Assessing the Comparative Efficacy of INP104 for Acute Treatment of Migraine Attacks: A Matching-Adjusted Indirect Comparison

Joshi S[1], Aurora SK[2], Wang S[3], Park JE[3], Wu P[3], Keeping ST[3], Bariahtaris S[2], Shrewsbury S[2]
[1]Dent Neurologic Institute, Amherst, NY, USA, [2]Impel NeuroPharma, Inc., Seattle, WA, USA, [3]Precision HEOR, Vancouver, BC, Canada

BACKGROUND

- Triptans are the most commonly prescribed drug class for the acute treatment of migraine, however 30-40% of patients with migraine do not respond adequately to triptans.[1]
- Other options include: calcitonin-gene related peptide (CGRP) antagonists (known as gepants), a new class of drugs that includes two oral agents, rimegepant and ubrogepant; a 5-HT1F receptor agonist, lasmiditan; and dihydroergotamine (DHE) nasal spray.
- Traditional DHE nasal spray primarily delivers drug to the lower nasal space, and is hindered by poor bioavailability and inconsistent response on pain-related outcomes. Therefore, an unmet need exists for more effective delivery of DHE that would be fast acting, and provide consistent and durable efficacy.[2]
- INP104 is a novel, self-administered drug-device combination product using a Precision Olfactory Delivery (I123 POD®) device to target delivery of dihydroergotamine mesylate to the upper nasal space.
- The phase 3, multicenter, 24/52-week, open-label STOP 301 study of INP104 enrolled patients with a documented diagnosis of migraine and at least two attacks/month during the previous six months (NCT03557333).
- In order to understand the comparative efficacy of INP104 versus other options for triptan-insufficient responders, relative treatment effects between comparator interventions need to be estimated.
- Since STOP 301 was a single-arm clinical trial, a traditional network meta-analysis would not be feasible; however, the availability of individual patient data (IPD) from the STOP 301 trial makes it possible to conduct a population-adjusted indirect comparison, a standard method to conduct indirect head-to-head comparisons.[3]

OBJECTIVE

To estimate the comparative efficacy for the acute treatment of migraine in terms of pain-related and symptom-related clinical outcomes with INP104 versus rimegepant, ubrogepant and traditional DHE nasal spray via a matching-adjusted indirect comparison (MAIC).

METHODS

Evidence base

- A systematic literature review (SLR) of clinical trials for the acute treatment of migraine was conducted to identify studies of DHE nasal spray and oral CGRP receptor antagonists.
- Data sources were MEDLINE (including Epub ahead of print), Embase, and the Cochrane Controlled Register of Trials (inception to May 2020) and relevant conference proceedings from 2018 to 2019.
- Abstracts and full-text articles were reviewed by two independent reviewers according to study eligibility criteria (**Table 1**). Data on key study characteristics, intervention details, patient characteristics and migraine-related outcomes were extracted

Matching-adjusted indirect comparison

- An MAIC approach was used to compare pain-related and symptom-related outcomes with INP104 versus rimegepant, ubrogepant and DHE nasal spray in a standard pairwise framework.
- IPD were available from STOP 301's full safety data set (n=354), of which 343 patients, who had outcome data and met the key inclusion criteria of the comparator studies, were eligible for the analysis.
- A logistic propensity score model was used to estimate weights for each patient in STOP 301 in order to adjust for differences between their characteristics and those of the populations in the comparator studies.
- Safety outcomes in STOP 301 were evaluated for multiple attacks over 24 and 52 weeks, whereas in comparators' trials, safety outcomes were assessed after either a single migraine or two migraines; given these differences, no comparisons of safety were conducted. Lasmiditan was not included in the MAIC due to the safety concerns which limit driving and other activities for 8 hours after dosing.
- Relevant effect modifiers and prognostic variables for adjustment were determined based on consultation with clinical experts and data availability i.e. characteristics had to be reported in both STOP 301 and the comparator trial(s). After review, the following factors were matched in the analyses: migraine history, use of concomitant preventative medication, and prior triptan use.
- Treatment comparisons were made based on differences between the weighted outcomes from STOP 301 and the observed outcomes from the comparator studies. Note: Baseline characteristics and outcomes were pooled by comparator when multiple studies were available. Logistic regression models were used to model treatment outcomes with relative treatment effects expressed as odds ratios (ORs) for INP104 relative to each comparator.

RESULTS

Table 1. Study eligibility criteria

Criteria	Description
Population	Adult patients (≥18 years) diagnosed with migraine (with or without aura)
Interventions	DHE nasal spray: • INP104 • Migranal® Oral CGRP antagonists: • rimegepant (75mg) • ubrogepant (50/100mg)
Comparators	• Placebo or usual care • Any intervention of interest • Any treatment that facilitates an indirect comparison
Outcomes	• Pain relief at 2 hours • Pain freedom at 2 hours • Sustained pain freedom at 2-24 and 2-48 hours • Freedom from most bothersome symptom at 2 hours • Freedom from individual migraine symptoms (photophobia, phonophobia, nausea, vomiting) at 2 hours • Treatment-emergent adverse events • Any adverse event reported by at least 5% of a trial arm
Study design	• Randomized controlled trials • Single-arm non-randomized controlled trials

Figure 1: Matching-adjusted indirect comparison of pain-related outcomes for INP104 compared with rimegepant, ubrogepant and DHE nasal spray*

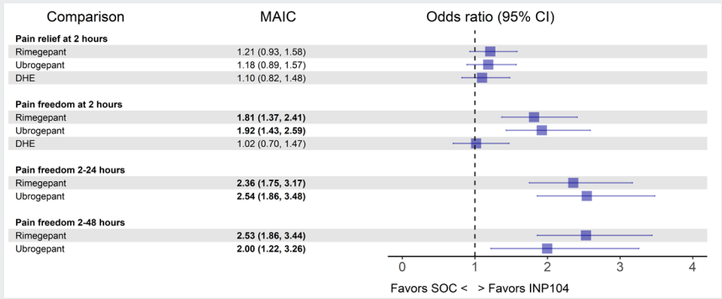
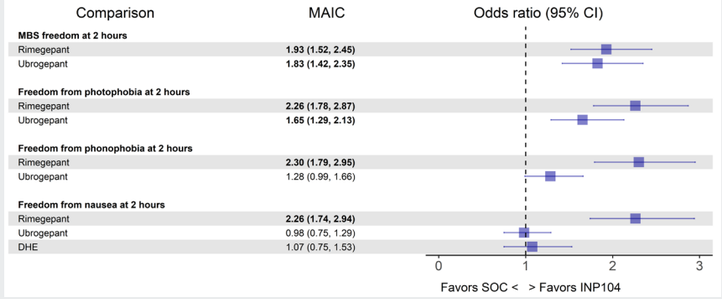


Figure 2: Matching-adjusted indirect comparison of symptom-related outcomes for INP104 compared with rimegepant, ubrogepant and DHE nasal spray**



Bold numbers indicate the odds ratios that are statistically significant (p<0.05). *Sustained pain freedom from 2-24 and 2-48 hours were not reported in studies of DHE nasal spray. **MBS freedom at 2 hours and freedom from photophobia and phonophobia at 2 hours were not reported in studies of DHE nasal spray. Abbreviations: CI, confidence interval; DHE, dihydroergotamine; MAIC, matching-adjusted indirect comparison; MBS, most bothersome symptom; SOC, standard of care

Table 2. Baseline patient characteristics of included studies in the MAIC

Trial		Characteristics, n (%)					
		N	Age mean (SD)	Male	Migraine history (year) mean (SD)	Use of concomitant preventive medication	Oral triptan use
INP 104	STOP 301 (1.45mg)	354	41.3 (11.1)	50 (14.1)	19.5 (12.1)	62 (17.5)	100 (28.2)
rimegepant	Study 301 (75mg)	543	41.9 (12.3)	79 (14.5)	--	--	--
	Study 302 (75mg)	537	40.2 (11.9)	58 (10.8)	--	89 (16.6)	--
	Study 303 (75mg)	669	40.3 (12.1)	101 (15.0)	--	--	--
	Marcus 2013 (75mg)	91	38.5 (11.9)	10 (11.0)	--	--	--
ubrogepant	ACHIEVE I (100mg)	485	40.6 (12.0)	67 (13.8)	18.9 (12.3)	100 (22.3)	202 (41.6)
	ACHIEVE I (50mg)	466	40.1 (11.7)	48 (10.3)	17.9 (11.9)	96 (22.7)	205 (44.0)
	ACHIEVE II (50mg)	488	41.2 (12.5)	44 (9.0)	18.1 (12.3)	116 (25.0)	191 (39.1)
	Voss 2016 (100mg)	102	41.9 (11.0)	12 (11.8)	--	--	64 (62.7)
	Voss 2016 (50mg)	106	40.7 (12.3)	14 (13.2)	--	--	68 (64.2)
	NCT01657370 (100mg)	27	--	9 (33.3)	--	--	--
	NCT01657370 (50mg)	28	--	2 (7.1)	--	--	--
Traditional DHE nasal sprays	Gallagher 1996 (1-2mg)	348	40.0 (--)	--	--	--	--
	Touchon 1996 (1-2mg)	133	42.0 (10.0)	22 (16.5)	Median: 17.0	34 (26.0)	--
	Boureau 2000 (1-2mg)	183	40.0 (11.0)	28 (15.3)	--	--	--

Abbreviations: DHE, dihydroergotamine; SD, standard deviation.

RESULTS

- The SLR identified 15 unique randomized controlled trials (RCTs) that assessed rimegepant, ubrogepant and traditional DHE nasal spray, and 11 of these trials were included in the MAICs after an assessment of the degree of overlap between these studies and STOP 301.
- The analysis set for the MAIC comprised IPD for INP104 and data for rimegepant (Study 301, Study 302, Study 303, and Marcus 2013), ubrogepant (ACHIEVE I, ACHIEVE II, Voss 2016, NCT01657370), and DHE nasal spray (Gallagher 1996, Touchon 1996, and Boureau 2000).
- Key patient characteristics from STOP 301 and the comparator studies are presented in **Table 2**.

Matching-adjusted indirect comparison

- INP104 improved pain-related outcomes relative to both rimegepant and ubrogepant, with a statistically significant increase in the probability of achieving pain freedom at 2 hours (rimegepant OR: 1.81 [95%CI: 1.37-2.41]; ubrogepant OR: 1.92 [95%CI: 1.43-2.59]), as well as sustained pain freedom from 2 to 24 hours (rimegepant OR: 2.36 [95%CI: 1.75 -3.17]; ubrogepant OR: 2.54 [95%CI: 1.86-3.48]) and 2 to 48 hours (rimegepant OR: 2.53 [95%CI: 1.86-3.44]; ubrogepant OR: 2.00 [95%CI: 1.22-3.26]) (**Figure 1**).
- Although favorable outcomes were also seen for INP104 for pain relief at 2 hours, these comparisons did not show statistically significant differences compared to the comparator interventions.
- Of the eight outcomes of interest, there was no data from clinical studies of traditional DHE nasal spray on five of these outcomes. Pain freedom at 2 hours was reported in only one of the three DHE nasal spray studies (Touchon 1996, OR: 1.02 [95%CI: 0.70-1.47]).
- For symptom-related outcomes, INP104 also showed statistically significant higher rates of freedom from most bothersome symptom at 2 hours (rimegepant OR: 1.93 [95%CI: 1.52-2.45]; ubrogepant OR: 1.83 [95%CI: 1.42-2.35]) and for freedom from photophobia at 2 hours (rimegepant OR: 2.26 [95%CI: 1.78-2.87]; ubrogepant OR: 1.65 [95%CI: 1.29-2.13]) when compared to the two gepants (**Figure 2**).
- For freedom from other individual symptoms at 2 hours such as phonophobia and nausea, only comparisons with rimegepant were statistically significant (phonophobia OR: 2.30 [95%CI: 1.79-2.95]; nausea OR: 2.26 [95%CI: 1.74, 2.94]).

DISCUSSION, LIMITATIONS AND CONCLUSIONS

- An unanchored population-adjusted indirect comparison is a standard approach to estimate the relative treatment effects between studies that do not share a common comparator arm. This type of analysis presumes that all relevant prognostic factors and effect modifiers have been accounted for in the model.
- The comparisons were also limited due to differences in the definition and availability of outcomes reported in the comparator studies. For example, comparisons with DHE nasal spray were not feasible for the majority of the outcomes due to lack of reporting, and safety outcomes could not be assessed due to differences with respect to the number of attacks evaluated in any of the comparator studies versus STOP 301.
- Among adult patients with migraine, compared with oral CGRP antagonists, treatment with INP104 led to significantly greater rates of pain freedom at 2 hours, sustained pain freedom at 24 and 48 hours, and reduction of MBS at 2 hours.

REFERENCES

1. Viana M, et al. Cephalalgia. 2013;33:891-896.
2. Silberstein SD, Shrewsbury SB, Hoekman J. Dihydroergotamine (DHE) - Then and Now: A Narrative Review. *Headache.* 2020;60(1):40-57.
3. Signorovitch JE, et al. Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research. Value in Health. 2012;15:940-947.