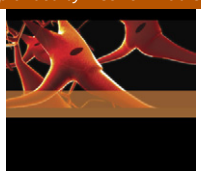
Epilepsy Research (2013) **103**, 2—30

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



REVIEW

Progress report on new antiepileptic drugs: A summary of the Eleventh Eilat Conference (EILAT XI)

Meir Bialer[a,*], Svein I. Johannessen[b], René H. Levy[c], Emilio Perucca[d], Torbjörn Tomson[e], H. Steve White[f]

[a] *Institute for Drug Research, School of Pharmacy and David R. Bloom Center for Pharmacy, Faculty of Medicine, Ein Karem, The Hebrew University of Jerusalem, 91120 Jerusalem, Israel*
[b] *The National Center for Epilepsy, Sandvika, and Department of Pharmacology, Oslo University Hospital, Oslo, Norway*
[c] *Department of Pharmaceutics and Neurological Surgery, University of Washington, Seattle, Washington, WA, USA*
[d] *Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, and National Institute of Neurology IRCCS C. Mondino Foundation, Pavia, Italy*
[e] *Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden*
[f] *Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, USA*

Received 13 September 2012; accepted 8 October 2012
Available online 4 December 2012

KEYWORDS
Antiepileptic drugs;
Drug development;
Epilepsy;
Pharmacology;
Clinical trials;
Conference

Summary The Eleventh Eilat Conference on New Antiepileptic Drugs (AEDs)-EILAT XI, took place in Eilat, Israel from the 6th to 10th of May 2012. About 100 basic scientists, clinical pharmacologists and neurologists from 20 countries attended the conference, whose main themes included ''Indications overlapping with epilepsy'' and ''Securing the successful development of an investigational antiepileptic drug in the current environment''. Consistent with previous formats of this conference, a large part of the program was devoted to a review of AEDs in development, as well as updates on AEDs introduced since 1994. Like the EILAT X report, the current manuscript focuses only on the preclinical and clinical pharmacology of AEDs that are currently in development. These include brivaracetam, 2-deoxy-glucose, ganaxolone, ICA-105665, imepitoin, NAX 801-2, perampanel and other AMPA receptor antagonists, tonabersat, valnoctamide and its homologue *sec*-propylbutylacetamide (SPD), VX-765 and YK3089. Since the previous Eilat conference, retigabine (ezogabine) has been marketed and four newer AEDs in development (NAX 810-2, SPD, tonabersat and VX-765) are included in this manuscript.

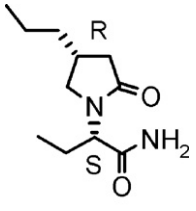
* Corresponding author. Tel.: +972 2 6758610; fax: +972 2 6757246.
E-mail address: bialer@md.huji.ac.il (M. Bialer).

0920-1211
http://dx.doi.org/10.1016/j.eplepsyres.2012.10.001

Contents

Brivaracetam (ucb34714)

Sarah Lu[a], Armel Stockis[b], Alain Matagne[b], Martin Johnson[a]
[a]UCB Pharma, Raleigh, NC, USA
[b]UCB Pharma, Braine-l'Alleud, Belgium



Brivaracetam

Introduction and rationale for development

Brivaracetam (UCB 34714) is a novel high-affinity synaptic vesicle protein 2A (SV2A) ligand (Kenda et al., 2004; Lynch et al., 2004). Brivaracetam also displays inhibitory activity at neuronal voltage-dependent sodium channels (Niespodziany et al., 2009; Zona et al., 2010). Brivaracetam is currently in Phase III development for epilepsy.

Pharmacology

The preclinical activity profile of brivaracetam in a wide range of animal models of focal and generalized seizures

Table 1 Anticonvulsant profile of investigational AEDs in mouse models.

Compound	Route	Time of test (min)	ED_{50}						TD_{50} (mg/kg)	In vivo activity in other model systems
			MES	s.c. PTZ	6 Hz, 22 mA	6 HZ, 32 mA	6 Hz, 44 mA	Audiogenic seizures		
Brivaracetam (UCB 34174)	i.p.	30	113	30	NT[4]	NT	4.4	2.4	55 (kindled mice)	Active in corneal kindled mouse (ED_{50}: 1.2 mg/kg), and on development of corneal kindling; active in phenytoin-resistant amygdala-kindled rat
2-Deoxy-D-glucose	i.p.	15—120	NT	NT	79.7	NT	NT	206	NA	
Ganaxolone	i.p.	30	29.7	3.5	NT	6.3	NT	NT	33.4	Active against bicuculline- and aminophylline-induced seizures (ED_{50}'s: 4.6 and 11.5 mg/kg, respectively)
ICA-105665	i.p.	30	8.1	13	NT	9.8	9.4	0.91	34	Elevates i.v. PTZ seizure threshold
Imepitoin (AWD 131—138 or ELB 138)	i.p.	30	94.	17	NT	NT	NT	2.6 (DBA); 5.0 (Frings)	176	Active in mouse and rat models of anxiety including innate fear and fear induced by open and high areas and light stimulation (e.g., elevated maze, light-dark chamber, social interaction test) at doses as low as 3 mg/kg, i.p. and p.o.
NAX 810-2	i.p.	60	>20	NT	NT	2.5	5.9	9.2	>32	Active in corneal kindled mouse (ED_{50}: 7.4 mg/kg); active in mouse formalin and carrageenan models of inflammatory pain
Perampanel (E2007)	i.p.	60	1.6	NT	NT	NT	NT	0.47	NT	
	p.o.	60	NT	0.94	NT	2.1	2.8	NT	1.8	
SPD	i.p.	15	71	62	NT	27	NT	20 (Frings)	*88*	Blocks minimal clonic seizures induced by s.c. picrotoxin and bicuculline and secondarily generalized seizures in the corneal kindled mouse with ED_{50}'s of 17, 94, and 39 mg/kg, respectively.
Tonabersat	i.p.	15—240	4.7	>250	NT	>5.0	NT	0.12	>250	Inhibits tonic but not myoclonic seizures induced by PTZ
VCD (rac)	i.p.	15	58	32		37	67		77	
(2S,3S)-VCD	i.p.	15	132	69	25	33	80		128	
(2R,3S)-VCD	i.p.	15	119	67	19	48	67		127	
YKP 3089	i.p.	15	9.8	28.5	11	17.9	16.5	NT	58	Anxiety; HI-induced lethality; s.c. picrotoxin-induced clonus

ED_{50}, median effective dose in mg/kg; TD_{50}, median toxic dose in mg/kg;HI, Hypoxia Ischemia; i.p., intraperitoneal; i.v., intravenous; p.o., per os; MED, median effective dose; NT, not tested; MES, maximal electroshock seizure; sc, subcutaneous; PTZ, pentylenetetrazol; SPD, *sec*-Butyl-propylacetamide; VCD, valnoctamide.

and epilepsy (Table 1) (Matagne et al., 2008) suggests potential broad spectrum activity with a potency and efficacy superior to levetiracetam. Data suggest that brivaracetam has anticonvulsant and disease-modifying effects against refractory self-sustaining status epilepticus in rats, and that brivaracetam is effective at lower doses when combined with low-dose diazepam (Wasterlain et al., 2009). The preclinical profile of brivaracetam has been summarized previously (Bialer et al., 2010).

Doses of brivaracetam that exert anticonvulsant effects in amygdala-kindled rats were devoid of negative impact on learning and memory performance in normal and amygdala-kindled rats evaluated in the Morris water maze (Detrait et al., 2010). Furthermore, brivaracetam did not affect long-term potentiation in hippocampal slices. These findings suggest that brivaracetam would not be expected to have detrimental effects on hippocampal-dependent cognitive function in patients with epilepsy.

A strong functional correlation between in vitro SV2A binding affinity and anticonvulsant potency in animal models of both focal and generalized epilepsy has been established (Kaminski et al., 2008). Consistent with these findings, ex vivo binding studies demonstrated that the time- and dose-dependency of brivaracetam binding to brain SV2A was correlated with seizure protection in audiogenic mice (Gillard et al., 2011). Brivaracetam was more potent and faster than levetiracetam in achieving maximal SV2A occupancy and seizure protection.

Simulations based on in vitro and ex vivo binding experiments in mice predicted that, at 50 mg/day, brivaracetam should occupy more than 80% of SV2A in patients with epilepsy (Gillard et al., 2011). Similarly, human brain concentrations of brivaracetam predicted using physiological models, combined with mouse ex vivo binding pharmacokinetic/pharmacodynamic modeling, estimated that brivaracetam 50 mg/day would occupy approximately 50% of SV2A in human brain (Brochot et al., 2010).

Toxicology

Brivaracetam demonstrated low acute oral toxicity in mice, rats, and dogs. Toxicology data have been summarized previously (Bialer et al., 2009).

Clinical pharmacokinetics

Brivaracetam is well absorbed from the gastrointestinal tract and shows linear pharmacokinetics following single oral doses up to 600 mg (Sargentini-Maier et al., 2007; von Rosenstiel and Perucca, 2009). The extent of binding to plasma proteins is small ($\leq$20%) (Sargentini-Maier et al., 2008a) and the volume of distribution is in the order of 0.6 L/kg (Rolan et al., 2008). The half-life of brivaracetam is about 8 h (Rolan et al., 2008; Sargentini-Maier et al., 2007).

Brivaracetam is eliminated primarily by biotransformation through hydrolysis of the acetamide group and CYP2C19-mediated hydroxylation (Sargentini-Maier et al., 2008a; von Rosenstiel and Perucca, 2009). The metabolites are pharmacologically inactive and do not accumulate in plasma to any significant extent (von Rosenstiel and Perucca, 2009; Sargentini-Maier et al., 2008a). After administration of a radiolabelled dose of brivaracetam, over 95% of the radioactivity is recovered in urine within 72 h, of which less than 10% is represented by unchanged drug (Rolan et al., 2008; Sargentini-Maier et al., 2008a). The CYP2C19 genetic polymorphism has only a modest influence on brivaracetam pharmacokinetics, with a 30% decrease in clearance of brivaracetam being reported in subjects with inactive *2 or *3 mutations (Stockis et al., 2011). As a result, no dose adjustments are considered necessary in subjects bearing CYP2C19 mutations (Bialer et al., 2010).

In population pharmacokinetic studies using data from patients included in Phase II and III trials, plasma brivaracetam levels were not found to be significantly affected by gender, age, race, dose, renal function (creatinine clearance), and concomitant AEDs, except for enzyme inducing AEDs which were associated with increased brivaracetam clearance (Bialer et al., 2010). The pharmacokinetic profile of brivaracetam in the elderly (Sargentini-Maier et al., 2008b) and in subjects with severe renal impairment not requiring dialysis (creatinine clearance < 15 mL/min, $n = 6$; 15—29 mL/min, $n = 3$) (Sargentini-Maier et al., 2012) did not differ to a major extent from those found in non-elderly healthy subjects. In subjects with severe hepatic impairment (Child-Pugh Class C), exposure to brivaracetam is increased by up to 50—60% compared with healtly control subjects (Stockis et al., 2008).

Drug interactions

In adjunctive-therapy trials in patients with epilepsy, brivaracetam treatment was found not to cause significant changes in the plasma concentrations of carbamazepine, lamotrigine, levetiracetam, monohydroxycarbazepine (licarbazepine), phenobarbital, phenytoin, topiramate, valproic acid, or zonisamide. The concentrations of the 10,11-epoxide metabolite of carbamazepine were increased at brivaracetam doses of $\geq$50 mg/day, and at doses of 100—150 mg/day it approached a concentration of 3.0 μg/mL, which is close to the upper limit of the range found in subjects not receiving brivaracetam. These data suggest that monitoring for potential carbamazepine-associated adverse effects is indicated when brivaracetam is added on to the therapeutic regimen of patients stabilized on high doses of carbamazepine (Bialer et al., 2010).

At a dose of 100 mg/day, brivaracetam did not modify the pharmacokinetics of the components of an oral contraceptive steroid (30 μg ethinylestradiol and 150 μg levonorgestrel) (Stockis et al., 2009). In the same study, the oral contraceptive did not affect trough brivaracetam concentrations.

Efficacy data

Phase IIb studies

Two randomized, double-blind, placebo-controlled adjunctive-therapy Phase IIB studies were completed in patients (16—65 years old) with partial-onset seizures (POS) uncontrolled despite treatment with up to 2 concomitant AEDs. In study N01193 (NCT00175825), which assessed brivaracetam doses of 5, 20, and 50 mg/day, the percent reduction over placebo in baseline-adjusted POS

frequency (primary efficacy endpoint) achieved statistical significance for the 50 mg/day dose ($p = 0.004$) (French et al., 2010). Secondary efficacy analysis (≥50% responder rate and median percent reduction from baseline in POS frequency/week) provided supportive evidence for the efficacy of brivaracetam 20 mg/day. In Study N01114 (NCT00175929), which assessed brivaracetam doses of 50 and 150 mg/day, no statistically significant difference between brivaracetam and placebo was found for the primary efficacy endpoint (Van Paesschen et al., 2007). However, a clear differentiation from placebo was found on several secondary efficacy endpoints for both brivaracetam doses.

Phase III fixed-dose studies

Two randomized, double-blind, placebo-controlled adjunctive-therapy Phase III trials were conducted in adults (16—70 years old) with refractory POS receiving up to 2 concomitant AEDs. In both trials, brivaracetam was administered b.i.d. for 12 weeks without titration and the primary efficacy endpoint was percent reduction over placebo in baseline-adjusted POS frequency. Statistical comparisons were conducted in a pre-defined order starting with 50 mg/day for both studies.

In study N01253 [NCT00464269], which assessed doses of 5, 20 and 50 mg/day in a total of 400 randomized patients, statistical significance versus placebo ($p = 0.02$) was reached for the primary efficacy endpoint for the 50 mg/day dose, but not for the lower doses (Biton et al., 2009). In study N01252 [NCT00490035], which investigated doses of 20, 50 and 100 mg/day in 399 patients, statistical significance versus placebo on the primary efficacy endpoint ($p = 0.261$) was not achieved for the predefined initial comparison at 50 mg/day (Biton et al., 2009). Statistical significance, however, was achieved for 100 mg/day at the nominal 0.05 significance level, a finding which was supported by the secondary efficacy analyses (≥50% responder rate and median percent POS frequency reduction) at the 100 mg/day dose (Bialer et al., 2010).

Phase III flexible-dose study

A prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial (N01254 [NCT00504881]) was conducted in adults (16—70 years) with uncontrolled POS or generalized seizures despite treatment with 1—3 concomitant AEDs (Kwan et al., 2010). Brivaracetam was initiated at 20 mg/day and increased stepwise to a maximum of 150 mg/day at the investigator's discretion. Four hundred and eighty patients were randomized (359 brivaracetam, 121 placebo); 431 (89.8%) with POS and 49 (10.2%) with primary generalized seizures. During the 16-week treatment period, median percent reduction from baseline in POS frequency/week was 26.9% for brivaracetam versus 18.9% for placebo ($p = 0.070$); 50% responder rates were 30.3% for brivaracetam versus 16.7% for placebo ($p = 0.006$). Preliminary data suggest potential efficacy of adjunctive brivaracetam in adults with generalized epilepsy. Of the 49 patients with primary generalized seizures, 34/36 (94.4%) who received brivaracetam and 13/13 (100%) who received placebo completed the 16-week treatment period (Kwan et al., 2010). Seizure types experienced during the baseline period were tonic-clonic (21 brivaracetam, 8 placebo), absence (12 brivaracetam, 6 placebo), tonic (6 brivaracetam, 1 placebo), myoclonic (5 brivaracetam, 0 placebo), clonic (1 brivaracetam, 2 placebo) and atonic (1 brivaracetam, 1 placebo). Median baseline generalized seizure days/week was similar in both groups (brivaracetam 1.42; placebo 1.47). Exploratory efficacy analysis showed that during the treatment period the median generalized seizure days/week decreased to 0.63 on brivaracetam and remained relatively stable on placebo (1.26). Median percentage reductions from baseline and ≥50% responder rates in generalized seizure days/week were higher on brivaracetam (42.6% and 44.4%, respectively) compared with placebo (20.7% and 15.4%, respectively). Three (8.3%) patients on brivaracetam were seizure-free during the entire treatment period compared with none on placebo.

Tolerability and adverse event profile

In all studies conducted to date, brivaracetam (5—150 mg/day) showed a favourable safety and tolerability profile (Brodsky et al., 2007; Biton et al., 2009). In the two Phase III fixed-dose studies, a similar proportion of patients on brivaracetam (range: 56.6—79.0%) reported at least one treatment-emergent adverse event (TEAE) compared with placebo (range: 53.0—70.4%). In all treatment arms, the proportion of completers was high (range: 84.5—94.0% for brivaracetam versus 92.0—94.9% for placebo) and few patients discontinued treatment due to TEAEs (range: 4.0—8.2%, for brivaracetam versus 2.0—4.0% for placebo). These favourable safety and tolerability results were confirmed by the Phase III flexible-dose trial, in which a similar proportion of brivaracetam and placebo patients reported at least one TEAE (66.0% vs 65.3%) (UCB, data on file). Completion rates were 90% for brivaracetam and 91.7% for placebo, and discontinuation rates for TEAEs were 6.4% for brivaracetam and 5.8% for placebo (Kwan et al., 2009). The majority of TEAEs reported in the Phase III trials were mild to moderate. Those reported most frequently were headache (range: brivaracetam 6.0—18.2%, placebo 9.0—19.8%), somnolence (range: brivaracetam 6.1—16.8%, placebo 4.1—7.1%), dizziness (range: brivaracetam 5.0—15.8%, placebo 5.0—9.2%), and fatigue (range: brivaracetam 3.0—13.0%, placebo 2.0—4.1%) (Biton et al., 2009; Kwan et al., 2009).

In a well controlled QT safety study in healthy subjects, brivaracetam (75 and 400 mg b.i.d.) was found not to affect cardiac repolarization (Rosillon et al., 2008).

Ongoing clinical studies

A Phase III, randomized, double-blind, placebo-controlled, fixed-dose study (N01358, NCT01261325) in adults with POS inadequately controlled with 1—2 concomitant AEDs has been initiated to evaluate the efficacy and safety of brivaracetam 100 and 200 mg/day as adjunctive treatment.

Three Phase III, open-label, multicenter, flexible-dose (up to a maximum dose of 150 mg/day) long-term follow-up trials (N01125, NCT00175916; N01199, NCT00150800;

N01315, NCT00761774) are ongoing to evaluate the long-term safety/tolerability and maintenance of efficacy of brivaracetam in patients with epilepsy who had participated in previous trials.

A multicenter, open-label, adjunctive-therapy randomized trial (N01258, NCT01405508) is ongoing to investigate the safety and tolerability of brivaracetam 200 mg/day administered intravenously as an infusion or bolus in adults with POS or generalized seizures.

A multicenter, open-label trial (N01263, NCT00422422) is ongoing to evaluate the steady state pharmacokinetics, safety, and preliminary efficacy of adjunctive brivaracetam in children with any type of epilepsy aged from at least 1 month to 16 years. The dose of brivaracetam is adjusted by body weight to achieve similar exposure to adults at doses of 50—200 mg/day.

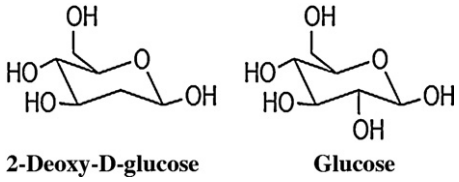
Acknowledgements

The authors thank Laurent Turet (UCB Pharma) for critical review and co-ordination of the manuscript preparation. Jenny Stewart, MSc, (QXV Communications, Macclesfield, UK) provided assistance in the manuscript preparation, which was funded by UCB Pharma.

2-Deoxy-D-glucose

Thomas Sutula[1,4], Elizabeth Hutchinson[1], Paul Rutecki[1], Elizabeth Meyerand[2,3], Carl E. Stafstrom[1]

Departments of Neurology[1], Medical Physics[2], and Bioengineering[3], University of Wisconsin, Madison WI, and NeuroGenomeX, Inc.[4], Madison, WI



2-Deoxy-D-glucose **Glucose**

Introduction

2-Deoxy-D-glucose is a glucose analogue and glycolytic inhibitor. The anticonvulsant and disease-modifying antiepileptic properties of 2-deoxy-D-glucose were defined in animal models during investigations aimed at elucidating the mechanisms underlying the efficacy of the ketogenic diet. 2-Deoxy-D-glucose is currently in preclinical development for the treatment of epilepsy. More detailed information on this compound can be found in the reports of previous Eilat conferences (Bialer et al., 2009 and 2010).

Pharmacology

Glycolytic inhibition by 2-deoxy-D-glucose

2-Deoxy-D-glucose undergoes activity-dependent uptake into cells through glucose transporters. It then undergoes phosphorylation to 2-deoxy-D-glucose-6-phosphate, which cannot undergo isomerization to fructose-6-phosphate, thereby preventing subsequent steps of glycolysis.

Anticonvulsant profile in experimental models

2-Deoxy-D-glucose displays both *acute* and *chronic* mechanisms of action in experimental in vivo models. In the mouse in vivo 6 Hz model, 2-deoxy-D-glucose acutely protected against seizures evoked by 6 Hz 22 mA corneal stimulation at doses of 75—300 mg/kg i.p. with an ED_{50} of 79.7 mg/kg (Table 1). The time to peak action was 15 min at a dose of 75 mg/kg i.p. and 1 h at a dose of 100 mg/kg i.p. 2-Deoxy-D-glucose protected against audiogenic seizures evoked in Frings mice 2 h after administration of 220—250 mg/kg i.p. The ED_{50} was 206.4 mg/kg, and the time to peak effect was 2 h at these doses. 2-Deoxy-D-glucose also demonstrated evidence of anticonvulsant activity against seizures evoked by pentylentetrazol at 30 min after administration at doses of 200—400 mg/kg i.p. and 50—400 mg/kg per os (p.o.), but overall the results were not sufficient to calculate an ED_{50} or a time to peak effect. There was no protective effect of 2-Deoxy-D-glucose against MES in rats when tested 15 min to 4 h after administration of 100—200 mg/kg p.o. (Stafstrom et al., 2009).

2-Deoxy-D-glucose displays in vivo chronic ''disease-modifying'' antiepileptic effects consisting of 2-fold slowing of progression of repeated seizures evoked by perforant path or olfactory bulb kindling (Garriga-Canut et al., 2006; Stafstrom et al., 2009). These effects have been observed at doses of 37.5—50 mg/kg administered 30 min prior to perforant path stimulation. In addition, effects on disease progression have been observed when 2-Deoxy-D-glucose was administered immediately after, and approximately 10 min after, evoked seizures (Sutula and Franzoso, 2008). This novel ''post-seizure'' action is most likely based on enhanced activity-dependent uptake of 2-Deoxy-D-glucose into those brain regions with increased energy demand; e.g., hyperactive neural circuits as occurs during seizures. This novel action of 2-Deoxy-D-glucose represents a potential opportunity for ''post-seizure'' anticonvulsant administration for the treatment of seizure clusters and status epilepticus. 2-Deoxy-D-glucose also reduces the latency to seizures evoked by pilocarpine and kainic acid (Lian et al., 2007).

Neuroprotective action in experimental traumatic brain injury (TBI)

2-Deoxy-D-glucose displays neuroprotective effects against the progressive structural damage in the frontal cortex or dorsal hippocampus after TBI induced by controlled cortical impact (CCI) model using Sprague Dawley rats. 2-Deoxy-D-glucose also displays neuroprotective effects following TBI in unique strains of rats bred for their susceptibility or resistance to kindling progression evoked by perforant path stimulation of the hippocampus (Hutchinson et al., 2010). After CCI, serial in vivo magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) performed over a 6 month period demonstrate progresively increasing ventricle volume, increasing hippocampal diffusion abnormalities, and evolving patterns of hippocampal and corpus callosum anisotropy. Brief treatment with 2-Deoxy-D-glucose (40 mg/kg at the time of injury and 250 mg/kg/day for 2 weeks) did not modify the severity of the initial injury.

However, this treatment with 2-Deoxy-D-glucose did reduce the progression of the observed structural damage that was assessed by MRI and DTI measures over the 6 month post-TBI observation period. Distinct patterns of structural abnormalities were observed in kindling-susceptible and kindling-resistant rat strains. Studies are underway to evaluate the possibility that treatment with 2-Deoxy-D-glucose might also have favorable effects on long-term consequences such as post-traumatic epilepsy and post-traumatic stress disorder.

Toxicology

Cardiac toxicity and increased incidence of pheochromocytomas were reported with chronic administration of 2-deoxy-D-glucose at doses of 0.25—0.4% of dietary intake (corresponding to total daily exposures of ~125—200 mg/kg/day). Reduced life-span was also reported at a daily dietary intake of 0.4% (Minor et al., 2010). Cardiotoxicity was accompanied by myofibrillar vesicular alterations consistent with autophagy, and subtle evidence of myofibrillar vesicular alterations was also reported at dietary exposures of about 20—25 mg/kg/day. As discussed in more detail in a previous report (Bialer et al., 2010), the reversibility and significance of these observations are currently under investigation.

Experiments in rodents using the Morris water maze test found no effects on spatial memory at doses nearly 30 times greater than the minimum dose required to reduce kindling progression (Bialer et al., 2010). Further, no effects on spatial memory at 15 min after treatment with 50 or 250 mg/kg, i.p. were observed. Dose-dependent effects in the open field tests were reported at doses of 250 mg/kg i.p., but not at doses of 50 mg/kg i.p. (Stafstrom et al., 2007; Ockuly et al., 2012).

Pharmacokinetics and cerebral uptake mechanisms

Intravenous 2-Deoxy-D-glucose (40 mg/kg) in normal human volunteers induces regional increases in cerebral blood flow in cingulate gyrus, sensorimotor cortex, superior temporal cortex, occipital cortex, basal ganglia, limbic system, and hypothalamus (Elman et al., 1999), which are likely to explain the shorter latencies of onset of behavioral seizures in response to intravenous administration of convulsants reported in some rodent studies (Gasior et al., 2010). In Phase I studies in human cancer patients, the half-life of of 2-Deoxy-D-glucose during 14 days of once daily oral dosing at 45 mg/kg was 7.3—8.2 h (Stein et al., 2010).

Tolerability and safety in clinical studies

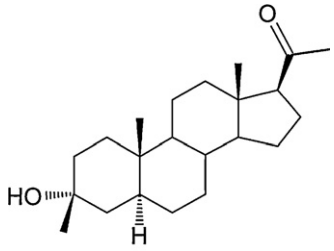
2-Deoxy-D-glucose has been evaluated in Phase I/II cancer trials and reported to be well tolerated in dose escalation studies up to 64 mg/kg/day for 5 to 8 weeks (Raez et al., 2007, Singh et al., 2005). In a recent open label multiple dose Phase I study in patients with prostate cancer, dose-limiting reversible toxicity of grade 3 asymptomatic QTc prolongation was seen in two patients treated at a dose of 60 mg/kg, but no evidence of QTc prolongation was observed at doses of 45 mg/kg (Stein et al., 2010).

Planned studies

Further preclinical toxicology and pharmacokinetic studies are planned. Planned clinical studies include, in addition to conventional trial designs in a variety of seizure types, protocols for administration during seizure clusters as well as status epilepticus (Bialer et al., 2010).

Ganaxolone

G. Farfel[a], J. Tsai[a], K. Shaw[a*], V. Nohria[b], M. A. Rogawski[c]
[a]Marinus Pharmaceuticals, Inc, Branford, CT, USA; [b]Mercer University, Atlanta, GA, USA; [c]Department of Neurology, School of Medicine, University of California, Davis, Sacramento, CA, USA; *Deceased.



Ganaxolone

Introduction

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is the 3β-methyl analog of the neurosteroid allopregnanolone, a metabolite of progesterone. Like other related neurosteroids, ganaxolone is not believed to have nuclear hormone activity and cannot be biotransformed to metabolites with such activity. Two Phase II clinical trials have shown that ganaxolone treatment significantly reduces mean weekly seizure frequency (WSF) in adults with POS when compared to placebo, with good tolerability and safety at doses of 1500—1625 mg/day. New data from a 104-week open-label extension of a 10-week double-blind randomized study in adults with POS show efficacy is sustained long-term while maintaining the tolerability profile seen in earlier studies. No new safety concerns were identified during extended treatment.

Pharmacology

Neurosteroids including ganaxolone have two separate effects on $GABA_A$ receptors: at low concentrations they potentiate the action of GABA and at higher concentrations directly activate the receptor; these actions occur at two distinct sites on the receptor complex that do not correspond with the modulatory sites of benzodiazepines and barbiturates (Hosie et al., 2006). Unlike benzodiazepines that are specific for synaptic $GABA_A$ receptors, neurosteroids modulate both synaptic and extrasynaptic $GABA_A$ receptors and their modulatory action is of greater magnitude for

extrasynaptic $GABA_A$ receptor isoforms that contain a δ subunit (Herd et al., 2007). These isoforms have decreased expression in rodent models of temporal lobe epilepsy (Joshi et al., 2011).

Ganaxolone has anticonvulsant and protective activity in diverse rodent seizure models, including clonic seizures induced by the chemoconvulsants pentylenetetrazol, bicuculline, flurothyl, *tert*-butylbicycloorthobenzoate, aminophylline; limbic seizures in the 6 Hz model; amygdala and cocaine-kindled seizures; and corneal kindled seizures (see Bialer et al., 2010 and Reddy and Rogwski, 2012). In female amygdala kindled mice, ganaxolone produced a dose-dependent suppression of behavioral and electrographic seizures (Reddy and Rogawski, 2010). In chronically treated rats, tolerance does not occur to the anticonvulsant activity of ganaxolone (Reddy and Rogawski, 2000).

Toxicology and safety pharmacology

There was little evidence of target organ or systemic toxicity associated with either single- or multiple-dose treatment with ganaxolone (6 months in rat and 1 year in dog) (Marinus Pharmaceuticals, data on file). Hematologic or serum chemistry parameters were not altered, and no anatomic changes were observed. Ganaxolone was not teratogenic in rats and mice and did not significantly affect the development of offspring. Specifically, there were no effects on fertility or embryofetal development in rats at doses of 40 mg/kg/day, and there were no effects on peri-postnatal development except a slight decrease in body weight (up to 6%) at this dose. In a neonatal rat study at a dose of 50 mg/kg/day, no adverse effects were obtained. In mice, no effects on embryofetal development were demonstrated at a higher dose of 300 mg/kg/day. Ganaxolone also showed no potential for mutagenicity or carcinogenicity. In studies performed to assess central nervous system behavioral effects in mice, ganaxolone showed less of an interaction with ethanol than did valproic acid in the hanging wire-mesh test of ataxia and ganaxolone affected cognitive function in an animal passive-avoidance paradigm only at doses causing ataxia. Dosing in toxicology and safety studies was limited only by sedation and, in rodents, by liver weight gain associated with CYP induction.

Clinical pharmacokinetics

Ganaxolone is a lipophilic, high clearance compound. After administration of a single dose of ganaxolone, plasma levels rapidly decline due to metabolism and tissue distribution followed by a longer elimination phase. Multiple dosing with the ganaxolone capsule formulation achieved steady state within 48 h when ganaxolone was dosed 200, 400, or 600 mg b.i.d. with a standard meal or snack, and the effective half-life was 7—10 h. Mean peak plasma concentrations (C_{max}) and $AUC_{(0-12)}$ at steady-state were close to dose-proportional (Marinus Pharmaceuticals, data on file; Bialer et al., 2010).

Because of its aqueous insolubility, formulation-dependent food effects have been observed where absorption is higher in the fed than in the fasted state. To enhance its bioavailability, ganaxolone has been formulated in a nanosized particulate suspension and a nanosized particulate capsule. The capsule formulation at a 400 mg dose gave approximately 2-fold higher AUC and 3-fold higher Cmax levels in a high-fat fed state compared to the fasted state. Based on C_{max}, AUC and trough levels at steady state, 400 to 600 mg b.i.d.dosing of the ganaxolone capsule formulation provides comparable ganaxolone exposure to 500 mg t.i.d. dosing of the suspension formulation (Marinus Pharmaceuticals, data on file; Bialer et al., 2010).

Drug interactions

Results of a midazolam interaction study (1042-0402) in normal volunteers with the capsule formulation of ganaxolone dosed 400 mg b.i.d. for 12 days indicated that ganaxolone is not a CYP3A4 inhibitor and showed low or no potential to induce CYP3A4 metabolism (<30% change in midazolam pharmacokinetic parameters comparing pre-ganaxolone dosing versus concomitant ganaxolone dosing at steady state). This result is consistent with in vitro studies showing that ganaxolone has low potential to affect the disposition of other drugs. However, data from the 1042-0600 study did show effects of concomitant administration of strong CYP3A4 inducers (carbamazepine and phenytoin) on ganaxolone pharmacokinetics (approximately 40% higher ganaxolone clearance than coadministration with other AEDs). In vitro studies have shown that the CYP3A4 inhibitor (ketoconazole) blocks the metabolism of ganaxolone (Marinus Pharmaceuticals, data on file).

Clinical efficacy

Prior to being acquired by the current sponsor, ganaxolone was studied in three open-label pediatric studies and a double-blind randomized pre-surgical study in adults and children with seizure disorders (Laxer et al., 2000; Kerrigan et al., 2000; Pieribone et al., 2007). A double-blind randomized trial in infantile spasms (West Syndrome) under the current sponsor was reported previously (Bialer et al., 2010).

The current sponsor has also completed a double-blind, placebo-controlled study of ganaxolone (1042-0600) as adjunctive therapy in adults with POS, which was originally reported in the summary from Eilat X (Bialer et al., 2010); additional information from a follow-on open label extension study is reported here. In the double-blind study, adult subjects aged 18—69 years, with POS with or without secondary generalization refractory to conventional AEDs were randomized in a 2:1 ratio to receive ganaxolone ($n = 98$) or placebo ($n = 47$). Baseline seizure frequency per 28 days was 6.5 in the ganaxolone group and 9.2 in the placebo group. Mean duration of illness was 25 years, and 75% of the study population took 2 or 3 concomitant AED medications. After an 8-week baseline period, participants were titrated to 1500 mg/day (3 divided doses with a 300 nm nanosized ganaxolone suspension formulation) over a 1—2-week period and maintained at that dose for an additional 8 weeks. Downward dose adjustments were permitted if necessary because of tolerability.

In this double-blind study, ganaxolone treatment produced an 18% decrease in mean weekly seizure frequency, compared with a 2% increase for placebo over the 10-week treatment period ($p = 0.014$). Responder rates (proportions of subjects with greater than 50% reduction in seizures during the maintenance phase) were 26% for the ganaxolone group versus 13% for placebo ($p = 0.057$). Of 131 completers, 94% entered a 104-week open-label extension study.

The objective of the open-label extension was to evaluate the long-term safety, tolerability and efficacy of ganaxolone at a target dose of 1500 mg/day. Subjects were dosed for a mean of 274 days (39 weeks). Most subjects (89%) reached 1500 mg/day and 72% were maintained on this dose before tapering. Thirty-eight subjects (30%) completed more than 52 weeks of treatment before the study was terminated for administrative reasons.

Efficacy in the open-label extension study was reported as the median and mean change in weekly seizure frequency at endpoint compared to the baseline from the beginning of the double-blind study. For all subjects at endpoint, median and mean improvement in weekly seizure frequency were 23% and 14% respectively. Subjects previously randomized to ganaxolone ($n = 79$) in the double-blind study had median improvement in weekly seizure frequency of 14% at endpoint while those randomized to placebo had median weekly seizure frequency improvement of 35% ($n = 41$). Twenty-four percent of all subjects met responder criteria (50% improvement) at endpoint, 29% having originally been randomized to placebo and 22% having been randomized to ganaxolone.

Tolerability and safety in clinical studies

More than 900 adults and children have been exposed to ganaxolone in Phase I and Phase II studies. The drug was found to be generally safe and well-tolerated at the doses used (for Phase II studies, up to 1875 mg/day in adults and up to 54 mg/kg/day in infants). Tolerability and safety in children and infants has been described previously (Bialer et al., 2009, 2010).

In the double-blind, randomized trial described above (study 1042-0600) in 147 adults, TEAEs reported by at least 5% of patients and at least twice as common in the ganaxolone group versus the placebo group were dizziness, fatigue (both 16% versus 8%) and somnolence (13% versus 2%). Seven percent of ganaxolone subjects and 6% of placebo subjects discontinued treatment due to TEAEs. There were no deaths during the study, and serious TEAEs occurred in 5% of ganaxolone versus 8% of placebo treated subjects. No clinically important trends were seen in clinical laboratory tests, electrocardiograms (ECGs), vital signs or body weight.

Ganaxolone continued to be safe and well tolerated in the open-label extension study. TEAEs reported in greater than 10% of subjects were headache (21%), convulsion (16%), fatigue (16%), fall (14%), nasopharyngitis (14%), dizziness (13%), contusion (12%), nasal congestion (10%). Serious TEAEs were reported in 14% of subjects, and 8% were not related to the underlying disease. Median weight change at endpoint was less than 0.5 kg. There were no trends of important changes in chemistry, hematology, vital signs, physical and neurological examinations, or ECGs. No new safety concerns were identified during extended treatment with ganaxolone for up to 104 weeks.

Conclusions and ongoing studies

Data from a 10-week, double-blind, placebo-controlled study of ganaxolone (1500 mg/day) as adjunctive therapy of adults with treatment-refractory POS as well as data from the 104-week open-label extension study show the drug to be efficacious, safe and well-tolerated. Importantly, there was no evidence of weight gain with extended exposure. The most recent clinical trial results in conjunction with several previous studies support development of ganaxolone for the adjunctive treatment of POS. Ganaxolone represents a new, mechanistically novel AED. The clinical information available indicates that the drug is safe in all infants, pediatrics and adults. Data from non-clinical studies suggest that ganaxolone may have low risk for use in pregnancy. Therefore, ganaxolone has the potential to provide important clinical benefit to subgroups of epilepsy patients who currently have limited treatment options.

Neurosteroids have also been proposed for study in a broad range of neurological and psychiatric conditions apart from epilepsy. Therapeutic utility may result from $GABA_A$ receptor modulation as well as effects on neuronal and glial differentiation, myelination, inflammation, and because of neuroprotective properties. Potential additional uses of ganaxolone are being explored through proof-of-concept studies in posttraumatic stress disorder and fragile X syndrome, which are currently in progress.

ICA-105665 (PF-04895162)

R. Roeloffs[1], D. S. Krafte[1], A. C. Gerlach[1] and G. C. Rigdon[2]
[1]Neusentis (a Pfizer Inc., Research Unit), Durham, NC USA
[2]Halcyon Drug Development, Inc., Wake Forest, NC USA

Introduction

ICA-105665 (PF-04895162) is a highly selective opener of neuronal Kv7 (KCNQ) potassium channels; the molecular components of the slow voltage-gated M current (Table 2). Its chemical structure has not yet been disclosed. A more detailed description of the preclinical pharmacology and toxicology may be found in Bialer et al., 2010. Clinical data have previously been presented in abstract form at the American Epilepsy Society meetings in 2009 and 2010 (Hetherington et al., 2009; Rigdon et al., 2009; Risner et al., 2009, and Biton et al., 2010).

Pharmacology

Anticonvulsant activity in animal models

In vivo, ICA-105665 protects against maximal electroshock (MES), scMetrazol, (scMet) 6 Hz and kindled seizures (Tables 1 and 3). In tests conducted by the sponsor, ED_{50}s were $\leq$1 mg/kg for s.c. pentylentetrazol and MES. The compound did not affect the ability of rats to maintain position on a rotorod at doses up to the highest dose tested (i.e., 100 mg/kg po).

Table 2 Anticonvulsant profile of investigational AEDs in rat models.

Compound	Route of administration	Time of test (min)	ED_{50} (mg/kg)				TD_{50} (mg/kg)	In vivo activity in other disease model systems actions
			MES	s.c. PTZ	Kindled rat (i.e., corneal, amygdala, hippocampal)	Spike-wave seizure model (GAERS, Lethargic mouse, GHB rat, WAG/Ri rat)	Behavioral toxicity (e.g., rotarod, observational, etc.)	
Brivaracetam	i.p.	60	N/A	N/A	44 mg/kg (amygdala)	2.6 mg/kg (GAERS)	163 mg/kg (Kindled rats) 177 mg/kg (GAERS)	Self-sustaining status epilepticus model (perforant path stimulation); diabetic and CCI models of neuropathic pain; and post-hypoxic myoclonus
	p.o.	60	N/A	N/A	45 mg/kg (amygdala)	N/A	N/A	
2-Deoxy-D-glucose	p.o.	15—240	No effect at doses up to 200 mg/kg	Partial protection at doses upto 400 mg/kg, p.o.	NT	NT	NT	Delays the acquisition of kindling induced by perforant path or olfactory bulb stimulation at doses of 37.5—50 mg/kg; neuroprotective in the CCI model of TBI
Ganaxolone	i.p.	30	7.8	N/A	4.5 (corneal)	NT	14.2	
ICA-105665	p.o.	60	11	Max. 25% protection at 160 mg/kg	NT	NT	>500	Increases latency to tonic extension in MES and tonic-clonic seizures in sc PTZ (ED50's: 0.9 and 0.7 mg/kg, respectively); active in lamotrigine-resistant kindled rat
	i.p.		N.T.	N.T.	<3.8 mg/kg in hippocampal rat against expression of seizures	N.T.		
Imepition (AWD 131—138 or ELB 138)	p.o.		21	16	Increases afterdischarge threshold at doses as low as 1 mg/kg; completely inhibits secondary generalization at 20 mg/kg, i.p.	Effective in WAG rat model of generalized absence at 3 mg/kg, p.o. (98% suppression of SWD observed at 30 mg/kg p.o.	>400	Blocks SWD induced by 25 mg/kg, i.p. dose of PTZ at 3 mg/kg, p.o.; Increases the PTZ seizure threshold in dogs by 33—59% after repeated oral administration of 5 mg/kg; prolongs kindling acquisition in amygdala kindled rat when administered prior to kindling stimulation

NAX 810-2	i.p.	0.25—24 h	NT	NT	NT	NT	>4.0 mg/kg	Elevates threshold for mechanical allodynia in rat sciatic nerve ligation model of neuropathic pain at 4.0 mg/kg
Perampanel (E2007)	p.o.	60	N.T.	N.T.	Increases afterdischarge threshold and decreases afterdischarge duration at 10 mg/kg; decreases behavioral seizure score and motor seizure duration at 5 and 10 mg/kg	No effect on SWD at doses between 1 and 10 mg/kg	9.14	
SPD	i.p.	15	20	62	19 mg/kg fully expressed hippocampal kindled rat secondarily generalized seizures SNL-ED_{50} = 49 mg/kg	NT	49	
	p.o,	60	29	82 and 18 (30 min)		NT	131	
Tonabersat	p.o.	15—240	2.1	>250	Inactive in hippocampal and LTG-resistant kindled rat	NT	>500	Dose-dependently elevates threshold for tonic extension seizures induced by electroshock and s.c. PTZ; blocks high K + bursting in rat hippocampal slices; suppresses neuron-glial communication via gap junctions; inhibits acute and chronic inflammation-induced expression of connexin-26
VCD	p.o.	60	29 (racemate) 34 ((2R,3S)-VCD) 64 ((2S,3S)-VCD)	54. (racemate) 11 ((2R,3S)-VCD) 33 ((2S,3S)-VCD)	SNL-ED_{50} = 29 mg/kg	NT	>100	Racemate and isomers of VCD were found to be active against tactile allodynia in Cheung model of neuropathic pain
(2R,3S)-VCD	i.p.	60	34	11	SNL-ED_{50} = 34 mg/kg			
(2S,3S)-VCD			64	33	SNL-ED_{50} = 65 mg/kg			

Table 2 (*Continued*)

Compound	Route of administration	Time of test (min)	ED_{50} (mg/kg)				TD_{50} (mg/kg)	In vivo activity in other disease model systems actions
			MES	s.c. PTZ	Kindled rat (i.e., corneal, amygdala, hippocampal)	Spike-wave seizure model (GAERS, Lethargic mouse, GHB rat, WAG/Ri rat)	Behavioral toxicity (e.g., rotarod, observational, etc.)	
YKP-3098	i.p.	15—240	NT	13.6	16.4 (hippocampal)	NT	38.9	Bennett and Chung models of chronic pain; Lithium-pilocarpine-induced status epilepticus
	p.o.	60	1.9	40% at 25	NT	NT	50.7	

i.p., intraperitoneal; i.v., intravenous; p.o., per os; MED, minimum effective dose; ED_{50}, median effective dose in mg/kg; TD_{50}, median toxic dose in mg/kg; MES, maximal electroshock seizure; sc, subcutaneous; PTZ, pentylenetetrazol; GAERS, genetic absence epileptic rat of Strasborg; N/A, not available; NT, not tested; CCI, controlled cortical impact, SPD, *sec*-Butylpropylacetamide; VCD, valnoctamide.

ICA-105665 was also tested by the Anticonvulsant Screening Project of the National Institute of Neurological Disorders & Stroke (ASP-NINDS, NIH). In mice, ICA-105665 was active in the MES, s.c. pentylentetrazol, 6 Hz psychomotor seizures, and audiogenic seizure tests. ICA-105665 elevated seizure threshold in the i.v. pentylenetetrazol assay. In rats, ICA-105665 did not produce signs of toxicity by the minimal motor impairment test at p.o. doses up to 500 mg/kg. It protected against MES-induced tonic extension seizures and was active in the hippocampal kindled rat model of POS. ICA-105665 was also active in the lamotrigine-resistant amygdala kindled rat model of pharmacoresistant epilepsy).

Mechanism of action

ICA-105665 opens cloned human neuronal Kv7 channels with EC50's of 0.3 μM (Kv7.2/7.3), 1.5 μM (Kv7.3/7.5) and 3.3 μM (Kv7.4). ICA 105665 did not interact with a variety of other ion channels, including the cardiac ion channels.

Toxicology

Safety pharmacology, 6 month rodent and 9 month non-rodent toxicity, as well as reproduction toxicity and genotoxicity studies required to meet International Conference on Harmonization (ICH) guidelines have been completed. Common findings at the higher doses in rodents have included decreased body weight gain and food consumption. In rodents and non-human primates, common clinical signs at the higher doses have included tremors, ataxia and hypoactivity.

Clinical pharmacokinetics

In healthy volunteers, ICA-105665 was well-tolerated following single oral doses up to 400 mg and multiple doses up to 600 mg/day (300 mg b.i.d.). The compound is highly bound (>99%) to plasma proteins, primarily albumin. Mean half-life values after oral administration ranged from 5 to 9.5 h Pharmacokinetics were linear after single and repeated doses, with area under the plasma concentration-time curve (AUC) and C_{max} values increasing approximately in proportion to dose. In 14 patients with epilepsy treated with 100 and 200 mg b.i.d. for 7 days, the mean half-life of ICA-105665 was similar to that found in healthy volunteers.

Drug interactions

Formal drug interaction studies have not been conducted. ICA-105665 at concentrations up to 30 μM (highest concentration tested) did not inhibit CYP enzymes or P-glycoprotein mediated transport, and studies conducted using fresh human hepatocytes indicate it is unlikely to induce liver enzymes.

Early Phase II study

To establish that ICA-105665 penetrates the blood-brain barrier and engages neuronal Kv7 channels, its ability to

reduce the photoparoxysmal EEG response was investigated in epilepsy patients with photosensitivity, using standardized methods (Kasteleijn-Nolst Trenité et al., 1996). Cohorts of 4—6 subjects (100, 200, 400 and 500 mg single dose) were tested, with a single subject being tested at 600 mg (ClinicalTrials.gov identifier: NCT00979004). Subjects were exposed to photic stimulation (2—60 flashes per second) 1—28 h after a single oral dose of placebo on Day 1 and ICA-105665 on Day 2. A single blind design was used; investigators and sponsor, but not subjects, were aware of treatment assignment. Decreases in the photosensitivity range (defined as a reduction in the standard photosensitivity range of at least 3 frequency steps at three or more hourly measurements after dosing, compared to the time-matched assessments on Day 1) occurred in 1of 4 subjects at 100 mg, 2 of 4 subjects at 400 mg, and 4 of 6 subjects at 500 mg The single subject that received 600 mg experienced a serious TEAE (see below) before undergoing photic stimulation. One of the tested subjects had a significant reduction in photoparoxysmal responses after a 100 mg dose and a complete abolishment of response 2 h after a 400 mg dose. The duration of response appeared to increase with dose. One patient in the 400 mg cohort and 2 patients in the 500 mg cohort maintained partial suppression of photosensitivity for >20 h

Tolerability and adverse event profile

Three Phase I studies focused on safety and pharmacokinetic parameters demonstrated good tolerability and potential for b.i.d. dosing without titration. In these studies, healthy volunteers tolerated single doses up to 400 mg and multiple doses up to 600 mg/day for 7 days; subjects with epilepsy tolerated 400 mg/day in 2 divided doses for 7 days. There were no dose-limiting toxicities, severe or life-threatening TEAEs, serious TEAEs, or discontinuations due to TEAEs, nor were there important trends or changes from baseline for clinical laboratory, vital signs, ECG, or physical examination findings. The most common TEAE in subjects who received ICA-105665 was headache. Other commonly reported TEAEs were generally CNS-related, including dizziness and somnolence. Dizziness appeared to be the first TEAE related to treatment.

In the Phase II study in photosensitive epilepsy, single doses of ICA-105665 ranging from 100 to 400 mg were well tolerated. The 500 mg dose was associated with TEAEs (especially dizziness) in most subjects and was defined as the maximum tolerated dose. A single subject with juvenile myoclonic epilepsy and a history of generalized tonic-clonic seizures received a single 600 mg dose of ICA-105665 and experienced a brief tonic-clonic seizure, and the study was terminated. The patient recovered uneventfully and the role of ICA-105665 in the event was not clear.

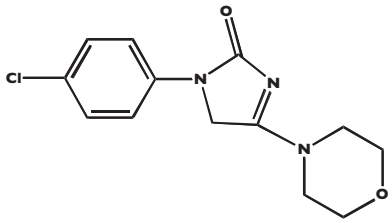
Planned studies

With the acquisition of Icagen by Pfizer, Inc., ICA-105665 is now formally part of the Pfizer portfolio and future clinical studies are being planned by the new project team.

Imepitoin

W. Löscher

Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine, Hannover, Germany



Imepitoin (AWD131-138 or ELB138)

Imepitoin (AWD 131—138 or ELB 138; 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one) is a new chemical entity that was previously presented at the EILAT IV and V conferences (Bialer et al., 1999, 2001). It was developed in the 1990s from a series of imidazolinones by Asta Medica and Arzneimittelwerk Dresden (AWD; later Elbion, Radebeul, Germany) (Rostock et al., 1998a). Furthermore, it was tested in the NINDS-sponsored Anticonvulsant Screening Project (ASP). Imepitoin was selected for further development because of its broad spectrum of anticonvulsant activity, high therapeutic index, and its efficacy in tests predictive for anxiolytic effects. It underwent Phase I clinical studies, but further clinical development for humans was suspended. However, interesting findings in dogs (see below) led Boehringer Ingelheim (Germany) to the decision to develop imepitoin as a new AED for canine epilepsy.

Pharmacology

Anticonvulsant activity in animal models

Imepitoin is active in primary screening tests for anticonvulsant activity in mice and rats using the maximal electroshock test (MES) and supramaximal stimulation with chemical convulsants such as pentylenetetrazol and bicuculline. Audiogenic clonic seizures in genetic models of epilepsy are potently inhibited, with ED_{50} values of 2.6 mg/kg i.p. in DBA/2 mice and 5.0 mg/kg, i.p. in Frings mice. In addition, imepitoin elevates the chemically-induced seizure threshold in the i.v. pentylenetetrazol test in mice. It also increases the pentylenetetrazol-induced seizure threshold in dogs after single doses and after prolonged oral treatment with 5 or 40 mg/kg b.i.d. (Löscher et al., 2004). In the MES threshold test in mice, imepitoin elevates the threshold for tonic hindlimb extension after i.p. and p.o. doses, starting at 30 and 50 mg/kg, respectively (Rostock et al., 1998a; Tober et al., 1998, 1999; Bialer et al., 1999). Imepitoin also exerts pronounced anticonvulsant effects in models for partial onset seizures. In fully amygdala-kindled rats, the threshold for induction of afterdischarges is increased dose dependently, with significant effects being already detectable at 1 mg/kg i.p., the lowest dose tested. Starting at 10 mg/kg i.p., imepitoin inhibits seizure severity after electrical stimulation at the elevated afterdischarge threshold current, whereas secondary generalization of the evoked kindled seizure is completely inhibited at 20 mg/kg i.p. Repeated treatment once daily with imepitoin during kindling

Table 3 Proposed mechanisms of action of investigational AEDs currently in development.

Compound	Proposed mechanism(s) of action
Brivaracetam	Binds to SV2A (IC_{50} = 0.08 μM) and inhibits voltage-dependent sodium channels (IC_{50} = 7 μM; max. effect: 65%)
2-Deoxy-D-glucose	Inhibits glycolysis; suppresses in vitro burst discharges induced by high potassium, 4-aminopyridine, bicuculline, and the mGluR1 agonist DHPG; blocks kindling acquisition by repressing expression of BDNF and TrKB
Ganaxolone	Directly activates and allosterically modulates $GABA_A$ receptors at $GABA_A$ receptors containing a δ subunits
ICA-105665	Selective activator of neuronal KCNQ (Kv7) potassium channels
Imepitoin (AWD 131—138 or ELB 138)	Low-affinity partial agonist at the benzodiazepine (BZD) recognition site of the $GABA_A$ receptor
NAX 810-2	Enhances galanin receptor neurotransmission by preferential activation of GalR2 receptors
Perampanel (E2007)	Non-competitive antagonist of AMPA-mediated glutamate receptors
sec-Butyl-propylacetamide (SPD)	Unknown
Tonabersat	Novel brain-specific binding site: suppresses neuron-glial communication via gap junctions; inhibits acute and chronic inflammation-induced expression of connexin-26
Valnoctamide (VCD)	Inhibits *myo*-inositol-1-phosphate synthase, unknown anticonvulsant and antiallodynic mechanism of action
VX-765	Anti-inflammatory; selective and reversible inhibitor of interleukin-converting enzyme
YKP 3089	Unknown

SV2A, synaptic vesicle protein 2A; IC50, inhibitory concentration to produce 50% inhibition; μM, micromolar; mGluR1, metabotropic glutamate receptor subtype 1; AMPA, (α-amino-3-hydroxy-5-5methyl-4-isoxazole propionic acid; BDNF, brain-derived neurotrophic factor; TrKB, tyrosine kinase B (high-affinity catalytic receptor for several neurotrophins including BDNF and neurotrophin 3 and 4); Nav, sodium channel isoform; $GABA_A$, γ-aminobutyric acid receptor; N-type, neuronal voltage-sensitive calcium channel; P/Q-type, purkinje/Q-type voltage-sensitive calcium channel; L-type, long-lasting type of voltage-sensitive calcium channel; SPD, *sec*-Butyl-propylacetamide; VCD, valnoctamide.

acquisition delays significantly the development of generalized motor seizures at 20 and 30 mg/kg i.p. Imepitoin decreases the number and duration of spontaneous spike-wave discharges in WAG rats, a model for absence epilepsy already at 3 mg/kg p.o., the lowest dose tested. After administration of 30 mg/kg p.o., spikes and waves are almost completely suppressed (98% inhibition of number and duration of discharges). In addition, imepitoin at a dose of 3 mg/kg p.o. inhibits the number and total duration of spikes and waves induced by i.p. administration of 25 mg/kg pentylentetrazol (Tober et al., 1999).

During repeated administration, no evidence of tolerance (i.e. no reduction of anticonvulsant activity) has been found in rodents and dogs, even when very high doses were given (Rostock et al., 1998b; Tober et al., 1998; Löscher et al., 2004). In particular, during 29 days of oral treatment at 100 mg/kg in mice, no decrease in the effect on the MES threshold was observed. In further experiments in mice, activity in the MES test was not reduced after administration of 100 mg/kg i.p. b.i.d. for 5 days. In the MES test with supramaximal stimulation in rats, no change in anticonvulsant activity was seen after administration of 28 and 100 mg/kg p.o. for 5 days (Rostock et al., 1998b; Tober et al., 1998; Bialer et al., 1999). In dogs, activity in the pentylenetetrazol seizure threshold test remained stable during treatment with 5 mg/kg or 40 mg/kg b.i.d. p.o. for 4 weeks (Löscher et al., 2004).

Activity profile in models of anxiolytic activity

Starting at dosages of 3 mg/kg i.p. and p.o., imepitoin is active in mouse and rat models predictive of anxiolytic activity, such as innate fear and fear induced by open and high areas, light stimulation and unfamiliar animals (elevated maze, light—dark chamber, social interaction test). In punishment tests, anxiety was clearly decreased only in the Vogel conflict test in rats (Rostock et al., 1998b).

Mechanism of action

Imepitoin acts as a low-affinity partial agonist at the benzodiazepine recognition site of the $GABA_A$ receptor (Rostock et al., 1998a; Sigel et al., 1998). At 10 μM, GABA currents are stimulated to 10—20% of the maximal stimulation achieved using diazepam. The threshold of stimulation is about 0.3—1.0 μM. The GABA-potentiating, anxiolytic, and anticonvulsant effects of imepitoin could be counteracted by the benzodiazepine antagonist flumazenil, indicating that the interaction of imepitoin with the benzodiazepine site may be the main mechanism of action of this novel drug.

One major disadvantage of drugs acting via the benzodiazepine site of GABA receptors is their tolerance, dependence, and abuse liability. Partial agonists at this site have been suggested to offer advantages over full agonists in this regard (Löscher et al., 1990; Costa and Guidotti, 1996; Mehta and Ticku, 1999). In line with this suggestion, imepitoin failed to produce benzodiazepine-like discriminative effects and drug self-administration behavior when tested in squirrel monkeys (Yasar et al., 2003). Furthermore, no loss of anticonvulsant efficacy during prolonged treatment or withdrawal symptoms on termination of treatment were observed in mice or dogs (Löscher et al., 2004).

In addition to its effects on $GABA_A$ receptors, imepitoin blocks voltage-activated Ca^{2+} channels in a dose-dependent

manner (Bialer et al., 1999). A significant block is found at 1 μM, and it is as yet unclear which channel subtype is affected. Imepitoin (1 and 100 μM) also antagonizes the increased firing of action potentials induced by corticotrophin-releasing factor (CRF) in locus coeruleus neurons of murine brain stem slices. This effect could contribute to the anxiolytic activity. Imepitoin has no effects on the normal frequency of action potential firing in these neurons.

Toxicology

The TD_{50} for motor impairment in the rotarod test is about 1000 mg/kg, p.o. in rats. This low neurotoxicity was confirmed in kindled rats with altered susceptibility to CNS adverse effects. The protective index, calculated as the ratio between the TD_{50} in the rotarod test and the dose inducing anticonvulsant and anxiolytic activity (3 mg/kg), is 333 in rats after p.o. administration. Consistent with the low neurotoxicity, imepitoin showed no measurable effects on basal synaptic transmission in rat brain slices with orthodromically evoked population spikes (Dost, unpublished results).

Pharmacokinetics

Imepitoin is absorbed rapidly and extensively in rats and dogs, and shows a high metabolic stability when tested in vitro with human liver microsomes and human liver slices (Bialer et al., 1999). Elimination half-lives in rats and dogs were dose-dependent, ranging from 1.1 to 6 h (Bialer et al., 1999; Löscher et al., 2004).

Efficacy and tolerability in dogs with epilepsy

Epilepsy is the most common chronic neurological disease in dogs (about 0.6—1% of the dog population) (Löscher et al., 1985; Podell, 1996). Currently, there is only one licensed AED for treatment of epileptic dogs, i.e., phenobarbital. Most other AEDs have too short half-lives in dogs (Frey and Löscher, 1985). About 70—80% of all dogs with epilepsy are not controlled by phenobarbital, and treatment is associated with adverse effects and the risk of severe withdrawal seizures upon termination of treatment. Thus, new treatments for canine epilepsy are urgently needed.

Based on the dose-finding experiments in a pentylentetrazol seizure model in dogs, b.i.d. oral dosing with imepitoin 10—30 mg/kg was used for first exploratory clinical trials in dogs with epilepsy (Löscher et al., 2004). In a prospective trial in dogs with newly diagnosed epilepsy, monotherapy with imepitoin markedly reduced seizure frequency and severity without significant difference to standard treatments (phenobarbital or primidone), but was much better tolerated than the standard drugs. In dogs with chronic epilepsy, most dogs exhibited a reduction in seizure frequency and severity during add-on treatment with imepitoin (Löscher et al., 2004).

Overall, the data in dogs demonstrate that the partial benzodiazepine receptor agonist imepitoin exerts significant anticonvulsant efficacy without tolerance in a dog seizure model as well as in epileptic dogs with spontaneously recurrent seizures. These data thus substantiate that partial agonism at the benzodiazepine site of $GABA_A$ receptors offers advantages versus full agonism and constitutes a valuable approach for treatment of seizures.

Based on these data, two large prospective and controlled multicenter trials were performed in epileptic dogs by Boehringer Ingelheim. The trials confirmed the efficacy and tolerability of imepitoin as a new AED for canine epilepsy. Currently, imepitoin (Pexion®) is in late stage development.

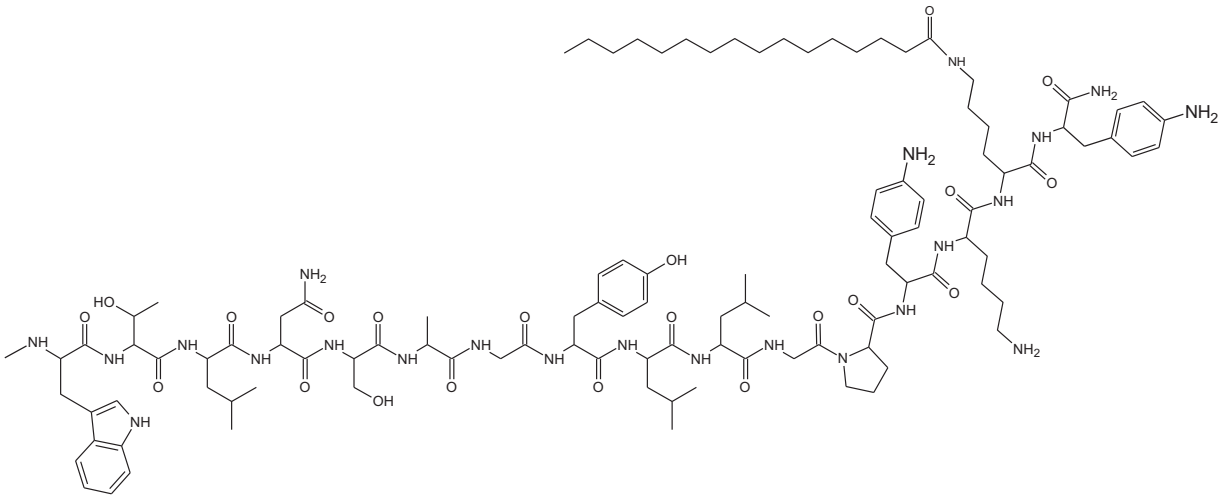
NAX 810-2

G. Bulaj[a], B.D. Klein[b,c], C.S. Metcalf[b], D. McDougle[b], M.D. Smith[c], L.Zhang[a], H.S. White[b,c]

[a] Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, USA

[b]NeuroAdjuvants, Inc. Salt Lake City, UT, USA

[c]Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, USA



NAX 810-2

Introduction and rationale for development

Galanin has been recognized as a potential anticonvulsant neuropeptide since the early work of Mazarati and coworkers (Mazarati et al., 1992; Mazarati et al., 1998, 2000). Galanin is one of several neuropeptides with demonstrated anticonvulsant activity (Robertson et al., 2010). Galanin is presumed to exert its biological activity through the activation of galanin receptor (GalR) subtypes 1 and 2; both of which are widely expressed in the CNS (Lang and Kofler, 2011). Early evidence demonstrating an the importance of both receptor types came from studies conducted in GalR1 knockout mice and in rats employing a GalR2 antisense approach (Mazarati et al. 2004a,b, 2006; Mazarati and Lu, 2005).

The development of galanin as an AED has been hampered by its marginal metabolic stability and inability to penetrate the blood-brain-barrier when delivered systemically. Further, activation of peripheral GalR1 results in the inhibition of insulin release and subsequent hyperglycemia. Modification of the galanin backbone led to the identification of a series of metabolically stable, blood-brain-barrier penetrant novel galanin agonists that demonstrate anticonvulsant activity following systemic administration (Bulaj et al., 2008; Zhang et al., 2009). The first candidate galanin analog to be extensively evaluated was the GalR1-receptor preferring analog NAX 5055 (Bialer et al., 2010). NAX 5055 was found to possess long-lasting and dose-dependent activity in the 6 Hz seizure model following i.v., i.p. s.c. and oral administration (White et al., 2009). NAX 5055 also exhibited potent efficacy in other models of epilepsy and pain. Unfortunately, NAX-5055 was subsequently shown to produce marked hyperglycemia that was associated with inhibition of insulin release. Subsequent investigations led to the discovery of NAX 810-2, a GalR2-preferring galanin agonist that displays similarly potent anticonvulsant activity in a battery of animal seizure and epilepsy models (Table 1).

Pharmacology

Structure—activity relationship studies demonstrated that the N-terminal fragment GAL(1—16) retains potent agonist activity at hippocampal galanin receptors. Based on that knowledge, the following modifications were introduced to the GAL(1—16) analogs: (1) the Gly1 residue was replaced by sarcosine as N-methylation of Gly1 maintains nanomolar galanin receptor affinity, but with an ~15-fold preference for GalR1 compared to GalR2. (2) ''atom shaving'' of this N-terminus substantially decreases GalR1 affinity while preserving relatively high GalR2 affinity (3) residues following critical Tyr9 were replaced by a combination of Lys residues and lipoamino acids, such as lysine-conjugated to long-chain carboxylic acids (Bulaj et al., 2008; Zhang et al., 2009; Robertson et al., 2010).

For lead optimization studies, approximately 40 new analogs targeting GalR2 were chemically synthesized on a solid support using standard Fmoc protocols and an automated peptide synthesizer. The peptides were purified by reversed-phase HPLC separations and their identities were confirmed by mass spectrometry. The new series of analogs were screened for anti-seizure activity in the mouse 6 Hz 32 mA test following i.p. administration. NAX 810-2 is an initial lead analog from this series that has undergone extended pharmacologic characterization.

Anticonvulsant profile in experimental models

As shown in Table 1, NAX 810-2 is potently active at both the 32 and 44 mA stimulation intensities in the mouse 6 Hz seizure model following i.p. administration and is effective in blocking sound-induced seizures in the Frings audiogenic seizure-susceptible mouse. NAX 810-2 is also potently active (Table 1) against the fully expressed seizure in the corneal kindled mouse model of partial epilepsy (Matagne and Klitgaard, 1998). In contrast, it is inactive at substantially higher doses (i.e., 20 mg/kg, i.p.) in the maximal electroshock test. In this respect, NAX 810-2 displays an anticonvulsant profile similar to the GalR1 preferring analog NAX 5055. NAX 810-2 has been evaluated in the rotarod test for motor impairment. In this particular test, the median toxic dose was estimated to be greater than 32 mg/kg, i.p. yielding a wide protective index ($PI = TD_{50}/ED_{50}$) of more than 10-fold for NAX 810-2 with the 6 Hz (32 mA) test.

As mentioned above, NAX 810-2 retains potent activity in the 6 Hz test even when the higher stimulation intensity (44 mA) is employed. The results obtained in the 6 Hz test are of particular interest because this model has evolved as a useful model for differentiating potential AEDs for treatment of refractory partial epilepsy (Barton et al., 2001). The overall prolife of NAX 810-2 in seizure models is unique compared to the majority of approved AEDs and most closely resembles that of levetiracetam. In addition to its anticonvulsant activity, the GalR1 preferring analog NAX 505-5 is effective in rodent models of acute and chronic pain (Bialer et al., 2010). Similarly, NAX 810-2 following systemic administration is potently active in mouse models of inflammatory pain (Table 1). It was active in the carrageenan assay and both the acute and chronic phases of formalin-induced pain in mice. The overall activity of NAX 810-2 supports the continued evaluation of these novel systemically active analogs targeting GalR2 for the treatment of epilepsy and pain.

Mechanisms of action

As described previously (Bialer et al., 2010), the GalR1 preferring analog NAX 5055 displays low nanomolar binding affinity for both GalR1 and GalR2 with Ki values of 3.5 and 51 nM, respectively. In contrast, NAX 810-2 possesses low nanomolar binding affinity for GalR2 (Ki value 31.7 nM) compared to GalR1 (Ki value 494 nM). Importantly, the GalR1 binding affinity of NAX 810-2 is reduced >100-fold compared to the GalR1-preferring agonist NAX 505-5. Both NAX 5055 and NAX 810-2 are presumed to exert their antiepileptic effects through selective interaction with these G-protein coupled galanin receptors. Studies in rat brain slice preparations have shown that galanin inhibits glutamate release (Zini et al., 1993). Further, activation of GalR2 has been shown to produce trophic effects in dorsal root ganglion neurons (Mahoney et al., 2003) and to be neuroprotective in hippocampal neurons (Elliott-Hunt et al., 2007). Therefore, a mechanistically novel therapy targeting GalR2 may possess disease modifying properties though these neuroprotective and anti-inflammatory effects.

Planned studies

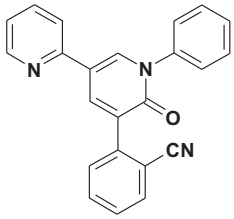
Ongoing studies will further define the efficacy and safety potential of NAX 810-2 and other leads from this new series targeting GalR2 for the treatment of pharmacoresistant POS. The preclinical development of a lead candidate targeting GalR2 is being advanced through IND filing supported by funding from a NINDS U01 translational research grant.

Acknowledgements

This work is supported by the grant U01 NS066991 from the NIH. G.B and H.S.W are scientific cofounders of NeuroAdjuvants, Inc

Perampanel (E2007)

David Squillacote, Medical Affairs, Eisai Inc., Woodcliff Lake, NJ, USA



Perampanel

Introduction and rationale for development

Perampanel (E2007) is an orally active, non-competitive, and highly selective antagonist of the glutamate AMPA receptor (Hanada et al., 2011). The AMPA receptor is a ligand-gated ion channel that has long been identified as a rational drug target for epilepsy. Excessive glutamate transmission is implicated in the initiation and spread of seizures, and as the AMPA receptor mediates the majority of fast synaptic transmission by glutamate it is theorized that an AMPA receptor antagonist will have anti-seizure activity (Rogawski and Loscher, 2004).

Perampanel is the first AMPA receptor antagonist to be submitted for regulatory approval for any indication. It is supported by a large dataset, from Phase I studies, Phase II studies in patients with multiple sclerosis, Parkinson disease, neuropathic pain and epilepsy, and a large Phase III program in patients with POS. Through this program, over 4600 subjects have been exposed to perampanel in clinical trials (Eisai, Data on File).

Pharmacology

Studies reported by Hanada et al. (Hanada et al., 2011) have demonstrated that perampanel is a potent AMPA receptor antagonist, inhibiting AMPA-mediated Ca^{2+} currents in vitro with an IC_{50} of 93 nM. Perampanel has no effect on NMDA-receptor-mediated currents at this concentration; a small inhibition is seen at 300-times this concentration (Hanada et al., 2011).

Further evidence of the selectivity of perampanel comes from ligand-binding studies, where perampanel, at a relatively high concentration of 10 μM, did not inhibit by $\geq$50% the binding of ligands to 86 different cellular targets (Eisai, Data on file).

Perampanel is thought to act via a non-competitive (allosteric) mechanism, binding to a separate site on the AMPA receptor from the glutamate-binding site. Rather than directly competing with glutamate to inhibit its binding to the AMPA receptor, perampanel binds to an allosteric site and thereby prevents glutamate from opening the receptor. In support of this allosteric mechanism, radiolabeled perampanel is not displaced from rat forebrain membranes by glutamate or AMPA but is displaced by known non-competitive AMPA receptor antagonists (Hanada et al., 2011).

Anticonvulsant profile in experimental models

The anti-seizure effects of perampanel across a range of animal models were reported in the previous Eilat report (Bialer et al., 2010) and these data have now been published in full (Hanada et al., 2011).

Other pharmacological properties

AMPA receptors, when activated, drive the generation of excitatory post-synaptic potentials (EPSPs) to propagate action potentials through networks of neurons. It is interesting, therefore, to explore the effects of perampanel in neuronal networks. Perampanel inhibits AMPA-receptor mediated EPSPs in hippocampal slices with no effect on NMDA- or kainate-receptor-mediated EPSPs, demonstrating selectivity for AMPA-type glutamate receptors (Ceolin et al., 2012)

Mechanism(s) of action

Perampanel, as noted earlier, reduces the ability of glutamate to activate AMPA receptors via a non-competitive mechanism (Hanada et al., 2011). The theoretical process by which this leads to clinical anti-seizure effects is by attenuating the neuronal hyperexcitability that characterizes epileptic brain regions. Glutamate is the predominant excitatory neurotransmitter in the brain, and AMPA receptors play a central role in seizure generation and spread (Rogawski and Loscher, 2004). Currently approved AEDs predominantly act pre-synaptically to reduce neuronal excitability (e.g. Na^+ channel blockers, K^+ channel openers), reduce neurotransmitter release (e.g. Ca^{2+} channel blockers, levetiracetam) or increase GABAergic inhibitory controls (benzodiazepines, tiagabine, vigabatrin). In contrast, perampanel acts post-synaptically to decrease excitability (Rogawski and Loscher, 2004).

One theoretical consequence of the non-competitive mechanism of action is that the ability to inhibit AMPA-receptor activation should be maintained even when glutamate concentrations are high (as occurs during seizure activity). In contrast, a competitive antagonist would be out-competed and displaced from the glutamate-binding site when glutamate concentrations are high, and competitive antagonism is, therefore, surmountable (Kenakin, 2006). The clinical implications of this are still being evaluated.

Toxicology

There have been no further toxicology studies since those reported in the previous report (Bialer et al., 2010).

Pharmacokinetics

The pharmacokinetics of perampanel in healthy volunteers were described in the previous report (Bialer et al., 2010). In summary, perampanel has a long half-life (~70–110 h), is metabolized primarily by CYP3A4, and steady state is achieved in 14 days with once-daily dosing (Eisai, Data on File, Bialer et al., 2010). Recently presented population pharmacokinetic analyses support a one-compartment model and indicate slightly lower clearance in females than males (Laurenza et al., 2011).

Drug interactions

In a population pharmacokinetic analysis, using pooled data from the 3 Phase III clinical trials, perampanel had no effect on the clearance of other AEDs (Laurenza et al., 2011). Clearance of perampanel was increased 2-fold by oxcarbazepine and phenytoin and increased 3-fold by carbamazepine (Laurenza et al., 2011).

There is a positive relationship between plasma perampanel concentration and clinical response. As average exposure to perampanel at steady state increased, seizure frequency decreased and the probability of an individual being a responder (≥50% reduction in seizure frequency) increased significantly. Concomitant AEDs had no effect on the exposure/efficacy relationship for seizure frequency or the probability of response at any given plasma concentration (Laurenza et al., 2011).

Efficacy data

Data from perampanel Phase II trials were reported in the previous Eilat report (Bialer et al., 2010) and have now been published (Krauss et al., 2011). Pharmacokinetic–pharmacodynamic (PK/PD) modeling from these Phase II trials established the no effect dose (2 mg/day), the minimum effective dose (4 mg/day), the mid effective dose (8 mg/day), and the high effective dose (12 mg/day).

Results from three Phase III trials in 1480 subjects have been presented (Study 304: French et al., 2012a; Study 305: French et al., 2012b and Study 306: Krauss et al., 2012). These trials all utilized similar trial designs, with a 6-week baseline period, a 6-week titration period, and a 13-week maintenance period. Patients were ≥12 years of age, with refractory POS, and already taking 1–3 AEDs. Unless stated otherwise, data are reported over the entire 19-week double-blind treatment period (titration + maintenance).

The first study to be reported (306, NCT00700310) investigated perampanel at doses of 2, 4 and 8 mg/day and placebo. The median percent change from baseline in seizure frequency was significantly greater with 4 and 8 mg/day perampanel (−23.3%, $p = 0.0026$ and −30.8%, $p < 0.0001$, respectively) but not 2 mg/day (−13.6%) compared to placebo (−10.7%). The responder rate was significantly higher during the maintenance period in the groups randomized to 4 and 8 mg/day perampanel (28.5%, $p = 0.0132$ and 34.9%, $p = 0.0003$, respectively) but not 2 mg/day (20.6%) compared to placebo (17.9%) (Krauss et al., 2012).

The next two studies confirmed the efficacy of the 8 mg/day dose and also included a higher dose (12 mg/day). Study 305 (NCT00699582) demonstrated a significant reduction in seizure frequency with perampanel 8 mg/day (median percent change from baseline: −30.5%, $p < 0.001$) and 12 mg/day (−17.6%, $p = 0.011$) versus placebo (−9.7%), and a significant increase in responder rate (33.3% at 8 mg/day, $p = 0.0018$ and 33.9% at 12 mg/day, $p = 0.0006$) versus placebo (14.7%) (French et al., 2012b).

Study 304 (NCT00699972) also demonstrated a significant reduction in seizure frequency with perampanel 8 mg/day (median percent change from baseline: −26.3%, $p = 0.0261$) and 12 mg/day (−34.5%, $p = 0.0158$) versus placebo (−21.0%) but responder rates (37.6% and 36.1%, respectively) were not significantly greater than the high placebo responder rate (26.4%) (French et al., 2012a). Placebo rates in study 304 were high, particularly in Central and South American study centers. Responder rates with perampanel were significantly higher than with placebo in the North American centers, but not the Central and South American centers. An explanation for this regional difference has not been forthcoming despite extensive analyses.

Tolerability and adverse event profile

Phase II studies showed that perampanel was tolerated at doses up to 12 mg/day (Krauss et al., 2011), and Phase III studies revealed no additional safety concerns. In the first Phase III study (306), the most common TEAEs (occurring in ≥10% of patients from any treatment group) were dizziness (27% with 8 mg/day versus 10% with placebo), somnolence (16% versus 7%) and headache (11% versus 9%) (Krauss et al., 2010). Serious TEAEs were not more frequent with study drug (3.6% with 8 mg/day) than with placebo (4.9%), and discontinuation rates due to TEAEs were low (7.1% with 8 mg/day versus 3.8% with placebo) (Krauss et al., 2012).

In studies 304 (French et al., 2012a) and 305 (French et al., 2012b), similar TEAEs were seen, and rates were generally higher with 12 mg/day than with 8 mg/day. In study 304, the most common TEAEs were dizziness (38.1% with 12 mg versus 9.9% with placebo), somnolence (17.2% versus 13.2%), irritability (14.2% versus 5.0%), headache (13.4% versus 13.2%), fall (12.7% versus 6.6%) and ataxia (11.9% versus 0%). Treatment discontinuations due to TEAEs were relatively low (placebo 5.8%, 8 mg/day 6.8%, 12 mg/day 17.9%) (French et al., 2012b).

In study 305, most TEAEs were of mild or moderate severity, and severe TEAEs were reported in only 6.6%, 9.3% and 10.7% of patients in the placebo, perampanel 8 mg/day and 12 mg/day groups, respectively (French et al., 2012b). The TEAEs that occurred in ≥10% of patients in any treatment group were dizziness (32.6% and 47.9% with perampanel 8 mg/day and 12 mg/day versus 7.4% for placebo), somnolence (12.4% and 18.2% versus 2.9%), fatigue (13.2% and 16.5% versus 8.1%), and headache (8.5% and 13.2% versus

13.2% with placebo) (French et al., 2012). The incidence of TEAEs was lower during the maintenance period: dizziness (5.1% and 14.4% versus 4.8% with placebo), headache (6.8%, and 4.8% versus 4.0%) and fatigue (4.2% and 6.7% versus 2.4%) (Ryvlin et al., 2011). The difference in TEAE rates between the titration period and the maintenance period might be explained by the somewhat rapid, forced titration paradigm of 2-mg increments each week over the 6 weeks of titration. Discontinuations due to TEAEs were higher in perampanel-treated patients compared with placebo (4.4%, 9.3%, and 19% with placebo, 8 mg, and 12 mg, respectively) (French et al., 2012b). Rash led to discontinuation in 1.6% perampanel patients versus 0% in placebo patients. No abnormal trends in laboratory tests, including QTc, were observed (French et al., 2012b).

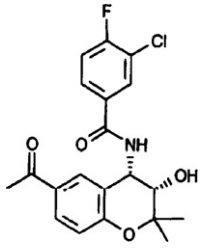
The number and rates of rash were low in all three studies without evidence of a dose response (Study 304: placebo = 3 (2.5%), perampanel = 5 (1.9%); Study 305: placebo = 2 (1.5%), perampanel 8 (3.2%); Study 306: placebo = 2 (1.1%), perampanel 9 (1.7%). There were no reports of Stevens-Johnson syndrome.

Planned studies

In addition to the open-label extensions of the perampanel Phase II and Phase III studies, two other trials are underway. The first (NCT01393743) will explore the efficacy and safety of adjunctive perampanel in primary generalized tonic–clonic seizures and aims to enroll 165 subjects. The second (NCT01161524) will explore the effect of perampanel on cognition and growth and evaluate its safety, tolerability, and pharmacokinetics in adolescents with refractory POS.

Tonabersat

Upsher Smith Laboratories, Minneapolis, Minnesota, USA
H. Steve White, PhD[1] and Paul Durham, PhD[2]
[1]Professor and Director, Anticonvulsant Drug Development Program, Department of Pharmacology Toxicology, University of Utah; [2]Professor and Director, Center of Biomedical and Life Sciences, Missouri State University



Tonabersat

Introduction and rationale for development

Tonabersat is one of a series of novel benzoylamino benzopyran compounds initially developed by SmithKline-Beecham for the treatment of migraine and epilepsy. The tonabersat binding site, primarily found in the brain, is distinct from that of other CNS pharmacologic agents, including antimigraine compounds, AEDs, amino acid analogues, and ion channel modulators. Tonabersat possesses a novel mechanism of action related to stereospecific activity at its binding site, which may be related to uncoupling of neuronal gap junctions. Further, this benzoylamino benzopyran class of compounds has been found to exhibit anti-seizure properties. The data described here detail the current studies evaluating the anti-seizure profile of tonabersat and its mechanism of action.

Pharmacology

In both mice and rats, standard in vivo and in vitro models were employed to establish the anti-seizure profile of tonabersat. These included, but were not limited to, models of generalized tonic-clonic seizures (MES, focal seizure with secondary generalization (6 Hz), POS with secondary generalization (hippocampal-kindled), and pharmacoresistant seizures with secondary generalization (lamotrigine-resistant kindled). Toxicity of tonabersat was assessed with the minimal motor impairment scale (MMI) or rotarod test, and minimal behavioral toxicity was subsequently quantitated (ED_{50} and TD_{50}) at the time of peak anticonvulsant effect. Additionally, MES data were used to correlate tonabersat plasma exposure with anti-seizure activity and model a relationship between efficacy and tonabersat brain/plasma concentrations.

The mechanism of action of tonabersat has been evaluated in an in vivo model of migraine. Briefly, Sprague-Dawley rats were injected with either tumor necrosis factor-α (TNF-α), capsaicin, or both agents (TNF-α CAP) to stimulate trigeminal ganglion neurons to induce an inflammatory reaction. Cell-cell communication was investigated with True Blue dye-coupling under basal and inflammatory conditions in the presence and absence of tonabersat (10 mg/kg ip). Further, the effects of inflammation and tonabersat on the expression of connexins (Cx) in trigeminal ganglion neurons and glia were evaluated by quantitative RT-PCR and immunohistochemistry (Damodaram et al., 2009) (Garrett and Durham, 2008).

Across a number of preclinical studies, tonabersat demonstrated a definitive anti-seizure profile. Tonabersat demonstrated a dose-dependent inhibition of electrographic bursting in the in vitro K^+ hippocampal brain slice model, with an $IC_{50} = 0.5\ \mu m$. While tonabersat was unable to reduce the frequency of bursting in entorhinal cortex/hippocampal brain slices, it did reduce individual burst duration by ~26%. In vivo, tonabersat demonstrated low toxicity with a $TD_{50} > 250$ mg/kg (mice) and >500 mg/kg (rats). Tonabersat significantly increased the threshold for electrically-induced tonic extension seizures. In this model, tonabersat displayed a long duration of action (e.g., up to 12 h). Further, tonabersat produced both time- and dose-dependent inhibition of tonic extension seizures in the rat MES model, which specifically correlated to tonabersat plasma and brain concentrations. While tonabersat was effective against audiogenic seizures (PI > 2000), it was not protective against 6 Hz (limbic) or clonic seizures induced by subcutaneous administration of picrotoxin or bicuculline. In addition, tonabersat did not

inhibit fully expressed seizures in either hippocampal or lamotrigine-resistant kindled rats. While tonabersat exhibited anti-seizure activity similar to other AEDs, it exhibited a higher PI.

TNF-α or capsaicin alone did not increase True Blue dye movement. In contrast, when simultaneous injection of TNF-α and capsaicin did increase dye movement between neuronal and satellite glial cells of the trigeminal ganglion (Damodaram et al., 2009). This finding provides evidence that activation of trigeminal ganglion neurons increase cellular communication between these cell types via gap junctions. RT-PCR and immunohistochemistry data demonstrate that Cx26, Cx36, and Cx40 are expressed in the trigeminal ganglions under basal conditions,(Damodaram et al., 2009, Garrett and Durham, 2008) and during inflammatory conditions the expression of these connexins is up-regulated. In the presence of tonabersat, the inflammatory-induced cellular communication between the neurons and satellite glia cells was abolished, and the increase in Cx26 expression was inhibited (Damodaram et al., 2009). Interestingly, the inhibitory effects of tonabersat on Cx26 expression were specific, as tonabersat did not inhibit the up-regulation of Cx36 or Cx40.

Pharmacokinetics and drug interactions

Initial studies evaluating the clinical pharmacokinetics and drug interaction potential of tonabersat (2—80 mg) in both healthy individuals and migraineurs were summarized in a previous Eilat conference report (Bialer et al., 2009).

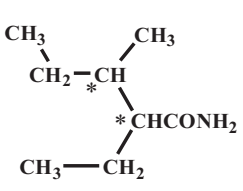
Planned studies

Tonabersat is currently being evaluated in Phase I studies as an investigational drug for the treatment of epilepsy.

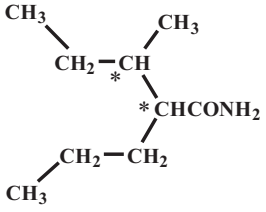
Valproic acid second generation derivatives

M. Bialer and B. Yagen

Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Israel



Valnoctamide (VCD)



sec-Butyl-propylacetamide (SPD)

Introduction

Since Eilat X (2010), significant progress has been made in the development of valnoctamide (VCD) as well as *sec*-butyl-propylacetamide (SPD), a one-carbon homologue of VCD (Bialer and White, 2010; White et al., 2012). VCD is a CNS-active chiral constitutional isomer of valpromide, the corresponding amide of valproic acid (VPA) that exhibits stereoselective pharmacokinetics in animals and humans (Bialer and Yagen, 2007; Bialer, 2012). Both VCD and SPD possess two chiral centers in their chemical structure (denoted above with the asterisk *). VCD (racemate) was commercially available as an anxiolytic drug (Nirvanil®) in several European countries from 1964 until as recently as 2005 (Bialer and Yagen, 2007; Bialer and White, 2010; Bialer, 2012), and it is now being developed for the treatment of bipolar disorder. VCD also has displayed potential in epilepsy and neuropathic pain.

Pharmacology

Anticonvulsant activity profile in experimental models

VCD (racemate and/or two of its individual enantiomers) demonstrated anticonvulsant activity in a wide array of anticonvulsant models in mice (MES, s.c. pentylentetrazol and 6 Hz psychomotor seizures) and rats (MES and s.c. pentylentetrazol) as described in the previous Eilat X Conference manuscript (Bialer et al., 2010).

As summarized in Table 1, SPD's anticonvulsant activity was defined in several rodent seizure and epilepsy models including: MES, 6 Hz psychomotor, s.c. pentylentetrazol, picrotoxin, bicuculline, audiogenic and corneal and hippocampal kindled seizures following i.p. administration (White et al., 2012). SPD was also evaluated for its ability to block benzodiazepine-resistant status epilepticus induced by pilocarpine (rats) and soman (rats and guinea pigs) following i.p. administration. SPD was tested for its ability to block excitotoxic cell death induced by the glutamate agonists N-methyl-D-Aspartate (NMDA) and kainic acid (KA) using organotypic hippocampal slices and status epilepticus-induced hippocampal cell death using Fluoro-Jade B staining. The cognitive function of SPD-treated rats that were protected against pilocarpine-induced convulsive status epilepticus was examined 10—14 days post SE using the Morris water maze.

SPD was highly effective and displayed a wide PI in the standardized seizure and epilepsy models employed (Table 1). SPD's wide PI values demonstrate that it is effective at doses well below those that produce behavioral impairment. Unlike VCD, SPD also displayed anticonvulsant activity in the rat lithium/pilocarpine model of status epilepticus. Thirty minutes after the induction of status epilepticus, the calculated rat ED_{50} for SPD against convulsive status epilepticus in this model was 84 mg/kg. SPD was not neuroprotective in the in vitro organotypic hippocampal slice preparation; however, it did display hippocampal neuroprotection in both in vivo status epilepticus models (i.e., lithium/pilocarpine and soman) and treatment after the onset of lithium/pilocarpine-induced status epilepticus with SPD resulted in cognitive sparing in the Morris water maze, an effect that was associated with its marked anti-seizure effect against pilocarpine-induced status epilepticus (White et al., 2012).

When administered 20 and 40 min after status epilepticus onset, SPD (100—174 mg/kg) produced long-lasting efficacy (e.g., 4—8 h) against soman-induced convulsive and electrographic status epilepticus in both rats and guinea pigs. SPD-ED_{50} values in guinea pigs were 67 mg/kg and 92 mg/kg

when administered at the onset of, or 40 min after, status epilepticus onset, respectively.

Overall, the results obtained in two highly treatment-resistant models of status epilepticus demonstrate that SPD is a broad-spectrum anti-seizure compound that blocks status epilepticus induced by pilocarpine and soman and affords in vivo neuroprotection that is associated with cognitive sparing. SPD activity against status epilepticus is superior to diazepam in terms of rapid onset, potency and its effect on animal mortality and functional improvement.

Other pharmacological properties: Reversal of tactile allodynia

The antiallodynic activity of VCD and two of its individual stereoisomers (2R,3S)-VCD and (2S,3S)-VCD in the spinal nerve ligation (or Chung) model for neuropathic pain in rats was described in the Eilat X Conference manuscript (Bialer et al., 2010). SPD's ED_{50} value in the spinal nerve ligation model of 49 mg/kg was very similar to that of VCD (ED_{50} = 52 mg/kg) (Kaufmann et al., 2009,2010).

Teratogenicity

The lack of notable teratogenicity of VCD and (2R,3S)-VCD and (2S,3S)-VCD in SWV/Fnn mice which are highly susceptible to VPA-induced teratogenicity was previously described (Bialer and Yagen, 2007; Bialer et al., 2010). Following a successful Phase IIa study in patients with mania funded by the Stanley Medical Research Institute (SMRI) (Bersudsky et al., 2010), the SMRI had a pre-IND meeting with the FDA-Division of Psychiatry Products. As requested by the FDA, the SMRI in collaboration with Yissum (Hebrew University Technology Transfer Company and VCD patents' owner) conducted teratogenicity studies comparing VCD to VPA (head-to-head) in mice, rats and rabbits at Covance Laboratories. In these additional studies, VCD in contrast to VPA failed to demonstrate teratogenic potential in mice and rabbits. In rats a modest teratogenic signal was observed at plasma concentrations 15-times higher than VCD therapeutic plasma levels.

A follow-up dose-response study with high doses of VCD and VPA in SWV/Fnn mice is currently in progress in the laboratory of Prof. Richard H. Finnell at the University of Texas in Austin, TX, USA. The study objective is to perform a comparative evaluation of VCD and VPA. Outcome measures of this study include assessment of: (a) neural tube defect response rates, and (b) soft tissue and skeletal integrity. Embryos will also be collected at critical times during development for genetic microarray studies to compare the impact on gene expression between a known teratogen, VPA, with VCD to see how they impact critical genetic pathways that regulate normal development.

Pharmacokinetics in experimental animals

The results of a previously conducted stereoselective pharmacokinetic analysis of VCD were summarized in the Eilat X Conference manuscript (Bialer et al., 2010).

SPD pharmacokinetics was also studied following i.p. administration 60 mg/kg to naïve male Sprague-Dawley rats. SPD was found to have a clearance of 0.3 L/h that was mainly metabolic, as only 0.1% of the SPD dose was excreted unchanged in the urine. In rats, SPD displayed a 7-fold higher clearance than VCD due to its higher lipophilicity. SPD volume of distribution was 3-times greater than that of VCD (White et al., 2012). As a consequence of these opposite trends in clearance and volume of distribution, SPD half-life was similar to that of VCD.

The relationship between the pharmacokinetic profile of SPD and its efficacy against soman-induced status epilepticus (PK-PD relationship) was evaluated. SPD (60 mg/kg, i.p.) was administered 20 min after the onset of status epilepticus. A PK-PD correlation (assuming linear pharmacokinetics) showed that SPD effective plasma levels in the soman-induced status epilepticus model ranged between 8—40 mg/L (20 min post seizure onset) and 12—50 mg/L (40 min post seizure onset). The time to peak effect (PD-t_{max}) occurred after the time of peak plasma levels (PK-t_{max}). This lag time may indicate a slow distribution of SPD to the extra-plasmatic active site responsible for SPD's anticonvulsant activity. This slower distribution to the active site may contribute to the fact that SPD's effect (responder rate) declined at a significantly slower rate than SPD plasma levels and in a few rats lasted for 24 hours when SPD was administered 20 min post status onset.

Clinical data

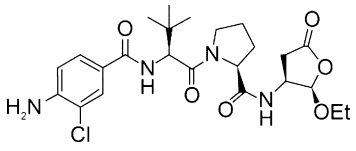
Recently, a successful double-blind controlled Phase IIa clinical trial funded by the SMRI with VCD racemate in patients with mania was completed (Bersudsky et al., 2010; Bialer et al., 2010). This study showed that VCD could be an important substitute to VPA in women of child-bearing age with bipolar disorder.It is worth emphasizing that based on head-to-head comparison with VPA in mice, rats and rabbits (unpublished data on file) VCD is the first potential effective mood stabilizer without significant teratogenicity in animal models.

Ongoing and planned studies

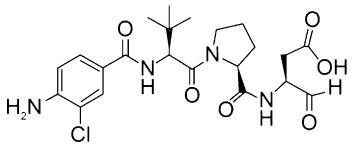
Although VPA is the most prescribed AED, its clinical use is restricted in women of child-bearing age and in children due to its teratogenicity and hepatotoxicity, respectively (Bialer and Yagen, 2007). The development of VCD and its introduction as a new and potentially non-teratogenic/non-hepatotoxic CNS agent that is more potent than VPA, may offer a safer alternative for the treatment of patients with bipolar disorder, epilepsy and neuropathic pain (Bialer and White, 2010). Following the successful Phase IIa clinical trial, VCD is currently undergoing a 3-week SMRI-funded Phase IIb, randomized double-blind multicenter study in 300 patients with bipolar manic episodes. The study is a 3-arm monotherapy parallel group trial in which patients are randomized to placebo (n = 120), VCD 1500 mg/day (n = 120) and risperidone, up to 6 mg/day (n = 60). The study's major objective is to evaluate the efficacy of VCD compared to placebo in patients with acute manic or mixed episodes. Risperidone is included as an active control to ascertain the trial's assay validity.

VX-765

French J[1], Martin M[2], Paskavitz J[2], Wright C[2].
[1]MDNYU Comprehensive Epilepsy Center, New York, NY, USA; [2]Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA.



VX-765



VRT-043198

Introduction and rationale for development

Although many treatments are available in the United States, there are approximately 800,000 patients with epilepsy that continue to have seizures despite treatment with 2 or more antiepileptic drugs (AEDs). Thus, there may be important components underlying the disease that are not being addressed by current therapies. There is increasing evidence that inflammation plays an important role in establishing and maintaining seizures (Perucca et al., 2007). Surgical specimens obtained from human brains of patients with treatment-resistant epilepsy show a number of inflammatory features, including elevated levels of interleukin converting enzyme (ICE, also known as caspase-1) and interleukin 1β (IL-1β) and an increase in IL-1β receptors (Ravizza et al., 2008; Vezzani et al., 2008). These human brain studies suggest that ICE/IL-1β may be involved in causing epilepsy, particularly epilepsy that is resistant to current treatments. Several nonclinical experiments support an important role for ICE/IL-1β systems in epilepsy and indicate that inhibition of ICE/IL-1β has therapeutic potential for treating epilepsy (Vezzani et al., 2008).

Pharmacology

VX-765 (developed by Vertex Pharmaceuticals Incorporated) is a selective and reversible inhibitor of interleukin-converting enzyme (ICE; srtucture above) (Wannamaker et al., 2007). VX-765 is currently in Phase 2 development.

Phase IIa study

A 6 week phase IIa randomized, double-blind, multicenter, placebo-controlled study was completed in subjects (18—64 years old) with treatment-resistant partial epilepsy receiving 1—4 concomitant AEDs. Treatment resistance was defined as failure to achieve seizure control despite adequate trials of 2 different AEDs. Subjects were randomized 4:1 to VX-765 900 mg tid, ($n = 48$) or placebo ($n = 12$). Subjects had to have at least 6 observable partial onset seizures (POS) during the 6 weeks between screening and the start of the treatment period (the ''baseline period''), and at least one seizure in 3 of the 6 weeks. The 6-week treatment period was followed by a 6-week observation period off study drug. The primary endpoint was safety and tolerability. Secondary endpoints included percent reduction in seizure frequency during the 6 week treatment period relative to the baseline period, percent of subjects with ≥50% reduction in seizure frequency (''responder-rate'') during the 6 week treatment period relative to the baseline period, and percent of subjects that become seizure-free during the last 2 weeks of the treatment period.

Safety and tolerability

A total of 35 subjects (72.9%) in the VX-765 group had at least 1 TEAE during the 6 week treatment period compared with 10 subjects (83.3%) in the placebo group. The most common TEAE was dizziness (16.7%). One subject in the VX-765 group had a rash that led to early discontinuation from treatment. Serious TEAE occurred in 6.3% (3/48) of VX-765 subjects (hernia surgery, pain, and acute worsening of complex partial seizures post-treatment) and 0% (0/12) of placebo subjects. All three serious TEAEs were determined by the need for hospitalization.

Efficacy results

A summary of the secondary efficacy assessments are shown in Table 4. The mean percent reduction in seizure rates were 15.6% in the VX-765 group and 7.0% in the placebo group. There was a ≥50% reduction in seizures in 18.8% of subjects in the VX-765 group versus 8.3% in the placebo group. The differences in reduction in seizure rate and 50% responder rates did not meet statistical significance between the two groups. Overall, 12.5% of the VX-765 subjects were seizure free during the last 2 weeks of treatment versus 0% in the placebo group.

Because animal data suggested a possible delayed effect of VX-765, a post hoc analysis was performed to determine whether stronger effects might be seen later in the treatment period. We evaluated a 4-week ''hybrid'' period consisting of the final 2 weeks of treatment plus the 2 week post-treatment (follow-up) period (Tables 5 and 6). During the hybrid period, there appeared to be a trend towards a better 50% responder rate in the VX-765 subjects (31.3% in the VX-765 group compared with 8.3% in the placebo group). These post hoc analyses suggest that there may be a delayed beneficial effect of VX-765 that persists for some time after drug is discontinued. Future studies can further evaluate these early observations.

Ongoing clinical studies

A double-blind, placebo-controlled, multicenter, international study in treatment resistant POS has been initiated (VX-765-402). This study is a 13-week dose-ranging study of VX-765, as adjunctive treatment, to evaluate the efficacy and safety in subjects with treatment-resistant partial onset seizures. However, on September 25, 2012, Vertex

Table 4 Summary of VX-765 efficacy results.

Endpoint, (%) (95% Cl)	Placebo $N = 12$	VX-765 $N = 48$	Treatment difference (VX-765 minus placebo)
% Reduction in seizure rate (mean)	7.0 (−22.3, 36.4)	15.6 (1.0, 30.2)	8.6 (−24.3, 41.5)
50% responder rate in treatment periord	8.3 (0.2, 38.5)	18.8 (8.9, 32.6)	10.5 (−18.9, 26.6)
% Seizure-free during last 2 weeks of treatment period	0 (0, 26.5)	12.5 (4.7, 25.2)	12.5 (−135, 25.0)

Table 5 Post hoc analyses of VX-765 efficacy results.

Endpoint, (%) (95% Cl)	Placebo $N = 12$	VX-765 $N = 48$	Treatment difference (VX-765 minus placebo)
% Reduction in seizure rate (mean) in hybrid period[a]	8.9 (−14.4,32.1)	29.4 (17.8, 41.0)	20.5 (−5.5, 46.6)
50% Responder rate in hybrid period[a]	8.3 (0.2, 38.5)	31.3 (18.7, 46.3)	23.0 (−8.4, 40.2)
% Seizure-free during last 2 weeks of follow-up period	0 (0, 26.5)	18.8 (8.9, 32.6)	18.8 (−8.5, 32.0)
% Seizure-free in hybrid period[a]	0 (0, 26.5)	6.3 (1.3, 17.2)	6.3 (−19.1, 17.2)

[a] Hybrid = last 2 weeks of treatment plus first 2 weeks of follow up. The hybrid period was 4 weeks relative to the 6 weeks of the baseline period.

Table 6 Comparison of VX-765 initial results with ''delayed effect'' model (post hoc analysis).

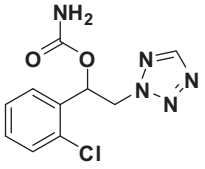
Endpoint, (%) (95% Cl)	Treatment period Treatment difference (VX-765 minus placebo)	Hibrid period Treatment difference (VX-765 minus placebo)
% Reduction in seizure rate (mean) [during treatment period vs. hybrid period]	8.6 (−24.3, 41.5)	20.5 (−5.5, 46.6)
50% Responder rate [during treatment period vs. hybrid period]	10.5 (−18.9, 26.6)	23.0 (−8.4, 40.2)
% Seizure-free [during last 2 weeks of follow-up period]	12.5 (−13.5, 25.0)	18.8 (−8.5, 32.0)
% Seizure-free [during last 4 weeks of treatmetn period vs. hybrid period]	2.1 (−24.4, 11.1)	6.3 (−19.1, 17.2)

made a business-related decision to stop enrollment in this study. Approximately 40 subjects were advancing through the 8-week baseline period and almost 20 subjects had been randomized into the treatment phase of the study.

Subjects will be permitted to stay in the study for its full planned duration. Though substantially underpowered for rigorous statistical analyses; data will be analyzed and thoroughly examined for safety assessments and potential effectiveness of treatment.

YKP3089

S. James Lee, Marc Kamin
SK Life Science Inc., Fair Lawn, New Jersey, USA



YKP3089

Introduction

YKP3089 is a novel tetrazole derived compound with one chiral center (denoted above with an asterisk). It is active in a broad range of animal models of epilepsy. It is currently in Phase II clinical development at SK Life Science.

Pharmacology

Anticonvulsant profile in experimental models

YKP3089 displays a broad-spectrum of anticonvulsant activity in rodent seizure and epilepsy models (Tables 1 and 2). It has been previously reported to prevent minimal electroshock-induced seizures in both mice and rats, with ED_{50} values of 9.8 mg/kg, i.p. and 1.9 mg/kg, p.o., respectively. In mice, YKP-3089 prevents minimal clonic seizures induced by subcutaneously administered pentylentetrazol and picrotoxin with ED_{50}'s of 28.5 and 34.5 mg/kg, i.p., respectively. YKP3089 was also effective against pentylentetrazol-induced clonic seizures and lithium/pilocarpine-induced status epilepticus in rats

following i.p. administration (ED_{50}: 14 and 7 mg/kg, i.p., respectively). YKP3089 was found to be effective in two models of POS, i.e., the hippocampal kindled rat (ED_{50} = 16.4 mg/kg, i.p.) and the mouse 6 Hz psychomotor seizure model (Tables 1 and 2). It is worth noting that little change in the potency of YKP3089 was observed in the 6 Hz test when the current was increased from 22 to 32, to 44 mA, with ED_{50}s of 11, 18 and 17 mg/kg, i.p. respectively.

Other pharmacological properties

As described previously, YKP3089 shows activity in mouse and rat models of anxiety and is more efficacious than gabapentin in the spinal nerve ligation (Bennett and Chung) model of neuropathic pain (Bialer et al., 2010). YKP3089 displays neuroprotective activity in the hypoxia-induced lethality mouse model.

Toxicology

YKP3089 was negative in all genotoxicity assays tested (Ames bacterial reverse mutation, mouse lymphoma and in vivo rat bone marrow micronucleus studies). No evidence of teratogenicity was observed in reproductive studies in rats and rabbits. YKP3089 did not affect cardiovascular functions in a telemetry cardiovascular study in monkeys.

Clinical pharmacokinetics

Following single oral administration, plasma YKP3089 levels were dose-proportional. In single dose studies, YKP3089 pharmacokinetic parameters were linear over a large dose range (5—750 mg), with a median time of peak concentration of 1.5—3.5 hours, a mean volume of distribution (Vd/F) of 37—55 L, a half-life of 30—75 h and a mean oral clearance (CL/F) of 0.63 L/h. In a multiple-dose 14-day study with once-daily dosing, both C_{max} and AUC correlated linearly with the dose over the range of 50 mg/day to 300 mg/day. There was no significant effect of food (high-fat diet) on YKP3089 pharmacokinetics.

Tolerability and adverse events profile

In Phase I healthy volunteer studies, YKP3089 was well-tolerated after single oral doses ranging from 5 mg to 750 mg In multiple ascending oral dose studies in healthy volunteers of 14—17 days duration, doses ranging from 50 mg/day to 200 mg/day were well tolerated. Doses of 250—300 mg/day were associated with a higher incidence of CNS-related TEAEs.They were mild to moderate in intensity and resolved rapidly. No clinically significant changes in ECGs or laboratory parameters were observed.

Ongoing Phase II study

A Phase II, multicenter, double-blind, randomized, placebo controlled trial to evaluate the efficacy and safety of adjunctive YKP3089 in subjects with treatment-resistant POS (NCT01397968) is ongoing.

Disclosure

M. Bialer has received in the last two years speakers or consultancy fees from Bial, BioAvenir, CTS Chemicals, Desitin, Medgenics, Rekah, Sepracor, Tombotech, UCB Pharma and Upsher Smith. He has been involved in the design and development of new antiepileptics and CNS drugs as well as new formulations of existing drugs.

S. I. Johannessen has served in the alst two years as a paid consultant to Bial.

R. H. Levy has been a consultant in the last year for the Metabolism and Transport Drug Interaction Database at the University of Washington and for Biocodex.**E. Perucca** received research grants from the European Union, the Italian Medicines Agency, the Italian Ministry of Health, and the Italian Ministry for Education, University and Research. He also received speaker's or consultancy fees and/or research grants from Bial, Eisai, GSK, Johnson & Johnson, Medichem, Novartis, Pfizer, Sun Pharma, Supernus, UCB Pharma, Upsher-Smith, Valeant, Vertex and Viropharma.

T. Tomson has received research grants and/or speakers honoraria from Eisai, GlaxoSmithKline, Janssen-Cilag Novartis, Sanofi-Aventis, Pfizer, and UCB-Pharma.

H. S. White has served within the last two years, as a paid consultant to Johnson and Johnson Pharmaceutical Research and Development, GSK Pharmaceuticals, Ono Pharmaceuticals, Valeant Pharmaceuticals, Eli Lilly & Co., and Upsher-Smith Laboratories, Inc. He is a member of the UCB Pharma Speakers Bureau and a member of the NeuroTherapeutics Scientific Advisory Board, and has received research funding from NeuroAdjuvants, Inc. H.S. White is also one of two scientific co-founders of NeuroAdjuvants, Inc., Salt Lake City, UT.

References

Barton, M.E., Klein, B.D., Wolf, H.H., White, H.S., 2001. Pharmacological characterization of the 6 Hz psychomotor seizure model of partial epilepsy. Epilepsy Res. 47, 217—227.

Bersudsky, Y., Applebaum, Y., Sharony, A., Mishory, A., Poderbeasky, A., Agam, G., Belmaker, R.H., 2010. Valnoctamide as valproate substitute with low teratogenic potential in mania: double blind controlled clinical trial. Bipolar Disorder 12, 376—382.

Bialer, M., Johannessen, S.I., Kupferberg, H.J., Levy, R.H., Loiseau, P., Perucca, E., 1999. Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV). Epilepsy Res. 34, 1—41.

Bialer, M., Johannessen, S.I., Kupferberg, H.J., Levy, R.H., Loiseau, P., Perucca, E., 2001. Progress report on new antiepileptic drugs: a summary of the Fifth Eilat Conference (EILAT V). Epilepsy Res. 43, 11—58.

Bialer, M., Johannessen, S.I., Levy, R.H., Perucca, E., Tomson, T., White, H.S., 2009. Progress report on new antiepileptic drugs: a summary of the Ninth Eilat Conference (EILAT IX). Epilepsy Res. 83, 1—43.

Bialer, M., Johannessen, S.I., Levy, R.H., Perucca, E., Tomson, T., White, H.S., 2010. Progress report on new antiepileptic drugs: a summary of the Tenth Eilat Conference (EILAT X). Epilepsy Res. 92, 89—124.

Bialer, M., White, H.S., 2010. Key factors in the discovery and development of new antiepileptic drugs (AEDs). Nat. Rev. Drug Discov. 9, 68—83.

Bialer, M., Yagen, B., 2007. Valproic acid — second generation. Neurotherapeutics 4, 130—137.
Bialer, M., 2012. Chemical properties of antiepileptic drugs (AEDs). Adv. Drug Deliv. Rev. 64, 887—895.
Biton, V., Werhahn, K.J., Johnson, M.E., Falter, U., Climos, K., Schelstraete, I., Brodsky, A., von Rosensteil, P., 2009. Brivaracetam as adjunctive treatment of refractory partial-onset seizures in adults: results from two randomized, double-blind, placebo-controlled trials. Epilepsia 50, 106—107.
Biton, V., Abou-Khalil, B., Kasteleijn-Nolst Trenité, D., French, J., Krauss, G., Rigdon, G., Moore, E., Hetherington, S., 2010. A Clinical Study of the Effect of ICA-105665 on Photic-induced Paroxysmal EEG Responses. American Epilepsy Society (Abst. 1.271).
Brochot, A., Zamacona, M., Stockis, A., 2010. Physiologically based pharmacokinetic/pharmacodynamic animal-to-man prediction of therapeutic dose in a model of epilepsy. Basic Clin. Pharmacol. Toxicol. 106, 256—262.
Brodsky, A., Costantini, C., von Rosenstiel, P., 2007. Safety and tolerability of brivaracetam (ucb 34714) as adjunctive treatment in adults with refractory partial-onset seizures. Epilepsia 48 (Suppl 6), 342.
Bulaj, G., Green, B.R., Lee, H.-K., Robertson, C.R., White, K., Zhang, L., Sochanska, M., Flynn, S.P., Scholl, E.A., Pruess, T.H., Smith, M.D., White, H.S., 2008. Design, synthesis, and characterization of high-affinity, systemically-active galanin analogues with potent anticonvulsant activities. J. Med. Chem. 51, 8038—8047.
Ceolin, L., Bortolotto, Z.A., Bannister, N., Collingridge, G.L., Lodge, D., Volianskis, A., 2012. A novel anti-epileptic agent, perampanel, selectively inhibits AMPA receptor-mediated synaptic transmission in the hippocampus. Neurochem. Int. ISSN 0197-0186, http://dx.doi.org/10.1016/j.neuint.2012.02.035 (accessed 10.03.12).
Costa, E., Guidotti, A., 1996. Benzodiazepines on trial: a research strategy for their rehabilitation. Trends Pharmacol. Sci. 17, 192—200.
Detrait, E.R., Leclercq, K., Löscher, W., et al., 2010. Brivaracetam does not alter spatial learning and memory in both normal and amygdala-kindled rats. Epilpesy Res. 91, 74—83.
Damodaram, S., Thalakoti, S., Freeman, S.E., Garrett, F.G., Durham, P.L., 2009. Tonabersat inhibits trigeminal ganglion neuronal-satellite glial cell signaling. Headache 49, 5—20.
Elliott-Hunt, C.R., Pope, R.J., Vanderplank, P., Wynick, D., 2007. Activation of the galaninreceptor 2 (GalR2) protects the hippocampus from neuronal damage. J. Neurochem. 100, 780—789.
Elman, I., Sokoloff, L., Adler, C.M., Weisenfeld, N., Brier, A., 1999. The effects of pharmacological doses of 2-deoxyglucose on cerebral blood flow in healthy volunteers. Brain Res. 815, 243—249.
French, J.A., Costantini, C., Brodsky, A., von Rosenstiel, P., N01193 Study Group, 2010. Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. Neurology 75, 519—525.
French, J., Krauss, G., Biton, V., Squillacote, D., Yang, H., Laurenza, A., Kumar, D., Rogawski, M.A., 2012a. Adjunctive perampanel for refractory partial-onset seizures: randomized Phase III study 304. Neurology 79, 589—596.
French, J., Krauss, G., Steinhoff, B.J., David Squillacote, D., Yang, H., Kumar, D., Laurenza, A., 2012b. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. Epilepsia, http://dx.doi.org/10.1111/j.1528-1167.2012.03638.x [Epub ahead of print].
Frey, H.-H., Löscher, W., 1985. Pharmacokinetics of anti-epileptic drugs in the dog: a review. J. Vet. Pharmacol. Ther. 8, 219—233.
Gasior, M., Yankura, J., Hartman, A.L., French, A., Rogawski, M., 2010. Anticonvulsant and proconvulsant actions of 2-deoxy-D-glucose glucose. Epilepsia 51, 1385—1394.
Garrett, F.G., Durham, P.L., 2008. Differential expression of connexins in trigeminal ganglion neurons and satellite glial cells in response to chronic or acute joint inflammation. Neuron Glia Biol. 4, 295—306.
Garriga-Canut, M., Schoenike, B., Qazi, R., Bergendahl, K., Daley, T.J., Pfender, R., Morrison, J.F., Ockuly, J., Stafstrom, C., Sutula, T., Roopra, A., 2006. 2-deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP - dependent metabolic regulation of chromatin structure. Nat. Neurosci. 9, 1382—1387.
Gillard, M., Fuks, B., Leclercq, K., Matagne, A., 2011. Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties. Eur. J. Pharmacol. 664, 36—44.
Hanada, T., Hashizume, Y., Tokuhara, N., Takenaka, O., Kohmura, N., Ogasawara, A., Hatakeyama, S., Ohgoh, M., Ueno, M., Nishizawa, Y., 2011. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. Epilepsia 52, 1331—1340.
Herd, M.B., Belelli, D., Lambert, J.J., 2007. Neurosteroid modulation of synaptic and extrasynaptic $GABA_A$ receptors. Pharmacol. Ther. 116, 20—34.
Hosie, A.D., Wilkins, M.E., da Silva, H.M.A., Smart, T.G., 2006. Endogenous neurosteroids regulate $GABA_A$ receptors through two discrete transmembrane sites. Nature 444, 486—489.
Hutchinson, E., Rutecki, P., Meyerand, M.E., Sutula, T., 2010. MRI and DTI markers for TBI-related brain tissue damage and plasticity in a rat CCI model demonstrate protective effects of 2DG. Program No. 356.9 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2010. www.sfn.org
Hetherington, S., Biton, V., Rigdon, G., Moore, E., and Wargin, W., 2009. A multiple, ascending-dose study of ICA-105665 in patients with epilepsy. American Epilepsy Society (Abst. 1.234), 2009.
Joshi, S., Rajasekaran, K., Kapur, J., 2011. GABAergic transmission in temporal lobe epilepsy: the role of neurosteroids. Exp. Neurol., http://dx.doi.org/10.1016/j.expneurol.2011.10.028.
Kaminski, R.M., Matagne, A., Leclercq, K., et al., 2008. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacology 54, 715—720.
Kasteleijn-Nolst Trenité, D.G.A., Marescaux, C., Stodieck, S., Edelbroek, P.M., Oosting, J., 1996. Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue levetiracetam. Epilepsy Res. 25, 225—230.
Kaufmann, D., Bialer, M., Yagen, B., Shimshoni, A., Devor, M., Yagen, B., 2009. Synthesis and evaluation of antiallodynic and anticonvulsant activity of novel amide and urea derivatives of valproic acid analogues. J. Med. Chem. 52, 7236—7248.
Kaufmann, D., Yagen, B., Minert, A., Wlodarczyk, B., Finnell, R.H., Schrig, V., Devor, M., Bialer, M., 2010. Evaluation of the antiallodynic, teratogenic and pharmacokinetic profile of stereoisomers of valnoctamide, an amide derivative of a chiral isomer of valproic acid. Neuropharmacology 52, 1228—1236.
Kenakin, T., 2006. A Pharmacology Primer. Theory, Applications, and Methods. Academic Press, Amsterdam.
Kenda, B.M., Matagne, A.C., Talaga, P.E., et al., 2004. Discovery of 4-substituted pyrrolidone butanamides as new agents with significant antiepileptic activity. J. Med. Chem. 47, 530—549.
Kerrigan, J.F., Shields, W.D., Nelson, T.Y., Bluestone, D.L., Dodson, W.E., Bourgeois, B.F., Pellock, J.M., Morton, L.D., Monaghan, E.P., 2000. Ganaxolone for treating intractable infantile spasms: a multicenter, open-label, add-on trial. Epilepsy Res. 42, 133—139.

Krauss, G.L., Bar, M., Biton, V., Klapper, J.A., Rektor, I., Vaiciene-Magistris, N., Squillacote, D., Kumar, D., 2011. Tolerability and safety of perampanel: two randomized dose-escalation studies. Acta Neurol. Scand. 125, 8—15.

Krauss, G.L., Serratosa, J.M., Villanueva, V., Endziniene, M., Hong, Z., French, J., Yang, H., Squillacote, D., Edward,s, H.B., Zhu, J., Laurenza, A., 2012. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 78, 1408—1415.

Kwan, P., Johnson, M.E., Falter, U., Pieteur, V.B., Brodsky, A., von Rosensteil, P., 2009. Safety and tolerability of brivaracetam as adjunctive treatment in adults with refractory epilepsy: randomized, double-blind, placebo-controlled trial. Epilepsia 50, 107—108.

Kwan, P., Johnson, M., Merschhemke, M., Lu, S., 2010. Adjunctive brivaracetam in adults with uncontrolled generalized seizures: sub-population analysis of the results of a randomized, double-blind, placebo-controlled trial. [Abstract]. http://www.aesnet.org/go/publications/aes-abstracts/abstract-search/mode/display/st/brivaracetam/sy/2010/sb/All/id/12467

Lang, R., Kofler, B., 2011. The galanin peptide family in inflammation. Neuropeptides 45, 1—8.

Laurenza, A., Ferry, J., Hussein, Z., 2011. Population pharmacokinetics and pharmacodynamics of perampanel: a pooled analysis from three phase III trials [Abstract 2.231] Abstract presented at AES 2011.

Laxer, K., Blum, D., Abou-Khalil, B.W., Morrell, M.J., Lee, D.A., Data, J.L., Monaghan, E.P., the Ganaxolone Presurgical Study Group, 2000. Assessment of ganaxolone's anticonvulsant activity using a randomized, double-blind, presurgical trial design. Epilepsia 41, 1187—1194.

Lian, X.Y., Khan, F.A., Stringer, J.L., 2007. Fructose-1,6-bisphosphate has anticonvulsant activity in models of acute seizures in adult rats. J. Neurosci. 27, 12007—12011.

Löscher, W., Schwartz-Porsche, D., Frey, H.-H., Schmidt, D., 1985. Evaluation of epileptic dogs as an animal model of human epilepsy. Arzneim-Forsch/Drug Res. 35, 82—87.

Löscher, W., Hönack, D., Scherkl, R., Hashem, A., Frey, H.-H., 1990. Pharmacokinetics, anticonvulsant efficacy and adverse effects of the β-carboline abecarnil, a novel ligand for benzodiazepine receptors, after acute and chronic administration in dogs. J. Pharmacol. Exp. Ther. 255, 541—548.

Löscher, W., Potschka, H., Rieck, S., Tipold, A., Rundfeldt, C., 2004. Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. Epilepsia 45, 1228—1239.

Lynch, B.A., Lambeng, N., Nocka, K., et al., 2004. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc. Natl. Acad. Sci. U. S. A. 101, 9861—9866.

Mahoney, S.A., Hosking, R., Farrant, S., Holmes, F.E., Jacoby, A.S., Shine, J., Iismaa, T.P., Scott, M.K., Schmidt, R., Wynick, D., 2003. The second galanin receptor GalR2 plays a key role in neurite outgrowth from adult sensory neurons. J. Neurosci. 15, 416—421.

Matagne, A., Margineanu, D.-G., Kenda, B., Michel, P., Klitgaard, H., 2008. Anti-convulsive and anti-epileptic properties of brivaracetam (ucb 34714), a high-affinity ligand for the synaptic vesicle protein, SV2A. Br. J. Pharmacol. 154, 1662—1671.

Matagne, A., Klitgaard, H., 1998. Validation of corneally kindled mice: a sensitive screening model for partial epilepsy in man. Epilepsy Res. 31 (1), 59—71.

Mazarati, A.M., Halászi, E., Telegdy, G., 1992. Anticonvulsive effects of galanin administered into the central nervous system upon the picrotoxin-kindled seizure syndrome in rats. Brain Res. 28, 164—166.

Mazarati, A.M., Liu, H., Soomets, U., Sankar, R., Shin, D., Katsumori, H., Langel, U., Wasterlain, C.G., 1998. Galanin modulation of seizures and seizure modulation of hippocampal galanin in animal models of status epilepticus. J. Neurosci. 18, 10070—10077.

Mazarati, A.M., Hohmann, J.G., Bacon, A., Liu, H., Sankar, R., Steiner, R.A., Wynick, D., Wasterlain, C.G., 2000. Modulation of hippocampal excitability and seizures by galanin. J. Neurosci. 15, 6276—6281.

Mazarati, A., Lu, X., Shinmei, S., Badie-Mahdavi, H., Bartfai, T., 2004a. Patterns of seizures, hippocampal injury and neurogenesis in three models of status epilepticus in galanin receptor type 1 (GalR1) knockout mice. Neuroscience 128, 431—441.

Mazarati, A., Lu, X., Kilk, K., Langel, U., Wasterlain, C., Bartfai, T., 2004b. Galanin type 2 receptors regulate neuronal survival, susceptibility to seizures and seizure-induced neurogenesis in the dentate gyrus. Eur. J. Neurosci. 19, 3235—3244.

Mazarati, A., Lu, X., 2005. Regulation of limbic status epilepticus by hippocampal galanin type 1 and type 2 receptors. Neuropeptides 39, 277—280.

Mazarati, A., Lundström, L., Sollenberg, U., Shin, D., Langel, U., Sankar, R., 2006. Regulation of kindling epileptogenesis by hippocampal galanin type 1 and type 2 receptors: The effects of subtype-selective agonists and the role of G-protein-mediated signaling. J. Pharmacol. Exp. Ther. 318, 700—708.

Mehta, A.K., Ticku, M.K., 1999. An update on GABA(A) receptors. Brain Res. Rev. 29, 196—217.

Minor, R.K., Smith, D.L., Sossang, A.M., Kaushik, S., Poosala, S., Spangler, E.L., Roth, G.S., Lane, M., Allison, D.B., deCabo, R., Ingraham, D., Mattison, J.A., 2010. Chronic ingestion of 2-deoxy-D-glucose induces cardiac vacuolization and increases mortality in rats. Toxicol. Appl. Pharm. 243, 332—339.

Niespodziany, I., Leclere, N., Matagne, A., Wolff, C., 2009. Brivaracetam modulates Na^+ currents expressed in a neuroblastoma cell line compared with carbamazepine. Epilepsia 50, 107.

Ockuly, J., Gielissen, J., Levenick, C., Zeal, C., Groble, K., Munsey, k., Sutula, T., Stafstrom, C.E., 2012. Behavioral and cognitive effects and safety profile of 2-deoxy-2-glucose (2DG) in adult rats. Epilepsy Res 101, 246—252.

Perucca, E., French, J., Bialer, M., 2007. Development of new antiepileptic drugs: challenges, incentives, and recent advances. Lancet Neurol. 6, 793—804.

Pieribone, V.A., Tsai, J., Soufflet, C., Rey, E., Shaw, K., Giller, E., Dulac, O., 2007. Clinical evaluation of ganaxolone in pediatric and adolescent patients with refractory epilepsy. Epilepsia 48, 1870—1874.

Podell, M., 1996. Seizures in dogs. Vet. Clin. North Am. Small Anim. Pract. 26, 779—809.

Raez, L.E., Langmuir, V., Tolba, K., Rocha-Lima, C.M., Papadopoulos, K., Kroll, S., Brawer, M., Rosenblatt, J., Ricart, A., Lampidis, T., 2007. Responses to the combination of the glycolytic inhibitor 2-deoxy-glucose (2DG) and docetaxel (DC) in patients with lung and head and neck (H/N) carcinomas. J. Clin. Onc. ASCO Ann. Meeting Proc. 25 (s18), 14025.

Ravizza, T., Noé, F., Zardoni, D., Vaghi, V., Sifringer, M., Vezzani, A., 2008. Interleukin Converting Enzyme inhibition impairs kindling epileptogenesis in rats by blocking astrocytic IL-1beta production. Neurobiol. Dis. 31, 327—333.

Reddy, D.S., Rogawski, M.A., 2000. Chronic treatment with the neuroactive steroid ganaxolone in the rat induces anticonvulsant tolerance to diazepam but not to itself. J. Pharmacol. Exp. Ther. 295, 1241—1248.

Reddy, D.S., Rogawski, M.A., 2010. Ganaxolone suppression of behavioral and electrographic seizures in the mouse amygdala kindling model. Epilepsy Res. 89, 254—260.

Reddy, D.S., Rogwski, M.A., 2012. Neurosteroids — Endogenous regulators of seizure susceptibility and role in the treatment of epilepsy (Chapter 77), Jasper's Basic Mechanisms of the Epilepsies, Fourth Edition. In: Noebels, J.L., Avoli, M., Rogawski, M.A., Olsen, R.W., Delgado-Escueta, A.V. (Eds.), Contemporary Neurology Series 80. Oxford University Press, pp. 984—1002.

Rigdon, G., Hetherington, S., Moore, E., Allison, M., Wargin, W., 2009. ICA-105665-02: Multiple, Ascending Dose Study: Healthy Volunteers. American Epilepsy Society (Abst. 1.233).

Risner, M., Rigdon, G., Moore, E., Allison, M., Wargin, W., Hetherington, S., 2009. A single ascending dose study of ICA-105665 in healthy volunteers. American Epilepsy Society (Abst. 1.228).

Robertson, C.R., Scholl, E.A., Pruess, T.H., Green, B.R., White, H.S., Bulaj, G., 2010. Engineering galanin analogues that discriminate between GalR1 and GalR2 subtypes and exhibit anticonvulsant activity following systemic delivery. J. Med. Chem. 53, 1871—1875.

Rogawski, M.A., Loscher, W., 2004. The neurobiology of antiepileptic drugs. Nat. Rev. Neurosci. 5, 553—564.

Rolan, P., Sargentini-Maier, M.L., Pigeolet, E., Stockis, A., 2008. The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy males. Br. J. Clin. Pharmacol. 66, 71—75.

Rosillon, D., Astruc, B., Hulhoven, R., Meeus, M.A., Troenaru, M.M., Watanabe, S., Stockis, A., 2008. Effect of brivaracetam on cardiac repolarisation-a thorough QT study. Curr. Med. Res. Opin. 24, 2327—2337.

Rostock, A., Tober, C., Dost, R., Rundfeldt, C., Bartsch, C., Egerland, U., Stark, B., Schupke, H., Kronbach, T., Lankau, H.-J., Unverferth, K., Engel, J., 1998a. AWD-131-138. Drugs Fut. 23, 253—255.

Rostock, A., Tober, C., Dost, R., Bartsch, R., 1998b. AWD 131-138 is a potential novel anxiolytic without sedation and amnesia: a comparison with diazepam and buspirone. Naunyn-Schmied. Arch. Pharmacol. 358 (Suppl. 1), R68.

Ryvlin, P., Lagae, L., Unterberger, I., Squillacote, D., Yang, H., Kumar, D., Laurenza, A., 2011. Perampanel as adjunctive therapy in patients with refractory partial-onset seizures: safety and tolerability analysis from a phase III trial [Abstract 2.236]. Abstract presented at AES 2011.

Sigel, E., Baur, R., Netzer, R., Rundfeldt, C., 1998. The antiepileptic drug AWD 131-138 stimulates different recombinant isoforms of the rat GABA(A) receptor through the benzodiazepine binding site. Neurosci. Lett. 245, 85—88.

Sargentini-Maier, M.L., Rolan, P., Connell, J., et al., 2007. The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. Br. J. Clin. Pharmacol. 63, 680—688.

Sargentini-Maier, M.L., Espie, P., Coquette, A., Stockis, A., 2008a. Pharmacokinetics and metabolism of ^{14}C-brivaracetam, a novel SV2A ligand, in healthy subjects. Drug Metab. Dispos. 36, 36—45.

Sargentini-Maier, M.L., Homery, M.C., Stockis, A., on behalf of the Brivaracetam N01118 Study Group, 2008b. Pharmacokinetics, safety and tolerability of brivaracetam in healthy elderly subjects. Epilepsia 49 (Suppl. 7), 452.

Sargentini-Maier, M.L., Sokalski, A., Boulanger, P., Jacobs, T., Stockis, A., 2012. Brivaracetam disposition in renal impairment. J. Clin. Pharmacol., http://dx.doi.org/10.1177/0091270011431457.

Singh, D., Banerji, A.K., Dwarakanath, B.S., et al., 2005. Optimizing cancer radiotherapy with 2-deoxy-D-glucose: dose escalation studies in patients with glioblastoma multiforme. Strahlenther Onkol. 181, 507—514.

Stafstrom, C., Ockuly, J., Valley, M., Roopra, A., Sutula, T., 2009. Novel anticonvulsant and antiepileptic properties of 2-deoxy-D-glucose in experimental epilepsy models. Ann. Neur. 65, 435—448.

Stafstrom, C.E., Ockuly, J.C., Gielissen, J., Levenick, C., Zeal, C., Sutula, T.P., 2007. 2-Deoxyglucose effects on spatial learning and exploratory behavior in rodents. Epilepsia 48 (Suppl. 6), 299.

Stein, M., Lin, H., Jeyamohan, C., Dvorzhinski, D., Gounder, M., Bray, K., Eddy, S., Goodin, S., White, E., DiPaola, R.S., 2010. Targeting tumor metabolism with 2-deoxyglucose in patients with castrate-resistant prostate cancer and advanced malignancies. Prostate 70, 1388—1394.

Stockis, A., Sargentini-Maier, M.L., Boulton, M., Horsmans, Y., 2008. Pharmacokinetics of brivaracetam in subjects with hepatic impairment and in matched healthy controls. Epilepsia 49 (Suppl. 7), 457.

Stockis, A., Hulhoven, R., Astruc, B., et al., 2009. Interaction study between brivaracetam and a combination oral contraceptive. Epilepsia 50 (Suppl. 10), 96.

Stockis, A., Watanabe, S., Rouits, E., Matsuguma, K., Irie, S., 2011. Double-blind, placebo-controlled single and multiple rising dose study of brivaracetam in healthy Japanese male subjects — influence of CYP2C19 genotype. [Abstract] http://www.aesnet.org/go/publications/aes-abstracts/abstract-search/mode/display/st/brivaracetam/sy/2011/sb/All/id/14664 UCB, Data on file.

Sutula, T., Franzoso, S., 2008. Dose-response and time course of action of disease-modifying effects of 2DG on kindling progression: effectiveness of administration after seizures. Epilepsia 49 (Suppl. 7), 382.

Tober, C., Rostock, A., Bartsch, R., 1998. AWD 131-138: a derivative of a series of imidazolinones with anticonvulsant activity. Naunyn-Schmied. Arch. Pharmacol. 358 (Suppl. 1), R68.

Tober, C., Rostock, A., White, H.S., Wolf, H.H., Bartsch, R., 1999. Anticonvulsant activity of AWD 131-138 in genetic animal models of epilepsy. Naunyn-Schmied. Arch. Pharmacol. 359 (Suppl. 3), R97.

Van Paesschen, W., Brodsky, A., von Rosenstiel, P., 2007. Efficacy and tolerability of 50 and 150 mg/day brivaracetam (UCB 34714) as adjunctive treatment in adults with refractory partial onset epilepsy. Epilepsia 48 (Suppl. 6), 329.

Vezzani, A., Balosso, S., Ravizza, T., 2008. The role of cytokines in the pathophysiology of epilepsy. Brain Behav. Immun. 22, 797—803.

von Rosenstiel, P., Perucca, E., 2009. Brivaracetam. In: Shorvon, S., Perucca, E., Engel Jr., J. (Eds.), The treatment of epilepsy. , 3 edn. Wiley-Blackwell, Chichester, pp. 447—457.

Wannamaker, W., Davies, R., Namchuk, M., Pollard, J., Ford, p., Ku, G., Decker, C., Charifson, P., Weber, P., German, U.A., Kuida, K., Randle, J.C.R., 2007. (S)-1-((S)-2-{[1-(4-amino-3-chloro-phenyl)-methanol]-amino}-3,3-dimethyl-butanoyl)-pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxo-tetrahydro-furan-3-yl)-amine (VX-765), an orally available selective interleukin (IL)-converting enzyme/caspase-1 inhibitor, exhibits potent anti-inflammatory activities by inhibiting the release of IL-1β and IL-18. J. Pharamcol. Exper Ther. 321, 509—516.

Wasterlain, C.G., Suchomelova, L., Matagne, A., Klitgaard, H., Niquet, J., Baldwin, R., 2009. Short-term and long-term effects of brivaracetam in an animal model of status epilepticus. Epilepsia 50 (Suppl. 10), 13.

White, H.S., Scholl, E.A., Klein, B.D., Flynn, S.P., Pruess, T.H., Green, B.R., Zhang, L., Bulaj, G., 2009. Developing novel antiepileptic drugs: characterization of NAX 5055, a systemically-active galanin analog, in epilepsy models. Neurotherapeutics 6, 372—380.

White, H.S., Alex, A.B., Pollock, A., Hen, N., Shekh-Ahmed, T., Wilcox, K.S., McDonough, J.H., Stables, J.P., Kaufmann, D., Yagen, B., Bialer, M., 2012. A new derivative of valproic acid amide possesses a broad-spectrum antiseizure profile and unique

activity against status epilepticus and organophosphate neuronal damage. Epilepsia 53, 134—146.

Yasar, S., Bergman, J., Munzar, P., Redhi, G., Tober, C., Knebel, N., Zschiesche, M., Paronis, C., 2003. Evaluation of the novel antiepileptic drug, AWD 131-138, for benzodiazepine-like discriminative stimulus and reinforcing effects in squirrel monkeys. Eur. J. Pharmacol. 465, 257—265.

Zhang, L., Robertson, C.R., Green, B.R., Pruess, T.H., White, H.S., Bulaj, G., 2009. Structural requirements for a lipoamino acid in modulating the anticonvulsant activities of systemically active galanin analogues. J. Med. Chem. 52, 1310—1316.

Zini, S., Roisin, M.P., Langel, U., Bartfai, T., Ben-Ari, Y., 1993. Galanin reduces release of endogenous excitatory amino acids in the rat hippocampus. Eur. J. Pharmacol. 15, 1—7.

Zona, C., Pieri, M., Carunchio, I., Curcio, L., Klitgaard, H., Margineanu, D.G., 2010. Brivaracetam (ucb 34714) inhibits Na^+ current in rat cortical neurons in culture. Epilepsy Res. 88, 46—54.