Impel Pharmaceuticals Announces First Patient Dosed in Phase 2a Study Evaluating INP105 to Treat Acute Agitation in Adolescents With Autism Spectrum Disorder (ASD)

July 19, 2022

CALM 201 Study to Explore the Safety and Efficacy of Single 5mg-Dose INP105 Compared to Placebo in Quickly Reducing Agitation in Participants with ASD

SEATTLE, July 19, 2022 (GLOBE NEWSWIRE) -- Impel Pharmaceuticals (NASDAQ: IMPL), a commercial-stage pharmaceutical company developing transformative therapies for people suffering from diseases with high unmet medical needs, today announced the first subject has been dosed in a Phase 2a proof-of-concept study of INP105, nasal olanzapine, a widely used atypical, second-generation antipsychotic. INP105 is being developed as an acute treatment for agitation in persons with autism spectrum disorder (ASD) using Impel's proprietary Precision Olfactory Delivery (POD®) technology which delivers drugs to the upper nasal space. Results are expected in Q1 2023.

CALM 201 (NCT05163717), "INP105 Proof-of-concept Study for the Acute Treatment of Agitation in Adolescents With ASD" is a Phase 2a, randomized, double-blind, placebo-controlled, single-dose, 2-way, 2-period crossover study designed to evaluate the safety, tolerability and exploratory efficacy using a number of adapted scales of a single dose of INP105 versus placebo in adolescents (12 to < 18 years of age) with ASD experiencing agitation.

"The initiation of this trial is an important milestone for Impel as we advance our second compound, INP105, and build on our Phase 1 results which demonstrated that INP105 reached peak plasma levels approximately twice as fast as intramuscular olanzapine - currently marketed as Zyprexa® - and ten-times faster than orally disintegrating tablets," said Adrian Adams, Chairman of the Board and Chief Executive Officer of Impel Pharmaceuticals. "Autism is the fastest-growing developmental disorder in the United States[1] and there is an unmet need to help those living with autism and its related effects. We are optimistic about the potential benefits of INP105 based on previous study results and the positive impact we have seen with the POD technology with Trudhesa®."

Approximately 1 in 54 children in the U.S. and 1 in 160 children worldwide have been identified with ASD according to the Centers for Disease Control and Prevention and World Health Organization, respectively. Acute agitation often manifests in patients with serious underlying mental health conditions such as bipolar I disorder or schizophrenia. Between 1.7 million and 7 million episodes of acute agitation have been reported to occur in U.S. hospitals and emergency room settings each year.[2] An ideal medication for acute agitation, according to a 2005 expert consensus, is easy-to-administer, non-traumatically administered, provides rapid calming without excessive sedation, has a swift onset of action with sufficient duration to prevent untimely recurrence and has low risk for adverse events (AEs) and drug interactions.[3]

"Crisis behaviors such as agitation and irritability are the most common of the behavioral patterns that may develop in persons with ASD, and while chronic oral daily dosing treatments have been approved to reduce irritability in youth, they have significant metabolic (weight gain and disturbed glucose regulation) and extrapyramidal (uncontrolled movements) side effects among others. There is an increasing desire to avoid chronic daily dosing, and instead find a safe and effective acute treatment targeting agitation in this population," said Stephen Shrewsbury, M.D., Chief Medical Officer of Impel. "Our hope is to create a medication that is easy-to-administer, provides rapid calming without excessive sedation, has a swift onset of action with sufficient duration to prevent untimely recurrence, and has minimal risk for adverse events and drug interactions. If successful, this trial will bring us one step closer to potentially helping millions of autistic people, their families, and caregivers better manage episodes of agitation."

"My team and I are pleased to be leading this important trial with Impel as they look to develop an olanzapine product that can be effective as a single dose in treating agitation episodes in adolescents with ASD," said Craig A. Erickson, M.D., Professor of Psychiatry, Cincinnati Children's Hospital and the University of Cincinnati College of Medicine, and one of two lead investigators of the CALM 201 study at the Cincinnati Children's Hospital Medical Center. "Agitation can display in a variety of ways from patient to patient – from maladaptive or challenging behaviors such as oppositional or interfering intensely repetitive behavior to more severe behaviors like dangerous self-injury or physical aggression.[4]"

Mathew Siegel, M.D., Associate Professor of Psychiatry and Pediatrics, Tufts University School of Medicine, the other lead investigator at Spring Harbor Hospital in Portland, agrees with Dr. Erickson and said that "there is a great need for a treatment option that alleviates acute agitation that negatively affects the quality of life of people with ASD and their families.[5]"

The primary objectives of the study, which is being conducted at Cincinnati Children's Hospital Medical Center, OH and Spring Harbor Hospital in Portland, ME, are to evaluate the incidences of AEs and serious AEs in the INP105 and placebo groups at 48 hours post-dose and overall, respectively. Secondary objectives are to explore the efficacy of treatment over two hours with a single dose of INP105 versus placebo on acute agitation in adolescents with ASD using validated observational assessment tools for aggression albeit in different diseases and populations. The total duration of each patient's participation will be no more than 18 days.

Further details of the CALM 201 study can be found on ClinicalTrials.gov.

About the Precision Olfactory Delivery (POD®) Technology
Impel's proprietary POD® technology is able to deliver a range of therapeutic molecules and formulations into the vascular-rich upper nasal space, believed to be a gateway for unlocking the previously unrealized full potential of these molecules. By delivering predictable doses of drug directly to the upper nasal space, Impel's precision performance technology has the goal of enabling increased and consistent absorption of drug, overriding the high

variability associated with other nasal delivery systems, yet without the need for an injection. While an ideal target for drug administration, to date no technology has been able to consistently deliver drugs to the upper nasal space. By utilizing this route of administration, Impel Pharmaceuticals has been able to demonstrate blood concentration levels for its investigational therapies that are comparable to intramuscular administration and can even reach intravenous-like systemic levels quickly, which could transform the treatment landscape for central nervous system and other disorders. Importantly, the POD technology offers propellant-enabled delivery of dry powder and liquid formulations that eliminates the need for coordination of breathing, allowing for self- or caregiver-administration in a manner that may improve patient outcome, comfort, and potentially, compliance.

About INP105

INP105 is a proprietary nasal formulation of olanzapine administered using Impel's novel POD® technology that is being developed for the potential treatment of agitation and aggression associated with autism spectrum disorder. The POD® is a novel, simple-to-use device designed to deliver consistent and predictable doses of drug. INP105 delivers olanzapine to the richly vascularized upper nasal space to offer rapid, consistent, and optimized bioavailability that can be administered by the patient or a caregiver. Olanzapine is the most used treatment for acute agitation, but its use is limited to intramuscular injection and in a hospital setting. INP105 is intended to be a preferred choice for the safe and rapid treatment of acute agitation and because it is designed to be non-invasive, it has the potential to expand the treatment setting beyond the emergency room, such as inpatient treatment or community care facilities and the patient's home.

About Acute Agitation

Acute agitation is defined as excessive motor activity associated with a feeling of inner tension, often manifesting in patients with a number of serious underlying mental health conditions such as bipolar I disorder or schizophrenia. Between 1.7 million and 7 million episodes of acute agitation have been reported, or estimated, to occur in U.S. hospitals and emergency room settings each year. This places a huge burden on emergency rooms, the healthcare systems and the friends and families of those afflicted and is responsible for many healthcare staff assaults and injuries. Recent market research confirmed acute agitation is also common in patients with autism with at least five million episodes of moderate or severe agitation occurring per year in the U.S.[6] The historic approach of "restrain and sedate" is being abandoned in favor of less coercive, more compassionate, de-escalation approaches that include less invasive pharmacologic interventions.

Trudhesa® Indication and Important Safety Information

Indication

Trudhesa® is used to treat an active migraine headache with or without aura in adults. Do not use Trudhesa to prevent migraine when you have no symptoms. It is not known if Trudhesa is safe and effective in children.

Important Safety Information

Serious or potentially life-threatening reductions in blood flow to the brain or extremities due to interactions between dihydroergotamine (the active ingredient in Trudhesa) and strong CYP3A4 inhibitors (such as protease inhibitors and macrolide antibiotics) have been reported rarely. As a result, these medications should not be taken together.

Do not use Trudhesa if you:

- Have any disease affecting your heart, arteries, or blood circulation.
- Are taking certain anti-HIV medications known as protease inhibitors (such as ritonavir or nelfinavir).
- Are taking a macrolide antibiotic such as clarithromycin or erythromycin.
- Are taking certain antifungals such as ketoconazole or itraconazole.
- Have taken certain medications such as triptans or ergot-type medications for the treatment or prevention of migraine within the last 24 hours.
- Have taken any medications that constrict your blood vessels or raise your blood pressure.
- Have severe liver or kidney disease.
- Are allergic to ergotamine or dihydroergotamine.

Before taking Trudhesa, tell your doctor if:

- You have high blood pressure, chest pain, shortness of breath, heart disease; or risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease or you are postmenopausal, or male over 40); or problems with blood circulation in your arms, legs, fingers, or toes.
- You have or had any disease of the liver or kidney.
- You are taking any prescription or over-the-counter medications, including vitamins or herbal supplements.
- You are pregnant, planning to become pregnant or are nursing, or have ever stopped medication due to an allergy or bad reaction.
- This headache is different from your usual migraine attacks.

The use of Trudhesa should not exceed dosing guidelines and should not be used on a daily basis. Serious cardiac (heart) events, including some that have been fatal, have occurred following the use of dihydroergotamine mesylate, particularly with dihydroergotamine for injection, but are extremely rare.

You may experience some nasal congestion or irritation, altered sense of taste, sore throat, nausea, vomiting, dizziness, and fatigue after using Trudhesa.

Contact your doctor immediately if you experience:

- Numbness or tingling in your fingers and toes
- Severe tightness, pain, pressure, heaviness, or discomfort in your chest

- Muscle pain or cramps in your arms or legs
- Cold feeling or color changes in 1 or both legs or feet
- Sudden weakness
- Slurred speech
- Swelling or itching

The risk information provided here is not comprehensive. To learn more, talk about Trudhesa with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at www.Trudhesa.com or 1-800-555-DRUG. You can also call 1-833-TRUDHESA (1-833-878-3437) for additional information.

About Impel Pharmaceuticals
Impel Pharmaceuticals is a commercial-stage pharmaceutical company developing transformative therapies for people suffering from diseases with high unmet medical needs, with an initial focus on diseases of the central nervous system. Impel offers, and is developing, treatments that pair its proprietary POD® technology with well-established therapeutics. In addition to Trudhesa® nasal spray, which is approved in the U.S. for the acute treatment of migraine with or without aura in adults, Impel is also developing INP105 for the acute treatment of agitation and aggression in patients with autism.

Cautionary Note on Forward-Looking Statements
This press release contains "forward-looking" statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995, including, but not limited to, the potential clinical benefits of Trudhesa®, the market opportunities of Trudhesa within the migraine market, the speed of uptake and market growth of Trudhesa, and the timing of announcements of clinical results and clinical development activities of Impel's product candidates. Forward-looking statements can be identified by words such as: "believe," "may," "will," "potentially," "estimate," "continue," "anticipate," "intend," "could," "would," "project," "plan," "expect" or the negative or plural of these words or similar expressions. These statements are subject to numerous risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including but not limited to, Impel's ability to maintain regulatory approval of Trudhesa, its ability to execute its commercialization strategy for Trudhesa, its ability to develop, manufacture and commercialize its other product candidates including plans for future development of its POD® devices and plans to address additional indications for which Impel may pursue regulatory approval, whether results of preclinical studies or clinical trials will be indicative of the results of future trials, and the effects of COVID-19 on its clinical programs and business operations. Many of these risks are described in greater detail in Impel's filings with the Securities and Exchange Commission. Any forward-looking statements in this press release speak only as of the date of this press release. Impel assumes no obligation to update forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

 To learn more about Impel Pharmaceuticals, please visit our website at https://impelpharma.com.

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[1] Autism Spectrum Disorder Foundation Website Homepage. Last Accessed May 31, 2022. https://myasdf.org/about-autism/

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[3] Allen MH, Currier GW, Hughes DH et al. *J Psychiatr Pract* 2005. 11(Suppl 1); 5-108

[4] Stark HK, Barnes JC, Young ND, and RL Gabriels, Brief Report: Understanding Crisis Behaviors in Hospitalized Psychiatric Patients with Autism Spectrum Disorder—Iceberg Assessment Interview*Journal of Autism and Developmental Disorders*. 2015;45(11):3468–3474.

[5] https://publications.aap.org/pediatrics/article-abstract/137/Supplement_2/S124/34019/Pharmacologic-Treatment-of-Severe-Irritability-and?redirectedFrom=fulltext?autologincheck=redirected

[6] ZS Market Research Analysis, N= 30 Interviews