Safety of INP104 in Migraine Patients With Cardiovascular Risk Factors: Post Hoc Subgroup Analysis of the Phase 3 STOP 301 Study

Rima M. Dafer, MD, MPH[1]; Gretchen E. Tietjen, MD[2]; John F. Rothrock, MD[3]; Joe Hirman, PhD[4]; Robert E. Vann, PhD[5]; Judie Gutierrez, PhD, MBA[5]; Sutapa Ray, PhD[5]; Sheena K. Aurora, MD[5]

[1]Rush University Medical Center, Chicago, IL, USA; [2]University of Toledo, Toledo, OH, USA; [3]Inova Health, Fairfax, VA, USA; University of Virginia School of Medicine, Charlottesville, VA, USA; [4]Pacific Northwest Statistical Consulting, Woodinville, WA, USA; [5]Impel Pharmaceuticals, Seattle, WA, USA

Introduction

- INP104 is a combination of dihydroergotamine mesylate (DHE) and the Precision Olfactory Delivery (POD®) device approved for the acute treatment of migraine with or without aura in adults[1]
- The safety and exploratory efficacy of INP104 has been previously reported in the Phase 3 STOP 301 trial[1]
- Although INP104 was well tolerated in the STOP 301 study, DHE is contraindicated in patients with cardiovascular (CV) disease or significant risk factors for CV disease because of a theoretical risk for arterial vasoconstriction[2]
- The CV safety of INP104 has been previously presented in 2 different studies
  - The Phase 1 study (STOP 101) showed no significant blood pressure increases or electrocardiogram (ECG) changes with INP104 in healthy participants[3]
  - The Phase 3 (STOP 301) study in patients with migraine who had no active CV disease or significant risk factors for CV disease demonstrated that only 1.4% of patients experienced a nonserious, vascular treatment-emergent adverse event (TEAE), and there were minimal changes in blood pressure and ECG parameters over 24 or 52 weeks. Further, INP104 overuse and use with triptans (contraindicated) did not lead to concerning TEAEs[4]
- Since migraine can be associated with a risk of CV events,[5,6] evaluating the safety of INP104 or any migraine treatment specifically in patients with any CV risk factors is warranted

Objective

- This post hoc subgroup analysis of the Phase 3 STOP 301 study evaluated the safety of INP104 in patients with migraine who had nonsignificant CV risk factors

Methods

Study Design

- STOP 301 was a Phase 3, open-label, single-group assignment study that assessed the safety, tolerability, and exploratory efficacy of INP104 (NCT03557333)
- The study was comprised of a 28-day screening period where patients used their best usual care to acutely treat migraine attacks (MAs), a 24-week treatment where INP104 was used to acutely treat MAs for all patients, and a 2-week post-treatment follow-up period for all patients
- A subset of patients continued into a treatment extension for 52 weeks
- Following the screening period, all eligible patients were provided with up to 3 doses/week of INP104 to nasally self-administer (1.45 mg in a dose of 2 sprays) with self-recognized MAs

Study Patients

- Eligible patients:
  - Were adult males or females aged 18-65 years
  - Had a documented diagnosis of migraine with or without aura not qualifying as chronic migraine per the International *Classification of Headache Disorders, 3rd edition, beta version*
  - Were in general good health, with no significant medical history or clinical abnormalities at baseline
  - Experienced ≥2 MAs per month for the previous 6 months and during screening
  - Completed eDiary entries on ≥23 of the 28 days during screening
- Exclusion criteria included:
  - Ischemic heart disease
  - Clinical symptoms or findings consistent with coronary artery vasospasm (including Prinzmetal's variant angina)
  - Significant risk factors for coronary artery disease (CAD)
  - Current use of tobacco products
  - Smoking history (≥10 cigarettes per day within the 12 months prior to screening)
  - History of diabetes
  - Known peripheral arterial disease
  - Raynaud's phenomenon
  - Vascular surgery (within 3 months prior to study start)
  - Potentially unrecognized CAD as demonstrated by history, physical examination, or screening ECG
- Patients with nonsignificant CV risk factors were included, such as a history of hypertension (if the hypertension was stable and well controlled on current therapies for >6 months provided that no other risk factors for CAD were present) or obesity

Results

Patient Disposition

- 360 patients were screened and enrolled into the 24-week treatment period
- 354 patients received at least 1 dose of INP104 and were defined as the 24-week full safety set
- Of these, 139 patients were identified as having ≥1 nonsignificant CV risk factors (Table 1)

Table 1. Nonsignificant CV Risk Factors (24-Week FSS)

Nonsignificant CV Risk Factor	n (%)
Obesity	80 (22.6)
Hypertension	33 (9.3)
Hyperlipidemia	19 (5.4)
Hypercholesterolemia	10 (2.8)
Gastric bypass	7 (2.0)
Bradycardia	6 (1.7)
Overweight	5 (1.4)
Mitral valve prolapse	4 (1.1)
Blood cholesterol increased; impaired fasting glucose; gastric banding[a]	3 (0.8)
Postural orthostatic tachycardia syndrome; tachycardia; cardiac murmur; heart rate irregular; hypertriglyceridemia; bronchitis chronic[a]	2 (0.6)
Bundle branch block right; heart valve incompetence; palpitations; sinus bradycardia; ventricular extrasystoles; type V hyperlipidemia; blood pressure increased; weight increased; abnormal weight gain; dyslipidemia; glucose tolerance impaired; hyperglycemia; insulin resistance; gestational diabetes; gestational hypertension; anesthesia procedure; cardiac ablation; poor peripheral circulation; prehypertension[a]	1 (0.3)

Note: More than one risk factor may have been present within a given patient.
[a]Each listed risk factor occurred in the number (%) of patients noted.
CV=cardiovascular; FSS=full safety set.

TEAEs in Patients With Nonsignificant CV Risk Factors Who Used INP104

- TEAEs were reported in 74.8% (n=104/139) of patients within this subgroup
- The most common (≥5%) TEAEs were nasal congestion (19.4%), upper respiratory tract infection (12.2%), abnormal product taste (7.9%), nasopharyngitis (6.5%), nasal discomfort (6.5%), nausea (6.5%), and urinary tract infection (5.0%)
- Few CV-related TEAEs occurred, including hypertension (2.9%), cardiac murmur (1.4%), bradycardia (0.7%), and sinus bradycardia (0.7%)
- TEAEs of interest are in Table 2

Table 2. TEAEs of Interest in Patients With Nonsignificant CV Risk Factors Who Used INP104 in the STOP 301 Study

System Organ Class Preferred Term, n (%)	N=139
Any Adverse Event	104 (74.8)
Cardiac disorders	2 (1.4)
Bradycardia	1 (0.7)
Sinus bradycardia	1 (0.7)
Investigations	9 (6.5)
Cardiac murmur	2 (1.4)
Blood glucose increased	1 (0.7)
Social circumstances	1 (0.7)
Menopause	1 (0.7)
Vascular disorders	4 (2.9)
Hypertension	4 (2.9)

Conclusion

- This is a post hoc subgroup analysis of all patients from STOP 301 with known nonsignificant CV risk factors
- Overall, the most frequently occurring TEAEs with INP104 use were not cardiac related in migraine patients with nonsignificant CV risk factors
- Further studies in patients with known stable CV risk factors in the absence of CV contraindications for DHE may be warranted

References

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