Patient Acceptability of a Novel Upper Nasal Delivery System for Dihydroergotamine Mesylate Using the Precision Olfactory Delivery (POD®) Device - Results From the Open-label STOP 301 Trial

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Introduction

- Migraine is a common, disabling primary headache disorder with ~1 billion individuals afflicted globally[1,2]
- Despite the recent approval of several, novel abortive treatments, patients remain dissatisfied with their current therapies and there is a high unmet need for effective and safe migraine treatment options[3,4]
- Dihydroergotamine (DHE) has long been used and recommended for the treatment of migraine (since 1946) due to its high response rate and sustained efficacy[5]
- However, DHE was originally only available by injection, which was invasive and could result in greater systemic side effects – especially with intravenous injection – such as nausea and vomiting[5,6]
- A nasal formulation of DHE mesylate (Migranal® [Bausch Health Companies, Inc. or its affiliates]) became available in 1997, but the therapeutic effect of Migranal was variable which may be due to inconsistent absorption of DHE from the lower nasal space[5,6]
- INP104 is a novel drug-device combination product that targets delivery of nasal DHE mesylate to the upper nasal cavity using a Precision Olfactory Delivery (POD) device[6]
- Now, delivery of drugs to the upper nasal space has the potential to provide greater, more consistent drug absorption, and thus, may reduce response variability and provide reliable relief in a non-invasive manner[6,7]
- INP104 was previously found to be readily absorbed and well tolerated in a Phase 1 study (STOP 101), with a favorable safety profile[6]
- INP104 was shown to reach intravenous DHE-like levels in the blood from 20 minutes-48 hours post-administration and displayed more consistent delivery compared to Migranal[6]
- STOP 301 is a pivotal Phase 3 safety study reviewed by the Food and Drug Administration to collect long-term safety data (over 24 and 52 weeks) on the use of INP104 for acute episodic migraine, with a focus on upper nasal space safety
- Exploratory efficacy data was also collected as part of the open-label design, and INP104 was compared against "best usual care" used during baseline with information collected in a daily diary

Objective

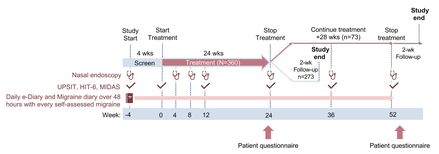
- To report the safety, tolerability, exploratory efficacy, and patient acceptability of POD-DHE mesylate (INP104) over 24 weeks from the pivotal, Phase 3 STOP 301 clinical trial

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 (NCT03557333) 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

- 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 over 52 weeks
- 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

Study Assessments

- 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 adverse event (AE) per the objective of this study
- Exploratory endpoints included a patient acceptability questionnaire
- Additional endpoints included exploratory efficacy outcomes, such as freedom from headache pain and most bothersome symptom (MBS) at 2 hours, pain relief at 2 hours, and sustained pain freedom through 24 hours during the 24-week treatment period

Results

Patient Disposition and Baseline Characteristics

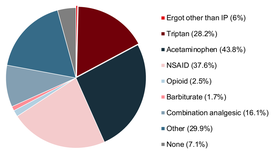
- 360 patients were screened and enrolled into the 24 week trial period
  - 354 patients who were enrolled and received at least 1 dose of INP104 comprised the Full Safety Set (FSS)
  - 262 patents completed the 24-week treatment period
    - Reasons for treatment discontinuation included withdrawal 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 is included in **Table 1** and **Figure 2**

Table 1. 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 2. STOP 301 Baseline Migraine Medication Types (FSS Population)



FSS, full safety set; IP, investigational product; NSAID, nonsteroidal anti-inflammatory drug.

Safety and Tolerability

- 36.7% and 34.1% of patients in the FSS and PSS populations, respectively, reported an INP104-related TEAE during the 24-week treatment period (**Figure 3**)
- There were no INP104-related serious AEs (SAEs) to date
- There were also no findings of concern during nasal endoscopy and olfactory function assessments (data not shown)

Figure 3. Treatment-Related TEAEs (24-Week FSS and PSS Populations)

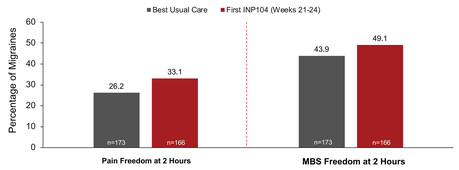
Treatment-Related TEAE (≥1% in FSS)	FSS n=354	PSS n=185
Any INP104-related TEAE, n (%)	130 (36.7)	63 (34.1)
Nasal congestion	53 (15.0)	23 (12.4)
Nausea	24 (6.8)	8 (4.3)
Nasal discomfort	18 (5.1)	10 (5.4)
INP104 taste abnormal	18 (5.1)	9 (4.9)
Vomiting	9 (2.5)	2 (1.1)
Olfactory test abnormal	8 (2.3)	6 (3.2)
Sinus congestion	7 (2.0)	3 (1.6)
Package-associated injury	6 (1.7)	5 (2.7)
Dizziness	5 (1.4)	2 (1.1)
Nasal mucosal disorder	5 (1.4)	3 (1.6)
Epistaxis	5 (1.4)	1 (0.5)
Dysgeusia	4 (1.1)	1 (0.5)
Rhinorrhea	4 (1.1)	1 (0.5)

FSS, full safety set; PSS, primary safety set; TEAE, treatment-emergent adverse event.

Exploratory Efficacy

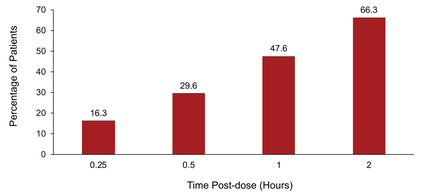
- 33.1% of patients achieved pain freedom at 2 hours post-INP104 nasal delivery (Weeks 21-24) compared to 26.2% on best usual care (baseline) (**Figure 4**)
- 49.1% of patients achieved freedom from their most bothersome symptom (MBS) at 2 hours post-INP104 nasal delivery (Weeks 21-24) compared to 43.9% on best usual care (baseline) (**Figure 4**)
- Additionally, 66.3% of patients achieved pain relief at 2 hours (**Figure 5**)
- Sustained pain freedom through 24 hours was also reported in the majority of patients, as 98.4% of patients were relapse-free of their migraine after using INP104 (Weeks 21-24) compared to 93.2% using best usual care (baseline) (**Figure 6**)

Figure 4. 2-Hour Pain Freedom and Most Bothersome Symptom (24-Week PSS Population, n=185)



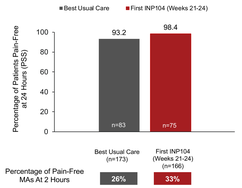
Note: Data is self-reported via a patient e-diary.
MBS, most bothersome symptom.

Figure 5. Pain Relief for First INP104 Treated Migraine (24-Week FSS Population, N=354)



Note: Pain Relief = Severe or Moderate pain decreased to Mild or None or Mild pain decreased to None.
Data is self-reported via a patient e-diary.
FSS, full safety set.

Figure 6. Sustained Pain Freedom Through 24 Hours (24-Week PSS Population)

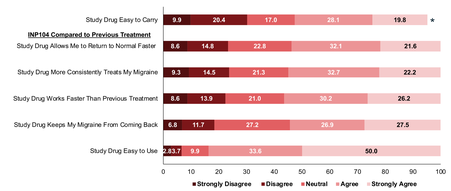


Note: Data is self-reported via a patient e-diary.
MA, migraine attack; PSS, primary safety set.

Patient Acceptability Questionnaire

- The patient acceptability questionnaire results are shown in **Figure 7**
  - The patient acceptability questionnaire demonstrated that the majority of patients agreed or strongly agreed that they found INP104 easy to use (~84%)
  - Compared to their previous treatment, the majority of patients found that INP104 kept their migraine from coming back and allowed them to return to normal activities of life faster
  - Further, patients reported faster and more consistent onset of effect with INP104 than with their previous best usual care treatment

Figure 7. Patient Acceptability Questionnaire (24-week FSS, N=354)



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

Conclusions

- STOP 301 was an open-label study of safety, tolerability, patient acceptability, and exploratory efficacy of long-term intermittent usage of nasal DHE mesylate (INP104) self administered over 24 and 52 weeks
- There were no new safety signals following delivery to the upper nasal space, and with a patient acceptability questionnaire, it was determined that the majority of patients found INP104, the combination product of POD and DHE mesylate, easy to use and preferred it over their current therapy
- Exploratory efficacy data suggests that INP104 resulted in pain freedom in 33.1% of patients, most bothersome symptom freedom in 49.1% of patients, and pain relief in 66.3% of patients at 2 hours
- Additionally, sustained pain freedom through 24 hours was also reported in the majority of patients with 98.4% of patients remaining relapse-free of their migraine after using INP104 for 24 weeks
- These results suggest that delivery to the upper nasal space may provide an effective, consistent, and well-tolerated alternative to acute oral and injectable treatments for migraine, while providing the reliable efficacy, speed, and potency of the long-established DHE molecule

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