IMPEL NEUROPHARMA ANNOUNCES POSITIVE PHASE 1 TRIAL FOR INP105 FOR THE TREATMENT OF ACUTE AGITATION IN BIPOLAR I DISORDER AND SCHIZOPHRENIA

Data Demonstrated Nasal Delivery of INP105 (POD-olanzapine) Achieved Peak Olanzapine Plasma Levels Twice as Fast as Intramuscular Injection, Ten-Times Faster than Orally-Disintegrating Tablets

Study Showed a Safety and Tolerability Profile Consistent with Currently Marketed Formulations of Olanzapine

SEATTLE, January 6, 2019 — Impel NeuroPharma, a Seattle-based, privately-held biopharmaceutical company focused on innovative therapies for the treatment of central nervous system (CNS) disorders, today announced positive results of a Phase 1 trial of INP105. INP105 is a drug-device combination which delivers an optimized formulation of olanzapine, the current gold standard of treatment for acute agitation, via Impel's proprietary Precision Olfactory Delivery, or POD®, nasal delivery device. INP105 is being studied for the treatment of acute agitation in bipolar I disorder and schizophrenia.

Results demonstrated that INP105 reached peak plasma levels (T_{max}) twice as fast as intramuscular olanzapine (Zyprexa®), and ten-times faster than orally-disintegrating tablets (ODT, Zyprexa Zydis®). Maximum and total plasma levels (C_{max} and AUC) were similar to intramuscular delivery and exceeded the total plasma levels for ODT. Pharmacodynamic measures of sedation, including Visual Analogue Scale (VAS), the Agitation and Calmness Evaluation Scale (ACES) and Digit Symbol Substitution Test (DSST) all showed a robust statistical significance compared to placebo.

"The results of this trial are very encouraging and initial conversations with the U.S. Food and Drug Administration have indicated the potential for a streamlined development program given the current unmet need for bipolar and schizophrenia patients who experience episodes of acute agitation," said Jon Congleton, President and Chief Executive Officer of Impel NeuroPharma. "We are excited that Impel NeuroPharma's drug-device clinical programs, including INP105, are progressing rapidly and we anticipate multiple data readouts and regulatory filings across the portfolio in the next 18-24 months."

In the trial, a randomized, double-blind, placebo-and-active controlled, two-period crossover design, the overall safety and tolerability profiles of INP105 were similar to Zyprexa and Zyprexa Zydis. The most common adverse events (at least two events for any treatment) were dizziness (including postural), headache, nasal congestion, rhinorrhea, hypotension, orthostatic hypotension, fatigue, restlessness, nausea and orthostatic tachycardia.

"Unfortunately, the mental health community still lacks an ideal pharmacological rescue treatment for acute agitation – one with a non-invasive route of administration but with rapid onset, adequate duration and good tolerability," said Michael H. Allen, M.D., Professor of Psychiatry and Emergency Medicine at the University of Colorado. "These data are encouraging as they indicate that INP105 may be able to help patients maintain consciousness and return to a tranquil state so healthcare professionals can better assess and treat them in both hospital and outpatient settings."

Acute agitation often manifests in people living with serious mental health conditions, such as bipolar I disorder or schizophrenia. Agitation episodes related to neuropsychiatric disorders account for approximately 1.7 million visits to the ER each year, placing a significant economic and resource burden on the healthcare system.[1] An ideal medication for acute agitation, according to a 2005 expert consensus, is easy-to-administer, non-traumatically administered, provides rapid tranquilization without excessive sedation, has a swift onset of action with sufficient duration to prevent untimely recurrence, and has low risk for adverse events and drug interactions.[2] Such an optimal medication could be suitable for administration earlier during an agitation episode, possibly avoiding the need for ER attendance, as well as reduce the need for injected drugs and the associated risks of needlestick injuries and assaults on healthcare staff.

About the Trial

The "SNAP 101" Trial (**S**afety and Tolerability of Intra**na**sal **P**OD-olanzapine) is evaluating the safety, tolerability and pharmacokinetic/pharmacodynamic (PK/PD) profile of INP105 at three ascending doses compared with two doses of Zyprexa® intramuscular (5 mg and 10 mg) and orally disintegrating Zyprexa Zydis® (10 mg) in 36 healthy volunteers. The aim of the SNAP 101 trial is to establish the safety and tolerability of INP105 while informing appropriate dosing for future studies based on the PK and PD profiles.

Further details of the SNAP 101 (INP105-101) study can be found on ClinicalTrials.gov.

About INP105

INP105 is a drug-device combination product being studied for the treatment of acute agitation associated with bipolar I disorder or schizophrenia. It is comprised of an intranasal formulation of olanzapine and Impel's proprietary Precision Olfactory Delivery, or POD, nasal delivery device. The POD device delivers olanzapine to the richly-vascularized upper nasal cavity offering rapid, consistent and optimized bioavailability that can be administered by the patient or a caregiver. Olanzapine is the most commonly used treatment for acute agitation, but its use is

limited to intramuscular injection. INP105 is intended to be suitable for use in the hospital emergency room setting as well as early in an episode where it could be self-administered in the patient's home or supportive care setting.

About Acute Agitation

Acute agitation is defined as excessive motor activity associated with a feeling of inner tension, often manifesting from a number of serious underlying mental health conditions such as bipolar I disorder or schizophrenia. Agitation episodes related to neuropsychiatric disorders account for 1.7 million visits to the emergency room (ER) in the US each year.[1] This places a significant burden on ERs, the healthcare system, and the friends and families of those afflicted, and is responsible for many healthcare staff assaults and injuries. 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.

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About Impel NeuroPharma

Impel NeuroPharma, Inc., is a privately-held, Seattle-based biotechnology company devoted to creating life-changing, innovative therapies for central nervous system (CNS) diseases. Impel NeuroPharma is currently investigating INP104 (POD-DHE) for acute migraine headache, INP103 (POD-levodopa) for reversal of OFF episodes in Parkinson's disease and INP105 (POD-olanzapine) for acute agitation in schizophrenia and bipolar disorders.

Impel's products utilize its novel, nasal drug-delivery Precision Olfactory Delivery, or POD, device technology to deliver liquid or dry powder forms of drug to the upper nasal cavity in a consistent and predictable manner.

 To learn more about Impel NeuroPharma, please visit our website at http://impelnp.com.

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

[2] The Diagnosis and Management of Agitation. Edited by Scott L. Zeller, Kimberly D. Nordstrom and Michael P. Watson. *Cambridge University Press* 2017, Page 1.