IMPEL NEUROPHARMA ANNOUNCES FDA SUBMISSION OF NEW DRUG APPLICATION FOR INP104 FOR THE ACUTE TREATMENT OF MIGRAINE

~The INP104 New Drug Application is Supported by Results from the Phase 3 STOP 301 Study~

~Dihydroergotamine mesylate (DHE) is Administered via Impel's Proprietary Precision Olfactory Delivery (POD®) Technology, the First and Only Delivery System to Utilize the Vascular-Rich Upper Nasal Space as a Potential Treatment Pathway~

SEATTLE, November 9, 2020 — Impel NeuroPharma, a late-stage biopharmaceutical company, today announced that it has submitted a New Drug Application (NDA) for INP104 (dihydroergotamine mesylate) or DHE to the U.S. Food and Drug Administration (FDA) for the acute treatment of migraine headaches with or without aura in adult patients. INP104 uses the Company's proprietary Precision Olfactory Delivery (POD) technology, a novel delivery system that uniquely targets the vascular-rich upper nasal space. Impel is focused on the development and commercialization of transformative therapies for patients living with central nervous system (CNS) disorders with high unmet medical needs and INP104 is the Company's first therapeutic candidate to be submitted for U.S. regulatory review.

"The submission of INP104 represents our first NDA and marks a major milestone for Impel as we rapidly advance our pipeline of differentiated, potentially transformative therapies for people living with CNS disorders," said Adrian Adams, chairman and chief executive officer of Impel NeuroPharma. "Based upon the previously reported positive results of the STOP 301 study, we believe that INP104 has the potential to provide an important new option for people who need a fast, effective, and consistently reliable acute treatment of migraine headaches."

The NDA submission for INP104 is supported by safety results from the pivotal Phase 3 STOP 301 study, in which over 5,650 migraine attacks were treated over 24 or 52 weeks. The study met its primary objectives, with no new safety signals or concerning trends in nasal safety findings observed for INP104 following delivery of DHE to the upper nasal space. For the 24-week Full Safety Set (FSS) (n=354), the majority of treatment-emergent adverse events (TEAEs) were mild and transient in nature. The most frequently reported TEAEs (≥5%) during the entire 24-week period were nasal congestion (16.7%), nausea (7.9%), nasal discomfort (5.4%), and abnormal taste (5.1%). No cardiac TEAEs were observed, and no significant changes in mean heart rate were observed over 24 weeks of treatment. No drug-related serious adverse events (SAEs) were observed over the entire 52-week study. Exploratory efficacy data in the FSS (n=354) observed that 66.3% of patients reported pain relief, 38% of patients reported pain freedom, and 52% had freedom from their most bothersome migraine symptom (MBS) at two hours following their first dose of INP104. In 85% of reported migraine attacks, patients did not require rescue medication. Initial onset of pain relief as early as 15 minutes was reported by 16.3% of patients, which continued to improve over time. The STOP 301 study is one of the largest longitudinal studies of DHE to date.

About the STOP 301 Study:

The Phase 3 STOP 301 study enrolled 360 patients at 36 sites in the U.S. who had a documented diagnosis of migraine headaches with or without aura, with at least two attacks per month for the previous six months. 354 patients received at least one dose of INP104 and comprised the Full Safety Set. 185 patients who took an average of two or more treatments of INP104 per 28-day period during the 24-week treatment period comprised the Primary Safety Set. Of those enrolled, 74% (n=262) of patients completed the 24-week treatment period. Reasons for treatment discontinuation included withdrawal by subject (n=25 [7.1%]), adverse events (n=24 [6.8%]), lack of efficacy (n=21 [5.9%]), lost to follow-up (n=11 [3.1%]), non-compliance/protocol violation (n=5 [1.4%]), and physician's decision (n=1 [0.3%]). A subset of 73 patients continued into a 28-week treatment extension period to 52 weeks total, of which 90% completed.

About INP104:

Impel NeuroPharma is developing INP104 with the goal to be a transformative new therapy for the acute treatment of migraine headaches. INP104 aims to optimize dihydroergotamine mesylate (DHE) for fast and lasting whole migraine relief, regardless of when in the migraine attack it is administered, without an injection. Importantly, INP104 is designed to deliver a lower dose of DHE compared to FDA-approved and investigational products. This may enable patients to benefit from the established efficacy of DHE, without the undesired side effects that may be experienced with delivery to the lower nasal space.

INP104 utilizes Impel's propellant-enabled POD technology to conveniently and consistently deliver optimal doses of DHE deep into the vascular rich upper nasal space, an ideal target for efficient drug administration, particularly for the majority of patients with migraine who experience nausea and/or vomiting during an attack, which presents limitations for the use of oral therapies, including triptans, CGRP inhibitors and ditans as well as other non-specific acute migraine medications.

About Migraine:

Migraine is a common and debilitating neurological disease characterized by recurrent episodes of severe head pain and associated with nausea, vomiting and sensitivity to light and sound.[i] Migraine affects approximately 39 million people in the U.S.[ii] Of the approximately 19 million diagnosed migraine patients, only four million are on prescription treatment.[iii] While triptans account for almost 70% of acute migraine therapies, approximately 30 to 40% of patients do not respond adequately to triptans and up to 79% of the patients who do respond to triptans report being dissatisfied with their current treatment and willing to try a new therapy.[iv]

Further, evidence suggests that gastroparesis, delayed emptying of the stomach, is a prevalent feature in migraine that may delay or reduce the absorption of oral medications, including triptans, gepants and ditans. This means that oral medications can remain in the stomach for hours, delaying symptom relief, leading to loss of confidence (about future administration) and prolonged suffering during the current migraine attack.[v]

About Impel NeuroPharma:

Impel NeuroPharma, Inc. is a privately held, Seattle-based biopharmaceutical company focused on developing transformative therapies for people living with central nervous system (CNS) and other disorders with high unmet medical needs. The Company is rapidly advancing a late-stage product pipeline

that optimizes the effectiveness of proven treatments for neurological conditions, including INP104 for acute migraine, INP107 for OFF episodes in Parkinson's disease, and INP105 for acute agitation associated with schizophrenia, bipolar I disorder and autism.

About the Precision Olfactory Delivery or POD® System

Impel's proprietary Precision Olfactory Delivery (POD®) system 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 is designed to enable increased and consistent absorption of drug, with the potential to outperform the high variability associated with other nasal delivery systems.

While an ideal target for drug administration, to date no other system has been developed to deliver drugs to the upper nasal space. By utilizing this route of administration, Impel NeuroPharma has been able to demonstrate blood concentration levels for its investigational therapies that are comparable to intramuscular (IM) administration and can even reach intravenous (IV)-like systemic levels quickly, which could transform the treatment landscape for many 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.

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[i] Mayo Clinic. Migraine Symptoms & Causes. Last Accessed October 26, 2020.
[ii] Migraine Research Foundation. Migraine Facts. Last Accessed October 26, 2020.
[iii] Data on file
[iv] Data on file
[v] Aurora S, et al. *Cephalalgia*. 2013; 33:408-415; Tokola RA et al. *Br J Clin Pharmacol*. 1984. 18:867-871; Volans GN. *Clin Pharmacokinet*. 1978 3:313-318