



Stopping Pain in Its Tracks: Optimizing Acute Migraine Therapy

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A white compass rose logo with eight points, enclosed in a circular border with small tick marks.

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A large, faint, light blue compass rose graphic is visible in the background on the right side of the slide.



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Learning
Objective **1**

Develop strategies to address the challenges in acute management of migraine.



Audience Response

What is correct about the calcitonin gene-related peptide (CGRP) receptor antagonist “gepant” class of agents in migraine?

- A. Dizziness is one of the prominent side effects.
- B. They are metabolized primarily by the kidneys.
- C. They are not contraindicated in patients with vascular disease.
- D. They should be avoided in patients with contraindications to triptans.
- E. I am not sure

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Patient Case: Migraine with Aura



- Laura is 29 yo female
- Migraine with aura since late teens
- Reports having 8 monthly migraine days (MMD)
- Works as a realtor
- Presents with request for better acute treatment and one that would be safe during pregnancy
- Past medical history (PMH):
 - Asthma
- Current Medications:
 - Ibuprofen 400mg q4h
 - Quit oral contraceptive pill (OCP) 6 months ago
- Allergies:
 - No known drug allergies (NKDA)

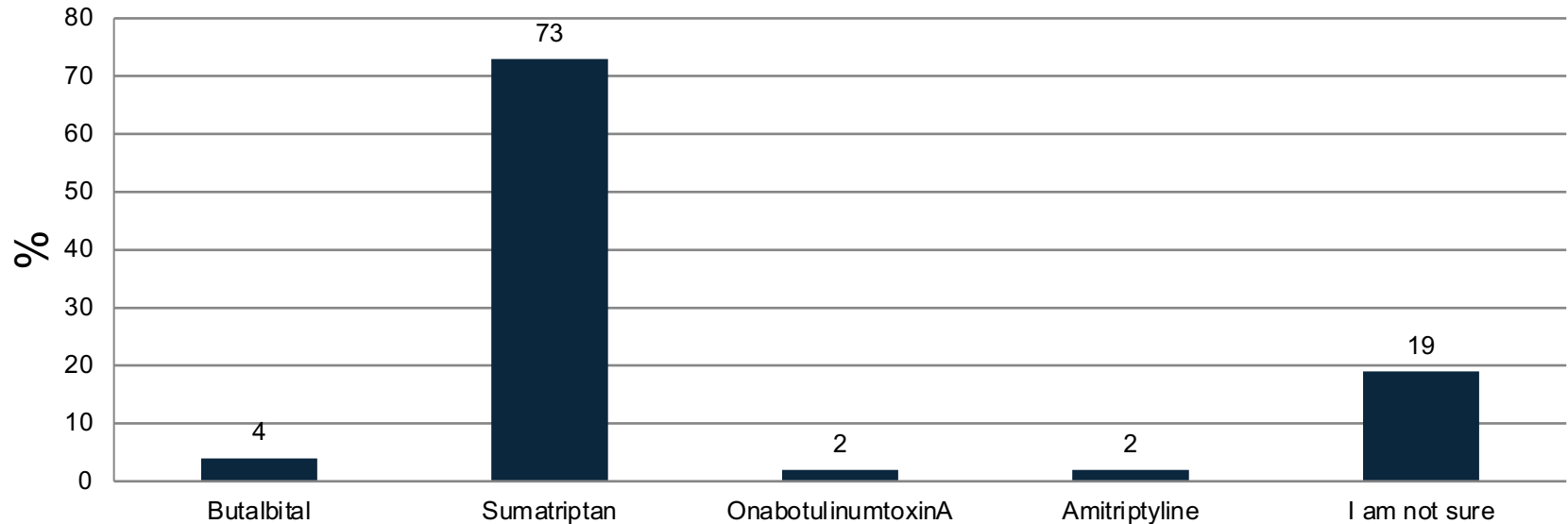
Audience Response

What would be your first line treatment choice for acute migraine treatment in our patient Laura?

- A. Butalbital
- B. Sumatriptan
- C. OnabotulinumtoxinA
- D. Amitriptyline
- E. I am not sure

Audience Response

What would be your first line treatment choice for acute migraine treatment in our patient Laura?



Psychosocial Burden of Migraines

- Estimated total direct cost of migraine \$9.2 Billion/year¹ in the US
- Increased risk of conditions^{2,3}:
 - Anxiety
 - Depression
 - Asthma
 - Epilepsy
 - Stroke
 - Sleep disorders



1. Raval AD, et al. *J Pain*. 2017;18(1):96-107. 2. Buse DC, et al. *J Headache Pain*. 2020; 21(1):109.
3. Steiner TJ, et al. *J Headache Pain*. 2019;20-57.

Migraine: Acute Goals of Therapy



- Restored ability to function
- Rapid relief from symptoms, including pain
- Decrease in rescue/repeat medications
- Optimal self-care and reduced subsequent use of resources
 - ↓ ED visits, diagnostic imaging, clinician + ambulatory infusion center visits
- Minimal adverse events
- Balance efficacy, side effects and costs

ED = emergency department

Ailani J, et al. *Headache*. 2021;68:1021-1039.

Migraine with Aura: ICHD-3 Diagnostic Criteria


- A. At least **2** attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
- Visual
 - Sensory
 - Speech and/or language
 - Motor
 - Brainstem
 - Retinal
- C. At least 3 of the following 6 characteristics:
- ≥ 1 aura symptoms (sx) spreads over ≥ 5 min
 - ≥ 2 aura sx occur in succession
 - Each aura sx lasts 5 to 60 min
 - At least one aura sx is unilateral
 - At least one aura sx is positive
 - Aura is accompanied, or followed within 60 minutes, by headache
- D. Not better accounted for by another ICHD-3 diagnosis

Migraine without Aura: ICHD-3 Diagnostic Criteria

- A. At least 5 attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hrs (when untreated or unsuccessfully treated)
- C. Headache has at least 2 of the following characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe pain intensity
 - Aggravation by or causing avoidance of routine physical activity
- D. During headache at least one of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis

Migraine Diagnosis: ID Migraine Screen

Patients answering “yes” to ≥ 2 of these questions probably have migraine.



Photophobia	Do lights bother you when you have a headache?
Impairment	Do you feel impaired or avoid activities when you have a headache?
Nausea	Do you have nausea when you have a headache?

Evidence for Acute Treatment Options

Established Efficacy		Probable Efficacy	
Migraine-Specific	Nonspecific	Migraine-Specific	Nonspecific
Triptans	NSAIDs: ASA, Celecoxib oral solution, diclofenac, ibuprofen, naproxen	Ergotamine + caffeine	NSAIDs: flurbiprofen,* ketoprofen,* ketorolac IM/IV*
Ergot derivative: DHE intranasal	Combination analgesic: APAP + ASA + caffeine	Ergot derivative: DHE IM/IV/SQ	Combination: APAP plus isometheptene,* or tramadol*, or codeine*
Gepants			Magnesium IV* (for migraine with aura)
Lasmiditan			Antiemetics: metoclopramide*, prochlorperazine*, promethazine,* chlorpromazine,* droperidol*

Established or Probable Efficacy based on American Academy of Neurology (AAN) scheme for classification of evidence;

* = Indications are not FDA approved for migraine.

ASA = acetylsalicylic acid; APAP = acetaminophen; DHE = dihydroergotamine; IM = intramuscular; IV = intravenous;

NSAID = non-steroidal anti-inflammatory drugs; SQ = subcutaneous

Ailani, et al. *Headache*. 2021;68:1021-1039; Mamura MJ, et al. *Headache*. 2015;55(1):3-20.

Summary of Acute Migraine Targets

Target	Medications	Contraindications/AEs
COX-1/COX-2 Inhibitors	Ketorolac, Indomethacin, Aspirin, Naproxen, Ibuprofen, Diclofenac, Celecoxib	Renal insufficiency, severe asthma, active PUD; AEs: acute kidney injury, nausea, and dyspepsia
Serotonin (5-HT) _{1B/1D} Receptor Agonist (RA) "Triptans"	Sumatriptan, Zoltriptan, Rizatriptan, Almotriptan, Eletriptan, Frovatriptan, Naratriptan	CVD, PAD, HTN, hemiplegic aura; AEs: sedation, HTN, nausea, "triptan sensation," serotonin syndrome
Serotonin (5-HT) _{1B/1D} RA, dopamine, adrenergic receptor "Ergotamine Derivatives"	DHE ergotamine/caffeine	CVD, HTN, coronary vasospasm, PAD, pregnancy; AEs: NV, flushing, diaphoresis
Serotonin (5-HT) _{1F} RA "Ditans"	Lasmitidan	AEs: CNS depression, dizziness, sedation (8-hour driving restriction, Schedule V controlled substance), NV, serotonin syndrome, medication overuse headache
Calcitonin gene-related peptide (CGRP) receptor antagonists "Gepants"	Ubrogepant, Rimegepant	Hypersensitivity to any ingredient; AEs: nausea

AEs = adverse events; CVD = cardiovascular disease; DHE = Dihydroergotamine; HTN = hypertension; NV = nausea & vomiting; PAD = peripheral artery disease; PUD = peptic ulcer disease.

Warner T, et al. 1999; Proc Natl Acad Sci U S A. 1999;96(13):7563-7568. Cameron C, et al. *Headache*. 2015;55 Suppl 4:221-235;

Lipton RB, et al. *J Fam Pract*. 2020;69(1 Suppl):S1-S7.

Reasons for Discontinuation of Acute Treatment

- ⊕ Inefficacy, inadequate pain relief
- 📄 Route of administration
- 💰 Cost
- 📦 Non-prescription (OTC) medication use
- ⚠️ Intolerability and safety concerns
- 🔄 Coexisting conditions, contraindications



Non-Oral Migraine Treatment Options

Ergots

- Nasal
- SQ/IM injection

Triptans

- Nasal sumatriptan, zolmitriptan
- SQ sumatriptan auto injector

NSAIDS

- SQ/IM injection

Neuromodulation

- eTNS, sTMS, nVNS, REN, eCOT-NS

eCOT-NS = external combined occipital and trigeminal neurostimulation ; eTNS = external trigeminal nerve stimulation; nVNS = non-invasive vagus nerve stimulation; REN = remote electrical neuromodulation; sTMS = single-pulse transcranial magnetic stimulation
Ailani J, et al. *Headache*. 2021;68:1021-1039. Daniel O, et al. *Expert Rev Med Devices*. 2021;18(4):333-342.

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Learning Objective **2**

Apply data on efficacy and safety of recently approved therapies for acute treatment of migraine to optimize treatment decisions for patients with migraine.



Laura: 18 months later



- 30yo female
- Migraine with aura
- Presenting post-childbirth (not nursing) with request for new acute option with less drowsiness.
- Medications:
 - Sumatriptan
- Allergies:
 - NKDA
- PMH:
 - Asthma
 - Gestational Diabetes

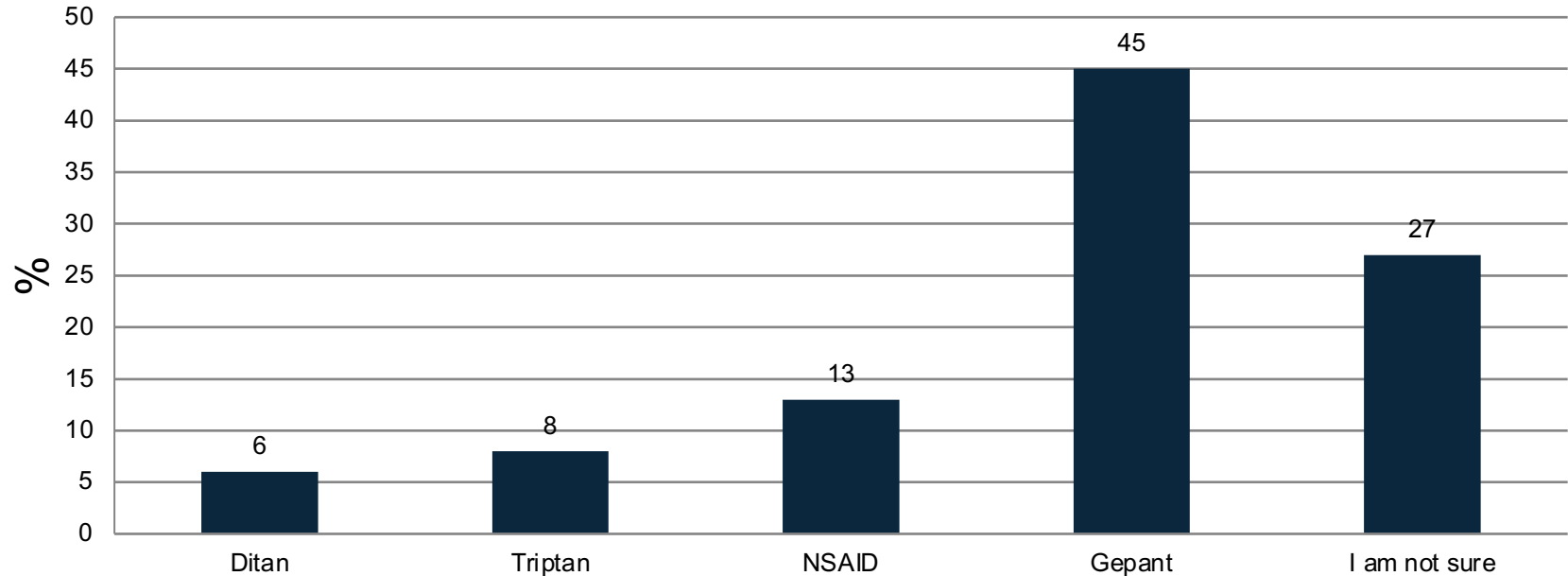
Audience Response

What medication class would you recommend for Laura now?

- A. Ditan
- B. Triptan
- C. NSAID
- D. Gepant
- E. I am not sure

Audience Response

What medication class would you recommend for Laura now?



Triptans in Acute Migraine: Systematic Review and Meta Analysis

Study Outcomes	Number of Studies/ Number of Participants	Percentage of Patients Responding to Treatment
Headache Relief at 2 Hours	96/56k	42-76% SD triptans vs 27% placebo
Freedom from Pain at 2 hours	88/51k	18-50% SD triptans vs 11% placebo
Sustained Headache Relief at 24 Hours	29/23k	29-50% SD triptans vs 17% placebo
Sustained Freedom From Pain at 24 Hours	42/28k	18-33% SD triptans vs 10% placebo
Use of Rescue Medications	88/48k	20-34% SD triptans vs 52% placebo

Placebo = placebo-controlled or active migraine treatment with other triptan agents, NSAIDs, aspirin, acetaminophen, ergots, opioids, or anti-emetics

Cameron C, et al. *Headache*. 2015;55 Suppl 4:221-235.

Phase 3 Studies for New Agents

Patient Population

- Migraine with or without aura for at least 1 year
- Over 18 years of age
- 3-8 migraine attacks per month
- Prevention medications were allowed during the study, if necessary

Primary Outcome Measures

- 2-hour pain-freedom
- 2-hour freedom from most bothersome symptom (MBS)

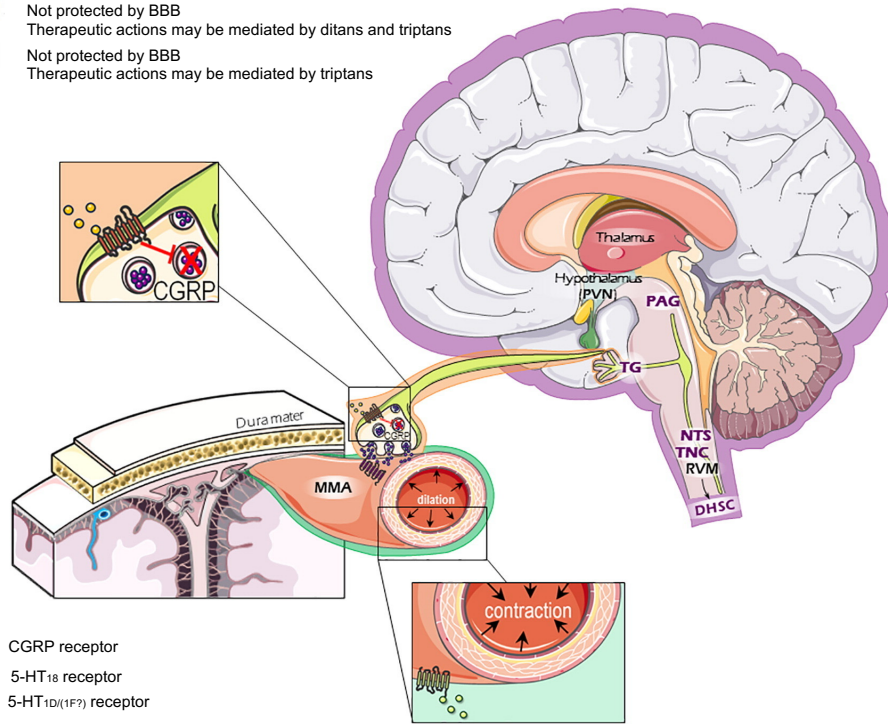
Patient Reported Outcomes

- Return to normal function
- Satisfaction with selected treatment
- Reduction in disability

Therapeutic Targets for Acute Migraine

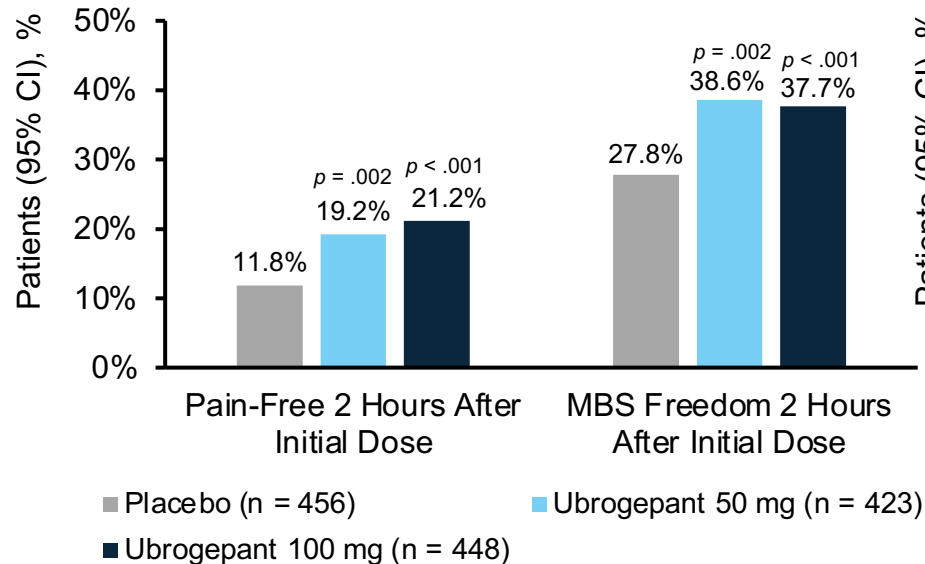
- Triptans: Serotonin 5-HT_{1B/1D} Receptor Agonist
- Ditans: Serotonin 5-HT_{1F} Receptor Agonist
- Gepants: CGRP Receptor Antagonist

- Protected by BBB
Therapeutic actions may be mediated by ditans and lipophilic triptans
- Not protected by BBB
Therapeutic actions may be mediated by ditans and triptans
- Not protected by BBB
Therapeutic actions may be mediated by triptans

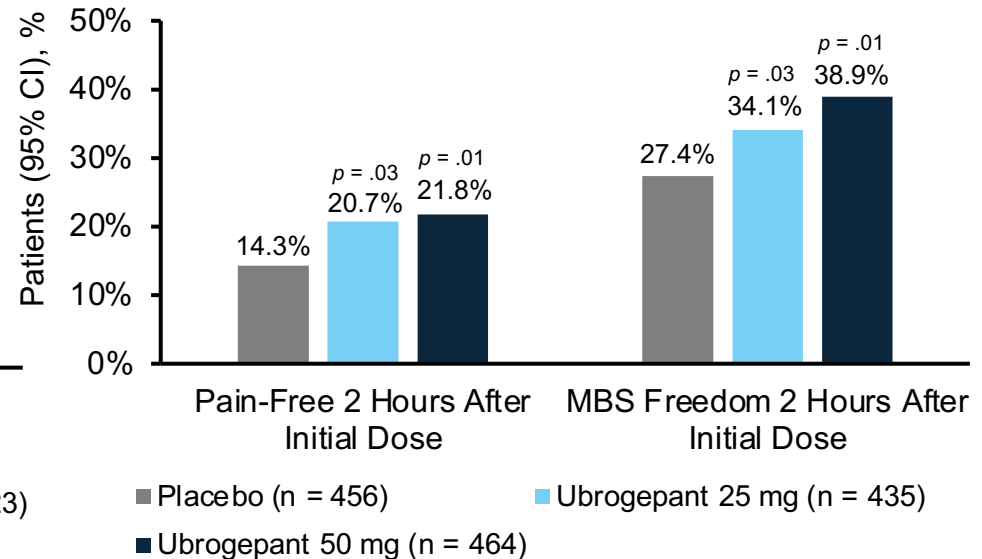


Ubrogepant: Primary Efficacy in Acute Migraine

ACHIEVE-I Primary Endpoints¹



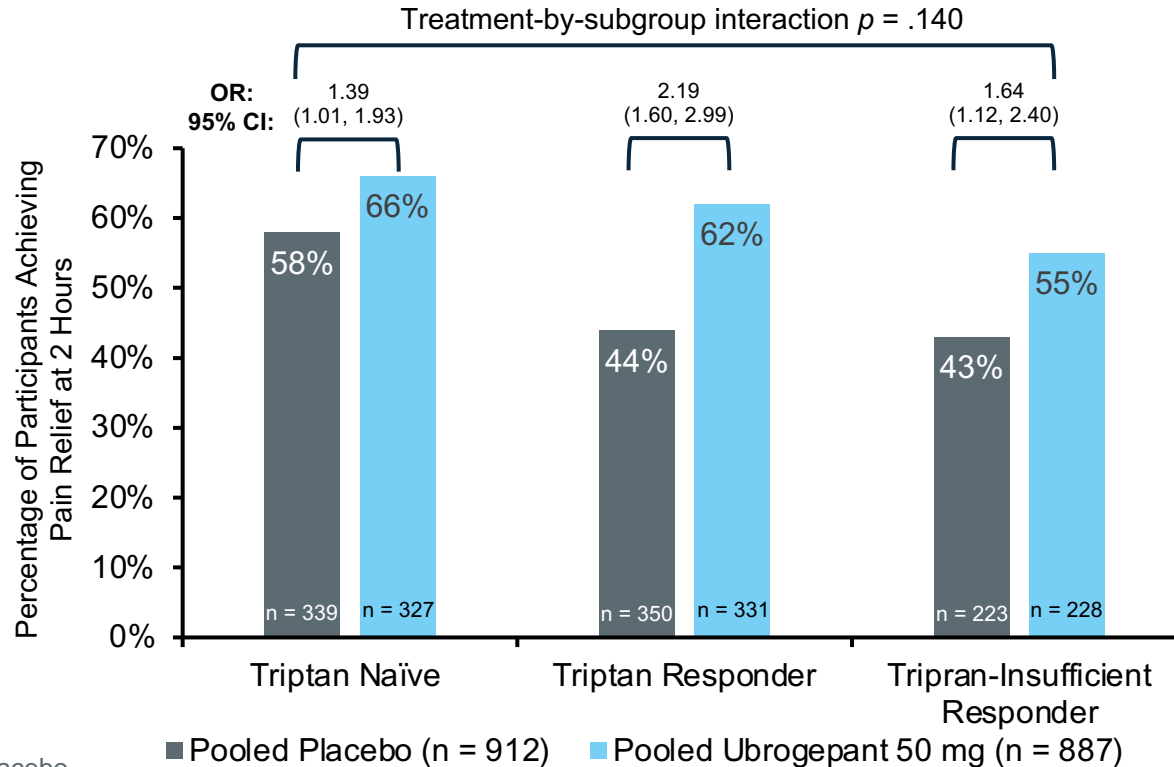
ACHIEVE-II Primary Endpoints²



P value compared to placebo; CI = confidence interval, MBS = Most Bothersome Symptom

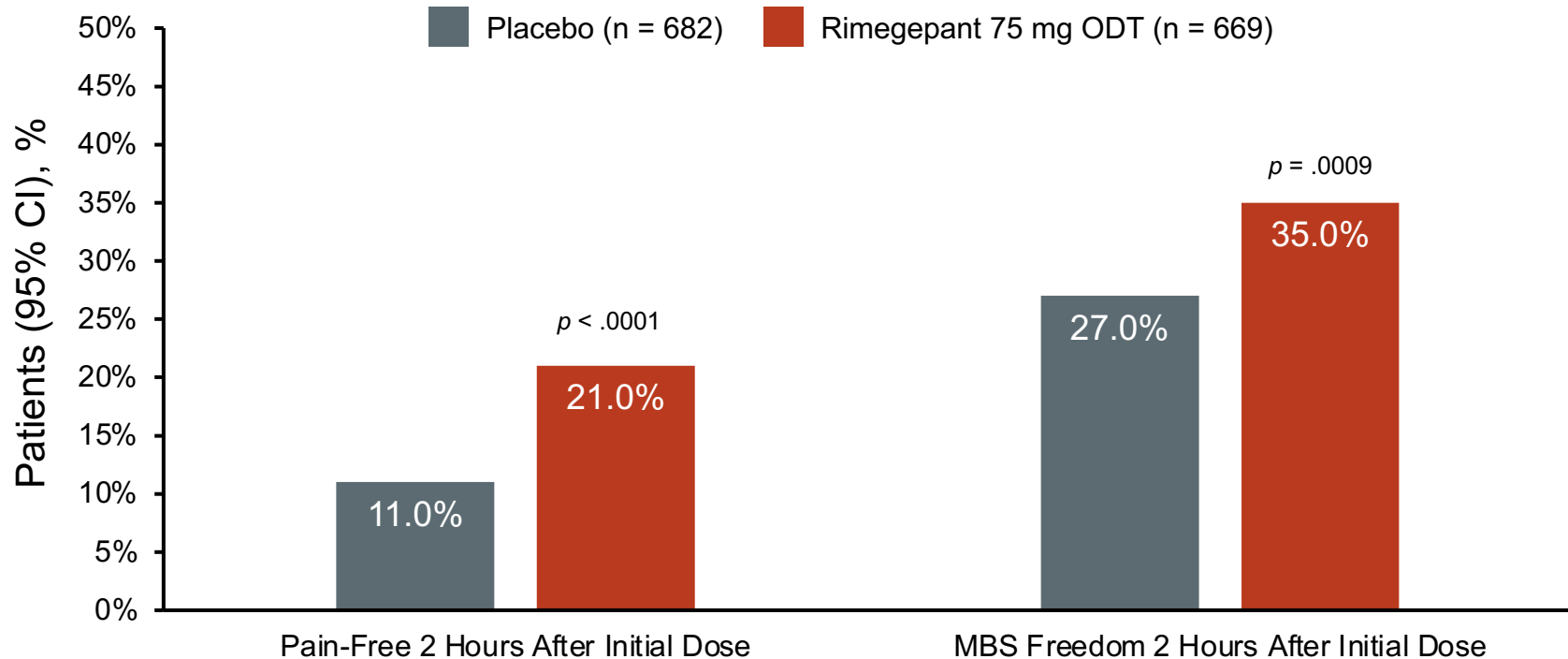
1. Dodick DW et al. *N Engl J Med*. 2019;381(23):2230-2241; 2. Lipton RB, et al. *JAMA*. 2019;322(19):1887-1898;
3. Ailani J, et al. *Headache*. 2020;60(1):141-152.

Ubrogепant: Post Hoc Analysis



P value compared to placebo.
Blumenfeld AM, et al. *Headache*. 2021;61(3):422-429.

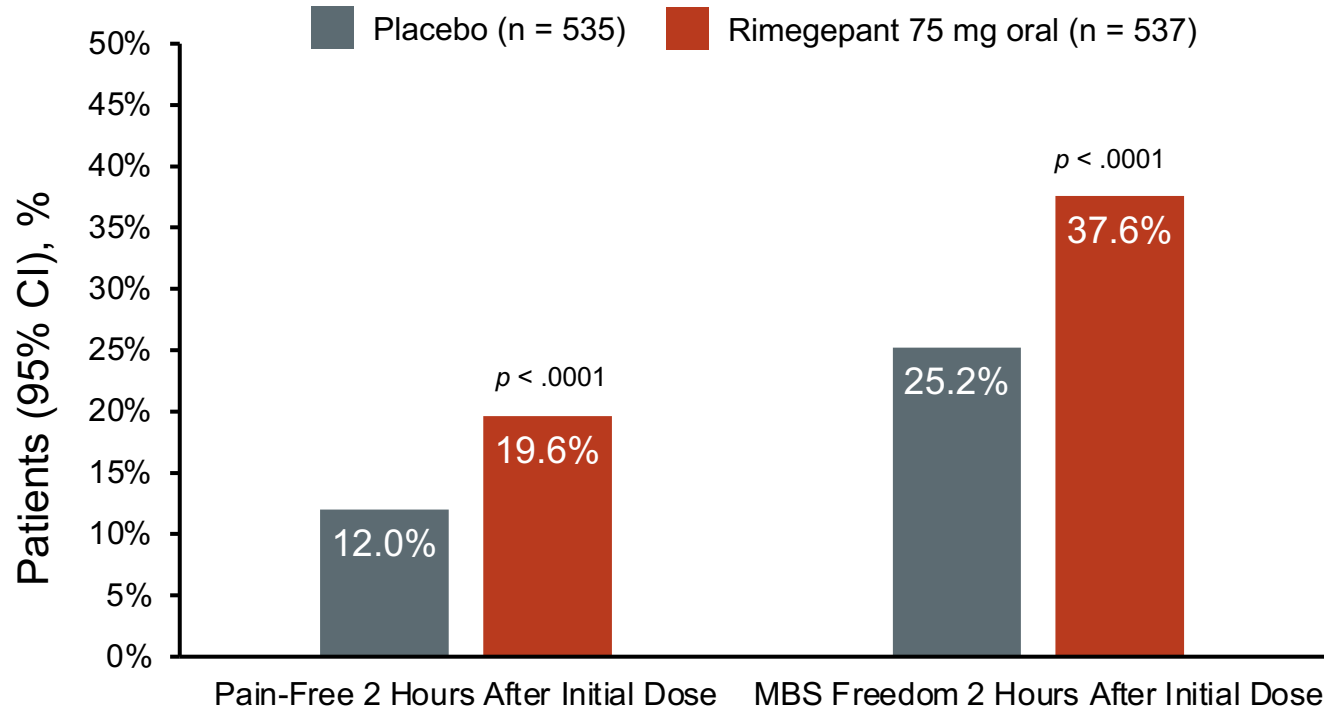
Rimegepant ODT: Primary Efficacy in Acute Migraine



P value compared to placebo. ODT = Orally Disintegrating Tablet

Croop R, et al. *Lancet*. 2019;394(10200):737-745.

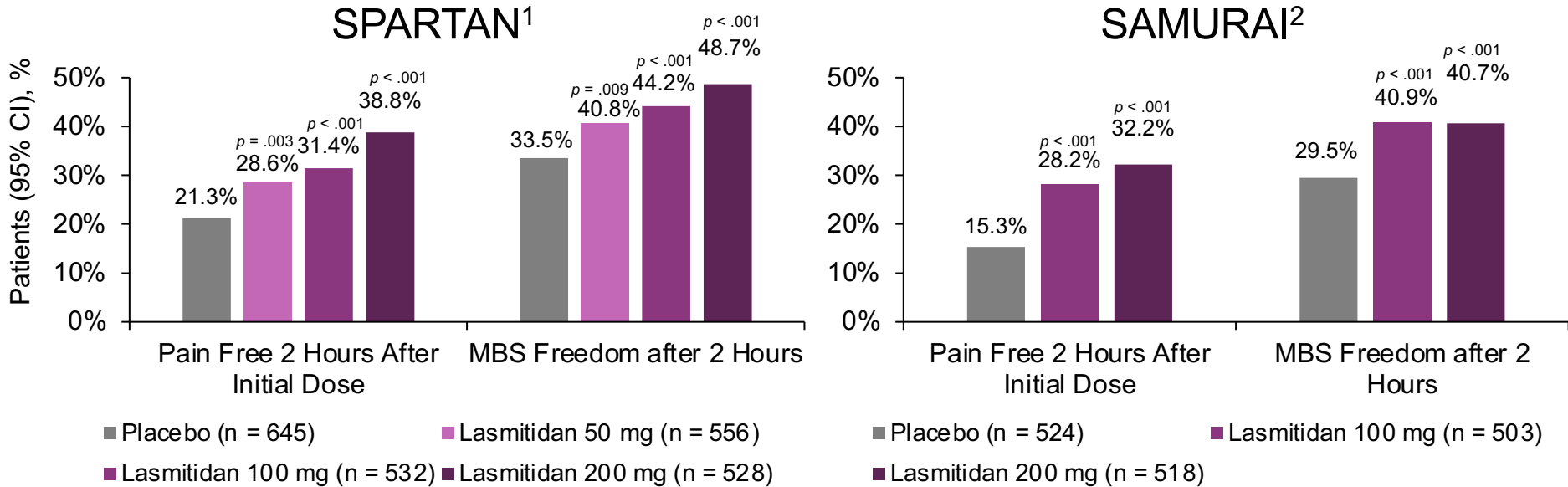
Rimegepant: Efficacy in Acute Migraine



P value compared to placebo.

Lipton RB, et al. *N Engl J Med*. 2019;381(2):142-149.

Lasmitidan: Primary Efficacy in Acute Migraine



P value compared to placebo.

1. Goadsby PJ, et al. *Brain*. 2019;142(7):1894-1904. 2. Kuca B, et al. *Neurology*. 2018;91(24):e2222-e2232.

Choosing New Acute Migraine Options

- Age > 18 and prescribed by a clinician
- Contraindications or intolerance to triptans
- Inadequate response to 2 more more oral triptans determined by either:
 - Validated acute treatment patient-reported outcome questionnaire
 - Clinician attestation

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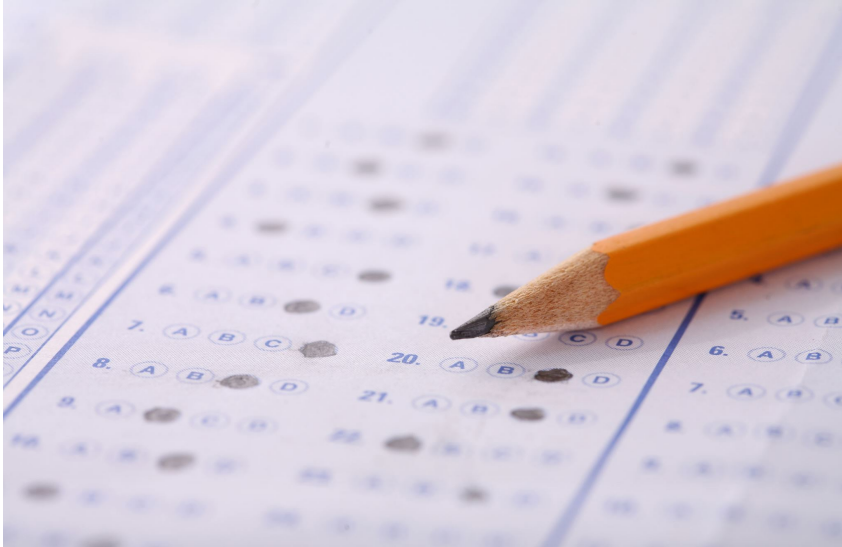


Learning
Objective **3**

Implement patient-centered approaches to individualize treatment strategies for patients with migraine.



Patient-Reported Outcome Questionnaires



Migraine Treatment Optimization Questionnaire ¹	mTOQ
Migraine Assessment of Current Therapy ²	Migraine-ACT
Patient Perception of Migraine Questionnaire ³	PPMQ-R
Functional Impairment Scale ⁴	FIS

1. Lipton RB, et al. *Cephalalgia*. 2009;29(7):751-759; 2. Dowson AJ, et al. *Curr Med Res Opin*. 2004;20(7):1125-1135; 3. Revicki DA, et al. *Headache*. 2006;46(2):240-252; 4. Diener H-C, et al. *Cephalalgia*. 2019;39(6):687-710.

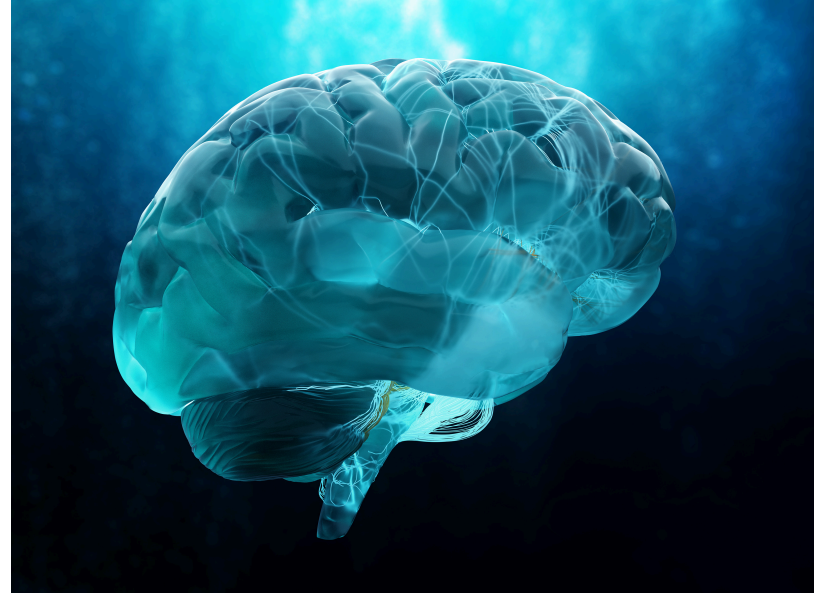
Treatment Considerations

Pharmacologic:

- Use of acute medications – avoid medication overuse
- Review need for preventive
- Trial and error – no one-size fits all

Nonpharmacologic:

- Neuromodulation
- Biobehavioral approaches
- Lifestyle changes



Lifestyle Modifications for Migraine

“SEEDS”

Sleep
Eat
Exercise*
Diary
Stress



Dietary
triggers:

Alcohol,
Tyramine



Caffeine

MSG



Aspartame

Skipping
meals



Other
Triggers:

Odors



Menses

Weather
changes



Sleep
apnea/insomnia

Exercise*



Stress

*Exercise triggers migraine in some persons, but regular exercise may help prevent migraine and should be encouraged.
Robblee J. et al. *Cleve Clin J Med.* 2019;86(11):741-749.

Patient-Centered Headache Diaries

- Helps patient recognize migraine attack patterns
 - Warning signs
 - Pain intensity
 - Timing
 - Duration
 - Symptoms
 - Triggers
- Evaluation of medication

Migraine Diary

Date	Day	Time	Severity	Sickness Vomit	Medication Name Dose	Time Taken	Side Effects	Notes: re activities/ events e.g. weather, work, Social, bowel movement, menstrual cycle
1								
2								
3								
4								
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the migraine trust

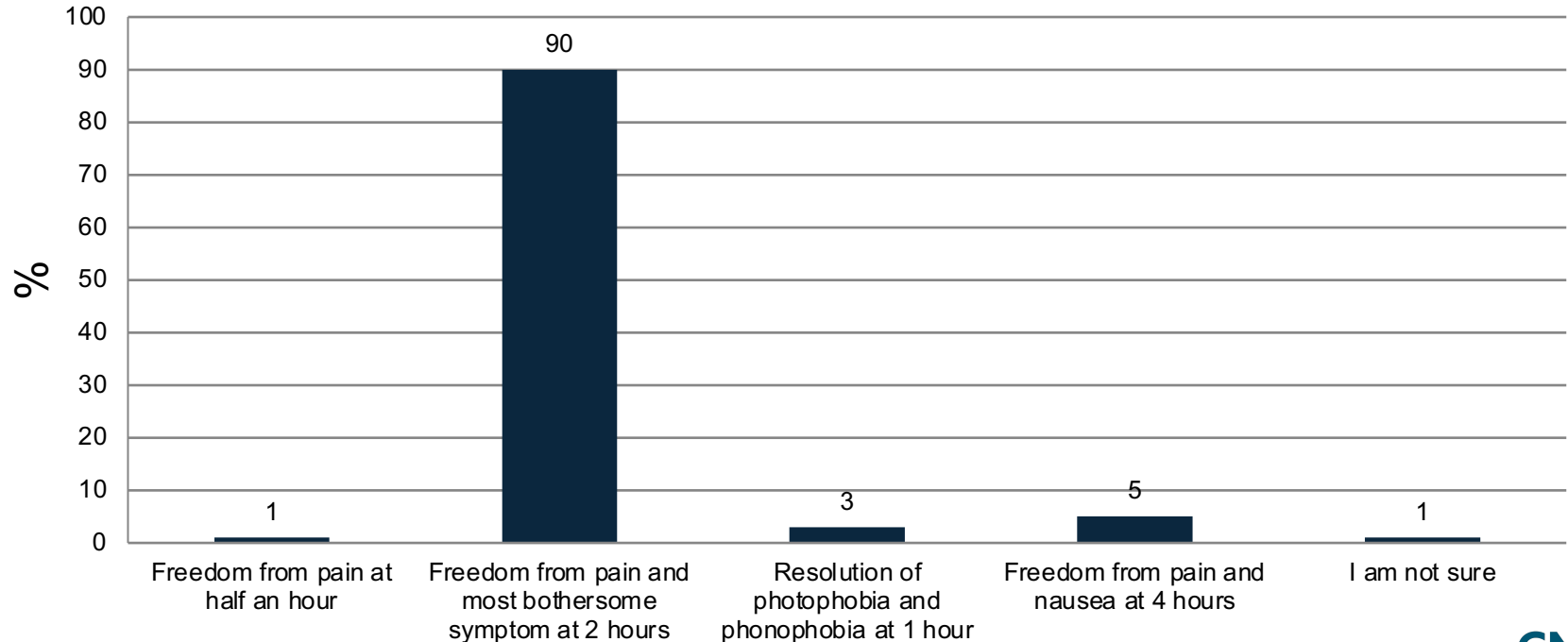
Audience Response

Which of the following is the primary endpoint of the Phase 3 clinical trials for recently approved lasmiditan, rimegepant, and ubrogepant?

- A. Freedom from pain at half an hour
- B. Freedom from pain and most bothersome symptom at 2 hours
- C. Resolution of photophobia and phonophobia at 1 hour
- D. Freedom from pain and nausea at 4 hours
- E. I am not sure

Audience Response

Which of the following is the primary endpoint of the Phase 3 clinical trials for recently approved lasmiditan, rimegepant, and ubrogepant?



Results recorded on December 8, 2021.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Ensure that accurate assessment/diagnosis and patient history are included in the management of acute migraine.
- Implement patient education on the frequency of use of preventive and acute medications and including lifestyle modifications for acute migraine, to avoid MOH.
- Individualize treatment plans for acute migraine with patient-reported outcomes such as a migraine-specific quality of life questionnaire to monitor treatment responses.

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AFTER THE SHOW

Questions & Answers

Recorded on December 8, 2021





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Migraine Hub

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<https://www.cmeoutfitters.com/migrainehub/>

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