

## RESEARCH SUBMISSION

# Pharmacokinetics and safety of ubrogepant when coadministered with calcitonin gene-related peptide-targeted monoclonal antibody migraine preventives in participants with migraine: A randomized phase 1b drug-drug interaction study

Abhijeet Jakate PhD<sup>1</sup> | Andrew M. Blumenfeld MD<sup>2</sup> | Ramesh Boinpally PhD<sup>1</sup> |  
Matthew Butler MD<sup>1</sup> | Lisa Borbridge MS<sup>3</sup> | Janette Contreras-De Lama PhD<sup>1</sup> |  
Danielle McGeeney BS<sup>1</sup> | Antonia Periclou PhD<sup>1</sup> | Richard B. Lipton MD<sup>4</sup>

<sup>1</sup>Clinical Pharmacology, AbbVie, Madison, NJ, USA

<sup>2</sup>Headache Center of Southern California, Carlsbad, CA, USA

<sup>3</sup>Bioanalysis, Non-clinical and Translational Sciences, AbbVie, Irvine, CA, USA

<sup>4</sup>The Saul R. Korey Department of Neurology, Department of Psychiatry and Behavioral Sciences, Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

## Correspondence

Janette Contreras-De Lama, Medical Affairs (Neurosciences - Migraine), US Medical Affairs, AbbVie, 2525 Dupont Drive, Irvine, CA 92612, USA.  
Email: janette.contrerasdelama@abbvie.com

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## Abstract

**Objective:** To evaluate the impact of two calcitonin gene-related peptide (CGRP)-targeted monoclonal antibodies (mAbs), erenumab and galcanezumab, on the pharmacokinetic (PK) profile, safety, and tolerability of ubrogepant.

**Background:** People taking CGRP-targeted mAbs for migraine prevention sometimes take ubrogepant, an oral small-molecule CGRP receptor antagonist, for acute treatment of breakthrough migraine attacks.

**Design:** In this two-arm, multicenter, open-label, phase 1b trial, adults with migraine were randomized to arm 1 (ubrogepant ± erenumab) or arm 2 (ubrogepant ± galcanezumab). The PK profile of ubrogepant was characterized for administration before and 4 days after CGRP-targeted mAb injection. Participants received single-dose ubrogepant 100 mg on day 1, subcutaneous erenumab 140 mg (arm 1) or galcanezumab 240 mg (arm 2) on day 8, and ubrogepant 100 mg once daily on days 12–15. In each study arm, serial blood samples were drawn on days 1 and 12 for measurement of plasma ubrogepant concentrations. The primary outcomes were area under the plasma ubrogepant concentration–time curve (AUC) from time 0 to  $t$  post-dose ( $AUC_{0-t}$ ) and from time 0 to infinity ( $AUC_{0-inf}$ ), and maximum plasma concentration ( $C_{max}$ ) of ubrogepant when ubrogepant was administered before or after a single dose of erenumab or galcanezumab. Vital signs and laboratory parameters were monitored.

**Results:** Forty participants enrolled (20 per arm; mean [standard deviation] ages, 32.2 [8.9] and 38.4 [8.8] years; 50% [10/20] and 60% [12/20] female in arms 1 and

**Abbreviations:**  $AUC_{0-inf}$ , area under the plasma concentration–time curve from time 0 to infinity;  $AUC_{0-t}$ , area under the plasma concentration–time curve from time 0 to time  $t$ ; CGRP, calcitonin gene-related peptide; CL/F, apparent total body clearance of drug from plasma after extravascular administration;  $C_{max}$ , maximum plasma concentration; CYP3A4, cytochrome P450 3A4; ECG, electrocardiogram; GI, gastrointestinal; ICHD-3, International Classification of Headache Disorders, 3rd edition; LSM, least-squares mean; mAb, monoclonal antibody; PK, pharmacokinetic/pharmacokinetics; SC, subcutaneous; SD, standard deviation;  $t_{1/2}$ , terminal elimination half-life; TEAE, treatment-emergent adverse event;  $t_{max}$ , median time to maximum plasma drug concentration;  $V_z/F$ , apparent volume of distribution during the terminal phase after extravascular administration.

Abhijeet Jakate and Antonia Periclou were employees of AbbVie at the time of this study.

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2, respectively). There were no significant differences in ubrogepant  $C_{\max}$  after versus before erenumab administration (geometric least-squares mean [LSM] ratio, 1.04 [90% CI, 0.93–1.16]), and no significant differences in  $AUC_{0-t}$  (1.06 [0.96–1.16]) or  $AUC_{0-inf}$  (1.05 [0.96–1.15]). Similarly, ubrogepant  $C_{\max}$  (1.00 [90% CI, 0.82–1.20]),  $AUC_{0-t}$  (1.05 [0.90–1.23]), and  $AUC_{0-inf}$  (1.05 [0.90–1.22]) geometric LSM ratios were statistically equivalent after galcanezumab versus ubrogepant alone. Treatment-emergent adverse events (TEAEs) were similar to those reported with each treatment alone. No serious TEAEs, TEAEs leading to discontinuation, or clinically relevant changes in laboratory parameters or vital signs were reported.

**Conclusions:** The PK profile of ubrogepant was not significantly changed and no safety concerns were identified when ubrogepant was coadministered with erenumab or galcanezumab.

#### KEYWORDS

calcitonin gene-related peptide, CGRP, erenumab, galcanezumab, headache, ubrogepant

## INTRODUCTION

Migraine is a prevalent, chronic neurologic disease characterized by recurrent attacks of headache pain accompanied by sensitivity to light and/or sound and/or nausea in various combinations.<sup>1,2</sup> Acute treatments for migraine, taken at the time of an individual attack, aim to provide rapid and consistent freedom from pain and associated symptoms.<sup>3</sup> Preventive treatments are taken on a regular schedule (i.e., daily or monthly) with the aim of reducing the overall frequency, severity, and duration of migraine attacks or headaches.<sup>3</sup> An estimated 39% of people with migraine meet criteria for offering or considering preventive treatment.<sup>4</sup> Inadequate treatment of migraine attacks may lead to uncontrolled migraine and medication overuse, potentially resulting in medication overuse headache, disease progression, and chronification, and further compounding the burden and disability of the disease.<sup>1,5-7</sup> Comprehensive management of migraine focuses on moving individuals closer to migraine freedom through a combination of acute and preventive treatments, as well as biobehavioral interventions.<sup>3,8</sup>

Inhibition of the calcitonin gene-related peptide (CGRP) pathway has emerged as a targeted approach for both acute and preventive treatment of migraine.<sup>9,10</sup> Four monoclonal antibodies (mAbs) targeting the CGRP ligand or the CGRP receptor (CGRP-targeted mAbs) are approved in the United States for the preventive treatment of migraine in adults.<sup>11-14</sup> In addition, several small-molecule CGRP receptor antagonists (i.e., gepants) have been explored for acute or preventive treatment of migraine,<sup>10</sup> including two that were approved in 2019 and 2020 for the acute treatment of migraine attacks.<sup>15,16</sup> While CGRP-targeted mAbs have demonstrated efficacy in reducing the frequency of migraine attacks,<sup>17-21</sup> most people who take them continue to experience breakthrough attacks that require acute treatment. Therefore, patients receiving preventive treatment with CGRP-targeted mAbs are candidates for coadministration of gepants. Because of their shared mechanism of action (blockade of CGRP pathways), it is unclear whether gepants will provide acute treatment benefits in

patients receiving CGRP-targeted mAb treatment. Anecdotal reports and clinical practice experience suggest that gepants are effective in patients receiving CGRP-targeted mAbs.<sup>22,23</sup> However, formal studies are needed to evaluate the potential for pharmacokinetic (PK) drug-drug interactions and the safety of their concomitant use.

Erenumab and galcanezumab are CGRP-targeted mAbs that are self-administered once monthly by subcutaneous (SC) injection for the preventive treatment of migraine in adults.<sup>11,12</sup> Erenumab targets the CGRP receptor, whereas galcanezumab targets the CGRP ligand and blocks its binding to the CGRP receptor. Both mAbs are large molecules (molecular weight, 147–150 kDa). Following a single dose of erenumab or galcanezumab, peak plasma concentrations are attained in approximately 5–6 days and their elimination half-lives are in the range of 27–28 days.<sup>11,12</sup> Erenumab is thought to be metabolized and eliminated through degradation or internalization of the erenumab-receptor complex at low concentrations and through the hepatic reticuloendothelial system at high concentrations.<sup>12,24</sup> Galcanezumab is likely metabolized and eliminated via degradation into small peptides and amino acids through the same catabolic pathways as endogenous immunoglobulin G.<sup>11</sup>

In contrast, ubrogepant is a small-molecule (molecular weight, 0.5496 kDa) CGRP receptor antagonist that is orally administered for acute treatment of migraine attacks.<sup>15,25</sup> Ubrogepant is rapidly absorbed after oral administration, with the 100 mg dose having a median time to maximum plasma drug concentration ( $t_{\max}$ ) of 1.7 h and a terminal elimination half-life ( $t_{1/2}$ ) between 5 and 7 h.<sup>15,26</sup> Ubrogepant concentrations associated with effective coverage of the CGRP receptor are attained within 10 to 15 min after oral dosing.<sup>27</sup> Ubrogepant has demonstrated no clinically relevant PK interactions with other acute treatments for migraine (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen,<sup>28</sup> and sumatriptan<sup>27</sup>) or with oral contraceptives.<sup>29</sup> Ubrogepant is primarily metabolized by cytochrome P450 3A4 (CYP3A4), and its primary circulating metabolites in human plasma are glucuronide conjugates (M15 and M20) of its oxidative metabolites (M9 and M8).<sup>30</sup> Accordingly, ubrogepant should not be administered with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) and dose modifications

are recommended when administered with weak and moderate CYP3A4 inhibitors and strong CYP inducers.

It is unlikely that CGRP-targeted mAbs will have meaningful drug–drug interactions with ubrogepant, a cytochrome P450 substrate, because they are not metabolized by cytochrome P450 enzymes.<sup>11,12</sup> However, no study has yet evaluated the PK profile of ubrogepant when taken following administration of a CGRP-targeted mAb. This study was conducted to test the hypothesis that the PK profile of single-dose ubrogepant is equivalent when administered before or after administration of a single dose of galcanezumab or erenumab in participants with migraine. Safety and tolerability were also evaluated.

## METHODS

### Study design

This was a two-arm, multicenter, open-label, fixed-sequence, phase 1b drug–drug interaction study (ClinicalTrials.gov identifier: NCT04179474) in adults with migraine. Eligible participants were randomized 1:1 to arm 1 (ubrogepant ± erenumab) or arm 2 (ubrogepant ± galcanezumab) via a computerized randomization scheme created by the sponsor. No allocation concealment method was employed. In both arms, the PK profile of plasma ubrogepant was established prior to and following administration of the CGRP-targeted mAb. Participants in arm 1 received a single oral dose of 100 mg ubrogepant alone under fasted conditions on day 1 and a single SC injection of 140 mg erenumab alone (not under fasted conditions) on day 8, followed by once-daily oral doses of 100 mg ubrogepant on days 12 through 15 under fasted conditions (Figure 1). Participants in arm 2 received a single oral dose of 100 mg ubrogepant alone under fasted conditions on days 1 and 2 consecutive SC injections of 120 mg galcanezumab alone (not under fasted conditions) on day 8,

followed by once-daily oral doses of 100 mg ubrogepant on days 12 through 15 under fasted conditions (Figure 1).

The study was conducted at two clinical sites in the United States (Spaulding Clinical, West Bend, Wisconsin, and Bio-Kinetic Clinical Applications LLC, Springfield, Missouri) between September 26, 2019 and December 23, 2019. The study protocol was approved by the institutional review board for each study center (Advarra IRB, Columbia, Maryland, USA, approved August 22, 2019; and Bio-Kinetic Clinical Applications IRB, Springfield, Missouri, USA, approved September 3, 2019) before study initiation, and all participants provided written informed consent. The study was conducted in conformance with the ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council of Harmonisation Good Clinical Practice guidelines, and applicable local laws and regulations. All authors had full access to the study data.

### Participants

Eligible participants were men or women aged 18–50 years with at least a 1-year history of migraine with or without aura that was consistent with a migraine diagnosis according to the International Classification of Headache Disorders, 3rd edition (ICHD-3).<sup>31</sup> Participants were required to have a history of migraine attacks typically lasting between 4 and 72 h if untreated or treated unsuccessfully, migraine attacks separated by at least 48 h of headache pain freedom, and at least two migraine attacks per month in the 2 months prior to screening. In addition, participants must have had a sitting pulse rate  $\geq 45$  beats per minute and  $\leq 100$  beats per minute at screening; body mass index of 18–40 kg/m<sup>2</sup> at screening; and negative drug test results for benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates,

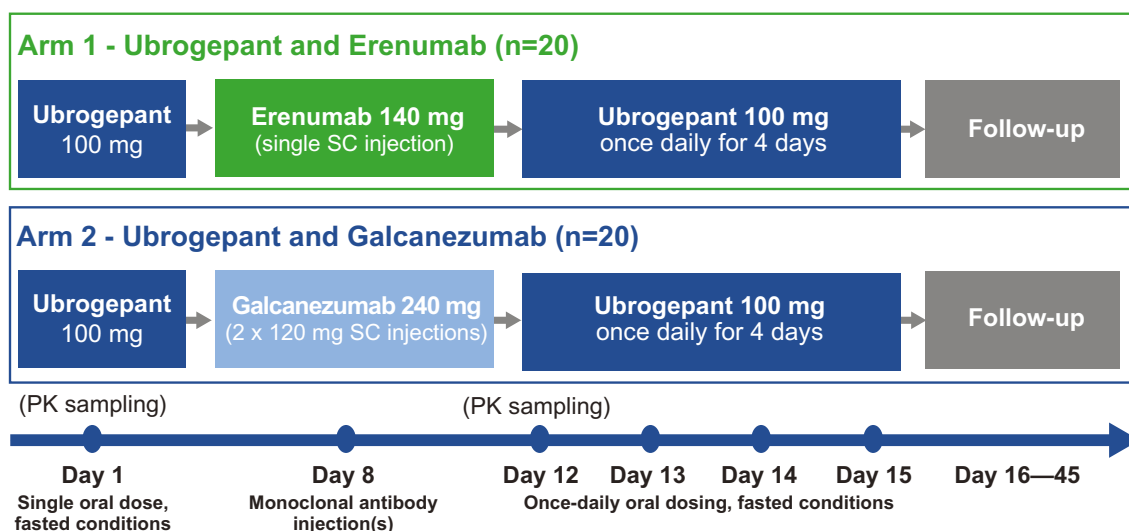


FIGURE 1 Study design. PK, pharmacokinetic; SC, subcutaneous [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

and phencyclidine at the screening and day -1 (unless explained by concomitant medication use, such as opioids prescribed for migraine pain). Participants were excluded if there was difficulty distinguishing migraine headache from tension-type headache or other headaches, or if they had a history of migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine as defined by ICHD-3; a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy as defined by ICHD-3; required hospital treatment of a migraine attack three or more times in the 6 months prior to screening; or clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to: clinically significant ischemic heart disease (e.g., unstable angina pectoris), clinically significant cardiac rhythm or conduction abnormalities (e.g., atrial fibrillation, second- or third-degree heart block), or risk factors for torsade de pointes (e.g., heart failure, hypokalemia, bradycardia), myocardial infarction, transient ischemic attack, or stroke within 6 months prior to screening, or heart failure as defined by the New York Heart Association functional classification system, class III or IV. Additional exclusion criteria were the presence of a chronic non-headache pain condition requiring daily pain medication (with the exception of pregabalin); a known hypersensitivity to CGRP receptor antagonists or CGRP-targeted mAbs; sitting systolic blood pressure  $\geq 160$  mm Hg or  $\leq 90$  mm Hg or sitting diastolic blood pressure  $\geq 100$  mm Hg or  $\leq 50$  mm Hg at screening; an abnormal electrocardiogram (ECG) result thought to be potentially clinically significant according to the investigator, or QT prolongation (QTcF  $\geq 450$  ms for men; QTcF  $\geq 470$  ms for women or uncorrected QT  $\geq 500$  ms) at screening and the presence of any clinically significant disease or other confounding pain syndromes, confounding psychiatric conditions, dementia, epilepsy, or significant neurological disorders other than migraine. Participants were not allowed to consume Seville oranges, beverages, or food containing quinine (bitter lemon, tonic water), poppy seeds, dietary supplements, or other foods or beverages that may affect drug-metabolizing enzymes and transporters (e.g., grapefruit juice), vegetables from the mustard green family (e.g., kale, broccoli), or charbroiled meats within 14 days prior to dosing and throughout the duration of the study. Participants were required to abstain from strenuous exercise or starting an intense exercise regimen for at least 7 days before blood collection for clinical laboratory tests on day 1 and throughout the duration of the study, including the follow-up period. Men and women of childbearing potential agreed to use an effective method of contraception; women were required to have a negative result from a serum pregnancy test at screening and a negative result from a serum or urine pregnancy test on day -1.

## Study procedures

Participants checked into the study center on days -1 and 7, and stayed overnight on days -1, 1, and 7 through 15. All participants received ubrogepant 100 mg administered under fasting conditions

(i.e., overnight fast for at least 10 h) with 240 ml of water on days 1, 12, 13, 14, and 15, with additional water restricted 1 h before and 1 h after administration of each dose. Participants fasted and remained seated upright and awake for an additional 4 h after ubrogepant dosing. While admitted in the study center, participants were provided with standardized low-fat (<20 g fat) meals at appropriate times each day. Participants in the erenumab arm received a single SC injection of erenumab 140 mg in the abdomen, thigh, or upper arm administered by the site staff on day 8. Participants in the galcanezumab arm received two consecutive SC injections ( $\leq 5$  min between injections) of galcanezumab 120 mg in the abdomen, thigh, back of the upper arm, or buttocks administered by the site staff on day 8.

## PK assessments

In both study arms, blood samples for the determination of ubrogepant concentrations were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 h post-dose on days 1 and 12. A total of 26 PK blood samples (4 ml each) were to be drawn from each participant. Blood collected for PK analyses was centrifuged within 30 min at no less than 2500 g for 10 min at approximately 4°C. Plasma samples were then flash-frozen and stored at approximately -20°C. PK plasma samples were analyzed using a validated liquid chromatography tandem-mass spectrometry method for ubrogepant. Sample pretreatment involved protein precipitation extraction of ubrogepant from human plasma samples. The stable isotope-labeled [ $D^3$ ]-ubrogepant was used as the internal standard. Samples were chromatographed using reverse-phase high-performance liquid chromatography on a Waters (Brussels, Belgium) XBridge C18 column (5  $\mu$ m, 2.1  $\times$  30 mm). Ubrogepant was detected using an Applied Biosystems Sciex API 5000 quadrupole mass spectrometer using a Turbo V ion source with electrospray ionization probe and operated in the positive ionization mode. The multiple reaction monitoring ion transition of  $m/z$  550  $\rightarrow$  264 was used for ubrogepant and  $m/z$  553  $\rightarrow$  267 was used for the internal standard. The lower limit of quantification (LLOQ) for ubrogepant was 1 ng/ml, with a linear calibration range from 1 to 1000 ng/ml.

## Endpoints

PK parameters of ubrogepant for the primary endpoint analysis included the area under the plasma concentration-time curve from time 0 to time  $t$  ( $AUC_{0-t}$ ), area under the plasma concentration-time curve from time 0 to infinity ( $AUC_{0-inf}$ ), and maximum plasma drug concentration ( $C_{max}$ ) of ubrogepant when ubrogepant and erenumab or ubrogepant and galcanezumab were coadministered and when ubrogepant was administered alone. Secondary PK endpoints were  $t_{max}$ ,  $t_{1/2}$ , apparent total body clearance of drug from plasma after extravascular administration (CL/F), and the apparent volume of distribution during the terminal phase after extravascular administration ( $V_z/F$ ) of ubrogepant when ubrogepant and erenumab or ubrogepant

and galcanezumab were coadministered and when ubrogepant was administered alone. Additional secondary endpoints were changes from baseline in vital signs, clinical laboratory measurements, physical examinations, and ECGs; the incidences, severity, and causality of treatment-emergent adverse events (TEAEs); and TEAEs leading to discontinuation from the study. Adverse events were monitored throughout the study and to day 45.

## PK and statistical analysis

All participants who received at least 1 dose of study treatment were included in the safety population. The PK population was defined as all participants who complied with the protocol and had an evaluable PK profile. The PK analysis population included all participants who had evaluable plasma PK parameters of ubrogepant for both ubrogepant alone and ubrogepant in combination with erenumab or galcanezumab.

Although the sample size for the study was not based on statistical power calculations, the inclusion of 40 participants (20 participants in each arm) was considered reasonable to achieve the objectives of the study. Enrollment of participants stopped when the target sample size was obtained.

The plasma PK parameters for ubrogepant were calculated using noncompartmental methods with Phoenix WinNonlin version 8.0 (Certara, Princeton, New Jersey, USA). All PK and safety parameters were summarized using descriptive statistics. Ubrogepant concentrations that were below the LLOQ were set to zero. Statistical analyses were performed using Phoenix WinNonlin version 8.0. For the estimation of the effects of erenumab or galcanezumab on the PK of ubrogepant,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  of ubrogepant were compared between the two treatment conditions (ubrogepant coadministered after the mAb versus ubrogepant administered alone) using a linear mixed-effects model with study treatment as a fixed effect and participant as a random effect in each arm of the study

for the PK analysis population. Statistical analysis was based on log-transformed values for the  $C_{max}$  and AUC parameters of ubrogepant. For each study arm, the two-sided 90% CI was constructed for the ratio of least-squares geometric means of  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  of ubrogepant in combination with the CGRP-targeted mAb on day 12 (test) versus ubrogepant alone on day 1 (reference). No effect of coadministration with CGRP-targeted mAbs on the PK of ubrogepant was concluded if the 90% CIs for the ratios of ubrogepant PK parameters for test versus reference study treatments were within the limits of 80%–125%.<sup>32</sup>

## RESULTS

### Participants

Of the 40 participants enrolled in the study, 20 were randomly allocated to the erenumab arm and 20 were randomly allocated to the galcanezumab arm (Figure 1). Demographic and baseline characteristics are shown in Table 1. Among all 40 enrolled participants, mean (standard deviation [SD]) age was 35.3 (9.3) years; 55% (22/40) of participants were women and 58% (23/40) were white. Demographic characteristics were similar between arms. Participant disposition is shown in Figure S1. One participant in the erenumab arm was discontinued from the study on day 7 because of a failed urine drug screen. One participant in the galcanezumab arm discontinued on day 10 for personal reasons. In each arm, a total of 19 participants completed all 3 treatment periods. There were no missing PK data.

### Effect of erenumab coadministration on the PK of ubrogepant

Mean ubrogepant plasma concentration–time profiles with and without coadministration of erenumab are presented in Figure 2A and PK

	Ubrogepant + erenumab arm (n = 20)	Ubrogepant + galcanezumab arm (n = 20)	Total (N = 40)
Age, years, mean (SD)	32.2 (8.9)	38.4 (8.8)	35.3 (9.3)
Sex, n (%)			
Female	10 (50)	12 (60)	22 (55)
Male	10 (50)	8 (40)	18 (45)
Race, n (%)			
White	12 (60)	11 (55)	23 (58)
Black/African American	7 (35)	9 (45)	16 (40)
Multiple	1 (5)	0	1 (3)
Ethnicity, n (%)			
Not Hispanic or Latino	20 (100)	16 (80)	36 (90)
Body mass index, kg/m <sup>2</sup> , mean (SD)	27.4 (4.6)	28.3 (6.6)	27.9 (5.6)

TABLE 1 Participant characteristics

Abbreviation: SD, standard deviation.

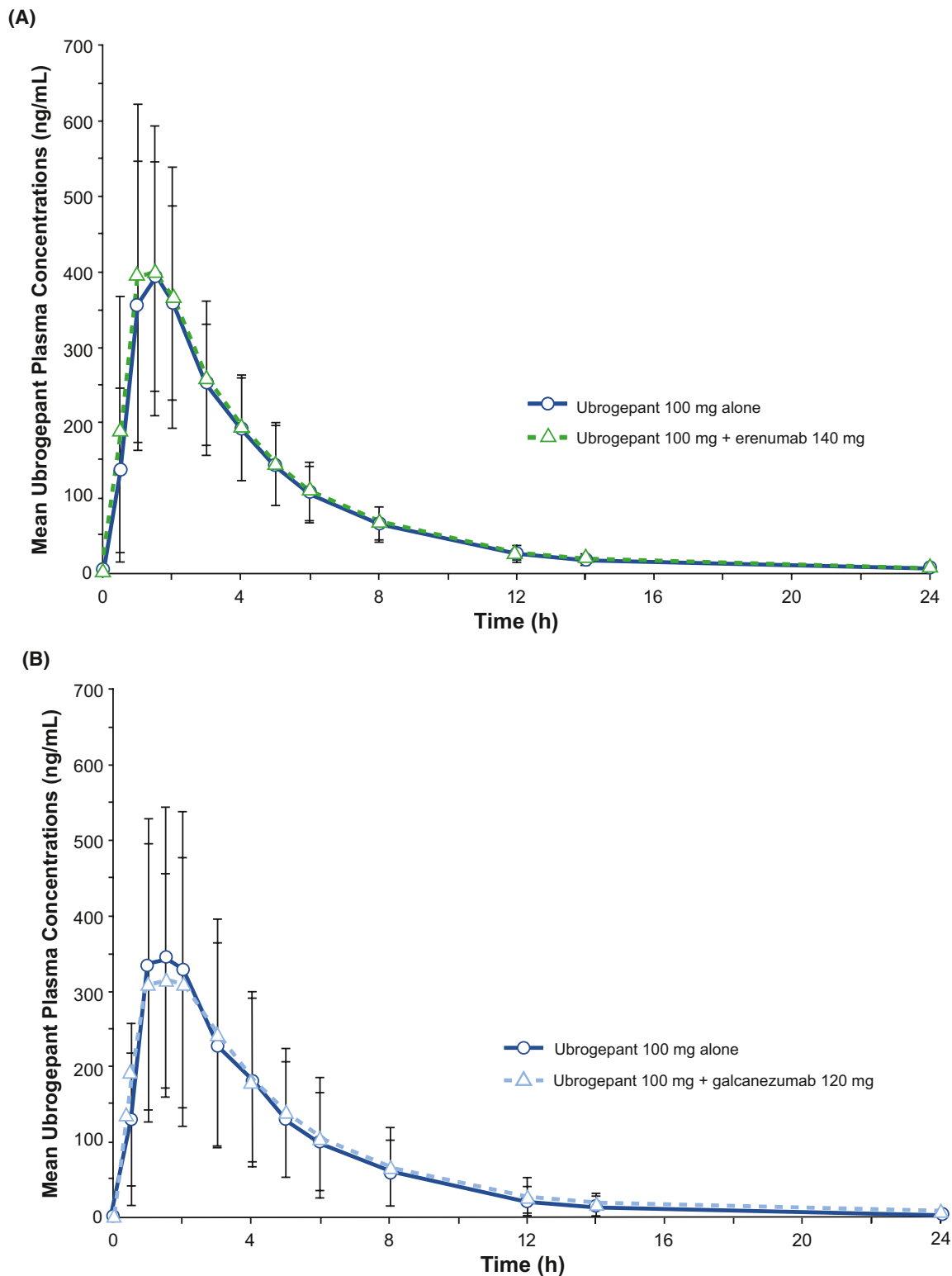


FIGURE 2 Mean ( $\pm$  SD) plasma ubrogepant concentration–time profiles with and without coadministration of (A) erenumab or (B) galcanezumab. SD, standard deviation [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

parameters are shown in Table 2. Median ubrogepant  $t_{\max}$  was 1.5 h with both treatment regimens. Ubrogapant  $t_{1/2}$  was 5.3 h after administration alone and 4.6 h after coadministration with erenumab. The geometric least-squares mean (LSM) value of ubrogepant  $C_{\max}$

was 4% higher,  $AUC_{0-t}$  was 6% higher, and  $AUC_{0-inf}$  was 5% higher when administered 4 days after erenumab injection compared with ubrogepant administered alone (Table 3). The 90% CIs for the geometric LSM ratios were contained within the 80%–125% range for



establishing equivalence for  $AUC_{0-\infty}$  (geometric LSM ratio, 1.05 [90% CI, 0.96–1.15],  $AUC_{0-t}$  (1.06 [0.96–1.16]), and  $C_{max}$  (1.04 [0.93–1.16]), suggesting no significant change in maximal concentrations or systemic exposure to ubrogepant.

### Effect of galcanezumab coadministration on the PK of ubrogepant

Mean ubrogepant plasma concentration–time profiles with and without coadministration of galcanezumab are presented in Figure 2B and PK parameters are shown in Table 4. Median ubrogepant  $t_{max}$  was 1.5 h with or without galcanezumab coadministration. Ubrogepant  $t_{1/2}$  was 5.0 h after being administered alone and 4.6 h after coadministration with galcanezumab. Geometric LSM ubrogepant  $C_{max}$  was similar (no change), whereas  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were higher by 5%, when administered 4 days after galcanezumab injection compared with ubrogepant administered alone (Table 5). The 90% CIs for the geometric LSM ratios fell well within the 80%–125% range of equivalence for  $AUC_{0-\infty}$  (geometric LSM ratio, 1.05 [90% CI, 0.90–1.22],  $AUC_{0-t}$  (1.05 [0.90–1.23]),

and  $C_{max}$  (1.00 [0.82–1.20]), suggesting no significant change in maximal concentrations or systemic exposure to ubrogepant.

### Safety

The incidence of TEAEs by study arm and treatment period is shown in Table 6. No serious TEAEs, TEAEs leading to discontinuation, or deaths were reported in either study arm. The most common TEAEs (>10% of patients) during the coadministration phases were constipation (11% [2/19]), nausea (11% [2/19]), and upper abdominal pain (11% [2/19]) when ubrogepant was coadministered with erenumab, and dizziness (11% [2/19]) when ubrogepant was coadministered with galcanezumab. A detailed table of all specific TEAEs and treatment-related TEAEs is presented in Table S1.

In arm 1, a total of three treatment-related TEAEs were reported in 2 of 20 participants (10%) after the single dose of ubrogepant alone. Seven treatment-related TEAEs were reported in 7 of 19 participants (37%) after the erenumab injection alone. Six treatment-related TEAEs were reported in 5 of 19 participants (26%) when ubrogepant was administered once daily for 4 days beginning 4 days after erenumab injection (Table 6). Gastrointestinal (GI) events (e.g., nausea, abdominal pain, and constipation) were the most common treatment-related TEAEs during coadministration of erenumab and ubrogepant (Table S1). One participant, a 30-year-old woman, reported multiple, mild treatment-related GI TEAEs on days 8 through 17 (flatulence, constipation, and abdominal pain).

In arm 2, no treatment-related TEAEs were reported after the single dose of ubrogepant alone. Four treatment-related TEAEs were reported in 3 of 20 participants (15%) after galcanezumab injections alone. Three treatment-related TEAEs were reported in 3 of 19 participants (16%) when ubrogepant was administered once daily for 4 days beginning 4 days after galcanezumab injection. GI events (e.g., abdominal discomfort and upper abdominal pain) and nervous system disorders were the most common treatment-related TEAEs during coadministration of galcanezumab and ubrogepant (Table S1).

No clinically relevant changes in laboratory parameters, vital signs, or ECG values were observed. Mean changes in blood pressure values during each treatment period are shown in Table 7. No potentially clinically significant increases in blood pressure occurred, except in one participant during concomitant treatment with

TABLE 2 Ubrogepant plasma PK parameters when administered alone or with erenumab

PK parameter	Ubrogepant alone (n = 20)	Ubrogepant + erenumab (n = 19)
$C_{max}$ , ng/ml	459.3 (168.6)	486.8 (201.5)
$AUC_{0-t}$ , ng•h/ml	1841.4 (490.2)	1960.0 (639.5)
$AUC_{0-\infty}$ , ng•h/ml	1878.3 (497.8)	1993.4 (639.2)
$t_{max}$ <sup>a</sup> , h	1.5 (1.0–3.0)	1.5 (0.5–3.0)
$t_{1/2}$ , h	5.3 (1.0)	4.6 (0.9)
$V_z/F$ , L	437.0 (158.1)	375.8 (161.4)
CL/F, L/h	57.4 (17.2)	54.7 (16.3)

Note: Values are arithmetic means (SD) unless otherwise indicated.

Abbreviations:  $AUC_{0-\infty}$ , area under the plasma concentration–time curve from time 0 to infinity;  $AUC_{0-t}$ , area under the plasma concentration–time curve from time 0 to time t; CL/F, apparent total body clearance of drug from plasma after extravascular administration;  $C_{max}$ , maximum plasma concentration; PK, pharmacokinetic; SD, standard deviation;  $t_{1/2}$ , terminal elimination half-life;  $t_{max}$ , time to maximum plasma concentration;  $V_z/F$ , apparent volume of distribution during the terminal phase after extravascular administration.

<sup>a</sup>Median (range).

TABLE 3 Statistical analysis of ubrogepant PK parameters with (test condition) and without (reference condition) erenumab

PK parameter	Geometric LSM		
	Ubrogepant + erenumab (test) (n = 19)	Ubrogepant alone (reference) (n = 20)	Geometric LSM ratio (90% CI) (test/reference)
$C_{max}$ , ng/ml	447.6	430.9	1.04 (0.93–1.16)
$AUC_{0-t}$ , ng•h/ml	1874.8	1776.2	1.06 (0.96–1.16)
$AUC_{0-\infty}$ , ng•h/ml	1910.0	1812.4	1.05 (0.96–1.15)

Abbreviations:  $AUC_{0-\infty}$ , area under the plasma concentration–time curve from time 0 to infinity;  $AUC_{0-t}$ , area under the concentration–time curve from time 0 to time t;  $C_{max}$ , maximum plasma concentration; LSM, least-squares mean; PK, pharmacokinetic.

erenumab and ubrogepant (diastolic blood pressure of 118 mm Hg [change from baseline, 22 mm Hg] early on day 13); all diastolic blood pressure values recorded in this participant later on days 13–16 were normal (range, 80–94 mm Hg). No participant met the hepatic laboratory criteria for a potential Hy's law case.

TABLE 4 Ubrogepant plasma PK parameters when administered alone or with galcanezumab

PK parameter	Ubrogepant alone (n = 20)	Ubrogepant + galcanezumab (n = 19)
$C_{max}$ , ng/ml	415.3 (225.6)	375.1 (152.1)
$AUC_{0-t}$ , ng•h/ml	1700.3 (913.4)	1758.1 (1033.4)
$AUC_{0-inf}$ , ng•h/ml	1732.2 (928.1)	1793.7 (1057.0)
$t_{max}$ , h <sup>a</sup>	1.5 (1.0–6.0)	1.5 (1.0–6.0)
$t_{1/2}$ , h	5.0 (1.5)	4.6 (1.4)
$V_z/F$ , L	568.7 (497.9)	449.3 (213.8)
CL/F, L/h	72.9 (38.1)	68.9 (28.1)

Note: Values are arithmetic means (SD) unless otherwise indicated. Abbreviations:  $AUC_{0-inf}$ , area under the plasma concentration–time curve from time 0 to infinity;  $AUC_{0-t}$ , area under the concentration–time curve from time 0 to time t; CL/F, apparent total body clearance of drug from plasma after extravascular administration;  $C_{max}$ , maximum plasma concentration; PK, pharmacokinetic; SD, standard deviation;  $t_{1/2}$ , terminal elimination half-life;  $t_{max}$ , time to maximum plasma concentration;  $V_z/F$ , apparent volume of distribution during the terminal phase after extravascular administration.

<sup>a</sup>Median (range).

## DISCUSSION

This study showed that the PK profile of ubrogepant is not significantly changed when ubrogepant is coadministered with either erenumab or galcanezumab. The median  $t_{max}$  was unchanged and exposure metrics ( $C_{max}$  and AUC) for plasma concentrations of ubrogepant were statistically equivalent after administration with or without each of the CGRP-targeted mAbs. The lack of a PK interaction is not surprising since the pathways for the elimination of ubrogepant and the CGRP-targeted mAbs are distinct.

The potential for pharmacodynamic interactions that may have safety consequences is less clear, given that both treatments act through CGRP blockade. In the current study, no safety concerns were identified during the 30-day follow-up when ubrogepant was administered once daily for 4 consecutive days after erenumab or galcanezumab. The TEAE profiles observed during single and concomitant administration were consistent with those reported in clinical trials when each medication was administered alone. In phase 3 trials, the most common TEAEs were nausea (4%), somnolence (2%), and dry mouth (2%) with ubrogepant 100 mg<sup>33</sup> and nausea (2%), dizziness (1%), and somnolence (1%) with ubrogepant 50 mg.<sup>34</sup> TEAEs reported in at least 2% of participants treated with erenumab 140 mg and at an incidence at least 2% greater than with placebo in phase 3 trials were injection-site reactions (5%), constipation (3%), and cramps/muscle spasms (2%)<sup>12,17,19</sup>; these events are consistent with the reports of GI TEAEs in the current study when ubrogepant was coadministered with erenumab. GI and other TEAEs are less common with galcanezumab, occurring at rates similar to those

TABLE 5 Statistical analysis of ubrogepant PK parameters with (test condition) and without (reference condition) galcanezumab

PK parameter	Geometric LSM		
	Ubrogepant + galcanezumab (test) (n = 19)	Ubrogepant alone (reference) (n = 20)	Geometric LSM ratio (90% CI) (test/reference)
$C_{max}$ , ng/ml	357.0	358.7	1.00 (0.82–1.20)
$AUC_{0-t}$ , ng•h/ml	1583.9	1508.0	1.05 (0.90–1.23)
$AUC_{0-inf}$ , ng•h/ml	1614.6	1541.3	1.05 (0.90–1.22)

Abbreviations:  $AUC_{0-inf}$ , area under the plasma concentration–time curve from time 0 to infinity;  $AUC_{0-t}$ , area under the concentration–time curve from time 0 to time t;  $C_{max}$ , maximum plasma concentration; LSM, least-squares mean; PK, pharmacokinetic.

TABLE 6 Summary of treatment-emergent adverse events by study arm and treatment period

	Ubrogepant single dose alone (Day 1)	CGRP-targeted mAb alone (Day 8)	Ubrogepant QD for 4 days after CGRP-targeted mAb coadministration (Days 12–15)
<b>Timing of TEAE collection</b>	<b>Days 1–7</b>	<b>Days 8–11</b>	<b>Days 12–16+</b>
<b>Erenumab arm</b>	<b>n = 20</b>	<b>n = 19</b>	<b>n = 19</b>
Any TEAE	7 (35)	8 (42)	7 (37)
Any treatment-related TEAE	2 (10)	7 (37)	5 (26)
<b>Galcanezumab arm</b>	<b>n = 20</b>	<b>n = 20</b>	<b>n = 19</b>
Any TEAE	2 (10)	3 (15)	4 (21)
Any treatment-related TEAE	0	3 (15)	3 (16)

Note: All values are n (%).

Abbreviations: CGRP, calcitonin gene–related peptide; mAb, monoclonal antibody; QD, once daily; TEAE, treatment-emergent adverse event.



TABLE 7 Summary of blood pressure results by study arm and treatment period

	Ubrogепant single dose alone (Day 1)	CGRP-targeted mAb alone (Day 8)	Ubrogепant QD for 4 days after CGRP-targeted mAb coadministration (Days 12–15)
<b>Timing of collection</b>	<b>Days 1–2</b>	<b>Days 8–9</b>	<b>Days 12–13</b>
<b>Erenumab arm</b>	<b>n = 20</b>	<b>n = 19</b>	<b>n = 19</b>
Systolic blood pressure, mm Hg			
Baseline (predose), mean (SD)	119.6 (13.8)	113.4 (12.9)	115.4 (14.6)
Change from baseline, mean (SD)			
2 h postdose	2.3 (13.0)	–1.3 (11.8)	–0.2 (6.7)
24 h postdose	–3.4 (13.0)	–0.8 (11.5)	–6.1 (8.5)
Diastolic blood pressure, mm Hg			
Baseline (predose), mean (SD)	77.9 (9.5)	73.8 (7.9)	74.2 (9.8)
Change from baseline, mean (SD)			
2 h postdose	1.6 (6.4)	–0.7 (5.7)	2.7 (5.0)
24 h postdose	–1.2 (8.1)	0.5 (6.0)	–0.8 (6.1)
<b>Galcañezumab arm</b>	<b>n = 20</b>	<b>n = 20</b>	<b>n = 19</b>
Systolic blood pressure, mm Hg			
Baseline (predose), mean (SD)	117.0 (12.3)	113.1 (11.4)	113.3 (10.8)
Change from baseline, mean (SD)			
2 h postdose	2.3 (8.5)	2.9 (9.4)	3.1 (9.8)
24 h postdose	0.1 (12.1)	–1.7 (9.0)	–0.9 (8.8)
Diastolic blood pressure, mm Hg			
Baseline (predose), mean (SD)	75.6 (8.5)	77.5 (7.3)	76.2 (7.6)
Change from baseline, mean (SD)			
2 h postdose	3.3 (5.0)	0.4 (5.8)	2.6 (6.5)
24 h postdose	–0.1 (6.5)	–2.3 (7.8)	–2.1 (8.3)

Abbreviations: CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; QD, once daily; SD, standard deviation.

observed with placebo in clinical trials<sup>20,21</sup>; this aligns with our observation of lower rates of TEAEs, including GI events, during coadministration of ubrogепant with galcañezumab compared with coadministration with erenumab. In general, the sum of safety and tolerability data for these US Food and Drug Administration-approved CGRP-targeted mAbs and gepants suggests that saturating the inhibition of the CGRP pathway is associated with minimal safety concerns.<sup>35,36</sup> Minimal safety data currently exist on concomitant use of gepants with CGRP-targeted mAbs. Rimegepant 75 mg was shown to be well tolerated when used concomitantly with erenumab (*n* = 7), fremanezumab (*n* = 4), or galcañezumab (*n* = 2) in a multicenter, long-term, open-label safety study.<sup>22</sup> However, additional studies are needed to fully characterize the potential impacts of long-term inhibition of the CGRP pathway.

CGRP is a potent vasodilator that may have a physiological role in protection against hypertension.<sup>37</sup> Thus, there is a theoretical risk that compounding CGRP blockade with multiple agents could lead to clinically relevant hypertension or other vascular events.<sup>35,38</sup> A recent analysis of vascular adverse events and blood pressure data from four double-blind, placebo-controlled studies of erenumab and their open-label extensions in patients with chronic or episodic migraine demonstrated no clinically relevant effects on blood pressure measurements in participants treated with erenumab compared with

placebo.<sup>39</sup> However, cases of new-onset hypertension and worsening of pre-existing hypertension reported during post-marketing use of erenumab have prompted a Warning and Precaution regarding hypertension in the erenumab prescribing information.<sup>12</sup> There were no clinically meaningful effects of concomitant use of ubrogепant and erenumab or galcañezumab on clinical data for blood pressure, vital signs, and ECGs in the current study. However, participants with pre-existing hypertension and cardiovascular disease were excluded and the study had a short duration of treatment and small sample size. It is possible that the shorter half-life of ubrogепant compared with erenumab (5–7 h versus. 28 days, respectively) may reduce the incremental risk of hypertension when ubrogепant is administered with erenumab. Additional studies are needed to evaluate the full safety profile when gepants are coadministered with CGRP-targeted mAbs.

Serum CGRP concentrations in cranial circulation have been shown to increase in response to trigeminal activation and during spontaneous migraine attacks.<sup>9,40,41</sup> It is unknown whether treatment with mAbs that target either CGRP or its receptor is associated with complete blockade of the CGRP pathway. The dose dependency of response and perhaps the low rates of 100% response with CGRP-targeted mAb treatment<sup>19,42</sup> suggest that coverage is likely incomplete. As a small molecule, ubrogепant may have access to a pool of

CGRP receptors that are not readily available to mAbs.<sup>23</sup> Thus, ubrogepant may theoretically have efficacy for acute treatment of migraine attacks in individuals who have benefited from CGRP-targeted mAb treatment. However, few data exist on the efficacy of gepants in people receiving CGRP-targeted mAb treatment. Concomitant use of rimegepant for the acute treatment of breakthrough migraine attacks during erenumab treatment was reported in two patients.<sup>23</sup> Together, these two patients treated a total of 16 migraine attacks that occurred while on erenumab. All 16 breakthrough attacks were treated successfully with rimegepant, although “successful treatment” was not explicitly defined in the publication. Neither patient reported any treatment-related adverse events. These observations suggest that there may be benefits of the concomitant use of a gepant and a CGRP-targeted mAb that could potentially involve additive effects, although the exact mechanisms are unclear.<sup>23</sup> Efficacy data were not collected in our study, and additional data are needed to evaluate the efficacy of ubrogepant for the acute treatment of breakthrough migraine attacks occurring while on preventive mAb treatments.

## Strengths and limitations

These data address a key data gap in the safety of coadministration of two classes of relatively new treatment options for migraine that target the same pathway. One strength of this study was the inclusion of participants with a history of migraine, in contrast to most drug–drug interaction studies, which are typically conducted in healthy adults. Additionally, ubrogepant was administered multiple times during the coadministration phase of the study at a frequency similar to anticipated real-world use.

There are several limitations of the current study. First, the sample size was relatively small, with 40 participants overall and 20 allocated to each treatment arm. While this population size was considered adequate for identifying potential PK interactions, it is insufficient for detecting potential safety issues. Second, this study did not evaluate the effect of ubrogepant on the PK profiles of the mAbs. Third, the study had a short duration of treatment and ubrogepant was administered at set time points, and not during a migraine attack, when CGRP levels may be elevated. Fourth, the efficacy of concomitant use for migraine relief was not evaluated. Last, as this study did not include a method of allocation concealment, we cannot rule out the potential impact of selection bias. Additional real-world data are needed to fully characterize the safety of ubrogepant with CGRP-targeted mAbs.

## Conclusion

The PK profile of ubrogepant did not change and no safety concerns were identified when ubrogepant was coadministered with erenumab or galcanezumab. The lack of PK interactions or new safety concerns provides some reassurance on the safety of concomitant use. However, broader safety conclusions will require longer term evaluation of concomitant use in larger populations.

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## CONFLICT OF INTEREST

Andrew M. Blumenfeld has served on advisory boards for, consulted for, and/or been a speaker or contributing author for AbbVie, Alder, Amgen, Biohaven, Lilly, Lundbeck, Novartis, Teva, Theranica, and Zoscana. He has received grant support from AbbVie and Amgen. Richard B. Lipton, MD, has received research support from the National Institutes of Health, the FDA, and the National Headache Foundation. He serves as consultant, advisory board member, or has received honoraria or research support from AbbVie/Allergan, Amgen, Biohaven, Dr. Reddy's Laboratories (Promius), electroCore, Eli Lilly, GlaxoSmithKline, Lilly, Lundbeck, Merck, Novartis, Teva, Vector, and Vedanta Research. He receives royalties from *Wolff's Headache*, 8th edition (Oxford University Press, 2009), and Informa. He holds stock/options in Biohaven and Ctrl M. Ramesh Boinpally, Matthew Butler, Lisa Borbridge, Janette Contreras-De Lama, and Danielle McGeeney are employees of AbbVie, and may hold AbbVie stock. Abhijeet Jakate and Antonia Periclou were employees of AbbVie at the time of this study, and may hold AbbVie stock.

## AUTHOR CONTRIBUTIONS

*Study concept and design:* Abhijeet Jakate, Ramesh Boinpally, Janette Contreras-De Lama, Antonia Periclou. *Acquisition of data:* Abhijeet Jakate, Lisa Borbridge, Danielle McGeeney. *Analysis and interpretation of data:* Abhijeet Jakate, Andrew M. Blumenfeld, Ramesh Boinpally, Matthew Butler, Lisa Borbridge, Janette Contreras-De Lama, Danielle McGeeney, Antonia Periclou, Richard B. Lipton. *Revising the manuscript for intellectual content:* Abhijeet Jakate, Andrew M. Blumenfeld, Ramesh Boinpally, Matthew Butler, Lisa Borbridge, Janette Contreras-De Lama, Danielle McGeeney, Antonia Periclou, Richard B. Lipton. *Final approval of the completed manuscript:* Abhijeet Jakate, Andrew M. Blumenfeld, Ramesh Boinpally, Matthew Butler, Lisa Borbridge, Janette Contreras-De Lama, Danielle McGeeney, Antonia Periclou, Richard B. Lipton.

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## INSTITUTIONAL REVIEW BOARD APPROVAL

Advarra IRB, Columbia, Maryland, USA, and Bio-Kinetic Clinical Applications IRB, Springfield, Missouri, USA.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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