Improvements in Disability and the Interictal Period With INP104: Results From the Phase 3 STOP 301 Study

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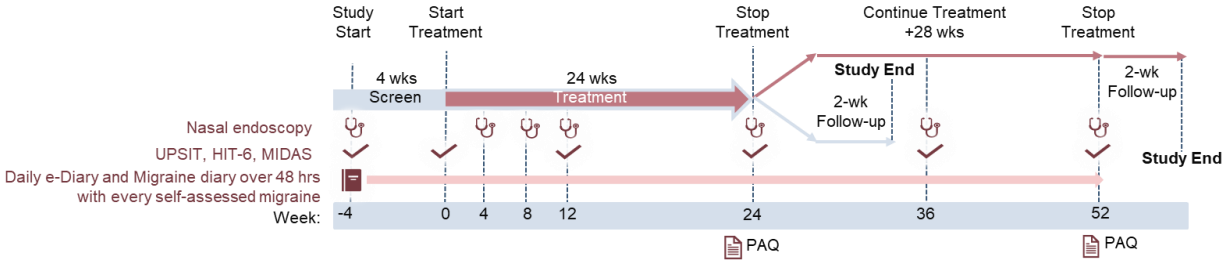
Introduction

- Migraine is a highly prevalent and debilitating condition that can result in significant functional, physical, emotional, economic, and social impairments[1-6]
- Migraine can place a substantial burden on individuals during (ie, the ictal period) and between (ie, the interictal period) migraine attacks (MAs)[3,7,8]
- The ictal burden is well recognized and easily understood, while the interictal burden is complex, can be extensive between defined MAs, and can impact other aspects of daily life[3,7,8]
- Several epidemiological studies have reported that it is common to experience anticipatory anxiety or depression about future MAs, which may negatively affect quality of life[3,5,7,8]
- An increase in the frequency of MAs may also increase disease burden, anxiety, and headache-related disability; given the unpredictable nature of migraine, some patients may overuse acute medications during headache-free periods out of anticipation or fear of a migraine developing—a morbidity known as cephalalgiaphobia—which may further impact their interictal burden[3-6, 9-13]
- Therefore, the need exists for new and effective acute therapies that will rapidly resolve migraine symptoms and provide a sustained benefit to potentially reduce interictal symptoms
- INP104 is a drug-device combination product for the acute treatment of migraine that delivers dihydroergotamine mesylate (DHE) to the previously underutilized upper nasal space using Precision Olfactory Delivery (POD®) technology[14]
- Previously presented exploratory efficacy data reported that INP104 was associated with improvements for both the first treated MA or across multiple MAs over 24 and 52 weeks[14-16]

Objective

- This post hoc analysis investigated headache-related disability, time between MAs, and frequency of MAs over 24 weeks, which were exploratory outcome measures relevant to interictal burden, from the Phase 3, STOP 301 study of INP104 for the acute treatment of migraine

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.

Methods

Study Design

- STOP (Safety and Tolerability of POD-DHE) 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 included 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 (**Figure 1**)
- Following 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
- After the screening period, 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 MBS severity 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 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

- Migraine Disability Assessment (MIDAS)
  - The MIDAS questionnaire is a validated, highly reliable instrument that measures headache-related disability with a grading system that categorizes disability as follows:
    - Grade I = minimal or infrequent disability (scores of 0-5); Grade II = mild or infrequent disability (scores of 6-10); Grade III = moderate disability (scores of 11-20); Grade IVa = severe disability (scores of 21-40); Grade IVb = severe disability (scores of 41-270)
  - It includes 5 scored questions that measure the number of days in the past 3 months that the patient experienced limitations in daily activities resulting from migraine
  - The MIDAS questionnaire was completed by patients during screening, at baseline, at Weeks 12 and 24, and if applicable, Weeks 36 and 52
- Monthly frequency of MAs over 24 weeks by 4-week intervals
- Time between MAs was determined during screening and Weeks 1-24 of INP104 treatment using Kaplan-Meier methods to estimate the median interval length

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Results

Patient Demographics and Disposition

- 360 patients were screened and enrolled in the 24-week treatment period; 354 were in the 24-week full safety set (FSS; self-administered ≥1 INP104 dose over 24 weeks) and 73 were in the 52-week FSS
- 262 and 66 patients completed the 24- and 52-week treatment periods, respectively
- For the 24-week FSS, the mean MIDAS total score for patients was 25.1 at baseline
  - Most frequent scores were Grade III (28.8%) and Grade IVa (27.7%), indicating moderate to severe disability at study initiation
- For the 52-week FSS, the mean MIDAS total score for patients was 24.6 at baseline
  - Most frequent scores were Grade III (31.5%) and Grade IVa (31.5%), indicating moderate to severe disability at study initiation (**Tables 1 and 2**)

MIDAS Scores Over 24 and 52 Weeks

- For the 24-week FSS, the mean MIDAS total score at Weeks 12 and 24 was 18.4 and 17.4, with a mean change from baseline of -5.5 and -7.4, respectively
  - Most patients had improved MIDAS scores of Grade III or better at Weeks 12 and 24
- At Weeks 12, 24, 36, and 52, the mean 52-week FSS MIDAS total score was 18.8, 20.3, 15.3, and 14.9, with a mean change from baseline of -5.8, -5.1, -7.8, and -8.9, respectively
  - Most patients had MIDAS scores of Grade III or better at Weeks 12, 24, 36, and 52 (**Tables 1 and 2**)

Table 1. MIDAS Scores Over 24 and 52 Weeks

Period		24-week FSS (N=354)	52-week FSS (N=73)
Baseline	n Mean (SD)	354 25.1 (22.3)	73 24.6 (20.2)
Week 12	n Mean (SD) Change from baseline, mean (SD)	283 18.4 (17.1) -5.5 (18.7)	73 18.8 (15.9) -5.8 (18.1)
Week 24	n Mean (SD) Change from baseline, mean (SD)	209 17.4 (16.5) -7.4 (17.6)	57 20.3 (16.2) -5.1 (18.6)
Week 36	n Mean (SD) Change from baseline, mean (SD)	-----	69 15.3 (11.2) -7.8 (15.1)
Week 52	n Mean (SD) Change from baseline, mean (SD)	-----	65 14.9 (12.0) -8.9 (15.8)

FSS = full safety set; MIDAS= Migraine Disability Assessment; SD = standard deviation.

Table 2. Category of MIDAS Scores Over 24 and 52 Weeks

Period		24-week FSS (N=354)	52-week FSS (N=73)
Baseline, n (%)	n	354	73
	I	38 (10.7)	4 (5.5)
	II	51 (14.4)	10 (13.7)
	III	104 (28.8)	23 (31.5)
	IVa	98 (27.7)	23 (31.5)
	IVb	65 (18.4)	13 (17.8)
Week 12, n (%)	n	283	73
	I	45 (15.9)	8 (11.0)
	II	62 (21.9)	17 (23.3)
	III	88 (31.1)	24 (32.9)
	IVa	65 (23.0)	19 (26.0)
	IVb	23 (8.1)	5 (6.8)
Week 24, n (%)	n	209	57
	I	39 (18.7)	7 (12.3)
	II	43 (20.6)	10 (17.5)
	III	72 (34.4)	22 (38.6)
	IVa	38 (18.2)	12 (21.1)
	IVb	17 (8.1)	6 (10.5)
Week 36, n (%)	n	-----	69
	I		9 (13.0)
	II		16 (23.2)
	III		28 (40.6)
	IVa		13 (18.8)
	IVb		3 (4.3)
Week 52, n (%)	n	-----	65
	I		8 (12.3)
	II		20 (30.8)
	III		23 (35.4)
	IVa		12 (18.5)
	IVb		2 (3.1)

FSS = full safety set; MIDAS= Migraine Disability Assessment; SD = standard deviation

Frequency of MAs Over 24 Weeks

- At baseline, the mean frequency of monthly MAs was 4.7
  - The mean frequency of monthly MAs by 4-week intervals was 3.7, 3.0, 2.6, 2.5, 2.4, and 2.4 at Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24, respectively (**Figure 2 and Table 3**)

Table 3. Frequency of Monthly MAs Over 24 Weeks (24-Week FSS, N=354)

Period		24-week FSS (N=354)	Week 24 Completers (N=262)
Baseline	n Mean (SD)	354 4.7 (2.30)	262 4.6 (2.32)
Weeks 1-4	n Mean (SD)	347 3.7 (2.05)	262 3.8 (2.10)
Weeks 5-8	n Mean (SD)	325 3.0 (2.08)	262 3.2 (2.04)
Weeks 9-12	n Mean (SD)	297 2.6 (1.97)	262 2.7 (1.95)
Weeks 13-16	n Mean (SD)	289 2.5 (1.89)	262 2.6 (1.87)
Weeks 17-20	n Mean (SD)	276 2.4 (1.89)	262 2.5 (1.88)
Weeks 21-24	n Mean (SD)	268 2.4 (1.85)	262 2.4 (1.84)

Note: Patients are only summarized within the months that they have completed.
FSS = full safety set; MA = migraine attack; SD = standard deviation.

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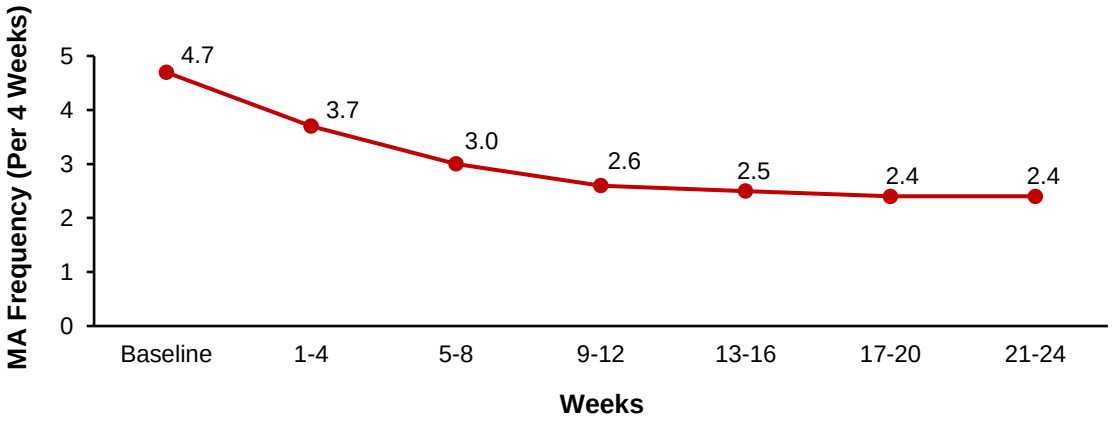
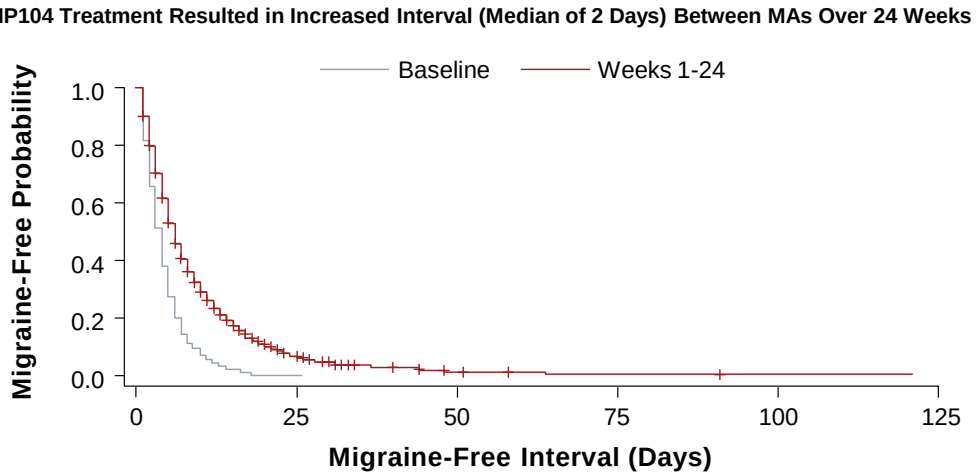
Figure 2. INP104 Reduced Migraine Frequency Over 3 Months and Reduction Was Sustained at 6 Months (24-Week FSS, N=354)



FSS = full safety set; MA = migraine attack.

Figure 3. Time Between MAs Over 24 Weeks (24-Week FSS, N=354)



FSS = full safety set; MA = migraine attack.

Time Between MAs Over 24 Weeks

- During Weeks 1-24, the median time between MAs was 6 days, compared with 4 days at baseline (**Figure 3**)

Conclusions

- Use of INP104 was associated with improvements in migraine-related disability as assessed by the MIDAS questionnaire
  - The mean MIDAS total score in both 24-week and 52-week FSS decreased at each post-baseline visit, with mean total scores suggestive of moderate residual disability
- Over 24 weeks, the frequency of monthly MAs decreased and the time between MAs was longer with INP104 use compared with baseline when patients used their best usual care
- A limitation of this study was the open-label design, which does not include a placebo control group for comparison; however, comparing INP104 with a patient's best usual care at baseline is reflective of a real-world setting
- Data reported here suggest that repeated acute use of INP104 may have positive effects on interictal burden by reducing migraine-associated disability, prolonging the headache-free period, and decreasing the number of MAs over time

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