IMPEL NEUROPHARMA ANNOUNCES PUBLICATION OF NARRATIVE REVIEW IN THE JOURNAL *HEADACHE* SUPPORTING NEED FOR NOVEL FORMULATIONS OF DIHYDROERGOTAMINE (DHE) IN ADDRESSING ACUTE TREATMENT OF MIGRAINE

DHE is Well-Tolerated and Demonstrates Reliable Benefits According to Review of More than 70 Years of Clinical Practice Data

DHE Offers Rapid Onset, Sustained Effects Lasting Up to 48 Hours and Works at Any Time Point After Migraine Onset

INP104, by Targeting the Upper Nasal Cavity, is Exploring a Lower Dose of Nasally Delivered DHE than FDA-Approved and Investigational Products in Development

SEATTLE, November 20, 2019 — Impel NeuroPharma, a late-stage biopharmaceutical company focused on the development and commercialization of transformative therapies for patients living with central nervous system (CNS) disorders with high unmet medical needs, today announced that a narrative review of dihydroergotamine (DHE) was published online in *Headache,* the official journal of the American Headache Society.

The analysis, conducted by Stephen Silberstein, M.D., of the Jefferson Headache Center at Thomas Jefferson University, Stephen Shrewsbury, M.D., Chief Medical Officer of Impel NeuroPharma and John Hoekman, PhD, Co-founder and Chief Scientific Officer of Impel NeuroPharma, is a narrative review of data supporting novel formulation and delivery approaches of DHE for the treatment of acute migraine. DHE was first introduced as a treatment for migraine in 1946.

“Analysis of the literature clearly demonstrates that DHE is a powerful tool for treating migraine, especially in patients who tend to be more difficult to treat, or whose disease is complicated by symptoms like allodynia (nerve hypersensitivity), or frequent recurrence,” said Dr. Silberstein. “Importantly, DHE offers rapid onset, durable effects and works at any point after migraine onset. Historically, the challenge has been finding the right dose paired with a non-invasive route of administration to unlock its full potential for broad, at home use.”

The publication, which can be accessed here, includes an overview of pharmacokinetic data supporting INP104, Impel's lead investigational drug candidate for the acute treatment of migraine. In STOP-101, a Phase 1 proof-of-concept trial, INP104 demonstrated an improvement in bioavailability (Cmax and AUC) over a currently approved dihydroergotamine mesylate nasal spray and showed systemic drug levels comparable to D.H.E. 45 (dihydroergotamine mesylate) IV injection after twenty minutes of administration.

"Extensive clinical experience with DHE strongly suggests that its potential benefits may best be realized through novel, non-injected routes of administration such as orally-inhaled and nasally-delivered DHE formulations. In addition to documenting a renewed interest in the clinical study and development of modern versions of DHE, the *Headache* publication offers strong evidence to support INP104, which is currently being developed by Impel," said Dr. Shrewsbury. "Over a decade of work has yielded this novel DHE product which has demonstrated similar plasma exposure levels to intravenous DHE from 20 minutes – only without the high peak plasma concentrations linked to unpleasant side effects, potentially addressing a long-standing clinical unmet need after many decades of DHE use."

INP104 utilizes the Company's Precision Olfactory Delivery (POD®) technology platform to deliver DHE to the richly vascularized upper nasal cavity. INP104 is currently being evaluated in the "STOP-301 Trial" (Safety and Tolerability of POD-DHE), a Phase 3, open-label safety and tolerability trial assessing long-term (24/52 week), intermittent use of INP104 for the treatment of acute migraine.

About INP104

INP104 is a drug-device combination product being studied for the treatment of acute migraine. It is comprised of a nasal formulation of dihydroergotamine (DHE) and Impel's proprietary Precision Olfactory Delivery, or POD®, device. The family of POD devices is designed to deliver consistent and predictable doses of drug. INP104, an investigational new drug, delivers DHE to the richly vascularized upper nasal cavity, offering the potential for rapid and consistent biodistribution without injection. DHE is an established and highly effective treatment option for acute migraine treatment.

The safety of INP104 is currently being investigated in the "STOP-301 Trial" (**S**afety and **To**lerability of **P**OD-DHE), a Phase 3, open-label safety and tolerability trial evaluating long-term (24/52 week), intermittent use of INP104 for the treatment of acute migraine.

About Acute Migraine

Migraine is a common and debilitating neurological disease characterized by recurrent episodes of severe head pain and associated with nausea, vomiting, sensitivity to light and to sound. Migraine affects approximately 39 million people in the United States. Of the approximately 19 million diagnosed migraine patients, only four million are on prescription treatment. While triptans account for almost 70 percent of migraine therapies, approximately 30 to 40 percent of patients do not respond adequately to triptans and up to 79 percent of the

treated patients report being dissatisfied with their current treatment and willing to try a new therapy.

About Impel NeuroPharma
Impel NeuroPharma, Inc., is a privately-held, Seattle-based biopharmaceutical 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) and INP107 (POD-carbidopa/levodopa) for reversal of OFF episodes in Parkinson's disease and INP105 (POD-olanzapine) for acute agitation in schizophrenia and bipolar I disorder.

Impel's product candidates are delivered via its proprietary Precision Olfactory Delivery, or POD®, technology which targets the richly vascularized upper nasal cavity with the goal of achieving enhanced bioavailability of therapeutic molecules.

IMPEL, POD and the IMPEL Logo are trademarks of Impel NeuroPharma, Inc. To learn more about Impel NeuroPharma, please visit our website at http://impelnp.com.

About Precision Olfactory Delivery or POD® Devices
Impel NeuroPharma's proprietary POD® nasal drug delivery device is designed to deliver drugs to the richly-vascularized upper nasal cavity to improve biodistribution and bioavailability of both small molecules and biologic drugs. By consistently and predictably delivering therapeutics to the upper nasal cavity, the POD device may improve overall bioavailability of drugs without IV injection. Impel has developed dry powder and liquid compatible POD devices to improve upon current treatment options for central nervous system (CNS) disorders.

Contact:
Melyssa Weible
Elixir Health Public Relations
Ph: (1) 201-723-5805
E: mweible@elixirhealthpr.com