New data for Vimpat (lacosamide) C-V showed sustained efficacy for up to 5 years

EurekAlert

ATLANTA, June 29, 2010 /EurekAlert!/ — New long term data showed that Vimpat® (lacosamide) C-V provided sustained reduction in seizure frequency for up to five years when used as an add-on treatment for uncontrolled partial onset seizures in adults with epilepsy. In addition post-hoc exploratory analyses showed that adjunctive lacosamide treatment reduced partial-onset seizure frequency and improved responder rates when added to a broad range of antiepileptic drugs (AEDs) including both traditional sodium channel-blocking agents* and those that act on non-sodium channel-targets. These and other data were presented this week at the 9th European Congress on Epileptology (ECE), in Rhodes, Greece.

"The new data showed that lacosamide provided long-term additional partial-onset seizure control when added to a broad range of AEDs and when current therapy was not enough," said Dr. Jacqueline French, Professor in the department of Neurology, NYU Comprehensive Epilepsy Center.

In addition, laboratory results of the first direct in-vitro comparison of lacosamide with other AEDs were also presented at the Congress and provided additional evidence of lacosamide's novel mode of action.

Vimpat is approved in the U.S. as an add-on therapy for the treatment of partial-onset seizures in people with epilepsy who are 17 years and older, and is available as oral tablets, oral solution and as an intravenous (IV) injection. In the European Union, Vimpat (film-coated tablets, syrup and solution for infusion) is approved as adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy, aged 16 years and older. The maximum recommended daily dose for Vimpat in the European Union and the U.S. is 400 mg/day. Vimpat solution for infusion may be used when oral administration is temporarily not feasible. Vimpat has a novel mechanism of action that is different from all currently available AEDs, although the precise mechanism by which Vimpat exerts its antiepileptic effect in humans is yet to be fully elucidated.

About the Data

Vimpat sustained efficacy for up to 5 years

Long term sustained efficacy has been reported in patients with partial-onset seizures who completed 1 to 5 years of adjunctive treatment with lacosamide.

Pooled data from 1,327 patients who took part in double-blind trials and/or corresponding open-label lacosamide trials were analyzed, and results for the first three months of treatment were compared with those of the last three months of

treatment in cohorts completing 1, 3 and 5 years of therapy.

Median percent reductions in seizure frequency for the first 3 months of treatment were 45.5%, 50.0% and 48.2% for the 1 (n=853), 3 (n=384) and 5 (n=67) year cohorts, respectively. These results compared with 52.4%, 72.7% and 71.8% during the last three months of treatment, demonstrating sustained effects over time.

The proportion of patients achieving a greater than or equal to 50% improvement in seizure frequency was also sustained in each cohort, ranging from 45.0%-50.3% for the first 3 months of treatment, compared to 51.8%-70.6% for the last 3 months.

Long-term efficacy of lacosamide for partial-onset seizures: An interim evaluation of completer cohorts exposed to lacosamide for up to 5 years
French J, Ben-Menachem E , Isojarvi J, Hebert D, Doty P
Platform session: Drug Therapy June 29th

Vimpat additional efficacy when added to a broad range of AEDs

Lacosamide reduced seizure frequency and improved responder rates in epilepsy patients with uncontrolled partial seizures regardless of the type of AED they were already taking.

Of 1,308 patients who took part in phase II/III placebo-controlled lacosamide trials, 82% were using at least one traditional sodium channel-blocking AED (eg, lamotrigine, oxcarbazepine, carbamazepine or phenytoin). Patients could also be taking other concomitant AEDs. In this group:

- Median percent reduction in seizure frequency per 28 days for lacosamide 200mg, 400mg and 600mg/day** was reduced by 33.3%, 39.0%, 42.7% respectively, compared to 18.9% with placebo ($p < 0.01$)
- 50% responder rates with lacosamide 200mg, 400mg and 600mg/day** compared to placebo were 33.3% ($p = 0.06$), 39.9% ($p < 0.01$) and 42.4% ($p < 0.01$) versus 22.7%
- The most common treatment-emergent adverse events (TEAEs) (greater than or equal to 10%) were dizziness, headache, nausea, diplopia and vomiting

Evaluation of lacosamide efficacy and safety as adjunctive therapy in patients receiving traditional sodium channel blocking AEDs
Isojarvi J, Hebert D, Doty P, Zackheim J, Davies K, Sake J-K, Eggert-Formella A
Poster session: Drug therapy I, P230: June 28th

In the 18% of patients taking only AEDs that act on non-sodium channel blocking AEDs (eg, valproate, levetiracetam, topiramate, zonisamide, gabapentin, pregabalin, phenobarbital, tiagabine and/or lorazepam):

- Median percent reduction in seizure frequency per 28 days for lacosamide

200mg, 400mg and 600mg/day** was reduced by 38.0% (p = 0.11), 62.5% (p < 0.01) and 79.0% (p < 0.01) compared with placebo (28.0%)
- 50% responder rates with lacosamide 200mg, 400mg and 600mg/day** compared to placebo were 41.9% (p=0.2), 62.3% (p< 0.01) and 79.2% (p < 0.01) versus 25.0%
- Lacosamide was generally well-tolerated, with 8.6% of patients withdrawing from treatment due to TEAEs; the most common TEAEs (greater than or equal to 10%, all lacosamide doses combined) were dizziness (15.3%), headache (12.3%) and fatigue (10.4%)

Lacosamide efficacy and safety in patients taking AEDs that act on non-sodium channel targets
Sake J-K, Hebert D, Doty P, Zackheim J, Eggert-Formella A , Davies K, Isojarvi J
Poster session: Drug therapy XI, P414: June 29th

Vimpat novel mode of action

The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. Results of the first direct comparison of lacosamide and other AEDs on voltage gated sodium channel inactivation provided additional evidence of its novel mode of action.

In laboratory studies the selective effects of lacosamide on voltage gated sodium channel slow inactivation parameters were compared to other AEDs that target the sodium channel (carbamazepine, phenytoin, lamotrigine, zonisamide and rufinamide). The study was performed in the N1E-115 mouse neuroblastoma cell line expressing native voltage gated sodium channels.

The electrophysiological results showed that lacosamide produced a significant and large change in neurophysiological parameters indicative of a selective enhancement of the slow inactivation of voltage gated sodium channels, while no such effect was seen with carbamazepine or zonisamide. Phenytoin, lamotrigine and rufinamide modified slow inactivation parameters in different ways from lacosamide.

Modulation of sodium channels is important for control of abnormal neuronal activity in the brains of people with epilepsy, and inactivation can occur via fast or slow mechanisms. While other sodium channel blocking AEDs act primarily via fast inactivation, the novel effect of Vimpat through the selective enhancement of slow inactivation is thought to control neuronal hyperexcitability without affecting normal nerve function.

Comparative study of lacosamide with other sodium channel blocking antiepileptic drugs on sodium current slow inactivation
Niespodziany I, Leclère N, Vandenplas C, Foerch P, Wolff C
Poster session: Drug therapy VI, P506: June 30th

Other UCB-supported lacosamide studies presented at the 9th European Congress on Epileptology included:

- A multicenter, open-label trial to assess the safety and tolerability of a single intravenous loading dose of lacosamide followed by oral maintenance as adjunctive therapy in patients with partial-onset seizures
  Fountain NB, Krauss G, Isojarvi J, Dilley D, Doty P, Rudd GD
  Poster session: Drug therapy XI, P416: June 29th
- Pharmacokinetic evaluation of oral lacosamide in Phase II/III clinical trials: a pooled analysis
  Cawello W, Andreas J-O, Hebert D, Eggert-Formella A
  Poster session: Drug therapy I, P227: June 28th
- Beta 1 Na+ channel subunit loss impairs the effects of CBZ but not lacosamide on repetitive firing via differential effects on persistent Na+ currents
  Uebachs M, Opitz T, Stoehr T , Niespodziany I, Wolff C, Beck H
  Poster session: Drug therapy VI, P499: June 30th

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[1] http://www.eurekalert.org/pub_releases/2010-06/cwgi-ndf062810.php