Reduced Nausea When Dihydroergotamine Mesylate Is Delivered by INP104

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Introduction

- Migraine is a debilitating condition, and nausea is a frequently associated symptom experienced by migraine patients (~60-95%)[1-5]
- In recent epidemiological studies, nausea was reported as the most bothersome symptom (MBS) by over 28% of respondents, and headache-related nausea was associated with significantly increased headache-related disability[3]
- Nausea associated with migraine can significantly impede migraine management by discouraging or delaying use of oral medications and/or limiting their absorption, resulting in slow onset of action. Consequently, headache severity may be prolonged and worsen, which may increase the duration of disability and disease burden[3,4,6,7]
- Dihydroergotamine mesylate (DHE) has a long, established history as an effective migraine therapy and is well-recognized by physicians[8]
- However, nausea is often reported with high peak plasma concentrations (C_{max}) of DHE by intravenous (IV) administration (30-63% in the literature), and the medication often requires pretreatment with an antiemetic[1,8-11]
- INP104 is a novel, investigational drug-device combination product that targets delivery of DHE to the upper nasal space using a gas-propelled Precision Olfactory Delivery (POD®) device[8,12]
- In a Phase 1 study, it was demonstrated that INP104 resulted in a C_{max} of only 10% that of IV DHE, but ~4-fold that of MIGRANAL® (Bausch Health Companies, Inc. or its affiliates), a currently approved nasal DHE product[11]
  - An antiemetic was given 5–10 minutes prior to dosing[11]
  - A low percentage of INP104 users reported nausea as a treatment-emergent adverse event (TEAE; 3.2%) compared to 9.4% of IV DHE users; all the nausea TEAEs in the IV DHE group were reported to be related to treatment, while none in the INP104 group were reported as related to treatment[11]
- INP104 was also found to be well tolerated in the recent Phase 3, STOP 301 open-label safety study[13]

Objective

- To report the rates of nausea from the long-term, Phase 3, STOP 301 study

Methods

Study Design

- A Phase 3, interventional, open-label, single-group assignment study (STOP 301) assessing the safety, tolerability, and exploratory efficacy of INP104 over 24 and 52 weeks was conducted at 38 US centers (NCT03557333)
- STOP 301 comprised a 4-week screening period, in which patients used their best usual care, 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
- Following the screening period, 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 migraine attacks over 24 weeks, with a subset over 52 weeks

Study Patients

- Patients were adult (18–65 years) males or females with a documented diagnosis of migraine, and displayed 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 (ICHD-3β)
- Patients were generally in good health and presented with no significant medical history or clinical abnormalities at baseline, which included no history of cardiovascular events

Study Outcome Measures

- The primary endpoint was to assess the safety and tolerability of INP104, which included collection of TEAEs from the time of patient consent until the last study follow-up visit, assessment of change in nasal mucosa as detected by nasal endoscopy, and change in olfactory function testing
- All reported TEAEs of nausea among INP104 users were also investigated as part of the safety evaluation
  - Pretreatment with an antiemetic was not required

Results

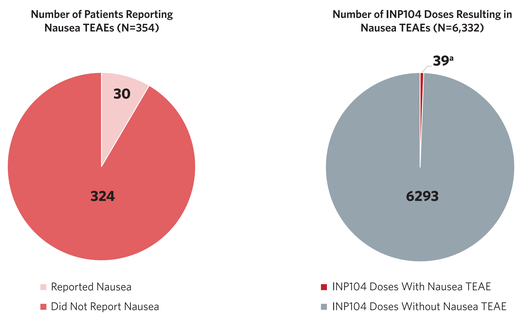
Safety Outcomes

- 354 patients comprised the full safety set (FSS), which was defined as enrolled patients who received ≥1 dose of INP104[13]
- More detailed safety data was previously presented, but briefly, 36.7% of patients reported an INP104-related TEAE during the 24-week treatment period, with nasal congestion being the most common (15%)[13]

Rates of Nausea

- Over 52 weeks, 6,332 doses of INP104 were self-administered, resulting in 39 nausea TEAEs reported by 30 patients (**Figure 1, Table 1**)
  - 0.6% (39/6332) of INP104 doses resulted in nausea (**Figure 1**)
  - Most nausea TEAEs were reported during the 24-week treatment period (28/39 events) and most (34/39 events) were considered related to INP104
  - 72% of nausea events were reported after the first (n=15), second (n=9), or third (n=4) dose of INP104 (28/39 events)

Figure 1. Nausea TEAEs Over 52 Weeks (FSS)



[a]39 nausea TEAEs were reported, which represents 39 INP104 doses.

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

Table 1. Patients With Nausea TEAEs Over 52 Weeks

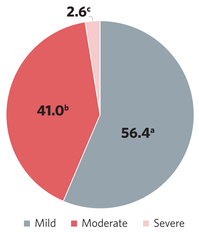
Patient No.	Severity	Duration (Days)	INP104 Doses at Start of TEAE	Related to INP104	INP104 Discontinued	Study Withdrawal
1	Mild	41	9	Possibly	Yes	Yes
2	Mild	143	2	Definitely	No	No
3	Mild	39	82	Probably	No	No
4	Moderate	2	2	Probably	No	No
	Moderate	2	2	Probably	No	No
	Moderate	2	2	Probably	No	No
	Moderate	2	3	Probably	No	No
	Moderate	2	4	Probably	Yes	No
5	Mild	144	1	Probably	No	No
6	Mild	1	1	Possibly	No	No
7	Moderate	56	1	Definitely	No	No
8	Moderate	87	6	Probably	No	No
9	Moderate	1	1	Possibly	No	No
10	Moderate	14	2	Definitely	Yes	Yes
11	Mild	57	1	Possibly	No	No
12	Mild	2	7	Unlikely	No	No
13	Mild	1	1	Definitely	No	No
	Mild	1	2	Definitely	Yes	Yes
14	Mild	2	3	Not related	No	No
15	Severe	1	1	Possibly	No	No
16	Mild	2	23	Not related	No	No
17	Moderate	100	10	Probably	No	No
18	Mild	Ongoing[a]	12	Probably	No	No
19	Moderate	360	1	Probably	No	No
20	Moderate	147	1	Probably	No	No
21	Mild	136	2	Possibly	No	No
22	Mild	1	1	Definitely	No	No
	Mild	1	2	Definitely	No	No
	Mild	1	3	Definitely	No	No
23	Moderate	Ongoing[a]	6	Not related	No	No
24	Mild	127	1	Probably	No	No
25	Moderate	1	14	Probably	No	No
26	Moderate	6	1	Probably	No	No
27	Mild	2	13	Not related	No	No
28	Moderate	2	1	Definitely	No	No
29	Mild	79	1	Possibly	No	No
30	Mild	1	1	Probably	No	No
	Mild	1	2	Probably	No	No
	Mild	1	3	Probably	No	No

[a]The TEAE was ongoing at the last contact with the patient.

TEAE = treatment-emergent adverse event.

- Most nausea TEAEs were mild (n=22) or moderate (n=16) in severity (**Figure 2, Table 1**)
  - 1 patient reported a nausea TEAE as severe (after the first dose), but self-administered another 19 doses and completed the study without further reports of nausea
- INP104-related nausea events were not particularly confined to those patients who reported nausea as their MBS at baseline
  - At baseline, nausea was reported as an MBS by 16.4% (58/354) of patients (24-week FSS)
  - Of the 30 patients who reported a nausea TEAE, 28% (7/30) reported having nausea as their MBS at baseline
- A small proportion of patients discontinued treatment (n=4; 1.1%) or withdrew from the study (n=3; 0.8%) due to nausea
- 3.1% (n=11) of patients used an antiemetic or antinauseant (24-week FSS)

Figure 2. Percentage of Nausea TEAEs by Severity Over 52 Weeks (FSS)



[a]n/N=22/39, [b]n/N=16/39, [c]n/N=1/39. Note: N is the number of nausea TEAEs.

TEAE = treatment-emergent adverse event.

Conclusions

- Nausea is widely reported to occur after IV administration of DHE[1,8-11]
- In the STOP 301 trial, pretreatment with an antiemetic was not required and less than 1% of INP104 doses resulted in nausea
- Further, only 0.8% of dosed patients withdrew from the trial because of a nausea TEAE
- The lower rates of nausea reported in this study may be due to the lower C_{max} observed with INP104 compared to IV DHE[11]
- This study demonstrates the possibility for a lower incidence of the self-limiting TEAE of nausea, with the potential to offer a viable delivery alternative to DHE users

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