

Company

Impel Pharmaceuticals Inc.

Drug or Device Name

Trudhesa®

Category

Medical Technology

Compound/Technical Name

Precision Olfactory Delivery (POD®) Technology

Trade Name

Trudhesa

Date of Approval

09/03/2021

Therapeutic Categories

Migraine

Indications

Trudhesa, the only product approved by the U.S. Food and Drug Administration utilizing POD technology, is indicated for the acute treatment of migraine with or without aura in adults.

Background

The approval of Trudhesa ushered in an entire new era of nasal drug delivery. POD technology eliminates the need for coordinating inhalation and breath-holding (a limitation from previous delivery systems targeting the upper nasal space), resulting in easy at-home administration, greater patient comfort and potentially improved compliance – all while achieving more consistent absorption and efficacy comparable to IV administration.

The easiest way to visualize the sheer magnitude of innovation in POD technology is by comparing its pharmacokinetic parameters with DHE delivered via IV and traditional nasal delivery systems, respectively (see attachments).

In results from the STOP 101 trial depicted above, Trudhesa avoided the undesirable high-peak plasma DHE concentration seen with IV administration while generating similar plasma levels from 30 minutes to 48 hours. It also achieved a four-fold increase in maximum DHE concentration and a three-fold increase in the total amount of DHE in the blood, compared with liquid DHE nasal spray using an identical formulation but less than three-quarters of the dose.

Additionally, exploratory efficacy data from the STOP 301 Phase 3 study found that Trudhesa resulted in

relief from migraine symptoms as early as 15 minutes after dosing, with more than half of people free from their most bothersome symptom at two hours. Importantly, rates of pain freedom were the same whether people took Trudhesa within two hours or several hours into a migraine attack.

Best said by Dr. Eric Baron, Cleveland Clinic neurologist and migraine thought leader: “What if I told you we now have a very easy to use nasal spray DHE with significantly greater effectiveness compared to [traditional nasal devices], with the same potency and effectiveness of IV DHE, but with much less side effects than IV DHE? Well, it’s happened with Trudhesa. And before you start telling yourself this is just another expensive repackaging of an old medicine that does the same thing, I have a spoiler alert... that’s far from accurate.”

Development

The POD technology was developed by John Hoekman, Ph.D., co-founder and Chief Technology and Development Officer at Impel Pharmaceuticals, while pursuing his thesis work in nasal drug delivery at the University of Washington. Intravenous delivery required costly, time-consuming in-patient visits, and oral medicines suffered from slow absorption and onset of action, and possible interactions with food or other orally administered drugs, side effects due to high systemic drug levels resulting from the need for larger doses to observe therapeutic effect.

While nasal delivery of drugs was not new, it was recognized as being especially challenging in terms of demonstrating efficacy equivalent to comparable IV/oral formulations, consistent patient outcomes, and improved tolerability profiles. These challenges could all be traced back to the place in the nose to which nearly every commercialized nasal spray delivered drug: the lower nasal space.

Delivering drug to the lower nasal space results in suboptimal absorption of drug, and with gravity leads to drug dripping out of the nostril or into the throat. Drug delivered to the lower nasal space can also get trapped in the mucus and cleared/swallowed by mucociliary clearance — a protective physiological mechanism that, unfortunately for drug developers, acts as a barrier to drug absorption in the nose.

The upper nasal space’s respiratory and olfactory epithelium areas are more permeable than the epithelium found in the lower nasal space, and the tissue architecture in the upper nasal space may render it more suitable for drug absorption. Hoekman’s solution was the POD technology, an approach that targeted the vascular-rich upper nasal space for the first time, providing IV-like outcomes in a convenient, easy-to-use nasal spray.

An urgent area of unmet need was for effective, consistent ways of delivering medicines for acute conditions that require therapies to provide a maximal benefit as quickly as possible. One of these conditions was migraine, a variable and complex disorder that may require drug targets with broader pharmacology to provide patients with full-spectrum relief, particularly for those patients with an incomplete, inconsistent, or lack of response to agents with more narrow pharmacological range.

Dihydroergotamine mesylate, or DHE, is regarded as one of the most effective medicines in treating migraine – it has a broad mechanism of action a long half-life with biphasic elimination, and has been shown to slowly dissociate from receptors, which may underlie its proven benefit in recurrent headache and multiple forms of difficult-to-treat migraine (e.g., menstrual migraine, medication overuse headache, triptan-resistant migraine, and severe or prolonged migraine). While its use had

been limited due to frequent adverse events, such as nausea and vomiting, inconvenience of IV administration, and a general preference for needle-free options, John and Impel realized that delivering it to the upper nasal space could make all the difference.

After 13 years of developing POD technology, Impel received U.S. FDA approval for Trudhesa in September 2021 for the acute treatment of migraine – marking the first drug-device combination product to use the POD technology and the first product to successfully and consistently deliver drug to the upper nasal space and achieve therapeutic benefit.

Innovation

The most immediate implication for future research on Trudhesa and POD technology is studying it in randomized, controlled clinical trials with other commonly used migraine medications.

To set the stage: IV DHE has always been considered one of the most effective medicines in treating migraines, and is often a go-to when other acute medicines won't work – it's one of the only options that can reverse late-stage migraine and thus is a staple in headache centers. Despite this, DHE has been historically underutilized outside of the clinic given the IV requirement and physician inexperience.

At the same time, the idea of a “migraine toolbox” has gained popularity amongst healthcare professionals over the past couple of years. The heterogeneity of migraine means there are no “one-size-fits-all” options, and as such a compelling case emerges to equip patients with a mix of triptans, NSAIDs, ditans, gepants and DHE in their toolkits.

Since Trudhesa was approved in September 2021, multiple post-hoc analyses from STOP 301 have shed light on its differentiated safety and efficacy profile compared to other DHE-based products, most notably in evaluations of its use with other commonly used migraine medications. These analyses have suggested that Trudhesa is safe to use with triptans, preventive CGRPs and gepants – and that further studies of these combinations are warranted.

Bottom line: now with an easier-to-use, more tolerable and less invasive form of DHE disposable to clinicians, it's important to understand how this differentiated DHE product interacts with other migraine mainstays – and having clinically validated evidence of its safety could transform this idea of a ‘toolbox’ approach by bringing DHE to the mainstream (so to speak) through non-expert prescribers.

The potential to improve human health leveraging the POD device go beyond the way Trudhesa has redefined expectations for nasal drug delivery in migraine. POD technology has the potential to transform the treatment of many acute conditions that require therapies to provide a maximal benefit as quickly as possible.

According to research, the global inhalation and nasal spray market size was \$30.5 billion in 2020, and expected to reach \$46.8 billion in 2028 – highlighting the breadth of medications that can currently be delivered nasally. POD technology is a novel approach to nasal delivery that addresses critical shortcomings of existing treatment mechanisms by depositing medicines directly and consistently into the vascular-rich upper nasal space where they can be readily absorbed.

The potential new applications of POD technology are substantial: it can deliver both liquid and dry

powder formulations of therapeutics, can be modified to accommodate formulation and molecular structure of a wide range of medical compounds, and has demonstrated the ability to deliver certain peptide and protein-based drugs that do not readily cross the blood-brain barrier. This capability opens the door to a wide array of potential investigational programs across many diseases.

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1. 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> 2. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 396:1204–1222 [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30925-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30925-9/fulltext) 3. R. B. Lipton, M. E. Bigal, M. Diamond, F. Freitag, M. L. Reed, W. F. Stewart. Migraine prevalence, Disease Burden, and the Need for Preventive Therapy. *Neurology* 2007;68;343-349 DOI: <https://n.neurology.org/content/68/5/343> 4. Lipton, R. B., Munjal, S., Buse, D. C., Alam, A., Fanning, K. M., Reed, M. L., Schwedt, T. J., & Dodick, D. W. (2019). Unmet Acute Treatment Needs From the 2017 Migraine in America Symptoms and Treatment Study. *Headache*, 59(8), 1310–1323. <https://doi.org/10.1111/head.13588> 5. Aurora S, et al. Gastric stasis in migraineurs: Etiology, characteristics, and clinical and therapeutic implications. *Cephalalgia*. 2013; 33:408–415 <https://journals.sagepub.com/doi/abs/10.1177/0333102412473371> 6. Tokola RA et al. Effect of migraine attacks on paracetamol absorption. *Br J Clin Pharmacol*. 1984. 18:867-871 <https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2125.1984.tb02557.x> 7. The American Headache Society Position Statement on Integrating New Migraine Treatments into Clinical Practice. *Headache: The Journal of Head and Face Pain*, 59: 1-18. <https://doi.org/10.1111/head.13456> 8. Aurora SK, et al. *J Headache Pain*. 2013;14(Suppl 1):P143. <https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/1129-2377-14-S1-P143> 9. Martin V, Hoekman J, Aurora SK, Shrewsbury SB. Nasal Delivery of Acute Medications for Migraine: The Upper Versus Lower Nasal Space. *J. Clin. Med*. 2021, 10, 2468. <https://doi.org/10.3390/jcm10112468> 10. Hoekman J, Ray S, Aurora SK, Shrewsbury SB. The Upper Nasal Space—A Novel Delivery Route Ideal for Central Nervous System Drugs. *US Neurology*. Volume 16. Issue 1. Spring 2020. <https://touchneurology.com/parkinsons-disease/journal-articles/the-upper-nasal-space-a-novel-delivery-route-ideal-for-central-nervous-system-drugs/> 11. Allen MH, Currier GW, Hughes DH et al. *J Psychiatry Pract* 2005. 11(Suppl 1); 5-108

Attachments

- 1653324253Trudhesa_Fact_Sheet_FINAL.pdf
- 1653324274IMP_TRU_Clamshell_Overhead_RGB_v6_sm_No_Shadow.png
- 1653324284IMP_TRU_Hero_01_Straight_Left_White_RGB_v5_sm_No_Shadow.png
- 1653324203Prix_Galien-_Impel_Implications.pdf