Advances in Epilepsy Treatment
New and Emerging AEDs

July 5, 2011

Raman Sankar, MD, PhD

David Geffen School of Medicine at UCLA

Los Angeles, California

Recent & Anticipated Approvals

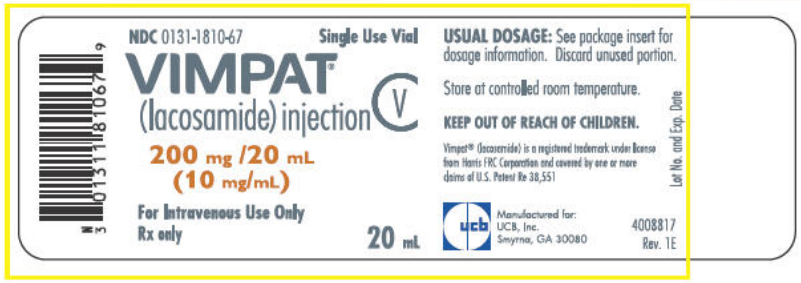
- **Lacosamide (Vimpat – UCB)**
- **Rufinamide (Banzel – Eisai)**
- **Ezogabine (Potiga – Valeant + GSK)**
- **Eslicarbazepine (Stedesa – Sunovion)**
- **Perampanel (Eisai)**
- **Brivaracetam (Rikelta – UCB)**

Lacosamide

VIMPAT® tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years

VIMPAT® injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years when oral administration is temporarily not feasible

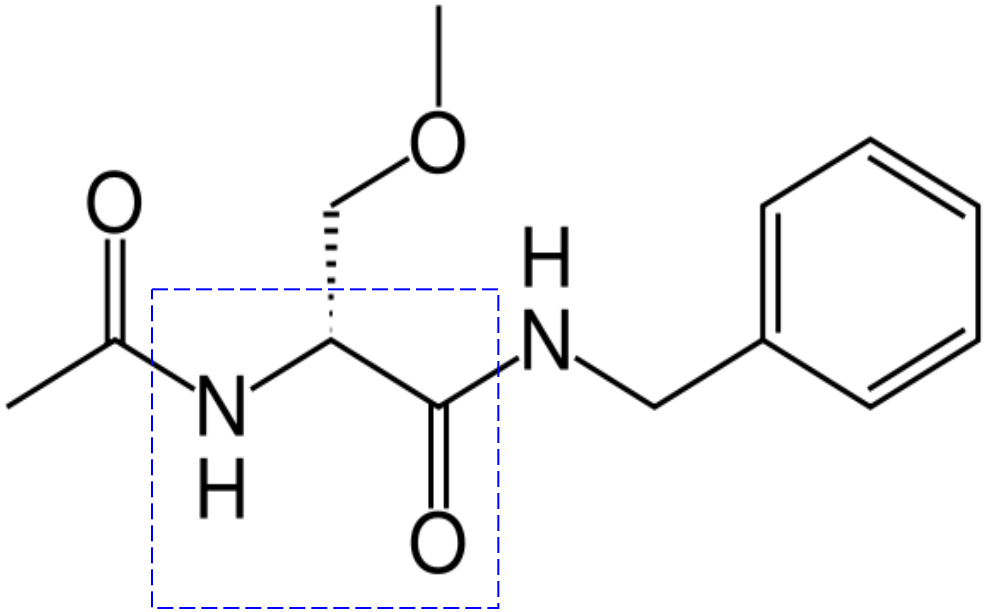

VIMPAT
(lacosamide) tablets
2 Week
Starter Kit
NDC 0131-2470-99
Rx only
Professional Sample
Not for Sale
2 Week
Starter Kit
VIMPAT
(lacosamide) tablets
NDC 0131-5410-70
VIMPAT
(lacosamide) oral solution
10 mg / mL
Rx only
ATTENTION PHARMACIST:
Each patient is required to receive the accompanying Medication Guide.
Manufactured for:
UCB, Inc
Smyrna, GA 30080
465 mL
VIMPAT
(lacosamide) injection
200 mg /20 mL
(10 mg/mL)
Intravenous Use Only
10 vials
VIMPAT
(lacosamide) injection
200 mg /20 mL
(10 mg/mL)
VIMPAT
(lacosamide) tablets
NDC 0131-2477-99
Rx Only
50 mg
5 sample cartons (14 tablets each)
VIMPAT
(lacosamide) tablets
50 mg
100 mg
150 mg
200mg
Rx only


NDC 0131-1810-67
Single Use Vial
VIMPAT
(lacosamide) injection
200 mg /20 mL
(10 mg/mL)
For Intravenous Use Only
Rx only
20 mL
USUAL DOSAGE: See package insert for dosage information. Discard unused portion.
Store at controlled room temperature.
KEEP OUT OF REACH OF CHILDREN.
Vimpat® (lacosamide) is a registered trademark under license from Harris FRC Corporation and covered by one or more claims of U.S. Patent Re 38,551
Manufactured for:
UCB, Inc.
Smyrna, GA 30080
4008817
Rev. 1E
Lot No. and Exp. Date


50
100
150
200

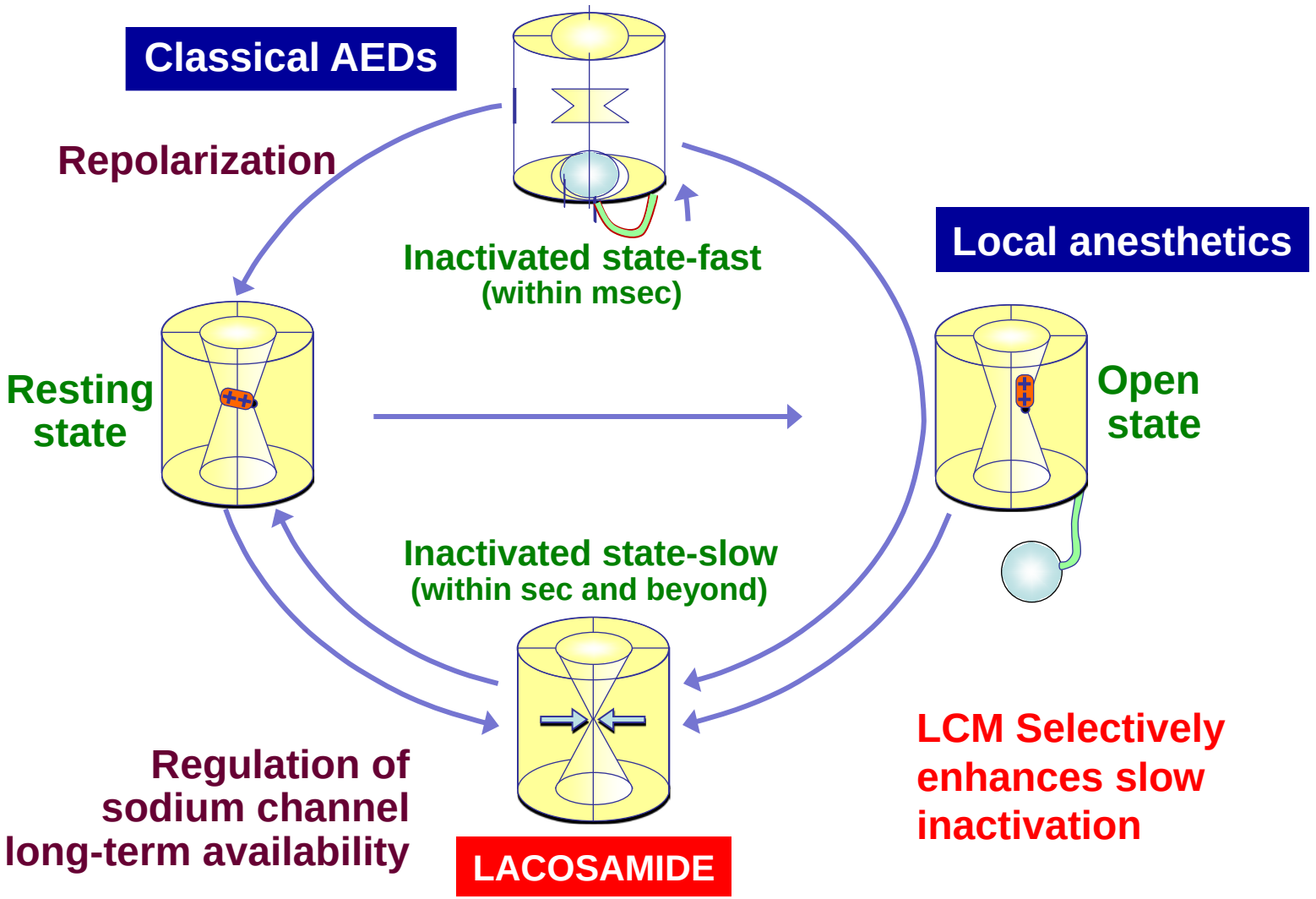
Lacosamide: The Molecule

- **Functionalized amino acid (Glycine derivative)**
- **R(+) configuration is active**
- **Molecular weight: 250.3 g/mol**
- **Aqueous solubility: ~25**



Beyreuther BK, et al. *CNS Drug Rev*. 2007;13(1):21–42.

Physiology of Voltage-Gated Sodium Channels



Adapted from Beyreuther et al.
CNS Drug Rev 2007;13(1):21–42.

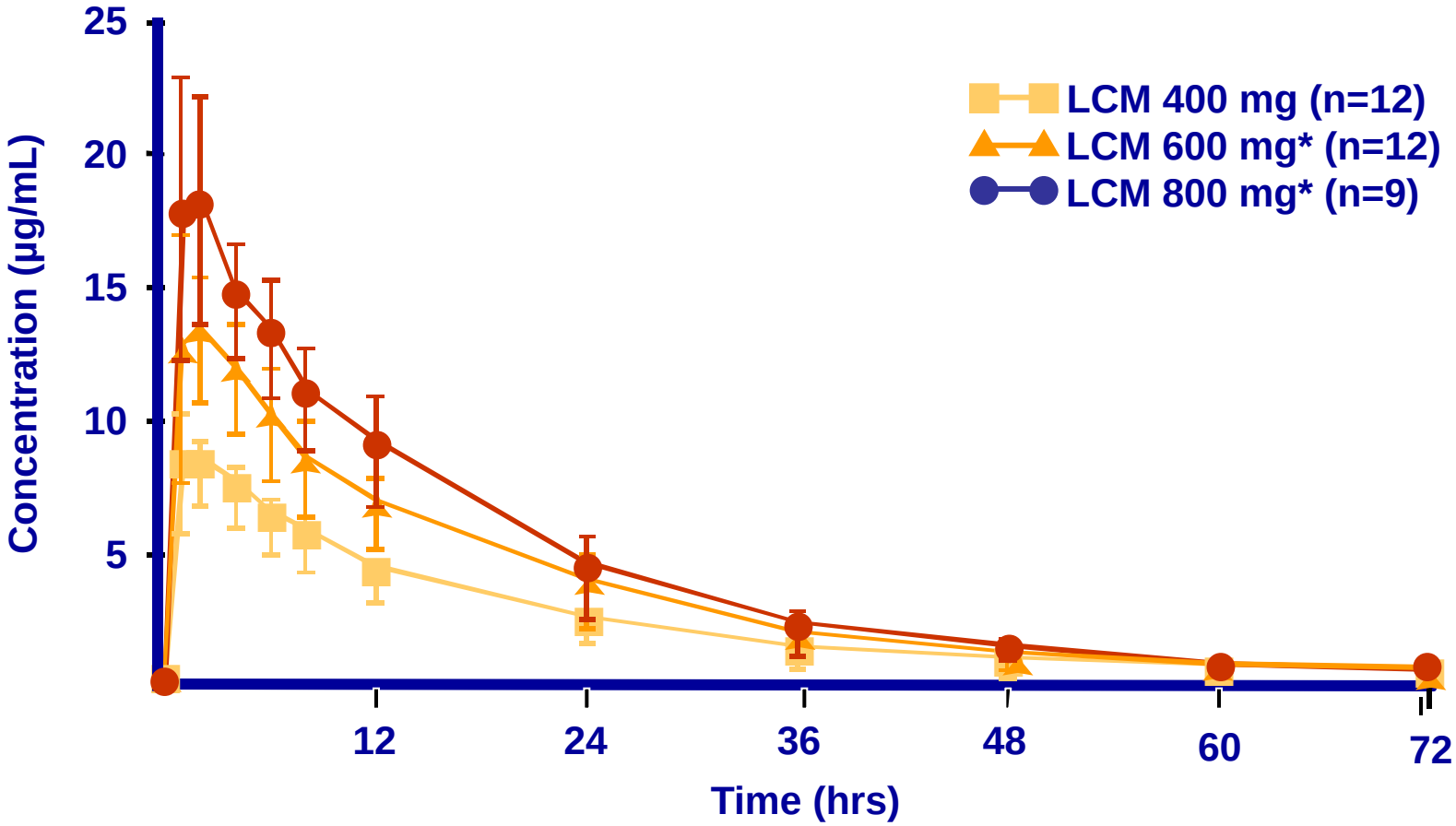
Pharmacokinetic Properties

- **Dose proportionality of C_{max} and AUC**
- **Low inter- and intra-subject variability of about 20%**
- **T_{max} between 1 and 4 hours after oral administration**
- **$T_{1/2}$ ~13 hours**
- **High oral bioavailability of approximately 100%**
- **95% of the dose is excreted in the urine**
- **Volume of distribution ~0.65 l/kg**
- **Low protein binding (<15%)**
- **Bioequivalence of oral and iv (30- and 60-minute infusion)**

AUC=area under plasma concentration–time curve; C_{max}=maximum observed plasma concentration; iv=intravenous; $T_{1/2}$=plasma terminal elimination half-life; T_{max}=time to C_{max}

UCB data on file:
Clinical Overview Epilepsy, p17–23.

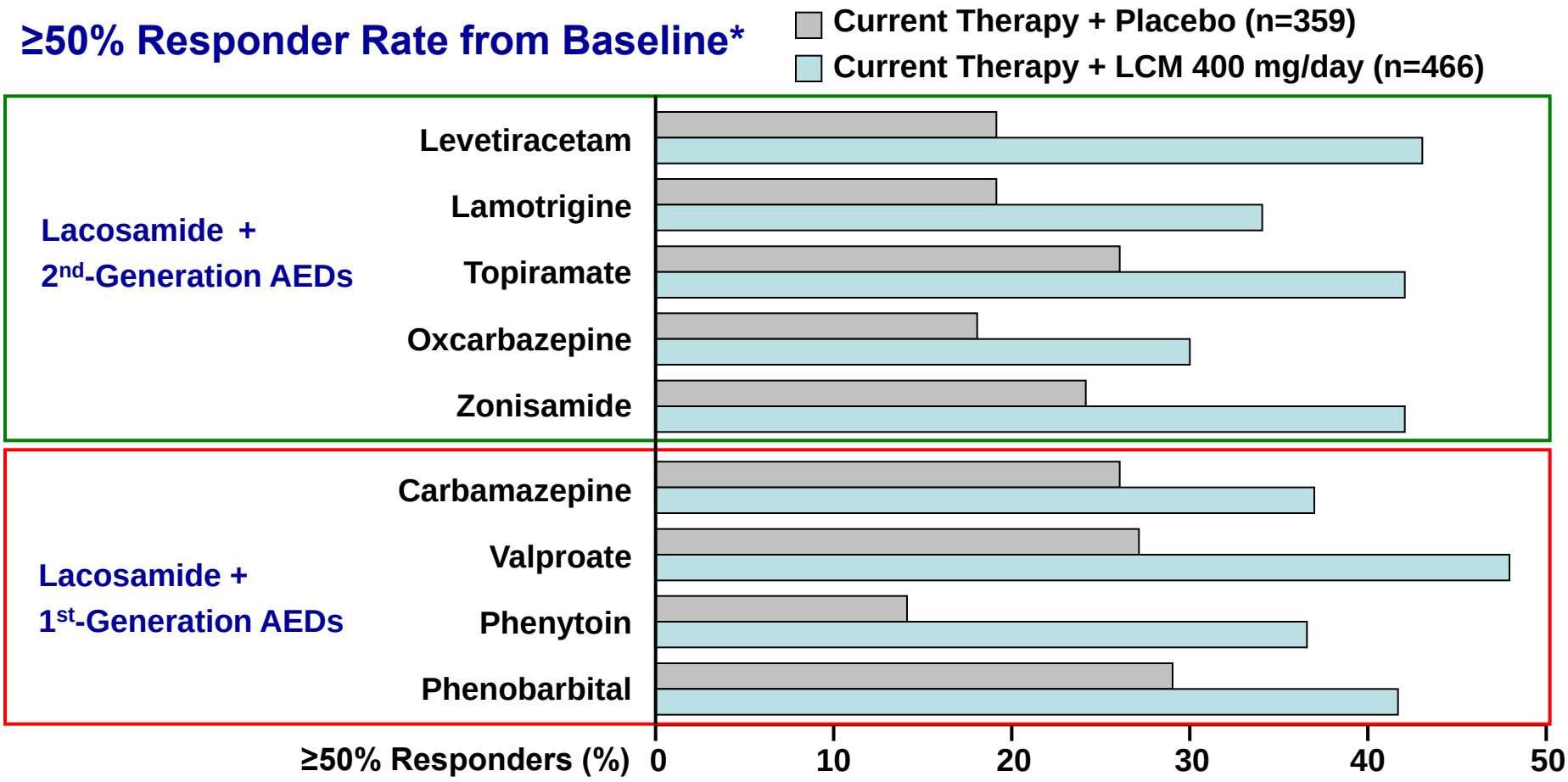
Plasma Concentrations Are Proportional After Single Dose Administration



*600 mg and 800 mg/d are above the approved maximum dose

UCB data on file: Summary Clinical Pharmacology p8–9.

Lacosamide Demonstrates Efficacy with a Broad Range of AEDs



*Per 28 days from baseline to maintenance. Intent-to-treat population. Most patients were taking >1 AED; therefore, these groups may not be mutually exclusive.

Data on file; UCB, Inc. Rosenfeld W, et al. Poster presented at: 62nd Annual American Epilepsy Society Meeting; December, 5-9, 2008; Seattle, WA. *Please see your UCB sales representative for full prescribing information.*

Drug-Drug Interaction Trials

- **In drug–drug interaction trials, no clinically significant PK interaction has been observed with:**
  - **Carbamazepine***
  - **Valproic acid**
  - **Omeprazole (inhibitor of CYP2C19)**
  - **Ethinylestradiol and levonorgestrel**
  - **Metformin**
  - **Digoxin**

*Available Population PK data indicate that the plasma concentrations of lacosamide may be decreased under concomitant treatment with carbamazepine, phenytoin, and phenobarbital. The influence is considered of minor clinical relevance and no dose adjustment is necessary.
PK=pharmacokinetic; PopPK=population pharmacokinetic analysis

Horstmann RP, et al. Presented at AES.
Kropeit D, et al. Presented at AES, 2005.
Thomas D, et al. Presented at AES, 2006

Drug-Drug Interaction Profile with Marketed AEDs

AED co-administered	Dose AED [mg/day]	Influence of LCM* on AED	Influence of AED on LCM*	Trial
Carbamazepine	1000–2200	No	No	SP586
Phenytoin	400	No	No	SP586
Carbamazepine	600–2400	No	No	SP607
Gabapentin	1200–3600	No	No	SP607
Lamotrigine	100–1200	No	No	SP607
Levetiracetam	1000–5000	No	No	SP607
Oxcarbazepine	900–3600	No	No	SP607
Phenytoin	200–700	No	No	SP607
Zonisamide	300–700	No	No	SP607

*200–600 mg/day,
SP586=multicenter, uncontrolled, ascending-dose trial to evaluate the tolerability, compatibilty, efficacy and PK of LCM as add-on therapy in patients with POS
SP607= multicenter, open-label, single-arm, dose-titration trial to determine the maximum tolerated dose of LCM (<600 mg/day) and evaluate efficacy of LCM as add-on therapy in patients with POS
AEDs=antiepileptic drugs; LCM=lacosamide; POS=partial-onset seizure

Thomas D, et al.
Poster presented at
AES, 2006 (abstract 2.235).

Treatment-Emergent Adverse Events **(Frequency ≥10% During Treatment Phase):** Titration Vs. Maintenance

	Titration (%)		Maintenance (%)	
MedDRA Preferred Term	Placebo n=364	Total Lacosamide n=944	Placebo n=337	Total Lacosamide n=781
Dizziness	7	25	2	8
Headache	6	9	5	6
Nausea	4	9	1	3
Diplopia	1	9	1	3
Vomiting	2	8	1	4
Fatigue	5	8	1	2
Coordination Abnormal	1	7	<1	3
Vision blurred	2	7	1	2
Tremor	3	5	1	2
Nystagmus	3	4	1	1

Injection: Dosing and Administration

- **200 mg of VIMPAT®/20 mL single-use vial**
  - **Concentration: 10 mg/mL**
  - **pH : 3.5-5.0***
- **Does not require additional dilution prior to administration or may be mixed with diluents**
  - **Compatible and stable with sodium chloride injection 0.9% (w/v), dextrose injection 5% (w/v), and lactated Ringer's injection**
- **Store at room temperature**
- **Infusion rate: At least 30 minutes**
- **1:1 dose conversion (oral ↔ injection)**

***Hydrochloric acid is used for pH adjustment.**

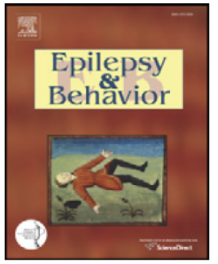
Summary of Efficacy and Safety of Lacosamide

- **LCM at doses of 200, 400 and 600 mg/day significantly reduced seizure frequency despite 1–3 concomitant AEDs**
- **LCM use was generally well tolerated and was associated with dose-related CNS and GI adverse events**
- **No clinically relevant influence of LCM on laboratory results, vital signs, ECG, or body weight was recorded**
- **Caution – when used with drugs that prolong PR interval – syncope risk. (e.g.) β-blockers, procainamide, quinidine, digitalis, verapamil, mexiletine, et cetera**

Contents lists available at ScienceDirect

Epilepsy & Behavior

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



Case Report

2010 Oct 20. [Epub ahead of print]

Does lacosamide aggravate Lennox–Gastaut syndrome? Report on three consecutive cases

Antonella Cuzzola [a,b], Edoardo Ferlazzo [c,*], Domenico Italiano [c], Rocco Salvatore Calabrò [c], Placido Bramanti [c], Pierre Genton [a]

[a] *Hôpital Henri Gastaut, Centre Saint-Paul, Marseille, France*
[b] *Division of Child Neurology and Psychiatry, University of Messina, Messina, Italy*
[c] *IRCCS Centro Neurolesi "Bonino-Pulejo," Messina, Italy*

- **3 patients with LGS, mid-twenties**
- **Tonic seizures increased in each, including when awake – no benefit in other types**
- **One experienced tonic status for 6 hours**

Contents lists available at ScienceDirect

Seizure

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

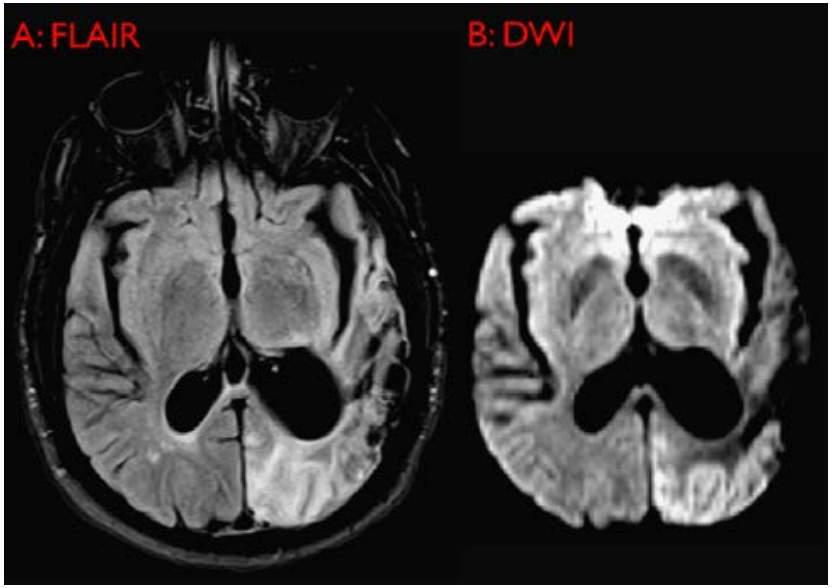
Case report

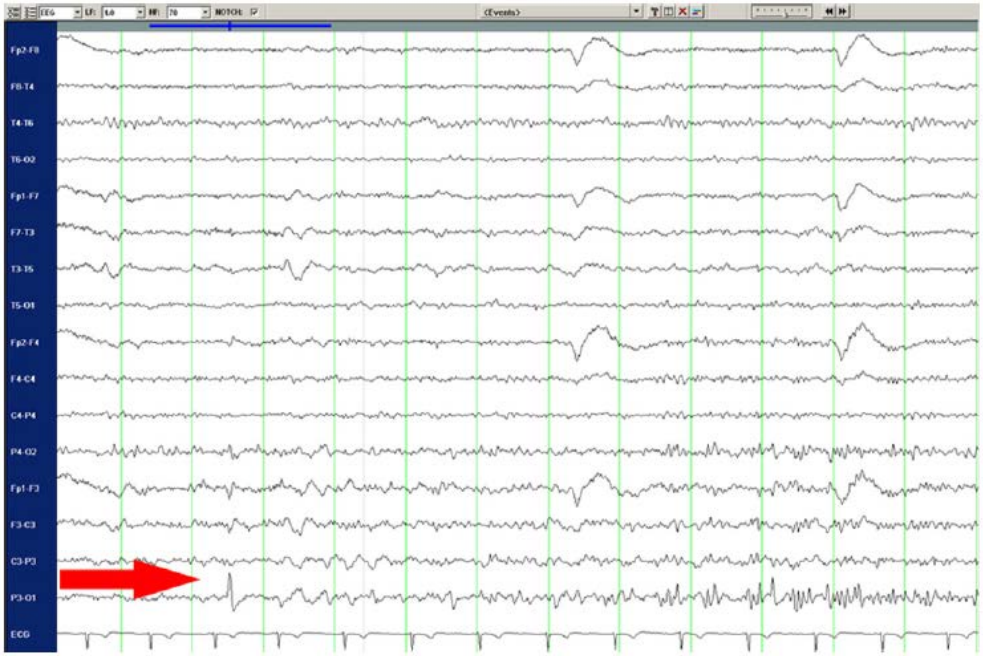
2010 Nov 23. [Epub ahead of print]

Successful treatment of refractory simple motor status epilepticus with lacosamide and levetiracetam

Leo L.K. Chen [a,b,*], Zulfi Haneef [a], Andrew Dorsch [a], Inna Keselman [a], John M. Stern [a]

[a] David Geffen School of Medicine at UCLA, Neurology, Los Angeles, CA, United States
[b] VA Greater Los Angeles Health Care System, Neurology, Los Angeles, CA, United States





Intravenous lacosamide for treatment of status epilepticus

2010 Sep 26. [Epub ahead of print]

Retrospective, n=39

Kellinghaus C, Berning S, Immisch I, Larch J, Rosenow F, Rossetti AO, Tilz C, Trinka E. Intravenous lacosamide for treatment of status epilepticus.
Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2010.01423.x.
© 2010 John Wiley & Sons A/S.

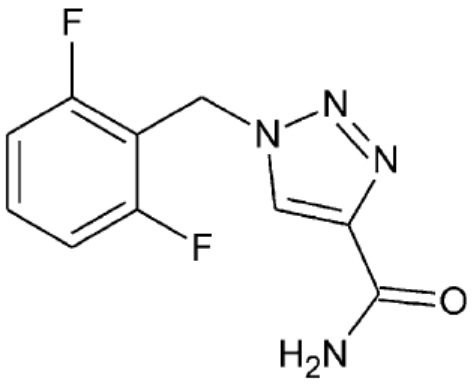
C. Kellinghaus[1], S. Berning[1], I. Immisch[2], J. Larch[3,4], F. Rosenow[2], A. O. Rossetti[5], C. Tilz[6], E. Trinka[3,4]

[1]Department of Neurology, Klinikum Osnabrück, Osnabrück; [2]Department of Neurology, University

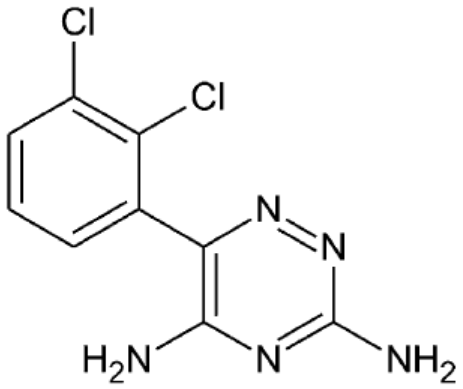
The success rate in patients receiving LCM as first or second drug was 3/5, as third drug 11/19, and as fourth or later drug 3/15. In five subjects, SE could not be terminated at all. No serious adverse events attributed to LCM were documented.

Conclusions Intravenous LCM may be an alternative treatment for established SE after failure of standard therapy, or when standard agents are considered unsuitable.

Rufinamide (Banzel™- Eisai)



Rufinamide



Lamotrigine

Rogawski MA

***Epilepsy Res*, 2006**

AED	Rotorod test TD_{50} (95% CI) mg/kg	MES test ED_{50} (95% CI) mg/kg	PI
Rufinamide	>500 <1,000	15.5 (12.5–18.1)	>32.2
Phenytoin	65.5 (52.5–72.1)	9.5 (8.1–10.4)	6.9
Phenobarbital	69.0 (62.8–72.9)	21.8 (15.0–25.5)	3.2
Valproate	425.8 (369–450)	272 (247–338)	1.6
Ethosuximide	440.8 (383–485)	1,000 no protection	<0.4

White SH et al., *Epilepsia*, 2008

Anticonvulsant Profile of Rufinamide

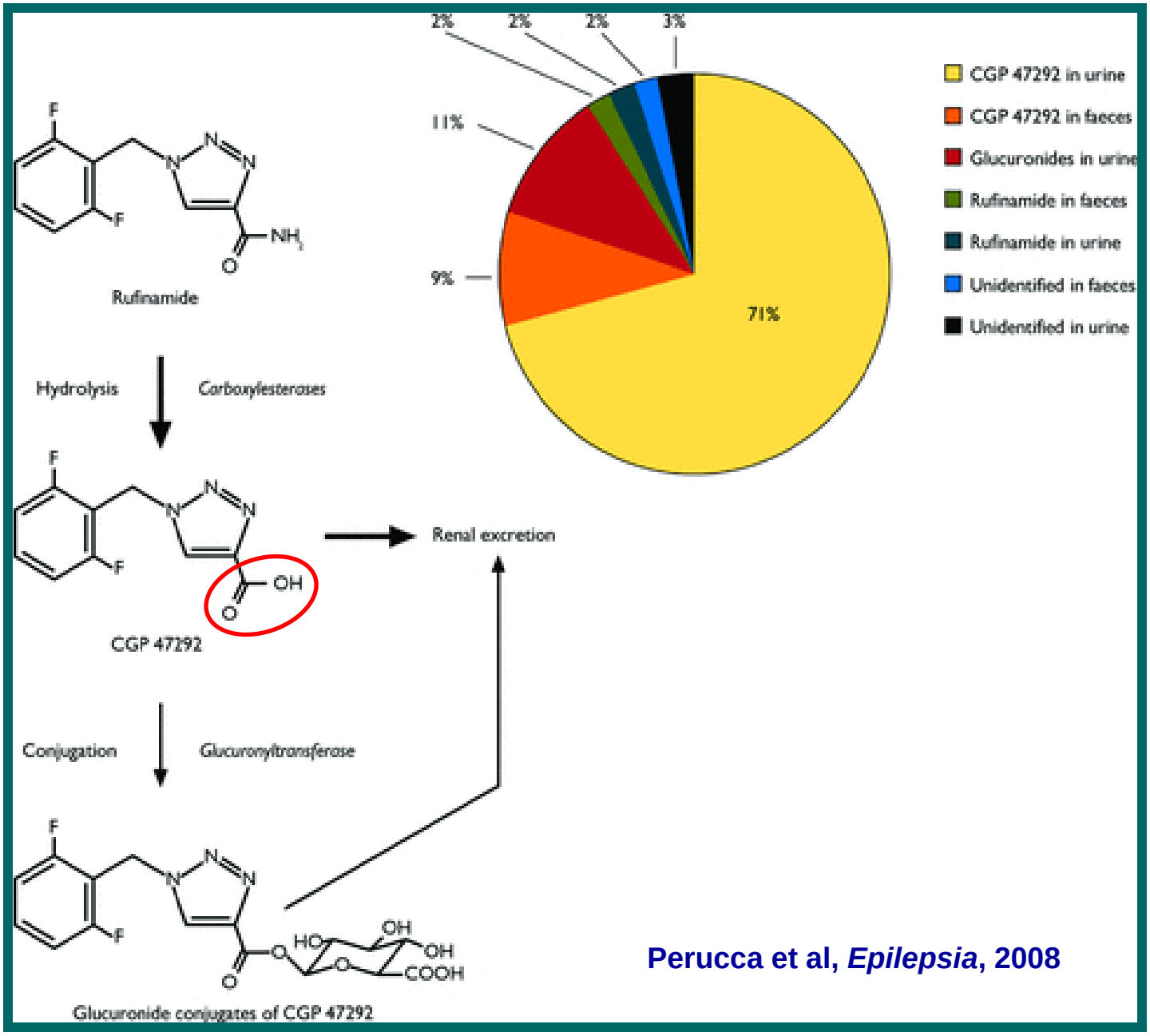
Table 2. Anticonvulsant activity and protective index of oral AEDs in mice

	Rotorod test	MES test		Pentylenetetrazol test	
AED	TD_{50} (95% CI) mg/kg	ED_{50} (95% CI) mg/kg	PI	ED_{50} (95% CI) mg/kg	PI
Rufinamide	>1,000	23.9 (19.3–28.6)	>41.9	45.8 (34.2–60.4)	>21.9
Phenytoin	86.7 (80.4–96.1)	9.0 (7.4–10.6)	9.6	>300	<0.3
Phenobarbital	96.8 (79.9–115)	20.1 (14.8–31.6)	4.8	12.6 (8.0–19.1)	7.7
Valproate	1,264.4 (800–2,250)	664.8 (605–718)	1.9	388.3 (349–439)	3.3
Ethosuximide	879.2 (840–934)	>2,000	<0.4	192.7 (159–218)	4.6

AED, antiepileptic drug; MES, maximal electroshock seizure; TD_{50}, the dose eliciting evidence of minimal neurotoxicity in 50% of animals; CI, confidence interval; ED_{50}, the dose of drug required to produce the desired end point in 50% of animals; and PI, protective index (ratio of TD_{50} to ED_{50}).

Rufinamide's protective index exceeds that of PHT in the MES test and that of ethosuximide and VPA in the PTZ test, suggesting a broad spectrum of action; MOA remains unclear – Na^+ channel antagonism has been demonstrated but may involve other mechanisms.

White SH et al., *Epilepsia*, 2008



Perucca et al, *Epilepsia*, 2008

Pharmacokinetics

- **Absorption**
  - Well absorbed after oral administration
  - At higher dose, dose-limited due to limited solubility
- **Distribution**
  - 34% protein binding (27% to albumin)
- **Metabolism**
  - Extensively metabolized through carboxylesterase(s) mediated hydrolysis
  - None of metabolites have anti-seizure activity
  - BANZEL™ (rufinamide) is slight inducer of CYP 4503A4 enzyme
- **Elimination/Excretion**
  - T_{max} = 4–6 hours
  - Half-life = 6–10 hours
  - Renal excretion was predominant route of elimination (85%)
- **No significant difference of PK profile as a function of age**
  - Ages 4 to 80 years

Arroyo S. *Neurotherapeutics*. 2007;4:155–62.
BANZEL™ (rufinamide) Prescribing Information.

Dosage and administration (in clinical trials)	
Lennox-Gastaut syndrome	Initial dosage: 10 mg/kg/day
	Maximum dosage: 45 mg/kg/day
Partial Seizures	Initial dosage: 200–1600 mg/day[a]
	Maximum dosage: 3200 mg/day
Route of administration	Oral
Pharmacokinetic profile (after a single oral 400mg dose in healthy adult volunteers)	
Mean maximum plasma concentration (C_{max})	3.03 μg/mL
Mean area under the plasma concentration-time curve from 0 to 48 hours	49.4 μg • h/mL
Mean time to C_{max}	6.56h
Mean elimination half-life	8.82h
Most frequent adverse events (incidence ≥10%)	
Lennox-Gastaut syndrome	Somnolence, vomiting
Partial seizures (pooled data)	Headache, dizziness, fatigue, nausea, somnolence, diplopia
a It should be noted that the upper limit recommendation for the initial rufinamide dosage will be lower than 1600 mg/day.	

Deeks & Scott
***CNS Drugs*, 2006**

ARTICLES

Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome

T. Glauser, MD
G. Kluger, MD
R. Sachdeo, MD
G. Krauss, MD
C. Perdomo, MS
S. Arroyo, MD, PhD

ABSTRACT

Background: Lennox–Gastaut syndrome is a catastrophic pediatric epilepsy syndrome characterized by multiple types of treatment-resistant seizures and high rates of seizure-related injury. Current available treatments are inadequate, leaving patients with few treatment options and opportunities.

Methods: We conducted a double-blind, randomized, placebo-controlled trial of the antiepileptic

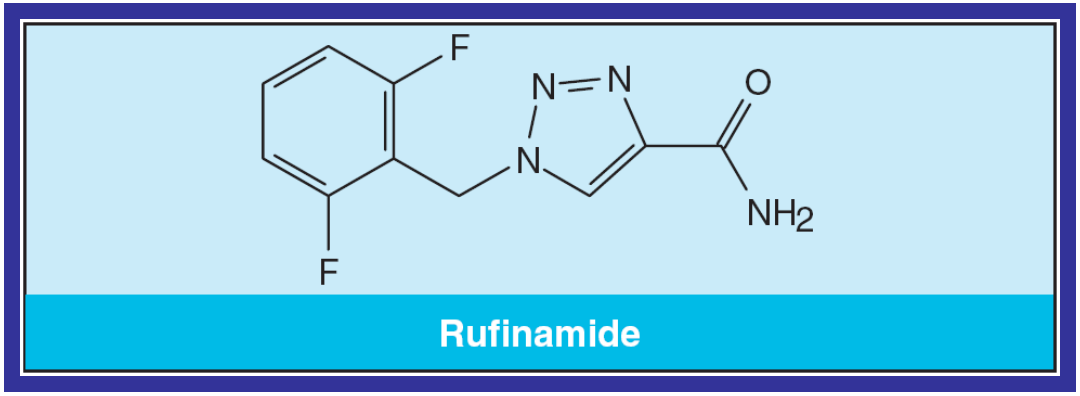


Table 1 Rufinamide dosing schedule

Trial day (titration phase)	Approximate dose (mg/kg/d)	Actual dose by body weight (mg/d)			
		18.0–29.0 kg	29.1–50.0 kg	50.1–70.0 kg	>70.0 kg
1–2	10	200	400	600	800
3–4	20	400	800	1,200	1,600
5–6	30	800	1,200	1,800	2,400
7	45	1,000	1,800	2,400	3,200

Glauser T et al, *Neurology*, 2008

Table 2 Patient demographic and baseline characteristics*

Characteristic	Rufinamide (n = 74)	Placebo (n = 64)
Sex, n (%)		
Male	46 (62.2)	40 (62.5)
Female	28 (37.8)	24 (37.5)
Race, n (%)		
White	62 (83.8)	53 (82.8)
Black	6 (8.1)	4 (6.3)
Other	6 (8.1)	7 (10.9)
Age, y		
Median (range)	13.0 (4.0–35.0)	10.5 (4.0–37.0)
4–<12, n (%)	31 (41.9)	33 (51.6)
12–<17, n (%)	19 (25.7)	17 (26.6)
≥17, n (%)	24 (32.4)	14 (21.9)

Glauser T et al, *Neurology*, 2008

Rufinamide in LGS

Figure 2 Median percentage reduction in total seizure frequency and tonic-atonic seizure frequency (per 28 days during the double-blind phase relative to baseline)

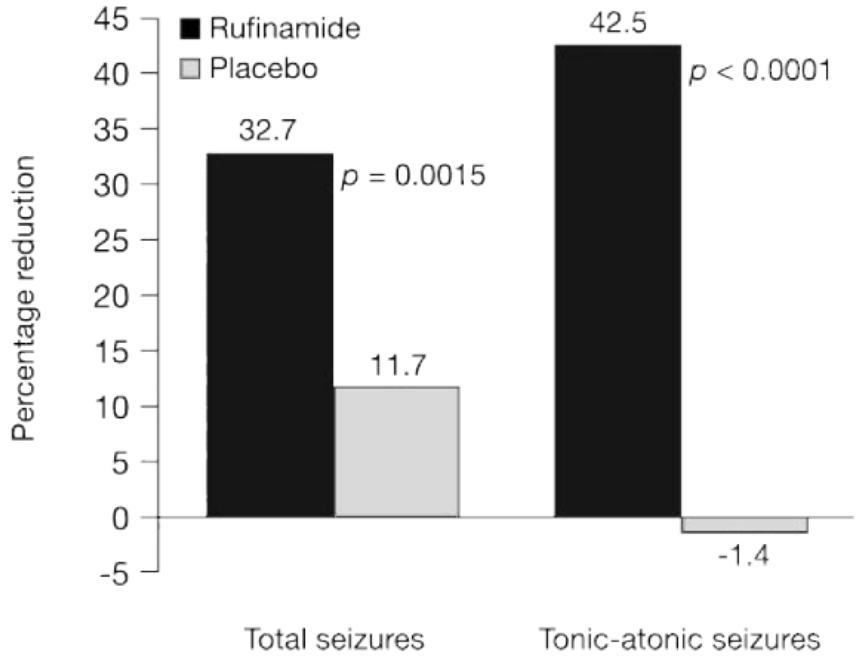
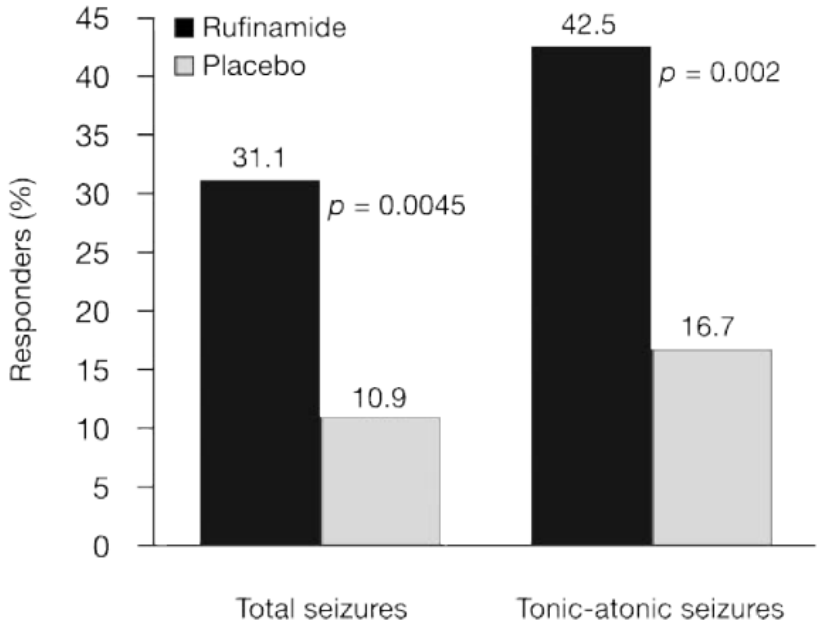
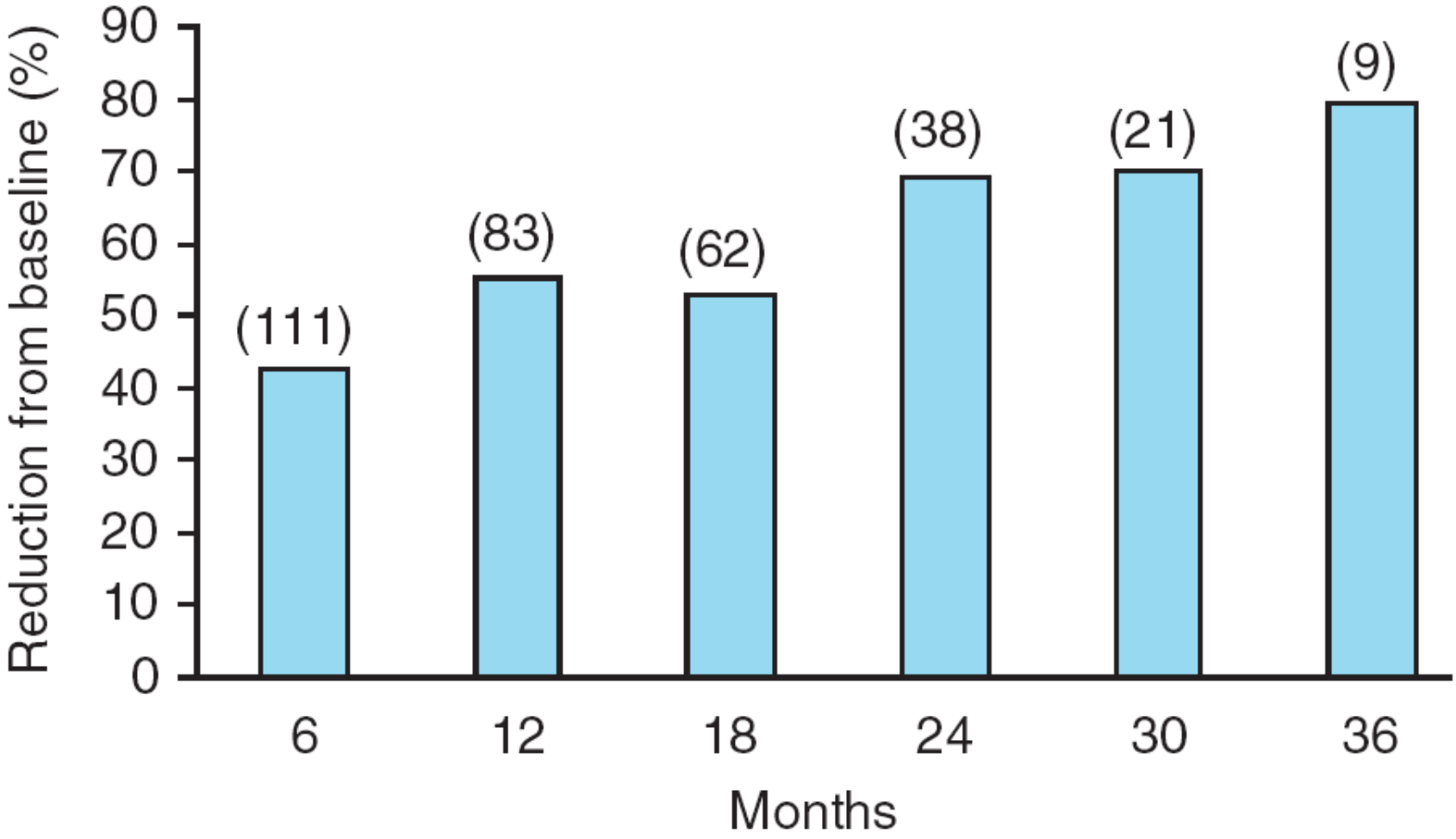


Figure 3 Percentage of patients (responders) who experienced at least a 50% reduction in tonic-atonic and total seizure frequency (per 28 days during the double-blind phase relative to baseline)

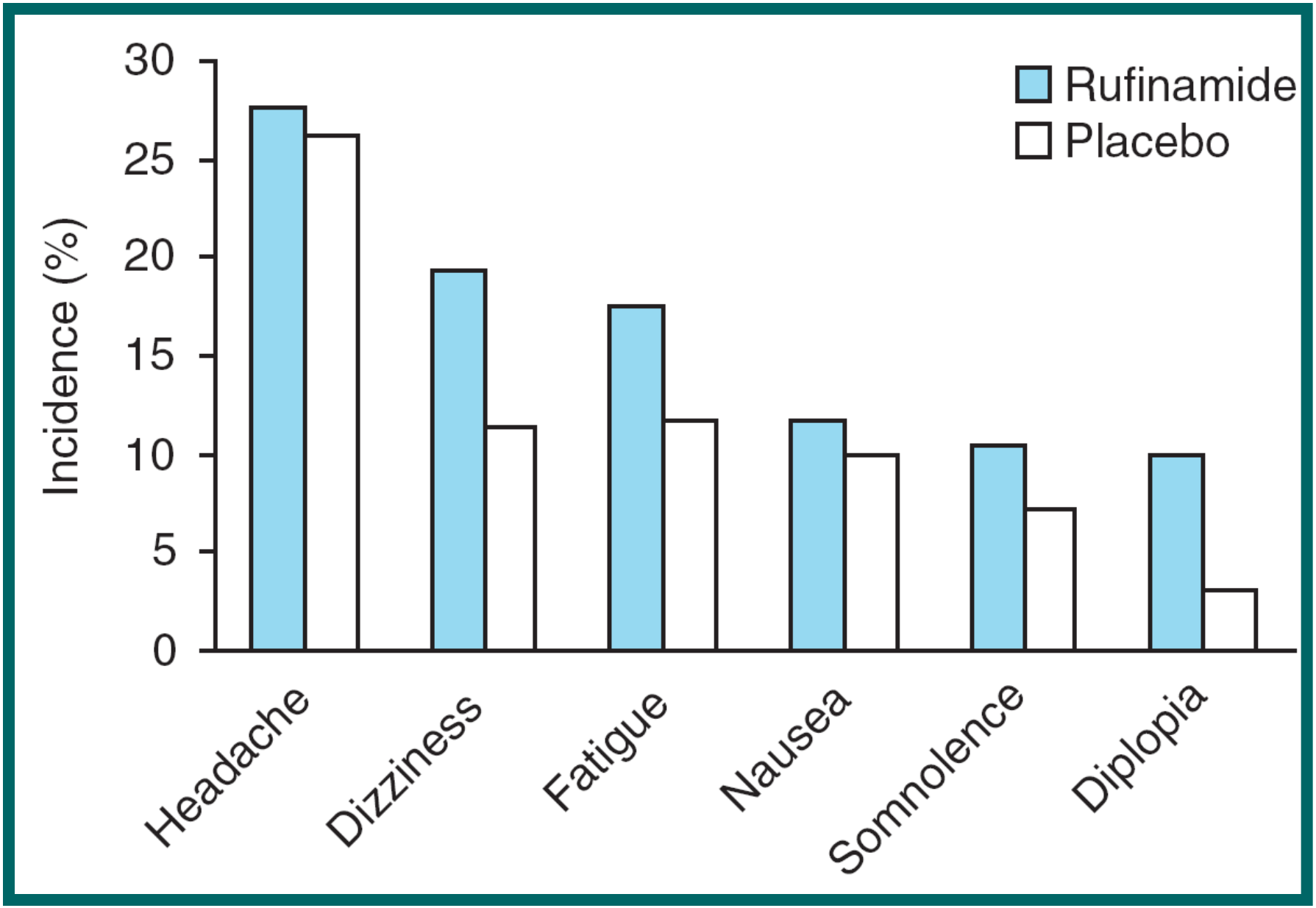


Glauser T et al, *Neurology*, 2008

Long-term efficacy of Rufinamide in Lennox-Gastaut Syndrome



Deeks & Scott, *CNS Drugs*, 2006



Deeks & Scott, *CNS Drugs*, 2006

AED Drug Interactions

AED Co-administered	Influence of BANZEL™ (rufinamide) on AED Concentration	Influence of AED on BANZEL (rufinamide) Concentration
Carbamazepine	Decrease by 7 to 13%	Decrease by 19 to 26% Dependent on dose of carbamazepine
Lamotrigine	Decrease by 7 to 13%	No Effect
Phenobarbital	Increase by 8 to 13%	Decrease by 25 to 46% Independent of dose or concentration of phenobarbital
Phenytoin	Increase by 7 to 21%	Decrease by 25 to 46% Independent of dose or concentration of phenytoin
Topiramate	No Effect	No Effect
Valproate	No Effect	Increase by < 16 to 70% Dependent on concentration of valproate
Primidone	Not Investigated	Decrease by 25 to 46% Independent of dose or concentration of primidone
Benzodiazepines	Not Investigated	No Effect

- Patients stabilized on BANZEL (rufinamide) before being prescribed valproate should begin valproate therapy at a low dose and titrate to a clinically effective dose. Similarly, patients on valproate should begin at a BANZEL (rufinamide) dose lower than 400 mg
- The effects of BANZEL (rufinamide) on the PK of other AEDs are unlikely to have clinical significance
- Potent P450 enzyme inducers appear to increase the clearance of BANZEL (rufinamide)

BANZEL™ (rufinamide) Prescribing Information.

Epilepsia, **47**(7):1153–1159, 2006
Blackwell Publishing, Inc.
© 2006 International League Against Epilepsy

The Effect of the New Antiepileptic Drug Rufinamide on Cognitive Functions

*†Albert P. Aldenkamp and ‡Willem C. J. Alpherts

**Department of Behavioural Sciences Epilepsy Centre Kempenhaeghe, Heeze; †Department of Neurology, Maastricht University Hospital, Maastricht; and ‡Department of Psychology 'SEIN, Heemstede, The Netherlands*

Conclusions: RUF is a new AED with no serious cognitive effects even in add-on treatment and even in the higher dose ranges.

Psychother Psychosom 2010;79:194–195
DOI: 10.1159/000296139

The Possible Antianxiety and Mood-Stabilizing Effects of Rufinamide

Maurizio Fava

Depression Clinical and Research Program, Massachusetts General Hospital, Boston, Mass., USA

Acta Neurol Scand 2010: 122: 202–208 DOI: 10.1111/j.1600-0404.2010.01334.x

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ACTA NEUROLOGICA
SCANDINAVICA

Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study

Kluger G, Glauser T, Krauss G, Seeruthun R, Perdomo C, Arroyo S. Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study.
Acta Neurol Scand: 2010: 122: 202–208.

G. Kluger[1], T. Glauser[2], G. Krauss[3], R. Seeruthun[4], C. Perdomo[5], S. Arroyo[6]

The Cost Effectiveness of Rufinamide in the Treatment of Lennox-Gastaut Syndrome in the UK

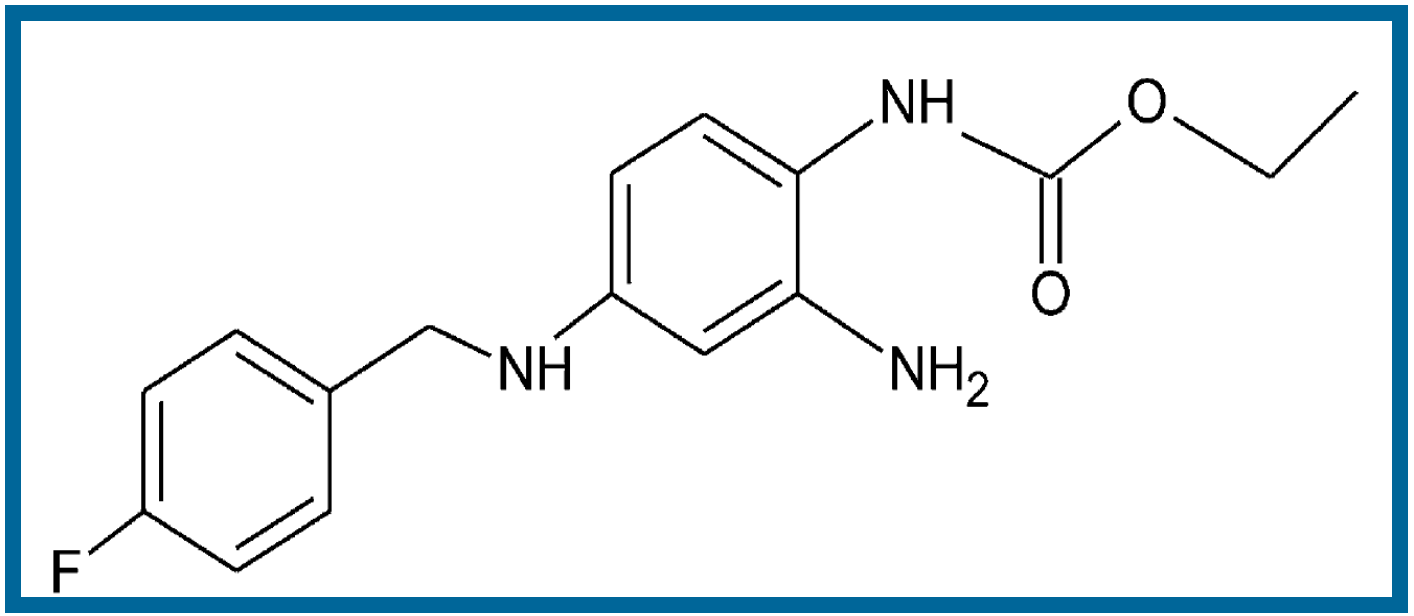
Ágnes Benedict,[1] *Lara Verdian*[2] and *Grant Maclaine*[2]

Pharmacoeconomics 2010; 28 (3): 185-199

Retigabine

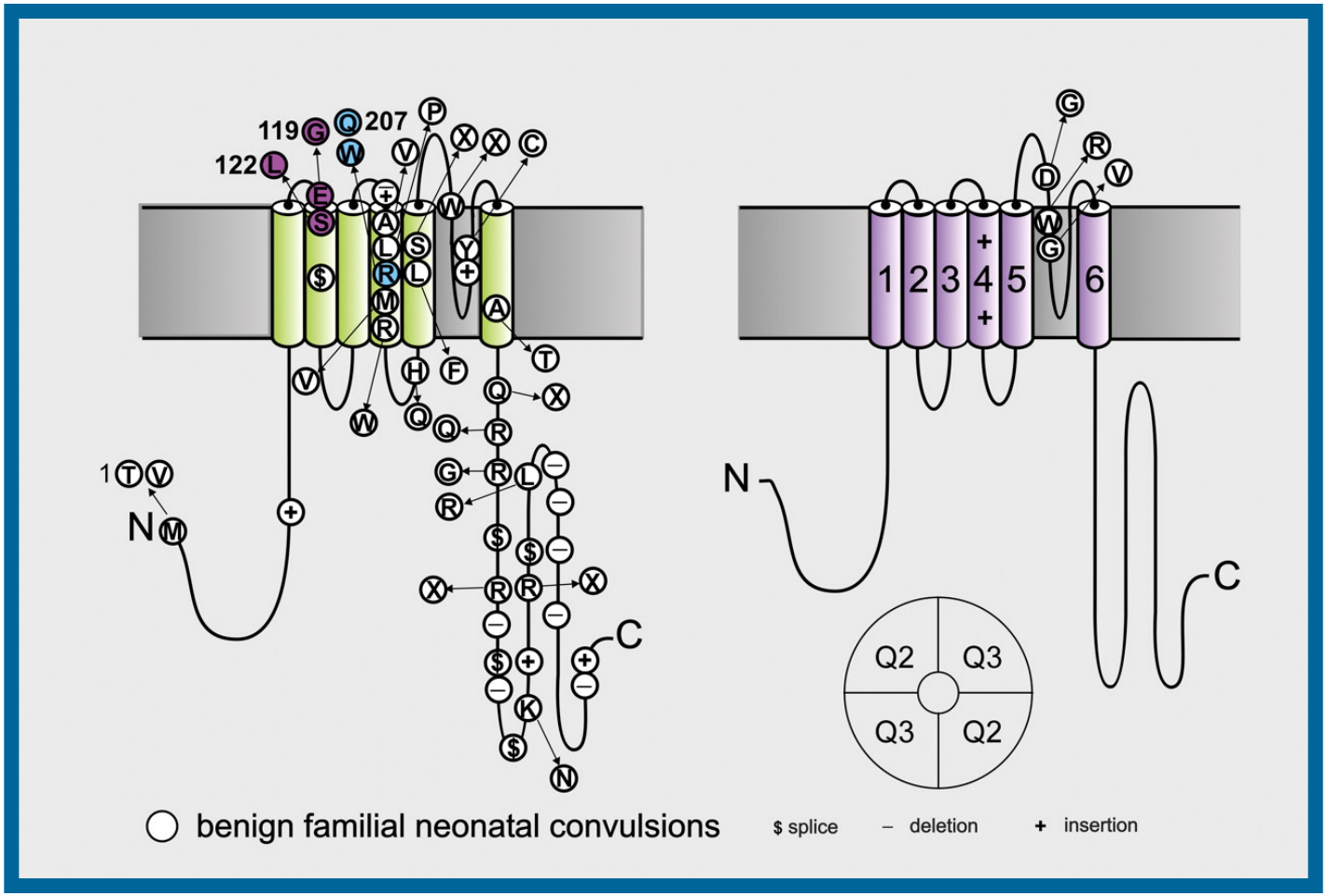
Ezogabine

US FDA Approval granted June 2011



Ezogabine - Potiga® (Valeant-GSK)

US FDA Approval granted June 2011



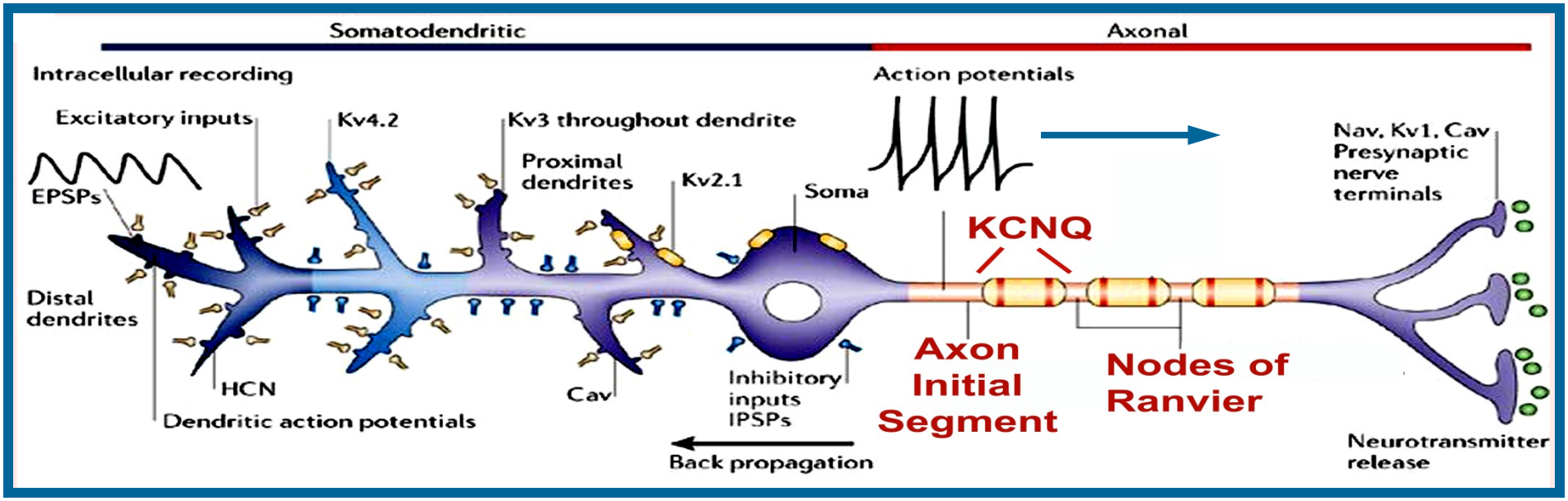
Maljevic, S. et al. *J Physiol* 2008;586:1791-1801

Epilepsia, 49(10):1777–1786, 2008
doi: 10.1111/j.1528-1167.2008.01674.x

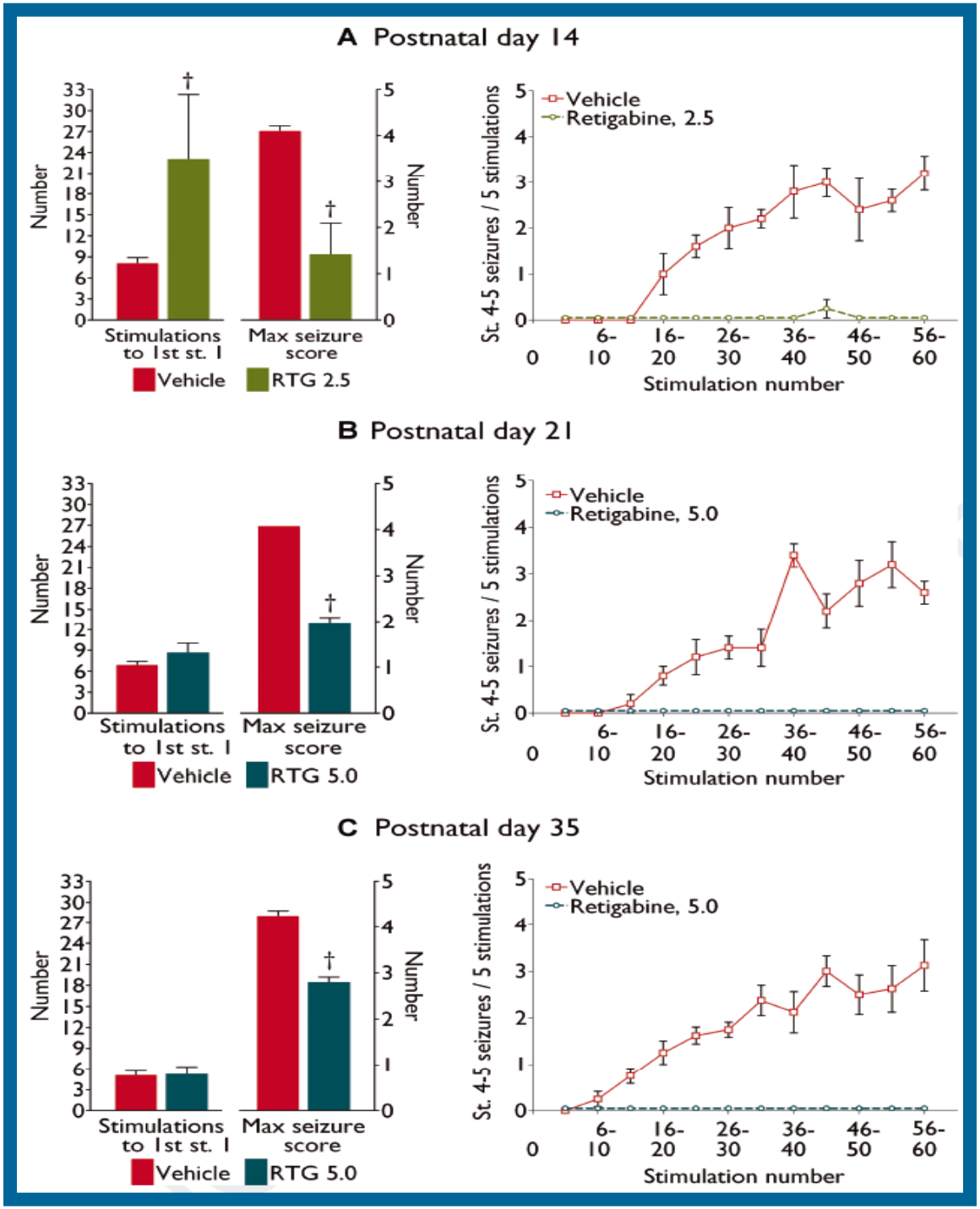
FULL-LENGTH ORIGINAL RESEARCH

Antiepileptogenic and antiictogenic effects of retigabine under conditions of rapid kindling: An ontogenic study

*Andrey Mazarati, †Jim Wu, *Don Shin, *‡Young Se Kwon, and *§Raman Sankar



Lai et al. *Nature Reviews Neuroscience* 2006: 7, 548–562



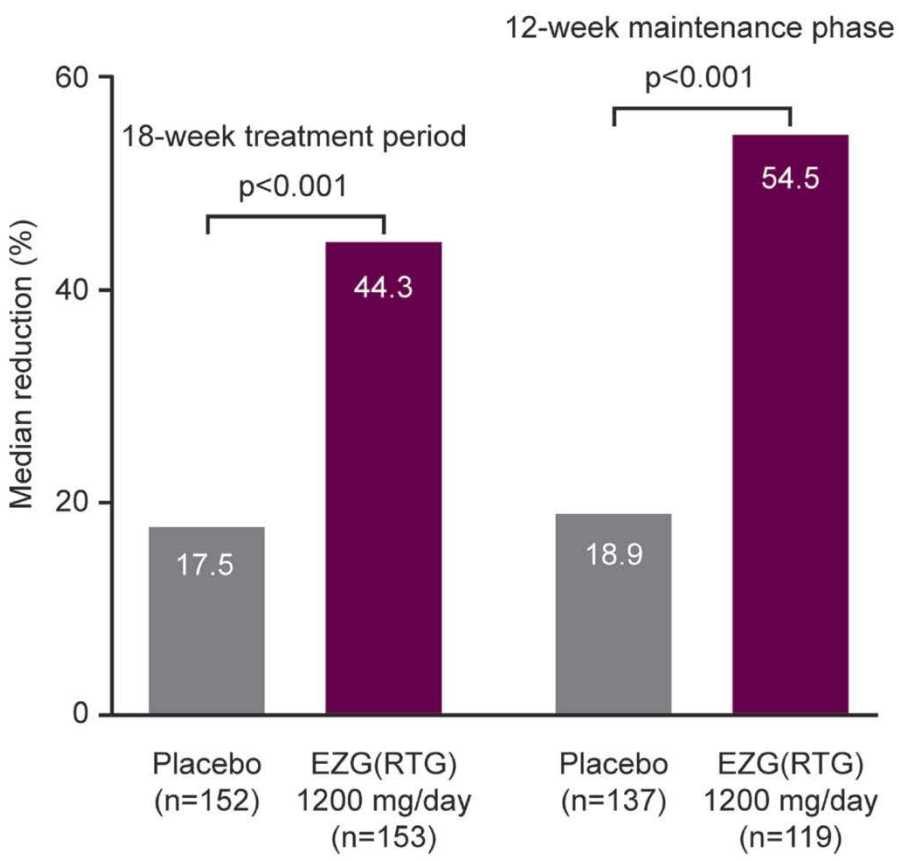
Mazarati et al., *Epilepsia*, 2008

Ezogabine Pharmacokinetics

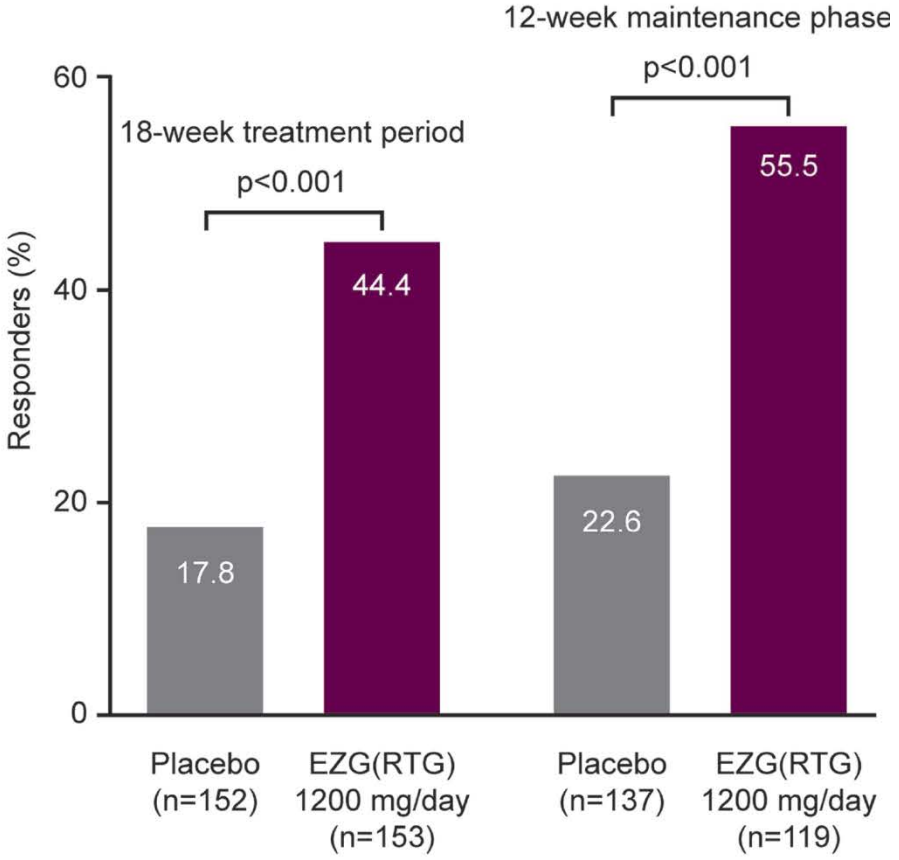
- **Extensive first-pass metabolism**
- **Protein binding about 80%**
- **Hydrolysis – acetylation & glucuronidation**
- **N-acetyl not especially active**
- **Clearance increased by PB, CBZ**
- **Not so much by VPA, LTG, TPM**

Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy

A Median percent reduction from baseline in 28-day seizure frequency



B Responder rate (≥50% reduction in total partial-seizure frequency from baseline; ITT population)



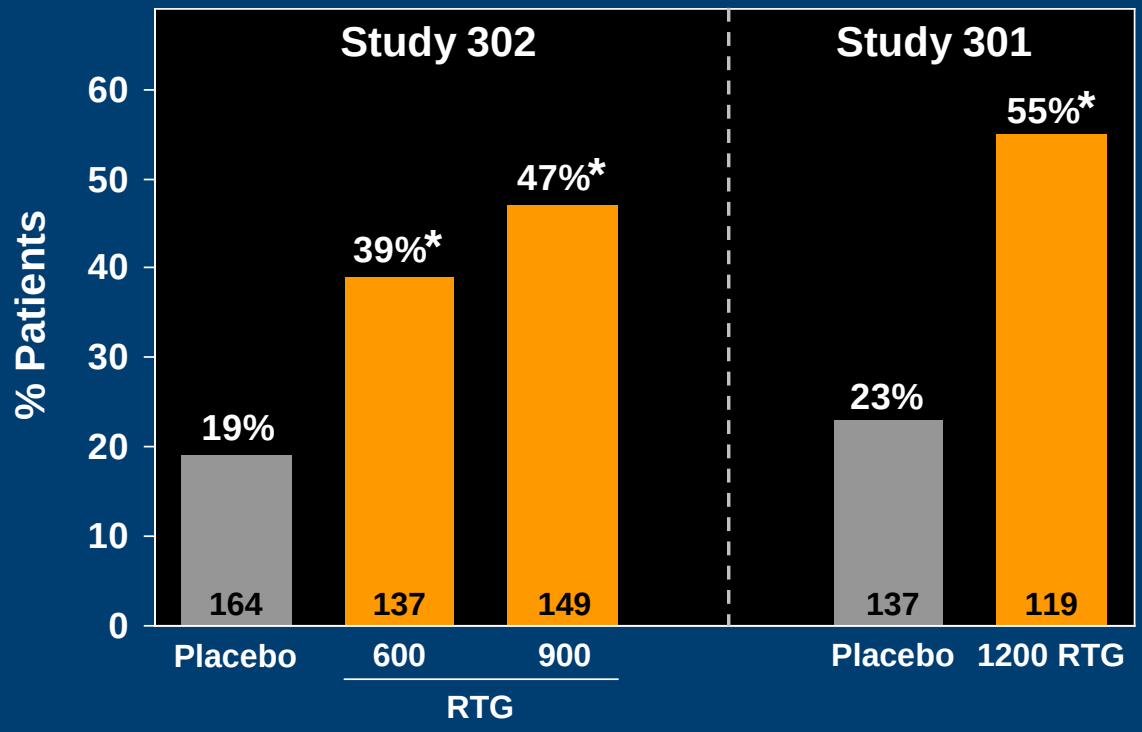
Phase III Trials: Overview

- Two Phase III studies with similar design
  - Randomized, double-blind, placebo-controlled
  - Adult patients with refractory partial-onset seizures on a stable regimen of 1 - 3 background AEDs
  - Primary endpoints and study design meet US and European regulatory guidance
- Study 302 (RESTORE 2):

  600 and 900 mg/day RTG vs placebo
- Study 301 (RESTORE 1):

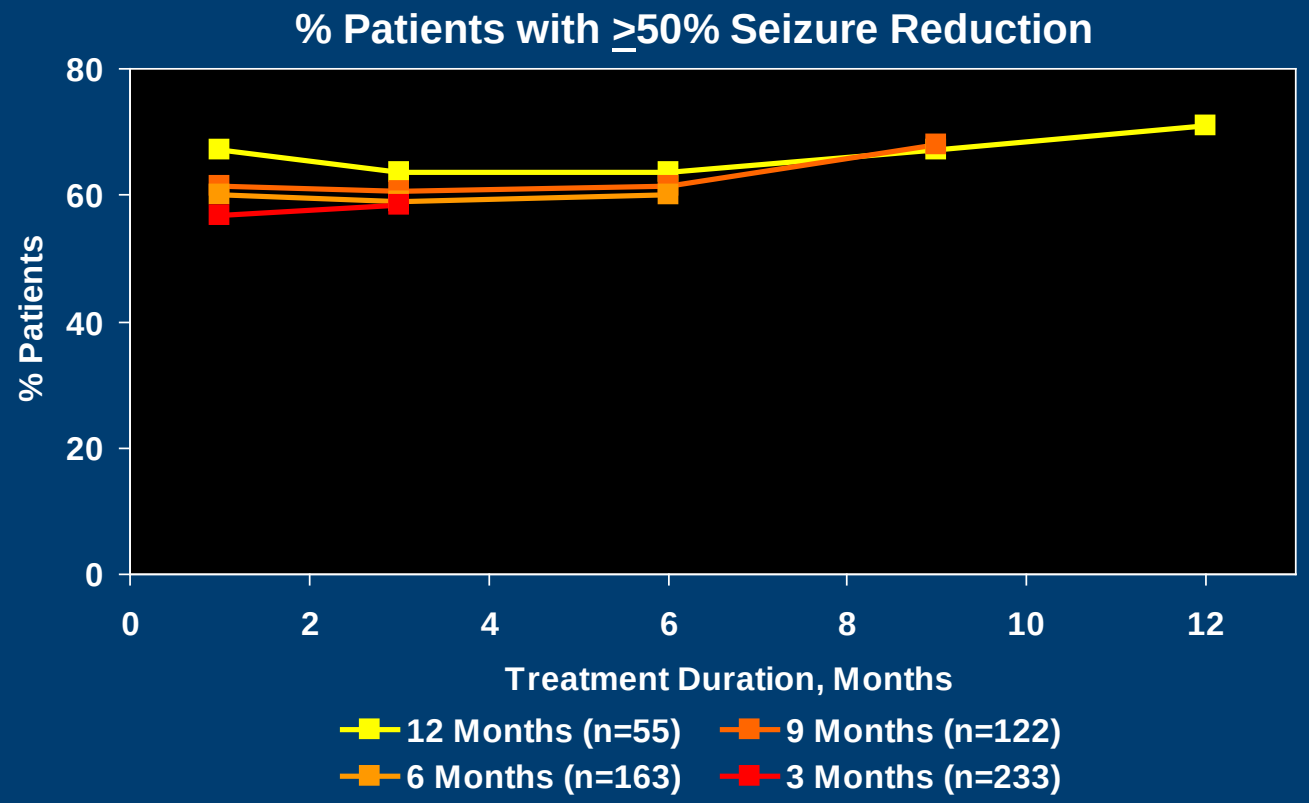
  1200 mg/day RTG vs placebo

Patients with ≥50% Seizure Reduction During Maintenance



*p<0.001
Fisher's exact test

Responder Rate Over Time by Duration of Retigabine Open-Label Exposure (Study 304)



Discontinuations Due to Adverse Events

- Adverse event as primary reason for discontinuation

	RTG		
Placebo (N=331)	**600 (N=181)**	**900 (N=178)**	**1200 (N=153)**
8%	14%	26%	27%

- Cause for discontinuation in >3% of patients
  - Dizziness*
  - Confusion*
  - Somnolence
  - Fatigue

***Dose-related**

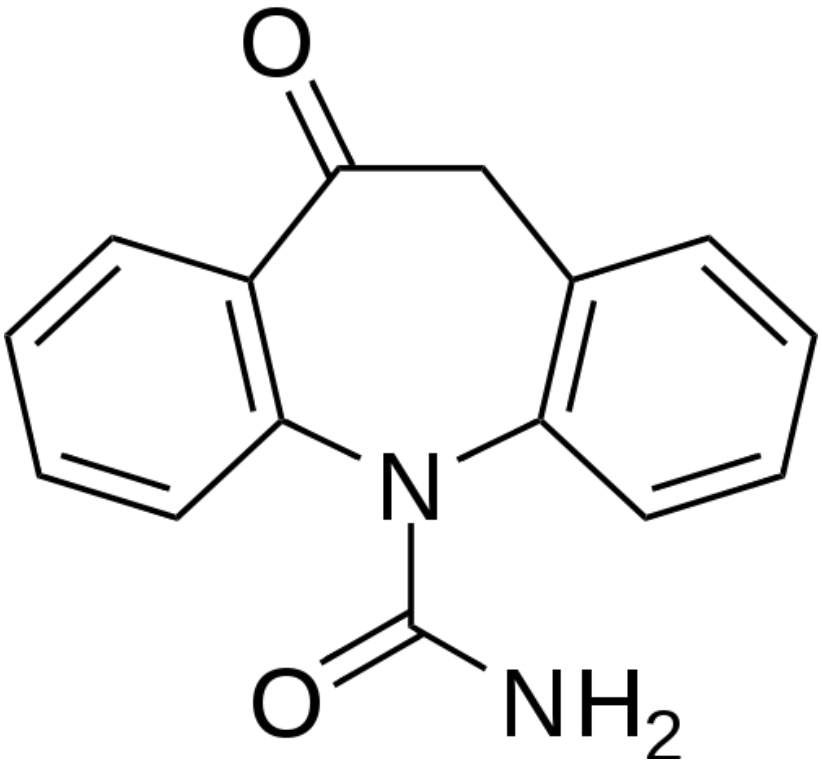
Conclusions

- All doses met primary efficacy endpoints
  - Statistically superior to placebo ($p<0.01$) at all doses
  - Clear dose-response established
- Generally well-tolerated
  - Adverse events mostly dose-related
  - Extensive safety experience
- Validates novel mechanism of action
- An important advance for epilepsy patients with refractory partial-onset seizures

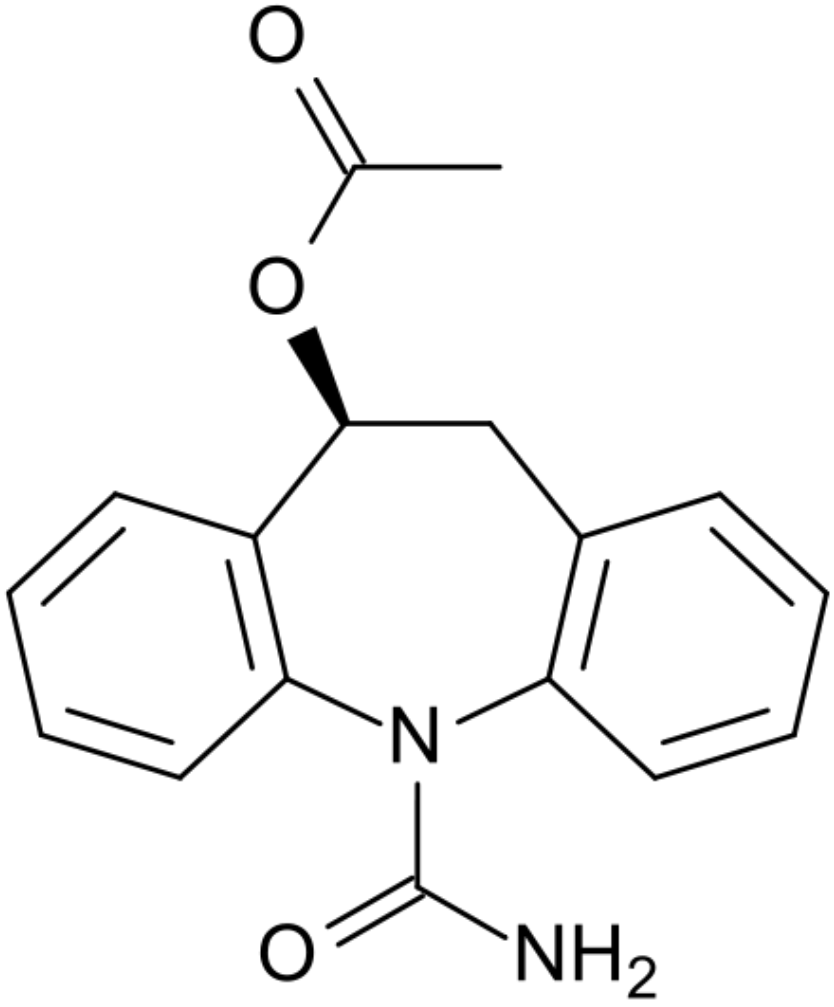
- Requires TID dosing
- Even with that 26% discontinued at 900 mg/d
- However, even 600 mg/d met efficacy criteria
- Will need to explore usage strategy for optimizing results

Eslicarbazepine

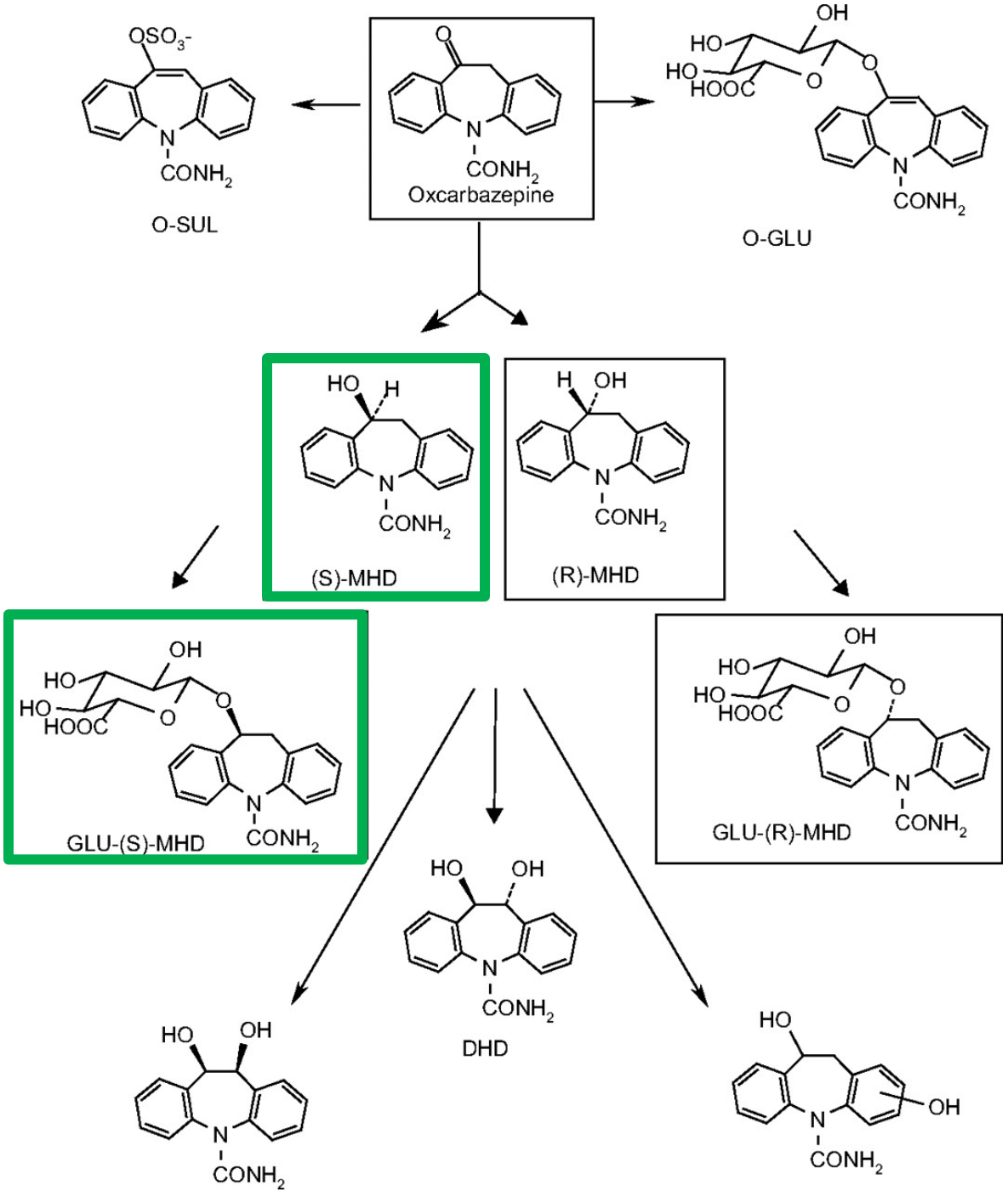
Stedesa™ - Sunovion



Oxcarbazepine



Eslicarbazepine


OSO3-
CONH2
O-SUL
O
CONH2
Oxcarbazepine
OH
HO
HO
HOOC
O
O
CONH2
O-GLU
HO
H
CONH2
(S)-MHD
H
OH
CONH2
(R)-MHD
OH
HO
HO
HOOC
O
O
CONH2
GLU-(S)-MHD
OH
HO
HO
HOOC
O
O
CONH2
GLU-(R)-MHD
HO
OH
CONH2
DHD
HO
OH
CONH2
HO
OH
CONH2

Pharmacokinetics

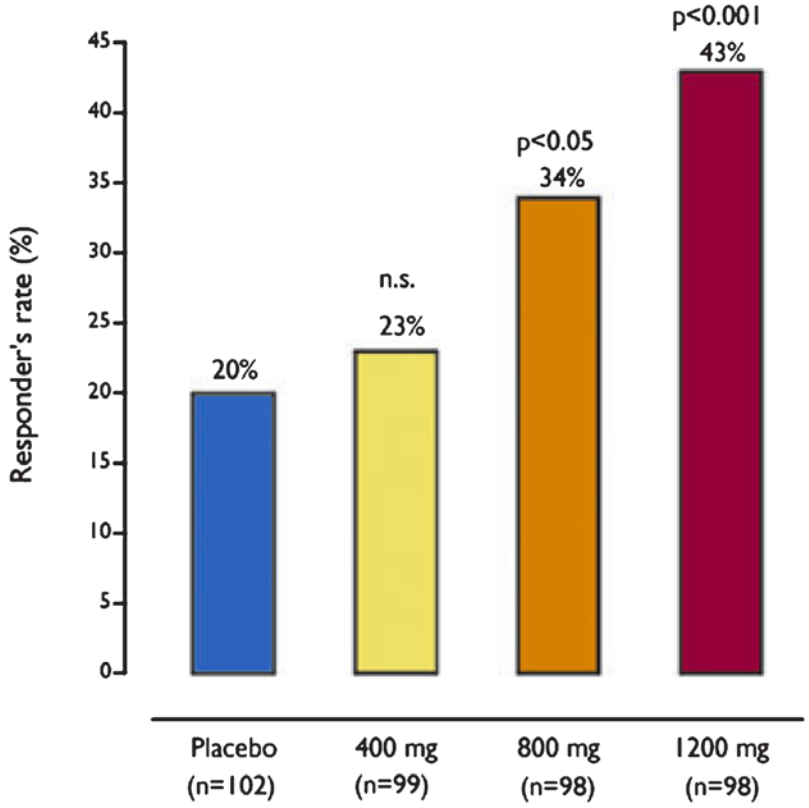
- **Peak concentration: 2-3 hrs after dose**
- **Low protein binding (<40%)**
- **Bioavailability >90%**
- **Rapid conversion to eslicarbazepine**
- **Excretion: 2/3 free; 1/3 as glucuronide**
- **Effective half life close to 20 hrs**
- **Steady state reached in 4-5 days**

1. In in vitro studies in human liver microsomes, eslicarbazepine had no relevant inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4 and CYP2C9, and only a moderate inhibitory effect on CYP2C19.
2. No significant induction of CYP1A2, CYP3A and phase II enzymes involved in the glucuronidation and sulfatation
3. No meaningful PK interaction with PHT or LTG

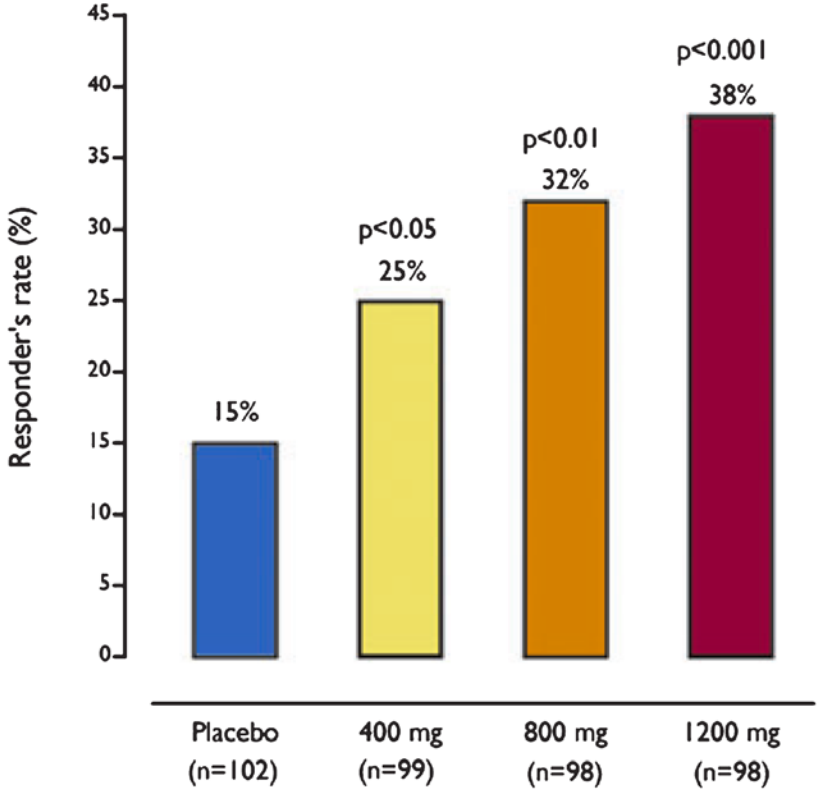
Epilepsia, 50(3):454–463, 2009
doi: 10.1111/j.1528-1167.2008.01946.x

Efficacy and safety of eslicarbazepine acetate

A



B

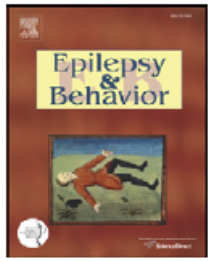


Epilepsy & Behavior 18 (2010) 366–373

Contents lists available at ScienceDirect

Epilepsy & Behavior

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



Effect of eslicarbazepine acetate and oxcarbazepine on cognition and psychomotor function in healthy volunteers

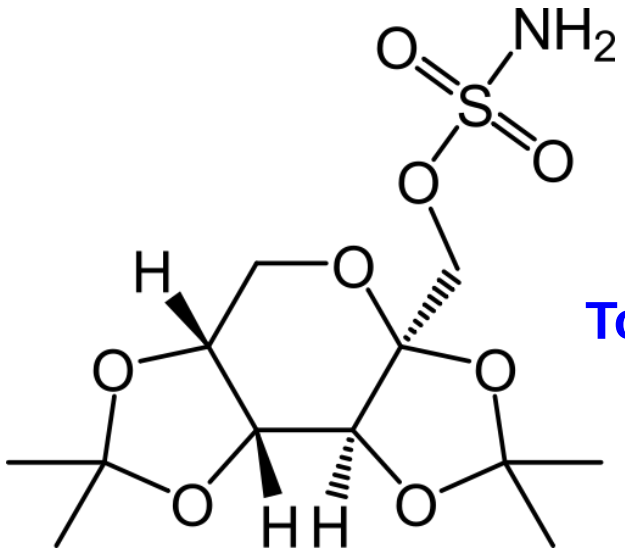
Denise Milovan [a], Luis Almeida [b,c], Myroslava K. Romach [a], Teresa Nunes [b], José Francisco Rocha [b], Marta Sokowloska [a], Edward M. Sellers [a], Patrício Soares-da-Silva [b,d,*]

- Two single-blind studies following single and repeated administration in healthy volunteers.
- The cognitive and psychomotor evaluation consisted of several computerized and paper-and-pencil measures.
- ESL and OXC had similar overall cognitive profiles and did not cause clinically relevant cognitive impairment.
- Incidence of adverse events lower with ESL than with OXC.

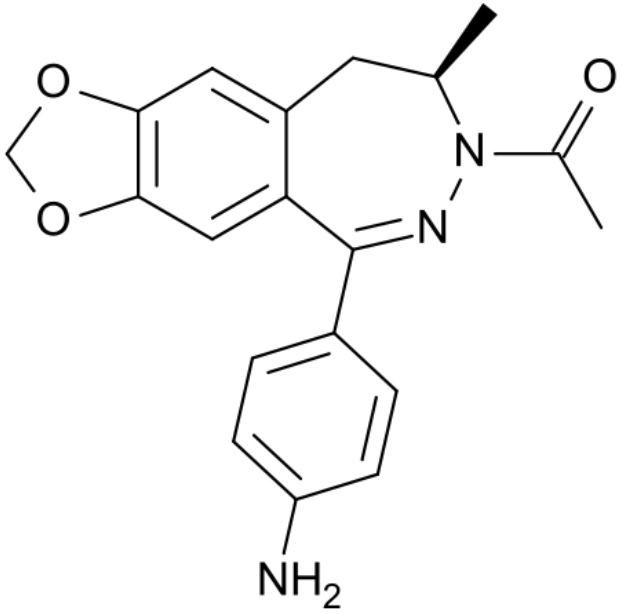
Eslicarbazepine – Advantages?

- **Once daily administration**
- **Possibly fewer adverse effects than OXC**
- **Incidence of hyponatremia may be lower**
- **May not exacerbate PGE compared to CBZ or PHT (??? Unpublished animal data)**
- **Many of the above will need validation in extended clinical use**

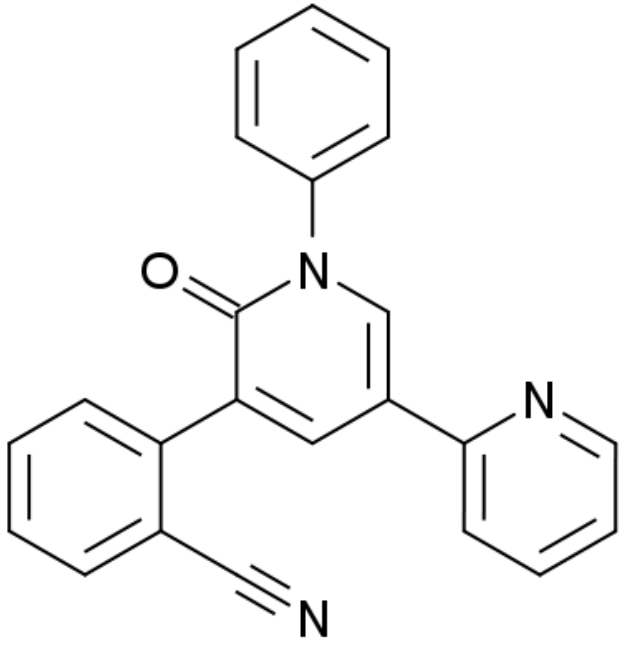
Perampanel



Topiramate



Talampanel



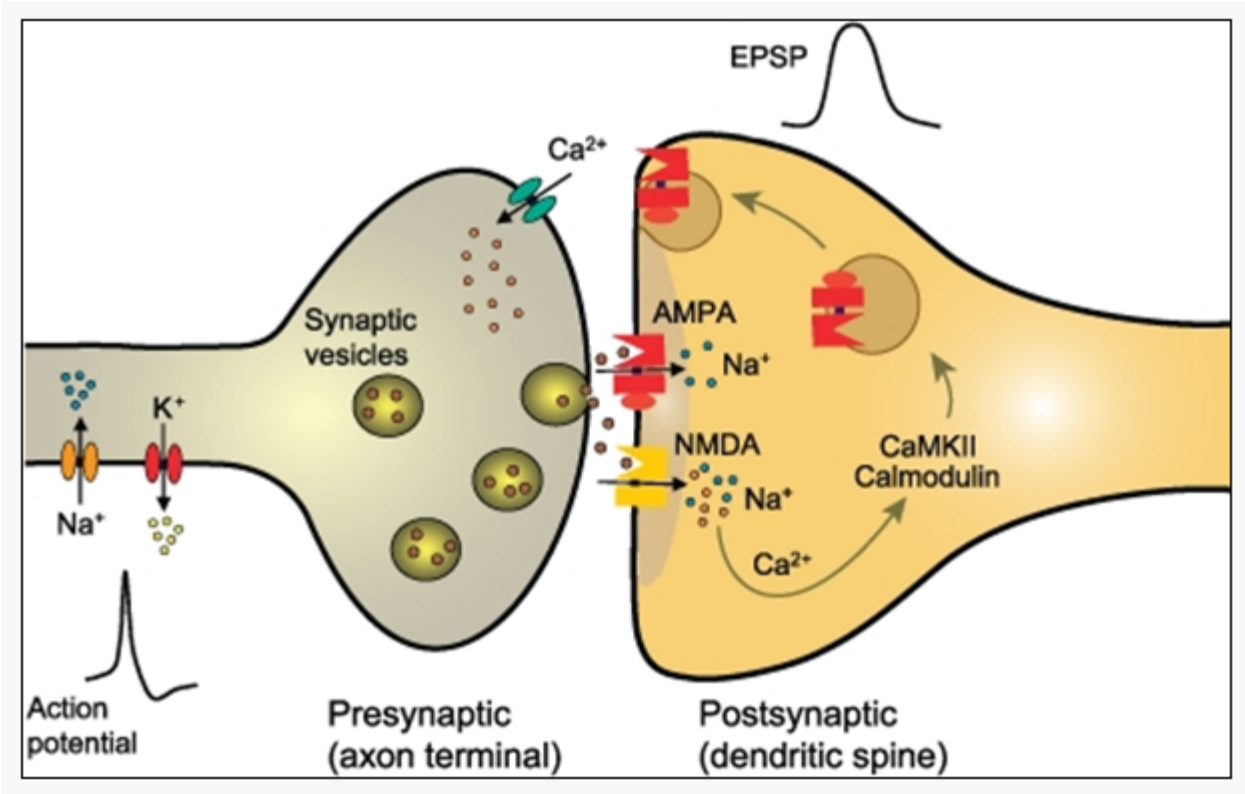
Perampanel

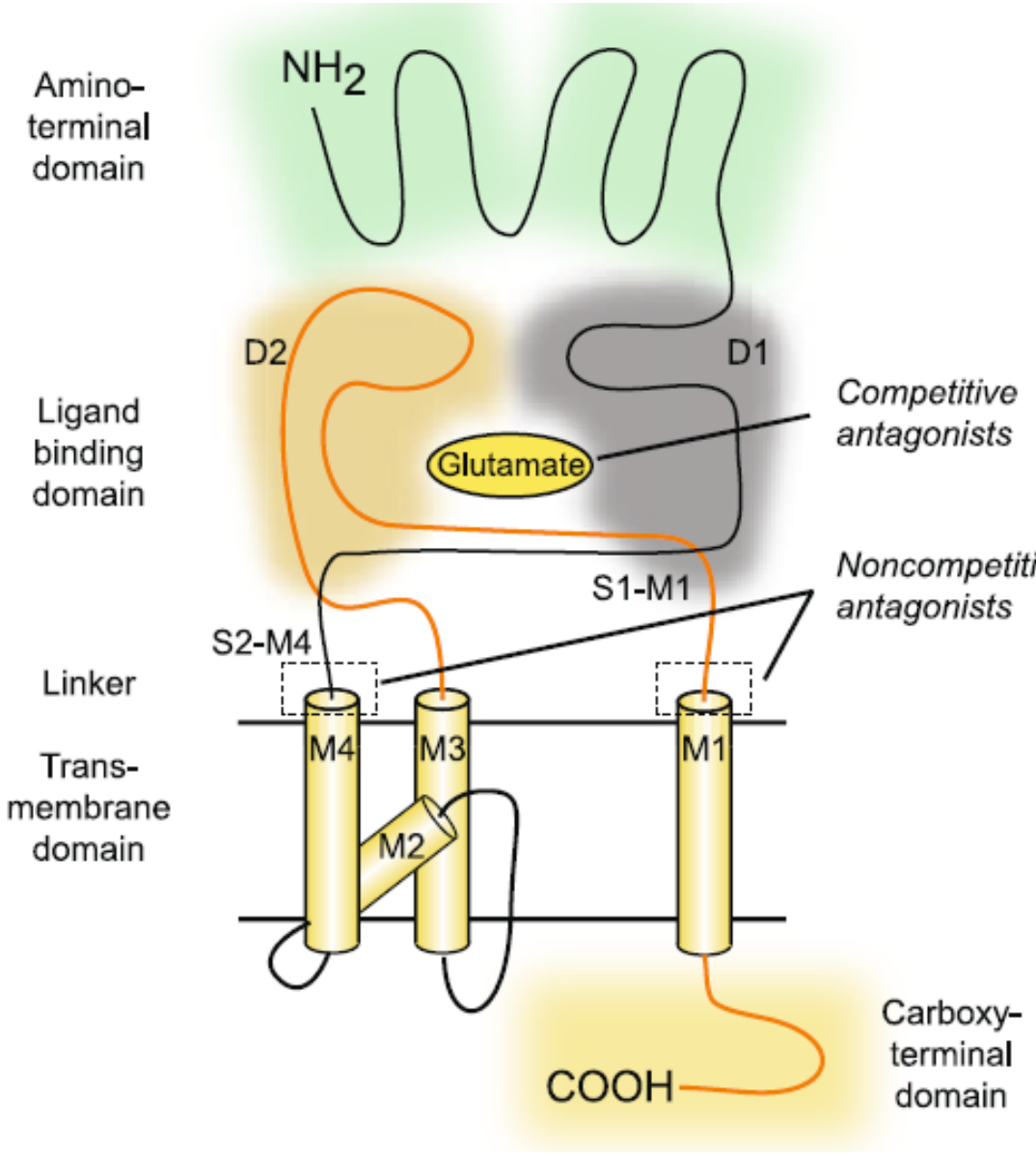
The Curious Recent History of AMPA-blockers

- **Talampanel**
- **Studied by Teva in failed studies for:**
  - **Malignant gliomas**
  - **Amyotropic Lateral Sclerosis**
- **Perampanel**
- **Studied by Eisai for Parkinson disease failed**
- **Epilepsy studies? US & Europe vs. Latin America**

Revisiting AMPA Receptors as an Antiepileptic Drug Target

Michael A. Rogawski





Talampanel
Perampanel

Perampanel

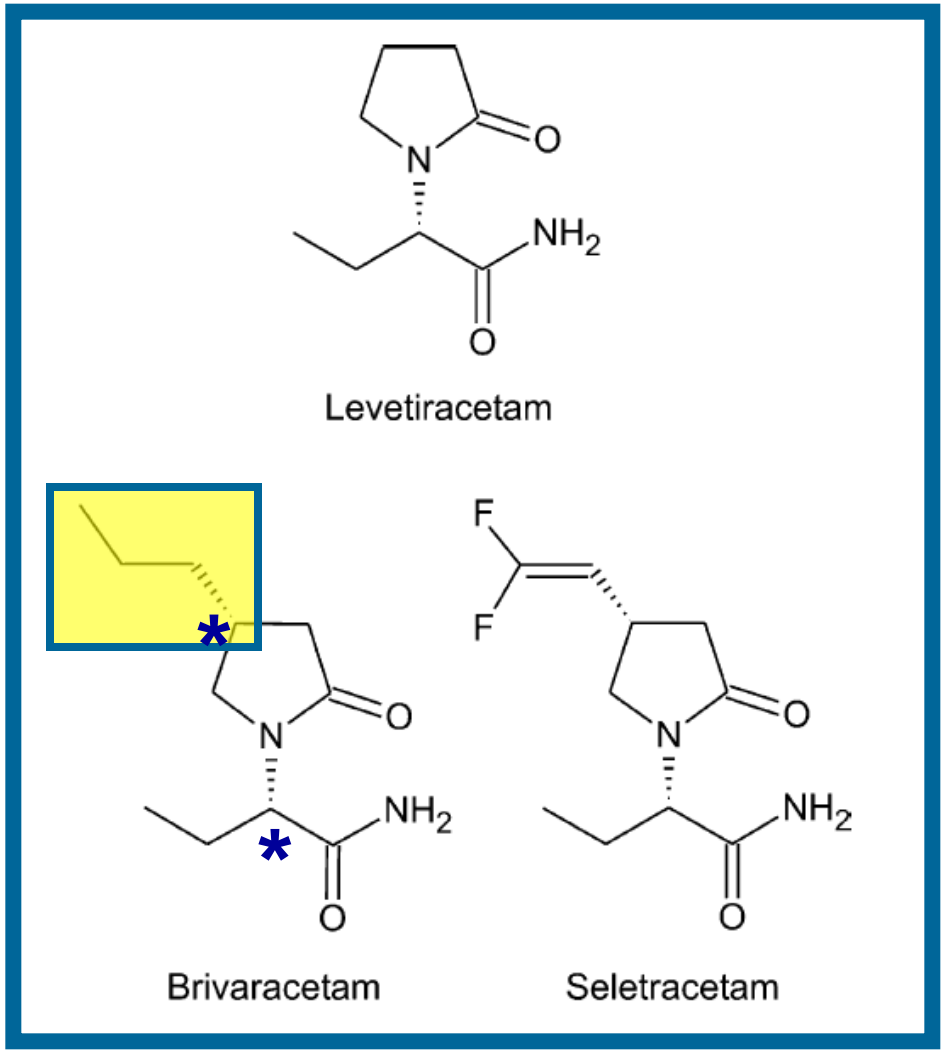
- **Rapid absorption**
- **Protein binding about 95%**
- **Half-life estimated at 70 hrs**
- **Once daily administration feasible**
- **Metabolism: hydroxylation by CYP3A4 and glucuronidation**

Perampanel Trials

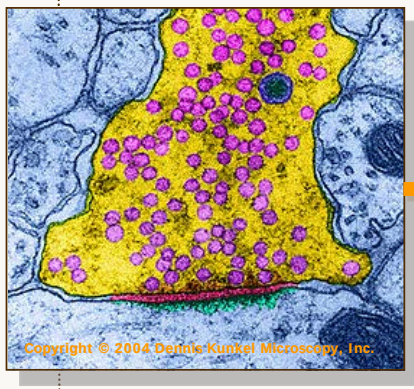
- **Phase II studies at 2, 4, 8, 10, and 12 mg/d**
- **Tolerated with some CNS side effects**
- **Phase III studies positive in US and Europe**
- **Did not differentiate in Latin American studies**
- **FDA submission expected this Summer**

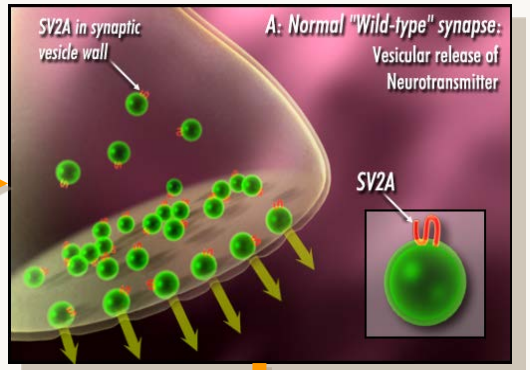
Brivaracetam

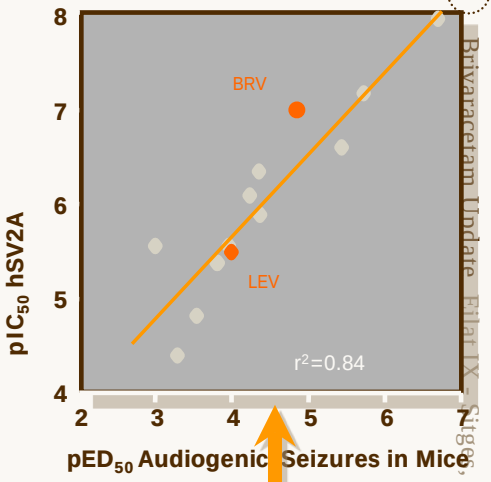
Rikelta™ - UCB

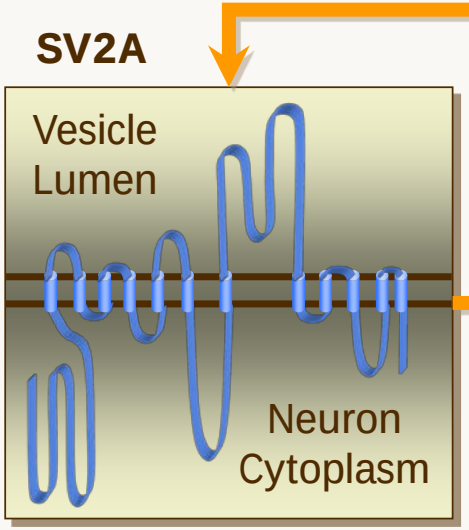

O
N
NH2
O
Levetiracetam
*
*
O
N
NH2
O
Brivaracetam
F
F
O
N
NH2
O
Seletracetam

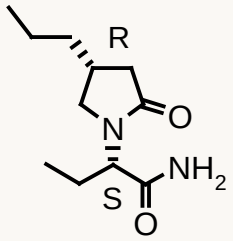
SV2A - a disease-relevant target for AEDs











Brivaracetam

Used with permission, Dennis Kunkel Microscopy, Inc.
Adapted from Lynch et al, PNAS 2004; 101:9861–6.

Mechanism of Action

SV2A (pKi)	7.1
Na^+ channel current (IC_{50} value [µM] and max. effect [%])	7 ~65%
HVA Ca^{2+} channel current (IC_{50} value [µM])	No effect up to 1 mM
LVA Ca^{2+} channel current (IC_{50} value [µM])	No effect up to 1 mM
GABA & glycine currents (IC_{50} value [µM])	No effect up to 100 µM
GABA/Glycine Zn2+ inhibition (IC_{50} value [µM])	0.1-1 µM

Epilepsy pharmacology

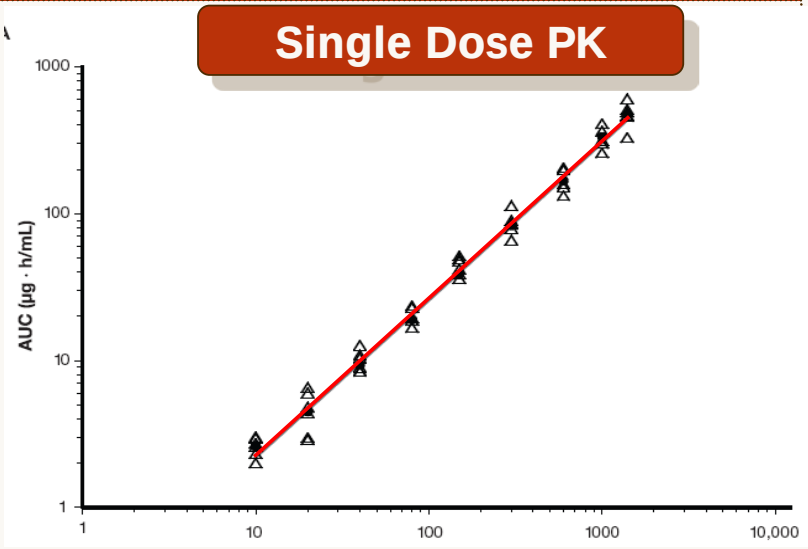
Models	ED50 (mg/kg)
Acute seizure	
MES (mice)	113
PTZ (mice)	30
Partial epilepsy	
6 Hz, 44 mA (mice)	4.4
Amygdala kindling (rats)	44
Corneal kindling (mice)	1.2
Generalized epilepsy	
Audiogenic Seizures (mice)	2.4
GAERS	2.6
Other models	
Post-hypoxic seizures/myoclonus (rats)	Abolished at 0.3 mg/kg
SSSE (rats)	Sz duration/cumulative sz time <5%of controls at 100 mg/kg

Matagne et al, Br J Pharmacol 2008
Tai and Truong, J Neural Transm 2007
Wasterlain et al, AES 2005, Abstract, Epilepsia 2005
UCB SA, Data on File

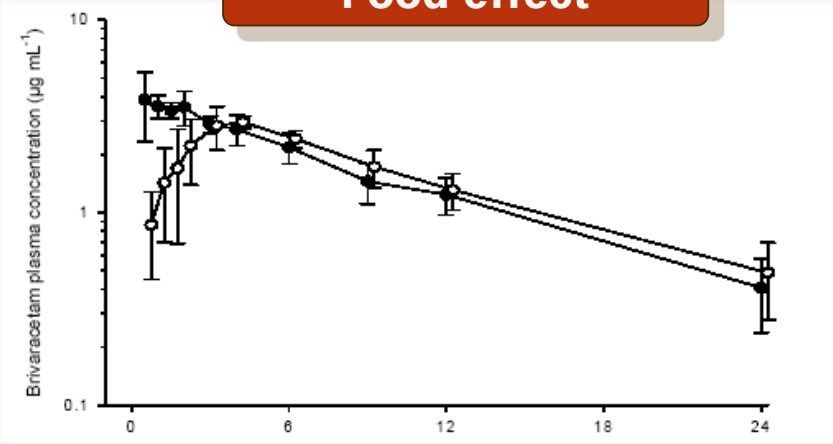
Pharmacokinetics: absorption / distribution

- Absorption
  - High bioavailability (~100%) with T_{max} <2hrs
  - T_{max} delayed / C_{max} reduced with high fat meal, no change in AUC
  - Linear PK across and beyond the therapeutic dose range
- Distribution
  - Volume of distribution close to total body water (0.52 l/kg)
  - Plasma protein binding <20%

Single Dose PK



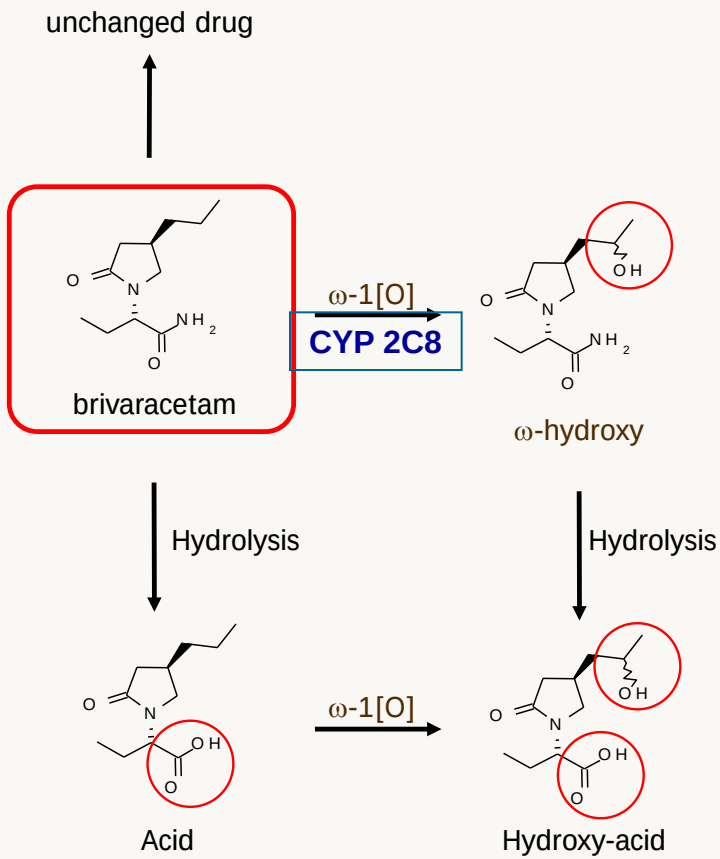
Food effect



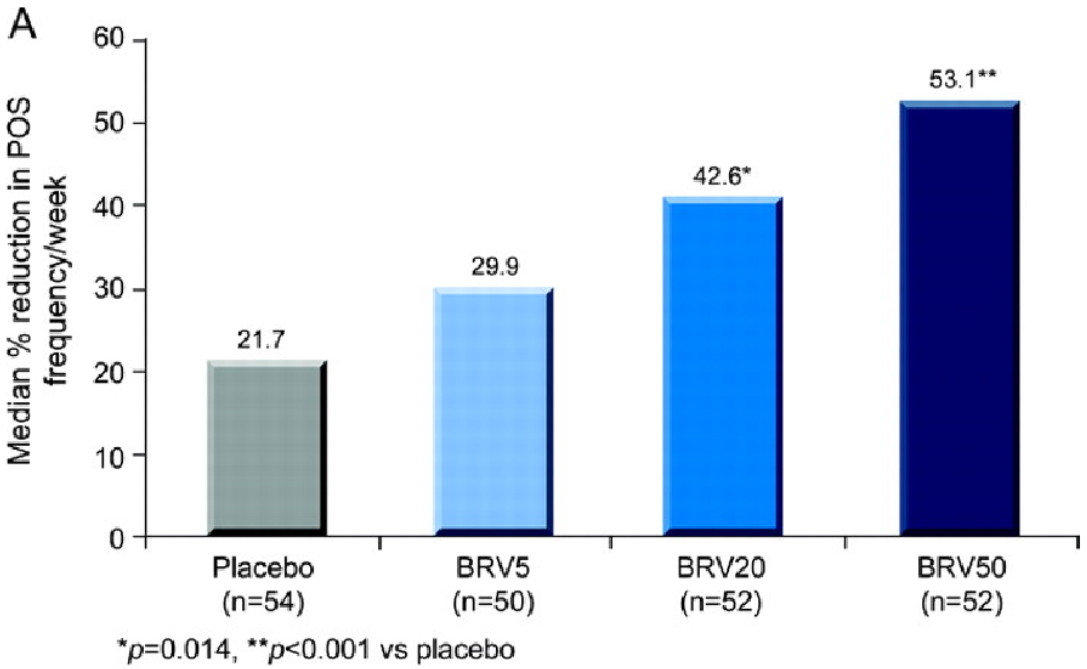
Sargentini-Maier et al, Br J Clin Pharmacol 2007
Sargentini-Maier et al, Drug Metab Dispos 2008

Major metabolic pathways

Urinary metabolites (% dose in 48 h)		
Parent	**9 %**	
Acid / conjugates	**38 %**	**inactive**
ω-hydroxy	**16 %**	**inactive**
Hydroxy-acid	**15 %**	**inactive**
Keto	**3.5 %**	**active**
Total identified	**89 %**	
Total radiocarbon	**92 %**	

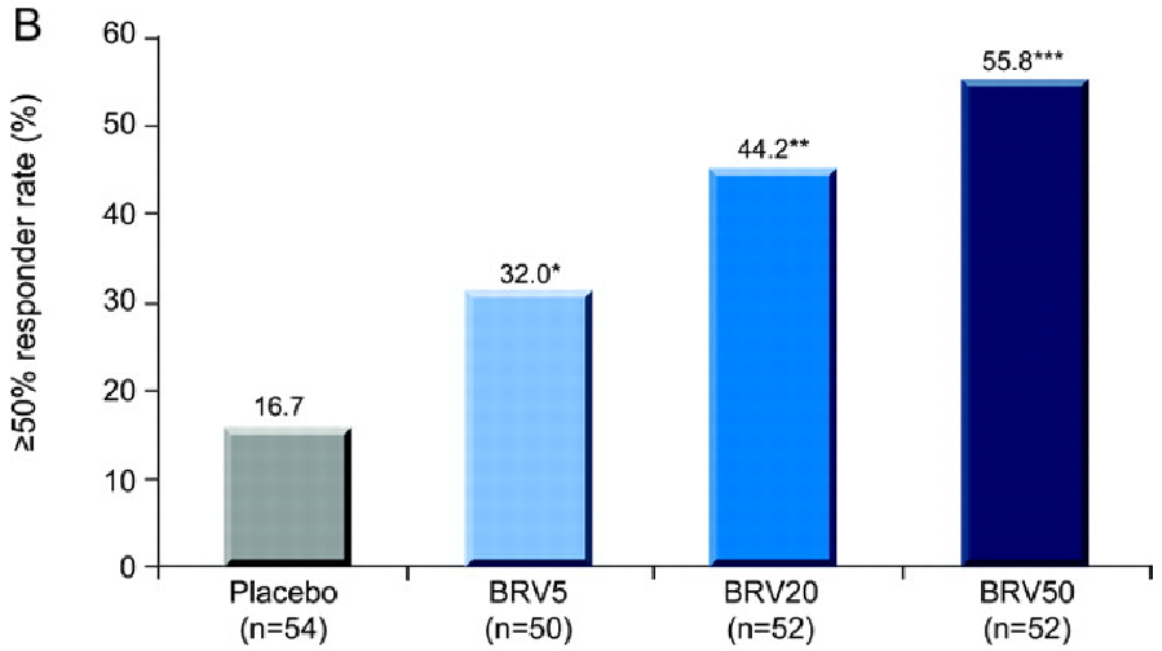


Sargentini-Maier et al, Drug Metab Dispos 2008



Phase II Data

French et al *Neurology* 2011



Phase II Data

French et al *Neurology* 2011

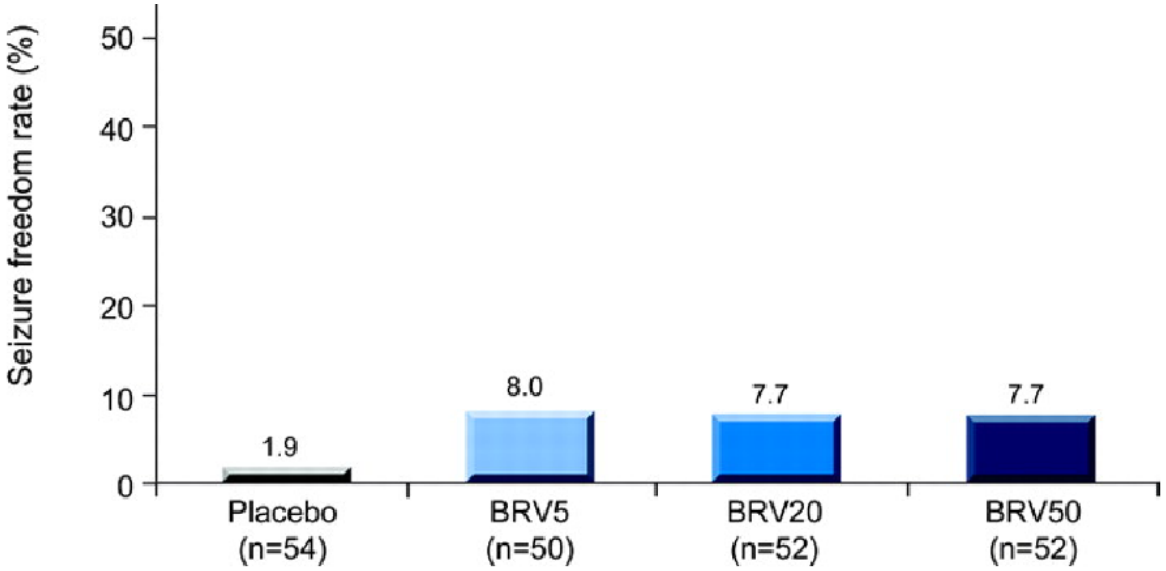


Table 3 Overall summary of TEAEs and TEAEs reported by ≥5% of patients in any treatment group (ITT population)[a]

	Placebo (n = 54)	BRV5 (n = 50)	BRV20 (n = 52)	BRV50 (n = 52)
At least 1 TEAE	29 (53.7)	26 (52.0)	29 (55.8)	28 (53.8)
Drug-related AEs	12 (22.2)	7 (14.0)	10 (19.2)	12 (23.1)
Headache	4 (7.4)	4 (8.0)	2 (3.8)	1 (1.9)
Somnolence	4 (7.4)	1 (2.0)	3 (5.8)	3 (5.8)
Influenza	4 (7.4)	4 (8.0)	0	1 (1.9)
Dizziness	3 (5.6)	1 (2.0)	0	4 (7.7)
Fatigue	2 (3.7)	0	2 (3.8)	3 (5.8)
Neutropenia	1 (1.9)	4 (8.0)	2 (3.8)	0
SAEs	0	0	1 (1.9)	0

Epilepsy Research (2010) 91, 74–83

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

Brivaracetam does not alter spatial learning and memory in both normal and amygdala-kindled rats

E.R. Detrait[a,*], K. Leclercq[a], W. Löscher[b], H. Potschka[b], I. Niespodziany[a], E. Hanon[a], R.M. Kaminski[a], A. Matagne[a], Y. Lamberty[a]

Epilepsia, 52(2):264–272, 2011
doi: 10.1111/j.1528-1167.2010.02746.x

FULL-LENGTH ORIGINAL RESEARCH

Neurocognitive effects of brivaracetam, levetiracetam, and lorazepam

*Kimford J. Meador, †Alan Gevins, ‡Philip T. Leese, §Christian Otoul, and *David W. Loring

*Neurology, Emory University, Atlanta, Georgia, U.S.A.; †San Francisco Brain Research Institute and SAM Technology, San Francisco, California, U.S.A.; ‡Quintiles, Overland Park, Kansas, U.S.A.; and §UCB Pharma, Braine-l'Alleud, Belgium

Conclusions

- In placebo controlled dose ranging studies in patients with refractory partial onset seizures brivaracetam has demonstrated very potent antiepileptic activity
- Phase II studies suggest 50 mg/d as the optimal dose
- A drug-drug interaction potential exists across the tested dose range
- BRV was well tolerated in the potential therapeutic dose-range
  - Low drop-out rate
  - AE rates on BRV not significantly different from placebo
- A phase 3 program with BRV as adjunctive therapy in patients with refractory partial onset seizures is ongoing

New and Pipeline AEDs

- **Of the AEDs discussed, many involve novel compounds and targets**
- **Others in the pipeline include variations of the old – new versions of CBZ, VPA, etc.**
- **Some “hiccups” in recent Phase III studies may reflect trends in studies more than the intrinsic properties of compounds**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Mattel Children's @ UCLA