

PULMATRIX Dihydroergotamine (DHE) and Migraine Key Opinion Leader Event

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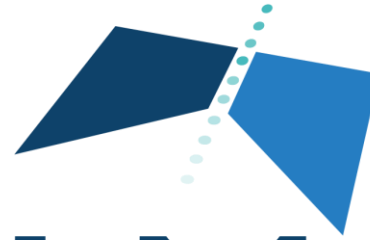
NASDAQ: PULM

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This presentation contains forward-looking statements. All statements other than statements of historical fact contained herein, including statements regarding our business plans or strategies, projected or anticipated benefits or other consequences of our plans or strategies, projected or anticipated benefits from acquisitions to be made by us, or projections involving anticipated revenues, earnings or other aspects of our operating results, are forward-looking statements. Words such as “anticipates,” “assumes,” “believes,” “can,” “could,” “estimates,” “expects,” “forecasts,” “guides,” “intends,” “is confident that,” “may,” “plans,” “seeks,” “projects,” “targets,” and “would,” and their opposites and similar expressions, as well as statements in future tense, are intended to identify forward-looking statements. Forward-looking statements should not be read as a guarantee of future performance or results and may not be accurate indications of when such performance or results will actually be achieved. Forward-looking statements are based on information we have when those statements are made or our management’s good faith belief as of that time with respect to future events and are subject to risks and uncertainties that could cause actual performance or results to differ materially from those expressed in or suggested by the forward-looking statements. A discussion of these and other factors, including risks and uncertainties with respect to Pulmatrix, Inc. (the “Company”), as set forth in the Company’s filings with the Securities and Exchange Commission (“SEC”), including the Company’s most recently filed Annual Report on Form 10-K, as may be supplemented or amended by the company’s Quarterly Reports on Form-10Q. Investors and security holders are urged to read these documents free of charge on the SEC’s website at <http://www.sec.gov>. Forward-looking statements contained in this presentation are made as of this date, and the Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise.

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CAUTION: We have not received approval from the FDA, or any other regulatory entity, to market our therapeutic candidates in the United States or in any other jurisdictions. Our therapeutic candidates, including PUR1900, PUR1800, and PUR3100 are classified by the FDA as investigational drugs and are limited by Federal (or United States) law to investigational use only and will require additional studies to make definitive conclusions and claims about such candidates’ safety or efficacy.



PULMATRiX

Our Mission

PULMATRiX is committed to the development and commercialization of novel and transformational medicines for patients all over the world, using our proprietary iSPERSE™ technology to optimally deliver both respiratory and non-respiratory therapies via the respiratory system.

Management Team

Deep expertise in respiratory diseases and drug delivery technology across all stages of development



Ted Raad – *CEO & Director*

- Previously Chief Business Officer of Pulmatrix
- 20 years of commercial healthcare and life sciences leadership experience
- Former Chief Commercial Officer at Option Care



Margaret Wasilewski, MD – *Chief Medical Officer*

- 25 years in pharmaceutical drug development
- Development experience in infectious disease, sepsis, neurology and rare disease
- Trained in Internal Medicine and Infectious Diseases with active board certification in Internal Medicine.



Aidan Curran, PhD – *Research & Scientific Affairs*

- Previously Director of Inhalation Technology at Huntingdon Life Sciences
- Spent over a decade in academic research and has more than 30 peer reviewed manuscripts



Michelle Siegert – *Finance*

- Joined Pulmatrix in 2010 and has held numerous roles of increasing responsibility
- 25+ years of financial, transactional and operational experience in both private and public companies



Peter Ludlum – *Interim Chief Financial Officer*

- Currently Senior Director at Danforth Advisors
- Extensive finance and accounting leadership experience with 17 years as a C-level executive in public, private, international, manufacturing, clean tech and life science companies



Jason Perry – *CMC & Pharmaceutical Development*

- 15 years of experience developing pharmaceutical products
- Prior formulation and process development roles at Alkermes advancing oral and inhaled dosage products



Steven Kramer – *Quality*

- 11+ years with Pulmatrix holding numerous roles
- Previously held positions at Alkermes and AMAG Pharmaceutical
- 15+ years experience in quality assurance & control

PUR3100

Inhaled Dihydroergotamine (DHE) for Treatment of Acute Migraine



~\$575M U.S. peak net revenue potential, a **1% total Rx share**, is a conservative forecast¹ that fully considers the competitive landscape and generic pressure



iSPERSE mitigates the manufacturing / device issues resulting in MAP0004 complete response and



Ph1 results: Safe, well tolerated, fastest non-IV T_{max} of any acute migraine therapy with a higher C_{max} than other non-IV DHE formulations including MAP0004



Potential Ph2 proof of concept efficacy study that could start as early as Q4 2023

¹ Source: Physician Interviews and Payer Interviews; ClearView Health Partners Analysis



PUR3100: Acute Treatment of Migraine

Large underserved market



Large Market

>1 billion worldwide
>38 million U.S.
Affects 3x's more women than men



Large Unmet Medical Need

75% of patients not actively treated with Rx's due to poor efficacy
80% of patients on Rx's would try new therapies



High Pharmacoeconomic Burden

\$38 billion annual cost – U.S. (healthcare & lost productivity)
~ 150 million lost workdays – U.S.



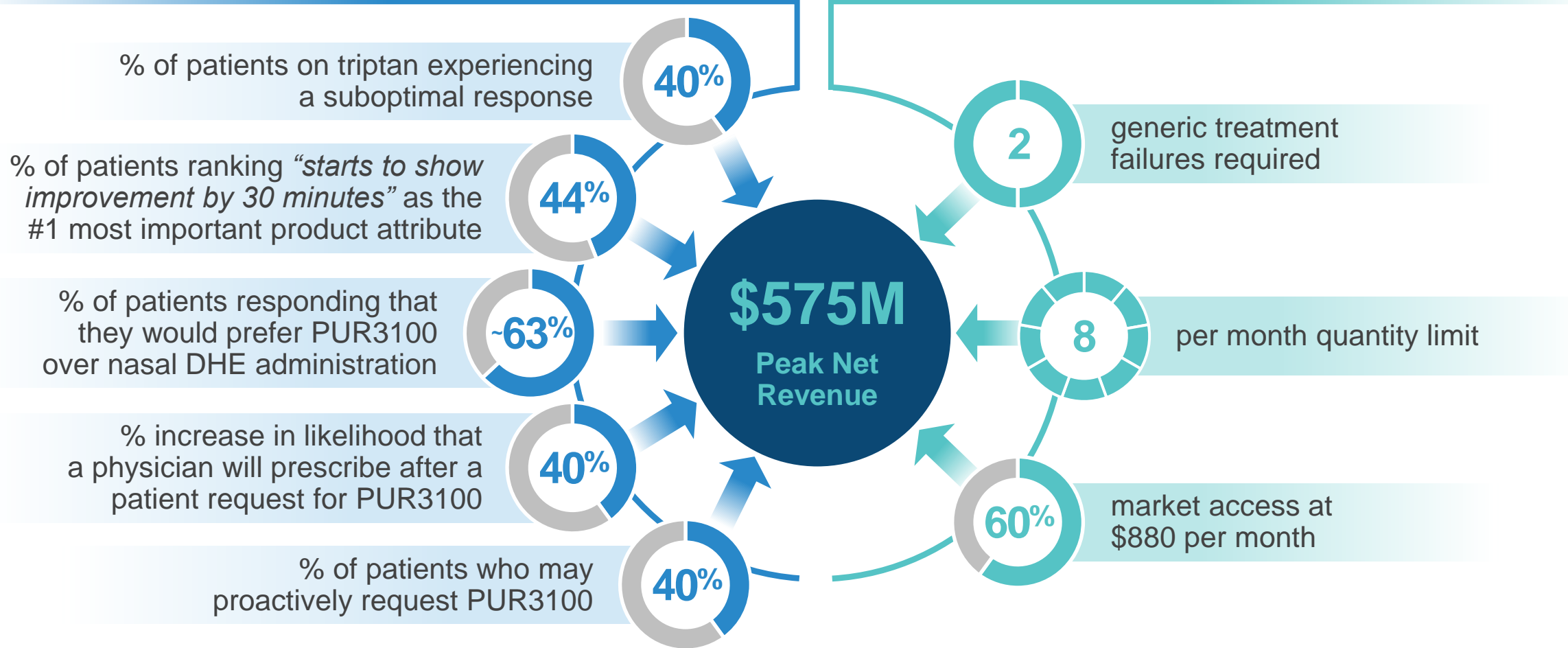
Acute Treatment

New preventative treatment options do not fully address the ongoing need for acute treatment of migraine
>50% of patients require acute care for breakthrough pain

PUR3100: \$575M Peak Net Revenue Potential at LOE in the U.S.

Physician and Patient Feedback

Payer Feedback



Source: Physician Interviews; Payer Interviews; Patient Research: ClearView Analysis. * Also includes discount for patient compliance, patient persistence, and gross-to-net adjustment and peak revenues expected at loss of market exclusivity, ~16 years post launch; Estimate based on ClearView Analysis, which took into account uninsured patients, patients who are unwilling to pay, and projected access restrictions placed by payers

Published Pain Freedom Data Earlier Than Two Hours

Drug/Route	Class	Dose	Pain Freedom <u>above Placebo</u> (%)				24h Rescue% ⁸
			0.5 hour	1 hour	2 hour	24 hour	
Rizatriptan Tablet/Wafer ^{1, 2}	Triptan	5mg	0	7	22	13	60 ⁴
		10mg	1	9	31	18	55 ⁴
Sumatriptan Nasal Spray ³		20mg	-	10	21	-	62 ⁴
Sumatriptan Tablet ³		50mg	-	3	17	10	50 ⁴
		100mg	-	5	21	16	44 ⁴
MAP0004 Inhaled ^{6, 7}	DHE	1mg	12 ⁶	15 ⁶	28 ⁶	15 ⁶	43 ⁷
Ubrogepant Oral tablet ⁵	CGRP	50mg	0	0	7	4	-
		100mg	0	0	9	7	-

PUR3100 is an investigational drug, the safety and efficacy of which has not been established.

- Indicates no reliable data available

¹Ferrari, M. D., et al. (2001). "Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials." *Cephalalgia* **21**(2): 129-136

²Ferrari demonstrated no difference in efficacy between tablet and wafer.

³Derry, C. J., et al. (2014). "Sumatriptan (all routes of administration) for acute migraine attacks in adults - overview of Cochrane reviews." *Cochrane Database of Systematic Reviews*(5).(moderate to severe pain)

⁴Data taken from product package insert separate from literature data and so may not be fully in agreement (likelihood of rescue needed estimated based on Kaplan-Meier plots)

⁵Dodick, D. W., et al. (2019). "Ubrogepant for the Treatment of Migraine." *New England Journal of Medicine* **381**(23): 2230-2241.

⁶Aurora, S. K., et al. (2009). "A Randomized, Double Blind, Placebo-Controlled Study of MAP0004 in Adult Patients With Migraine." *Headache: The Journal of Head and Face Pain* **49**(6): 826-837.

⁷Aurora, S. K., et al. (2011). "MAP0004, Orally Inhaled DHE: A Randomized, Controlled Study in the Acute Treatment of Migraine." *Headache: The Journal of Head and Face Pain* **51**(4): 507-517.

⁸Rescue medication defined as addition dose of drug or other rescue agent

Dr. Stewart J. Tepper

Professor of Neurology at the Geisel School of Medicine at Dartmouth College in Hanover, New Hampshire



Dr. Tepper is Director of the Dartmouth Headache Center in the Department of Neurology of Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire. Dr. Tepper received his undergraduate degree *cum laude* in the study of the nervous system/psychobiology from Yale College, New Haven, Connecticut, and attended Cornell University Medical College in New York City. He completed his Neurology residency at the Longwood Area Harvard program, Boston, Massachusetts, and has been board certified in Headache Medicine since 2006.

Dr. Tepper was Director of the Scottsdale Headache Symposium CME course of the American Headache Society from 2008 to 2020. He was Editor-in-Chief of the journal *Headache Currents* and Associate Editor for the journal *Headache* from 2012-2020. He has published more than 470 peer-reviewed manuscripts, editorials, and books on headache medicine. Dr. Tepper serves on the Executive Board of Directors and is the Corporate Liaison for the American Headache Society. He serves on the AHS Education, Exhibits, and Finance Committees. He also serves on the Governance Committee and Board of Directors of the American Migraine Foundation.

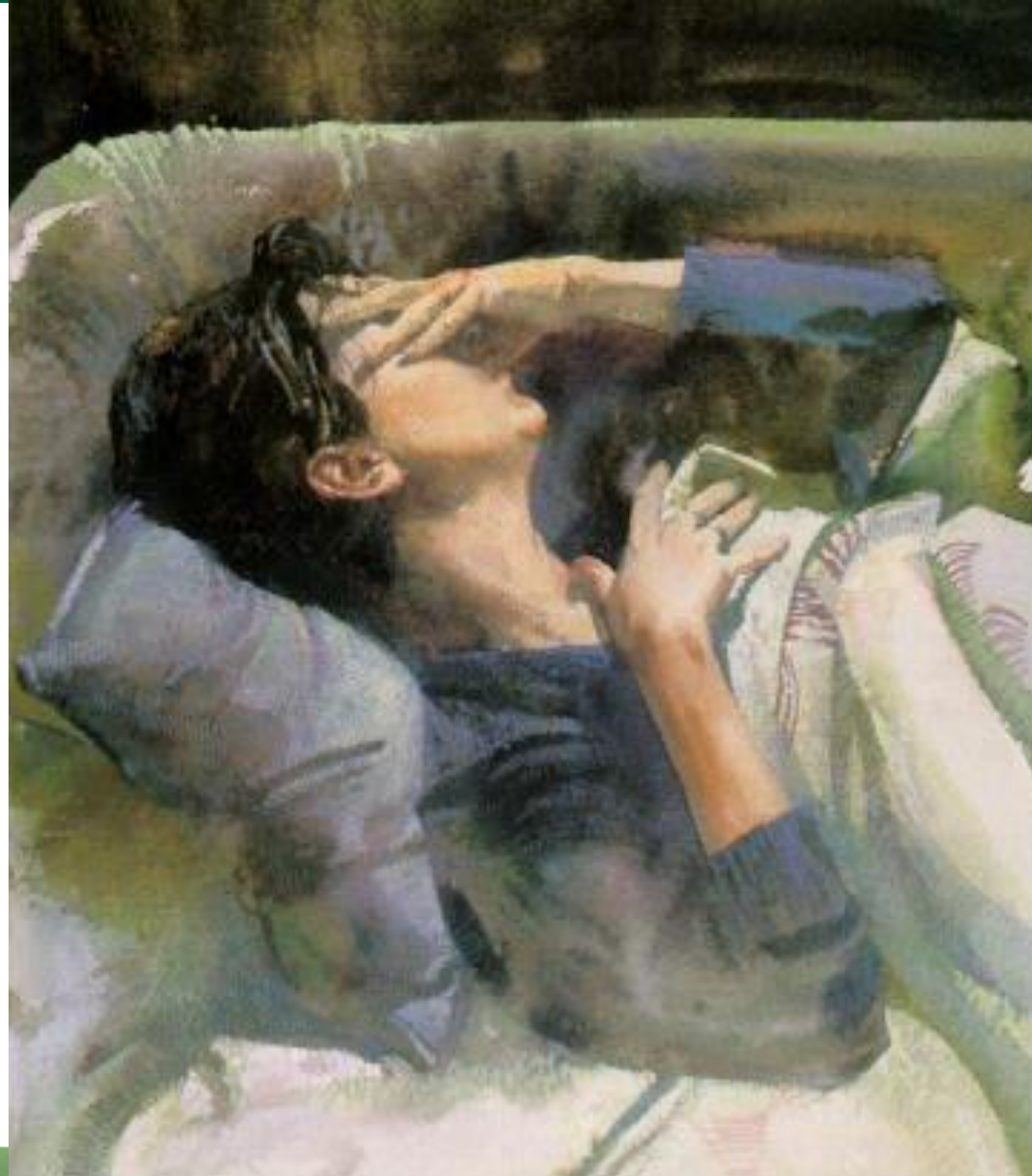
Migraine Current Treatment Landscape and Unmet Medical Needs



Stewart J. Tepper, MD
Professor of Neurology
Geisel School of Medicine at Dartmouth

Why is Migraine Important?

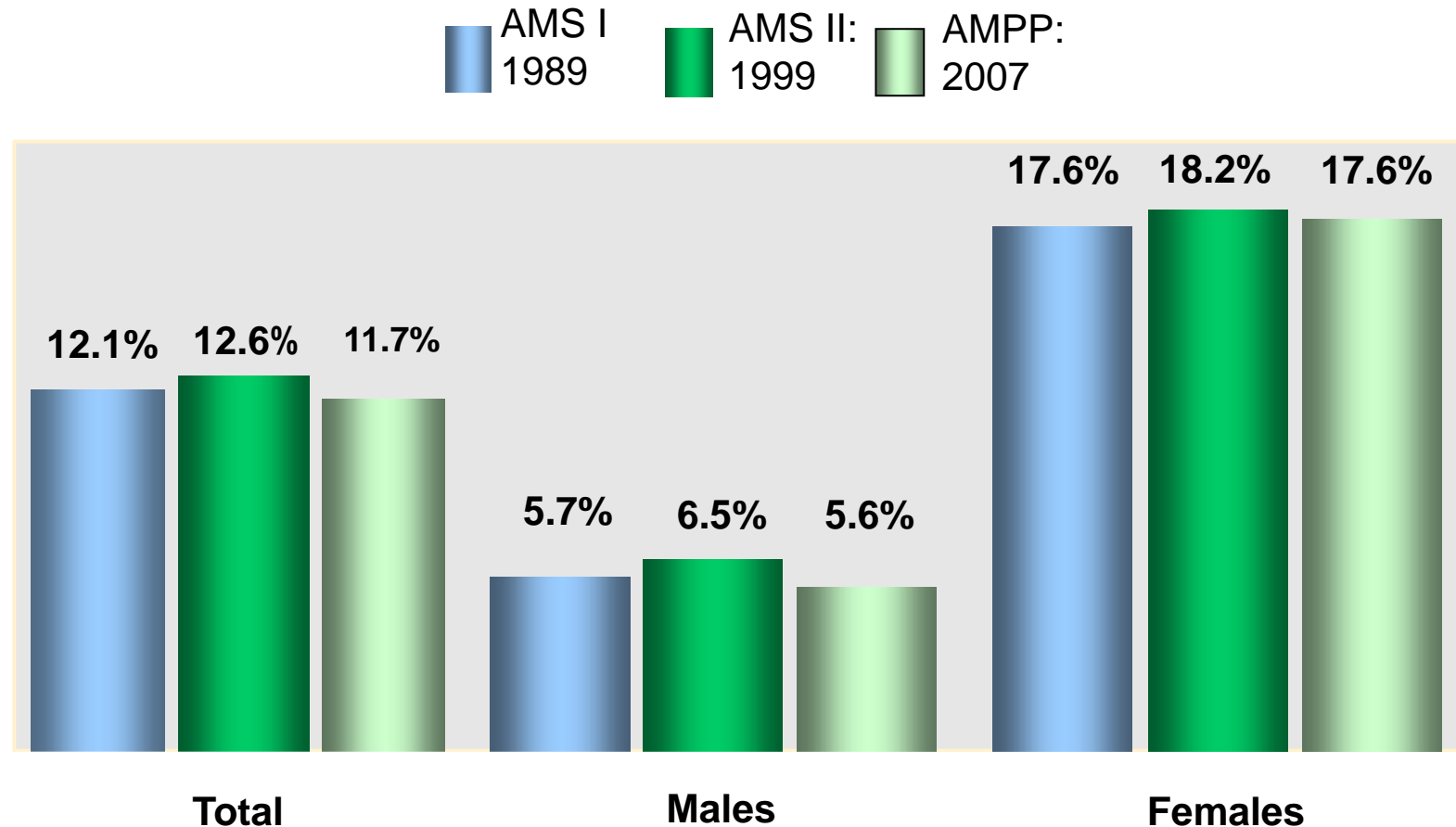
- It is very **common**
- It is very **disabling**
- It is very **treatable**



Prevalence and Incidence of Migraine



Migraine Prevalence: 3 Population-Based Studies: The Most Common Neurological Illness



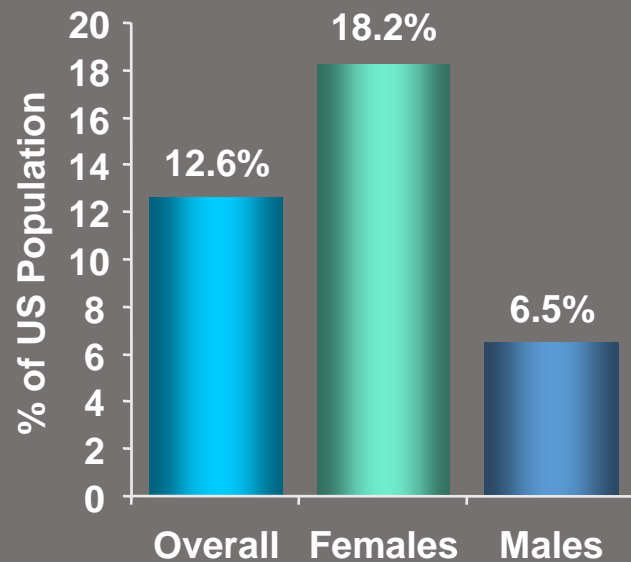
Stewart et al. *JAMA*. 1992;267:64-69.

Lipton et al. *Headache*. 2001;41:646-657.

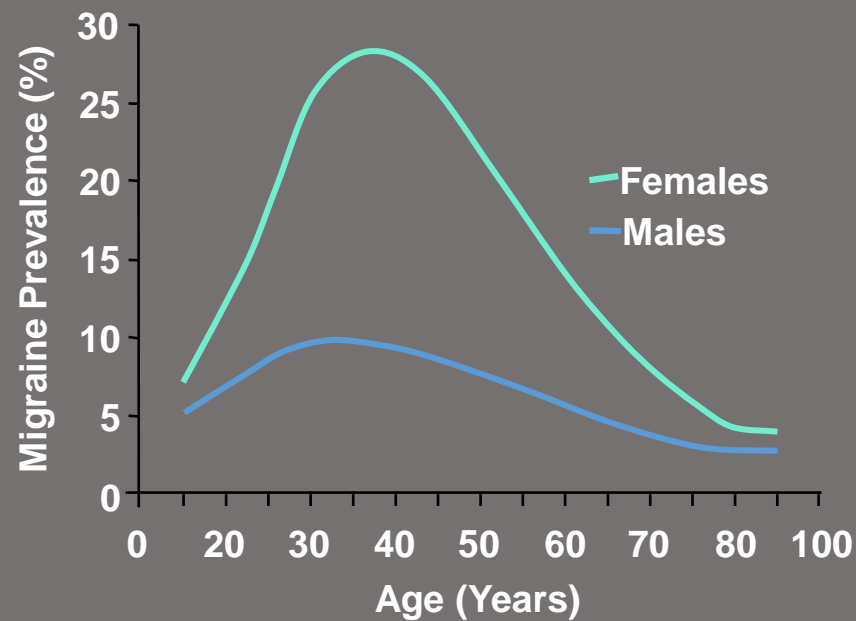
Lipton et al. *Neurology*. 2007;68:343-349.

Migraine is Most Common in Women and During Peak Productive Years

Prevalence of Migraine



Age-Associated Prevalence of Migraine

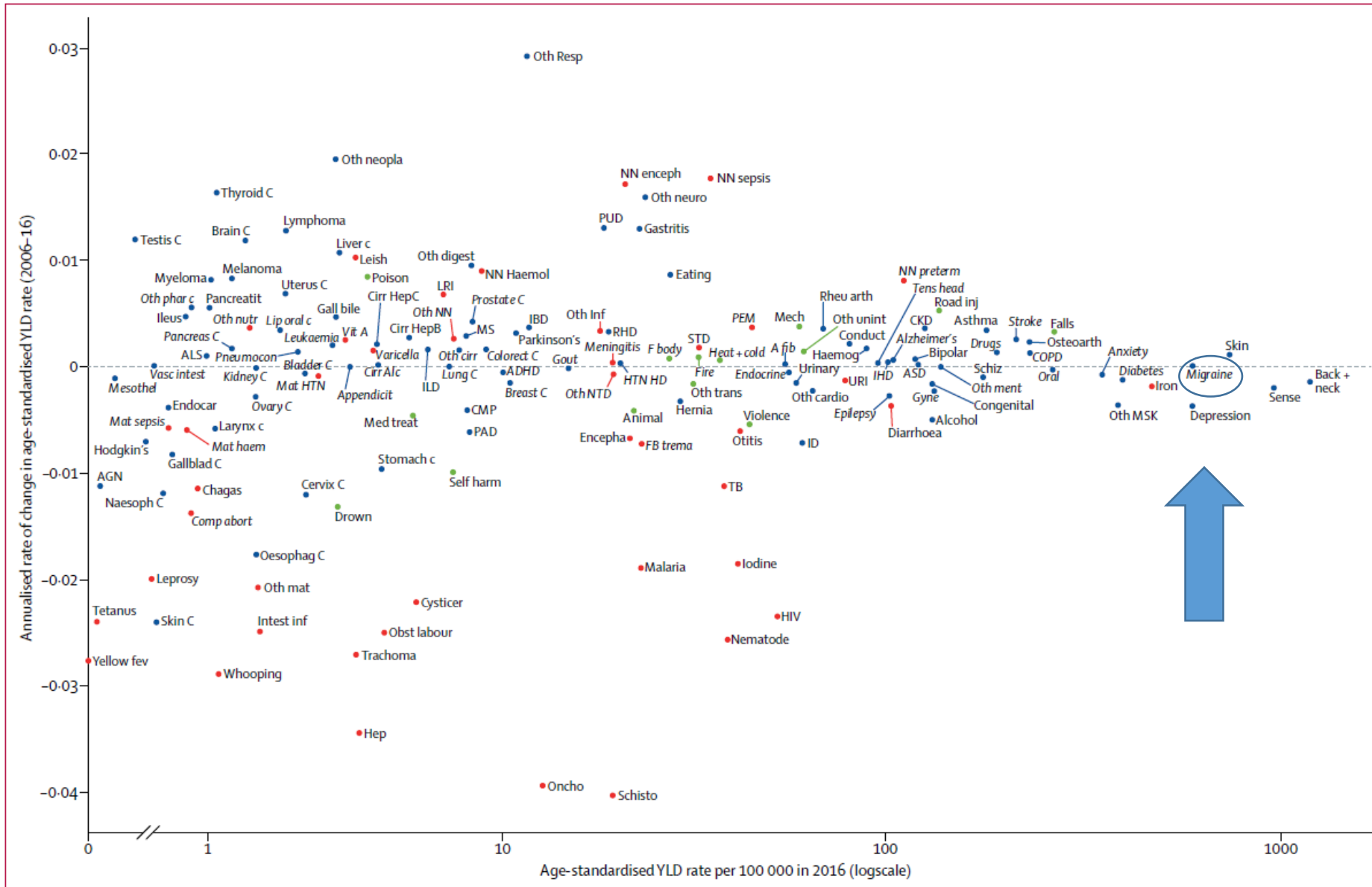


Lipton RB et al. *Headache*. 2001;41:646-657. (AMS II)

Global Prevalence: World Health Organization (WHO), 2016

- In 2016, had migraine #6 of the 10 greatest causes of years lived with disability
- Migraine was one of the two leading causes of YLDs in developed countries, and in the top five worldwide
- “Migraine (including medication-overuse headache, which is a form of chronic migraine) has become the second largest cause of disability in 2016”.

Migraine Years Lived with Disability (YLDs): WHO (2016)



Lancet 2017;390:1211-1259.

Acute Migraine Treatment



Clinical Goals for Acute Treatment of Migraine

- Pain-Free within 2 hours
- Freedom from Most Bothersome Symptom within 2 hours, picked by patients from sensitivity to light, sensitivity to noise, or nausea
- Lack of adverse events, good tolerability, and good safety
- A complete response, one and done, defined as a sustained 2-24 hour, Pain-Free response:
 - Pain-Free within 2 hours
 - No recurrence of headache for the next 22 hours
 - No use of additional medication or rescue medication for the next 22 hours
- Works deep in a migraine, when a patient is disabled, including waking up with a full-blown migraine or later in the day when the attack has peaked
- Works fast
- Works in the setting of nausea and vomiting

Triptans, Ergots, NSAIDs

- Triptans and ergots are serotonin (5-HT)_{1B/D} agonists
- Ergots also have non-serotonin activity
- Both classes inhibit release of CGRP
- NSAIDs inhibit migraine inflammation

Triptan Groups

Group 1

Faster onset, high potency

- Sumatriptan (IMITREX)- oral, liquid nasal, nasal powder, SC
- Sumatriptan/naproxen (TREXIMET)- oral
- Zolmitriptan (ZOMIG)- oral, liquid nasal
- Rizatriptan (MAXALT)- oral
- Almotriptan (AXERT)- oral
- Eletriptan (RELPAX)- oral

Group 2

Slower onset, lower potency

- Naratriptan (AMERGE)-oral
- Frovatriptan (FROVA)- oral

Gepants and Lasmiditan

- Gepants (ubrogepant/UBRELVY[®] and rimegepant/NURTEC[®]) are only dosed orally and have a slower onset of action (20% pain free at 2h)
 - Gepants block the CGRP receptor, so they only work in those with a CGRP biology
- Lasmiditan (REYVOW[®]) is FDA scheduled, associated with significant dizziness and drowsiness, and patients are forbidden to drive for 8 hours after taking a REYVOW tablet
 - Lasmiditan works with a serotonin mechanism

Currently Available Ergots

- Ergotamine tartrate (CAFERGOT®)
- Dihydroergotamine (DHE):
 - Injectable: SC, IV
 - Liquid nasal (MIGRANAL®, TRUDHESA®)



Unmet Acute Treatment Needs

- Access
- Triptans don't work deep into a migraine (central sensitization)
- Triptans are associated with migraine recurrence requiring re-treatment, often up to 40%
- Triptans are associated with genesis of acute medication overuse headache and chronic migraine
- Lack of good non-oral formulations beyond tablets (some patients do not like liquid nasal or injections)
- Triptans are either ineffective or poorly tolerated in 20-25% of patients

Unique Properties of DHE

DHE

- Works in the brain and outside the brain
- Targets multiple receptors to provide optimal response
- Fast onset:
 - MAP pulmonary DHE showed pain freedom in <30 minutes
- Complete response:
 - Pain free within 2 hours (or before) without headache recurrence, use of a second dose, or rescue medication (2-24 hour sustained pain freedom)
- Works deep in attacks when patients are most disabled, during central sensitization
- Perfect for migraine upon awakening (50% of migraine attacks)
- Perfect for long duration attacks such as menstrual migraine which occurs in 66% of women with migraine (12% of the population)
- Wake up, throw up, back up

Non-Oral Delivery

- Useful with nausea and vomiting
- Bypasses the gut
- Can be quicker in onset
- Useful in migraines with quick time to peak intensity
- Useful when patients are disabled by pain and migraine associated symptoms (central sensitization)

Liquid Nasal DHE as MIGRANAL®

Liquid nasal DHE as MIGRANAL® is available only in a patient-unfriendly device, delivers inconsistent results, and is ridiculously expensive (Valeant/Bausch)

During a migraine, the patient must:

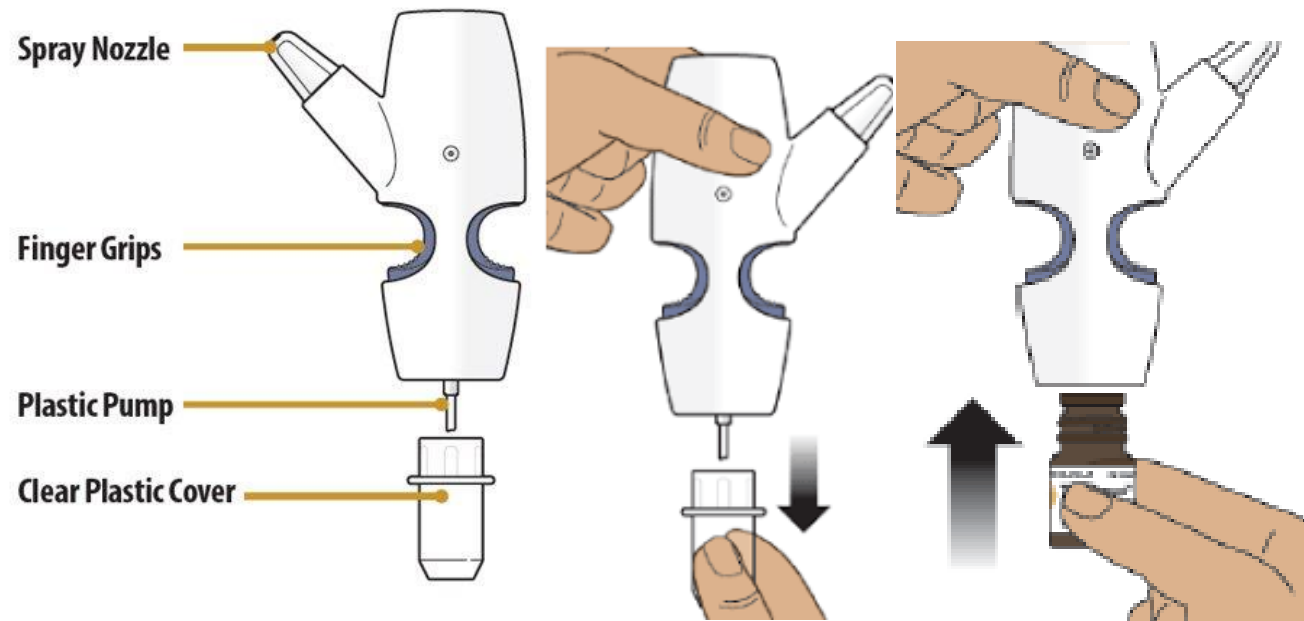
1. Remove the tin collar and not get cut
2. Remove the rubber stopper
3. Remove the top and bottom of sprayer
4. Screw into the glass ampule
5. Prime 4 times
6. One spray each nostril, do not sniff
7. Time 15 minutes
8. Repeat one spray each nostril, do not sniff
9. 4 sprays = one dose



Liquid Nasal DHE as TRUDHESA®

1. Open Liquid DHE vial: Remove the collar and rubber stopper
2. Remove plastic cover from the TRUDHESA device at the bottom
3. Screw on liquid DHE vial from the bottom
4. Prime the device
5. Spray once in both nostrils
6. Throw it away

(4 to a box)



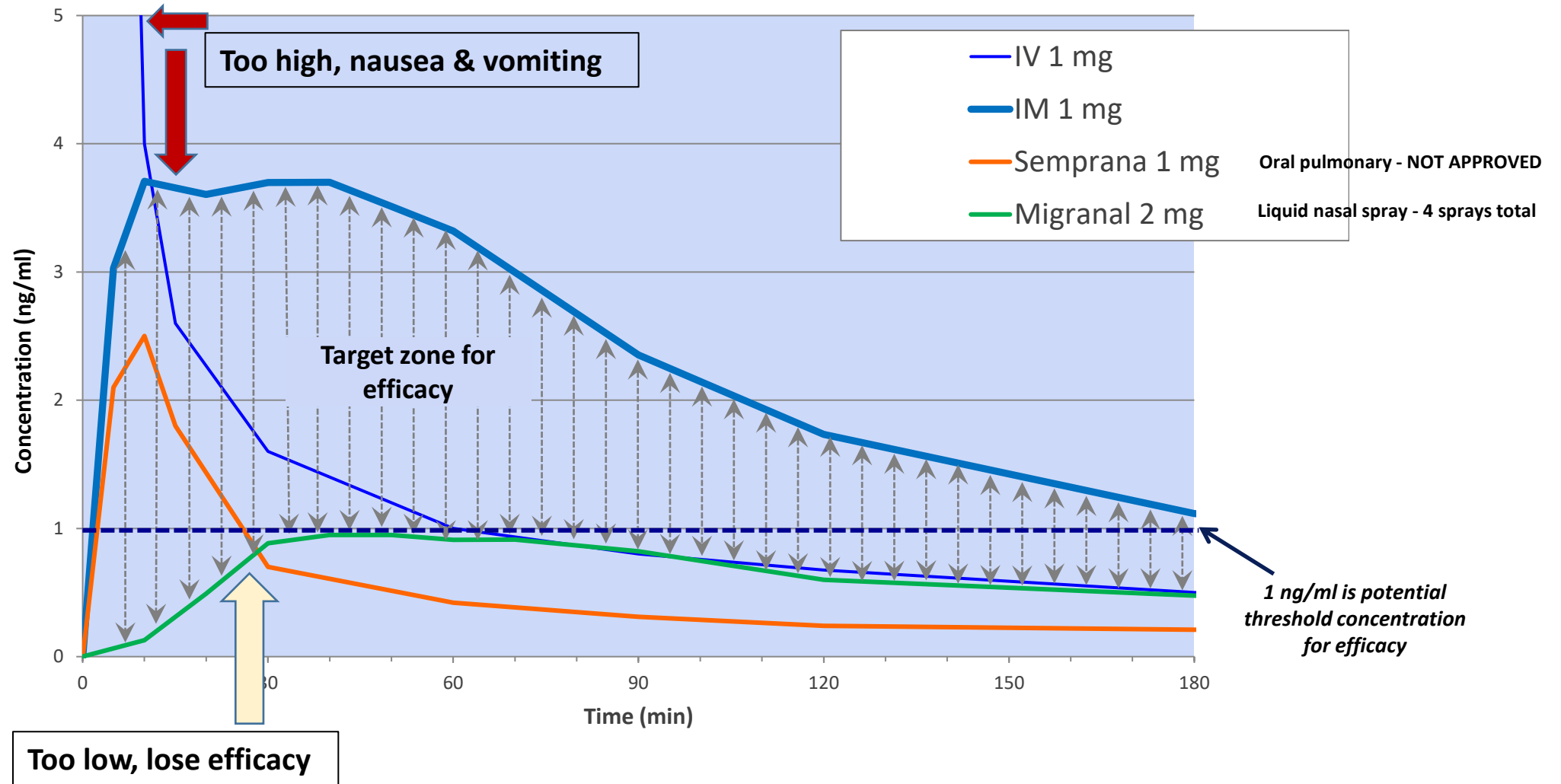
Summary of Acute Landscape and Unmet Needs

- Triptans do not work deep into attacks, can be poorly tolerated, are associated with recurrence and transformation to chronic migraine, and have poor non-oral formulations
- Gepants have a CGRP biology with 20% 2-hour Pain-Free
- Lasmiditan, which works on serotonin, is associated with dizziness and drowsiness and patients cannot drive for 8 hours, so can't be used in the day
- Current ergot delivery can be challenging and can be excessively expensive
- Some patients do not like nasal sprays or injections
- Non-oral acute medication delivery is a significant unmet need, given common morning attacks, nausea, vomiting, and quick time-to-peak intensity

Exposure and Efficacy: Thoughts on the Pharmacokinetics of DHE

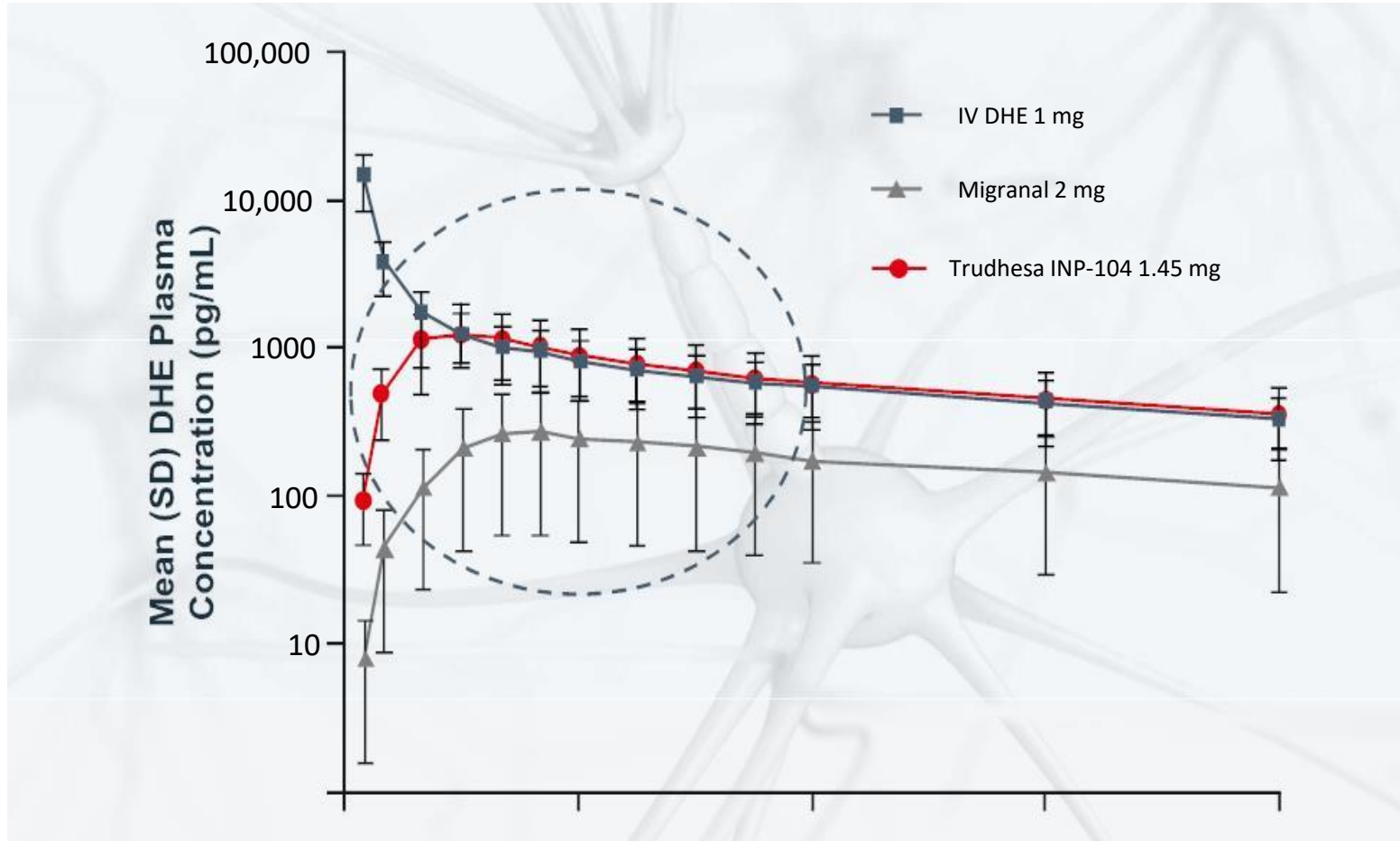


DHE Pharmacokinetics 1: IV/ IM/ MAP Inhalable/ MIGRANAL[®] Nasal



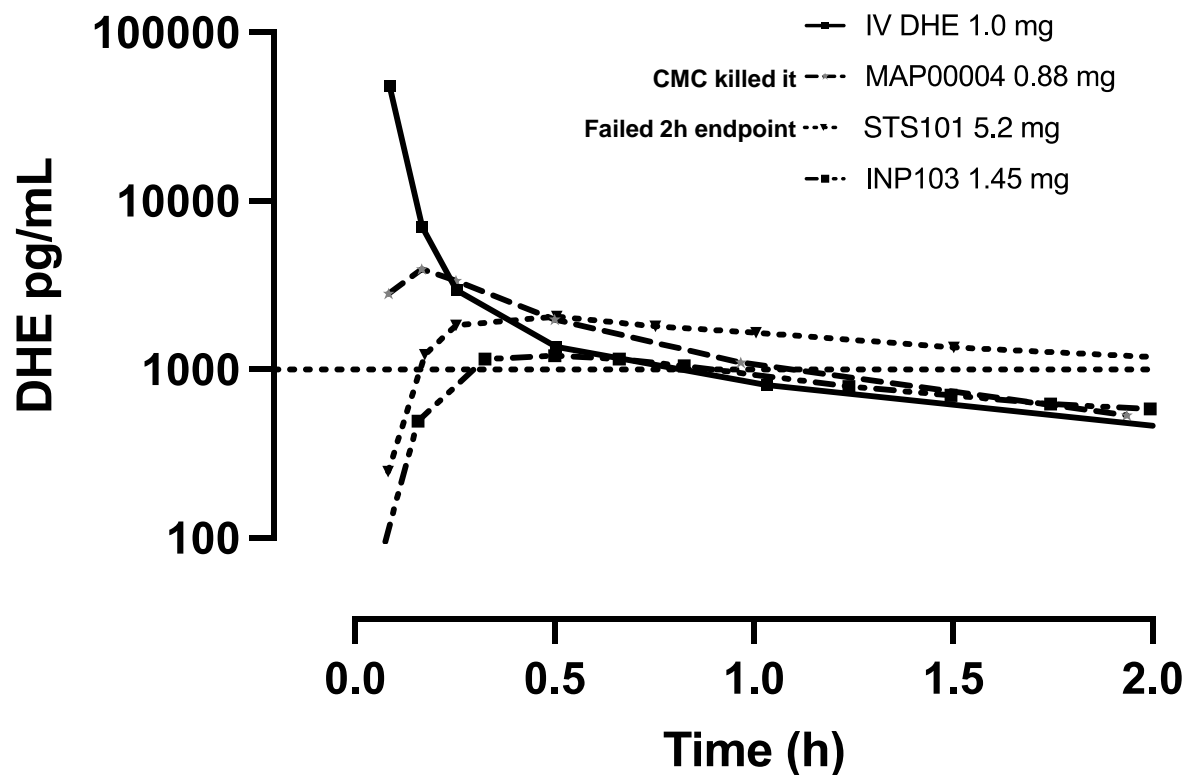
Kellerman et al., J Aerosol Pulm Drug Deliv 2013; Aurora et al., Headache 2011; Silberstein et al., Headache 2007; Edwards et al., Headache 2001; Humbert et al., Clin Pharm Ther 1996; Schran et al., Curr Ther Res 1994; Gallagher et al., Arch Neurol 1996

DHE pK 2: IV/ MIGRANAL Nasal/ TRUDHESA® Nasal



Shrewsbury SB, et al. *Headache*. 2019;59:394-409; Kellerman DJ, et al. *J Aerosol Med Pulm Drug Deliv*. 2013;26:297-306; Aurora SK, et al. *Headache*. 2009;49:826-837.

DHE pK: IV/ MAP inhalable/ Satsuma Nasal/ TRUDHESA®



Formulation	Nominal Dose (mg)	C _{max} (pg/mL)	T _{max} (min)	AUC _{0-2h} (pg.h/mL)	Therapeutic Gain over Placebo at 2h
IV DHE ^{1,2}	1.0	44,000	7	7,700 ³	-
MAP0004 ^{1,2}	1.0	2,500	12	1,400 ³	24% ⁶
STS101 ⁴	5.2	2,175	30	3,000 ³	3% ⁷
INP104 ⁵	1.45	1,301	30	1,600 ³	38% ^{8,9}
Migranal ⁴	2.0	300	47	375 ³	

1. Shrewsbury, S. B., et al., *Headache* **48**, 355–67 (2008).
2. Kellerman, D. J., et al., *J Aerosol Med Pulm D* **26**, 297–306 (2013).
3. AUC_{0-2h} estimated from published data
4. Albrecht, D., et al., *Headache* **60**, 701–712 (2020).
5. Shrewsbury, S. B., et al., *Headache J Head Face Pain* **59**, 394–409 (2019).
6. Aurora, S. K. et al. *Headache: J Head Face Pain* **51**, 507–517 (2011).
7. STS101 Phase 3 Summit Trial
8. Smith, T. R. et al. *Headache J Head Face Pain* **61**, 1214–1226 (2021).
9. Results is expressed as total response as no placebo was included

Conclusions on pK

- We want **lower C_{\max} to avoid AEs** (<5,000 pg/ml)
- Do we want a **T_{\max} to avoid AEs** (>10 minutes) ?
- We want **optimal C_{\max} for efficacy** (2,000-2,500 pg/ml)
- Prefer **inhalable** to parenteral or nasal

Thank You!



Margaret Wasilewski, MD

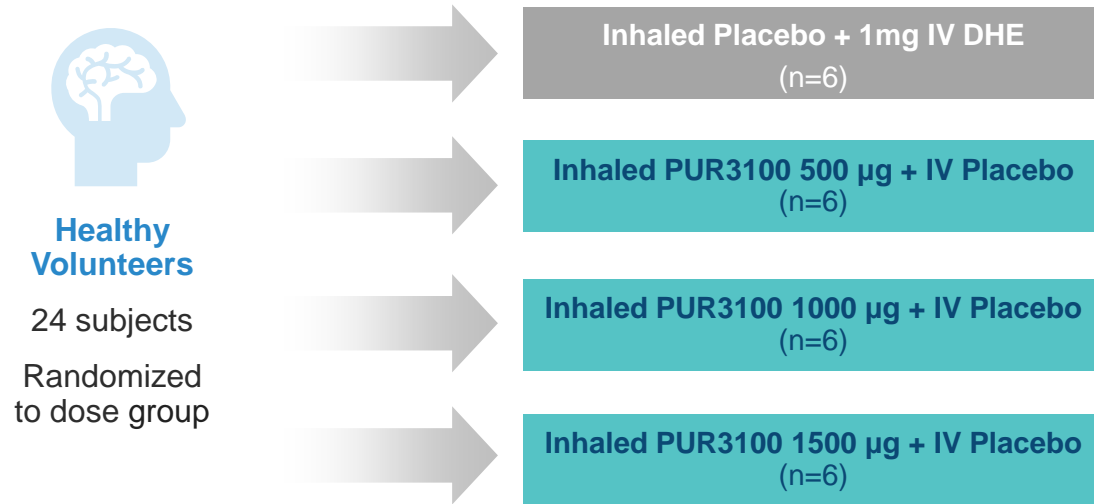
Pulmatrix Chief Medical Officer



PUR3100 Phase 1 Clinical Study to Evaluate Safety, Tolerability and Pharmacokinetics

Objective to demonstrate safety and comparative bioavailability of PUR3100 (pulmonary inhaled) relative to IV DHE

Randomized Double-blind, Double-dummy Single Dose Study in 24 Healthy Volunteers



Initial Phase 1 Study

- IV DHE or 1 of 4 doses of PUR3100 with matching placebo
- Assessment of safety, tolerability, and PK after administration of single dose
- PK data from IV DHE allows for preliminary assessment of comparable bioavailability between IV DHE and PUR3100



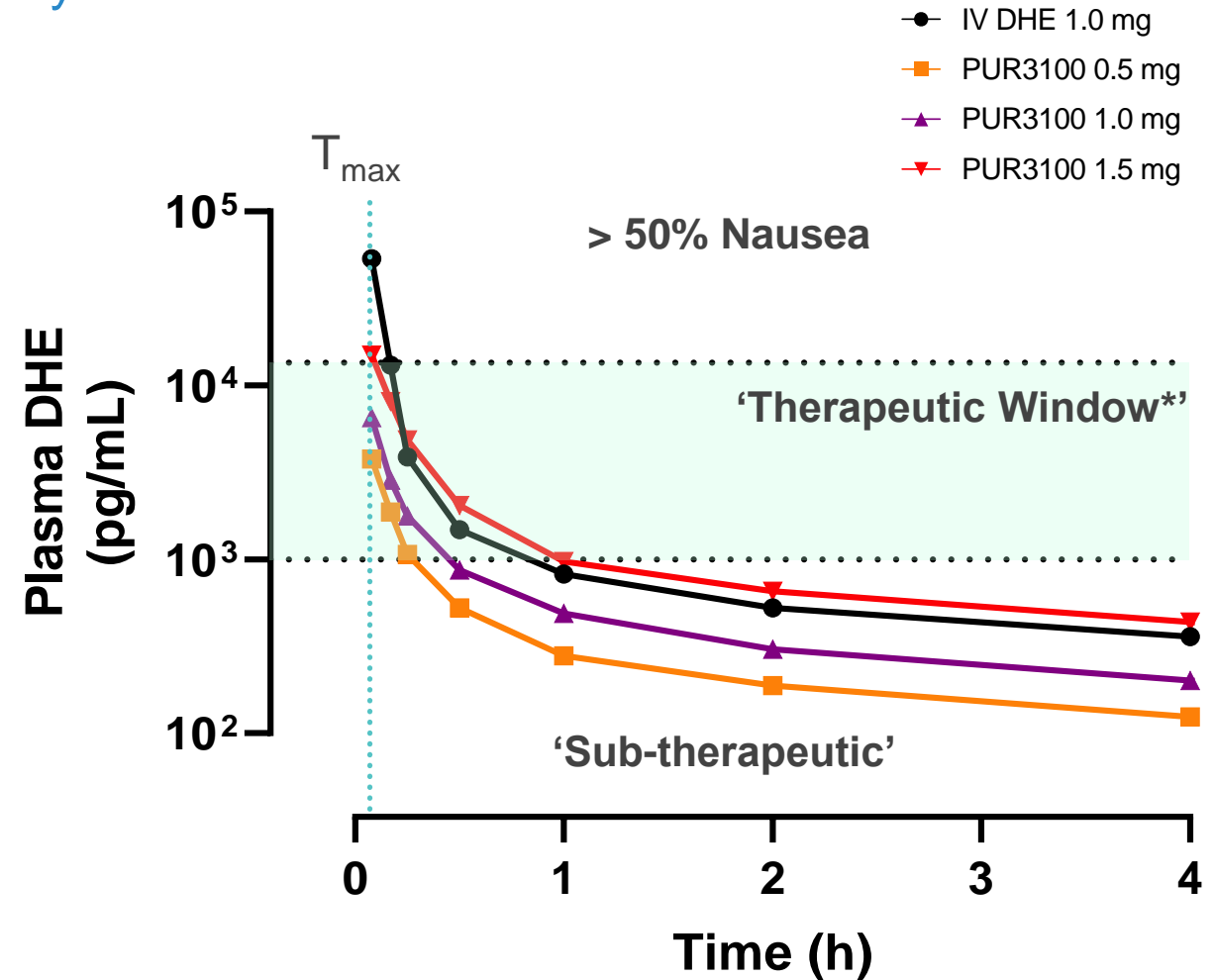
PUR3100 Achieved All Phase 1 Study Objectives and TPP

Objectives & Target Product Profile	Results
To determine the safety and tolerability of single doses of inhaled PUR3100 in healthy adult subjects	<ul style="list-style-type: none"> No vomiting was observed in the PUR3100 dose groups compared to IV DHE. Lower incidence of nausea in all of the PUR3100 dose groups relative to IV DHE.
To characterize the systemic pharmacokinetics (PK) of single doses of inhaled PUR3100 in healthy adult subject	<ul style="list-style-type: none"> PUR3100 achieves higher than projected C_{max} and T_{max} at 5 min after dose – ‘IV-like profile’
C_{max} therapeutic window between ~1,000 pg/mL and ~13,500 pg/mL	<ul style="list-style-type: none"> All three doses achieved ‘therapeutic’ exposure levels (>1000 pg/mL)
From TPP – T_{max} <15 minutes hoping for <10 minutes based on animal data comparison and MAP0004 T_{max} of 12 min	<ul style="list-style-type: none"> All PUR3100 doses had T_{max} within 5 min after dose
To explore the comparative PK of inhaled PUR3100 versus IV D.H.E. 45. Overall AUC not to exceed that of IV DHE while maintaining a lower C_{max} for safety	<ul style="list-style-type: none"> Kinetics showed superior C_{max} with similar AUC relative to IV DHE and similar T_{max}

PUR3100 Four Hour Exposure Profile is Similar to IV

Equivalent T_{max} with C_{max} below the range typically associated with nausea

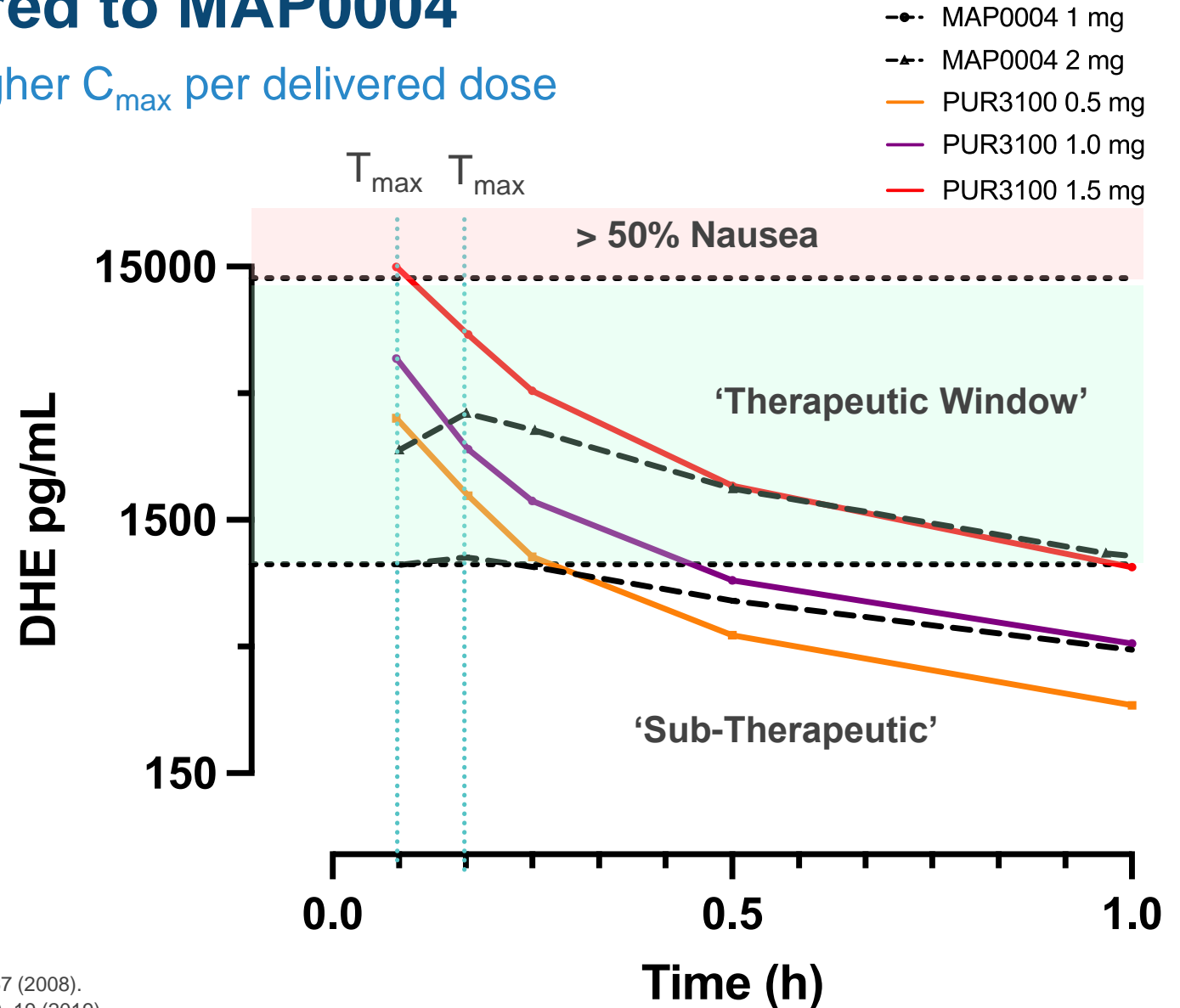
- T_{max} is at the first time point (5 min) for all subjects at all PUR3100 doses
- C_{max} at every dose is in the 'therapeutic window'
- The kinetic profile matches that of IV and differs from all other routes, including MAP0004
- PK profile of major metabolite, is similar to IV DHE 45



PUR3100 Kinetics Compared to MAP0004

PUR3100 is quicker to T_{max} and has higher C_{max} per delivered dose

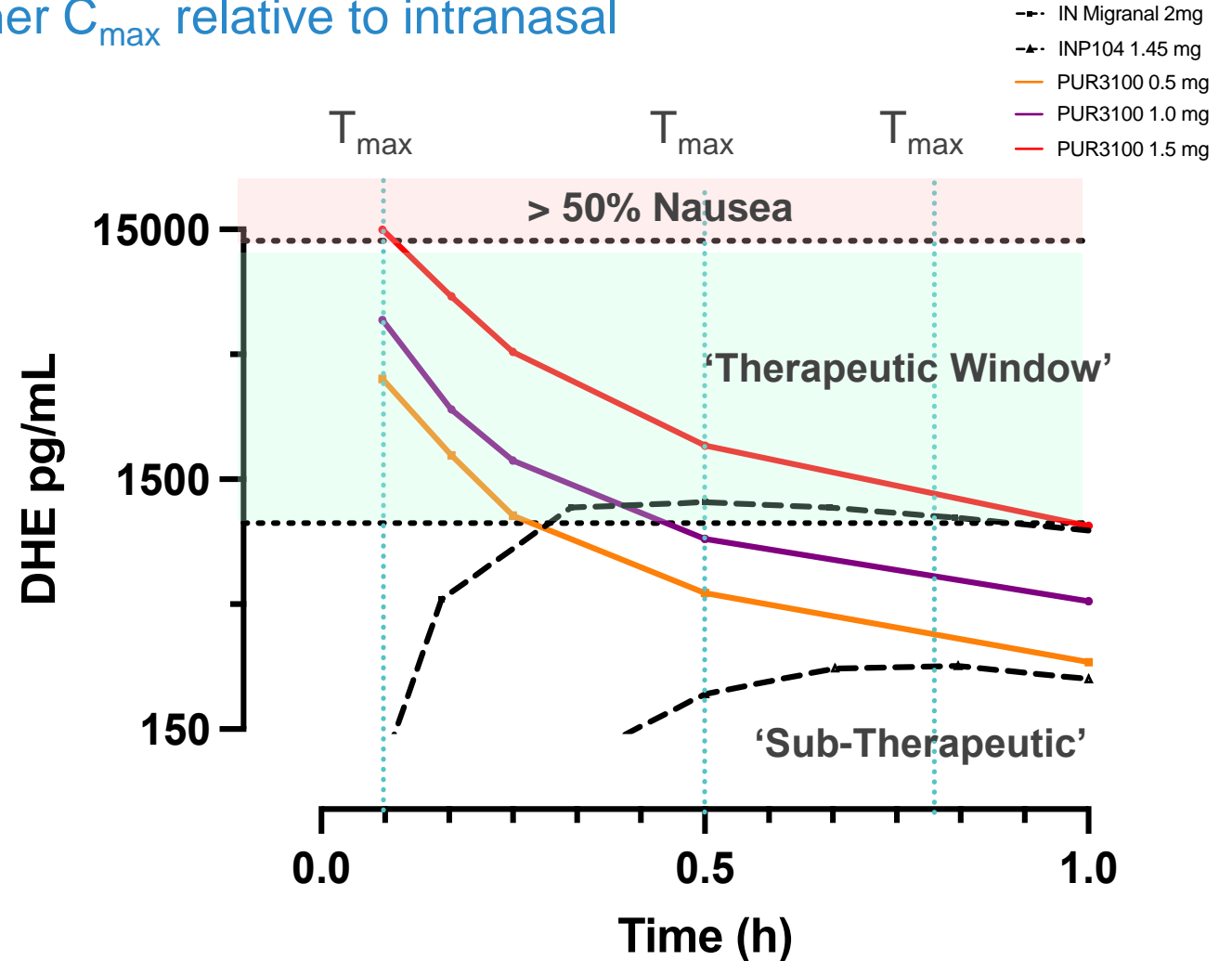
- T_{max} at 5 min for all PUR3100 doses versus 12 minutes in MAP Phase 1 study¹ (MAP Ph3 dose intermediate)
- Similar AUC at equivalent dose but with higher C_{max} with PUR3100
- Higher and faster exposure may drive faster receptor binding² and increase rate of pain relief
- DHE binds slowly but tightly resulting in longer duration of effect³



PUR3100 Has Improved Kinetics to Marketed DHE Therapies

PUR3100 is quicker to T_{max} and has higher C_{max} relative to intranasal

- T_{max} at 5 min for all PUR3100 doses versus 30 minutes for INP104¹ and 50 minutes for Migranal¹
- Substantially higher C_{max} than IN formulations with similar AUC
- Substantially faster and greater C_{max} potentially could translate into better treatment effects^{2, 3}



PUR3100: No Vomiting and Less Nausea Than IV DHE

Subject number	Active medication	C _{max} (ng/mL)	Duration of Dose (min)	Time to Nausea after dose (min)		
120	IV D.H.E. 45 1 mg	SNR	4	6	Nausea	chest tightness
109	IV D.H.E. 45 1 mg	112000	3	5	Nausea	suprapubic pain
105	IV D.H.E. 45 1 mg	100000	3	30	Nausea	Vomit
103	IV D.H.E. 45 1 mg	50800	4	4	Nausea	
123	IV D.H.E. 45 1 mg	49100	4	7	Nausea	
114	IV D.H.E. 45 1 mg	25300	5	12	Nausea	Vomit
220	IV D.H.E. 45 1 mg	11700	4			
115	PUR3100 1.5 mg	19300	5			
108	PUR3100 1.5 mg	18800	4			
101	PUR3100 1.5 mg	17700	6	37	Nausea	
111	PUR3100 1.5 mg	14500	4			
117	PUR3100 1.5 mg	10500	4			
122	PUR3100 1.5 mg	9090	5	6	Nausea	
116	PUR3100 1.0 mg	12200	4			
107	PUR3100 1.0 mg	10700	4	3	Nausea	
102	PUR3100 1.0 mg	7270	4			
110	PUR3100 1.0 mg	4130	4			
121	PUR3100 1.0 mg	3270	4			
118	PUR3100 1.0 mg	1520	7			
119	PUR3100 0.5 mg	SNR	4	9	Nausea	
106	PUR3100 0.5 mg	5150	5			
104	PUR3100 0.5 mg	4980	4			
112	PUR3100 0.5 mg	3960	5			
124	PUR3100 0.5 mg	3490	3	67	Nausea	GI upset
113	PUR3100 0.5 mg	2680	4			
219	PUR3100 0.5 mg	2370	4			

Nausea Incidence in Relation to C_{max}

C _{max} (pg/mL)	Nausea incidence n/N (%)
< 14,500	3/16 (19%)
> 14,500	6/8 (75%)
> 9,000	8/14 (57%)
< 9,000	1/10 (10%)



PUR3100 is an investigational drug, the safety and efficacy of which has not been established.

*Duration of Dose = T₀ – IV end. Where T₀ is the start time of first inhalation and IV end is the end time of the IV administration.

*Time to Nausea after dose = AE onset – T₀. Where T₀ is the start time of first inhalation and AE onset is the time of Nausea onset.

SNR = sample not received – data excluded from PK analysis; TEAE=treatment emergent adverse event

Migraine – Pulmonary Inhaled DHE Therapy Potential Advantages

What Do Patients Want?

1	2	3	4	5
Fast Acting Pain Relief (15–30 Minutes)	Effective When Taken at Any Time During a Migraine	Long Lasting Relief	Ease of Dosing	Minimal Impact on Patient’s Regular Activities
Fast onset of action through early T_{max} and sustained target engagement ^{1,2}	Migraine upon awakening, quick to peak intensity, rescue for breakthrough	24+ hour headache relief through sustained target engagement ^{1,3}	Inhaled preferred over intranasal, convenient device and administration	Absence of: nausea, lethargy, medication overuse, dysgeusia ⁴



1. Aurora, S. K., et al. (2011). "MAP0004, Orally Inhaled DHE: A Randomized, Controlled Study in the Acute Treatment of Migraine." *Headache: The Journal of Head and Face Pain* 51(4): 507-517.
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Thank You!

Questions?

