Impel Pharmaceuticals to Present Trudhesa® Data at the 64th Annual Meeting of the American Headache Society

June 9, 2022

Oral Presentation Showcases Early Ability to Predict Responders to Trudhesa

New Analysis Suggest Patient-Reported Benefits of Long-Term Use with Trudhesa

Two Additional Analyses Demonstrate Trudhesa Efficacy Regardless of Current Preventive Therapies or Prior Acute Treatments

SEATTLE, June 09, 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 that it will present one oral presentation and three poster presentations from the pivotal, 52-week long, open-label, Phase 3 STOP 301 trial exploring the safety and exploratory efficacy of Trudhesa® (dihydroergotamine mesylate [DHE]) nasal spray (0.725 mg per spray), at the 64TH Annual American Headache Society (AHS) Scientific Meeting, taking place June 9-12, 2022, in Denver, Colorado.

Sara Sacco, M.D., a neurologist with the Carolinas Headache Clinic, Charlotte, North Carolina, and lead author on the prediction of response analysis abstract, will present an American Academy of Neurology (AAN) encore analysis from the pivotal, Phase 3 STOP 301 trial, aimed to determine if early treatment response to Trudhesa could predict response over consecutive migraine attacks.

“As a clinician, I see patients who are cycling through migraine medications without relief while the disease continues to cause disabling pain and limits their ability to live their daily lives,” says Dr. Sacco. “These data suggest that patients who respond to Trudhesa during the first two migraine attacks will continue to respond long-term. This, coupled with the new analysis showing self-reported improvements in disability and headache days with long-term Trudhesa use, equips clinicians with new information to improve therapeutic decision making, especially for non-responders to triptans or medications targeting calcitonin gene-related peptide, or CGRP. Patients are seeing relief of symptoms, improved predictability of response to treatment, and a reduction of disabilities due to their migraine with Trudhesa.”

Using Impel’s proprietary Precision Olfactory Delivery (POD®) technology, Trudhesa delivers dihydroergotamine mesylate — a proven, well-established therapeutic for the acute treatment of migraine for adults—quickly to the bloodstream through the vascular-rich upper nasal space. Trudhesa bypasses the gut and reduces potential absorption issues, offering rapid, sustained, and consistent symptom relief without nausea commonly associated with older migraine medications, even when administered outside the traditional window of efficacy for a migraine attack. Drug delivery via the POD technology enables rapid absorption and provides enhanced bioavailability and reaches intravenous (IV)-like systemic levels quickly, which could transform the treatment landscape.

“DHE is a well-established molecule, but many patients and clinicians do not know that it can now be administered at home and no longer needs to be administered via IV. With Trudhesa, we can now prescribe this highly effective medication, delivered directly to the upper nasal space achieving IV like levels utilizing Impel’s proprietary POD technology. In addition, there were no new safety concerns, and the therapy was well tolerated in a home setting with limited side effects,” said Sheena K. Aurora, M.D., Vice President Medical Affairs, Impel Pharmaceuticals. “This data at AHS, adds to the growing body of evidence supporting a novel method of DHE delivery that can be used regardless of the severity of a migraine attack or the time at which Trudhesa is administered.”

All presentations will be accessible on the AHS website at www.americanheadachesociety.org. Presentation details are highlighted below.

Oral Presentation:

- The analysis that Dr. Sacco will discuss found that patients who self-report mild or no pain at two hours for their first three Trudhesa-treated migraine attacks are extremely likely (>89%) to respond to Trudhesa treatment. Those with no or mild pain for their first two Trudhesa treated migraine attacks were also likely (>75%) to respond to Trudhesa treatment. Results suggest that if Trudhesa provides pain relief for the first two to three migraine attacks, it is likely a patient will respond to Trudhesa with long-term use, which is informative for clinical decision making.[1]
    - **Session title: Industry-Submitted Abstracts**
    - **Presentation Title:** “Early Prediction of Response to INP104 for the Acute Treatment of Migraine”
    - **Presentation Time:** Saturday, June 11, 9-9:10 a.m. Mountain Time (MT)

Poster Presentations:

- This analysis looked to determine report scores for each item of the Migraine Disability Assessment Scale (MIDAS) questionnaire following long-term use with Trudhesa for the acute treatment of migraine. The review suggests that long-term treatment with Trudhesa was associated with improvements in scores of several individual MIDAS items of productivity and disability, as well as a decrease in the number of headache days over 24 and 52 weeks, leading to a

reduction in overall patient burden.[2]

- **Presentation Title:** “Improvements in Productivity and Disability with INP104 as Assessed by the Migraine Disability Assessment Scale (MIDAS): Results from the Phase 3 STOP 301 Study”; **Poster** #P-176
- **Presentation Time:** Saturday, June 11, 1:00-2:15 p.m. Mountain Time (MT)

- This analysis evaluated data from the STOP 301 trial to determine the efficacy of Trudhesa in patients who did or did not use concomitant migraine preventive medications over 24-week period. Treatment with Trudhesa over 24 weeks demonstrated improvements in self-reported pain and most bothersome symptom freedom at 2 hours post-Trudhesa with most of the concomitant migraine preventive groups analyzed. Results suggest that Trudhesa may be an effective acute therapy for migraine in patients who are concurrently using preventive therapies.[3]
  - **Presentation Title:** “Exploratory Efficacy of INP104 in Patients Using Concomitant Preventive Migraine Medications”; **Poster** #P-174
  - **Presentation Time:** Saturday, June 11, 1:00-2:15 p.m. Mountain Time (MT)

- An additional AAN encore presentation from the pivotal, Phase 3 STOP 301 trial, will look at the exploratory efficacy of Trudhesa treatment over 24 weeks based on acute medications used prior to Trudhesa. There are many evidence-based migraine acute treatments currently available and these are either migraine non-specific (i.e., non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) or migraine-specific (i.e., triptans, DHE). Since there are numerous acute therapies available, it is important to determine if the efficacy of Trudhesa is impacted by prior acute treatment history. Acute therapies most commonly used prior to initiation of treatment with Trudhesa were acetaminophen, NSAIDs, and triptans. This analysis suggests that Trudhesa is an effective treatment for migraine patients who have previously used a variety of acute therapies.[4]
  - **Presentation Title:** “Exploratory Efficacy of INP104 in Migraine Patients by Prior Treatment”; **Poster** #P-173
  - **Presentation Time:** Friday, June 10, 1:30-2:30 p.m. Mountain Time (MT)

About STOP 301

The new drug application for Trudhesa included the results of the Phase 3, open-label, pivotal safety study, STOP 301, which is the largest longitudinal study ever conducted with DHE using nasal spray delivery.[5] More than 5,650 migraine attacks were treated over 24 or 52 weeks during the study. The primary objective of the study was to assess the safety and tolerability of Trudhesa. Exploratory objectives included efficacy assessments of migraine measures and a patient acceptability questionnaire. In the trial, Trudhesa was generally well tolerated and exploratory efficacy findings showed it provided rapid, sustained, and consistent symptom relief. Unlike some oral acute treatments that need to be taken within one hour of attack onset to be most effective, the STOP 301 study reported Trudhesa offered consistent efficacy even when taken late into a migraine attack.[6]

There were no serious Trudhesa-related treatment-emergent adverse events (TEAEs) observed in the STOP 301 study and the majority of TEAEs were mild and transient in nature.[7] Some of the most frequently reported Trudhesa-related TEAEs (≥2%) during the entire 52-week study period were nasal congestion (17.8%), nausea (6.8%), nasal discomfort (6.8%), abnormal olfactory test (6.8%) and vomiting (2.7%).[8]

In the STOP 301 study, patient-reported exploratory efficacy findings reported that more than a third of patients (38%) had pain freedom,[9] two-thirds (66%) had pain relief,[9] and more than half (52%) had freedom from their most bothersome migraine symptom[10] at two hours after their first dose of Trudhesa. For one in six patients (16%), pain relief started as early as 15 minutes.[11] Of patients who were pain free at two hours after their first migraine attack, 98 percent were still pain free at 24 hours,[11] and 95 percent were still pain free through two days respectively, during weeks 21-24.[12] The great majority of patients (84%) reported that Trudhesa was easy to use and preferred it over their current therapy. [13]

About Migraine

Approximately 31 million adults in the U.S. are living with migraine,[14] and there is a need for more treatment options. In a survey of nearly 4,000 U.S. patients using oral acute prescription medication for migraine, 96 percent said they were dissatisfied with at least one aspect of their treatment —including lack of sustained relief, inconsistent relief, and lack of relief from a rapid-onset attack. Nearly half (48%) said they can still have pain two hours after taking medication and 38 percent say their headache returns within 24 hours of getting relief.[15] Additionally, there is a need for non-oral routes of administration given the high prevalence of gastrointestinal issues among people with migraine.

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 (IM) administration and can even reach intravenous (IV)-like systemic levels quickly, which could transform the treatment landscape for central nervous system (CNS) 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 Trudhesa® (dihydroergotamine mesylate) Nasal Spray

Trudhesa® nasal spray (0.725 mg per spray) is approved by the U.S. Food and Drug Administration for the acute treatment of migraine with or without

aura in adults in the U.S. Using Impel's proprietary POD® technology, Trudhesa gently delivers DHE—a proven, well-established therapeutic[6]—quickly to the bloodstream through the vascular-rich upper nasal space. Trudhesa bypasses the gut and potential absorption issues, offering the potential for rapid, sustained, and consistent relief without injection or infusion, even when administered hours after the start of a migraine attack.[16]

Trudhesa is a single use, drug-device combination product containing a vial of DHE (4 mg DHE in a 1 mL solution that is clear and colorless to faintly yellow) and a POD® device. Prior to initiation of Trudhesa, a cardiovascular evaluation is recommended. For patients with risk factors predictive of coronary artery disease who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of Trudhesa take place in the setting of an appropriately equipped healthcare facility.

Trudhesa is designed to be self-administered. Once assembled, Trudhesa should be primed before initial use by releasing 4 sprays. A patient should use Trudhesa immediately after priming. The recommended dose of Trudhesa is 1.45 mg administered as two metered sprays into the nose (one spray of 0.725 mg into each nostril). The dose may be repeated, if needed, a minimum of one hour after the first dose. A patient should not use more than two doses of Trudhesa within a 24-hour period or three doses within a 7-day period. A patient should use or discard Trudhesa within eight hours once the vial has been opened or the product has been assembled. A consumer assembly video is available on www.TRUDHESA.com and please refer to the Instructions for Use for more details.

About Dihydroergotamine Mesylate (DHE)

DHE was approved for the treatment of migraine in 1946 and has more than 70 years of therapeutic use.[6] Migraine treatment with DHE has demonstrated efficacy independent of when the treatment is initiated.[17] Unlike other available treatments for migraine, DHE is known to bind to multiple receptors theorized to be implicated in migraine onset and duration.[12]

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.

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

---

[1] Sacco S.; Vann R.; Ray S.; Shrewsbury SB; Aurora, S. Early Prediction Of Response To INP104 For The Acute Treatment Of Migraine. AHS 2022 Annual Conference, June 9-12, 2022.

[2] Treppendahl C.; Buse D.; Vann R.; Fitzpatrick C.; Murphy M.; Shrewsbury SB.; Aurora SK.; Improvements in Productivity and Disability With INP104 as Assessed by the Migraine Disability Assessment Scale (MIDAS): Results From the Phase 3 STOP 301 Study. AHS 2022 Annual Conference, June 9-12, 2022.

[3] Grant J.; Vann R.; Fitzpatrick C.; Lieu TM.; Shrewsbury SB.; Aurora SK. Exploratory Efficacy of INP104 in Patients Using Concomitant Preventive Migraine Medications. AHS 2022 Annual Conference, June 9-12, 2022.

[4] Bilchik T.; Vann R.; Ray S.; Shrewsbury SB.; Aurora S. Exploratory Efficacy of INP104 in Migraine Patients By Prior Treatment. AHS 2022 Annual Conference, June 9-12, 2022.

[5] On file at Impel

[6] Smith TR.; Winner P.; Aurora SK.; Jeleva M.; Hocevar-Trnka J.; Shrewsbury SB.; STOP 301: A Phase 3, Open-Label Study Of Safety, Tolerability, And Exploratory Efficacy Of INP104, Precision Olfactory Delivery (POD®) Of Dihydroergotamine Mesylate, Over 24/52 Weeks In Acute Treatment Of Migraine Attacks In Adult Patients. *Headache*. 2021; 00: 1– 13. https://doi.org/10.1111/head.14184

[7] Impel Neuropharma. (2020). INP104-301. Table 3.4.5.

[8] Impel Neuropharma. (2020). Clinical Study Report, Protocol No. INP104-301. Version 1.0. Tables 14.3.1.1.3b.

[9] Impel Neuropharma. (2020). INP104-301. Table 3.3.1.

[10] Impel Neuropharma. (2020). INP104-301. Table 3.3.4.

[11] Shrewsbury SB.; Hoekman J.; Jeleva M.; Hocevar-Trnka J.; Hoekman J.; Shrewsbury SB.; A Long Term, Open Label Study of Safety and Tolerability of Precision Olfactory Delivery of DHE in Acute Migraine (STOP 301): Clinical Results, PainWEEK Live Virtual Conference Sept 11-13, 2020

[12] Impel Neuropharma. (2020). INP104-301. Table 3.3.6.

[13] Impel Neuropharma. (2020). Clinical Study Report, Protocol No. INP104-301. Version 1.0. Tables 14.3.11.1a

[14] Lipton RB.; Bigal ME.; Diamond M.; Freitag F.; Reed ML.; Stewart VF.; Migraine Prevalence, Disease Burden, And The Need For Preventive Therapy. *Neurology* 2007;68;343-349 DOI: 10.1212/01.wnl.0000252808.97649.21

[15] Impel Neuropharma. (2020). INP104-301. Table 3.8.2.

[16] Aurora SK; et al. *J Headache Pain*. 2013;14(Suppl 1):P143.

[17] Impel Neuropharma. (2020). INP104-301. Table 3.3.6.