Safety of Concomitant Triptan and INP104 Use From the Phase 3 STOP 301 Study in Migraine Patients

Alexander Feoktistov, MD[1]; Robert E. Vann, PhD[2]; Judie Gutierrez, PhD, MBA[2]; Sutapa Ray, PhD[2]; Sheena K. Aurora, MD[2]

[1]Synergy Integrative Headache Center, Northfield, IL, USA; [2]Impel Pharmaceuticals, Seattle, WA, USA

Introduction

- INP104 is a drug-device combination product that delivers dihydroergotamine mesylate (DHE) to the upper nasal space using Precision Olfactory Delivery (POD®) technology and is approved for the acute treatment of migraine with or without aura in adults[1,2]
- Safety and exploratory efficacy results for INP104 as an acute therapy for migraine from the Phase 3 STOP 301 study have been previously published[1]
- Because DHE and triptans act on 5-HT1B/1D receptor subtypes, which contributes to their vasoconstrictive effects, administering triptans within 24 hours of DHE use is contraindicated in DHE product labels and was not permitted during the STOP 301 trial[2,3-6]
- During the STOP 301 study, a small group of patients used triptans within 24 hours of INP104 during the treatment period despite being instructed against doing so; therefore, understanding the safety of concomitant triptan and INP104 use is an important topic for the patient-physician dialogue

Objective

- To report safety in patients with migraine who used a triptan within 24 hours of INP104 administration

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 design included a 28-day screening period during which patients used their best usual care to acutely treat migraine attacks (MAs), a 24-week treatment period for all eligible patients during which INP104 was used to acutely treat MAs, and a 2-week post-treatment follow-up period for all patients. A subset of patients continued into a treatment extension to 52 weeks
- Following the screening period, all eligible patients were provided with up to 3 doses per week of INP104 to nasally self-administer (1.45 mg in a dosage of 2 sprays) with self-recognized MAs. Dosing was limited to ≤2 doses per 24 hours and ≤3 doses per 7 days
- Only non-ergot, non-triptan acute therapies for migraine were allowed as rescue medication after 2 hours of INP104 administration. A single additional dose of INP104 was also permitted after 2 hours

Study Patients

- Eligible patients were adults (aged 18-65 years) with a documented diagnosis of migraine with or without aura not qualifying as chronic migraine based on the *International Classification of Headache Disorders, 3rd edition, beta version*; were in general good health; had no significant medical history or clinical abnormalities at baseline; were required to experience ≥2 MAs per month for the previous 6 months and during screening, and were required to complete eDiary entries on ≥23 of 28 days during screening
- Exclusion criteria included patients with 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, history of diabetes, known peripheral arterial disease, Raynaud's phenomenon, vascular surgery (within 3 months prior to study start), or potentially unrecognized CAD as demonstrated by history, physical examination, or screening electrocardiogram (ECG)
- Patients with non significant cardiovascular risk factors were eligible, such as a history of controlled hypertension (if the hypertension was stable and well controlled on current therapies for >6 months, provided no other risk factors for CAD were present)

Results

- Over 24 weeks, 354 patients self-administered ≥1 dose of INP104
- Despite being instructed NOT to take triptans during the treatment period, 10 patients used triptans within 24 hours of INP104 use on ≥1 occasion
  - Triptans included sumatriptan (n=5), rizatriptan (n=2), and eletriptan (n=1); 2 patients did not list the triptan they used
  - 6 patients who used triptans were also using serotonin and norepinephrine reuptake inhibitors or selective serotonin reuptake inhibitors during the study
- Seven of the 10 patients reported 15 treatment-emergent adverse events (TEAEs); only 2 TEAEs occurred within 24 hours of concomitant triptan-INP104 use (Table)
  - One patient reported nasal congestion (possibly INP104 related) on the day of INP104 administration, which resolved before subsequent triptan use on the following day (~6 hours later)
  - One patient reported epistaxis 2 days after concomitant triptan and INP104 use (unlikely related to INP104 or INP104-triptan use because epistaxis is not anticipated for either product)
- The remaining 5 patients had various TEAEs that were not temporally related to triptan-INP104 use (Table)
- No TEAEs related to blood pressure, pulse, or ECG parameters were reported, and any variance was within normal clinical limits

Table: Patients Who Used a Triptan Within 24 Hours of INP104 Administration

Patient	Number of Times Triptan Used Within 24 Hours of INP104	TEAE During Study? (Yes/No)	TEAE Preferred Term	TEAE Related to INP104	Temporal Association of TEAE to Triptan Use Within 24 Hours? (Yes/No)
1	1	Yes	Retinal detachment	Not related	No
2	4	Yes	Status migrainosus	Not related	No
3	1	Yes	Nasal congestion	Possibly	TEAE on day of INP104 use; resolved before triptan use the following day
			Nasal congestion	Possibly	No
			Nasal congestion	Possibly	No
			Nasal congestion	Possibly	No
4	15	Yes	Olfactory test abnormal	Not related	No
5	1	Yes	Hemorrhoids	Not related	No
			Large intestine polyp	Not related	No
			Streptococcal pharyngitis	Not related	No
			Cough	Not related	No
6	2	Yes	Nasal congestion	Probably	No
			Package product-associated injury (finger cut from INP104 packaging)	Definitely	No
7	1	Yes	Epistaxis	Unlikely	2 days after triptan and INP104 use
			Influenza	Not related	No
8	2	No	NA	NA	NA
9	1	No	NA	NA	NA
10	1	No	NA	NA	NA

NA=not applicable; TEAE=treatment-emergent adverse event.

Conclusions

- Although in a small population, no significant safety concerns emerged consequent to off-protocol concomitant use of triptans and INP104 during the STOP 301 study
- Only 2 TEAEs occurred within 24 hours of concomitant triptan-INP104 use: nasal congestion (possibly INP104 related) and epistaxis (unlikely related to INP104 or INP104-triptan use because epistaxis is not anticipated for either product)
- Results reported here provide clinical data on concomitant triptan and INP104 use and can help facilitate the patient-physician dialogue

References

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