Single Therapeutic and Supratherapeutic Doses of Ubrogepant Do Not Affect Cardiac Repolarization in Healthy Adults: Results From a Randomized Trial

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Ubrogepant is a novel, oral calcitonin gene–related peptide receptor antagonist currently under US Food and Drug Administration (FDA) review for the acute treatment of migraine attacks. This double-blind, four-period crossover study compared the cardiac repolarization effect of therapeutic (100 mg) and supratherapeutic (400 mg) ubrogepant doses vs. placebo in healthy adults. Moxifloxacin 400 mg was used as an open-label active control, and the primary end point was change from baseline in Fridericia-corrected QT intervals (ΔQTcF). Assay sensitivity was demonstrated via statistically significant QTcF prolongation with moxifloxacin vs. placebo. After single oral doses of ubrogepant, the least squares mean placebo-corrected ΔQTcF ($\Delta\Delta$QTcF) and 90% confidence intervals (CIs) did not exceed the 10-millisecond regulatory threshold at any timepoint. The 90% CI upper bounds were 2.46 milliseconds and 2.69 milliseconds for ubrogepant 100 and 400 mg, respectively. Categorical and concentration-based analyses were consistent with the primary result, showing no significant impact of ubrogepant on cardiac repolarization.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The effect of ubrogepant on cardiac repolarization has not been evaluated in a thorough QT clinical study.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study assessed whether therapeutic (100 mg) and supratherapeutic (400 mg) doses of ubrogepant had any clinically relevant effect on cardiac repolarization in healthy adults.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The effects of therapeutic and supratherapeutic doses of ubrogepant on cardiac repolarization in healthy adult participants were not clinically relevant in comparison with placebo.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Due to the poor cardiac safety profile of triptans, a commonly used acute treatment for migraine attacks, people with migraine may be concerned about the cardiac safety of new migraine medications. This study addresses the QT prolongation potential of therapeutic and supratherapeutic doses of ubrogepant and showed that cardiac repolarization is unlikely to be a safety concern associated with the use of ubrogepant. These results provide additional support for an overall favorable safety profile of ubrogepant for the acute treatment of migraine attacks.

Migraine is a prevalent chronic disease with episodic attacks that are characterized by incapacitating neurological symptoms such as headache pain, sensitivity to light and sound, and nausea.[1] An estimated 12.3% of adults in the United States experience migraine attacks, resulting in a great individual, familial, and societal burden.[2–5]

Commonly used acute treatments for migraine include triptans, opioids, nonsteroidal antiinflammatory drugs, combination analgesics, and barbiturates; however, the utility of these treatments is limited by inadequate efficacy, poor tolerability, and cardiovascular contraindications.[6–10] Among these types of medications, only triptans were developed specifically for the acute treatment of migraine attacks, targeting the serotonin pathway in accordance with the vascular theory of migraine pathology.[11,12] Despite the widespread use of triptans in the treatment of migraine, the vasoconstrictive properties that drove their development are also the basis for their contraindication in patients with ischemic heart disease, uncontrolled hypertension, and cerebrovascular disease.[12] The shortcomings of acute treatments for migraine attacks underscore the need for new options with improved efficacy and tolerability profiles.

The evolving understanding of migraine has led to a focus on the calcitonin gene–related peptide (CGRP), a potent vasodilatory neurotransmitter that is highly expressed in pain-sensitive trigeminal sensory neurons that innervate the dural and meningeal blood vessels.[13–15] Evidence of CGRP's role in migraine includes studies showing induction of headache and migraine via infusion of CGRP in people with a history of migraine, pathological release of CGRP during the headache phase of a migraine attack, and relief from attacks after treatment with oral CGRP receptor antagonists.[16–19]

Ubrogepant is an orally delivered, potent, and specific CGRP receptor antagonist that is anticipated to be a first-in-class CGRP-targeted medication for the acute treatment of migraine attacks. Clinical data have shown ubrogepant to be effective for the acute treatment of migraine attacks, providing patients with substantial symptomatic relief and enabling return to function. In phase III, randomized, multicenter studies (ACHIEVE I and II), ubrogepant was found to be a safe and effective oral treatment for migraine attacks.[20,21] The current study assessed whether therapeutic (100 mg) and supratherapeutic (400 mg) doses of ubrogepant had any clinically relevant effect on cardiac repolarization in comparison with placebo. In addition, the pharmacokinetics (PK), safety, and tolerability of single doses of ubrogepant (100 mg and 400 mg) were evaluated. Moxifloxacin 400 mg was chosen as an active control because it is known to produce an increase in QTc interval in healthy adult participants at a time to maximum plasma drug concentration (t_{max}) of approximately 2 hours postdose.[22–24]

METHODS

Study design

In accordance with the US Food and Drug Administration's (FDA's) E14 guidance regarding clinical evaluation of QT/QTc prolongation,[25] this phase I, randomized, double-blind, single-center, single-dose, placebo-controlled and active-controlled, four-period crossover trial was conducted in healthy adults to evaluate the impact of ubrogepant on cardiac repolarization, as determined by measurement of the QT interval corrected for heart rate using the Fridericia formula (QTcF). Eligible participants were randomized to 1 of 12 treatment sequences (**Table S1**), with ubrogepant and placebo administered in a double-blind manner and moxifloxacin administered in an open-label fashion. There was a 7-day washout period between each of the four treatments, with a total treatment period of 24 days (day −1 to day 23).

This study was conducted in conformance with the ICH E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or US laws and regulations, whichever afforded the greater protection to the individual. The investigator obtained approval of the study protocol from a properly constituted institutional review board prior to initiating the study, and written informed consent was required from participants before participating in any study-related procedures.

Participants

Enrolled participants were aged 18 through 45 years, were nonsmokers, had a body mass index of 18–30 kg/m², and had a supine pulse rate of 50–100 beats per minute during the vital signs assessment at screening. Agreement to use an effective method of contraception as defined in the protocol was required from those with reproductive potential.

The exclusion criteria included hypersensitivity to CGRP receptor antagonists; clinically significant findings regarding disease state, physical examination, medical history, or standard clinical laboratory parameters; supine systolic blood pressure ≤ 90 or ≥140 mmHg or diastolic blood pressure ≤50 mmHg or ≥ 90 mmHg at screening; potentially

clinically significant electrocardiography; history of cardiovascular disease, including but not limited to long QT syndrome (or family history of long QT syndrome), cardiac arrhythmia, orthostatic hypotension, and coronary artery or valvular disease; clinical condition or previous surgery that could affect absorption, distribution, biotransformation, or excretion of ubrogepant or moxifloxacin; concomitant medications within 14 days or hormonal drug products within 30 days before dosing; consumption of foods that could affect drug metabolizing enzymes and transporters within 14 days before dosing; consumption of caffeine-containing or xanthine-containing compounds within 48 hours before dosing; participation in a blood or plasma donation program within 60 or 30 days, respectively, before dosing; participation in any other clinical investigation requiring repeated blood or plasma draws within 60 days before dosing; and history of substance abuse within 5 years of screening or positive result at screening or admission for specific drugs of abuse. Furthermore, given the known sex differences in human electrocardiogram (ECG) measurements,[26] in particular, the finding that women have longer QTc intervals than men, the exclusionary and safety ECG QTcF cutoff for women was set at a slightly higher range than for men (450 milliseconds for men vs. 470 milliseconds for women).

The study was conducted at a single clinical research center, where for each treatment participants were admitted and administered investigational products, underwent PK sample collections, Holter ECG recordings, and safety assessments, and were released after their 25-hour Holter ECG recording in each study period. Participants had a follow-up period for clinical chemistry assessments 30 (±2) days after the last dose.

Treatments

The four treatments were a single 100 mg ubrogepant therapeutic dose administered as two tablets of 50 mg each plus six matching placebo tablets (double-blind treatment), a single 400 mg ubrogepant supratherapeutic dose administered as eight tablets of 50 mg each (double-blind treatment), a single placebo dose of eight matching tablets (double-blind treatment), and a single 400 mg moxifloxacin dose administered as a single tablet (open-label treatment). All treatments were administered orally in accordance with the randomization scheme with approximately 240 mL of water. Participants were required to undergo a 10-hour fast prior to each dosing (days 1, 8, 15, and 22) and to maintain the fast for 4 hours postdose.

Outcomes

The primary outcome was the change in QTcF interval from baseline (ΔQTcF) following administration of ubrogepant and placebo. For this pharmacodynamic (PD) analysis, continuous ECGs were obtained via 12-lead Holter ECG readers. Holter ECG readers rendered continuous ECGs from approximately 30 minutes before dose to 25 hours postdose, with participants remaining supine for at least 10 minutes before each timepoint until approximately 5 minutes after the timepoint. ECG extractions were obtained at 0 hour (before dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose. Example ECG recordings for a representative participant at 2 hours postdose is shown in **Figure S1**. At each timepoint, ECGs were extracted in triplicate within a 5-minute window; the middle ECG was collected at the nominal timepoint. Baseline QTcF interval for each treatment period was calculated from the mean of nine predose measurements (triplicate readings taken 20 minutes, 10 minutes, and immediately before dosing) taken on days 1, 8, 15, and 22. A central ECG laboratory was employed to minimize variability. The ECG readers (n = 6) were blinded to all study and participant information. All the ECG readers were cardiologists, and the same blinded ECG reader interpreted and reviewed all study-related ECGs for one participant.

The secondary outcomes were evaluated using plasma concentrations of ubrogepant and moxifloxacin and safety assessments. Blood samples (6 mL) were collected on days 1, 8, 15, and 22 at 0 hour (before dose) and

postdose at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours. Blood samples were centrifuged to obtain plasma samples, which were flash-frozen and stored at −70°C until analysis. The limit of quantitation was 1 ng/mL for ubrogepant and 25 ng/mL for moxifloxacin. Plasma concentrations of ubrogepant and moxifloxacin were determined using validated liquid chromatography with tandem mass spectrometry methods.[27]

Safety was assessed by monitoring adverse events (AEs), clinical laboratory tests, vital signs, safety ECGs, and physical examinations. The safety ECG was a standard 12-lead ECG performed in the supine position to measure the following parameters in lead II or lead III: heart rate, PR interval, QRS duration, QT interval, and QTcF interval.

Randomization and blinding

Enrollment numbers were assigned sequentially to participants and randomization occurred via a computerized scheme that was blinded. The clinical site and study participants were blinded with respect to ubrogepant and placebo treatments. Moxifloxacin was administered in an open-label fashion. The central ECG readers were blinded to all study and participant information (e.g., study design, study drug assignment, times and days of treatments and assessments, participant number and demographics). The bioanalytical team measuring plasma concentrations of ubrogepant and moxifloxacin as well as the sponsor's bioanalytical representatives were unblinded to the samples.

Statistical analyses

A sample size of 72 participants for enrollment was planned, assuming a 20% dropout rate, which would yield a total of 58 participants completing the study. A sample size of 58 would ensure at least a 90% probability that 90% confidence intervals (CIs) were below 10 milliseconds at all timepoints, assuming a true difference in QTcF interval change from baseline between ubrogepant doses and placebo of 3 milliseconds at all timepoints. A sample size of 58 participants completing would also ensure at least 80% probability of detecting a 5-millisecond true mean difference between moxifloxacin and placebo for at least one timepoint after multiplicity adjustment, assuming a true difference in QTcF interval change from baseline between moxifloxacin and placebo of 9 milliseconds at the time of maximum moxifloxacin plasma concentrations (2 and 3 hours postdose).

Additional assumptions used in sample size determination were a standard deviation (SD) of 10 milliseconds for the change in QTcF interval from predose baseline, an average correlation of 0.40 among measurements in the same period, and an average correlation of 0.15 among measurements in different periods.

The PD population consisted of all participants who received study treatment and had nonmissing QTcF intervals at baseline and at least one postdose QTcF interval for at least one treatment period; the PK population consisted of all participants with evaluable PK parameters for ubrogepant and/or moxifloxacin; and the safety population consisted of all participants who received at least one dose of study treatment.

A linear mixed-effects model that included treatment, sequence, period, and gender as fixed factors, predose baseline for the period and mean predose baseline across periods as covariates, and participant as a random effect was used to determine the treatment effect of ubrogepant (each dose) vs. placebo and the treatment effect of moxifloxacin vs. placebo in QTcF interval change from predose baseline at each postdose timepoint ($\Delta\Delta$QTcF). The least squares mean estimate of $\Delta\Delta$QTcF and a two-sided 90% CI for each postdose timepoint were calculated. The effect of ubrogepant on QTcF interval was evaluated by comparing the largest upper limit of the two-sided 90% CI for each ubrogepant dose vs. placebo, compared with a threshold of 10 milliseconds.

To assess assay sensitivity, the time-matched mean difference between moxifloxacin and placebo in QTcF interval change from baseline was determined, and the effect of moxifloxacin on QTcF interval was evaluated by comparing the largest lower limit of the $\Delta\Delta$QTcF two-sided 90% CIs at 2 and 3 hours, with a threshold value of 5 milliseconds. Assay sensitivity

was established if the null hypothesis that the difference between moxifloxacin and placebo in QTcF interval change from baseline was < 5 milliseconds at both the 2-hour and 3-hour timepoints was rejected using the Hochberg procedure.

To enable categorical assessments, extreme QTcF intervals were defined as those greater than 450, 480, or 500 milliseconds, and changes from baseline in QTcF intervals were defined as those greater than 30 or 60 milliseconds. The number and percentage of participants that met the above criteria at scheduled ECG timepoints was summarized.

Descriptive statistics were presented for each ubrogepant dose and for moxifloxacin for the following: plasma drug concentration at each timepoint, all PK parameters, and safety parameters (clinical laboratory variables, vital signs, and safety ECG parameters). The number of participants with potentially clinically significant postbaseline values was also summarized for the safety parameters. PK parameters were derived from plasma concentrations of ubrogepant and moxifloxacin: area under the plasma drug concentration-time curve from time 0 to time t (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$), maximum plasma drug concentration (C_{max}), time to reach C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), and terminal elimination rate constant (λ_z). The following PK parameters were derived for ubrogepant only: apparent total body clearance (CL/F) and apparent volume of distribution (V_z/F). Values for λ_z, $AUC_{0-\infty}$, or $t_{1/2}$ that exhibited a terminal log-linear phase in the concentration-vs.-time profile or yielded an r^2 value of the regression for λ_z of 0.8 or more were reported. $AUC_{0-\infty}$, CL/F, and V_z/F were reported if the extrapolated AUC was less than 20%. A linear mixed effects model with sequence, treatment, and period as fixed effects and participant nested within sequence as a random effect was used to evaluate dose proportionality between the ubrogepant 100 mg and 400 mg doses based on log-transformed, dose-normalized C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ parameters. PK analyses were performed using Phoenix WinNonlin version 6.3 (Certara, L.P., Princeton, NJ, USA).

Treatment-emergent AEs were summarized by incidence and distribution. Descriptive statistics for clinical laboratory values and vital signs at all assessment points were compiled and evaluated for potential clinical significance.

RESULTS
Baseline demographics and study flow

A total of 84 participants (53 men and 31 women) were enrolled and received at least one dose of study treatment (**Table 1**). Evaluable pharmacodynamic (PD) and PK assessments were available for 78 participants after administration of ubrogepant 100 mg, 76 participants after administration of ubrogepant 400 mg, and 72 participants after administration of moxifloxacin 400 mg, and there were 74 participants with evaluable PD assessments after placebo administration. Overall, 67 (79.8%) participants completed all treatment periods, with 17 participants discontinuing the trial: 9 due to protocol violations (positive urine drug screen), 3 due to adverse events (AEs), 2 due to consent withdrawal, 2 due to loss to follow-up, and 1 due to investigator's decision.

Assay sensitivity

The least squares mean estimate of change from baseline in QTcF interval (ΔQTcF) after single-dose moxifloxacin 400 mg, at the prespecified 2-hour and 3-hour timepoints, was statistically different from placebo, with the least squares mean differences from placebo ($\Delta\Delta$QTcF) and lower bounds of the two-sided 90% CIs (7.50 milliseconds at 2 hour, 7.91 milliseconds at 3 hour) above the 5-millisecond threshold (**Figure 1** and **Table S2**).

Table 1 Demographics and baseline characteristics

	Placebo (n = 74)	Ubrogepant 100 mg (n = 78)	Ubrogepant 400 mg (n = 76)	Moxifloxacin 400 mg (n = 72)	Total (N = 84)
Age[a] (years)					
Mean (SD)	29.0 (7.5)	29.2 (7.4)	29.2 (7.3)	29.1 (7.3)	29.3 (7.5)
Sex, n (%)					
Male	46 (62.2)	50 (64.1)	47 (61.8)	44 (61.1)	53 (63.1)
Female	28 (37.8)	28 (35.9)	29 (38.2)	28 (38.9)	31 (36.9)
Race, n (%)					
White	32 (43.2)	35 (44.9)	30 (39.5)	31 (43.1)	36 (42.9)
Black or African-American	39 (52.7)	40 (51.3)	43 (56.6)	38 (52.8)	45 (53.6)
Asian	3 (4.1)	3 (3.8)	3 (3.9)	3 (4.2)	3 (3.6)
Ethnicity, n (%)					
Hispanic or Latino	9 (12.2)	10 (12.8)	8 (10.5)	8 (11.1)	10 (11.9)
Not Hispanic or Latino	65 (87.8)	68 (87.2)	68 (89.5)	64 (88.9)	74 (88.1)
Weight (kg)					
Mean (SD)	73.5 (11.6)	73.8 (11.6)	74.1 (11.6)	74.1 (11.5)	73.5 (11.6)
Height (cm)					
Mean (SD)	171.0 (8.9)	171.2 (8.9)	171.3 (9.1)	171.0 (9.0)	171.0 (8.8)
BMI (kg/m^2)					
Mean (SD)	25.11 (3.1)	25.14 (3.2)	25.22 (3.1)	25.32 (3.1)	25.10 (3.1)

N = number of participants in the safety population. n = number of participants in the specific category. BMI, body mass index; SD, standard deviation.
[a]Age relative to informed consent date.

Pharmacodynamics

After single oral doses of ubrogepant 100 or 400 mg, the least squares mean differences from placebo ($\Delta\Delta$QTcF) and upper bounds of two-sided 90% CIs were lower than the 10-millisecond threshold at all timepoints (**Figure 2** and **Table 2**). The values of the upper bounds of the two-sided 90% CIs at the maximum $\Delta\Delta$QTcF (2.46 milliseconds for ubrogepant 100 mg, 2.69 milliseconds for ubrogepant 400 mg at 24 hour) were below the 10-millisecond threshold, demonstrating the absence of an effect of single-dose ubrogepant 100 or 400 mg on QTcF interval. A scatterplot of least squares mean
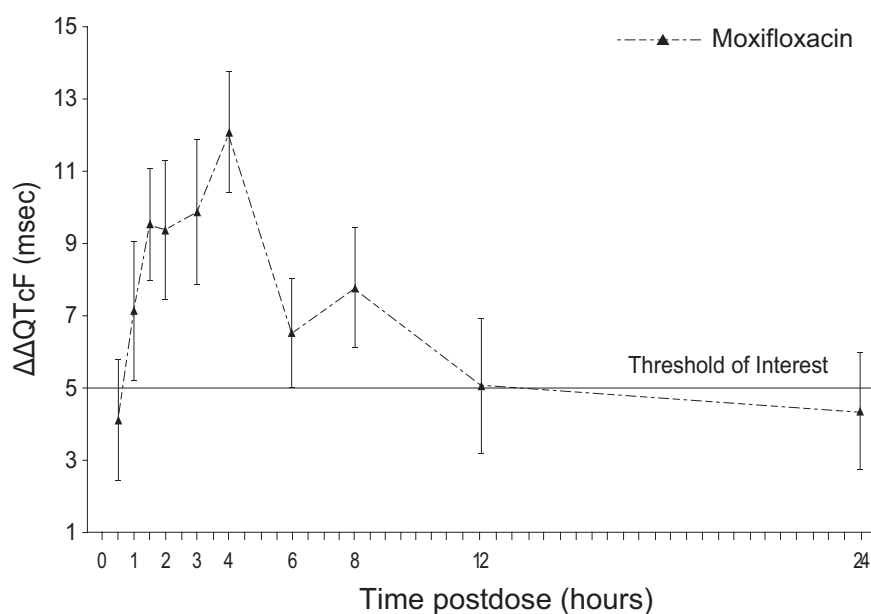

Figure 1 Placebo-corrected least squares mean (90% confidence interval) change from predose baseline in time-matched QTcF interval following moxifloxacin administration (pharmacodynamic population).
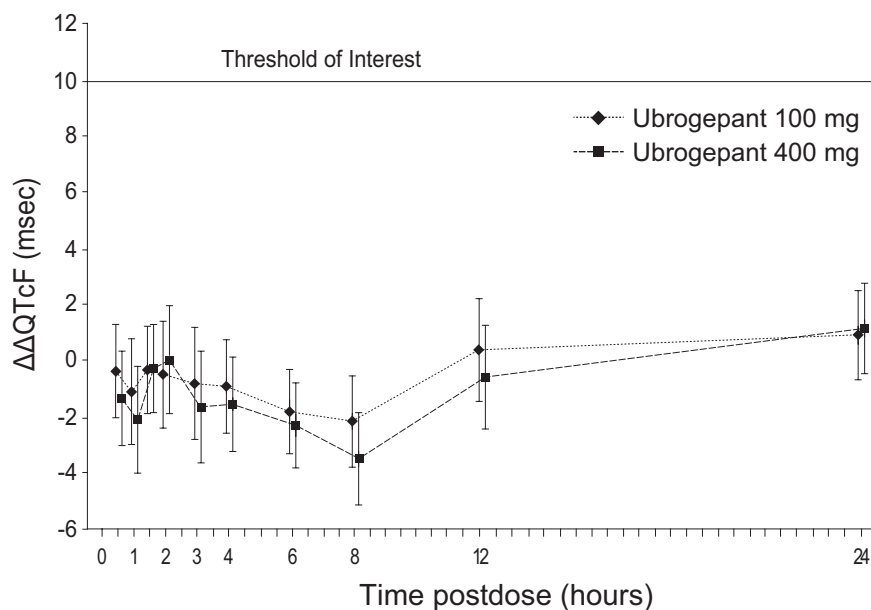
Figure 2 Placebo-corrected least squares mean (90% confidence interval) change from predose baseline in time-matched QTcF interval following ubrogepant (100 and 400 mg) administration (pharmacodynamic population).

Table 2 Mean ΔΔQTcF interval at each timepoint following single doses of ubrogepant 100 mg or ubrogepant 400 mg (PD (pharmacodynamic) population)

Postdose timepoint (hours)	Ubrogepant 100 mg (n = 78)	Ubrogepant 400 mg (n = 76)
	LS mean difference (90% CI)	
0.5	−0.46 (−2.15, 1.23)	−1.44 (−3.14, 0.27)
1	−1.21 (−3.11, 0.70)	−2.20 (−4.12, −0.29)
1.5	−0.41 (−1.97, 1.15)	−0.35 (−1.93, 1.22)
2	−0.58 (−2.49, 1.33)	−0.05 (−1.97, 1.88)
3	−0.89 (−2.89, 1.11)	−1.74 (−3.76, 0.27)
4	−1.00 (−2.66, 0.67)	−1.65 (−3.33, 0.03)
6	−1.92 (−3.44, −0.41)	−2.41 (−3.94, −0.89)
8	−2.25 (−3.90, −0.60)	−3.60 (−5.27, −1.94)
12	0.31 (−1.53, 2.16)	−0.67 (−2.53, 1.20)
24	0.85 (−0.75, 2.46)	1.07 (−0.55, 2.69)

ΔΔQTcF, placebo-corrected change from baseline in time-matched QTcF interval; CI, confidence interval; LS, least squares.

ΔΔQTcF intervals vs. plasma ubrogepant concentrations showed no trends in ΔΔQTcF with increasing plasma drug concentrations (**Figure 3**).

Categorical analyses

In the categorical analysis of QTcF, no participant had a QTcF interval greater than 500 milliseconds at any timepoint. An extreme value of QTcF interval change from baseline greater than 30 milliseconds was reported in one participant who received ubrogepant 100 mg, one participant who received ubrogepant 400 mg, and one participant who received moxifloxacin 400 mg. No participant had a QTcF interval change from baseline greater than 60 milliseconds.

Pharmacokinetics

Ubrogepant was rapidly absorbed: median t_{max} was 1.67 and 2.08 hours for the 100 and 400 mg doses, respectively. The mean elimination half-life of ubrogepant was 4.41 and 5.06 hours for the 100 and 400 mg doses, respectively. Mean plasma concentration-time profiles and PK parameters of ubrogepant following single-dose administration of 100 or 400 mg ubrogepant are shown in **Figure S2** and **Table 3**, respectively. Mean plasma concentration-time profiles and PK parameters for moxifloxacin following single-dose administration of moxifloxacin 400 mg are shown in **Figure S3** in and **Table 3**, respectively. Ubrogepant maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in a dose-proportional manner from 100 to 400 mg (**Table S3**).

Safety

There were no serious AEs or deaths during the study. The incidence of treatment-emergent AEs (TEAEs) was low and generally comparable between treatment groups (**Table 4**). The most commonly reported TEAEs (≥ 2% in any active treatment and with incidence greater than that for placebo) were gastrointestinal disorders such as nausea and upper abdominal pain (placebo, 2.7% (n = 2), ubrogepant 100 mg, 3.8% (n = 3), ubrogepant 400 mg, 3.9% (n = 3), moxifloxacin, 5.6% (n = 4)) and nervous system disorders such as headache and dizziness (placebo, 2.7% (n = 2), ubrogepant 100 mg, 3.8% (n = 3), ubrogepant 400 mg, 2.6% (n = 2), moxifloxacin, 5.6% (n = 4)). A summary of all TEAEs is provided in **Table S4**.

Treatment-related TEAEs were infrequent and balanced across the treatment groups. Three participants discontinued due to an AE, one for hypoesthesia and two for QT interval prolongation.

One event of QT prolongation was reported on day 15 (period 3, moxifloxacin dosing visit) in a 29-year-old male who received
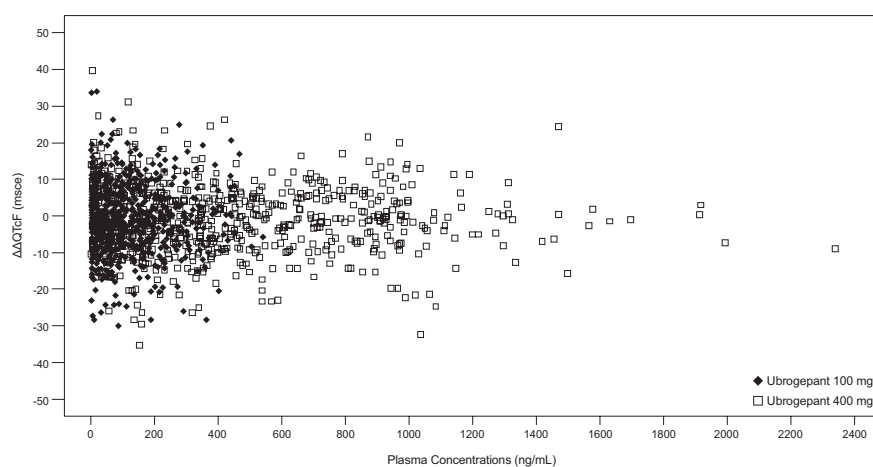
Figure 3 Scatterplot of ΔΔQTcF vs. plasma ubrogepant concentrations (pharmacodynamic population). ΔΔQTcF, placebo-corrected change from baseline in time-matched QTcF interval.

Table 3 Pharmacokinetic (PK) parameters following single-dose administration of ubrogepant 100 mg, ubrogepant 400 mg, or moxifloxacin 400 mg (PK population)

PK parameter, mean (SD)	Ubrogepant 100 mg ($n = 78$)	Ubrogepant 400 mg ($n = 76$)	Moxifloxacin 400 mg ($n = 72$)
C_{max} (ng/mL)	274.25 (99.25)	1029.75 (428.79)	1660.40 (422.36)
AUC_{0-t} (ng·h/mL)	1220.57 (430.26)	4998.22 (1935.06)	18393.27 (4693.84)
$AUC_{0-\infty}$ (ng·h/mL)	1249.39 (433.97)	5127.06 (1979.76)	25702.00 (5678.68)
t_{max} (hour)[a]	1.67 (1.08–6.08)	2.08 (0.58–5.00)	2.08 (0.58–8.08)
$t_{1/2}$ (hour)	4.41 (1.11)	5.06 (1.77)	9.56 (0.83)
V_z/F (L)	561.40 (238.88)	662.67 (384.10)	—
CL/F (L/hour)	88.95 (29.26)	89.24 (34.05)	—

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

Table 4 Summary of adverse events by treatment (safety population)

n (%)	Placebo ($n = 74$)	Ubrogepant 100 mg ($n = 78$)	Ubrogepant 400 mg ($n = 76$)	Moxifloxacin 400 mg ($n = 72$)
TEAEs[a]	11 (14.9)	6 (7.7)	11 (14.5)	8 (11.1)
Treatment-related TEAEs[a]	7 (9.5)	4 (5.1)	7 (9.2)	7 (9.7)
AEs leading to discontinuation[b]	1 (1.4)	1 (1.3)	1 (1.3)	0

Participants were counted only once within each category. A TEAE was assigned to the treatment before the onset of AE. AE, adverse event; TEAE, treatment-emergent AE.
[a]Events that began or worsened on or after the treatment start date in the first period and within 30 days of the treatment start date in the last period.
[b]Discontinuation events that occurred within the treatment start date in the first period to 30 days after treatment start date in the last period.

ubrogepant 100 mg in period 1 (day 1) and placebo in period 2 (day 8). QTcF at baseline was 436 milliseconds. At his period 3 visit (dosing with moxifloxacin), before moxifloxacin treatment, the participant was noted to have a QTcF of 460 milliseconds. One hour following dosing with moxifloxacin, the participant's QTcF was 468 milliseconds, with two repeat ECGs demonstrating QTcF values of 473 milliseconds and 466 milliseconds. The participant was treated with two infusions of 1000 mL of intravenous sodium chloride and the event was reported to have resolved by the following day. The subject subsequently was discontinued from the study.

The second event of QT prolongation was reported on day 15 (period 3, moxifloxacin dosing visit) in a 45-year-old female who received placebo in period 1 (day 1) and ubrogepant 400 mg in period 2 (day 8). QTcF at baseline was 429 milliseconds. At her period 3 visit (dosing with moxifloxacin), before moxifloxacin treatment, the participant was noted to have a QTcF of 443 milliseconds. One hour following treatment with moxifloxacin, the participant's QTcF was 480 milliseconds, and two repeat ECGs both demonstrated QTcF values of 473 milliseconds. The participant was treated with two infusions of 1000 mL of intravenous

sodium chloride, and the event resolved the same day. The subject subsequently was discontinued from the study.

There were no clinically meaningful mean changes from baseline or relevant trends in any laboratory parameters, vital sign parameters, or safety ECG measurements.

DISCUSSION

The results of this study, which was conducted in accordance with International Council for Harmonisation (ICH) requirements for safety evaluation of investigational medications, suggest that ubrogepant has no clinically relevant effect on cardiac repolarization. Ubrogepant is a novel, oral CGRP receptor antagonist that was developed to mitigate the pathological effects of CGRP in migraine without triggering vasoconstriction. It is intended for the acute treatment of migraine attacks and has demonstrated safety and efficacy in clinical trials.[20,21]

Assay sensitivity for the measurement of QTcF intervals in this study was demonstrated by a statistically significant prolongation of the baseline-corrected QTcF interval of the active control (moxifloxacin 400 mg) vs. placebo based on the lower limit of the two-sided 90% CIs being above the 5-millisecond threshold at the prespecified timepoints of 2 and 3 hours postdose. Moxifloxacin PK parameters were consistent with values reported in the literature for mean AUC (20,300–44,600 ng·hour/mL)[22,23,28] and mean C_{max} (1620–3800 ng/mL).[22,23,28] The mean $t_{1/2}$ of moxifloxacin (9.56 hours) was within the range reported in one study (9.0–12.8 hours)[28] but below that reported in another (12.1–19.1 hours)[22] and in the moxifloxacin labeling (11.5–15.6 hours).[23] This is likely due to the fact that PK sampling in the current study was limited to 24 hours postdose.

Systemic exposure to ubrogepant (AUC) and C_{max} increased in a dose-proportional manner in the dose range of 100–400 mg. These results are in agreement with previous clinical studies in which ubrogepant was administered as single (100–400 mg) or daily (40–400 mg) doses.[29,30] Therapeutic (100 mg) and supratherapeutic (400 mg) doses of ubrogepant had no impact on cardiac repolarization in healthy adult participants, as demonstrated by the absence of any ΔΔQTcF reaching the 10-millisecond threshold for the upper limit of the two-sided 90% CIs. Both doses of ubrogepant were well tolerated in healthy adult participants; incidence of TEAEs was low and comparable among treatments, and no clinically meaningful changes from baseline were observed for laboratory or vital sign parameters.

Nonclinical studies evaluated ubrogepant for any effect on human Ether-à-go-go-Related Gene (hERG) channels heterologously expressed in Chinese hamster ovary K1 (CHO-K1) cells using standard whole-cell voltage-clamp techniques (data on file, Allergan plc). Ubrogepant inhibited hERG current, with an half maximal inhibitory concentration (IC_{50}) value of 63μM, suggesting no impact of ubrogepant on the hERG channel at clinically relevant concentrations (approximately 0.3μM). In addition, ubrogepant demonstrated no impact on arterial blood pressure parameters (systolic blood pressure, diastolic blood pressure, and mean blood pressure), heart rate, electrocardiograph parameters (PR, QRS, RR and QT/QTcI intervals), QT:RR interval relationship, respiratory parameters (rate and depth of respiration), and body temperature in a combined cardiovascular–respiratory telemetry study in rhesus monkeys (data on file, Allergan, plc). These results are further supported by the current study data in healthy adult participants.

In completed clinical trials, ubrogepant administered at doses of 50 or 100 mg (ACHIEVE I) or 25 or 50 mg (ACHIEVE II) to treat single migraine attacks was effective, safe, and generally well tolerated in adult patients with a history of migraine.[20,21] Patients in each study were allowed a second optional dose after 2 hours if needed to treat the migraine attack, resulting in the largest potential cumulative dose of 200 mg per day—half the 400 mg dose that showed no impact on cardiac repolarization in the current study. These trials also detected no clinically relevant changes in laboratory parameters, vital signs, or safety ECGs.

A potential limitation of the study was the enrollment of healthy adult participants, a population that may not share the same cardiovascular conditions or comorbidities as the real-world population of people with migraine. However, in accordance with ICH regulatory guidance, QTc studies are performed in healthy adult participants to minimize confounding variables.[25]

Another potential limitation was the substantially larger proportion of male participants vs. female participants (63.1% vs. 36.9%), given the greater prevalence of migraine in females than males: males represented 17% of the study population in a large ($N = 107,122$), retrospective study of commercial and Medicare Supplemental–insured adults who had a prescription claim for a migraine medication from 2008 through 2011.[31] Because the PK characteristics of ubrogepant are similar in males and females, however, the impact of this limitation is likely to be minimal. Furthermore, the E14 guidance from the FDA and the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use regarding clinical evaluation of QT/QTc prolongation encourages including both genders in a thorough QT study, and states that gender-based analysis is not expected when the primary analysis is negative and there is no evidence suggesting gender differences.[25] Finally, the upper bounds of the two-sided 90% CIs at the maximum ΔΔQTcF for both ubrogepant doses were well below the 10-millisecond threshold that would have indicated an effect of potential clinical significance, and a larger proportion of females would be unlikely to have affected this finding.

In conclusion, in this thorough QT study in which assay sensitivity was demonstrated with moxifloxacin, single doses of therapeutic (100 mg) and supratherapeutic (400 mg) ubrogepant did not affect cardiac repolarization and were safe and well tolerated in healthy adults. Furthermore, dose-proportional increases in C_{max} and AUC were seen in the dose range of 100–400 mg of ubrogepant.

SUPPORTING INFORMATION

Figure S1. Individual ECG (electrocardiogram) recordings at 2 hours; for example, adult male participant following administration of (**a**) placebo, (**b**) moxifloxacin, (**c**) ubrogepant 100 mg, and (**d**) ubrogepant 400 mg.
Figure S2. Mean (SD) plasma ubrogepant concentration over time on (**a**) a linear scale and (**b**) a semi-logarithmic scale (PK (pharmacokinetic) population).

Figure S3. Mean (SD) plasma moxifloxacin concentration over time on (**a**) a linear scale and (**b**) a semi-logarithmic scale (PK (pharmacokinetic) population).

Table S1. Study treatments.

Table S2. Mean ∆∆QTcF interval over time following a single dose of 400 mg moxifloxacin (PD (pharmacodynamic) population).

Table S3. Dose proportionality results following single-dose administration of ubrogepant 100 or 400 mg (PK (pharmacokinetic) population).

Table S4. Treatment-emergent adverse events by treatment, system organ class, and preferred term (safety population).

AUTHOR CONTRIBUTIONS
A.J., R.B., M.B., K.L., D.M., and A.P. wrote the manuscript; A.J., A.P., and R.B. designed the research; A.J., K.L., and M.B. analyzed the data.

DATA AVAILABILITY STATEMENT
Data reported in this manuscript are available within the article (and/or) its supplementary materials. Allergan will share de-identified patient-level data and/or study-level data, including protocols and clinical study reports, for phase II–IV trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The indication studied in the trial must have regulatory approval in the United States and/or the European Union and the primary manuscript from the trial must be published prior to data sharing. To request access to the data, the researcher must sign a data use agreement. All shared data are to be used for noncommercial purposes only. More information can be found on http://www.allerganclinicaltrials.com/.

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia* **38**, 1–211 (2018).
2. Buse, D.C. *et al*. Impact of migraine on the family: Perspectives of people with migraine and their spouse/domestic partner in the CaMEO study. *Mayo Clin. Proc.* **91**, 596–611 (2016).
3. Lampl, C. *et al*. Interictal burden attributable to episodic headache: findings from the Eurolight project. *J. Headache Pain* **17**, 9 (2016).
4. Vos, T. *et al*. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2163–2196 (2012).
5. Buse, D.C. *et al*. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention study. *Headache* **52**, 1456–1470 (2012).
6. Becker, W.J. Acute migraine treatment in adults. *Headache* **55**, 778–793 (2015).
7. Holland, S., Fanning, K.M., Serrano, D., Buse, D.C., Reed, M.L. & Lipton, R.B. Rates and reasons for discontinuation of triptans and opioids in episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. *J. Neurol. Sci.* **326**, 10–17 (2013).
8. Messali, A.J. *et al*. Treatment persistence and switching in triptan users: a systematic literature review. *Headache* **54**, 1120–1130 (2014).
9. Serrano, D., Buse, D.C., Manack Adams, A., Reed, M.L. & Lipton, R.B. Acute treatment optimization in episodic and chronic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* **55**, 502–518 (2015).
10. Martelletti, P. Acute treatment of migraine: quo vadis? *Expert. Opin. Pharmacother.* **18**, 1035–1037 (2017).
11. Humphrey, P.P. The discovery of a new drug class for the acute treatment of migraine. *Headache* **47** (suppl. 1), S10–S19 (2007).
12. Goadsby, P.J., Lipton, R.B. & Ferrari, M.D. Migraine—current understanding and treatment. *N Engl. J. Med.* **346**, 257–270 (2002).
13. Goadsby, P.J., Holland, P.R., Martins-Oliveira, M., Hoffmann, J., Schankin, C. & Akerman, S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol. Rev.* **97**, 553–622 (2017).
14. Iyengar, S., Ossipov, M.H. & Johnson, K.W. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. *Pain* **158**, 543–559 (2017).
15. Eftekhari, S., Salvatore, C.A., Calamari, A., Kane, S.A., Tajti, J. & Edvinsson, L. Differential distribution of calcitonin gene-related peptide and its receptor components in the human trigeminal ganglion. *Neuroscience* **169**, 683–696 (2010).
16. Lassen, L.H., Haderslev, P.A., Jacobsen, V.B., Iversen, H.K., Sperling, B. & Olesen, J. CGRP may play a causative role in migraine. *Cephalalgia* **22**, 54–61 (2002).
17. Goadsby, P.J., Edvinsson, L. & Ekman, R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann. Neurol.* **28**, 183–187 (1990).
18. Ho, T.W. *et al*. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet* **372**, 2115–2123 (2008).
19. Hewitt, D.J. *et al*. Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. *Cephalalgia* **31**, 712–722 (2011).
20. Dodick, D.W. *et al*. Ubrogepant for the acute treatment of migraine: efficacy, safety, tolerability, and functional impact outcomes from a single attack phase III study, ACHIEVE 1 [abstract IOR-01LB]. *Headache* **58**, 1287–1288 (2018).
21. Lipton, R.B. *et al*. Efficacy, safety, and tolerability of ubrogepant for the acute treatment of migraine: Results from a single attack phase III study, ACHIEVE II [abstract PS111LB]. *Headache* **58**, 1315–1316 (2018).
22. Stass, H. & Kubitza, D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J. Antimicrob. Chemother.* **43** (suppl. B), 83–90 (1999).
23. Avelox [package insert]. (Merck & Co., Inc., Whitehouse Station, NJ, 2016).
24. Démolis, J.L., Kubitza, D., Tennezé, L. & Funck-Brentano, C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin. Pharmacol. Ther.* **68**, 658–666 (2000).
25. US Food and Drug Administration. Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf> (2005). Accessed October 9, 2019.
26. Salama, G. & Bett, G.C. Sex differences in the mechanisms underlying long QT syndrome. *Am. J. Physiol. Heart Circ. Physiol.* **307**, H640–H648 (2014).

27. Li, C.C. *et al*. Population PK analyses of Ubrogepant (MK-1602), a CGRP receptor antagonist: enriching in-clinic plasma PK sampling with outpatient dried blood spot sampling. *J. Clin. Pharmacol.* **58**, 294–303 (2018).

28. Burkhardt, O. *et al*. Single- and multiple-dose pharmacokinetics of oral moxifloxacin and clarithromycin, and concentrations in serum, saliva and faeces. *Scand. J. Infect. Dis.* **34**, 898–903 (2002).

29. Ankrom, W. *et al*. Multiple, once-daily, oral doses of 150 mg ubrogepant administered for 28 days are generally well tolerated, with no clinically significant elevation of alanine aminotransferase in healthy adult males [abstract]. *Neurology* **92** (suppl. 15), P2.10-024 (2019).

30. Bondiskey, P. *et al*. Single and multiple doses of ubrogepant are not associated with a clinically significant elevation of alanine aminotransferase in healthy adult males [abstract]. *Neurology* **92** (suppl. 15), P1.10.014 (2019).

31. Woolley, J.M., Bonafede, M.M., Maiese, B.A. & Lenz, R.A. Migraine prophylaxis and acute treatment patterns among commercially insured patients in the United States. *Headache* **57**, 1399–1408 (2017).