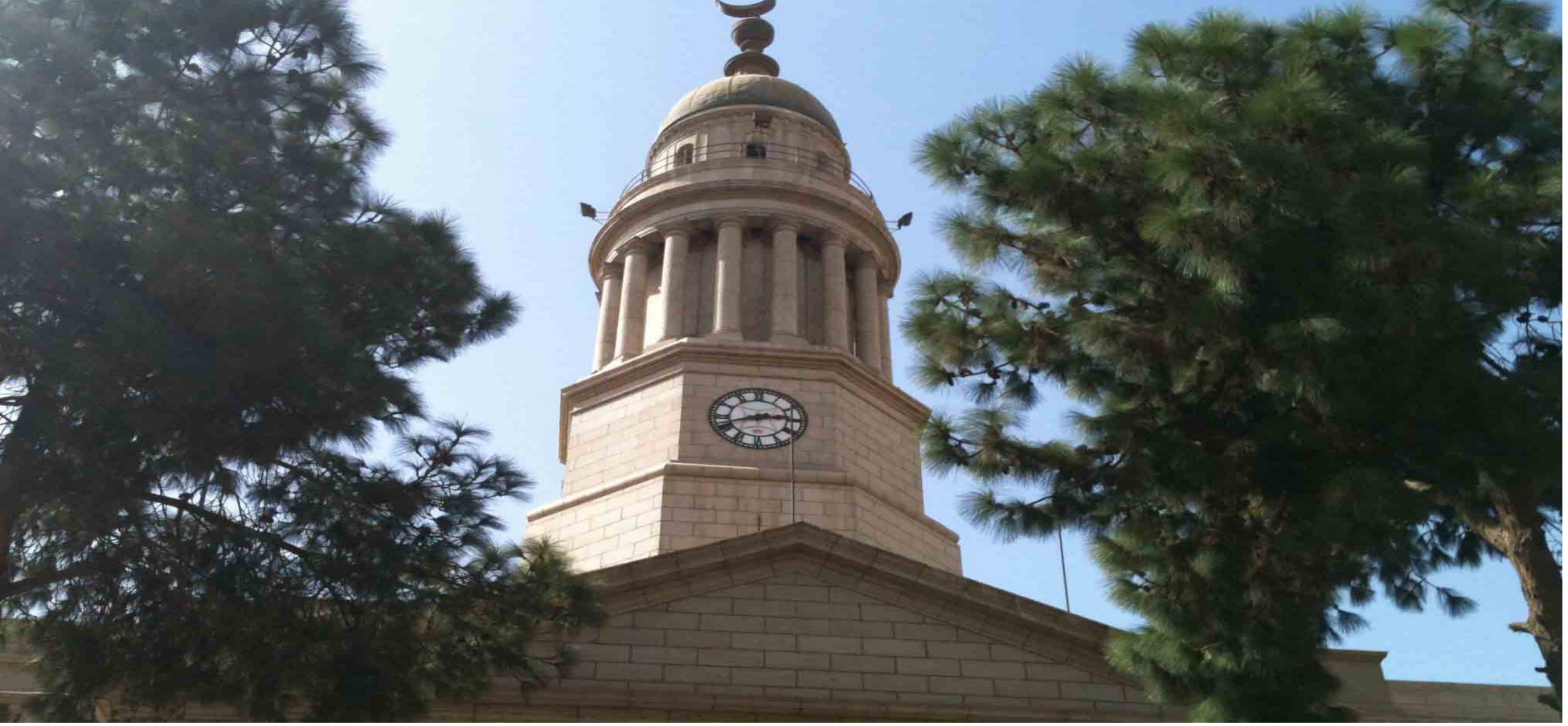
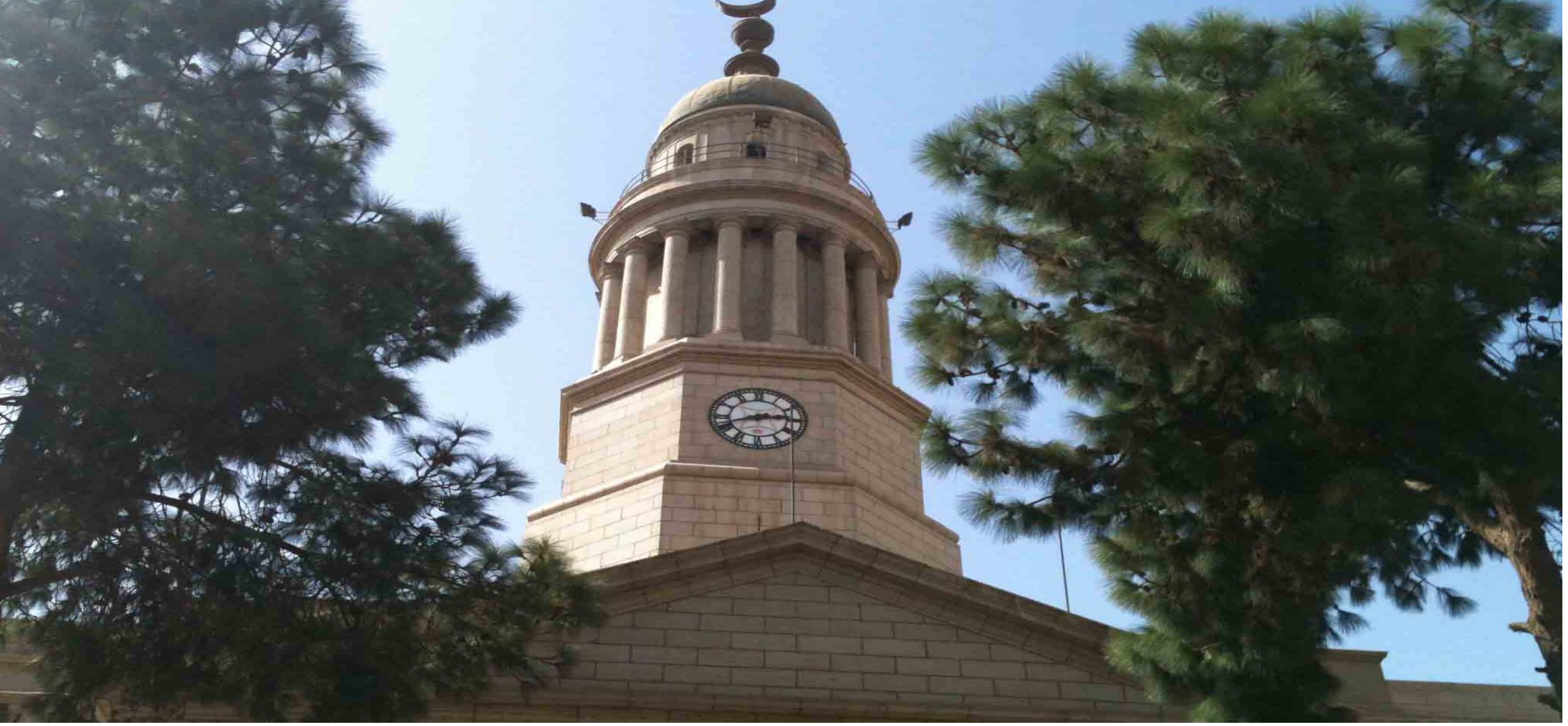


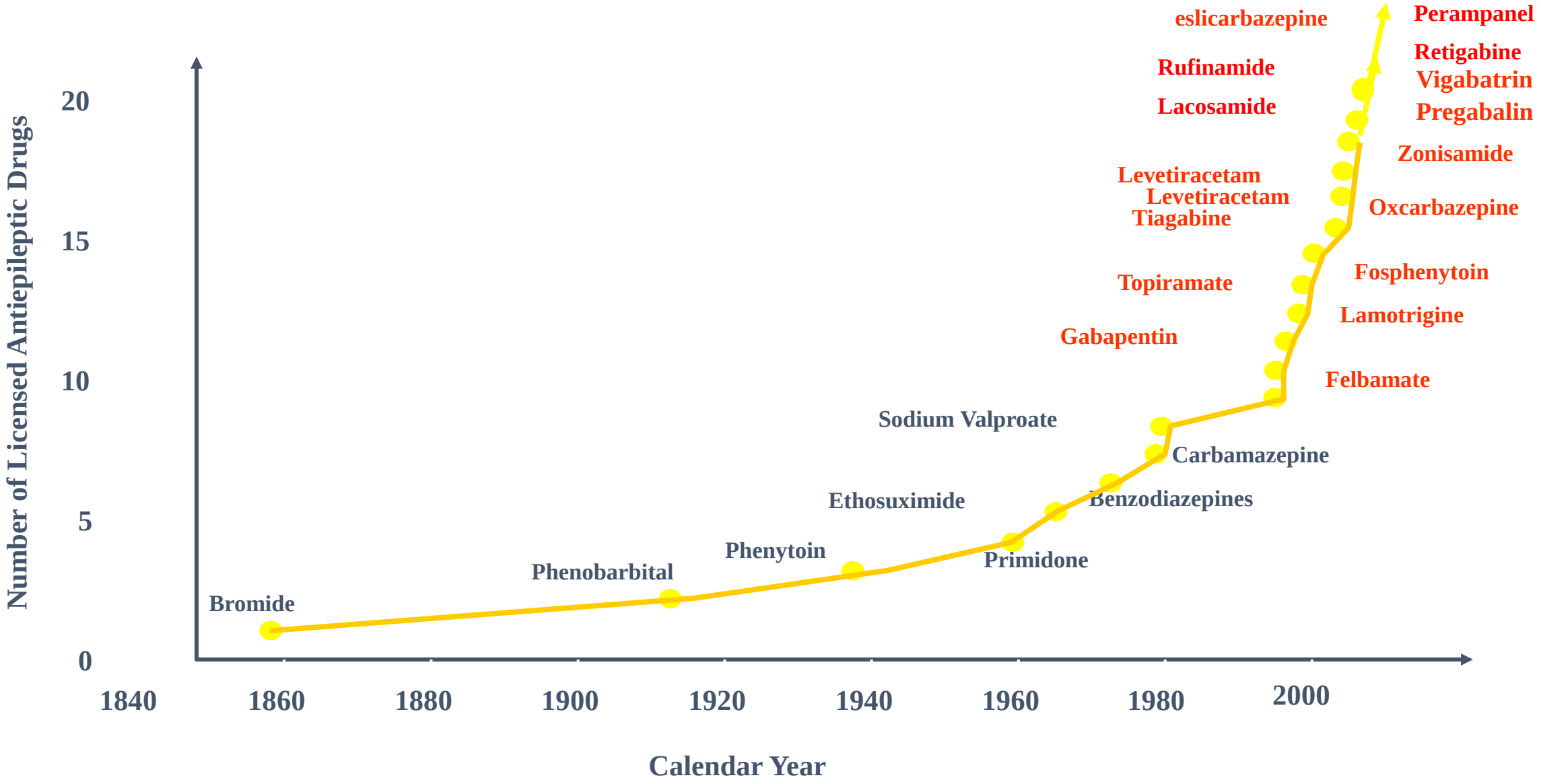
Eslicarbazepine acetate



Amr Hasan, M.D.

Associate Professor of Neurology - Cairo University

ANTIEPILEPTIC DRUG DEVELOPMENT

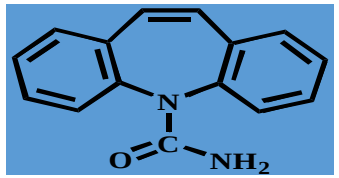


Generation of AED	AED	Year of introduction
First generation	Bromide	1857
	PB	1912
	PHT	1939
	PRM	1960
	STM†	1960
	CBZ	1965
	VPA	1970
Second generation	VGB†	1989
	OXC	1990
	LTG	1991
	GBP	1994
	FBM†	1994
	TPM	1995
	TGB†	1996
	LEV	2000
	PGB	2005
	ZNS	2007
	STP†	2007
	RUF†	2007
Third generation	ESL	2010
	LCM	2010
	RTG (ezogabine)	2011

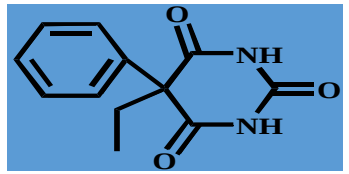
Mechanism	AED
Sodium channel (fast inactivation)	PHT, CBZ, LTG, OXC, RFN, ESL, ZNS
Sodium channel (slow inactivation)	LCM
Calcium channel blockade (high-voltage activated)	GPN, PGB
Calcium channel blockade (low-voltage activated)	ESM, VPA
$GABA_A$ receptor activation	PB, BNZ
GABA transporter blockade	TGB
GABA transaminase inhibition	VGN
SV2A modulation	LEV
Multiple targets	VPA, FBM, TPM, ZNS
Potassium channel opener	RTB
NMDA blockade	FBM
AMPA receptor blocker	PML

Compounds which are second or third generation derivatives of AEDs introduced before 1970

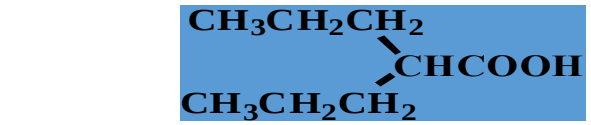
1st Generation AED



CarbamazepineeTegretol ™

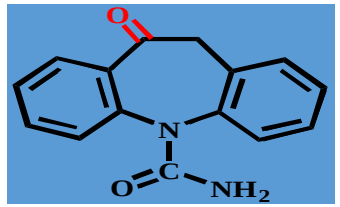


Phenobarbital

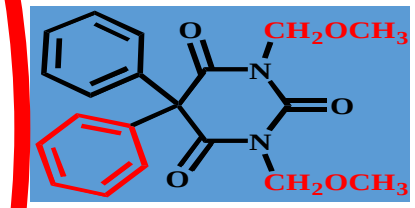


Valproic Acid Depakote ™

2nd Generation AED



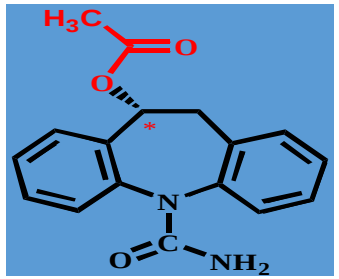
Oxcarbazepine



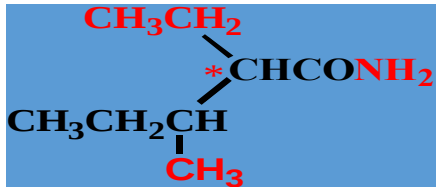
T2000

Valrocemide (SPD–493)

3rd Generation AED



Eslicarbazepine Acetate (BIA 2-093)



Valnoctamide

Perucca et al, Lancet Neurol, 2007

Eslicarbazepine acetate

- CHEMICAL STRUCTURE
- PHARMACOKINETICS
- PHARMAKODYNAMICS
- CLINICAL TRIALS
- DOSAGE AND ADMINSTRATION

Eslicarbazepine acetate
chemical structure

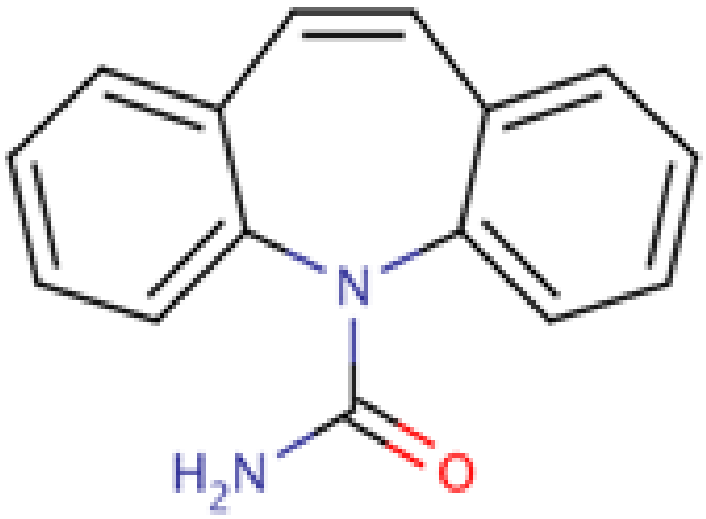
- Eslicarbazepine acetate (ESL) [(S)-()-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide].

- ESL shares with **carbamazepine** and **oxcarbazepine** the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11-position.

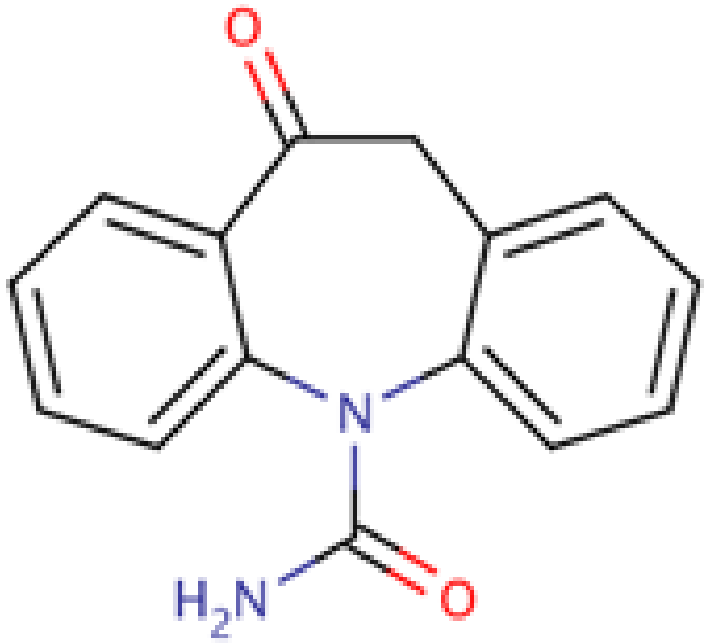
- This molecular variation results in **differences in metabolism, preventing the formation of toxic epoxide metabolites** such as carbamazepine-10,11 epoxide.

Eslicarbazepine acetate

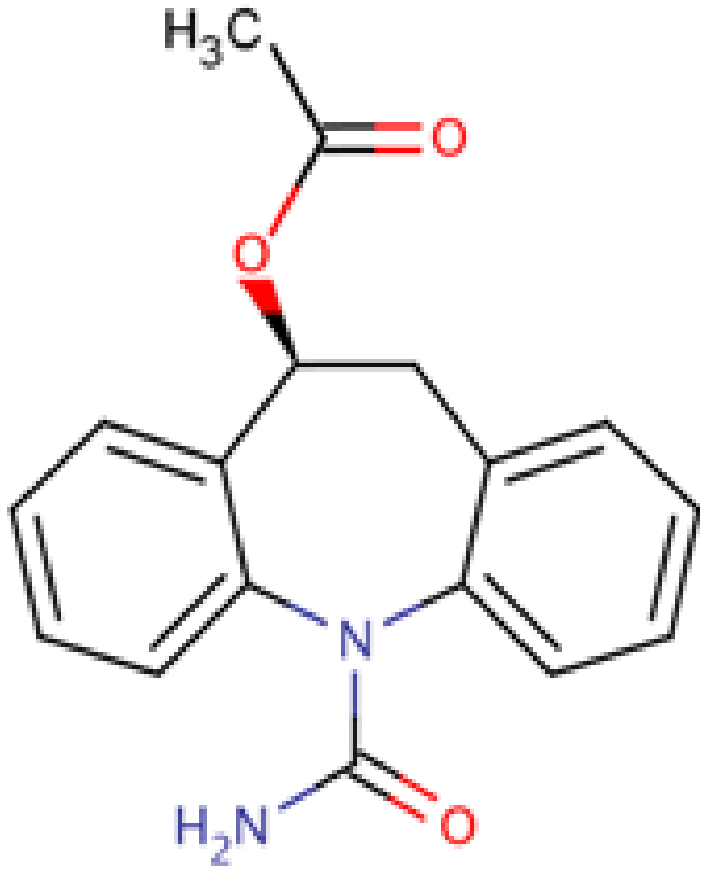
chemical structure



Carbamazepine (CBZ)

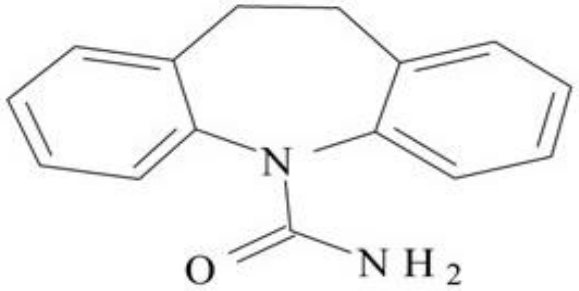


Oxcarbazepine (OXC)

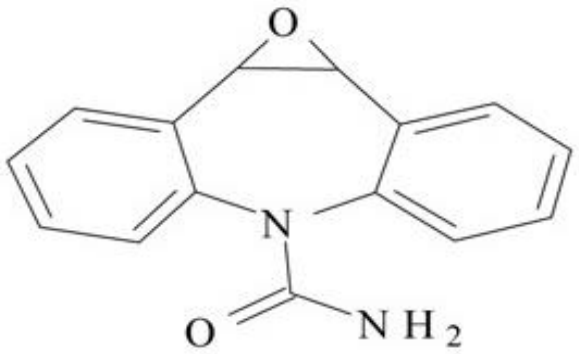


Eslicarbazepine Acetatate (ESL)

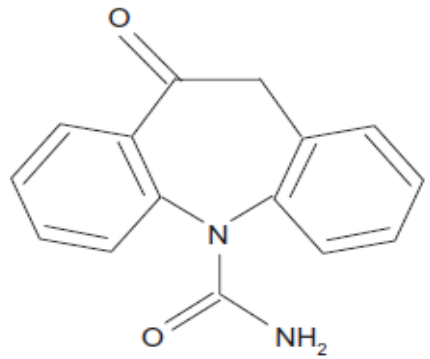
Eslicarbazepine acetate
chemical structure



Carbamazepine



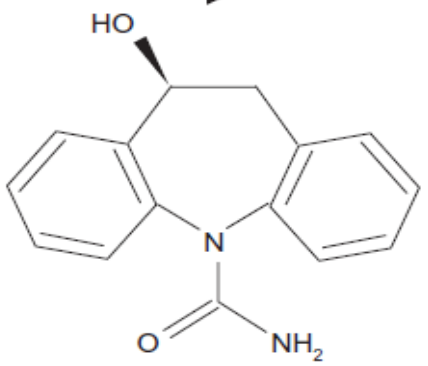
Carbamazepine -10,11-epoxide



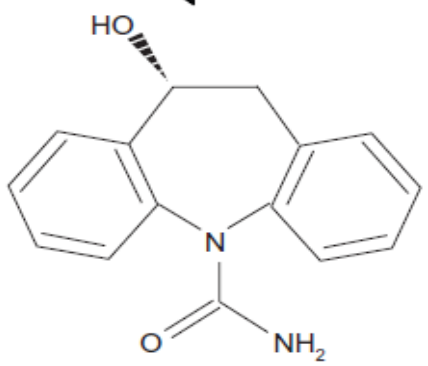
Oxcarbazepine

75%–80%

20%–25%



S(+)-Licarbazepine

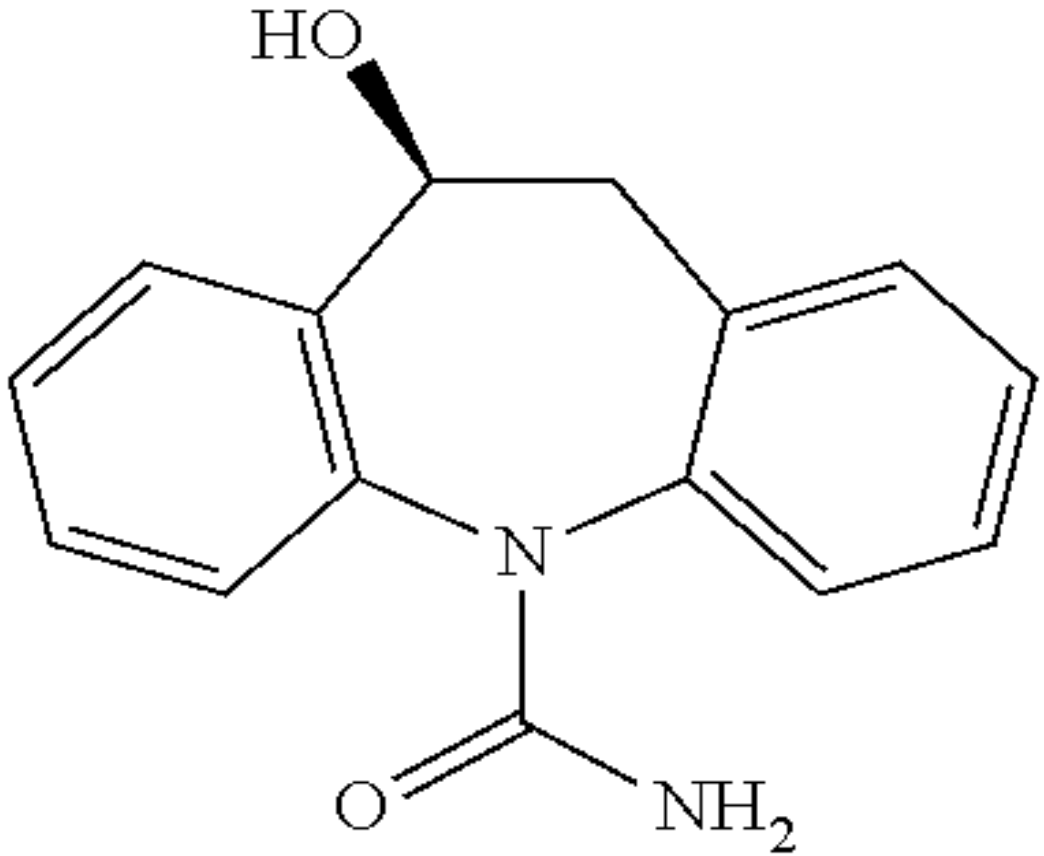


R(−)-Licarbazepine

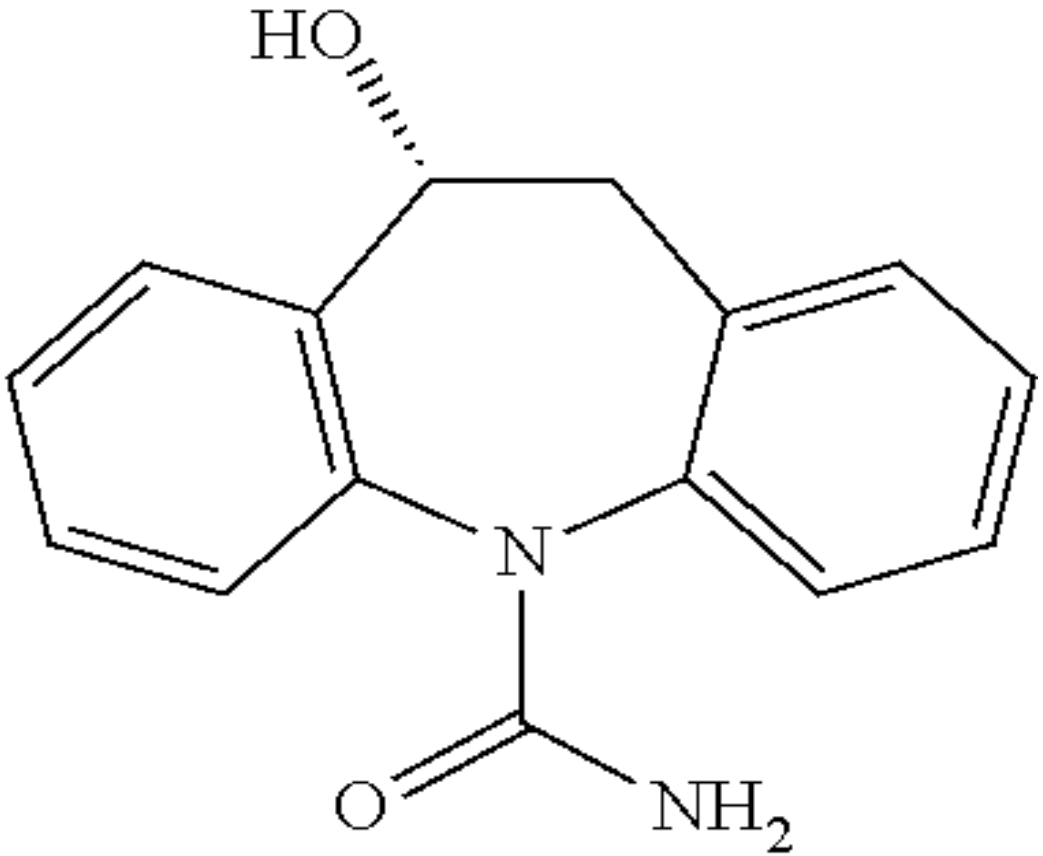
Vol. 4, 88–96, January 2007 c The American Society for Experimental NeuroTherapeutics, Inc

Eslicarbazepine acetate

chemical structure



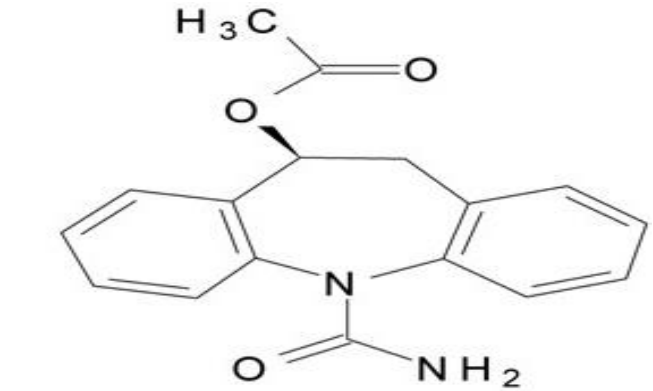
S-licarbazepine



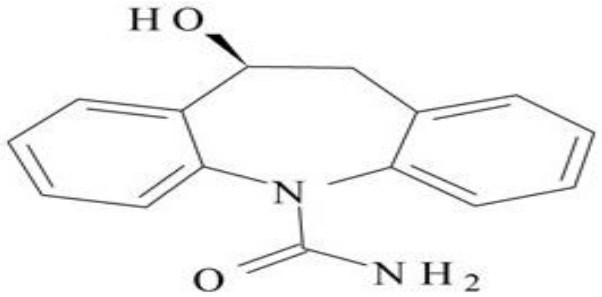
R-licarbazepine

Eslicarbazepine acetate

chemical structure



Eslicarbazepine acetate

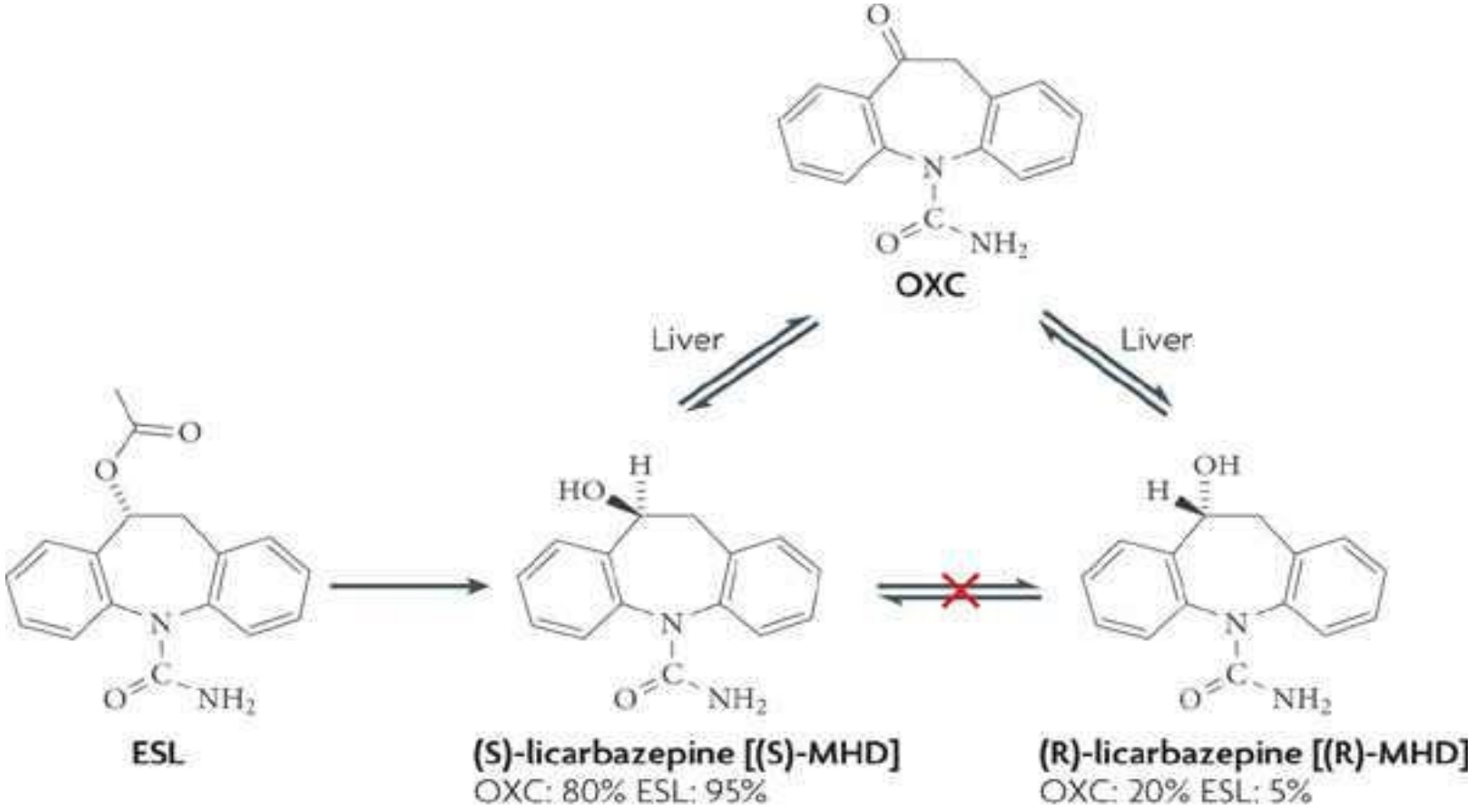


S(+)-licarbazepine

Vol. 4, 88–96, January 2007 c The American Society for Experimental NeuroTherapeutics, Inc

Eslicarbazepine acetate

chemical structure



Nature Reviews | Drug Discovery

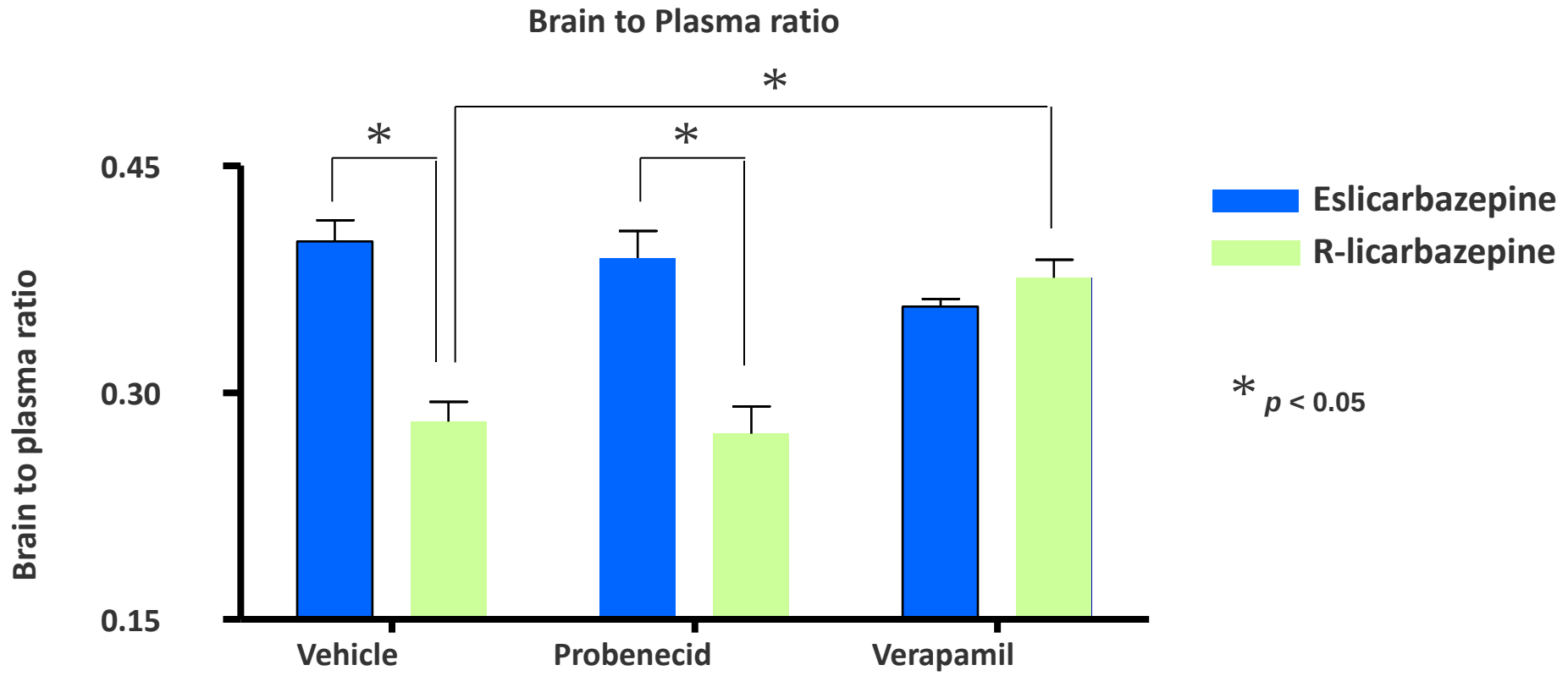
Eslicarbazepine acetate

ESL was developed with the expectation that S-licarbazepine would be

- More ***effective*** than R-licarbazepine.
- Better ***tolerated*** than R-licarbazepine.
- ***Cross*** the blood brain barrier more ***efficiently*** than R-licarbazepine.

Higher Brain/Plasma Exposure Ratio of Eslicarbazepine[1]

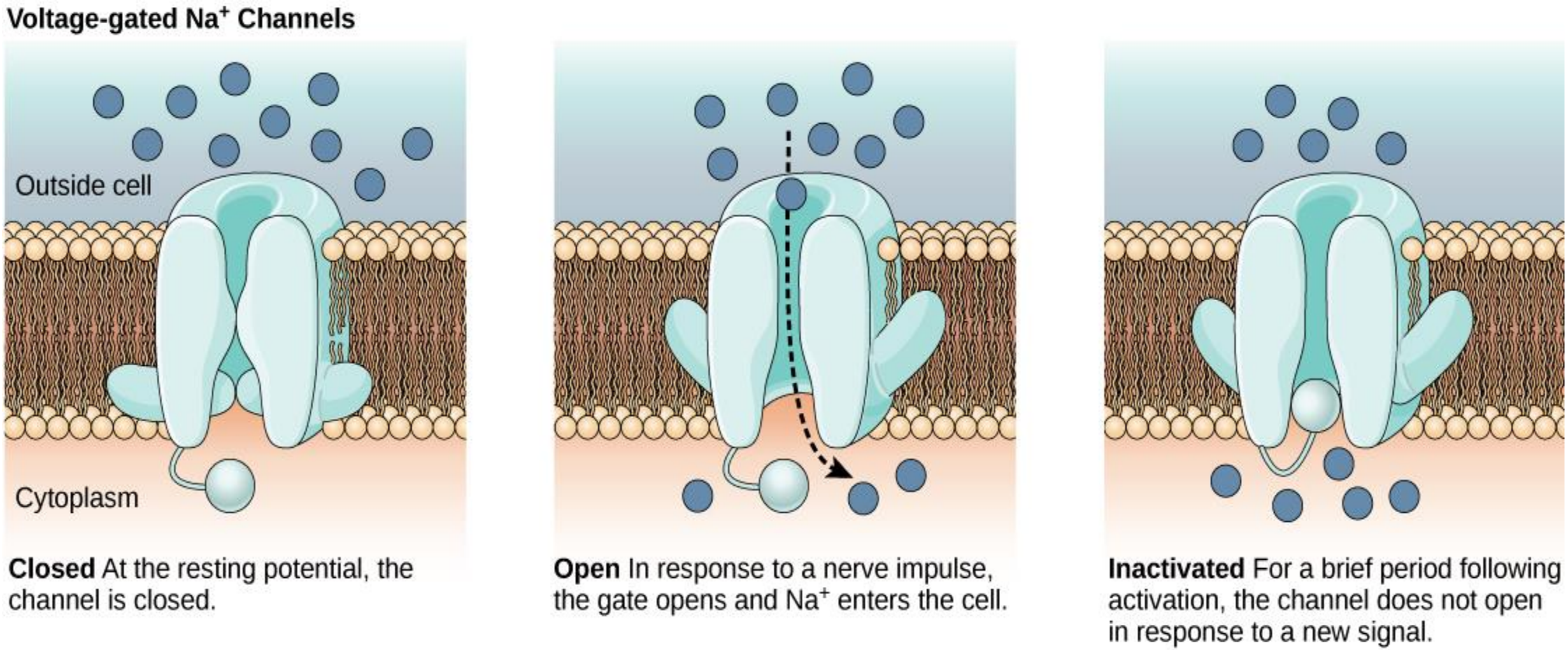
Brain exposure of Eslicarbazepine is twice that of R-licarbazepine[1]



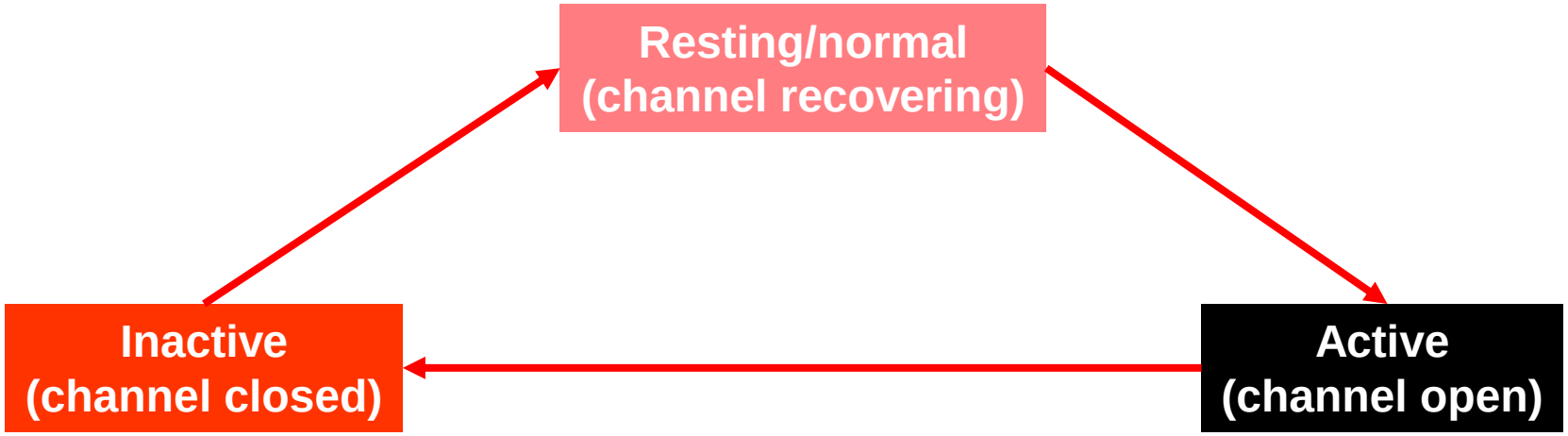
Lower brain exposure of R-licarbazepine is due to its susceptability to be back transported by P-glycoprotein (a verapamil-sensitive process)

1.Almeida L, Bialer M, Soares-da-Silva P. Eslicarbazepine Acetate pp 485 - 498
The Treatment of Epilepsy, 3rd edition, Ed. Shorvon S, Perucca E, Engel J 2009 Blackwell Publishing,

Firing Sequence of Voltage-gated Sodium Channels (VGSC)



Firing Sequence of Voltage-gated Sodium Channels (VGSC)



- ESL, CBZ and OXC competitively inhibit the VGSC by binding with the receptor in its inactive state, prolonging the period between successive firings.

1.Bonifacio MJ, *et al.* Epilepsia 2001;42(5):600-608

Eslicarbazepine acetate

Mechanism of action

ESL stabilizes the inactive form of the sodium channel, preventing its return to the active state, and sustains repetitive neuronal firing.

ESL has a much higher affinity for the inactivated state of the channel compared with the resting state.

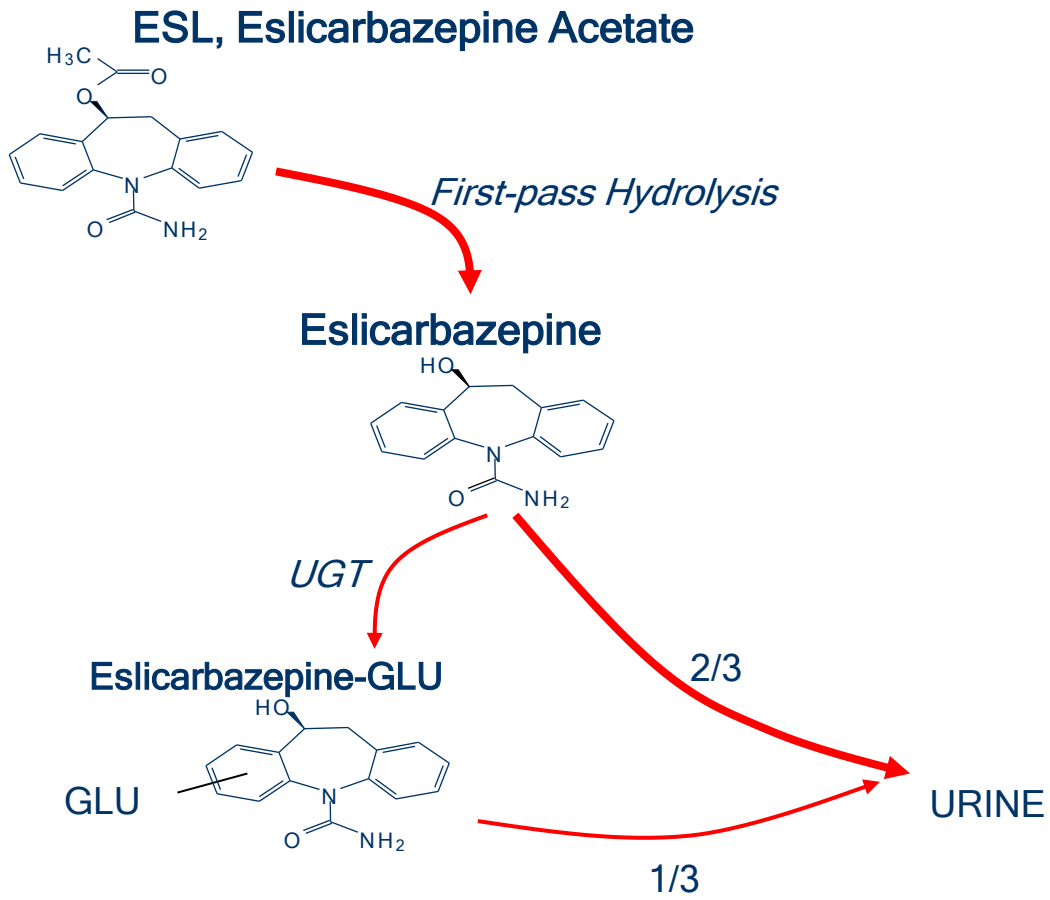
The affinity of ESL for resting channels is about threefold lower than that of CBZ.

This profile suggests that ESL has an enhanced inhibitory selectivity for rapidly firing neurons over those displaying normal activity.

Eslicarbazepine Acetate

Metabolic Profile

- Eslicarbazepine is the predominant metabolite in both plasma and urine[1]
- Glucuronidation is the main metabolic pathway[2]
- Eslicarbazepine and its glucuronide correspond to 92% of the total drug material excreted in urine[2]
- The main metabolic pathway of ESL generates no epoxide metabolites, which are associated with toxic effects[3]



1. Maia J, *et al.* Int J Clin Pharmacol Therapeut 2008 ;46(3):119-130
2. Almeida L, *et al*. Eur J Clin Pharmacol 2008;64:267-273
3. Bialer M, *et al.* Epilepsy Res 2007;73(1):1-52

Eslicarbazepine Acetate

Pharmacokinetics

Bioavailability	Complete
Peak plasma concentration	1–4 h
Plasma protein binding	<40%
Half-life	13–20 h
Serum concentrations	5–9 mcg/ml
“Therapeutic range”	Not established
Plasma clearance	20–30 ml/min
Elimination	Hydroxylation, conjugation –> renal excretion

Eslicarbazepine acetate

Drug-Drug Interaction

ESL has a favorable drug-drug interaction profile due to its low protein binding and minimal effect on the hepatic cytochrome P450 enzymatic system (CYP).

In vitro studies have shown that ESL has a moderate inhibitory effect on the CYP 2C19, and no relevant inhibitory effect on the CYP 1A2, CYP 2A6, CYP 2B6, CYP 2D6, CYP 2E1, CYP 3A4, CYP 2C9.

Eslicarbazepine acetate

Drug-Drug Interaction

Concomitant use with phenytoin resulted in a 33% decrease of the ESL exposure.

underlying mechanism is probably enzymatic induction of glucuronidation, and other inducers such as phenobarbital or CBZ have a similar effect.

Steady dosage of ESL increased the levels of phenytoin and phenobarbital, possibly due to inhibition of the CYP 2C19.

Eslicarbazepine acetate

Drug-Drug Interaction

Oral contraceptives

Patients who are taking ESL and hormonal contraceptives need to be vigilant as ESL interact with these agents.

Female patients taking ESL at a dose of 1200 mg once daily were found to have a 37% and 42% decrease in the systemic exposure to levonorgestrel and ethinyloestradiol respectively.

Studies evaluating eslicarbazepine as adjunctive treatment in adults with partial-onset epilepsy

Study	Study design	Pts, n	Mean duration of epilepsy (y)	Randomized Tx (Dose in mg/day)	Duration of Tx (weeks)	Results: reduction in seizure frequency	Results: response rate
Dose response study	R, DB, PC, MC	143	18.7	Placebo ESL once daily ESL twice daily (dose titrated from 400 mg to 800 mg to 1,200 mg)	12	N/A	28% 54% (*P*=0.008) 41% (*P*=0.12)
BIA-2093-301	R, DB, PC, MC	402	21.0	Placebo ESL 400 mg ESL 800 mg ESL 1,200 mg	12	16% 26% (*P*>0.05) 36% (*P*=0.0028) 45% (*P*=0.0003)	20% 23% 34% 43%
BIA-2093-302	R, DB, PC, MC	393	23.9	Placebo ESL 400 mg ESL 800 mg ESL 1,200 mg	12	5% 21% (*P*>0.05) 33% (*P*<0.01) 33% (*P*<0.0003)	18% 20% 32% 35%
BIA-2093-303	R, DB, PC, MC	252	23.0	Placebo ESL 800 mg ESL 1,200 mg	12	17% 38% (*P*<0.05) 42% (*P*<0.05)	23% 35% 38%
Extension of BIA-2093-302	R, OL, MC	325	24.1	ESL 800 mg	52	41% from baseline	53%

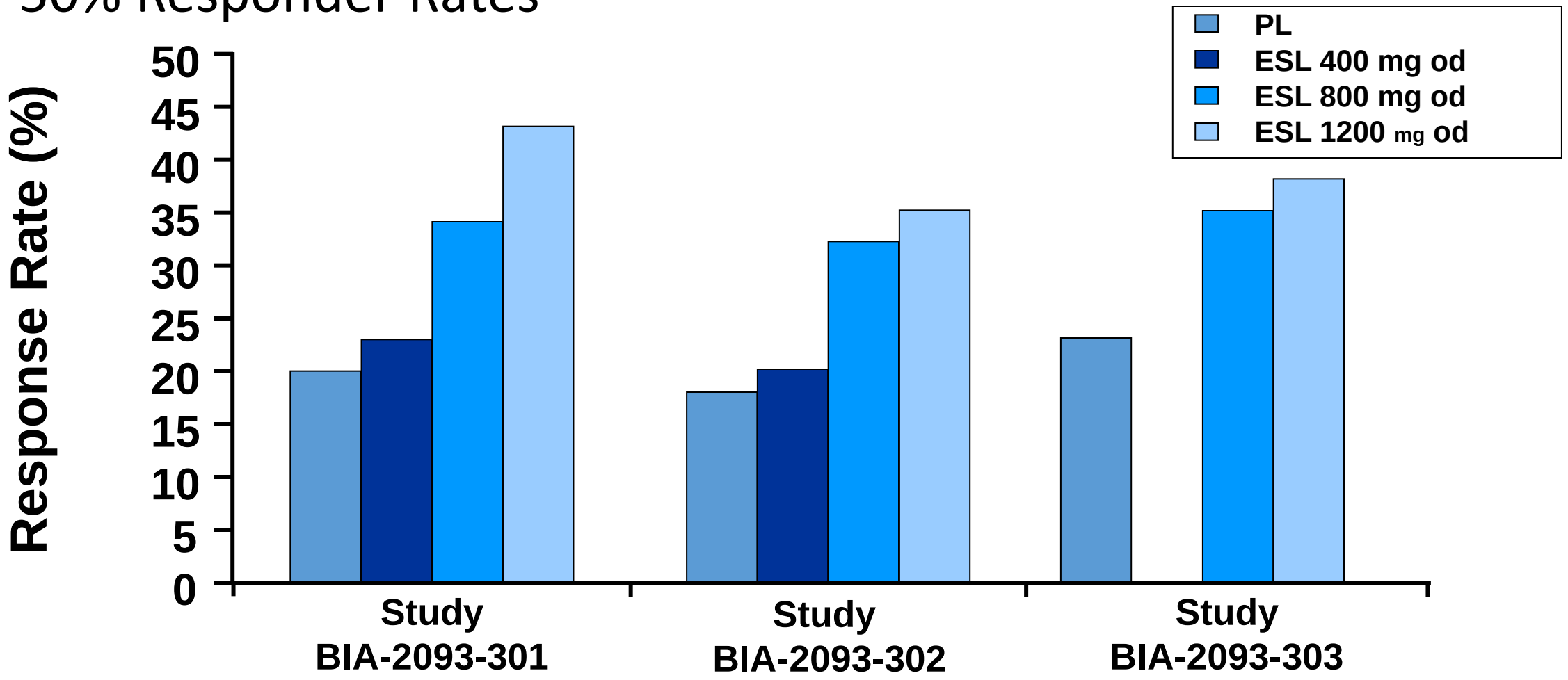
Abbreviations: DB=double-blind, ESL=eslicarbazepine acetate, MC=multi-center, N/A=not available, OL=open-label, PC=placebo-controlled, R=randomized, Tx-treatment

High Completion Rates for Phase III 1-Year Open-Label Extension [1-3]

1-year Open-Label Extension	BIA-2093-301[1]	BIA-2093-302[2]	BIA-2093-303[3]
Number of patients enrolled (Total 833)	314	325	194
Patients who completed 1 year (Total 612)	239	223	150
Completion rate (73.5%)	76.1%	68.6%	78.5%
Median dose of ESL	800 mg	800 mg	800 mg

1. Halász P, *et al.* Epilepsia. 2008;49(suppl.7):435-436
2. Gabbai AA ,*et al.* Epilepsia. 2008;49(suppl.7):432-433
3. Lopes-Lima J, *et al.* Epilepsia. 2008;49(suppl.7):441-442

Results from 3 Eslicarbazepine Pivotal Trials: 50% Responder Rates



800 mg and 1200 mg doses were statistically significant; 400 mg was not.

Verrotti et al, Epilepsy Research 2014: 108: 1-10

Incidence rate of CNS-related TEAEs affecting >2% of patients in any group[1,2]

Treatment-emergent adverse events (%)	Placebo (N=289)	400 mg (N=196)	800 mg (N=284)	1200 mg (N=280)
Dizziness	7.3	13.3	21.1	28.9
Somnolence	9.3	10.7	13.0	15.0
Headache	8.7	8.7	10.2	13.6
Diplopia	1.7	5.1	8.1	8.6
Abnormal coordination	2.1	3.1	5.3	6.1
Blurred vision	1.0	4.1	3.9	3.9
Vertigo	0.3	2.0	1.8	3.9
Depression	0.3	3.1	0.7	1.8
Convulsion	2.1	1.5	1.1	0.7

1.Elger C, *et al.* Epilepsia. 2008;49(suppl.7):428-429
2.Data on file. BIAL-ESL Phase III - Integrated Clinical Report

Side effects

- **Most common Side effects: dizziness, sleepiness, headache, nausea, vomiting, double vision, abnormal coordination**
- **Low incidence of low blood sodium(0.6-1.3%)**
- **Not associated with changes in total cholesterol, low density lipoprotein (LDL) levels, and glucose**
- **No effect on body weight**
- **Rash in 3%**

Verrotti et al, Epilepsy Research 2014: 108: 1-10

Epilepsia, 51(10):1963–1969, 2010
doi: 10.1111/j.1528-1167.2010.02660.x

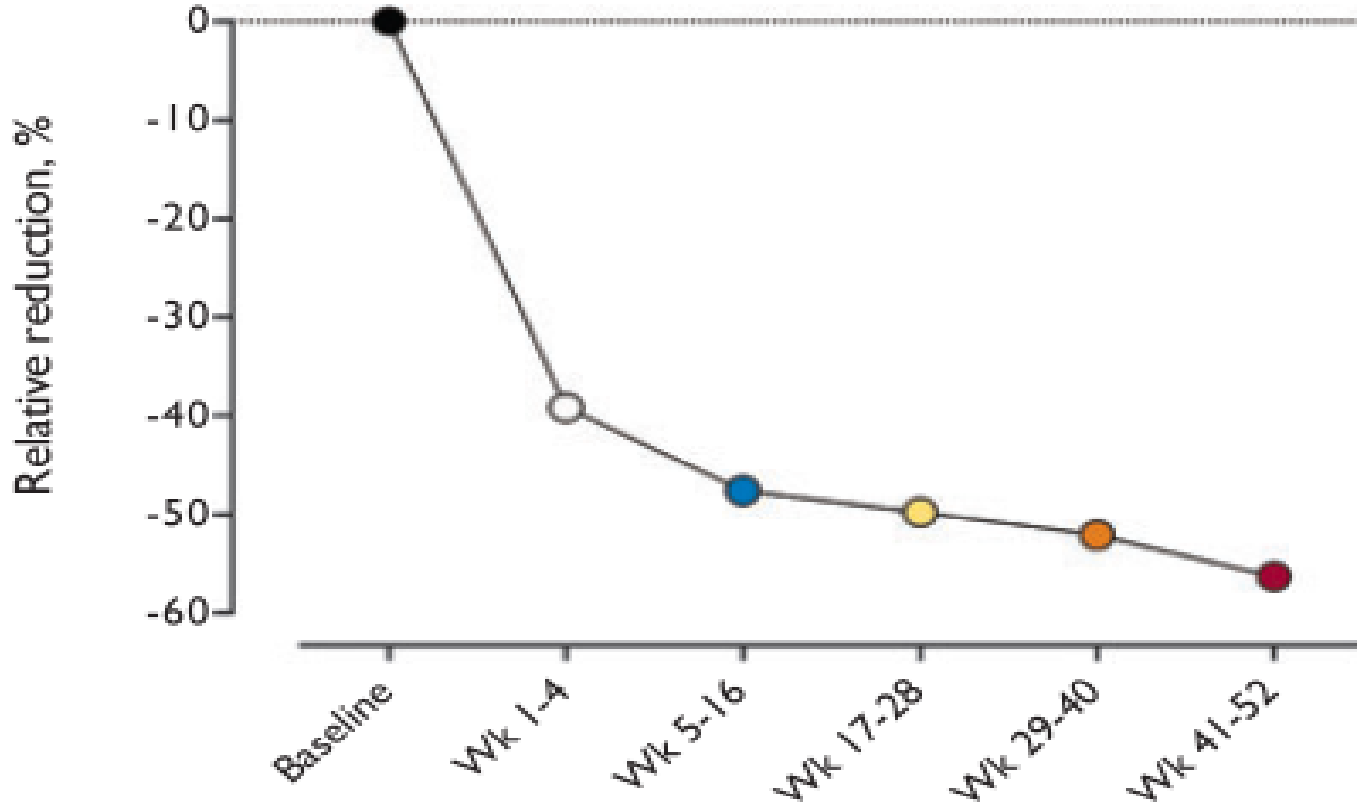
FULL-LENGTH ORIGINAL RESEARCH

Long-term efficacy and safety of eslicarbazepine acetate: Results of a 1-year open-label extension study in partial-onset seizures in adults with epilepsy

*Peter Halász, †Joyce A. Cramer, ‡Danilo Hodoba, §Anna Członkowska, ¶Alla Guekht, #Joana Maia, **Christian Elger, ††Luis Almeida, and #‡‡Patricio Soares-da-Silva, on behalf of the BIA-2093-301 Study Group

*National Institute of Psychiatry and Neurology, Budapest, Hungary; †Yale University School of Medicine, New Haven, Connecticut, U.S.A.; ‡Clinical Psychiatric Hospital Vrapce, Zagreb, Croatia; §Institute of Psychiatry and Neurology, Warsaw, Poland; ¶Russian State Medical University, Moscow, Russia; #BIAL – Portela & Co, SA, S Mamede do Coronado, Portugal; **University of Bonn, Bonn, Germany; ††University of Aveiro, Aveiro, Portugal; and ‡‡University of Porto, Porto, Portugal

Median relative seizure frequency reduction by period (ITT population).
Wk, week of treatment.



Epilepsia, 51(10):1963–1969, 2010 doi: 10.1111/j.1528-1167.2010.02660.x

Epilepsy Research (2010) 89, 278—285

journal homepage: www.elsevier.com/locate/epilepsyres

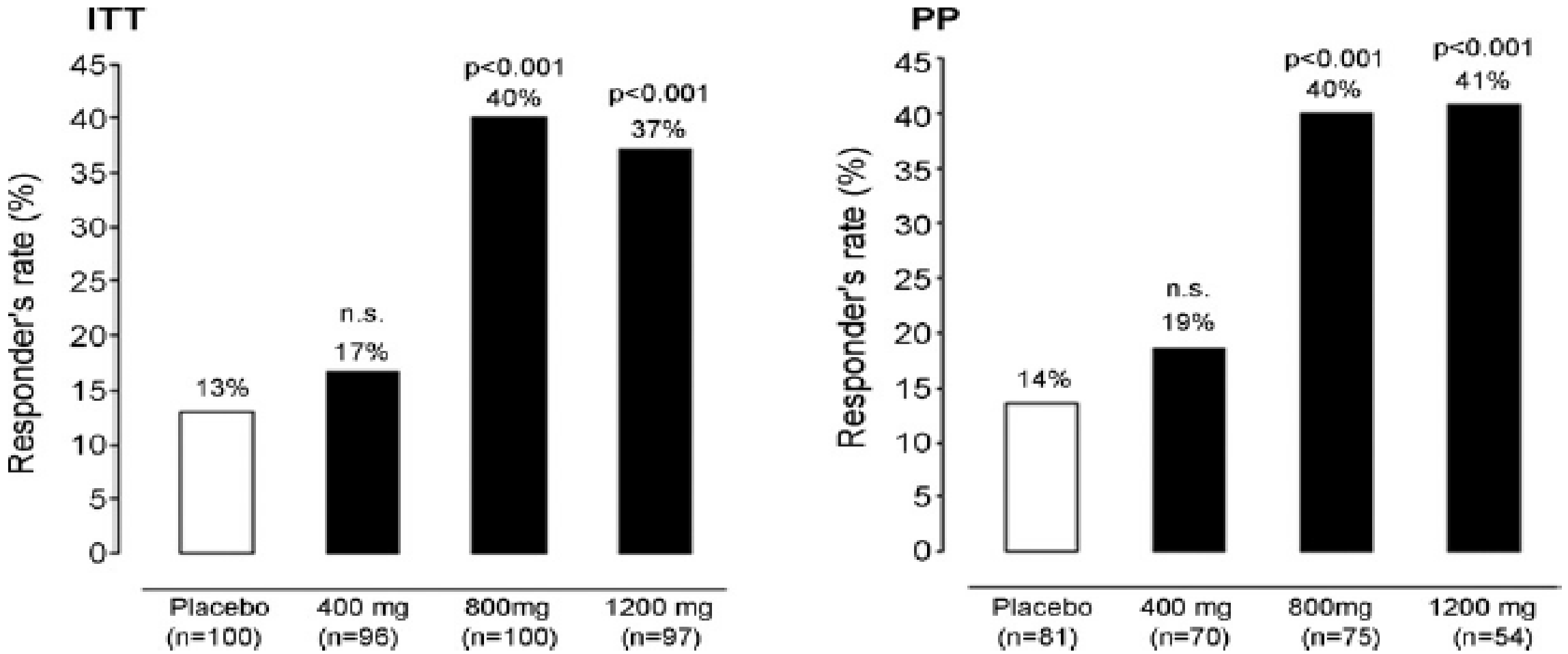
Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy☆

E. Ben-Menachem[a,1], A.A. Gabbai[b,1], A. Hufnagel[c,1], J. Maia[d,1], L. Almeida[e,1], P. Soares-da-Silva[d,f,*,1]

[a] *Department of Clinical Neuroscience and Physiology, Sahlgren Academy, Sahlgren University Hospital, Göteborg, Sweden*
[b] *Centro de Estudos em Neurologia da Escola Paulista de Medicina, Federal University of S. Paulo, S. Paulo, Brazil*
[c] *Department of Neurology, University of Essen, Essen, Germany*
[d] *Department of Research and Development, BIAL — Portela & Co, SA, S Mamede do Coronado, Portugal*
[e] *Health Sciences Section, University of Aveiro, Portugal*
[f] *Institute of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Portugal*

Received 11 December 2009; received in revised form 17 January 2010; accepted 18 January 2010
Available online 17 March 2010

EFFICACY



Epilepsy Research (2010) **89**, 278—285

Safety

Overall, an analysis of TEAEs of special interest revealed no specific concerns with respect to the safety of ESL.

In particular, ESL was associated with very few psychiatric events and revealed no relevant differences in the incidence of AEs among the 4 treatment groups. Incidence of rash was low (1%).

There were no changes in laboratory parameters that indicated a safety concern regarding risk of hyponatraemia or lipid profile abnormalities, nor were there any clinically relevant differences in vital signs, body weight, or ECGs during the study.

Epilepsy Research (2010) **89**, 278—285

Acta Neurol Scand 2009: 120: 281–287 DOI: 10.1111/j.1600-0404.2009.01218.x

ACTA NEUROLOGICA
SCANDINAVICA

Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures

Gil-Nagel A, Lopes-Lima J, Almeida L, Maia J, Soares-da-Silva P, on behalf of the BIA-2093-303 Investigators Study Group. Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures.
Acta Neurol Scand 2009: 120: 281–287.

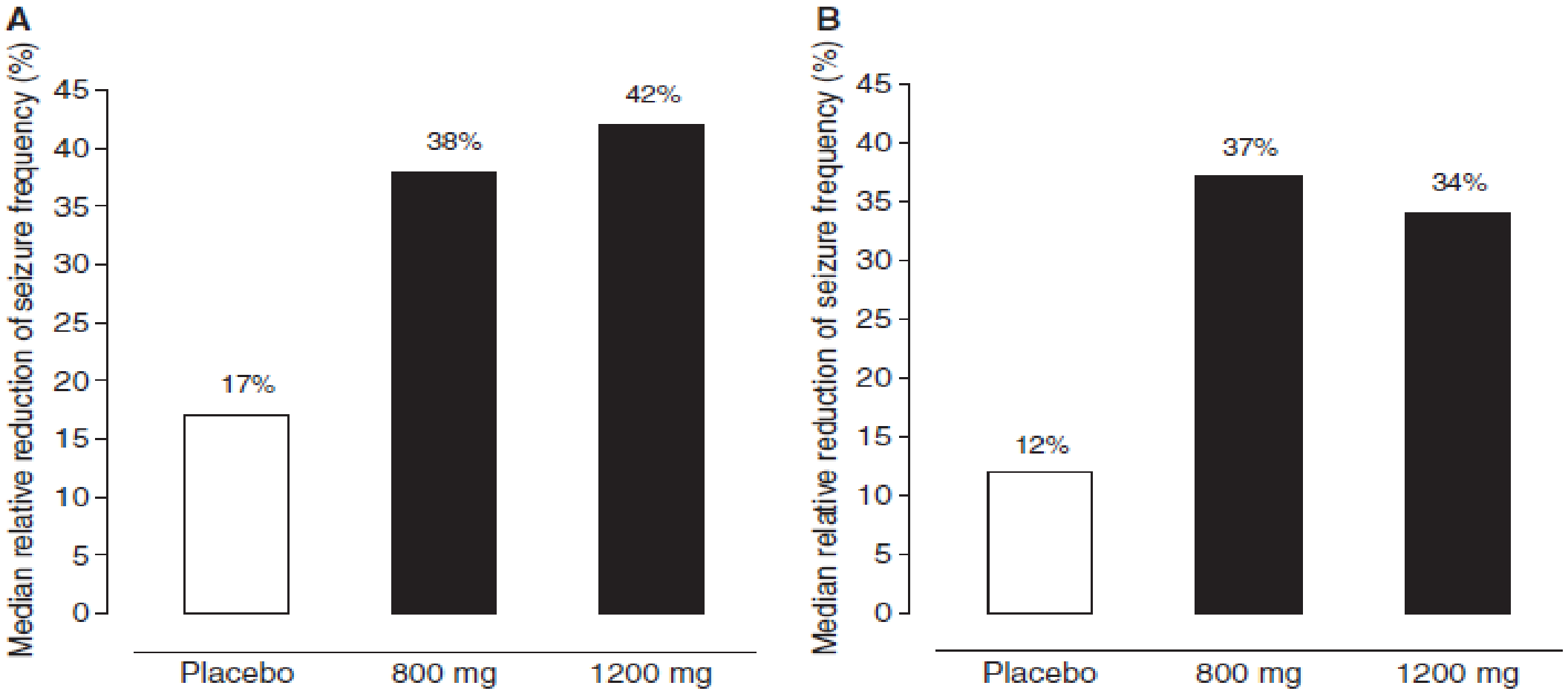
Study Population and Methods

- Gil-Nagel et al[3] evaluated the effects of adjunctive eslicarbazepine acetate therapy on seizure frequency and treatment-emergent adverse events (TEAEs) in patients inadequately controlled with other AEDs, including carbamazepine.
- Patients were pooled from two phase III multicenter studies.
- Must have had four or more documented partial-onset seizures over 4 weeks while using 1–3 AEDs
- Randomized to 400, 800, or 1,200 mg/d of the drug or placebo and followed for a 12-week maintenance period and a 4-week tapering period

Results

- Compared with placebo, 800 and 1,200 mg/d of eslicarbazepine acetate led to a significant reduction in seizure frequency in patients, including those taking carbamazepine.
- The frequency of TEAEs and TEAEs leading to drug discontinuation increased with the dose of eslicarbazepine acetate administered, especially among patients taking > 800 mg/d of carbamazepine concomitantly.
- Most frequent TEAEs observed with eslicarbazepine acetate: dizziness, diplopia, headache, somnolence, and nausea

Efficacy



Median relative reduction in seizure frequency for the maintenance period (A) and for the titration plus maintenance
periods (B) (ITT population).

Conclusions

Once-daily treatment with ESL 800 and 1200 mg was effective and generally well tolerated. Therefore, a once-daily dose of 800 mg ESL appears to offer the optimal initial treatment regimen, with the option of titrating to 1200 mg (based on individual response and tolerability), if increased efficacy is necessary.

Eslicarbazepine Acetate in Partial-Onset Epilepsy – Summary of Results[1]

- **Long apparent half life of 13-20h**
- **Studied as adjunctive therapy in a population of 1,049 refractory partial-onset epilepsy patients**
  - Enrolled by 125 sites distributed by 23 countries
- **800 mg and 1200 mg once-daily reduced partial-onset seizures**
  - Maintained reduction in seizure frequency during a 1-year open-label treatment period
  - Consistent results between different studies, subpopulations
- **Tolerability and safety profile**
  - Few discontinuations due to adverse events
  - Low incidence of serious dermatologic reactions and hyponatremia
  - Changes in serum lipids, ECG parameters, body weight similar to placebo

Jacobson et al. BMC Neurology (2015) 15:46
DOI 10.1186/s12883-015-0305-5

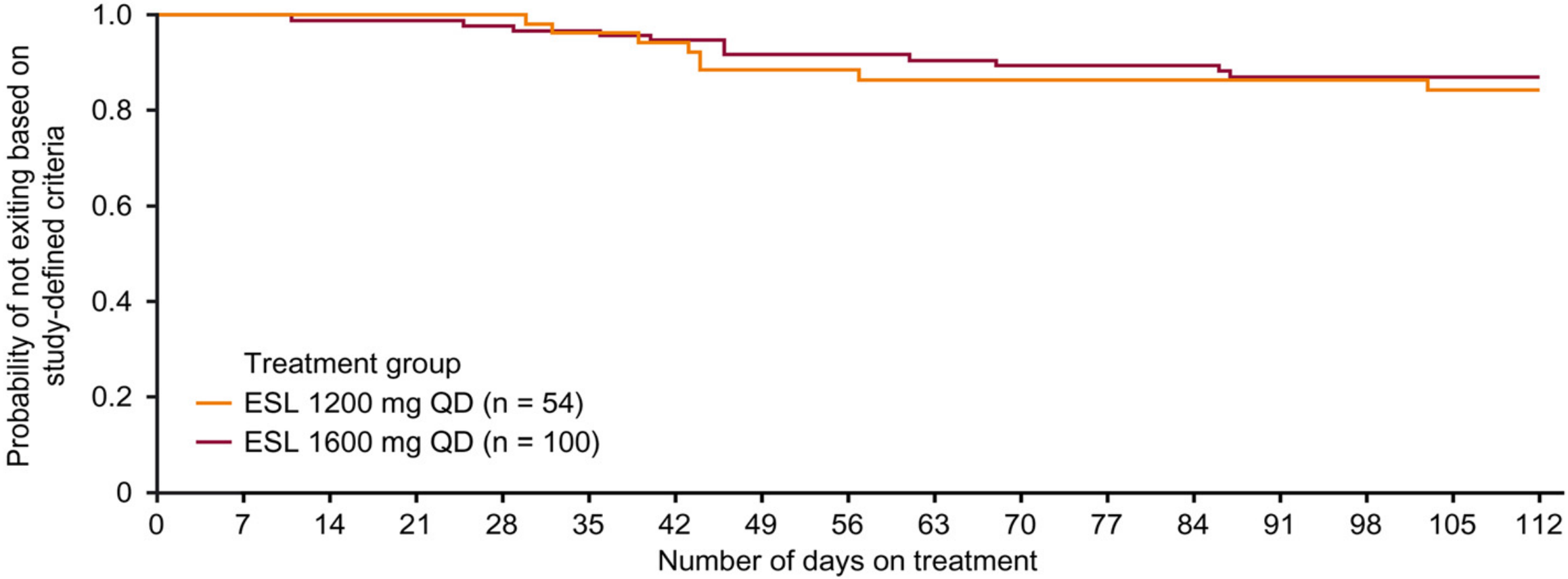
BMC Neurology

RESEARCH ARTICLE Open Access

Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a historical-control phase III study

Mercedes P Jacobson[1*], Ladislav Pazdera[2], Perminder Bhatia[3], Todd Grinnell[4], Hailong Cheng[4], and David Blum[4] on behalf of the study 046 team

The efficacy of ESL monotherapy for seizure control



Kaplan–Meier plot of time to exit (EFF population). EFF = efficacy; ESL = eslicarbazepine acetate; QD = once-daily.

Jacobson et al. BMC Neurology (2015) 15:46 DOI 10.1186/s12883-015-0305-5

Conclusions

BMC Neurology

The results of this phase III study demonstrate that ESL monotherapy, following conversion from other adjunctive AEDs, was effective based on comparison with a historical control.

Additionally, during ESL monotherapy a substantial fraction of patients experienced a reduction in seizure frequency compared with baseline.

The relatively high completion rate and the side effect profile of ESL at doses of 1200 and 1600 mg QD indicate that ESL was efficacious and well tolerated when used as monotherapy.

These findings indicate that ESL monotherapy was efficacious and well tolerated in this study.

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Sunovion Announces FDA Approval of a New Indication for Aptiom® (eslicarbazepine acetate) as Monotherapy for Partial-Onset Seizures

Published: Aug 28, 2015 11:16 a.m. ET

Only exclusively once-daily, non-extended release antiepileptic drug (AED) now FDA-approved as both monotherapy and adjunctive therapy for partial-onset seizures

DOSING& ADMINISTRATION

- **The recommended starting dose is 400 mg PO once daily.**
- **After one week, increase the dose to the recommended maintenance dose of 800 mg PO once daily.**
- **Treatment may be initiated at 800 mg PO once daily if the need for additional seizure reduction outweighs an increased risk of adverse effects during initiation.**
- **The maximum recommended dosage of 1200 mg PO daily may be beneficial for some patients; however this dosage is associated with an increase in adverse events.**
- **A dosage of 1200 mg/day should only be initiated after a patient has tolerated 800 mg/day for at least one week.**

Is it better than CBZ and OXC?

- Once daily administration
- Unlike CBZ, ESL is not metabolized into the CBZ 10,11-epoxide, an active and potentially toxic compound.
- As a result, ESL has very low enzyme-inducing activity of the cytochrome P450 enzymatic system and does not induce its own metabolism.
- Favorable drug-drug interaction profile
- Less effect on blood chemistry (sodium)
- Smoother release may reduce side effects related to fluctuation of drug levels in bloodstream

THANK YOU