This supplement was sponsored by Allergan plc, with medical writing and editorial assistance by Peloton Advantage, an OPEN Health company. It was edited and peer reviewed by *The Journal of Family Practice*.

SUPPLEMENT TO
THE JOURNAL OF FAMILY PRACTICE®
VOL 69, NO 1 | JAN/FEB 2020 | MDEDGE.COM/FAMILYMEDICINE

A SPECIAL SUPPLEMENT ON

Migraine Management

Treatment Patterns and Unmet Needs in the Acute Treatment of Migraine

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KEY TAKEAWAYS

- The main goals of acute treatment of migraine are to rapidly and consistently treat the attack with minimal recurrence and minimal adverse events while restoring the patient's ability to function and minimizing use of additional rescue medications and resources. However, available specific and nonspecific options for the acute treatment of migraine may not provide sufficient relief for all patients and may lead to adverse events.
- Some commonly used acute treatments for migraine have limitations and precautions: Triptans are contraindicated for patients with a history of cardiovascular (CV) events; nonsteroidal anti-inflammatory drugs (NSAIDs) may need to be avoided or used with caution in patients with gastrointestinal (GI) or cardiovascular conditions.
- Oral triptans are the most commonly prescribed acute medication for migraine attacks. However, there are challenges with efficacy and tolerability.
- Migraine-specific agents, including calcitonin gene–related peptide (CGRP) receptor antagonists (gepants) are in late-stage development to provide more acute treatment options for people with migraine.

INTRODUCTION

Migraine is a chronic disease defined by recurrent attacks, which may include pulsating unilateral headache lasting 4 to 72 hours, with associated symptoms that may include nausea, phonophobia, photophobia, and—in about a quarter of cases—aura.[1,2] The disabling symptoms of migraine are associated with negative effects in many aspects of life, including physical and mental health, relationships, career, and financial well-being.[3-6] The Global Burden of Diseases, Injuries, and Risk Factors Study ranked migraine as the second leading cause of disability worldwide, with more than 1 billion individuals reporting migraine annually.[7]

Migraine management includes both acute and preventive treatments. Acute treatments are designed to relieve pain and restore ability to function after an individual migraine attack. In contrast, preventive treatments are aimed at reducing the frequency, severity, and duration of attacks.[8-10] Several domains of unmet treatment need have been identified (**TABLE 1**), although the definitions of these domains vary across studies.[11,12] One study found that 62% of patients with migraine have 1 or more of the criteria for an unmet acute treatment need.[12] This article reviews data on current treatment patterns and unmet needs in the acute treatment of migraine attacks.

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ACKNOWLEDGMENTS

This manuscript was sponsored by Allergan plc, Dublin, Ireland. Medical writing and editorial assistance was provided to the authors by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and was funded by Allergan plc. All authors met the authorship criteria of the International Committee of Medical Journal Editors. Neither honoraria, nor other form of payment, was made for authorship.

CONFLICTS OF INTEREST

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Dawn C. Buse, PhD, has received grant support and honoraria from Allergan, Avanir, Amgen, Biohaven, Eli Lilly and Company, and Promius and for work on the editorial board of *Current Pain and Headache Reports*.

Aubrey Manack Adams, PhD, and **Janette Contreras-De Lama, PhD,** are employees and stockholders of Allergan plc.

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CURRENT OPTIONS FOR ACUTE TREATMENT OF MIGRAINE

The main goals of acute treatment of migraine are to rapidly and consistently relieve pain and associated symptoms, and to restore function while minimizing attack recurrence, the need for rescue treatments, and side effects.[8,13-15] Acute treatment options for migraine include migraine-specific medications, nonspecific analgesics, and medications for associated symptoms such as nausea.[13] Migraine-specific acute medications modulate pain pathways involved in migraine and include triptans (eg, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) and ergots (ergotamine tartrate, dihydroergotamine).[16] Nonspecific acute medications include simple analgesics (aspirin, acetaminophen), NSAIDs (eg, diclofenac, ibuprofen, naproxen; both over-the-counter and prescription), opioids (eg, butorphanol nasal spray), barbiturates, and combination products (eg, acetaminophen/aspirin/caffeine).[8,16] Current acute treatment options often are insufficient to meet the goals of migraine management.[11,17] In development are several investigational migraine-specific agents, including CGRP receptor antagonists (gepants) and 5-hydroxytryptamine 1F receptor agonists (ditans).[18] One of the gepants, ubrogepant, is the first oral, small-molecule CGRP receptor antagonist approved by the US Food and Drug Administration (FDA) for the acute treatment of migraine, providing another option to help meet the goals of treatment.

Real-world patterns and unmet acute treatment needs for migraine

The majority of individuals experiencing migraine attacks do not use acute prescription medication for headache treatment.[19,20] The large, longitudinal, Chronic Migraine Epidemiology and Outcomes (CaMEO) study evaluated self-reported headache symptoms and severity in a sample representative of the US population.[21] Of 13,624 respondents with migraine, 8784 (64.5%) reported they had never used an acute prescription medication for migraine attacks, 3121 (22.9%) were current users of acute prescription medication for migraine, and 1719 (12.6%) had used acute prescription medication for migraine but were no longer doing so and were considered discontinuers (**TABLE 2**).[19]

Of the current users of acute prescription medications, 47.2% were taking a triptan, 37.3% an opioid, and 31.9% a prescription NSAID. Despite current use of an acute prescription medication, this cohort continued to be substantially impacted by their migraine attacks (**TABLE 2**).[19] Approximately 51% of current users of acute prescription medications were experiencing 5 or more headache days per month, 60% reported moderate-to-severe headache-related disability (Migraine Disability Assessment Scale [MIDAS] grade III/IV), and at least one-third had comorbid depression (37%; score ≥10 on 9-item Patient Health Questionnaire [PHQ-9]) and/or anxiety (33%; score >10 on 7-item Generalized Anxiety Disorder scale [GAD-7]). Of those who had discontinued their acute prescription medication, only 21.3% reported headache alleviation as the reason for discontinuation; 28.2% had discontinued because of lack of efficacy, and 24.9% because of tolerability issues or adverse events.[19] Data on acute treatment patterns were similar in the Migraine in America Symptoms and Treatment (MAST) study, a longitudinal study evaluating symptoms, management approaches, and unmet needs among US adults with migraine.[20] Use of preventive medications for migraine is rare, with approximately 12% of people with migraine reporting current use of a preventive medication.[20,22]

Upon discontinuation of acute prescription medication, the majority of individuals continue to experience substantial migraine-related disability.[19] In the CaMEO study, 37.6% of respondents who had discontinued acute prescription medications still experienced at least 5 headache days per month, and 41.7% reported moderate or severe migraine-related disability (MIDAS grade III/IV; **TABLE 2**).[19] Approximately one-third had moderate-to-severe depression (33%) and/or moderate-to-severe anxiety (30%) as assessed with the PHQ-9 and the GAD-7, respectively.[19]

TABLE 1 General domains of unmet treatment need in people with migraine[11,12]

Domains of unmet treatment need
• Disability related to headache
• Lack of optimization of current acute treatment
• Dissatisfaction with current acute treatment
• Acute medication overuse
• Excessive use of opioids or barbiturates
• Emergency department or urgent care use for headache
• Cardiovascular events indicating possible contraindication to triptan use
• Gastrointestinal conditions indicating possible relative contraindication to nonsteroidal anti-inflammatory drug use

LIMITATIONS OF CURRENT OPTIONS FOR ACUTE TREATMENT OF MIGRAINE

Commonly used acute medications have limitations. Although triptans are a mainstay of acute treatment, they are associated with suboptimal efficacy and/or tolerability in many patients.[23-25] The triptans and ergot alkaloids have precautions and contraindications regarding use in patients with CV risk factors and/or CV disease (CVD), and NSAIDs are

TABLE 2 **Headache characteristics in respondents with migraine, by acute prescription use category in CaMEO study[19a]**

	Use of acute prescription medication		
	Never (n=8784)	Discontinued (n=1719)	Current[b] (n=3121)
Monthly headache days, %			
0–4	74.9	62.4	49.3
5–9	14.5	18.7	23.2
10–14	5.4	7.9	12.1
≥15	5.3	11.0	15.5
MIDAS grade III/IV, %	28.8	41.7	59.8
Moderate-to-severe depression (PHQ-9 score >10), %	27.6	33.0	37.4
Moderate-to-severe anxiety (GAD-7 score >10), %	26.6	30.0	33.0

Abbreviations: CaMEO, Chronic Migraine Epidemiology and Outcomes; GAD-7, 7-item Generalized Anxiety Disorder scale; ICHD-2, *International Classification of Headache Disorders, 2nd edition*; MIDAS, Migraine Disability Assessment Scale; PHQ-9, 9-item Patient Health Questionnaire.

[a]The CaMEO study was a large epidemiologic, longitudinal, Web-based study that used quota sampling to identify respondents who met modified ICHD-2 migraine criteria, including episodic and chronic migraine. It was designed to characterize self-reported headache symptoms and severity in a sample representative of the US population.

[b]Current users were those who self-reported that they currently used these medications or had them on hand.

associated with a risk of potentially serious GI, renal, and CV side effects.[15,26] Most of the current acute treatment options should not be used more than 10 to 15 days per month, as high levels of use can exacerbate headache and lead to medication overuse headache (MOH).[1] Opioids and barbiturates are often used,[27] but are not recommended for acute treatment of migraine.[28]

Insufficient response to triptans

Oral triptans are the most commonly prescribed acute medications for migraine,[19,24,25,29,30] are considered the standard of care, and are an essential part of management for many people with migraine. However, there are challenges with suboptimal efficacy and/or tolerability.[23-25] The MAST study found that 55.2% of those who had tried an oral triptan discontinued it.[25,30] The most frequently reported reason for discontinuing was perceived lack of efficacy (38.4%), followed by side effects (22.8%).[25,30] The most common side effects associated with discontinuation were dizziness (37.4%), nausea (30.7%), and fatigue (26.2%).[25,30] Furthermore, at least 1 triptan sensation symptom (eg, chest tightness) was reported by 46.5% of those currently using an oral triptan.[25,30]

According to a study of a US claims database of 40,892 patients who received a new triptan prescription during the period 2001–2005, 54% did not renew it within 2 years of the initial fill.[31] The majority (67%) of patients switched to a nonspecific acute medication, often an opioid (34%) or an NSAID (23%), at the time of first refill.[31] Approximately 26% of patients discontinued acute prescription treatment for migraine attacks, and another 7% switched to a different triptan.[31]

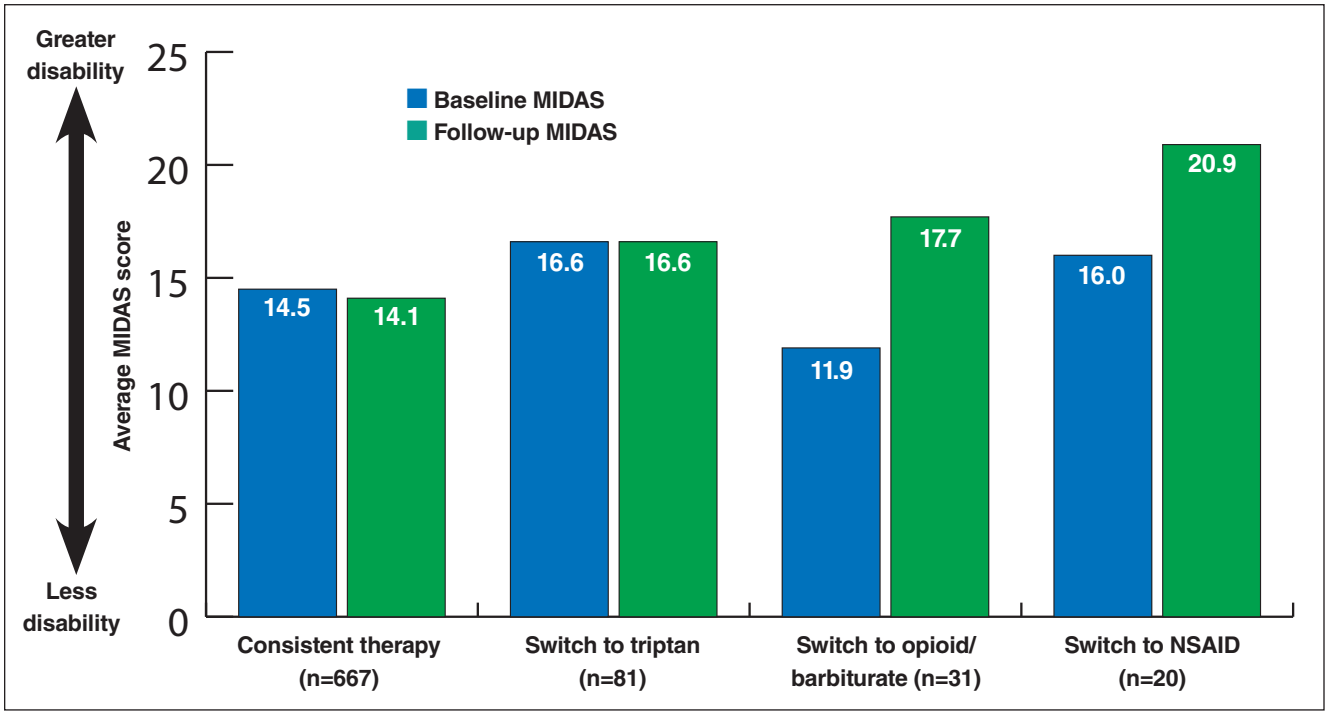
In a large observational study, switching among triptans did not improve headache-related disability.[32] An analysis of data from the American Migraine Prevalence Prevention (AMPP) study showed that changing from one triptan to another, or staying with the same triptan, was not associated with improvement in headache-related disability over 1 year of follow-up (**FIGURE 1**).[32]

Risk of medication overuse and medication overuse headache

Regular overuse of certain acute medications (including triptans, ergotamine, opioids, and combination products) on 10 or more days per month is often defined as medication overuse.[1,33,34] Longitudinal studies have demonstrated that medication overuse is associated with increasing headache frequency and the development of chronic migraine, characterized by headache on 15 or more days per month.[35]

In the CaMEO study, among people with migraine taking acute prescription drugs for migraine, nearly 1 in 5 respondents met criteria for medication overuse as defined in the *International Classification of Headache Disorders, 3rd edition* (ICHD-3).[1] Compared with respondents who were not overusing medication, those overusing had significantly higher rates of depression (53.8% vs 27.7%; $P<.001$), anxiety (48.6% vs 25.9%; $P<.001$), headache-related disability (73.1% vs 31.6%; $P<.001$), emergency department (ED) and urgent

FIGURE 1 Average baseline and follow-up MIDAS scores



Abbreviations: AMPP, American Migraine Prevalence and Prevention; MIDAS, Migraine Disability Assessment Scale; NSAID, nonsteroidal anti-inflammatory drug.

Average baseline and follow-up MIDAS scores in patients who were consistent with their use of acute medications, compared with patients who switched from one triptan to another, from a triptan to an opioid or a barbiturate, or from a triptan to an NSAID. Data from AMPP, a longitudinal study that followed a random sample of 24,000 adults by annual mailed questionnaires during period 2005–2009.[32]

care use in the preceding 6 months (12.8% vs 3.3%; $P<.001$), and severe migraine-associated burden as indicated on the Migraine Interictal Burden Scale (MIBS) questionnaire (48.6% vs 18.7%; $P<.001$).

Thus, people who overuse acute medication for migraine represent a population whose treatment needs are not being met by currently available treatments.

Patients with cardiovascular and gastrointestinal risk factors

Options for acute treatment are limited for patients with underlying CVD or multiple CV risk factors and for patients with certain GI conditions (**TABLE 3**). The vasoconstrictive mechanism of action of triptans and ergots is the basis for their labels' specific CV contraindications. For example, use of triptans is contraindicated in people with a history of coronary artery disease, coronary artery vasospasm, stroke, transient ischemic attack, peripheral vascular disease, and uncontrolled hypertension.[36-41] Rare but serious CV adverse events have been observed with triptans in clinical practice,[42] and FDA product labeling for this drug class recommends that patients with CV risk factors should have a CV evaluation before receiving triptans.[36-41] Significant blood pressure elevation has also been reported on rare occasions with triptans, and this medication class is contraindicated in patients with uncontrolled hypertension.[36-41] Labels for NSAIDs also carry a boxed warning regarding an association with increased risks of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal.[26] These CV contraindications and precautions apply to a substantial proportion of the population with migraine. An analysis of data from the AMPP study estimated that 70% of people with migraine have at least 1 CV risk factor, 40% at least 2, and 20% at least 3.[43] Furthermore, migraine itself, particularly migraine with aura, is a risk factor for CVD events, including myocardial infarction and stroke, and is associated with increased CV mortality.[44-46] The lack of acute treatment options for people with both migraine and CV risk factors has a significant impact. According to recent CaMEO study findings, respondents with both migraine and at least 1 CV comorbidity were 56% more likely than those without a CV comorbidity to be using an opioid for headache (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.28-1.90).[47]

TABLE 3 **Cardiovascular and gastrointestinal conditions associated with limitations to use of prescription medications for acute treatment of migraine**[26,36,56,57]

Triptans	Ergotamine derivatives	NSAIDs
Use is contraindicated in patients with:		
• History of: - Coronary artery disease - Coronary artery vasospasm - Stroke - Transient ischemic attack - Hemiplegic or basilar migraine • Wolff-Parkinson-White syndrome • Arrhythmias associated with cardiac accessory conduction pathway disorders • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension	• Ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) • Clinical symptoms or findings consistent with coronary artery vasospasm, including Prinzmetal variant angina • Uncontrolled hypertension • Hemiplegic or basilar migraine • Peripheral arterial disease	• Treatment of perioperative pain in setting of coronary artery bypass graft surgery
Use with caution in patients with:		
Multiple CV risk factors • High Framingham CV disease risk score[43]: - Women: ≥21 - Men: ≥16	Multiple CV risk factors • High Framingham CV disease risk score[43]: - Women: ≥21 - Men: ≥16	• Known CV disease or risk factors for CV disease • Hypertension • Fluid retention or heart failure • History of ulcer disease or GI bleeding • High Framingham CV disease risk score[43]: - Women: ≥21 - Men: ≥16

Abbreviations: CV, cardiovascular; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Labels for NSAIDs warn of the increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of stomach or intestines.[26] Prescription NSAIDs are associated with up to a 4-fold increased risk of GI bleeding and perforation, and this risk increases greatly with age.[48] For patients who are elderly, and for those who have CV risk factors or are at risk of GI bleeding, the drug label strongly advises against using NSAIDs.[26] In the CaMEO study, 14.4% of respondents reported a GI condition (eg, treated GERD [gastroesophageal reflux disease], diagnosed ulcer, ulcerative colitis, Crohn disease) representing a relative contraindication to NSAID use. Use of barbiturates, opioids, or NSAIDs was nearly twice as common among respondents with a relative GI contraindication as among those without one (34.8% vs 17.8%). Safe and effective treatment options are needed for patients with both migraine and CVD or CV risk and for those with GI risk factors.

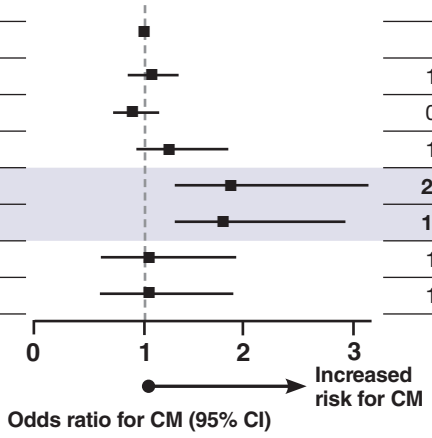
Opioids and barbiturates for acute treatment of migraine attacks

Consensus guidelines of the American Academy of Neurology, the European Federation of Neurological Societies, and other organizations recommend against using opioids or barbiturates for the acute treatment of migraine.[49-51] Opioids and barbiturates have limited efficacy in the acute treatment of migraine attacks and do not treat associated symptoms.[16,27,50,51] Furthermore, their use is associated with increased risk of migraine progression, from episodic to chronic (**FIGURE 2**).[35,52]

Despite recommendations against opioid use, people who go to the ED to have a migraine attack treated are often prescribed opioids. According to a recent analysis of data obtained from a Web-based survey conducted in 2018 of a representative US sample, the ratio of opioids to triptans prescribed in the ED for migraine in patients with ≥4 monthly headache days was 2.4.[53] In a retrospective chart review of 574 patients who visited the ED for acute treatment of primary headache between May 2011 and September 2012, 24% of cases were diagnosed as migraine.[54] Among patients with migraine, 13.8% were given opioid-containing products for the acute treatment of migraine.[54] Patients given opiates first had significantly higher rates of

FIGURE 2 **Medication use for episodic migraine in 2005 as a predictor of chronic migraine in 2006. AMPP study data captured on 2 most frequently used medications[35]**

	Headache status in 2006		
	CM (n=209)[a]	EM (n=6805)[b]	
Medication	**Mean monthly days of exposure in 2005 (SD)**		**Odds ratio for CM (95% CI)**
APAP[a]	12.77 (10.13)	6.36 (7.52)	1 (reference)
APAP + aspirin + caffeine	9.97 (8.09)	5.4 (6.68)	1.06 (0.79, 1.42)
NSAIDs	13.88 (10.77)	7.81 (8.35)	0.85 (0.63, 1.17)
Triptans	6.8 (7.23)	4.8 (11.87)	1.25 (0.89, 1.75)
Barbiturates	**10.74 (6.73)**	**6.55 (11.57)**	**2.06 (1.34, 3.17)[c]**
Opiates	**9.91 (16.58)**	**7.57 (12.63)**	**1.98 (1.38, 2.83)[c]**
Isometheptenes	8.63 (10.93)	3.88 (7.64)	1.02 (0.50, 2.11)
Ergotamines	8.63 (10.93)	4.34 (9.77)	1.01 (0.51, 2.01)



Abbreviations: AMPP, American Migraine Prevalence and Prevention; APAP, N-acetyl-para-aminophenol (acetaminophen); CI, confidence interval; CM, chronic migraine; EM, episodic migraine; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

[a]Individuals with new-onset chronic migraine in 2006 who had episodic migraine in 2005.

[b]Individuals with episodic migraine in 2006 who had episodic migraine in 2005.

[c]Results were statistically significant.

return ED visits within 7 days (7.6% vs 3%; *P*=.033) compared with those given nonopioid recommended medications.[54] In the CaMEO study, respondents who used opioids for acute treatment of migraine attacks, compared with opioid nonusers, were 73% more likely to seek headache treatment at an emergency facility (OR, 1.73; 95% CI, 1.30-2.31). The combination of frequent ED visits by those who use opioids for migraine and the high likelihood of obtaining an opioid prescription in the ED has contributed to the high rate of opioid use.[55]

CONCLUSIONS

Significant unmet needs exist for users of acute prescription medications for the treatment of migraine attacks. Both current and discontinued users of acute medications have high headache-related disability and comorbid anxiety and depression. In addition, effective and safe treatment options are limited for people with migraine who have CV event histories and/or CV and GI risk factors. Increased health care professional awareness of low rates of prescription renewal, high rates of continued disability, and high rates of acute medication overuse may inform optimal treatment selection and improve outcomes for people with migraine. The lack of acute treatment optimization and the high rates of opioid and barbiturate use underscore the need for better acute treatment options for people with migraine. The development of migraine-specific agents, including CGRP receptor antagonists (gepants) for the acute treatment of migraine attacks could alter the treatment paradigm for migraine and fill the gap of the long-unmet need of these patients. Ubrogepant, a selective CGRP receptor antagonist designed to address these needs, was recently approved by the FDA for the acute treatment of migraine. The pharmacology, clinical pharmacokinetic characteristics, and clinical efficacy and tolerability of ubrogepant are described in detail in subsequent sections of this supplement. ●

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Pharmacology and Pharmacokinetics of Ubrogepant: A Potent, Selective Calcitonin Gene-Related Peptide Receptor Antagonist for the Acute Treatment of Migraine

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KEY TAKEAWAYS

- Recognize the role of calcitonin gene-related peptide (CGRP) in the pathogenesis of migraine.
- Understand the in vitro and in vivo pharmacokinetic (PK) properties of ubrogepant.
- Consider the benefits of ubrogepant relative to other available therapies for the acute treatment of migraine.

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ACKNOWLEDGMENTS

This manuscript was sponsored by Allergan plc, Dublin, Ireland. Medical writing and editorial assistance was provided to the authors by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and was funded by Allergan plc. All authors met the authorship criteria of the International Committee of Medical Journal Editors. Neither honoraria, nor other form of payment, was made for authorship.

CONFLICTS OF INTEREST

Andrew M. Blumenfeld, MD, within the past 12 months, has served on advisory boards, consulted, and/or been a speaker or contributing author for Alder, Allergan, Amgen, Biohaven, Lilly, Novartis, Teva, Theranica, and Zoscano. He has received grant support from Allergan and Amgen.

Lars Edvinsson, MD has given talks sponsored by Amgen, Novartis, and Teva.

Abhijeet Jakate, PhD, and **Pradeep Banerjee, PhD** are employees and stockholders of Allergan plc.

INTRODUCTION

Migraine is a common neurobiological disease characterized by recurrent attacks of moderate to severe headache that are often accompanied by sensitivity to external stimuli, nausea, vomiting, and/or photophobia and phonophobia.[1,2] Migraine comprises up to 4 phases that often overlap: a prodromal phase, an aura phase, a headache phase, and a postdromal phase.[3] The complex pathogenesis of this disabling disease involves a variety of neurotransmitters,[4] including serotonin, nitric oxide, pituitary adenylate cyclase activating peptide (PACAP), and CGRP.[2,5] CGRP is highly expressed in the trigeminal ganglion and nerve, which have a key role in migraine pathogenesis. It is thought that central nervous system (CNS) activation of the trigeminal ganglion results in CGRP activation of the trigeminovascular pathway, ultimately leading to headache pain.[6]

Currently prescribed acute treatments for migraine attacks can be migraine-specific (eg, triptans and ergotamines that target serotonin neurotransmitter receptors) or migraine-nonspecific (eg, opioids, nonsteroidal anti-inflammatory drugs [NSAIDs], and combination products, such as acetaminophen/aspirin/caffeine and butalbital/aspirin/caffeine, that target analgesic and pro-inflammatory pathways).[7,8] However, current acute treatments for migraine may be (1) poorly tolerated and associated with risk of medication overuse headache, (2) ineffective, or (3) contraindicated in people with cardiovascular conditions, owing to effects on the vasculature (eg, vasoconstriction), all of which limit their utility (see article in this supplement by Lipton et al).[8-11] Consequently, effective and well-tolerated medications that lack the vasoconstrictive actions of triptans and ergotamines and that do not have the potential for overuse issues are needed for the acute treatment of migraine attacks.[9] In this article, we provide a review of the pharmacology and clinical PK characteristics of ubrogepant, a selective CGRP receptor antagonist that could address these needs. Ubrogepant was recently approved by the US Food and Drug Administration (FDA) for the acute treatment of migraine.

TABLE 1 **In Vitro binding affinity and potency of ubrogepant**

Cloned Receptor	CGRP K_i[a,b] (nM)	cAMP IC_{50}[a,c] (nM)	cAMP + HS IC_{50}[a,d] (nM)
Human CGRP (CLR/RAMP1)	0.07 ± 0.006	0.081 ± 0.005	0.19 ± 0.01
CGRP receptor in other species			
Rhesus CGRP	0.079 ± 0.005	0.07 ± 0.02	0.3 ± 0.01
Rat CGRP	9.6 ± 1.1	—	—
Mouse CGRP	11.6 ± 1.1	—	—
Rabbit CGRP	11 ± 0.5	—	—
Dog CGRP	47 ± 4	—	—
Other CGRP family receptors			
Calcitonin	—	20,284 ± 7470	—
Adrenomedullin 1	—	>20,000	—
Adrenomedullin 2	2059 ± 122	1,591 ± 185	—
Amylin 1	8.2 ± 1.6	8.4 ± 0.6	—
Amylin 3	—	219 ± 57	—

Abbreviations: cAMP, cyclic adenosine monophosphate; CGRP, calcitonin gene-related peptide; CLR, calcitonin receptor-like receptor; hCGRP, human CGRP; HEK, human embryonic kidney cell; HS, human serum; IC_{50}, 50% inhibitory concentration; RAMP, receptor activity-modifying protein; SEM, standard error of mean.

[a]Mean value ± SEM.

[b]The K_i value for inhibition of ^{125}I-hCGRP binding was determined using membranes from HEK293 cells stably expressing the cloned receptor.

[c]Inhibition of CGRP-induced cAMP production in HEK293 cells stably expressing the cloned receptor.

[d]Assay conditions are as for footnote c but were determined in the presence of 50% HS.

Source: Data on File, Allergan plc, Madison, NJ.

CGRP is a 37-amino acid neuropeptide expressed in multiple nervous system regions, is known to be associated with migraine pathophysiology, and has been identified as a therapeutic target for migraine.[6,12-15] Many lines of evidence indicate that CGRP is a potent vasodilator and neurotransmitter that has an important role in migraine pathogenesis.[3,6,12,16] For example, serum CGRP concentrations increase in the jugular venous system in response to trigeminal nerve activation during the headache phase of migraine attacks.[17-19] In addition, exogenously administered CGRP can induce headache as well as delayed migraine-like attacks in people with migraine.[20,21] Several oral small-molecule CGRP receptor antagonists (called gepants) have been evaluated for their efficacy and safety in the acute treatment of migraine.

PHARMACOLOGY

In vitro

Ubrogepant has a high affinity for the human CGRP receptor, inhibiting binding of human CGRP to both native and recombinant human CGRP receptors with a K_i of 0.07 nM (**TABLE 1**). Binding of ubrogepant to CGRP receptors is highly species-specific for human and nonhuman primates relative to CGRP receptors of other species (**TABLE 1**) (Data on File, Allergan plc, Madison, NJ). Other clinically active small-molecule CGRP antagonists share this feature, which has been attributed to a species-specific residue in the CGRP receptor protein believed to be the site of antagonist binding.[6,22] In a pharmacology screen of enzymes, receptors, and ion channels, no off-target binding affinity of ubrogepant was identified, except for a micromolar affinity for dopamine transporters (DAT; K_i=4.4 μM) (Data on File, Allergan plc, Madison, NJ), which may be biologically irrelevant, since it is highly unlikely that such high brain concentrations of ubrogepant will be reached in humans.

Ubrogepant is a potent and competitive CGRP receptor antagonist. It was shown to have subnanomolar potency for blocking human α-CGRP-stimulated cyclic adenosine monophosphate (cAMP) responses in human CGRP receptor-expressing human embryonic kidney (HEK) 293 cells (cAMP IC_{50} [50% inhibitory concentration]=0.08 nM; **TABLE 1**) (Data on File, Allergan plc, Madison, NJ), which was similar to the IC_{50} values observed in the same assay system with other gepants, including telcagepant (2.2 nM),[23] MK-3207 (0.12 nM),[24] and rimegepant (0.14 nM).[25] Ubrogepant was highly selective for the human CGRP receptor in the cAMP assay, showing minimal antagonist activity at most of the other receptors in the CGRP family (ie, calcitonin, adrenomedullin 1 and 2 receptors) and low nM antagonist activity at the amylin 1 receptor (**TABLE 1**), although the role of the amylin 1 receptor in migraine is poorly understood. The high potency of ubrogepant was maintained in the same functional assay carried out in the presence of 50% human serum

(IC_{50}=0.19 nM; **TABLE 1**), suggesting that its activity is not significantly affected by plasma protein binding in vivo (Data on File, Allergan plc, Madison, NJ).

In vivo

The ability of ubrogepant to function as a CGRP receptor antagonist was evaluated in vivo in the rhesus monkey capsaicin-induced dermal vasodilation (CIDV) pharmacodynamic assay.[26] In this model, therapeutic concentrations were considered to be represented by the estimated plasma concentration of ubrogepant required for inhibition of 90% of the CIDV response (EC_{90}), which was approximately 29 nM.

Overall, ubrogepant has exhibited similar oral bioavailability in the rat (F=22%) and rhesus monkey (F=24%). Ubrogepant had a lower potential to form reactive metabolites than did first-generation small-molecule CGRP antagonists in mechanistic studies. In addition, drug-induced liver injury (DILI) simulations based on in vitro data predicted no liver enzyme elevations for ubrogepant at clinically relevant doses. Results of nonclinical safety pharmacology studies indicated that ubrogepant had no adverse cardiovascular, neurobehavioral, or respiratory effects in rats and dogs. Ubrogepant did not exhibit vasoconstrictor effects when it was administered at therapeutic concentrations in isolated human coronary, cerebral, and middle meningeal arteries.[27] Ubrogepant exhibited limited brain penetration (cerebrospinal fluid to plasma ratio of 0.03) and low CGRP receptor occupancy in monkeys, and showed no CNS adverse effects or potential for abuse in rodents or monkeys (Data on File, Allergan plc, Madison, NJ).

CLINICAL PHARMACOKINETICS

The PK profile of oral ubrogepant was evaluated in 18 phase 1 studies in healthy volunteers (Data on File, Allergan plc, Madison, NJ). Oral ubrogepant is rapidly absorbed under fasting conditions, with a median time to maximum plasma drug concentration (t_{max}) of 1.7 hours (range, 1.1–6.1 hours) and a terminal elimination half-life of 4.4 hours (**TABLE 2**).[28] These PK properties make ubrogepant suitable for acute dosing/treatment. A PK study of ubrogepant and sumatriptan in healthy adults demonstrated that the median t_{max} of ubrogepant 100 mg alone (1.5 hours; range, 1–4 hours) was similar to that of sumatriptan 100 mg alone (1 hour; range, 0.5–5 hours).[29]

The maximum plasma concentration (C_{max}) of ubrogepant after a 100 mg dose was 274.2 ng/mL, with an area under the plasma drug concentration-time curve (AUC) of 1249.4 ng•hr/mL. Pharmacokinetics of ubrogepant were dose proportional in the dose range of 1 mg to 400 mg. No accumulation was noted after repeated once-daily dosing, and steady state was achieved within 2 days of dosing.[28]

TABLE 2 Clinical pharmacokinetic parameters of plasma ubrogepant following administration of single oral doses of ubrogepant 100 mg to healthy fasted participants[28]

Pharmacokinetic parameter	Ubrogepant 100 mg (N=78)
C_{max}, ng/mL[a]	274.2 (99.3)
AUC_{0-t}, ng•h/mL[a]	1220.6 (430.3)
$AUC_{0-\infty}$, ng•h/mL[a]	1249.4 (434)
t_{max}, h[b]	1.7 (1.1, 6.1)
$t_{1/2}$, h[a]	4.4 (1.1)
V_z/F, L[a]	561.4 (238.9)
CL/F, L/h[a]	89 (29.3)

Abbreviations: AUC_{0-t}, area under the plasma concentration time curve from time 0 to time t; $AUC_{0-\infty}$, area under the plasma concentration time curve from time 0 to infinity; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}; V_z/F, apparent volume of distribution.

Source: Jakate A, Boinpally R, Butler M, Lu K, McGeeney D, Periclou A. Single therapeutic and supra-therapeutic doses of ubrogepant do not affect cardiac repolarization in healthy adults: results from a randomized trial. *Clin Pharmacol Ther.* 2019; published online ahead of print, October 19. doi:10.1002/cpt.1696.

[a]Mean (SD).

[b]Median (min, max).

Ubrogepant is metabolized primarily by cytochrome P450 3A4 (CYP3A4), with the glucuronide conjugates (M15 and M20) of the oxidative metabolites (M9 and M8) being the primary circulating metabolites in human plasma. These metabolites are cleared from plasma within 6 hours. Ubrogepant is eliminated mostly via the biliary/fecal route (≈83%), with the renal route accounting for less than 10% of elimination (Data on File, Allergan plc, Madison, NJ).

A population PK study of data combined from phase 1, 2, and 3 studies of ubrogepant included a quantitative assessment of the impact of covariates, such as food intake, formulation, hepatic impairment status, race, body weight, creatinine clearance (CL_{CR}), concurrent migraine, health status, and sex, on the PK of ubrogepant. Renal function (as measured by CL_{CR}) did not have a statistically significant effect on any structural PK parameter. The apparent central volume of distribution was 16.6% lower in females than in males, translating into a projected increase in C_{max} of less than 20%, which is not considered clinically relevant. With regard to race, the apparent volume of distribution was 6.5% lower in Asian than non-Asian participants, but was not different between Caucasian and black participants. In addition, body weight, age, concurrent migraine, and health status (ie, healthy participant vs migraine patient) did not have any clinically relevant impact on systemic exposure to ubrogepant. The analysis also determined that coadministration of mild CYP3A4 inhibitors (alprazolam, azithromycin, cimetidine, fluvoxamine, isonia-

zid, and ranitidine) had no effect on ubrogepant clearance. Based on these results, no dosage adjustments of ubrogepant are needed due to differences in sex, race, weight, and age, or due to mild or moderate hepatic or renal impairment, food consumption, or concomitant use with mild CYP3A4 inhibitors (Data on File, Allergan plc, Madison, NJ).

While no effect on ubrogepant clearance was found with coadministration of mild CYP3A4 inhibitors, ubrogepant should not be used with strong CYP3A4 inhibitors (eg., ketoconazole, itraconazole, clarithromycin). Coadministration of ubrogepant with ketoconazole resulted in a 9.7-fold increase in ubrogepant $AUC_{0-\infty}$ and a 5.3-fold increase in ubrogepant C_{max}. Coadministration of ubrogepant with verapamil (a moderate CYP3A4 inhibitor) showed a 3.5-fold increase in ubrogepant $AUC_{0-\infty}$ and a 2.8-fold increase in ubrogepant C_{max} (Data on File, Allergan plc, Madison, NJ).

Coadministration of ubrogepant with rifampin, a strong CYP3A4 inducer, resulted in an 80% reduction in ubrogepant exposure (Data on File, Allergan plc, Madison, NJ). In patients concomitantly using CYP3A4 inducers, loss of ubrogepant efficacy is expected. No clinically relevant drug-drug interactions have been noted with oral contraceptives, acetaminophen, sumatriptan, naproxen, or esomeprazole (**TABLE 3**). An open-label PK study of the effect of multiple doses of ubrogepant on the single-dose PK of a commonly used oral contraceptive (ethinyl estradiol [EE] 0.035 mg/norgestimate [NGM] 0.25 mg) in healthy postmenopausal or oophorectomized women demonstrated that ubrogepant has no potential for clinically significant drug-drug interactions with oral contraceptives containing EE/NGM.[30]

The population PK analysis found that moderate or severe hepatic impairment had an impact on oral apparent clearance that translated into increases in AUC_{0-24hr} of 21% for moderate impairment and 60% for severe impairment, suggesting that severe hepatic impairment may be a clinically relevant covariate for ubrogepant exposure. The potential for increased exposure to ubrogepant in patients with severe hepatic impairment was further evaluated in a phase 1 study of ubrogepant 100 mg in patients with impaired hepatic function compared with healthy participants. The rate (C_{max}) and extent ($AUC_{0-\infty}$) of systemic exposure to ubrogepant were significantly higher (40% and 115%, respectively) in patients with severe hepatic impairment than in participants with normal hepatic function. Patients with moderate hepatic impairment had a 25% higher C_{max} and a 52% higher $AUC_{0-\infty}$ than participants with normal hepatic function (Data on File, Allergan plc, Madison, NJ).

No hepatic safety concerns were identified in two phase 1 studies of ubrogepant in healthy volunteers. In a single-center, randomized, double-blind, placebo-controlled phase 1 study in 32 healthy adult males, administration of ubrogepant 150 mg once daily for 28 days did not have a clinically meaningful effect on serum alanine aminotransferase levels.[31] Results of a multicenter, randomized, double-blind, placebo-controlled, phase 1 study in 518 healthy adults demonstrated that frequent, intermittent dosing of ubrogepant 100 mg (ie, 2 days on treatment and 2 days off treatment for a total of 28 days of dosing in a 56-day treatment period) was safe and well tolerated in healthy participants, and no hepatic safety concerns were identified.[32]

With regard to cardiac safety, ubrogepant had no effect on cardiac repolarization in healthy adults. A phase 1, single-center, single-dose, double-blind, placebo- and active-controlled crossover study in 84 healthy male and female participants showed that therapeutic (100 mg) and supratherapeutic (400 mg) doses of ubrogepant did not cause any relevant change in placebo- and baseline-corrected QTcF intervals.[28] Ubrogepant has not been tested in patients with known atherosclerotic disease, such as coronary artery disease; however, erenumab, a monoclonal antibody directed against CGRP receptors, has been studied in a placebo-controlled, single-dose study of patients with stable angina, and no significant differences between treatment groups in reported adverse events were noted.[33] In addition, in dogs with coronary artery stenosis and serial atrial pacing–evoked regional myocardial ischemia, intravenous and intra-atrial administration of a CGRP receptor antagonist ($CGRP_{8-37}$) had no effect on paced coronary flow or myocardial ischemia severity.[34]

TABLE 3 Summary of ubrogepant drug-drug interactions of interest[30]

Coadministered Agent(s)	Effect on Ubrogepant
Mild CYP3A4 inhibitors	No effect on clearance
Moderate CYP3A4 inhibitors	↑ $AUC_{0-\infty}$ ↑ C_{max}
Strong CYP3A4 inhibitors	↑ $AUC_{0-\infty}$ ↑ C_{max}
Strong CYP3A4 inducers	↓ Exposure
Acetaminophen	No clinically relevant interactions
Sumatriptan	No clinically relevant interactions
Naproxen	No clinically relevant interactions
Oral contraceptives	No clinically relevant interactions
Esomeprazole	No clinically relevant interactions

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration time curve from time 0 to infinity; C_{max}, maximum plasma concentration.

Source: Data on File, Allergan plc, Madison, NJ; Li CC, Palcza J, Xu J, et al. Absence of clinically significant drug interactions with coadministration of ubrogepant and an ethinyl estradiol/norgestimate oral contraceptive in healthy female subjects: a phase 1 pharmacokinetic analysis [abstract]. *Neurology*. 2019;92(15 suppl):P1.10-018.

Further, no definitive ubrogepant-related muscle enzyme elevation has been identified in healthy human adults exposed to clinical doses of ubrogepant (Data on File, Allergan plc, Madison, NJ). Ubrogepant has not been studied in pregnant women or women who are breastfeeding. Ubrogepant does not cause excessive somnolence or dizziness; thus, no driving precautions are needed (Data on File, Allergan plc, Madison, NJ). Ubrogepant is not a scheduled drug.

SUMMARY AND CONCLUSIONS

Ubrogepant is a competitive, potent, selective, orally administered, small-molecule CGRP receptor antagonist or gepant that has been approved by the US FDA for the acute treatment of migraine attacks. Its mechanism of action specifically targets the underlying disease pathophysiology in migraine, thus distinguishing ubrogepant from the serotonergic and vasoconstrictive actions of the triptans, and its short terminal elimination half-life of 5 hours makes it uniquely suited for acute treatment of migraine. Its molecular structure provides efficacy, while minimizing the potential for hepatotoxicity and cardiovascular adverse effects. Overall, these demonstrated pharmacologic properties further establish ubrogepant as a rational agent for the acute treatment of migraine attacks that may help to address the unmet need of patients who do not use available acute treatments for migraine attacks due to lack of efficacy, side effects, or risk factors that preclude their use. The properties of ubrogepant have translated to good tolerability and efficacy for the acute treatment of migraine in multiple, large, double-blind, placebo-controlled trials, the results of which are reviewed by Drs. Dodick and Ailani in a separate article in this supplement. ●

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Clinical Efficacy and Safety of Ubrogepant for the Acute Treatment of Migraine

David W. Dodick, MD; Jessica Ailani, MD

KEY TAKEAWAYS

- Ubrogepant is a small-molecule oral calcitonin gene–related peptide (CGRP) receptor antagonist which has demonstrated efficacy for the acute treatment of migraine.
- Ubrogepant is well tolerated, with no safety concerns demonstrated in pivotal clinical trials in people with migraine.

INTRODUCTION

A significant unmet need exists for users of acute medications for the treatment of migraine attacks, many of whom continue to have high headache-related disability with use of currently available acute medications (eg, triptans, ergotamine derivatives, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids).[1,2] These medications may be ineffective and/or associated with undesirable side effects in a significant proportion of people with migraine.[3-5] Most of the current acute treatment options also increase the risk of medication overuse headache when used 10 to 15 or more days per month.[6] CGRP receptor antagonism is a promising therapeutic approach for the acute treatment of migraine attacks.[7] Ubrogepant is a novel, small-molecule, oral CGRP receptor antagonist that has demonstrated good tolerability and efficacy for the acute treatment of migraine attacks in clinical trials.[8-10] Here, we review efficacy and safety outcomes from the phase 3 clinical trial program for ubrogepant.

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ACKNOWLEDGMENTS

This manuscript was sponsored by Allergan plc, Dublin, Ireland. Medical writing and editorial assistance was provided to the authors by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and was funded by Allergan plc. The authors acknowledge Aubrey Manack Adams and Janette Contreras-De Lama for providing the historical background and clinical knowledge related to the development of ubrogepant. All authors met the authorship criteria of the International Committee of Medical Journal Editors. Neither honoraria, nor other form of payment, was made for authorship.

CONFLICT OF INTEREST

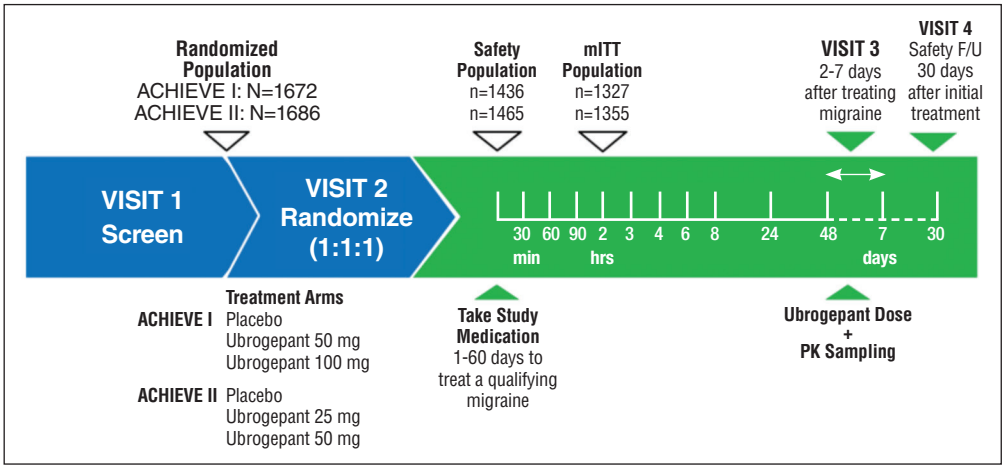
David W. Dodick, MD, reports the following conflicts: Personal fees: Amgen, Association of Translational Medicine, University Health Network, Daniel Edelman Inc., Autonomic Technologies, Axsome, Aural Analytics, Allergan, Alder BioPharmaceuticals, Biohaven, Charleston Laboratories, Dr Reddy's Laboratories/Promius, Electrocore LLC, Eli Lilly, eNeura, Neurolief, Novartis, Ipsen, Impel, Satsuma, Supernus, Sun Pharma (India), Theranica, Teva, Vedanta, WL Gore, Nocira, PSL Group Services, University of British Columbia, XoC, Zosano, ZP Opco, Foresite Capital, Oppenheimer, Upjohn (Division of Pfizer), Pieris, Revance, Equinox, Salvia, Amzak Health. CME fees or royalty payments: HealthLogix, Medicom Worldwide, MedLogix Communications, Mednet, Miller Medical, PeerView, WebMD Health/Medscape, Chameleon, Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket, Global Scientific Communications, Global Life Sciences, Global Access Meetings, UpToDate (Elsevier), Oxford University Press, Cambridge University Press, Wolters Kluwer Health; Stock options: Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien, GBS/Nocira, Matterhorn/Ontologics, King-Devick Technologies; Consulting without fee: Aural Analytics, Healint, Second Opinion/Mobile Health, Epien; Board of directors: Epien, Matterhorn/Ontologics, King-Devick Technologies. Patent: 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis; Research funding: American Migraine Foundation, US Department of Defense, PCORI, Henry Jackson Foundation; Professional society fees or reimbursement for travel: American Academy of Neurology, American Brain Foundation, American Headache Society, American Migraine Foundation, International Headache Society, Canadian Headache Society.

Jessica Ailani, MD, has served as a consultant for Alder, Allergan, Alpha Sites Consulting, Aptus, Amgen, Biohaven, Electrocore, Eli Lilly and Company, Impel, Promius, Revance, Satsuma, Teva, Neurodiem, and Zosano; been involved with CME programming with Avent (CME content and speaker's fee), Miller Communications (CME content and speaker fee), Forefront (CME content and speaker fee), and Peer View (CME speaker fee); been a speaker for Allergan, Amgen, Electrocore, Eli Lilly and Company, Promius, and Teva; received grant support from the American Migraine Foundation, Allergan, Biohaven, and Eli Lilly and Company; received honorarium for writing in *Neurology Times*; and provided editorial services to *Current Pain and Headache Reports*.

UBROGEPANT: SMALL-MOLECULE CGRP RECEPTOR ANTAGONIST

Ubrogepant belongs to the "gepant" medication class, a group of small molecules that compete with CGRP for a binding site on the CGRP receptor complex (consisting of the calcitonin receptor-like receptor and receptor activity modifying protein 1).[11,12] The pharmacologic profile of ubrogepant is reviewed in detail in the companion manuscript in this supplement titled, "Preclinical Pharmacology and Pharmacokinetics of Ubrogepant: A Potent, Selective Calcitonin Gene–Related Peptide Receptor Antagonist for the Acute Treatment of Migraine."

FIGURE 1 Design of the ACHIEVE I and II phase 3 clinical trials of ubrogepant[9,10]



Abbreviations: F/U, follow-up; mITT, modified intent-to-treat; PK, pharmacokinetic.

SELECTION OF CLINICAL TRIAL PRIMARY ENDPOINTS FOR ACUTE TREATMENTS OF MIGRAINE

The US Food and Drug Administration and International Headache Society (IHS) guidelines recommend using freedom from headache pain (defined as reduction from moderate/severe pain to no pain) 2 hours after dosing and absence of the most bothersome migraine-associated symptom 2 hours after dosing as co-primary endpoints for controlled trials of acute medications for migraine.[13,14] The co-primary endpoints for the phase 3 clinical trial program for ubrogepant adhered to these guidelines. The measure of pain relief (reduction in headache severity from moderate/severe to mild or none) was also included as a secondary outcome in the ubrogepant clinical trial program, as it can provide insight into a drug's pain-relieving effect at a specific point in time. Early clinical trials that assessed the efficacy of triptans for the treatment of moderate or severe migraine attacks focused on assessing headache response (pain relief) at 2 hours.[15,16] Given the different *response* definitions, "headache response" rates in early clinical trials of triptans are consistently greater than response rates based on pain freedom.[16]

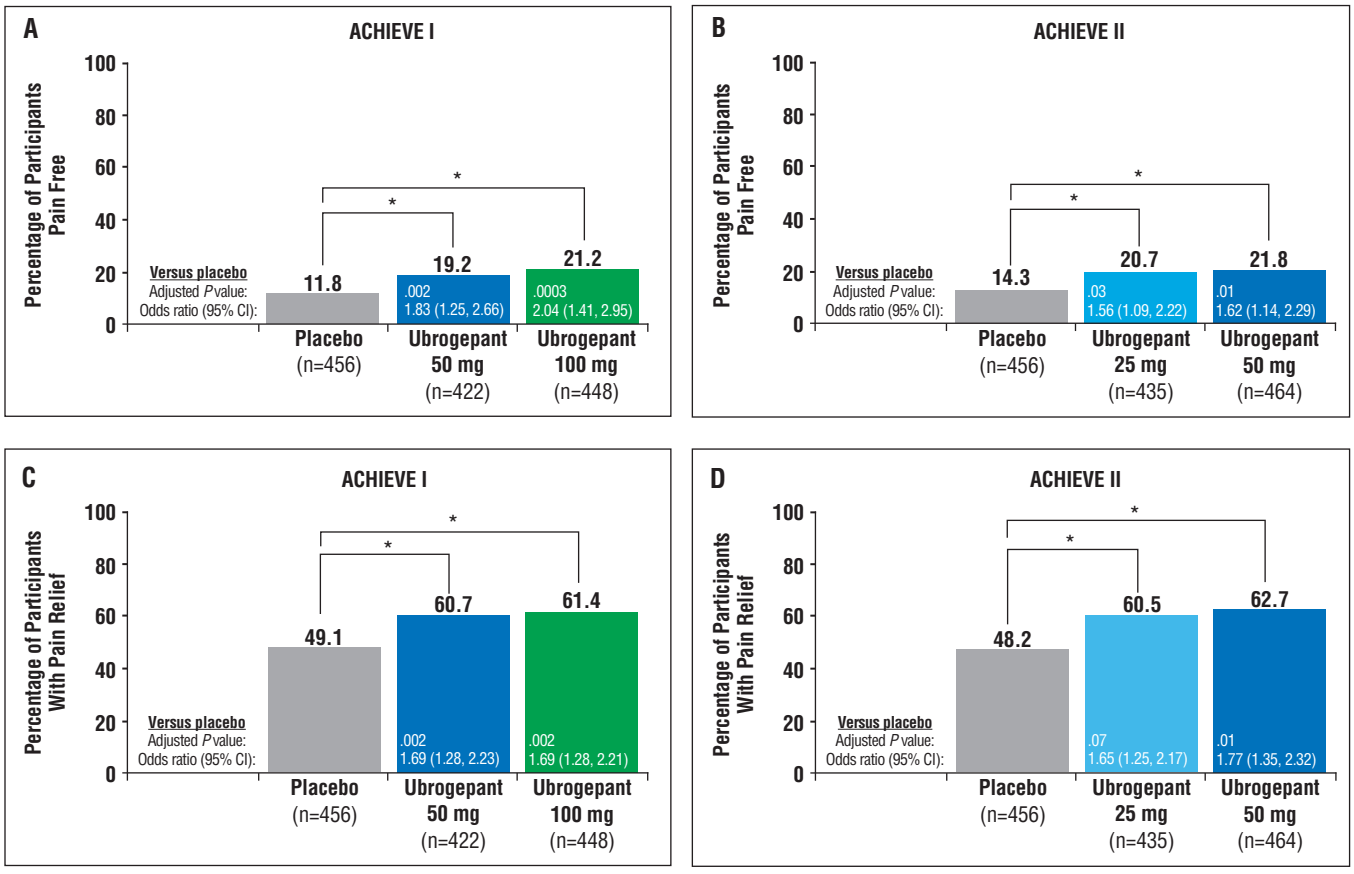
CLINICAL TRIAL PROGRAM FOR UBROGEPANT: ACHIEVE I AND II

Two phase 3, multicenter, randomized, double-blind, placebo-controlled trials (ACHIEVE I and II) investigated the efficacy, safety, and tolerability of ubrogepant for the acute treatment of a single migraine attack (**FIGURE 1**).[9,10] The co-primary efficacy outcomes of both ACHIEVE I and II were pain freedom and absence of the most bothersome migraine-associated symptom 2 hours post initial dose. Participants were instructed to take the blinded study medication (placebo or ubrogepant [50 mg or 100 mg in ACHIEVE I; 25 mg or 50 mg in ACHIEVE II]) as soon as possible within 4 hours after the onset of a qualifying migraine attack, characterized by moderate or severe migraine headache severity and presence of at least 1 migraine-associated symptom of photophobia, phonophobia, or nausea. An optional second dose of study medication or rescue medication was allowed for the treatment of moderate or severe headache from 2 to 48 hours after the initial dose. For those who chose to take the optional second dose of study medication, participants in the ubrogepant groups were randomized to receive either placebo or ubrogepant for the second dose. All participants in the placebo group received placebo for the optional second dose. Participants who opted not to take the second dose of study medication could take rescue medication to treat their moderate or severe migraine headache beginning 2 hours after initial treatment. Rescue medication options included acetaminophen, NSAIDs, opioids, anti-emetics, or triptans. Once participants had taken rescue medication, they could not take an optional second dose of study medication. Rescue medication could be taken if needed 2 hours after the second dose of study medication. Adverse events (AEs) were recorded 48 hours after initial dose and optional second dose of study medication and within 30 days after any dose.

Participant characteristics

The trials enrolled 3358 adults with a history of migraine with or without aura who had experienced 2 to 8 migraine

FIGURE 2 Headache pain freedom 2 hours post initial dose in ACHIEVE I (A) and ACHIEVE II (B) and pain relief 2 hours post initial dose in ACHIEVE I (C) and ACHIEVE II (D)[9,10]



*Indicates statistical significance based on adjusted *P* value.

attacks monthly with moderate to severe headache pain in the previous 3 months. Demographic characteristics were similar in ACHIEVE I and II. The mean age was 41-42 years and the majority of participants were Caucasian (82%–83%) and female (88%–90%).

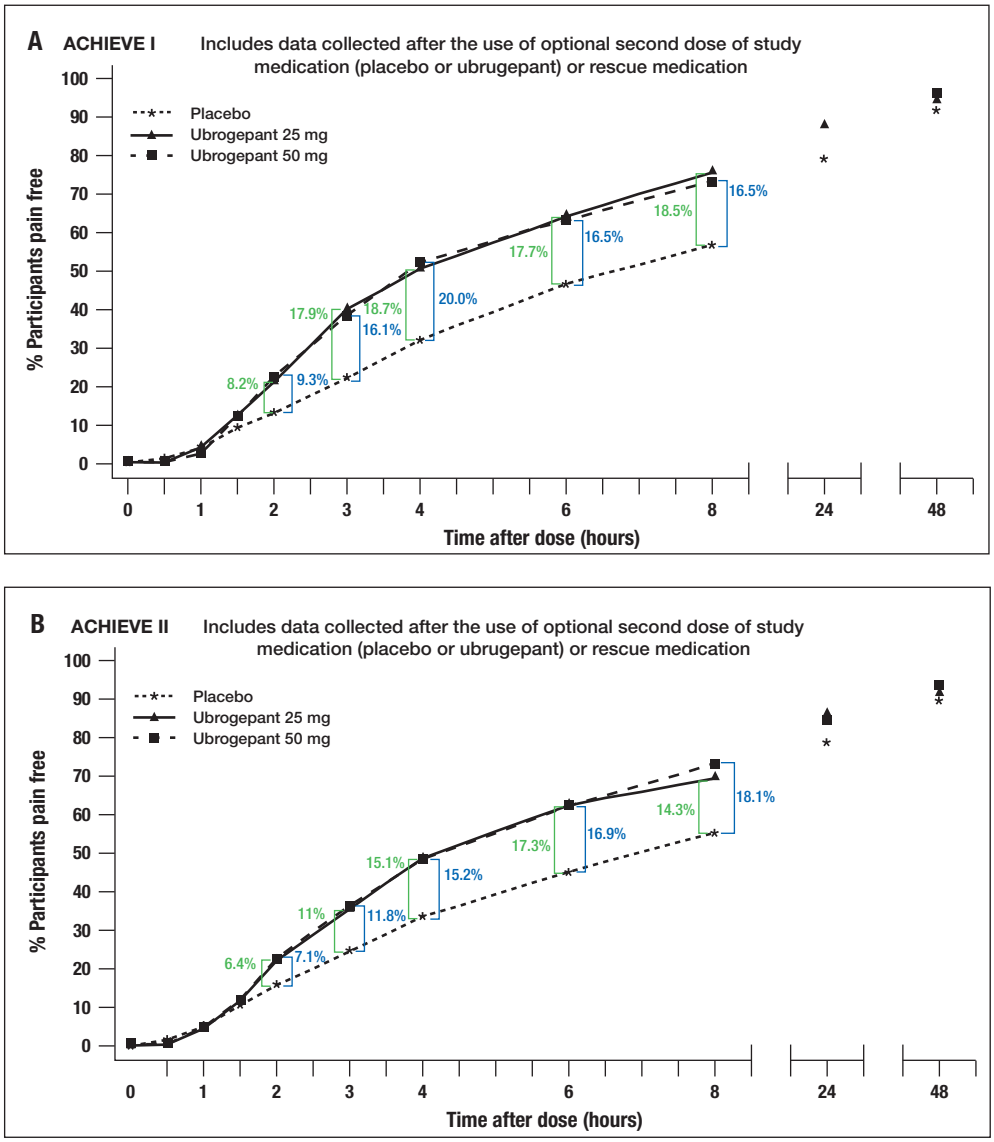
Migraine attack characteristics

In ACHIEVE I and II, respectively, 79% (n/N=1327/1672) and 80% (1355/1686) of randomized participants treated a qualifying migraine attack with study medication and were evaluable for efficacy (mITT population). Of those, 23% to 24% reported current use of a preventive migraine medication (eg, β-blocker, tricyclic antidepressant, topiramate, valproic acid, onabotulinumtoxinA). Immediately before treating the qualifying migraine attack, approximately 60% of participants rated their migraine headache pain as moderate and approximately 40% rated it as severe. Ninety percent of participants reported the presence of photophobia at the time of the qualifying attack, while approximately 80% reported phonophobia and slightly more than 60% reported nausea at attack baseline. The most frequently reported most bothersome migraine-associated symptom was photophobia (56%–57%), followed by phonophobia (22%–26%) and nausea (17%–21%).

Primary efficacy results

In each trial, the percentage of participants reporting pain freedom 2 hours post initial dose was significantly greater in the ubrogepant 50 mg arm than the placebo arm (ACHIEVE I: 19.2% vs 11.8%, adjusted *P*=.002; ACHIEVE II: 21.8% vs 14.3%, adjusted *P*=.01; **FIGURE 2A-B**).[9,10] Pain freedom 2 hours post initial dose was also significantly greater with ubrogepant 100 mg than placebo (21.2% vs 11.8%, adjusted *P*=.0003) in ACHIEVE I and with ubrogepant 25 mg than placebo (20.7% vs 14.3%, adjusted *P*=.03) in ACHIEVE II. In both trials, ubrogepant efficacy over placebo improved beyond the 2-hour time point, with maximum efficacy and separation between ubrogepant and placebo groups observed from 3 to 8 hours after the initial dose (**FIGURE 3**).

FIGURE 3 **Kaplan-Meier plots of time to pain freedom after initial dose in ACHIEVE I (A) and ACHIEVE II (B) including data collected after use of an optional second dose of study medication or rescue medication[9,10]**



Panel A is from N Engl J Med, Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM, Szegedi A. Ubrogepant for the Treatment of Migraine, 381(23), 2230-2241. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The proportion of participants reporting absence of the most bothersome migraine-associated symptom (photophobia, phonophobia, or nausea) at 2 hours was significantly greater in the ubrogepant 50 mg groups of ACHIEVE I (38.6%, adjusted *P*=.002) and ACHIEVE II (38.9%, adjusted *P*=.01) than placebo (27.8% and 27.4%, respectively). In ACHIEVE I, ubrogepant 100 mg also significantly improved the rate of alleviation of the most bothersome symptom at 2 hours compared with placebo (37.7% vs 27.8%, adjusted *P*=.002). In ACHIEVE II, 34.1% of participants treated with ubrogepant 25 mg reported absence of the most bothersome symptom at 2 hours compared with 27.4% in the placebo group, although the between-group difference was not statistically significant (adjusted *P*=.07).

Secondary efficacy results

Secondary efficacy outcomes in ACHIEVE I and II included pain relief at 2 hours, sustained pain relief from 2 to 24 hours, sustained pain freedom from 2 to 24 hours, and absence of photophobia, phonophobia, and nausea 2 hours post initial dose (**TABLE 1**). In ACHIEVE I and II, respectively, 61% and 63% of participants in the ubrogepant 50 mg groups reported pain relief at 2 hours, compared with 49% and 48% of participants in the placebo group (ACHIEVE I, OR [odds ratio] [95% CI, confidence interval]: 1.69 [1.28, 2.23], adjusted *P*=.002; ACHIEVE II: 1.77 [1.35, 2.32], adjusted *P*=.01; **FIGURE 2C-D**).[9,10] Significantly greater proportions of participants also reported sustained pain relief from 2 to 24 hours in the 50 mg groups of ACHIEVE I and II than in their respective placebo groups (adjusted *P*≤.01; **TABLE 1**). In ACHIEVE I, 61% of participants in the ubrogepant 50 mg group reported pain relief at 2 hours, compared with 49% of participants in the placebo group (OR [95% CI]: 1.69 [1.28, 2.21], adjusted *P*=.002). Responder rates for ubrogepant 100 mg were also significantly greater than placebo for sustained pain freedom and pain relief from 2 to 24 hours, and absence of photophobia (adjusted *P*≤.004; **TABLE 1**). Statistical comparisons between

TABLE 1 Secondary efficacy outcomes of ACHIEVE I and II[9,10]

Secondary efficacy variables	ACHIEVE I			ACHIEVE II		
	Placebo (n=456)	Ubrogepant 50 mg (n=423)	Ubrogepant 100 mg (n=448)	Placebo (n=456)	Ubrogepant 25 mg (n=435)	Ubrogepant 50 mg (n=464)
Pain relief[a] at 2 hours, n/N1 (%)[b]	224/456 (49.1)	256/422 (60.7)	275/448 (61.4)	220/456 (48.2)	263/435 (60.5)	291/464 (62.7)
Odds ratio (95% CI)[c]		1.69 (1.28, 2.23)	1.69 (1.28, 2.21)		1.65 (1.25, 2.17)	1.77 (1.35, 2.32)
Adjusted *P* value		.002	.002		.07	.01
Sustained pain relief[d] from 2 to 24 hours, n/N1 (%)[e]	93/447 (20.8)	150/413 (36.3)	165/434 (38)	93/443 (21)	138/424 (32.5)	165/449 (36.7)
Odds ratio (95% CI)[c]		2.25 (1.65, 3.07)	2.39 (1.77, 3.24)		1.82 (1.33, 2.48)	2.16 (1.59, 2.92)
Adjusted *P* value		.002	.002		.07	.01
Sustained pain freedom[f] from 2 to 24 hours, n/N1 (%)[g]	39/452 (8.6)	53/418 (12.7)	68/441 (15.4)	37/451 (8.2)	55/432 (12.7)	66/457 (14.4)
Odds ratio (95% CI)[c]		1.57 (1.01, 2.44)	1.95 (1.28, 2.97)		1.62 (1.04, 2.53)	1.85 (1.20, 2.83)
Adjusted *P* value		.06	.004		.07	.01
Absence of photophobia at 2 hours, n/N1 (%)[h]	143/456 (31.4)	172/423 (40.7)	205/448 (45.8)	162/456 (35.5)	171/435 (39.3)	203/464 (43.8)
Odds ratio (95% CI)[i]		1.63 (1.22, 2.19)	1.81 (1.36, 2.42)		1.28 (0.96, 1.72)	1.52 (1.14, 2.02)
Adjusted *P* value		.06	.004		.18	.02
Absence of phonophobia at 2 hours, n/N1 (%)[h]	215/456 (47.1)	245/423 (57.9)	244/448 (54.5)	211/456 (46.3)	233/435 (53.6)	251/464 (54.1)
Odds ratio (95% CI)[i]		1.56 (1.16, 2.09)	1.47 (1.10, 1.95)		1.38 (1.04, 1.83)	1.39 (1.05, 1.84)
Adjusted *P* value		.06	.06		.11	.04
Absence of nausea at 2 hours, N1/n (%)[h]	284/456 (62.3)	297/423 (70.2)	310/448 (69.2)	319/456 (70)	307/435 (70.6)	331/464 (71.3)
Odds ratio (95% CI)[i]		1.31 (0.96, 1.79)	1.35 (1.00, 1.83)		1.10 (0.81, 1.49)	1.12 (0.83, 1.51)
Adjusted *P* value		.10	.10		.95	.95

[a]Pain relief = Reduction of a moderate or severe migraine headache to a mild headache or to no headache.

[b]N1 = Number of participants with non-missing pain severity assessment at or before 2 hours after initial dose in the modified intent-to-treat population.

[c]Odds ratio (95% CI) and *P* value are based on logistic regression with treatment group, historical triptan response, use of medication for migraine prevention, and baseline headache severity as explanatory variables.

[d]Sustained pain relief = Pain relief at 2 hours with no administration of either rescue medication or the second dose of study medication, and with no occurrence thereafter of a moderate or severe headache during the relevant number of hours after dosing with study medication.

[e]N1 = Number of participants with determinable sustained pain relief from 2 to 24 hours after initial dose in the modified intent-to-treat population. Determinable cases = participants for whom sustained pain relief from 2 to 24 hours status could be determined based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

[f]Sustained pain freedom = Pain freedom at 2 hours with no administration of either rescue medication or the second dose of study medication, and with no occurrence thereafter of a mild, moderate, or severe headache during the relevant number of hours after dosing with study medication.

[g]N1 = Number of participants with determinable sustained pain freedom from 2 to 24 hours after initial dose in the modified intent-to-treat population.

[h]N1 = Number of participants with non-missing postdose photophobia, phonophobia, or nausea assessment at or before 2 hours after (respectively for each measure listed).

[i]Odds ratio, 95% CI, and *P* value are based on logistic regression with treatment group, historical triptan response, use of medication for migraine prevention, baseline headache severity, and baseline presence/absence of the migraine-associated symptom at interest (photophobia, phonophobia, or nausea) as explanatory variables.

the 25 mg dose and placebo were not made for secondary outcomes in ACHIEVE II because the co-primary outcomes of pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours were not met for this dose.

Time course of efficacy

The time to reach pharmacologically effective concentrations of ubrogepant is approximately 11 minutes, based on the inhibition of human capsaicin-induced dermal vasodilation model, a pharmacodynamic measure of CGRP blockade (EC_{90}=13 ng/mL).[17] Based on a pooled analysis of the ubrogepant 50 mg (n=887) and the placebo (n=912) data from the ACHIEVE I and II trials, at 30 minutes, pain relief was reported by 19% of participants administered ubrogepant 50 mg, with statistically significant pain relief observed by

1 hour (ubrogepant 50 mg, 43%; placebo, 37%; OR [95% CI]: 1.30 [1.06, 1.59], *P*=.0104) and maintained through 48 hours.[17] At 1 hour, absence of the most bothersome migraine-associated symptom was reported by 17% of participants administered ubrogepant 50 mg, with statistically significant absence of the most bothersome symptom observed by 1.5 hours (ubrogepant 50 mg, 28%; placebo, 22%; OR [95% CI]: 1.42 [1.14, 1.77], *P*=.002) and maintained through 48 hours. At 1.5 hours, pain freedom was reported by 12% of participants administered ubrogepant 50 mg, with statistically significant pain freedom observed by 2 hours (ubrogepant 50 mg, 20%; placebo, 13%; OR [95% CI]: 1.72 [1.33, 2.22], *P*<.0001) and maintained through 48 hours. With the 100 mg dose in ACHIEVE I, significant differences from placebo were observed as early as 1.5 hours post dose for the outcomes of pain relief (ubrogepant 100 mg, 52%; placebo, 44%; OR [95% CI]: 1.36 [1.03, 1.78], *P*=.03) and absence of the most bothersome migraine-associated symptom (ubrogepant 100 mg, 28%; placebo, 22%; OR [95% CI]: 1.41 [1.03, 1.93], *P*=.03) and 2 hours post dose for pain freedom (ubrogepant 100 mg, 21%; placebo, 12%; OR [95% CI]: 2.04 [1.41, 2.95], *P*=.0001). Statistical comparisons were not made for the 25 mg dose.

Efficacy of an optional second dose of ubrogepant

Participants who had an inadequate response to their initial dose could elect to take an optional second dose of study medication in ACHIEVE I and II if their pain was still moderate or severe or if, after initial pain relief at 2 hours, their pain returned to moderate or severe within 2 to 48 hours after the initial dose. Participants who were randomized to ubrogepant were randomly assigned to receive ubrogepant or placebo (1:1) for their blinded optional second dose of study medication. Participants randomized to placebo received placebo for their blinded optional second dose. In pooled analyses, 39.8% (353 of 887) of participants who took ubrogepant 50 mg initially opted to take a second dose of the study medication compared with 44.8% (409 of 912) of those who took placebo. A significantly greater proportion of participants who were randomly assigned to ubrogepant 50 mg for their second dose of study medication achieved 2-hour pain freedom (n=53/156, 34%; OR [95% CI]: 2.85 [1.81, 4.50], *P*<.0001), compared with those randomly assigned to placebo for their second dose of study medication (n=25/131, 19%). Response rates in those who achieved pain relief 2 hours after their initial dose were also significantly greater after the optional second dose of ubrogepant 50 mg (n=41/75, 55% pooled; OR [95% CI]: 2.85 [1.81, 4.50], *P*<.0001), compared with participants who received ubrogepant 50 mg for their initial dose and placebo for their optional second dose (n=19/57, 33% pooled). Response rates were greater for those who received ubrogepant 25 mg or 100 mg for their second dose compared with placebo; however, the differences were not significant.

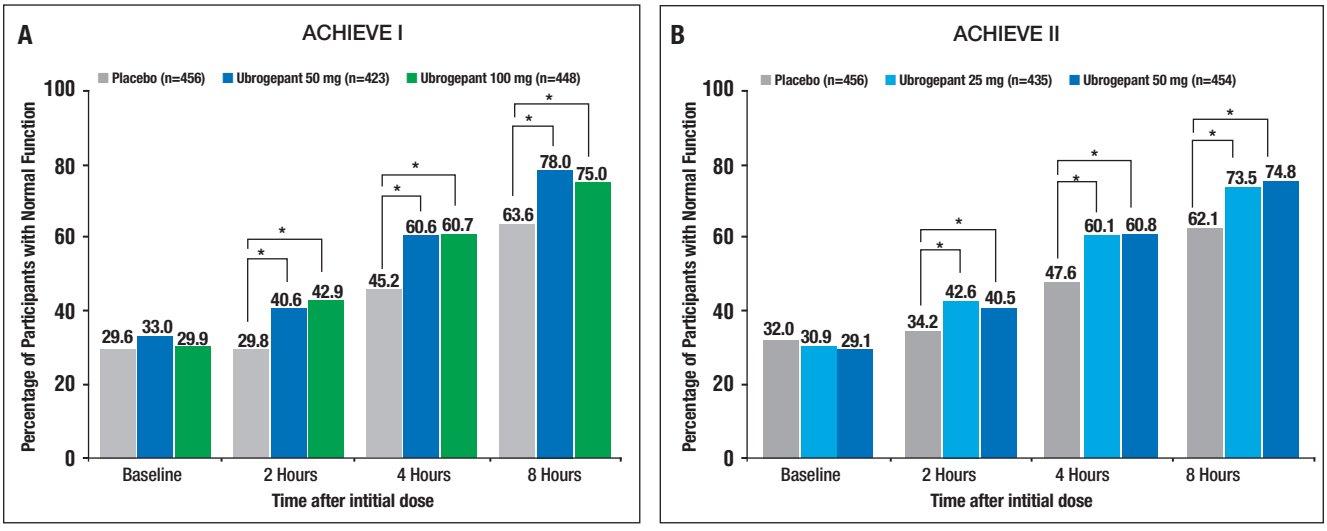
Functional improvement

One of the main goals of acute treatment of migraine attacks is to restore the ability to function.[2,18-20] ACHIEVE I and II demonstrated that treatment with ubrogepant improved the ability to function in daily activities, as assessed using the Functional Disability Scale. In both trials, the proportion of participants who reported being able to function normally was significantly greater in all ubrogepant arms at 2, 4, and 8 hours post initial dose compared with their respective placebo arms (*P*≤.01; **FIGURE 4**). Eight hours post dose, 78% and 75% of participants in the ubrogepant 50 mg groups and 64% and 62% in the placebo groups reported being able to function normally in ACHIEVE I and II, respectively (OR [95% CI]: 2.11 [1.54, 2.89], *P*<.0001, and 2.02 [1.49, 2.73], *P*<.0001, respectively). In ACHIEVE I, 75% of participants in the ubrogepant 100 mg group and 64% in the placebo group reported normal function at 8 hours (OR [95% CI]: 1.78 [1.32, 2.41], *P*=.0002). In ACHIEVE II, normal function was achieved by 74% in the ubrogepant 25 mg group and 62% in the placebo group at 8 hours (OR [95% CI]: 1.93 [1.42, 2.61]).

Efficacy in triptan non-responders

A prespecified analysis was conducted on subpopulations of participants who were previous (past 6 months) or current users of a triptan and were *triptan responders* (defined as having achieved pain freedom 2 hours post dose more than half of the time) or *triptan insufficient-responders* or *contraindicated* (did not achieve pain freedom 2 hours post dose on more than half of those occasions, discontinued a triptan because of lack of efficacy or side effects, or never used a triptan because of contraindications), and participants who were *triptan-naïve* (no prior exposure to triptans, excluding participants for whom triptans were contraindicated). At baseline in ACHIEVE I and II, respectively, 40% and 35% of participants were triptan responders, 27% and 23% were triptan insufficient-responders or contraindicated, and 32% and 42% were triptan-naïve. Among triptan insufficient-responders or contraindicated, response rates for 2-hour pain freedom were significantly greater in the pooled ubrogepant 50 mg group (16%) than in the pooled placebo group (8%; OR [95% CI]: 2.16 [1.19, 3.95]), rates of absence of the most bothersome migraine-associated symptom were greater in the pooled ubrogepant 50 mg group (36%) than in the placebo

FIGURE 4 **Patient-reported outcome of ability to function normally assessed using the Functional Disability Scale in ACHIEVE I (A) and ACHIEVE II (B)[9,10]**



*$P \leq .01$.

group (23%; OR [95% CI]: 1.76 [1.16, 2.68]), and a greater percentage of participants in the pooled ubrogepant 50 mg group (55.3%) reported pain relief at 2 hours compared with participants in the placebo group (42.6%; OR [95% CI]: 1.64 [1.12, 2.40]). In ACHIEVE I, triptan insufficient-responders treated with ubrogepant 100 mg vs placebo had higher rates of pain freedom (14% vs 6%; OR [95% CI]: 2.49 [1.00, 6.22]) and absence of the most bothersome symptom (30% vs 22%; OR [95% CI]: 1.50 [0.84, 2.70]) at 2–hours. In ACHIEVE II, triptan insufficient-responders in the ubrogepant 25 mg vs placebo groups had greater rates of pain freedom (18% vs 10%; OR [95% CI]: 1.81 [0.80, 4.08]) and absence of the most bothersome symptom (37% vs 25%; OR [95% CI]: 1.65 [0.90, 3.05]) at 2 hours. Response rates were also greater in the ubrogepant groups than in the placebo groups in the triptan responder and triptan-naïve subgroups. The magnitude of effect (ubrogepant vs placebo) was not significantly different among the 3 subgroups for pain freedom (P=.2898) or absence of the most bothersome migraine-associated symptom (P=.7045), indicating a comparable treatment effect regardless of historical triptan experience. Placebo response rates were lowest in the triptan insufficient-responder group and highest in the triptan-naïve group. The high proportion of triptan-naïve participants (32%-42%) may have contributed in part to the high response rates in the placebo-treated participants in the ACHIEVE trials.

SAFETY PROFILE OF UBROGEPANT IN ACHIEVE I AND II

Overall, treatment-emergent AEs (TEAEs) were reported in 13% (185/1436) and 11% (158/1465) of treated participants in any group within 48 hours of the initial or optional second dose of study medication in ACHIEVE I and II, respectively. The most commonly reported TEAEs (≥2%) were nausea (placebo, 1.6%; ubrogepant 50 mg, 1.7%, ubrogepant 100 mg, 4.1%), somnolence (0.8%; 0.6%; 2.5%), and dry mouth (0.4%; 0.6%; 2.1%) in ACHIEVE I and nausea (placebo, 2%; ubrogepant 25 mg, 2.5%; ubrogepant 50 mg, 2%) and dizziness (1.6%; 2.1%; 1.4%) in ACHIEVE II (**TABLE 2**). The most common treatment-related TEAEs were nausea (placebo, 1.6%; 50 mg, 1.5%; 100 mg, 3.3%), somnolence (0.8%; 0.6%; 2.3%), and dry mouth (0.4%; 0.6%; 1.4%) in ACHIEVE I and nausea (placebo, 1.8%; 25 mg, 1.9%; 50 mg, 1.8%) and dizziness (1.2%; 1.7%; 1.4%) in ACHIEVE II. No serious AEs were reported within 48 hours post dose in either trial. A total of 6 participants experienced serious AEs across ACHIEVE I and II. One serious AE (seizure in 1 participant in the ubrogepant 100 mg group) was judged by the investigator to be related to treatment; the case was confounded by possible alprazolam withdrawal. No participants discontinued because of AEs in either trial. Monitoring of hepatic laboratory values (eg, alanine aminotransferase/aspartate aminotransferase [ALT/AST], alkaline phosphatase, and total bilirubin levels) indicated no clinically relevant signs of hepatotoxicity.

LONG-TERM SAFETY

A phase 3, multicenter, open-label, 52-week extension, long-term safety trial randomized adults with migraine with or without aura 1:1:1 to usual care (n=417), ubroge-

TABLE 2 Summary of adverse events by treatment group in ACHIEVE I and II[9,10]

	ACHIEVE I, n (%)			ACHIEVE II, n (%)			
Time frame AE	Placebo (n=485)	Ubrogepant 50 mg (n=466)	Ubrogepant 100 mg (n=485)		Placebo (n=499)	Ubrogepant 25 mg (n=478)	Ubrogepant 50 mg (n=488)
WITHIN 48 HOURS AFTER INITIAL OR OPTIONAL SECOND DOSE OF STUDY MEDICATION							
TEAEs[a]	62 (12.8)	44 (9.4)	79 (16.3)		51 (10.2)	44 (9.2)	63 (12.9)
TEAEs in ≥2% of participants in any group							
Nausea	8 (1.6)	8 (1.7)	20 (4.1)	Nausea	10 (2)	12 (2.5)	10 (2)
Somnolence	4 (0.8)	3 (0.6)	12 (2.5)	Dizziness	8 (1.6)	10 (2.1)	7 (1.4)
Dry mouth	2 (0.4)	3 (0.6)	10 (2.1)				
Treatment-related TEAEs[a]	41 (8.5)	27 (5.8)	58 (12)		30 (6)	30 (6.3)	42 (8.6)
Treatment-related TEAEs in ≥2% of participants in any group							
Nausea	8 (1.6)	7 (1.5)	16 (3.3)	Nausea	9 (1.8)	9 (1.9)	9 (1.8)
Somnolence	4 (0.8)	3 (0.6)	11 (2.3)	Dizziness	6 (1.2)	8 (1.7)	7 (1.4)
Dry mouth	2 (0.4)	3 (0.6)	7 (1.4)				
WITHIN 30 DAYS AFTER ANY DOSE							
TEAEs[a]	113 (23.3)	126 (27)	139 (28.7)		112 (22.4)	105 (22)	133 (27.3)
TEAEs in ≥2% of participants in any group							
Nausea	12 (2.5)	9 (1.9)	23 (4.7)	Upper respiratory tract infection	9 (1.8)	6 (1.3)	13 (2.7)
Somnolence	4 (0.8)	4 (0.9)	12 (2.5)	Nausea	10 (2)	14 (2.9)	12 (2.5)
Dry mouth	3 (0.6)	3 (0.6)	10 (2.1)	Nasopharyngitis	1 (0.2)	5 (1)	11 (2.3)
Upper respiratory tract infection	8 (1.6)	5 (1.1)	10 (2.1)	Dizziness	9 (1.8)	11 (2.3)	10 (2)
Treatment-related TEAEs[a]	49 (10.1)	36 (7.7)	68 (14)		39 (7.8)	34 (7.1)	54 (11.1)
Serious AE[b]	0	3 (0.6)	2 (0.4)		0	1 (0.2)	0
Death[b]	0	0	0		0	0	0
AE leading to discontinuation[c]	0	0	0		0	0	0

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

[a] Events that began or worsened on or after the treatment start date and within 30 days of the treatment end date for participants without the safety follow-up visit. For participants with the safety follow-up visit, events that occurred at or before the safety follow-up visit are considered.

[b] Events that occurred on or after the treatment start date and within 30 days of the treatment end date for participants without the safety follow-up visit. For participants with the safety follow-up visit, events that occurred at or before the safety follow-up visit are considered.

[c] Discontinuation events that occurred between the treatment start date and the safety follow-up visit or within 30 days after the treatment end date for participants without the safety follow-up visit.

Participants are counted only once within each category.

pant 50 mg (n=404), and ubrogepant 100 mg (n=409).[21] TEAEs were reported by 268 participants (66%) receiving ubrogepant 50 mg and 297 (73%) receiving ubrogepant 100 mg; the most common TEAE was upper respiratory tract infection (<12%), with a similar incidence observed across dose groups.[21] Treatment-related AEs were reported by 42 participants (10%) who received ubrogepant 50 mg and 43 (11%) who received ubrogepant 100 mg. Serious AEs occurred in 9 participants (2%) in the ubrogepant 50 mg and 12 (3%) in the ubrogepant 100 mg group; the investigator considered 1 case of sinus tachycardia occurring in the ubrogepant 50 mg group related to treatment. There were 20 cases of ALT/AST levels of ≥3 times the upper limit of normal: 4/398 (1%) in the usual care, 5/399 (1.3%) in the ubrogepant 50 mg, and 11/406 (2.7%) in the ubrogepant 100 mg group.[21]

There was no evidence of medication overuse developing over the course of the 1-year trial. Most participants in

TABLE 3 Adverse events by cardiovascular risk category: pooled analysis of ACHIEVE I and II[23]

	Moderate to high CV risk (n=311)				Low CV risk (n=920)				No CV risk factors (n=1670)			
		Ubrogepant				Ubrogepant				Ubrogepant		
AE Type, n (%)	POOLED Placebo (n=100)	25 mg (n=51)	POOLED 50 mg (n=100)	100 mg (n=60)	POOLED Placebo (n=335)	25 mg (n=145)	POOLED 50 mg (n=300)	100 mg (n=140)	POOLED Placebo (n=549)	25 mg (n=282)	POOLED 50 mg (n=554)	100 mg (n=285)
AEs that occurred within 48 hours after initial or optional second dose of study medication												
TEAEs[a]	9 (9)	4 (7.8)	15 (15)	8 (13.3)	38 (11.3)	12 (8.3)	14 (4.7)	24 (17.1)	66 (12)	28 (9.9)	60 (10.8)	47 (16.5)
Treatment-related TEAEs[a]	8 (8)	2 (3.9)	11 (11)	7 (11.7)	25 (7.5)	7 (4.8)	25 (5.7)	19 (13.6)	38 (6.9)	21 (7.4)	41 (7.4)	32 (11.2)
Serious AEs[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Triptan-associated TEAEs	0 (0)	2 (3.9)	0 (0)	1 (1.7)	2 (0.6)	0 (0)	0 (0)	1 (0.7)	3 (0.5)	1 (0.3)	0 (0.5)	3 (1.1)
AEs that occurred within 30 days after any dose												
TEAEs[a]	32 (32)	11 (21.6)	29 (29)	13 (21.7)	74 (22.1)	28 (19.3)	79 (26.3)	45 (32.1)	119 (21.7)	66 (23.4)	151 (27.3)	81 (28.4)
Treatment-related TEAEs[a]	11 (11)	3 (5.9)	14 (14)	7 (11.7)	31 (9.2)	9 (6.2)	20 (6.7)	26 (18.6)	46 (8.4)	22 (7.8)	56 (10.1)	35 (12.3)
Serious AEs[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	3 (0.5)	2 (0.7)
Triptan-associated TEAEs	0 (0)	2 (3.9)	1 (1)	1 (1.7)	3 (0.9)	0 (0)	0 (0)	2 (1.4)	4 (0.7)	1 (0.3)	0 (0)	4 (1.4)

Abbreviations: AE, adverse event; CV, cardiovascular; TEAE, treatment-emergent adverse event.

Triptan-associated AEs included the following individual AEs: chest pain, chest discomfort, throat tightness, asthenia, paresthesia, dysesthesia, and hyperesthesia.

[a] Events that began or worsened on or after the treatment start date and within 30 days of the treatment end date for participants without the safety follow-up visit. For participants with the safety follow-up visit, events that occurred at or before the safety follow-up visit are considered.

[b] Events that occurred on or after the treatment start date and within 30 days of the treatment end date for participants without the safety follow-up visit. For participants with the safety follow-up visit, events that occurred at or before the safety follow-up visit are considered.

Participants are counted only once within each category.

the pooled ubrogepant group treated fewer than 8 attacks per month during each month of the trial (month 1: 99.4% [808/813]; month 12: 93.6% [584/624]).

SAFETY IN PARTICIPANTS WITH CV RISK FACTORS

In ACHIEVE I and II, participants were categorized as having moderate to high, low, or no cardiovascular (CV) risk factors at baseline using an algorithm based on the National Cholesterol Education Program.[22] Of the 2901 participants in the pooled safety population for ACHIEVE I and II, 11% were categorized as having moderate to high CV risk (n=311), 32% as having low CV risk (n=920), and 58% as having no CV risk factors (n=1670).[23] The incidence of TEAEs in the ubrogepant treatment groups was comparable across CV risk categories and did not differ greatly vs placebo (**TABLE 3**). All 6 of the participants who experienced serious AEs within 30 days of dosing (5 in ACHIEVE I and 1 in ACHIEVE II) were categorized as having no CV risk factors. Thus, the safety profile of ubrogepant among participants with high CV risk was similar to that among those with low or no CV risk. The rate of TEAEs in the Cardiac Disorder System Organ Class (eg, palpitations) was low and similar in the ubrogepant and placebo treatment groups and there were no treatment-related cardiovascular serious AEs.

DISCUSSION

Ubrogepant is an orally administered, small-molecule CGRP receptor antagonist (ie, gepant) for the acute treatment of migraine. With its anti-CGRP mechanism of action, ubrogepant differs from triptans, ergots, NSAIDs, analgesics, and opioids and offers a novel, therapeutic alternative to commonly prescribed acute treatments, especially when efficacy is limited, potential adverse events are considered, or con-

traindications exist. Despite the range of medications available for the acute treatment of a migraine attack, there is an unmet need for agents with better efficacy, safety, and tolerability profiles. These unmet needs are reviewed in detail in the companion manuscript in this supplement titled, "Treatment Patterns and Unmet Needs in the Acute Treatment of Migraine."

Ubrogepant has demonstrated excellent tolerability in phase 3 trials. Furthermore, pooled analyses indicate that ubrogepant is well tolerated in people with moderate to high CV risk. In addition to the single-attack trials, a trial of long-term safety and tolerability has provided important data on ubrogepant use over the course of 1 year.[21] Additional studies of safety and efficacy are needed in populations who were not included in the pivotal trials, such as pregnant and nursing women.

In conclusion, ubrogepant is an orally administered, small-molecule CGRP receptor antagonist for the acute treatment of migraine. The co-primary efficacy outcomes of 2 phase 3 trials of ubrogepant were met for the 50 mg and 100 mg doses, as were a range of clinically important secondary outcome measures, demonstrating clinically meaningful improvements 2 hours after an initial dose. Ubrogepant was well tolerated, with no safety concerns identified. With its novel mechanism of action, ubrogepant provides a promising new treatment option for the acute treatment of migraine that could provide a unique benefit beyond the current migraine-specific acute treatments. ●

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A guide to understanding

migraine disease

What is migraine?

- Migraine is thought to be caused by a process in the brain that leads to the release of pain-producing substances around the nerves and blood vessels.[1]
- Migraine is characterized by repeated attacks, often with symptoms, like pulsating, one-sided headache pain, sensitivity to light and sound, nausea, and vomiting.
- Chronic migraine is a subset of migraine with 15 or more headache days per month for more than 3 months and 8 or more migraine headache days per month.[2]

1 in 7
people have migraine
(1 billion people worldwide)

- Migraine is the 2nd leading cause of years lived with disability.[3]
- Linked to lower quality of life and negative impact on family, society, and the economy, that can be improved with proper treatment.

Who has migraine?

- More common in women than men.
- Mostly people between 35 to 45 years old.
- Often begins in puberty.

Phases of a migraine attack

Prodrome	Aura *(for some)*	Headache	Postdrome
• Irritability, fatigue, difficulty concentrating, food cravings • Lasts a few hours to several days	• Visual disturbances, temporary sight loss, numbness or tingling • Lasts 5-60 minutes	• Pulsating, one-sided pain • Nausea, vomiting • Sensitivity to light, smell, and sound • Lasts 4-72 hours	• Inability to concentrate • Fatigue • Depressed or excited mood • Lasts 24-48 hours

What should I do if I think that I, or someone I know, has migraine?

1. Schedule a headache-focused appointment with your doctor to discuss symptoms and diagnosis.
2. Review screening tools to get an idea of questions your doctor may ask to assess your headaches.
   - https://headaches.org/resources/headache-tests/
3. Keep a diary of your migraine attacks and symptoms. Be sure to capture date, time, duration, symptoms, and possible triggers (see sample below).

Share this with your doctor and ask about next steps.

Sample Headache Journal

Date	Start time	End time	Symptoms (eg, sensitivity to light or sound, nausea, headache severity)	Possible triggers (eg, exercise, foods/beverages, hormones, stress, sleep, light)	Treatments (eg, medication, lifestyle changes)

References: 1. World Health Organization. Fact Sheets: Headache Disorders. https://www.who.int/news-room/fact-sheets/detail/headache-disorders. Accessed November 19, 2019; 2. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.; 3. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2018;17(11):954-76.

A guide to treating migraine attacks

Migraine treatment should be individualized. If your treatment isn't working well, or if there are too many side effects, ask your health care provider about other options.

Migraine treatment options

- Lifestyle changes
- Medication
- Education, support, and follow-up

Types of medication

Acute medications

- Taken just before a migraine attack starts or when it has already begun.
- May stop or reduce headache pain but does not prevent a future migraine attack.

Preventive medications

- Taken to prevent future migraine attacks.

Goals of acute treatment

- Treat attacks fast and consistently.
- Restore ability to function normally.
- Minimize side-effects.

Types of acute medications

Non-specific
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- Acetaminophen

Migraine-specific
- Triptans
- Ditans*
- Gepants

*Under review by the Drug Enforcement Agency to determine abuse potential.

Controlled**
- Opioids
- Barbiturates

**Typically prescribed in the emergency room and not for routine use.

How do I know if my current migraine treatment is effective?

Keep a log of your migraine attacks and treatments:

1. Capture date, time, duration, symptoms, and possible triggers (see sample below).
2. Record any treatments you use along with a description of how you feel.
3. Document any recent changes to your lifestyle.

Share this with your doctor and ask about next steps.

Date	Start time	End time	Symptoms (eg, sensitivity to light or sound, nausea, headache severity)	Possible triggers (eg, exercise, foods/beverages, hormones, stress, sleep, light)	Treatments (eg, medication, lifestyle changes)

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