Comparison of Early Plasma Exposure of DHE Following Delivery by Nasal, Oral Inhalation or Intravenous Administration

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Introduction

- Acute treatment of migraine remains a clinical challenge despite the availability of multiple treatment options. Approximately 40% of respondents in a survey of patients with acute migraine reported dissatisfaction with current treatment options, suggesting the opportunity for outcome improvement in acute migraine patients (Lipton, 2013).
- Dihydroergotamine (DHE) is a semi-synthetic, hydrogenated ergot alkaloid derivative that has been extensively used in the treatment of migraine pain, beginning in 1946 (Horton, 1945; Silberstein, 2003).
- Currently marketed DHE products in the US include injectable DHE (D.H.E. 45 for IV, SC or IM delivery) and nasal DHE (Migranal).
- DHE delivered nasally to the lower nasal cavity (Migranal) using a traditional nasal spray applicator results in low and variable bioavailability (32%, US PI 2017; 13% to 101% Migranal SBA 20148) and inconsistent efficacy. Further, patients and physicians report issues of "spillage" after administration, likely contributing to variability in absorption and efficacy (Humbert, 1996).
- IV, IM, and SC DHE are used most often in the emergency room or by headache specialists after other treatments have failed; however, injection is typically not a favored route of administration by patients experiencing migraine. Further, IV DHE, because of its high peak plasma concentration (C_{max}), has more side effects than other formulations.
- An orally inhaled DHE product (MAP0004) was developed to provide an alternative to nasal delivery or injection that would result in rapid and consistent absorption of DHE. MAP0004 was clinically developed but never marketed due to CMC challenges. DHE was contained within the hydrofluoroalkane (HFA) canister in the MAP0004 product.
- For migraine treatments, it is critical to address migraine pain in the first two hours, where changes at the molecular level in neurons located in the trigeminal ganglion and spinal trigeminal nucleus cause hypersensitivity to internal and external factors (Burstein, 2011) and so delayed treatment may impact outcome. However, DHE, unlike other medications, has been shown to be effective even if administered outside this critical window (Tepper 2011).
- For DHE, it has been reported that plasma exposure in the first two hours following administration is critical for pain relief and is related to the side effect profile (Kellerman, 2013).
- Nasal DHE products in development include INP104, STS101 and DFN-19.
- Impel is developing INP104, an innovative drug-device combination product that consists of a liquid DHE formulation administered by the I123 Precision Olfactory Delivery (POD®) device that addresses the low bioavailability and high variability in nasal administration observed with traditional nasal sprays.

Nasal Delivery of DHE

- Comparison of DHE 2-hour pain relief and pain-free rates for nasal and orally inhaled administration for treatment of acute migraine (**Table 1**).

Table 1. Rates of Pain Relief, Pain Freedom, and Treatment Effect at 2 Hours With Nasal or Orally Inhaled DHE for Acute Migraine

Drug (Reference)	Pain Relief (%)	Treatment Effect (%)*	Pain Freedom (%)	Treatment Effect (%)*
MAP0004 1 mg [Orally inhaled] (Aurora, 2009)	72	39	44	37
MAP0004 2 mg [Orally inhaled] (Aurora, 2009)	65	32	35	28
MAP0004 1 mg [Orally inhaled] (Aurora, 2011)	59	24	28	18
Migranal Nasal Spray 2.0 mg [Study 1] (US PI, 2017)	61	38	NR	NR
Migranal Nasal Spray 2.0 mg [Study 3] (US PI, 2017)	32	12	NR	NR

NR = not reported.
* Treatment effect = active treatment minus placebo

- DHE plasma exposure in the first 2 hours after drug delivery is critical to migraine pain relief (FDA Migraine guidance, 2018), justifying an emphasis on AUC_{0-2h} and C_{max} when assessing novel DHE products.
- Further, while C_{max} is likely important for efficacy, research suggests that a high C_{max} may also predict a high rate of adverse events (Shrewsbury et al, 2008; Jividen, 2011; Silberstein, et al, 2014).

INP104, a Novel Nasal DHE Product

- INP104, a novel drug-device combination product in Phase 3 clinical development, targets delivery of a liquid DHE formulation to the upper nasal cavity using the Precision Olfactory Delivery (POD®) device.
- The POD device technology targets consistent and efficient delivery of drugs to the vascular rich upper nasal space (**Figure 1**).
- This region of the nasal cavity with thinner and more consistent mucosa has many advantages for drug delivery including reduced overall variability and improved bioavailability by minimizing the amount of drug that drips out of the nose or runs into the posterior pharynx after nasal administration.
- With INP104, the POD system maintains DHE and HFA propellant separate until actuation.
- Actuation propels a focused stream containing DHE to the olfactory epithelium of the upper nasal space where rapid absorption into the systemic circulation occurs.
- No product has previously utilized the upper nasal space for systemic drug delivery.

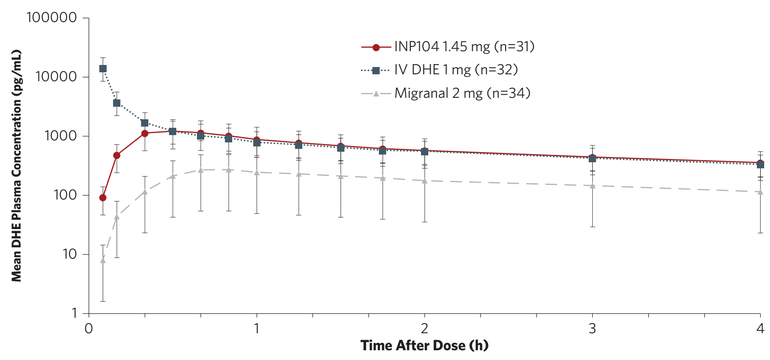
Figure 1. Illustration of the Target Delivery Area of the POD Device (right) and the To-Be-Marketed I123 POD Device (left)

Objective & Methods

- Using data obtained from the STOP 101 study (Shrewsbury et al, 2019) and other literature reports, the objective of this analysis was to compare PK parameters, plasma exposure in the first 2 hours, and adverse events following administration of:
  - DHE by INP104 (Precision Olfactory Delivery [POD®]), 1.45 mg
  - Migranal® Nasal Spray, 2 mg
  - D.H.E. 45® (IV), 1 mg
  - MAP0004 (oral inhalation), 1 mg or 2 mg nominal (Aurora, 2009)
  - STS101, 6 mg (Albrecht, 2019)
- In addition, trends in the literature of DHE PK, efficacy, and adverse events related to C_{max} were reported.

Results

Figure 2. Mean Plasma DHE Concentrations From 0-4 hrs From the INP104-101 Study (Safety Population)



From Shrewsbury et al, 2019

- AUC_{0-2h} following administration of INP104 (1.45 mg), Migranal (2 mg), and D.H.E. 45 (1 mg IV) was 1595, 387.5, and 3022 h*pg/mL, respectively, in the STOP 101 trial (**Table 2**, PK Population).
- A literature report describing the PK of orally inhaled DHE 1 mg states an AUC_{0-2h} value of 1447 h*pg/mL (Kellerman et al, 2013), similar to that reported for INP104.
- C_{max} values were highest following D.H.E. 45 (IV) at 14190 pg/mL followed by INP104 at 1281 pg/mL and Migranal at 299.6 pg/mL (**Table 2**, PK Population).

Table 3. Incidence of Most Common TEAEs

	Number (%) of Subjects						
	INP104 1.45 mg (n=31)[a]	IV DHE 1 mg (n=32)[a]	DHE Nasal Spray 2 mg (n=34)[a]	MAP0004 1 mg (n=6)[b]	MAP0004 2 mg (n=12)[b]	IV DHE 1 mg (n=16)[b]	STS101 6 mg[c] (n=27)
Any TEAE event	15 (48.4)	21 (65.6)	14 (41.2)	5 (83.3)	8 (66.7)	16 (100)	16 (39)
Somnolence	4 (12.9)	9 (28.1)	5 (14.7)	NR	NR	NR	NR
Headache	2 (6.5)	6 (18.8)	3 (8.8)	1 (16.7)	2 (16.7)	3 (18.8)	NR
Dizziness	NR	5 (15.6)	1 (2.9)	1 (16.7)	2 (16.7)	7 (43.8)	NR
Nausea	1 (3.2)	3 (9.4)	1 (2.9)	NR	NR	10 (62.5)	NR
Vomiting	NR	2 (6.3)	1 (2.9)	NR	NR	2 (12.5)	NR
Diarrhea	NR	NR	2 (5.9)	NR	NR	1 (6.3)	NR
Abdominal pain	NR	1 (3.1)	NR	NR	1 (8.3)	NR	2 (4.9)
Nasal Discomfort	1 (3.2)	0	0	NR	NR	NR	14 (34.1)

NR = not reported.
[a]IV, INP104, Migranal – Shrewsbury 2019; [b]IV, Orally inhaled – Shrewsbury, 2008; [c]6 mg dihydroergotamine mesylate = 5.2 mg dihydroergotamine free base – Albrecht, 2019.

- STS101 plasma exposure is lower than expected given the high dose, which is 3-fold higher than Migranal and 4-fold higher than INP104. The AUC_{0-2hr} is 2-fold higher than necessary when comparing to the MAP0004 reports; higher exposure levels may result in a higher incidence of AEs.

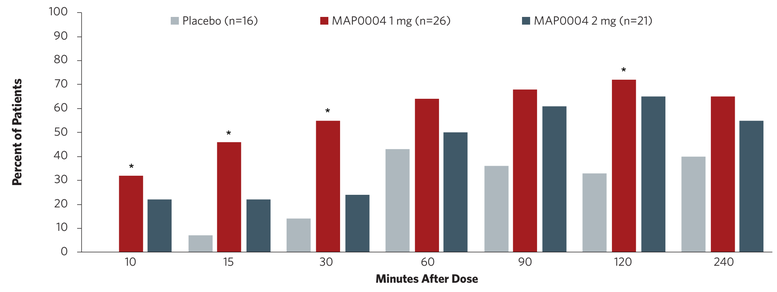
Table 2. Literature Comparison of Mean PK Parameters for Different Formulations of DHE

Parameter	IV	INP104	INP104	Migranal	IM/SC	Orally Inhaled (MAP0004)			STS101	
									Part 1	Part 2
Subject Population	PK	Safety[a]	PK	PK	---	---	---	---	---	---
Dose (nominal, mg)	1	1.45	1.45	2	1	1[3]	2[3]	1[8]	6.0[c]	6.0[c]
T_{max} (h) (median)	0.083	0.5	0.5	0.783	0.37-0.40	0.2	0.1	0.15	0.5	0.5
C_{max} (pg/mL)	14190	1301	1281	299.6	2900-3200	1145	2921	2720	1870	2175
AUC_{0-inf} (h*pg/mL)	7490	6275	6153	2199	9210-9360	3129	7668	4472	10150	12030
AUC_{0-2} (h*pg/mL)	3022	1603	1595	387.5	Not available	---	---	1447	NR	2979
F (%)	100[b]	---	58.9	15.2	NR	NR	NR	NR	NR[d]	NR[d]

NR = not reported.
IV, INP104, Migranal – Shrewsbury 2019; IM/SC – Schran 1994; Orally inhaled – Shrewsbury, 2008; Kellerman, 2013 ; STS101 - Albrecht, 2019
[a]Safety population includes all subjects randomized. PK population includes only those subjects that completed all three arms of the STOP 101 study.
[b]Bioavailability was calculated relative to IV in the STOP 101 clinical study.
[c]6 mg dihydroergotamine mesylate = 5.2 mg dihydroergotamine free base.
[d]This information was not reported by Satsuma. However, when relative bioavailability is calculated against IM in the STS101 study, it is similar to Migranal.

- Research from a Phase 2 trial with 1 mg MAP0004 reports onset of pain relief in migraineurs as early as 10 minutes and only 1 incidence of nausea (Aurora et al, 2009; **Figure 3**).
- A higher rate of adverse events was reported following 2 mg MAP0004 absent any therapeutic gain. The 2 mg nominal dose was suggested to have no additional benefit (Aurora et al, 2009; **Table 3**; **Figure 3**).
- A pooled analysis of 5 studies in 163 healthy subjects administered inhaled DHE by MAP0004 found that the incidence of nausea was related to peak DHE concentrations (Silberstein et al, 2014). The probability of nausea with inhaled DHE is greater than 50% at a C_{max} that exceeds 13,400 pg/mL (Silberstein et al, 2014).

Figure 3. Percent of Patients Achieving Pain Relief With MAP0004 and Placebo



From Aurora et al, 2009; *p<0.05 vs. placebo

- The authors concluded that:
  - Based on the results of the MAP0004 study (Aurora, 2009), it was proposed that the optimal dose for treating acute migraine appeared to be a systemic equivalent of 1 mg nominal dose, achieving approximately 1/3 of the AUC_{0-inf} 1 mg IV DHE dose and a C_{max} of 1/30th of the IV dose.

Conclusions

- A goal for acute migraine products to enable potential pain relief is to achieve high plasma exposure within the first 2 hours after a dose.
- INP104 improves bioavailability of DHE approximately 4-fold compared to delivery by a typical nasal spray or STS101, and 20 min after dosing, plasma levels observed are similar to IV DHE.
- In particular, delivery of DHE by the POD device results in high plasma exposure to DHE in the first 2 hours after administration similar to inhaled DHE (MAP0004), a product with reported migraine pain relief as early as 10 minutes (Aurora, 2009; Kellerman, 2013).
- An approximate 10-fold reduction in the C_{max} following INP104 administration compared with IV DHE may also lead to a more favorable tolerability profile compared with IV DHE, similar to MAP0004 (1 mg).

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