UPSHER-SMITH PRESENTS FAVORABLE PHASE I DATA FOR USL261, A NOVEL FORMULATION OF INTRANASAL MIDAZOLAM, AT 66TH ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

USL261 Demonstrates Promising PK, PD and Safety Profiles in Patients with Epilepsy

Philadelphia - April 29, 2014 – Upsher-Smith Laboratories, Inc., (Upsher-Smith) today announced that Phase I data for USL261 (investigational intranasal midazolam) in patients with epilepsy were presented at the 66th Annual American Academy of Neurology (AAN) meeting in Philadelphia. The results demonstrated that USL261 at a single dose of up to 7.5 mg was rapidly absorbed and exhibited a short half-life. Additionally, USL261 was generally well tolerated in patients with epilepsy and demonstrated a rapid onset of pharmacodynamic effects with return to baseline function by 4 hours post dose.

USL261 is an investigational formulation of midazolam being developed for the intranasal rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity, including seizure clusters or acute repetitive seizures. It is intended to be delivered intranasally without active inhalation by the patient.

USL261 has been granted orphan drug designation for this use by the Food and Drug Administration (FDA) and is currently the subject of a global Phase 3 clinical trial – ARTEMIS I – being conducted under a Special Protocol Assessment (SPA) agreement with the FDA. An open-label safety extension study to ARTEMIS I is also underway. The multicenter study will evaluate the long-term safety and tolerability of USL261 in the treatment of seizure clusters.

“Patients and caregivers need alternatives, such as intranasal formulations, to rectal diazepam, the only approved out-of-hospital treatment for bouts of increased seizures. The results of a recently completed Phase I study of USL261 in patients show that the investigational drug, given at clinically relevant doses, is rapidly absorbed with an onset of pharmacodynamic effects within 10 minutes following administration,” said James Cloyd, PharmD, Professor and Lawrence C. Weaver Endowed Chair-Orphan Drug Development, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota. “Adverse effects appeared modest and were consistent with known benzodiazepine adverse effects. Findings presented at AAN support the continued development of USL261 for outpatient rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity.”

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About the Study

The randomized, phase 1, open-label, inpatient study enrolled 90 patients with epilepsy between the ages of 12 and 65 years old on stable antiepileptic drug (AED) regimens. Patients were administered a single dose of 2.5 mg, 5.0 mg, or 7.5 mg USL261 by unit-dose nasal-spray. Data presented are based on a subset analysis.

Pharmacodynamic assessments of sedation and psychomotor performance were conducted before and after dosing. Onset of pharmacodynamic effects were observed as early as 10 minutes after dosing with USL261, and sedation and psychomotor performance scores returned to near baseline levels by four hours after drug administration. USL261 was generally well tolerated in patients with epilepsy.

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.

USL261, at a single dose of up to 7.5 mg, was rapidly absorbed and exhibited a short half-life in patients with epilepsy. Both maximum plasma concentration and area under the curve increased with increasing doses for midazolam and its major metabolite.

Abstracts of the poster presentations can be found online at: www.aan.com.

- Safety and Pharmacodynamics of USL261, a Novel Intranasal Formulation of Midazolam, in Subjects with Epilepsy
  P3.277. Session P3: Epilepsy and Clinical Neurophysiology: AED
- Pharmacokinetics of USL261, a Novel Intranasal Formulation of Midazolam, in Subjects with Epilepsy

About Epilepsy

Epilepsy is a medical condition that is characterized by recurrent seizures. More than two million people in the U.S. are estimated to be affected by epilepsy with about 150,000 new cases of epilepsy diagnosed each year. Epilepsy can be associated with profound physical, psychological and social consequences that negatively impact people’s lives.

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.

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. 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 Central Nervous System Pipeline**

On March 11, 2014 Upsher-Smith received approval from the U.S. Food and Drug Administration (FDA) for USL255, an extended-release formulation of topiramate. Upsher-Smith’s clinical development pipeline includes two investigational drugs that are being studied for the management of seizure disorders. The pipeline includes USL261, an investigational intranasal midazolam for the rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity, often called seizure clusters, which is the subject of an ongoing international Phase 3 clinical trial (ARTEMIS1) with an open-label safety extension study. In addition, USL260 (tonabersat) is in early clinical development as a potential first-in-class neuronal gap junction modulator.

**About Upsher-Smith**

Upsher-Smith Laboratories, Inc., founded in 1919, is a growing pharmaceutical company dedicated to its mission of Advancing Pharmacotherapy. Improving Life™. With capabilities ranging from early-stage research to delivering on-market products, Upsher-Smith is committed to offering quality products that enable people to live life to its greatest potential. Upsher-Smith’s approach to product development and partnering has resulted in a broad range of both branded and generic therapeutic solutions to address patients’ needs. The Company has a particular focus on developing therapies for people living with central nervous system (CNS) conditions, such as seizure disorders, and has a robust pipeline of promising CNS compounds in various stages of development. For more information, visit www.upsher-smith.com.

### References


