Effects of CYP3A4 and P-glycoprotein inhibition or induction on the pharmacokinetics of ubrogepant in healthy adults: Two phase 1, open-label, fixed-sequence, single-center, crossover trials

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Abstract

Background: Ubrogepant is metabolized by cytochrome P450 3A4 (CYP3A4) and is a P-glycoprotein (P-gp) substrate.

Objective: To assess effects of multiple-dose moderate-strong CYP3A4 and strong P-gp inhibitors and inducers on ubrogepant pharmacokinetic (PK) parameters.

Methods: Two phase 1, open-label, fixed-sequence, single-center, crossover trials enrolled healthy adults to receive ubrogepant 20 mg with/without verapamil 240 mg (a moderate CYP3A4 inhibitor) or ketoconazole 400 mg (a strong CYP3A4 and P-gp transporter inhibitor) (Study A), or ubrogepant 100 mg with/without rifampin 600 mg (a strong CYP3A4 inducer and P-gp inducer) (Study B). Outcomes included ubrogepant PK parameters (area under plasma concentration-time curve, time 0 through infinity [AUC₀–∞], peak plasma concentration [Cmax]), and safety (treatment-emergent adverse events [TEAEs]). PK parameters were compared between ubrogepant with/without coadministered medications using linear mixed-effects models. Cmax and AUC₀–∞ least-squares geometric mean ratios (GMR) of ubrogepant with/without coadministration were constructed.

Results: Twelve participants enrolled in Study A and 30 in Study B. AUC₀–∞ and Cmax GMR (90% CI) were 3.53 (3.32–3.75) and 2.80 (2.48–3.15), respectively, for ubrogepant with verapamil; 9.65 (7.27–12.81) and 5.32 (4.19–6.76) with ketoconazole; and 0.22 (0.20–0.24) and 0.31 (0.27–0.36) with rifampin. TEAEs were predominantly mild; no treatment-related serious TEAEs or TEAE-related discontinuations occurred.

Conclusion: The PK of ubrogepant were significantly affected by the concomitant use of CYP3A4 moderate-strong inhibitors and strong inducers.

Keywords

CGRP antagonist, CYP3A4 protein inhibition/induction, drug-drug interactions, ketoconazole, migraine, rifampin, Uburogepant, verapamil

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Introduction

Migraine is a chronic, debilitating disease that affects over 1 billion people worldwide.¹ Migraine attacks are recurrent, often severe headaches that can be associated with nausea, phonophobia, and photophobia.² In addition to the increased disability and impaired health-related quality of life imposed upon individuals with migraine,³–⁶ this chronic disease is associated with high societal burden in the form of high direct and indirect costs of care.⁷–¹⁰

Most acute treatment strategies for migraine attacks involve the use of combination therapies, with triptans and nonsteroidal anti-inflammatory drugs as mainstay first-line therapies.¹¹ Treatment plans are individualized based on clinical factors and patient preference.¹² Treatment plans must also accommodate the use of concomitant medications for comorbidities, which are common in individuals with migraine.⁹,¹⁰

Ubrogepant is a potent, highly selective, oral calcitonin gene–related peptide (CGRP) receptor antagonist (gepant) approved by the US Food and Drug Administration (FDA) for the acute treatment of migraine with or without aura in adults.¹³,¹⁴ The safety and efficacy of ubrogepant have been established in phase 3 clinical trials in adults with migraine.¹⁵–¹⁷ Administered orally, ubrogepant is absorbed with maximum plasma concentrations (Cmax) at 1.5 h (tmax; time to maximum plasma concentration) and a terminal elimination half-life (t½) of 5–7 h.¹⁴ Ubrogepant is primarily metabolized by cytochrome P450 3A4 (CYP3A4) and is also a substrate for the efflux pump P-glycoprotein (P-gp), an ATP-binding cassette transport protein.¹⁸,¹⁹

The CYP3A4 metabolic pathway is shared by many medications, and CYP3A4-mediated drug-drug interactions (DDIs) have been observed with medications used to treat headache.²⁰ Indeed, DDIs can be a major reason for headache treatment failures.²⁰ Coadministration of a medication that is a CYP3A4 substrate with a CYP3A4 inducer can lead to reduced therapeutic efficacy, and coadministration with a CYP3A4 inhibitor can potentiate side effects.²⁰ Similarly, DDIs can occur when P-gp substrates are coadministered with P-gp inhibitors or inducers.²¹ The objective of these 2 studies was to assess the effects of multiple-dose verapamil (a moderate CYP3A4 inhibitor), ketoconazole (a strong CYP3A4 and P-gp transporter inhibitor), and rifampin (a strong CYP3A4 inducer and P-gp inducer) on single-dose pharmacokinetic (PK) parameters, safety, and tolerability of ubrogepant.

Methods

Study designs

Two open-label, fixed-sequence, single-center, phase 1 crossover trials were conducted. Study A (verapamil and ketoconazole) comprised 3 treatment periods. In period 1, participants received a single oral dose of ubrogepant 20 mg on day 1 (dosed as two 10 mg tablets). Period 2 commenced at least 3 days after period 1 dosing, and participants received oral doses of verapamil 240 mg once daily (QD) for 7 days with a single oral dose of ubrogepant 20 mg coadministered on day 5. In period 3, which started at least 14 days after the last dose of verapamil in period 2, participants received oral doses of ketoconazole 400 mg QD for 5 days with a single dose of ubrogepant administered on day 2. Ubrogepant was administered under fasted conditions. A lower 20 mg dose of ubrogepant was chosen in this study to provide a safety margin for a potential higher than predicted increase in exposure with ketoconazole coadministration. Additionally, a lower dose would allow any increases in ubrogepant exposure to occur within what has been observed to be a linear dose-response range. The half-life of verapamil increases with consecutive dosing and requires multiple days to reach steady state.²²,²³ Therefore, the potential DDI between ubrogepant and verapamil was evaluated after 5 days of 240 mg daily doses of verapamil. CYP3A4 inhibition by ketoconazole appears to be related to dose and duration.²⁴ As the intent of this study was to investigate the effect of multiple doses of ketoconazole on ubrogepant single-dose PK, the administration of 2 doses of ketoconazole prior to obtaining ubrogepant PK data was sufficient.

Study B (rifampin) had 2 treatment periods. In period 1, participants received a single oral dose of ubrogepant 100 mg on day 1 (dosed as two 50 mg tablets). Period 2 began after a washout of at least 8 days, and participants received an oral dose of rifampin 600 mg QD for 5 days (days 9–13) with a single oral dose of ubrogepant 100 mg coadministered with rifampin 600 mg on day 14. Ubrogepant 100 mg is the highest dose approved for clinical use, and ubrogepant showed no accumulation with once daily repeated dosing. Repeated once-daily doses of 600 mg rifampin for 5 days are required to achieve maximal effect on induction of CYP3A4 and P-gp.²⁵ All treatments were received under fasted conditions.

These studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent before any trial-specific procedures were initiated. Study A received Institutional Review Board approval from Chesapeake Research Review, Inc., Columbia, Maryland, USA, and Study B obtained approval from IntegReview IRB, Austin, Texas, USA.

Participants

Healthy adults aged 19–50 years for Study A or 18–45 years for Study B were eligible to participate. Participants had to be continuous nonsmokers without nicotine-containing product use for at least 3 months before dosing in Study A or the previous 2 years for Study B. For Study A, participants had to have body mass index between 18.5 and 32.0 kg/m², and for Study B, a body mass index between 18.0 and 30.0 kg/m² was required. Exclusion criteria for both studies
including: hypersensitivity to any study drug; exposure to hepatitis B virus, hepatitis C virus, or HIV; and use of any drug or substance known to affect CYP enzymes or P-gp.

**Outcomes**

Outcome measures included PK parameters calculated from ubrogepant plasma concentrations, and safety. In Study A, blood samples for PK were collected before dosing and at 20 min, 40 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 32 h after dosing in all periods, also at 48 and 72 h post-dose in period 2, and also at 48, 72, and 96 h post-dose in period 3. In Study B, blood samples for PK testing were collected on day 1 in period 1 and day 14 in period 2 before ubrogepant dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 h after dosing. Uburogepant concentrations in plasma were quantified using validated liquid chromatography with tandem mass spectrometry detection methods. Samples in Study A were analyzed by Merck Research Laboratories (Oss, Netherlands); the lower limit of quantitation (LLOQ) was 1 ng/mL for these assays. Samples in Study B were analyzed by Algorithmica Pharma (Laval, Quebec, Canada); the LLOQ was 0.1 ng/mL for ubrogepant and 1 ng/mL for rifampin.

Safety was assessed by monitoring treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory tests, vital signs, ECGs, and physical examinations. Clinical laboratory values were considered to be potentially clinically significant (PCS) if they met either the low or high PCS criteria assigned for each laboratory parameter. Vital sign values meeting both the actual value and change from baseline PCS criteria were categorized as PCS. ECG values meeting either the actual value or change from baseline PCS high criteria were labeled PCS.

**Statistical analysis**

Sample size was calculated from a power analysis based on estimates of the area under the concentration-time curve from time 0 to infinity (AUC\(_{0-\infty}\)) and C\(_{\text{max}}\) from prior studies. For Study A, assuming a true within-subject variance of 0.00511 for In-AUC\(_{0-\infty}\) and 0.0538 for In-C\(_{\text{max}}\), with \(n = 10\) completed subjects and \(\alpha = 0.05\), then there is a 99.99\% and 84.65\% probability that the upper bound of the 90\% CI for the true geometric mean AUC\(_{0-\infty}\) and C\(_{\text{max}}\) ratios (ubrogepant with verapamil/ubrogepant alone), respectively, will fall below 4.00, given that the true geometric mean ratio (GMR) is 3.00. If the true GMR of AUC\(_{0-\infty}\) and C\(_{\text{max}}\) is below 3.68 and 3.06, respectively, there is at least 80\% probability that the upper bound of the 90\% CI will fall below 4.00. For Study B, the sample size was determined considering that the within-participant coefficient of variation for the C\(_{\text{max}}\) and AUC parameters of ubrogepant was 8\% to 16\% in the evaluation of verapamil impact on ubrogepant PK, and 33\% to 39\% in the evaluation of ketoconazole impact on ubrogepant PK.

Assuming a within-participant coefficient of variation of 25\% in this study, and a ratio for ubrogepant with rifampin vs ubrogepant alone of 1.0, a sample size of 30 participants completing the trial was required to ensure a probability of at least 90\% that the 90\% CIs for the geometric means (GMs) were calculated for AUC\(_{0-\infty}\) and C\(_{\text{max}}\). Comparisons between ubrogepant with or without concomitantly administered medications for AUC\(_{0-\infty}\) and C\(_{\text{max}}\) used linear mixed-effects models with treatment as fixed effect and participant as a random effect; statistical inference was based on log-transformed values. Two-sided 90\% CIs were constructed for the least squares GMR of C\(_{\text{max}}\) and AUC of ubrogepant with each comparator and ubrogepant alone. C\(_{\text{max}}\) and t\(_{\text{max}}\) data were calculated from the observed ubrogepant plasma concentration-time data and reported without imputation for missing data. TEAEs were categorized based on the Medical Dictionary for Regulatory Activities version 15.0 for Study A and version 20.0 for Study B. The PK analysis was conducted on the PK population, which included all participants who received at least 1 dose of ubrogepant and had evaluable PK parameters, and the safety analysis was conducted on the safety population, which comprised all participants who received at least 1 dose of study medication in both Study A and Study B. PK parameters were analyzed using WinNonlin (Certara USA, Inc., Princeton, New Jersey, USA) version 5.2 (Study A) or 6.3 (Study B).

**Results**

**Participants**

Study A was conducted between December 3, 2012, and February 19, 2013, at a single trial site (Celerion, Lincoln, Nebraska, USA). Study B was conducted between June 27, 2017, and August 9, 2017, at a single trial site (Clinical Pharmacology of Miami, Miami, Florida, USA). Twelve participants enrolled in Study A and 30 enrolled in Study B (Figure 1). In Study A, 11 of 12 participants completed the trial. One participant completed all study procedures except for follow-up (discontinued due to a fatal motor vehicle accident prior to follow-up). Twenty-seven of 30 participants completed Study B. Three participants discontinued the trial because of loss to follow-up (\(n = 1\)) and participant decision (\(n = 2\)). In both studies, most participants were male (58\% in Study A, 60\% in Study B) and most were white (83\% in Study A, 87\% in Study B) (Table 1). The PK and safety analysis sets comprised all 12 participants in Study A and all 30 participants in Study B.
PK of ubrogepant coadministered with verapamil
(Study A)

The plasma concentration-time profiles of single-dose ubrogepant 20 mg following administration alone and coadministered with multiple-dose verapamil 240 mg, a moderate CYP3A4 inhibitor, are shown in Figure 2. Verapamil increased AUC₀⁻¹₀⁻∞ of ubrogepant by 3.5-fold and increased peak concentrations by 2.8-fold (Table 2). Terminal $t_{1/2}$ of ubrogepant was longer when coadministered with verapamil (4.2 h) compared with ubrogepant alone (2.5 h).

The plasma concentration-time profiles are shown for single-dose ubrogepant 20 mg administered alone (blue squares) or following administration of multiple doses of verapamil 240 mg (green circles) in healthy participants ($n = 12$). Data are represented on linear scale and semi-log scale (inset). Error bars represent SD. SD, standard deviation.

PK of ubrogepant coadministered with ketoconazole
(Study A)

Plasma concentration-time profiles of single-dose ubrogepant 20 mg alone and following coadministration with multiple-dose ketoconazole 400 mg, a strong CYP3A4 and P-gp inhibitor, are shown in Figure 3. Ketoconazole appeared to have substantially increased the levels of ubrogepant, with $C_{\text{max}}$ increasing 5.3-fold and AUC₀⁻¹₀⁻∞ increasing 9.7-fold in the presence of ketoconazole (Table 3). Terminal $t_{1/2}$ of ubrogepant was longer when coadministered with ketoconazole (5.9 h) compared with ubrogepant administered alone (2.5 h).

The plasma concentration-time profiles are shown for single-dose ubrogepant 20 mg administered alone (blue squares) or following administration of multiple doses of ketoconazole 400 mg (orange circles) in healthy participants ($n = 12$). Data are represented on linear scale and semi-log scale (inset). Error bars represent SD. SD, standard deviation.

PK of ubrogepant coadministered with rifampin
(Study B)

The plasma concentration-time profiles of ubrogepant 100 mg alone and following coadministration with multiple
doses of rifampin 600 mg, a strong CYP3A4 and P-gp
inducer, are shown in Figure 4. The overall exposure of
ubrogepant (AUC) decreased by 78% when coadministered
with multiple doses of rifampin compared with ubrogepant
administered alone (Table 4). The mean ubrogepant C_max
decreased by 69% when coadministered with rifampin
compared with administration of ubrogepant alone. The
median t_max of ubrogepant was slightly shorter when coadministered with rifampin compared with ubrogepant admin-
istered alone (1.5 h vs 2.0 h). Terminal t_1/2 of ubrogepant
was shorter when coadministered with rifampin (3.0 h)
compared with ubrogepant administered alone (4.4 h).

The plasma concentration-time profiles are shown for
single-dose ubrogepant 100 mg administered alone (blue
squares) or following administration of multiple doses of
rifampin 600 mg (lavender circles) in healthy participants
(n = 30). Data are represented on linear scale and semi-
log scale (inset). Error bars represent SD. SD, standard
deviation.

Safety results
In Study A, a single oral dose of ubrogepant appeared to be
safe and generally well tolerated when coadministered with
multiple doses of verapamil or ketoconazole in healthy
adults. Eleven participants reported a total of 39 TEAEs.
Nine TEAEs were considered treatment related, and all
were related to verapamil only (Supplemental Table S1).
Most TEAEs were mild in severity, and the most com-
monly reported TEAE was headache. One participant had
a fatal SAE after dosing but before the follow-up visit
(traffic accident) that was considered not related to study

Table 2. PK parameters of ubrogepant alone or coadministered with verapamil (n = 12).

| PK parameter       | Ubrogepant       | Ubrogepant + Verapamil | GMR (90% CI) |
|--------------------|------------------|------------------------|--------------|
| AUC_0-<inf>∞</inf>, ng•h/mL, mean (SD) | 213.2 (71.4) | 742.0 (212.7) | 3.53 (3.32, 3.75) |
| C_max, ng/mL, mean (SD) | 45.2 (15.0) | 124.8 (36.4) | 2.80 (2.48, 3.15) |
| t_max, h, median (range) | 2.00 (1.00–4.00) | 2.00 (1.03–4.00) | — |
| Apparent terminal t_1/2, h, mean (SD) | 2.52 (0.56) | 4.29 (0.91) | — |

AUC_0-<inf>∞</inf>: area under the plasma concentration-time curve from time 0 to infinity; C_max: maximum plasma concentration; GMR: ratio of geometric least-
squares mean (ubrogepant + verapamil/ubrogepant); PK: pharmacokinetic; SD: standard deviation; t_1/2: half-life; t_max: time to maximum plasma
concentration.
intervention. No other SAEs, deaths, or discontinuations due to a TEAE occurred in Study A. Additionally, no participants experienced elevations in serum transaminases or bilirubin greater than or equal to two-fold ULN, and there were no treatment-related changes in laboratory values, vital signs, or ECG parameters.

In Study B, a single oral dose of ubrogepant appeared to be safe and generally well tolerated when coadministered with multiple doses of rifampin. Six participants reported at least 1 TEAE during the trial, most commonly headache (Supplemental Table S2). All TEAEs were considered to be treatment related, and all were mild in severity. No SAEs, deaths, or discontinuations for a TEAE occurred in Study B. Changes from baseline in laboratory values, vital signs, and ECG parameters were not clinically meaningful.

**Discussion**

Systemic exposure of single-dose ubrogepant was increased following coadministration with both verapamil and ketoconazole administered as multiple doses to reach maximal levels of CYP3A4 inhibition. Verapamil was selected as a moderate CYP3A4 inhibitor for this study because it has been used in the past for the preventive treatment of migraine, and could potentially be used in combination with ubrogepant. A 3.5-fold increase in ubrogepant exposure (AUC<sub>0-∞</sub>) was seen with concomitant verapamil, a moderate CYP3A4 inhibitor. Based on these findings, dose modification of ubrogepant is recommended when coadministered with a moderate CYP3A4 inhibitor (Table 5).

Ketoconazole dose (400 mg) and duration of dosing (administered daily for 2 days before ubrogepant...
administration) were selected to achieve maximal CYP3A4 inhibition. At the time that this study was conducted, ketoconazole was included in the list of index CYP3A4 inhibitors in the FDA guidance and was widely used in drug metabolism and drug interaction studies because of its potency as a strong CYP3A4 inhibitor. Exposure of ubrogepant (AUC₀–∞) was more than 9 times higher following coadministration with the strong CYP3A4 and P-gp inhibitor ketoconazole. Concomitant use of ubrogepant with strong CYP3A4 inhibitors is contraindicated (Table 5). The increased exposure of ubrogepant with concomitant verapamil or ketoconazole, together with the increased t₁/₂, suggest interactions at both first-pass and systemic levels. CYP3A4 is also expressed in the gut wall, and selective inhibition or induction of gut enzymes could affect the bioavailability of orally administered ubrogepant.

A decrease in ubrogepant exposure (78% decrease in AUC₀–∞ and 69% decrease in Cₘₐₓ) was observed following coadministration with the strong CYP3A4 and P-gp inducer rifampin. This decrease in ubrogepant exposure is expected to reduce clinical efficacy, and the concomitant use of strong CYP3A4 inducers with ubrogepant should be avoided (Table 5). Taken together, these findings suggest CYP3A4 and P-gp transport play important roles in the absorption and elimination of ubrogepant.

A single oral dose of ubrogepant appeared to be safe and generally well tolerated when coadministered with multiple oral doses of verapamil, ketoconazole, or rifampin in healthy adults. The incidence of AEs was generally low, with headache being the most common TEAE in both studies, reported by 3 participants with verapamil coadministration, 1 participant with ketoconazole coadministration,

### Table 4. PK parameters of ubrogepant alone or coadministered with rifampin (n = 30).

| PK parameter | Ubrogepant | Ubrogepant + Rifampin | GMR (90% CI) |
|--------------|------------|-----------------------|--------------|
| AUC₀–∞, ng·h/mL, mean (SD) | 1908.31 (834.95) | 397.13 (144.28) | 0.22 (0.20, 0.24) |
| Cₘₐₓ, ng/mL, mean (SD) | 415.89 (197.55) | 136.07 (96.18) | 0.31 (0.27, 0.36) |
| tₘₐₓ, h, median (range) | 2.00 (1.00–4.00) | 1.50 (0.50–6.00) | — |
| Apparent terminal t₁/₂, h, mean (SD) | 4.36 (0.75) | 3.04 (0.64) | — |

AUC₀–∞: area under the plasma concentration-time curve from time 0 to infinity; Cₘₐₓ: maximum plasma concentration; GMR: ratio of geometric least-squares mean (ubrogepant + rifampin/ubrogepant); PK: pharmacokinetic; SD: standard deviation; t₁/₂: half-life; tₘₐₓ: time to maximum plasma concentration.

![Figure 4. Plasma concentration-time profiles for ubrogepant alone or coadministered with rifampin.](image-url)
Table 5. Ubrogepant dose modifications for drug interactions.14

| Concomitant drug          | Initial dose | Second dose (if needed)* |
|---------------------------|--------------|--------------------------|
| Moderate CYP3A4 inhibitorsb | 50 mg        | Avoid within 24 h         |
| Weak CYP3A4 inhibitors    | 50 mg        | 50 mg                    |
| Strong CYP3A4 inducersd   | 50 mg        | Avoid concomitant use    |
| Weak and moderate CYP3A4 inducersa | 100 mg | 100 mg                  |
| BCRP and/or P-gp only inhibitorsf | 50 mg | 50 mg                   |

BCRP: breast cancer resistance protein; P-gp: P-glycoprotein.

*Second dose may be taken at least 2 h after the initial dose.

bModerate CYP3A4 inhibitors include cyclosporine, ciprofloxacin, fluconazole, fluvoxamine, and grapefruit juice.

cNo dedicated drug interaction study was conducted with ubrogepant and weak CYP3A4 inhibitors.

dStrong CYP3A4 inducers include phenytoin, barbiturates, rifampin, and St. John’s Wort.

fNo dedicated drug interaction study was conducted with ubrogepant and moderate or weak CYP3A4 inducers.

*Use of BCRP and/or P-gp only inhibitors (eg, quinidine, carvedilol, eltroomboapag, curcumin) may increase the exposure of ubrogepant.

and 1 participant when ubrogepant was coadministered with rifampin. All TEAEs were predominantly mild in intensity, and there were no SAEs, deaths, or discontinuations due to a treatment-related TEAE. In phase 3 clinical trials of ubrogepant for the acute treatment of migraine, TEAEs occurring in at least 2% of ubrogepant-treated (50 mg and 100 mg) participants and at a greater frequency than placebo included nausea (2% and 4%), somnolence (2% and 3%), and dry mouth (<1% and 2%).15,16

The recommended dosage of ubrogepant is 50 or 100 mg administered orally, with a second dose, if needed, that may be administered at least 2 h after the initial dose.14 The maximum dose in a 24-h period is 200 mg. Use of ubrogepant with strong CYP3A4 inhibitors is contraindicated and use with CYP3A4 inducers should be avoided. With a moderate CYP3A4 inhibitor, the lower 50 mg dose of ubrogepant is recommended; in addition, it is recommended to not take a second dose within 24 h. With a weak CYP3A4 inhibitor, the lower 50 mg dose of ubrogepant is also recommended, with an option for taking a second dose within 24 h if needed. An initial and second dose of ubrogepant 100 mg is recommended with a weak or moderate CYP3A4 inducer.

Triptans are widely used for the acute treatment of migraine. Whereas one of the more commonly prescribed triptans, sumatriptan, is metabolized primarily by monoamine oxidase A, other triptans (such as frovatriptan and eletriptan) are metabolized via the CYP pathway.30–32 Additionally, topiramate is commonly used for the preventive treatment of migraine and can be associated with induction of CYP3A4 at higher doses.33 Clinicians should be aware of potential interactions among multiple acute treatments or between an acute and preventive medication when managing individuals with migraine, and adjust ubrogepant dose as appropriate (Table 5).

A potential limitation of the current study is the small sample size in both Study A (N = 12) and Study B (N = 30). With a smaller sample in Study A, there potentially could be a reduced chance of detecting a significant effect. However, despite the smaller sample size, a robust and consistent effect was observed with both moderate and strong CYP3A4 inhibitors in this study. Both study populations included more men than women (58% men in Study A and 60% men in Study B) and included participants with a relatively high mean BMI (25.0 kg/m² in Study A and 27.4 kg/m² in Study B). Individuals with migraine are disproportionately female, with migraine prevalence estimated to be 3 times higher in women than in men.34,35 Women have a higher expression of hepatic CYP3A4 and lower P-gp levels compared with men.36,37 Higher BMI has been found to be associated with reduced hepatic CYP3A4 activity and lower clearance of CYP3A4 substrates.38,39 However, a population PK study of ubrogepant found no clinically relevant impact of sex, race, body weight, or age on ubrogepant PK.18

These studies evaluated the impact of moderate and strong CYP3A4 inhibition, strong CYP3A4 induction, and P-gp inhibition and induction on ubrogepant PK, allowing for a broad characterization of the impact of altered CYP3A4 and P-gp–mediated elimination of ubrogepant. The safety profile of ubrogepant, which has been established in people with migraine up to a maximum dose of 200 mg in a 24-h period, combined with efficacy demonstrated with the 50 mg and 100 mg doses, allows for administration, with dose modifications, even in individuals with concomitant use of weak or moderate CYP3A4 inhibitors. Study A evaluated the impact of CYP3A4 inhibitors on a 20 mg dose of ubrogepant, while Study B evaluated the impact of a CYP3A4 inducer on a 100 mg dose of ubrogepant. Although the ubrogepant dose differed between the 2 studies and Study A evaluated a lower ubrogepant dose than the 50 mg or 100 mg recommended dose, no differences in the relationship of this interaction would be expected at a higher dose.

Conclusion

Ubrogepant exposure increased when coadministered with moderate and strong CYP3A4 inhibitors and decreased when coadministered with a strong CYP3A4 inducer. As is required with all medications that are metabolized by CYP3A4 and/or are substrates of P-gp, care must be taken to ensure that the ubrogepant dose is appropriately modified or not administered with medications that may result in clinically significant underexposure or overexposure of ubrogepant, and review and monitoring of medications used by individuals with migraine are warranted.19,40,41
Clinical implications

- Ubrogepant, a calcitonin gene–related peptide (CGRP) receptor antagonist that is indicated for the acute treatment of migraine with or without aura in adults, is primarily metabolized by cytochrome P450 3A4 (CYP3A4) and is a P-glycoprotein substrate.
- This drug-drug interaction study showed that ubrogepant exposure is increased when ubrogepant is coadministered with moderate/strong CYP3A4 inhibitors and decreased when coadministered with strong CYP3A4 inducers.
- Use of ubrogepant is contraindicated with strong CYP3A4 inhibitors and should be avoided with strong CYP3A4 inducers.

Authors’ note
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Data sharing statement
AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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Supplemental material
Supplemental material for this article is available online.

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