Patient Acceptability of a Novel Upper Nasal Delivery System for DHE – Using the Precision Olfactory Delivery (POD®) Device (INP104)

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Introduction

- Migraine is a debilitating condition with a significant patient and socioeconomic burden, and dissatisfaction with current therapies persists as a high unmet need[1-4]
- Dihydroergotamine (DHE) has a long-established history as an effective migraine therapy, especially when administered intravenously; however, the intravenous formulation, impractical for self-administration at home, can be associated with side effects such as nausea and vomiting[5,6]
- In 1997, a nasal formulation of DHE mesylate that targets the lower nasal space (Migranal® [Bausch Health Companies, Inc. or its affiliates]) was developed, but it had variable efficacy because of both drug loss and low bioavailability[5,6]
- INP104 is a novel drug-device combination product that targets delivery of DHE mesylate to the upper nasal cavity using a Precision Olfactory Delivery (I123 POD®) device, with which greater, more consistent drug absorption occurs following noninvasive administration[6,7]
- STOP 301 was an open-label, pivotal Phase 3 study that assessed safety, tolerability, and exploratory efficacy following a single-dose administration of 1.45 mg INP104 in patients with migraine compared to a baseline period using their best usual care over 24 and 52 weeks[8]
  - No major safety concerns were identified during this long-term safety study, including adverse events (AEs) related to the upper nasal space[8]
  - Over the 24-week treatment period, INP104 also led to consistent and sustained improvements in patient-reported pain freedom, most bothersome symptom freedom, pain relief, and headache recurrence[8]
- As part of the STOP 301 study, patient acceptability of INP104 drug delivery to the olfactory epithelium with the POD device was determined through a patient survey. We report those results here for the 24-week time period

Objective

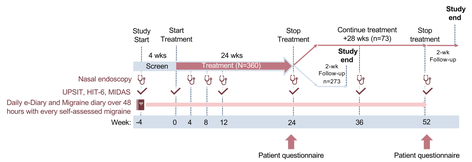
- To assess the patient acceptability of POD DHE (INP104) over 24 and 52 weeks in the pivotal Phase 3 STOP 301 study

Methods

Study Design

- This was a pivotal Phase 3, interventional, open-label, single-group assignment study, assessing the safety, tolerability, patient acceptability, and exploratory efficacy of INP104 (NCT 03557333) over long-term use
- The study was comprised of a 4-week screening period, a 24-week treatment period for all patients, a treatment extension to 52 weeks for a subset of the patients, and a 2-week post-treatment follow-up period (**Figure 1**)

Figure 1. Study Design



HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; UPSIT, University of Pennsylvania Smell Identification Test; wk, week.

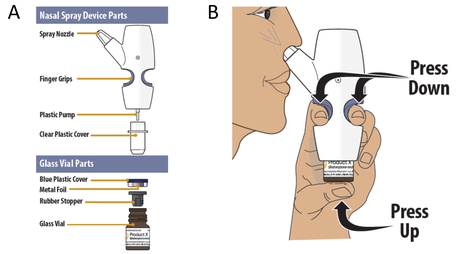
Study Patients

- Patients had a documented diagnosis of frequent migraine, defined as suffering a minimum of 2 migraines, with or without aura, each month not qualifying as chronic headache during the previous 6 months per the *International Classification of Headache Disorders,* version 3 beta
- Patients were adult (18-65 years) males or females in general good health, with no significant medical history or clinical abnormalities at baseline, which includes no history of cardiovascular events
- Patients were excluded if they had medication overuse headache, trigeminal autonomic cephalalgias, migraine aura without headache, hemiplegic migraine, or migraine with brainstem aura
- Patients with significant nasal congestion/blockage or abnormalities of the septum, as well as those with hypersensitivity to ergot alkaloids, failure of response to intravenous DHE, ongoing use of triptan or ergot-based medications, or other prohibited medications were further excluded

Study Treatments and Assessments

- During the 28-day (4-week) screening period, patients were on a current "best usual care" treatment
- After the screening period, all patients were provided with up to 3 doses/week of INP104 to nasally self-administer (1.45 mg in a dose of 2 puffs, one puff to each nostril) with all self-recognized migraine attacks over 24 weeks, with a subset continuing over 52 weeks (**Figure 2**)
- Dosing was limited to no more than 2 doses within a 24-hour period, 3 doses within a 7-day period, or 12 doses per 4-week period
- Primary endpoints included the number of patients reporting treatment-emergent adverse events (TEAEs, serious or non-serious), change in nasal mucosa, and change in olfactory function
  - Migraines were not included within the definition of an AE per the objective of this study
- Exploratory endpoints included efficacy measures and a patient acceptability questionnaire
  - A 6-question patient acceptability questionnaire was administered at Week 24 and 52 (**Table 1**)

Figure 2. Illustration of INP104 Drug-Device Product and Actuation of INP104



A) Diagram of the INP104 drug-device product
B) Diagram of how to dose with INP104

Table 1. Patient Acceptability Questionnaire

	Questions	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1	The study drug is easy to use					
2	The investigational product works faster compared to my previous prescription migraine medication(s)*					
3	The investigational product keeps my migraine from coming back for a longer time than previous prescription migraine medications I've used*					
4	With the investigational product I can return to normal activities faster (school/work/leisure activities) compared to my previous prescription migraine medication(s)*					
5	Compared to previous migraine prescription medications, the investigational product more consistently relieves each one of my migraine headaches*					
6	The investigational product was very convenient to carry with me and use outside of my home					

*INP104 compared to previous treatment (best usual care).

Results

Patient Disposition and Baseline Characteristics

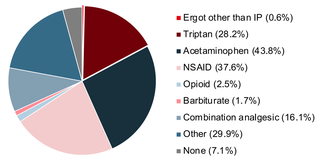
- 360 patients were screened and enrolled into the 24-week treatment period
  - 354 patients who were enrolled and received at least 1 dose of INP104 comprised the full safety set (FSS)
  - 262 patents completed the 24-week treatment period
    - Reasons for treatment discontinuation included withdrawal by subject (n=25 [7.1%]), AEs (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%])
  - 185 patients who took an average of 2 or more treatments with INP104 per the 28-day period during the 24-week treatment period comprised the primary safety set (PSS)
- Demographic characteristics for the patients enrolled in the 24-week treatment period for the FSS population are included in **Table 2** and **Figure 3**

Table 2. STOP 301 Baseline Demographics Overview

Baseline Demographics Overview	FSS (N=354)
Age, Years, Mean (SD)	41.3 (11.12)
Female, n (%)	304 (85.9)
Migraines During 28-day Screening Period, Mean (SD)	4.60 (2.313)
Most Bothersome Symptom, n (%)	
Photophobia	175 (49.4)
Nausea	58 (16.4)
Phonophobia	50 (14.1)
Foggy thinking	19 (5.4)
Vomiting	9 (2.5)
Visual change	9 (2.5)
Fatigue	6 (1.7)
Dizziness/vertigo	4 (1.1)
Sensitivity to touch	2 (0.6)
Other	22 (6.2)

FSS, full safety set; SD, standard deviation.

Figure 3. STOP 301 Baseline Migraine Medication Types (FSS Population)

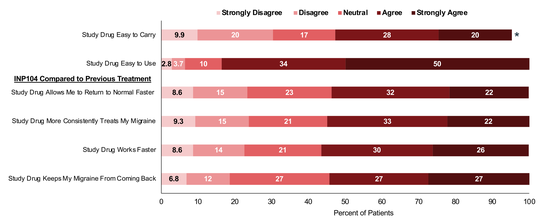


Note: 13 patients in total used non-oral acute migraine treatments (triptans) at baseline in the FSS, of which 5 patients were using a nasal triptan.
FSS, full safety set; IP, investigational product; NSAID, nonsteroidal anti-inflammatory drug.

Patient Acceptability Questionnaire

- The patient acceptability questionnaire results are shown in **Figure 4**
  - 48% of patients agreed/strongly agreed that INP104 was easy to carry
  - 84% of patients agreed/strongly agreed that INP104 was easy to use
  - Compared to their previous best usual care:
    - 54% of patients agreed/strongly agreed that INP104 allowed them to return to normal activities faster
    - 56% and 55% of patients agreed/strongly agreed that INP104 worked faster and more consistently, respectively
    - 54% of patients agreed/strongly agreed that INP104 lasted longer

Figure 4. Patient Acceptability Questionnaire (24-week FSS, N=354)



*Remaining 5% never used INP104 outside of the home.
Note: Data are self-reported via a patient e-diary.
FSS, full safety set.

Conclusions

- STOP 301 was an open-label study of the safety and tolerability of chronic intermittent usage of nasal DHE mesylate (INP104) for 24 or 52 weeks
- With a patient acceptability questionnaire it was determined that most patients reported this novel drug-device (INP104) to be easy to carry and easy to use
- Compared to their previous medications, the majority of patients found that INP104 kept their migraine from coming back and allowed them to return to normal activities of daily living faster, and that INP104 worked faster and more consistently
- The data collected from this patient acceptability questionnaire were also used to optimize the instructions for use and conduct further human factors testing
- Overall, these results suggest that upper nasal delivery may provide an effective and well-tolerated alternative to acute oral treatments for migraine, while providing the reliable efficacy of the long-established DHE molecule

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