STOP 101: A Phase 1, Randomized, Open-Label, Comparative Bioavailability Study of INP104, Dihydroergotamine Mesylate (DHE) Administered Intranasally by a 1123 Precision Olfactory Delivery (POD®) Device, in Healthy Adult Subjects

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Objective. — Investigate the safety and pharmacokinetics (PK) of INP104, intranasal dihydroergotamine mesylate (DHE) administered via a Precision Olfactory Delivery (POD®) device, (Impel NeuroPharma, Seattle, WA) vs intravenous (IV) DHE and DHE nasal spray (Migranal®) in healthy adult subjects.

Methods. — This was a Phase 1, open-label, randomized, single-dose, 3-period, 3-way crossover study. Subjects received a single dose of A) INP104 1.45 mg (a drug-device combination product composed of DHE and the 1123 POD device); B) DHE 45® Injection (IV) 1.0 mg; and C) DHE by Migranal® Nasal Spray 2.0 mg. Plasma levels of DHE and the major bioactive metabolite, 8′OH-DHE, were measured, and PK parameters were determined for both. Comparative bioavailability (BA) was assessed by calculating the ratio of the geometric means between treatments for C max and AUC 0-inf on the ln-transformed data. Safety was assessed from adverse events, vital signs, electrocardiograms, and clinical laboratory values.

Results. — Thirty-eight subjects were enrolled, 36 were dosed with at least 1 IP and 27 were included in the evaluation of PK and comparative BA. DHE plasma levels following INP104 1.45 mg administration reached 93% of C max by 20 minutes and were comparable to IV DHE 1.0 mg by 30 minutes (1219 ng/mL for INP104 vs 1224 ng/mL for IV DHE), which was the T max for INP104. From 30 minutes onward, DHE levels for INP104 closely matched those of IV DHE to 48 hours, the last time point measured. In comparison, the C max for Migranal was 299.6 pg/mL (approximately 4-fold less than INP104) and occurred at 47 minutes, 17 minutes later than INP104. Plasma DHE AUC 0-inf for INP104, IV DHE, and Migranal, respectively, were 6275, 7490, and 2199 h•pg/mL.

Conclusion. — INP104 met the predefined statistical criteria for comparative bioavailability with IV DHE and Migranal. The shorter time to reach C max and at 4 times the plasma concentration of DHE in comparison to Migranal combined with a favorable tolerability profile support further investigation of INP104 as an effective, well tolerated, and non-invasive treatment for acute episodic migraine.

Key words: bioavailability, dihydroergotamine, intranasal, migraine, pharmacokinetics

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INTRODUCTION

Migraine in 2018 remains a serious cause of disability, affecting predominantly young adults in their most productive years when they are aged between 30 and 39,1,3 with approximately 14% or 1 in 7 of adults in the United States affected (migraine or severe headache),1 and is the second leading cause of years lived with disability (YLDs), a key metric in measuring the economic impact of diseases.1

On a national scale, visits to the emergency room (ER) for migraine are estimated to cost between $646 million and $1.94 billion5 each year in the United States, and combined with headache, migraine was the fourth leading cause of ER visits4 in 2009–2010, accounting for 3.1% of all ER visits.5 More than one-third of subjects report 4 or more acute episodes per month.6 Nearly half, 42%, of migraineurs, still report dissatisfaction with the degree of relief their treatment provides; over a third (37%) with the speed of effect, half (50%) that their pain recurred, and 42% with the need for a second dose.7 Thus, the disease remains a significant challenge to the health care system.

Dihydroergotamine (DHE) has been available for treating migraine in the United States since 1946.8,9 It is well-known to most headache specialists and still used as an effective treatment when given by injection by either intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes.10 DHE binds with high affinity to serotonin 5-HT1Dα and 5-HT1Dβ receptors as well as 5-HT1A, 5-HT2A, and 5-HT2C receptors, noradrenaline α2A, α2B, and α1 receptors, and dopamine D2L and D3 receptors.11,12 The antimigraine effects of DHE are hypothesized to occur from activation of 5-HT1D receptors located on intracranial blood vessels, leading to vasoconstriction, or from activation of 5-HT1D receptors on sensory nerve endings of the trigeminal system resulting in inhibition of pro-inflammatory neuropeptide release.12 DHE is unique in being effective when given either early in an attack, or late,13 to those already receiving prophylactic treatment,14 to those with prolonged attacks,15 and to triptan resistant migraineurs,16 leading to high rates of sustained relief.17 These features may be due to the slow dissociation of DHE from the receptors, where DHE has a considerably longer dissociation half-life compared to sumatriptan (1.38 and 1.28 hours for DHE from the 5-HT1B and 5-HT1D receptors, respectively, compared to 0.17 and 0.09 hours, respectively, for sumatriptan).17

Two DHE products are available in the United States, an injectable and an intranasal product. DHE delivered by a traditional nasal spray pump (Migranal) has been available in the United States since gaining US Food and Drug Administration (FDA) approval in August 1997.18 However, the bioavailability of the nasal spray is variable and low, at only approximately 32% of the injectable formulation,18 with a delayed peak plasma concentration and slow onset of action.10 In addition, greater intra-patient and inter-patient variability has been reported, perhaps due to delivery to the lower nasal cavity, where variable amounts of the deposited product are lost, described as “spillage” by subjects.19

Self-administration of DHE by subcutaneous or intramuscular injection is known to be effective,20,21 but it is invasive and can be difficult for the patient to safely and accurately self-administer during a migraine episode.10 Nausea and vomiting are reported in at least 50% of patients with IV DHE use, likely attributed to the high Cmax following IV administration,22,23 and the majority of patients require concomitant use of antiemetics to manage nausea,10 which limits the use of DHE injectables for treating acute migraine. Nevertheless, IV DHE remains an important and popular option for headache specialists because of its reliable efficacy,24 with several studies reporting its efficacy in acute migraine treated in the ER10 or with patients presenting with “recalcitrant migraine.” Oral DHE is not available in the United States but is still available in many other countries despite its low oral bioavailability of 0.1%–1.5%,25 although Europe ended its chronic oral use for prophylaxis in 2013.26

In the last decade, a novel inhaled version of DHE, MAP0004, went through clinical development.23,27,28

Conflict of Interest: SBS, MJ, KHS, and JH are full-time employees and own stock in Impel NeuroPharma. JL is a full-time employee of Nucleus Network.

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This product showed promise, as it combined IV-like efficacy but with much lower (on the order of 1/30th) $C_{\text{max}}$ and (~1/4th) AUC$_{0-2}$. MAP0004 was self-administered without injection and low rates of nausea were reported. In a Phase 1 study of MAP0004, DHE was delivered by 6 actuations (1.32 mg fine particle dose), giving a lower $C_{\text{max}}$ (at 1/9th of the level, 5241 pg/mL vs 45,289 pg/mL) but a higher AUC$_{0-48h}$ compared with 1.0 mg IV DHE (~12% higher at 10,892 pg*h/mL vs 9683 pg*h/mL). The incidence of nausea and vomiting was also less in these healthy volunteers (25% and 8.3% for nausea and vomiting, respectively, with MAP0004 1.32 mg, compared to 62.5% and 12.5% with 1.0 mg IV DHE). At a lower dose of 4 inhalations (fine particle dose of 0.88 mg DHE, giving $C_{\text{max}}$ of 3648 pg/mL and an AUC$_{0-48}$ of 7472 pg*h/mL), there was no incidence of nausea or vomiting in these volunteers despite no pretreatment with an antiemetic, suggesting the higher $C_{\text{max}}$ of the IV DHE could have been the cause of the nausea and vomiting. MAP0004 (developed as Levadex and subsequently Semprana) has not been approved in any market and clinical development has ceased, since after a successfully completed clinical development program, content uniformity on the canister filling and standardization of actuation remained problematic, leading to a third Complete Response Letter (denying the New Drug Application) from the FDA. This denial for chemistry, manufacturing, and controls (CMC) issues left the headache community without access to a consistently effective, rapidly acting, non-injective form of DHE for migraine treatment.

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. Deposition in the vestibule region of the nasal cavity can also lead to drug dripping out of the nose or down the back of the throat, leading to inconsistencies in dose available for absorption. Drug delivery to the highly vascularized olfactory epithelium of the upper nasal cavity might lead to more consistent and predictable systemic absorption.

The Precision Olfactory Delivery, or POD®, device is a nasal drug delivery platform supporting individualized designs for delivering either liquid or powder drug formulations of small or large molecules to the upper turbinate region and upper nasal cavity in a consistent and predictable manner for improved biodistribution, which in turn should yield improved clinical outcomes. By delivering drugs to the upper nasal cavity, the POD device platform takes advantage of the rich vasculature found in the olfactory region. In addition, since a gas, hydroxyfluoroalkane (HFA), propels drug into the nasal cavity upon activation of the device, the POD device technology offers an easy and consistent dose administration (without requiring coordination of breathing during dosing, similar to Migranal, but unlike some other nasally administered antimigraine drugs, such as ONZETRA® Xsail®). Unlike the MAP0004 product where the DHE was suspended in the HFA, which was believed to have led to the CMC challenges, the INP104 product keeps the drug separate from the propellant until the time of delivery. The POD device delivery platform has the potential to improve the nasal delivery and systemic uptake of many existing and novel therapeutics, leading to improved clinical outcomes compared to traditional nasal pumps.

INP104 is a drug-device combination product being developed by Impel NeuroPharma, to provide migraine patients with or without aura, with a consistent, non-injectable and user-friendly DHE treatment option. It consists of a liquid DHE formulation administered by the I123 POD device that has been developed to address the low bioavailability and variability in nasal administration observed with traditional nasal sprays. By delivering the drug payload to the upper nasal cavity instead of to the nasal vestibule as traditional nasal sprays do, INP104 may avoid drug dripping out of the nose or into the nasopharynx, increasing systemic availability and maybe reducing the adverse event of taste disturbance. The formulation of DHE administered by INP104 is identical to the formulation approved and used in Migranal with no changes to the formulation or the primary container closure system.

In this study, 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 (Migranal) 2.0 mg in healthy adult subjects were compared. Additionally, the pharmacokinetics of 8′-OH-DHE, an active metabolite of DHE, were also compared. For the purposes of this study, the DHE delivered by the POD device will be referred to as INP104 and the traditional liquid Migranal nasal spray as Migranal, to differentiate this nasal delivery from the POD nasal delivery.

METHODS

Study Design.—This was a Phase 1, open-label, randomized, single-dose, 3-period, 3-way crossover study. The study was conducted in accordance with the Declaration of Helsinki, the National Health and Medical Research Council National Statement on Ethical Conduct in Research Involving Humans (2007), Good Clinical Practices, the International Conference on Harmonization guidelines, and the Australian Therapeutic Goods Administration. The protocol was reviewed and approved by a human research ethics committee, and written informed consent was obtained from each subject before study enrollment.

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 (Fig. 1) with a 7-day washout between treatments. Treatments were (A) INP104 1.45 mg; (B) IV DHE 1.0 mg; and (C) Migranal 2.0 mg. All subjects were observed as inpatients for 48 hours after each dosing. Follow-up evaluations occurred 7 days after each dosing.

Study Subjects.—Participants aged 18–55 years, with a body mass index (BMI) of 18–32 kg/m², and in good general health with no significant medical history in the opinion of the experienced Principal Investigator, including recent migraine were eligible. Subjects had clinical laboratory values within normal range, or if out of normal range, considered not clinically significant by the Investigator, and a negative urine drug screen and alcohol breath test at screening. Subjects were willing to refrain from smoking for the duration of the study. Female subjects of childbearing potential agreed to use 2 methods of adequate contraception during the study and for 30 days after the last dose of DHE received. Male subjects and their partners agreed to use 2 forms of effective methods of contraception during the study and for 90 days after study completion.

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). Also excluded were those with a positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HCV); those with ischemic heart disease or clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal’s variant angina; those with hypertension, known peripheral arterial disease, Raynaud’s phenomenon, sepsis, history of vascular surgery or severely impaired hepatic or renal function; history or presence of alcohol or drug abuse within 2 years; active infection or history of recurrent infections; or subjects with any underlying physical, psychological, or medical condition including laboratory abnormality that could interfere with the conduct of the study. Subjects with a known hypersensitivity to ergot alkaloids or metoclopramide were also excluded. Subjects were required
to refrain from caffeine within 48 hours of each study period and throughout confinement. Use of any relevant prescription or over-the-counter medication, foods (e.g., grapefruit juice) or supplements (including herbal) within 14 days of randomization, in particular, those affecting the cytochrome P450 3A4 (CYP3A4) pathway as well as any recent investigational drug product was prohibited. Lastly, subjects were excluded for any nasal congestion or physical blockage in either nostril, or for deviated nasal septum.

**Study Treatments.**—INP104 was self-administered with 1 spray in each nostril, delivering a total of 1.45 mg DHE. IV DHE 1.0 mg was administered in a volume of 1.0 mL by IV infusion over 1 minute. Migranal 2.0 mg was self-administered by 2 sprays to each nostril (4 sprays total). One spray to each nostril was delivered initially, followed 15 minutes later by an additional spray to each nostril, according to the Migranal instructions for use. Pretreatment by an antiemetic (metoclopramide 10 mg, delivered by slow IV push over 1–2 minutes, 5–10 minutes prior to DHE dosing) was added to the study protocol at the request of the Human Research Ethics Committee to increase subject tolerability and safety by reducing the nausea and vomiting often associated with IV DHE administration, but was given in all 3 treatment periods to ensure bioanalytical conditions remained consistent between treatments.

**Study Assessments.**—At screening, medical history and physical examination, 12-lead electrocardiogram (ECG), vital signs (blood pressure, heart rate, respiratory rate, temperature), clinical laboratory (hematology, chemistry, urinalysis), HIV and hepatitis B and C status, urine drug screen and alcohol breath test, and serum pregnancy test and follicle-stimulating hormone (postmenopausal women) were obtained.

Vital signs were recorded at each of the 3 visits prior to initiation of dosing and at 5, 10, 20, 30, 40, and 50 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 8, 12, 24, 36, and 48 hours post dose. Physical examination and clinical laboratory assessments were performed pre-dose and at 4, 24, and 48 hours after each dosing. An ECG was performed at screening and at 1, 4, 24, and 48 hours. Adverse events were elicited routinely throughout each study period. Blood samples were collected within 15 minutes prior to dosing and at 5, 10, 20, 30, 40, and 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.

**Bioanalytical and PK Methods.**—Quantitative liquid chromatography, tandem mass spectrometry (LC-MS/MS) was used to determine plasma levels of DHE and 8′-OH-DHE. Stable labeled internal standards were used, and extraction was performed by the following method: a plasma sample volume of 200 µL was aliquoted into a 1.2 mL 96-well plate and mixed with 25.0 µL of internal standard solution and 175 µL of water. The mixture was transferred to 400 µL Isolute SLE+ supported liquid extraction plate using a Tomtec Quadra 96 liquid handler. Methyl tert-butyl ether was used to elute the analytes and internal standards, which were collected in a new plate, evaporated to dryness, and reconstituted. Samples were analyzed on a Waters Acquity liquid chromatograph interfaced with a Thermo Scientific TSQ Vantage triple quadrupole mass spectrometer with ESI ionization. Each extracted sample was injected onto a BEH C18 column (2.1 × 50 mm; 1.7 µm) equilibrated at 30°C. A gradient method was used that was linear over the standard concentration ranges studied of the analytes (10 to 10,000 pg/mL DHE and 20 to 20,000 pg/mL for 8′-OH-DHE). Replicate analyses over 36 runs of quality control samples showed assay accuracy of −1.1% to 3.2% and −0.7% to 4.7% and assay precision of 2.4%–3.8% and 2.7%–5.2% for DHE and 8′-OH-DHE, respectively.

For the comparative BA assessment, PK parameters, determined using WinNonLin v6.3 (Pharsight Corporation, Mountain View, CA, USA) non-compartmental analysis, for parent DHE and 8′-OH-DHE from individual participants included: maximum observed plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the concentration-time curve calculated using linear-up log-down trapezoidal summation from time 0 to time of last measurable concentration (AUC0-t), area under the drug concentration-time curve from time 0 to infinity (AUC0-inf) calculated as AUC0-t + Ct/ke; apparent terminal elimination rate constant (keq) calculated by linear regression of the terminal
linear portion of the log concentration vs. time curve, apparent elimination half-life ($t_{1/2}$) calculated as $\ln(2)/k_{el}$; apparent clearance (CL/F) calculated as $\text{Dose} / \text{AUC}_{0\text{-inf}}$; and apparent volume of distribution at the terminal phase (Vz/F) calculated as $\text{Dose} / (k_{el} \times \text{AUC}_{0\text{-inf}})$. Values for $k_{el}$, $t_{1/2}$, AUC$_{0\text{-inf}}$, CL/F, and Vz/F for an individual’s treatment arm were only to be reported if the following criteria for the log-linear phase for the concentration-time data were met: (1) a minimum of 3 measurable concentration-time points during the log-linear portion of the terminal elimination phase excluding $C_{\text{max}}$, and adjusted $r^2 > 0.8$ for the regression of the log concentration-time data during the terminal elimination phase had a negative slope for log regression fit. PK parameters were summarized by individual and administration method using descriptive statistics (arithmetic means, standard deviation [SD], coefficients of variation [CV], sample size [N], minimum, maximum, median and geometric mean). Geometric mean was calculated for AUC$_{0\text{-t}}$, AUC$_{0\text{-inf}}$ and $C_{\text{max}}$.

**Statistical Analysis.**—Sample size was estimated from the point estimate of the ratio of geometric means for AUC$_{0\text{-last}}$, AUC$_{0\text{-inf}}$ and $C_{\text{max}}$ of DHE using SAS Proc POWER (SAS Institute, Cary, NC, USA). Assuming intrasubject variability of 60%, geometric mean ratios for INP104:IV DHE and INP104:Migranal of 80% and 120%, respectively, a sample size of 30 subjects was sufficient to achieve 80% power. 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$_{0\text{-t}}$, AUC$_{0\text{-inf}}$, and $C_{\text{max}}$. Each ANOVA included calculation of least squares mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. Only subjects who had sufficient PK sample collection to generate the key PK parameters (AUC$_{0\text{-t}}$, AUC$_{0\text{-inf}}$, and $C_{\text{max}}$) for each administration method were included in the ANOVA analysis. Ratios of geometric means were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC$_{0\text{-t}}$, AUC$_{0\text{-inf}}$ and $C_{\text{max}}$. These ratios were expressed as a percentage relative to the reference treatment (INP104 [test]/DHE for IV injection [reference] and INP104 [test]/Migranal [reference]). Treatment comparison (<test>/<reference>) by analysis of variance of log-transformed parameters was completed using SAS Proc GLM (SAS Institute), then back-transformed. Consistent with the 2 one-sided tests for bioequivalence, 90% confidence intervals were obtained for the ratio of geometric means for AUC$_{0\text{-t}}$, AUC$_{0\text{-inf}}$ and $C_{\text{max}}$. Since 2 one-way comparisons were performed that accounted for sequence effects, slight differences in the INP104 geometric means were generated for each analysis.

**RESULTS**

**Subject Disposition and Baseline Characteristics.**—Of 38 participants who were enrolled and randomized (Intent-to-treat [ITT] population), 2 subjects withdrew prior to receiving any IP (1 prior to metoclopramide pre-treatment; 1 after), therefore, 36 received at least 1 dose of any 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 participants who received all 3 treatments (including the 1 non-compliant subject who completed all 3 dosings but failed to return for their last follow-up visit) 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 6 treatment sequences and are summarized in Table 1. There were equal numbers of males and females (n = 19 each [50%]). The mean age was 28.9 years (median 28 years; minimum 18, maximum 47), which was similar across all 6 sequences. A mean body weight of 70.2 ± 11.1 kg and BMI of 23.3 ± 3.2 kg/m$^2$ was observed for all participants, which was similar by sequence assignment, and the majority of participants were white (63.2%) and non-Hispanic (100.0%). The safety population (n = 36) consisted of all subjects who received 1 or more dose of IP. Their demographics were very similar (data not shown) with an equal number of males and females (n = 18 each), a mean age across
Pharmacokinetic Analysis of DHE (Safety Population).—Following administration of INP104 1.45 mg, DHE plasma levels quickly increased to 93% of C_max at 20 minutes, peaked at 30 minutes (median T_max), and closely matched the levels of IV DHE 1.0 mg from 30 minutes (1219 ng/mL for INP104 vs 1224 ng/mL for IV DHE) to 48 hours (Fig. 2). The mean C_max for INP104 was 1301 pg/mL (Table 2). Following IV DHE, T_max occurred at 5 minutes (first time point assessed) and the mean C_max was at least 10-fold higher (14,190 pg/mL) than INP104. In comparison, the mean C_max following Migranal was 299.6 pg/mL (>4-fold lower than INP104) and was not achieved until 47 minutes. Plasma DHE AUC_0-inf was 6275, 7490, and 2199 h*pg/mL for INP104, IV DHE, and Migranal, respectively (Table 2). INP104 displayed more consistent delivery compared to Migranal based on the lower intersubject CV% for C_max (51.4% vs 91.8%) and AUC_0-inf (41.8% vs 74.7%). Plasma DHE half-lives were similar for the 3 products at 11.8, 14.2, and 10.4 hours for INP104, IV DHE and Migranal, respectively.

Pharmacokinetic Analysis of 8′-OH-DHE (Safety Population).—Mean plasma concentration profiles for 8′-OH-DHE were consistent with the parent compound, DHE (Fig. 3), but plasma concentrations of 8′-OH-DHE were at least 20–30-fold lower than DHE for all 3 treatments. The route of administration (IN vs IV) did not affect the relative level of the metabolite compared to the parent compound. The C_max for 8′-OH-DHE after INP104, IV DHE, and Migranal administrations was 55.9 pg/mL, 387.4 pg/mL, and 38.8 pg/mL, respectively. Due to the low levels of the metabolite, in particular during the elimination phase, calculation of AUC_0-inf is not presented (Table 3).

Pharmacokinetic Analysis of DHE (PK Population) and Comparative Bioavailability.—Pharmacokinetic parameters for the PK population (subjects who received all 3 treatments, N = 27) were similar to those for the safety population, albeit the differences between treatments were in general slightly smaller (Table 4). Using the PK population, a comparative bioavailability assessment was performed to demonstrate that the exposure to DHE following administration of INP104 falls between that of DHE 45 (IV) and Migranal, which was a primary objective of the study. The ratio of

| Number of subjects | All | ABC | ACB | BAC | BCA | CAB | CBA |
|--------------------|-----|-----|-----|-----|-----|-----|-----|
| Male:Female        | 38  | 7   | 6   | 6   | 7   | 6   | 6   |
| Age, years†        | 28.9 ± 6.1 | 28.4 ± 6.2 | 33.3 ± 9.2 | 28.9 ± 2.0 | 30.0 ± 6.2 | 25.8 ± 3.9 | 28.0 ± 5.9 |
| Weight, kg†        | 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 |
| Body mass index, kg/m²† | 23.3 ± 3.2 | 24.8 ± 3.7 | 23.9 ± 4.3 | 23.6 ± 4.3 | 22.5 ± 3.2 | 23.1 ± 3.0 | 22.1 ± 2.3 |

Table 1.—Baseline Characteristics (ITT Population)

†Mean ± standard deviation.
geometric means (percent) for $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ was 7.88% and 74.2%, respectively, for INP104: IV DHE, and 445% and 308% for INP104: Migranal (Table 5). The upper bound of the one-sided 90% CI for the ratio of geometric means of INP104: IV DHE for $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ was ≤125%. The lower bound of the one-sided 90% CI for ratio of geometric means of INP104: Migranal for $C_{\text{max}}$ and $AUC_{0-\text{inf}}$ was ≥80%. Based upon this evaluation, where the upper bound of the 90% confidence interval of INP104 to IV DHE ratio of geometric means for DHE $AUC_{0-\text{inf}}$ and $C_{\text{max}}$ were ≤125% and the lower bound of the 90% confidence interval of INP104 to Migranal ratio of geometric means for DHE $AUC_{0-\text{inf}}$ and $C_{\text{max}}$ were ≥80%, the primary comparative BA assessment was established to demonstrate a scientific bridge of INP104 to the reference products, D.H.E. 45 and Migranal. Lastly, the absolute bioavailability of INP104 and Migranal were calculated using geometric means from the PK

Fig. 2.—Mean plasma concentrations for DHE from 0 to 4 hours (top) and 0 to 48 hours (bottom).
population. The absolute bioavailability for INP104 was 58.9%, whereas it was 15.2% for Migranal.

DHE exposure in the first 2 hours after administration is proposed to be critical for pain relief.22 As such, emphasis on AUC 0-2h is justified and was examined in this study post hoc. The AUC 0-2h was 1595, 3019, and 428.7 h*pg/mL, respectively, for INP104, IV DHE, and Migranal for the PK population, which represented 26%, 41%, and 19.4% of the AUC 0-inf for these treatments, respectively. This result for INP104 is similar to that shown for the MAP0004 product, which yielded an AUC0-2h of 1447 h*pg/mL, representing 32.4% of the AUC 0-inf.22 The comparative bioavailability of INP104 vs IV DHE and Migranal in the first 2 hours is presented graphically in Figure 4.

Tolerability.—Across all 3 treatments, a total of 98 events occurred in 29 (80.6%) participants and all except 1 were of mild or moderate severity (Table 6). One serious TEAE of acute myeloid leukemia was noted at the follow-up visit after the subject completed all 3 dosings in the study, but this event was considered unrelated to the last study drug administered (INP104). The frequency of treatment emergent adverse events (TEAEs) (whether or not related to treatment) was similar following administration of INP104 or Migranal, whereas the frequency increased approximately 1.5-fold following administration of IV DHE. Across all 3 treatment groups in the safety population, 19/36 (52.8%) participants reported TEAEs that were considered (probably or possibly) related to study drug, with a higher incidence following IV DHE (16/32, [50.0%]) compared to INP104 (6/31, [19.4%]) and Migranal (4/34, [11.8%]) (Table 6). All TEAEs reported as probably related to the study drug occurred in 5 (15.6%) participants following administration of IV DHE. One participant experiencing a moderate AE of dysphoria prior to administration of INP104 subsequently withdrew due to the AE, which was deemed unrelated to study drug. One participant withdrew after experiencing a mild AE of drowsiness following 50% administration of Migranal; this was deemed unlikely related to study drug. No deaths or life-threatening AEs were reported. No clinically significant changes in vital signs, clinical laboratory values or ECG were observed.

Subjects were asked which delivery device they preferred after receiving DHE with all 3 products: the POD device, traditional Migranal, or IV injection. INP104 (POD device) was preferred by 69%, whereas 24% favored the traditional Migranal, and 7% preferred the IV injection. Importantly, 77% of subjects reported nasal dripping after Migranal use, compared to only 32% for INP104. Additionally, 56% of subjects reported drug running down the back of the throat after dosing with Migranal, whereas only 32%
noted this with INP104. The POD device was found to provide a very satisfactory or quite satisfactory experience by 68% of subjects and was reported to be very easy to use by 71%, compared to 53% and 53%, respectively, for Migranal.

**DISCUSSION**

Migraine is reported to impact up to 15% of the population worldwide. In the Global Burden of Disease Study, migraine is ranked as a leading cause of years lost to disability, unquestionably having a major impact on health-related quality of life. Migraine represents an enormous socioeconomic burden to the individual as well as to society, estimated to be between $646 Million and $1.94 Billion in just ER visits in the United States alone.

Triptans are the standard of care for treating acute episodic migraine, but their oral administration is often hampered by the nausea and vomiting that can accompany migraine. Triptans may also cause

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**Fig. 3.**—Mean plasma concentrations for 8′-OH DHE from 0 to 4 hours (top) and 0 to 36 hours (bottom).
neurological side effects and a low but increased risk for cardiovascular events. Further, 30%–40% of patients experience inadequate pain relief and fail to achieve pain-free status with triptans and may have an increased risk of medication-overuse headache. While ergot alkaloids, specifically DHE (first approved in 1946), have been available for decades to treat acute migraine and offer an alternative to triptans, use of existing IV, subcutaneous (SC), intramuscular (IM), and nasal formulations of DHE is limited by patient concerns about ease of use and consistency of response, in addition to safety/tolerability concerns from both patients and health care practitioners. Consequently, alternatives are needed for treating acute migraine that are effective, convenient, well tolerated, and safe, and deliver a reliable dose of DHE with low variability in the PK profile to avoid large variation in DHE exposure that could lead to efficacy or tolerability issues. These challenges led to the clinical development program for an orally inhaled version of DHE (MAP0004, or Levadex or as latterly developed by Allergan, Semprana), which sought to overcome some of the challenges with current DHE modes of administration. However, the

| Table 3.—Summary of Pharmacokinetic Parameters for 8′-OH-DHE (Safety Population) | Mean ± Standard Deviation |
|---|---|---|
| | INP104 1.45 mg | IV DHE 1.0 mg | Migranal 2.0 mg |
| C<sub>max</sub>, pg/mL† | 55.9 ± 26.2 | 387.4 ± 112.6 | 38.8 ± 15.4 |
| AUC<sub>0-last</sub>, h*pg/mL | 414.5 ± 463.6 | 500.9 ± 367.1 | 351.3 ± 354.0 |
| T<sub>max</sub>, h (median [min, max]) | 1.33 (0.33, 4.08) | 0.08 (0.07, 2.05) | 1.93 (0.70, 4.08) |
| T<sub>1/2</sub>, h | 16.9 ± 9.5 | 10.5 ± 4.8 | 18.8 ± 4.2 |
| K<sub>e</sub>, L/h | 0.06 ± 0.05 | 0.08 ± 0.05 | 0.04 ± 0.01 |
| CL/F, L/h | 1748 ± 1700 | 1263 ± 757 | 1498 ± 651 |
| Vz/F, L | 29550 ± 9792 | 15580 ± 4464 | 38240 ± 8817 |

†n = 29, 31, and 10 for C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-last</sub> for INP104, IV DHE, and Migranal, respectively. n = 20, 25, and 4 for the remaining pharmacokinetic parameters for INP104, IV DHE, and Migranal, respectively. PK parameters for 8′-OH-DHE for the PK population were not calculated as there were insufficient data.

| Table 4.—Summary of Pharmacokinetic Parameters for DHE (PK Population) | Mean ± Standard Deviation |
|---|---|---|
| | INP104 1.45 mg (n = 27) | IV DHE 1.0 mg (n = 27) | Migranal 2.0 mg (n = 27) |
| C<sub>max</sub>, pg/mL | 1281 ± 682 | 14,620 ± 4906 | 329 ± 261 |
| C<sub>max</sub>, CV (%) | 53.3 | 33.6 | 79.4 |
| AUC<sub>0-2h</sub>, h*pg/mL | 1595 ± 800.9 | 3019 ± 513.4 | 428.7 ± 317.8 |
| AUC<sub>0-last</sub>, h*pg/mL | 5807 ± 2623 | 6967 ± 1095 | 1999 ± 1433 |
| AUC<sub>0-inf</sub>, h*pg/mL | 6153 ± 2721 | 7381 ± 1139 | 2208 ± 1488 |
| AUC<sub>0-inf</sub> CV (%) | 44.2 | 15.4 | 67.4 |
| T<sub>max</sub>, h (median [min, max]) | 0.50 (0.33, 0.78) | 0.08 (0.07, 0.10) | 0.67 (0.50, 1.8) |
| T<sub>1/2</sub>, h | 11.9 ± 2.9 | 14.5 ± 3.6 | 10.6 ± 3.0 |
| K<sub>e</sub>, L/h | 0.06 ± 0.01 | 0.05 ± 0.01 | 0.07 ± 0.03 |
| CL/F, L/h | 280 ± 238 | 119 ± 19 | 1208 ± 869 |
| Vz/F, L | 4546 ± 2994 | 2505 ± 769 | 16,370 ± 9122 |
| Absolute Bioavailability (%) | 58.9 | 100 | 15.2 |
Table 5.—Plasma DHE Comparative Bioavailability Assessment for INP104 vs Migranal, INP104 vs IV DHE, and Migranal vs IV DHE

| PK Parameter | INP104 (Geometric Mean) | Migranal (Geometric Mean) | Ratio of Geometric Means (%) | One-sided 90% CI for Ratio of Geometric Means (%) (Lower, Upper) |
|--------------|-------------------------|---------------------------|-------------------------------|-------------------------------------------------------------|
| AUC<sub>0-2h</sub> (h*pg/mL) | 1417.47 | 339.59 | 417.41 | 309.46, 563.01 |
| AUC<sub>0-last</sub> (h*pg/mL) | 5193.62 | 1575.94 | 329.56 | 243.58, 445.88 |
| AUC<sub>0-inf</sub> (h*pg/mL) | 5562.29 | 1808.75 | 307.52 | 233.96, 404.21 |
| C<sub>max</sub> (pg/mL) | 1130.65 | 254.04 | 445.06 | 326.51, 606.67 |

| PK Parameter | INP104 (Geometric Mean) | IV DHE (Geometric Mean) | Ratio of Geometric Means (%) | One-sided 90% CI for Ratio of Geometric Means (%) (Lower, Upper) |
|--------------|-------------------------|-------------------------|-------------------------------|-------------------------------------------------------------|
| AUC<sub>0-2h</sub> (h*pg/mL) | 1397.20 | 3021.33 | 46.25 | 36.96, 57.87 |
| AUC<sub>0-last</sub> (h*pg/mL) | 5119.19 | 6978.17 | 73.36 | 58.56, 91.91 |
| AUC<sub>0-inf</sub> (h*pg/mL) | 5485.08 | 7392.37 | 74.20 | 60.00, 91.76 |
| C<sub>max</sub> (pg/mL) | 1114.64 | 14,140.25 | 7.88 | 6.16, 10.09 |

| PK Parameter | Migranal (Geometric Mean) | IV DHE (Geometric Mean) | Ratio of Geometric Means (%) | One-sided 90% CI for Ratio of Geometric Means (%) (Lower, Upper) |
|--------------|-------------------------|-------------------------|-------------------------------|-------------------------------------------------------------|
| AUC<sub>0-2h</sub> (h*pg/mL) | 338.76 | 2972.02 | 11.40 | 8.80, 14.77 |
| AUC<sub>0-last</sub> (h*pg/mL) | 1574.69 | 6861.74 | 22.95 | 17.64, 29.85 |
| AUC<sub>0-inf</sub> (h*pg/mL) | 1807.65 | 7277.14 | 24.84 | 19.53, 31.59 |
| C<sub>max</sub> (pg/mL) | 253.84 | 13,918.36 | 1.82 | 1.39, 2.40 |

Treatment comparison (<test>/<reference>) by analysis of variance (ANOVA) of log-transformed parameters. Comparisons of INP104 vs Migranal, INP104 vs IV DHE, and Migranal vs IV DHE were performed independently. The INP104 geometric mean values differ between the respective comparisons due to the use of a 3-period 6 sequence design, inclusion of sequence, and subject nested within sequence in the ANOVA model and the conduct of independent statistical comparisons.

CI = confidence interval.

Correction made after first online publication on January 28, 2019: “14,187.47” changed to “1417.47” in first row of table.

Fig. 4.—DHE AUC<sub>0-2h</sub> for INP104, IV DHE, and Migranal. The box horizontal lines represent 25th, 50th, and 75th percentiles, and the end bars represent 10th and 90th percentiles.
product, despite successful clinical studies,\textsuperscript{23,27,28} has failed to win approval in the United States, due to problems in CMC.

The results from this study showed that INP104, which delivers a total dose of 1.45 mg DHE by 1 spray to each nostril by the novel POD device, produced

Table 6.—Summary of Treatment-Emergent Adverse Events (TEAEs) and Incidence of TEAEs Occurring in at Least 2 Participants in Any Treatment Group and All Treatment Related TEAEs

|                                         | INP104 (n = 31) | IV DHE (n = 32) | Migranal (n = 34) |
|----------------------------------------|-----------------|-----------------|-------------------|
| Any TEAE event                         | 15 (48.4)       | 24 (65.6)       | 14 (41.2)         |
| Discontinued for AE                    | 1 (3.2)         | 0               | 1 (2.9)           |
| Serious AE                             | 1 (3.2)         | 0               | 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)           |
| Hot flush                              | 0               | 3 (9.4)         | 0                 |
| Any related TEAE                       | 6 (19.4)        | 11 (34.4)       | 4 (11.8)          |
| Headache                               | 1 (3.2)         | 5 (15.6)        | 1 (2.9)           |
| Somnolence                             | 1 (3.2)         | 4 (12.5)        | 1 (2.9)           |
| Dizziness                              | 0               | 5 (15.6)        | 0                 |
| Mental impairment                      | 0               | 1 (3.1)         | 0                 |
| Lethargy                               | 0               | 1 (3.1)         | 0                 |
| Nausea                                 | 0               | 3 (9.4)         | 1 (2.9)           |
| Vomiting                               | 0               | 2 (6.3)         | 1 (2.9)           |
| Abdominal pain                         | 0               | 1 (3.1)         | 0                 |
| Restlessness                           | 0               | 2 (6.3)         | 1 (2.9)           |
| Agitation                              | 0               | 1 (3.1)         | 0                 |
| Oropharyngeal pain                     | 0               | 1 (3.1)         | 0                 |
| Nasal discomfort                       | 1 (3.2)         | 0               | 0                 |
| Intranusal paresthesia                 | 0               | 0               | 1 (2.9)           |
| Fatigue                                | 1 (3.2)         | 0               | 0                 |
| Feeling hot                            | 0               | 1 (3.1)         | 0                 |
| URTI*                                  | 0               | 0               | 1 (2.8)           |
| Gastroenteritis viral                  | 1 (3.2)         | 0               | 0                 |
| Myalgia                                | 0               | 1 (3.1)         | 0                 |
| Musculoskeletal discomfort             | 0               | 1 (3.1)         | 0                 |
| Metrorrhagia                           | 1 (3.2)         | 0               | 1 (2.9)           |
| Breast tenderness                      | 0               | 0               | 1 (2.9)           |
| Hot flush                              | 0               | 2 (6.3)         | 0                 |
| Pruritus                               | 1 (3.2)         | 0               | 0                 |

\textsuperscript{1}URTI = upper respiratory tract infection.
plasma DHE exposure that was comparable to IV DHE after only 30 minutes and matched those levels through to 48 hours, with a similar AUC_{0-inf} compared to IV DHE (6275 h*pg/mL vs 7490 h*pg/mL, respectively). DHE exposure in the first 2 hours (AUC_{0-2h}) following dosing is reported to be critical for pain relief and in this study at a mean level of 1595 h*pg/mL was similar to that reported with the orally inhaled MAP0004 product (mean 1447 pg*h/mL). As a nasal spray, INP104 displayed substantially higher (3-fold) and more consistent plasma DHE exposure compared with the higher dose of 2.0 mg of Migranal, which requires 4 sprays over 15 minutes to deliver 2.0 mg. In this study, INP104 had an absolute bioavailability of 58.9% vs 15.2% for Migranal. Therefore, the POD device, by depositing 1.45 mg of DHE 2–3 cm deeper/higher in the nose than Migranal 2.0 mg, effected vast improvements in bioavailability.

Following IV dosing, plasma concentrations of the metabolite, 8′-OH-DHE, peaked rapidly at approximately 0.2 hours and then declined in a monoexponential manner. The decline in 8′-OH-DHE concentrations generally paralleled that of DHE. 8′-OH-DHE concentrations after INP104 peaked at about 1 hour and declined slowly thereafter. At C_{max}, plasma concentrations of DHE were at least 20-fold higher than 8′-OH-DHE concentrations after both IV and INP104 administration. The majority of subjects (24/34) that received Migranal did not produce high enough plasma concentrations of 8′-OH-DHE (due to low levels of absorption of the parent compound) to calculate the key PK parameters C_{max}, AUC_{0-last}, and T_{max}. Overall, plasma levels of the metabolite compared to DHE indicated there was no substantial difference in the conversion of DHE to the metabolite between the 3 treatments.

In terms of tolerability, the incidence of adverse events with INP104 1.45 mg was lower than with IV DHE 1.0 mg and generally comparable to Migranal 2.0 mg. Of note, IV DHE was administered over 1 minute in this study vs the recommended 5 minute administration time to better match the administration time of INP104. A key advantage of nasal delivery of DHE for acute migraine is that it avoids the initial high peak concentrations of IV DHE that are associated with higher rates of adverse events, a favorable result which is similar to that seen with the MAP0004 product. Interestingly, in this study, despite pre-treatment with an antiemetic, the treatment related TEAE of vomiting was reported by 2 (6.3%) subjects shortly after IV DHE administration. It was also reported by 1 subject after Migranal (at a delayed time of 34 hours post dosing), but by no subjects with INP104. The reports for treatment related TEAE of nausea were 0 (0.0%), 3 (9.4%), and 1 (2.9%), respectively, for INP104, IV DHE, and Migranal. In this study, peak concentrations of DHE delivered by IV were at least 10-fold higher than observed with INP104, which likely contributed to the higher incidence of adverse events with IV DHE compared with INP104.

In conclusion, these results demonstrate that INP104 provides a PK profile of DHE that is comparable to IV DHE, except for a lower peak concentration, a favorable reduction that should result in a lower incidence of AEs associated with DHE. INP104 displayed a favorable T_{max} of 30 minutes, substantially faster than Migranal and with low variability in plasma DHE concentrations indicating consistent delivery. It is anticipated that the DHE levels observed following administration by INP104 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 treatment of migraine.

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