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Single-Dose Pharmacokinetics and Safety of Ubrogepant in Adults With Hepatic Impairment: Results From an Open-Label, Phase 1 Trial

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Abstract

Ubrogepant is an oral calcitonin gene–related peptide receptor antagonist approved for the treatment of acute migraine headaches. Ubrogepant demonstrated efficacy and safety in 2 pivotal phase 3 studies (N = 2240) that led to its approval. Here, we report the pharmacokinetics and safety results from a phase 1 study in which participants with severe (n = 4), moderate (n = 8), or mild (n = 8) hepatic impairment and matched participants with normal hepatic function (n = 8) were administered a single dose of 100 mg of ubrogepant. Twenty-eight participants aged 36 to 70 years were enrolled and completed the study. In participants with mild, moderate, or severe hepatic impairment, ubrogepant systemic exposure (area under the plasma concentration–time curve) increased by 7%, 52%, and 115%, respectively, compared with participants with normal hepatic function (≈1600 ng • h/mL). Peak exposure increased by 1%, 18%, and 26%, respectively, in participants with mild, moderate, or severe hepatic impairment compared to those with normal hepatic function (≈400 ng/mL). Plasma protein binding did not change significantly across groups. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Dose adjustment (50 mg) is recommended for patients with severe hepatic impairment. Single doses of ubrogepant 100 mg were safe, and all the enrolled participants, regardless of hepatic function, completed the study.

Keywords

CGRP receptor antagonist, hepatic impairment, pharmacokinetics, ubrogepant

Ubrogepant is a novel calcitonin gene–related peptide (CGRP) receptor antagonist that was developed for the acute treatment of migraine.[1] CGRP is a neuropeptide implicated in the pathophysiology of migraine. CGRP levels in the cranial circulation are increased during a migraine attack, and exogenously administered CGRP has been shown to trigger migraine-like headache.[2] CGRP is present in the majority (80%-90%) of trigeminal Aδ fibers that innervate the dura, suggesting that these fibers may be involved in sterile neurogenic inflammation and migraine pain transmission.[3] Furthermore, the CGRP receptor is present on human meningeal and cerebral blood vessels. These observations suggest that CGRP-mediated activation of the trigeminovascular system may play a key role in migraine pathogenesis and that inhibition of CGRP function may yield a novel therapeutic approach to treating migraine.

The ability of CGRP inhibition to induce pain relief in acute migraine was established by Boehringer Ingelheim using an IV formulation of BIBN4096BS,[4] and replicated by Merck & Co., Inc., with an oral formulation of telcagepant,[5] a highly selective CGRP receptor antagonist. Telcagepant was superior to placebo

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in phase 3 studies in the primary end points of 2-hour pain freedom, 2-hour pain relief, and absence of associated symptoms at 2 hours (photophobia, phonophobia, and nausea), as well as the key secondary end point of 24-hour sustained pain freedom.[5] Telcagepant administration has been associated with serum alanine aminotransferase increases, as was administration of a second CGRP receptor antagonist, MK-3207.[6] For this reason, the development of these compounds was suspended.

In contrast, ubrogepant administration has not been associated with a deleterious effect on the liver in either nonclinical or clinical studies.[6–11] In these clinical studies, single, oral doses of 1 to 400 mg of ubrogepant and multiple oral doses of ubrogepant up to 400 mg once daily for 10 consecutive days and 150 mg once daily for 28 consecutive days have been evaluated.[9,10,12] Ubrogepant was generally safe and well tolerated in these studies with no serious adverse events (AEs), discontinuations due to AEs, or abnormal standard clinical laboratory findings.[9,10,12] Dose-proportional pharmacokinetics (PK) were noted in the dose range of 1 to 400 mg.[12] Ubrogepant is rapidly absorbed, with maximum plasma concentrations achieved in 0.5 to 1.5 hours following oral administration.[12] Ubrogepant is metabolized to an inactive metabolite almost exclusively by cytochrome P450 (CYP) 3A4 with subsequent glucuronidation.[6,12] Ubrogepant has a short terminal elimination half-life of 5 to 7 hours, with no accumulation after once-daily repeated dosing.[12] Ubrogepant is mainly metabolized by hepatic CYP isozymes.[12] In healthy participants, concomitant administration of a strong CYP3A4 inhibitor (eg, ketoconazole) or a strong CYP3A4 inducer (eg, rifampin) demonstrated an increase in ubrogepant exposure by up to 9.7-fold or a decrease in exposure by 78%, respectively.[13] Considering this, it is likely that patients with varying degrees of hepatic impairment might achieve higher systemic concentrations of ubrogepant. Understanding the impact of concomitant medication and/or hepatic impairment will help guide clinicians on the potential need for dose adjustments. Therefore, the study reported herein characterized the safety, tolerability, and PK profile of ubrogepant in participants with mild, moderate, or severe hepatic impairment as compared to participants with normal hepatic function.

Methods

Study Design

This study was conducted in accordance with the respective protocols, International Council for Harmonization Good Clinical Practice guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. The study protocols were approved by the institutional review board (IntegReview IRB, Austin, Texas) at the study sites (Clinical Pharmacology of Miami, LLC, Miami, Florida; and Orlando Clinical Research Center, Orlando, Florida). All participants gave written informed consent before participation in the study.

The phase 1, multicenter, open-label, single-dose, nonrandomized, parallel-group study reported herein intended to enroll 24 male and female participants with hepatic impairment (8 mildly impaired, 8 moderately impaired, and 8 severely impaired) and 8 healthy male and female participants with normal hepatic function. The study design was chosen in accordance with the requirements of the US Food and Drug Administration guidance.[14] All participants received a single, oral dose of 100 mg (2 × 50-mg tablets) of ubrogepant with 240 mL of water under fasted conditions on day 1 and remained fasted for 4 hours following dosing. The ubrogepant dose of 100 mg was selected, because it was the highest clinical dose of ubrogepant evaluated in phase 3 studies.[9] Because minimal to no accumulation is expected after once-daily repeated dosing for ubrogepant,[12] a single-dose study is considered adequate to satisfy the objectives of the study. The planned duration of each participant's participation in the study was 4 days (day –1 [day before drug administration] through the last PK sample on day 3), excluding the screening period and 30-day follow-up period.

Participants with hepatic impairment were categorized according to the Child-Pugh classification. Participants with moderate hepatic impairment (Child-Pugh B classification) were not enrolled until 4 participants with mild hepatic impairment (Child-Pugh A classification) had completed the study; participants with severe hepatic impairment (Child-Pugh C classification) were not to be enrolled until 4 participants with moderate hepatic impairment had completed the study. Enrollment for the moderate and severe hepatic impairment groups began after the safety/tolerability/PK profile of ubrogepant was established in mild and moderate hepatically impaired participants, respectively. Healthy participants with normal hepatic function were recruited after participants with hepatic impairment had been enrolled in the study, in order to match them as closely as possible to the hepatically impaired participants with respect to age, weight, and sex. Participants with normal hepatic function were matched specifically according to age, not to exceed 5 years between the means of the normal group and the 3 hepatically impaired groups; weight range, which deviated <20% between the means of the normal group and the 3 hepatically impaired groups; and sex as much as possible to match the ratio of the normal hepatic function group to the 3 hepatically impaired groups.

Participants

Male or female participants, aged 18 through 75 years (inclusive), were to be enrolled in the study if they were a nonsmoker or light smoker (<10 cigarettes/day within 1 week before ubrogepant administration), had a body mass index ≥18 and ≤42 kg/m^2, had a sitting pulse rate ≥50 beats per minute and ≤100 beats per minute during the vital sign assessment at screening, had a negative pregnancy test at screening and day –1 (women only), agreed to use effective methods of contraception, agreed not to become pregnant or have their partners become pregnant, and signed the informed consent form and had the mental capability to understand it. Key exclusion criteria included known hypersensitivity to CGRP receptor antagonist; positive test for drugs of abuse or history of substance abuse within the previous 2 years; clinically significant disease state; an abnormal electrocardiogram (ECG) result; exposure to hepatitis B virus, hepatitis C virus, or HIV; and abnormal and clinically significant results from any screening tests (eg, physical, laboratory, medical history). In addition to these criteria, participants with hepatic impairment had chronic liver disease and/or cirrhosis documented by at least 1 of the following: liver biopsy with histologic findings consistent with cirrhosis; computed tomographic or ultrasonographic evidence of liver disease with or without portal hypertension; physical examination and clinical and laboratory evidence of chronic liver disease or colloid shift on a liver-spleen scan, and could not have gastrointestinal hemorrhage because of esophageal varices, peptic ulcers, or Mallory-Weiss syndrome within 6 months before day 1; an acute exacerbation of liver disease within 4 weeks of dosing; ascites requiring paracentesis within 1 week of dosing or during the study period; or a Child-Pugh score >13.

All concomitant medication use was reviewed by the investigator in consultation with the sponsor before enrollment. No concomitant medications, with the exception of those medications prescribed as therapy for hepatic cirrhosis or other concurrent diseases common in this patient population, were permitted during the study.

Assessments and Bioanalysis

Safety assessments were monitored throughout the study duration and included: AEs, physical examinations, vital signs (pulse rate, blood pressure, respiration rate, and body temperature), 12-lead ECG, and clinical laboratory tests (hematology, biochemistry, serum pregnancy test, and urinalysis). An AE (classified by preferred term) that occurred during the treatment period was considered treatment emergent (TEAE) if it was not present before the dosing of ubrogepant or if it was present before the dosing of ubrogepant but increased in severity during the treatment period. An AE that occurred >30 days after the last dose of ubrogepant was not counted as a TEAE. Efficacy was not monitored in this study.

PK sampling was done at the following times to determine ubrogepant plasma concentrations: starting on day 1 at 0 hour (before dosing) and 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, 24, 30, 36, and 48 hours after dosing. Sampling was also done at the following times for plasma protein binding determinations: day 1 at 0 hour (before dosing) and 2 hours after dosing. PK and protein-binding blood samples were drawn at the nominal times specified above, relative to the dosing time, and the actual time of the blood draw was recorded. All predose samples were drawn within 15 minutes before the dosing time, and predose protein binding samples were externally spiked with known quantities of ubrogepant. Plasma protein binding was performed using rapid equilibrium dialysis (Thermo Fisher Scientific, Waltham, Massachusetts). Equal volumes (20 μL) of phosphate buffered saline (PBS) and human plasma were added to the receiver and donor side, respectively, and incubated at 37°C and 100 rpm on a shaking water bath for 11 hours. After dialysis of the clinical study samples, 20 μL of dialyzed plasma from the donor side was mixed with 180 μL of blank human plasma and 200 μL of PBS. Dialyzed buffer from the receiver side was mixed with 100 μL of blank plasma. Aliquots (50 μL) of matrix matched receiver and donor side samples were treated with an equal volume of PBS, mixed, and then spiked with internal standard ([D3]-ubrogepant) followed by protein precipitation with acetonitrile, centrifugation, and dilution of the supernatant into 0.1% formic acid in water in preparation for quantification of ubrogepant. Plasma samples were also spiked with [D3]-ubrogepant followed by protein precipitation (600 μL) with acetonitrile, supernatant harvested (17 μL), and prepared for analysis by addition of 200 μL of 0.1% formic acid in 20:80 acetonitrile/water.

The ubrogepant concentrations in plasma and protein binding plasma samples were analyzed at Keystone Bioanalytical, Inc. (North Wales, Pennsylvania) using validated liquid chromatography–tandem mass spectrometry assays on a Sciex API 5500 quadrupole mass spectrometer (Applied Biosystems, Foster City, California) coupled to a Turbo V ion source with positive-mode electrospray ionization. Reversed-phase chromatography was performed on a ZORBAX eclipse plus C18 (50 × 3 mm; Agilent, Santa Clara, California) column. For plasma, analytes were chromatographed with a 2.7-minute, linear gradient consisting of 0.1% formic acid in water and 0.1% formic acid in acetonitrile. For plasma-binding samples, a 1.2-minute linear gradient using water and 0.05% formic acid in

acetonitrile was used. Analyte detection was achieved through multiple reaction monitoring of ubrogepant (550 → 267) and the internal standard (553 → 267). Collision energies for both ubrogepant and the internal standard were 45. Standard curves for plasma- and protein-binding samples were prepared in the range of 1 to 1000 ng/mL and 0.1 to 100 ng/mL, respectively. Intra- and interassay variability for the analyses herein were <4% and <5.6% (plasma) and <5.4% and <6.2% (protein binding), respectively. The lower limit of quantitation for ubrogepant was 1 ng/mL for plasma PK analysis and 0.1 ng/mL for the protein-binding analysis.

Pharmacokinetic and Safety Parameters

The principal parameters describing the PK of ubrogepant were derived from plasma concentrations using noncompartmental analysis with the software program Phoenix WinNonlin version 8.0 (Certara, Princeton, New Jersey). The actual sampling times were used in the calculations of PK parameter values; nominal sample times were used in the calculation of descriptive statistics for plasma concentration data. The following PK parameters were calculated using a model-independent approach based on standard Phoenix WinNonlin equations: area under the plasma concentration–time curve from time 0 to time t ($AUC_{0\text{-}t}$) and from time 0 to infinity ($AUC_{0\text{-}\infty}$), maximum plasma drug concentration (C_{max}), time of maximum plasma drug concentration (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{\frac{1}{2}}$), and apparent total body clearance of drug from plasma after extravascular administration (CL/F). The $AUC_{0\text{-}t}$ was calculated by using the linear-log trapezoidal rule. Estimates of $t_{\frac{1}{2}}$ were calculated based on λ_z. The λ_z was determined by performing a regression analysis on the terminal linear phase of semilogarithmic plots of individual concentration-time data using a minimum of 3 concentration-time points in the elimination phase excluding C_{max}. No value of λ_z, $AUC_{0\text{-}\infty}$, or $t_{\frac{1}{2}}$ was reported for cases that did not exhibit a terminal log-linear phase in the concentration-time profile or if the r^2 value of the regression for λ_z was <0.8. If the extrapolated AUC was >20%, the $AUC_{0\text{-}\infty}$ and CL/F values were listed by participant but excluded from descriptive statistics. Safety measures included AE recording, clinical laboratory determinations, vital sign parameters, ECG results, and physical examination findings.

Statistical Analyses

Two populations were used in the statistical analysis of this study. For the PK population, all participants who had evaluable PK parameters for ubrogepant were included, and for the safety population, all participants who received a dose of ubrogepant were included. Individual and descriptive statistics for "percent-bound" ubrogepant values obtained from the protein-binding samples at the 2-hour time point were presented for all participants by hepatic function group. Individual and descriptive statistics for ubrogepant plasma concentration–time data were presented for all participants by hepatic function group in the PK population in a tabular form and displayed graphically by participant group. All postdose time points for which no sample was collected were treated as missing. No value was imputed for these missing values. Concentrations below the limit of quantitation were reported as 0 for calculating descriptive statistics and in graphs depicting arithmetic means. Descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, maximum, median, and minimum) were calculated for all plasma PK parameters such as C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, λ_z, $t_{1/2,}$ t_{max}, and CL/F. The geometric mean was also reported for C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and CL/F.

PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) for ubrogepant were compared using an analysis of variance model with hepatic function group as a fixed effect. Statistical inference was based on log-transformed values for the C_{max} and AUC parameters. The 2-sided 90%CI was constructed for the geometric mean ratio (GMR) of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for each hepatically impaired group (test) vs the normal hepatic function group (reference). An exact Wilcoxon 2-sample test was performed to compare the difference in median t_{max} for each hepatically impaired group and the normal hepatic function group. Statistical analyses of safety outcomes were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Participants

A total of 28 participants (8 participants each in the healthy, mild, and moderate hepatic impairment groups and 4 in the severe hepatic impairment group) were enrolled in the study. Due to challenges finding sufficient participants with severe hepatic impairment, enrollment was stopped after 4 of the planned 8 participants in that group had entered the study. All 28 participants who entered the study received study treatment and were included in the safety and PK population analyses; all participants completed the study.

Demographics and baseline characteristics are summarized in Table 1. Overall, characteristics were well balanced across the hepatic impairment groups and healthy participants. Mean age was 56.7 years overall (range, 36-70 years), and half the participants were women. While the overall sex ratio was balanced, the majority of the mild hepatic impairment group were women (75%) and of the majority of the severe hepatic

Table 1. Summary of Demographics and Baseline Characteristics of Study Population

Parameter	Normal Hepatic Function	Hepatic Impairment			Total
		Mild	Moderate	Severe	
Number of participants	8	8	8	4	28
Age, y					
Mean (SD)	58.1 (2.8)	54.0 (8.3)	57.8 (7.6)	57.0 (9.6)	56.7 (6.9)
Median	59.5	56.0	58.0	58.0	58.5
Min, max	54, 61	36, 62	45, 70	46, 66	36, 70
Sex, n (%)					
Male	4 (50.0)	2 (25.0)	5 (62.5)	3 (75.0)	14 (50.0)
Female	4 (50.0)	6 (75.0)	3 (37.5)	1 (25.0)	14 (50.0)
Race, n (%)					
White	8 (100.0)	8 (100.0)	6 (75.0)	4 (100.0)	26 (92.9)
Black/African American	0	0	0	1 (12.5)	1 (3.6)
Multiple	0	0	0	1 (12.5)	1 (3.6)
Ethnicity, n (%)					
Hispanic or Latino	5 (62.5)	4 (50.0)	5 (62.5)	3 (75.0)	17 (60.7)
Not Hispanic or Latino	3 (37.5)	4 (50.0)	3 (37.5)	1 (25.0)	11 (39.3)
Weight, kg					
Mean (SD)	79.4 (8.4)	85.0 (16.8)	85.1 (22.6)	85.8 (8.1)	83.6 (15.5)
Median	76.2	86.7	80.8	86.0	80.0
Min, max	72.6, 93.2	62.4, 113.0	55.0, 123.0	75.6, 95.4	55.0, 123.0
Height, cm					
Mean (SD)	167.8 (11.6)	164.5 (5.3)	168.5 (6.7)	168.9 (11.1)	167.2 (8.3)
Median	166.6	166.3	169.5	169.3	167.5
Min, max	148.0, 182.0	157.0, 172.3	155.5, 176.0	155.0, 182.0	148.0, 182.0
Body mass index, kg/m^2					
Mean (SD)	28.3 (2.4)	31.3 (5.4)	29.9 (7.5)	30.3 (4.1)	29.9 (5.2)
Median	28.0	31.9	27.9	29.6	28.8
Min, max	25.7, 33.3	22.4, 41.3	20.4, 41.6	26.2, 35.8	20.4, 41.6

SD, standard deviation.

impairment group were men (75%). Most participants were White (92.9%), and mean weight was 83.55 kg.

Participants with hepatic impairment were allowed to continue taking medications prescribed for their hepatic disease or other concurrent diseases common in this population. No concomitant medications were administered to participants with normal hepatic function during the study.

Ubrogepant PK

The mean plasma ubrogepant concentration–time profiles in participants with varying degrees of hepatic impairment and with normal hepatic function are presented in Figure 1. Hepatic impairment appears to increase both the rate and extent of absorption of ubrogepant. However, the extent of increase in systemic exposure of ubrogepant was marginal in mild hepatic impairment. A summary of the mean PK parameters for ubrogepant when administered to participants with varying degrees of hepatic impairment and in participants with normal hepatic function is presented in Table 2. The differences in median t_{max} for participants with mild, moderate, or severe hepatic impairment as compared to participants with normal hepatic function were –0.25, +0.25, and –0.25 hours, respectively. Comparison of t_{max} in participants with mild, moderate, and severe hepatic impairment to participants with normal hepatic function using an exact Wilcoxon 2-sample test resulted in *P* values of 0.3503, 0.9385, and 0.3737, respectively. Thus, median ubrogepant t_{max} and the mean apparent terminal $t_{1/2}$ of ubrogepant were generally similar in participants with hepatic impairment and in participants with normal hepatic function. The C_{max} and the overall systemic exposure ($AUC_{0-\infty}$) of ubrogepant increased with higher degree of hepatic impairment. CL/F was similar between the mild hepatic impairment (66.38 ± 26.15 L/h) and normal hepatic function group (69.01 ± 23.54 L/h); however, CL/F for the moderate (49.78 ± 23.84 L/h) and severe (31.23 ± 7.49 L/h) hepatic impairment groups was lower compared to participants with normal hepatic function.

Statistical comparisons of the PK parameters for participants with varying degrees of hepatic impairment and normal hepatic function including the ratio

Table 2. Ubrogepant PK Parameters Following Single-Dose, Oral Administration of Ubrogepant 100 mg in Participants With Mild, Moderate, or Severe Hepatic Impairment and in Participants With Normal Hepatic Function

PK Parameter	Mild Hepatic Impairment Group	Moderate Hepatic Impairment Group	Severe Hepatic Impairment Group	Normal Hepatic Function Group
C_{max}, ng/mL	411.36 ± 189.51	479.96 ± 188.78	509.27 ± 75.78	405.76 ± 218.89
AUC_{0-t}, ng • h/mL	1745.23 ± 767.40	2784.87 ± 2021.70	3310.82 ± 704.12	1587.83 ± 529.76
$AUC_{0-\infty}$, ng • h/mL	1764.09 ± 775.00	2815.22 ± 2056.88	3327.31 ± 704.93	1598.02 ± 532.55
t_{max}, h[a]	1.50 (1.00-2.00)	2.00 (1.00-3.00)	1.50 (0.50-2.00)	1.75 (1.00-4.00)
$t_{1/2}$, h	6.56 ± 5.93	5.95 ± 2.68	5.62 ± 0.62	5.60 ± 3.68
CL/F, L/h	66.38 ± 26.15	49.78 ± 23.84	31.23 ± 7.49	69.01 ± 23.54
Free fraction in plasma, %	10.2 ± 1.3	11.8 ± 1.0	14.7 ± 0.9	10.7 ± 1.5

AUC_{0-t}, area under the plasma concentration–time curve from time 0 to time t; $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 to infinity; CL/F, apparent total body clearance of drug from plasma after extravascular administration; C_{max}, maximum plasma drug concentration; PK, pharmacokinetic; t_{max}, time of maximum plasma drug concentration; $t_{1/2}$, terminal elimination half-life.
All values reported are arithmetic mean ± standard deviation of the pharmacokinetic population unless otherwise noted.
[a]Median (range).

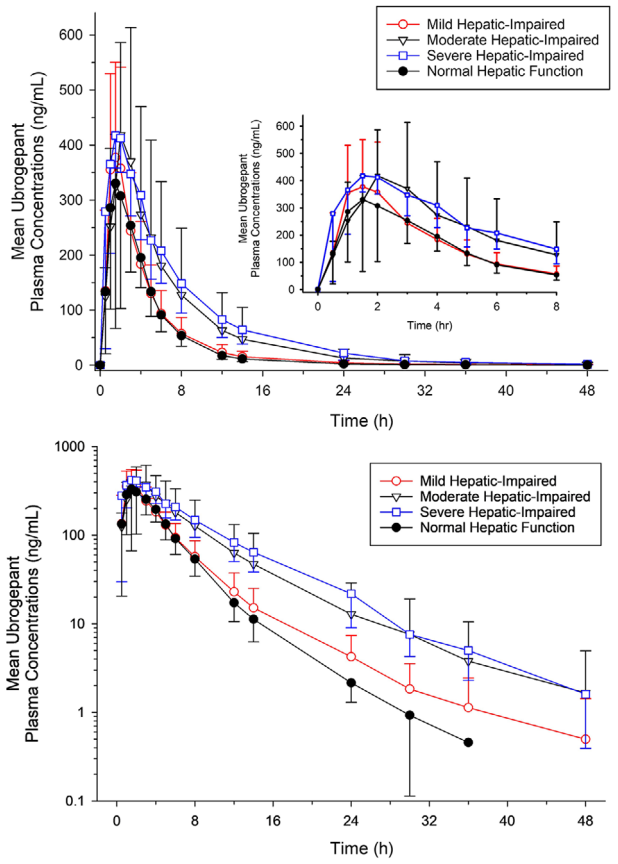

Figure 1. Mean ± SD plasma ubrogepant concentration-time profiles following single-dose, oral administration of 100 mg of ubrogepant in participants with mild, moderate, or severe hepatic impairment and in participants with normal hepatic function (N = 8 in each group and N = 4 in severe hepatic impairment group) (top panel: linear scale; bottom panel: semilogarithmic scale).

of geometric means and 90%CI are presented in Table 3. Participants with mild hepatic impairment had 4% higher C_{max} and 7% higher $AUC_{0-\infty}$ when compared to participants with normal hepatic function after administration of a single oral dose of 100 mg of ubrogepant. The increase in C_{max} and $AUC_{0-\infty}$ was slightly higher in participants with moderate hepatic impairment, with a 25% higher C_{max} and 52% higher $AUC_{0-\infty}$. As compared to participants with normal hepatic function, those with severe hepatic impairment showed a significantly higher C_{max} and $AUC_{0-\infty}$ of 40% and 115%, respectively.

Ubrogepant Plasma Protein Binding

The percent bound of ubrogepant was determined using equilibrium dialysis in the 2-hour samples. In participants with hepatic impairment who were administered a single oral dose of 100 mg of ubrogepant, the percentage of protein-bound ubrogepant calculated as the arithmetic mean ± standard deviation was 89.8% ± 1.3%, 88.2% ± 1.0%, and 85.3% ± 0.9% in mild, moderate, and severe hepatic-impaired groups, respectively, as compared to 89.3% ± 1.5% in participants with normal hepatic function. Plasma protein binding was generally similar across all hepatic-impaired groups as well as in participants with normal hepatic function.

Safety

No deaths, severe AEs, or withdrawals due to AEs occurred during the study. TEAEs of mild to moderate intensity occurred in 5 of the total 28 participants (17.9%) in the study. The 5 participants with TEAEs had mild or moderate hepatic impairment. The only TEAE experienced by more than a single participant was headache, in 2 of 28 participants (7.1%). Both headaches were mild, self-limiting events that resolved

Table 3. Summary of Comparison of Plasma Ubrogepant PK Parameters Following Single-Dose, Oral Administration of Ubrogepant 100 mg in Participants With Mild, Moderate, or Severe Hepatic Impairment to Participants With Normal Hepatic Function

		Geometric LSM		Ratio of Geometric Means	
Hepatic Group	PK Parameter	Test	Reference	Test/Reference	90%CI
Mildly impaired	C_{max}, ng/mL	375.33	359.86	1.04	0.72-1.51
	AUC_{0-t}, ng • h/mL	1608.58	1512.10	1.06	0.72-1.57
	$AUC_{0-\infty}$, ng • h/mL	1625.33	1522.28	1.07	0.72-1.58
Moderately impaired	C_{max}, ng/mL	449.39	359.86	1.25	0.86-1.81
	AUC_{0-t}, ng • h/mL	2299.44	1512.10	1.52	1.03-2.24
	$AUC_{0-\infty}$, ng • h/mL	2319.45	1522.28	1.52	1.03-2.25
Severely impaired	C_{max}, ng/mL	505.35	359.86	1.40	0.89-2.21
	AUC_{0-t}, ng • h/mL	3249.97	1512.10	2.15	1.33-3.46
	$AUC_{0-\infty}$, ng • h/mL	3266.51	1522.28	2.15	1.33-3.46

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

within a day and without intervention. There were no clinically relevant changes in laboratory parameters, vital signs, or ECG measurements.

Discussion

Ubrogepant is indicated for acute treatment of migraine. It is not intended for continuous administration on a daily basis. Thus, the effect of hepatic impairment on the PK of ubrogepant as well as the safety and tolerability was assessed following a single 100-mg dose of ubrogepant in healthy participants with normal hepatic function and participants with impaired hepatic function. Because ubrogepant is mainly metabolized by hepatic CYP isozymes,[12] it was considered likely that patients with varying degrees of hepatic impairment might achieve higher systemic concentrations of ubrogepant. The results of this study confirmed that the rate (C_{max}) and extent ($AUC_{0-\infty}$) of ubrogepant systemic exposures increased with severity of hepatic impairment compared with participants with normal hepatic function. Although time to reach C_{max} was similar across all hepatic function groups, C_{max} and $AUC_{0-\infty}$ of ubrogepant were significantly higher in participants with moderate and severe hepatic impairment. This could be due to reduction in first-pass metabolism of ubrogepant as well as reduction in systemic clearance. Systemic clearance of ubrogepant for the moderate (49.78 $\pm$ 23.84 L/h) and severe (31.23 $\pm$ 7.49 L/h) hepatic impairment groups was lower compared to participants with normal hepatic function (69.01 $\pm$ 23.54 L/h). Accordingly, the GMR of C_{max} and $AUC_{0-\infty}$ in participants with moderate hepatic impairment, compared to participants with normal hepatic function were 1.25 (90%CI, 0.86-1.81) and 1.52 (90%CI, 1.03-2.25), respectively. The GMR of C_{max} and $AUC_{0-\infty}$ in participants with severe hepatic impairment, compared to participants with normal hepatic function were 1.40 (90%CI, 0.89-2.21) and 2.15 (90%CI, 1.33-3.46), respectively. Plasma protein binding was similar in participants with impaired hepatic function when compared to participants with normal hepatic function, suggesting that minor changes in the extent of plasma protein binding of ubrogepant due to hepatic impairment may not have contributed to changes in systemic exposure.

Due to doubling of systemic exposure of ubrogepant in severe hepatic-impaired participants, lower 50-mg dose is recommended for such patients. Although the upper bound of 90%CI for the GMR of $AUC_{0-\infty}$ in participants with severe hepatic impairment compared to participants with normal hepatic function was 3.46, further reduction of dose may not be needed due to the wide therapeutic window for ubrogepant. A supratherapeutic dose of 400 mg of ubrogepant was safe and well tolerated in healthy participants in the thorough QT study[15] and for 10 days in the multiple-ascending-dose study.[16] Furthermore, a dose of 50 mg of ubrogepant has been evaluated in 2 pivotal phase 3 studies and was found to be efficacious compared to placebo.[9,10]

Ubrogepant was well tolerated in healthy participants and in participants with mild to severe hepatic impairment. The incidence of TEAEs was low (17.9% overall), with only mild headaches occurring in >1 participant (2 participants total). No deaths, serious AEs, or withdrawals due to AEs occurred during the study. There was no indication of worsening tolerance with increasing hepatic impairment.

Conclusions

No dose adjustment for ubrogepant is recommended for patients with mild or moderate hepatic impairment;

dose adjustment (50 mg) is recommended for patients with severe hepatic impairment. Single doses of ubrogepant 100 mg were safe and well tolerated when administered to healthy participants with normal hepatic function and participants with impaired hepatic function.

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