A Long-term, Open-label Safety and Tolerability Study of Precision Olfactory Delivery of DHE in Acute Migraine Treatment (STOP 301): Exploratory Efficacy Results

Sheena Aurora, MD[1]*; Timothy R. Smith, MD[2]; Maria Jeleva, PhD[1]; Jasna Hocevar-Trnka, MD[1]; John Hoekman, PhD[1]; Stephen Shrewsbury, MB ChB[1]
[1]Impel NeuroPharma, Seattle, WA, USA; [2]StudyMetrix Research, St. Peters, MO, USA
*Presenting author

Introduction

- Patients continue to report dissatisfaction with acute treatment options for migraine[1,2]
- Gastrointestinal (GI) symptoms and comorbidities frequently accompany migraine and may affect the absorption of oral medications and/or lead to patient reluctance to use oral therapies[3-7]
- INP104, an investigational drug-device combination product that targets dihydroergotamine (DHE) mesylate to the upper nasal cavity using Precision Olfactory Delivery (POD®) technology, is a nasal product that bypasses the GI tract and increases systemic absorption of drug[3,8,9]
- Results from a Phase 1 study (STOP 101) showed that INP104 reached intravenous (IV) DHE-like blood levels from 20 minutes to 48 hours with a lower C_{max} and incidence of adverse events (AEs) than IV DHE[8]
- While the primary focus of the pivotal STOP 301 study was to assess upper nasal space safety and tolerability, which was previously presented,[10] it also included exploratory efficacy of INP104 for the acute treatment of migraine

Objective

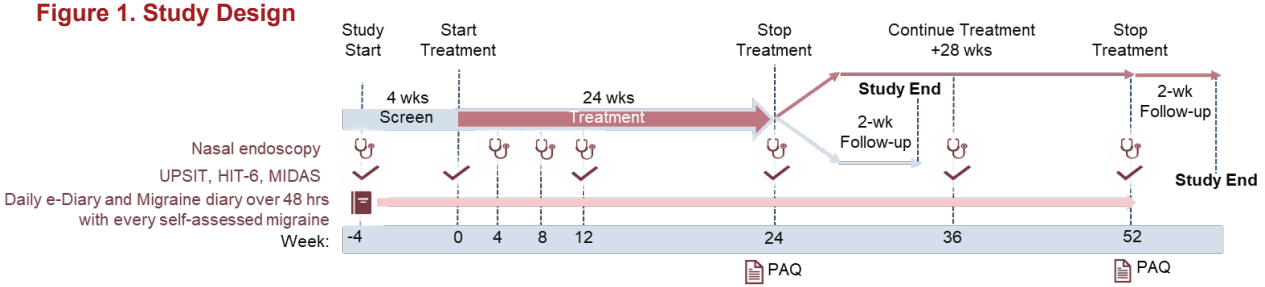
- To report INP104 exploratory efficacy from the Phase 3 STOP 301 study over 24 weeks

Methods

Study Design

- This was a Phase 3, interventional, open-label, single-group assignment study, assessing the safety, tolerability, and exploratory efficacy of INP104 (NCT03557333)
- The study comprised a 4-week screening period, where patients used their best usual care, 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**)
- Following 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 sprays) with all self-recognized migraine attacks (MAs) over 24 weeks, with a subset over 52 weeks
- Daily eDiaries were completed to capture headache and migraine details, headache medication usage, and most bothersome symptom (MBS) severity

Figure 1. Study Design



HIT-6 = Headache Impact Test-6; MIDAS = Migraine Disability Assessment; PAQ = patient acceptability questionnaire; UPSIT = University of Pennsylvania Smell Identification Test; wk = week.

from screening through the 24-week visit and, if applicable, the 52-week visit

Study Patients and Assessments

- Patients were adult (18-65 years) males or females who had a documented diagnosis of frequent migraine, with 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 in general good health, with no significant medical history or clinical abnormalities at baseline, which included no history of cardiovascular events
- Self-reported exploratory endpoints included efficacy outcomes of pain and MBS freedom at 2, >2-4 and >4 hours, pain relief at 2 hours, use of rescue medication, and sustained pain freedom through 24 and 48 hours during the 24-week treatment period
- Statistical comparisons to best usual care during baseline were not performed because patients were permitted to administer acute therapies (sometimes more than one) of their choosing to treat their MAs during baseline

Results

Patient Disposition and Baseline Characteristics

- 360 patients were screened and enrolled into the 24-week treatment period
  - –354 patients received ≥1 dose of INP104 (24-week full safety set [FSS])
  - –73 patients continued into the 28-week extension period (52-week FSS)
- 262 patients completed the 24-week treatment period
- Demographic characteristics for the 24-week FSS are included in **Table 1**

Table 1. STOP 301 Baseline Demographics Overview

24-Week Full Safety Set (N=354)	
Age, Years, Mean (SD)	41.3 (11.12)
Female, n (%)	304 (85.9)
MAs During Screening, 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)

MA = migraine attack; SD = standard deviation.

Safety and Tolerability

- INP104-related treatment-emergent adverse events (>3%) were nasal congestion (15%), nausea (6.8%), and nasal discomfort and unpleasant taste (5.1% each)
- There were no INP104-related serious AEs (SAEs) and no findings of concern during nasal endoscopy and olfactory function assessments (data not shown)

Exploratory Efficacy

- 4,515 self-reported MAs were treated with INP104 over 24 weeks

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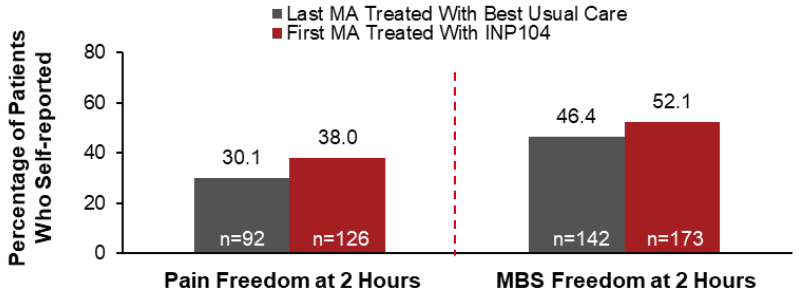
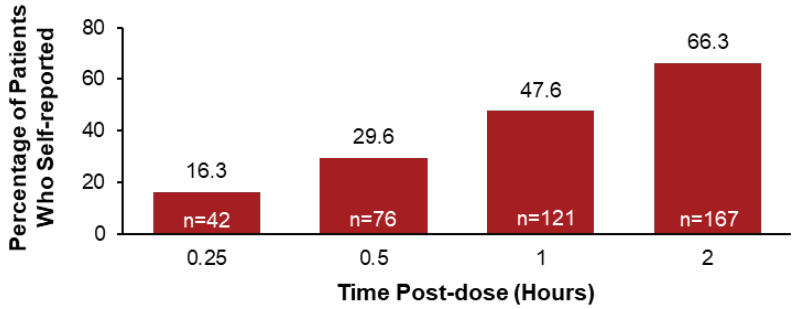
- 38.0% and 52.1% of patients reported pain freedom and MBS freedom at 2 hours for their first INP104-treated MA, respectively, compared to 30.1% and 46.4% on best usual care for their last treated MA (baseline), respectively (**Figure 2**)
- For patients who treated their first MA with INP104 >2 hours from migraine start, pain freedom was reported in 39.4% and 30.9% of patients and MBS freedom in 57.6% and 40.0% at >2-4 and >4 hours from migraine initiation, respectively
- 66.3% of patients reported pain relief at 2 hours for their first INP104-treated MA (**Figure 3**)
- 35% and 32% of patients reported sustained pain freedom at 24 and 48 hours, respectively, over 24 weeks (**Figure 4**)
- Only 15% of MAs (649/4,257) required rescue medication over 24 weeks, with the majority using non-INP104 medications (90.9%; a second INP104 dose was allowed within 24 hours)

Figure 2. 2-hour Pain Freedom and MBS Freedom (24-week FSS, N=354)



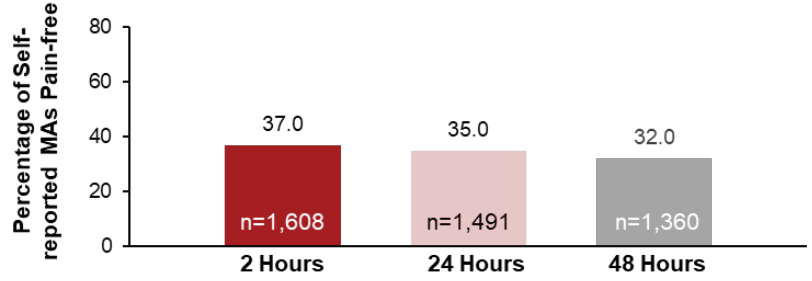
FSS = full safety set; MA = migraine attack; MBS = most bothersome symptom.

Figure 3. Pain Relief for the First INP104-treated MA (24-week FSS, N=354)



Note: Pain Relief = Severe or Moderate pain decreased to Mild or None or Mild pain decreased to None.
FSS = full safety set; MA = migraine attack.

Figure 4. Sustained Pain Freedom, Weeks 1-24 (24-week FSS; N=4,295 MAs)



FSS = full safety set; MA = migraine attack.

Conclusion

- STOP 301 was an open-label study of safety, tolerability, and exploratory efficacy of long-term intermittent usage of nasal DHE mesylate (INP104) self-administered over 24 and 52 weeks
- The use of INP104 was associated with improvements in several migraine measures of exploratory efficacy, and was well tolerated with no new safety signals following delivery to the upper nasal space
  - Pain freedom was self-reported in 38% of patients, MBS freedom in 52.1%, and pain relief in 66.3% at 2 hours for the first INP104-treated MA
  - Pain and MBS freedom were not very different whether patients administered INP104 within 2 hours of migraine initiation or beyond for their first MA
  - Additionally, sustained pain freedom was self-reported in 35% and 32% of MAs at 24 and 48 hours, respectively, and there was a low incidence of rescue medication use over 24 weeks
- DHE may provide well-tolerated, clinically meaningful, and sustained relief as an acute treatment for migraine when targeted to the upper nasal space

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