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Lundbeck Reports Positive Phase III Study Results for Clobazam in the Adjunctive Treatment of Seizures Associated with Lennox-Gastaut Syndrome

Two highest dosages of clobazam as add-on therapy achieved a robust statistically significant reduction in average weekly rate of drop seizures, compared with placebo[1]

77.6 percent of patients who received high-dosage clobazam achieved a 50 percent or greater reduction in average weekly rate of drop seizures[1]

Lundbeck Inc. anticipates NDA submission by year end

San Antonio, Texas, December 4, 2010 – Today, Lundbeck Inc. presented positive data from its pivotal phase III study to determine the efficacy and safety profiles of the investigational compound clobazam as adjunctive therapy in treating seizures associated with Lennox-Gastaut syndrome (LGS). In the study, clobazam met its primary efficacy endpoint and was further supported by several key secondary efficacy endpoints.[1] LGS is a rare and severe form of epilepsy that is typically diagnosed in childhood and persists into adulthood.[2,3] Results from this largest clinical trial to date in LGS patients were presented at the 64th annual meeting of the American Epilepsy Society in San Antonio, Texas (Poster No. 1.283).[1,4]

This prospective, double-blind, placebo controlled study randomized 238 patients diagnosed with LGS to one of three different dosages of clobazam or placebo. Efficacy analyses were done for the modified intent to treat population (mITT), which included all randomized patients who had baseline data, at least one dose of study drug and at least one daily seizure measurement during the maintenance period (N=217).[1]

Data from the study's primary endpoint showed that the high (1.0 mg/kg/day; N=49) and medium (0.5 mg/kg/day; N=58) dosages of clobazam, evaluated versus placebo (N=57), met a robust statistically significant ($p \leq 0.01$) reduction in the average weekly rate of drop seizures from the 4-week baseline period compared to the 12-week maintenance period. Patients in the high-dosage clobazam group achieved a mean decrease in average weekly rate of drop seizures of 68.3 percent ($p<0.0001$ vs. placebo) while those in the medium-dosage arm had an average decrease of 49.4 percent ($p=0.0015$ vs. placebo).[1]

A secondary endpoint of the study was responder rates. For each group treated with one of the three different dosages of clobazam, the percentage of patients with a decrease in average weekly rate of drop seizures of ≥25%, ≥50%, ≥75% or 100% from baseline to the maintenance period was compared to placebo. Among patients in the high-dosage arm, 77.6 percent had a 50 percent or greater reduction ($p<0.01$); 63.3 percent had a 75 percent or greater reduction ($p<0.01$); and 24.5 percent achieved 100 percent reduction. Among patients in the medium-dosage arm, 58.6 percent had a 50 percent or greater reduction ($p<0.05$); 37.9 percent had a 75 percent or greater reduction ($p<0.01$); and 12.1 percent achieved 100 percent reduction. The logistic regression model used in this study was unable to provide valid p-value estimates for the 100 percent response thresholds due to the small number of patients enrolled in this group.[1]

"LGS is a devastating form of epilepsy associated with multiple types of seizures, including dangerous drop seizures which may cause falls that often result in injury. This can take a tremendous toll on even the strongest families," said Joan A. Conry, MD, professor of neurology at Children's National Medical Center in Washington, D.C., and a principal investigator in the study. "While several medications are approved in the U.S. for treatment of LGS, many patients continue to have seizures due to the intractable nature of the disease. The focus on this small patient population and the results of this study provide hope for LGS patients, their families and the medical community."

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The study also evaluated the effect of clobazam in decreasing total seizures (drop and non-drop) as another key secondary endpoint. Robust statistical significance was observed in patients who received the high- and medium-dosage clobazam ($p<0.01$ in each arm versus placebo).[1]

In the study, the most common treatment emergent adverse events (AEs) included somnolence, lethargy, drooling, fever, and constipation. Serious AEs occurring in ≥2 patients were lobar pneumonia and pneumonia, which occurred in both clobazam and placebo treatment arms.[1]

"Lundbeck makes several treatment options available in the U.S. for people affected by epilepsy, and the development of clobazam for those with LGS represents our ongoing commitment to making a difference in the lives of those affected by rare and challenging seizure disorders," said Timothy M. Cunniff, PharmD, vice president of global regulatory affairs at Lundbeck. "We are encouraged by these phase III results and look forward to submitting an NDA very soon for clobazam."

About the Study
This phase III trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of clobazam as adjunctive therapy in patients with LGS. Patient age ranged from 2-54, with a mean age at baseline of 12.4 years. Patients were included if they were being treated with one to three antiepileptic drugs (AEDs) at stable dosages for ≥30 days before screening and had ≥2 drop seizures per week during the 4-week baseline period.[1]

Prior to randomization, patients were stratified by weight (12.5 kg to ≤30 kg, >30 kg) and then randomized to placebo (N=59) or one of three dosages of clobazam: low (N=58 at 0.25 mg/kg/day up to a maximum of 10 mg per day), medium (N=62 at 0.5 mg/kg/day; maximum daily dosage of 20 mg per day), and high (N=59 at 1.0 mg/kg/day; maximum daily dosage of 40 mg). Of 238 patients randomized, a total of 217 comprised the modified intent to treat (mITT) population, which included all randomized patients who had baseline data, ≥1 dose of study drug, and ≥1 daily seizure measurement during the maintenance period. A total of 177 patients completed the study. Statistical significance for the primary efficacy endpoint was prespecified as $p\leq0.01$ to be considered robust statistical evidence in a single multi-center study, and $p\leq0.05$ for secondary measures.[1]

About Clobazam
Clobazam is a 1,5-benzodiazepine that potentiates the inhibitory action of gamma-aminobutyric acid (GABA) by binding to GABA-A receptors.[5,6] Additionally, research has identified three subtypes of the benzodiazepine omega receptor (ω).[5] Diffusely distributed throughout the CNS, these ω receptors demonstrate a variety of pharmacological effects.[6] In non-clinical studies, clobazam was shown to have higher affinity for the ω_2 compared to the ω_1 receptor.[5] The precise mechanism of action by which clobazam exerts its antiepileptic effects is unknown.

The current study is part of a clinical development program to obtain FDA approval for clobazam as adjunctive treatment for patients with LGS. Clobazam is marketed outside of the U.S. in more than 100 countries under various brand names, including Frisium® or Urbanyl®. Brand names listed are property of their owners.

About Lennox-Gastaut Syndrome (LGS)
Lennox-Gastaut syndrome (LGS) is a rare[2] and severe form of epilepsy[7] characterized by multiple types of seizures, mental retardation or regression, and abnormal electroencephalogram (EEG) with generalized slow spike and wave discharges (1.5-2 Hz).[8] Responsible for 1-4 percent of all childhood epilepsies, LGS typically occurs between two and eight years of age (peak onset occurs from 3-5 years).[2,8] Eighty percent of those with LGS will have continued seizures throughout childhood and into their adult years.[2] LGS is associated with multiple seizure types,[8] including atonic, tonic and myoclonic seizures, which can all cause falls, or "drop attacks", that are associated with a high rate of recurrent injuries.[9] Prognosis for individuals with LGS varies, and complete recovery, including freedom from seizures and normal development, is uncommon.[7]

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About Lundbeck Inc.
Headquartered in Deerfield, Illinois, Lundbeck Inc., a wholly-owned subsidiary of H. Lundbeck A/S, is committed to providing innovative specialty therapies that fulfill unmet medical needs of people with central nervous system (CNS) disorders and rare diseases for which few, if any, effective treatments are available. For more information, please visit www.lundbeckinc.com.

About Lundbeck
H. Lundbeck A/S (LUN.CO, LUN DC, HLUKY) is an international pharmaceutical company highly committed to improving the quality of life for people suffering from central nervous system (CNS) disorders. For this purpose, Lundbeck is engaged in the research, development, production, marketing and sale of pharmaceuticals across the world. The company's products are targeted at disorders such as depression and anxiety, schizophrenia, insomnia, Huntington's, Alzheimer's and Parkinson's diseases.

Lundbeck was founded in 1915 by Hans Lundbeck in Copenhagen, Denmark. Today Lundbeck employs approximately 5,900 people worldwide. Lundbeck is one of the world's leading pharmaceutical companies working with CNS disorders. In 2009, the company's revenue was DKK 13.7 billion (approximately EUR 1.8 billion or USD 2.6 billion). For more information, please visit www.lundbeck.com.

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Sources

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