
Review Article

Dihydroergotamine (DHE) – Then and Now: A Narrative Review

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Objective.—To provide a narrative review of clinical development programs for non-oral, non-injectable formulations of dihydroergotamine (DHE) for the treatment of migraine.

Background.—Dihydroergotamine was one of the first “synthetic drugs” developed in the 20th century for treating migraine. It is effective and recommended for acute migraine treatment. Since oral DHE is extensively metabolized, it must be given by a non-oral route. Intravenous DHE requires healthcare personnel to administer, subcutaneous/intramuscular injection is challenging to self-administer, and the approved nasal spray formulation exhibits low bioavailability and high variability that limits its efficacy. Currently there are several attempts underway to develop non-oral, non-injected formulations of DHE.

Method.—A systematic search of MEDLINE/PubMed and ClinicalTrials.gov databases, then narrative review of identified reports, focusing on those published in the last 10 years.

Results.—Of 1881 references to DHE from a MEDLINE/PubMed search, 164 were from the last 10 years and were the focus of this review. Further cross reference was made to ClinicalTrials.gov for 19 clinical studies, of which some results have not yet been published, or are studies that are currently underway. Three nasal DHE products are in clinical development, reawakening interest in this route of delivery for migraine. Other routes of DHE administration have been, or are being, explored.

Conclusion.—There is renewed appreciation for DHE and the need for non-oral, non-injected delivery is now being addressed.

Key words: acute migraine, clinical, dihydroergotamine, intranasal delivery

(*Headache* 2020;60:40-57)

INTRODUCTION

Ergotamine has historically been used to treat migraine since the middle ages, and as a pharmaceutical since 1926,¹ but is limited by poor tolerability (nausea,

vomiting, and cardiovascular effects), thus attempts were made to synthesize compounds with the same efficacy but reduced safety concerns. Dihydroergotamine (DHE) was synthesized by Stoll and Hofmann in 1943 and was

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Accepted for publication October 14, 2019.

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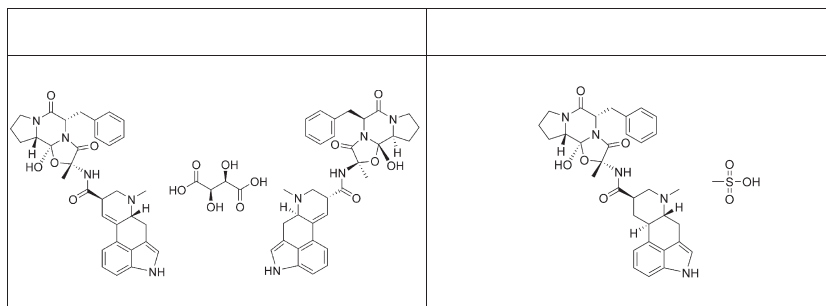


Fig. 1.—The molecular structures of (A) ergotamine (tartrate) and (B) dihydroergotamine (mesylate).

the 45th experimental modification hence the original intravenous (IV) formulation was branded as D.H.E. 45[®]. This modified molecule is more potent than ergotamine as an alpha-adrenergic antagonist (but less potent as an arterial vasoconstrictor), from which it is derived and causes less nausea and vomiting.² DHE was originally envisaged as an antihypertensive agent, but it was later shown to be highly effective in treating migraine at the Mayo Clinic.³ DHE has a chemical structure similar to many naturally occurring neurotransmitters (eg, epinephrine, norepinephrine, dopamine, and serotonin) and as a result binds to a broad range of receptors (Fig. 1).⁴ DHE was approved in 1946 as one of the first drugs of the post-World War II era and continues to be a choice today for acute migraine, status migrainosus, and cluster headaches. DHE is erratically absorbed through the gut with absorption ranging from 10 to 60% and extremely poor oral bioavailability (0.07-0.14%),⁵ and therefore this molecule is limited to non-oral routes of administration. IV administration of DHE is especially effective for treating acute migraine and has a high response rate. Other routes of administration such as nasal delivery (Migranal) have been approved but report 32% bioavailability⁶ and variable pharmacokinetics (PK) that create therapeutic challenges (eg, unpredictable clinical response or adverse events). Thus, an unmet need exists for more effective and consistent delivery

of DHE that provides improved safety, tolerability, and ease of use while retaining its efficacy. In the last decade, an orally inhaled version of DHE (suspended in hydrofluoroalkane [HFA] propellant), MAP0004 showed promise with a successful clinical development program but failed to overcome manufacturing issues so has never been approved. Now, with renewed interest in the disease, at least 3 companies are developing nasally delivered options of DHE while other non-oral, non-injected products are also in development.

This narrative review will highlight the development of non-oral, non-injected DHE programs for acute migraine and summarize the status of the 5 programs in development (3 nasal, 2 in late stage clinical, 1 microneedle patch, and 1 sublingual film) and the 1 oral inhalation formulation. These are the currently, or recently active, development programs identified for DHE which attest to the considerable interest in this 70-year old molecule.

METHOD

A literature search of MEDLINE and PubMed similar to the one conducted by Silberstein and Kori 2013,⁷ revealed 1881 publications with the search term DHE (20 September 2019). When the search was narrowed to DHE and last 10 years, 164 records were obtained. These were manually reviewed and categorized as: chemistry (6), case series (15), reviews including

Conflict of Interest: SDS has received honoraria from Alder Biopharmaceuticals; Allergan, Inc; Amgen; Avanir Pharmaceuticals, Inc; Curelator, Inc; Dr. Reddy's Laboratories; eNeura Inc; electroCore Medical, LLC; Impel NeuroPharma, Inc., Lilly USA, LLC; Medscape, LLC; National Institute of Neurological Disorders and Stroke; Supernus Pharmaceuticals, Inc; Teva Pharmaceuticals; Theranica; and Trigemina, Inc. SBS and JH are full time employees and own stock in Impel Neuropharma, Inc. that is developing INP104. SBS was also a full time employee of MAP Pharmaceuticals 2005-08.

Funding: Impel NeuroPharma, Seattle, WA.

guidelines that many of which were in pediatrics (73), cluster headache or other headache syndromes (8), other Central Nervous System indications and experiments (6), epidemiology and health outcomes work (5), novel randomized controlled clinical studies including 1 double blind, double dummy study comparing oral sumatriptan to an “oral ergotamine preparation” from Bosnia-Herzegovina,⁸ which is not further discussed (6), preclinical work (13), letters (2), and not relevant (17) (for example: signaling pathways in bovine sperm motility, environmental residue detection, DHE tartrate for treatment of lung cancer, and genetic mapping of *Plasmodium falciparum*). Within the past 10 years the only novel clinical research published were 12 papers from MAP Pharmaceuticals (MAP0004) and 1 from Impel NeuroPharma (INP104). Another company, Satsuma presented data on their nasal DHE product at the American Headache Society Annual meeting in July 2019. These are further discussed in this narrative review below.

MIGRAINE

Migraine is very common with a worldwide prevalence of 14.3%;⁹ and along with severe headache is estimated to affect 1 in every 6 adult Americans.¹⁰ A 2016 report found that migraine remained one of the leading causes of disability worldwide¹¹ and the third leading cause of disability worldwide for those aged 15-49 years.⁹ The social and economic burden of migraine remains substantial from lost productivity and functionality, reduced quality of life (QoL), and enormous economic burden.¹² In the United States, the direct and indirect cost burden of acute migraine is substantial,¹³ with migraine patients experiencing high levels of lost days at work, which is associated with significantly higher indirect costs and higher levels of healthcare utilization. In the United States alone, annual costs for healthcare and lost productivity from migraine are estimated at \$36 billion (Migraine Research Foundation), while in Europe, annual direct, indirect, and societal costs of migraine are estimated at €27 billion.¹⁴

TREATMENT OF MIGRAINE

Dihydroergotamine has accumulated over 70 years of clinical practice data demonstrating that it is a safe

and reliable treatment when delivered consistently. When given IV, DHE achieves adequate blood levels to treat acute migraine and provide rapid and sustained relief. The supportive body of clinical evidence for DHE is vast and impressive and suggests a risk profile that some compared to the triptans.¹⁵ For many years, until the advent of the triptans, the ergotamines were the only specific antimigraine drugs.¹⁶

Nowadays, treatment of acute episodic migraine often begins with one of the triptans,¹⁷ which have made a significant impact on the management of migraine as evidenced by the number of different molecules that have been developed. They are now available as inexpensive generics, yet only 1 in 5 patients actually use them.¹⁸ The limitations of triptans include need for early dosing (within an attack), inadequate response, and headache recurrence that result in poor adherence and discontinuation.¹⁹⁻²¹ Triptans fail to relieve migraine in >30% of acute migraine patients^{22,23} with headache recurrence occurring in approximately one-third.²² Almost 50% of acute migraine patients experience frequent nausea that contributes to the burden of migraine,²⁴ and leads to anxiety about taking any oral medication during an attack. In a survey from 3 headache centers, 42% of migraineurs reported dissatisfaction with their treatment, 37% were dissatisfied with the onset of effect, 50% with headache recurrence, and 42% with the need for a second dose of medication.²⁵ A survey of over 8200 U.S. migraine sufferers reported that current treatments for acute migraine were associated with inadequate 2-hour pain-free response (56%), inadequate 24-hour pain relief (53.7%), and headache recurrence (25.7%).²⁶ This may be partly explained by inter- and intra-subject variability.

Two new classes of drugs are being developed for the treatment of acute migraine, the ditans and the small-molecule calcitonin gene-related peptide antagonists, or gepants (not to be confused with monoclonal antibodies being developed, or already approved, for preventive treatment of migraine). The ditans and gepants are alternatives to triptans for acute migraine treatment, but lasmiditan, rimegepant, and ubrogepant are not more effective than most triptans or DHE (Table 1).²⁷⁻³⁸ Acute migraine treatment continues to be a challenge, and a need exists for additional (preferably non-oral, non-injected) acute migraine treatments.³⁹

Table 1.—Rates of Pain Relief, Pain Freedom, and Treatment Effects (Active Minus Placebo Rates) at 2 Hours With Various Acute Non-Injected Migraine Treatments

Drug/Dose (Reference)	Relief (%)	Treatment Effect (%)	Freedom (%)	Treatment Effect (%)
Levadex (orally inhaled DHE 1.0 mg) ²⁷	59	24	28	18
Migranal 2.0 mg (Study 1)†	61	38		
Migranal 2.0 mg (Study 2)†	47	14	Not reported	Not reported
Migranal 2.0 mg (Study 3)†	32	12		
Migranal 2.0 mg (Study 4)†	30	10		
Sumatriptan 100 mg ²⁸	59	30	29	19
Rizatriptan 10 mg ²⁹	88.1	No placebo	60.9	No placebo
Ubrogepant ³⁰			25.5	16.6
Rimegepant (Study 303) ³¹	59.3	10.0	21.2	10.3
Rimegepant (Study 302) ³²	58.1	15.3	19.6	7.6
Rimegepant (Study 301) ³³	56.0	10.3	19.2	5.0
Lasmiditan 200 mg ³⁴	59.5	17.3	32.2	16.9
Lasmiditan 200 mg ³⁵	65.0	17.3	38.8	17.5

†Data for the 4 Migranal studies are taken from the current Migranal Prescribing information. The original publications references 36-38.

DHE – EARLY CLINICAL DATA

Dihydroergotamine was first used to treat migraine in 1945,³ and was approved in 1946. A prospective, double-blind, crossover study was conducted on the effectiveness of DHE vs active control for acute migraine treatment (n = 37) in the emergency department; patients could be pretreated with IV prochlorperazine.⁴⁰ Importantly for patients, by 60 minutes after treatment, those receiving DHE first had significantly better relief of pain than those receiving it later. The authors concluded that treatment with IV prochlorperazine and DHE was safe and effective. A series of 55 patients with intractable migraine were given DHE IV every 8 hours (with metoclopramide) for up to 2 days and compared to 54 age- and sex-matched patients treated with diazepam.⁴¹ With DHE, 49/55 patients became headache-free by 48 hours, with 39 reporting sustained benefit up to 16 months. In contrast, only 7/54 diazepam-treated patients became headache-free. The DHE plus metoclopramide regimen quickly became popular and was known as the “Raskin protocol” and many headache clinics established infusion centers where patients could receive IV DHE. However, not all agree with the conclusion of the trial based on the methodology.⁴²

DHE - BROAD RECEPTOR BINDING PROFILE

Dihydroergotamine is an agonist at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors but also binds to 5-HT_{1A}, 5-HT_{2A} as well as to adrenergic, cholinergic, and dopaminergic receptors.⁴³ This may result in greater efficacy in patients inadequately responding to triptans,⁴⁴ for example, in patients with recurrent or prolonged migraine and those experiencing allodynia⁴⁵ who are often less responsive to triptans.^{46,47} Once bound, DHE dissociates slowly from 5-HT_{1B/1D} receptor sites.⁴⁸ DHE has a considerably longer dissociation half-life compared to sumatriptan, 1.38 and 1.28 hours for DHE from the 5-HT_{1B} and 5-HT_{1D} receptors, respectively, compared to 0.17 and 0.09 hours, respectively, for sumatriptan.⁴⁹

BENEFITS OF DHE

Systemic DHE has a rapid onset and sustained effects lasting up to 48 hours and which may be exerted at any time point after migraine onset, from early (within 2 hours) and up to 8 hours after onset.⁵⁰ DHE is often effective in patients who wake with migraine (a large subset – 48%),⁵¹ are triptan resistant, have menstrual migraine, allodynia or severe and/or prolonged migraine,^{45,47,50,52-56} or have cluster headache.⁵⁷ DHE

has minimal risk of medication overuse headache.⁵⁶ Repetitive IV DHE was effective in 100% of inpatients with cluster headache.⁵⁸ DHE has high rates of sustained migraine relief.⁴⁹ In an animal model, DHE reversed central sensitization, even after established, while a triptan was ineffective.⁵⁹

The following sections will outline some of the data that supports how DHE can meet many of these criteria, and new products can overcome the inconsistency and other drawbacks of the currently marketed nasal spray. Many of these points were addressed in a recent review of DHE use.⁶⁰

DHE – CURRENTLY AVAILABLE PRODUCTS

The following section compares and contrasts formulations of DHE that have been approved and are currently marketed.

D.H.E. 45[®]

D.H.E. 45 is available for IV, subcutaneous (SC), or intramuscular (IM) administration. IV DHE is used most often in the emergency room or by headache specialists, often after other treatments have failed.⁶¹ IV infusion of DHE 1 mg/8 hours for 1-3 days in the hospital setting has a very high response rate for refractory migraine patients: 97% pain reduction, 60-78% pain freedom.^{62,63} However, IV DHE, because of its high

peak plasma concentration (C_{max}), has more systemic side effects than other formulations.^{43,44,64} Despite these drawbacks it remains a popular choice in specialist Headache centers.^{55,61} The IV route remains the fastest, most effective method of administering DHE but requires appropriate facilities and trained healthcare staff able to establish IV access and then administer on a doctor's orders. IV DHE is typically administered in intermittent or bolus injections in the emergency room or infusion center, or continuously in inpatient settings for the treatment of status migrainosus.

SC and IM DHE have limited efficacy due to needle phobia and poor tolerability, including local irritation that limit injectable formulations.⁷ Pharmacokinetic parameters for injected DHE preparations are presented in Table 2.

DHE – NASAL: MIGRANAL[®]

DHE nasal spray (Migranal[®]), was approved in December 1997 as a noninjectable version of DHE to overcome the limitations of IV administration. The product comes as a clear, colorless to light yellow solution in an amber glass vial containing DHE mesylate 4 mg, caffeine (anhydrous) 10 mg, dextrose (anhydrous) 50 mg, carbon dioxide, and water up to 1 mL. The nasal spray delivers formulation to the lower nasal cavity. However, this region of the nose has thick, ciliated

Table 2.—Comparison of Pharmacokinetic Parameters for Different Formulations of DHE

Program	INP104†		IM/SC‡		MAP0004§,¶			STS101††		
Route/Product	IV	Nasal INP104	Migranal	IM/SC‡	Orally Inhaled§			STS101	IM	Migranal
Dose (mg)	1	1.45	2	1	1§	2§	1¶	6††	1	2
T_{max} (h)	0.1	0.5	0.8	0.25-0.5	0.2	0.2	0.15	0.5	0.25	1.0
C_{max} (pg/mL)	14,620	1281	329	2900-4400	1145	3648	2720	2175	3368	961
CV (%)	33	53	79	—‡	—	—	43	41	25	76
AUC _{0-inf} (h*pg/mL)	7381	6153	2208	13,600	3129	8116	4472	12,030	13,650	6496
CV (%)	15	44	67	—‡	—	—	38	39	16	55
AUC ₀₋₂ (h*pg/mL)	3019	1595	428.7	—	—	—	1513	2979	4791	1316
CV (%)	17	50	74	—‡	—	—	45	39	19	75

†PK population.⁶⁶

‡NA – CV (or SD) not available.⁴⁴

§Shrewsbury et al (2008).⁶⁸

¶Mean of data from 6 trials with 1 mg MAP0004 for C_{max} , 4 trials for AUC_{0-inf} and 1 trial for AUC₀₋₂.⁶⁵

††Data presented at AHS Meeting, July 2019. 5.2 mg DHE = 6.0 mg DHE Mesylate.⁶⁷

pseudostratified columnar epithelium⁶⁹ along with a mucus layer.⁷⁰ This contributes to low systemic bioavailability (32%), significant “spillage”⁷¹ along with inter-subject differences in self-administration, leading to suboptimal therapeutic effects, and rhinitis, which is a common adverse event (AE) (26%).⁶ Drug deposition and coalescence in the vestibule region, from the cloud-like plume of the liquid spray in the lower nasal cavity, can lead to drug loss,^{70,72,73} as it runs out onto the upper lip or down the back of the nasopharynx, leading to reports of disturbed taste 8% and abdominal pain (0.1-1.0%).

Migranal 2.0 mg was shown to be effective in 4 randomized, double-blind, placebo-controlled studies in the United States.⁶ Headache response (rather than pain freedom) was reported at 2 hours as significant in the first trial only and at 4 hours in 3 out of 4 trials. Response rates and therapeutic gain (active – placebo response) are summarized in Table 3. The therapeutic gain varied from as little as 10% (2-hour response in trial 4) to as much as 42% (4-hour response in trial 1), suggesting a variability in response that might translate into a lack of clinical reliability – especially in the initial 2 hours after dosing.

DHE – IN DEVELOPMENT

MAP0004 (Levadox/Semprana).—MAP Pharmaceuticals developed an orally inhaled formulation of supercritical fluid processed DHE particles suspended

in HFA propellant (MAP0004) and completed a comprehensive preclinical and clinical development program with the product. The New Drug Application was filed but has never been approved with the Food and Drug Administration citing manufacturing concerns (content uniformity from an improved canister filling process and standards for device actuation) in a complete response letter issued in June 2014. No issues related to clinical safety or efficacy were cited, but further development appears to have been terminated. However, the pharmacokinetic and pharmacodynamic data generated with MAP0004 is relevant to current DHE development programs and had not been generated for the original DHE 45 approval in 1946 or for the subsequent Migranal approval in 1997. Much of what we now know about DHE has come from these relatively recent studies. Results from the MAP0004 Phase 1 studies demonstrated a rapid T_{max} and lower C_{max} for orally inhaled DHE vs IV DHE, but with comparable exposure (area under the concentration-time curve [AUC]) and improved tolerability.^{65,68,74,75} The mechanism for the improved tolerability for MAP0004 vs IV DHE was attributed to a substantially lower peak DHE concentration with less binding to receptor sites (that require a high DHE concentration) contributing to reduced adverse effects with MAP0004.^{43,64}

In a 2-dose period, randomized, double-blind, placebo-controlled Phase 2 study in patients with acute migraine, an early onset of action (10 minutes) was

Table 3.—Migranal Response Rates in 4 Randomized, Placebo-Controlled Trials⁵

Study/Ref	Arm	Number Enrolled	2 Hours Response (%)	Therapeutic Gain (%)	4 Hours Response (%)	Therapeutic Gain (%)
1	Migranal	105	61*	38	70**	42
	Placebo	98	23		28	
2	Migranal	103	47	14	56*	21
	Placebo	102	33		35	
3	Migranal	50	32	12	48*	26
	Placebo	50	20		22	
4	Migranal	47	30	10	47	17
	Placebo	50	20		30	

* $P < .01$.

** $P < .001$.

Data for the 4 Migranal studies are taken from the current Migranal Prescribing information. The original publications references 36-38.

demonstrated with MAP0004 1.0 mg nominal dose (0.5 mg systemic equivalent dose), significant 2-hour pain relief and pain freedom as well as sustained pain relief and pain freedom.⁷⁶ Both a higher (2.0 mg) and lower (0.5 mg) nominal dose were explored, but neither were found to improve on the efficacy/tolerability ratio seen with the 1.0 mg dose which had previously generated a C_{max} of $\sim 1/30$ th of the 1.0 mg IV dose but an AUC_{0-inf} of $\sim 1/3$ rd.

The 1.0 mg nominal dose was selected as optimal and used in a pivotal, double-blind, randomized, placebo-controlled study of 792 acute migraine patients, where MAP0004 was significantly more effective than placebo for 2-hour pain relief and pain freedom as well as absence of phonophobia, photophobia, and nausea at 2 hours; significant pain relief and pain freedom was achieved for 30 minutes with MAP0004 vs placebo.²⁷ Further, results from a post hoc analysis found that pain relief was independent of the time of MAP0004 administration during the migraine attack,⁵⁰ even >8 hours from headache onset.⁶⁹ The pulmonary safety of orally inhaled DHE was demonstrated in a placebo-controlled study of MAP0004 in asthmatic patients.⁷⁷ In addition, a pooled analysis of 4 PK studies with MAP0004 suggested that AUC_{0-2} was the most important parameter for predicting pain relief.⁶⁵ From this pooled analysis, nausea was reported. In patients with a DHE C_{max} exceeding 13,400 pg/mL it was reported in 50%, but in patients with a DHE C_{max} of under 5,000 pg/mL it was reported in less than 2%.⁷⁸

Although the clinical program for MAP0004 successfully demonstrated efficacy and tolerability,^{27,76} after 3 complete response letters from the Food and Drug Administration, MAP0004 was not approved because of manufacturing issues with the delivery system. Thus, while MAP0004 was a promising formulation for administering DHE, and was until recently still awaited eagerly,⁷⁹ the regulatory experience highlights the challenges with the approval of a combination of drug-device product with a complex delivery system and drug stability in HFA propellant. Currently no alternative orally inhaled DHE products are in development, but that situation may change.

Research with MAP0004 in head-to-head studies with IV DHE had addressed some of the concerns about DHE safety, especially with regard to cardiovascular effects, yet this still remains a concern.

DHE – CARDIAC SAFETY

5-HT_{1B} and 5-HT_{2A} receptors are present on the smooth muscle in the coronary arteries, but to a lower extent than on cranial arteries. This has been responsible for anxiety about the cardiac safety of DHE. To address this concern, as part of the development of MAP0004, competitive binding of MAP0004 was investigated at a range of receptors: adrenergic ($\alpha 1$ [non-specific], $\alpha 2A$, $\alpha 2B$, $\alpha 2C$, β), dopaminergic (D; D1, D2, D3), and serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₄, 5-HT_{5A}, 5-HT₆, 5-HT₇) for the parent DHE as well as the major metabolite, 8'-hydroxy-DHE (8'OH-DHE).⁴³ This was complemented by functional binding studies for the serotonergic, adrenergic, and muscarinic receptors. At concentrations found with IV DHE (C_{max} : 53,000 pg/mL), DHE was active at all serotonergic receptors (except 5-HT₃ and 5-HT₄) and at adrenergic ($\alpha 1$, $\alpha 2A$, $\alpha 2B$, $\alpha 2C$) and dopamine D3 receptors. In contrast, at plasma levels of 4300 pg/mL (C_{max} of 4 actuations of MAP0004), significant receptor binding was seen at 5-HT_{1B} and 5-HT_{1D} only with similar limited functional binding profiles. This occurred at a similar AUC_{0-48} of 9683 vs 7472 pg*h/mL for IV DHE and MAP0004. No activity was noted with the respective plasma C_{max} of 8'OH-DHE bio-active metabolite. Thus, similar total exposure (AUC) with reduced peak plasma exposure (C_{max}) of DHE led to a difference in receptor engagement that could potentially reduce the theoretical cardiovascular risk associated with IV DHE. Consistent with this, the Phase 1 study reported fewer AEs in healthy volunteers for MAP0004 – with dizziness reported by 44% with IV DHE compared to only 8% with 4 actuations of MAP0004, paresthesia (31% vs 0%), nausea (63% vs 0%), and emesis (13% vs 0%).

Following satisfactory preclinical work, a randomized, double blind, 3-period clinical study investigating cardiac safety was undertaken. MAP0004, IV DHE or placebo were given to 24 healthy volunteers at 0 and 3 hours and PK, ECG, and Doppler echocardiogram-derived measures of pulmonary arterial systolic pressure (PASP) were recorded.⁷⁴ The change in PASP was significant with IV DHE (AUC_{0-2h} of 2857 mm Hg*min, $P = .001$), but not with MAP0004 (2624 mm Hg*min) compared to placebo (2453 mm Hg*min), with no

other clinically significant changes in a cardiac parameters. No significant ECG changes were observed. Even supratherapeutic doses of MAP0004 did not affect the QT interval.⁸⁰ Mean changes in blood pressure, both systolic (SBP) and diastolic (DBP), 15 minutes after IV DHE were 6-12 mm Hg, compared to 3-5 mm Hg for SBP and 1-2 mm Hg for DBP with MAP0004, which were similar to placebo. The PK data confirmed the high C_{max} seen with IV administration (58,321 pg/mL) compared to the C_{max} with MAP0004 (2475 pg/mL after first dose and 3063 pg/mL after second dose) that was effective in the clinical studies.^{27,76} A recent review examined the evidence of cardiovascular safety concerns with DHE (and triptans) and suggested that evidence for harm with these 5HT agonists is missing⁸¹ even for those suffering from what is now classified as Migraine with Brainstem Aura (MBA) or Hemiplegic Migraine.⁸² The final concluding statement from the review reminded us of the primary role of neuronal processes in the pathophysiology of migraine, rather than vascular. A further drug-drug interaction (DDI) study showed that co-administration of ketoconazole, a powerful CYP3A4 inhibitor, with orally inhaled DHE did not affect the PK of DHE suggesting that the customary DHE label contraindication is unnecessary.⁸³

PHARMACOLOGY OF NASAL DRUG DELIVERY

The nasal cavity has been proposed as an entry point for therapeutics into the systemic circulation, but most programs, like Migranal[®], have targeted the lower nasal cavity. Drug absorption via the upper nasal cavity is currently not utilized as a route for systemic drug delivery but offers a desirable alternative for achieving systemic drug effects because of the highly vascular nature of the upper nasal cavity, good tissue permeability, and avoidance of first pass hepatic metabolism.⁸⁴⁻⁸⁶ Drug delivery via the thinner, but highly vascularized olfactory epithelium of the upper nasal cavity, may lead to more consistent and predictable systemic absorption⁸⁷ than via the lower nasal cavity. Limited and inconsistent systemic absorption have been reported with the traditional nasal sprays that were originally developed and successfully used for treating local nasal disease – such as allergic rhinitis, where systemic absorption was neither sought nor desired.

Once delivered to this olfactory epithelium deeper in the nose, the likelihood of it dripping out of the front of the nose, or down the back of the throat, may be reduced (Fig. 2) compared to traditional nasal sprays. The primary challenge, in achieving significant absorption, is depositing drugs in the upper nasal cavity. Due to the complex architecture of this area, drugs delivered with standard nasal devices such as droppers, sprays, or pumps typically deposit less than 5% of the active drug into the upper nasal cavity, and thus do not consistently or effectively get enough drug to this surface for absorption and hence into the body. Three companies are currently developing nasal DHE products, of which 2 of those are now in phase 3 of clinical development.

INP104

Impel NeuroPharma has, since 2011, been developing the Precision Olfactory Delivery or POD[®] nasal drug delivery platform designed to utilize the rich vasculature found in the olfactory region,^{87,88} allowing for consistent, predictable delivery, and improved bioavailability.⁸⁹ By keeping the HFA propellant and the drug (either in liquid or powder form) separate until the point of delivery, the POD system overcomes the significant chemistry, manufacturing, and controls (CMC) challenge of dose uniformity and stability of drugs for airway delivery that MAP0004 encountered. INP104 uses exactly the same formulation for the DHE drug product that is used in the currently approved Migranal product but administered by the POD device to deliver a larger fraction of DHE to the upper nasal region, above the middle turbinate (Fig. 3) using a low velocity plume of ambient temperature propellant to push a narrow, focused plume to this space (Fig. 4). This leads to a very different PK profile compared to the same formulation delivered by a “traditional” nasal spray. A single 1.45 mg dose administered with POD delivers peak plasma concentrations of DHE that are up to 10-fold lower compared with 1.0 mg IV DHE, but from 20 minutes onward, the PK profile is similar to IV DHE⁶⁶ with an AUC_{0-2} that is similar to that of MAP0004. INP104 also provides a more reproducible dose delivery than Migranal.⁶⁶

Results from a Phase 1 study (NCT03401346) demonstrate a substantially lower peak plasma DHE concentration but comparable exposure (AUC) with

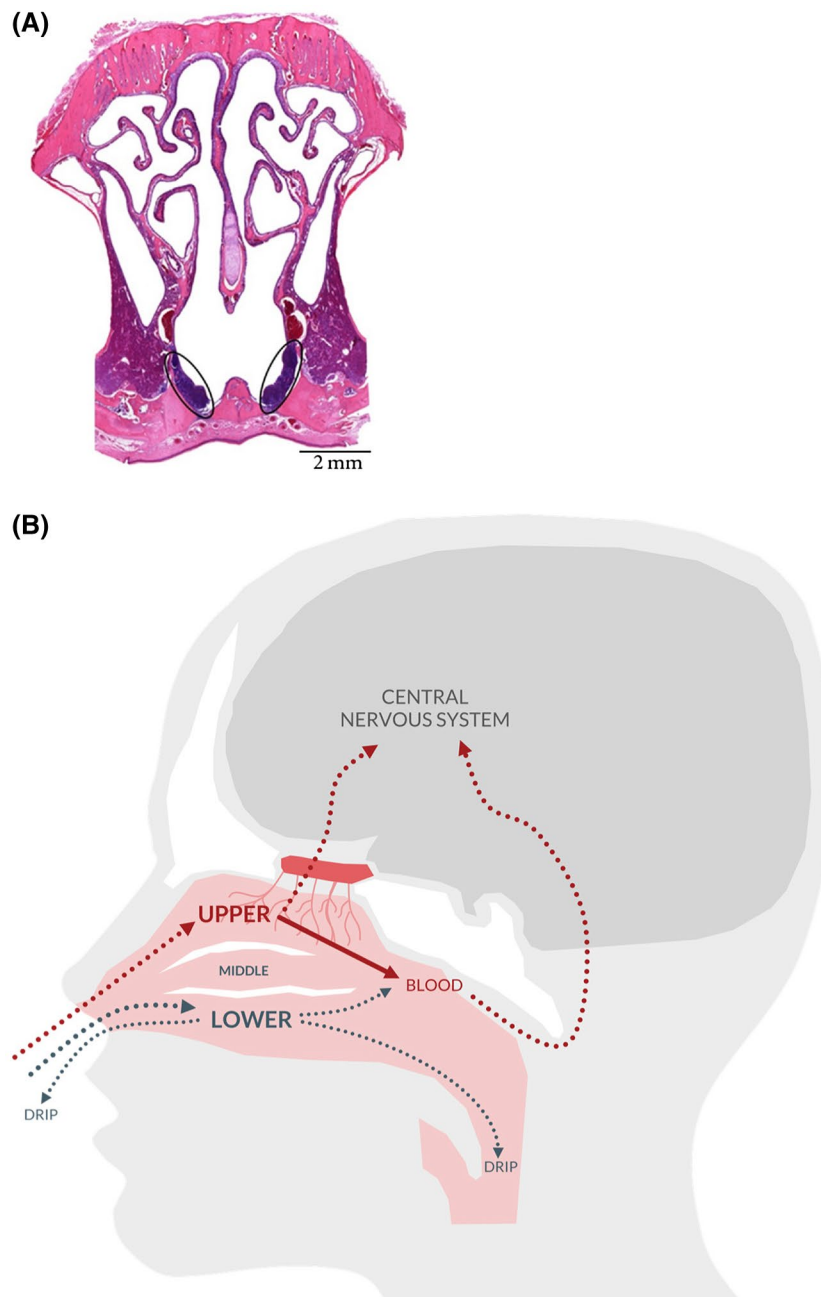


Fig. 2.—(A) Cross section of the nose; (B) disposition of drugs administered by nasal delivery (lower nasal space – targeted by traditional atomizers and upper nasal space – targeted by POD).

INP104 vs IV DHE.⁶⁶ (Fig. 5). In this study, INP104, which utilized the same formulation as Migranal but at <75% of the dose, achieved a 4-fold improvement in DHE C_{max} and a 3-fold improvement in DHE AUC compared to Migranal, matching the IV DHE profile from 20 minutes to 48 hours. This was accomplished by pushing the DHE formulation approximately 3 cm

deeper than traditional nasal sprays, delivering the majority of DHE into the upper nasal space.

The incidence of any treatment-related AE was 19.4% with INP104, 34.4% with IV DHE, and 11.8% with Migranal.⁶⁶ Drug leakage out of the nose or into the nasopharynx after nasal administration with INP104 was reduced compared to Migranal. Subject

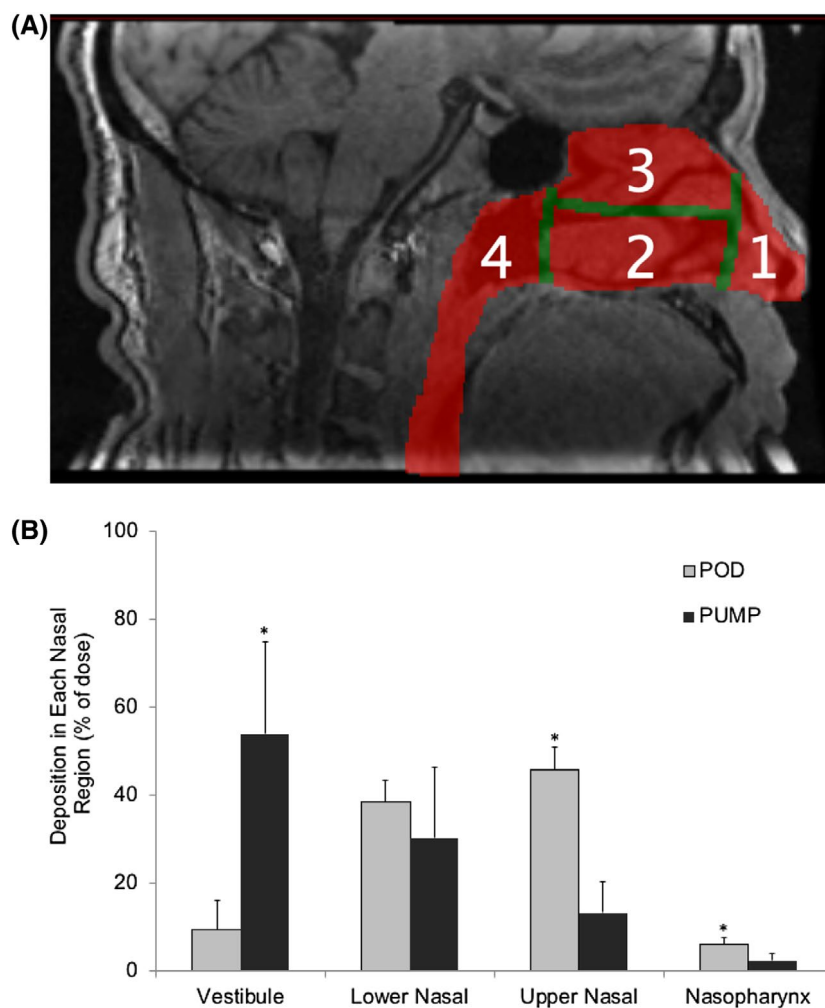


Fig. 3.—Intranasal delivery of MAG-3 (technetium-99m labeled peptide) by POD vs a nasal pump as determined by SPECT imaging in 7 healthy subjects.⁸⁸ (A) For the determination of nasal deposition, the nasal cavity was sectioned into the nasal vestibule (1), the lower turbinate region (2), the upper turbinate/olfactory region (3), and the nasopharynx (4). These sections were defined based on the nasal anatomy observed in MRI images. (B) Nasal deposition quantitation. The POD device led to significantly ($*P < .05$) higher deposition in the upper nasal cavity/olfactory region (upper nasal) compared to the traditional PUMP. A majority of the PUMP dose was administered into the vestibule region.⁸⁹

self-reporting of “nose dripping” after a single dose was 32.3% with INP104 and 76.5% with Migranal.⁶⁶ Further analysis of the cardiovascular safety data from STOP101 indicated brief but statistically significant changes in (peripheral) blood pressure observed after IV dosing that were not seen with either nasal administration.⁹⁰

STOP 301, a Phase 3 study with INP104 for the treatment of acute migraine headache, has completed enrolling (NCT03557333) to assess safety and tolerability over 24/52 weeks. The trial incorporates nasal endoscopy and the University of Pennsylvania Smell

Identification Test (UPSIT) to examine olfactory mucosal integrity and function. In addition, STOP-301 is capturing efficacy endpoints via an e-diary, as well as assessing healthcare utilization and QoL.

STS101

Satsuma Therapeutics is developing a proprietary powder formulation of DHE (mixed with microcrystalline cellulose, tribasic calcium phosphate, and possibly anhydrous caffeine – their patent covers both with and without options) and a small, compact, plastic “squeeze bottle” device with a one way valve developed by Shin

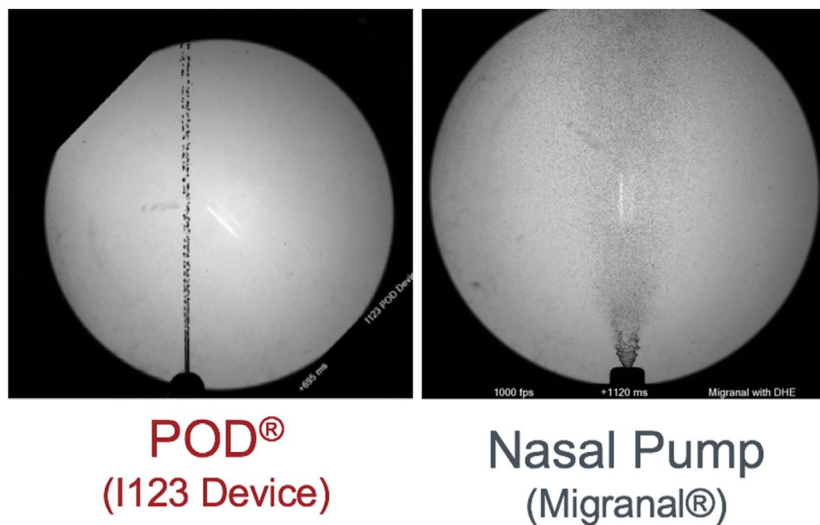


Fig. 4.—Contrasting plumes of DHE propelled from POD (left panel) and migranal nasal spray (right panel). [Color figure can be viewed at wileyonlinelibrary.com]

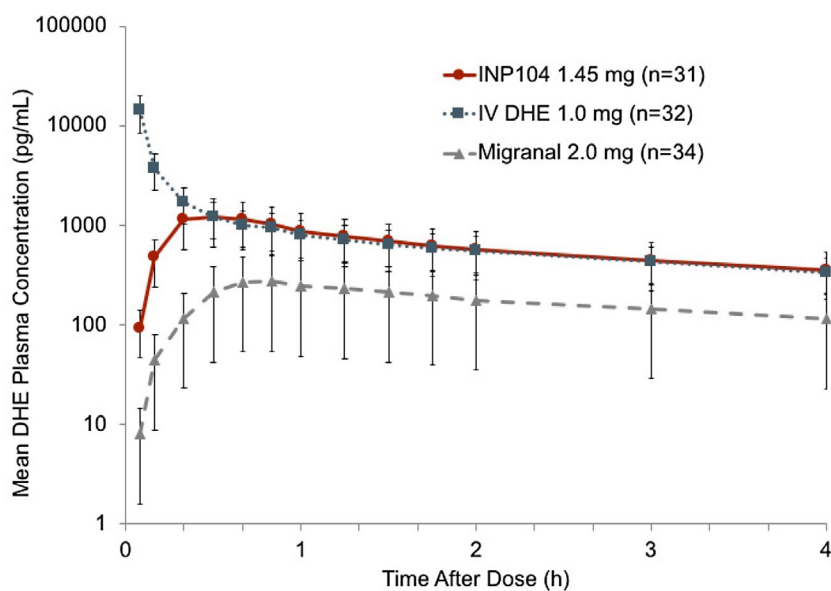


Fig. 5.—Plasma DHE concentrations following administration of single doses of INP104, IV DHE, and DHE nasal spray (top) (republished with permission).⁶⁶

Nippon Biomedical Laboratories (SNBL). A phase 1 PK study (NCT03874832) has been completed and a large phase 3 single dose, efficacy, and safety trial (NCT03901482) is underway. The phase 1, 2-period, 3 single dose, PK, and safety study was completed at the Quotient phase 1 unit in Florida in early 2019 with 1.3, 2.6, or 5.2 mg of STS101 (equivalent to 1.5, 3.0, and 6.0 mg of DHE mesylate) tested in Period 1 and

then comparing STS 5.2 mg in Period 2 to 1.0 mg DHE mesylate given IM or 2.0 mg DHE mesylate nasal spray.

The results were presented at the American Headache Society meeting in Philadelphia in July 2019.⁶⁷ STS101 5.2 mg generated a DHE C_{max} of 2175 pg/mL at a median T_{max} of 0.5 hour, compared to values of 3368 pg/mL for 1.0 mg IM DHE and 961 pg/mL for Migranal (Table 2). AUC_{0-inf} of

12,030 pg*h/mL was similar to that following IM 13,650 pg*h/mL and approximately double that of Migranal 2.0 mg at 6496 pg*h/mL. The AUC_{0-2} of STS101 5.2 mg was 2979 pg*h/mL compared to 4791 pg*h/mL with 1 mg IM DHE and 1316 pg*h/mL with Migranal nasal spray. Overall, the plasma exposure to DHE and the C_{max} were lower than expected, given the high dose of STS101 (6 mg DHE mesylate) when compared to Migranal 2 mg. Further, the profile of the 8'OH-DHE metabolite was not reported but is anticipated to be significant, given this higher dose of DHE mesylate (6.0 mg) administered compared to all other DHE nasal or injectable products. Also not reported was absolute (or relative to IM) bioavailability, though estimates suggest that the bioavailability for STS101 is less than reported for Migranal. In this study, 39% of STS101 subjects reported a TEAE, vs 18.5% with Migranal and 15.4% with IM DHE. Nasal discomfort at 34.1% (Migranal 7.4%), dysgeusia 22.0%, rhinorrhea 14.6%, rhinalgia 12.2%, and nasal congestion 12.2% suggest local irritation with the novel powder formulation may occur although all AEs were mild; none led to withdrawal and no SAEs were reported. On the basis of these results, Satsuma are now embarking on a large phase 3 safety and efficacy study, comparing 2 doses of STS101 to placebo in 1140 migraineurs in their EMERGE study (NCT03901482). Full publication of the Phase 1 data is awaited with interest.

These 2 nasal delivery programs are tackling the shortcomings of Migranal in different ways and both generate plasma levels of DHE that, based on the MAP experience, should be effective. INP104 delivers 1.45 mg of DHE to the upper nasal space and Satsuma are delivering 6.0 mg of DHE mesylate (as their high dose) in an ongoing study. Long term safety information with both products may be revealing.

DFN-19

Promius Pharma (website), indicate a DHE based nasal spray in phase 2 of clinical development, however there are no active, or completed, clinical trials registered on ClinicalTrials.gov, no publications about the product, and no further information available apart from a mention in a corporate presentation to investors in 2015 and a patent.⁹¹ However, that patent is broad

and provides for a range of dosing administration times (<15 minutes), delivered in <4 sprays (Line 22) by a pre-primed device (Line 16) at doses of 0.5 to 2.0 mg (Line 35), with one or more of a variety of stabilizers (30 acids alone are mentioned in the patent [Line 79]), preservatives (Line 174), and viscosity enhancing agents (Line 176), but leading to a plasma level of 700 pg/mL 10% faster than Migranal (Line 201), a C_{max} of "at least about" 10% higher (Line 212), 20% higher (Line 221), or 30% higher (Line 222) with 10% less coefficient of variation than Migranal (Line 224). Line 417 (Example 38-40) describes sparging with nitrogen and dissolving DHE, caffeine, and dextrose to create a clear drug solution to which citric acid monohydrate, trisodium citrate dihydrate, and Vitamin E TPGS (a water soluble Vitamin E derivative, D-alpha-tocopheryl polyethylene glycol succinate) were added. Clinical data with DFN-19 is eagerly awaited.

OTHER NON-ORAL DHE PROGRAMS

A team from the Georgia Institute of Technology published PK results for a DHE-loaded dissolving polyvinylpyrrolidone microneedle patch (MNP) in hairless rat.⁹² DHE was loaded onto the MNPs and after ex vivo experiments in pig skin and in vitro dissolution work, 15 hairless male Sprague-Dawley rats were administered 50 mcg of DHE as IV (1 mg/mL) (n = 5), SC (n = 5) or the DHE MNP which was left in place for 30 minutes, and in all animals, PK blood draws were taken for up to 360 minutes post dosing. The resulting PK parameters showed C_{max} with MNP to be ~5% that of IV (at 7.1 and 141 ng/mL respectively) and ~70% of SC (at 10.7 ng/mL), but with more similar AUC (at 1259, 1751, and 1304 ng*min/mL for MNP, IV, and SC respectively). The T_{max} was noted to be 37.5 min (MNP), 23.8 min (SC), and 2 min (IV), suggesting that the DHE MNP (although only produced at laboratory scale for this study), if scalable and once manufactured under GMP conditions, could be a viable alternative route of DHE administration.

Another team, based in Turkey, more recently reported the PK results of a DHE-loaded maltodextrin-pullulan sublingual film in rabbits.⁹³ After developing 16 different laboratory formulations of maltodextrin, pullulan, and propylene glycol (as plasticizer) to find the optimum disintegration, tensile

strength, and dissolution at 10 minutes parameters, a formulation was selected that when cut into 2 cm² DHE-loaded patches, delivered 23.35% of the dose with a T_{max} at 20 minutes. In an in vivo experiment, 12 anesthetized female New Zealand rabbits were given IV DHE (n = 6) or the sublingual film (n = 6) and blood drawn over the subsequent 8 hours. The results reported C_{max} of 12.8 ng/mL for IV vs 0.85 ng/mL for the sublingual film, and AUC_{0-480} of 14.3 vs 3.3 ng·h/mL, respectively, with a T_{max} of 5 (first blood draw) and 20 minutes for IV and sublingual film, respectively.

WHAT DO PATIENTS WANT?

Recent market research⁹⁴ with patients experiencing migraines has identified the following attributes as most important for a successful acute migraine treatment:

- Fast acting (15-30 minutes)
- Able to be taken at any time during the migraine
- One medication that could relieve all migraine symptoms
- Long lasting relief (12-24 hours)
- Providing complete or near complete relief
- Having few or minor side effects
- Low cost/ insurance coverage
- Ability to take medication and continue regular activities.

Current approved formulations of DHE deliver some but not all of the above attributes. Non-oral, non-injected DHE promised (with the MAP0004 program) to deliver these benefits but was not able to overcome manufacturing challenges. Two nasal products are in late stage clinical development with competing products. Other non-oral, non-injected formulations are in earlier stages of development but all believe that DHE is an underused and underappreciated drug in today's armamentarium.

SUMMARY

DHE is effective for the treatment of acute migraine even in patients with difficult to treat migraines such as the presence of allodynia (or frequent recurrence)⁵⁶ or when administered late in an attack.⁷² IV DHE is effective for treating migraine with a rapid

onset of action, a sustained effect, and independence to time of migraine onset,⁶¹ but high peak plasma concentrations often cause nausea and vomiting that requires pretreatment with an antiemetic.^{43,95,96} IV DHE requires establishing IV access and close monitoring for side effects and is not suitable for "at home" administration. A DHE formulation that provides similar plasma exposure to IV DHE but without the high peak plasma concentrations offers a desirable efficacy and safety profile for treating acute migraine with rapid onset and sustained migraine relief with a lower risk of recurrence and good tolerability.

The past 2 decades have seen attempts to develop orally inhaled and nasally delivered DHE formulations. Orally inhaled DHE showed good efficacy and tolerability for acute migraine, but was never able to solve CMC challenges. However, previous concern about the cardiovascular safety of DHE was investigated during the clinical development of MAP0004 and demonstrated that lowering the peak plasma concentration of DHE while maintaining similar early and total exposure to IV DHE is able to reduce cardiovascular (and gastrointestinal) side effects.⁷⁴ This has led to a better understanding of how to harness the power of DHE without compromising on efficacy, safety and tolerability.

While, traditional nasal spray delivery systems may not deliver adequate, consistent, or predictable levels of DHE to the systemic circulation,⁶⁶ at least 2 different novel nasally administered DHE products are in clinical development, one with fully published PK data.⁶⁶ The safety of DHE when delivered into the upper nasal space is currently being investigated in one repeat dosing Phase 3 safety study of 1.45 mg DHE mesylate (STOP 301) in 360 patients with migraine over 24/52 weeks utilizing nasal endoscopy and the assessment of olfactory function. Meanwhile a large single, "high dose" (believed to be 6.0 mg of DHE mesylate) or "low dose" of nasal powder is being studied in a safety and efficacy study vs placebo in ~1140 patients with migraine a different formulation and device. Thus, improved delivery of DHE to the nose may unlock the potential of DHE delivery for acute migraine in the home setting. INP104, by utilizing targeted upper nasal delivery, is exploring this novel target area for administration of a lower dose of DHE than the existing approved nasal spray.

STS101 is aiming to improve efficacy by delivering a much larger dose (3 times the dose of Migranal). Other formulations of this established and trusted molecule are in earlier development but may in time provide even more non-oral, non-injected alternatives for the 1 in 10 of the population that suffer from migraine.

Acknowledgment: The authors would like to acknowledge the editorial assistance of Richard S. Perry, PharmD in the development of this manuscript, which was supported by Impel NeuroPharma, Seattle, WA.

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REFERENCES

1. Tfelt-Hansen P, Saxena PR, Dahlföf C, et al. Ergotamine in the acute treatment of migraine: A review and European consensus. *Brain*. 2000;123(Pt 1): 9-18.
2. Lipton RB, Ergotamine tartrate and dihydroergotamine mesylate: Safety profiles. *Headache*. 1997; 37:S33-S41.
3. Horton BT, Peters GA, Blumenthal LS. A new product in the treatment of migraine: A preliminary report. *Mayo Clin Proc*. 1945;20:241-248.
4. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: History, pharmacology, and efficacy. *Headache*. 2003;43:144-166.
5. Little PJ, Jennings GL, Skews H, Bobik A. Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol*. 1982;13:785-790.
6. *Migranal (R) Nasal Spray 2 mg Prescribing Information*. US (Bausch Health Companies Inc) Rev. 07/2019.
7. Silberstein SD, Kori SH. Dihydroergotamine: A review of formulation approaches for the acute treatment of migraine. *CNS Drugs*. 2013;27:385-394.
8. Miljković S, Smajlović D, Tirić Campara M, et al. The first comparative double-blind trial on efficacy and safety of ergotamine based five-component combination and sumatriptan in migraine without aura. *Hippokratia*. 2018;22:17-22.
9. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211-1259.
10. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Figures and trends from government health studies. *Headache*. 2018;58:496-505.
11. Global Burden of Disease 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;16:877-897.
12. Hazard E, Munakata J, Bigal ME, Rupnow MF, Lipton RB. The burden of migraine in the United States: Current and emerging perspectives on disease management and economic analysis. *Value Health*. 2009;12:55-64.
13. Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. *Headache*. 2018;58:700-714.
14. Bloudek LM, Stokes M, Buse DC, et al. Cost of healthcare for patients with migraine in five European countries: Results from the International Burden of Migraine Study (IBMS). *J Headache Pain*. 2012;13: 361-378.

15. Mathew PG, Krel R, Buddhdev B, et al. A retrospective analysis of triptan and DHE use for basilar and hemiplegic migraine. *Headache*. 2016;56:841-848.
16. Tfelt-Hansen PC, Koehler PJ. History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward. *Cephalalgia*. 2008;28:877-886.
17. 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.
18. Chu MK, Buse DC, Bigal ME, Serrano D, Lipton RB. Factors associated with triptan use in episodic migraine: Results from the American Migraine Prevalence and Prevention study. *Headache*. 2012;52:213-223.
19. Messali AJ, Yang M, Gillard P, et al. Treatment persistence and switching in triptan users: A systematic literature review. *Headache*. 2014;54:1120-1130.
20. Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. *Headache*. 2014;54:278-289.
21. Lipton RB, Hutchinson S, Ailani J, et al. Discontinuation of acute prescription medication for migraine: Results from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study. *Headache*. 2019. doi:10.1111/head.13642.
22. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: Detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia*. 2002;22:633-658.
23. Viana M, Genazzani AA, Terrazzino S, Nappi G, Goadsby PJ. Triptan nonresponders: Do they exist and who are they? *Cephalalgia*. 2013;33:891-896.
24. Lipton RB, Buse DC, Saiers J, Fanning KM, Serrano D, Reed ML. Frequency and burden of headache-related nausea: Results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2013;53:93-103.
25. Bigal M, Rapoport A, Aurora S, Sheftell F, Tepper S, Dahlof C. Satisfaction with current migraine therapy: Experience from 3 centers in US and Sweden. *Headache*. 2007;47:475-479.
26. Lipton RB, Munjal S, Buse DC, Fanning KM, Bennett A, Reed ML. Predicting inadequate response to acute migraine medication: Results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2016;56:1635-1648.
27. Aurora SK, Silberstein SD, Kori SH, et al. MAP0004, orally inhaled DHE: A randomized, controlled study in the acute treatment of migraine. *Headache*. 2011;51:507-517.
28. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Oral triptans (serotonin, 5-HT_{1B/1D} agonists) in acute migraine treatment: A meta-analysis of 53 trials. *Lancet*. 2001;358:1699-1675.
29. Ng-Mak DS, Hu XH, Chen Y, Ma L, Solomon G. Times to pain relief and pain freedom with rizatriptan 10 mg and other oral triptans. *Int J Clin Pract*. 2007;61:1091-1111.
30. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. *Cephalalgia*. 2016;36:887-898.
31. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: A randomised, phase 3, double-blind, placebo-controlled trial. *Lancet*. 2019;394:737-745.
32. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019;381:142-149.
33. Lipton RB, Conway CM, Stock EG, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the acute treatment of migraine: Results from a phase 3, double-blind, randomized, placebo-controlled trial (study 301). Poster #PS123LB presented at the 2018 American Headache Society Annual Meeting, June 2018.
34. Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB. Lasmiditan is an effective acute treatment for migraine. A phase 3 randomized study. *Neurology*. 2018;91:e2222-e2232.
35. Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142:1894-1904.
36. Gallagher RM. Acute treatment of migraine with dihydroergotamine nasal spray. *Arch Neurol*. 1996;53:1285-1291.
37. The Dihydroergotamine Nasal Spray Multicenter Investigators. Efficacy, safety, and tolerability of dihydroergotamine nasal spray in the treatment of acute migraine. *Headache*. 1995;35:177-184.
38. Ziegler D, Ford R, Kriegler J, et al. Dihydroergotamine nasal spray for the acute treatment of migraine. *Neurology*. 1994;44:447-453.
39. Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs

- among persons with episodic migraine: Results of the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2013;53:1300-1311.
40. Callahan M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. *Headache*. 1986;26:168-171.
 41. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. *Neurology*. 1986;36:995-997.
 42. Bekan G, Tfelt-Hansen P. Is the generally held view that intravenous dihydroergotamine is effective in migraine based on wrong "general consensus" of one trial? A critical review of the trial and subsequent quotations. *Headache*. 2016;56:1482-1491.
 43. Cook RO, Shrewsbury SB, Ramadan NM. Reduced adverse event profile of orally inhaled DHE (MAP0004) vs IV DHE: Potential mechanism. *Headache*. 2009;49:1423-1434.
 44. Baron EP, Tepper SJ. Orally inhaled dihydroergotamine: Reviving and improving a classic. *Future Neurol*. 2011;6:327-333.
 45. Tepper SJ, Kori SH, Borland SW, et al. Efficacy and safety of MAP0004, orally inhaled DHE in treating migraines with and without allodynia. *Headache*. 2012;52:37-47.
 46. Silberstein SD, Young WB, Hopkins MM, Gebeline-Myers C, Bradley KC. Dihydroergotamine for early and late treatment of migraine with cutaneous allodynia: An open-label pilot trial. *Headache*. 2007;47:878-885.
 47. Kori S, Tepper S, Boland S, Wang M, Hu B, Silberstein S. Evaluation of efficacy and safety of Levadex (MAP0004) in reversing central sensitization and treating migraine in established allodynic patients. *J Headache Pain*. 2010;11(Suppl. 1):466.
 48. Tfelt-Hansen PC. Relatively slow and long-lasting antimigraine effect of dihydroergotamine is most likely due to basic pharmacological attributes of the drug: A review. *Cephalalgia*. 2013;33:1122-1131.
 49. Kori S, Zhang J, Kellerman D, Armer T, Goadsby P. Sustained pain relief with dihydroergotamine in migraine is potentially due to persistent binding to 5-HT_{1B} and 5-HT_{1D} receptors. *J Headache Pain*. 2013;14(Suppl. 1):P75.
 50. Tepper SJ, Kori SH, Goadsby PJ, et al. MAP0004, orally inhaled dihydroergotamine for acute treatment of migraine: Efficacy of early and late treatments. *Mayo Clin Proc*. 2011;86:948-955.
 51. Fox AW, Davis RL. Migraine chronobiology. *Headache*. 1998;38:436-441.
 52. Aurora S, Lu B, Connors E, Li X, Kellerman D, Kori S. Analysis of subjects with menstrually related migraine vs non-menstrually related migraine treated with MAP0004. *J Headache Pain*. 2013;14(Suppl. 1):P143.
 53. Kellerman D, Chang J, Kori J, Chen S. A long-term open-label study assessing the safety and tolerability of LEVADEX® orally inhaled dihydroergotamine in adult migraineurs. *Ann Neurol*. 2010;68:S17.
 54. Kori S, Connors E, Zhou J, Lu B, Borland S. Efficacy of MAP0004 in treating severe pain. *J Headache Pain*. 2013;14(Suppl. 1):P208.
 55. Kori SH, Tepper ST, Saper J, et al. Levadex efficacy in treating resistant migraine. *Ann Neurol*. 2010;68:S14.
 56. Saper JR, Silberstein S, Dodick D, Rapoport A. DHE in the pharmacotherapy of migraine: Potential for a larger role. *Headache*. 2006;46(Suppl. 4):S212-S220.
 57. Magnoux E, Zlotnik G. Outpatient intravenous dihydroergotamine for refractory cluster headache. *Headache*. 2004;44:249-255.
 58. Mather PJ, Silberstein SD, Schulman EA, Hopkins MM. The treatment of cluster headache with repetitive intravenous dihydroergotamine. *Headache*. 1991;31:525-532.
 59. Burstein R, Jakubowski M. Analgesic triptan action in an animal model of intracranial pain: A race against the development of central sensitization. *Ann Neurol*. 2004;55:27-36.
 60. Piechal A, Blecharz-Klin K, Mirowska-Guzel D. Dihydroergotamine (DHE) – Is there a place for its use? *J Pre-Clin Clin Res*. 2018;12:149-157.
 61. Nagy AJ, Gandhi S, Bholra R, Goadsby PJ. Intravenous dihydroergotamine (DHE) for inpatient management of refractory primary headaches. *Neurology*. 2011;77:1827-1832.
 62. Ford RG, Ford KT. Continuous intravenous dihydroergotamine in the treatment of intractable headache. *Headache*. 1997;37:129-136.
 63. Kabbouche M, Khoury CK. Management of primary headache in the emergency department and inpatient headache unit. *Semin Pediatr Neurol*. 2016;23:40-43.
 64. Dahlöf C, Maassen Van Den Brink A. Dihydroergotamine, ergotamine, methysergide and sumatriptan – Basic science in relation to migraine treatment. *Headache*. 2012;52:707-714.
 65. Kellerman DJ, Forst A, Combs DL, Borland S, Kori S. Assessment of the consistency of absorption of dihydroergotamine following oral inhalation: Pooled results from four clinical studies. *J Aerosol Med Pulm Drug Deliv*. 2013;26:297-306.

66. Shrewsbury SB, Jeleva M, Satterly KH, Lickliter J, Hoekman J. STOP 101: A phase 1, randomized, open-label, comparative bioavailability study of INP104, dihydroergotamine mesylate (DHE) administered intranasally by a I123 Precision Olfactory Delivery (POD®) device, in healthy adult subjects. *Headache*. 2019;59:394-409.
67. Albrecht D, Iwashima M, Dillon D, Harris S, Levy J. Pharmacokinetics and safety of intranasal dihydroergotamine powder (STS101). Poster presented at American Headache Society 61st Annual Scientific Meeting 11-14 July, 2019.
68. 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.
69. Lochhead J, Thorne R. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev*. 2012;64:614-628.
70. Pu Y, Goodey AP, Fang X, Jacob K. A comparison of the deposition patterns of different nasal spray formulations using a nasal cast. *Aerosol Sci Technol*. 2014;48:930-938.
71. Humbert H, Cabiatic MD, Dubray C, Lavene D. Human pharmacokinetics of dihydroergotamine administered by nasal spray. *Clin Pharmacol Ther*. 1996;60:265-275.
72. Tepper SJ. Clinical implications for breath-powered powder sumatriptan intranasal treatment. *Headache*. 2013;53:1341-1349.
73. Newman LC. Why triptan treatment can fail: Focus on gastrointestinal manifestations of migraine. *Headache*. 2013;53(Suppl. 1):11-16.
74. Noveck RJ, Douglas PS, Chow SC, Mangum B, Kori S, Kellerman DJ. Assessing acute systemic effects of an inhaled drug with serial echocardiography: A placebo-controlled comparison of inhaled and intravenous dihydroergotamine. *Drug Des Dev Ther*. 2013;7:619-625.
75. Shrewsbury SB, Kori SH, Miller SD, Pedinoff A, Weinstein S. Randomized, double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of MAP0004 (orally-inhaled DHE) in adult asthmatics. *Curr Med Res Opin*. 2008;24:1977-1985.
76. 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.
77. Shrewsbury SB, Stonerook M, Okikawa JK. Intrapulmonary and intravenous administrations of dihydroergotamine mesylate have similar cardiovascular effects in the conscious dog. *Br J Pharmacol*. 2008;154:1254-1265.
78. Silberstein SD, Basile AS, Kellerman D, Davar G. Relationship between plasma dihydroergotamine (DHE) concentrations and the occurrence of nausea after treatment with orally inhaled DHE. Presented at the 2014 American Headache Society Annual Meeting, June 2014.
79. Vandebussche N, Goadsby PJ. The discovery and development of inhaled therapeutics for migraine. *Expert Opin Drug Discov*. 2019;14:591-599.
80. Kori S, Kellerman DJ, Voloshko P, Haugen G. Effects of a supratherapeutic dose of investigational orally inhaled dihydroergotamine (MAP0004) on QT interval: A randomized, double-blind, active- and placebo-controlled crossover study in healthy volunteers. *Clin Ther*. 2012;34:1920-1928.
81. Mathew PG, Klein BC. Getting to the heart of the matter: Migraine, triptans, DHE, ditans, CGRP antibodies, first/second-generation gepants, and cardiovascular risk. *Headache*. 2019;59:1421-1426.
82. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
83. Kellerman DJ, Kori S, Forst A, et al. Lack of drug interaction between the migraine drug MAP0004 (orally inhaled dihydroergotamine) and a CYP3A4 inhibitor in humans. *Cephalalgia*. 2012;32:150-158.
84. Ghori MU, Mahdi MH, Smith AM, Conway BR. Nasal drug delivery systems: An overview. *Am J Pharmacol Sci*. 2015;3:110-119.
85. Mittal D, Ali A, Md S, Baboota S, Sahni JK, Ali J. Insights into direct nose to brain delivery: Current status and future perspective. *Drug Deliv*. 2014;21:75-86.
86. Singh M, Kaur R, Rajput R, Singe SP, Rachana M. Intranasal drug delivery – New concept of therapeutic implications for effective treatment of CNS disorders. *IJPSR*. 2017;8:3194-3205.
87. Hoekman JD, Ho R, JY. Enhanced analgesic responses following preferential delivery of morphine and fentanyl to the olfactory epithelium. *Anesth Analg*. 2011;113:641-651.
88. Hoekman J, Brunelle A, Hite M, Kim P, Fuller C. SPECT imaging of direct nose-to-brain transfer

- of MAG-3 in man. Poster W4009 presented at the American Association of Pharmaceutical Scientists Annual Meeting, San Antonio, Texas, November 10-14, 2013.
89. Hoekman J, Brunelle A, Hite M, Kim P, Fuller C. Usability and tolerability study in human subjects with a novel precision olfactory delivery (POD) device. Poster M1050 presented at the American Association of Pharmaceutical Scientists Annual Meeting, San Antonio, Texas, November 10-14, 2013.
90. Craig K, Hoekman J, Jeleva M, Satterly K, Shrewsbury S. Cardiovascular profile of dihydroergotamine mesylate (DHE) delivered by INP104 compared to D.H.E. 45® for injection from the INP104-101 clinical trial. Presented at the 2019 American Headache Society Annual Meeting, June 2019.
91. Narashima Murthy A, Gupta P, Jana A, Vallabhadas Rathi V, Karanth G, Raghuvanshi RS. *International Publication No. WO2019008439*; 2019. Available at: <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019008439>. Accessed September 20, 2019.
92. Tas C, Joyce JC, Nguyen HX, et al. Dihydroergotamine mesylate-loaded dissolving microneedle patch made of polyvinylpyrrolidone for management of acute migraine therapy. *J Con Rel*. 2017;268:159-165.
93. Esim O, Ozkan CK, Kurbanoglu S, et al. Development and *in vitro/in vivo* evaluation of dihydroergotamine mesylate loaded maltodextran-pullulan sublingual films. *Drug Dev Ind Pharm*. 2019;45:914-921.
94. Shrewsbury SB, Ray S. Impact and burden of episodic, acute migraine (I-BEAM): A patient experience study. IHC 2019 Abstracts. *Cephalalgia*. 2019;39(Suppl. 1):124.
95. Chou DE, Tso AR, Goadsby PJ. Aprepitant for the management of nausea with inpatient IV dihydroergotamine. *Neurology*. 2016;87:1613-1616.
96. Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral dihydroergotamine for acute migraine headache: A systematic review of the literature. *Ann Emerg Med*. 2005;45:393-401.