UPSHER-SMITH PRESENTS FAVORABLE PHASE I DATA FOR USL261, A NOVEL FORMULATION OF INTRANASAL MIDAZOLAM, IN PATIENTS WITH EPILEPSY

Presentations to Include Late-Breaking Abstracts at 66th Annual Meeting of the American Epilepsy Society

December 3, 2012 – Upsher-Smith Laboratories, Inc., (Upsher-Smith) announced that Phase I data for USL261 (intranasal midazolam) in patients with epilepsy were presented at the American Epilepsy Society Annual Meeting in San Diego, CA. The results demonstrated that maximum midazolam plasma concentrations were rapidly achieved after dosing with USL261. Additionally, both midazolam and its metabolite were rapidly eliminated. Single doses up to 7.5 mg were generally well-tolerated with no significant adverse events.

USL261 is a novel, investigational formulation of the benzodiazepine midazolam, delivered intranasally for the outpatient rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity, often called seizure clusters or acute repetitive seizures. It is intended to be administered by a caregiver without active inhalation by the patient. USL261 is also the subject of the ongoing, global Phase III ARTEMIS1 (Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray) Trial.

"At Upsher-Smith, we are dedicated to researching new treatment options for people living with challenging central nervous system conditions like epilepsy," said William Pullman, MB BS, BMedSc, PhD, FRACP, Chief Scientific Officer at Upsher-Smith. "The data presented at AES from the development program for USL261 support the safety profile and favorable pharmacokinetics/pharmacodynamics of USL261 both in healthy volunteers, and more importantly, in patients with epilepsy. These findings support the further development of USL261 for outpatient seizure rescue in patients with intermittent bouts of increased seizure activity, a population for which few treatment options are currently available."

About the Study

The randomized, open-label, inpatient study enrolled 90 male and female patients with epilepsy between the ages of 12 and 62 years old on stable antiepileptic drug (AED) regimens. Patients were administered a single dose of 2.5 mg (n=18), 5.0 mg (n=36), or 7.5 mg (n=36) USL261 by a unit-dose nasal spray device. Pharmacodynamic assessments of sedation and psychomotor performance were conducted before and after dosing.

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Investigators concluded that the onset of pharmacodynamic effects were seen as early as 10 minutes after dosing with USL261, and scores of each instrument returned to near baseline levels by four hours after the administration of USL261. USL261 at doses up to 7.5 mg was generally well-tolerated and did not result in excessive or prolonged sedation or psychomotor impairment.

For the assessment of the pharmacokinetics, venous blood samples were collected before dosing and at set time points after dosing for a period of 12 hours to determine plasma concentrations of midazolam and its major metabolite, 1-hydroxymidazolam (1-OHMZ).

Investigators concluded that consistent with results in healthy volunteers, midazolam $C_{\text{max}}$ was rapidly achieved after dosing with USL261 in subjects with epilepsy, and both midazolam and 1-OHMZ were rapidly eliminated, with mean $t_{1/2}$ between three and four hours. In general, midazolam $C_{\text{max}}$ and AUC$_{0-\infty}$ for both compounds increased with dose, but dose-proportionality analysis was inconclusive.

The results, consistent with findings in healthy volunteers, demonstrated that peak concentrations of midazolam were rapidly achieved, resulting in a rapid onset of pharmacodynamic effects. Additionally, both midazolam and its major metabolite were rapidly eliminated, which may have limited the incidence of adverse effects.

More information about the presentations, including full abstracts, is available on the AES website at www.aesnet.org.

USL261 is the subject of the ongoing global Phase III ARTEMIS1 (Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray) Trial. More information about the trial, including key eligibility requirements, is available at www.clinicaltrials.gov (NCT# 01390220) and at www.seizureclusterstudy.com.

About Epilepsy

Epilepsy is a medical condition that causes seizures affecting a variety of cognitive and physical functions. More than two million people in the U.S are estimated to be affected by epilepsy with about 200,000 new cases of epilepsy diagnosed each year.  

About Seizure Clusters

Seizure clusters, also referred to as acute repetitive seizures or increased bouts of seizure activity, are multiple seizures which occur over a relatively brief period of time with a pattern distinguishable from the usual seizure pattern. Typically, there is recovery between seizures.

Reports of seizure cluster prevalence vary, but it has been estimated that approximately 22% of the intractable epilepsy population (approximately 152,000 people) experience them.
Seizure emergencies, such as repetitive seizures and seizure clusters, are serious medical events requiring immediate treatment to reduce the risk of morbidity and mortality. Inadequate treatment of seizure clusters may potentially impact the safety of an epilepsy patient, may result in emergency room visits, and/or may evolve into status epilepticus, a potentially life-threatening condition. Benzodiazepines are the treatment of choice for management of acute seizures. Prehospital treatment with benzodiazepines has been shown to reduce seizure activity significantly compared with seizures that remain untreated until the patient reaches the emergency department; however, currently available options are underused. It is important to treat seizure emergencies early for many reasons, including findings that patients treated within 30 minutes of seizure onset are more responsive to first-line treatment.

Market research has shown that patients and caregivers would prefer a rescue medication for seizure clusters that could be administered in any setting and that provides effective and rapid seizure termination in an easy-to-use, non-invasive form of administration. Physicians, much like patients and caregivers, have expressed interest in a non-invasive rescue therapy for use outside of the hospital.

**Upsher-Smith’s CNS Pipeline**

Upsher-Smith is developing USL261 (midazolam) for the rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity, often called seizure clusters or acute repetitive seizures. USL261 has been granted orphan drug designation for this use by the FDA and Upsher-Smith will be seeking approval for this indication.

Currently, the only product approved in the U.S. to control bouts of increased seizure activity must be delivered rectally, which may be undesirable to some individuals. In contrast, USL261 (midazolam) is a benzodiazepine in an investigational formulation that is delivered intranasally. It is intended to be administered by a caregiver in an outpatient setting for the rescue treatment of seizure clusters without active inhalation by the patient.

In addition to USL261, Upsher-Smith’s central nervous system pipeline in clinical development includes USL255, an investigational extended-release topiramate for the management of epilepsy in adults, which is being studied in an ongoing international Phase III clinical trial. Another Upsher-Smith development program involves USL260 (tonabersat), an investigational drug in Phase I of development that is a potential first-in-class neuronal gap junction modulator that is also being explored as a potential treatment for epilepsy.

On August 14, 2012, the company completed its acquisition of UK-based Proximagen Group plc, a European biotechnology company focused on the development and commercialization of novel therapeutics for diseases of the central nervous system and inflammation.
About Upsher-Smith

Upsher-Smith, founded in 1919, is an independent and privately-owned specialty pharmaceutical company headquartered in Maple Grove, Minnesota that focuses on product growth and innovation for branded, branded-generic and generic pharmaceuticals. Upsher-Smith has a particular focus on providing therapies to assist people suffering from central nervous system diseases (including epilepsy, Parkinson's disease and Alzheimer's disease) and also markets products relating to cardiology, dermatology and women's health. In addition to products currently marketed, Upsher-Smith has an emerging neurology pipeline with three products in clinical development, two of which are in Phase III clinical trials. For more information, visit www.upsher-smith.com.

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References


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