American Academy of Neurology (AAN) 2020 Annual Meeting
Poster #2625

Comparison of Early Plasma Exposure to DHE for Marketed and Development Stage Nasal, Inhalation, and Injectable Products

Kelsey Satterly[1*], Stephen Shrewsbury[1], John Hoekman[1]

[1]Impel NeuroPharma, Seattle, WA

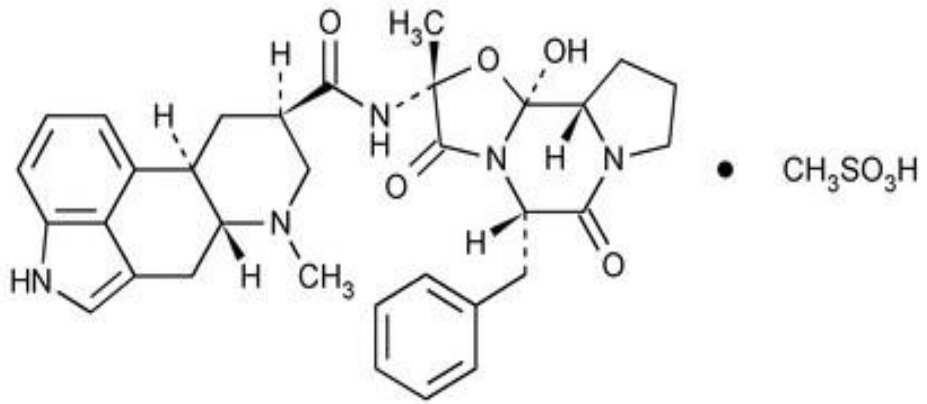
*Presenting Author

Disclosures and Acknowledgments

KS, SS, and JH are employees of and stockholders in Impel NeuroPharma, Inc.

Introduction & Background

- Acute treatment of migraine remains a clinical challenge despite the availability of multiple treatment options.
- Dihydroergotamine 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).
- **Rapid plasma exposure to dihydroergotamine in the first 2 hours following administration may predict success of treatment and may be related to the side-effect profile** (Kellerman, 2013).



Dihydroergotamine mesylate

Objective

Using data obtained from:

- STOP 101 study of INP104 (Shrewsbury et al, 2019)
- Published literature for nasal, inhaled or injectable DHE

The objective of this analysis is to compare PK parameters, plasma exposure in the first 2 hours, and adverse events following administration of DHE mesylate 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
- STS101 (nasal powder), 6 mg

INP104 targets the upper nasal cavity

$AUC_{0\text{-}2hr}$ of INP104 is Similar to Inhaled DHE and Cmax of INP104 is ~10-fold Lower than IV DHE

Parameter	IV[a]	INP104[a]	INP104[a]	Migranal[a]	Orally Inhaled (MAP0004) [b,c]			STS101[d]
Subject Population	PK	PK	Safety	PK	---	---	---	PK
N	27	27	31	27	6	6	66	27
Dose* (nominal, mg)	1.0	1.45	1.45	2.0	1.0	2.0	1.0	6.0
T_{max} (median, hr)	0.083	0.5	0.5	0.783	0.2	0.1	0.15	0.5
C_{max} (pg/mL)	14190	1281	1301	299.6	1145	2921	2720	2175
$AUC_{0\text{-}inf}$ (h*pg/mL)	7490	6153	6275	2199	3129	7668	4472	12030
$AUC_{0\text{-}2\ hr}$ (h*pg/mL)	3022	1595	1603	387.5	---	---	1447	2979
F (Bioavailability, %)	100	58.9	---	15.2	NR	NR	~38%	NR[e]

References: [a]Shrewsbury, 2019; [b]Shrewsbury, 2008; [c]Kellerman, 2013; [d]Albrecht, 2020; [e]Not reported but can be estimated as relative bioavailability against IM, approximately 15-20%.
*Dose = DHE mesylate. NR = not reported.

Key Takeaways: Efficient Delivery of DHE by INP104 Results in Optimal PK Parameters to Maximize Potential Efficacy and Minimize AEs

- Results from a Phase 2 trial with 1 mg MAP0004 reported onset of pain relief in migraineurs as early as 10 minutes and only 1 incident of nausea (Aurora et al, 2009). INP104 and 1 mg MAP0004 have similar $AUC_{0\text{-}2hr}$ values.
- Given the ~10-fold reduction in INP104 C_{max} compared to IV DHE, tolerability may be improved for INP104 and similar to DHE nasal spray and inhaled DHE (MAP0004).
- INP104 improves bioavailability of DHE by ~3 to 4-fold compared to a Migranal nasal spray or STS101 (nasal powder).
- By ~20 min following dosing, INP104 plasma levels are similar to IV DHE, but the high C_{max} following IV is avoided by INP104 administration.
- 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 (MAP0004 2 mg; Aurora, 2009).

Adverse Events (AEs) Associated with High DHE C_{max}

	INP104 (n=31) [a]	IV DHE (n=32) [a]	IV DHE (n=16) [c]	DHE Nasal Spray (n=34) [a]	MAP0004 (n=6) [b]	MAP0004 (n = 12) [b]	STS101 (n=41) [d]
Dose (mg)	**1.45**	**1.0**	**1.0**	**2.0**	**1.0**	**2.0**	**6.0**
Number (%) of Subjects							
Any TEAE event	15 (48.4)	21 (65.6)	16 (100)	14 (41.2)	5 (83.3)	8 (66.7)	16 (39.0)
Nasal discomfort	1 (3.2)	0	0	0	0	0	14 (34.1)
Dysgeusia	0	0	0	0	2 (33.3)	2 (16.7)	9 (22.0)
Dizziness	0	5 (15.6)	7 (43.8)	1 (2.9)	1 (16.7)	2 (16.7)	NR
Nausea	1 (3.2)	3 (9.4)	10 (62.5)	1 (2.9)	0	0	NR
Vomiting	0	2 (6.3)	2 (12.5)	1 (2.9)	0	0	NR

References: [a]Shrewsbury, 2019; [b]Shrewsbury, 2008; [c]Kellerman, 2013; [d]Albrecht, 2020. NR = not reported.

Key Takeaways

- Rapid plasma exposure to DHE in the first 2 hours following administration may predict success of treatment for DHE products and may be related to the side-effect profile (Kellerman, 2013).
- INP104, a drug-device combination product utilizing POD device technology to efficiently deliver DHE as shown using bioavailability, achieves IV-like plasma levels of DHE by 20 minutes following administration.
- An approximate 10-fold reduction in the C_{max} following INP104 vs. IV DHE may also lead to a more favorable tolerability profile (Shrewsbury, 2019).
- Increasing the dose of DHE to achieve plasma exposure above a threshold in the first two hours may not result in result in therapeutic gain, as demonstrated in MAP0004 (Aurora, 2009) and Migranal (Gallagher, 1996) reports, and may lead to a higher incidence of adverse events.