Retigabine

Roger J. Porter,^{*} Virinder Nohria,[†] and Chris Rundfeldt[‡]

^{*}Department of Pediatrics, School of Medicine, Emory University, Atlanta, Georgia 30322; [†]111 Skyline View Road, Franklin, North Carolina 28734; and [‡]elbion AG, Meissner Straße 191, D-01445, Radebeul, Germany

Summary: Retigabine is a novel antiseizure drug that acts through potassium channels and has activity in a broad range of animal models of epilepsy. It is also effective in several preclinical pain models. The drug has been extensively studied in phase I and II studies, with very promising results. The maximal tolerated dose

for most patients is 1,200 mg/day. Adverse effects have been largely CNS-related and mild; most have occurred during the titration periods in the various studies. At present, retigabine is in two pivotal phase III studies. **Key Words:** Retigabine, potassium channels, partial-onset seizures, epilepsy.

INTRODUCTION

The most refractory seizure type in humans is the complex partial seizure. Patients with this epileptic disorder not only suffer the immediate consequences of having unpredictable attacks with alteration of consciousness, but also suffer socially, with limitations on such matters as insurance, job availability, and driving.

The development of new antiseizure drugs has been an ongoing effort of both the U.S. government and of pharmaceutical companies since the 1940s. In spite of these efforts, hundreds of thousands of patients worldwide continue to suffer uncontrolled partial seizures. It is in this context that retigabine is being vigorously pursued as a highly promising potential new drug.

CHEMISTRY

Retigabine, *N*-(2-amino-4-(4-fluorobenzylamino)phenyl)carbamic acid ethyl ester (D-23129), is a white to slightly colored, odorless, tasteless, and nonhygroscopic crystalline powder with a melting point of 138–145°C. It is made in a two-step synthesis, using commercially available starting materials, followed by recrystallization and drying, yielding drug substance with high purity. Three polymorphic forms (modifications) are known for retigabine. Crystal modification A was selected for development (FIG. 1).

PHARMACOLOGY

Retigabine was identified using an *in vivo* screening approach driven by pharmacophore modeling. This strategy differs from common target-driven research programs. Although rational and straightforward in strategy, target-driven screening approaches involve a number of risks. First of all, target-driven programs can run only on known targets; that is, the identified drug acts only via a known target already utilized by established drugs.¹ Such compounds may deliver incremental improvement for the treatment of epilepsy and may have a distinct and potentially better side-effect profile, but they are unlikely to be of great advantage for the treatment of drug-refractory epilepsy, which is the central medical need in this field.

A second risk is that a newly identified target, which therefore lacks clinical validation, fails to deliver a compound that is both active and safe in patients. An example for such a program was the identification of the NMDA receptor for the treatment of epilepsy.² The high hopes generated in preclinical, mechanism-driven models with regard to activity and side-effect profile did not translate into clinical utility.

A third risk is that, even though epilepsy is a heterogeneous disease, target-directed programs are aimed at finding compounds with high selectivity for one target. Resulting compounds may fail due to lack of efficacy or safety in a field patient population. Indeed, most currently successful drugs marketed for the treatment of epilepsy address more than one target, contributing to the overall activity and tolerability.

Address correspondence and reprint requests to: Roger J. Porter, M.D., Adjunct Professor of Neurology, University of Pennsylvania, Philadelphia, PA 19104-4283. E-mail: rjportermd@aol.com.

FIG. 1. Chemical structure of retigabine, *N*-(2-amino-4-(4-fluorobenzylamino)phenyl)carbamic acid ethyl ester. Molecular weight: 303.3 g/mol. Molecular formula: $C_{16}H_{18}FN_3O_2$.

To overcome these risks, the screening strategy that resulted in the discovery of retigabine was designed to identify compounds with potent activity in animal models of epileptic seizures that are distinct from known anticonvulsants—that is, compounds that do not interact with the mechanisms of action of known anticonvulsants. With this strategy, it is possible to find potentially innovative drugs that interact with targets as yet unknown and that are active in validated animal models of epileptic seizures. This primary screening approach was supported by the U.S. National Institutes of Health within the antiepileptic drug development (ADD) program.³

Flupirtine, a centrally acting analgesic with what was at the time an unknown mechanism of action,⁴ was identified within the ADD program as an active compound in a number of screening models. Because the compound was (and is) marketed in Germany and several countries as an analgesic, its potential use as antiepileptic could be immediately evaluated in a small clinical trial. Indeed, flupirtine was found to be active; however, the doses used in this trial exceeded the doses established for analgesic activity.⁵ Given these data, flupirtine fulfilled the criteria for a starting point for structural optimization aiming at a derivative with higher anticonvulsant activity, better tolerability, and reduced analgesic potential. The subsequent program, driven by quantitative structure activity studies and pharmacophore modeling,⁶ yielded retigabine.

In animal models of epileptic seizures, retigabine was shown to have a very broad spectrum of activity, in that the compound was active in nearly every model tested. It was effective in primary screening tests in mice and rats.⁷ It blocked seizures in both the maximal electroshock model (MES) (tonic hindlimb extension) and pentylenetetrazole (PTZ)-induced seizure model (clonus threshold).⁸ The former results suggest that the drug is effective against generalized tonic-clonic human seizures (similar to carbamazepine, phenytoin, and valproate), and the latter suggests activity against generalized absence or myoclonic seizures (similar to valproate and ethosuximide).⁹

In a comparison of anticonvulsant activity of retigabine with the activity of standard anticonvulsants in the traditional MES test, retigabine was effective in both mice and rats after either oral or intraperitoneal administration. The protective index (PI) calculated from the

TD_{50} in the rotarod test (i.e., the dose inducing adverse effects on the rotarod in 50% of animals) and the ED_{50} in the MES reached 2.2 and 2.4 in mice and 2.0 and 29.1 in rats after intraperitoneal and oral administration, respectively. The PI values in mice are more favorable for retigabine than for valproate, but do not reach the PI values of phenytoin or carbamazepine.⁷

Threshold variants of the MES and PTZ seizure models are commonly used to determine the minimal dose of a compound capable of exerting anticonvulsant activity. In such tests, the dose necessary to increase seizure threshold by 50% (TID_{50}) above the control is determined. Such threshold doses are thought to yield plasma levels in animals that are more reflective of clinically relevant plasma levels than those following supramaximal doses. Retigabine was very effective in elevating the threshold for MES-induced seizures in mice and rats, yielding a significant increase after application of 1 and 0.5 mg/kg, respectively. The PI calculated from the TID_{50} in the MES and the TD_{50} in the rotarod test was in the same range as the ratios for the standard anticonvulsants phenobarbital, carbamazepine, phenytoin, and valproate. Retigabine was also effective in elevating the intravenously infused dose of PTZ that is needed to induce generalized clonic seizures in mice, with a TID_{50} of 5 mg/kg.⁷ In addition, retigabine exhibited anticonvulsant activity against penicillin, picrotoxin, kainite, and intracerebroventricularly administered NMDA, but not against bicuculline- or strychnine-induced seizures.^{7,10,11}

The models mentioned thus far are models of epileptic seizures, but not of epilepsy. Furthermore, the models were identified and characterized using established anticonvulsants.¹² Because the medical need is to find drugs that are active in patients with drug-refractory epilepsy, it would be advantageous to find drugs that are active in more closely disease-related models, and even further in models of drug-refractory epilepsy.

Genetic epilepsy models, kindling models, and models of epileptogenesis after neurochemical induction of status epilepticus serve the purpose of being more closely related to epilepsy as a disease, but the issue of identifying animal models of resistance to drug treatment still remains a challenge. Amygdala kindling has been frequently discussed as a potential model of resistance to drug treatment, but so far this has not been proven. Other models represent treatment-resistant discharges in brain slices, but it remains to be validated whether the data generated can be translated into clinical success. To evaluate the potential of retigabine, it was tested in all of these models.

Two commonly used genetic models of epilepsy are audiogenic seizure-susceptible DBA/J2 mice and genetically epilepsy-prone (GEPR) rats. Retigabine effectively suppressed sound-induced seizures in both.^{13,14} It

showed a greater potency against the moderate seizures of GEPR-3s than in the severe seizures of GEPR-9s, which is suggestive of a broad-spectrum anticonvulsant profile.¹³

Retigabine was also potently active in several different kindling models. Kindling involves a progressive potentiation of seizure susceptibility as a result of initially subconvulsive electrical or chemical stimulation. The increased seizure susceptibility persists even if stimulation is stopped, resembling epileptogenesis. Indeed, if stimulation is continued, spontaneous recurrent seizures develop. The most common paradigm is amygdala kindling, which is considered the most predictive animal model of human complex partial seizures.^{9,12} Retigabine was very potent and effective in this model. At doses as low as 0.01 mg/kg, retigabine increased the electrical threshold for induction of afterdischarges.¹⁵ At 5 mg/kg, the compound not only increased the threshold for afterdischarges by 450% but also reduced seizure severity and seizure duration. This dose was free of side effects in kindled rats.

Because epileptic seizures are thought to be initiated by an epileptogenic disturbance surpassing an endogenous threshold,¹⁶ even a modest increase in threshold might yield full seizure control. If kindled animals are stimulated 20% above their individual seizure threshold, full suppression of seizures is obtained in most animals even with doses of 0.01 mg/kg. In contrast to most other anticonvulsants, retigabine was found to be more potent in kindling models than in other seizure models, such as MES. Retigabine was also active in two other kindling models, namely, hippocampal kindling in rats¹⁷ and corneal kindling in mice.

The potent activity of retigabine in kindling models may be taken as a hint that this compound may be suitable for the treatment of drug-refractory epilepsy. The potential utility for refractory epilepsy was further substantiated in *in vitro* models of treatment-resistant epileptiform discharges. In one model, a reduction of magnesium induces late recurrent discharges in entorhinal cortex, which could be suppressed by retigabine but not by conventional anticonvulsants¹⁸; similarly, entorhinal cortex discharges induced by 4-aminopyridine were also suppressed.¹⁹ Retigabine was also capable of suppressing different discharge patterns in cortical tissue excised from drug-refractory patients undergoing surgical removal of the epileptic focus.²⁰

The amygdala kindling model has been discussed also as a model of epileptogenesis. Because repetitive stimulations are needed to induce the persistent hyperexcitability, it is possible to try to prevent this process. A common approach is daily administration of the anticonvulsant, prior to the kindling stimulus. Retigabine (5 mg/kg i.p.) was capable of potently suppressing the development of hyperexcitability. If treatment was termi-

nated after 22 days and kindling stimulation was resumed after a wash-out period of 1 week, retigabine-treated rats behaved similarly to nonkindled rats, in that the number of stimulations needed to reach the first stage 5 seizure was comparable—indicating suppression of epileptogenesis.

To further evaluate the performances of retigabine in this model, the compound was administered daily (with valproic acid as reference) immediately after the kindling stimulus, to see whether the proposed neuronal plasticity induced by kindling could be modulated independently of the occurrence of afterdischarges. Neither valproic acid at 200 mg/kg i.p. nor retigabine was capable of modulating the kindling process in this setup.²¹ These data indicate that a full seizure control is likely the best approach to prevent epileptogenesis or progression of the disease.

Mechanism of action of retigabine

Based on the particular profile of retigabine in seizure models and models of epilepsy, it was concluded that the compound likely differs in mechanism of action of conventional anticonvulsants. Indeed, retigabine was found not to interact with NMDA or kainite-induced currents in rat cortical neurons and to have only very weak blocking effects on neuronal sodium and mixed calcium currents at 100 μ mol/L.²² Retigabine was found to potentiate GABA-induced currents in rat cortical neurons. This effect was insensitive to the benzodiazepine binding site antagonist flumazenil, indicating that the compound differs from benzodiazepines.

The extent of activity of retigabine on GABA-induced currents was likely not sufficient to explain the broad-spectrum activity of retigabine in animal models.²² Indeed, retigabine was found to activate neuronal potassium channels in different cell preparations.^{23,24} The channel targeted was later identified as a member of the KCNQ channel, lately renamed the Kv7 channel.²⁵ The concentration needed to activate this potassium channel was more than 30-fold lower than concentrations needed to potentiate GABA-induced currents.²² Kv7 channels were identified to be the molecular correlate of the M-current; that is, retigabine acts as an M-current activator. This channel has long been known to control excitability of neuronal cells. Furthermore, mutation of Kv7 channel subunits has been identified in a hereditary epilepsy syndrome, benign familial neonatal convulsions (BFNC).²⁶

Mutations identified in either of the two genes identified in BFNC pedigrees result in a moderate reduction of the function of the heteromultimeric Kv7.2/3 channel.²⁷ Although these data strengthen the role of Kv7 channels in epilepsy and support the idea that the activity of retigabine is mediated primarily by this target, it could further be shown that retigabine was also capable of activating the mutated heteromultimeric Kv7.2/3 channel

(T.J. Jentsch and C. Rundfeldt, 2000, unpublished observation). Retigabine thus is capable of selectively reverting the deficit induced by a gene defect, without gene therapy.

The role of Kv7 channels for neuronal excitability has been subject to intensive research and, based on the target information, additional medical uses could be identified for retigabine.²⁸ Although the analgesic activity of retigabine was reduced compared to that of flupirtine, it was found to be particularly active in models of neuropathic pain,^{29,30} and the activity could be reversed using the KCNQ channel blocker linopirdine.³⁰ Because neuronal potassium channels, including Kv7 channels, are discussed as potential targets for neuroprotection, retigabine was evaluated in three models of neurodegeneration. It was found to reduce infarct size in a model of permanent medial cerebral artery occlusion; it reversed functional deficits induced by unilateral carotid artery occlusion²⁴; and in a model of kainic acid-induced status epilepticus, retigabine partially prevented the severe neurodegeneration resulting from the prolonged status.³¹

Kv7.3 and Kv7.5 subunits are expressed in bladder and in intestinal smooth muscle. Retigabine is capable of relaxing bladder strips, and the compound was therefore proposed to be of utility of treatment of urinary incontinence³² and irritable bowel syndrome.³³

Retigabine activates Kv7.4 channels also. This subunit is selectively expressed in auditory pathways and it was proposed that activation of this channel may be beneficial for treatment of auditory system disorders, including deafness and tinnitus.³⁴

In summary, in addition to its anticonvulsant activity, retigabine may be of utility in neuropathic pain, in stroke and other neurodegenerative disorders, in the treatment of tinnitus and progressive hearing loss, and in the treatment of urinary incontinence.

Animal toxicology

Retigabine has thus far proven to be a safe drug. Animal studies of cardiovascular function have not demonstrated any liability. The drug does, in rodents, cause inhibition of bladder contractions and decreased micturition; this may be related to the drug's ability to hyperpolarize bladder muscle. Early suggestions of genotoxicity were not borne out by subsequent testing; expert opinion suggests that there is no evidence of genotoxicity. Carcinogenicity testing is under way.

CLINICAL STUDIES

Clinical pharmacology

Eighteen human volunteer studies and more than five human clinical studies have been performed with retigabine. This brief monograph will now concentrate on human data. Retigabine is readily absorbed, with a $T_{\max}$

of 1–2 hours. Levels increase linearly with dose following both single and multiple dose administration. The major metabolite is N-acetyl-retigabine, which is also linear with dose. Both retigabine and its metabolite were eliminated with an elimination half-life ($T_{1/2}$) of ~ 8 hours. Exposure was not modified by a high-fat meal. Protein binding is low and does not exceed 80%.

Metabolism is extensive, but is almost exclusively phase II in nature, and not through oxidative (P450) mechanisms.

Phase II studies

Two major phase II studies have been conducted with retigabine. The first, which will be referred to as phase IIa, was a dose-finding and drug-interaction study. The second, referred to as phase IIb, was a definitive controlled study in complex partial seizures.

Two fundamental issues need to be resolved prior to entering into definitive studies with new antiepileptic drugs (AEDs). The failure of investigators to consider these two issues often leads either to failed studies or null results because of inadequate drug delivery.

The first of these two issues is drug dose. Most antiepileptic drugs have a narrow therapeutic range, especially for patients with refractory disease. This means that the new drug (assuming that it is not a miracle drug) needs to be tested—at least in part—near to the maximal tolerated dose. This will give the drug its best chance to show efficacy, especially in the refractory patients who are usually first to be tested in AED drug development.

The second issue to be resolved is the potential for drug–drug interactions. A major problem arises when the new drug increases the levels of the concomitant medications. The clinical trial may then be criticized, should appropriate measures not be taken, as a study in which the new drug merely increased the levels (and possibly the efficacy) of older drugs already in place.

Both of these issues were addressed by the phase IIa study (led by R.C. Sachdeo) designed to evaluate both the maximal tolerated dose of retigabine and the drug interactions of retigabine with phenytoin, carbamazepine, valproic acid, and topiramate.³⁵ In this study, 60 patients with epilepsy were studied on a stable, single AED (one of the four just listed). After establishing the pharmacokinetics of the background AED, retigabine was added stepwise up to the maximal tolerated dose. Thereafter, the concomitant AED was decreased in a similar stepwise fashion, to attempt retigabine monotherapy. Pharmacokinetics parameters were measured throughout the process, to obtain data on the effect of retigabine on four AEDs and to evaluate the effect of four AEDs on retigabine. The study showed a terminal $T_{1/2}$ of 9 hours for retigabine; it also demonstrated linear dose proportionality up to 1,200 mg.³⁵ The only observed interaction was a slight increase in retigabine

clearance by phenytoin and carbamazepine. Overall, very few patients tolerated doses $>1,200$ mg/day.

With the maximal tolerated dose established, and with basic drug–drug interactions now known, and with the knowledge that these interactions will not interfere with a controlled clinical trial, phase IIb was undertaken.

Phase IIb was a four-arm, double-blind, placebo-controlled study of 399 patients with partial-onset seizures.³⁶ In this study, retigabine was well tolerated and produced a dose-dependent reduction in partial-onset seizures. Further description of this study is embargoed, however, because a report from the study is currently in review for publication.

Phase III program

A phase III program has been launched and is known as RESTORE (Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy). This program consists of two double-blind, placebo-controlled studies. More than 800 patients with partial-onset seizures with or without secondary generalization who have had epilepsy for at least 2 years and have failed adequate therapeutic trial with two antiepileptic drugs will participate in these two studies. At the time of inclusion in the study, patients may be on one, two, or three antiepileptic drugs. Each study has an 8-week baseline period, followed by a titration period to achieve the target dose and then a 12-week maintenance period. The primary outcome is median percent reduction in monthly total partial seizure frequency during the entire double-blind period, compared with baseline period. The key secondary outcome is the percentage of patients with $\geq 50\%$ reduction in monthly total partial seizure frequency during the maintenance period, compared with the baseline period. One study is being conducted in North America and South America and the other in Europe, South Africa, Israel, and Australia.

CONCLUSION

Retigabine is a very promising drug for partial-onset seizures, now in the late stages of clinical development. It has a novel mechanism of action and an excellent safety profile. It promises to be an important addition to the antiseizure armamentarium of the practicing physician. Furthermore, the mechanism of retigabine suggests that the drug may be effective in a wide variety of other disorders, from pain to urinary incontinence.

REFERENCES

1. Löscher W. New visions in the pharmacology of anticonvulsion. *Eur J Pharmacol* 1998;342:1–13.
2. Rogawski MA. Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines. *Trends Pharmacol Sci* 1993;14:325–331.
3. Kupferberg HJ. Antiepileptic drug development program: a cooperative effort of government and industry. *Epilepsia* 1989;30(suppl 1):S51–S56.
4. Jakovlev V, Achterrath-Tuckermann U, von Schlichtegroll A, Stroman F, Thieme K. General pharmacologic studies on the analgesic flupirtine [In German]. *Arzneimittelforschung* 1985;35:44–55.
5. Seaman CA, Sheridan PH, Engel J, Molliere M, Narang PK, Nice FJ. Flupirtine. In: Meldrum BS, Porter RJ, editors. *New anticonvulsant drugs*. Current Problems in Epilepsy 4. London: Libbey, 1986. p. 135–146.
6. Seydel JK, Schaper KJ, Coats EA, et al. Synthesis and quantitative structure–activity relationships of anticonvulsant 2,3,6-triaminopyridines. *J Med Chem* 1994;37:3016–3022.
7. Rostock A, Tober C, Rundfeldt C, et al. D-23129: a new anticonvulsant with a broad spectrum activity in animal models of epileptic seizures. *Epilepsy Res* 1996;23:211–223.
8. Tober C, Rundfeldt C, Rostock A, Bartsch R. The phenyl carbamic acid ester D-23129 is highly effective against amygdale kindled seizures in rats. *Eur J Pharmacol* 1994;7(suppl):212. Abstract.
9. Löscher W, Schmidt D. Strategies in antiepileptic drug development: is rational drug design superior to random screening and structural variation? *Epilepsy Res* 1994;17:95–134. Review.
10. Nickel B, Shandra A, Godlevsky L, Mazarati A, Kupferberg H, Szelenyi I. Anticonvulsant activity of D-20443. *Naunyn Schmiedeberg's Arch Pharmacol* 1993;347(suppl):R142. Abstract.
11. Nickel B, Shandra A, Godlevsky L, Mazarati A, Kupferberg H, Szelenyi I. Antiepileptic activity of a new drug: D-20443. *Epilepsia* 1993;34(suppl 1):95. Abstract.
12. Löscher W, Schmidt D. Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. *Epilepsy Res* 1988;2:145–181.
13. Dailey JW, Cheong JH, Ko KH, Adams-Curtis LE, Jobe PC. Anticonvulsant properties of D-20443 in genetically epilepsy-prone rats: prediction of clinical response. *Neurosci Lett* 1995;195:77–80.
14. Tober C, Rundfeldt C, Rostock A, Bartsch R. The phenyl carbamic acid ester D-23129 is highly effective in epilepsy models for generalized and focal seizures at nontoxic doses. *Abstr Soc Neurosci* 1994;20:1641. Abstract.
15. Tober C, Rostock A, Rundfeldt C, Bartsch R. D-23129: a potent anticonvulsant in the amygdala kindling model of complex partial seizures. *Eur J Pharmacol* 1996;303:163–169.
16. Engel J. Clinical aspects of epilepsy. *Epilepsy Res* 1991;10:9–17.
17. Ganguly A, Wolf HH, White HS. Investigational anticonvulsant D-23129 inhibits limbic behavioral seizures in hippocampal kindled rats. *Epilepsia* 1995;36(suppl 4):49. Abstract.
18. Armand V, Rundfeldt C, Heinemann U. Effects of retigabine (D-23129) on different patterns of epileptiform activity induced by low magnesium in rat entorhinal cortex hippocampal slices. *Epilepsia* 2000;41:28–33.
19. Armand V, Rundfeldt C, Heinemann U. Effects of retigabine (D-23129) on different patterns of epileptiform activity induced by 4-aminopyridine in rat entorhinal cortex hippocampal slices. *Naunyn Schmiedeberg's Arch Pharmacol* 1999;359:33–39.
20. Straub H, Kohling R, Hohling J, et al. Effects of retigabine on rhythmic synchronous activity of human neocortical slices. *Epilepsy Res* 2001;44:155–165.
21. Tober C. Investigations of the effects of retigabine in the amygdala kindling model in rats [dissertation]. Leipzig, Germany: University of Leipzig, 1997.
22. Rundfeldt C, Netzer R. The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells transfected with human KCNQ2/3 subunits. *Neurosci Lett* 2000;282:73–76.
23. Rundfeldt C. The new anticonvulsant retigabine (D-23129) acts as an opener of K⁺ channels in neuronal cells. *Eur J Pharmacol* 1997;336:243–249.
24. Rundfeldt C. Characterization of the K⁺ channel opening effect of the anticonvulsant retigabine in PC12 cells. *Epilepsy Res* 1999;35:99–107.
25. Rundfeldt C, Netzer R. Investigations into the mechanism of action of the new anticonvulsant retigabine: interaction with GABAergic and glutamatergic neurotransmission and with voltage gated ion channels. *Arzneimittelforschung* 2000;50:1063–1070.

26. Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. *Science* 1998;279:403–406.
27. Schroeder BC, Kubisch C, Stein V, Jentsch TJ. Moderate loss of function of cyclic-AMP-modulated KCNQ2/KCNQ3 K⁺ channels causes epilepsy. *Nature* 1998;396:687–690.
28. Gribkoff VK. The therapeutic potential of neuronal KCNQ channel modulators. *Expert Opin Ther Targets* 2003;7:737–748.
29. Blackburn-Munro G, Jensen BS. The anticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain. *Eur J Pharmacol* 2003;460:109–116.
30. Dost R, Rostock A, Rundfeldt C. The anti-hyperalgesic activity of retigabine is mediated by KCNQ potassium channel activation. *Naunyn Schmiedebergs Arch Pharmacol* 2004;369:382–390.
31. Ebert U, Brandt C, Löscher W. Delayed sclerosis, neuroprotection, and limbic epileptogenesis after status epilepticus in the rat. *Epilepsia* 2002;43(suppl 5):86–95.
32. Argentieri TM, Sheldon JH, Bowlby MR, inventors; American Home Products Corporation, assignee. Methods for modulating bladder function. US patent 6 348 486. Feb. 19, 2002.
33. Burbridge SA, Clare JJ, Cox B, Dupere J, Hagan RM, Xie X. New uses for potassium channel openers. WO Patent WO1407768. January 11, 2001.
34. Kharkovets T, Hardelin JP, Safieddine S, et al. KCNQ4, a K⁺ channel mutated in a form of dominant deafness, is expressed in the inner ear and the central auditory pathway. *Proc Natl Acad Sci U S A* 2000;97:4333–4338.
35. Sachdeo RC, Ferron GM, Partiot AM, et al. An early determination of drug-drug interactions between valproic acid, phenytoin, carbamazepine, or topiramate and retigabine in epileptic patients. *Neurology* 2001;56:A331–A332. Abstract.
36. Porter R, Alves W, Nohria V; on behalf of the 2005 study group. Poster abstract 01175 [CD-ROM]. 2005 World Congress of Neurology, 5–11 Nov. 2005, Sydney, Australia. *J Neurol Sci* 2005; 15(suppl 1):S1–S526.