CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	211765
Link to EDR	\\CDSESUB1\evsprod\NDA211765\0001
Submission Date	Dec 26, 2018
Submission Type	505(b)(1) Standard Review
Brand Name	UBRELVY™
Generic Name	Ubrogepant
Dosage Form and Strength	50 mg or 100 mg taken orally with or without food when needed
Route of Administration	Oral tablets
Proposed Indication	Acute treatment of migraine with or without aura in adults
Applicant	Allergan Sales, LLC.
Associated IND	IND 113924
OCP Review Team	Bilal AbuAsal, PhD., Atul Bhattaram, PhD., Sreedharan Sabarinath, PhD.
OCP Final Signatory	Mehul Mehta, PhD.

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1. EXECUTIVE SUMMARY

The Applicant, Allergan Sales, LLC., is seeking approval for Ubrogepant (UBRELVY™) via 505(b)(1) pathway for the acute treatment of migraine with or without aura in adults. Ubrogepant is a small molecule, oral CGRP receptor antagonist. A large body of evidence suggests that CGRP plays a central role in the pathogenesis of migraine. Multiple CGRP inhibitors have been approved recently for migraine prevention in adults. UBRELVY™ will be supplied as 50 or 100 mg oral tablets.

To demonstrate efficacy, the applicant is relying on two pivotal, double-blind, placebo-controlled, single attack studies (Studies UBR-MD-01 and UBR-MD-02) in migraine patients. These studies evaluated the safety and efficacy of 25 mg and 50 mg doses of ubrogepant (Study UBR-MD-02) and 50 mg and 100 mg doses of ubrogepant (Study UBR-MD-01).

Studies UBR-MD-01 and UBR-MD-02 demonstrated that both 50 mg and 100 mg doses were superior to placebo for the acute treatment of migraine based on the co-primary efficacy endpoints (pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose of investigational product). Study UBR-MD-02 demonstrated that 25 mg was superior to placebo for the co-primary endpoint pain freedom at 2 hours after the initial dose; however, statistical significance was not achieved for the absence of most bothersome migraine-associated symptom-m at 2 hours after the initial dose. The applicant is seeking approval for 50 mg and 100 mg doses. A second dose may be administered 2 hours after the initial dose. The maximum daily dose should not exceed 200 mg.

The application includes 18 Phase 1 studies, two Phase 2 studies in migraine patients, and one long term open label extension study, in addition to the pivotal efficacy/safety studies. The primary focus of this review is to evaluate the appropriateness of the proposed dosing regimen and to evaluate the need for dose adjustments based on intrinsic and extrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under this NDA and recommends the approval of 50 and 100 mg doses for the acute treatment of migraine with or without aura in adults.

Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of UBRELVY™ for the acute treatment of migraine was demonstrated in two randomized, double- blind, placebo-controlled, multi-center, single migraine attack studies. The applicant is seeking approval of 50 and 100 mg doses that demonstrated efficacy based on the co-primary endpoints (pain freedom and absences of most bothersome symptom at 2 hours).

General dosing instructions	50 mg or 100 mg taken orally with or without food. If required, a second dose may be administered 2 hours after the initial dose. The maximum daily dose should not exceed 200 mg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose adjustment is needed for the following intrinsic factors: • **Severe hepatic impairment (Child-Pugh C)**: Use 50 mg dose. If required, a second 50 mg dose may be administered 2 hours after the initial dose. • **Severe renal impairment (CLcr 15-29 mL/min)**: Use 50 mg dose. If required, a second 50 mg dose may be administered 2 hours after the initial dose. UBRELVY should be avoided in patients with ESRD (CLcr <15) • **End Stage Renal Disease (ESRD, CLcr <15 mL/min)**: Avoid UBRELVY in patients with ESRD. Dose adjustment is needed for the following extrinsic factors: • **Strong CYP3A4 inhibitors**: Contra-indicated with concomitant use of strong CYP3A4 Inhibitors. • **Moderate CYP3A4 inhibitors**: Use 50 mg dose and avoid taking a second dose within 24 hours, if using concomitant moderate CYP3A4 inhibitors. • **Weak CYP3A4 inhibitors**: Use 50 mg dose when concomitantly used with weak CYP3A4 inhibitors. If required, a second 50 mg dose is allowed 2 hours after the initial dose. • **BCRP or P-gp only inhibitors**: Use 50 mg dose when concomitantly used with BCRP or P-gp only inhibitors. If required, a second 50 mg dose is allowed 2 hours after the initial dose. • **Strong CYP3A4 Inducers**: In patients taking strong CYP3A4 inducers, loss of ubrogepant efficacy is expected. Concomitant use of ubrogepant with strong CYP3A4 inducers should be avoided. • **Moderate and weak CYP3A4 inducers**: Coadministration of ubrogepant with mild and moderate CYP3A4 inducers was not adequately evaluated. If use of mild and moderate CYP3A4 inducers cannot be avoided, use 100 mg dose of ubrogepant. If required, a second 100 mg dose may be administered 2 hours after the initial dose.

Labeling	The review team recommends changes to the USPI to reflect the recommended dose optimizations based on intrinsic and extrinsic factors described above.
Bridge between the to-be-marketed and clinical trial formulations	The bridge between the to-be marketed (TBM) tablets and clinical trial (CT) tablets is acceptable. Bioequivalence was demonstrated between the 50-mg and 100-mg strengths of the TBM tablets and the 50-mg strength of the CT tablets used in Phase 3 efficacy trials. A consult for site inspection for the pivotal PK bridging study 3110-103-002 was sent to the Office of Study Integrity and Surveillance (OSIS). OSIS recommended accepting data without an on-site inspection because this site was recently inspected and the outcome from the inspection was classified as No Action Indicated (NAI). Please refer to section 3.3.5 for details.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Ubrogepant is an oral, calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology. CGRP levels in the cranial circulation are increased during a migraine attack and CGRP itself has been shown to trigger migraine-like headache.

Absorption:

Ubrogepant is rapidly absorbed following oral administration of UBRELVY™ with peak plasma concentrations observed by around 1.5 hours post dose. Ubrogepant displays dose proportional pharmacokinetics within the dose range of 1 to 400 mg.

Food Effect:

When UBRELVY™ was administered with a high-fat meal, the time to maximum ubrogepant plasma concentration was delayed by about 2 hours and resulted in a 22% reduction in C_{max} with no change in AUC. The phase III studies were conducted without regard to food, however only about 10-13 % of patients reported taking ubrogepant within 2 hours of a high fat meal. The impact of meals on the efficacy of ubrogepant cannot be fully evaluated using available information. Since an adequate evaluation of the impact of food on the efficacy of ubrogepant is not possible, the review team is relying on the overall efficacy results from the Phase III studies that were conducted without any restriction on food. Thus, ubrogepant can be taken with or without food, just as studied in Phase III.

Distribution:

Plasma protein binding of ubrogepant is 87% in vitro. The mean apparent central volume of distribution of ubrogepant (V/F) after single dose oral administration is approximately 350 L.

Metabolism and Elimination:

Results from an ADME study (MK-1602 P009) showed that ubrogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (ubrogepant), and 2 glucuronide conjugate metabolites were the most prevalent circulating components in human plasma. The glucuronide metabolites are not expected to contribute to the pharmacological activity of ubrogepant since they are reported as about 6000-fold less potent in the CGRP receptor binding assay. These metabolites are more hydrophilic than ubrogepant and have only about 30% the exposure of ubrogepant. Therefore, the DDI liability of these metabolites are considered low.

Excretion:

The elimination half-life of ubrogepant is approximately 5-7 hours. The mean apparent oral clearance (CL/F) of ubrogepant is approximately 89 L/hr. Ubrogepant is excreted mostly via the biliary/fecal route, while the renal route is a minor route of elimination. Based on results from Study MK-1602 P009, following single oral dose administration of radio-labelled [^{14}C]- ubrogepant to healthy male subjects, approximately 42% and 6% of the dose was recovered as unchanged ubrogepant in feces and urine, respectively.

Special Populations:

Hepatic Impairment:

Results from a dedicated hepatic impairment study (Study UBR-PK-01) conducted in otherwise healthy participants with pre-existing mild (Child-Pugh Class A), moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, ubrogepant exposure was increased by 7%, 50% and 115%, respectively relative to healthy control subjects. There were no major changes to plasma protein binding or elimination half-life in subjects with hepatic impairment relative to healthy controls.

Renal Impairment:

Renal route of elimination plays only a minor role in the clearance of ubrogepant. In a radiolabeled study, only about 9.5% of the total administered radioactivity was recovered in urine, and most radioactivity (~83%) was found in the fecal samples. A dedicated clinical pharmacology study to evaluate the impact of renal impairment on the pharmacokinetics of ubrogepant was not conducted. Instead, a population PK approach was used to assess the impact of renal impairment on ubrogepant exposure (Report UBR-MS-01). Rrenal function (measured by creatinine clearance estimated with Cockcroft-Gault (C-G) equation) did not have a statistically significant effect the clearance of ubrogepant in patients with mild and moderate renal impairment (CLcr 30-89 mL/min). Patients with severe renal impairment or ESRD (CLcr ≤ 30 mL/min) were not studied. Dose adjustment is required in patients with severe renal impairment. UBRELVY should be avoided in patients with ESRD (CRcl <15 ml/min). Please refer to section 3.3 for details.

Sex, Age, Race and Body Weight:

Study MK-1602 P003 evaluated the effect of sex and age on the pharmacokinetics of ubrogepant. The geometric mean ratio (GMR) for elderly female/elderly male, 65-80 years old, was 0.8 for both $AUC_{0\text{-}inf}$ and C_{max}. The PK characteristics of ubrogepant are similar in elderly men and women.

The $AUC_{0\text{-}inf}$ of ubrogepant following a single oral dose of 40 mg in elderly participants appeared to be just slightly higher (GMR of 1.28) compared to that in young males, while the C_{max} appeared to be similar (GMR of 1.01) (Study MK-1602 P003). The mean C_{max} of ubrogepant was unchanged while mean $AUC_{0\text{-}inf}$ was 21% lower in healthy Japanese participants compared to healthy Caucasian participants (Study 3110-101-002).

The impact of body weight on exposure was evaluated using PopPK analysis. This analysis also included race, age and sex and was shown to have no significant impact on ubrogepant systemic exposure. Please refer to section 3.3 for details.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose for the acute treatment of migraine is 50 mg or 100 mg taken orally with or without food. If required, a second dose may be administered 2 hours after the initial dose. The maximum daily dose should not exceed 200 mg.

2.2.2 Therapeutic individualization

CYP3A4 Inhibitors:

Strong CYP3A4 inhibitors:

Co-administration of ubrogepant with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 9.7-fold increase in ubrogepant $AUC_{0\text{-}inf}$ and a 5.3-fold increase in ubrogepant C_{max}. Concomitant use of ubrogepant is contraindicated with strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin, etc.).

Moderate CYP3A4 inhibitors:

Co-administration of ubrogepant with verapamil (a moderate CYP3A4 inhibitor) showed a 3.5-fold increase in ubrogepant $AUC_{0\text{-}inf}$ and a 2.8-fold increase in C_{max}. Patients concomitantly using moderate CYP3A4 inhibitors should be advised to use ubrogepant 50 mg and avoid a second dose within 24 hours.

Weak CYP3A4 inhibitors:

No dedicated drug interaction study was conducted with ubrogepant and weak CYP3A4 inhibitors. As a result, patients are recommended to use 50 mg dose strength with concomitant use of weak CYP3A4 inhibitors. If required, administration of a second 50 mg dose 2 hours after the initial dose is allowed.

CYP3A4 Inducers:

Strong CYP3A4 inducers:

Co-administration of ubrogepant with rifampin, a strong CYP3A4 inducer, resulted in an 80% reduction in ubrogepant exposure. Taking strong CYP3A4 inducers (e.g., phenytoin, barbiturates,

rifampin, St. John's Wort) may result in loss of ubrogepant efficacy. Therefore, avoid concomitant use of ubrogepant with strong CYP3A4 inducers.

Weak or moderate CYP3A4 inducers:

Coadministration with weak or moderate CYP3A4 inducers was not evaluated. According to the FDA Guidance for Clinical Drug Interaction Studies[1], a moderate inducer is expected to decrease the AUC of a sensitive index CYP substrate by ≥ 50% to < 80%. A weak inducer is expected to decrease the AUC of a sensitive index CYP substrate by ≥ 20% to < 50%. If concomitant use of mild or moderate CYP3A4 inducers cannot be avoided, use 100 mg dose of ubrogepant in these patients. If required, a second dose can be administered 2 hours after the initial dose.

P-gp only Inhibitors:

Ubrogepant is a P-gp substrate and concomitant administration with P-gp inhibitors can increase the exposure of ubrogepant. No clinical studies were conducted with a P-gp only inhibitor and ubrogepant. Drug interaction with verapamil (a combined P-gp inhibitor and moderate CYP3A4 inhibitor) resulted in a 3.5-fold increase in exposure. This increase in exposure can be due to the combined P-gp/CYP3A4 inhibition and the relative contribution of P-gp inhibition needs to be segregated to provide dose adjustment recommendation with P-gp only inhibitors. In order to segregate the relative contribution of P-gp vs CYP3A4 inhibition and predict the highest possible contribution of P-gp inhibition the review team used the following approach.

The maximal contribution of P-gp inhibition can be predicted when the lowest possible contribution of CYP3A4 is assumed. Since ubrogepant can be considered as a sensitive CYP3A4 substrate, drug interaction due to CYP3A4 only inhibition with moderate CYP3A4 inhibitors like verapamil is expected to result in at least 2-fold increase in exposure (the range for moderate CYP3A4 inhibitors is 2-5-fold increase in exposure for sensitive CYP3A4 substrates). With this assumption of about 2-fold increase in exposure due to CYP3A4 inhibition by verapamil, the expected maximal increase in exposure due to P-gp only inhibition to give the observed drug interaction result will be less than 2-fold. In addition, based on the ADME study, the fraction absorbed of ubrogepant is at least 58%. This also suggest that that intestinal P-gp inhibition can enhance systemic availability of ubrogepant by about 42% as a conservative assumption. Based on this, a P-gp only inhibition is unlikely to result in more than 2-fold increase in ubrogepant exposure. Thus, the review team recommends 50 mg dose of ubrogepant with concomitant use of P-gp only inhibitors (e.g. quinidine). If required, administration of a second 50 mg dose 2 hours after the initial dose is allowed. Even if the impact of P-gp inhibition is much lower than the assumed 2-fold, the 50 mg dose is expected to provide comparable efficacy to the 100 mg dose based on results from registration trials.

BCRP Transporter Inhibitors:

BCRP is an efflux transporter expressed in same tissues as with P-gp. Accordingly, the same rationale discussed above about fraction absorbed calculation for P-gp only inhibitors can be used to provide dose adjustment recommendation for BCRP inhibitors. Thus, the review team

[1] Clinical Drug Interaction Studies-Study Design, Data Analysis, and Clinical Implications Guidance for Industry (https://www.fda.gov/media/82734/download)

recommends 50 mg dose with concomitant use of BCRP inhibitors (e.g. eltrombopag, curcumin). If required, administration of a second 50 mg dose 2 hours after the initial dose is allowed.

Hepatic Impairment:

A clinical study in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) showed that the exposure to ubrogepent increased by 7, 50 and 115% respectively relative to healthy controls. No dose adjustments are required in subjects with mild or moderate hepatic impairment. Patients with severe hepatic impairment should be advised to use ubrogepant 50 mg dose. If required, a second 50 mg dose may be administered 2 hours after the initial dose.

Renal Impairment:

Renal elimination is a minor excretion pathway for ubrogepant. No dedicated renal impairment study was conducted for ubrogepant. However, a PopPK analysis did not reveal a difference in the pharmacokinetics of ubrogepant in subjects with mild or moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function. Therefore, no dose adjustment is required for patients with mild or moderate renal impairment. Patients with severe renal impairment or ESRD were not studied during the clinical development of ubrogepant. Therefore, we recommend the use of 50 mg dose in subjects with severe renal impairment (CLcr 15-29 mL/min). If required, a second 50 mg dose may be administered 2 hours after the initial dose. Patients with ESRD should avoid use of UBRELVY.

Age, Body Weight, Sex and Race:

No dose adjustment is required for patients based on age, gender and race. This recommendation is based on the results from clinical pharmacology studies (See Section 3.3.3) and PopPK analyses.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

- UBRELVY™ can be administered without regard to food.
- Dose adjustment is not required for mild or moderate hepatic/renal impairment or based on demographic factors such as age, sex, race, and body weight.
- In patients with severe hepatic impairment (Child-Pugh C) or severe renal impairment (CRcl 15-29 mL/min), use only 50 mg dose. If required, an optional second 50 mg dose is allowed 2 hours after the initial dose. Avoid use in patients with ESRD.
- Use of UBRELVY™ with strong CYP3A4 inhibitors is contraindicated.
- Patients who are concomitantly taking moderate CYP3A4 inhibitors should be advised to use 50 mg dose and avoid taking a second dose within 24 hours.
- Patients are recommended to use 50 mg dose strength with concomitant weak CYP3A4 inhibitors and the optional second dose is allowed.
- Use 50 mg dose with concomitant P-gp only inhibitors (e.g. quinidine) or BCRP inhibitors (e.g. eltrombopag, curcumin) and the optional second dose is allowed 2 hours after the initial dose.

- In patients taking strong CYP3A4 inducers (e.g., phenytoin, barbiturates, rifampin, St. John's Wort), loss of ubrogepant efficacy is expected and concomitant use of UBRELVY™ with strong CYP3A4 inducers should be avoided.
- Coadministration with weak or moderate CYP3A4 inducers was not evaluated. If use of weak or moderate CYP3A4 inducers cannot be avoided, use 100 mg dose of UBRELVY™. If required, an optional second 100 mg dose is allowed 2 hours after the initial dose.
- No clinically significant pharmacokinetic interactions were observed when ubrogepant was co-administered with oral contraceptives containing norgestimate and ethinyl estradiol, acetaminophen, naproxen, sumatriptan or esomeprazole (a proton pump inhibitor).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Ubrogepant is a small molecule CGRP receptor antagonist and is formulated as immediate release tablets for oral administration. Ubrogepant is available in two strengths: 50 mg and 100 mg.

The clinical development program to demonstrate the safety/efficacy for ubrogepant consisted of two Phase 3 registration studies (Studies UBR-MD-01 and UBR-MD-02) and two Phase 2 studies (Studies MK-1602 and MK-1602) in patients with migraine. The application also includes 18 Phase 1 studies and one open label extension study in migraine patients. Key design features for these studies are summarized in Section 4.4.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Ubrogepant is an oral, calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology. CGRP levels in the cranial circulation are increased during a migraine attack and CGRP itself has been shown to trigger migraine-like headache.
Active Moieties	Ubrogepant is the active moiety. No active metabolites were reported for ubrogepant.
QT Prolongation	No significant QTc prolongation effect of ubrogepant (100 mg and 400 mg) was detected in a TQT study UBR-PK-02 (See QT-IRT Review dated 05/22/2019).
General Information	
Bioanalysis	The concentrations of ubrogepant in human plasma were measured using a validated LC-MS/MS method. Please refer to Section 4.1 for details.
Healthy Volunteers vs. Patients	PK is similar between migraine patients and healthy subjects.
Dose Proportionality	Dose proportional PK over a dose range of 1-400 mg.
Accumulation	No accumulation is noted after repeated once daily dosing. Steady state is achieved within one day.

Variability	The coefficient of variation (CV%) was around 31% and 37% for $AUC_{0\text{-}inf}$ and C_{max} respectively.
Absorption	
Bioavailability	The absolute oral bioavailability of ubrogepant was not determined.
T_{max}	Median T_{max} values ranged from 0.67 to 1.50 hours post dose.
Food effect (high-fat meal) GMR relative to fasted state for tablets	High-fat meal delays Tmax by ~2 h and reduces C_{max} by 22% with no major change in AUC.
Distribution	
Volume of Distribution	Apparent central volume of distribution was estimated to be 350 L.
Plasma Protein Binding	87% (at concentrations ranging from 0.1 to 10 µM).
Substrate transporter systems	Ubrogepant is a substrate for P-gp, BCRP. It is also a weak substrate for OATP1B1, OATP1B3, and OAT1, but not a substrate of OAT3 in transporter assays. Ubrogepant is not an inhibitor of P-gp, BCRP, BSEP, MRP3, MRP4, OAT1, OAT3 transporters, but is a weak inhibitor of OATP1B1, OATP1B3, and OCT2 transporters.
Elimination	
Mean Terminal Elimination half-life	Approximately 5-7 hours
Metabolism	
Primary metabolic pathway(s) [*in vitro*]	CYP3A4 is the primary enzyme involved in the metabolism of ubrogepant.
Inhibitor/Inducer	• Ubrogepant is not an inhibitor of CYP1A2, 2B6, or 3A4 and is a weak inhibitor of CYP2C8, 2C9, 2D6, 2C19, MAO-A and UGT1A1. • Ubrogepant is not an inducer of CYP3A4, 1A2 or 2B6 at concentrations achieved after 100 mg oral administration.

Excretion	
Primary excretion pathways	Ubrogepant is mainly cleared through metabolism. Fecal excretion accounted for about 83% of the dose while recovery from urine was about 9.5%. About 42% and 6% of the dose was recovered as unchanged ubrogepant in feces and urine, respectively.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness of ubrogepant for the treatment of acute migraine is from two Phase III studies, UBR-MD-01 and UBR-MD-02. These are identically designed, randomized, double-blind, placebo-controlled, single-attack studies for the acute treatment of migraine with or without aura. Study UBR-MD-01 assessed the efficacy and safety of 50 mg and 100 mg doses of ubrogepant, while Study UBR-MD-02 included 25 mg and 50 mg doses of ubrogepant respectively. A total of 1917 patients received ubrogepant in these studies (478 patients on 25 mg Ubrogepant is a small molecule CGRP receptor antagonist, 954 patients on 50 mg, and 485 patients on 100 mg).

The pivotal studies enrolled patients 18 to 75 years who had a history of migraine with or without aura for at least 1 year. This is consistent with a diagnosis according to the International Classification of Headache Disorders criteria (ICHD-3 beta, 2013)[2]. Patients had to have experienced between 2 to 8 migraine attacks with moderate to severe headache pain in each of the 3 months before screening.

In each study, the co-primary efficacy endpoints of pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose of investigational product) demonstrated statistically significant treatment differences for ubrogepant 50 mg and 100 mg doses when they were compared with placebo. In Study UBR-MD-02, ubrogepant 25 mg demonstrated superiority over placebo for the co-primary endpoint of pain freedom at 2 hours after the initial dose, but not for absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose Table 1. Since the 25 mg dose did not meet statistical significance for the absence of the most bothersome migraine-associated symptom at 2 hours, the applicant is seeking approval for only the 50 mg and 100 mg dose levels. The applicant also reported that a greater percentage of patients in the ubrogepant 25 mg dose group took rescue medication (defined broadly as acute migraine treatment and/or optional second dose of ubrogepant 2 hours after the initial dose) compared with patients in the ubrogepant 50 mg or 100 mg dose groups (Table 2 Use of Rescue Medication (Acute Migraine Treatment and/or Optional Second Dose) - Studies UBR-MD-01 and UBR-MD-02 (mITT Population)Table 2.Summary of efficacy results are presented in Table 1

[2] https://ichd-3.org/1-migraine/

Table 1. Summary of efficacy results from Studies UBR-MD-01 and UBR-MD-02

Efficacy Endpoint	UBR-MD-01			UBR-MD-02		
	Pairwise Comparisons (UBR vs. PBO)			Pairwise Comparisons (UBR vs. PBO)		
Statistics	PBO (N = 456)	UBR 50 mg (N = 423)	UBR 100 mg (N = 448)	PBO (N = 456)	UBR 25 mg (N = 435)	UBR 50 mg (N = 464)
Primary Efficacy Endpoints						
Pain Freedom at 2 Hours						
Responder, n (%)	54 (11.8)	81 (19.2)	95 (21.2)	65 (14.3)	90 (20.7)	101 (21.8)
Odds Ratio (95% CI)		1.83 (1.25, 2.66)	2.04 (1.41, 2.95)		1.56 (1.09, 2.22)	1.62 (1.14, 2.29)
Adjusted P-value		0.0023[a]	0.0003[a]		0.0285[a]	0.0129[a]
Absence of Most Bothersome Migraine-associated Symptom at 2 Hours						
Responder, n (%)	126 (27.8)	162 (38.6)	169 (37.7)	125 (27.4)	148 (34.1)	180 (38.9)
Odds Ratio (95% CI)		1.70 (1.27, 2.28)	1.63 (1.22, 2.17)		1.37 (1.02, 1.83)	1.65 (1.25, 2.20)
Adjusted P-value		0.0023[a]	0.0023[a]		0.0711	0.0129[a]

Source: Summary of clinical efficacy; Table 3-2; Page 42/112. Link:\\cdsesub1\evsprod\da211765\0001\m2\27-clin-sum\summary-clin-efficacy-migraine.pdf

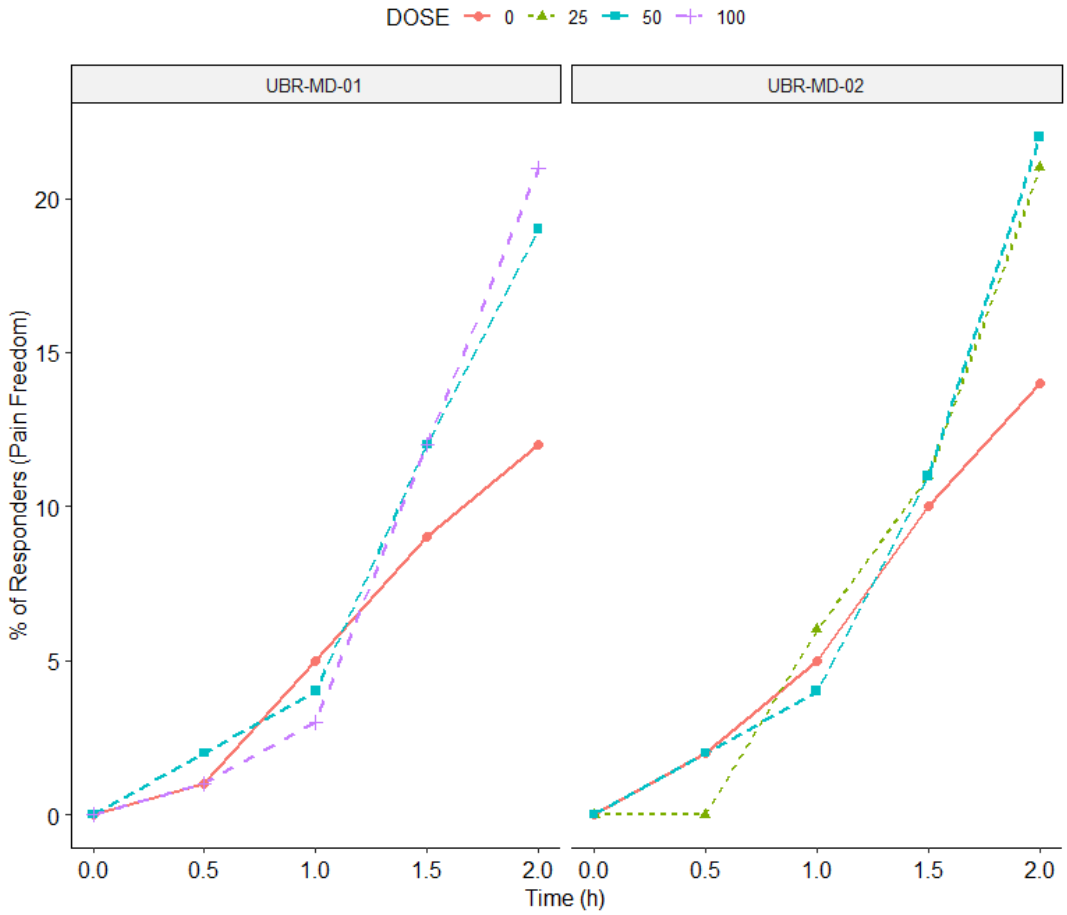
Table 2 Use of Rescue Medication (Acute Migraine Treatment and/or Optional Second Dose) - Studies UBR-MD-01 and UBR-MD-02 (mITT Population)

Hours Post Dose	Study UBR-MD-01			Study UBR-MD-02		
	PBO (N = 456)	UBR 50 mg (N = 423)	UBR 100 mg (N = 448)	PBO (N = 456)	UBR 25 mg (N = 435)	UBR 50 mg (N = 464)
Within 24 Hours						
Took Rescue Medication	72.4%	54.6%	54.0%	68.4%	59.1%	53.0%
P-value		< 0.0001	< 0.0001		0.0045	< 0.0001

Source: Clinical overview, Table 4-5, Page 32. Link: \\cdsesub1\evsprod\NDA211765\0001\m2\25-clin-over

The time-course of pain freedom compared to placebo provided additional support for efficacy for all three dose levels and is presented in Figure 1 below.

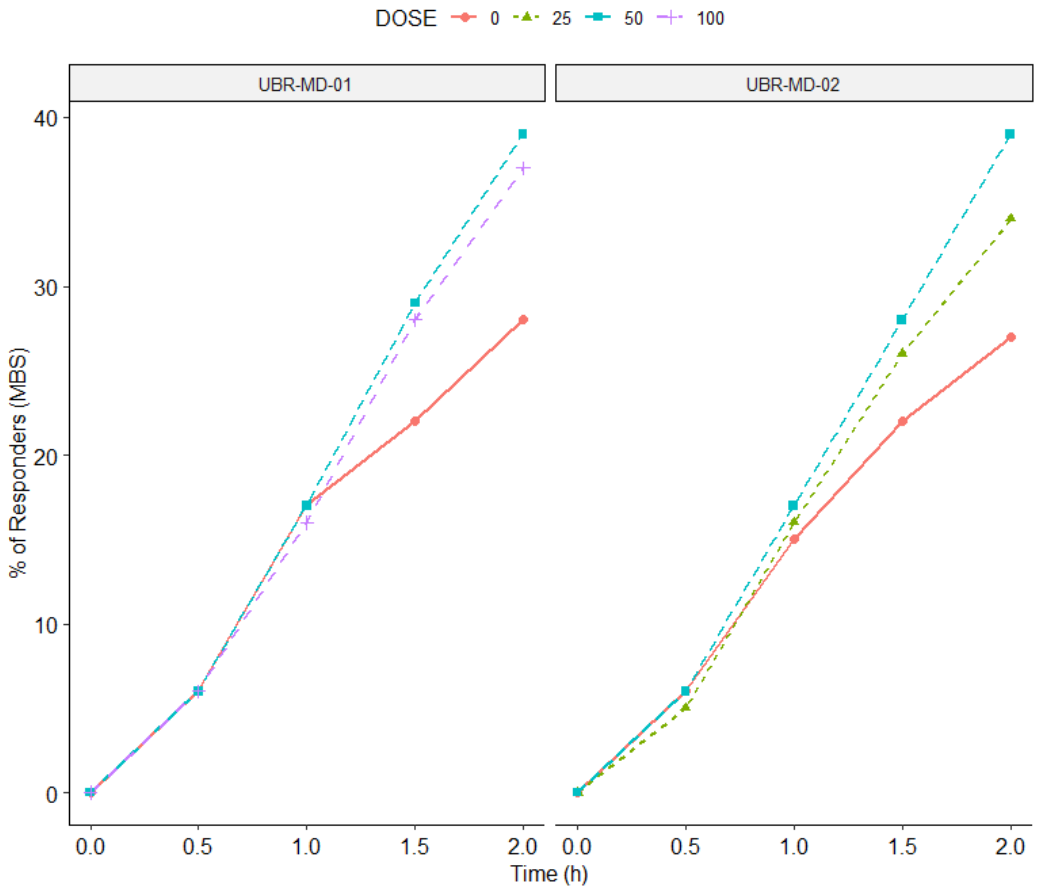
Figure 1. Percentage of patients with pain freedom, by dose over time in Studies UBR-MD-01 and UBR-MD-02



Source: Figure generated by FDA reviewer from studies UBR-MD-01 and UBR-MD-02.

Proportion of subjects with most bothersome symptom (MBS)-freedom over time supports the efficacy of ubrogepant at all dose levels when compared to placebo (Figure 2).

Figure 2. Percentage of patients with MBS-freedom over time, by dose in Studies UBR-MD-01 and UBR-MD-02



Source: Figure generated by FDA reviewer from studies UBR-MD-01 and UBR-MD-02.

Safety assessments across the clinical studies showed ubrogepant as well tolerated and safe in patients and in healthy participants across a broad range of doses up to 400 mg (See clinical safety review for details).

Ubrogepant was administered in dosing schedules that included an initial dose that was randomized and an optional second dose of ubrogepant 2 hours after the initial dose to treat a single migraine attack within 24 hours. Longer-term studies included dosing schedules that included high-frequency dosing of 100 mg ubrogepant for 8 weeks in a Phase 1 hepatic safety study (3110-105-002) and intermittent dosing for the treatment of up to 8 migraine headaches per month for up to 1 year in the Phase 3 long-term extension study (UBR-MD-04). As per the clinical review team, analysis of the AEs did not suggest any safety concerns with intermittent dosing of ubrogepant. Cardiovascular and hepatic safety was closely examined in this clinical program and no major safety issues related to ubrogepant were identified across all dose levels.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, studies UBR-MD-01 and UBR-MD-02 demonstrated that ubrogepant 50 mg and 100 mg are superior to placebo for the acute treatment of migraine for both pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose (See Section 3.3.1). Even though ubrogepant 25 mg dose was superior to placebo for pain freedom at 2 hours after the initial dose in Study UBR-MD-02, absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose did not meet prespecified statistical acceptance criteria (See Biometrics review in DARRTS dated 12/11/2019 for details).

Participants in these studies were allowed to have an optional second dose of ubrogepant at least two hours after the initial dose or rescue medication if required. However, efficacy analysis is limited to the initial dose only. The patients who elected to have the optional second dose of ubrogepant contributed to the safety information that supported the proposed maximum daily dose of 200 mg.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, dose optimization is required for subjects with severe hepatic impairment (Child-Pugh C) and severe renal impairment (creatinine clearance 15-30 mL/min). no dose adjustments are needed based on age, body weight, sex or race.

Hepatic Impairment:

The applicant conducted a dedicated Phase I study to evaluate the effect of hepatic impairment on the pharmacokinetics of ubrogepant after a single oral dose of 100 mg in healthy subjects with normal hepatic function (N=8) and in patients with mild (N=8), moderate (N=8) or severe (N=4)-hepatic function impairment (Study UBR-PK-01). Thorough PK blood samples were collected up to 48 hours post dose after dosing on Day 1.

Participants with mild hepatic impairment had 4% higher C_{max} and 6% higher AUC when compared to participants with normal hepatic function. The increase in C_{max} and AUC was higher in participants with moderate hepatic impairment, with a 25% higher C_{max} and 52% higher AUC. As compared to participants with normal hepatic function, those with severe hepatic impairment showed a significantly higher C_{max} and AUC of 40% and 115%, respectively. No significant difference in protein binding was observed across the different hepatic impairment groups. No dose adjustments are required for mild or moderate hepatic impairment. However, due to a two-fold increase in ubrogepant systemic exposure in severe hepatic impairment, such patients should be advised to use only 50 mg ubrogepant and if required, a second 50 mg dose is allowed 2 hours after initial dosing.

Renal Impairment:

The renal route elimination is a minor excretion pathway for ubrogepant (<10%). A clinical pharmacology study to evaluate the impact of renal impairment on the pharmacokinetics of ubrogepant was not conducted. Instead, a population PK approach (Report UBR-MS-01) was used

to assess the impact of renal impairment on the exposure of ubrogepant. About 265 patients with mild renal impairment and 18 patients with moderate renal impairment were included in this analysis. Renal function, as measured by creatinine clearance estimated using the Cockcroft-Gault (C-G) equation did not have a statistically significant effect on the clearance (CL/F) for patients with mild and moderate renal impairment. Based on that no dose adjustment is proposed for patients with mild and moderate renal impairment (CLcr 30-89 mL/min).

Patients with severe renal impairment or ESRD (CLcr <15 mL/min) were not included in any of the studies with ubrogepant. As a cautionary measure based on ADME information, we recommend the use of only 50 mg dose of ubrogepant in subjects with severe renal impairment (CLcr 15-29 mL/min). If required, an optional 50 mg second dose is allowed two hours after the initial dose in these subjects. Avoid use in patients with ESRD (CLcr <15 mL/min).

Race:

Study 3110-101-002 evaluated the effect of race on ubrogepant PK in healthy adult Japanese and Caucasian subjects. A single dose of 25 mg, 50 mg or 100 mg of ubrogepant was administered under fasting conditions in healthy, male and female, Japanese and Caucasian participants. The ratios of geometric means [90% CI] for ubrogepant Cmax and AUC0-inf for Japanese versus Caucasian were 1.01 [0.68, 1.49] and 0.79 [0.56, 1.11], respectively. Race is not considered as a significant covariate for ubrogepant exposure, and no dose adjustment is needed.

Sex and Age:

Study MK-1602 P003 evaluated the effect of age and sex on the pharmacokinetics, safety and tolerability of ubrogepant in healthy elderly male and elderly female subjects. A total of 16 subjects, divided by sex into 2 panels of 8 subjects each received a single oral dose of ubrogepant 40 mg (n = 6 per panel) or matching placebo (n = 2/panel) in a randomized fashion.

The systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) values in elderly males was slightly higher on average, than those in elderly female subjects. The geometric mean ratio (elderly female/ elderly male) was 0.83 for both $AUC_{0\text{-}inf}$ and C_{max} and 90% CI were (0.62-1.11) and (0.6-1.15) for AUC and C_{max} respectively. Overall, PK characteristics of ubrogepant are similar in elderly men and women. In assessment of age, the $AUC_{0\text{-}inf}$ of ubrogepant following a single oral dose of 40 mg in elderly participants appeared to be slightly higher (GMR of 1.28 and 90 CI [1.0-1.6]) compared to that in young participants in study MK-1602 P002, while Cmax appeared to be similar (GMR of 1.01 and 90% CI [0.76-1.34]).

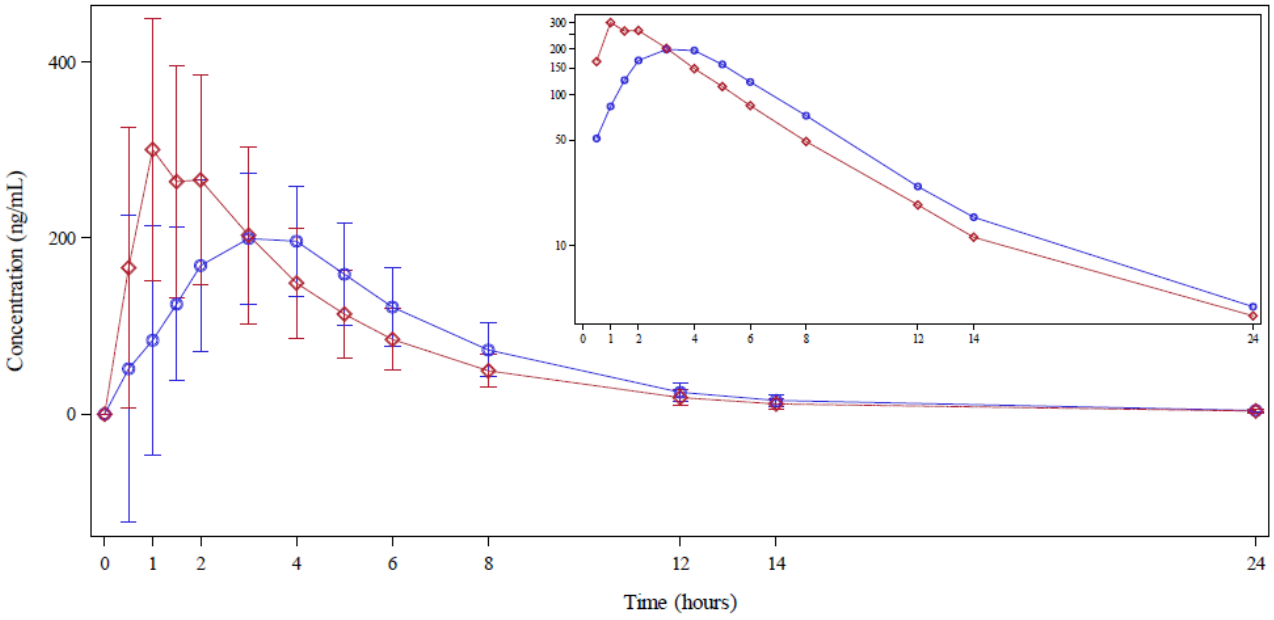
Additional evaluation of the effect of intrinsic factors was conducted as part of the population PK analysis. Population PK analysis concluded that age, weight, and sex are not expected to significantly affect the exposure of ubrogepant. The reported differences in exposure across these intrinsic factors are minimal and are not expected to be significant considering the safety and efficacy for the doses tested in efficacy trials.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food effect:

Co-administration of ubrogepant with a standard high-fat meal delayed the time to maximum ubrogepant plasma concentrations (T_{max}) by 2 hours and resulted in a 22% reduction in C_{max} with no change in ubrogepant AUC (Study 3110-103-002)Figure 4. The mean plasma ubrogepant concentration - time profiles in the fasted and fed state are shown in Figure 3.

Figure 3 Mean (±SD) plasma concentration (ng/mL)-time (hours) profiles of ubrogepant in the fasted state (red lines) and fed state (blue lines).



Source: Figure 14.2.2.1 & 14.2.2.2, Page 131 of 431 ISR 3110-103-002.

In Phase III studies ubrogepant was administered without regard to food. Patients were instructed to document if the drug was administered on fed state (defined high fat/high calorie meal within 2 hours of investigational product) or fasted state. About 10-13% of the patients reported taking high fat/high calorie food within 2 hours of taking ubrogepant on the day of migraine attack.

The subgroup analyses of pain freedom at 2 hours and absence of most bothersome migraine-associate symptom at 2 hours by dose in Studies UBR-MD-01 and UBR-MD-02 are shown below (Table 3, Table 4, Table 5 and Table 6). There appeared to be a higher placebo response in patients who had high fat/high calorie food in Study UBR-MD-02. Per sponsor' analysis, the treatment-by-subgroup interaction was not significant in Study UBR-MD-01 (p = 0.2730), and in Study UBR-MD-02 (p = 0.3195). However, due to the availability of efficacy data from only 10-13% of the patients who took high fat/high calorie food within 2 hours of taking ubrogepant, no meaningful conclusion regarding the effect of food intake on efficacy can be derived. As noted in

previous sections, the Phase III studies were conducted without regard to food. Considering the overall efficacy results from these studies the review team recommends administering ubrogepant without regard to food for the treatment of acute migraine.

Table 3. Subgroup Analysis: Pain Freedom at 2 Hours After Initial Dose by Food Intake, Modified Intent-to-Treat Population (Study UBR-MD-01)

	Placebo (N=456)	**50 mg (N=423)**	**100 mg (N=448)**
Participants Who Took High Fat/High Calorie Food			
Responder, n (%)	9 (13.4)	15 (28.8)	8 (17.4)
Non-responder, n (%)	58 (86.6)	37 (71.2)	38 (82.6)
Participants Who Did Not Take High Fat/High Calorie Food			
Responder, n (%)	45 (11.6)	66 (17.8)	86 (21.5)
Non-responder, n (%)	344 (88.4)	304 (82.2)	314 (78.5)

Source: Table 2-1.1.8 Page 13 of 58 in appendix-tables.pdf (ISE; 5.3.5.3)

Table 4. Absence of Most Bothersome Migraine-Associated Symptom at 2 Hours After Initial Dose by Food Intake Modified Intent-to-Treat Population (Study UBR-MD-01)

	Placebo (N=456)	**50 mg (N=423)**	**100 mg (N=448)**
Participants Who Took High Fat/High Calorie Food			
Responder, n (%)	18 (26.9)	21 (41.2)	14 (30.4)
Non-responder, n (%)	49 (73.1)	30 (58.8)	32 (69.6)
Participants Who Did Not Take High Fat/High Calorie Food			
Responder, n (%)	108 (27.9)	140 (38.0)	154 (38.5)
Non-responder, n (%)	279 (72.1)	228 (62.0)	246 (61.5)

Source: Table 2-1.1.9 Page 38 of 58 in appendix-tables.pdf (ISE; 5.3.5.3)

Table 5. Subgroup Analysis: Pain Freedom at 2 Hours After Initial Dose by Food Intake Modified Intent-to-Treat Population (Study UBR-MD-02)

	Placebo (N=456)	**50 mg (N=423)**	**100 mg (N=448)**
Participants Who Took High Fat/High Calorie Food			
Responder, n (%)	13 (23.2)	14 (24.6)	14 (20.3)
Non-responder, n (%)	43 (76.8)	43 (75.4)	55 (79.7)
Participants Who Did Not Take High Fat/High Calorie Food			
Responder, n (%)	52 (13.1)	76 (20.1)	87 (22.0)
Non-responder, n (%)	345 (86.9)	302 (79.9)	308 (78.0)

Source: Table 2-1.2.8 Page 21 of 58 in appendix-tables.pdf (ISE; 5.3.5.3)

Table 6. Absence of Most Bothersome Migraine-Associated Symptom at 2 Hours After Initial Dose by Food Intake Modified Intent-to-Treat Population (Study UBR-MD-02)

	Placebo (N=456)	**50 mg (N=423)**	**100 mg (N=448)**
Participants Who Took High Fat/High Calorie Food			
Responder, n (%)	15 (26.8)	19 (33.3)	29 (42.0)
Non-responder, n (%)	41 (73.2)	38 (66.7)	40 (58.0)
Participants Who Did Not Take High Fat/High Calorie Food			
Responder, n (%)	109 (27.5)	129 (34.2)	151 (38.3)
Non-responder, n (%)	288 (72.5)	248 (65.8)	243 (61.7)

Source: Table 2-2.2.9 Page 47 of 58 in appendix-tables.pdf (ISE; 5.3.5.3)

Drug-Drug Interactions:

CYP3A4 modulators:

Clinical drug interaction studies were conducted to assess the impact of CYP3A4 modulators on the PK of ubrogepant (Table 7). Study UBR-PK-09 evaluated the effect of 600 mg rifampin once daily (induction of CYP3A4 and P-gp) on a single 100 mg dose of ubrogepant. Study P018 evaluated the effect of multiple doses of 240 mg once daily verapamil and 400 mg once daily ketoconazole (moderate and strong CYP3A4 inhibitors respectively) on the single-dose PK of 20 mg ubrogepant.

Co-administration of ubrogepant with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 9.7-fold increase in ubrogepant AUC_{inf} and a 5.3-fold increase in ubrogepant C_{max}. Ubrogepant should not be used with strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, etc.).

Moderate CYP3A4 inhibition with verapamil resulted in about 3.5-fold and 2.8-fold increase in AUC_{inf} and C_{max} of ubrogepant, respectively relative to ubrogepant administered alone. Patients concomitantly using moderate CYP3A4 inhibitors such as verapamil should be advised to use ubrogepant 50 mg and avoid a second dose within 24 hours. This proposal will limit the maximum daily dose of ubrogepant to 50 mg, which is 4 folds lower than the 200 mg maximal allowed daily dose for the general population. Thus, the proposed dose adjustment with moderate CYP3A4 inhibitors will match exposure from 200 mg total dose allowed in a day in the general population.

Table 7 Drug interactions with CYP3A4 modulators

CYP3A4 Modulator	PK Parameter	GMR	90% CI lower	90% CI upper
Verapamil (Moderate Inhibitor)	C_{max}	2.80	2.48	3.15
	AUC_{inf}	3.53	3.32	3.75
Ketoconazole (Strong Inhibitor)	C_{max}	5.32	4.19	6.76
	AUC_{inf}	9.65	7.27	12.81
Rifampin (Strong Inducer)	C_{max}	0.31	0.27	0.36
	AUC_{inf}	0.22	0.20	0.24

GMR: Geometric mean ratio, CI: Confidence interval
Source: Study MK-1602 P018 CSR, Study UBR-PK-09 CSR

No dedicated drug interaction study was conducted with weak CYP3A4 inhibitors. Weak inhibitors are defined as inhibitors causing up to 2-fold increase in exposure of probe sensitive substrates. Ubrogepant can be considered as a sensitive CYP3A4 substrate and the potential increase in ubrogepant exposure with weak CYP3A4 inhibitors can therefore be only up to 2-fold. Based on this, the review team recommends 50 mg dose of ubrogepant with concomitant weak CYP3A4 inhibitors. Optional second dose 2 hours after the initial dosing is allowed.

Co-administration of ubrogepant with rifampin, a strong CYP3A4 and P-gp inducer, resulted in about 78 % reduction in ubrogepant AUC_{inf} and 69 % reduction in C_{max} compared to administration of ubrogepant alone. Reduction in exposure to this extent seen with strong CYP3A4 inducers is expected to result in loss of efficacy for ubrogepant. Therefore, coadministration of ubrogepant with strong CYP3A4 inducers should be avoided.

Coadministration of ubrogepant with mild or moderate CYP3A4 inducers was not studied. Since ubrogepant can be considered as a sensitive CYP3A4 substrate (i.e., mainly eliminated by CYP3A4 metabolism and strong CYP3A4 inhibition resulted in about 10-fold increase in its exposure), drug interaction with weak or moderate inducers are expected to reduce ubrogepant exposure by 20-50% or 50-80% respectively. Since both 50 mg and 100 mg dose are considered safe and effective, we believe the high dose of 100 mg can be used if concomitant use of weak or moderate CYP3A4

inducers cannot be avoided. A second 100 mg dose is allowed 2 hours after the initial dose, if required.

Other Drug Interaction Studies:

Naproxen

Co-administration of 100 mg ubrogepant and 500 mg naproxen did not significantly affect the PK of either drugs relative to when they were administered alone in a single dose cross-over study in healthy adult subjects (Study 3110-102-002).

Oral contraceptive (OC)

The effect of 50 mg once daily ubrogepant for 14 days on a single dose of oral contraceptive (0.035 mg ethinyl estradiol/0.25 mg norgestimate) administered on Day 10 was tested in 22 post-menopausal or oophorectomized female subjects. The PK of ubrogepant was not affected by concomitant OC administration. However, the Cmax of ethinyl estradiol decreased by 26% when given with 50 mg dose of ubrogepant. The GMR for AUC of ethinyl estradiol and AUC and Cmax of norgestimate were within 80-125% (See Table below). The 26% reduction in Cmax for ethinyl estradiol was not considered clinically significant especially because its AUC was not significantly affected.

It should be noted that the clinical drug interaction study was conducted with 50 mg dose of ubrogepant and not with the highest 100 mg dose. CYP3A4-mediated metabolism is the major pathway of oxidative metabolism of oral contraceptives (i.e. norelgestromin and ethinyl estradiol). In-vitro induction studies with human hepatocytes was conducted and assessment based on mRNA fold of change (non-clinical reportPK002) concludes that ubrogepant is unlikely to be a significant CYP3A inducer at 100 mg dose level.

PH mediated interaction with Esomeprazole, a Proton Pump Inhibitor (PPI)

Study UBR-PK-10 evaluated the effect of multiple daily dose of esomeprazole magnesium (40 mg Nexium® 24HR capsules) on single-dose ubrogepant 10-0 mg in healthy adult participants. Ubrogepant AUC0-inf was 10% lower and Cmax was 23% lower when co-administered with esomeprazole magnesium as compared with ubrogepant administered alone. As a result, PH-mediated drug interaction due to proton pump inhibitor is unlikely and ubrogepant can be taken without regard to PPI administration.

In conclusion, no significant interactions are expected with oral contraceptives, acetaminophen, sumatriptan, naproxen. Results of all the drug interaction studies are presented in Table 8,Table 9

Table 8 Clinical drug interaction study results for ubrogepant as a victim

Perpetrator Drug	Ubrogepant PK Parameter	GMR	90 % CI
Naproxen 500 mg	C_{max}	0.94	0.85-1.04
	AUC_{inf}	1.05	1.00-1.11
Oral Contraceptive (OC)	C_{max}	0.97*	0.85-1.11
	AUC_{24h}	1.02*	0.96-1.08
Acetaminophen	C_{max}	1.42	1.29-1.57
	AUC_{inf}	1.43	1.36-1.51
Esomeprazole	C_{max}	0.77	0.67-0.89
	AUC_{inf}	0.9	0.83-0.98
Sumatriptan	C_{max}	0.76	0.70-0.85
	AUC_{inf}	1.05	1.00-1.11

*ubrogepant PK on Day 10 with OC/ ubrogepant PK on Day 1 given alone

Table 9 Clinical drug interaction study results with ubrogepant as a perpetrator

Victim Drug	PK Parameter of victim drug	GMR	90 % CI
Naproxen (500 mg)	C_{max}	0.87	0.83-0.92
	AUC_{inf}	1.01	0.99-1.04
Ethinyl estradiol (0.035 mg)*	C_{max}	0.74	0.69-0.79
	AUC_{inf}	0.97	0.93-1.01
Norelgestromin (0.25 mg)*	C_{max}	0.96	0.91-1.01
	AUC_{inf}	0.91	0.82-1.00
Sumatriptan	C_{max}	0.96	0.85-1.08
	AUC_{inf}	1	0.94-1.04
Acetaminophen	C_{max}	0.76	0.66-0.87
	AUC_{inf}	0.93	0.91-1.04

*PK of OC alone/PK of OC given on Day 10 with daily 50 mg ubrogepant for 14 days

Source: Tables generated by FDA reviewer from data sets with DDI individual study reports listed in Table1

In Vitro Studies:

In vitro studies showed that ubrogepant is a substrate of hepatic uptake transporters OATP1B1 and OATP1B3. Review of these in vitro uptake studies in OATPB1/B3 transfected cells showed that transfected cells had only 2-fold higher uptake when compared to mock cells. This suggests that ubrogepant is a weak substrate of OATPB1/B3 transporters and a significant clinical drug interaction with OATPB1/B3 inhibitors and ubrogepant is unlikely.

Ubrogepant is also a substrate of efflux transporters P-gp and BCRP and use of inhibitors of BCRP or P-gp transporters can increase the exposure of ubrogepant. No clinical drug interaction studies were conducted with BCRP or P-gp only inhibitors. The review team proposed the use of 50 mg dose of ubrogepant with concomitant BCRP and/or P-gp only inhibitors. This is based on conservative predictions of the maximum possible drug interaction as explained in Section 2.2.2.

Additional in-vitro studies showed that ubrogepant is not anticipated to be a perpetrator of drug interactions through CYP450s, MAO-A, or UGT1A1 inhibition and is not a time-dependent inhibitor of CYP3A4. Following incubations of ubrogepant (0.1 – 20 µM) with cryopreserved human hepatocytes it was found that ubrogepant is not an inducer of CYP3A4 or CYP1A2 or CYP2B6 in human hepatocyte incubations at clinically relevant concentrations.

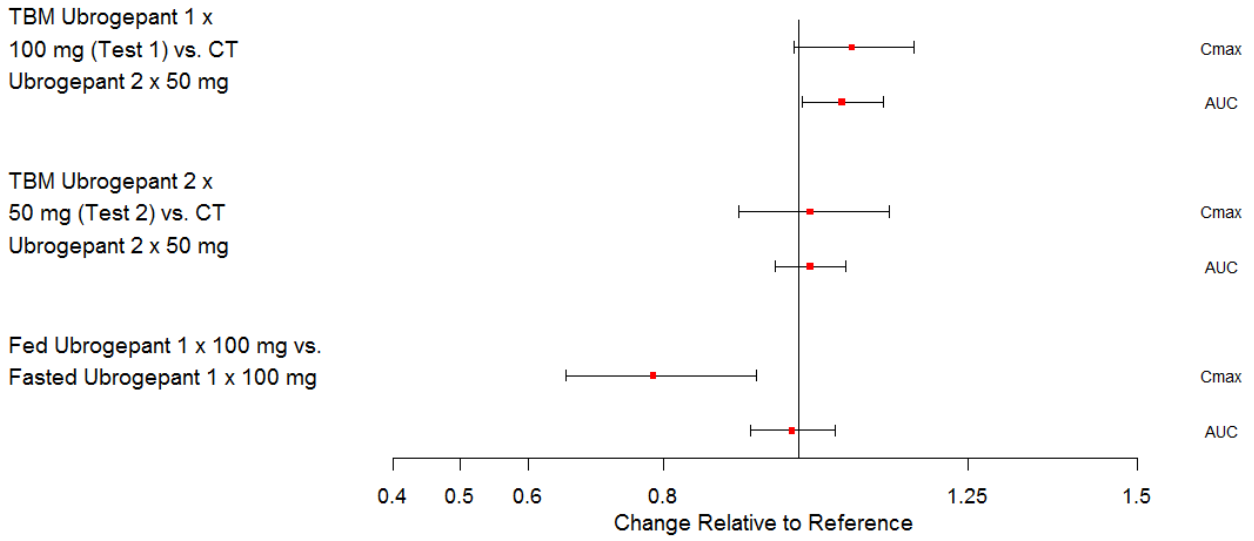
3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

PK bridging of the clinical trial formulation to the to-be-marketed formulation was evaluated in Study 3110-103-002. This study was a Phase 1, 2-Part, single-center, single-dose, open-label, randomized, bioequivalence study comparing two strengths of the to-be-marketed tablet formulation of ubrogepant versus the clinical trial tablet formulation and the effect of food on the to-be-marketed tablet formulation in healthy adult participants.

Part A of this study evaluated the bioequivalence of the 100 mg and 50 mg strengths of the to-be-marketed (TBM) tablets against 50 mg clinical trial (CT) tablets. Part B of the study was a food effect PK study evaluating the effect of a standard high-fat breakfast on the bioavailability of 100 mg TBM tablet. Results of this study established bioequivalence between the clinical trial formulation and the to be marketed formulation. Results of this study is presented in Figure 4.

A consult for site inspection for the pivotal PK bridging study 3110-103-002 was sent to the Office of Study Integrity and Surveillance (OSIS). OSIS recommended accepting data without an on-site inspection because this site was recently inspected and the outcome from the inspection was classified as No Action Indicated (NAI).

Figure 4. Comparison of TBM vs. CT formulations and food effect of the TBM formulation



Source: Figure generated by FDA reviewer from data sets submitted with report for study 3110-103-002.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

PK analysis conducted and included in this submission used validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) assays for the quantification of ubrogepant. All sample analysis was conducted in accordance with FDA Guidance for Industry, Bioanalytical Method Validation (May 2018) and approved Standard Operating Procedures effective at each site. Sample pre-treatment involved the protein precipitation extraction of Ubrogepant from 0.100 mL of human plasma and MK-1602-D3 was used as the internal standard (IS). The compounds were identified and quantified using reversed-phase HPLC with MS/MS detection over a theoretical concentration range of 1 ng/mL to 1000 ng/mL for ubrogepant.

Details of the method performance characteristics, including selectivity, lower limit of quantitation, precision, accuracy, extraction recovery, dilution factor, matrix effects, in-process stability, and frozen stability for quantitation of ubrogepant are provided in Table 10.

Table 10, Summary of the bioanalytical method validation

Parameter	Value
Analyte	Ubrogepant
Internal standard (IS)	[D3]-MK-1602
Limit of quantitation (ng/mL)	1 ng/mL
Average recovery of drug (%)	94.0 – 96.5%
Average recovery of IS (%)	102.7%
Standard curve concentrations (pg/mL) and linearity r^2	Standards: 1, 2, 5, 10, 20, 50, 100, 300, 700, 850, 1000 ng/mL (r^2=0.99)
QC concentrations (ng/mL)	3, 500, 750 ng/mL
QC Intraday precision range (%)	2.4 – 2.8%
QC Intraday accuracy range (%)	96.6 – 100.0%
QC Interday precision range (%)	3.3 – 3.9%
QC Interday accuracy range (%)	101.2 – 102.6%
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24.1 hours

Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Ubrogepant: 144 days Internal Standard: 397 days
Processed stability (hrs) (equivalent to post-preparative stability)	97.3 hours
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days) **(equivalent to long-term stability of analyte in matrix)**	-20°C: 199 days -80°C: 199 days
Selectivity	No significant interference observed in 10 blank lots.

4.2 Clinical PK and/or PD Assessments

NA

4.3 Population PK Analyses

4.3.1. Sponsor's Population PK analysis:

A population pharmacokinetic (Pop-PK) model was developed to support dose adjustment justification as part of the ubrogepant new drug application (NDA). The applicant also performed exposure-response analyses using the Pop-PK approach. For this NDA, only the Pop-PK model was reviewed.

Objective:

The goal of this current analysis is to describe the PK of ubrogepant in adult healthy volunteers and migraine patients. This overall goal has been achieved through the following sub-objectives:

- To build a Pop-PK model in order to describe the plasma concentration of ubrogepant over time in adults.
- To assess the impact of intrinsic and extrinsic factors (e.g. body weight, age, formulation, food, race, liver impairment, creatinine clearance) on the PK of ubrogepant in adults.
- Evaluate the labeling statements based on Pop-PK analysis

Labeling statements in Section 12.3 of the proposed label based on population pharmacokinetic analyses:

Specific Populations

Patients with Renal Impairment:

(b) (4)

Other Specific Populations:

(b) (4)

Method:

Pop-PK model describing ubrogepant PK in healthy volunteers and migraine patients after single or multiple dose administration of ubrogepant formulations was developed using NONMEM (Version 7.3 or higher).

Table 11Model development was carried out using first order conditional estimation with interaction (FOCE-I). In a first step, the structural model was built and a flexible transit compartment absorption model (TCAM) was used to describe absorption. Various models for inter-individual variability and residual variability were investigated to obtain a stable model. As a second step, the included covariate relationships were re-examined using the Phase 1 data-set and the need for inclusion of additional covariates (i.e., food intake, formulation, hepatic impairment status and race) was evaluated. It should be noted that log-transformed concentrations were used in the final model.

Once the structural model had been established, the PK data obtained in the Phase 2 and 3 studies were included. The inter-individual variability (IIV) and residual variability models were further updated to account for differences in the ubrogepant PK in the Phase 1 versus Phase 2 and 3 studies. Once the structural model was identified, the predictive value of individual patient characteristics was assessed using a covariate search.

During model development, a difference in objective function value (OFV), ΔOFV of 6.63 was used between two nested models differing in one parameter (corresponding to a nominal $P < 0.01$).

For the stepwise covariate modeling (SCM), a difference in OFV, ΔOFV of 6.63 was used for an effect to be included in the model during forward inclusion and ΔOFV of 10.8 (corresponding to a nominal $P < 0.001$) for retention of an effect during backward elimination. The final model was determined on the basis of maximized likelihood (lowest stable OFV).

Table 11 summarizes the main design aspects of the studies that were included in the analyses. A total of 17,187 PK observations from 2,287 subjects were included in model development. Out of these, 6,782 PK observations from 1,811 subjects came from the Phase 3 studies. In Phase 3 studies, sparse PK samples were collected

In Phase 3 a PK sub-study with serial PK samples of ubrogepant was conducted in visit 3 in 1216 patients. Six blood samples were collected from each patient (predose; 0.5, 1, 2, and 4 hours post dose; and at any time between 5 and 12 hours post dose. In addition, For the subset of patients who consented to participate in the PK sub-study, 2 PK samples were collected by the patients after treating a qualifying migraine (at 2 hours post-dose and 4 to 12 hours post-dose).

Model development was carried out using first order conditional estimation with interaction (FOCE-I). In a first step, the structural model was built and a flexible transit compartment absorption model (TCAM) was used to describe absorption. Various models for inter-individual variability and residual variability were investigated to obtain a stable model. As a second step, the included covariate relationships were re-examined using the Phase 1 data-set and the need for inclusion of additional covariates (i.e., food intake, formulation, hepatic impairment status and race) was evaluated. It should be noted that log-transformed concentrations were used in the final model.

Once the structural model had been established, the PK data obtained in the Phase 2 and 3 studies were included. The inter-individual variability (IIV) and residual variability models were further updated to account for differences in the ubrogepant PK in the Phase 1 versus Phase 2 and 3 studies. Once the structural model was identified, the predictive value of individual patient characteristics was assessed using a covariate search.

During model development, a difference in objective function value (OFV), ΔOFV of 6.63 was used between two nested models differing in one parameter (corresponding to a nominal $P < 0.01$).

For the stepwise covariate modeling (SCM), a difference in OFV, ΔOFV of 6.63 was used for an effect to be included in the model during forward inclusion and ΔOFV of 10.8 (corresponding to a nominal $P < 0.001$) for retention of an effect during backward elimination. The final model was determined on the basis of maximized likelihood (lowest stable OFV).

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Table 11: Summary of the characteristics of the studies used for Pop-PK analyses

Phase	Study ID	Study Design	NONMEM Dataset Created by	N Subjects Providing Data	PK Data	PD Data
1	P002	HV,SD and MD PK, S&T	(b) (4)	34	x	
1	P003	HV, SD PK in elderly 65-80 y S&T		12	x	
1	P004	HV, 28-day MD in HV 18-50 y, S&T		22	x	
1	P005	MD DDI with Oral Contraceptives in Postmenopausal/Oophorectomized Healthy Females		22	x	
1	P010	Biocomparison study in HV 18-50 y		15	x	
1	UBR-PK-02	TQT Study		72	x	
1	3110-101-002	SD PK biocomparison		48	x	
1	UBR-PK-01	Hepatic Impairment		32	x	
1	3110-103-002	HV, Pivotal BE Study		30	x	
1	UBR-PK-05	DDI Sumatriptan		30	x	
1	3110-105-002	Placebo-controlled Safety Study		500	x	
2	P006	Ph2b popPK & Efficacy in Patients w Acute Migraine 18-65 y & efficacy		630		x
2	P007	Ph2b popPK & Efficacy in Patients w Acute Migraine 18-65 y		163	x	x
3	UBR-MD-01	Safety, Tolerability and Efficacy study in Acute Migraine		~ 1,650	x	x
3	UBR-MD-02	Safety, Tolerability and Efficacy study in Acute Migraine		~ 1,650	x	x

S&T&E = safety, tolerability and efficacy. DDI = drug-drug-interaction, SD = single dose, MD = multiple dose, HV = healthy volunteers

Source: UBR-MS01 CSR, Page 23/284, Table1

Model Diagnostics and Qualification

Graphical assessment of goodness of fit, diagnostic plots of observed data vs. population prediction (PRED) and individual prediction (IPRED) were examined for adequate fit. Plots of conditional weighted residual (CWRES) versus PRED and versus time. In addition, visual predictive check (VPC) was performed using VPC tool in PSN. The observed data was overlaid with median and 2.5th and 97.5th percentiles of the observed data. The 95% CIs around the corresponding percentiles for the simulated data was included. The percentiles of the observed data should preferably be included in the 95% CI of the corresponding percentiles of the simulated data. The final model was determined based on successful numerical convergence, acceptable parameter precision (relative standard errors <50%), low condition number (<1000) and biological plausibility of parameter values.

Results:

Subjects' baseline continuous and categorical covariates are presented in Table 12 and Table 13 and Table 14

Table 12 Summary of baseline continuous covariates for subjects included in pop-PK analysis

Study	Phase I	P007	UBR-MD-01	UBR-MD-02	All
	(N=346)	(N=130)	(N=883)	(N=928)	(N=2287)
Age (yr)					
Mean (SD)	37.7 (13)	37.1 (12)	40.4 (12)	41.4 (12)	40.2 (12)
Median (range)	35 (18 - 73)	35 (18 - 65)	39 (18 - 75)	41 (18 - 75)	39 (18 - 75)
Weight (kg)					
Mean (SD)	75.5 (13)	79.1 (22)	83.5 (23)	82.1 (21)	81.5 (21)
Median (range)	75.1 (48.7 - 123)	75.4 (46 - 168)	79.4 (40.4 - 219)	78.8 (40.8 - 176)	78 (40.4 - 219)
Gender					
Female	122 (35.3%)	109 (83.8%)	775 (87.8%)	842 (90.7%)	1848 (80.8%)
Male	224 (64.7%)	21 (16.2%)	108 (12.2%)	86 (9.3%)	439 (19.2%)
Race					
Asian	32 (9.2%)	3 (2.3%)	13 (1.5%)	7 (0.8%)	55 (2.4%)
Black	109 (31.5%)	20 (15.4%)	127 (14.4%)	138 (14.9%)	394 (17.2%)
Caucasian	186 (53.8%)	82 (63.1%)	724 (82.0%)	771 (83.1%)	1763 (77.1%)
Multiple	2 (0.6%)		8 (0.9%)	7 (0.8%)	17 (0.7%)
Native American	11 (3.2%)	23 (17.7%)	7 (0.8%)	3 (0.3%)	44 (1.9%)
Other	6 (1.7%)	2 (1.5%)			8 (0.3%)
Pacific Islander			4 (0.5%)	2 (0.2%)	6 (0.3%)
Height (cm)					
Mean (SD)	171 (9.4)	166 (8)	166 (8.3)	165 (8.4)	166 (8.7)
Median (range)	170 (147 - 201)	165 (147 - 188)	165 (141 - 198)	165 (136 - 203)	165 (136 - 203)
CL_{cr} (mL/min)					
Mean (SD)	120 (34)	127 (40)	144 (56)	144 (53)	139 (52)
Median (range)	114 (48.9 - 263)	121 (64 - 282)	133 (35.5 - 475)	132 (48.5 - 416)	127 (35.5 - 475)

Source: UBR-MS01 CSR, Page 30/284, Table 4

Table 13 Summary of baseline categorical covariates for subjects included in the PK analysis

Study	Phase 1	P007	UBR-MD-01	UBR-MD-02	All
Hepatic Impairment					
Normal function	326 (94.2%)	130 (100.0%)	882 (99.9%)	928 (100.0%)	2266 (99.1%)
Mild impairment	8 (2.3%)		1 (0.1%)		9 (0.4%)
Moderate impairment	8 (2.3%)				8 (0.3%)
Severe impairment	4 (1.2%)				4 (0.2%)
Health					
Healthy Volunteer	326 (94.2%)				326 (14.3%)
Patient	20 (5.8%)	130 (100.0%)	883 (100.0%)	928 (100.0%)	1961 (85.7%)
Migraine					
No Migraine	346 (100.0%)		16 (1.8%)	16 (1.7%)	378 (16.5%)
Migraine Attack		130 (100.0%)	867 (98.2%)	912 (98.3%)	1909 (83.5%)
Caffeine					
No Caffeine	346 (100.0%)	109 (83.8%)	883 (100.0%)	928 (100.0%)	2266 (99.1%)
Taking Caffeine		21 (16.2%)			21 (0.9%)
Fed Status					
Fasted	334 (96.5%)	53 (40.8%)	782 (88.6%)	799 (86.1%)	1968 (86.1%)
Small Snack		34 (26.2%)			34 (1.5%)
Light Meal	3 (0.9%)				3 (0.1%)
Small or Medium Meal		31 (23.8%)			31 (1.4%)
Large Meal		12 (9.2%)			12 (0.5%)
High Fat	9 (2.6%)		101 (11.4%)	129 (13.9%)	239 (10.5%)

Source: UBR-MS01 CSR, Page 30/284, Table 4

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Table 14 Summary of patients taking selected concomitant medication by study

Study	UBR-MD-01	UBR-MD-02	All
	(N=883)	(N=928)	(N=1811)
Alprazolam			
Not taking	852 (96.5%)	894 (96.3%)	1746 (96.4%)
Taking	31 (3.5%)	34 (3.7%)	65 (3.6%)
Azithromycin			
Not taking	882 (99.9%)	927 (99.9%)	1809 (99.9%)
Taking	1 (0.1%)	1 (0.1%)	2 (0.1%)
Chlorzoxazone			
Not taking	883 (100.0%)	928 (100.0%)	1811 (100.0%)
Cimetidine			
Not taking	882 (99.9%)	928 (100.0%)	1810 (99.9%)
Taking	1 (0.1%)		1 (0.1%)
Fluvoxamine			
Not taking	882 (99.9%)	928 (100.0%)	1810 (99.9%)
Taking	1 (0.1%)		1 (0.1%)
Isoniazid			
Not taking	882 (99.9%)	928 (100.0%)	1810 (99.9%)
Taking	1 (0.1%)		1 (0.1%)
Ranitidine			
Not taking	865 (98.0%)	921 (99.2%)	1786 (98.6%)
Taking	18 (2.0%)	7 (0.8%)	25 (1.4%)

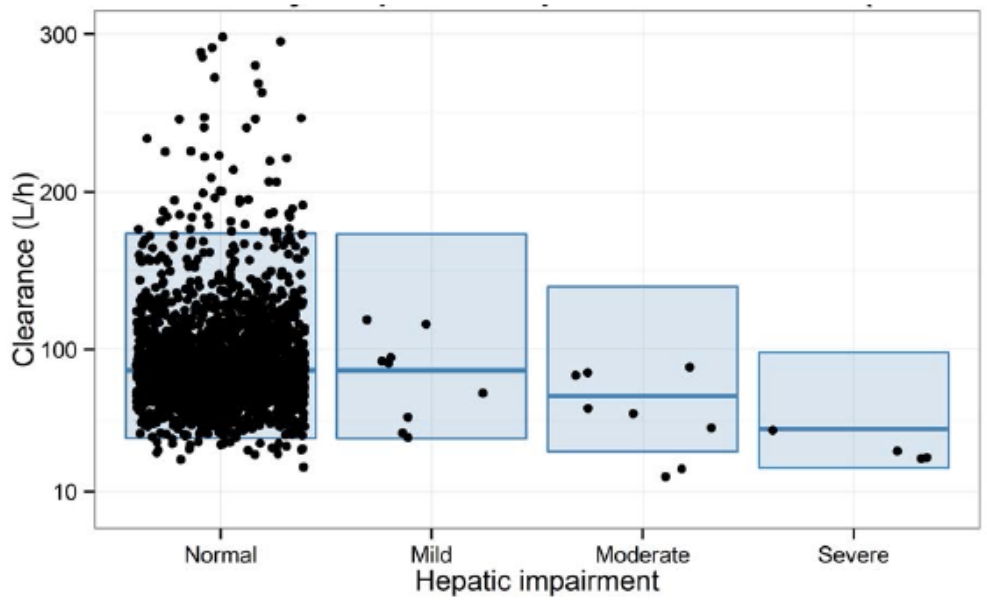
Source: UBR-MS01 CSR, Page 32/284, Table 5

The overall PK profile was best described by a two-compartment model with linear elimination from the central compartment (run320). A TCAM model was used to describe the ubrogepant absorption (see Figure 9 and Table 15). Residual variability was included as a log-additive error model (i.e. proportional error model in the normal domain).

Covariate Exploration

Hepatic function had a significant effect on CL/F; more so, when hepatic impairment was moderate or severe. CL/F was found to be the same for normal liver function and mildly hepatic impaired patients (CL/F = 94 L/h). CL/F decreased with increasing hepatic impairment, with CL/F estimated at 76.3 L/h for moderately impaired and 53.5 L/h for severely impaired patients. In this analysis, the patients with mild moderate and severe hepatic Figure 5 impairment were 8, 4 and 4 respectively Figure 5.

Figure 5 Effect of Hepatic Impairment on the Ubrogepant CL/F.



Dots: represent individual parameter estimates; **Shaded box area:** confines the 90% prediction interval of the predicted covariate effect relationship of the final model; **Horizontal line:** median of the 90% prediction interval

Source: UBR-MS01 CSR, Page 61/284, figure 19

Mild CYP3A4 inhibitors as concomitant medications were not formally tested given the fact that the data did not suggest a relationship with ubrogepant CL/F.

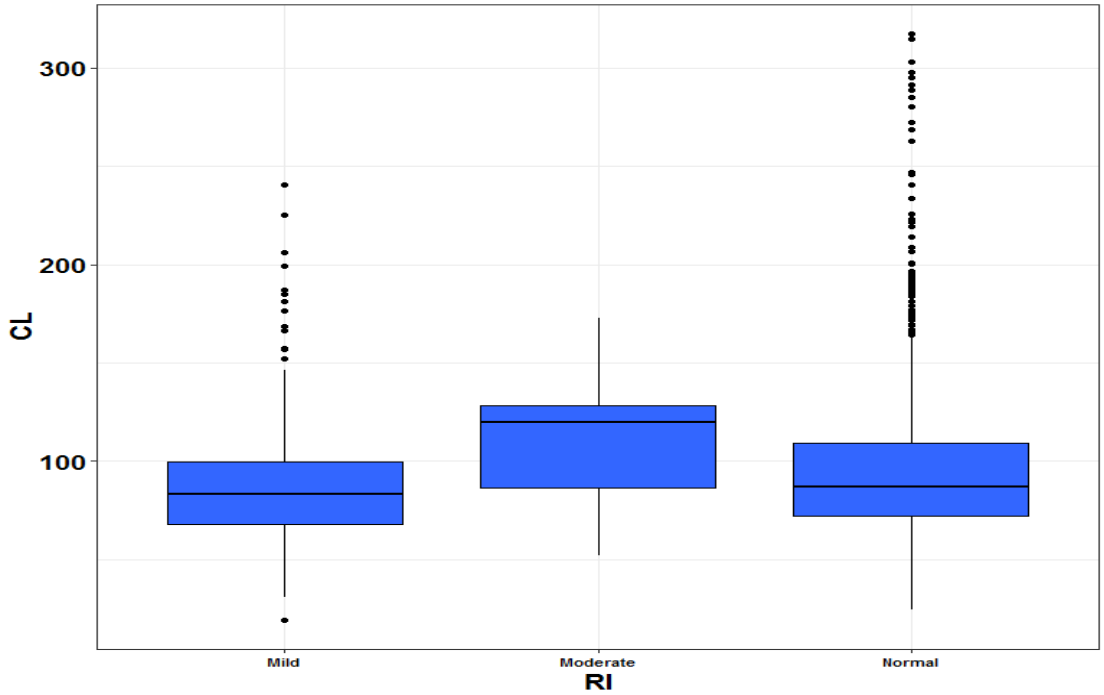
Reviewer comment:

This conclusion was not accepted by review team. This is because Phase III trials were a single attack trial and the timing of these week inhibitor administration relative to ubrogepant administration is not included in the analysis. (b) (4)

Covariate analysis suggested that renal impairment (characterized based on estimated creatinine clearance (Clcr) using the Cockcroft-Gault (C-G) equation) did not affect the exposure of ubrogepant. 18 patients with moderate renal impairment and 265 subjects with mild renal impairment were included in the analysis. CL/F was found to be similar for subjects with normal renal function when compared with patients with mild and moderate renal impairment. CL/F was

87 L/h, 87 and 93 L/h for subjects with normal, mild and moderate renal impairment respectively. The study did not enroll subjects with severe or end stage renal disease. Based on previous clinical pharmacology studies ubrogepant is eliminated through metabolism. Renal impairment is unlikely to affect clearance of ubrogepant Figure 6.

Figure 6 Effect of renal impairment on ubrogepant CL/F (L/h).



Source: FDA reviewer analysis

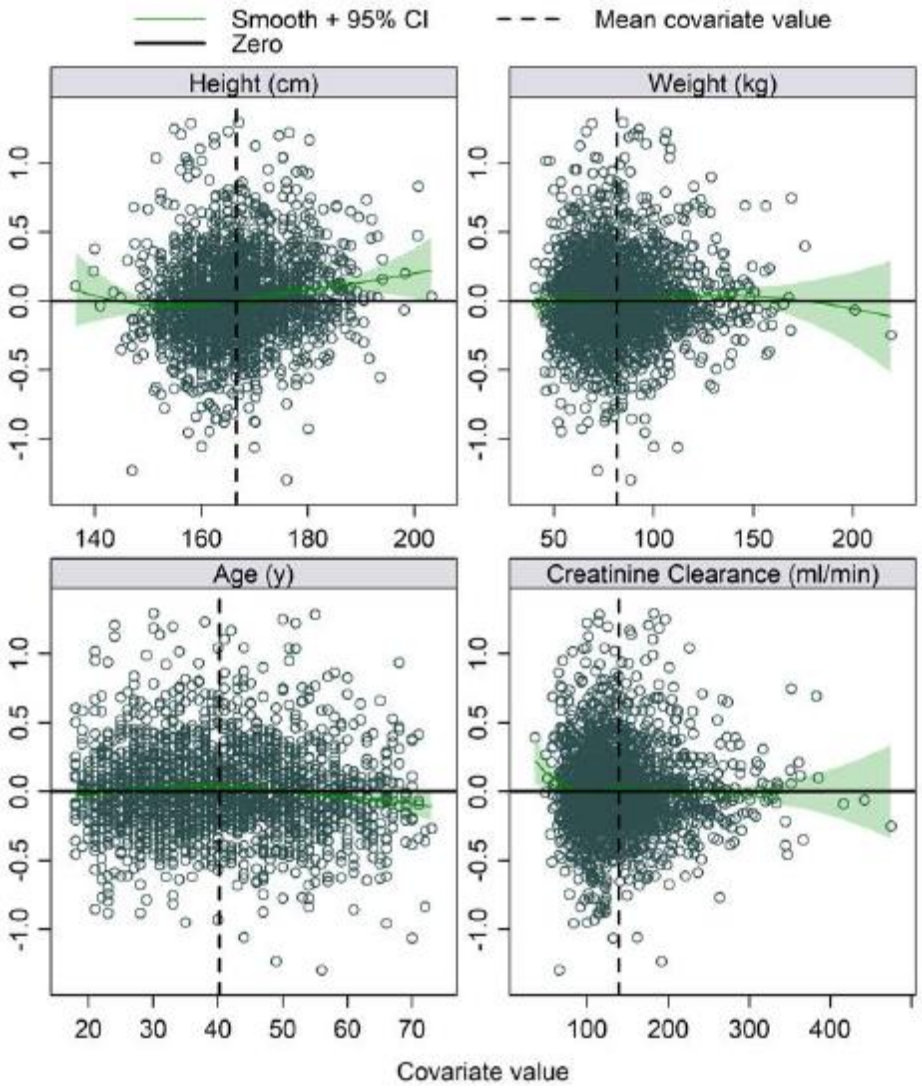
Weight was not found to have a significant impact on V1/F or CL/F. Therefore, the effect of WT on V1/F was not considered to be included in further model development. Distributions of ETAs versus continuous covariates show the absence of effect of these covariates on ubrogepant PK parameters CL/F (Figure 7) and V1/F (Figure 8).

Mild CYP3A4 inhibitors as concomitant medications were not formally tested given the fact that the data did not suggest a relationship with ubrogepant CL/F.

Reviewer comment:

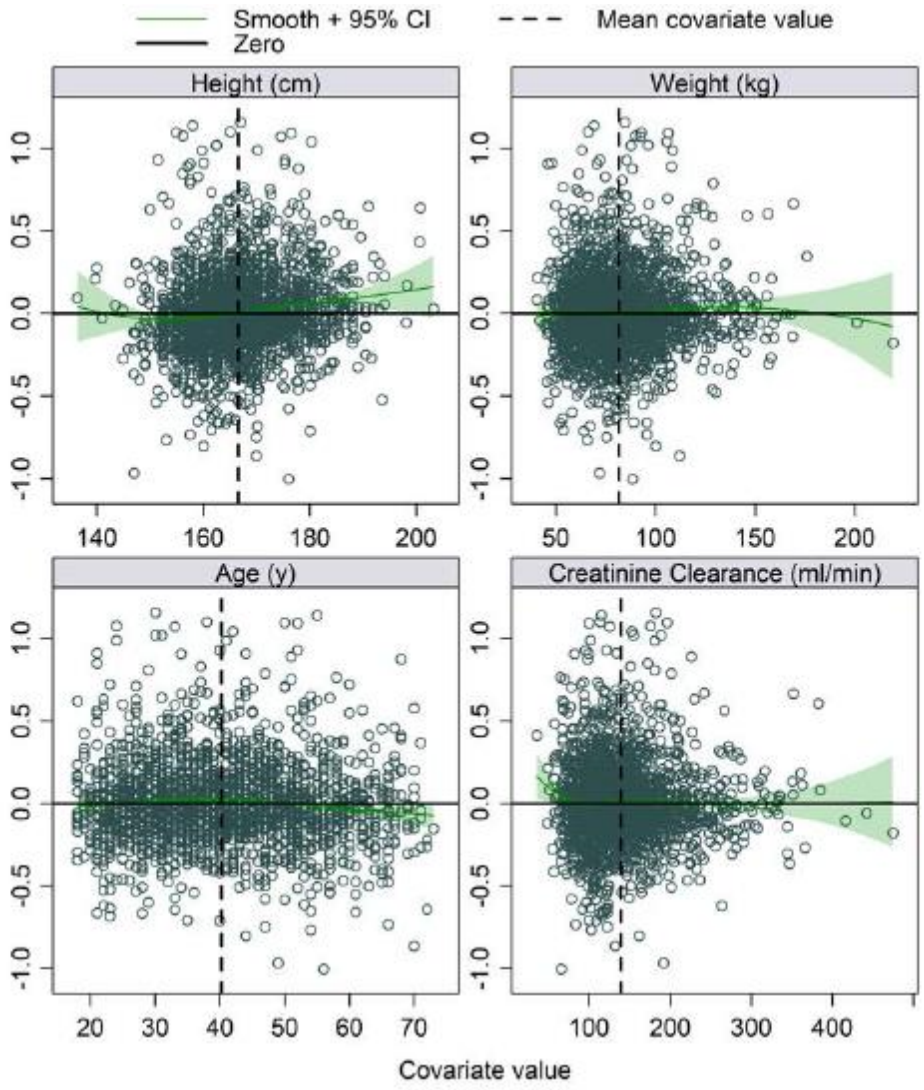
This conclusion was not accepted by review team. This is because Phase III trials were a single attack trial and the timing of these week inhibitor administration relative to ubrogepant administration is not recorded. (b) (4)

Figure 7: Distribution of ETA1 (CL/F) versus continuous covariates in the final model.



Source: UBR-MS01 CSR, Page 56/284, figure 13

Figure 8 Distribution of ETA2 (V1/F) versus continuous covariates - Final model

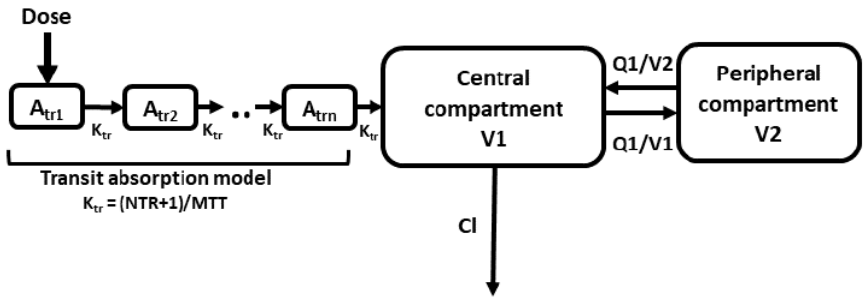


Source: UBR-MS01 CSR, Page 57/284, figure 14

Asians, were found to influence V1/F. However, this effect was insignificant. V1/F was also slightly influenced by gender. V1/F was found to be 16.6% lower in females and 6.5% lower in Japanese subjects.

Intake of a meal resulted in a slower absorption (2.2-fold longer MTT). With food, Cmax was estimated to be 22.6% lower while Tmax was estimated to be almost doubled (increase from 1.3h to 2.4h) and AUC0-24h decreased with 6.6%. This is similar to findings from dedicated food effect study. Finally, the there was no difference in the PK parameters of ubrogepant between healthy and migraine patients.

Figure 9 Model structure of final model



$\mathbf{A_{trn}}$: Amount in Transit Compartment n, $\mathbf{K_{tr}}$: Transit Compartment Rate, **NTR**: Number of Transit Compartments, **MTT**: Mean Transit Time, **Cl**: Clearance, **V1**: Central Volume of Distribution, **V2**: Peripheral Volume of Distribution, **Q1**: Intercompartmental Clearance.

Source: UBR-MS01 CSR, Page 49/284, figure 7

Table 15. Parameter estimates of the final full Pop-PK model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Apparent systemic clearance ($L \cdot h^{-1}$)	86.9	.....	(83.1 - 91)
θ_2	Apparent central volume of distribution (L)	350.	.....	(333 - 369)
θ_3	Intercompartmental clearance ($L \cdot h^{-1}$)	11.8	.....	(10.9 - 12.8)
θ_4	Apparent peripheral volume of distribution (L)	377.	.....	(316 - 451)
θ_5	Blood Plasma ratio	0.674	.....	(0.652 - 0.696)
θ_6	Number of transit compartments	2.16	.....	(2.12 - 2.21)
θ_7	Mean transit time (h)	0.667	.....	(0.634 - 0.702)
θ_8	Any meal on MTT	2.18	.....	(2.14 - 2.21)
θ_9	Any meal on F1	0.936	.....	(0.905 - 0.969)
θ_{10}	(b) (4)	0.667	.....	(0.648 - 0.687)
θ_{11}		1.18	.....	(1.14 - 1.21)
θ_{13}		1.15	.....	(1.12 - 1.19)
θ_{14}	Moderate hepatic impairment on CL/F	0.809	.....	(0.709 - 0.924)
θ_{15}	Severe hepatic impairment on CL/F	0.571	.....	(0.405 - 0.806)
θ_{16}	Asian on V1/F	0.935	.....	(0.846 - 1.03)
θ_{17}	Proportional error Phase 1	0.400	0.3	(0.398 - 0.402)
θ_{18}	Proportional error Phase 2 and 3	0.663	0.7	(0.655 - 0.672)
θ_{19}	Proportional error Phase 2 and 3 with migraine	1.54	1.1	(1.51 - 1.57)
θ_{20}	Box-Cox transformation V1/F	6.25	.....	(4.66 - 8.38)
θ_{21}	Sex effect on V1/F	0.834	.....	(0.805 - 0.865)
$\omega_{1.1}$	$\omega^2_{CL/F}$	0.176	5.4	(0.157 - 0.194)
$\omega_{2.1}$	$covariance\omega^2_{CL/F}\omega^2_{V1/F}$	0.136	5.9	(0.12 - 0.151)
$\omega_{2.2}$	$\omega^2_{V1/F}$	0.121	7.9	(0.102 - 0.14)
$\omega_{3.3}$	$\omega^2_{Q/F}$	0.237	14.1	(0.171 - 0.303)
$\omega_{4.4}$	$\omega^2_{V2/F}$	0.367	33	(0.13 - 0.604)
$\omega_{5.5}$	ω^2_{MTT}	0.705	4.1	(0.648 - 0.762)

Parameter values for the structural PopPK model. k_a: absorption rate. CL/F: apparent systemic clearance. V_1/F: apparent central volume of distribution. V_2/F: apparent peripheral volume of distribution. Q/F: apparent intercompartmental clearance. ω^2_X: variance of the IIV of parameter X, covariance $\omega^2_X\omega^2_Y$: covariance of the IIV of parameters X and Y, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

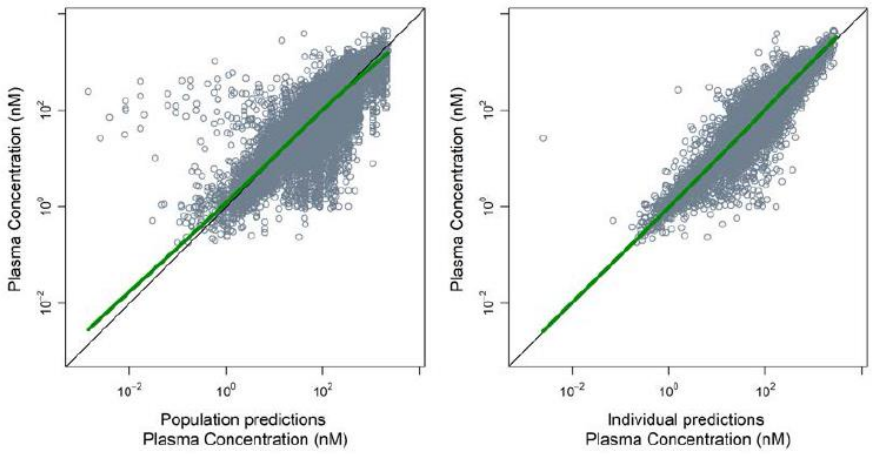
Source: UBR-MS01 CSR, Page 51/284, Table 13

Graphical Assessment of Goodness of Fit

The final model demonstrated appropriate agreement between predicted and observed data values (Figure 10). The CWRES are randomly scattered around the predicted range (Figure 11) and

across time Figure 12. Overall, the diagnostic plots of residuals indicated that there is no structural bias or substantial lack of fit in the final model.

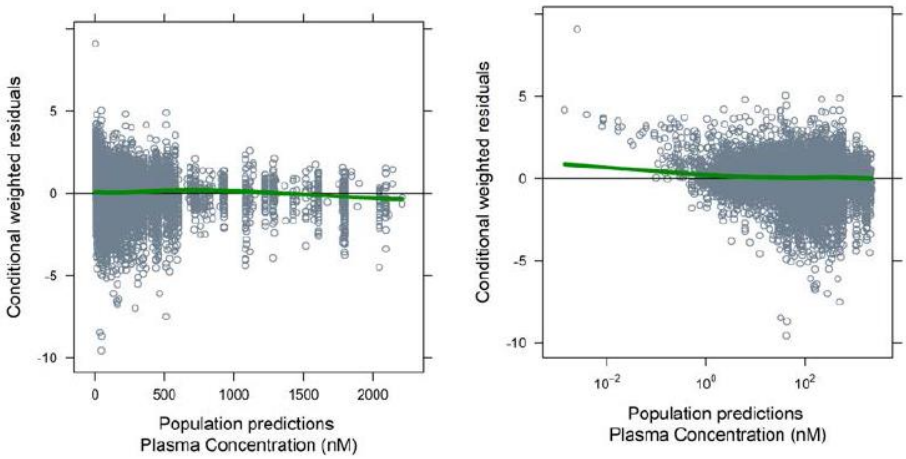
Figure 10 Observations (DV) versus population and individual predictions - Final model



Green line: Loess smooth **Black line:** Line of identity

Source: UBR-MS01 CSR, Page 53/284, figure 8

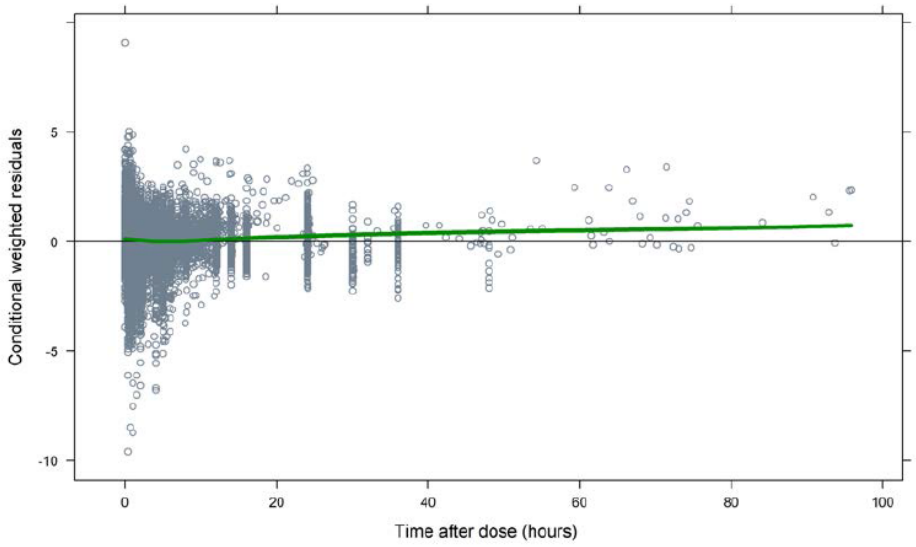
Figure 11 Conditional weighted residuals versus predictions - Final model



Green line: Loess smooth, left: Linear scale, right:Logarithmic x-axis

Source: UBR-MS01 CSR, Page 53/284, figure 9

Figure 12 Conditional weighted residuals versus time after dose - Final model



Source: UBR-MS01 CSR, Page 54/284, figure 10

Reviewer Comment:

The review team explored the outlier data in the upper left corner of the population predicted vs. observed concentration plot (DV vs. PRED). After additional analysis it was found that these data are coming from 66 subjects out of 2287 subjects (2.8%). Exploration of covariates and demographic of these subjects was conducted by the review team to identify any difference in covariate estimates between this group and the general population that may cause this trend, however no unique difference was observed for these subjects when compared to the general population. The mean and median values of continuous covariates are presented in Table 16*. Also, there are no unique distribution in race, sex as categorical covariate. In general, this small subset of data is unlikely to affect the final conclusions from this analysis.*

Table 16 Covariates of outlier data

	Mean	Median
Weight (kg)	82.3	82.9
Age (year)	42.8	42.5
CLcr (ml/min)	133.4	165
Height (cm)	165.6	170.2

Source: Reviewer Analysis

Conclusions

- Ubrogepant PK was well-characterized by a two-compartment PK model with linear elimination. A transit compartment model was used to describe the ubrogepant absorption after oral administration.

- Renal function (as measured by creatinine clearance) did not affect ubrogepant clearance. However only subjects with normal, mild (n=265) and moderate (n=18) renal impairment were enrolled in phase III studies. The effect of severe renal impairment or ESRD patients was not evaluated.
- Based on a screening performed with Phase 3 concomitant medications, co-medication of mild CYP3A4inhibitors (alprazolam, azithromycin, cimetidine, fluvoxamine, isoniazid and ranitidine) did not affect ubrogepant clearance. However, phase III trials were a single attack trials and the timing of these week inhibitor administration relative to ubrogepant administration is not included in the analysis. (b) (4)
- Subjects with moderate or severe hepatic impairment were found to have a 19.1% and 42.9% lower clearance. This is in alignment with results from dedicated hepatic impairment study.
- Weight was not found to have a significant impact on V1/F or CL/F .
- Asians and females were estimated to have a slightly higher Cmax as compared to other race categories and males, respectively, while Tmax (1.3h) and AUC0-24h remained unaffected. This effect was not significant and not clinically relevant.
- The impact of food on Cmax and AUC0-24h, as determined by population PK analysis, is consistent with the results from the phase 1 study 'Assessment of the Bioequivalence of To-Be-Marketed Tablets versus the Clinical Trial Tablets of Ubrogepant and food effect on the To Be-Marketed Tablets' (3110-103-002). Cmax was estimated to be 22.6% lower while typical Tmax was estimated to increase from 1.3h to 2.4h (slower absorption) with 6.6% decrease in AUC0-24h.

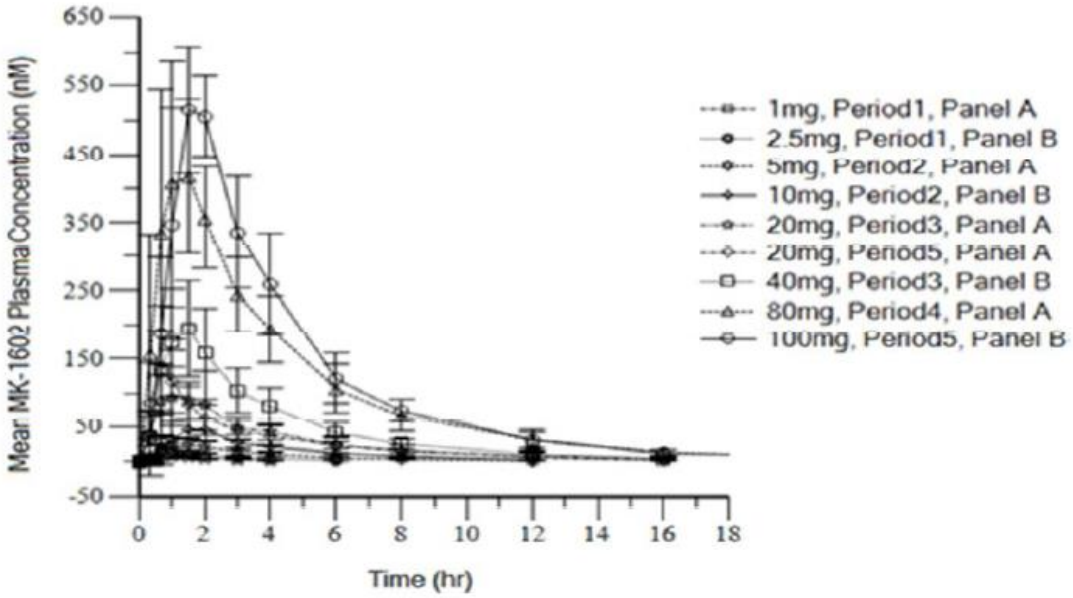
4.4 Summary of Individual Clinical Pharmacology and Efficacy Studies

Study/Report	Study Description
Disposition and metabolism Study	
P009	ADME Mass balance study. 50 mg single radiolabeled dose
Healthy Subject PK, PD, and Tolerability	
P001	Single ascending dose study. (1, 2.5, 5, 10, 20, 40, 80, 100 mg)
P002	SAD and MAD in healthy subjects (SD: 40, 100, 200, 400 mg, MAD: 100, 200, 400 QD x 10d)
P003	Elderly subject study: Single dose of 40mg in healthy volunteers age 65 – 80
3110-101-002	Race study: PK of Japanese vs Caucasian: single dose of 25, 50 and 100 mg
Hepatic safety in healthy subjects	
P004	Hepatic safety: Multiple dose study of 150 mg/day x 28 days in healthy
3110-105-002	Hepatic Safety Study: Multiple-dose, placebo-controlled, 8-week study Participants randomized to the ubrogepant arm received ubrogepant 100 mg on each of 2 consecutive days, followed by 2 consecutive days of placebo, alternating for a total of 8 weeks. Participants randomized to the placebo arm received 2 placebo tablets every day for a total of 8 weeks.
Bio-Pharm and PK Bridging	
3110-103-002	To-Be-Marketed BE & food effect study. 2 strengths of to-be-marketed tablet vs clinical trial tablet
MK-1602 P010	Formulation bridging study of 3 (b) (4) formulations and 1 (b) (4) tablet
Drug Interaction Studies	
P005	Oral Contraceptive drug interaction: Multiple dose of 50 mg ubrogepant with single dose norgestimate and ethinyl estradiol
P018	Drug interaction with Verapamil and Ketoconazole (CYP3A4 inhibitors): Multiple doses of verapamil and ketoconazole on single-dose PK of ubrogepant
UBR-PK-04	Acetaminophen: Single-dose acetaminophen (1000 mg) and ubrogepant (100 mg)
UBR-PK-09	Drug interaction with rifampin: Induction of CYP3A4 and P-gp x 5 days, single 100 mg dose of ubrogepant
UBR-PK-10	Drug interaction with Esomeprazole:Multiple dose of S-omeprazole 40 mg QD and single dose of (ubrogepant 100 mg)
UBR-PK-05	Drug interaction with sumatriptan: Single-dose sumatriptan (100 mg) and ubrogepant (100 mg)

3110-102-002	Drug interaction with Naproxen: Single-dose Naproxen (500 mg) and ubrogepant (100 mg)
Thorough QT Study	
UBR-PK-02	TQT study: Single dose study at therapeutic (100mg) and supra therapeutic (400mg) dose levels
Phase 2 placebo-controlled Studies	
MK-1602 P006	Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group single attack migraine study in adults (Placebo, 1mg, 10mg, 25mg, 50 mg, 100mg, N:640)
MK-1602 P007	Phase 2b, multicenter, randomized, double-blind, placebo controlled, parallel group single attack study in adults. This was 3 doses single attack study (Placebo, 1mg, 10mg, 25mg, 50 mg, 100mg, N:164). Dose 1: Taken at onset of migraine of moderate or severe intensity Dose 2: Taken the evening before Visit 2 Dose 3: Taken at Visit 2
Phase 3 Registration Studies	
UBR-MD-01	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group single attack migraine study in adults 18-75 years with a history of migraine with or without aura for ≥ 1 year (consistent with ICHD-3 beta criteria), had 2-8 migraine attacks of moderate-severe headache pain in each of the 3 months before screening. (Doses: 50 and 100 mg, N=1436)
UBR-MD-02	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group single attack migraine study in adults 18-75 years with a history of migraine with or without aura for ≥ 1 year (consistent with ICHD-3 beta criteria), had 2-8 migraine attacks of moderate-severe headache pain in each of the 3 months before screening. (Doses: 50 and 100 mg, N=1465)
UBR-MD-04	52-week, long-term, multi-dose safety, Phase 3, multicenter, randomized, open-label extension; adult participants with migraine with or without aura who completed Study UBR-MD-01 or Study UBR-MD-02. Randomization to the ubrogepant arms (50 and 100 mg) was blinded

4.4 PK Profiles of Ubrogepant from Selected Studies.

Figure 13 Arithmetic Mean (SD) Ubrogepant Plasma Concentration vs. Time Profiles Following Single Dose Administration of 1 to 100 mg of Ubrogepant in Fasted Healthy Subjects (n=6 /dose)



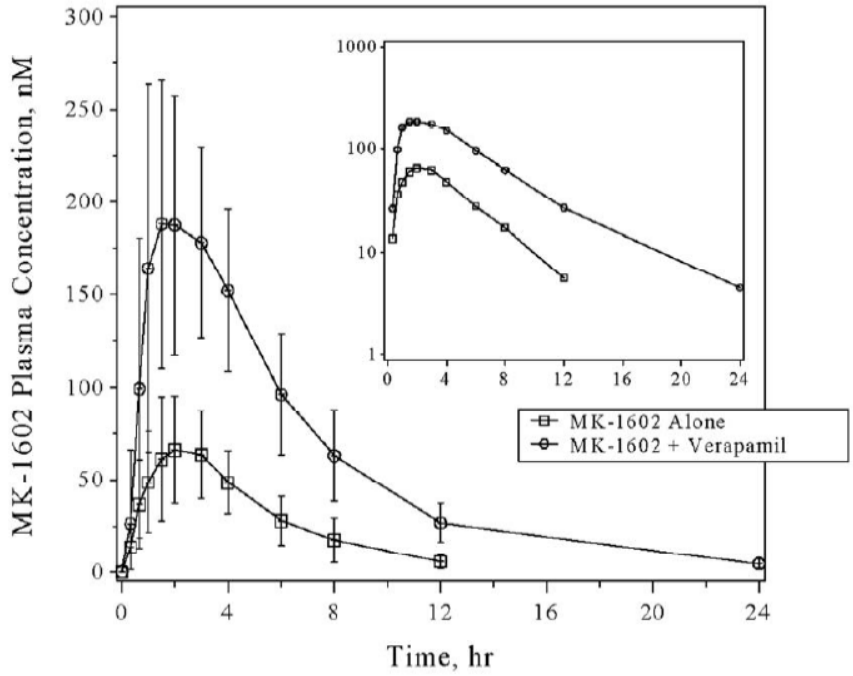
Source: Study MK-1602 P001 CSR, Figure 14.2-1, Module 5.3.3.1

Table 17 Arithmetic Mean ± SD Pharmacokinetic Parameter Values of Ubrogepant Following Administration of Single Oral Doses.

Dose (mg)	N	$AUC_{0-\infty}$ (ng•hr/mL)	AUC_{0-24hr} (ng•hr/mL)	C_{max} (ng/mL)	C_{2hr} (ng/mL)	T_{max} (hr)[a]	Apparent Terminal $t_{1/2}$ (hr)[b]
1	6	13.0 ± 2.7	10.4 ± 2.0	5.2 ± 1.1	2.5 ± 0.5	0.83 (0.33 – 1.50)	2.04 ± 0.69
2.5	6	26.3 ± 11.0	22.9 ± 10.3	9.5 ± 4.8	4.4 ± 1.6	0.83 (0.67 - 1.00)	2.42 ± 0.71
5	6	61.0 ± 20.0	57.7 ± 19.0	17.6 ± 7.0	11.5 ± 4.0	1.25 (0.67 - 2.00)	3.21 ± 0.66
10	6	113.8 ± 50.7	109.9 ± 51.4	29.2 ± 9.4	25.8 ± 9.3	1.50 (1.00 - 2.00)	3.15 ± 0.52
20 (Panel A, Period 3)	6	251.7 ± 85.7	245.7 ± 82.4	69.2 ± 20.9	46.9 ± 25.6	1.00 (0.67 - 2.00)	3.65 ± 0.89
20 (Panel A, Period 5)[c]	6	249.5 ± 107.2	245.7 ± 106.1	74.7 ± 29.5	35.4 ± 10.9	0.67 (0.67 – 1.50)	3.40 ± 0.78
40	6	435.3 ± 147.3	433.6 ± 145.6	116.5 ± 42.1	86.8 ± 36.3	1.50 (0.67 - 2.00)	3.10 ± 0.34
80	6	1104.7 ± 299.0	1071.7 ± 295.1	258.9 ± 54.7	195.7 ± 40.8	1.00 (0.67 – 2.00)	7.36 ± 3.94
100	6	1242.1 ± 252.3	1214.6 ± 245.7	299.5 ± 21.7	277.5 ± 32.0	1.50 (1.00 – 2.00)	5.61 ± 3.40
10 (Fed)	6	120.4 ± 46.9	119.3 ± 48.0	17.3 ± 6.4	14.4 ± 8.0	3.00 (1.00 – 4.00)	2.88 ± 0.33

Source: Study MK-1602 P001 CSR, Table 14.2-1 through 14.2-9, Module 5.3.3.1.

Figure 14 Mean (SD) Plasma Concentration-Time Profiles of Ubrogepant Following the Administration of a Single Oral Dose of 20 mg Ubrogepant Alone and Following the Administration of a Single Oral Dose of 20 mg Ubrogepant With Multiple Oral Doses of 240 mg Verapamil (N=12)



Source: Study MK-1602 P018 CSR, Figure 11-1, Module 5.3.3.4

Table 18 Statistical Comparisons of Plasma Pharmacokinetics of Ubrogepant Following the Administration of a Single Oral Dose of 20 mg Ubrogepant Alone and Following the Administration of a Single Oral Dose of 20 mg Ubrogepant With Multiple Oral Doses of 240 mg Verapamil

Ubrogepant Pharmacokinetic Parameter	Ubrogepant Alone (Reference)			Ubrogepant With Verapamil (Test)			Ubrogepant With Verapamil/ Ubrogepant Alone		Pseudo Within Subject %CV[a]
	N	AM	SD	N	AM	SD	GMR	90% CI[b]	
$AUC_{0-\infty}$ (ng•hr/mL)	12	213.2	71.4	12	742.0	212.7	3.53	(3.32, 3.75)	8.32
C_{max} (ng/mL)	12	45.2	15.0	12	124.8	36.4	2.80	(2.48, 3.15)	16.26
T_{max}(hr)[c]	12	2.00	(1.00, 4.00)	12	2.00	(1.03, 4.00)			
Apparent terminal $t_{1/2}$ (hr)	12	2.52	0.56	12	4.29	0.91			

Source: Study MK-1602 P018 CSR, Table 11-1 and Table 11-3, Module 5.3.3.4

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