# Cardiovascular Safety Results of INP104 (POD-DHE) From the STOP 301 Phase 3 Study

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## Introduction

- Dihydroergotamine (DHE) has long been used and recommended for the treatment of migraine due to its high response rate and sustained efficacy[1]
- However, despite over 70 years of clinical experience, DHE product labels warn of potential cardiovascular (CV) and peripheral ischemic events[1,2]
- INP104 is a novel, investigational drug-device combination product that targets delivery of DHE mesylate to the upper nasal space using a gas-propelled Precision Olfactory Delivery (POD®) device, version I123[1,3]
- A Phase 1 study (STOP 101) found INP104 to be well tolerated and readily absorbed, showing ~1/10 of the $C_{max}$ of intravenous (IV) DHE mesylate, yet approaching IV-like levels at 20 minutes, and matching IV levels from 30 minutes onward[4]
- Phase 1 data showed significant blood pressure increases with IV DHE mesylate, but not with INP104, and no electrocardiogram (ECG) changes were observed[5]
- STOP 301 was a pivotal Phase 3 safety study on the use of INP104 for the acute treatment of migraine over 24 and 52 weeks

## Objective

- To report the cardiovascular results of INP104 from the STOP 301 study

## Methods

### Study Design

- This was a pivotal Phase 3, interventional, open-label, single-group assignment study, assessing the safety, tolerability, exploratory efficacy, and patient acceptability of INP104 over long-term use (NCT03557333)
- The study comprised a 4-week screening period, 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 for all patients
- Although the primary focus of this study was on nasal safety (integrity and function), CV effects (treatment-emergent adverse events [TEAEs], concomitant medication use, vital signs, and ECGs) were regularly collected and reviewed against preexisting conditions, concomitant medication use, and INP104 exposure

### Study Patients and Treatment

- Patients were adult (18-65 years) males and females with a documented diagnosis of migraine, defined as experiencing a minimum of 2 migraine attacks, with or without aura, each month not qualifying as chronic migraine 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
- Patients were excluded if they had a history of CV events or presented with significant risk factors for CV disease
  - Patients with a history of hypertension could enroll if hypertension was stable and well controlled on current therapies for >6 months, provided no other risks were present
- After an initial 4-week screening period, patients were provided with up to 3 doses/week of INP104 to nasally self-administer (one dose is one spray to each nostril, delivering a total of 1.45 mg DHE mesylate) with self-recognized migraine attacks over 24 weeks, with a subset over 52 weeks
- Dosing was limited to no more than 2 doses within a 24-hour period or 3 doses within a 7-day period

### Study Assessments

- The primary endpoint was to assess the safety and tolerability of INP104, which included adverse event (AE) collection from the time of patient consent until the last study follow-up visit, nasal endoscopy, and olfactory function testing
- Secondary endpoints
  - Vital signs, including blood pressure, were collected every 4 weeks starting at the 4-week screening period
  - 12-lead ECGs were performed at the 4-week screening period, at baseline (Week 0), Week 24, and Week 52

## Results

### Patient Disposition and Baseline Characteristics

- 360 patients were screened and enrolled into the 24-week treatment period
  - 354 patients who received at least 1 dose of INP104 were defined as the 24-week full safety set (FSS)
- 262 patients completed the 24-week treatment period

### Adverse Events

- No serious AEs were considered related to INP104 use

### Cardiac TEAEs

- No patient experienced a cardiac-related TEAE over 24 weeks

### Vascular TEAEs

- Over 24 weeks, 5 patients (1.4%) experienced vascular TEAEs (**Table 1**)
- 4 patients (1.1%) experienced (mild) hypertension
  - 2 patients (Patients 2 and 3) had ongoing hypertension at the start of the study for which they were receiving treatment
  - Worsening hypertension for Patient 2 was assessed as related to INP104; however, the event resolved with additional treatment after 116 days
  - Of the 4 hypertensive patients, 3 completed the study and 1 withdrew due to pregnancy
- 1 patient (0.3%) experienced a hematoma that was not related to INP104, but was sustained during a motorcycle accident

### Blood Pressure and ECG

- Overall, minimal mean changes from baseline were observed for systolic and diastolic blood pressure and for median heart rate, aggregate PR interval, QRS duration, QT interval, QT corrected with Fridericia's formula (QTcF), and RR interval over 24 weeks (**Table 2 and 3**)
- No patient had an overall interpretation of an abnormal clinically significant ECG or experienced a TEAE associated with an abnormal ECG

### Concomitant Medication Use

- INP104 overuse and use with triptans (contraindicated) did not lead to concerning TEAEs

**Table 1. Vascular TEAEs Overview (24-Week FSS, N=354)**

| Patient | Duration (Days) | INP104 Doses at TEAE Start | Related to INP104 | Relevant Medical History | Relevant Prior Treatment |
|---|---|---|---|---|---|
| **Hypertension (mild)** | | | | | |
| 1 | Ongoing[a] | 10 | No | None | None |
| 2[b] | 116 | 17 | Yes | Hypertension | Hydrochloro-thiazide/ irbesartan |
| 3[b] | Ongoing[a] | 6 | No | Obesity, Hypertension | Amlodipine |
| 4 | Ongoing[a] | 22 | No | None | None |
| **Hematoma** | | | | | |
| 5 | Ongoing[a] | 11 | No | None | None |

[a]The TEAE was ongoing as of last contact with patient.

[b]Verbatim term was worsening hypertension.

FSS = full safety set; TEAE = treatment-emergent adverse event.

**Table 2. Mean Systolic and Diastolic Blood Pressure (24-Week FSS, N=354)**

| Week | Systolic BP (mmHg, Mean ± SD) | Diastolic BP (mmHg, Mean ± SD) |
|---|---|---|
| Baseline[a] | 118.1 ± 12.44 | 77.3 ± 9.67 |
| 4[b] | 117.6 ± 12.38 | 77.1 ± 8.99 |
| 8[b] | 117.9 ± 13.34 | 77.0 ± 9.38 |
| 12[b] | 116.9 ± 12.67 | 76.1 ± 9.25 |
| 16[b] | 118.2 ± 12.88 | 77.5 ± 9.17 |
| 20[b] | 117.4 ± 12.35 | 76.9 ± 8.69 |
| 24[b] | 117.0 ± 12.55 | 76.7 ± 8.96 |
| 26 (Follow-up) | 116.8 ± 12.51 | 77.0 ± 8.72 |

[a]Baseline is defined as the last non-missing observation prior to the date of patient's enrollment into the study on Day 0.

[b]Post-baseline only includes data from patients who started the first INP104 on/before the visit evaluated.

BP = blood pressure; FSS = full safety set; SD = standard deviation.

**Table 3. Mean ECG Parameters (24-Week FSS, N=354)**

| Parameter | Baseline[a] (Mean ± SD) | Week 24[b] (Mean ± SD) | End of Period (24-Wk Trt, Mean ± SD)[b,c] |
|---|---|---|---|
| Median Heart Rate (beats/min) | 69.7 ± 11.27 | 69.4 ± 10.61 | 69.5 ± 10.54 |
| PR Interval, Aggregate (msec) | 154.9 ± 20.89 | 153.2 ± 21.80 | 153.1 ± 21.19 |
| QRS Duration, Aggregate (msec) | 88.6 ± 9.88 | 88.3 ± 10.76 | 88.8 ± 10.13 |
| QT Interval, Aggregate (msec) | 391.6 ± 28.08 | 392.1 ± 27.19 | 390.6 ± 27.12 |
| QTcF Interval, Aggregate (msec) | 410.9 ± 18.84 | 410.6 ± 19.58 | 409.6 ± 19.11 |
| RR Interval, Aggregate (msec) | 878.58 ± 144.11 | 877.90 ± 127.76 | 877.53 ± 129.98 |

[a]Baseline is defined as the last non-missing observation prior to the date of patient's enrollment into the study on Day 0.

[b]Post-baseline only includes data from patients who started the first IP on/before the visit evaluated

[c]End of period (24-Wk Trt) is defined as the last assessment with non-missing values during the 24-week treatment period.

FSS = full safety set; IP = investigational product; min = minute; msec = millisecond; QTcF = QT interval corrected for heart rate with Fridericia's formula; SD = standard deviation; Trt = treatment; Wk = week.

## Conclusions

- Although patients with active CV disease were excluded from the STOP 301 study, no significant AEs were noted in the peripheral or CV system even in patients with CV risk factors or concomitant triptan use
- INP104 displayed few treatment-related vascular events and no treatment-related cardiac events
- INP104 was well tolerated when taken as directed in the STOP 301 study

### References

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