Safety, Tolerability and Comparative Bioavailability of a Novel Intranasal DHE Product (INP104)

Shrewsbury SB,[1] Jeleva M,[1] Satterly KH,[1] Lickliter J,[2] Hoekman J[1]

[1]Impel NeuroPharma, Seattle, WA; [2]Nucleus Network, Melbourne, Australia

Introduction

Migraine remains a serious cause of disability.[1,2] Up to 42% of migraineurs still report dissatisfaction with their treatment,[3] over a third (37%) with the speed of effect and half (50%) were dissatisfied that their pain recurred.

Dihydroergotamine (DHE) is effective for acute migraine and is recommended as an alternative to triptans.[4] DHE is available in multiple formulations: SC, IM, limited by slow absorption; nasal spray formulations limited by low bioavailability, and IV administration limited by difficulty self-administering and high rates of adverse events.[5] MAP Pharmaceuticals developed an inhaled DHE product (MAP0004, Levadex®, Semprana®) with encouraging PK[6] which was successful in clinical studies at relieving migraine[7,8] but the NDA was rejected three times by 2014 due to CMC issues[9] which remained unresolved in 2017[10]. Separating drug (DHE) from propellant (HFA) and delivering to the upper nasal cavity may avoid these issues and provide an improved route of administration for DHE.

Drug absorption via the nasal cavity is an underutilized route for systemic drug delivery, primarily because of difficulty with achieving significant and consistent absorption through the ciliated, pseudostratified columnar (respiratory) epithelium in the lower nasal space.[11] The Precision Olfactory Delivery or POD® device is a nasal drug delivery platform designed to deliver drugs to the upper turbinate region and upper nasal cavity in a consistent and predictable manner for improved biodistribution, which should yield improved clinical outcomes.[12,13]

INP104 is an innovative drug-device combination product that consists of a liquid DHE formulation administered by the I123 POD device that addresses the low bioavailability and high variability in nasal administration observed with traditional nasal sprays. By delivering the drug to the upper nasal cavity, INP104 may improve systemic availability and reduce reported adverse events of taste disturbance and avoid drug dripping out of the nose or into the nasopharynx after nasal administration, reported with traditional nasal sprays.

Impel NeuroPharma is developing INP104 to provide migraine patients with a non-injectable and user-friendly DHE delivery option. This study compared the safety, tolerability, and bioavailability of DHE following single dose administration of INP104 1.45 mg to that of IV DHE 1.0 mg and DHE nasal spray 2.0 mg in healthy adult subjects.

Methods

Study Design

- Phase 1, open-label, randomized, single-dose, 3-period, 3-way crossover study.
- Subjects were screened up to 21 days before study dosing and were randomized in a 3-treatment, 3-period, balanced crossover study of 6 sequences (**Figure 1**) with a 7-day washout between treatments.

Figure 1. Treatment Sequences

	Treatment		
Sequence	1	2	3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A

A) INP104 1.45 mg
B) DHE IV injection 1.0 mg
C) DHE Nasal Spray 2.0 mg

Study Subjects

- Adults aged 18 to 55 years, body mass index (BMI) of 18-32 kg/m^2, and in good general health with no significant medical history
- Subjects were excluded for a recent history of migraine (at least 1 attack in the past 6 months or receiving antimigraine prophylaxis) and its variants including hemiplegic migraine and basilar migraine (migraine with brain stem aura).
- Subjects with a known hypersensitivity to ergot alkaloids or metoclopramide were also excluded.

Study Treatments

- INP104 was self-administered with the dose split between nostrils, with one spray in each nostril, delivering a total of 1.45 mg DHE.
- IV DHE 1.0 mg was administered in a volume of 1 mL over a 1-minute infusion.
- DHE nasal spray 2.0 mg was self-administered by one spray to each nostril, followed 15 minutes later by an additional spray to each nostril (4 sprays total).
- Pretreatment with an antiemetic (metoclopramide 10 mg, delivered by slow IV push over 1-2 min, 5 to 10 minutes prior to DHE dosing) was given in all three treatment arms.

Study Assessments

- Medical history and physical examination, 12-lead electrocardiogram (ECG), vital signs (blood pressure, heart rate, respiratory rate, temperature), clinical laboratory (hematology, chemistry, urinalysis), and adverse events were assessed.
- Blood samples were collected within 15 minutes prior to dosing and at 5, 10, 20, 30, 40, 50 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 8, 12, 24, 36 and 48 hours relative to the start of each dosing to determine DHE and 8'OH-DHE plasma concentrations.
- Quantitative liquid chromatography, tandem mass spectrometry was used to measure plasma levels of DHE and 8'OH-DHE.
- Pharmacokinetic parameters for DHE and 8'OH-DHE were determined.

Statistical Analysis

- Analysis of variance (ANOVA) with effects for sequence, subject nested within sequence, period, and treatment were performed on the ln-transformed DHE (and 8'OH-DHE) AUC_{0-t}, AUC_{0-inf}, and C_{max}.
- Least squares mean (LSM), the difference between treatment LSM, and the standard error associated with the difference were calculated (DHE only).
- Ratios of geometric means for DHE were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and expressed as a percentage relative to the reference treatment (INP104 [test]/ DHE for IV injection [reference] and INP104 [test]/ DHE nasal spray [reference]).
- 90% confidence intervals (CI) were obtained for the ratio of DHE geometric means for AUC_{0-t}, AUC_{0-inf}, and C_{max}.
- Phoenix WinNonlin V6.3 (Pharsight Corporation, Mountain View, CA, USA) was used for analyses.

Results

Subject Disposition and Baseline Characteristics

- 38 subjects were screened, randomized, and enrolled in the study (intent-to-treat population [ITT]).
- 2 subjects withdrew before receiving any investigational product (one after receiving IV metoclopramide); thus, 36 received at least one dose of any investigational study treatment and were included in the safety population.
- Within the ITT population, the reasons for study discontinuation included withdrawal of consent (n=5 [13.2%]), adverse events (n=3 [7.9%]), physician's decision (n=1 [2.6%]), and non-compliance / protocol violation (n=1 [2.6%]).
- The PK population consisted of 27 subjects who received all three treatments and provided a sufficient number of blood samples for non-compartmental analysis.
- Demographic characteristics for the 38 subjects in the ITT population were consistent across the six treatment sequences (**Table 1**).

Table 1. Baseline Characteristics (ITT Population)

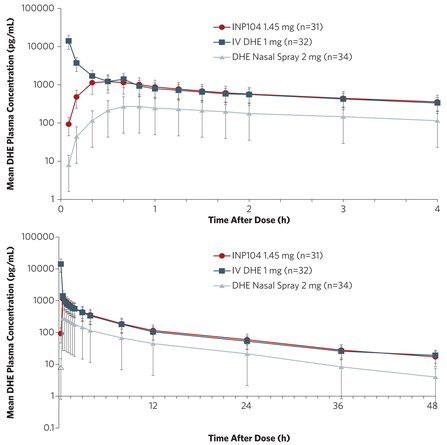
Order of Treatment	All	ABC	ACB	BAC	BCA	CAB	CBA
Number of Subjects	38	7	6	6	7	6	6
Male:female	19:19	6:1	2:4	2:4	3:4	2:4	4:2
Age, years[a]	28.9 ± 6.1	28.4 ± 6.2	33.3 ± 9.2	28.0 ± 2.0	30.0 ± 6.2	25.8 ± 3.9	28.0 ± 5.9
Range, years	18 – 47	18 – 39	21 – 47	25 – 31	23 – 40	22 – 32	18 – 34
Race, n (%)							
White	24 (63.2)	2 (28.6)	4 (66.7)	5 (83.3)	4 (57.1)	5 (83.3)	4 (66.7)
Asian	10 (26.3)	4 (57.1)	2 (33.3)	0	1 (14.3)	1 (16.7)	2 (33.3)
Black or African American	3 (7.9)	0	0	1 (16.7)	2 (28.6)	0	0
Other	1 (2.6)	1 (14.3)	0	0	0	0	0
Weight, kg[a]	70.2 ± 11.1	75.3 ± 13.7	68.4 ± 8.4	74.5 ± 11.7	66.6 ± 10.8	66.8 ± 12.7	69.6 ± 9.6
Range	52.0 – 96.2	53.9 – 96.2	58.6 – 82.3	55.1 – 89.3	52.0 – 83.1	52.5 – 85.0	55.7 – 84.0
Body mass index, kg/m^2[a]	23.3 ± 3.2	24.8 ± 3.7	23.9 ± 4.3	23.6 ± 3.2	22.5 ± 3.2	23.1 ± 3.0	22.1 ± 2.3
Range	18.4 – 31.8	19.9 – 29.7	19.8 – 31.8	18.8 – 27.6	18.4 – 26.8	20.7 – 28.7	18.8 – 25.1

[a]Mean ± standard deviation

Pharmacokinetic Analysis

- Following administration of INP104 1.45 mg, DHE plasma levels rapidly increased and were comparable to IV DHE 1.0 mg by 30 minutes, which was the T_{max} for INP104, and then closely followed the levels of IV DHE to 48 hours (**Figure 2**).
- By 20 minutes, plasma levels following INP104 administration were >92% of C_{max}.

Figure 2. Mean Plasma Concentrations for DHE From 0-4 h (top) and 0-48 h (bottom) [Safety Population]



- DHE AUC was comparable for INP104 and IV DHE (**Table 2**).
- Plasma DHE half lives were similar for the 3 products

Table 2. Summary of Pharmacokinetic Parameters for DHE (PK Population)

	Mean ± Standard Deviation Coefficient of Variation (%)		
	INP104 1.45 mg (n=27)	IV DHE 1.0 mg (n=27)	DHE Nasal Spray 2.0 mg (n=27)
C_{max}, pg/mL	1281 ± 682 53.3	14620 ± 4906 33.6	329 ± 261 79.4
AUC_{0-last}, h*pg/mL	5807 ± 2623 45.2	6967 ± 1095 15.7	1999 ± 1433 71.7
AUC_{0-inf}, h*pg/mL	6153 ± 2721 44.2	7381 ± 1139 15.4	2208 ± 1488 67.4
T_{max}, h	0.5 ± 0.14 27.6	0.1 ± 0.01 7.6	0.8 ± 0.30 36.0
$T_{1/2}$, h	11.9 ± 2.9 24.0	14.5 ± 3.6 24.7	10.6 ± 3.0 28.4
K_{el}, L/h	0.061 ± 0.013 21.3	0.051 ± 0.014 26.6	0.070 ± 0.026 36.4
CL/F, L/h	280 ± 238 85.1	119 ± 19 15.9	1208 ± 869 72.0
Vz/F, L	4546 ± 2994 65.9	2505 ± 769 30.7	16370 ± 9122 55.7

C_{max} = maximum observed plasma concentration; T_{max} = time to maximum plasma concentration; AUC_{0-last} = area under the concentration-time curve from time 0 to last measurable concentration; AUC_{0-inf} = area under the drug concentration-time curve from time 0 to infinity; K_{el} = apparent terminal elimination rate constant; $T_{1/2}$ = apparent elimination half-life; CL/F = apparent clearance; Vz/F = apparent volume of distribution at the terminal phase

- The ratio of geometric means for C_{max} and AUC_{0-inf} was 0.08 and 0.74 for INP104: IV DHE, and 4.45 and 3.08 for INP104: DHE nasal spray (**Table 3**).
- INP104 displayed more consistent delivery compared to DHE nasal spray based on the lower inter-subject %CV for C_{max}.

Table 3. Geometric Mean and Geometric Mean Ratios, Intrasubject CV%, and Confidence Intervals for Comparison of INP104 vs. DHE Nasal Spray and INP104 vs. IV DHE (PK Population)

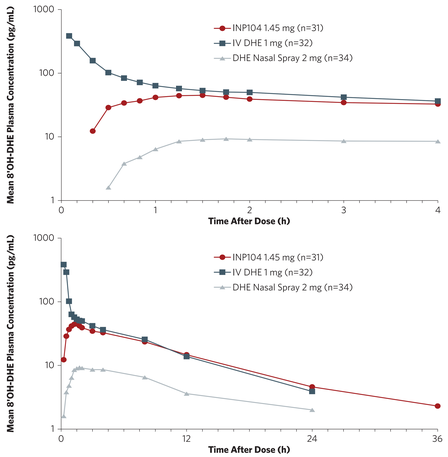
	INP104	DHE Nasal Spray	Ratio of Geometric Means for INP104/DHE Nasal Spray, (CV %)	One-sided 90% Confidence Intervals for Ratio of Geometric Means
C_{max}, pg/mL	1130.7	254.0	4.451 (72.0)	3.265, 6.067
AUC_{0-last}, h*pg/mL	5193.6	1575.9	3.296 (69.9)	2.436, 4.459
AUC_{0-inf}, h*pg/mL	5562.3	1808.8	3.075 (62.0)	2.340, 4.042
	INP104	**IV DHE**	**Ratio of Geometric Means for INP104/IV DHE**	**One-sided 90% Confidence Interval for Ratio of Geometric Means**
C_{max}, pg/mL	1114.6	14140.3	0.079 (55.2)	0.062, 0.101
AUC_{0-last}, h*pg/mL	5119.2	6978.2	0.734 (49.8)	0.586, 0.919
AUC_{0-inf}, h*pg/mL	5485.1	7392.4	0.742 (46.6)	0.600, 0.918

- Mean plasma concentration profiles for 8'OH-DHE were calculated (**Figure 3**) and compared post hoc and found to be consistent with the parent compound, DHE, but were at least 20-30 fold lower after both INP104 and IV DHE administration (**Table 4**).

Table 4. Summary of Pharmacokinetic Parameters for 8'OH-DHE (Safety Population)

	Mean (Standard Deviation)		
	INP104 1.45 mg	IV DHE 1.0 mg	DHE Nasal Spray 2.0 mg
No. with data	29	31	10
C_{max}, pg/mL	55.9 ± 26.2	387.4 ± 112.6	38.8 ± 15.4
AUC_{0-last}, h*pg/mL	415 ± 463	500.9 ± 367.1	351.3 ± 354.0
T_{max}, h	1.4 ± 0.7	0.1 ± 0.4	2.3 ± 1.3
No. with data	20	25	4
AUC_{0-inf}, h*pg/mL	1137 ± 625	934.3 ± 501.7	1309 ± 415
$T_{1/2}$, h	16.9 ± 9.6	10.5 ± 4.8	18.8 ± 4.2
K_{el}, L/h	0.06 ± 0.052	0.08 ± 0.045	0.04 ± 0.01
CL/F, L/h	1748 ± 1700	1263 ± 757	1498 ± 651
Vz/F, L	29550 ± 9792	15580 ± 4464	38240 ± 8817

Figure 3. Mean Plasma Concentrations for 8'OH-DHE From 0-4 h (top) and 0-36 h (bottom)



Tolerability

- 98 adverse events occurred in 29 (80.6%) subjects, all of mild or moderate severity except one of severe intensity that was also an SAE (**Table 5**).
- The one serious adverse event (considered not related of acute myeloid leukemia) was reported after the subject had completed all three treatments, with INP104 being the last treatment received.
- The frequency of treatment-emergent adverse events (TEAEs) was roughly equivalent following administration of INP104 and DHE nasal spray, whereas the frequency increased approximately 1.5-fold following administration of IV DHE.
- Across all 3 treatment groups, 14 (38.9%) participants reported TEAEs that were possibly related to study drug, with a higher incidence following IV DHE (11, [34.4%]) compared to INP104 (6, [19.4%]) and DHE nasal spray (4, [11.8%]).
- All TEAEs reported as probably related to the study drug occurred in 5 (15.6%) participants following administration of IV DHE.

Table 5. Summary of Treatment-Emergent Adverse Events (TEAE) and Incidence of TEAEs Occurring in at Least 2 Participants in Any Treatment Group (Safety Population)

	Number (%) of Subjects		
	INP104 (n=31)	IV DHE (n=32)	DHE Nasal Spray (n=34)
Any TEAE event	15 (48.4)	21 (65.6)	14 (41.2)
Discontinued for AE	0	0	1 (2.9)
Serious TEAE	1 (3.2)	0	0
Possibly Related TEAE	6 (19.4)	11 (34.4)	4 (11.8)
Probably Related TEAE	0	5 (15.6)	0
Somnolence	4 (12.9)	9 (28.1)	5 (14.7)
Headache	2 (6.5)	6 (18.8)	3 (8.8)
Dizziness	0	5 (15.6)	1 (2.9)
Nausea	1 (3.2)	3 (9.4)	1 (2.9)
Vomiting	0	2 (6.3)	1 (2.9)
Diarrhea	0	0	2 (5.9)
Myalgia	2 (6.5)	1 (3.1)	0
Musculoskeletal stiffness	0	0	2 (5.9)
Restlessness	0	4 (12.5)	1 (2.9)
Catheter site related reaction	2 (6.5)	0	0
Upper respiratory tract infection	0	0	2 (5.9)
Hot flush	0	3 (9.4)	0

Summary

- INP104 DHE delivered intranasally by the POD device, produced plasma DHE exposure that was comparable to IV DHE by and after 30 minutes.
- INP104 displayed substantially higher and more consistent plasma DHE exposure compared to DHE nasal spray.
- The incidence of adverse events with INP104 1.45 mg was lower than with IV DHE 1.0 mg and generally comparable to DHE nasal spray 2.0 mg.
- Despite pre-treatment with an antiemetic, vomiting was reported by 2 (6.3%) subjects with IV DHE, 1 subject (2.9%) with DHE nasal spray (34 hours after dosing and unrelated to treatment) but no subjects with INP104.
- In conclusion, INP104 provides a PK profile of DHE that is comparable to IV DHE, except for a lower plasma C_{max}, a favorable reduction that should result in a lower incidence of AEs associated with DHE and similar to that seen with MAP0004 that was developed for the same indication (but has not won approval). INP104 displayed a rapid T_{max} of 30 minutes, substantially faster than DHE nasal spray and low variability in plasma DHE concentrations indicating consistent delivery.
- It is anticipated that the DHE levels observed following INP104 delivery will provide rapid, durable and predictable pain control without the use of a needle.
- Future studies are planned with migraine patients to support INP104 as an effective, reliable, safe and patient friendly treatment for acute migraine.

References

1. Barch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache* 2015 Feb;55(2): 356.
2. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* 2017;16(11):877-897.
3. Bigal M, Rapoport A, Aurora S, et al. Satisfaction with current migraine therapy: Experience from 3 centers in US and Sweden. *Headache*. 2007;47:475-479.
4. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3-20.
5. Silberstein SD, Kori SH. Dihydroergotamine: a review of formulation approaches for the acute treatment of migraine. *CNS Drugs*. 2013;27:385–94.
6. Shrewsbury SB, Cook RO, Taylor G, Edwards C, Ramadan NM. Safety and pharmacokinetics of dihydroergotamine mesylate administered via a novel (Tempo®) inhaler. *Headache* 2008;48:355-367.
7. Aurora SK, Rozen TD, Kori SH, Shrewsbury SB. A randomized, double blind, placebo-controlled study of MAP0004 in adult patients with migraine. *Headache* 2009;49:826–837.
8. Aurora SK, Silberstein SD, Kori SH, Tepper SJ et al. MAP0004, orally inhaled DHE: A randomized , controlled study in the acute treatment of migraine. *Headache* 2011;51:507-517.
9. https://www.fiercebiotech.com/regulatory/fda-hands-out-its-third-rejection-for-allergan-s-migraine-drug-semprana.
10. https://www.biospace.com/article/allergan-r-and-d-chief-company-forges-ahead-with-migraine-treatments/ .
11. Lochhead J, Thorne R. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev.* 2012;64:614-28.
12. Hoekman J, Brunelle A, Hite M, et al. Usability and tolerability study in human subjects with a novel precision olfactory delivery (POD) device. Presented at AAPS Annual Meeting, November 10-14, 2013, San Antonio, TX.
13. Hoekman JD, Hu RJY. Enhanced analgesic responses following preferential delivery of morphine and fentanyl to the olfactory epithelium. *Anesth Analg.* 2011;113(3):641-51. 2011;113(3):641-51.

Presented at the American Headache Society 60th Annual Meeting, June 28–July 1, 2018, San Francisco, CA