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Role of MRGPRX2 in Migraine

April 13, 2026

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Agenda and Speakers

Introduction	**Luis Peña**
Overview of Migraine	**Stewart Tepper, MD**
Role of Mast Cells and MRGPRX2 in Migraine	**Greg Dussor, PhD**
EVO756 Migraine Development Program	**Jeegar Patel, PhD**
Closing Remarks	**Luis Peña**

EVMN Speakers

Luis Peña
Evommune
President & CEO

Jeegar Patel, PhD
Evommune CSO

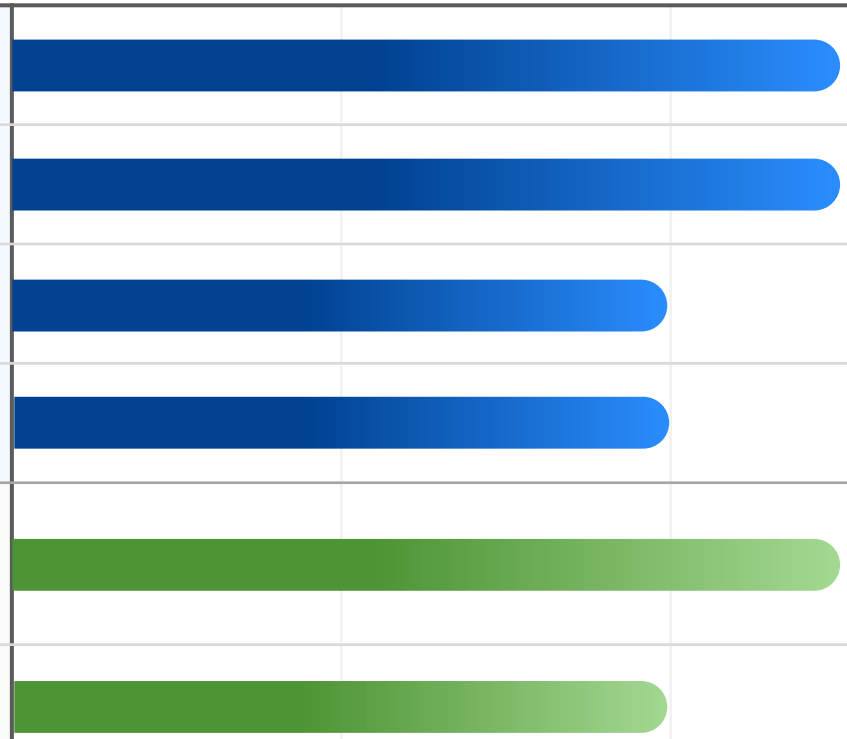
Guest Speakers

Stewart Tepper, MD
VP, NEINH
Professor of Neurology, Dartmouth

Greg Dussor, PhD
Professor, UT Dallas

Our Inflammation Portfolio

Program / Target	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Next Anticipated Milestone
EVO756 MRGPRX2	Chronic Spontaneous Urticaria					• Phase 2b Data (Q2 2026)
	Atopic Dermatitis					• Phase 2b Data (H2 2026)
	Migraine					• Phase 2 Trial Initiation (mid-2026)
	Other Indications					• Phase 2 Trial Initiation (2027)
EVO301 IL-18	Atopic Dermatitis					• Positive Phase 2a POC: Full data to be presented at an upcoming medical meeting • Phase 2b Trial planning underway
	Ulcerative Colitis					• Phase 2 Trial planning underway



Advancing Multiple Preclinical Programs Toward Clinical Proof-of-Concept

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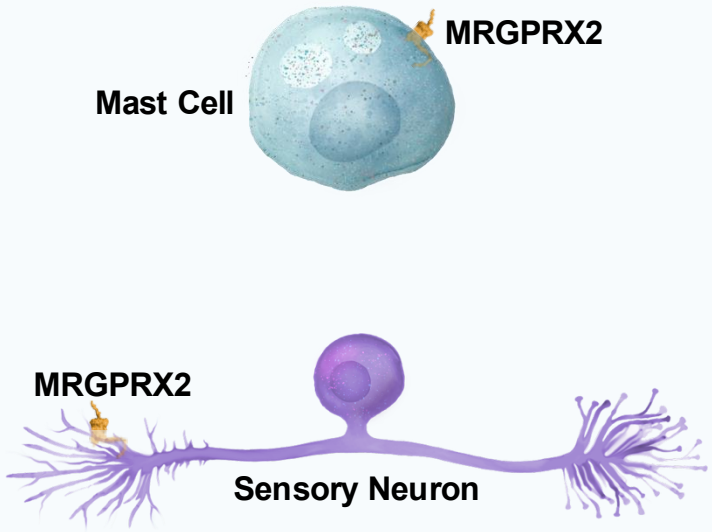
EVO756: Broad Spectrum Oral Anti-Inflammatory Potential

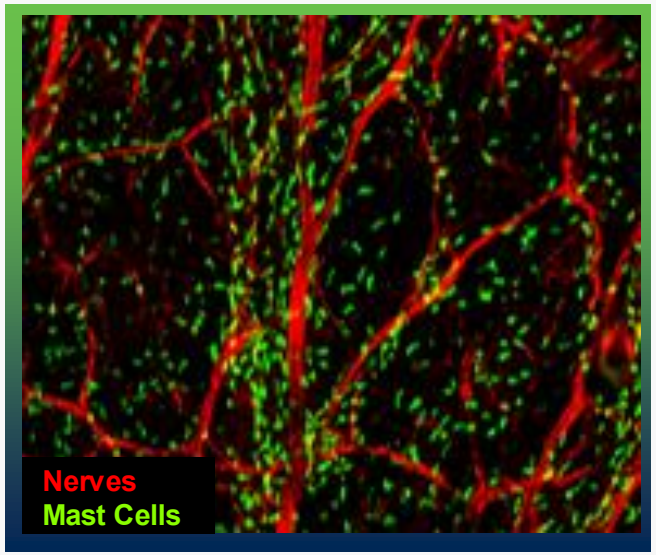
Potential First-Line Oral Across Several Specialties

- Potent and highly selective small molecule
- Oral convenience could drive adoption across multiple indications
- Anticipate favorable safety and tolerability profile

MRGPRX2 Expressed on Both Mast Cells and Sensory Neurons



Mast Cells and Sensory Neurons Are Found in Close Proximity



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EVO756 Development Roadmap: Demonstrate Proof-of-Concept and Expand into Additional Indications

Cutaneous	Neurological	Respiratory	Other
✓ Chronic Urticarias	✓ Migraine[2]	○ Asthma	○ Irritable Bowel Syndrome
✓ Atopic Dermatitis[1]			○ Interstitial Cystitis

EVO756 Development Strategy

Initially pursue inflammatory diseases with:

- Underserved patient population
- Economic viability
- Well-defined clinical and regulatory development pathway

1. Proof-of-concept based on skin challenge test in healthy volunteers. 2. Proof-of-concept supported by positive clinical data for PACAP (MRGPRX2 ligand) inhibition in migraine prophylaxis (Lundbeck)

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MRGPRX2 is a Novel Migraine Target with Potential to Address Neuroinflammatory and Mast Cell Drivers of Migraine

Strong Scientific Rationale for EVO756 in Migraine

Disease-Relevant Expression	MRGPRX2 is expressed in human trigeminal neurons and meningeal mast cells
Preclinical Validation	*in vivo* headache models support pathogenic role for MRGPRX2
Translational Insights	Multiple MRGPRX2 ligands induce migraine in humans
Clinical Proof-of-Concept	mAb inhibition of MRGPRX2 ligand (PACAP) shows clinical benefit

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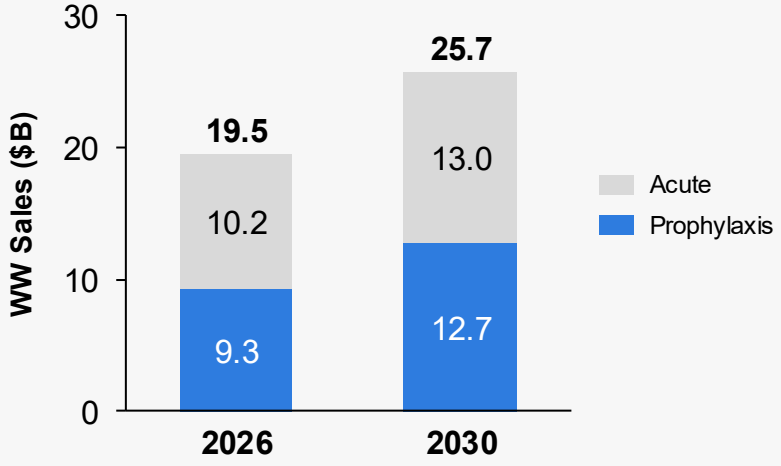
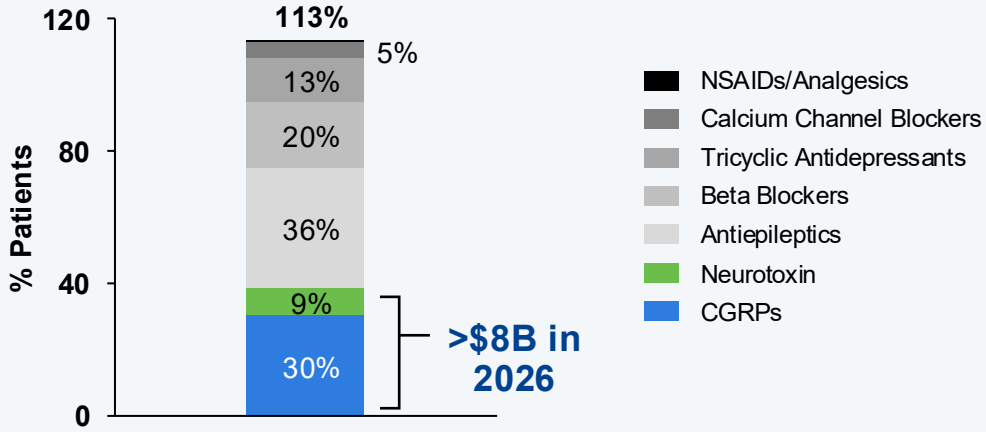
High Demand for Preventative Migraine Therapy

Prevention Drives ~50% of Migraine Market Value



>75M People Living with Migraine Worldwide

Most Patients Remain on Legacy Preventives — Targeted Therapies Drive Sales



~20M Global Patients Eligible for Preventative Therapy

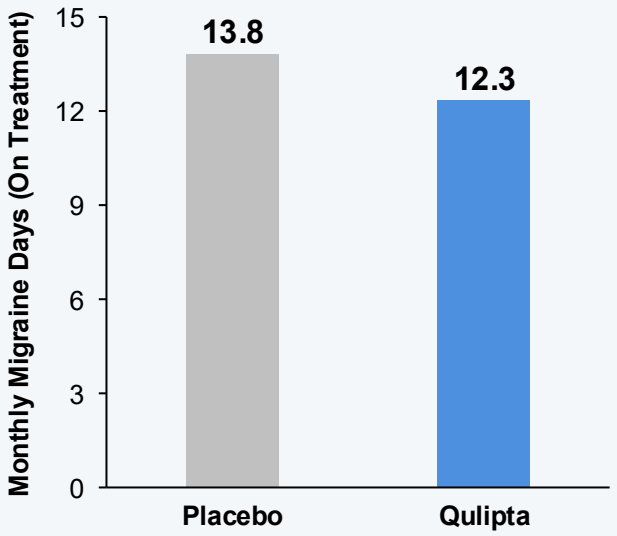
Source: Clarivate "Migraine: Disease Landscape and Forecast" (February 2026). Note: Sales represent 7 Major Markets (US, EU5, Japan); Percent of patients by therapy type exceeds 100% due to co-prescribing; % patient numbers by therapy reflect US patient breakdown.

Innovation in Migraine Prevention Has Been Limited to CGRPs

Preventive Innovation has Clustered Around a Single Target (CGRP)

Advanced Treatments	Class	Route of Administration
QULIPTA (atogepant) tablets	CGRP	Oral QD
Nurtec ODT		Oral EOD
vyepti		IV
Emgality		SC
aimovig erenumab		SC
AJOVY		SC
BOTOX onabotulinumtoxinA	Neurotoxin	IM

Migraine Burden Persists Despite Oral CGRP Therapy



- Many chronic patients still experience >12 monthly migraine days on treatment

High Unmet Need in Migraine Prevention

Limited Therapeutic Diversity

- Only CGRP inhibitors and neurotoxin

Inadequate Efficacy

- ~45% of patients do not achieve 50% improvement

Tolerability Challenges Remain

- CGRPs associated with constipation, hypertension, Raynaud's, nausea, allergic and injection site reactions

Source: Qulipta Prescribing Information from pivotal trial in chronic migraine patients.

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OVERVIEW OF MIGRAINE

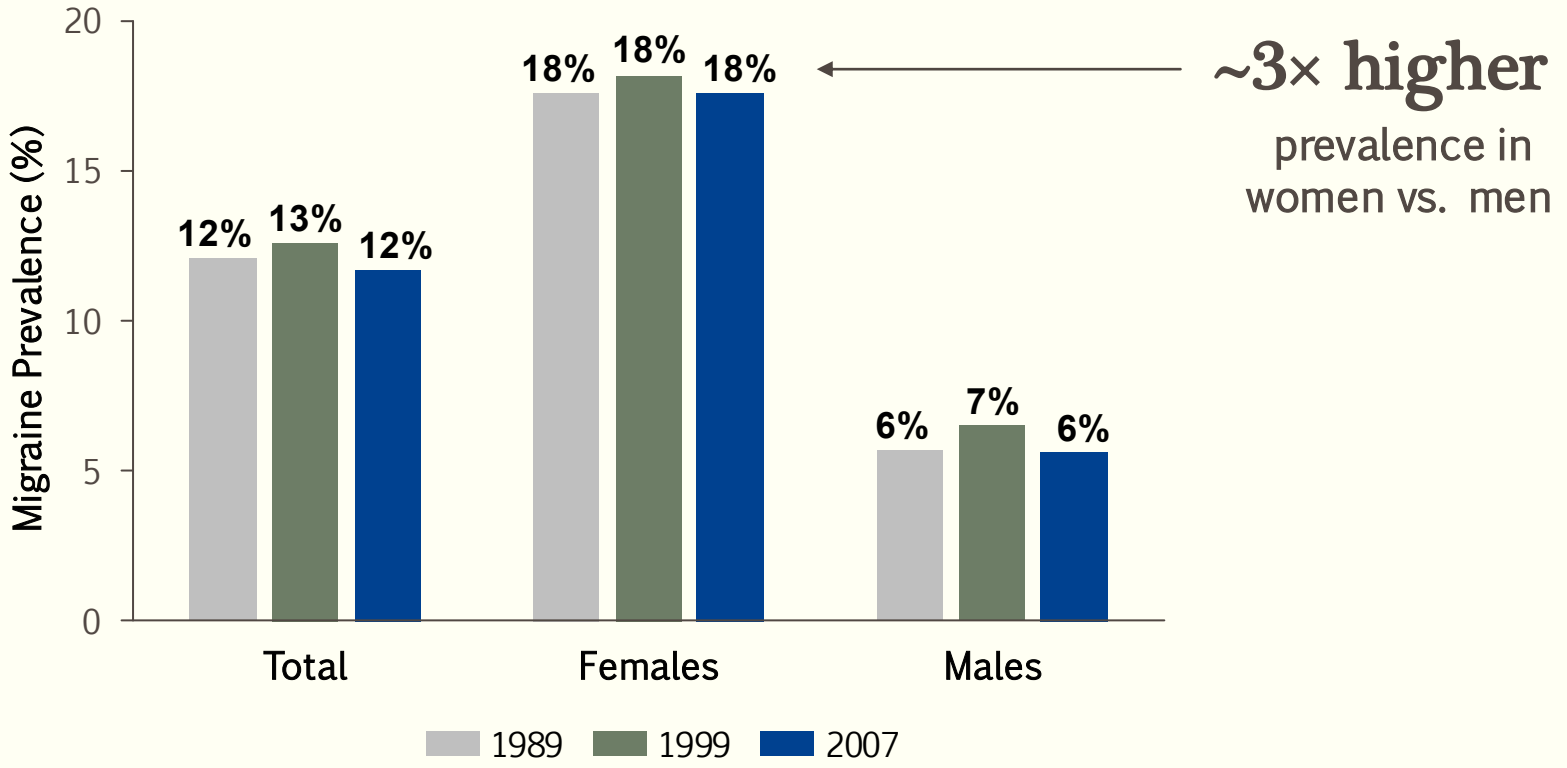
Stewart Tepper, MD

Vice President, The New England Institute for Neurology and Headache

Professor of Neurology, Geisel School of Medicine at Dartmouth

Migraine is Highly Prevalent and Disproportionately Affects Women

Population-Based Studies Show Consistent Prevalence



Sources: Stewart *et al.* (1992; PMID1727198); Lipton *et al.* (2001 PMID11554951); Lipton *et al.* (2007, PMID17261680).

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High Prevalence Impacts Patients and Communities

Scale of Disease

- ~25% of the population has migrainous illness
  - ~12% episodic, ~2-4% chronic
  - Additional 10–20% meet criteria for probable migraine[1]
- ~40M migraineurs in the U.S. (>75M globally)
- Prevalence peaks during prime working-age years

Clinical and Societal Impact

Daily Functioning

- 3rd Leading cause of *disability*

Work & Career

- 50% report *reduced productivity*

Emotional Well-Being

- Elevated rates of *anxiety* and *distress*

Social Life & Family

- Missed events and *reduced participation*

1. Headache disorder symptoms missing one migraine criterion, also felt to be a type of migraine; Sources: Lipton *et al.* (2001, PMID11554951); Lipton *et al.* (2007, PMID17261680); Diamond *et al.* (2007, PMID17371352).

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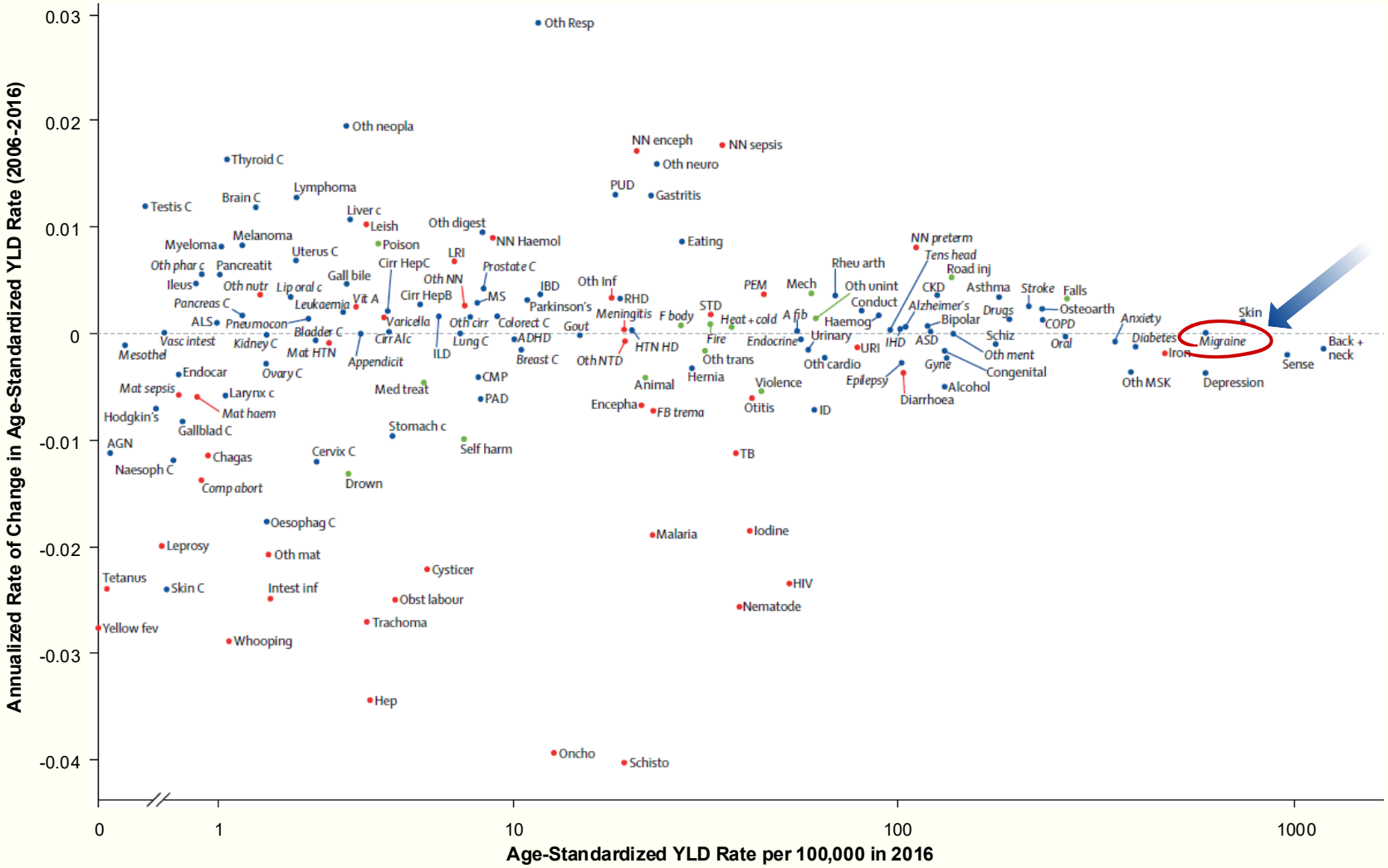
Migraine is a Leading Cause of Disability Worldwide

Global burden of disease study across 328 conditions



YLD = Years Lived with Disability. Source: *The Lancet* (2017, PMID28919117).

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Frequent Attacks Drive Meaningful Functional Impairment

Burden exceeding many chronic systemic conditions

Attack Frequency

- **25%:** ≥4 severe attacks per month
- **35%:** 1-4 attacks per month
- **38%:** <1 attack per month

Daily Life

- **3.8–5.6:** days per year bedrest per patient
- Many patients report impaired functioning between attacks

Impact

- **~74M:** days of restricted activity annually
- **~112M:** bedridden days annually
- **>180M:** days per year of impaired or lost function

Sources: Lanteri-Minet *et al.* (2024, PMID:39160483). Lipton *et al.* (2001, PMID11554951); Stang and Osterhaus (1993, PMID8436495); Cull *et al.* (1992).
Note: impact metrics pertain to U.S.

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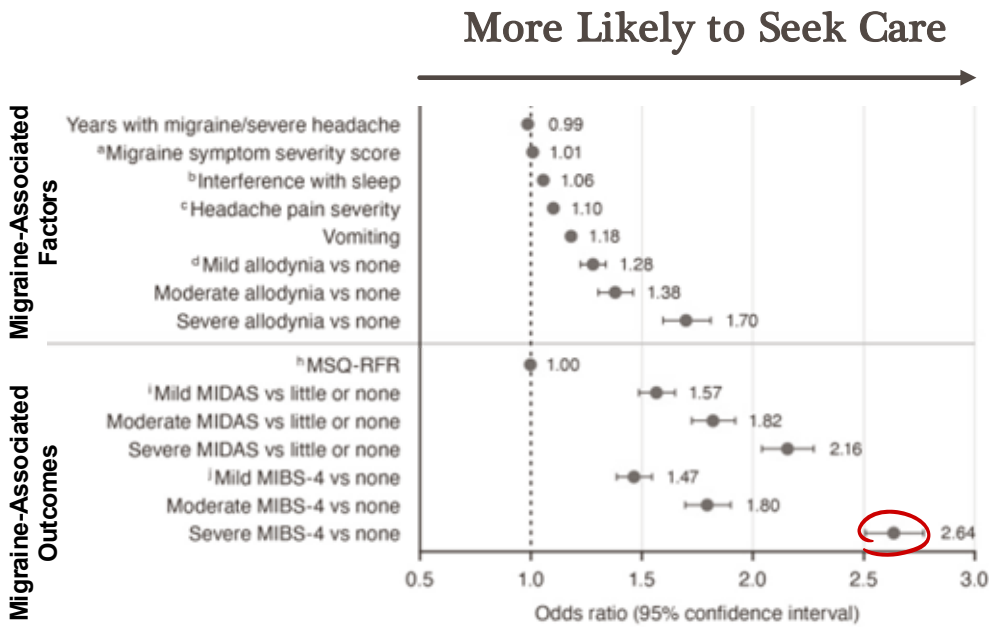
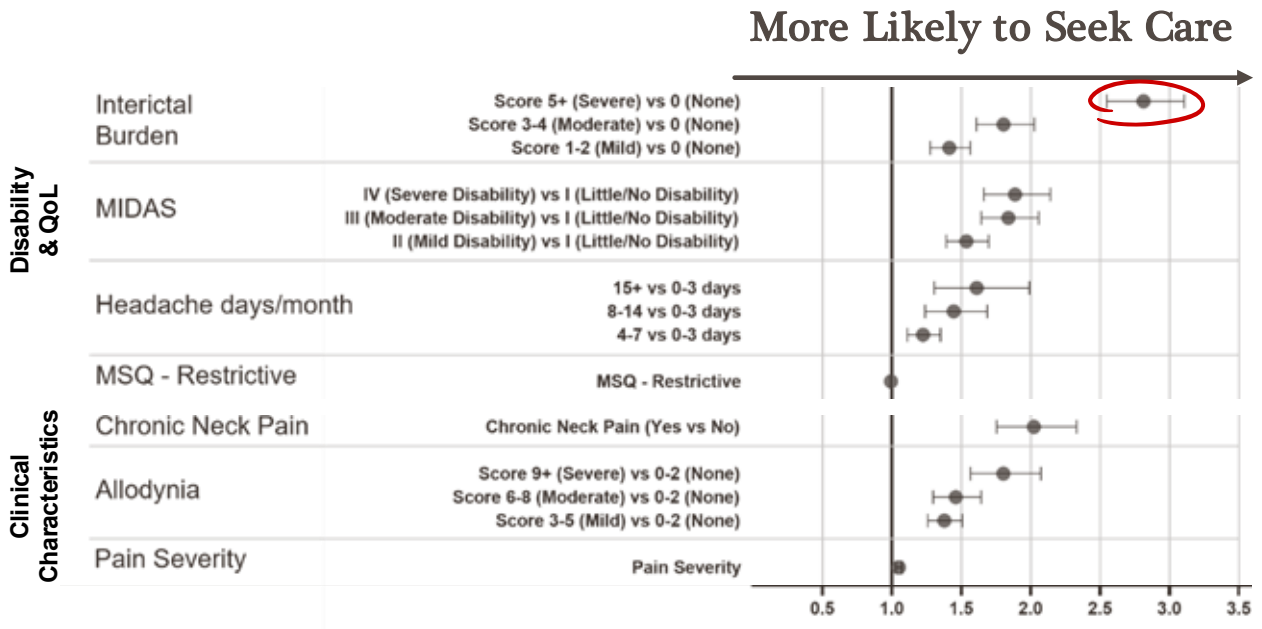
Interictal Burden is the Primary Driver of Treatment-Seeking in Migraine

What Brings Patients to Care is Not Just Attacks — It's Persistent Functional Impairment





Note: The OVERCOME study evaluated ~100,000 participants with migraine in the US, EU, and Japan. Sources: Ashina S *et al.* (2024; PMID38785227); Pascual *et al.* 18th Biennial MTIS 2022; Sep 8 – 11, 2022. MTIS22-EP-018.

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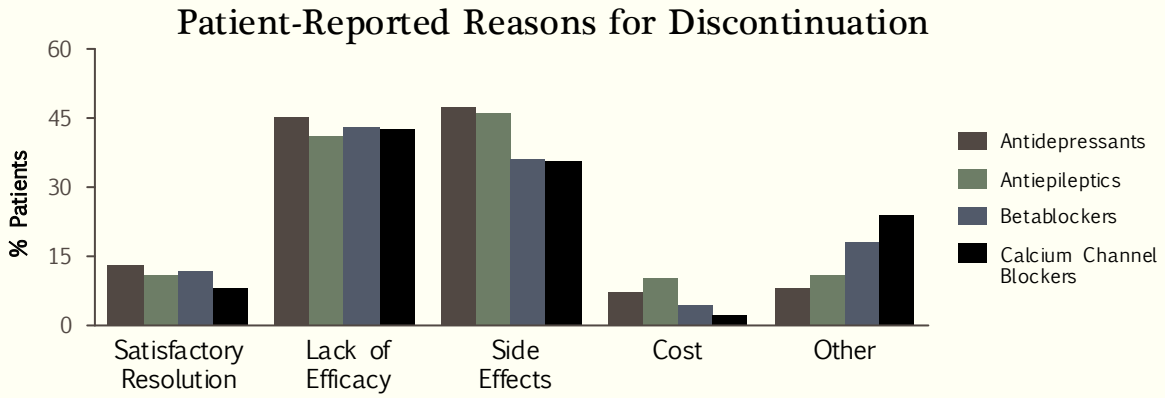
Step Therapy Fails Patients with Migraine

New AHS guidelines recommends removal of non-specific step therapy

Legacy Preventives Lack Efficacy and are Rarely Sustained



- >80% patients discontinue traditional non-specific preventive therapy within 1 year; sign of significant clinical futility
- Discontinuation driven by lack of efficacy and poor tolerability

Treatment Paradigm is Shifting Away from Step Therapy

- Historically required failure of ≥2 non-specific therapies before CGRP access
- 2024 AHS position statement eliminates step-through requirements
- Payers increasingly aligning with guideline and professional society position – based recommendations for access

Step therapy delays access to effective treatment in a high-burden, low-adherence disease

Charles *et al*, (2024). Calcitonin gene-related peptide targeting therapies are a first line option for the prevention of migraine: an American Headache Society position statement update (2024); Hepp *et al*. (2015, PMID25164920); Blumenfeld *et al*. (2013, PMID23458496).

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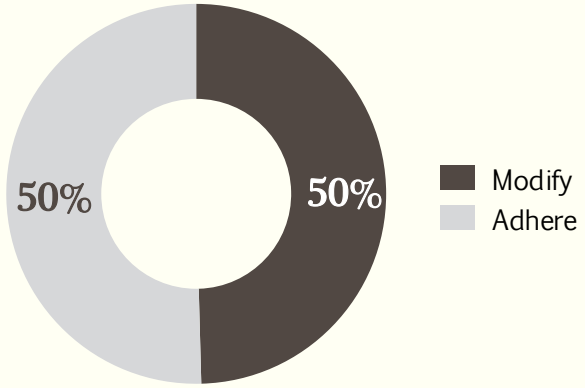
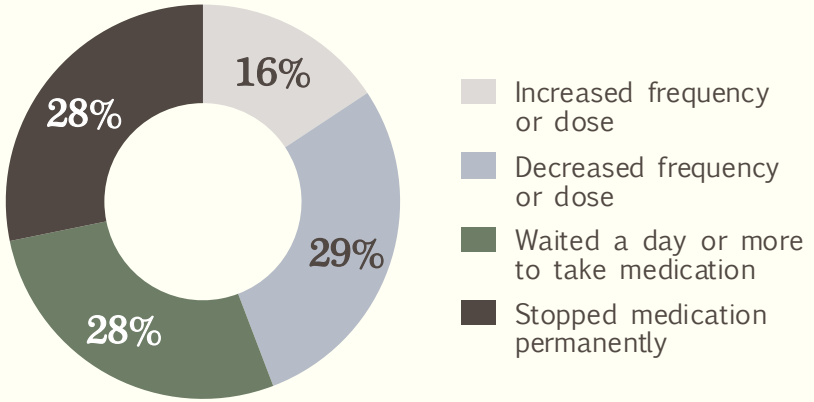
Patients Frequently Self-Manage Preventive Therapy Without Medical Guidance

50% of Patients Modify Preventive Therapy without Physician Consultation



- Self-adjustment of these medications poses the potential for serious health effects[1]
- Treatment modifications primarily driven by lack of efficacy and adverse events

Modifications Reflect Instability in Disease Control



- ~28% stop therapy entirely
- ~45% change dose or frequency
- ~28% delay or skip dosing

Unsupervised treatment changes introduce risk and reflect inadequate disease control

Note: Serious health effects may include withdrawal seizures from abrupt discontinuation or precipitous lowering of anti-epilepsy drug dosing and/or withdrawal arrhythmias from acute stopping of a β-blocker. Source: Real-world prospective observational study: Kawata *et al.* (2021, PMID 33594686).

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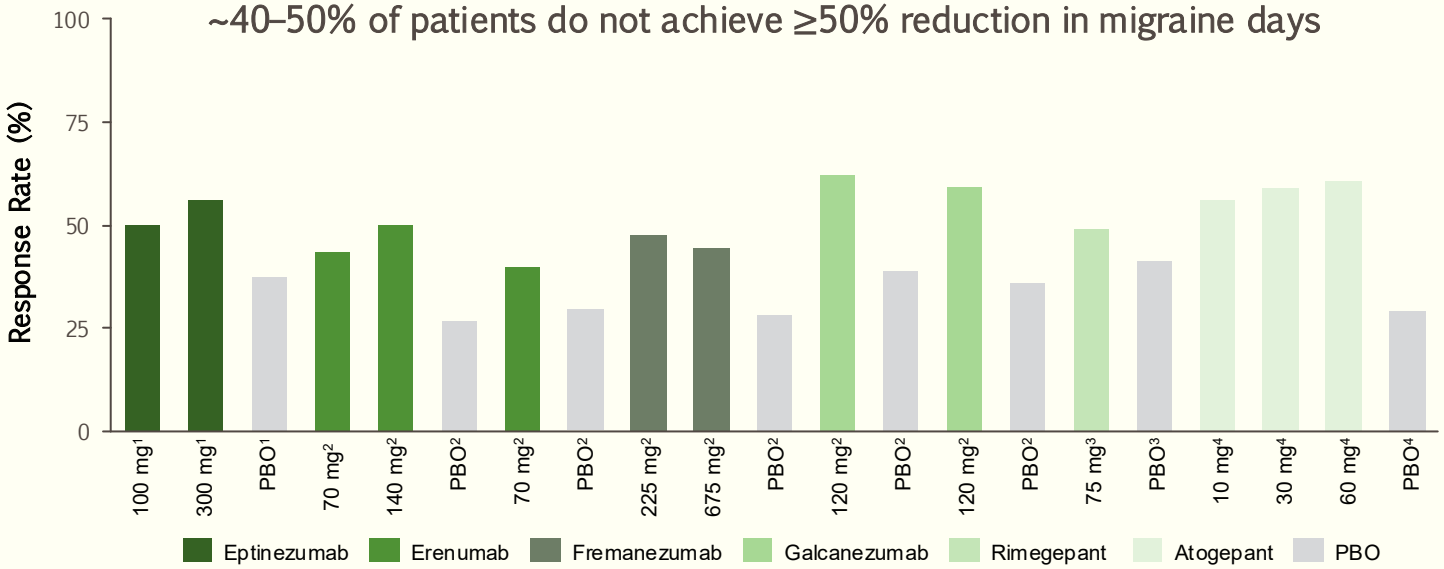
CGRP: Scientifically and Clinically Proven — Yet Substantial Room for Improvement, Especially for Oral Options

Human Biology Established CGRP as a Key Migraine Driver…

- CGRP levels rise during migraine attacks and normalize after treatment with abortives
- IV CGRP can trigger migraine headaches in humans
- Multiple monoclonal CGRP antibodies and oral gepants reduce monthly migraine days

… However Clinical Response to CGRP Inhibitors Often Incomplete



- Additionally, many chronic patients continue to experience >10 migraine days/month
- Tolerability and persistence challenges limit real-world benefit

Clinical data from pivotal trials of CGRPs approved for migraine prevention (episodic data shown). Sources: PMID33211930, Prescribing Information for Rimegepant, Atogepant. 1. Q12W. 2. Q4W. 3. QOD. 4. QD.

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Special Articles

Cephalalgia
An International Journal of Headache

International Headache Society

Setting higher standards for migraine prevention: A position statement of the International Headache Society

Cephalalgia
2025, Vol. 45(2) 1–11

DOI: 10.1177/03331024251320608
journals.sagepub.com/home/cep
Sage

Simona Sacco[1], Messoud Ashina[2,3], Hans-Christoph Diener[4], Faraidoon Haghdoost[5], Mi Ji Lee[6], Teshamae S. Monteith[7], Bronwyn Jenkins[8], Mario F. P. Peres[9], Patricia Pozo-Rosich[10,11], Raffaele Ornello[1], Francesca Puledda[12], Fumihiko Sakai[13], Todd J. Schwedt[14], Gisela Terwindt[15], Gloria Vaghi[16,17], Shuu-Jiun Wang[18,19,20], Fayyaz Ahmed[21], and Cristina Tassorelli[16,17]

"The opportunity for a more fulfilling ***migraine-free life***, with potential impact on society as a whole"

- The goal should be migraine freedom in prevention, and even with anti-CGRP therapies, we are ***not there yet!***

Key Clinical Insights

- Migraine is the most common neurologic illness and a leading cause of disability, with profound impact on patients, families, and society
- Interictal burden—the pervasive impact between attacks—is a primary driver of treatment-seeking
- Older non-specific preventive therapies are limited by modest efficacy, tolerability issues, and low adherence
- Low cost is irrelevant if therapies are not used or not tolerated
- The AHS position statement now calls for migraine-specific therapies as first-line, rather than step edits through non-specific options
- Significant unmet need remains for new targeted therapies and for oral options
- The goal of care is migraine freedom

Role of Mast Cells and MRGPRX2 in Migraine

Greg Dussor, PhD

Professor, Department of Neuroscience
The University of Texas at Dallas

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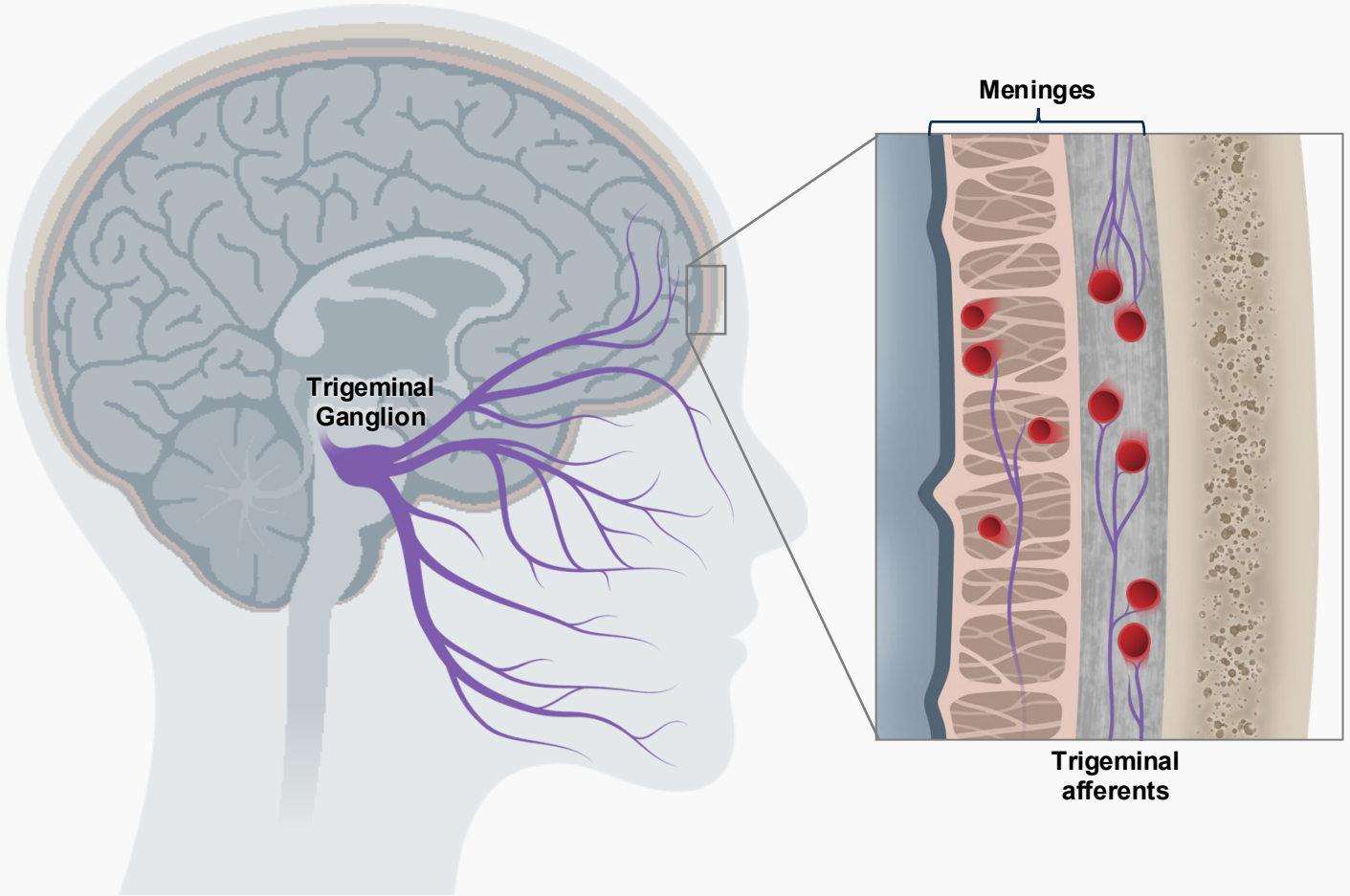
Migraine Pain Arises from Activation of the Trigeminovascular System



Key Events in a Migraine Attack

- Migraine involves heightened sensitivity of sensory pathways
- Pain arises from activation of trigeminal afferents that innervate the meninges
- Activated trigeminal neurons release neuropeptides — CGRP, PACAP, VIP, Substance P
- These signals are transmitted centrally and perceived as pain

Trigeminal Neurons and Meningeal Mast Cells Increasingly Recognized as Key Components of Migraine Biology

Right Time, Right Place

- Abundant in meninges and perivascular spaces – regions innervated by trigeminal neurons

Neuroimmune Communication

- Trigeminal neuropeptides (CGRP, PACAP, VIP, Substance P) activate mast cells

Release Nociceptive Mediators

- Histamine, cytokines and proteases sensitize sensory neurons

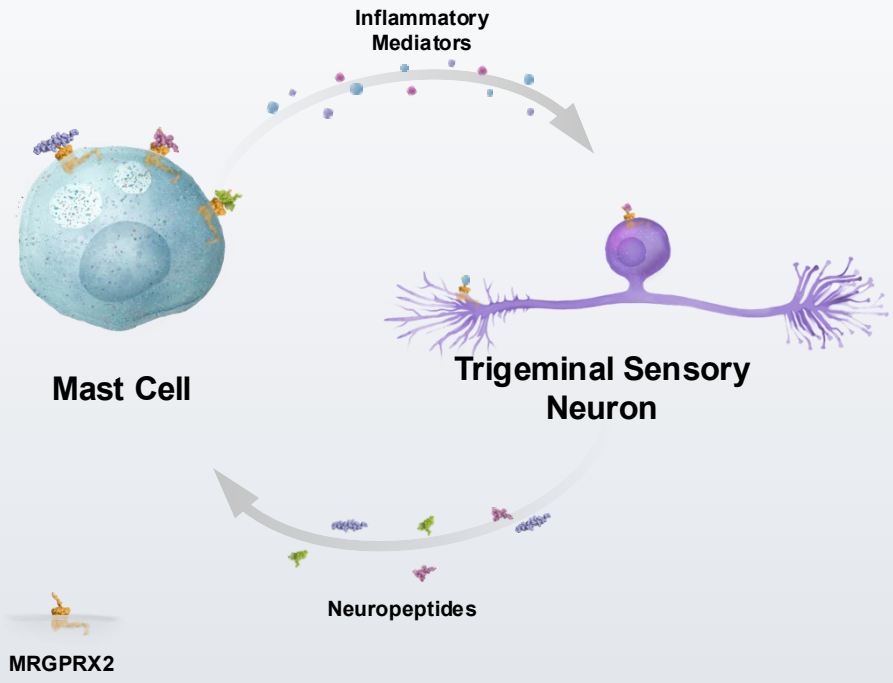
Positive Feedback Loop

- Increasing and sustaining migraine pain

Translational Support Emerging

- Mast cell activation linked to migraine-like responses in animal models and human tissue

Dynamic Cross-Talk Between Meningeal Mast Cells and Trigeminal Sensory Neurons



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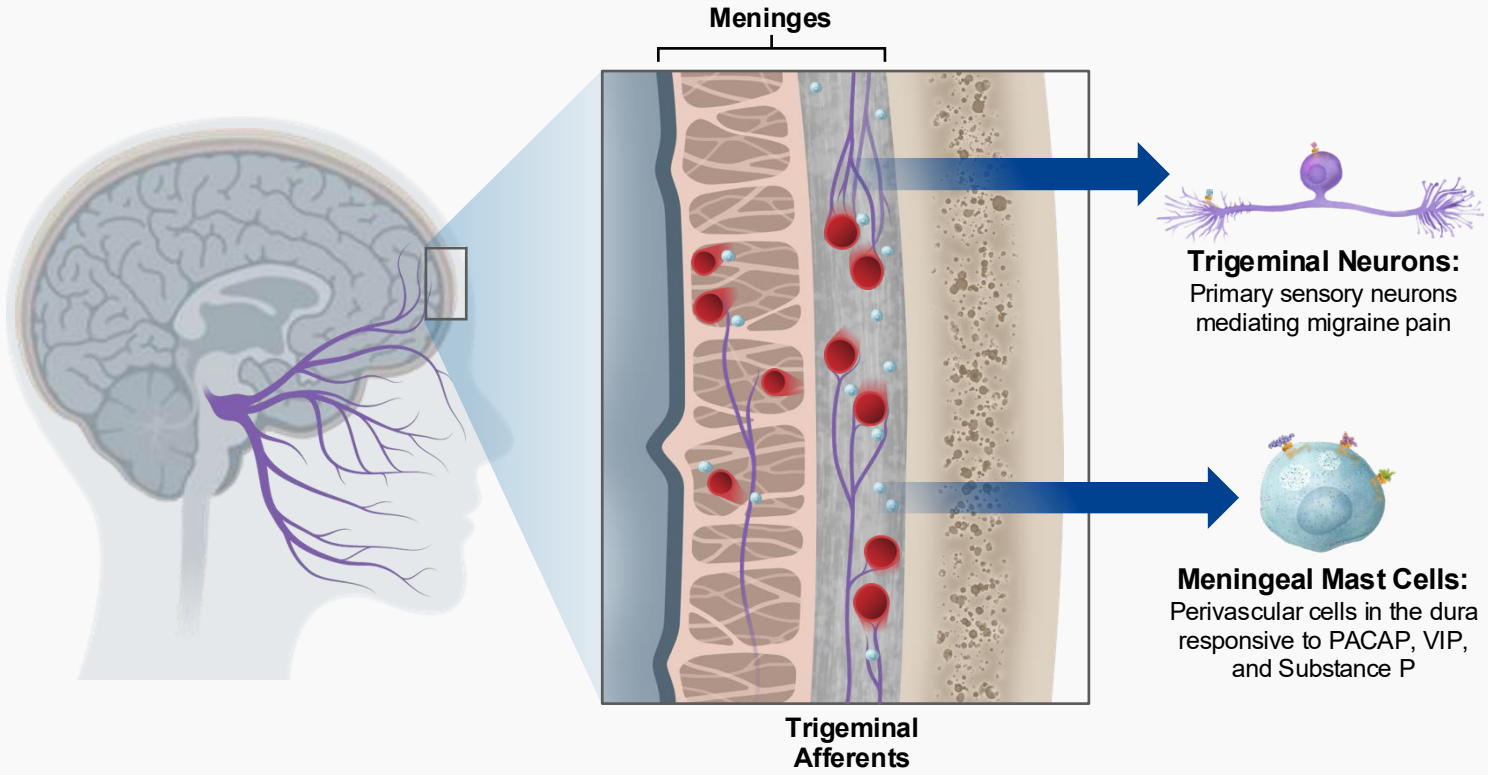
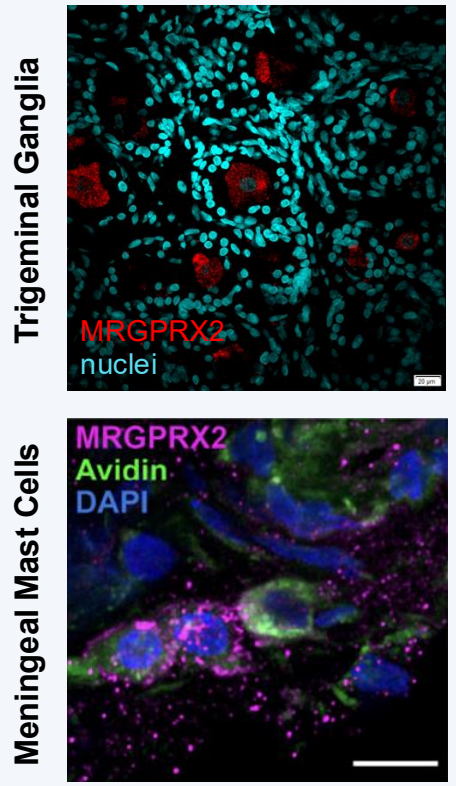
MRGPRX2: Positioned to Address Neuronal and Mast Cell Drivers of Migraine

MRGPRX2 Mediates Neuropeptide Signaling Associated with Migraine (PACAP, VIP, Substance P)



Expression Confirmed in Disease-Relevant Tissues



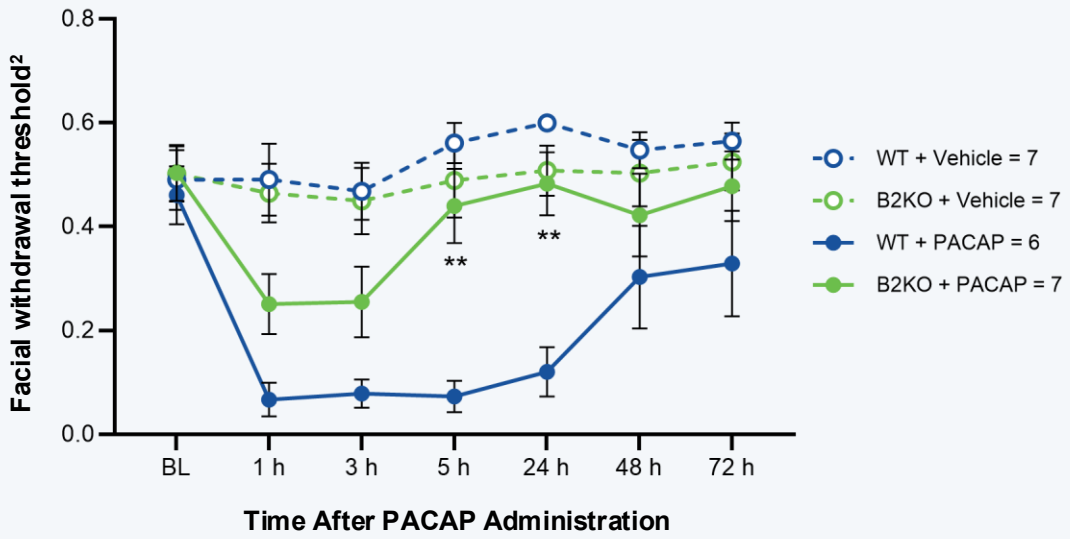
Source: Evommune internal data (trigeminal neurons; *in situ* hybridization on human tissue samples), PMID40712576 (meningeal mast cells)

PACAP Triggers Migraine via MRGPRX2[1] as Primary Receptor *in vivo*

MRGPRX2 Ligand PACAP Induces Headache *in vivo*

1. PACAP injected directly to meninges of wild type and knockout models
2. Facial withdrawal threshold used as functional pain readout

Knockout of MRGPRX2[1] Reduced PACAP-Induced Migraine Symptoms



- *in vivo* data support functional role of MRGPRX2[1] signaling in migraine

1. Mrgprb2 is rodent homologue. 2. In grams, measured via Orbital von Frey assessment. Source: Internal Evommune data. Confirms data published in PMID37516794.

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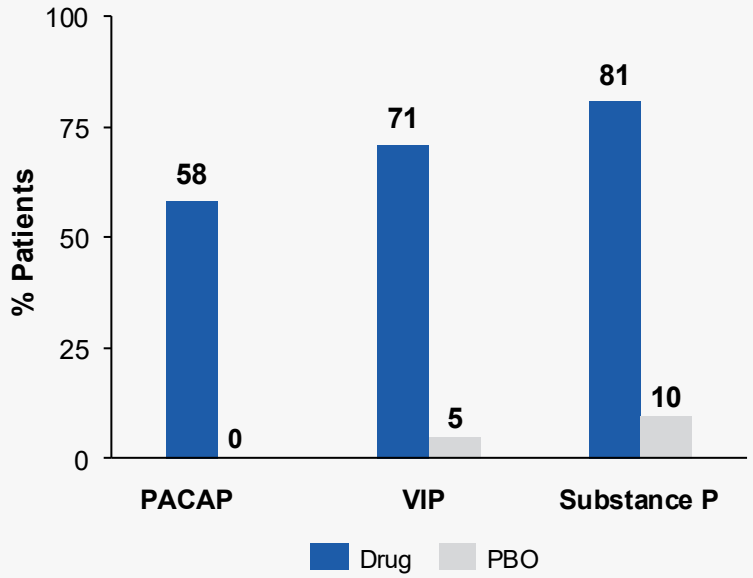
MRGPRX2 Ligands Induce Migraine in Humans

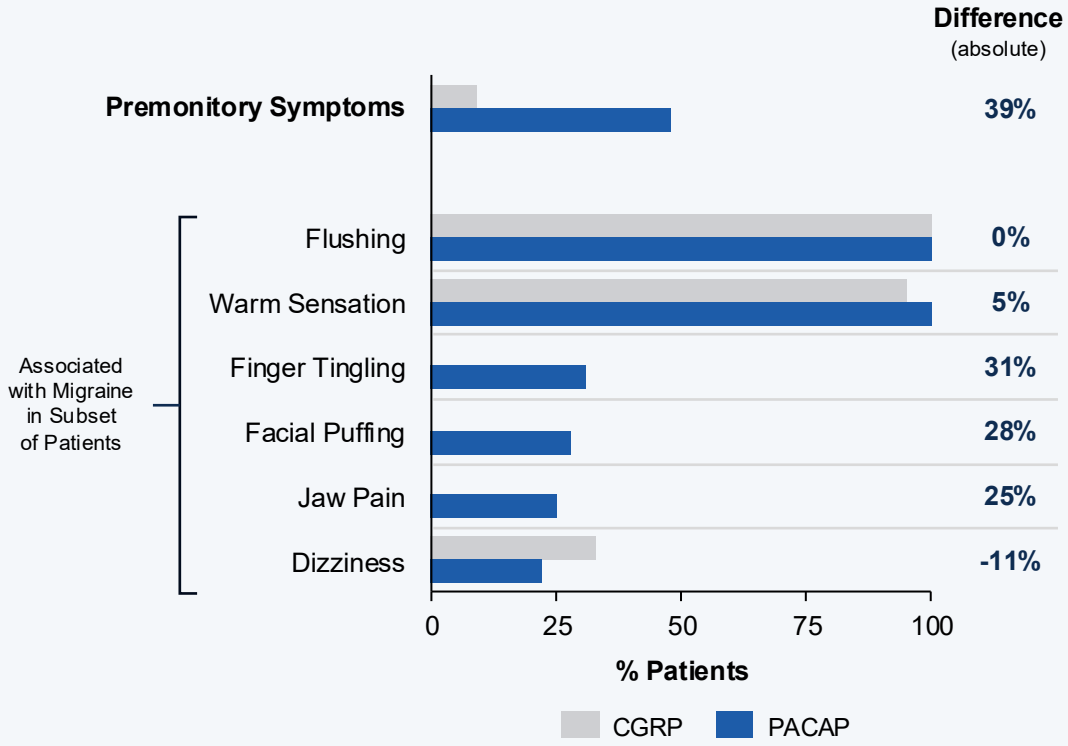
PACAP, VIP, Substance P are Known MRGPRX2 Agonists

PACAP, VIP, Substance P Infusion all Induce Migraine-Like Headache in Migraineurs



- Similar to CGRP, which induces migraine in ~2/3 patients

PACAP-Induced Headaches More Closely Recapitulate Migraine Features vs. CGRP



Note: Data shown from PACAP-38; PACAP-27 also induces migraine. Sources: Adapted from PMID19052139, PMID34357396, PMID37009867, Al-Khazali *et al.*, (2026). Note that there have been multiple studies inducing headache/migraine with ligands and experimental paradigms / results differed. Data shown represent cumulative observations pooled across multiple trials and cannot support definitive conclusions.

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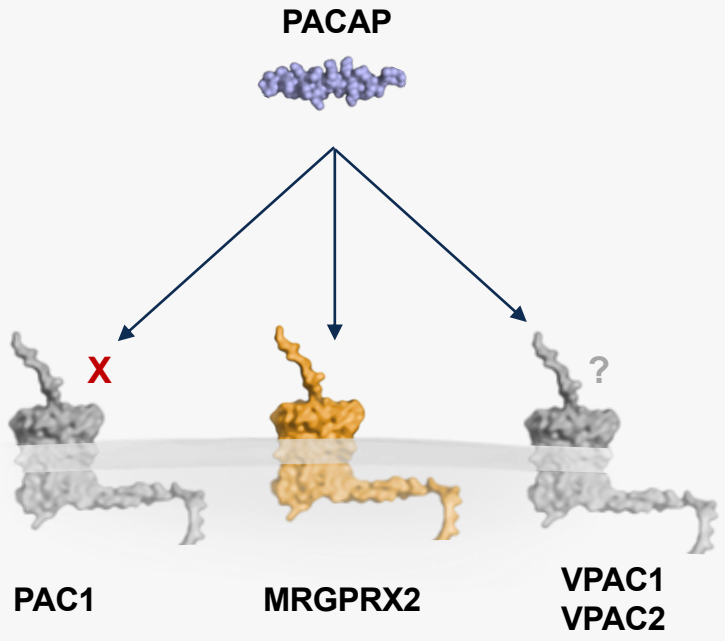
PACAP Likely Induces Migraine in Humans Through MRGPRX2 as Primary Receptor

PACAP Impact in Migraine Is Primarily through MRGPRX2



PACAP Receptor	Relevant Tissue Expression	Preclinical Evidence?	Clinical Validation In Migraine?
PAC1	**Neurons**[1]	Limited	✗
VPAC1 **VPAC2**	**Cranial vessels** Neurons (?)	Limited	*Not evaluated*
MRGPRX2	**Mast Cells** **Sensory Neurons**	✓	**TBD**

1. Trigeminal sensory neurons, brainstem pain circuits, hypothalamus, cortex, thalamus. Note: In addition to MRGPRX2 PACAP binds PAC1, VPAC1, VPAC2, but PAC1 inhibition (Amgen's AMG301: PAC1 blocking mAb.) does not show therapeutic benefit in migraine. Sources: PMID33231489, PMID39085771, PMID37706270.

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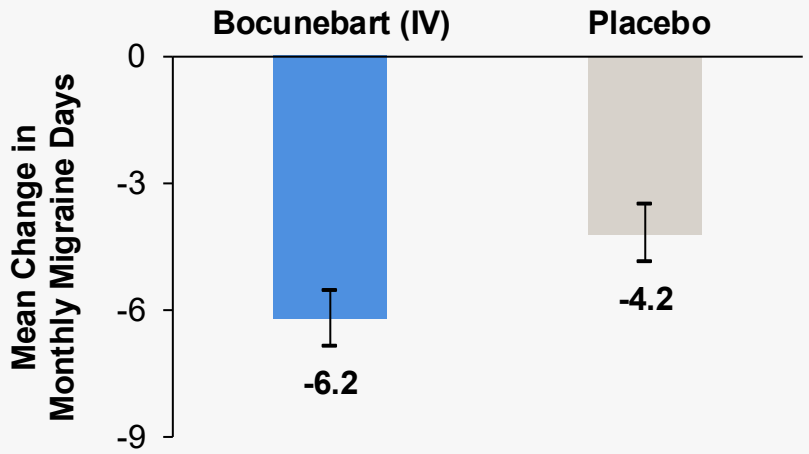
PACAP Inhibition Achieves CGRP-Like Efficacy in Migraine Prophylaxis

Lundbeck's Bocunebart Reduced Monthly Migraine Days by ~2



- Magnitude of benefit consistent with marketed CGRP inhibitors

Second Neuropeptide Axis Validated in Migraine Prevention

- PACAP is a key neuropeptide trigger of migraine attacks
- Antibody blockade reduced migraine frequency in controlled clinical study
- Effect size falls within range observed for approved CGRP therapies

Note: Lundbeck's bocunebart is a humanized mAb that neutralizes PACAP. Results above from Phase 2 a study in migraine prophylaxis (HOPE; N=237; single IV administration of bocunebart in patients that were a mix of episodic and chronic migraineurs). Source: Clinicaltrials.gov NCT05133323. Direct comparisons cannot be made in the absence of head-to-head trials because of differences in trial design, patient population and other factors.

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EVO756 Migraine Development Program

Jeegar Patel, PhD

Evommune CSO

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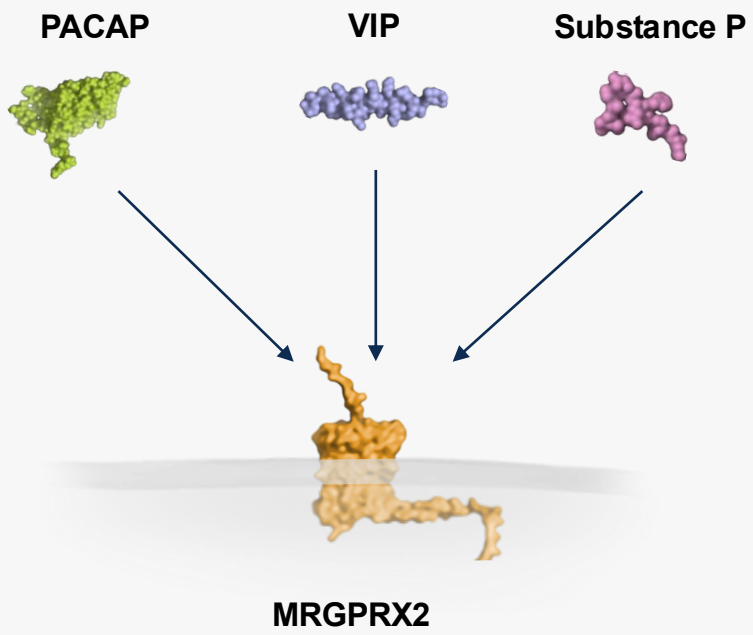
MRGPRX2 Inhibition May Offer Broader Migraine Benefit than Targeting PACAP Alone

3 Neuropeptides that Trigger Migraine Signal Through MRGPRX2



Neuropeptide	Preclinical Evidence	Induced Headache in Humans	Clinical Validation
PACAP	✓	✓	✓
VIP	✓	✓	TBD
Substance P	✓	✓	TBD

Note that PACAP also binds PAC1, VPAC1, VPAC2, but PAC1 inhibition does not show therapeutic benefit in migraine.

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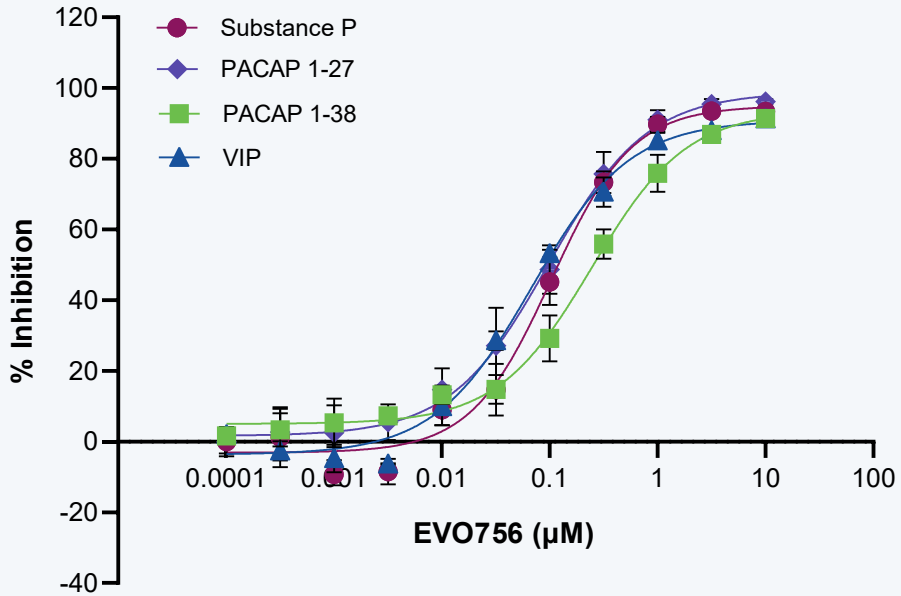
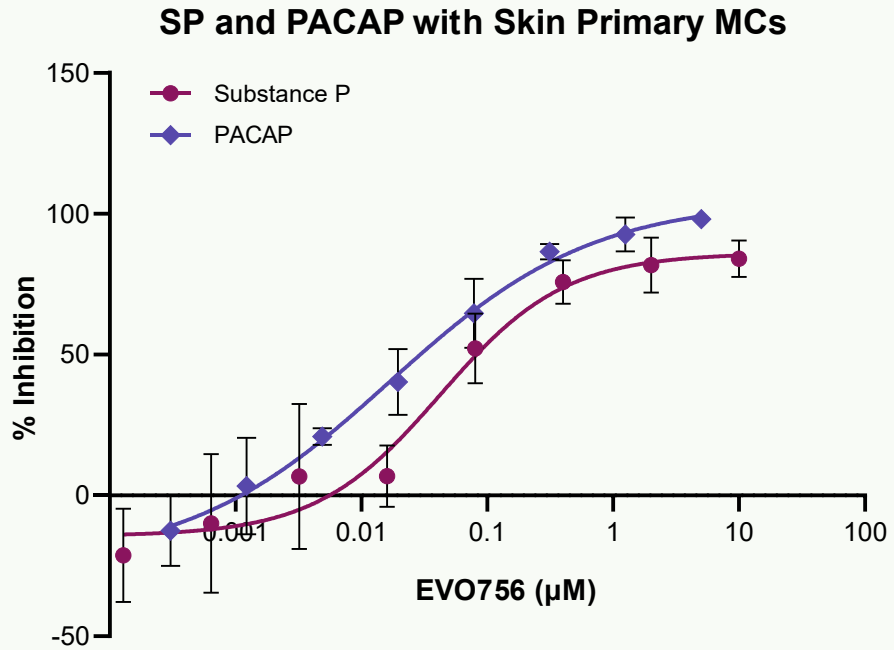
EVO756 Potently (low nM) Inhibits PACAP, Substance P and VIP-Induced MRGPRX2 Activation *in vitro*

EVO756 Inhibits Migraine Relevant Endogenous Ligands in X2-CHO Cells



EVO756 Inhibits PACAP and SP-Induced Primary Human Mast Cell Activation *in vitro*



All assays (agonists) run at ≥EC80. Primary skin MC: CD63; similar experiment run on primary skin mast cells with CD107a with similar results.

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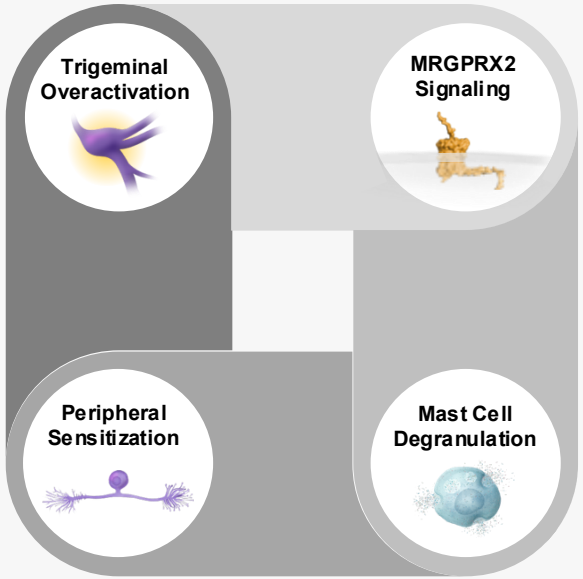
EVO756 Positioned for Broader Efficacy Than Single-Ligand Strategies

Self-Reinforcing Neuroinflammatory Cycle in Migraine



- Blocking MRGPRX2 may disrupt the feedback loop that sustains migraine

EVO756 has Front-Line Therapy Potential in Migraine

Dual Action MOA

- Dampens neuroinflammatory signaling and attenuates neuronal sensitization

Multi-Neuropeptide Coverage

- Blocks multiple migraine-triggering pathways simultaneously

Mechanistic Breadth

- Supports potential for efficacy across diverse migraine endotypes

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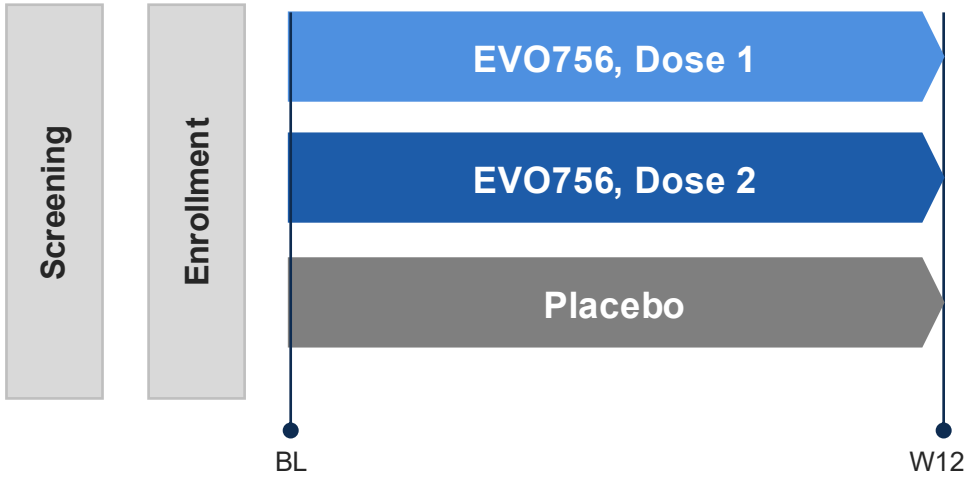
Phase 2b Dose-Ranging Trial in Migraine Prophylaxis

Initiation Expected Mid-2026

Adults with Refractory Migraine ≥6 Days/Month

(N ≈ 330)

Randomized, Double-Blind, Placebo-Controlled Trial



Exploring daily doses up to 100 mg

Primary Endpoint

- Mean CFB in MMD

Key Secondary Endpoints

- ≥50%, ≥75% reduction in MMD
- CFB in MHDs and MMD
- CFB in monthly acute migraine medication use

Exploratory Endpoints

- Patient subtyping
- Changes in biomarkers
- Change in migraine-specific QoL

BL = Baseline; CFB = change from baseline; MMD = monthly migraine days; MHD = monthly headache days; QoL = quality of life

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Closing Remarks

Luis Peña

Evommune President & CEO

EVO756 Well-Positioned to be Meaningful Potential New Therapy in Migraine Prophylaxis

Compelling Biology

- MRGPRX2 ligands **induce migraine in humans**
- Inhibition of MRGPRX2 Ligand PACAP **demonstrated clinical benefit**

Differentiated Profile

- Novel dual mechanism may **address broad population** with potential for **efficacy comparable or superior to CGRPs**
- **Well tolerated** to date, with no SAEs observed

Convenience

- **65% of patients prefer oral therapies** over injectables or IV

Substantial Opportunity

- **>10M patients** eligible for preventative therapy
- **~60% remain untreated** with advanced therapies

Evommune internal estimation from DRG, Evaluate Pharma and KOL interviews; Biohaven Market Research 2021.
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Role of MRGPRX2 in Migraine

April 13, 2026