STOP 301: Open-label Safety and Tolerability of Chronic Intermittent Usage for 24/52 Weeks of INP104 [Nasal Dihydroergotamine Mesylate (DHE) Administered by Precision Olfactory Delivery (POD®) Device] in Migraine Headache

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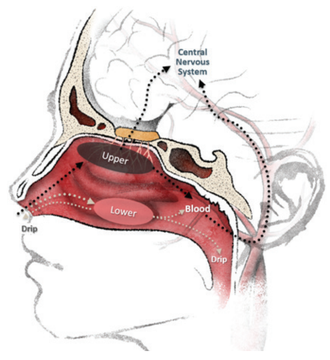
Introduction

- Migraine remains a serious cause of disability (Burch et al, 2018; Global Burden of Disease Study, 2017).
- Up to 42% of migraineurs report dissatisfaction with their treatment (Bigal et al, 2007; Holland et al, 2013; Wells et al, 2014), over a third (37%) with the speed of effect (Bigal et al, 2007), and half were dissatisfied that their pain recurred (Bigal et al, 2007).
- Intravenous (IV) DHE is an effective abortive therapy, however, the nasal formulation, Migranal®, has poor bioavailability and hence variable efficacy.
- INP104 is an innovative drug-device combination product that consists of a liquid DHE formulation administered by the I123 Precision Olfactory Delivery (POD®) device that addresses the low bioavailability and high variability in nasal administration observed with traditional nasal sprays.
- The POD device technology targets consistent and efficient delivery of drugs to the vascular rich upper nasal space (**Figure 1**).
- The upper nasal cavity has many advantages for drug delivery including higher, more consistent bioavailability – likely attributable to the highly vascularized nature of this region combined with a reduction in the amount of drug that can drip out of the nose or run into the posterior pharynx after administration to this region.
- These factors make the upper nasal cavity a desirable route of administration for drugs where rapid absorption and onset of effect and lower doses (related to a reduction in the amount of drug that drips out) are beneficial.
- The POD device technology utilized in INP104 maintains DHE nasal solution (NS) and HFA propellant separate until actuation.
- Actuation propels a focused stream of DHE NS to the olfactory epithelium.
- No product has previously utilized the upper nasal space for systemic drug delivery.

Figure 1. Illustration of I123 POD Device and Target Delivery Area

A. INP104 drug-device combination product ready for use

B. Diagram of the nasal space (lower = target of most "nasal sprays"; upper = target for POD delivery)



- PK data from the pivotal PK (STOP 101) study demonstrated that in healthy subjects, INP104 (1.45 mg) had a 3-fold greater $AUC_{0\text{-}inf}$ and a 4-fold greater C_{max} than Migranal 2 mg as a result of delivery technology (Shrewsbury et al, 2019).
- Safety data from STOP 101 showed fewer treatment-related adverse events with INP104 than IV DHE.
- The STOP 301 study was designed to assess the safety of chronic, repetitive administration of DHE NS on olfactory epithelium integrity and function.
- Despite the open label design, STOP 301 will also explore the efficacy and consistency of INP104 over time (24 or 52 weeks).

Objectives

- Assess the safety and tolerability of INP104

Exploratory Objective

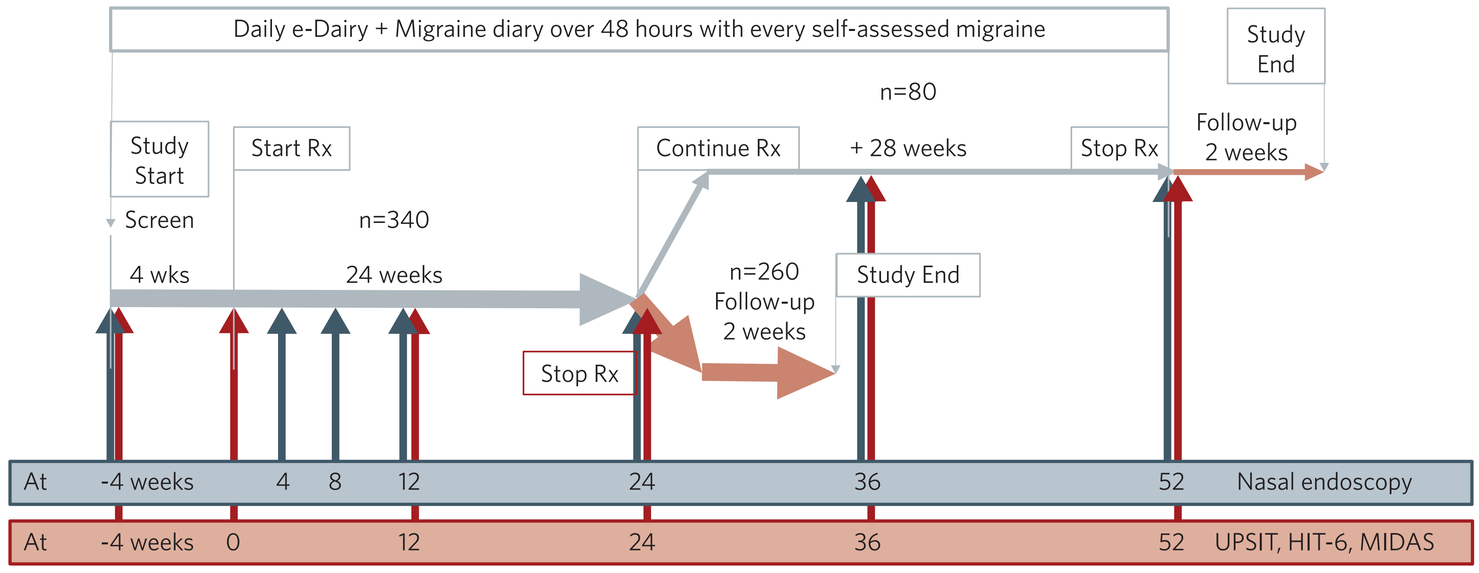
- Evaluate the efficacy of INP104 for treating acute episodic migraine attacks

Methods

Study Design

- Open-label, single-group assignment, safety, tolerability and exploratory efficacy study

Figure 2. STOP301 Study Design



- The study will comprise a 4-week screening period, a 24-week or 52 week treatment period, and a 2-week post-treatment follow-up period (**Figure 2**)
- Approximately 340 patients will enter the 24 week study, allowing at least 150 to each be exposed to INP104, at least twice per month on average, for 24 weeks
- Of the 340 enrolled, approximately 80 will enter into a further 28 week treatment period with the goal of 50 patients completing 52 weeks of exposure with on average having migraines twice per month or more for the study duration.
- Patients will be enrolled at approximately 40 study sites in the U.S. ClinicalTrials.gov Identifier: NCT03557333

Study Treatments

- INP104 administering DHE 1.45 mg nasally
- Patients will use no more than:
  - 2 doses within a 24-hour period
  - 3 doses in a 7-day period
  - 12 doses in a 4-week period

Patient Selection Criteria

Inclusion Criteria
Adults age 18 to 65 years
ICHD diagnosis of migraine with or without aura with at least 2 attacks/month for previous 6 months
At least 2 attacks during a 28-day screening period
>80% eDiary compliance
Exclusion Criteria
Trigeminal autonomic cephalalgias
Migraine aura without headache, hemiplegic migraine or migraine with brainstem aura
Chronic migraines, medication overuse headache or other chronic headache syndromes (at least 15 headache days in screening)
Status migrainosus
Coronary artery disease (CAD), symptoms or findings consistent with coronary artery vasospasm, including Prinzmetal's variant angina
Significant risk factors for CAD, current tobacco user, smoking history (at least 10 cigarettes/day within the last 12 months), history of diabetes, peripheral arterial disease, Raynaud's phenomenon
Potentially unrecognized CAD on history, examination, or ECG
Abnormal, clinically significant laboratory tests at screening
Recent acute illness or uncontrolled infection
Recurrent sinusitis or epistaxis or chronic rhinosinusitis with nasal polyp
Significant nasal congestion, physical blockage in either nostril, significantly deviated nasal septum, septal perforation, or any pre-existing upper nasal mucosal abnormality
Triptan or ergot use >12 days/month in the 2 months prior or during screening
Use of barbiturates/barbiturate containing compounds or opiates >7 days/month or unstable usage pattern in 2 months prior to or during screening.

Study Assessments

Assessments	Screen	Baseline	Treatment Period										Follow Up
Week	-4	0	4	8	12	16	20	24/ EOT	26	36	42	52/ EOT	54
Safety/ tolerability	X	X	X		X	X	X	X	X	X	X	X	X
Nasal endoscopy	X		X	X	X			X		X		X	
UPSIT	X	X			X			X		X		X	X
MIDAS and HIT-6	X	X			X			X		X		X	
eDiary review		X	X	X	X	X	X	X		X	X	X	

- Olfactory mucosal integrity and function will be assessed by endoscopy of the upper (and lower) nasal spaces and by University of Pennsylvania Smell Identification Test (UPSIT) at intervals throughout exposure (Doty et al, 1984). (**Figure 2**)

Outcome Measures

Primary

- Adverse events
- Change in olfactory function (UPSIT)
- Change in nasal mucosa determined by nasal endoscopy (QSS-NM; Shrewsbury et al, 2019) (**Table 1**)

Table 1. Quantitative Scoring Scale for Evaluation of Nasal Mucosa (QSS-NM)

Finding	Grading Criteria
Mucosal Irritation	Scored from 0 = none to 4 = septal perforation
Epistaxis (frank bleeding or dried blood clot)	Scored 0 = none to 3 = severe (ER visit or hospitalization)
Mucosal Edema Nasal Discharge Mucosal Crusting	Scored as 0 = none, 1 = mild, 2 = moderate or 3 = severe

Secondary

- Change in vital signs, physical examination, 12-lead ECG, and laboratory evaluations

Exploratory

- Change in healthcare utilization
- Product acceptability questionnaire

Exploratory Efficacy

- Freedom/relief from most bothersome symptom (MBS) and pain at 2 hours
- Change in frequency and severity of pain and MBS at other time points
- Change in frequency and severity of nausea, phonophobia, and photophobia
- Change in frequency and severity of migraine by eDiary
- Incidence of pain relapse at 24 and 48 hours
- Change in headache-related disability
  - Migraine Disability Assessment (MIDAS; Stewart et al, 1999)
  - Headache Impact Test (HIT-6; Yang et al, 2011)
- Change in concomitant migraine medication use

Summary

- Nasal drug delivery has been an underutilized route of administration focused primarily on local treatments (to the lower, anterior nasal space) with traditional nasal sprays.
- Nasal delivery by the POD device is effective for delivering drugs to the upper nasal space leading to rapid and consistent systemic absorption.
- STOP 301 is designed to assess safety, tolerability and explore efficacy of repeat administration of DHE drug to the upper nasal space.
- Findings from STOP 301 are expected to confirm the safety/ tolerability profile of INP104 and its efficacy for treating acute episodic migraine.
- Topline results are expected by the end of 2019.

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