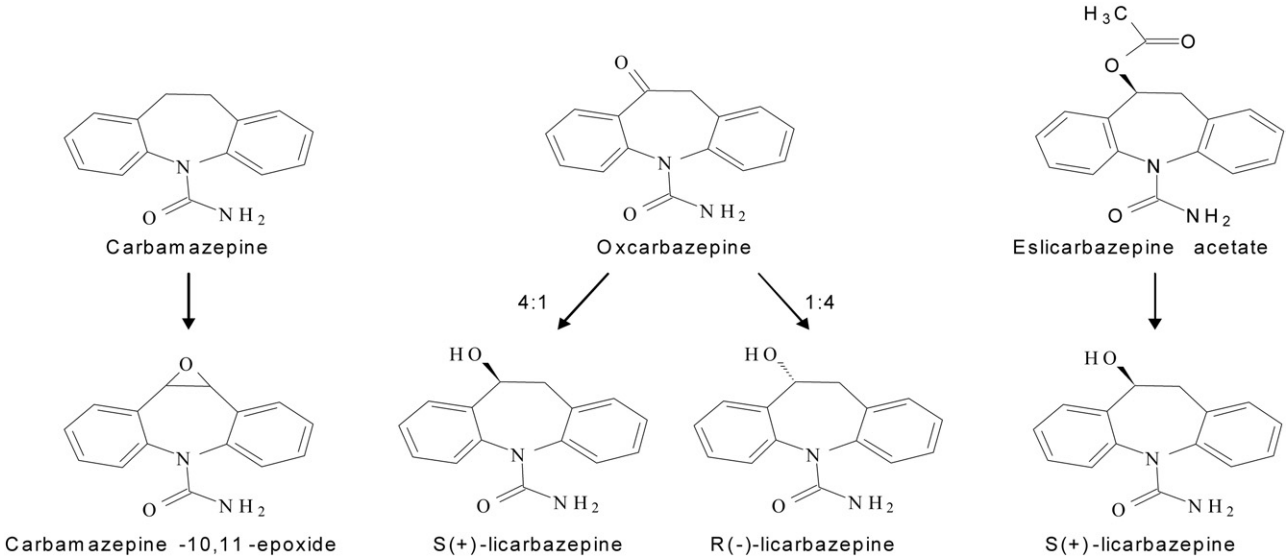

FIG. 1. Chemical structure and main metabolic pathway of carbamazepine, oxcarbazepine, and eslicarbazepine acetate.

with benzodiazepine, GABA, and glutamate receptors.[2,8–10]

In comparison with CBZ and OXC, ESL was found to cause less neurological impairment to rats after intraperitoneal administration and, consequently, has a higher protective index.[1] (The protective index is the ratio of the median toxic dose to the median effective dose: PI = TD_{50}/ED_{50}). In a study in cultured hippocampal neurons, ESL was less neurotoxic than CBZ or OXC.[11]

ESL and its metabolites were tested in several models predictive of anticonvulsant efficacy. In the maximal electroshock seizure (MES) test in rat, ESL was found to be equally potent to CBZ and more potent than OXC at 2 and 4 h after administration by gastric tube; however, at 8 h after administration, the three drugs were equipotent. ESL and CBZ were similarly effective in preventing development of kindling seizures in kindled rats (amygdala kindling in rats mimics complex partial seizures in humans). ESL also showed protective effect against seizures induced by several chemoconvulsants in rats or mice: metrazole, bicuculline, picrotoxin, and 4-aminopyridine (4-AP).[12]

Also evaluated were the effects of oral treatment with ESL on a whole-animal model in which partial seizures can be elicited repeatedly on different days without changes in threshold or seizure patterns. In animals treated with threshold doses of picrotoxin (perfused through the hippocampus), the average number of seizures was 2.3 ±1.2, and average seizure duration was 39.5 ± 8.4 s. Pretreatment with an ESL dose of 30 mg/kg 2 h before picrotoxin microperfusion prevented seizures in 75% of rats. Lower doses (3 and 10 mg/kg) did not suppress seizures; however, after administration of 10 mg/kg, significant reductions in seizure duration (24.3 ± 6.8 s) and seizure number (1.6 ± 0.3) were observed. No adverse effects of ESL were observed in the behavioral and EEG patterns studied, including sleep–wakefulness cycle, at the doses studied.[13]

Intrahippocampal microperfusion of latrunculin A (4 μmol/L) induces long-term changes in neuronal excitability, leading to the onset of sporadic spontaneous seizures. At oral doses of 10 and 30 mg/kg, ESL resulted in marked attenuation of seizures induced by latrunculin A microperfusion in the rat hippocampus.[14] The molecular mechanisms behind latrunculin A seizures are still unknown, but the increase in extracellular glutamate concentrations observed during latrunculin A microperfusion are completely reversed by ESL.[14] This fits well with the observation that ESL is a potent blocker of the 4-aminopyridine- or veratridine-evoked release of glutamate.[9]

Pharmacokinetics and metabolic profile

When a chiral method is used, the assay can distinguish between eslicarbazepine (S-licarbazepine or S-MHD) and its R-enantiomer (R-licarbazepine or R-MHD). Pharmacokinetic studies in humans using such an assay have shown that ESL is rapidly and extensively metabolized to the active metabolite eslicarbazepine (FIG. 1).[15–17] This metabolite is responsible for approximately 95% of total systemic drug exposure after oral administration of ESL; R-licarbazepine and OXC are minor metabolites.[15–17] Plasma levels of parent drug (ESL) usually remained below the limit of quantification.

In some early clinical pharmacokinetic studies, a nonchiral drug assay was used. This method does not allow the separation of S-licarbazepine and R-licarbazepine, and the enantiomeric mixture has been reported as BIA 2-005. In single-dose and multiple-dose studies with ESL in healthy subjects administered with single oral doses

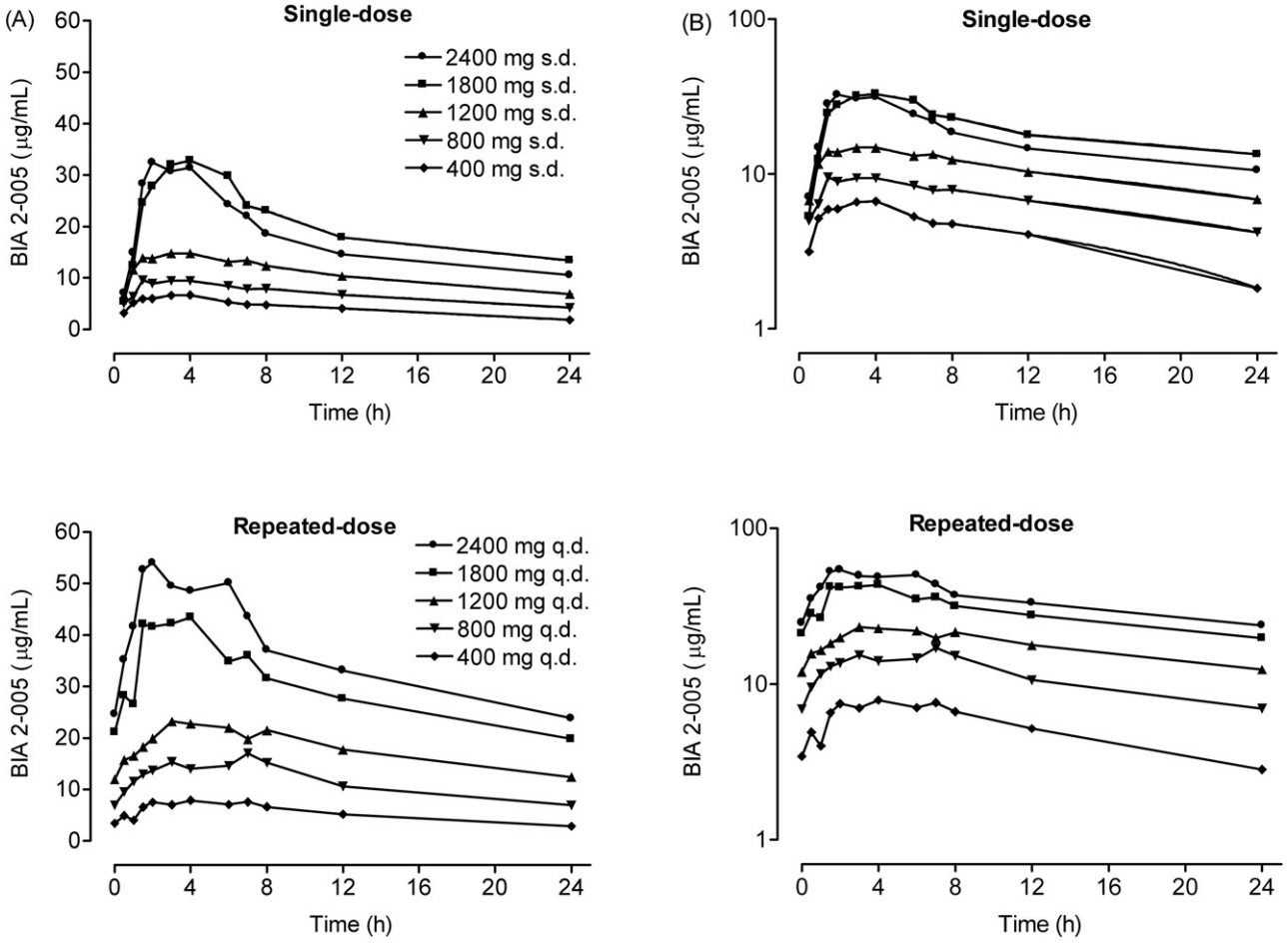

FIG. 2. Mean 24-h plasma concentration-time profiles of the active moiety BIA 2-005 after oral administration of single dose (s.d.) and last dose of an 8-day once-daily (q.d.) regimen of eslicarbazepine acetate to healthy male subjects (n = 6 per dose group). (A) Linear scale. (B) Semilog scale.

ranging from 20 mg to 2400 mg[4,18] and with multiple-dose studies ranging from 200 mg 2× daily (b.i.d.) to 2400 mg 1× daily (q.d.),[5,18] ESL was extensively metabolized to BIA 2-005.

The plasma concentration *versus* time profiles of BIA 2-005 after single and repeated (8-day treatment) doses are shown in Figure 2. The main pharmacokinetic parameters after a single dose and after the last dose of an 8-day treatment are given in Tables 1 and 2. Both the rate and the extent of systemic exposure to BIA 2-005 in-

TABLE 1. *Main Pharmacokinetic Parameters of BIA 2-005 After Single-Dose Administration of Eslicarbazepine Acetate to Healthy Male Subjects*

Dose*	Mean C_{max}, μg/mL (%CV)	Median t_{max}, h (range)	Mean AUC_{0-24h}, μg · h/mL (%CV)	Mean apparent $t_{1/2}$, h (%CV)
20 mg	0.3 (18.7)	0.8 (0.5–0.8)	2.4 (16.2)	**9.1 (15.9)**
50 mg	0.9 (24.7)	0.8 (0.5–2)	6.7 (12.7)	8.1 (9.1)
100 mg	1.5 (13.8)	1.5 (0.5–2)	16.4 (11.7)	9.3 (8.7)
200 mg	2.9 (16.2)	1.5 (0.8–2.5)	30.5 (23.7)	8.4 (18.8)
400 mg	5.2 (11.6)	4 (4–5)	81.5 (10.8)	11.7 (18.6)
600 mg	8.5 (20.0)	4 (0.5–5)	119.7 (17.4)	12.3 (14.8)
900 mg	15.0 (18.2)	2.3 (0.8–4)	210.3 (10.6)	16.3 (31.9)
1200 mg	18.6 (16.3)	4 (2–6)	285.7 (16.7)	16.5 (6.8)
1800 mg	34.6 (16.3)	3.5 (3–6)	507.6 (17.0)	11.8 (11.7)
2400 mg	35.9 (42.6)	3 (1.5–6)	445.6 (26.1)	11.1 (21.1)

AUC = area under the plasma concentration-time curve over the dosing interval specified in the subscript, C_{max} = maximum plasma concentrations, CV = coefficient of variation, $t_{1/2}$ = elimination half-life. * n = 6 per dose group.

TABLE 2. *Main Pharmacokinetic Parameters of BIA 2-005 After Last Dose of an 8-Day Treatment with Eslicarbazepine Acetate in Healthy Male Subjects*

Dose*	Mean C_{max}, μg/mL (%CV)	Median t_{max}, h (range)	Mean AUC_{0-24h}, μg · h/mL (%CV)	Mean apparent $t_{1/2}$, h (%CV)
200 mg b.i.d.	6.7 (23.6)	2.75 (1–4)	63.1 (12.7)	9.40 (16.7)
400 mg q.d.	8.8 (16.0)	3 (0.5–7)	126.3 (11.7)	9.50 (18.8)
800 mg q.d.	18.7 (14.0)	3.5 (1–7)	268.4 (10.3)	12.3 (22.9)
1200 mg q.d.	25.5 (10.8)	3 (0.5–6)	423.0 (10.9)	13.1 (20.1)
1800 mg q.d.	47.7 (23.3)	2 (0.5–4)	740.3 (19.6)	11.3 (28.8)
2400 mg q.d.	56.5 (20.0)	2 (1.5–8)	905.9 (12.8)	10.4 (24.1)

AUC = area under the plasma concentration-time curve over the dosing interval specified in the subscript, C_{max} = maximum plasma concentrations, CV = coefficient of variation, $t_{max} = t_{1/2}$ = elimination half-life. * $n = 6$ per dose group.

creased in an approximately dose-proportional manner after single and repeated administration. BIA 2-005 accumulated in plasma after repeated administration. The mean observed accumulation (R_o) was 3.0 after 200 mg b.i.d., and 1.4, 1.7, 1.7, 1.5, and 2.1 after 400, 800, 1200, 1800, and 2400 mg q.d, respectively. Steady-state plasma BIA 2-005 concentrations were attained at 4–5 days of q.d. dosing, consistent with an effective elimination half-life ($t_{1/2}$) on the order of 20–24 h. Renal clearance of BIA 2-005 from plasma was approximately 20–30 mL/min. Renal clearance of BIA 2-005 appeared to be constant over the dose range studied. The total amount of BIA 2-005 recovered in urine was approximately 20% within 12 h after the dose and 40% within 24 hours after.[5] The dose-proportionality for BIA 2-005 (after single and repeated doses) is in accordance with the concept of linearity regarding its pharmacokinetic behavior (rate and extent of systemic exposure).

The effect of systemic exposure to eslicarbazepine after administration of q.d. and b.i.d. regimens of ESL was investigated in an unpublished study by our group in 11 healthy subjects. That study consisted of 8-day treatment periods separated by a washout period of 10–15 days. In each treatment period, the volunteers received either an oral dose of ESL 900 mg q.d. or ESL 450 mg b.i.d.. ESL was extensively and rapidly metabolized to eslicarbazepine (S-licarbazepine), the main active metabolite. After the last dose of the ESL 900 mg q.d. regimen, eslicarbazepine maximum plasma concentration (C_{max}) was 22.2 ± 7.3 μg/mL (mean ± SD), and the area under the plasma concentration-time curve over the dosing interval (AUC_τ) was 294.0 ± 58.4 μg · h/mL; after the last dose of the ESL 450 mg b.i.d. regimen, the corresponding values were C_{max} = 16.7 ± 4.0 μg/mL and AUC_τ = 142.1 ± 25.9 μg · h/mL. The rate of systemic exposure to eslicarbazepine, as assessed by C_{max}, was 33% higher after ESL 900 mg q.d. in comparison with ESL 450 mg b.i.d. The extent of systemic exposure to eslicarbazepine during a 24-h interval, as assessed by comparing the AUC_τ of the ESL 900 mg q.d. regimen (AUC_{0-24h}) with twice the AUC_τ of the ESL 450 mg b.i.d. regimen (2 × AUC_{0-12h}), was 3% higher after ESL 900 mg q.d. than after ESL 450 mg b.i.d.

A study showed that oral suspension 50 mg/mL and tablets strengths 200 mg and 800 mg are bioequivalent.[6]

The effect of age and gender on the pharmacokinetics of ESL was investigated in a study in 12 young (18–40 years) and 12 elderly (65 years or more) healthy subjects.[15,17] In each age group, six subjects were female and six were male. That study consisted of a single-dose period (600 mg; phase A) and a multiple-dose period (600 mg q.d. for 8 days; phase B), separated by 4 days. Plasma concentration-time profiles of eslicarbazepine after phase A single dose and phase B last dose are presented in Figure 3. After a 600-mg single dose, mean C_{max} and AUC from 0 to infinity ($AUC_{0-\infty}$) were, respectively, 9.9 μg/mL and 180.9 μg · h/mL in young subjects and 9.5 μg/mL and 196.0 μg · h/mL in elderly subjects, and a corresponding 9.3 μg/mL and 171.9 μg · h/mL in men and 10.1 μg/mL and 205.0 μg · h/mL in women. After multiple dosing, steady-state plasma concentrations were attained at 4–5 days of administration in both age and sex groups, consistent with an effective half-life in the order of 17–18 h.

After the last dose of phase B, mean C_{max} and $AUC_{0-\infty}$ of eslicarbazepine were, respectively, 17.3 μg/mL and 296.7 μg · h/mL in young subjects and 15.1 μg/mL and 294.3 μg · h/mL in elderly subjects, and a corresponding 15.5 μg/mL and 295.8 μg · h/mL in men and 16.8 μg/mL and 295.2 μg · h/mL in women. After the single dose (phase A), the eslicarbazepine C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ elderly/young geometric mean ratio (GMR) with 95% confidence interval (95% CI) was, respectively, 0.95 (0.81, 1.14), 1.02 (0.86, 1.24), and 1.06 (0.88, 1.32); the corresponding female/male GMR (95% CI) was 1.09 (0.87, 1.43), 1.16 (0.95, 1.48), and 1.17 (0.90, 1.63). After the last dose of phase B, the eslicarbazepine C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ elderly/young GMR (95% CI) was, respectively, 0.88 (0.77, 1.03), 0.98 (0.90, 1.09), and 1.01 (0.89, 1.18); the corresponding female/male GMR (95% CI) was 1.10 (0.98, 1.27), 1.04 (0.88, 1.28), and 1.01 (0.83, 1.30). It was concluded that

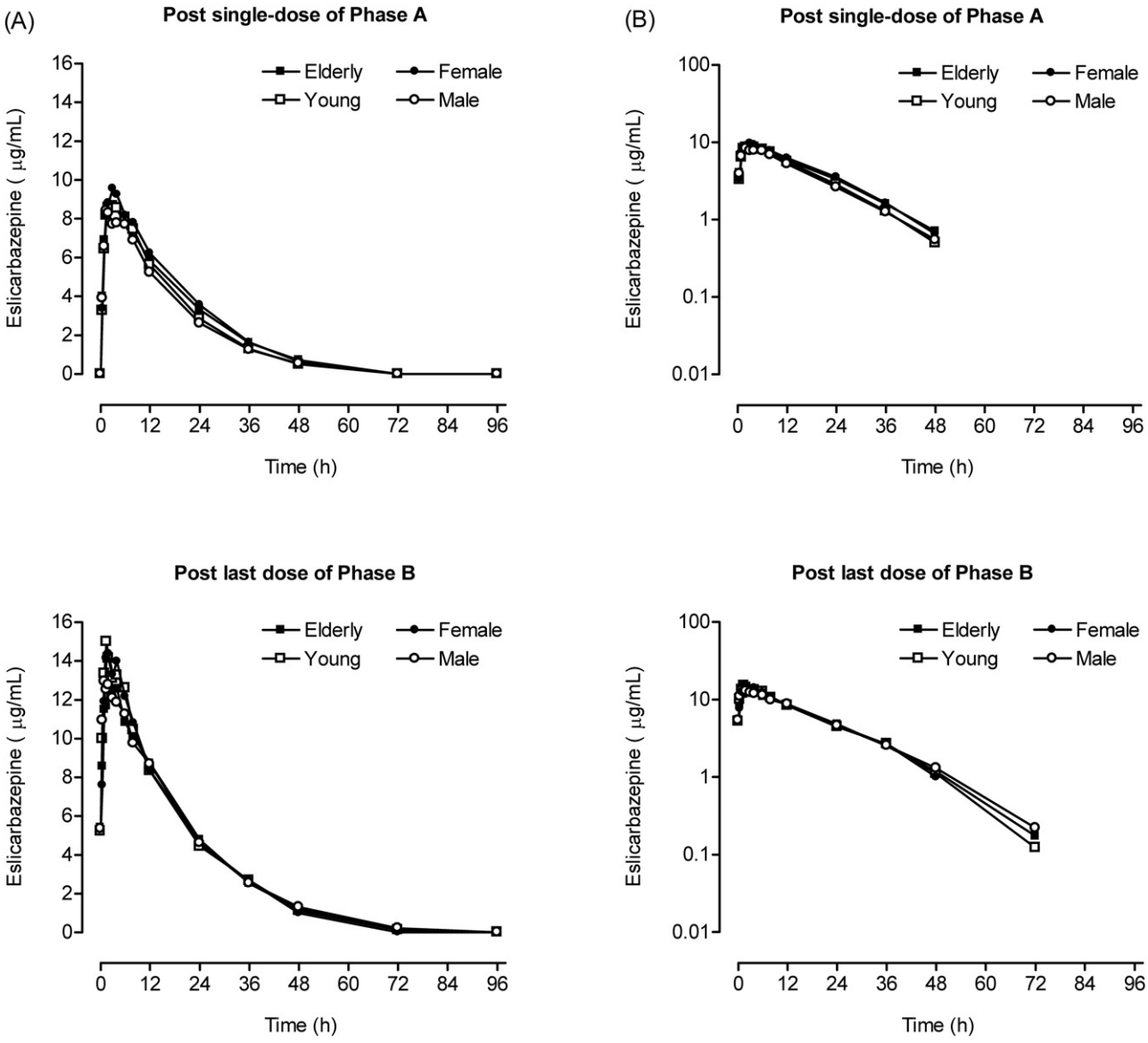

FIG. 3. Mean plasma concentration–time profile of the active moiety eslicarbazepine after a 600-mg single dose (phase A) and after the last dose of an 8-day once-daily 600-mg dose regimen (phase B) of eslicarbazepine acetate to young and elderly healthy subjects (n = 12 per age group; n = 12 per gender group). (A) Linear scale. (B) Semilog scale.

no dosage adjustment on the basis of age or gender is necessary. [15,17]

Drug interactions

In vitro studies with human plasma showed that the binding of eslicarbazepine to plasma proteins is relatively low (30%) and is not affected by the presence of warfarin, diazepam, digoxin, phenytoin, and tolbutamide, and that the binding of warfarin, diazepam, digoxin, phenytoin, and tolbutamide is not affected by the presence of eslicarbazepine (unpublished observations).

The interaction of eslicarbazepine with other drugs and enzymes has been also evaluated *in vitro*. Eslicarbazepine appeared to have no relevant effect on the activity of the cytochrome P450 (CYP) isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP4A9/11; the uridine diphosphate-5′-glucuronosyltransferases (UGT) UGT1A1 and UGT1A6; and the epoxide hydrolase (EH) of human hepatic microsomes. The most significant effect was a moderate inhibition (38% reduction) of CYP2C9-mediated tolbutamide 4-hydroxylation and a mild activation (39% increase) of UGT1A1-mediated ethinylestradiol glucuronidation (unpublished observations). Another study investigated the potential for eslicarbazepine to induce hepatic drug metabolizing enzymes using freshly isolated human hepatocytes (unpublished observations). Those *in vitro* findings suggested that it is unlikely that

eslicarbazepine will significantly induce the metabolism of drugs coadministered during clinical use that undergo metabolism through CYP1A2, CYP3A4, and phase 2 hepatic enzymes.

The effect of food on the ESL pharmacokinetics was investigated in a randomized, two-way crossover study in 12 healthy subjects.[19] That study consisted of two consecutive treatment periods separated by a washout of 14 days or more. In each of the study periods, subjects were administered a single dose of ESL 800 mg after either a standard high-fat content meal or 10 h of fasting. The nonchiral assay was used, and therefore the active moiety was reported as BIA 2-005. The BIA 2-005 C_{max} was 12.8 ± 1.8 (mean ± SD) in fed (or Test) conditions and 11.3 ± 1.9 μg/mL in fasting (or Reference) conditions; the corresponding $AUC_{0-\infty}$ was 242.5 ± 32.1 (Test) and 243.6 ± 31.1 μg · h/mL (Reference). The point estimate and 90% confidence interval, or PE (90% CI), of the Test/Reference C_{max} GMR was 1.14 (1.04, 1.25); the PE (90% CI) for the $AUC_{0-\infty}$ Test/Reference ratio was 1.00 (0.95, 1.04). Bioavailability of ESL administered in fed and fasting conditions was similar, and bioequivalence was accepted for both $AUC_{0-\infty}$ and C_{max} because the 90% CI lies within the usual acceptance range of 0.80, 1.25.[20] No statistically significant differences were found in t_{max} (i.e., time of occurrence of C_{max}).

The effect of ESL on the digoxin pharmacokinetics was investigated in a randomized, double-blind, placebo-controlled, two-way crossover study in 12 healthy subjects.[21] That study consisted of two 8-day treatment periods separated by a washout of 10 or more days. During each treatment period, subjects received either a daily oral dose of ESL 1200 mg q.d. or a placebo (PLA) concomitantly with a digoxin q.d. dose of 0.5 mg/day on days 1 and 2, and 0.25 mg/day on days 3–8. Minimum (predose) serum digoxin concentrations (C_{min}) at days 6, 7, and 8 were, respectively, 445, 452, and 633 pg/mL with PLA and 475, 522, and 561 pg/mL with ESL. The PE (90% CI) values of PLA/ESL C_{max} and AUC_{0-24} were 0.85 (0.68, 1.07) and 0.96 (0.90, 1.03), respectively. The observed 15% decrease in C_{max} of digoxin when digoxin was administered concomitantly with ESL is not expected to affect digoxin efficacy, because the extent of exposure (as assessed by AUC_{0-24}) was similar. It was concluded that, at the dose of 1200 mg q.d., ESL had no relevant effect on the steady-state extent of systemic exposure to digoxin.

The effect of ESL on the warfarin pharmacokinetics and pharmacodynamics was investigated in a multiple-dose, open-label, single-period study consisting of three consecutive phases:

Phase A: run-in warfarin dose-finding phase, aimed at identifying the warfarin daily dose that stabilizes the INR between 1.3 and 1.8 (minimum of 16 days and up to 21 days).

Phase B: warfarin pharmacokinetics and international normalized ratio (INR) profiling before, during, and after a 7-day multiple-dose treatment with ESL in which subjects received ESL 1200 mg q.d. concomitantly with their individualized dose of warfarin defined in the run-in phase A, the aim of which was to assess whether ESL affects INR and levels of warfarin when added to concomitant warfarin therapy.

Phase C: a 7-day period in which subjects received warfarin alone at their individualized doses, aimed at assessing whether ESL affected INR and levels of warfarin when it was removed from concomitant warfarin therapy.

The C_{max} of S-warfarin was reached at a time t_{max} between 1.0 and 4.0 h after the dose (median of 1.0 h). Thereafter, plasma S-warfarin concentrations declined in a multiphasic manner with a mean apparent terminal $t_{1/2}$ of 27.0 h (day 1 of phase B) and 24.5 h (day 8 of phase B). Systemic exposure (C_{max} and AUC_{0-24}) to S-warfarin decreased after administration of ESL concomitantly with warfarin. The PE (90% CI) of the AUC_{0-24} ratio of Test (warfarin plus ESL: day 8 of phase B) over Reference (= warfarin alone: day 1 of phase B) was 0.77 (0.72, 0.82). For the C_{max} ratio, PE was 0.81 and 90% CI was 0.76, 0.86. No statistical difference was found between t_{max} values. C_{max} of R-warfarin was reached t_{max} between 1.0 and 4.0 h after the dose (median of 1.0 h) at day 1 of phase B and between 1.0 and 8.0 h after the dose (median of 1.0 h) at day 8. Thereafter, plasma R-warfarin concentrations declined in a multiphasic manner, with a mean $t_{1/2}$ of 33.7 h on day 1 of phase B and 31.8 h on day 8. Systemic exposure (C_{max} and AUC_{0-24}) to R-warfarin did not significantly change after administration of ESL concomitantly with warfarin. The PE (90% CI) was 0.98 (0.92, 1.04) for AUC_{0-24} and 0.97 (0.91, 1.02) for C_{max}. No statistical difference was found between t_{max} values for R-warfarin.

During the three last days of phase A (warfarin, administered alone) and of phase B (ESL administered with warfarin), the INR values were 1.45 ± 0.10 (mean ± SD) and 1.51 ± 0.25, respectively. The small increase of 4.0% in the INR value appears to have no clinical or statistical significance (90% CI: −1.03, 9.12) and thus we conclude that there was no significant pharmacodynamic interaction between ESL and warfarin. In phase C, after discontinuation of ESL administration, a slight INR decrease was found: −5.42% (90% CI: −8.85, −1.98).

In an unpublished study by our group, administration of ESL 1200 mg q.d. concomitantly with a hormonal oral contraceptive containing 30 μg ethinylestradiol and 150

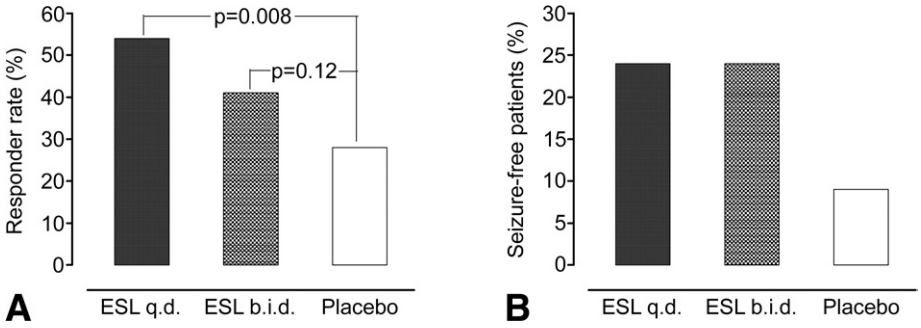

FIG. 4. **A**, Responder rate (i.e., proportion of patients with at least 50% decrease in number of seizures) and; **B**, proportion of seizure-free patients in a phase II study with eslicarbazepine acetate (ESL) in patients with refractory partial-onset epilepsy. q.d. = ESL up to 1200 mg once daily, b.i.d. = ESL up to 600 mg twice daily.

μg levonorgestrel was shown to decrease the plasma concentrations of the two hormonal components when Test (ESL plus oral contraceptive) and Reference (oral contraceptive alone) were compared. In this study, mean levonorgestrel C_{max} decreased 13% (Test/Reference PE: 0.87; 90% CI: 0.79, 0.95) and AUC_{0-24} decreased 24% (PE: 0.76; 90% CI: 0.68, 0.86) after administration of ESL. In a published study with OXC, the reported decrease in the AUC of levonorgestrel was 47%.[22] In the ESL study, mean C_{max} ethinylestradiol decreased 20% (PE: 0.80; 90% CI: 0.79–0.95) and AUC_{0-24} decreased 32% (PE: 0.76; 90% CI: 0.68–0.86) after administration of ESL. With OXC, the reported decrease in the AUC of ethinylestradiol was 47%.[22] No statistically significant difference was found between t_{max} values for levonorgestrel and ethinylestradiol after administration of ESL.

CYP3A4 in the liver is responsible for the 2-hydroxylation of ethinylestradiol, the main route of elimination of the steroid.[23] The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Ethinylestradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation. The metabolism of levonorgestrel is more complex than that of ethinylestradiol: it involves reduction of the unsaturated ketone ring A as well as 2- and 6-hydroxylation, followed by conjugation.[24] Most of the metabolites that circulate in the blood are sulfates, whereas excretion occurs predominantly in the form of glucuronides.

Because a significant proportion of ethinylestradiol and levonorgestrel metabolism occurs during the first pass in the liver, induction of metabolism provides an explanation not only for the decrease in extent of exposure (as assessed as AUC) but also for the reduced peak plasma concentration (assessed as C_{max}) after absorption.[24] The mostly likely explanation is that the decrease in plasma ethinylestradiol and levonorgestrel was due to induction of the CYP3A4 isoenzymes involved in their oxidation.[22] Although the decrease in the extent of exposure to levonorgestrel and ethinylestradiol after ESL was approximately half that reported with OXC,[22] it may be concluded that concomitant administration of ESL and hormonal contraceptives can render these contraceptives less effective.

In a phase II study in patients (unpublished observations), administration of ESL 400 mg, 800 mg, and 1200 mg q.d or divided in two doses (b.i.d.) did not significantly affect the mean trough serum concentrations of valproate. The concomitant administration of ESL q.d. did not affect the lamotrigine concentrations over time, but when ESL was administered b.i.d., a significant decrease in the lamotrigine concentrations was found. Topiramate concentrations were significantly affected by the concomitant administration of ESL (q.d. or b.i.d.), but the decrease was more marked in the b.i.d. dosing. However, these results must be considered merely exploratory, and further and more reliable data will come from the currently ongoing phase III clinical trial program.

Efficacy data

Results are available for a multicenter, double-blind, randomized, placebo-controlled study in 143 patients with at least four partial-onset seizures per month in spite of treatment with one or two AEDs.[25] That study consisted of a 12-week treatment period followed by a 1-week tapering off. Patients were randomly assigned to one of three groups: treatment with ESL q.d. (n = 50), ESL b.i.d. (n = 46), or placebo (PLA, n = 47). For the first 4 weeks, daily doses were 400 mg; doses were then titrated up to 800 mg and 1200 mg at 4-week intervals. Statistical analysis was performed in the intent-to-treat population (all randomized patients with at least one administration of study medication). Proportion of responders (patients with a ≥50% reduction in seizure frequency) had been defined as the primary endpoint.

The main efficacy results are presented in Figure 4. The percentage of responders at the end of the treatment period *versus* baseline showed a statistically significant difference between ESL 1200 mg q.d. and PLA groups (54% *versus* 28%; P = 0.008); the difference between the ESL 600 mg b.i.d. (41%) and PLA did not reach

TABLE 3. *Summary of Treatment-Emergent Adverse Events in a Phase II Study with Eslicarbazepine Acetate in Epileptic Patients*

	Eslicarbazepine acetate q.d.	Eslicarbazepine acetate b.i.d.	Placebo
Sample size, no. of patients	50	46	47
Any AE, no. (%)	19 (38.0)	19 (41.3)	21 (44.7)
Discontinued due to AE, no. (%)	3 (6.0)	4 (8.7)	4 (8.5)
Discontinued due to SFI, no. (%)	0 (0.0)	2 (4.3)	1 (2.1)
AEs possibly related to treatment and occurring in >1 patient, no. (%)			
Headache	1 (2.0)	4 (8.7)	1 (2.1)
Dizziness	1 (2.0)	3 (6.5)	0 (0.0)
Nausea	2 (4.0)	3 (6.5)	2 (4.3)
Somnolence	3 (6.0)	1 (2.2)	0 (0.0)
Vomiting	0 (0.0)	3 (6.5)	0 (0.0)
Hair loss	1 (2.0)	2 (4.3)	0 (0.0)
Dry mouth	0 (0.0)	2 (4.3)	0 (0.0)
Concentration impaired	0 (0.0)	2 (4.3)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	2 (4.3)
CK increase	1 (2.0)	0 (0.0)	1 (2.1)
Drowsiness	1 (2.0)	0 (0.0)	1 (2.1)

Some subjects reported more than one adverse event.
AE = adverse event, b.i.d. = twice daily, CK, creatine kinase, q.d. = once daily, SFI = seizure frequency increase.

statistical significance ($P = 0.12$). During weeks 1–4 (400 mg/day), no significant differences in responder rate were found. During weeks 5–8 (800 mg/day), the proportion of responders reached 58% in the ESL q.d., compared with 38% in the PLA groups ($P = 0.04$); no statistical difference was found between the ESL b.i.d. and PLA groups ($P = 0.36$). A significantly higher proportion of responders in weeks 5–8 was found in the ESL q.d. group, compared with the ESL b.i.d. groups (58.0 *versus* 32.6%, respectively, $P = 0.022$). In each of the three 4-week periods, the ESL q.d. group showed a significantly higher reduction in seizure number than the ESL b.i.d. group ($P = 0.037$, 0.018, and 0.002, respectively).

Results from three ongoing phase III placebo-controlled studies in refractory adult epileptic patients, which are expected to be available in 2007, will define the position of ESL in the therapy of patients with epilepsy. Other ongoing or planned studies include phase II/III studies in epileptic children, monotherapy studies in adult epileptic patients, and phase II studies in acute mania and recurrence prevention in bipolar disorder.

Exposure, tolerability, and side-effects

More than 1800 subjects have been enrolled in ESL clinical studies performed to date or currently ongoing, and more than 1200 of these have been exposed to single or repeated doses of ESL. In human pharmacology studies in healthy subjects, the highest dosage used was 2400 mg q.d. for 8 days.[18] In add-on studies in epileptic patients, ESL has been used in doses up to 1200 mg/day concomitantly with one or two antiepileptic drugs in standard therapeutic doses.[25] The longest exposure to ESL as add-on therapy in epileptic patients is approximately 20 months.

In human single-dose and multiple-dose pharmacology studies up to 2400 mg in healthy subjects, ESL was generally well tolerated.[4,5,18] Adverse events were generally mild in severity. The most commonly reported adverse events were headache, somnolence, dizziness, and paresthesia circumoral, lips, or tongue. In a study in elderly *versus* young subjects, all healthy, no significant difference in tolerability was found between elderly and young.[15] No drug-related serious adverse events were reported. No abnormal trends nor abnormal vital signs were found in the safety clinical laboratory tests. There were no clinically significant electrocardiographic abnormalities, nor was there evidence of QT interval prolongation.

In a phase II study in epileptic patients (TABLE 3), the proportion of patients reporting at least one adverse event and the incidence of adverse events was not significantly different between the ESL q.d., ESL b.i.d., and placebo groups.[25] The most reported adverse events were nausea, headache, dizziness, and somnolence. Most adverse events were mild in intensity and no drug-related serious adverse events occurred. No abnormal trends in the safety clinical laboratory tests or in vital signs were found.

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