Exploratory Efficacy of INP104 by Migraine Attack Severity and Time of Dosing: Results From the Phase 3 STOP 301 Study

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Introduction

- Oral drug delivery of acute medications for migraine may not be best suited for individuals with underlying autonomic dysfunction, gastrointestinal (GI) symptoms, or GI comorbidities; these conditions may affect drug absorption and lead to decreased use of oral therapies by patients[1-4]
- Dihydroergotamine mesylate (DHE) is an efficacious acute therapy for migraine that clinicians are familiar with because of its long history of demonstrating sustained benefits, even when used in patients with difficult-to-treat migraine attacks (MAs)[5,6]
- Some acute therapies are reported to be effective when administered early in an MA or when the MA is still of mild severity, but DHE has shown efficacy in treating MAs regardless of time of dosing[7-11]
- When administered intravenously (IV), DHE is associated with a high response rate, but its use may be limited by adverse events, such as nausea and vomiting, suggested to be due to its high maximum serum concentration (C_{max}), and is considered invasive; because it is being given IV, it is not suitable for at-home use[5,12]
- INP104 is a drug-device combination product that delivers DHE to the upper nasal space using Precision Olfactory Delivery (POD®) technology, which avoids possible GI issues and may be a suitable option for patients seeking an alternative to oral acute therapies[2,12,13]
- Results from a Phase 1 study (STOP 101) showed that INP104 achieved IV DHE-like blood levels from 30 minutes to 48 hours, but with a lower C_{max} (~1/10th of IV DHE) and adverse event rate than IV DHE[13]
- The Phase 3 study (STOP 301) of INP104 for the acute treatment of migraine evaluated the safety, tolerability, and exploratory efficacy of repeat use of INP104 over 24 and 52 weeks, with some of the data having been previously reported[14]

Objective

- This post hoc analysis investigated self-reported exploratory efficacy for INP104-treated MAs based on severity and time of INP104 administration

Methods

Study Design

- STOP 301 was a Phase 3, interventional, open-label, single-group assignment study that assessed the safety, tolerability, and exploratory efficacy of INP104 (NCT03557333)
- The study consisted of a 4-week screening period in which patients used their best usual care, a 24-week treatment period for all patients, a treatment extension to 52 weeks offered to the first 73 patients completing 24 weeks AND meeting compliance (and other) criteria, and a 2-week post-treatment follow-up period for all patients
- Based on FDA guidance, we were required to generate data in ≥150 patients using INP104 at least twice per month for 6 months and in an optional 50 patients (using INP104 twice per month for 12 months) for the 28-week extension
- Following screening, all patients were provided with up to 3 doses per week of INP104 to nasally self-administer (1.45 mg in a dose of 2 sprays) with self-recognized MAs
- Daily eDiaries were completed to capture headache and migraine details, headache medication usage, and most bothersome symptom (MBS) severity with each MA from screening through 24 weeks and, if applicable, 52 weeks

Study Patients

- Eligible patients were adult males or females aged 18 to 65 years with a documented diagnosis of migraine with or without aura not qualifying as chronic migraine based on the *International Classification of Headache Disorders*, version 3 beta
- Patients were required to have experienced ≥2 MAs but <14 headache days per month for the previous 6 months and during screening, and to have completed eDiary entries on ≥23 of 28 days during screening for eligibility
- Patients were in general good health, with no significant medical history or clinical abnormalities at baseline, which included no history of cardiovascular events

Study Outcome Measures

- Exploratory measures presented here included the following self-reported efficacy outcomes:
  - Pain and MBS freedom at 2 hours based on migraine severity before INP104 treatment over 24 weeks
  - Pain and MBS freedom at 2 hours when INP104 was administered between 2 and 4 hours and >4 hours from migraine onset for the first INP104-treated MA and based on migraine severity before INP104 treatment
  - Pain relief (ie, a decrease from severe or moderate pain to mild or no pain, or a decrease from mild pain to no pain) over 2 hours for MAs of any severity and for moderate to severe MAs for the first INP104-treated MA
- Maximum severity of headache pain is the worst severity score among all MAs during the screening period
  - For each MA, the worst severity score is identified at any point during a MA (ie, event onset, medication administration, post-dose time points at 15 minutes, 30 minutes, 1, 2, 8, 24, and 48 hours)
- Because patients were permitted to administer acute therapies of their choice—sometimes more than 1—to treat their MAs during baseline, statistical comparisons to best usual care during baseline were not planned or possible

Results

Patient Demographics and Disposition

- 360 patients were screened and enrolled in the 24-week treatment period

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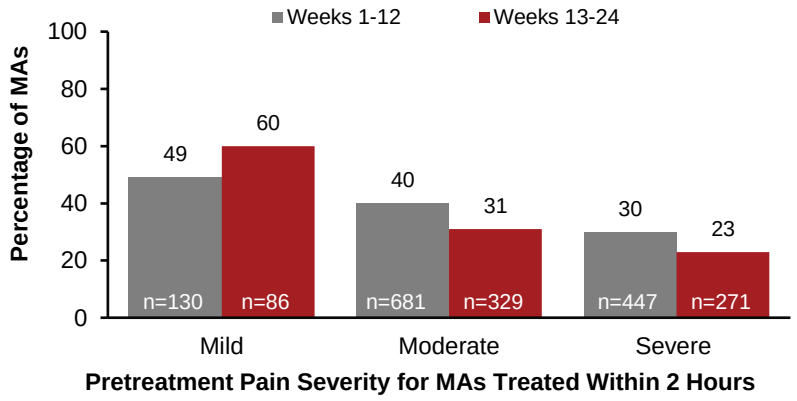
- 354 patients self-administered ≥1 dose of INP104 over 24 weeks (24-week full safety set [FSS]), and 73 patients continued into the 28-week extension period (52-week FSS)
- 262 and 66 patients completed the 24- and 52-week treatment periods, respectively
- Most patients in the 24-week FSS were female (85.9%), with a mean age of 41.3 years, and had a long history of migraine (mean, 19.5 years); they experienced an average of 4.6 MAs during the 28-day screening period
- During screening, maximum severity of headache pain was reported as severe, moderate, and mild by 65.3% (n=231), 32.2% (n=114), and 2% (n=7) of patients, respectively
- 4515 MAs were treated with INP104 during the 24-week treatment period, with 1099, 855, 708, 653, 618, and 582 MAs treated with INP104 during Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24, respectively

Pain Freedom, MBS Freedom, and Pain Relief by MA Severity

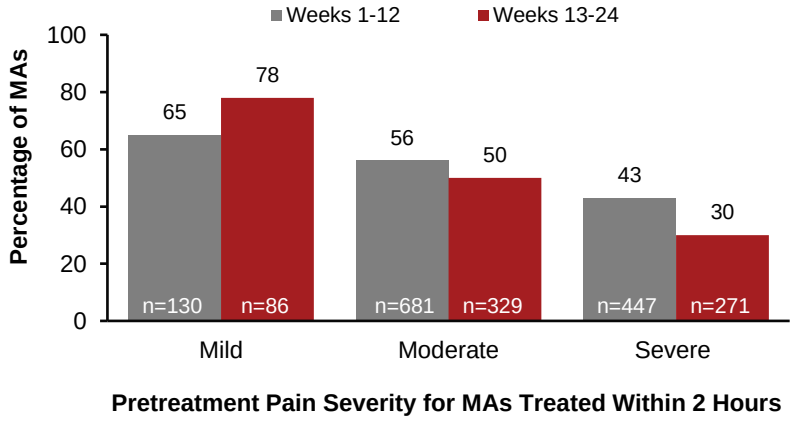
- Of the MAs reported as mild, moderate, or severe before INP104 treatment, self-reported pain and MBS freedom at 2 hours were as follows:
  - Pain freedom: 49%, 40%, and 30% of MAs during Weeks 1-12 and 60%, 31%, and 23% of MAs during Weeks 13-24, respectively (**Figure 1**)
  - MBS freedom: 65%, 56%, and 43% of MAs during Weeks 1-12 and 78%, 50%, and 30% of MAs during Weeks 13-24, respectively (**Figure 2**)
- For the first INP104-treated MA, initial onset of pain relief was self-reported as early as 15 minutes by 16.3% of patients and at 2 hours by 66.3% of patients
- Pain relief for only moderate or severe MAs was self-reported by 17.3% of patients at 15 minutes and by 68.9% of patients at 2 hours (**Figure 3**)

Figure 1. Pain Freedom at 2 Hours by Pretreatment Pain Severity for MAs Treated Within 2 Hours Over 24 Weeks (24-Week FSS)



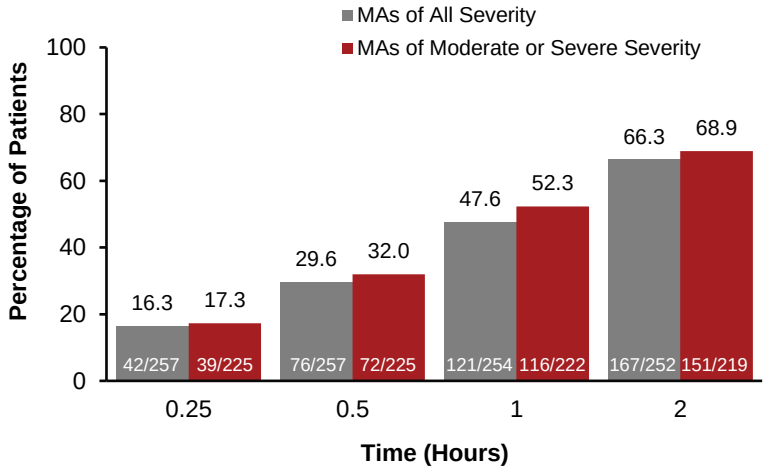
Note: Data are self-reported; n refers to the number of INP104-treated MAs.
FSS = full safety set; MA = migraine attack.

Figure 2. MBS Freedom at 2 Hours by Pretreatment Pain Severity for MAs Treated Within 2 Hours Over 24 Weeks (24-Week FSS)



Note: Data are self-reported; n refers to the number of INP104-treated MAs.
FSS = full safety set; MA = migraine attack; MBS = most bothersome symptom.

Figure 3. Pain Relief for the First INP104-Treated MA by Severity (24-Week FSS)



Note: Data are self-reported; numbers in the bars denote n/N. Only patients with Time 0 pain assessments and pain assessments at the post-treatment time points are included in the analysis.
FSS = full safety set; MA = migraine attack.

Pain and MBS Freedom by Time of Dosing

- For patients who treated their first MA with INP104 >2 hours after migraine onset, self-reported pain and MBS freedom at 2 hours were as follows:
  - Pain freedom: 39.4% and 30.9% of patients who treated their MA >2-4 and >4 hours from migraine onset, respectively
  - MBS freedom: 57.6% and 40.0% of patients who treated their MA >2-4 and >4 hours from migraine onset, respectively (**Figure 4**)

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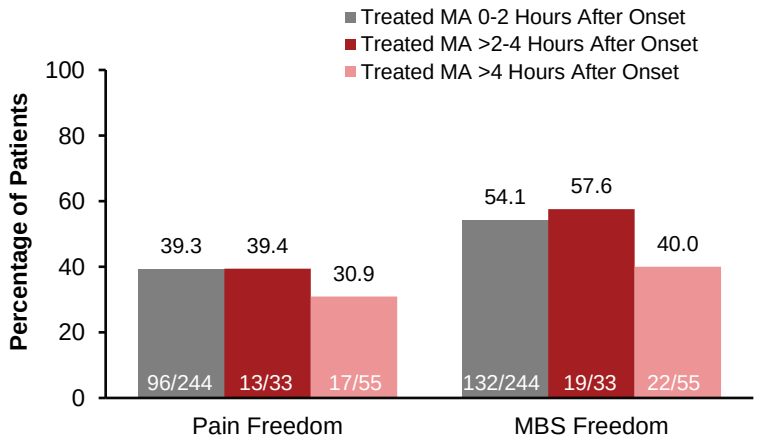
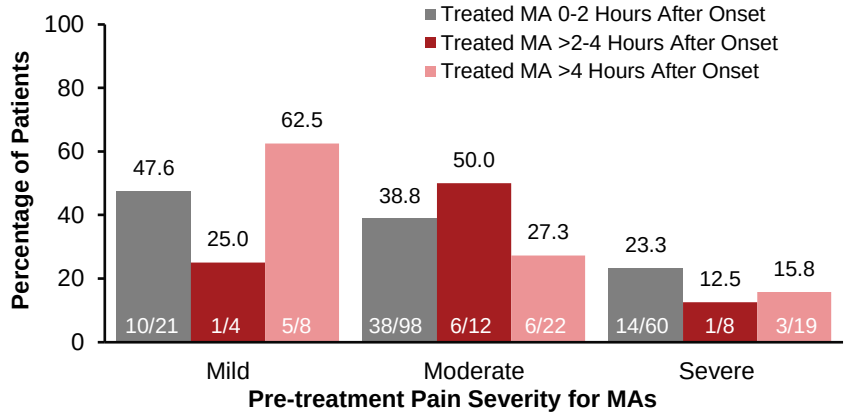
- Of the MAs reported as mild, moderate, or severe before INP104 treatment, self-reported pain and MBS freedom at 2 hours for the first-treated MA were as follows:
  - Pain freedom: 25.0%, 50.0%, and 12.5% of patients who treated their MA >2-4 hours and 62.5%, 27.3%, and 15.8% of patients who treated their MA >4 hours after onset, respectively (**Figure 5**)
  - MBS freedom: 75.0%, 58.3%, and 37.5% of patients who treated their MA >2-4 hours and 50.0%, 27.3%, and 42.1% of patients who treated their MA >4 hours after onset, respectively (**Figure 6**)

Figure 4. Pain and MBS Freedom at 2 Hours for the First INP104-Treated MA by Time of Dosing (24-Week FSS)



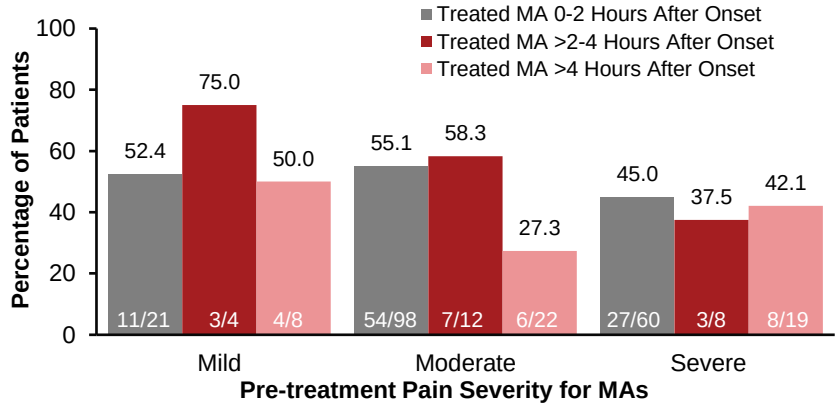
Note: Data are self-reported; numbers in the bars denote n/N. Although 354 patients treated ≥1 MA with INP104, only 332 patients treated their first MA with INP104.
FSS = full safety set; MA = migraine attack.

Figure 5. Pain Freedom at 2 Hours for the First INP104-Treated MA by Time of Dosing and Pre-treatment Pain Severity (24-Week FSS)



Note: Data are self-reported; numbers in the bars denote n/N. This analysis does not include patients with an unknown pre-treatment pain severity (n=80).
FSS = full safety set; MA = migraine attack.

Figure 6. MBS Freedom at 2 Hours for the First INP104-Treated MA by Time of Dosing and Pre-treatment Pain Severity (24-Week FSS)



Note: Data are self-reported; numbers denote n/N. This analysis does not include patients with an unknown pre-treatment pain severity (n=80).
FSS = full safety set; MA = migraine attack; MBS = most bothersome symptom.

Conclusions

- Over 24 weeks, pain and MBS freedom at 2 hours after INP104 use was self-reported in patients who experienced MAs of all severities
- Pain relief as early as 15 minutes and up to 2 hours regardless of pain intensity was self-reported with INP104 use for the first INP104-treated MA
- Most patients treated their first MA with INP104 within 2 hours of onset (as instructed), but INP104 provided a similar benefit at later administration time points
- Results suggest that INP104 may be a promising acute treatment for migraine patients with all levels of symptom severity and that it can be efficaciously administered with no treatment window limitations

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