

CTI Perspectives

Neurological Disorders - May , 2009

Highlights

- Adjunctive Eslicarbazepine Effective for Refractory Partial Seizures
- Lacosamide Effective as Adjunctive Therapy in Partial Seizures

Research & Development Updates

- Bapineuzumab
- Eslicarbazepine
- HSP 10

Ongoing Trials

Market News

Meetings Diary

©2009 Adis International BV

Highlights

Adjunctive Eslicarbazepine Effective for Refractory Partial Seizures

Adjunctive **eslicarbazepine** [Bial] 800 and 1200 mg/day are more effective than placebo, and are generally well tolerated, as adjunctive therapy for the treatment of patients with refractory partial-onset seizures, suggest the results of a multinational study.

A total of 402 patients were recruited to the study from 40 centres in Europe, which compared adjunctive eslicarbazepine 400, 800 and 1200 mg/day. The primary endpoint of the study was seizure frequency. Adjunctive eslicarbazepine 800 and 1200 mg/day, but not 400 mg/day were more effective than placebo; the log-transformed seizure frequency was 7.64, 6.73, 5.66 and 5.35 in the placebo and eslicarbazepine 400, 800 and 1200 mg/day groups, respectively ($p < 0.01$ for 800 mg/day vs placebo and $p < 0.001$ for 1200 mg/day vs placebo). Adjunctive eslicarbazepine was also generally well tolerated. The discontinuation rates due to adverse events were 4%, 4%, 8% and 20% in the placebo, and eslicarbazepine 400, 800 and 1200 mg/day groups, respectively. The adverse events that occurred in more than 10% of patients were dizziness, headache and diplopia, and most were mild to moderate.

The authors of the study noted that "ESL [eslicarbazepine], 800 and 1,200 mg once-daily, was well tolerated and more effective than placebo in patients who were refractory to treatment with one or two concomitant AEDs [anti-epileptic drugs]."

Clinical relevance: A

Adis score: 81

801142487

Eslicarbazepine is a sodium channel antagonist being developed as adjunctive treatment for partial seizures by Bial and Sepracor. Eslicarbazepine is designed for once-daily administration with improved anticonvulsant activity, and offers other clinical benefits such as a lowered risk of drug-drug interactions and adverse events commonly associated with conventional antiepileptic drugs carbamazepine and oxcarbazepine. Eslicarbazepine does not degrade into toxic metabolites such as epoxides, which are known to occur with these well known dibenzazepines. The current study, as well as two other phase III studies, are being used to support a New Drug Application, which is expected to be filed with the US FDA in early 2009.

Lacosamide Effective as Adjunctive Therapy in Partial Seizures

Adjunctive **lacosamide** is effective and generally well tolerated in patients with uncontrolled partial seizures, suggest the results of a multinational phase III study.

A total of 485 patients from 75 centres were recruited to the study, which assessed the efficacy, tolerability and pharmacokinetics of adjunctive lacosamide treatment. The primary endpoints of the study were changes from baseline in seizure frequency and the response rate, both measured at 28 days. Adjunctive lacosamide was found to be effective, with changes from baseline in seizure frequency of 36.4% in the lacosamide 400 mg/day group, and 35.3% in the 200 mg/day group, compared with 20.5% in the placebo group (both $p < 0.05$), and response rates of 41% in the 400 mg/day group ($p = 0.001$) and 35% in the 200 mg/day group ($0.05 < p < 0.10$), compared with 26% of patients in the placebo group. Adjunctive lacosamide showed dose-proportional pharmacokinetics, with drug concentrations remaining stable over the 12-week maintenance period. Lacosamide did not appear to have significant effects on concentrations of concomitant antiepileptic drugs. Lacosamide was generally well tolerated, with withdrawal rates due to adverse events of 15% in the 400 mg/day group, 6% in the 200 mg/day group and 5% in the placebo group. Serious adverse events occurred in 9%, 8% and 4%, respectively. Dosage-related adverse events included dizziness, nausea and vomiting

The authors of the study commented that "results of this trial demonstrated the efficacy and tolerability of adjunctive lacosamide 200 and 400 mg/day and support that lacosamide may be an advantageous option for the treatment of partial-onset seizures in patients with epilepsy."

Adis score: 84

801142486

©2009 Adis International BV

Research & Development Updates

Bapineuzumab

Bapineuzumab may improve cognitive outcomes in patients with mild-to-moderate Alzheimer's disease, suggest the results of a study presented at the 61st Annual Meeting of the American Academy of neurology.

In the modified intention-to-treat population, pre-specified primary efficacy analyses, bapineuzumab did not achieve statistical significance for the primary endpoint (change from baseline in ADAS-Cog and DAD scores). However, post-hoc analyses showed favourable trends for ADAS-Cog and NTB.

801142595

Bapineuzumab is a humanised monoclonal antibody administered by intravenous infusion, designed to specifically target amyloid-beta ($A\beta$) in the brain. Wyeth Pharmaceuticals and Elan Corporation are co-developing this product for the treatment of Alzheimer's disease. The product is undergoing phase-III development for Alzheimer's disease worldwide. A subcutaneous formulation of bapineuzumab is also undergoing clinical development in the US.

Eslicarbazepine

Refer to highlights

Clinical relevance: A

Adis score: 81

801142487

HSP 10

HSP 10 5 mg once or twice-weekly is well tolerated in patients with relapsing-remitting or secondary progressive multiple sclerosis, indicate the results of a phase II study.

A total fo 50 patients were recruited from two Australian sites for the study, which assessed the

tolerability of HSP 10. HSP 10 5mg once or twice weekly appeared well tolerated, with no significant differences from placebo in adverse event rates.

The authors of the study concluded "Cpn 10 [HSP 10] is safe and well tolerated when administered to patients with MS for 3 months, however, a further extended phase II study primarily focused on efficacy is warranted."

801139944

Australia-based-biotechnology company CBio is developing heat shock protein (HSP) 10 for the treatment of inflammatory-mediated disorders including multiple sclerosis, rheumatoid arthritis, graft versus host disease and plaque psoriasis. CBio's HSP 10 is a recombinant form of human HSP 10 produced in bacteria; it differs from natural HSP 10 by one alanine residue, added to replace the missing acetyl group as a result of bacteria deficiencies in protein modification. HSPs 10 and 60 were originally thought to only be involved in protein folding. However, both proteins have exhibited immunomodulatory activity. In particular, HSP 10 appears to have an immunosuppressant effect by acting on multiple mediators of the innate immune system.

©2009 Adis International BV

Ongoing Trials

Table 1 summarises activity of randomised clinical trials in *Neurological Disorders* identified over the past month.

Drug(s)	Indication	Study Status	Sponsor	Reference
ACR-16	Huntington's disease	Completed	NeuroSearch	700024191
Cladribine	Multiple sclerosis	Recruiting	EMD Serono, Merck Serono	700013158
Donepezil	Alzheimer's disease	Active, no longer recruiting	Eisai, Eisai Medical Research	700029200
Fingolimod	Multiple sclerosis	Active, no longer recruiting	Novartis	700020922
Interferon beta-1a, glatiramer acetate	Multiple sclerosis	Active, no longer recruiting		700012549
Interferon beta-1a	Multiple sclerosis	Active, no longer recruiting	EMD Serono	700036972
Lamotrigine	Partial seizures	Completed	GlaxoSmithKline	700021166
Lorazepam	Seizures	Completed		700036834
Pimavanserin	Psychotic disorders, Parkinson's disease	Active, no longer recruiting	ACADIA Pharmaceuticals	700025256
Rasagiline	Parkinson's disease	Completed	Eisai, Teva Pharmaceutical Industries	700016476
Rivastigmine	Incidence of various toxicities	Active, no longer recruiting	Novartis, Ono Pharmaceutical	700027379
Rosiglitazone vs donepezil	Alzheimer's disease	Completed	GlaxoSmithKline	700021156
Rosiglitazone	Incidence of various toxicities in patients with Alzheimer's disease	Discontinued	GlaxoSmithKline	700024447
Rosiglitazone	Incidence of various toxicities	Discontinued	GlaxoSmithKline	700028530
Rotigotine	Parkinson's disease	Completed	Schwarz Pharma AG	700026649
Safinamide	Parkinson's disease	Recruiting	EMD Serono	700042778
Topiramate	Gilles de la Tourette's syndrome	Completed	Ortho-McNeil	700014626

Drug(s)	Indication	Study Status	Sponsor	Reference
Topiramate	Gilles de la Tourette's syndrome	Completed	Ortho-McNeil	700017173

©2009 Adis International BV

Market News

Table 2 summarises milestones in *Neurological Disorders* drug development in key markets that have been identified over the last month.

Drug	Indication	Milestone	Reference
Dronabinol/cannabidiol [Sativex; Laboratorios Almirall]	Spasticity associated with Multiple Sclerosis	Regulatory submissions filed in the United Kingdom and Spain	Laboratorios Almirall
Fampridine [Acorda Therapeutics]	Multiple sclerosis	New Drug Application accepted by the US FDA	Acorda Therapeutics
Lamotrigine [Lamictal; GlaxoSmithKline]	Seizures	Orally disintegrating formulation approved by the US FDA	GlaxoSmithKline Eurand
Valproic acid [Valproate semisodium, divalproex; Impax]	Seizures	Generic formulation approved by the US FDA	IMPAX Laboratories

©2009 Adis International BV

Meetings Diary

Meeting	Location	Dates	Contact
Annual Meeting of the Royal College of Psychiatrists	Liverpool, England	2-5 Jun 2009	www.rcpsych.ac.uk/events
13th International Congress of Parkinson's Disease and Movement Disorders	Paris, France	7-11 Jun 2009	http://www.movementdisorders.org
19th Meeting of the European Neurological Society	Milan, Italy	20-24 Jun 2009	www.ensinfo.org
9th World Congress of Biological Psychiatry	Paris, France	28 Jun - 2 Jul 2009	http://www.wfsbp-congress.org
28th International Epilepsy Congress	Budapest, Hungary	28 Jun - 2 Jul 2009	http://www.epilepsybudapest2009.org/
International Conference on Alzheimer's Disease and Related Disorders	Vienna, Austria	11-16 Jul 2009	http://www.alz.org/icad
Mayo Clinic Neurology in Clinical Practice 2009	Chicago, Illinois, USA	16-18 Jul 2009	http://www.mayo.edu/cme/neurology-neurologic-surgery.html
59th Annual Conference of the Canadian Psychiatric Association	St. John's, Newfoundland, Canada	27-30 Aug 2009	http://www.cpa-apc.org
14th Congress of the International Headache Society	Philadelphia, Pennsylvania, USA	10-13 Sep 2009	http://www.americanheadachesociety.org
22nd Annual Congress of the European College of Neuropsychopharmacology	Istanbul, Turkey	12-16 Sep 2009	http://www.ecnp.nl

13th Congress of the European Federation of Neurological Societies	Florence, Italy	12-15 Sep 2009	http://www.kenes.com/efns2009/index.asp
2nd European Conference on Schizophrenia Research	Berlin, Germany	21-23 Sep 2009	http://www.schizophrenianet.eu
6th World Congress on Depressive Disorders and International Symposium of PTSD	Mendoza, Argentina	24-26 Sep 2009	http://www.mendoza2009.org/english/index.htm
3rd World Congress on Controversies in Neurology		8-11 Oct 2009	http://www.comtecmed.com/cony
134th Annual Meeting of the American Neurological Association	Baltimore, Maryland, USA	11-14 Oct 2009	
38th Annual Meeting of the Child Neurology Society	Louisville, Kentucky	14-17 Oct 2009	www.childneurologysociety.org
19th World Congress of Neurology	Bangkok, Thailand	24-30 Oct 2009	http://www.wcn2009bangkok.com
56th Annual Meeting of the American Academy of Child and Adolescent Psychiatry	Honolulu, Hawaii, USA	27 Oct - 1 Nov 2009	http://www.aacap.org
2009 Scottsdale Headache Symposium	Scottsdale, Arizona	6-8 Nov 2009	www.americanheadachesociety.org
6th International Congress on Vascular Dementia	Barcelona, Spain	19-22 Nov 2009	http://www.kenes.com/vascular
17th WFN World Congress on Parkinson's Disease and Related Disorders	Miami Beach, Florida, USA	13-16 Dec 2009	
62nd Annual Meeting of the American Academy of Neurology	Toronto, Ontario, Canada	10-17 Apr 2010	http://am.aan.com
11th International Child Neurology Congress	Cairo, Egypt	2-7 May 2010	http://www.icnc2010.com/
163rd Annual Meeting of the American Psychiatric Association	New Orleans, Louisiana, USA	22-27 May, 2010	http://www.psych.org
23rd Annual Congress of the European College of Neuropsychopharmacology	Amsterdam, The Netherlands	28 Aug - 1 Sep 2010	http://www.ecnp.nl
60th Annual Conference of the Canadian Psychiatric Association	Toronto, Ontario, Canada	23-26 Sep 2010	http://www.cpa-apc.org
57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry	Boston, Massachusetts, USA	14-17 Oct 2010	http://www.aacap.org
164th Annual Meeting of the American Psychiatric Association	Honolulu, Hawaii	14-19 May 2011	http://www.psych.org
24th Annual Congress of the European College of Neuropsychopharmacology	Paris, France	3-7 Sep 2011	http://www.ecnp.nl
61st Annual Conference of	Edmonton,	15-18	http://www.cpa-apc.org

the Canadian Psychiatric Association	Alberta, Canada	Sep 2011	
58th Annual Meeting of the American Academy of Child and Adolescent Psychiatry	Toronto, Ontario, Canada	18-23 Oct 2011	http://www.aacap.org
25th Annual Congress of the European College of Neuropsychopharmacology	Vienna, Austria	13-17 Oct 2012	http://www.ecnp.nl
26th Annual Congress of the European College of Neuropsychopharmacology	Barcelona, Spain	5-9 Oct 2013	http://www.ecnp.nl

©2009 Adis International BV