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RESEARCH SUBMISSIONS

STOP 301: A Phase 3, open-label study of safety, tolerability, and exploratory efficacy of INP104, Precision Olfactory Delivery (POD®) of dihydroergotamine mesylate, over 24/52 weeks in acute treatment of migraine attacks in adult patients

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Abstract

Objective: To report the safety, tolerability, exploratory efficacy, and patient acceptability of INP104 for the acute treatment of migraine from the Phase 3 STOP 301 trial.

Background: Dihydroergotamine (DHE) has long been used to treat migraine, but intravenous administration is invasive, frequently associated with adverse events (AEs), and not suitable for at-home administration. INP104 is an investigational drug device that delivers DHE mesylate to the upper nasal space using a Precision Olfactory Delivery technology and was developed to overcome the shortcomings of available DHE products.

Methods: STOP 301 was an open-label, 24-week safety study, with a 28-week extension period. After a 28-day screening period where patients used their "best usual care" to treat migraine attacks, patients were given INP104 (1.45 mg) to self-administer nasally with self-recognized attacks. The primary objective of this study was to assess safety and tolerability, with a specific focus on nasal mucosa and olfactory function. Exploratory objectives included efficacy assessments of migraine measures and a patient acceptability questionnaire.

Results: A total of 360 patients entered the 24-week treatment period, with 354 patients dosing at least once. INP104-related treatment-emergent AEs were reported by 36.7% (130/354) of patients, and 6.8% (24/354) discontinued treatment due to AEs over 24 weeks. No new safety signals were observed following delivery to the upper nasal space. Pain freedom, the most bothersome symptom freedom, and pain relief at 2 h post-INP104 were self-reported by 38.0% (126/332), 52.1% (173/332), and 66.3% (167/252) of patients, respectively. A low recurrence rate at 24 and 48 h was observed

Abbreviations: AE, adverse event; C_{max}, maximum observed plasma concentration; DHE, dihydroergotamine; FDA, Food and Drug Administration; FSS, full safety set; GI, gastrointestinal; ICHD, *International Classification of Headache Disorders*; IV, intravenous; MBS, most bothersome symptom; PAQ, patient acceptability questionnaire; POD, Precision Olfactory Delivery; PSS, primary safety set; QSS-NM, Quantitative Scoring Scale for Evaluation of the Nasal Mucosa; TEAE, treatment-emergent adverse event; UPSIT, University of Pennsylvania Smell Identification Test.

(7.1% [9/126] and 14.3% [18/126], respectively). Most patients found INP104 easy to use and preferred it over their current therapy.

Conclusions: INP104 has the potential to deliver rapid symptom relief, without injection, that is well tolerated and suitable for outpatient use. Results suggest INP104 may be a promising treatment for patients with migraine.

KEYWORDS
dihydroergotamine, efficacy, migraine, Precision Olfactory Delivery, safety/tolerability, upper nasal space

INTRODUCTION

While intravenous (IV) dihydroergotamine (DHE) mesylate has a long, established history as an effective migraine therapy, its use as an acute treatment can be limited by the high rate of nausea and vomiting reported by patients, which often requires pretreatment with antiemetics.[1–5] Furthermore, IV DHE mesylate needs to be administered in emergency room settings or by headache specialists, limiting convenience.[2,6] There have been attempts to develop alternative delivery systems of DHE mesylate, including nasal and orally inhaled, to overcome the limitations of IV administration, but these products have variable clinical response, presence of adverse events (AEs), or insurmountable manufacturing challenges. INP104 is an investigational, novel drug device from Impel NeuroPharma that targets delivery of DHE mesylate to the upper nasal cavity using Precision Olfactory Delivery (POD®) technology.[4] Targeting drug delivery to the upper nasal space may achieve greater, more consistent drug absorption, which can reduce response variability and provide reliable, noninvasive relief.[4,7–9] Although conventional nasal sprays deliver drugs to the nasal vestibule, INP104 was designed to deliver a liquid DHE mesylate formulation administered by the I123 POD device to the upper nasal space.[8] This delivery system aims to prevent any drug spillage out of the nose or into the nasopharynx to both increase systemic availability and possibly reduce the rate of adverse taste, which may be shortcomings of the older nasal product, MIGRANAL® (Bausch Health Companies, Inc. or its affiliates, Bridgewater, NJ, USA).[2,4,10] Importantly, the POD system eliminates the need for patients to coordinate breathing or orient their head in a specific position by using metered, propellant-powered delivery, which allows for easy administration by the patients and/or caregivers.[9,11] Whereas previous attempts to develop aerosolized versions of DHE mesylate failed because of manufacturing issues, the POD technology keeps the drug and propellant separated until the point of use, thereby avoiding concerns about stability and consistent dosing when suspended in the propellant.[9,12,13]

INP104 was found to reach efficacious blood levels and was well tolerated in healthy volunteers in a Phase 1 study (STOP 101), with a favorable safety profile making it suitable for at-home use.[4] Pharmacokinetic parameters of 1.45 mg of INP104 were compared with 1.0 mg of IV DHE mesylate and 2.0 mg of MIGRANAL. DHE plasma levels following INP104 administration reached 93% of maximum observed plasma concentration (C_{max}) by 20 min and were comparable with IV DHE mesylate by 30 min and up to 48 h. Compared with MIGRANAL, INP104 delivered DHE mesylate more consistently and had improved bioavailability—absolute bioavailability was 58.9% for INP104 versus 15.2% for MIGRANAL.[4] The incidence of nausea and vomiting was lower with INP104 (3.2% and 0%, respectively) than with IV DHE mesylate (9.4% and 6.3%, respectively), both after pretreatment with an antiemetic, likely attributable to the lower (~1/10) peak concentration of DHE mesylate from INP104.[4]

Epidemiologic studies demonstrate underutilization of prescription-abortive therapies, high levels of unmet need, and significant patient dissatisfaction with current treatments.[14–16] Most migraine therapies do not address the full spectrum of migraine symptoms, and patients often discontinue treatment because of lack of efficacy, headache recurrence, and accompanying AEs such as nausea.[17,18] DHE has uniquely shown sustainable benefit for migraine symptoms when administered during multiple phases of migraine, and furthermore provides benefits even in difficult-to-treat migraine.[2,3,19–24] DHE slowly dissociates from 5-$HT_{1B/1D}$ receptors, which may explain its sustained antimigraine effects.[25] In the pivotal STOP 301 study, long-term safety data on the use of INP104 for the acute treatment of migraine were collected. The primary focus was upper nasal space safety and tolerability, but it also included exploratory efficacy using patients' best usual care at baseline compared to INP104-treated attacks over 24 and 52 weeks.

METHODS

Study design

This was a pivotal Phase 3, interventional, open-label, single-group assignment study, assessing the safety, tolerability, and exploratory efficacy of INP104 over long-term use (NCT03557333). The study protocol was reviewed by an appropriately constituted Institutional Review Board and the Food and Drug Administration (FDA) and was initiated on July 13, 2018, and completed on March 17, 2020, at 38 centers across the United States (US). All patients signed an informed consent form prior to study-related procedures being performed. The study included a 28-day screening period, during which patients were on current best "standard of care acute reliever" as a nonblinded "active control," henceforth referred to as "best usual care." Following the baseline period, eligible patients were equipped with a POD device for training purposes. All patients self-administered INP104 through 24 weeks, with a 28-week treatment continuation (52-week period) for a subset of

patients, followed by a 2-week posttreatment follow-up. Patients were required to reconsent after the 24-week treatment period if continuing to the 52-week period (Figure 1). Per FDA guidance, we were required to generate data in ≥150 patients using INP104 at least twice/month for 6 months, and in an optional 50 patients (using INP104 twice/month for 12 months) for the 28-week extension. Patients in the 52-week period completed the study around the same time as the last of the enrolled patients completed 24 weeks, and therefore only one database lock occurred for both groups. The overall study duration was a maximum of 58 weeks, with the majority of patients completing 30 weeks. All patients were required to complete 9 visits during the 24-week treatment period, and 12 visits if continuing through the 52-week period.

Study outcome measures

Primary endpoints included the number of patients reporting treatment-emergent AEs (TEAEs, serious or nonserious), change in nasal mucosa as detected by nasal endoscopy, and change in olfactory function, as measured by the University of Pennsylvania Smell Identification Test (UPSIT) during, and at the end of, 24 and 52 weeks. The UPSIT is a validated tool for olfactory function assessment.[26] Change in nasal mucosa was evaluated with the novel Quantitative Scoring Scale for Evaluation of the Nasal Mucosa (QSS-NM), which was adapted from the Modified Lund-Kennedy Scoring (MLKS) system that is familiar to otolaryngologists.[27] Migraine attacks (unless of unusual severity or frequency) were not included within the definition of an AE. The investigator determined the severity, seriousness, and relatedness of an AE to treatment. Secondary endpoints included vital signs, physical examinations, electrocardiograms, and laboratory evaluations. All nasal endoscopies were performed by a board-certified/eligible otolaryngologist. Exploratory endpoints included a patient acceptability questionnaire (PAQ), which included nine questions assessing the patient's impression of INP104 usability and effectiveness, administered to those who completed the study at Weeks 24 and 52, or completed an early termination visit from the study. The PAQ was summarized for the frequency of response to each question (strongly agree, agree, neutral, disagree, strongly disagree). Additional exploratory endpoints included self-reported efficacy outcomes, such as pain and most bothersome symptom (MBS) freedom at 2, >2–4, and >4 h, pain relief at 2 h, and recurrence of migraine pain through 24 and 48 h. Pain relief was defined as a decrease from severe or moderate pain to mild or no pain, or a decrease from mild pain to no pain. Recurrence was defined as a migraine that was pain free at 2 h post-INP104 administration, followed by the onset of a new headache prior to 24 or 48 h.

Study patients

Eligible patients were adult (18–65 years) males or females with a documented diagnosis of migraine (by *International Classification of Headache Disorders* [ICHD] 3β criteria) with or without aura, with ≥2 attacks per month (maximum of 14 headache days/month) for the previous 6 months and also during the 28-day screening prior to Visit 2. All attacks experienced during screening were recorded in an eDiary, and daily entries were completed on ≥23 of 28 days prior to Visit 2 for eligibility. Patients were generally in good health, with no clinical abnormalities at baseline, provided a written informed consent and negative urine drug screen, and were willing to attend necessary study visits. Patients of childbearing potential were willing to use adequate contraception during the study and for 30 days after completion. Exclusion criteria are listed in Table 1.

Study treatment

This was a single-arm, open-label study, with INP104 dispensed every 4 weeks in the 24-week treatment period, and at Weeks 24, 36, and 42 for patients enrolled in the 52-week period. Patients

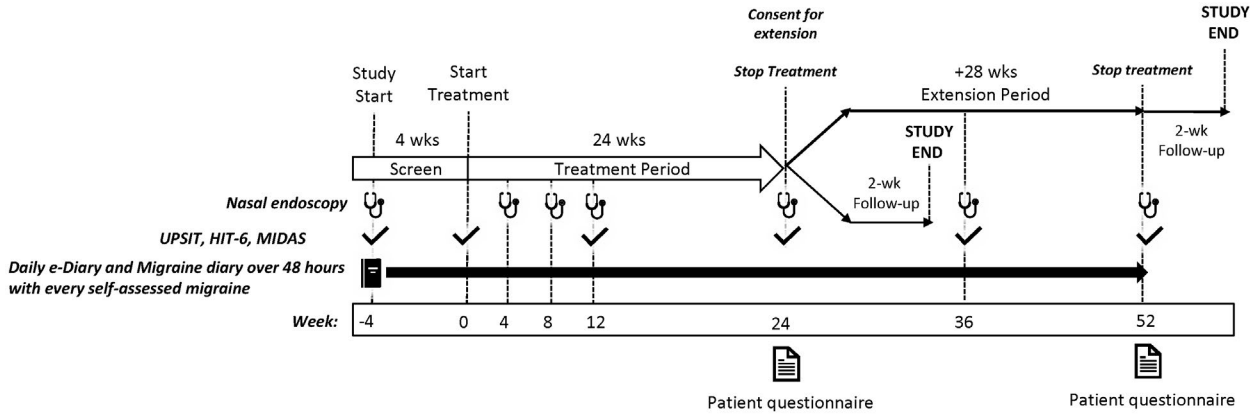

FIGURE 1 Study design. HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; UPSIT, University of Pennsylvania Smell Identification Test; wk, week

TABLE 1 Exclusion criteria

Patients with trigeminal autonomic cephalalgias (including cluster headache, hemicrania syndromes, and short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing), migraine aura without headache, hemiplegic migraine, or migraine with brainstem aura (previously referred to as basilar migraine), per ICHD-3β criteria
Patients with chronic migraine, medication overuse headache, or other chronic headache syndromes (and/or patients with ≥15 headache days per 28 days in screening), per ICHD-3β criteria
Patients with status migrainosus in the 3 months prior to screening or during the screening period
Positive test for human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C antibodies
Patients with ischemic heart disease or patients who have clinical symptoms or findings consistent with coronary artery vasospasm, including Prinzmetal variant angina
Patients with significant risk factors for coronary artery disease, current use of tobacco products, smoking history (of at least 10 or more cigarettes per day within the last 12 months prior to screening), or history of diabetes, known peripheral arterial disease, Raynaud phenomenon, sepsis or vascular surgery (within 3 months prior to study start), or severely impaired hepatic or renal function
Patients with a history of hypertension may be enrolled if the hypertension is stable and well controlled on current therapies for >6 months, provided no other risk factors for coronary artery disease are present
Patients with potentially unrecognized coronary arterial disease as demonstrated by history, physical examination, or screening ECG
Abnormal, clinically significant laboratory tests at screening, including but not limited to alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2x upper limit of normal or serum creatinine >1.5x upper limit of normal
Any acute illness or uncontrolled infection within 28 days prior to Day 1; however, potential patients who have experienced a mild, self-limiting illness that has resolved at least 7 days prior to Day 1 may be included
Patients with recurrent sinusitis or epistaxis, or chronic rhinosinusitis with nasal polyp (unless surgically resolved >3 months prior to screening)
Significant nasal congestion, physical blockage in either nostril, significantly deviated nasal septum, septal perforation, or any preexisting upper nasal mucosal abnormality on endoscopy scoring 1 or more (except score 1 is allowed for mucosal edema)
Patients who have previously shown hypersensitivity to ergot alkaloids or any of the ingredients in the drug product
Patients who have previous documented failure of response to IV DHE mesylate for the treatment of migraine
Use of any triptan or ergot-based medication or medication strongly or moderately affecting CYP3A4 cytochrome P450 metabolic pathway within 2 days prior to the baseline visit (Visit 2). This exclusion criterion does not apply to prescription contraceptives
Use of any medications prohibited by protocol
Use of triptan or ergot-based medication >12 days per month in the 2 months prior to screening or during the screening period
Use of barbiturates/barbiturate-containing compounds or opioids (including tramadol or tapentadol) greater than 7 days per month (cumulative) or unstable usage pattern in the 2 months prior to screening or during screening
History or presence of alcoholism or drug abuse within the 2 years prior to the first study drug administration or a positive result on the urine drug test at the screening visit (positive urine drug screens with a medical explanation may be discussed with the Medical Monitor for potential inclusion)
Females who are pregnant, or planning to get pregnant, or are lactating while participating in this clinical study
Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 28 days or five half-lives (whichever is longer) prior to screening is prohibited
Patients with any underlying physical, psychological, or medical condition that, in the opinion of the investigator, would make it unlikely that they would comply with the study
Failure to satisfy the investigator of fitness to participate for any other reason

Abbreviations: DHE, dihydroergotamine; ECG, electrocardiogram; ICHD, *International Classification of Headache Disorders*; IV, intravenous.

were instructed to self-administer INP104 1.45 mg when they experienced a recognizable migraine (even if pain was still mild) as one spray in each nostril. Dosing was limited to ≤2 doses per 24 h and ≤3 doses per 7 days. INP104 was the first acute treatment administered unless dosage limits had been reached. INP104 was not used as a second-line acute therapy. During the treatment period, only non-ergot, non-triptan acute treatment for migraine was allowed and only after 2 h from INP104 administration had elapsed as a rescue medication for patients who still had headache pain, or, alternatively, a single additional dose of INP104 may have been taken after 2 h. Such use was recorded in the eDiary.

Data collection

eDiaries were completed daily to capture headache and migraine details, headache medication usage, and MBS severity from screening through the 24-week visit and, if applicable, the 52-week visit. An entry for each headache, whether treated or not, was completed. Patients completed headache eDiary entries on an episodic basis, to capture information about any headache that did occur; the time it occurred and, if applicable, the acute treatment (INP104 or non-INP104) administered. If acute treatment was used, patients completed a postdose eDiary at 15, 30 min,

1, and 2 h after taking acute treatment, and up to 8, 24, and 48 h if the headache was still ongoing at those respective time points. Patients were asked to rate symptom severity at each postdose time point. Patients completed an evening eDiary each evening to encourage daily interaction with the eDiary regardless of whether they experienced a headache.

Statistical analyses

The sample size calculation was not based on statistical inference (Type I error or power considerations), as this was an open-label safety study. The first version of the study protocol called for an enrollment of ~200 patients with the goal of having ≥150 patients complete 24 weeks of treatment, each having an average of ≥2 attacks per 28-day period (the primary safety set [PSS]). The study protocol was then amended to enroll ~240 patients, with the final version amended to enroll ~340 patients to ensure the PSS was met, since it was observed as the study progressed that treatment with INP104 was associated with decreased migraine frequency while patients remained in the study, which threatened the original goal. Additionally, ≥80 patients were expected to be enrolled into an additional 28 weeks of treatment with the goal of ≥50 patients completing a total of 52 weeks of treatment, with each patient having an average of ≥2 attacks per 28-day period.

All patients who were enrolled and received ≥1 dose of INP104 were defined as the 24-week full safety set (FSS), whereas the 52-week FSS comprised all patients who qualified, consented, enrolled into, and received ≥1 dose of INP104 in the additional 28-week treatment period. The FSS was inclusive of the PSS. The 24-week PSS included all patients who had an average of ≥2 treatments with INP104 per 28-day period during the 24-week treatment period, remained in the study, attended the Week 24 visit, and received ≥12 INP104 treatments by the Week 24 visit. The 52-week PSS included all patients who signed the extension informed consent form at 24 weeks and had an average of ≥2 INP104 treatments per 28-day period during the full 52-week treatment period, remained in the study, attended the Week 52 visit, received ≥26 INP104 treatments during the full 52-week treatment period, and received ≥7 INP104 treatments between Weeks 24 and 52.

This is a primary analysis of data, with a post hoc analysis of exploratory efficacy data collected via the eDiary. Safety and exploratory efficacy endpoints were analyzed using descriptive statistics, including number, mean, standard deviation, standard error, median, minimum, and maximum using SAS software version 9.4. Baseline for non-diary-based endpoints was the last observation prior to, or on the day of, enrollment into the study on Day 0. If no measurement of a parameter was collected before patient enrollment on Day 0, the baseline measurement was set to "missing." For eDiary-based endpoints, baseline was calculated for each patient by averaging the results recorded within 28 days prior to patient enrollment in the study on Day 0. For endpoints that incorporated the timing after INP104 administration, their baseline data were based on the assessments that followed the "best usual care" treatment the patient used for their migraine within the baseline period. The 24-week treatment period began on Day 0. If the patient did not continue into the additional 28-week treatment period, all data after Day 0 were included in the 24-week treatment period. If the patient continued into the additional 28-week treatment period, then the 24-week treatment period ended on the date of the Week 24 visit. The 28-week extension period began upon the signing of the consent form at the Week 24 visit and included all data thereafter. For exploratory efficacy endpoints, analyses were based on responses to the treatment of individual attacks, specifically, the last "best usual care"-treated attack of the baseline period and the first INP104-treated attack of the open-label study period. As these analyses only count one migraine per patient, the number of attacks and the number of patients included in these analyses will be the same (i.e., these can be considered both patient-level and migraine-level analyses). Comparisons with best usual care during baseline were not included for all measures in this analysis set because patients were permitted to administer acute therapies (sometimes more than one) of their choice to treat their attacks during baseline. Continuous safety data were summarized with descriptive statistics and categorical safety data by frequency counts and percentages.

RESULTS

Patient disposition and demographics

A total of 893 patients consented and screened for the 24-week treatment period, of whom 533 (59.7%) were screen failures due to failed entry criteria, of which the most common (≥10% of patients) were failure to complete the eDiary on 25/28 days (39.2%; 209/533), and even after this criterion was relaxed to 23/28 days, a further 5.1% (27/533) failed; willingness to attend visits (13.9%; 74/533); and significant nasal abnormalities meeting exclusion criteria (11.8%; 63/533). Thus, 360 patients were enrolled, with 354 patients comprising the 24-week FSS. Furthermore, 73 patients continued into the 52-week treatment period, with 73 patients forming the 52-week FSS (Figure 2). Demographic characteristics for patients are shown in Table 2. The majority of patients in the 24-week treatment period were female (86%), had an average age of 41 years, and 31% of their migraine attacks occurred with aura. The average number of migraine headaches during the screening period was 4.60, and the maximum severity of headache pain was severe for 65.3% of attacks. The most frequently reported MBSs at the screening visit were photophobia (49.4%), nausea (16.4%), and phonophobia (14.1%), and the maximum severity was "severe" in 37.3%, 19.5%, and 31.4% of attacks, respectively. Medications used before treatment initiation included acetaminophen (43.8%), nonsteroidal anti-inflammatory drugs (37.6%), triptans (28.2%), and

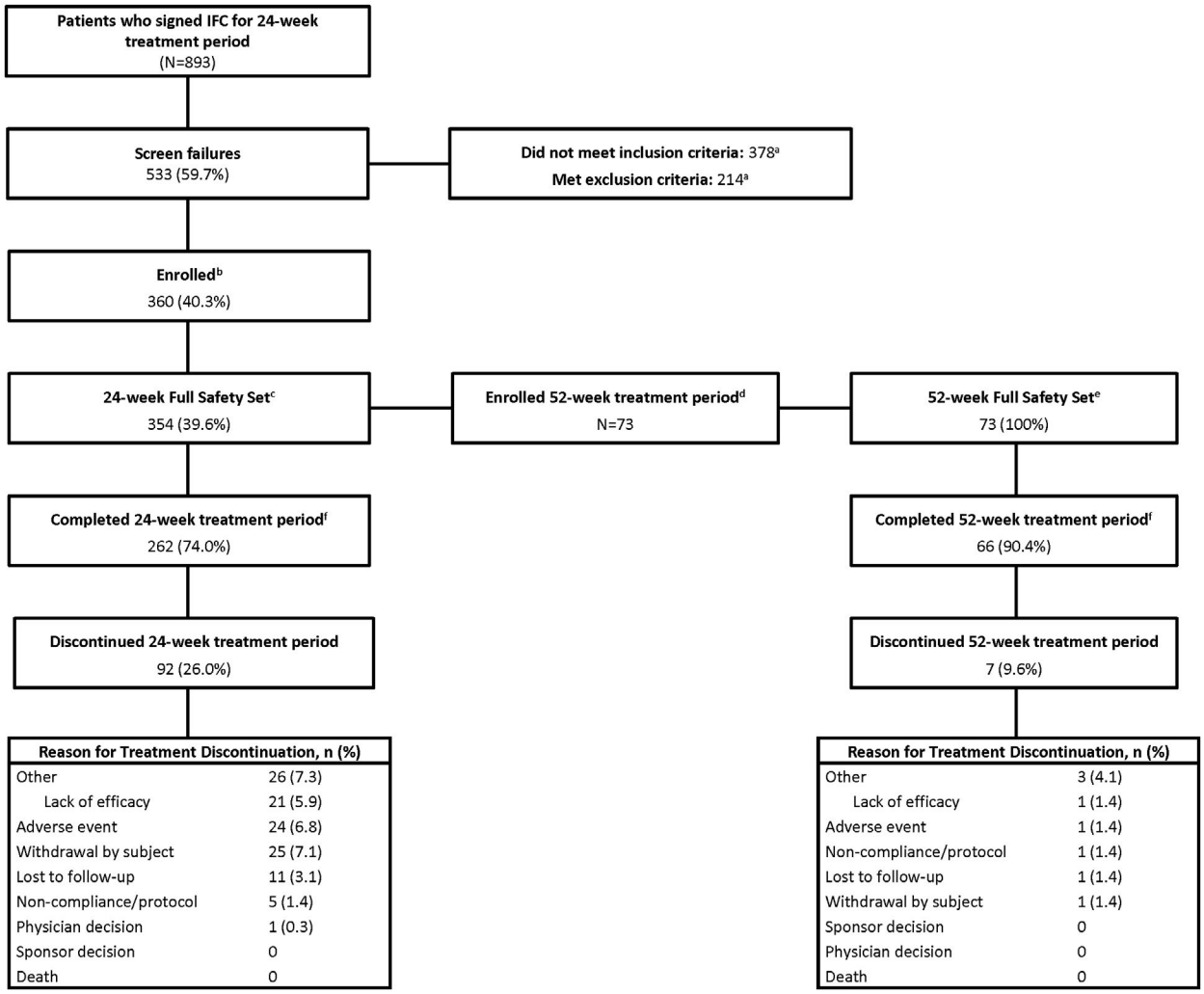

FIGURE 2 Patient disposition. [a]A patient is counted multiple times if multiple inclusion/exclusion criteria failed. [b]Included all patients who signed the ICF and were provided INP104. [c]Included all patients who were enrolled and received at least one dose of INP104. [d]Included all patients who signed the extension ICF at the Week 24 visit to continue into the extension and were provided with INP104. [e]Included all patients who were enrolled, received at least one dose of INP104 in the additional 28-week treatment period, and signed the extension ICF. [f]Included patients who continued INP104 treatment throughout the study period. ICF, informed consent form

combination analgesics (16.1%). Combination analgesics could include various assortments of medications such as acetylsalicylic acid, paracetamol, caffeine, butalbital, hydrocodone bitartrate, dichloralphenazone, and others. Thirteen patients in total used nonoral acute migraine treatments (triptans) at baseline, of whom five patients used a nasal triptan.

Safety outcomes

INP104 was well tolerated, with a total of 68.1% of patients reporting TEAEs in the 24-week FSS. INP104-related TEAEs were experienced by 36.7% of patients, the most common being nasal congestion (15%), nausea (6.8%), nasal discomfort (5.1%), and abnormal taste (5.1%) (>3% of patients; Table 3). In the 52-week FSS, 45.2% of patients reported INP104-related TEAEs. Of the 360 enrolled patients, 74% completed the 24-week treatment period, with reasons for treatment discontinuation including withdrawal by patient (7.1%), AEs (6.8%), lack of efficacy (5.9%), lost to follow-up (3.1%), noncompliance/protocol violation (1.4%), and physician's decision (0.3%). The most frequent nasal and gastrointestinal (GI) TEAEs that led to treatment discontinuation included nasal congestion (1.4%), nasal discomfort (1.1%), nausea (1.1%), and sinus congestion (0.6%). Of the 73 patients who entered the 28-week extension period, 90.4% of patients completed the 52-week treatment period (FSS), with reasons for treatment discontinuation including withdrawal by patient (1.4%), AEs (1.4%; asymptomatic olfactory test abnormal), lack of efficacy (1.4%), lost to follow-up (1.4%), and noncompliance/protocol violation (1.4%) (Figure 2). No serious treatment-related TEAEs were reported in either the 24-week or the 52-week treatment period.

Collectively, nasal-related TEAEs, upper nasal endoscopy (QSS-NM), and UPSIT scores suggested no significant change in

TABLE 2 Baseline characteristics and demographics for the 24- and 52-week treatment periods

	24-week treatment period (Weeks 1–24; FSS, *N* = 354)	52-week treatment period (Weeks 1–52; FSS, *N* = 73)
Age, years		
Mean (SD)	41.3 (11.1)	44.6 (10.2)
Sex, *n* (%)		
Female	304 (85.9)	60 (82.2)
Male	50 (14.1)	13 (17.8)
Race, *n* (%)		
White	266 (75.1)	57 (78.1)
Black/African American	79 (22.3)	15 (20.5)
Asian	3 (0.8)	1 (1.4)
American Indian or Alaska Native	3 (0.8)	0
Native Hawaiian or Other Pacific Islander	1 (0.3)	0
Multiple	2 (0.6)	0
Other	0	0
BMI (kg/m^2)[a]		
Mean (SD)	30.4 (7.5)	29.1 (6.3)
Duration of migraine history, years[b]		
Mean (SD)	19.5 (12.1)	22.0 (11.6)
Migraine headaches during baseline, *n*		
Mean (SD)	4.6 (2.3)	4.9 (2.6)
MIDAS	*n* = 351[h]	*n* = 72[h]
Mean (SD)	25.3 (22.3)	24.9 (20.1)
HIT-6		
Mean (SD)	63.9 (5.4)	64.6 (5.2)
Percentage pain-free 2 h postmigraine medication (non-IP)[c]		
Mean (SD)	24.9 (32.2)	20.2 (31.5)
Percentage MBS-free 2 h postmigraine medication (non-IP)[c]		
Mean (SD)	38.9 (38.0)	35.9 (37.3)
Percentage of migraine attacks with aura		
Mean (SD)	31.0 (40.5)	32.0 (41.6)
Maximum severity of headache pain, *n* (%)[d]	*n* = 352[h]	
Moderate	114 (32.2)	18 (24.7)
Severe	231 (65.3)	52 (71.2)
Maximum severity of MBS category, *n* (%)[d,e]	*n* = 352[h]	
Moderate	150 (42.4)	29 (39.7)
Severe	142 (40.1)	33 (45.2)
Maximum severity of nausea, *n* (%)[d]	*n* = 352[h]	
Moderate	146 (41.2)	32 (43.8)
Severe	69 (19.5)	16 (21.9)
Maximum severity of photophobia, *n* (%)[d]	*n* = 352[h]	
Moderate	131 (37.0)	25 (34.2)
Severe	132 (37.3)	33 (45.2)
Maximum severity of phonophobia, *n* (%)[d]	*n* = 352[h]	
Moderate	131 (37.0)	31 (42.5)
Severe	111 (31.4)	24 (32.9)

(Continues)

TABLE 2—Continued

	24-week treatment period (Weeks 1–24; FSS, *N* = 354)	52-week treatment period (Weeks 1–52; FSS, *N* = 73)
MBS subcategories, *n* (%)[e]		
Nausea	58 (16.4)	16 (21.9)
Vomiting	9 (2.5)	0
Light sensitivity	175 (49.4)	42 (57.5)
Sound sensitivity	50 (14.1)	7 (9.6)
Visual change	9 (2.5)	2 (2.7)
Dizziness/vertigo	4 (1.1)	1 (1.4)
Fatigue	6 (1.7)	2 (2.7)
Slowed/foggy thinking	19 (5.4)	1 (1.4)
Sensitivity to touch	2 (0.6)	1 (1.4)
Other	22 (6.2)	1 (1.4)
Migraine medication usage, *n* (%)[f]		
Ergot other than IP	2 (0.6)	0
Triptans	100 (28.2)	21 (28.8)
Acetaminophen	155 (43.8)	38 (52.1)
NSAIDs	133 (37.6)	23 (31.5)
Opioid	9 (2.5)	4 (5.5)
Barbiturate	6 (1.7)	1 (1.4)
Combination analgesic[g]	57 (16.1)	14 (19.2)
Other	106 (29.9)	25 (34.2)
None	25 (7.1)	3 (4.1)

Abbreviations: BMI, body mass index; FSS, full safety set; HIT-6, Headache Impact Test-6; IP, investigational product; MBS, most bothersome symptom; MIDAS, Migraine Disability Assessment; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

[a]BMI = (weight in kg)/(height in cm/100)^2.

[b]Duration of migraine history is calculated as (age at informed consent − age at diagnosis of migraine).

[c]Percentages are based on all treated migraine attacks.

[d]Maximum severity of a symptom (headache pain, MBS, nausea, photophobia, phonophobia) is the worst severity score among all migraine attacks within 28 days prior to patient's enrollment to the study on Day 0. For each migraine, the worst severity score is identified at any point during the course of a migraine event (i.e., event onset, medication administration, postdose time points at 15, 30 min, 1, 2, 8, 24, 48 h(s)). For the numeric value of each severity level, 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe.

[e]MBS is a patient-level assessment identified at screening.

[f]Only counted once if a patient took multiple medications within the same type.

[g]Combination analgesics could include various assortments of medications such as acetylsalicylic acid, paracetamol, caffeine, butalbital, hydrocodone bitartrate, dichloralphenazone, and others.

[h]Only 351 patients provided baseline MIDAS for the 24-week period, and 72 for the 52-week period; otherwise, baseline data were provided by all 354/73 patients. A total of 352 patients provided data on migraine symptom severity in the 24-week period, whereas all 73 provided it for the 52-week period.

olfactory mucosal integrity or functional disturbance over 24 weeks of treatment in the FSS. The majority of patients had scores indicating no upper mucosal irritation, epistaxis, or nasal discharge (>95% of patients) as assessed by the QSS-NM scoring system. UPSIT scores revealed no significant olfactory changes (defined as a decrease of 5 points or more) and remained in the normal range (~35–40) for the average age of the study population.[26] A Nasal Safety Review Committee consisting of three independent otolaryngologists reviewed the nasal safety data and suggested INP104 was safe and tolerable on the nasal mucosa. In their opinion, no further nasal toxicology studies would be required in future clinical trials with this product and monitoring of TEAEs was sufficient for monitoring upper nasal safety.[28]

Exploratory efficacy outcomes

A total of 5099 doses of INP104 were self-administered by 354 patients over the first 24 weeks of the study to treat 4515 migraine attacks and 90 headaches (nonmigraine) based on the evidence collected in the eDiaries. Two hours after a single dose of INP104, 38% and 52.1% of patients self-reported pain and MBS freedom with their first INP104-treated attack, whereas 30.1% and 46.4% who treated their last migraine in the screening period self-reported pain and MBS freedom at 2 h on best usual care (baseline; Figure 3). For patients who administered a single dose of INP104 for their first treated attack greater than 2 h from migraine

TABLE 3 Safety summary for the 24- and 52-week treatment periods

Treatment-related TEAEs	24-week treatment period (Weeks 1–24; FSS, *N* = 354)	52-week treatment period (Weeks 1–52; FSS, *N* = 73)
Any INP104-related TEAE, *n* (%)	130 (36.7)	33 (45.2)
Nasal congestion	53 (15.0)	13 (17.8)
Nausea	24 (6.8)	5 (6.8)
Nasal discomfort	18 (5.1)	5 (6.8)
INP104 taste abnormal	18 (5.1)	3 (4.1)
Vomiting	9 (2.5)	2 (2.7)
Olfactory test abnormal	8 (2.3)	5 (6.8)
Sinus congestion	7 (2.0)	–
Package-associated injury	6 (1.7)	4 (5.5)
Dizziness	5 (1.4)	3 (4.1)
Nasal mucosal disorder	5 (1.4)	1 (1.4)
Epistaxis	5 (1.4)	1 (1.4)
Dysgeusia	4 (1.1)	1 (1.4)
Rhinorrhea	4 (1.1)	1 (1.4)

Note: Treatment-related TEAEs reported in ≥1% of patients in the 24-week treatment period (FSS).

Abbreviations: FSS, full safety set; TEAE, treatment-emergent adverse event.

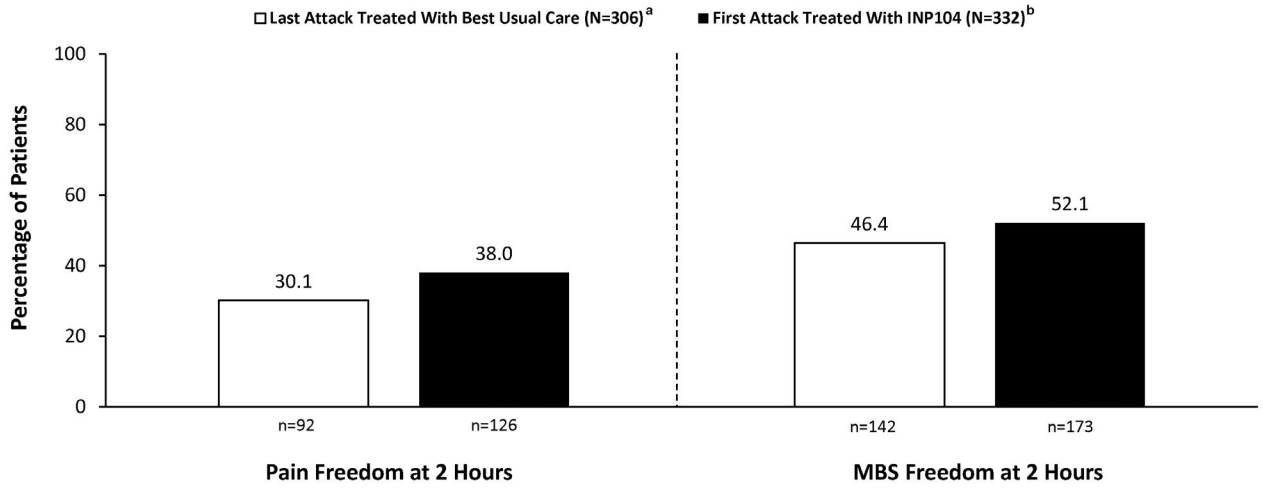

FIGURE 3 Two-hour pain and most bothersome symptom (MBS) freedom from the first migraine attack treated with INP104 and the last migraine attack treated with best usual care at baseline (full safety set). [a]Twenty-one patients did not provide data and were excluded from the analysis. [b]Fifteen patients did not provide data and were excluded from the analysis

initiation, pain freedom was self-reported in 39.4% and 30.9% of patients and MBS freedom in 57.6% and 40.0% at >2–4 h and >4 h from migraine initiation, respectively (Figure 4). The percentage of patients who self-reported pain relief for their first INP104-treated attack at 2 h was 66.3% (Figure 5). Of the 38% of patients who self-reported 2-h pain freedom for their first INP104-treated attack, only 7.1% and 14.3% of patients self-reported recurrence of migraine at 24 and 48 h post-INP104 administration, respectively (Figure 6).

Patient acceptability

The PAQ at Week 24 for the FSS demonstrated that the majority of patients agreed or strongly agreed that INP104 was easy to use (~84%). Compared with their previous treatment, the majority of patients found that INP104 kept their migraine from coming back for a longer time and allowed them to return to normal activities of daily living faster. Furthermore, patients reported faster and more consistent onset of effect with INP104 than with their previous best usual care treatment.

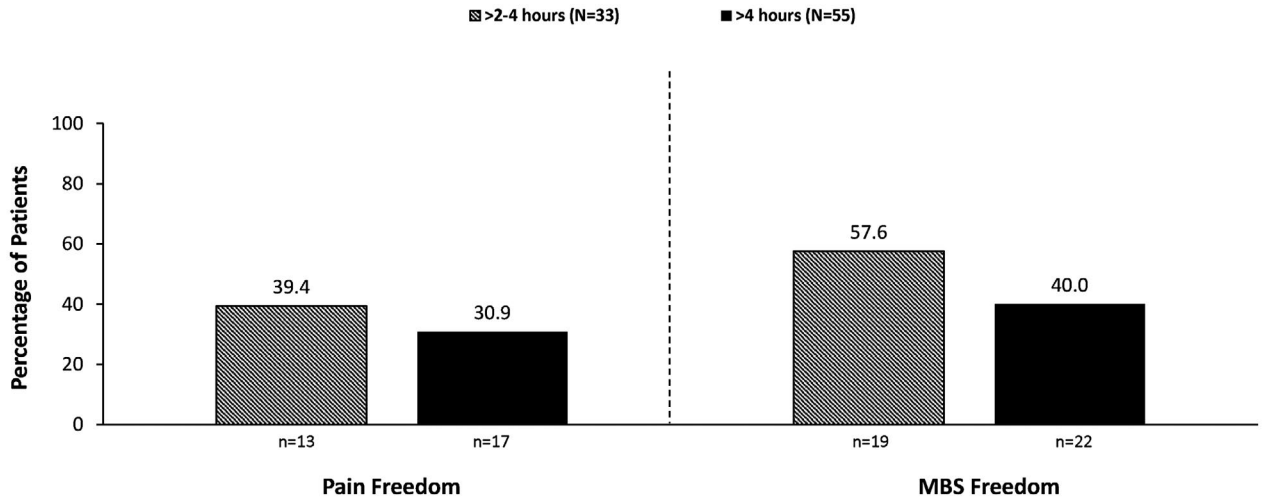

FIGURE 4 Pain and most bothersome symptom (MBS) freedom by INP104 treatment time for the first INP104-treated migraine attack (full safety set). Although 354 patients treated at least one migraine with INP104, only 332 patients treated their first migraine with INP104, of whom 244 treated within 2 h and are therefore not represented in this figure

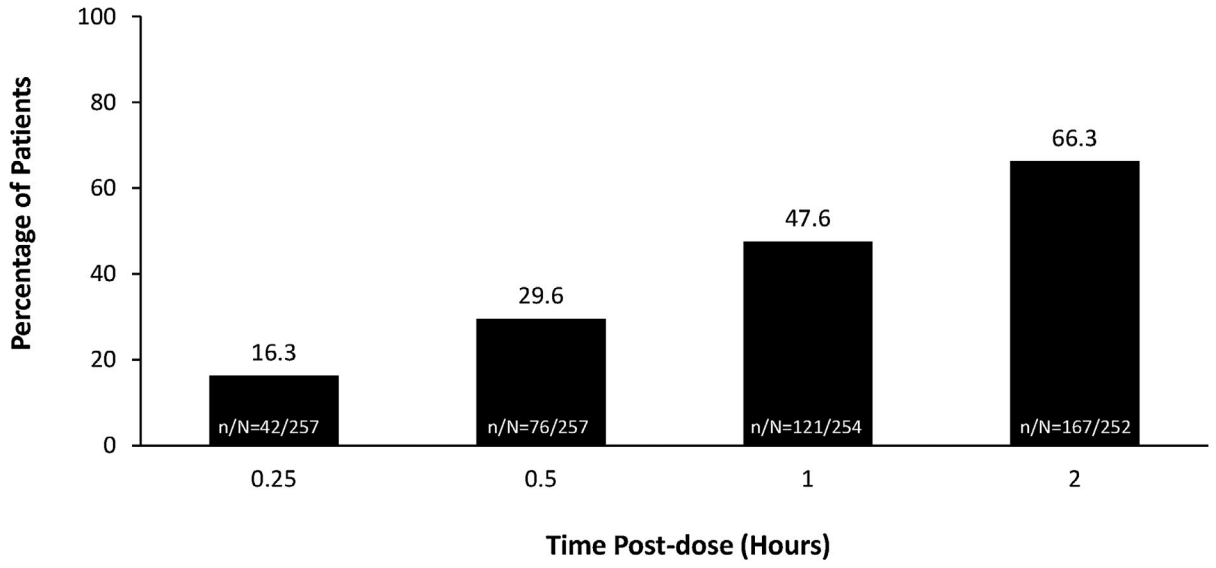

FIGURE 5 Pain relief for the first INP104-treated migraine attack (full safety set). Only patients with Time 0 pain assessments and pain assessments at the posttreatment time points are included in the analysis

DISCUSSION

The results of this Phase 3 study support the long-term safety of INP104, DHE mesylate delivered through the POD device. Throughout the initial 24-week treatment period and the full 52-week treatment period, INP104 was well tolerated, with no serious AEs related to study treatment reported. Furthermore, nasal endoscopy did not reveal clinically significant changes to the nasal mucosa, and olfactory function assessment did not reveal any abnormalities. In addition to the long-term safety and tolerability of INP104, patient-reported exploratory efficacy outcomes were assessed. The use of INP104 was associated with improvements in migraine measures for the first INP104-treated attack, and the PAQ indicated that patients generally had a positive perception of INP104 over the long-term study. Furthermore, there was a high rate of treatment completion, with 74% of patients completing the 24-week period. Of those who completed 24 weeks, 73 entered the 28-week extension, and of those, 90.4% completed. Interestingly, this is the first study to report a reduction in migraine frequency when treating repeated migraine attacks with DHE mesylate, perhaps suggesting sustained pain relief may lead to a reduction in frequency of those attacks and is worthy of further exploration. Collectively, these results support the long-term safety and patient acceptability of INP104.

There are perceived safety concerns with DHE use; however, when using recommended doses and in patients without

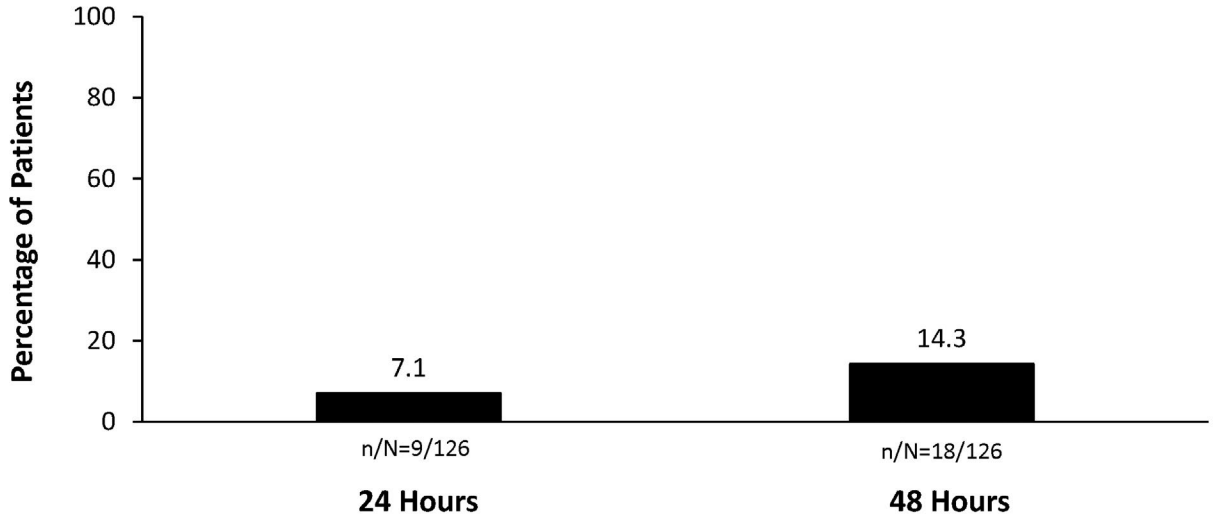

FIGURE 6 Recurrence rates for the first INP104-treated migraine attack (full safety set). The eDiary did not capture 24- and 48-h pain measurements if a patient was pain free at 2 h. Hence, a migraine is considered as having recurred if it was pain free at 2 h after INP104 administration and there was onset of a new headache prior to 24 or 48 h after INP104 administration

contraindications, IV or nasal DHE (currently approved options available in the US) have proven to be safe with over 70 years of clinical use.[2,5,29] INP104 was developed not only to improve convenience in use but also to improve the tolerability of DHE mesylate in currently marketed products. In addition, the STOP 101 study demonstrated a fourfold increase in C_{max} and a threefold increase in exposure over time (based on area under the curve) using the same formulation, but less than 75% of the dose, as in MIGRANAL (1.43 mg vs 2.0 mg), both self-administered by nasal delivery in the same naïve, healthy adult volunteers.[4] AE severity and frequency associated with DHE depend on the administration route and duration of exposure.[1,5,29,30] Nausea is C_{max} related and is typically observed with IV formulations,[1,5,29] with minimal nausea observed with other administration routes.[5,29,31] Therapeutic levels of DHE mesylate are quickly achieved with INP104 without the C_{max} spike seen with IV DHE mesylate,[4,5,31] and only 6.8% of patients reported nausea with INP104 in this study. An AE of abnormal taste was low for INP104 in this study, 5.1% ($n = 18$). This is most likely attributable to INP104 targeting the upper nasal space, which reduces the degree of nasal drip. These incidences are lower than the 10% and 8% of patients who experienced nausea and altered sense of taste, respectively, with MIGRANAL use.[10]

A significant number of patients are unsatisfied with current treatment options, or do not achieve optimal relief despite the use of triptans, which have been considered the standard of care for acute treatment of migraine.[14,15,32–34] Additionally, there is an increasing understanding that oral delivery may not always be optimal, and new (noninjected and nonoral) options for improving migraine symptoms remain an unmet need. DHE products can serve as an alternative to current treatments, yet existing formulations have elicited patient concerns regarding reliable, consistent effects, in addition to tolerability concerns.[2,4,5] The POD technology delivers DHE mesylate to the upper nasal space in a consistent and predictable manner.[4,7–9] Here we report the exploratory efficacy for the first INP104-treated attack, which was associated with 38%, 52.1%, and 66.3% of patients self-reporting pain freedom, MBS freedom, and pain relief 2 h after a single dose of INP104, respectively. Unlike some triptans, and more recently ubrogepant, for which rates of efficacy are highest when used early in an attack or when the attack is still mild, DHE has been shown to effectively treat attacks irrespective of time of dosing.[21,35–37] The efficacy of INP104 was not very different if patients administered within 2 h of migraine initiation or beyond.

INP104 may provide greater convenience than IV DHE mesylate and be more efficacious for patients who do not respond well to oral acute therapies for migraine. In this study, most patients reported that INP104 was easy to use, which suggests that on-demand availability of DHE may be important to patients and may have important implications during the COVID-19 pandemic.[38] GI symptoms may present with migraine, possibly arising from autonomic dysfunction, and include nausea, vomiting, diarrhea, reflux, and constipation. In addition, various GI conditions are frequently observed as comorbid conditions in patients with migraine.[39–48] Gastric motility issues, nausea, and vomiting associated with some comorbid GI conditions may affect not only the absorption of oral migraine drugs but also a patient's willingness to take an oral medication.[49,50] In this study, a comorbid history of GI disorders was reported by 38.4% of patients in the 24-week FSS. Patients with migraine and GI comorbidities may not obtain relief from migraine symptoms using an oral therapy; INP104 is a well-tolerated, nonoral alternative treatment that may benefit these patients.

This study has limitations that may influence the interpretation of the results. First, this was an open-label trial with no placebo control group for comparison of safety and exploratory efficacy measures. However, comparing INP104 to a patient's best usual care at baseline is reflective of a real-world setting. Second, this study

was limited to one geographic location, which may affect the generalizability of the results. Third, on average, patients in this study had a long history of migraine; therefore, patients with new-onset migraine were not assessed. Lastly, patients with chronic migraine were excluded.

CONCLUSION

INP104 has the promise to deliver speed and potency in providing acute relief of migraine symptoms without an injection. No major safety concerns were identified during this long-term safety study, including those relating to AEs of the upper nasal space. Patients were generally enthusiastic and satisfied with the long-term use of INP104. These data suggest that INP104 may be a well-tolerated acute treatment option for migraine.

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CONFLICT OF INTEREST

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INSTITUTIONAL REVIEW BOARD APPROVAL

IRB approval was granted by Advarra.

AUTHOR CONTRIBUTIONS

Study concept and design: Timothy R. Smith, Paul Winner, Sheena K. Aurora, Maria Jeleva, Jasna Hocevar-Trnka, Stephen B. Shrewsbury. *Acquisition of data*: Timothy R. Smith, Paul Winner, Sheena K. Aurora, Maria Jeleva, Jasna Hocevar-Trnka, Stephen B. Shrewsbury. *Analysis and interpretation of data*: Timothy R. Smith, Paul Winner, Sheena K. Aurora, Maria Jeleva, Jasna Hocevar-Trnka, Stephen B. Shrewsbury. *Drafting of the manuscript*: Timothy R. Smith, Paul Winner, Sheena K. Aurora, Maria Jeleva, Jasna Hocevar-Trnka, Stephen B. Shrewsbury. *Revising it for intellectual content*: Timothy R. Smith, Paul Winner, Sheena K. Aurora, Maria Jeleva, Jasna Hocevar-Trnka, Stephen B. Shrewsbury. *Final approval of the completed manuscript*: Timothy R. Smith, Paul Winner, Sheena K. Aurora, Maria Jeleva, Jasna Hocevar-Trnka, Stephen B. Shrewsbury.

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