CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	Division of Neurology Products/Office of New Drugs
Reviewer Name(s)	Laura Jawidzik, MD
Review Completion Date	12/19/2019
Established/Proper Name	Ubrogepant
(Proposed) Trade Name	Ubrelvy
Applicant	Allergan Sales, LLC
Dosage Form(s)	Tablet
Applicant Proposed Dosing Regimen(s)	50 mg or 100 mg orally; a second dose may be administered at least 2 hours after the initial dose; maximum 200 mg daily
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura
Recommendation on Regulatory Action	Approval of 25 mg, 50 mg, and 100 mg
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acute migraine with or without aura in adults

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Glossary

AC	advisory committee
ADaM	analysis data model
AE	adverse event
AHS	American Headache Society
AAN	American Academy of Neurology
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
DMC	data monitoring committee
DBP	diastolic blood pressure
DBTP	double-blind treatment phase
DM	demographics
DME	designated medical event
DNP	Division of Neurology Products
ECG	electrocardiogram
eCTD	electronic common technical document
eDiary	electronic diary
EOP2	end-of-phase 2
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HLT	high level term

HR	heart rate
ICH	International Council for Harmonization
ICHD-3	International Classification of Headache Disorders 3rd edition
IHS	International Headache Society
IND	Investigational New Drug Application
IP	investigational product
IR	information request
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
LOCF	last observation carried forward
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NDA	new drug application
NME	new molecular entity
NSAID	non-steroidal anti-inflammatory disorder
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	pain relief
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCS	Summary of Clinical Safety
SBO	small bowel obstruction

SBP	systolic blood pressure
SDTM	study data tabulation model
SGE	special government employee
SMQ	standard MedDRA queries
SOC	standard of care
SPF	sustained pain freedom
SPR	sustained pain relief
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Ubrogepant (previously MK-1602 and AGN-241688) is a small molecule, orally administered, calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a potent vasodilator in the cerebral, coronary, and renal vascular beds (Russell et al. 2014). CGRP has been shown to have a role in migraine pathophysiology. Plasma CGRP levels increase during migraine attacks and infusion of CGRP has been shown to induce migraine-like attacks in susceptible people (Hansen et al. 2010). Ubrogepant competes with the binding of CGRP and inhibits the function of CGRP at its receptor.

The applicant has proposed a dose of 50 mg or 100 mg orally with the option of a second dose to be administered at least two hours after the first dose with a maximum daily dose of 200mg. Three doses (i.e., 25 mg, 50 mg, 100 mg) were evaluated in pivotal clinical efficacy studies. Ubrogepant is intended to be prescribed for the acute treatment of migraine with or without aura.

Ubrogepant is a new molecular entity (NME). There are no FDA-approved orally administered, small molecule, CGRP receptor antagonists for the acute treatment of migraine. There are three FDA-approved monoclonal antibodies (i.e., erenumab, fremanezumab, and galcanezumab) that act on the CGRP pathway and are indicated for the preventive treatment of migraine.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support approval. The applicant provided data from two adequate and well-controlled studies that demonstrated that ubrogepant is effective for the acute treatment of migraine as compared to placebo. The applicant established effectiveness utilizing the co-primary endpoints that the Division considers clinically meaningful. The applicant has demonstrated statistical significance for the 50 mg and 100 mg doses on the co-primary endpoints: pain freedom at 2 hours, and absence of most bothersome symptom at two hours. In addition, the applicant has demonstrated statistical significance for the 25 mg dose on the endpoint pain freedom at 2 hours and nominal significance on the absence of most bothersome symptoms at 2 hours. I recommend approval of all three doses of ubrogepant (25 mg, 50 mg, and 100 mg) for the acute treatment of migraine in adults.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Ubrogepant is a small molecule, orally administered, calcitonin gene-related peptide (CGRP) receptor antagonist. It is intended to be prescribed for the acute treatment of migraine with or without aura.

Migraine is a very common, chronic neurological condition with a broad spectrum of frequency and severity. It is characterized by recurrent attacks of headache with accompanying symptoms of nausea, vomiting, photophobia, and phonophobia. These attacks are of moderate to severe intensity and can at times be disabling and impact the quality of patients' lives. There are many FDA-approved drugs for the acute treatment of migraine. The classes of drugs used to treat acute migraine include triptans, ergotamines, nonsteroidal anti-inflammatory medications (NSAIDs), as well as combination products. They all have limitations, especially related to safety and tolerability.

The efficacy of ubrogepant was demonstrated in two nearly identically designed randomized clinical studies that primarily differed in the doses studied. Both studies evaluated the effect of ubrogepant on a single migraine attack. The co-primary endpoints used by the applicant are described in the Migraine Guidance for Industry and are accepted by the Division as clinically meaningful endpoints. One study evaluated a 25 mg and 50 mg dose, and the other evaluated a 50 mg and 100 mg dose. The applicant has demonstrated statistical significance for the 50 mg and 100 mg doses on the co-primary endpoints: pain freedom at 2 hours, and absence of most bothersome migraine symptom (i.e., phonophobia, photophobia, or nausea) at two hours. In addition, the applicant has demonstrated statistical significance for the 25 mg dose on the endpoint pain freedom at 2 hours and nominal significance on the absence of most bothersome symptoms at 2 hours. Compared with placebo-treated patients, 6-10% more ubrogepant-treated patients were pain free at 2 hours and 7-12% more were free from their most bothersome symptom at 2 hours.

The safety profile of ubrogepant was characterized in two pivotal studies, a long-term open-label study with repeat dosing, and a dedicated hepatic safety study. No major, serious toxicities were identified in these trials. Common adverse events in clinical trials that occurred in ≥1% of ubrogepant-treated patients included viral infections, nausea, somnolence, confusion, dizziness, dry mouth, and abdominal pain. Clinical studies included generally younger, healthy patients and effectively excluded patients with major cardiovascular disease.

I recommend a postmarketing requirement (PMR) for a pregnancy registry and outcome study along with the required Pediatric Research Equity Act (PREA) PMRs for the study of pediatric migraine. These PMRs combined with enhanced pharmacovigilance, and product labeling will

address the risks associated with ubrogepant in the postmarket setting.

I recommend approval of all three doses of ubrogepant (25 mg, 50 mg, and 100 mg) for the acute treatment of migraine in adults. There is a small, but notable dose-dependent increase in the incidence of nausea and somnolence. Patients should have access to the lowest effective dose in case of intolerable side effects at higher doses or in case an unexpected safety signal arises in the post market setting.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Migraine is a very common, chronic neurological disease with a broad spectrum of frequency, and severity. It is characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with other symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last anywhere from 4 hours to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache. Migraine is more frequent in females than in males. In a large U.S. population-based study, the one-year prevalence of migraine was 18% in females and 7% in males and 12% overall (Lipton et al. 2001). Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton et al. 2007).	Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are many FDA-approved therapies for the treatment of acute migraine, as well as many others that are used off-label. FDA-approved therapies include ergotamines, triptans, NSAIDs (both OTC and prescription), devices, and combination products. Triptans are contraindicated in patients with a history of coronary artery disease, peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, transient ischemic attack, and stroke. Ergotamines are contraindicated in patients with cardiovascular disease. NSAIDs have an increased risk of serious gastrointestinal and cardiovascular adverse events.	Additional treatments for the acute treatment of migraine would be desirable, especially for patients with contraindications to currently available treatments.
Benefit	The applicant conducted two pivotal efficacy studies that demonstrate the efficacy of ubrogepant for the acute treatment of migraine. For both studies, the applicant utilized the co-primary endpoints of migraine pain freedom at 2 hours and the absence of the most bothersome symptoms at 2 hours. Studies MD-01 and MD-02 both provide evidence that 50 mg of ubrogepant is an effective dose for the acute treatment of migraine. Study MD-01 shows that the 100 mg dose is an effective dose for the treatment of migraine as well. Study MD-02 included a 25 mg dose which showed statistical significance for the endpoint pain freedom at 2 hours, and nominal significance for the endpoint absence of most bothersome symptoms at 2 hours. Compared with placebo-treated patients, 6-10% more ubrogepant-treated patients were pain free at 2 hours and 7-12% more were free from their most bothersome symptom at 2 hours. The efficacy of ubrogepant is also supported by the results of several key secondary endpoints. Ubrogepant 100 mg reached statistical significance on pain relief, sustained pain relief, sustained pain freedom, and absence of photophobia with nominal significance on absence of phonophobia and nausea. Ubrogepant 50 mg reached statistical significance on pain relief and sustained pain relief in both studies, and in study MD-02 also reached statistical significance on sustained pain freedom, absence of photophobia, and phonophobia. Because of the testing procedure for the	The efficacy of ubrogepant for the acute treatment of a migraine attack in patients with migraine with and without aura has been established. Ubrogepant-treated patients are more likely than placebo-treated patients to be migraine pain free and free of their most bothersome migraine symptom at 2 hours after dosing. I recommend the doses of ubrogepant for approval to be 25 mg, 50 mg, and 100 mg.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	multiplicity adjustment, the 25 mg dose reached only nominal significance on the following secondary endpoints: pain relief, sustained pain relief, sustained pain freedom, and phonophobia. Compared to placebo-treated patients, 12-15% of ubrogepant-treated patients experienced pain relief at 2 hours, and 12-17% experienced sustained pain freedom at 24 hours. Subgroup analyses suggest absent to reduced efficacy in patients ≥ age 65, male patients, and obese patients. In the two pivotal studies, the 50 mg and 100 mg doses performed similarly. From 50 mg to 100 mg, there is almost no increase in efficacy, and the dose response is quite flat. From 25 mg to 50 mg, there is a slight increase in efficacy on the MBS endpoint, but almost no increase in efficacy on pain freedom at 2 hours.	
Risk and Risk Management	No serious safety issues related to the use of ubrogepant were identified during this review. Several theoretical safety issues related to the use of CGRP receptor antagonists were reviewed in detail: cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, and liver toxicity. No clear safety signals were detected upon review of these issues. Common adverse events in clinical trials that occurred in ≥1% of ubrogepant-treated patients included viral infections, nausea, somnolence, confusion, dizziness, dry mouth, and abdominal pain. Clinical trials included generally younger, healthy patients and effectively excluded patients with major cardiovascular disease. Although small, there was a dose-dependent increase in the incidence of nausea and somnolence as compared to placebo.	Ubrogepant has an acceptable safety profile for the migraine population. However, safety issues have not been adequately evaluated in the population of patients with major cardiovascular disease. Enhanced pharmacovigilance will be used to address potential safety issues associated with the theoretical cardiovascular risk associated with CGRP receptor antagonism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	A Medication Guide does not appear to be needed. A pregnancy registry and outcome study will be a postmarketing requirement.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a very common, chronic neurological disease with a broad spectrum of frequency and severity. Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives.

Migraine is a disease characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last from 4 to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.

Migraine is more frequent in females than in males. In a large U.S. population-based study, the one-year prevalence of migraine was 18% in females, 7% in males, and 12% overall (Lipton et al. 2001). Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton et al. 2007). Although the prevalence of migraine declines with age, prevalence estimates in the population age 60 years and older is about 5% for females, and 1.6% for males (Lipton et al. 2007). Another estimate by Bigal and Lipton (2006) shows that the prevalence of migraine in the age 70 years and older population is about 4% with a 2% prevalence for males, and 5% prevalence for females.

2.2. Analysis of Current Treatment Options

There are many FDA-approved therapies including drugs and devices for the treatment of acute migraine, as well as many other drugs that are used off-label. The American Headache Society (AHS) published an assessment of the evidence for the acute treatment of migraine in 2015 (Marmura et al. 2015).

The evidence assessment classifies the following drugs as having Level A evidence (established as effective): acetaminophen, dihydroergotamine (DHE), aspirin, diclofenac, ibuprofen, naproxen, butorphanol nasal spray, triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan), and combination acetaminophen/aspirin/caffeine, sumatriptan/naproxen.

The following drugs and combination products are considered by this assessment to have Level B evidence (probably effective): chlorpromazine, droperidol, metoclopramide, prochlorperazine, flurbiprofen, ketoprofen, ketorolac, IV magnesium, isometheptene,

dihydroergotamine (SC, IV, IM); ergotamine/caffeine; tramadol/acetaminophen; and codeine/acetaminophen.

The following drugs and combination products are considered by this assessment to have Level C evidence (possibly effective): valproate (IV), phenazone, codeine, ergotamine, butorphanol (IM), meperidine, methadone, tramadol, dexamethasone, lidocaine (intranasal); butalbital/acetaminophen/caffeine, and butalbital/acetaminophen/caffeine/codeine.

A subset of the above listed drugs is FDA-approved for the treatment of acute migraine (Table 1). Although there are numerous options for the acute treatment of migraine, the current FDA-approved treatments all have some limitations especially related to safety and tolerability of the treatment.

Table 1 Summary of FDA-Approved Treatments for Acute Migraine

Product Type	Product Name(s)	Year of Initial Approval	Administration	Important Safety and Tolerability Issues
Ergotamine	DHE	1946	Injection; nasal spray	Contraindicated in cardiovascular disease; fibrotic complications may occur with prolonged use
Triptans	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	1995	Tablets, nasal spray, SC injection, nasal powder	Contraindicated in patients with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic/basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings in patients with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage or stroke
NSAIDs	Diclofenac, Ibuprofen (OTC)	2009	Oral dissolving packet, tablet	Cardiovascular risk for thrombotic events, myocardial infarction and stroke; gastrointestinal adverse events
Devices	GammaCore, Cerena, Cefaly	2013	Various	Contraindicated in patients with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices (Cerena); Contraindicated with recent trauma to skull/face or with skin conditions/rashes (Cefaly)
Combination products	Excedrin migraine, sumatriptan/ naproxen	2008	Tablets	Same as triptan/NSAID risks
5-HT1F receptor agonist	Lasmiditan	2019	Oral	Sedation; serotonin syndrome; abuse potential

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ubrogepant is an NME and is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 113924 was opened for ubrogepant on January 3, 2012, for the acute treatment of migraine. At that time, the sponsor of the IND was Merck. The primary safety concern was the potential for hepatotoxicity because of a potential class effect seen with other small molecule CGRP receptor antagonists. The 'May Proceed' notification was issued February 3, 2012.

In March 2016, the Division had a Type B end-of-phase 2 (EOP2) meeting with the applicant. At the EOP2 meeting, the Division and the applicant discussed the design of the two single-attack, phase 3 studies. The Division told the applicant that to get a labeling claim for triptan non-responders, evidence would need to come from a superiority study in which patients with a historical non-response to triptans were randomized to ubrogepant or to a triptan. The Division also recommended inclusion of a 25 mg arm into the pivotal studies as the 25 mg dose showed evidence of efficacy in phase 2 studies and the Division noted that if an unexpected safety issue was identified with the higher doses, the 25 mg dose may still be a viable option. The Division told the applicant that description of a second dose could be considered in labeling if there is adequate safety and efficacy data to support the description.

In April 2017, the Division sent the applicant a letter addressing the need for an adequate safety database to assess the potential for hepatoxicity with the use of ubrogepant. The applicant was asked to address the safety of the product for patients who use acute migraine medication on a daily or nearly daily basis (i.e., 20 to 30 days per month). The Division recommended that the applicant either enrich the long-term extension study with frequent users or conduct a three-month safety study in 300 patients taking ubrogepant daily or near daily.

In May 2017, the Division notified the applicant that a human abuse potential and human physical dependence study would not be required unless abuse-related adverse events were observed during phase 3 clinical studies.

In October 2017, the Division provided the applicant with feedback on the proposed study to evaluate hepatic liability in very frequent users of ubrogepant. The Division recommended that the applicant follow patients for at least 2 months after discontinuation of study medication to

potentially capture any delayed hepatotoxicity from the use of ubrogepant. The applicant declined this recommendation and opted to follow them for one month after discontinuation.

In May 2018, the Division had a Type C meeting with the applicant to again discuss the proposed safety database for ubrogepant. The Division reiterated that the applicant would need data on patients taking ubrogepant on a daily or near daily basis and that this data would need to be available at the time of the application, in advance of the 120-day safety update.

In August 2018, the pre-NDA meeting was held with the applicant. The Division and the applicant came to agreement on the proposed safety pools and analyses for the pools.

Summary of dates for regulatory interactions:
Initial IND: January 3, 2012
End of phase 2 meeting: March 17, 2016
Pre-NDA meeting: August 30, 2018
NDA filing: December 26, 2018

3.3. Foreign Regulatory Actions and Marketing History

Ubrogepant is not approved or marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of four clinical sites and also conducted an inspection of the applicant, Allergan Sales. Two sites were inspected for each of the two pivotal studies, MD-01 and MD-02. OSI concluded that the inspected sites conducted the study adequately, and that these sites and the data generated by the applicant were acceptable.

4.2. Product Quality

Please see the Integrated Quality Review.

4.3. Nonclinical Pharmacology/Toxicology

Please see the review by Dr. Edmund Nesti, nonclinical reviewer.

4.4. Clinical Pharmacology

Please see the review by Dr. Bilal AbuAsal, clinical pharmacology reviewer. I have summarized some of the major findings from his review in this section.

Ubrogepant is rapidly absorbed with a median Tmax of 0.7 to 1.5 hours post-dose. The α half-life of ubrogepant is about 3 hours and a β half-life (terminal phase) of about 5-7 hours. Steady state is reached within 1 day of dosing. Ubrogepant exhibits dose proportional increases in exposure with increased dosing over the range of doses 1 to 400mg.

CYP3A4 is the primary enzyme involved in the metabolism of ubrogepant. Ubrogepant is extensively, and almost exclusively metabolized by CYP3A4. Co-administration with a strong CYP3A4 inducer may cause a loss of efficacy.

Food effect evaluation for the 100 mg dose showed that administration of ubrogepant with a high-fat meal delayed the time to maximum plasma concentrations by about two hours and reduced the Cmax by about 22% with no change in the AUC.

The applicant conducted study UBR-PK-01 in hepatically impaired patients with pre-existing mild, moderate, or severe hepatic impairment. Per the applicant, ubrogepant exposure increased by 7%, 50%, and 115% in these patients, respectively. The applicant proposes no dose adjustment for patients with mild or moderate hepatic impairment and proposes the use of 50 mg for patients with severe hepatic impairment. The applicant did not conduct a pharmacokinetic study in renally impaired patients.

4.5. Devices and Companion Diagnostic Issues

N/A

4.6. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Clinical Trials Relevant to Treatment of Acute Migraine

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients treated	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
UBR-MD-01	Randomized, double-blind, placebo-controlled (pivotal efficacy)	50 mg or 100 mg orally	Pain freedom at 2 hours; freedom from MBS	Single attack; optional second dose	1436	Hx of episodic migraine; 18 to 75 years	89/1
UBR-MD-02	Randomized, double-blind, placebo-controlled (pivotal efficacy)	25 mg or 50 mg orally	Pain freedom at 2 hours; freedom from MBS	Single attack; optional second dose	1380	Hx of episodic migraine; 18 to 75 years	99/1
Studies to Support Safety							
UBR-MD-04	Open-label extension; repeat dosing	50 mg, 100 mg, or 'usual care'	Safety/tolerability	Up to 8 attacks per month for one year; optional second dose	1080	Hx of episodic migraine; 18 to 75 years	99/1
P004	Randomized, double-blind, placebo-controlled	150 mg orally	Safety	28 days	32	Healthy volunteers	1/1
P006	Randomized, double-blind, placebo-controlled (dose-ranging)	1mg, 10mg, 25 mg, 50 mg, or 100 mg orally	Pain freedom at 2 hours; (did not assess MBS)	Single attack; no second dose option	640	Hx of episodic migraine; 18 to 65 years	58/1
P007	Randomized, double-blind, placebo-controlled (dose-ranging)	1mg, 10mg, 25 mg, 50 mg, or 100 mg orally	Pain freedom at 2 hours; (did not assess MBS)	Single attack; no second dose option	165	Hx of episodic migraine; 18 to 65 years	20/1
3110-105-002	Randomized, double-blind, placebo-controlled (hepatic safety study)	100 mg orally	Safety	56 days	516	Healthy volunteers	6/1

5.2. Review Strategy

The applicant has proposed the 50 mg and 100 mg dose as the to-be-marketed doses. There are two pivotal studies that assess the 50 mg dose, and one pivotal study (MD-01) that assesses the 100 mg dose. One of the pivotal studies (MD-02) also assesses a 25 mg dose. This review will evaluate the data for both pivotal studies to determine which doses are approvable based on their efficacy and safety profiles. For efficacy, studies MD-01 and MD-02 will be reviewed.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. UBR-MD-01: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to evaluate the effect of ubrogepant compared to placebo for the acute treatment of a single migraine attack and to evaluate the safety and tolerability of ubrogepant.

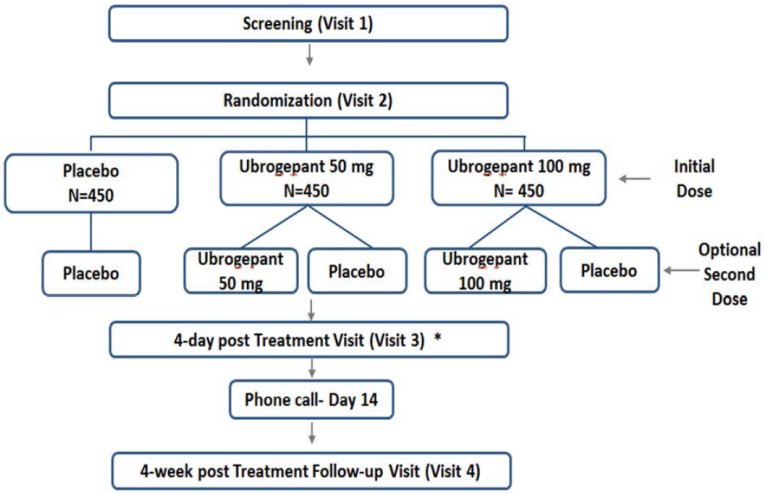
Trial Design

Study MD-01 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of patients with a history of migraine with or without aura. The study was conducted at 89 centers in the United States. In this study, patients treated a single qualifying migraine with a dose of ubrogepant or placebo. Patients were randomized in a 1:1:1: ratio to receive either placebo, ubrogepant 50 mg, or ubrogepant 100 mg. Randomization was stratified by previous response to triptans and current use of preventive medication. After a patient was randomized into the study, the patient had sixty days to treat a qualifying migraine with investigational product (IP). Patients were discontinued from the study if they did not treat a qualifying migraine during this time. Patients had the option to take a second dose of IP or rescue medication if needed. At the initial randomization visit, patients were randomized to either active treatment or placebo. Those patients randomized to active treatment were also randomized to either placebo or active treatment for the blinded optional second dose (Figure 1). Patients initially randomized to placebo were given placebo for the blinded optional second dose. Patients who completed the double-blind treatment period had the option to continue into the open-label extension study.

Basic Study Design

Screening period: up to 14 days prior to randomization
Treatment period: up to 60 days to treat a single migraine attack
Follow-up: 4 weeks

Figure 1 Study Flow Chart



This figure was taken from the protocol for study UBR-MD-01

Reviewer's comment: The study flow chart for study MD-02 is the same with the exception of the doses studied. In study MD-02, 25 mg and 50 mg were studied.

Diagnostic Criteria

The applicant utilized the International Classification of Headache Disorders, 3rd edition, beta for the diagnosis of migraine.

Treatment of a Qualifying Migraine

Patients had 60 days to treat a qualifying migraine attack at home. Patients were instructed to treat a migraine when the following conditions were met:

-migraine is moderate to severe in intensity
-presence of at least one migraine associated symptoms (i.e., photophobia, phonophobia, or nausea)
-migraine started less than 4 hours ago

-no prohibited medications were taken
-new headache (i.e., no other headache in the prior 48 hours)

Patients rated the severity of their headache at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose. Patients also recorded their migraine-associated symptoms at the same time points. The most bothersome migraine-associated symptom was to be identified pre-dosing.

Key Inclusion Criteria

1. Male or female ages 18 to 75
2. At least 1-year history of migraine with or without aura
3. Migraine onset before age 50

Key Exclusion Criteria

1. Chronic migraine in the 6 months prior to screening
2. Using acute medications for the treatment of headache for ≥10 days per month in any of the 3 months prior to screening (including acetaminophen, NSAIDs, triptans, ergotamine, opioids, or combination analgesics)
3. History of hemiplegic migraine, or retinal migraine
4. History of a trigeminal autonomic cephalgia, cranial neuropathy, or new persistent daily headache
5. Clinically significant ECG abnormality
6. A QTcF >450msec for males or QTcF>470msec for females
7. Clinically significant cardiovascular or cerebrovascular disease including the following: ischemic heart disease, unstable angina, cardiac rhythm or conduction abnormalities such as atrial fibrillation, second-degree or third-degree heart block, risk factors for Torsades (e.g. heart failure, hypokalemia, bradycardia); myocardial infarction, transient ischemic attack, or stroke within 6 months prior to screening; heart failure class III or IV
8. Hypertension
9. Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease; history of malignancy
10. Pain syndromes, psychiatric conditions, dementia, or epilepsy
11. Significant risk of self-harm
12. Patients who have participated in a study using injectable monoclonal antibodies blocking the CGRP pathway

Dose Selection

In a phase 2 study, the applicant evaluated ubrogepant 1, 10, 25, 50, and 100 mg compared to placebo for the treatment of acute migraine. The results showed that ubrogepant 25, 50, and

100 mg were significantly better than placebo for the endpoint pain freedom at 2 hours. Initially the applicant planned to evaluate 50 mg and 100 mg in the pivotal efficacy studies; however, the Division recommended inclusion of a 25 mg arm into pivotal studies as this dose also showed efficacy.

Study Treatments/Blinding

This was a double-blind placebo-controlled trial. IP was administered in 50 mg tablets or matching placebo. All patients were instructed to take two tablets regardless of dose group.

Assignment to Treatment

An automated interactive web response system (IWRS) was used to manage randomization and treatment assignment. All patients who met study entry criteria were randomized and provided enough IP to treat one migraine attack. Patients were randomized in a 1:1:1 ratio to either placebo, 50 mg, or 100 mg of ubrogepant.

Randomization was stratified by previous response to triptans (i.e., responder, insufficient-responder, triptan naïve) and current use of preventive medications (yes/no).

Dose Modification/Dose Discontinuation

The dosage of IP was fixed and could not be adjusted.

Procedures and Schedule

The schedule of study procedures and assessments is summarized in Table 3. I have modified the table from the applicant's materials to only include key assessments.

Table 3 Schedule of Procedures and Assessments for Study MD-01

	Screening (Visit 1)	Randomization (Visit 2)	Treatment (Day 1)	Day 4 Post-Treatment (Visit 3)	4- Week Safety Follow-Up (Visit 4)
Vital signs, pregnancy test, C-SSRS	x	x		x	x
ECG, physical exam	x			x	
Labs	x			x	

	Screening (Visit 1)	Randomization (Visit 2)	Treatment (Day 1)	Day 4 Post-Treatment (Visit 3)	4- Week Safety Follow-Up (Visit 4)
IP dispensed		x			
IP administered			x		

Dietary Instructions

Patients were to refrain from consuming grapefruit or grapefruit juice until the completion of the study. Patients were asked to refrain from consuming caffeine for at least 2 hours after taking IP.

Concurrent Medications

Patients requiring daily intake of antacids, proton pump inhibitors, and histamine H2 antagonists were excluded.

The following medications were prohibited 30 days prior to screening and throughout the study:

-CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, diltiazem, verapamil, aprepitant, cyclosporine, nefazadone, cimetidine, quinine, and HIV protease inhibitors)
-CYP3A4 inducers (e.g. barbiturate, phenobarbital, primidone, glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort)

The following medications were allowed but prohibited within 48 hours prior to taking IP: triptans, ergots, opioids, NSAIDs, analgesics, antiemetics, and proton pump inhibitors.

The following medications were allowed but were prohibited within 24 hours prior to taking IP: antacids or H2 blockers.

Daily aspirin use was allowed as was daily use of pregabalin.

SSRIs and SNRIs were allowed provided that the dose was stable for at least 60 days prior to screening. These medications could not be initiated during the study.

Standard migraine preventive treatments were allowed provided that the dose was stable for at least 30 days prior to screening. Preventive medications could not be initiated during the study.

Treatment Compliance

Compliance was monitored by counting the number of tablets dispensed and returned.

Rescue Medication

Rescue medication could only be taken beginning two hours after the initial dose of IP was taken. Patients could either take rescue medication, or the optional second dose of IP. If the optional second dose of IP were taken, then rescue medication could be taken beginning two hours after the second dose of IP.

Rescue medication could include triptans, ergotamine, NSAIDs, acetaminophen, or opioids.

Subject Completion/Discontinuation/Withdrawal

Patients could voluntarily withdraw from the study at any time. The reason for discontinuation was to be documented on the eCRF. All randomized patients who discontinued prematurely were to be seen for a final assessment. If the patient discontinued from the study after IP was taken, the patient was expected to return for the follow-up safety visit.

Study Endpoints

Co-Primary Endpoints

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

Secondary Endpoints

1. Pain relief two hours after the initial dose
2. Sustained pain relief (SPR) from 2 to 24 hours after the initial dose
3. Sustained pain freedom (SPF) from 2 to 24 after the initial dose
4. Absence of photophobia at 2 hours after the initial dose
5. Absence of phonophobia at 2 hours after the initial dose
6. Absence of nausea at 2 hours after the initial dose

Definition of Pain Freedom

Defined as the reduction in headache severity from moderate or severe pain at baseline to no pain at two hours after the initial dose.

Definition of Pain Relief

Defined as the reduction in headache severity from moderate or severe pain to mild or no headache at two hours after the initial dose.

Definition of Sustained Pain Freedom

Defined as pain freedom with no administration of either rescue medication or second dose of IP, and with no occurrence of a headache of any intensity from 2 to 24 hours after the initial dose.

Definition of Sustained Pain Relief

Defined as pain relief with no administration of either rescue medication or second dose of IP, with no occurrence of a headache of moderate or severe intensity from 2 to 24 hours after the initial dose.

Statistical Analysis Plan

Analysis Populations

Table 4 Analysis Sets for Study MD-01

Analysis Set	Definition
Intent-to-treat (ITT)	All randomized patients
Modified intent-to-treat (mITT)	All randomized patients who received at least 1 dose of IP, recorded a baseline migraine severity measurement, and had ≥ 1 post-dose migraine severity or migraine-associated symptom measurement at or before the 2-hour timepoint.
Safety	All patients who received ≥1 dose of IP

Sample Size Estimation

The applicant hypothesized that a sample size of 550 randomized patients per treatment group would provide at least 85% power to detect a treatment difference between each of the two ubrogepant doses (assumed to be equally effective) and placebo for the co-primary endpoints, and at least 70% power to detect a treatment difference for the secondary efficacy endpoints. The applicant assumed a 10% response rate for placebo and a 24% response rate for ubrogepant-treated groups.

Hypothesis Testing

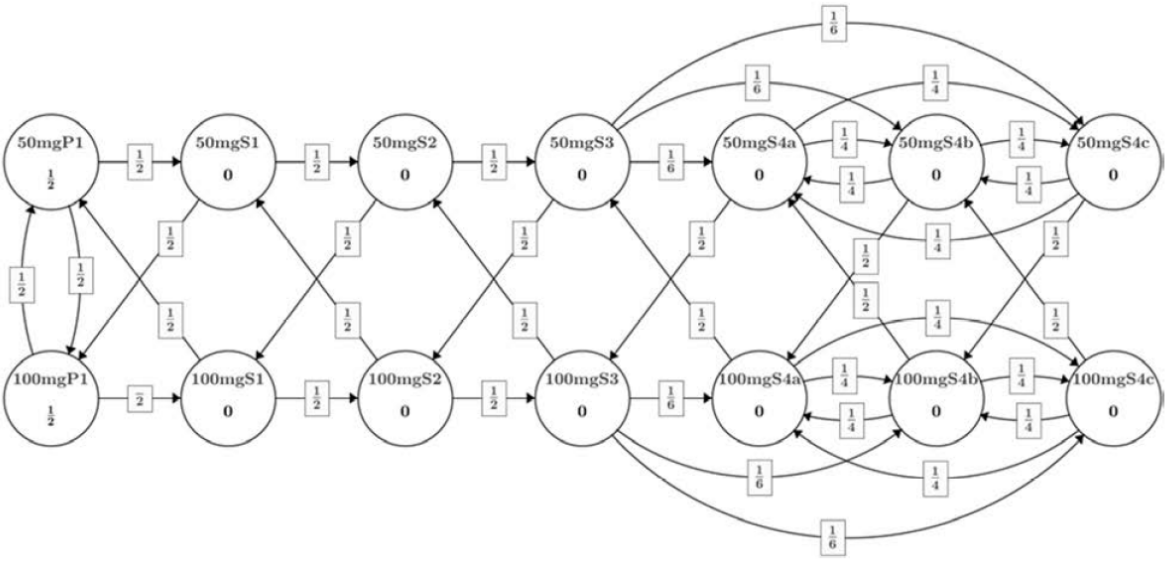
The applicant hypothesized that at least one ubrogepant dose would be superior to placebo in the acute treatment of migraine.

Efficacy analyses were based on the mITT population, which consisted of all randomized patients who received at least 1 dose of IP, recorded a baseline migraine headache severity measurement, and had ≥ 1 post-dose migraine headache severity or migraine-associated symptom measurement at or before the 2-hour timepoint.

The primary and secondary efficacy endpoints were analyzed using a logistic regression model. A graphical approach by Bretz was used to control the overall type-I error rate at alpha=0.05 for multiple comparisons across two ubrogepant doses versus placebo and the primary and secondary endpoints (Figure 2). The co-primary efficacy endpoints served as the gatekeepers of the secondary endpoints. No interim analyses were planned.

For analyses of sustained efficacy endpoints, only patients for whom all data (i.e., headache severity, headache recurrence, use of rescue medication, and use of optional second dose) was available were included in the analyses.

Figure 2 Testing Procedure for Multiple Comparisons



This figure is taken from the SAP for study MD-01

Pre-Specified Methods for Handling Missing Data

The last-observation-carried-forward (LOCF) was the primary imputation method for missing post-treatment values. Pre-specified sensitivity analyses for the primary efficacy endpoints imputed patients with missing data at 2 hours as non-responders, provided that the patients had at least 1 post-dose value before the 2-hour time point. Per recommendation from the Division, the applicant added in additional sensitivity analyses using a generalized linear mixed model assuming missing-at-random for the co-primary endpoints.

For sensitivity analyses of the sustained endpoints, patients were assumed to be non-responders if the sustained efficacy endpoints could not be determined.

Reviewer Comment: Missing data should be minimal for an acute migraine trial. Several sensitivity analyses were planned by the applicant, and additional analyses were performed by the statistician to explore the missing data. Please see the statistical review by Dr. Jinnan Liu.

Protocol Amendments

Three protocol amendments were made to the original protocol which was released on April 29, 2016. Protocol amendment 1 was dated June 9, 2016. Protocol amendment 2 dated November 4, 2016, added an exclusion criterion to the protocol whereby patients with chronic migraine would be excluded from the study and patients who had received injectable CGRP monoclonal antibodies would also be excluded from the study. Protocol amendment 3 dated May 19, 2017, increased the planned sample size from 1350 to 1650 patients.

The original SAP was amended twice. The first amendment was dated January 5, 2017. SAP amendment 1 updated the sample size to 550 patients per treatment arm from 450 patients per treatment arm. This amendment also re-ordered the secondary efficacy endpoints and updated the power calculations based on the new sample size. SAP amendment 2, dated May 17, 2017, updated the missing data handling of the sustained efficacy endpoints.

Reviewer's comment: Protocol amendment 2 excluded patients who had received injectable CGRPs; therefore, no safety or efficacy data is available for the concomitant use of the CGRP monoclonal antibodies and ubrogepant.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was conducted in compliance with ICH E6 guidelines for good clinical practice (GCP). The applicant asserts that investigators obtained institutional review board (IRB) approval prior to study initiation.

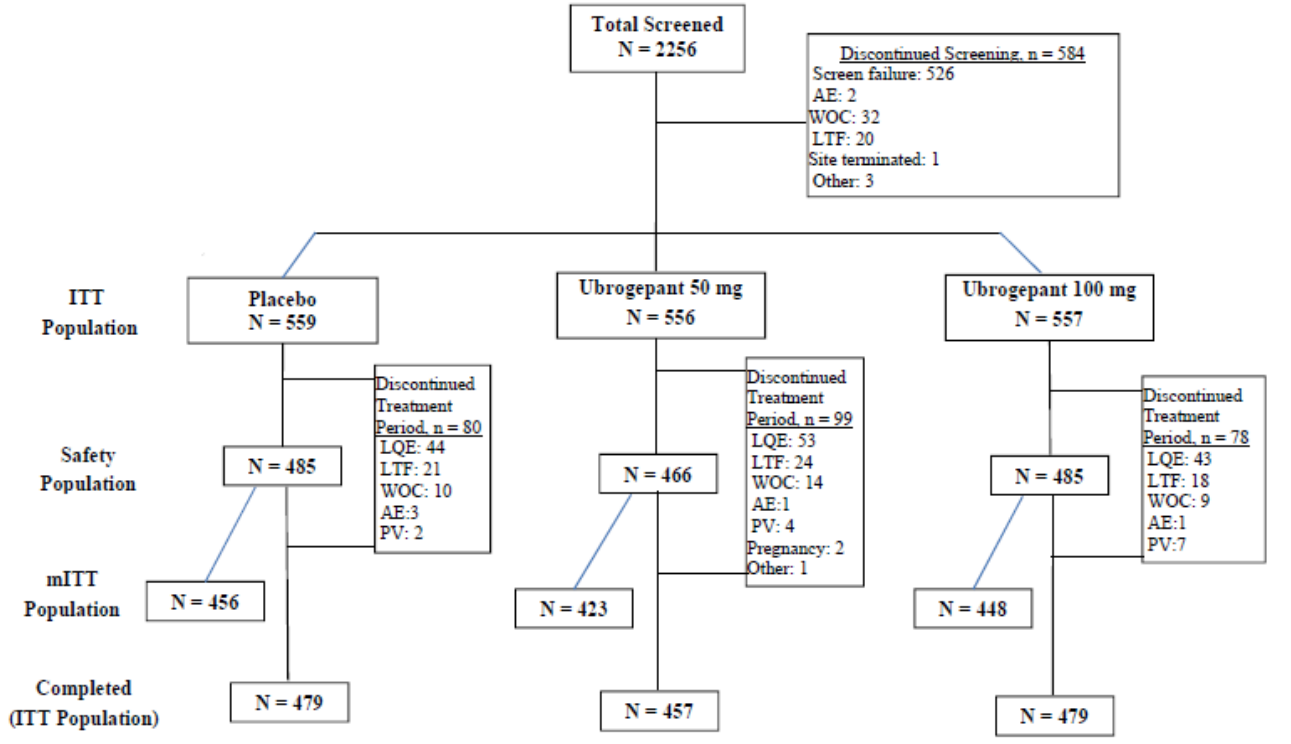
Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Screened: 2256
Randomized: 1672 (placebo: 50 mg: 100 mg 559: 556: 557)
Received at least 1 dose of double-blind IP: 1436 (placebo: 50 mg: 100 mg 485: 466: 485)
mITT population: 1327 (placebo: 50 mg: 100 mg 456: 423: 448)

Figure 3 Study MD-01: Patient Disposition Flow Chart



AE = adverse event; ITT = intent to treat; LTF = lost to follow-up; LQE = lack of qualifying event; mITT = modified intent to treat; PV = protocol violation; WOC = withdrawal of consent

This figure was adapted from the CSR for study MD-01

There were 1436 patients who took IP, but only 1327 who are included in the mITT. A total of 109 patients who took IP were excluded from the mITT (Table 5).

Table 5 Study MD-01: Randomized Patients Excluded from the mITT Population

Reason for Exclusion	Number of Patients
Did not take study medication	236
Did not record baseline migraine headache severity	19
Did not record post-dose migraine severity before 2-hour time point	90

This table was adapted from an IR response dated April 11, 2019, eCTD 0010

Protocol Violations/Deviations

The most common protocol deviation was use of a prohibited concomitant medication (Table 6). Overall the protocol deviations were low, generally balanced among treatment arms, and not expected to affect the primary efficacy outcome.

Table 6 Study MD-01: Protocol Deviations/Violations in the ITT Population

Protocol Deviation	Placebo N=559 n(%)	50 mg N=556 n(%)	100 mg N=557 n(%)
Exclusion criteria	5 (0.9)	7 (1.3)	11 (2.0)
Prohibited concomitant medication	23 (4.1)	15 (2.7)	29 (5.2)
Informed consent	16 (2.9)	12 (2.2)	12 (2.2)
Pregnancy	2 (0.4)	3 (0.5)	1 (0.2)

This table was adapted from the CSR for study MD-01, Table 10-3.

Table of Demographic Characteristics

No baseline imbalance in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 7) or baseline migraine characteristics (Table 8).

Table 7 Demographic Characteristics of All Randomized Patients (ITT) for Study MD-01

Demographic Parameters	Placebo (N=559) n (%)	Treatment Group		
		50 mg (N=556) n (%)	100 mg (N=557) n (%)	Total (N=1672) n (%)
Sex				
Male	68 (12.2)	63 (11.3)	78 (14.0)	209 (12.5)
Female	491 (87.8)	493 (88.7)	479 (86.0)	1463 (87.5)
Age				
Mean years (SD)	41.1 (11.9)	40.2 (12.0)	40.7 (12.4)	40.7 (12.1)
Median (years)	40.0	39.0	40.0	40.0
Min, max (years)	18, 74	18, 70	18, 75	18, 75
Age Group*				
18 to 40	287 (51.3)	300 (54.0)	285 (51.2)	872 (52.2)
41 to 64	253 (45.3)	241 (43.3)	251 (45.1)	745 (44.6)
65 to 75	19 (3.4)	15 (2.7)	21 (3.8)	55 (3.3)
Race				
White	471 (84.3)	459 (82.6)	447 (80.3)	1377 (82.4)
Black or African American	65 (11.6)	77 (13.8)	88 (15.8)	230 (13.8)
Asian	10 (1.8)	9 (1.6)	8 (1.4)	27 (1.6)
American Indian or Alaska Native	3 (0.5)	3 (0.5)	5 (0.9)	11 (0.7)
Native Hawaiian or Other Pacific Islander	3 (0.5)	1 (0.2)	5 (0.9)	9 (0.5)
Other/Multiple	7 (1.3)	7 (1.3)	4 (0.7)	18 (1.1)
Ethnicity				
Hispanic or Latino	60 (10.7)	67 (12.1)	66 (11.8)	193 (11.5)
Not Hispanic or Latino	499 (89.3)	489 (87.9)	491 (88.2)	1479 (88.5)
Concomitant preventive medication	123 (22.0)	120 (21.6)	120 (21.5)	363 (21.7)
Yes	123 (22.0)	120 (21.6)	120 (21.5)	363 (21.7)
Body Mass Index (BMI) kg/m²				
Mean (SD)	30.0 (7.4)	30.1 (7.9)	30.2 (7.8)	30.1 (7.7)
Median	28.6	28.7	28.6	28.7
Min, Max	18, 64	15, 60	17, 62	15, 64

This table was adapted from the CSR for study MD-01, table 14.1-2.1.A
*Age group was calculated by the reviewer in JMP using ADSL for MD-01, analysis by planned treatment

Table 8 Study MD-01: Baseline Migraine Characteristics for the mITT Population

	Placebo N=456 n(%)	50 mg N=423 n(%)	100 mg N=448 n(%)
Migraine headache severity			
Moderate	287 (62.9)	260 (61.5)	288 (64.3)
Severe	169 (37.1)	163 (38.5)	160 (35.7)
Most bothersome symptom (MBS)			
Photophobia	254 (55.7)	248 (58.6)	246 (54.9)
Phonophobia	98 (21.5)	82 (19.4)	116 (25.9)
Nausea	102 (22.4)	90 (21.3)	86 (19.2)
Missing	2 (0.4)	3 (0.7)	0

This table is adapted from the CSR for study MD-01, table 14.1-6.1

Table 9 Study MD-01: Migraine History (Safety Population)

	Placebo N=485	50 mg N=466	100 mg N=485
Duration of Migraine History			
Median (years)	16.9	16.0	17.0
Migraine Diagnosis			
Without aura n(%)	261 (53.8)	259 (55.6)	276 (56.9)
With aura n(%)	85 (17.5)	87 (18.7)	86 (17.7)
Both	139 (28.7)	120 (25.8)	123 (25.4)
Average Frequency of Mod to Sev Migraines in the Last 3 months			
Median	4	4	4
Min, Max	2, 8	2, 8	2, 8

This table is adapted from the CSR for study MD-01, table 14.1-4.2

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatments in this study were placebo, 50 mg of ubrogepant, or 100 mg of ubrogepant. The IP was distributed in 50 mg tablets, so to maintain the blind all patients were given two tablets of IP to be taken to treat a single migraine. Treatment compliance was assessed when patients returned unused IP to the study site. Of the 1436 patients who took IP, the majority (98.5%) were compliant with taking both tablets of IP. Approximately 1% of patients in each treatment arm took only 1 tablet for the initial dose.

About 22% of patients were taking concomitant migraine preventive medications. The percentage of patients was balanced across all three treatment groups (Table 7).

Use of rescue medication will be discussed in the efficacy results for the secondary endpoints related to sustained pain freedom and sustained pain relief.

Reviewer's comment: The percentage of patients who were not compliant with taking both tablets at the time of the acute migraine was equally distributed across all three treatment arms. It is unlikely that this small percentage of patients should affect the primary efficacy analysis.

Efficacy Results – Primary Endpoint

The co-primary endpoints for this study were as follows:

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

The efficacy analyses were based on the mITT population. Baseline was defined as the last non-missing efficacy assessment before the initial dose of IP. Statistically significant results were observed for both the 50 mg and 100 mg doses compared to placebo for both co-primary efficacy endpoints (Table 10). These results were verified by the statistical reviewer, Dr. Jinnan Liu. She confirmed the applicant's analysis and calculation of the unadjusted (raw) p-values.

Table 10 Study MD-01: Results for the Co-Primary Efficacy Endpoints (mITT Population)

	Placebo N=456	50 mg N=423	100 mg N=448
Pain Freedom at 2 hours			
Responders, n(%)	54 (11.8)	81 (19.2)	95 (21.2)
Odds Ratio		1.8	2.0
(95% CI)		(1.3, 2.7)	(1.4, 3.0)
Adjusted p-value*		0.0023	0.0001
Unadjusted p-value		0.0017	0.0003
NNT**		13.5	10.6
Absence of MBS at 2 hours			
Responders, n(%)	126 (27.8)	162 (38.2)	169 (37.7)
Odds Ratio		1.7	1.6
(95% CI)		(1.3, 2.3)	(1.2, 2.2)
Adjusted p-value*		0.0023	0.0023

Unadjusted p-value		0.0003	0.0008
NNT**		9.6	10.1

This table was adapted from the clinical overview, Table 4-1
*Adjusted p-values are from hypothesis testing using a graphical approach with closed testing procedure to control for multiplicity. Unadjusted p-value refers to the raw p-value before testing procedures to control for multiplicity are applied**Number-needed-to-treat (NNT) was calculated by the reviewer

Data Quality and Integrity

No major data quality issues were identified during the review of study MD-01.

The data quality and analysis quality are adequate. The statistical reviewer was able to perform independent review using the applicant's submitted datasets and confirm the results of the applicant's analyses.

Efficacy Results – Secondary and other relevant endpoints

The following were the secondary endpoints:

1. Pain relief two hours after the initial dose
2. Sustained pain relief from 2 to 24 hours after the initial dose
3. Sustained pain freedom from 2 to 24 after the initial dose
4. Absence of photophobia at 2 hours after the initial dose
5. Absence of phonophobia at 2 hours after the initial dose
6. Absence of nausea at 2 hours after the initial dose

Ubrogepant 100 mg demonstrated statistically significant findings on 4 out of the 6 secondary endpoints, while ubrogepant 50 mg demonstrated statistically significant findings on 2 out of the 6 secondary endpoints (Table 11). For the 100 mg dose, statistically significant findings were demonstrated on the following endpoints: pain relief, sustained pain relief, sustained pain freedom, and absence of photophobia at 2 hours. For the 50 mg dose, statistically significant findings were demonstrated on the following endpoints: pain relief, and sustained pain relief. Ubrogepant 100 mg showed nominal significance over placebo for absence of phonophobia and nausea 2 hours after the initial dose. Ubrogepant 50 mg showed nominal significance over placebo for SPF 2-24 hours, and absence of photophobia and phonophobia at 2 hours. There was no significant difference versus placebo for ubrogepant 50 mg for absence of nausea.

Table 11 Study MD-01: Secondary Endpoints Reaching Statistical Significance

	Pain Relief (PR)	SPR (2 to 24 hours)	SPF (2 to 24 hours)	Photophobia	Phonophobia	Nausea
50 mg	x	x	y	y	y	
100 mg	x	x	x	x	y	y

SPR: sustained pain relief; SPF: sustained pain freedom
X= statistical significance; y=nominal significance

Table 12 summarizes the results of the secondary endpoints for study MD-01. I have noted using x and y as per table 11 which results were statistically significant versus those that have nominal significance.

Table 12 Study MD-01: Results for the Secondary Endpoints

	Placebo N=456	50 mg N=423	100 mg N=448
Pain Relief at 2 hours			
Responders, n(%)	224 (49.1)	256 (60.7)	275 (61.4)
Odds Ratio		1.7	1.7
(95% CI)		(1.3, 2.2)	(1.3, 2.2)
Adjusted p-value*		0.0023[x]	0.0023[x]
Unadjusted p-value		0.0002	0.0002
NNT**		8.6	8.1
SPR from 2-24 hours			
Responders, n(%)	93 (20.8)	150 (36.3)	165 (36.8)
Odds Ratio		2.3	2.4
(95% CI)		(1.7, 3.1)	(1.8, 3.2)
Adjusted p-value*		0.0023[x]	0.0023[x]
Unadjusted p-value		<0.0001	<0.0001
SPF from 2-24 hours			
Responders, n(%)	39 (8.6)	53 (12.7)	68 (15.4)
Odds Ratio		1.6	2.0
(95% CI)		(1.0, 2.4)	(1.3, 3.0)
Adjusted p-value*		0.0577	0.0037[x]
Unadjusted p-value		0.0436[y]	0.0018
Absence of photophobia			
Responders, n(%)	143 (31.4)	172 (40.7)	205 (45.8)
Odds Ratio		1.6	1.8

	Placebo N=456	50 mg N=423	100 mg N=448
(95% CI)		(1.2, 2.2)	(1.4, 2.4)
Adjusted p-value*		0.0577	0.0037[x]
Unadjusted p-value		0.0011[y]	<0.0001
Absence of phonophobia			
Responders, n(%)	215 (47.1)	245 (57.9)	244 (54.5)
Odds Ratio		1.6	1.5
(95% CI)		(1.2, 2.1)	(1.1, 2.0)
Adjusted p-value*		0.0577	0.0577
Unadjusted p-value		0.0033[y]	0.0091[y]
Absence of nausea			
Responders, n(%)	284 (62.3)	297 (70.2)	310 (69.2)
Odds Ratio		1.3	1.4
(95% CI)		(1.0, 1.8)	(1.0, 1.8)
Adjusted p-value*		0.0962	0.0962
Unadjusted p-value		0.0835	0.0481[y]

This table was adapted from the clinical overview, Table 4-1 and Table 11-1 from the CSR for study MD-01
* Adjusted p-values are from hypothesis testing using a graphical approach with closed testing procedure to control for multiplicity; Unadjusted p-value refers to the raw p-value before testing procedures to control for multiplicity are applied
**NNT was calculated by the reviewer
X=statistically significant; y=nominally significant

Reviewer's comment: The analyses of the secondary endpoints were verified by the statistical reviewer. Dr. Liu's review verified the adjusted and unadjusted (raw p-values) for the secondary endpoints for study MD-01.

Dose/Dose Response

This will be addressed in section 7.1.4.

Sensitivity Analyses Conducted on Study MD-01

The applicant conducted a sensitivity analysis on the primary endpoint of pain freedom at 2 hours. This analysis utilized the mITT population, and patients who were missing the 2-hour time point were assumed to be non-responders (

Appears this way on original

Table 13). This result was consistent with the primary efficacy analysis and was confirmed by the statistical reviewer, Dr. Jinnan Liu.

Table 13 Study MD-01: Sensitivity Analysis of the Primary Endpoint: Missing Assumed as Non-Responders

	Placebo N=456	50 mg N=423	100 mg N=448
Pain Freedom at 2 hours			
Responders, n(%)	50 (11.0)	76 (18.0)	90 (20.1)
Odds Ratio		1.8	2.1
(95% CI)		(1.3, 2.7)	(1.4, 3.0)
p-value		0.0021	0.0001

This table is adapted from table 11-4 from the CSR for study MD-01.

In a written communication to the applicant regarding study MD-02, dated May 24, 2018, the Division requested that the applicant conduct additional sensitivity analyses on the co-primary endpoints assuming different missing data mechanisms. The Division did not specify which assumptions should be made. The applicant opted to conduct a sensitivity analysis on the missing data assuming missing-at-random for both studies (Table 14). This analysis was confirmed by the statistical reviewer and supports the conclusion that the 50 mg and 100 mg doses are effective on the primary endpoint, migraine pain freedom two hours after dosing.

Table 14 Study MD-01 Sensitivity Analysis of the Primary Endpoint: Missing at Random

	Placebo N=456	50 mg N=423	100 mg N=448
Pain Freedom at 2 hours			
Responders, % (n)	9.5	16.4	18.1
Odds Ratio		1.9	2.1
(95% CI)		(1.3, 2.7)	(1.4, 3.1)
p-value		0.0016	0.0001

This table is adapted from table 14.2-5.1 from the CSR for study MD-01.

Dr. Liu conducted additional sensitivity analyses on the co-primary endpoints to evaluate patients who used rescue medication prior to the 2-hour timepoint measurement. In these sensitivity analyses, Dr. Liu counted patients who took rescue medication prior to the 2-hour time point measurement as treatment failures. The results of these additional sensitivity analyses were consistent with the results of the primary endpoint.

Additional Analyses Conducted on the Individual Trial

Endpoints discussed in this section were not included in the testing hierarchy and therefore not controlled for type-1 error. The p-values reported in this section are not included in the graphical approach to multiplicity testing.

Use of Rescue Medication: defined as either the optional second dose of IP or another medication for the acute treatment of migraine or both, within 24 to 48 hours of the initial dose of IP.

Within 24 hours of taking the initial dose of IP, 72.4% of patients in the placebo arm took rescue medication compared to 54.6% and 54.0% of patients in the ubrogepant 50 mg and 100 mg treatment arms, respectively (Table 15). For the analysis presented in Table 15, rescue medication here is inclusive of taking either the optional second dose of IP or taking another medication for the acute treatment of migraine.

Table 15 Study MD-01: Use of Rescue Medication

	Placebo N=456	50 mg N=423	100 mg N=448
Within 24 hours			
Took Rescue Medication, n(%)	330 (72.4%)	231 (54.6)	242 (54.0)
Difference from PBO		-17.8%	-18.4%
Odds Ratio (95% CI)		0.44 (0.33, 0.59)	0.44 (0.33, 0.59)
p-value		<0.001[y]	<0.001[y]

Y=nominal p-values; this endpoint was not included in the graphical approach to multiplicity testing
This table was adapted from the CSR for study MD-01, table 11-15.

Reviewer's comment: Patients who took ubrogepant 50 mg or 100 mg were less likely to take rescue medication than patients who took placebo.

Optional Second Dose: Patients could take an optional second dose of IP starting at 2 hours after the initial dose of IP and up to 48 hours after the initial dose of IP. Patients who took the second dose of IP could not take other rescue medication for at least two hours following the second dose of IP. Patients could take the optional second dose if they continued to have a moderate to severe headache, or if a moderate to severe headache returned within 2 to 48 hours after the initial dose.

In Table 16, if we first consider those patients who did not respond to the initial dose of IP (line 1), then those patients who took the drug and provided a two-hour assessment could be considered the mITT. For a variety of reasons, there is a huge loss of patients from the group of patients who did not respond to the initial dose of IP to the mITT (approximately 52%). There is

about a 20% loss of patients from what we could call the safety population (i.e., those who took the optional second dose) to the mITT.

Table 16 Study MD-01: Use of Optional Second Dose

	Placebo N=456	50 mg N=423	100 mg N=448
Patients who did not respond to initial dose of IP	402	342	353
Took optional second dose	207/402 (51.5%)	174/342 (50.9%)	188/353 (53.3%)
Took UBR-PBO		70	100
Took UBR-UBR		104	88
Took Optional Second Dose and had non-missing 2-hour measurement (mITT)	173/207 (83.6%)	136/174 (78.2%)	147/188 (78.2%)
Took UBR-PBO		52/70 (74.3%)	79/100 (79.0%)
Took UBR-UBR		84/104 (80.8)	68/88 (77.3%)

This table was adapted from the CSR for study MD-01, tables 11-15 and 11-19

For patients initially treated with ubrogepant 100 mg who took the optional second dose of IP, there appears to be no additional benefit incurred with taking an additional 100 mg (Table 17). There may be some marginal benefit to an additional dose of 50 mg for those who have already taken 50 mg.

Table 17 Study MD-01: Results of the Analysis of the Optional Second Dose on Pain Freedom

	PBO/PBO	50 mg/PBO	50 mg/50 mg	100 mg/PBO	100 mg/100 mg
Responder	25/173 (15%)	10/52 (19.2%)	27/84 (32.1%)	19/79 (24.1%)	18/68 (26.5%)
Diff from UBR/PBO			12.9%		2.4%
*NNT			7.8		41.8
OR (95% CI)			2.15 (0.92, 5.0)		1.12 (0.52, 2.4)
p-value			0.08		0.78

This table was adapted from the CSR for study MD-01, table 11-19. Per the applicant, odds ratio (95% CI) and p-value are based on logistic regression with treatment sequence, historical triptan response, use of medication for migraine prevention, and pain severity at time of optional second dose as explanatory variables.
*NNT was calculated by the reviewer.

Reviewer's comment: At the EOP2, the applicant asked if the option for repeat dosing could be included in the product label at a minimum of 2 hours after the first dose, if needed. The Division told the applicant that to include efficacy data, patients that received active study drug would have to be re-randomized to a second dose of medication and be evaluated for pain-freedom at two hours post-dose. The applicant randomized patients at the start of the study to initial treatment and optional treatment. Patients were not re-randomized at the time they opted to take the second dose of IP. Patients did not have to take an additional dose of IP. They could opt to take either their own rescue medication or use another dose of IP. I think this analysis is quite limited and minimal conclusions should be drawn as there are many factors that could have influenced the reason why patients opted to take (or not take) the second dose of IP. Many patients (about half) who could have potentially taken the second dose were lost in this scenario. Of those who did opt for the second dose of IP, efficacy data is not available on about 20%. The optional second dose could be taken any time after the 2-hour efficacy endpoint was measured. This resulted in a wider time window in which the second dose could be taken, and potentially results in a wider range of maximum exposure achieved with a second dose.

6.2 UBR-MD-02: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

6.2.1. Study Design

Trial Design

Study MD-02 was identically designed to study MD-01. The primary difference was in the doses studied. In study MD-01, the doses studied were 50 mg and 100 mg vs placebo. In study MD-02, the doses studied were 25 mg and 50 mg vs placebo. For this study, a total of 100 study centers in the United States screened patients, and 99 of them randomized at least one patient to treatment.

Please refer to section 6.1.1 Study Design for UBR-MD-01 as these elements are all applicable to study MD-02 with the exception of the doses chosen for the treatment arms.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the study was conducted in compliance with ICH E6 guidelines for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted. The applicant asserts that investigators obtained institutional review board (IRB) approval prior to study initiation.

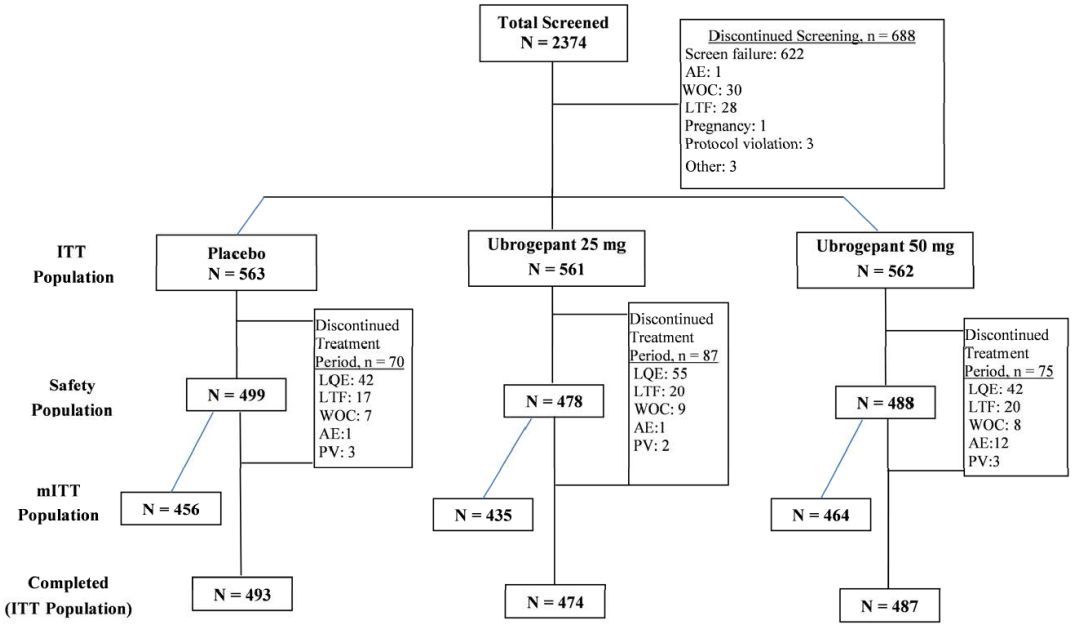
Financial Disclosure

Please see Appendix section 13.2

Patient Disposition

Screened: 2374
Randomized: 1686 (placebo: 25 mg: 50 mg 563: 561: 562)
Received at least 1 dose of double-blind IP: 1465 (placebo: 25 mg: 50 mg 485: 466: 485)
mITT population: 1355 (placebo: 50 mg: 100 mg 456: 423: 448)

Figure 4 Study MD-02: Patient Disposition Flow Chart



AE = adverse event; ITT = intent to treat; LQE = lack of qualifying event; LTF = lost to follow-up; mITT = modified intent to treat; PV = protocol violation; WOC = withdrawal of consent

This figure was taken from the CSR for study MD-02

There were 1465 patients who took IP, but only 1355 who are included in the mITT. A total of 110 patients who took IP were excluded from the mITT (Table 18).

Table 18 Study MD-02: Randomized Patients Excluded from the mITT Population

Reason for Exclusion	Number of Patients
Did not take study medication	221
Did not record baseline migraine headache	15
Did not record postdose migraine severity	95

This table was adapted from an IR response dated April 11, 2019, eCTD 0010

Protocol Violations/Deviations

The most common protocol deviation was use of a prohibited concomitant medication. Overall the protocol deviations were low, generally balanced among treatment arms, and not expected to affect the primary efficacy outcome (Table 19).

Table 19 Study MD-02: Protocol Deviations/Violations in the ITT Population

Protocol Deviation	Placebo N=563 n(%)	25 mg N=561 n(%)	50 mg N=562 n(%)
Exclusion criteria	10 (1.8)	5 (0.9)	10 (1.8)
Wrong IP treatment	0	1 (0.2)	1 (0.2)
Prohibited concomitant medication	25 (4.4)	21 (3.7)	34 (6.0)
Informed consent	9 (1.6)	7 (1.2)	10 (1.8)
Pregnancy	0	2 (0.4)	0

This table was adapted from the CSR for study MD-02, Table 10-3

Table of Demographic Characteristics

No baseline imbalance in the demographics were noted between placebo and treatment groups in the demographic characteristics or the baseline migraine severity characteristics (Table 20 and Table 21).

Table 20 Study MD-02: Demographic Characteristics of All Randomized Patients (ITT)

Demographic Parameters	Placebo (N=563) n (%)	Treatment Group		
		25 mg (N=561) n (%)	50 mg (N=562) n (%)	Total (N=1686) n (%)
Sex				
Male	69 (12.3)	60 (10.7)	65 (11.6)	194 (11.5)
Female	494 (87.7)	501 (89.3)	497 (88.4)	1492 (88.5)
Age				
Mean years (SD)	41.5 (12.2)	41.6 (12.3)	41 (12.4)	41.4 (12.3)
Median (years)	41.0	41.0	41.0	41.0
Min, max (years)	18, 73	18, 71	18, 75	18, 75
Age Group*				
18 to 40	269 (47.8)	274 (48.8)	277 (49.3)	820 (48.6)
41 to 64	283 (50.3)	267 (47.6)	262 (46.6)	812 (48.2)
65 to 75	11 (2.0)	20 (3.6)	23 (4.1)	54 (3.2)
Race				
White	449 (79.8)	467 (83.2)	456 (81.1)	1372 (81.4)
Black or African American	94 (16.7)	82 (14.6)	93 (16.5)	269 (16.0)
Asian	8 (1.4)	6 (1.1)	5 (0.9)	19 (1.1)
American Indian or Alaska Native	4 (0.7)	1 (0.2)	4 (0.7)	9 (0.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Other/Multiple	7 (1.2)	4 (0.7)	3 (0.5)	14 (0.8)
Ethnicity				
Hispanic or Latino	116 (20.6)	129 (23.0)	125 (22.2)	370 (21.9)
Not Hispanic or Latino	447 (79.4)	432 (77.0)	437 (77.8)	1316 (78.1)
Concomitant preventive medication				
Yes	135 (24.0)	135 (24.1)	135 (24.0)	405 (24.0)
Body Mass Index (BMI) kg/m²				
Mean (SD)	29.7 (7.6)	29.5 (7.2)	30.4 (7.4)	29.9 (7.4)
Median	28.3	28.1	29.4	28.7
Min, Max	16, 74	17, 66	16, 67	16, 74

This table was adapted from the CSR for study MD-02, table 14.1-2.1.A
*Age group was calculated by the reviewer in JMP using ADSL for MD-02, analysis by planned treatment

Table 21 Study MD-02: Baseline Migraine Characteristics for the mITT Population

	Placebo N=456 n(%)	25 mg N=435 n(%)	50 mg N=464 n(%)
Migraine headache severity			
Moderate	258 (56.6)	257 (59.1)	289 (62.3)
Severe	198 (43.4)	178 (40.9)	175 (37.7)
Most bothersome symptom (MBS)			
Photophobia	245 (53.7)	257 (59.1)	265 (57.1)
Phonophobia	136 (29.8)	102 (23.4)	115 (24.8)
Nausea	75 (16.4)	75 (17.2)	83 (17.9)
Missing	0	1 (0.2)	1 (0.2)

This table is adapted from the CSR for study MD-02, table 14.1-6.1

Table 22 Study MD-02: Migraine History (Safety Population)

	Placebo N=499	25 mg N=478	50 mg N=488
Duration of Migraine History			
Median (years)	17	17	16
Migraine Diagnosis			
Without aura n(%)	264 (52.9)	237 (49.6)	249 (51.0)
With aura n(%)	113 (22.6)	128 (26.8)	106 (21.7)
Both	122 (24.4)	113 (23.6)	133 (37.3)
Average Frequency of Mod to Sev Migraines in the Last 3 months			
Median	4	4	4
Min, Max	2, 8	2, 8	2, 8

This table is adapted from the CSR for study MD-02, table 14.1-4.2

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatments in this study were a single tablet of placebo, 25 mg of ubrogepant, or 50 mg of ubrogepant. The IP was distributed in 25 mg or 50 mg tablets or matching placebo. This study differed from study MD-01 in which two tablets needed to be taken to maintain the blind. In study MD-02, compliance with taking two tablets was not an issue as only one tablet was needed to be taken at migraine onset in study MD-02.
About 24% of patients were taking concomitant migraine preventive medications. The percentage of patients was balanced across all three treatment groups (Table 20).

Use of rescue medication will be discussed in the efficacy results for the secondary endpoints related to sustained pain freedom and sustained pain relief.

Efficacy Results – Primary Endpoint

The co-primary endpoints for this study were as follows:

1. Pain freedom two hours after the initial dose
2. Absence of most bothersome symptom (MBS) two hours after the initial dose

The efficacy analyses were based on the mITT population. Statistically significant results were observed for the 25 mg and 50 mg doses on the endpoint for pain freedom at 2 hours. However, the 25 mg dose had only nominal significance on absence of MBS at 2 hours after adjustments for multiplicity. These results were verified by the statistical reviewer, Dr. Jinnan Liu. She confirmed the applicant's analysis and calculation of the unadjusted (raw) p-values.

Table 23 Study MD-02: Results for the Co-Primary Efficacy Endpoints

	Placebo N=456	25 mg N=435	50 mg N=464
Pain Freedom at 2 hours			
Responders, n(%)	65 (14.3)	90 (20.7)	101 (21.8)
Odds Ratio		1.6	1.6
Adjusted p-value*		0.0285	0.0129
Unadjusted p-value		0.0143	0.0065
(95% CI)		(1.1, 2.2)	(1.1, 2.3)
NNT**		15.6	13.3
Absence of MBS at 2 hours			
Responders, n(%)	125 (27.4)	148 (34.1)	180 (38.9)
Odds Ratio		1.4	1.7
Adjusted p-value*		0.0711	0.0129
Unadjusted p-value		0.0355	0.0065
(95% CI)		(1.0, 1.8)	(1.3, 2.2)

	Placebo N=456	25 mg N=435	50 mg N=464
NNT**		14.9	8.7

This table was adapted from the clinical overview, Table 4-1
*Adjusted p-values are from hypothesis testing using a graphical approach with closed testing procedure to control for multiplicity; Unadjusted p-value refers to the raw p-value before testing procedures to control for multiplicity are applied; Both the adjusted and raw p-values are calculated using a logistical regression model. **Number-needed-to-treat (NNT) was calculated by the reviewer.

Data Quality and Integrity

The data quality and analysis quality are adequate. The statistical reviewer was able to perform independent review using the applicant's submitted datasets and confirm the applicant's analysis results.

Efficacy Results – Secondary and other relevant endpoints

The following were the secondary endpoints:

1. Pain relief two hours after the initial dose
2. Sustained pain relief from 2 to 24 hours after the initial dose
3. Sustained pain freedom from 2 to 24 after the initial dose
4. Absence of photophobia at 2 hours after the initial dose
5. Absence of phonophobia at 2 hours after the initial dose
6. Absence of nausea at 2 hours after the initial dose

Ubrogepant 50 mg demonstrated statistically significant findings on 5 out of the 6 secondary endpoints, while ubrogepant 25 mg demonstrated statistically significant findings on none of the secondary endpoints. Response rates for ubrogepant 25 mg were not statistically significant after multiplicity adjustment because 25 mg failed to reach statistical significance on the co-primary endpoint, specifically the MBS. The co-primary endpoints served as the gatekeeper for testing the secondary endpoints, so the testing procedures stopped after the analysis of the primary endpoint for the 25 mg dose.

Table 24 Study MD-02: Secondary Endpoints Reaching Statistical Significance

	Pain Relief (PR)	SPR (2 to 24 hours)	SPF (2 to 24 hours)	Photophobia	Phonophobia	Nausea
25 mg	y	y	y		y	
50 mg	x	x	x	x	x	

SPR: sustained pain relief; SPF: sustained pain freedom

x=statistically significant
y=nominally significant

Ubrogepant 50 mg showed nominal significance compared to placebo on absence of nausea. Ubrogepant 25 mg showed nominal significance compared to placebo on all the secondary endpoints except for absence of photophobia.

Table 25 Study MD-02: Results for the Secondary Endpoints

	Placebo N=456	25 mg N=435	50 mg N=464
Pain Relief at 2 hours			
Responders, n(%)	220 (48.2)	263 (60.5)	291 (62.7)
Odds Ratio		1.7	1.8
(95% CI)		(1.3, 2.2)	(1.4, 2.3)
Adjusted p-value		0.0711	0.0129[x]
Unadjusted p-value		0.004[y]	<0.0001
NNT*		8.1	6.9
SPR from 2-24 hours			
Responders, n(%)	93 (21.0)	138 (32.5)	165 (36.7)
Odds Ratio		1.8	2.2
(95% CI)		(1.3, 2.5)	(1.6, 2.9)
Adjusted p-value		0.0711	0.0129[x]
Unadjusted p-value		<0.0002[y]	<0.0001
SPF from 2-24 hours			
Responders, n(%)	37 (8.2)	55 (12.7)	66 (14.4)
Odds Ratio		1.6	1.9
(95% CI)		(1.0, 2.5)	(1.2, 2.8)
Adjusted p-value		0.0711	0.0129[x]
Unadjusted p-value		0.0317[y]	0.0051
Absence of photophobia			
Responders, n(%)	162 (35.5)	171 (39.3)	203 (43.8)
Odds Ratio		1.3	1.5
(95% CI)		(1.0, 1.7)	(1.1, 2.0)
Adjusted p-value		0.18	0.02[x]
Unadjusted p-value		0.09	<0.001
Absence of phonophobia			
Responders, n(%)	211 (46.3)	233 (53.6)	251 (54.1)
Odds Ratio		1.4	1.4
(95% CI)		(1.0, 1.8)	(1.0, 1.8)

	Placebo N=456	25 mg N=435	50 mg N=464
Adjusted p-value		0.1066	0.0440[x]
Unadjusted p-value		0.0266[y]	0.0220
Absence of nausea			
Responders, n(%)	319 (70.0)	307 (70.6)	331 (71.3)
Odds Ratio		1.1	1.1
(95% CI)		(0.8, 1.5)	(0.8, 1.5)
Adjusted p-value		0.9522	0.9522
Unadjusted p-value		0.5410	0.4761

This table was adapted from the clinical overview, Table 4-1
*NNT was calculated by the reviewer; Unadjusted p-value refers to the p-value before testing procedures to control for multiplicity are applied
x=statistically significant
y=nominally significant

Reviewer's comment: The analyses of the secondary endpoints were verified by the statistical reviewer. Dr. Liu's review verified the adjusted and unadjusted (raw) p-values for the secondary endpoints for study MD-02.

Dose/Dose Response

This will be addressed in section 7.1.4.

Sensitivity Analyses Conducted on Study MD-02

The applicant conducted a sensitivity analysis on the primary endpoint of pain freedom at 2 hours. This analysis utilized the mITT population, and patients who were missing the 2-hour time point were assumed to be non-responders (Table 26). This analysis supports the conclusion that the 25 mg and 50 mg doses are effective on the primary endpoint, migraine pain freedom two hours after dosing. This result was confirmed by Dr. Liu, statistical reviewer.

Table 26 Sensitivity Analysis of the Primary Endpoint: Missing Assumed as Non-Responders

	Placebo N=456	25 mg N=435	50 mg N=464
Pain Freedom at 2 hours			
Responders, n(%)	59 (12.9)	85 (19.5)	97 (20.9)
Odds Ratio		1.6	1.7
(95% CI)		(1.1, 2.3)	(1.2, 2.5)
p-value		0.010	0.003

This table is adapted from Table 11-4 in the CSR for study MD-02.

In a written communication to the applicant regarding study MD-02, dated May 24, 2018, the Division requested that the applicant conduct additional sensitivity analyses on the co-primary endpoints assuming different missing data mechanisms. The Division did not specify which assumptions should be made. The applicant opted to conduct a sensitivity analysis on the missing data assuming missing at random (Table 27). This analysis was confirmed by the statistical reviewer and supports the conclusion that the 25 mg and 50 mg doses are effective on the primary endpoint, migraine pain freedom two hours after dosing.

Table 27 Sensitivity Analysis of the Primary Endpoint: Missing at Random

	Placebo N=456	25 mg N=435	50 mg N=464
Pain Freedom at 2 hours			
Responders, n(%)	12.1	18.1	18.8
Odds Ratio		1.6	1.7
(95% CI)		(1.1, 2.3)	(1.2, 2.4)
p-value		0.010	0.004

This table is adapted from Table 11-5 in the CSR for study MD-02.

Dr. Liu conducted additional sensitivity analyses on the co-primary endpoints to evaluate patients who used rescue medication prior to the 2 -hour timepoint measurement. In these analyses, Dr. Liu counted patients who took rescue medication prior to the 2-hour timepoint measurement as treatment failures. The results of the additional sensitivity analyses for the co-primary endpoint pain freedom at 2 hours were consistent with the results of the primary analysis. However, the p-value for the sensitivity analysis for MBS freedom at 2 hours is larger than 0.05 (p=0.0514) when considering patients who took rescue medication as treatment failures.

Additional Analyses Conducted on the Individual Trial

Endpoints discussed in this section were not included in the testing hierarchy and therefore not controlled for type-1 error. The p-values reported in this section are unadjusted.

Use of Rescue Medication: defined as either the optional second dose of IP or another medication for the acute treatment of migraine or both, within 24 to 48 hours of the initial dose of IP.

Within 24 hours of taking the initial dose of IP, 68% of patients in the placebo arm took rescue medication compared to 59% and 53% of patients in the ubrogepant 25 mg and 50 mg treatment arms, respectively (Table 28). For the analysis shown in Table 28, rescue medication

here is inclusive of taking either the optional second dose of IP or taking another medication for the acute treatment of migraine.

Table 28 Study MD-02: Use of Rescue Medication

	Placebo N=456	25 mg N=435	50 mg N=464
Within 24 hours			
Took Rescue Medication, n(%)	312 (68.4)	257 (59.1)	246 (53.0)
Difference from PBO		-9.3%	-15.4%
Odds Ratio (95% CI)		0.7 (0.5, 0.9)	0.5 (0.4, 0.7)
p-value		0.005	0.0001

This table is adapted from Table 11-17 in the CSR for study MD-02.

Optional Second Dose: Patients could take an optional second dose of IP starting at 2 hours after the initial dose of IP and up to 48 hours after the initial dose of IP. Patients who took the second dose of IP could not take other rescue medication for at least two hours following the second dose of IP. Patients could take the optional second dose if they continued to have a moderate to severe headache, or if a moderate to severe headache returned within 2 to 48 hours after the initial dose.

In Table 29, if we first consider those patients who did not respond to the initial dose of IP (i.e., not pain free at 2 hours) (line 1), then those patients who took the drug and provided a two-hour assessment would be considered the mITT. For a variety of reasons, there is a huge loss of patients from the population who did not respond initially to the IP to mITT population (approximately 51%). There is about a 20% loss of patients from the population who took the optional second dose to the mITT.

Table 29 Study MD-02: Use of Optional Second Dose

	Placebo N=456	25 mg N=435	50 mg N=464
Patients who did not respond to initial dose of IP	391	345	363
Took optional second dose	202/391 (51.7%)	180/345 (52.2%)	179/363 (49.3%)
Took UBR-PBO		88	94
Took UBR-UBR		92	85

Took Optional Second Dose and had non-missing 2-hour measurement (mITT)	164/202 (81.2%)	149/180 (82.8%)	151/179 (84.4%)
Took UBR-PBO		66/88 (75.0%)	79/94 (84.0%)
Took UBR-UBR		83/92 (90.2%)	72/85 (84.7%)

This table was adapted from the CSR for study MD-02, tables 11-17 and 11-21

For patients initially treated with ubrogepant who took the optional second dose of IP, there appears to be very little additional benefit incurred with taking an additional 25 mg. There may be some additional benefit to an additional dose of 50 mg for those who have already taken a dose of 50 mg.

Table 30 Study MD-02: Results of the Analysis of the Optional Second Dose on Pain Freedom

	PBO/PBO	25 mg/PBO	25 mg/25 mg	50 mg/PBO	50 mg/50 mg
Responder	25/164 (15.2%)	15/66 (22.7%)	25/83 (30.1%)	15/79 (19.0%)	26/72 (36.1%)
Diff from UBR/PBO			7.4%		17.1%
NNT			13.5		5.8
OR (95% CI)			1.6 (0.7, 3.4)		2.2 (1.0, 4.7)
p-value			0.3		0.04

This table was adapted from the CSR for study MD-02, table 11-21. Per the applicant, odds ratio (95% CI) and p-value are based on logistic regression with treatment sequence, historical triptan response, use of medication for migraine prevention, and pain severity at time of optional second dose as explanatory variables.

Reviewer's comment At the EOP2, the applicant asked if the option for repeat dosing could be included in the product label at a minimum of 2 hours after the first dose, if needed. The Division told the applicant that to include efficacy data, patients that received active study drug would have to be re-randomized to a second dose of medication and be evaluated for pain-freedom at two hours post-dose. The applicant randomized patients at the start of the study to initial treatment and optional treatment. Patients were not re-randomized at the time they opted to take the second dose of IP. Patients did not have to take an additional dose of IP. They could opt to take either their own rescue medication or use another dose of IP. I think this analysis is quite limited and minimal conclusions should be drawn as there are many factors that could have influenced the reason why patients opted to take (or not take) the second dose of IP. Many patients (about half) who could have potentially taken the second dose were lost in this scenario. Of those who did opt for the second dose of IP, efficacy data is not available on about 20%. The optional second dose could be taken any time after the 2-hour efficacy endpoint was measured. This resulted in a wider time window in which the second dose could be taken, and potentially results in a wider range of maximum exposure achieved with a second dose.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

For both pivotal efficacy studies (MD-01 and MD-02), the applicant used the co-primary endpoints as outlined by the Migraine Guidance for Industry. These co-primary endpoints were pain freedom and absence of most bothersome symptom at 2 hours after dosing. These two studies were identically designed except for the doses studied. The treatment effect measured in each of the two pivotal studies was statistically significant for each of the co-primary endpoints for the 50 mg and 100 mg doses. Additionally, the 25 mg dose reached statistical significance for pain freedom at 2 hours, but only nominal significance for absence of MBS at 2 hours.

Table 31 Summary of Findings for the Co-Primary Endpoints for Studies MD-01 and MD-02

	PBO MD-02	25 mg MD-02	50 mg MD-02	PBO MD-01	50 mg MD-01	100 mg MD-01
Pain free at 2 hours (%)	14.3	20.7	21.8	11.8	19.2	21.2
Treatment effect (%)		6.4	7.5		7.4	9.4
Absence of MBS at 2 hours (%)	27.4	34.1	38.9	27.8	38.2	37.7
Treatment effect (%)		6.7	11.5		10.4	9.9

Reviewer created summary table

7.1.2. Secondary and Other Endpoints

Both studies included the same secondary endpoints: pain relief at 2 hours, sustained pain relief at from 2 to 24 hours, and sustained pain freedom from 2 to 24 hours as well as absence of photophobia, phonophobia, and nausea at 2 hours. Table 32 summarizes which doses reached statistical or nominal significance on each of the key secondary endpoints.

Table 32 Summary of Findings for Secondary Endpoints

	Pain Relief (PR)	SPR (2-24 hours)	SPF (2-24 hours)	Photophobia	Phonophobia	Nausea
25 mg (MD-02)	y	y	y		y	
50 mg	x	x	x	x	x	

(MD-02)						
50 mg (MD-01)	x	x	y	y	y	
100 mg (MD-01)	x	x	x	x	y	y

SPR: sustained pain relief; SPF: sustained pain freedom; x-statistically significant; y-nominally significant

In study MD-01, ubrogepant 100 mg showed nominal significance over placebo for absence of phonophobia and nausea 2 hours after the initial dose. Ubrogepant 50 mg showed nominal significance over placebo for SPF 2-24 hours, and absence of photophobia and phonophobia at 2 hours. There was no significant difference versus placebo for ubrogepant 50 mg for absence of nausea. In study MD-02, ubrogepant 50 mg showed statistical significance on all secondary endpoints except freedom from nausea.

Table 33 Summary of the Treatment Effect for Each Key Secondary Endpoint

	PBO MD-02	25 mg MD-02	50 mg MD-02	PBO MD-01	50 mg MD-01	100 mg MD-01
Pain relief (%)	48.2	60.5	62.7	49.1	60.7	61.4
Treatment effect (PBO-UBR %)		12.3	14.5		11.6	12.3
SPR at 24 hrs(%)	21.0	32.5	36.7	20.8	36.3	38.0
Treatment effect (PBO-UBR %)		11.5	15.7		15.5	17.2
SPF at 24 hrs (%)	8.2	12.7	14.4	8.6	12.7	15.4
Treatment effect (PBO-UBR %)		4.5	6.2		4.1	6.8
Photophobia (%)	35.5	39.3	43.8	31.4	40.7	45.8
Treatment effect (PBO-UBR %)		3.8	8.3		9.3	5.1
Phonophobia (%)	46.3	53.6	54.1	47.1	57.9	54.5
Treatment effect (PBO-UBR %)		7.3	7.8		10.8	7.4
Nausea (%)	70.0	70.6	71.3	62.3	70.2	69.2
Treatment effect (PBO-UBR %)		0.6	1.3		7.9	6.9

This table was adapted from the SCE. Treatment effect (%) was calculated by the reviewer

7.1.3. Subpopulations

The applicant performed subpopulation analyses on pooled data for studies MD-01 and MD-02. Only results for the 50 mg dose will be reported in this section as this was the only dose common to the two studies. I will present the applicants results of the pooled analyses by age, and sex, as well as my analysis by BMI ≥30 kg/m².

Analyses Pooled by Age

The applicant conducted pooled analyses by age for patients ≥65 years for pain freedom at 2 hours and absence of most bothersome symptom. It appears that there is no treatment effect in patients over age 65. For both co-primary endpoints, the results showed a treatment effect in favor of placebo.

Table 34 Pooled Analyses of the Co-primary Endpoint Efficacy Results

	Placebo	50 mg
Pain Freedom at 2 hours		
N1 (patients ≥65)	23	26
Responders, n(%)	6 (26.1)	3 (11.5)
Odds Ratio		0.36
(95% CI)		(0.1, 1.7)
Treatment effect (%)		-14.6%
Absence of MBS at 2 hours		
N1 (patients ≥65)	23	25
Responders, n(%)	9 (39.1)	9 (36.0)
Odds Ratio		0.89
(95% CI)		(0.3, 2.9)
Treatment effect (%)		-3.1%
Pain Freedom at 2 hours		
N1 (patients <65)	889	860
Responders, n(%)	113 (12.7)	179 (20.8)
Odds Ratio		1.8
(95% CI)		(1.4, 2.3)
Treatment effect (%)		8.1%
Absence of MBS at 2 hours		
N1 (patients <65)	887	858
Responders, n(%)	242 (27.3)	333 (38.8)
Odds Ratio		1.7
(95% CI)		(1.4, 2.1)

Treatment effect (%)		11.5%

This table was adapted from the SCE tables 3-19 and 3-22

Reviewer's comment: This analysis is not powered to detect a treatment effect in the patient population over age 65. However, it is still an interesting and somewhat concerning finding. (b) (4) *This finding potentially alters the risk-benefit profile for treatment of patients over age 65.*

Analyses Pooled by Sex

The applicant conducted pooled analyses by sex for pain freedom at 2 hours and absence of most bothersome symptom. It appears that there is no treatment effect in male patients.

Table 35 Pooled Analyses of the Co-Primary Endpoint Efficacy Results by Sex

	Placebo	50 mg
Pain Freedom at 2 hours		
Responders, n (%) Male	17 (16.5)	14 (16.7)
Treatment effect (%)		0.2
Responders, n (%) Female	102 (12.6)	168 (20.9)
Treatment effect (%)		8.3
Absence of MBS at 2 hours		
Responders, n (%) Male	34 (33.0)	28 (33.7)
Treatment effect (%)		0.7
Responders, n (%) Female	217 (26.9)	314 (39.3)
Treatment effect (%)		12.4

This table was adapted from the SCE tables 3-20 and 3-23

Reviewer's comment: Again, this analysis was not powered to detect a treatment effect in the male population. However, it is still an interesting and somewhat concerning finding. (b) (4)

Analysis Pooled by BMI

I conducted an analysis of the co-primary endpoints on patients who had a BMI ≥ 30 kg/m² (Table 36). This was the median BMI in the two pivotal studies.

Table 36 Pooled Analyses of the Co-Primary Endpoint Efficacy Results by BMI

	Placebo	50 mg
Pain Freedom at 2 hours		
N1 (BMI ≥30 kg/m²)	369	398
Responders, n(%)	51 (13.8)	63 (15.8)
Treatment effect (%)		2.0
Absence of MBS at 2 hours		
N1 (BMI ≥ 30 kg/m²)	367	397
Responders, n(%)	98 (10.4)	138 (34.8)
Treatment effect (%)		24.4
Pain Freedom at 2 hours		
N1 (BMI <30 kg/m²)	535	479
Responders, n(%)	68 (12.7)	117 (24.4)
Treatment effect (%)		11.7
Absence of MBS at 2 hours		
N1 (BMI <30 kg/m²)	533	477
Responders, n(%)	150 (28.1)	202 (42.3)
Treatment effect (%)		14.2

Reviewer created table from ISE ADAM dataset ADEFF join with ADSL where PARAMCD=PAINFRE or AMBTS and AVISIT=2

Reviewer's comment: (b) (4) *The applicant did not include analyses by BMI, so I conducted this analyses to see if efficacy would be affected by body weight with the use of ubrogepant. There appears to be reduced efficacy for pain freedom at 2 hours, but a preserved treatment effect for absence of MBS at 2 hours. The reason for that discrepancy is not clear.*

7.1.4. Dose and Dose-Response

In addition to the two pivotal studies, the applicant also conducted a phase 2 dose finding study of ubrogepant for the acute treatment of migraine. In study P006, the applicant evaluated doses of 1mg, 10mg, 25 mg, 50 mg, and 100 mg. Patients received a single dose of IP to treat a migraine. In this study, 100 mg showed statistically significant findings on pain freedom at 2 hours while 25 mg and 50 mg had nominal significance on pain freedom at 2 hours. Absence of MBS was not evaluated.

In the two pivotal studies, the 50 mg and 100 mg doses performed similarly. In fact, the confidence intervals in study MD-01 for the 50 mg and 100 mg almost completely overlap for

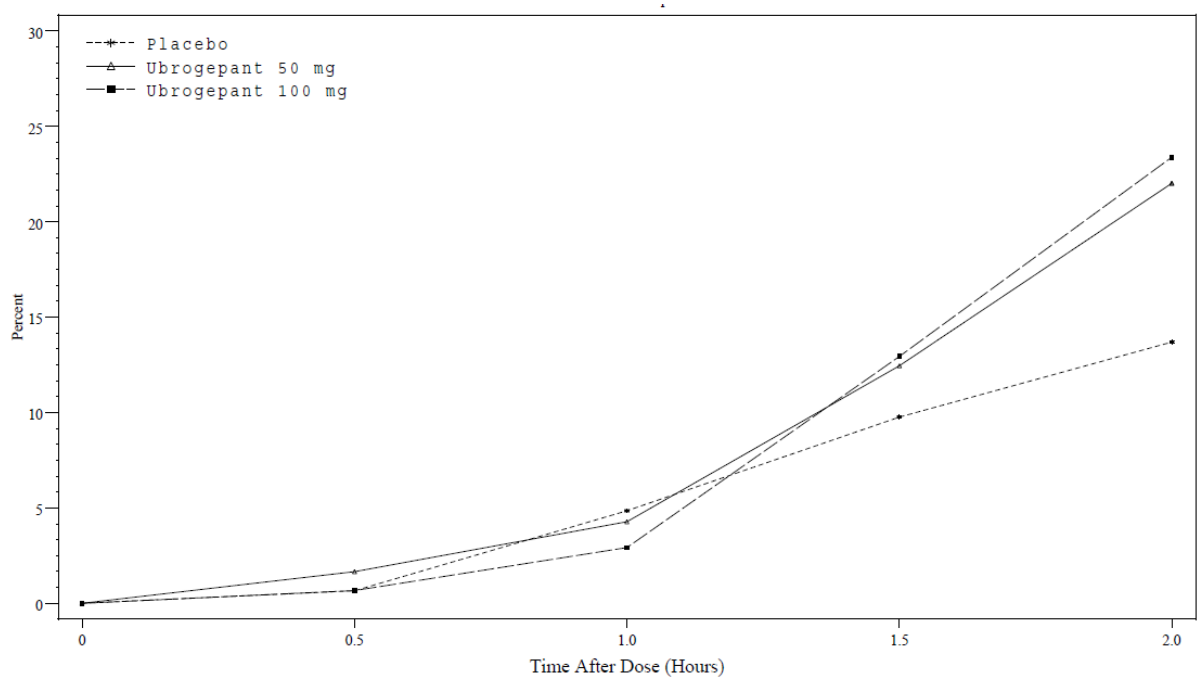
the endpoint absence of MBS. For study MD-02, the confidence intervals for the 25 mg and 50 mg dose almost completely overlap for the endpoint pain freedom at 2 hours. From 50 mg to 100 mg, there is almost no increase in efficacy, and the dose response is quite flat. From 25 mg to 50 mg, there is a slight increase in efficacy on the MBS endpoint, but almost no increase in efficacy on pain freedom at 2 hours.

7.1.5. Onset and Durability of Efficacy Effects

Onset of Effect

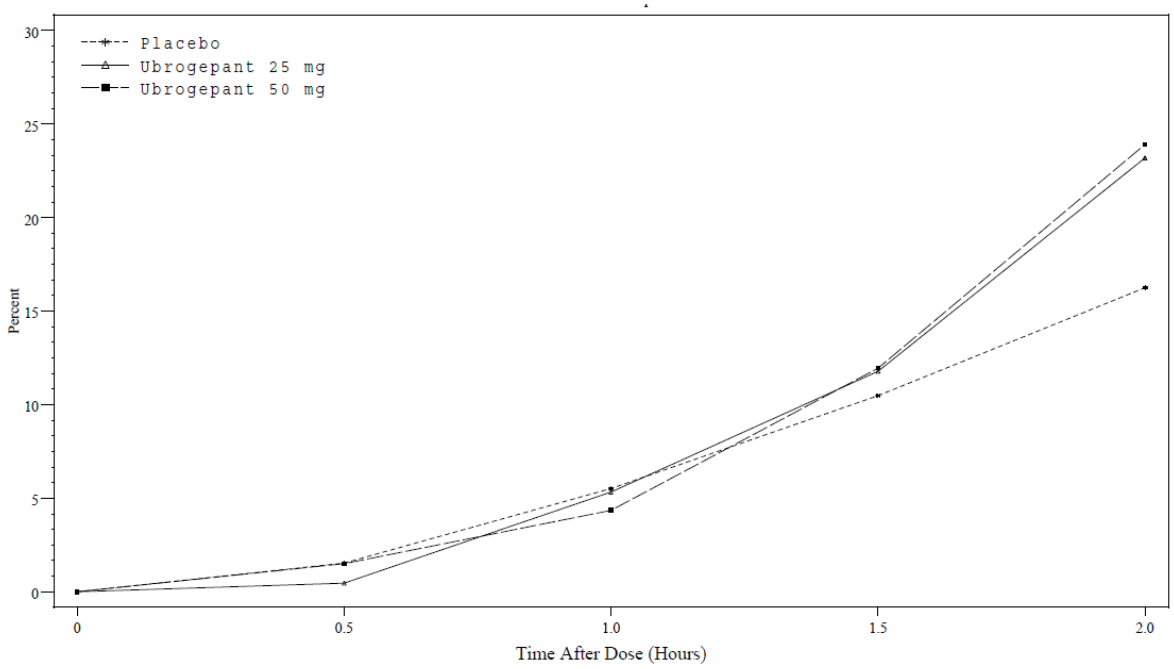
The onset of effect appears to begin at 1.5 hours after the initial dose was taken. This corresponds to the median time of Tmax. The separation from placebo occurs at about 1.5 hours after the administration of ubrogepant for the time to pain freedom. This is evident in the individual studies, as well as the pooled data for the 50 mg dose (Figure 5, Figure 6, and Figure 7).

Figure 5 Study MD-01: Time to Pain Freedom



This figure was taken from the CSR for study MD-01, figure 14.2-3.1

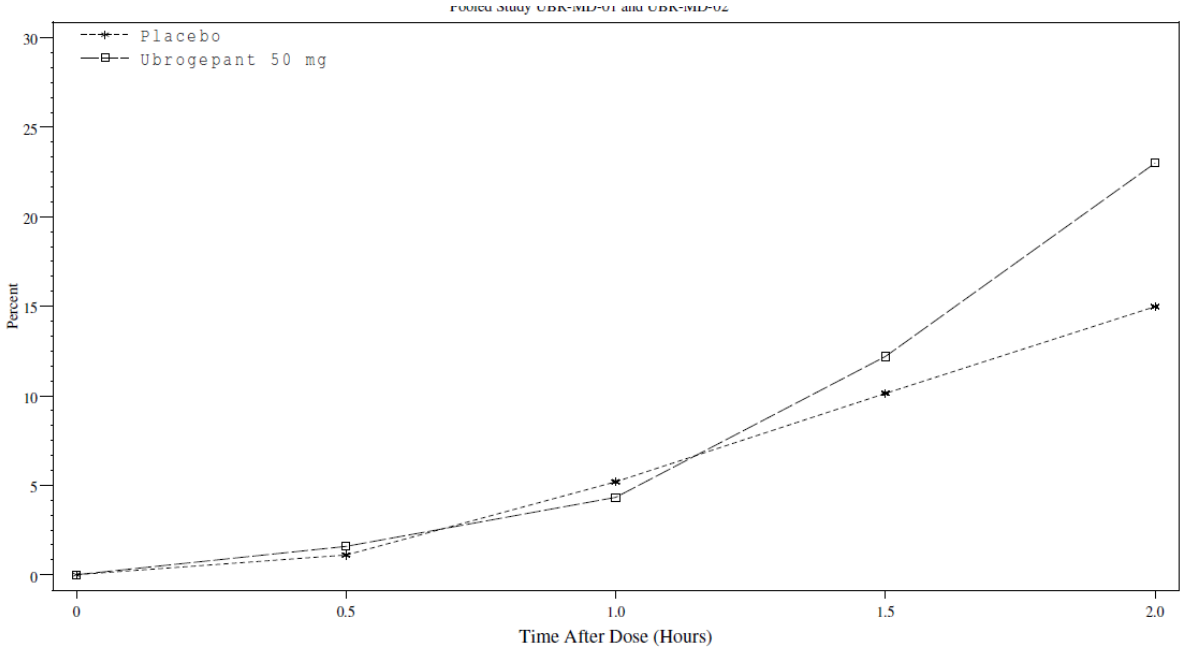
Figure 6 Study MD-02: Time to Pain Freedom



This figure was taken from the CSR for Study MD-02, figure 14.2-3.1

Figure 7 Time to Pain Freedom (Pooled Data from MD-01 and MD-02)

APPEARS THIS WAY ON ORIGINAL



This figure was taken from SCE figure 2-1.1

Durability of Effect

The applicant evaluated the secondary endpoint sustained pain freedom from 2 to 24 hours. Sustained pain freedom is defined as pain freedom with no administration of either rescue medication or second dose of IP, and with no occurrence of a headache of any intensity for 2 to 24 hours after the dose of IP is taken. For those patients receiving ubrogepant 13 to 15% experienced sustained pain freedom as compared to 8 to 9% of patients receiving placebo. When examining those patients who were pain free at 2 hours, almost all of the patients who were pain free at 2 hours were pain free at 24 hours whether the patient took ubrogepant or placebo. Of the patients receiving ubrogepant who were pain free at 2 hours, 61 to 72% experienced sustained pain freedom compared to 57 to 72% who received placebo. In other words, pain freedom at 2 hours was predictive of pain freedom at 24 hours whether active drug or placebo was taken.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The applicant attempted to capture the population that will most likely benefit from the use of ubrogepant. However, there are few issues that may arise in the postmarketing setting when the drug becomes more widely available that were not captured in the development program. The development plan included some patients over age 65. The limited efficacy data on this population suggests that there is no treatment effect in patients age 65 and older. There is limited data to inform on the safety of the product in patients over age 65. This could

potentially alter the risk-benefit ratio in patients over age 65. In addition, patients who are obese (BMI ≥30 kg/m²) have a reduced treatment effect, most notably on the endpoint pain freedom at 2 hours. This may be problematic in the U.S. population where approximately 40% of the population is obese.

7.3. Integrated Assessment of Effectiveness

The applicant has submitted enough evidence to meet the statutory evidentiary standard. Studies MD-01 and MD-02 both provide evidence that 50 mg of ubrogepant is an effective dose for the acute treatment of migraine. Study MD-01 shows that the 100 mg dose is an effective dose for the treatment of migraine as well. Study MD-02 included a 25 mg dose which showed statistical significance for the endpoint pain freedom at 2 hours, and nominal significance for the endpoint absence of most bothersome symptoms at 2 hours. The efficacy of ubrogepant is also supported by the results of several key secondary endpoints. Ubrogepant 100 mg reached statistical significance on pain relief, sustained pain relief, sustained pain freedom, and absence of photophobia with nominal significance on absence of phonophobia and nausea. Ubrogepant 50 mg reached statistical significance on pain relief and sustained pain relief in both studies, and in MD-02 also reached statistical significance on sustained pain freedom, absence of photophobia, and phonophobia. In study MD-01, the 50 mg dose reached only nominal significance on certain secondary endpoints that otherwise showed statistical significance in study MD-02 because of the testing procedure for multiplicity. In addition, because of multiplicity adjustment, the 25 mg dose in study MD-02 reached only nominal significance on freedom from MBS at 2 hours and on the following secondary endpoints: pain relief, sustained pain relief, sustained pain freedom, and phonophobia.

Subgroup analyses suggest absent to reduced efficacy in patients ≥ age 65, male patients, and obese patients. While these analyses were not powered to detect a difference from placebo, the results are notable (b) (4) In the two pivotal studies, the 50 mg and 100 mg doses performed similarly on the co-primary endpoints. From 50 mg to 100 mg, there is almost no increase in efficacy, and the dose response is quite flat. From 25 mg to 50 mg, there is a slight increase in efficacy on the MBS endpoint, but almost no increase in efficacy on pain freedom at 2 hours.

From my review of the pivotal studies presented in section 6 and summarized in section 7, I recommend approval of all three doses of ubrogepant (25 mg, 50 mg, and 100 mg) for the acute treatment of migraine with and without aura in adults. In my opinion, the studies demonstrate that all three doses are efficacious for the acute treatment of migraine and the lowest efficacious dose should be made available for patients.

8. Review of Safety

8.1. Safety Review Approach

The safety review includes studies MD-01, MD-02, MD-04, P0004, P006, P007, and 3110-105-002. The applicant has defined the safety population as any patient who received one or more doses of IP from these studies.

Table 37 Clinical Studies Contributing to the Integrated Review of Safety

Study	Dose	Patients in double-blind safety set	Patients in open-label safety set
MD-01	Placebo, 50 mg, 100 mg	placebo (485), ubrogepant 50 mg (466), ubrogepant 100 mg (485)	N/A
MD-02	Placebo, 25 mg, 50 mg	placebo (499), ubrogepant 25 mg (478), ubrogepant 50 mg (488)	N/A
MD-04	50 mg or 100 mg	N/A	usual care (417), ubrogepant 50 mg (404), ubrogepant 100 mg (409)
P004	Placebo or 150 mg	placebo (10), ubrogepant 150 mg (22)	N/A
P006	Placebo, 1, 10, 25, 50, 100 mg	placebo (113), ubrogepant 1 mg (107), ubrogepant 10 mg (108), ubrogepant 25 mg (103), ubrogepant 50 mg (107), ubrogepant 100 mg (102)	N/A
P007	Placebo, 1, 10, 25, 50, 100 mg	placebo (28), ubrogepant 1 mg (28), ubrogepant 10 mg (26), ubrogepant 25 mg (28), ubrogepant 50 mg (28), ubrogepant 100 mg (27)	N/A
3110-105-002	Placebo, 100 mg	placebo (260), ubrogepant 100 mg (256)	N/A

The applicant presented the safety analyses in pools: Group 1, 1a, 2, 3, 4, and 5. DNP and Allergan discussed and agreed upon the safety pools during the pre-NDA meeting. The pools are as follows:

Group 1: 4 single-attack migraine studies consisting of data from the 2 pivotal studies (MD-01, and MD-02) and from the 2 dose-ranging studies (P006 and P007) with 2581 patients exposed to ubrogepant
Group 1a: only the 2 pivotal studies with 1917 patients exposed to ubrogepant
Group 2: 52-week, long-term, open-label, extension study; patients could treat up to 8 migraines per month, optional second dose allowed with 813 patients exposed to ubrogepant
Group 3: study 3110-105-002; 8-week intermittent dosing with 100 mg of ubrogepant with 256 exposed to ubrogepant
Group 4: study P004, dosing with ubrogepant 150 mg daily for 28 days
Group 5: pooled safety data from phase 1 clinical pharmacology studies

In this review, I summarize information from the applicant's materials, and supplement them with analyses that I conducted using data from the Summary of Clinical Safety (SCS), the Integrated Summary of Safety (ISS), the 120-day safety update, and the applicant provided datasets. The applicant's datasets were initially analyzed by the Office of Computational Science (OCS) JumpStart team. There were data quality issues found for study MD-02. There were 19 patients whose data were included in the SDTM datasets but were omitted from the ADAM datasets. These data quality issues were corrected prior to the filing meeting.

The analyses that I performed on the applicant-provided datasets were carried out using the JMP software program. The primary safety data comes from Group 1a, pooled data from the pivotal studies. Analyses were conducted primarily on the applicant identified pools. For the adverse event section in this review, I focus on events reported from all the migraine studies to identify commonly reported events and infrequent events of potential concern. I present data from the controlled phase of the migraine studies to identify relative differences in risk by treatment for drug-relatedness.

Anticipated areas of interest for the safety review

The safety concerns that are theoretically associated with CGRP inhibition are cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal. CGRP is a potent vasodilator. The theoretical concern is that CGRP receptor antagonism during times of ischemia may prevent compensatory vasodilatation from occurring. Another potential safety concern is hepatic injury. This concern has arisen with small molecule CGRP receptor inhibitors that were previously in development. Drugs from the 'gepant' class of CGRP receptor antagonists have been reported to cause elevated liver enzymes in the setting of daily use (Yao et al).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 3624 people took at least one dose of ubrogepant during development. Of these, 1567 received at least one dose of ubrogepant 100 mg, the highest dose proposed for marketing.

Table 38 Safety Population, Size, and Denominators for Ubrogepant Across Studies

Safety Database for Ubrogepant		
Clinical Trial Groups	Ubrogepant	Placebo
Group 1	2581	1125
Group 1a	1917	984
Group 2	813	0
Group 3	256	260
Group 4	22	10
Group 5	436	136

The data in this table is adapted from Table 5-3 in the clinical overview.

From the Division's perspective, as per the migraine guidance, to be counted in the long-term safety database, adult patients should treat, on average, a minimum of two migraine attacks per month. Study MD-04 provided the long-term safety data to meet this requirement (Table 39).

Table 39 Study MD-04: Overall Extent of Exposure Per Migraine Guidance

	Total	100 mg	50 mg
≥6 months intermittent treatment	691 (421*)	352 (216*)	339 (205*)
≥12 months intermittent treatment	458 (281*)	232 (147*)	226 (134*)

This table was adapted from Table 14.3-1.2 from the CSR for Study MD-04

*Number treating ≥2 migraine attacks per month on average
This table is adapted from Table 5-2 in the clinical overview

At the time of the 120-day safety update, the overall extent of exposure was largely unchanged.

The number of patients dosed intermittently for up to 6 months was unchanged. The number of patients who dosed intermittently with ubrogepant for ≥12 months increased from 458 to 607 at the time of the completion of study MD-04 (Table 40).

Table 40 Overall Extent of Continuous Exposure (120-Day Safety Update)

	Total	100 mg	50 mg
≥12 months intermittent treatment	607 (364*)	315 (195*)	292 (169*)

*Number treating ≥2 migraine attacks per month on average
This table is adapted from Table 1-1 from the 120-day safety update, eCTD 0012

In the open-label study, MD-04, the majority of patients treated ≥2 and <8 migraines per month. Table 41 shows the number of patients who treated a given average number of attacks per month with ubrogepant over the entire duration of the study. Table 42 shows the number of patients who treated a maximum given number of attacks in at least one month of treatment with ubrogepant. For example, 29 patients treated ≥8 migraines per month for at least one month with ubrogepant 50 mg. However, no patients treated an average of ≥8 migraines per month for every month during the study with ubrogepant 50 mg.

Table 41 Study MD-04: Distribution of Patients by Average Number of Treated Attacks per Month

Average number of attacks per month	50 mg N=404 n(%)	100 mg N=409 n(%)
>0 and <2	177 (43.8)	173 (42.3)
≥2 and <4	164 (40.6)	168 (41.1)
≥4 and <6	57 (14.1)	57 (13.9)
≥6 and <8	6 (1.5)	10 (2.4)
≥8	0	1 (0.2)

This table is adapted from Table 7-8 from the CSR for study MD-04

Table 42 Study MD-04: Distribution of Patients by Maximum Number of Attacks Treated per Month

Maximum number of attacks per month	50 mg N=404 n(%)	100 mg N=409 n(%)

>0 and <2	40 (9.9)	23 (5.6)
≥2 and <4	124 (30.7)	136 (33.3)
≥4 and <6	133 (32.9)	129 (31.5)
≥6 and <8	78 (19.3)	81 (19.8)
≥8	29 (7.2)	40 (9.8)

This table is adapted from Table 7-9 from the CSR for study MD-04

Reviewer's comment: The applicant has included a statement in the label that the safety of (b) (4) *in a 30-day period has not been established. This statement is somewhat misleading. Technically the data shown above (Table 41 and Table 42) support the use of ubrogepant to treat up to 8 migraines a month (i.e., 8 to 16 doses of ubrogepant in 28 days). I think the statement in the label should state: "The safety of treating more than 8 migraines per month has not been established." The applicant does have safety data on use of ubrogepant for 14 out of 28 days per month in healthy volunteers, but not in migraine patients. However, given the concern for medication overuse in patients using acute migraine medications, it would be more prudent to use the safety data from patients using the drug to treat migraines rather than the healthy volunteer studies.*

8.2.2. Relevant characteristics of the safety population:

Migraine occurs more commonly in women than in men. The prevalence of the disease peaks in the fourth decade of life. The demographic characteristics in the ubrogepant development program are not entirely representative of the intended treatment population. Migraine is more prevalent in women than men (3:1), but the ratio in these studies of women to men is on the order of 6:1 or 7:1. The racial distribution of the study population is similar to the U.S. population (https://www.census.gov/quickfacts/fact/table/US/PST045218) with the exception of Asians being somewhat underrepresented. The age of patients enrolled in the studies was appropriate. The applicant allowed patients up to age 75 to enroll. However, the selection criteria for the migraine studies resulted in a relatively healthy population. The migraine studies excluded patients with the following disorders: unstable angina, chronic pain syndromes, major psychiatric disorders, seizure disorders, major neurological disorders, or hepatic disease. Patients with myocardial infarction, TIA, stroke, within 6 months of the study were excluded also. This may limit the generalizability of the safety data to the larger population when considering that postmarketing use will be much less restrictive.

The demographic characteristics of the patients who received at least one dose of IP are presented below (Table 43).

Table 43 Group 1a: Summary of Demographic Characteristics for the Safety Analysis Set

Demographic Parameters	Placebo	Treatment Group	Total

	N=984 n (%)	25 mg N=478 n (%)	50 mg N=954 n (%)	100 mg N=485 n (%)	N=2901 n (%)
Sex					
Male	112 (11.4)	47 (9.8)	92 (9.6)	67 (13.8)	318 (11.0)
Female	872 (88.6)	431 (90.2)	862 (90.4)	418 (86.2)	2583 (89.0)
Age					
Mean years (SD)	41.3 (11.9)	41.6 (12.4)	40.7 (12.1)	40.6 (12.0)	41.0 (12.1)
Median (years)	41.0	41.0	40.0	40.0	40.0
Min, max (years)	18, 74	18, 71	18, 75	18, 75	18, 75
Age Group*					
18 to 40	491 (49.9)	236 (49.4)	491 (51.5)	245 (50.5)	1463 (50.4)
41 to 64	468 (47.6)	225 (47.1)	431 (45.2)	225 (46.4)	1349 (46.5)
65 to 75	25 (2.5)	17 (3.6)	32 (3.3)	15 (3.1)	89 (3.1)
Race					
White	809 (82.2)	399 (83.5)	781 (81.9)	392 (80.8)	2381 (82.1)
Black or African American	139 (14.1)	67 (14.0)	148 (15.5)	75 (15.5)	429 (14.8)
Asian	16 (1.6)	6 (1.3)	9 (0.9)	7 (1.4)	38 (1.3)
American Indian or Alaska Native	6 (0.6)	1 (0.2)	5 (0.5)	4 (0.8)	16 (0.6)
Native Hawaiian or Other Pacific Islander	3 (0.3)	1 (0.2)	2 (0.2)	4 (0.8)	10 (0.3)
Multiple	11 (1.1)	4 (0.8)	9 (0.9)	3 (0.6)	27 (0.9)
Ethnicity					
Hispanic or Latino	152 (15.4)	110 (23.0)	162 (17.0)	56 (11.5)	480 (16.5)
Not Hispanic or Latino	832 (84.6)	368 (77.0)	792 (83.0)	429 (88.5)	2421 (83.5)
BMI (kg/m^2)					
Mean (SD)	29.9 (7.6)	29.6 (7.0)	30.4 (7.8)	30.4 (8.0)	30.1 (7.6)
Median	28.5	28.4	29.2	28.8	28.7
Min, Max	16, 74	17, 63	15, 67	17, 62	15, 74

This table was adapted from ISS appendix Table 3-1a.1.1
*This category was calculated by the reviewer using dataset ADSL submitted in eCTD 0005

8.2.3. Adequacy of the safety database:

The overall exposure to ubrogepant fulfills the minimum ICH guidelines for repeated intermittently used medications (i.e., 1500 exposed overall, 300 to 600 exposed for 6 months, and 100 exposed for one year). The applicant has also fulfilled the requirements as outlined in the Guidance for Industry- Migraine: Developing Drugs for Acute Treatment (Table 39 and Table

40). The guidance recommends that applicants should obtain safety data on at least 100 patients treating, on average, at least two migraine attacks per month for one year with a substantial experience at the highest dose and highest frequency of administration proposed for marketing. The median BMI is fairly reflective of the U.S. population. Major cardiovascular disease, which will be discussed in detail in section 8.5.1, is not represented. The applicant followed patients for up to one month after receiving ubrogepant. The drug has a 5 to 7-hour half-life. This should more than adequately capture AEs while the drug is present in the body.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Allergan's datasets were assessed by the Office of Computational Science using the JumpStart program. As noted above, quality issues with the datasets for study MD-02 were identified and corrected prior to filing. There were 19 patients whose data were in SDTM datasets, but not ADAM datasets.

8.3.2. Categorization of Adverse Events

Adverse events were assessed primarily through the analysis of AEs reported in the 48 hours following administration of IP or the optional second dose of IP. An AE was considered treatment emergent if it were present after the initial dose of IP or worsened in severity if previously present.

The applicant defined adverse events (AEs) as any untoward medical occurrence in a clinical trial subject whether or not it is related to study treatment. Progression or worsening of the disease under study is not reported as an adverse event unless the disease progression is greater than the anticipated natural course of the disease. At each visit, the investigator was instructed to query for adverse events by asking each patient a general, non-directed question: "How have you been feeling since the last visit?" This was to be followed by directed question and examination.

Serious adverse events (SAEs) were defined as any event that results in any of the following outcomes: death, life-threatening, inpatient hospitalization, persistent or significant disability/incapacity, or a congenital birth defect. Other events were considered SAEs if they required medical or surgical intervention to prevent one of the outcomes listed above.

The applicant considered all cancer adverse events as SAEs and any abortion (spontaneous or non-spontaneous) as an SAE.

AEs of Interest

The following adverse events were considered events of special interest: any post-treatment ALT or AST ≥3xULN, any potential Hy's law case, and any suicidal ideation with intent.

8.3.3. Routine Clinical Tests

In studies MD-01 and MD-02, blood and urine samples were collected at screening, 4 days after treatment, and at the 4-week safety follow-up visit. In study MD-04, blood and urine samples were collected at screening and then monthly, and at the 4-week safety follow-up visit. Hematology, chemistry and urinalysis were conducted on the samples at these visits.

Table 44 Clinical Laboratory Tests

Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, high density lipoprotein, low density lipoprotein, total triglycerides
Hematology	Hemoglobin; hematocrit; red blood cell count; red blood cell indices; white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count
Urinalysis	Urine dipstick for specific gravity, pH, protein, glucose, ketones, bilirubin, and blood; microscopic exam
Coagulation	INR (at screening)
Serology	anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody
Urine drug screen	Screening for drugs of abuse (e.g., marijuana, cocaine, phencyclidine, amphetamines, barbiturates, opiates, and benzodiazepines)

Vital Signs

Vital sign measurements, including sitting and standing blood pressure, sitting and standing heart rate, respiratory rate, temperature, body weight, and height. In studies MD-01 and MD-02, vital signs were collected at screening, 4 days after treatment, and at the 4-week safety follow-up visit. In study MD-04, vital signs were collected at screening, then monthly, and at the 4-week safety follow-up visit.

8.4. Safety Results

8.4.1. Deaths

There was one death during the clinical development program. During a phase 1 study, a 35-year-old male died in a motor vehicle accident. The subject had received ketoconazole 400mg

once daily for 5 days, with a single dose of ubrogepant 20mg on day 2 of the 5-day dosing of ketoconazole. The accident occurred 14 days after administration of the last dose of ketoconazole.

Reviewer's comment: This death is unlikely to be related to the use of ubrogepant. The half-life of ubrogepant is 5-7 hours. Ubrogepant is expected to be completely cleared from the body in less than 3 days. In the setting of ketoconazole, the half-life of ubrogepant is expected to be increased. However, ubrogepant is expected to be cleared from the body well before 14 days after administration.

8.4.2. Serious Adverse Events

The double-blind placebo-controlled data was examined for imbalances between placebo treated patients and patients treated with ubrogepant. Because there were so few SAEs, I did not present them by individual study, but instead presented the pooled data for all four phase 2 and phase 3 studies (Group 1).

There were 2581 patients in Group 1 who were treated with at least one dose of ubrogepant. There were no patients who experienced an SAE within 48 hours of dosing with IP. There were 13 SAEs reported by 7 patients within 30 days of dosing with ubrogepant, and none reported in the placebo group. A single patient experienced 7 of the 13 SAEs. The other 6 SAEs were as follows: myoclonus, spontaneous abortion, appendicitis (2), pericardial effusion, and seizure.

Reviewer's comment: The half-life of ubrogepant is 5-7 hours. Five half-lives are about 35 hours after administration. By 49 hours after administration, all of the drug should be cleared from the body (7 half-lives). SAEs that occurred after 48 hours of dosing with IP are likely not drug-related.

The single patient who experienced 7 SAEs (ligament sprain, loss of consciousness, renal hematoma, splenic rupture, syncope, traumatic renal injury, and road traffic accident) was involved in a bicycle accident where she went head first over the handle bars of her bicycle. The accident occurred 14 days after the last dose of ubrogepant.

There were 813 patients in Group 2, which consisted of patients in the long-term safety study MD-04. In Group 2, there were 30 SAEs experienced by 21 patients (i.e., 9 patients receiving 50 mg and 12 patients receiving 100 mg of ubrogepant). One patient experienced 6 SAEs: acute respiratory failure, cholecystitis acute, cholelithiasis, diabetic ketoacidosis, pneumonia, and sepsis. One patient reported 3 episodes of acute pancreatitis. This case will be discussed below (Patient (b) (6)) in narratives of selected SAEs.

Table 45 Group 2 SAEs: Open-Label Experience

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	50 mg N=404 n(%)	100 mg N=409 n(%)	Total N=813 n(%)
Cardiac Disorders	1 (0.2)	0	1 (0.1)
Sinus tachycardia	1 (0.2)	0	1 (0.1)
Gastrointestinal Disorders	1 (0.2)	5 (1.2)	6 (0.7)
Colitis	0	1 (0.2)	1 (0.1)
Hiatal hernia	0	1 (0.2)	1 (0.1)
Intestinal obstruction	1 (0.2)	0	1 (0.1)
Acute pancreatitis	0	3 (0.7)	3 (0.4)
General and Administration Site	1 (0.2)	1 (0.2)	2 (0.2)
Gait disturbance	1 (0.2)	0	1 (0.1)
Non-cardiac chest pain	0	1 (0.2)	1 (0.2)
Hepatobiliary Disorders	2 (0.5)	2 (0.5)	4 (0.5)
Acute cholecystitis	1 (0.2)	1 (0.2)	2 (0.2)
Cholelithiasis	1 (0.2)	1 (0.2)	2 (0.2)
Immune system disorders	1 (0.2)	0	1 (0.1)
Device allergy	1 (0.2)	0	1 (0.1)
Infections and infestations	3 (0.7)	2 (0.5)	5 (0.6)
Gastroenteritis	0	1 (0.2)	1 (0.1)
Pelvic inflammatory disease	1 (0.2)	0	1 (0.1)
Pneumonia	1 (0.2)	1 (0.2)	2 (0.2)
Post procedural infection	1 (0.2)	0	1 (0.1)
Sepsis	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	0	0	1 (0.1)
Subdural hematoma	0	0	1 (0.1)
Metabolism and nutrition disorders	0	1 (0.2)	1 (0.1)
Diabetic ketoacidosis	0	1 (0.2)	1 (0.1)
Nervous system disorders	0	1 (0.2)	1 (0.1)
Hemiparesis	0	1 (0.2)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	3 (0.7)	3 (0.4)
Abortion	0	1 (0.2)	1 (0.1)
Spontaneous abortion	0	1 (0.2)	1 (0.1)
Ectopic pregnancy	0	1 (0.2)	1 (0.1)
Psychiatric disorders	1 (0.2)	0	1 (0.1)
Substance induced mood disorder	1 (0.2)	0	1 (0.1)
Suicidal ideation	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (0.1)

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	50 mg N=404 n(%)	100 mg N=409 n(%)	Total N=813 n(%)
Acute respiratory failure	0	1 (0.2)	1 (0.1)
Vascular disorders	1 (0.2)	0	1 (0.1)
Hypertensive crisis	1 (0.2)	0	1 (0.1)
# of SAEs	11	19	30
# of patients	9	12	21

Reviewer created table

Narratives of Selected SAEs

Seizure

Patient (b) (6)

This 44-year-old female was participating in the PK portion of study MD-01 when she experienced a seizure. The patient received two doses of ubrogepant 100 mg in the double-blind treatment period without any adverse events. Three days later, the patient took ubrogepant 100 mg for the PK portion of the study. Approximately 5 hours after taking the study drug, the patient experienced what sounds like a focal dyscognitive seizure (formerly known as complex partial seizure) with secondary generalization. The patient was reported to be taking alprazolam 1mg tablets one to three times a day. On the day prior to the seizure, she took only 1mg, and on the day of the seizure she had not taken any alprazolam.

Reviewer's comment: This case is confounded by the use of alprazolam. Abrupt discontinuation of benzodiazepines can precipitate seizures. One would expect, however, that a seizure related to medication use (or abrupt discontinuation of use) would result in a generalized seizure, rather than a seizure with focal features. This seizure was alternately described as staring or raising her right arm at the onset suggesting a focal onset with rapid generalization rather than being generalized at onset which makes a drug effect less likely. Given that patients with epilepsy were excluded from pivotal studies, I cannot completely exclude a role for ubrogepant in lowering the seizure threshold in patients who are prone to seizures.

Elevated Liver Enzymes

1. Patient (b) (6)

This is a 56-year-old male who was participating in the open-label study MD-04 when he presented to the emergency room with severe epigastric pain, nausea, and vomiting. The patient had a medical history of cholelithiasis, morbid obesity (BMI 48.2 kg/m²) and Type 2 diabetes. He was admitted to the hospital and diagnosed with acute cholecystitis and diabetic ketoacidosis. He had an ultrasound showing a dilated common bile duct and intrahepatic dilatation. Three days later the patient underwent laparoscopic cholecystectomy, after which his liver enzymes declined rapidly, except for ALT which remained mildly elevated, but eventually normalized. Peak liver enzymes were as follows: ALT 467 U/L; AST 464 U/L; Tbili 4.2 mg/dl. His ALT was mildly elevated at screening and remained mildly elevated during participation in study MD-02 and MD-04.

Reviewer's comment: This case does not appear to be a drug-induced liver injury secondary to ubrogepant. The patient had an alternative explanation for his elevated liver enzymes.

2. Patient (b) (6)

This 48-year-old female was participating in the double-blind period of study MD-01 when she experienced right lower quadrant pain. This event occurred 33 days after the last dose of ubrogepant 100 mg. CT scan showed possible appendicitis. Her liver enzymes rose to ALT 580 (>10x ULN) and AST 965 (>28x ULN) and her lipase rose to 2908. Her total bilirubin remained normal. She underwent a laparoscopic appendectomy. The pathology interpretation was acute appendicitis. She was also diagnosed with a concomitant pancreatitis and treated aggressively for this as well. The patient had a prior history of chronic pancreatitis.

The patient had two other events that were called acute on chronic pancreatitis while she was participating in the open-label study. The second event occurred two days after the last dose of ubrogepant 100 mg. The patient was experiencing abdominal pain and went to the ER. She underwent CT scan of the abdomen and pelvis which did not show signs of pancreatitis but did show intra- and extra-hepatic biliary ductal dilatation. Abdominal ultrasound showed hepatic steatosis. A third and fourth event of abdominal pain occurred 10 and 19 days respectively after her last dose of ubrogepant. Both events were treated in the ER as recurrent events of acute on chronic pancreatitis, but no work up was done, other than lab work, to confirm. Lipase was mildly elevated in both cases.

Reviewer's comment: This patient's elevated liver enzymes are unlikely to be secondary to ubrogepant. The patient had another diagnosis that potentially caused the elevated liver enzymes. The event occurred well after 5 half-lives had passed since the last dose of

ubrogepant. It is unlikely the other episodes of abdominal pain/pancreatitis were related to ubrogepant. Two episodes occurred more than one week after the last dose, and the other episode of abdominal pain may have been incorrectly attributed to pancreatitis because of the patient's history of recurrent acute on chronic pancreatitis.

Colitis

Patient (b) (6)

This 47-year-old female with a BMI of 33 kg/m² was participating in the open-label study MD-04 when she experienced a severe case of colitis. Her last dose of ubrogepant 100 mg was taken approximately 3 weeks prior to the episode. She was hospitalized with bloody diarrhea and underwent a CT of abdomen and pelvis that showed colonic wall thickening. She was also found to have fatty infiltration of the liver and mild hepatic steatosis. The colitis resolved after three days and the patient was discontinued from ubrogepant.

Reviewer's comment: The case is concerning for possible ischemic colitis. However, it is unlikely to be related to ubrogepant. The event occurred 3 weeks after her last dose of ubrogepant. The half-life of the drug is 5-7 hours.

Hypertensive Crisis

This 50-year-old female was participating in the open-label study MD-04 when she experienced hypertensive crisis. She had no prior history of hypertension or cardiovascular disease. The patient last took ubrogepant on (b) (6), and experienced dizziness, blurred vision, and nausea on (b) (6). She was admitted to the hospital with chest pain and elevated systolic blood pressure around 200 mmHg. She was given IV labetolol and started on metoprolol and lisinopril. She was discharged on (b) (6). Blood pressure the day after discharge was 157/89 (sitting). She remained on lisinopril and continued on ubrogepant. She treated an additional three migraines with ubrogepant 50 mg from (b) (6) through (b) (6). During that time blood pressure ranged from 121-134/76-88.

Reviewer's comment: A cause for the patient's hypertensive crisis was not provided so a role for ubrogepant cannot be definitively excluded. However, in this case it is unlikely to be related to ubrogepant. The hypertensive crisis occurred about two months after the last dose of ubrogepant.

Designated Medical Events (DMEs)

I searched the ISS database (Group 1 and Group 2) for DMEs using the MedDRA-Based Adverse

Event Diagnostics (MAED) software. The following PTs for DMEs were found in ubrogepant-treated patients: pancreatitis (3), neutropenia (4), acute kidney injury (2), rhabdomyolysis (5), and seizure (1). For the cases of rhabdomyolysis, 3 of the 5 cases were attributed to exertion or exercise. Not all of the DMEs were coded as SAEs.

Pancreatitis

One patient experienced an episode of pancreatitis that was reported as 'mild'. This occurred 9 days after the last dose of ubrogepant 25 mg. The patient was obese and had a history of cholecystectomy and cholelithiasis. A second patient who had a history of pancreatitis experienced an episode of pancreatitis during the open-label study. She did not discontinue the study and continued to treat more than 35 migraines after the pancreatitis resolved without further episodes of pancreatitis. This patient eventually discontinued treatment due to severe hypothyroidism.

Neutropenia

There were four patients who experienced AEs of neutropenia. One patient had neutropenia at baseline that worsened slightly after taking ubrogepant 10mg and remained low at the conclusion of the study. The second patient experienced neutropenia approximately 30 days after taking a single dose of ubrogepant 25 mg. The third patient experienced mild neutropenia while taking 50 mg of ubrogepant during the open-label study. The neutropenia resolved, and she was able to continue on the same dose without a further episode of neutropenia. The fourth patient experienced a moderate neutropenia during the safety follow-up visit (33 days after the last dose of ubrogepant) which resolved by a follow-up visit three weeks later.

Acute kidney injury

There were two patients who experienced acute kidney injury (AKI). There were two patients who had an elevated creatinine during the double-blind treatment period. For both patients the AKI resolved within one week. Both patients continued to receive ubrogepant in the open-label study without any further episodes of AKI.

120-Day Safety Update

There were no additional deaths, SAEs, or discontinuations due to adverse events at the time of the 120-day safety update.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The applicant reported that only one patient discontinued from the single attack studies (P006, P007, MD-01, and MD-02) due to adverse events. However, when examining the ISS database for these four studies (Group 1), there are 7 patients who are noted to have 'drug withdrawn' due to adverse events (Table 46). Overall, the rate of withdrawal of IP due to AEs was low, and there was no clear pattern or AE that frequently led to withdrawal during the DBTP.

Table 46 Group 1: Drug Withdrawn Due to Adverse Events in the DBTP

Adverse Event (Preferred Term)	Placebo N=1125	50 mg N=1089	100 mg N=614
Arthralgia	1 (0.1)	0	0
Cardiac flutter	0	1 (0.1)	0
Dry mouth	1 (0.1)	0	0
Eye pruritis	0	1 (0.1)	0
Eyelid edema	0	1 (0.1)	0
Muscle twitching	0	0	1 (0.2)
Myalgia	1 (0.1)	0	0
Rash	2 (0.2)	0	0
Vomiting	1 (0.1)	1 (0.1)	0
Total # of AEs	6 (0.5)	4 (0.4)	2 (0.3)
Total # of patients	3 (0.3)	3 (0.3)	1 (0.2)

Reviewer created table from ISS dataset ADAE where AEACN='drug withdrawn'

The open-label exposure (Group 2) was also examined for discontinuations due to adverse events, or withdrawal of IP due to adverse events. Overall the rates of discontinuation of IP due to AEs was low. There were 4 patients who withdrew from ubrogepant due to nausea/vomiting. This is notable as nausea is one of the adverse drug reactions with imbalance compared to placebo and is discussed in section 8.4.5.

Table 47 Group 2: Drug Withdrawn Due to AEs (Open-Label Experience)

Adverse Event (Preferred Term)	50 mg N=404	100 mg N=409	Total N=813
Abortion	0	1 (0.2)	1 (0.1)
ALT increased	0	2 (0.5)	2 (0.2)
AST increased	0	2 (0.5)	2 (0.2)
Back pain	0	1 (0.2)	1 (0.1)
Cholelithiasis	0	1 (0.2)	1 (0.1)

Colitis	0	1 (0.2)	1 (0.1)
Diabetes mellitus	1 (0.2)	0	1 (0.1)
Dizziness	1 (0.2)	0	1 (0.1)
Ectopic pregnancy	0	1 (0.2)	1 (0.1)
Electrocardiogram abnormal	0	1 (0.2)	1 (0.1)
Extrasystoles	0	1 (0.2)	1 (0.1)
Fall	0	1 (0.2)	1 (0.1)
Gait disturbance	1 (0.2)	0	1 (0.1)
Hemiparesis	0	1 (0.2)	1 (0.1)
Hypoesthesia	1 (0.2)	0	1 (0.1)
Hypothyroidism	0	1 (0.2)	1 (0.1)
Idiopathic intracranial hypertension	1 (0.2)	0	1 (0.1)
Intestinal obstruction	1 (0.2)	0	1 (0.1)
Major depression	0	1 (0.2)	0
Migraine with aura	1 (0.2)	0	1 (0.1)
Mitral valve incompetence	0	1 (0.2)	0
Nausea	2 (0.5)	1 (0.2)	3 (0.4)
Palpitations	0	1 (0.2)	0
Papilledema	1 (0.2)	0	0
Paresthesia	1 (0.2)	0	1 (0.1)
Pruritus	0	1 (0.2)	0
Thrombocytopenia	1 (0.2)	0	1 (0.1)
Urticaria	1 (0.2)	0	1 (0.1)
Vomiting	1 (0.2)	0	1 (0.1)
# of AEs	14	19	33
# of patients	9	13	22

Reviewer created table using ISS dataset ADAE where AEACN=drug withdrawn

Review of Notable Discontinuations

There was one patient in the open-label period of study MD-04 who experienced a small bowel obstruction (SBO) and discontinued from the study because of the obstruction. The last dose of ubrogepant was about 4 weeks prior to the diagnosis of bowel obstruction. The patient was being treated at the time for a *Clostridium difficile* infection.

Reviewer's comment: A theoretical risk of CGRP antagonism is decreased gastric motility and bowel obstruction. However, in this case, it is unlikely that ubrogepant was related to the bowel obstruction. The patient was diagnosed with C. diff infection that is a risk factor for

development of SBO. The last dose of ubrogepant was taken considerably more than 5 half-lives prior to the development of the bowel obstruction.

8.4.4. Significant Adverse Events

AEs Leading to Dose Interruption

In Group 2 (open-label study MD-04), there were 11 AEs experienced by 9 patients leading to dose interruption. These AEs were as follows: blood pressure increased, electrocardiogram abnormal, subdural hematoma, dizziness, non-cardiac chest pain, vomiting, neutropenia, radius fracture, CPK increased, and abnormal weight gain (2).

AEs by Intensity

The applicant categorized adverse events as mild, moderate, or severe in intensity. The following definitions were applied:

Mild: awareness of sign or symptoms, but easily tolerated
Moderate: discomfort enough to cause interference with usual activity
Severe: incapacitating with inability to work or do usual activity

In the DBTP, the majority of AEs were of mild intensity (Table 48). There was a slight increase in the percentage of moderate intensity AEs in the 50 mg and 100 mg dose arms as compared to placebo and a slight increase in the percentage of patients in those arms experiencing moderate intensity AEs compared to placebo.

Table 48 Group 1: AEs by Intensity in the DBTP

	Placebo		25 mg		50 mg		100 mg	
	AEs N=421 n(%)	Pts N=1125 n(%)	AEs N=261 n(%)	Pts N=609 n(%)	AEs N=511 n(%)	Pts N=1089 n(%)	AEs N=329 n(%)	Pts N=614 n(%)
Mild	296 (70.3)	204 (18.1)	191 (73.2)	117 (12.2)	334 (60.6)	219 (20.1)	218 (66.3)	131 (21.3)
Moderate	108 (25.7)	86 (7.6)	59 (22.6)	46 (7.6)	161 (31.5)	114 (10.5)	99 (30.1)	71 (11.6)
Severe	17 (4.0)	12 (1.1)	8 (3.1)	3 (0.5)	16 (3.1)	14 (1.3)	12 (3.6)	8 (1.3)

Reviewer created table from Group 1 ADAE

Table 49: Group 2: AEs by Intensity in the Open-Label Period

	50 mg	100 mg

	AEs N=975 n(%)	Pts N=404 n(%)	AEs N=1177 n(%)	Pts N=409 n(%)
Mild	553 (56.7)	199 (49.3)	670 (56.9)	224 (54.8)
Moderate	386 (39.6)	165 (40.8)	432 (36.7)	191 (46.7)
Severe	36 (3.7)	23 (5.7)	75 (6.4)	34 (8.3)

Reviewer created table from Group 2 ADAE where STUDYID=UBR-MD-04, and TRTEMFL=Y, analysis of AESEV by TRT02A

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs in the ISS database occurring in more than 1% of ubrogepant-treated patients were as follows: various types of infections, gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), somnolence, fatigue, confusion, dizziness, dry mouth, and paresthesia (Table 50). This table captures AEs that occurred with the first 30 days after treatment. Some of these occurred at rates similar to placebo. I evaluated the rates of TEAEs in Group 1a, which only includes the two pivotal efficacy studies, and reported the TEAEs that demonstrate an imbalance as compared to placebo (Table 52). This table captures AEs that occurred within the first 48 hours after dosing.

Table 50 Group 1: TEAEs in the DBTP occurring in **≥1%** of Ubrogepant-Treated Patients

	Placebo N=1125	25 mg N=609	50 mg N=1089	100 mg N=614
Infection, all	72 (6.4)	44 (7.2)	90 (8.3)	49 (8.0)
Nausea, vomiting	33 (3.4)	24 (4.6)	37 (3.4)	33 (5.4)
URI, cold, rhinitis, flu-like illness	44 (2.9)	27 (3.9)	57 (5.2)	29 (4.7)
Somnolence, fatigue, sedation	23 (2.0)	17 (2.0)	27 (2.5)	26 (4.2)
Confusion, delirium, disorientation	18 (1.6)	12 (1.6)	15 (1.4)	22 (3.6)
Dizziness	20 (1.9)	16 (1.9)	21 (1.9)	17 (2.8)
Dry mouth	14 (1.2)	6 (1.0)	10 (0.9)	16 (2.6)
Abdominal pain, distention	10 (0.9)	7 (1.2)	7 (0.6)	11 (1.8)
Diarrhea, colitis, gastroenteritis	12 (1.1)	12 (2.0)	15 (1.4)	10 (1.6)
Asthenia, fatigue, malaise	20 (1.8)	7 (1.2)	15 (1.4)	10 (1.6)
Paresthesia, hypoesthesia	8 (0.7)	2 (0.3)	0 (0)	7 (1.1)

Reviewer created table from ISS dataset ADAE for Group 1 using FDA-created queries where TRTEMFL=Y. This includes studies P006, P007, MD-01, and MD-02

Table 51 Group 1: TEAEs in the DBTP occurring in **≥1%** of Ubrogepant-Treated Patients with Risk Difference **≥1%**

	Placebo N=1125	25 mg N=609	50 mg N=1089	100 mg N=614	Risk Difference		
					25 mg	50 mg	100 mg
Infection, all	72 (6.4)	44 (7.2)	90 (8.3)	49 (8.0)	1	2	2
Nausea, vomiting	33 (3.4)	24 (4.6)	37 (3.4)	33 (5.4)	1	0	2
URI, cold, rhinitis, flu-like illness	44 (2.9)	27 (3.9)	57 (5.2)	29 (4.7)	1	1	1
Somnolence, fatigue, sedation	23 (2.0)	17 (2.0)	27 (2.5)	26 (4.2)	1	0	2
Confusion, delirium, disorientation	18 (1.6)	12 (1.6)	15 (1.4)	22 (3.6)	0	0	2
Dizziness	20 (1.9)	16 (1.9)	21 (1.9)	17 (2.8)	1	0	1
Dry mouth	14 (1.2)	6 (1.0)	10 (0.9)	16 (2.6)	0	0	1
Abdominal pain, distention	10 (0.9)	7 (1.2)	7 (0.6)	11 (1.8)	0	0	1
Diarrhea, colitis, gastroenteritis	12 (1.1)	12 (2.0)	15 (1.4)	10 (1.6)	1	0	1

Reviewer created table from ISS dataset ADAE for Group 1 using FDA-created queries where TRTEMFL=Y. This includes studies P006, P007, MD-01, and MD-02

Table 52 Group 1a: TEAEs in the DBTP occurring in **≥1%** of Ubrogepant-Treated Patients with Risk Difference **≥1%**

	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%)	100 mg N=485 n(%)	Risk Difference		
					25 mg	50 mg	100 mg
Nausea, vomiting	22 (2.2)	12 (2.5)	19 (2.0)	20 (4.1)	0	0	2
Nausea	18 (1.8)	12 (2.5)	18 (1.9)	20 (4.1)	0	0	2
Somnolence*	12 (1.2)	8 (1.7)	17 (1.8)	16 (3.3)	0	1	2
Confusion**	10 (1.0)	4 (0.8)	9 (0.9)	14 (2.9)	0	0	2
Somnolence/Confusion	16 (1.6)	8 (1.7)	18 (1.9)	18 (3.7)	0	0	2
Dizziness	12 (1.2)	10 (2.1)	12 (1.3)	7 (1.4)	1	0	0
Dry mouth	9 (0.9)	1 (0.2)	4 (0.4)	10 (2.1)	0	0	1

Reviewer created table from ISS dataset ADAE for Group 1a using FDA-created queries where TRTEMFL=Y and AE48HRFL=Y. This includes studies MD-01, and MD-02
*Somnolence includes the following PTs: somnolence, sedation, fatigue

**Confusion includes the following PTs: somnolence, disorientation, lethargy, altered state of consciousness, confusional state, mental impairment, disturbance in attention

I conducted an AE analysis of the patients who took the optional second dose of IP (Table 53). The majority of patients who took the optional second dose did so between two and four hours after the initial dose of IP. There appears to be in increase in the rate of dizziness and somnolence in the patients who opted to take the second dose.

Table 53 Group 1a: TEAEs in the DBTP occurring in **≥1%** of Ubrogepant-Treated Patients with Risk Difference **≥1%** (Only Patients who Took the Optional Second Dose)

	Placebo N=446 n(%)	25 mg N=194 n(%)	50 mg N=374 n(%)	100 mg N=199 n(%)	Risk Difference		
					25 mg	50 mg	100 mg
Dyspepsia*	11 (2.5)	9 (4.6)	14 (3.7)	10 (5.0)	2	1	3
Nausea, vomiting	10 (2.2)	9 (4.6)	11 (2.9)	7 (3.5)	2	1	1
Dizziness	6 (1.3)	7 (3.6)	7 (1.9)	6 (3.0)	2	1	2
Somnolence**	5 (1.1)	3 (1.5)	12 (3.2)	6 (3.0)	0	2	2
Confusion***	4 (0.9)	2 (1.0)	4 (1.1)	6 (3.0)	0	0	2
Asthenia****	2 (0.4)	2 (1.0)	9 (2.4)	3 (1.5)	1	2	1

Reviewer created table from ISS dataset ADAE for Group 1a using FDA-created queries where TRTEMFL=Y and ADSL dataset where OPDOSETK=Y. This includes studies MD-01, and MD-02.
*Dyspepsia includes the following PTs: dyspepsia, nausea, vomiting, and gastritis.
**Somnolence includes the following PTs: somnolence, sedation, fatigue
***Confusion includes the following PTs: somnolence, disorientation, lethargy, altered state of consciousness, confusional state, mental impairment, disturbance in attention
****Asthenia includes the following PTs: asthenia, fatigue, malaise, muscular weakness, sedation, and sluggishness

The applicant conducted a randomized, double-blind, placebo-controlled study for hepatic safety in healthy volunteers. I have reviewed the TEAEs for that study as well. Nausea appears to have an imbalance as compared to placebo in the pivotal trials; however, nausea is a common symptom in migraine. I evaluated study 3110-105-002 using the FDA-created queries for common adverse events to see if nausea still showed an imbalance compared to placebo in a large study of healthy volunteers. Patients in this study received placebo, or ubrogepant 100 mg for two days on followed by two days of placebo over the course of 2 months. In this study, there was no imbalance seen in the PT for nausea. However, there was an imbalance for the PT nausea compared to placebo in the pooled data from the other phase 1 studies (Table 55).

Table 54 Group 3: TEAEs in the DBTP occurring in **≥1%** of Ubrogepant-Treated Patients with Risk Difference **≥1%**

	PBO N=260 n(%)	100 mg N=256 n(%)	Risk Difference
Headache	26 (10)	30 (11.7)	2
Somnolence/fatigue	6 (2.3)	11 (4.3)	2
Nausea	11 (4.2)	10 (3.9)	0
Abdominal pain	2 (0.8)	10 (3.9)	3
Dizziness	4 (1.5)	9 (3.5)	2
Dry mouth	3 (1.2)	3 (1.2)	0
Somnolence only	0	4 (1.6)	2
Bleeding	1 (0.4)	5 (2.0)	2
Depression	0	3 (1.2)	1

Reviewer created table from ISS dataset ADAE for Group 3 using FDA-created queries

The most common TEAEs in pooled phase 1 studies (Group 5) were headache, and nausea (Table 55). Nausea, vomiting, fatigue, headache, and dizziness all showed imbalance as compared to placebo.

Table 55 Group 5: TEAEs in Pooled Phase 1 Studies occurring in **≥1%** of Ubrogepant Treated Patients with Risk Difference **≥1%**

	PBO N=136 n(%)	Ubrogepant (all) N=436 n(%)	Risk Difference
Nausea	2 (1.5)	13 (3.0)	2
Vomiting	1 (0.7)	8 (1.8)	1
Fatigue	0	6 (1.4)	1
Headache	7 (5.1)	28 (6.4)	1
Dizziness	0	6 (1.4)	1

This table was adapted from the SCS, table 6-2.

The most common TEAEs in the open-label study (Group 2) are shown in (Table 56). Those queries that showed an imbalance as compared to placebo in the controlled studies including healthy volunteer studies are italicized.

Table 56 Group 2: TEAEs in Open-Label Study MD-04

	50 mg N=405 n(%)	100 mg N=409 n(%)
Infection (all)	174 (43.0)	195 (47.7)
Nausea, vomiting	22 (5.4)	23 (5.6)
LFTs abnormal	9 (2.2)	18 (4.4)
Headache	11 (2.7)	16 (3.9)
CPK increased	9 (2.2)	15 (3.7)
Cough	9 (2.2)	15 (3.7)
Anxiety	7 (1.7)	13 (3.2)
Dizziness	5 (1.2)	13 (3.2)
Renal stone	4 (1.0)	13 (3.2)
Hypertension	15 (3.7)	12 (2.9)
Arthritis/arthralgia	12 (3.0)	12 (2.9)
Somnolence/sedation/fatigue	14 (3.5)	11 (2.7)
Abdominal pain/distension	11 (2.7)	11 (2.7)

Reviewer created table from ISS dataset ADAE for Group 3 using FDA-created queries

Table 57 Suggested Adverse Event Table for the FDA-Approved Label

	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%)	100 mg N=485 n(%)	Risk Difference		
					25 mg	50 mg	100 mg
Nausea	18 (1.8)	12 (2.5)	18 (1.9)	20 (4.1)	0	0	2
Somnolence*	12 (1.2)	8 (1.7)	17 (1.8)	16 (3.3)	0	1	2
Dizziness	12 (1.2)	10 (2.1)	12 (1.3)	7 (1.4)	1	0	0
Dry mouth	9 (0.9)	1 (0.2)	4 (0.4)	10 (2.1)	0	0	1

*Somnolence includes the following PTs: somnolence, sedation, fatigue

Reviewer's comment: The applicant's suggested table includes nausea, somnolence, and dry mouth. My recommendation is to include these three AEs and dizziness (Table 57). These AEs occurred at a rate of at least 2% in ubrogepant-treated patients, and with at least 1% difference from placebo. I also recommend a statement stating there was an increase in dizziness and somnolence seen in those patients who opted to take a second dose. Alternatively, dizziness could be removed from the common AE table if the 25mg dose is not approved, and a statement regarding the increase in dizziness in those who took a second dose could be included.

8.4.6. Laboratory Findings

Mean Change from Baseline Analyses

I reviewed the applicant's analyses for mean changes from baseline for Group 1 and Group 1a (ISS tables 8-1.5.1 and 8-1a.5.1). See Table 44 for individual listings of each laboratory parameter that the applicant tested. I did not detect any clinically meaningful mean changes from baseline compared to placebo in the applicant's analyses for the following: hematology, chemistry, and urinalysis with the exception of creatine kinase (CK).

In Group 1 there was an increase in the mean change from baseline for all doses of ubrogepant compared to placebo at the day 4 post-dose measurement and the 4-week follow up (Table 58). When examining the median changes, there does not appear to be a clinically significant difference. The trend also does not appear to be dose dependent. It appears that the mean changes have been skewed by outlier values from patients who experienced rhabdomyolysis (5). There were two patients in the 50 mg group who experienced exercise-induced rhabdomyolysis. In Group 1 a, there was no notable difference between ubrogepant-treated patients and placebo-treated patients in clinically significant postbaseline elevations in CK (Table 59).

Table 58 Group 1: Mean Change from Baseline in CK

CK (U/L)	PBO N=1125	25 mg N=609	50 mg N=1089	100 mg N=614
Change from baseline (day 4)				
Mean	-1.1	8.5	17.2	6.6
Median	0	2	1	0
Min, Max	-1284, 813	-484, 1235	-521, 14875	-1120, 2002
Change from baseline (4-week follow up)				
Mean	2.8	11.2	9.4	2.5
Median	0	0	0	0
Min, Max	-1402, 1711	-592, 3586	-478, 3414	-1123, 416

This table was adapted from the ISS table 8-1.5.1

Table 59 Group 1a: Clinically Significant Postbaseline CK Elevations

CK	Placebo N=984	25 mg N=478	50 mg N=954	100 mg N=485
>2.0 x ULN	28/954 (2.9)	21/471 (4.5)	31/927 (3.3)	20/473 (4.2)

This table was adapted from the ISS table 8-1a.2.1

Analyses Focused on Outliers

I summarized post-baseline transaminase elevations in patients participating in the DBTP (Group 1a), open-label (Group 2), and the smaller hepatic safety study (Group 4). These tables summarize any elevation in AST or ALT after the patient received at least one dose of ubrogepant. This analysis does not take into account baseline AST or ALT.

Table 60 Group 1a: Post Baseline AST, ALT, and Tbili Elevations in the DBTP

	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%)	100 mg N=485 n(%)
AST				
≥3x ULN	0	0	2 (0.2)	1 (0.2)
≥5x ULN	0	0	0	1 (0.2)
≥10x ULN	0	0	0	1 (0.2)
≥20x ULN	0	0	0	1 (0.2)
ALT				
≥3x ULN	2 (0.2)	0	3	3 (0.6)
≥5x ULN	0	0	0	2 (0.4)
≥10x ULN	0	0	0	1 (0.2)
≥20x ULN	0	0	0	0
TBili				
≥1.5xULN	3 (0.3)	2 (0.4)	3 (0.3)	2 (0.4)
≥ 2xULN	0	1 (0.2)	2 (0.2)	0

Reviewer created table combining JumpStart outputs for studies MD-01 and MD-02

Table 61 Group 2: Post Baseline AST, ALT, and Tbili Elevations in Open-Label

	50 mg N=404 n(%)	100 mg N=409 n(%)	Usual Care N=417 n(%)
AST			
≥3x ULN	2 (0.5)	9 (2.2)	2 (0.5)
≥5x ULN	1 (0.3)	4 (1.0)	1 (0.2)
≥10x ULN	0	2 (0.5)	0
≥20x ULN	0	1 (0.2)	0
ALT			
≥3x ULN	4 (1.0)	8 (2.0)	4 (1.0)

≥5x ULN	2 (0.5)	4 (1.0)	1 (0.2)
≥10x ULN	0	1 (0.2)	0
≥20x ULN	0	0	0
TBili			
≥ 1.5xULN	5 (1.2)	2 (0.5)	3 (0.7)
≥ 2xULN	3 (0.7)	2 (0.5)	1 (0.2)
≥ 3xULN	1 (0.3)	1 (0.2)	0

Reviewer created table adapted from JumpStart outputs for study MD-04

In addition, the applicant conducted a small study in healthy volunteers who received ubrogepant 150 mg daily or placebo for 28 day. There was no evidence of hepatotoxicity in this small safety study.

Table 62 Group 4 Post Baseline AST, ALT, and TBili Elevations in the DBTP (Study P004)

	Placebo N=10 n(%)	150 mg N=22 n(%)
AST		
≥3x ULN	0	1 (4.5)
≥5x ULN	0	0
≥10x ULN	0	0
ALT		
≥3x ULN	0	0
≥5x ULN	0	0
≥10x ULN	0	0
TBili (mg/dl)		
≥ 1xULN	0	0
≥1.5xULN	0	0
≥ 2xULN	0	0

This table was adapted from output provided by the JumpStart service.

Investigation-Related Adverse Events

In Group 1a, investigation-related AEs were low in the DBTP with no notable imbalances compared to placebo (Table 63).

Table 63 Group 1a: Investigation-Related AEs in the DBTP

Preferred Term	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%)	100 mg N=485 n(%)
ALT increased	3 (0.3)	0	6 (0.6)	3 (0.6)
AST increased	0	0	4 (0.4)	0
Blood alk phos increased	1 (0.1)	0	0	0
Blood bilirubin increased	1 (0.1)	0	0	0
Blood cholesterol decreased	0	0	1 (0.1)	0
Blood cholesterol increased	0	0	1 (0.1)	0
Blood CPK increased	8 (0.8)	2 (0.4)	6 (0.6)	1 (0.2)
Blood phosphorus decreased	1 (0.1)	0	0	0
Blood potassium increased	1 (0.1)	0	0	0
Blood pressure diastolic increased	0	0	1 (0.1)	1 (0.2)
Blood pressure increased	2 (0.2)	0	1 (0.1)	1 (0.2)
Blood triglycerides decreased	0	0	1 (0.1)	0
Blood triglycerides increased	2 (0.2)	0	4 (0.4)	0
Blood uric acid increased	1 (0.1)	1 (0.2)	0	0
Body temperature increased	0	0	0	1 (0.2)
Creatinine renal clearance decreased	0	1 (0.2)	0	1 (0.2)
Creatinine renal clearance increased	2 (0.2)	0	0	0
Glomerular filtration rate decreased	1 (0.1)	0	0	1 (0.2)
Hemoglobin decreased	0	0	1 (0.1)	0
Heart rate increased	0	0	3 (0.3)	4 (0.8)
Hepatic enzyme increased	0	0	0	1 (0.2)
High density lipoprotein decreased	0	0	1 (0.1)	0
High density lipoprotein increased	1 (0.1)	0	0	0
Lipase increased	0	0	0	1 (0.2)
Low density lipoprotein decreased	0	0	1 (0.1)	0
Low density lipoprotein increased	1 (0.1)	0	0	0
Mean cell volume decreased	0	0	2 (0.2)	0
Peripheral pulse decreased	0	0	1 (0.1)	0
Platelet count increased	0	0	1 (0.1)	0

Preferred Term	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%)	100 mg N=485 n(%)
Protein urine present	1 (0.1)	0	0	0
Red blood cells urine	1 (0.1)	0	0	0
Urinary casts	1 (0.1)	0	0	0
Weight decreased	0	0	0	1 (0.2)
Weight increased	1 (0.1)	0	0	1 (0.2)

Reviewer created table from ISS dataset ADAE for Group 1a where TRTEMFL=Y and AEBODSYS=investigations.

8.4.7. Vital Signs

Vital signs including sitting and standing blood pressure, heart rate, respiratory rate, temperature, height, and weight were measured according to the schedule of assessments (see Section 6 under Study Design for a summary of the schedule of assessments).

I reviewed the applicant's analyses of vital signs. Ubrogepant did not appear to have clinically meaningful changes in mean systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, or weight (analyses not shown). I reviewed the analyses presented for both Group 1a (ISS tables), Group 2 (CSR for MD-04), and Group 3 (CSR for 3110-105-002).

The applicant collected orthostatic vital signs in phase 1, 2, and 3 studies. I reviewed the outlier analyses for orthostatic vital signs (Table 5-1 from the SCS), as well as the analyses presented for phase 1 studies (P001, P002, and P004). Ubrogepant did not appear to have clinically meaningful changes in orthostatic vital signs.

Potentially Clinically Significant Changes in Vital Signs

The applicant was asked to provide a table with the number and percentage of patients with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Heart rate: <60bpm and > 100bpm

The applicant provided this table in the ISS for Group 1a (Table 64) and in the CSR for studies MD-04 for Group 2 (Table 65) and Group 3 study 3110-105-002 (Table 66). I reviewed these tables and did not detect any imbalance between ubrogepant and placebo for SBP, DBP, and HR outliers.

Table 64 Group 1a: Outlier Analyses of Blood Pressure and Heart Rate

	Placebo N=972 n(%)	25 mg N=474 n(%)	50 mg N=941 n(%)	100 mg N=479 n(%)
SBP				
<90mmHg	24 (2.5)	6 (1.3)	12 (1.3)	2 (0.4)
>140mmHg	66 (6.8)	29 (6.1)	63 (6.7)	33 (6.9)
>160mmHg	2 (0.2)	2 (0.4)	7 (0.7)	1 (0.2)
DBP				
<50mmHg	2 (0.2)	2 (0.4)	3 (0.3)	1 (0.2)
>90mmHg	106 (10.9)	40 (8.4)	99 (10.5)	58 (12.1)
>100mmHg	6 (0.6)	0	12 (1.3)	7 (1.5)
HR				
<60bpm	94 (9.7)	46 (9.7)	57 (6.1)	39 (8.1)
>100bpm	32 (3.3)	16 (3.4)	34 (3.6)	18 (3.8)

This table was adapted from the ISS table 9-1a.5.1. Vital signs noted in this table were taken while sitting.

Table 65 Group 2: Outlier Analyses of Blood Pressure and Heart Rate

	Usual Care N=417 n(%)	50 mg N=404 n(%)	100 mg N=409 n(%)
SBP			
<90mmHg	18 (4.5)	28 (7.0)	17 (4.2)
>140mmHg	79 (19.8)	66 (16.5)	80 (19.7)
>160mmHg	7 (1.8)	4 (1.0)	9 (2.2)
DBP			
<50mmHg	7 (1.8)	6 (1.5)	5 (1.2)
>90mmHg	107 (26.9)	112 (28.0)	121 (29.8)
>100 mmHg	11 (2.8)	11 (2.8)	12 (3.0)
HR			
<60bpm	53 (13.3)	40 (10)	46 (11.3)
>100bpm	102 (25.6)	100 (25.0)	112 (27.6)

Adapted from CSR table 14.3-8.1 for study MD-04. Vital signs noted in this table were taken while sitting.

Table 66 Group 3: Outlier Analyses of Blood Pressure and Heart Rate

	Placebo	100 mg

	N=260 n(%)	N=256 n(%)
SBP		
<90mmHg	12/258 (4.7)	10/256 (3.9)
>140mmHg	22/258 (8.5)	21/256 (8.2)
>160mmHg	6/258 (2.3)	1/256 (0.4)
DBP		
<50mmHg	3/258 (1.2)	4/256 (1.6)
>90mmHg	19/258 (7.4)	13/256 (5.1)
>100mmHg	4/258 (1.6)	2/256 (0.8)
HR		
<60bpm	70/258 (27.1)	68/256 (26.6)
>100bpm	15/258 (5.8)	9/256 (3.5)

Adapted from the CSR table 12-16 for study 3110-105-002. Vital signs noted in this table were taken while sitting.

Vital Signs in Phase 1 Clinical Studies

Study P001

No clear pattern for mean changes from baseline in SBP and DBP were noted in the single ascending dose study P001 (Table 67 and Table 68).

Table 67 Study P001: Mean Changes from Baseline in SBP in mmHg

	Placebo N=10	80 mg N=6	100 mg N=6
Time in hours			
0.5	0.97	-0.11	-2.89
1	5.97	1.56	0.78
1.5	1.17	0.56	-1.72
2	3.57	0.56	3.44
3	-0.63	2.89	-4.89
4	3.67	2.06	-0.39
6	4.77	-1.28	-1.56
8	4.67	-0.44	-3.39
12	6.27	2.06	0.11

24	6.27	4.72	-0.56

This table was adapted from the CSR for study P001. SBP was measured in a semi-recumbent position

Table 68 Study P001: Mean Changes from Baseline in DBP in mmHg

	Placebo N=10	80mg N=6	100mg N=6
Time in hours			
0.5	3.03	0.78	-0.33
1	4.13	5.11	1.33
1.5	-0.47	2.11	1.33
2	0.13	2.94	0.17
3	-0.77	6.11	1.50
4	1.53	1.94	0.67
6	-2.47	-1.89	-8.00
8	-2.77	-3.89	-2.83
12	-1.37	-4.39	-0.67
24	0.83	1.28	-0.67

This table was adapted from the CSR for study P001. DBP was measured in a semi-recumbent position

Study P002

In the multiple ascending dose study P002, subjects were administered IP for 10 consecutive days. In this study, the 400 mg dose exhibited elevated mean changes from baseline in systolic and diastolic blood pressure (Table 69 and Table 70) when taken in the semi-recumbent position. This mean elevation peaked at day 5 (data not shown) with a mean change from baseline in SBP of 13.67 mmHg and DBP of 14.61 mmHg. This trend was also noted for the 400 mg dose when the diastolic blood pressure was taken in a standing position, but was not noted when the systolic blood pressure was taken in a standing position

Table 69 Study P002: Mean Changes from Baseline in SBP in mmHg

	Placebo N=8	100 mg N=6	200 mg N=6	400 mg N=6
Time				
Day 1, 1 hour	-0.58	-2.06	2.94	8.33
Day 1, 2 hours	2.67	2.78	4.94	3.00
Day 1, 4 hours	3.04	2.11	3.44	5.17
Day 1, 8 hours	2.04	-5.72	1.44	4.83
Day 1, 24 hours	-0.21	-1.39	1.11	0.33
Day 10, 1 hour	0.04	-0.89	-2.72	4.67
Day 10, 2 hours	0.17	-2.22	-0.72	5.00

Day 10, 4 hours	3.67	-1.39	1.28	6.33
Day 10, 8 hours	-2.08	-7.06	-4.39	6.33
Day 10, 24 hours	-1.21	-2.56	-0.56	-1.33

This table was adapted from the CSR for study P002. SBP was measured in a semi-recumbent position

Table 70 Study P002: Mean Changes from Baseline in DBP in mmHg

	Placebo N=8	100 mg N=6	200 mg N=6	400 mg N=6
Time				
Day 1, 1 hour	3.54	-1.50	1.11	7.28
Day 1, 2 hours	6.17	3.33	2.61	6.78
Day 1, 4 hours	1.67	0.33	6.11	5.94
Day 1, 8 hours	-1.46	-7.33	-2.72	1.78
Day 1, 24 hours	1.29	-4.33	-0.72	0.61
Day 10, 1 hour	2.04	-0.33	-1.72	4.61
Day 10, 2 hours	0.42	0	0.44	5.94
Day 10, 4 hours	0.42	-1.83	-0.39	6.61
Day 10, 8 hours	3.04	-4.00	-3.72	2.94
Day 10, 24 hours	-1.96	1.33	-3.56	-4.39

This table was adapted from the CSR for study P002. DBP was measured in a semi-recumbent position

Study P004

In study P004, placebo or 150 mg of ubrogepant was administered for 28 consecutive days. No clear pattern for mean changes from baseline in SBP and DBP were noted in this study.

Table 71 Study P004: Mean Changes from Baseline in SBP in mmHg

	Placebo N=10	150 mg N=22
Time		
Day 1, 1 hour	-5.30	-2.06
Day 1, 2 hours	-4.47	-1.74
Day 1, 12 hours	-5.47	-2.79
Day 1, 24 hours	-5.47	0.21
Day 28, 1 hours	-2.87	-2.02
Day 28, 2 hour	-5.07	-0.29
Day 28, 12 hours	-6.97	-3.61
Day 28, 24 hours	-5.47	-2.52

This table was adapted from the CSR for study P004. SBP was measured in a semi-recumbent position

Table 72 Study P004: Mean Changes from Baseline in DBP in mmHg

	Placebo N=10	150 mg N=22
Time		
Day 1, 1 hour	-4.85	-0.12
Day 1, 2 hours	-4.53	-0.44
Day 1, 12 hours	-10.93	-4.58
Day 1, 24 hours	-7.23	-1.44
Day 28, 1 hours	-5.83	-0.17
Day 28, 2 hour	-5.13	-1.67
Day 28, 12 hours	-8.43	-3.94
Day 28, 24 hours	-8.53	-2.03

This table was adapted from the CSR for study P004. DBP was measured in a semi-recumbent position

Study 3110-105-002

Study 3110-105-002 was designed primarily as a hepatic safety study to assess the safety of taking near daily dosing of ubrogepant. Healthy volunteers took placebo or ubrogepant 100 mg for two days on and two days off for 8 weeks. These subjects were evaluated in the study center one to two times per week for 56 days for safety assessments and on-site dosing.

Table 73 Study 3110-105-002: Mean Changes from Baseline in SBP in mmHg (Sitting)

	PBO N=260	100 mg N=256
Day 14: Change from baseline		
Mean	1.4	1.1
Median	1.0	1.0
Min, Max	-32, 43	-28, 40
Day 28: Change from baseline		
Mean	1.1	1.1
Median	1.0	1.0
Min, Max	-42, 41	-27, 43
Day 56: Change from baseline		
Mean	-0.5	-0.1

Median	-1.0	0
Min, Max	-34, 32	-30, 24

Adapted from Table 14.3-5.1 from the CSR for study 3110-105-002

Table 74 Study 3110-105-002: Mean Changes from Baseline in DBP in mmHg (Sitting)

	PBO N=260	100 mg N=256
Day 14: Change from baseline		
Mean	0.6	1.4
Median	0	1.0
Min, Max	-17, 22	-20, 30
Day 28: Change from baseline		
Mean	0.7	0.9
Median	1.0	0.0
Min, Max	-26, 23	-28, 25
Day 56: Change from baseline		
Mean	-0.1	0.3
Median	0	-1.0
Min, Max	-22, 25	-19, 25

Adapted from Table 14.3-5.1 from the CSR for study 3110-105-002

Reviewer's comment: The only notable trends in mean changes in SBP and DBP from baseline were seen with the 400 mg dose in study P002 when the drug was taken for 10 consecutive days. The maximum dose planned for marketing is 100 mg with the option for a second dose (maximum 200 mg in 24 hours). At the doses planned for marketing there do not appear to be any notable mean changes from baseline in SBP or DBP.

8.4.8. Electrocardiograms (ECGs)

The applicant provided summary statistics for the PR interval, QRS complex, the QT, and the QTcF. This included analyses of the mean changes from baseline and outlier analyses. I did not detect any clinically significant changes in PR, QRS, or QT intervals or in the analysis of ECG-related AEs.

Mean Changes in ECG Intervals

There were no clinically significant changes from baseline in mean HR, PR interval, QRS, or QTcF as compared to placebo in Group 1a (Table 75) or Group 2 (Table 76).

Table 75 Group 1a: Mean Changes in ECG Intervals (Day 4 Measurement)

	PBO N=984	25 mg	50 mg	100 mg
PR	-0.6	-0.5	0.3	-0.4
QRS	0	0	0.4	0.7
QT	-7.8	-6.0	-6.5	-6.0
QTcF	-2.6	-1.5	-0.9	-0.6

This table is adapted from the ISS Table 10-1a.4.1.

Table 76 Group 2: Mean Changes in ECG Intervals (End of Study Visit)

	Usual Care	50 mg	100 mg
PR	0.1	0.4	-0.5
QRS	1.5	1.1	0.7
QT	-5.2	-4.3	-5.4
QTcF	0.4	1.2	0.5

This table is adapted from Table 14.3-6.3 from the CSR for study MD-04.

Analyses Focused on Outliers

Table 77 Group 1a: Max QTcF Post-Baseline and Max Increase from Baseline

QTcF (msec)	Placebo N=969 n(%)	25 mg N=468 n(%)	50 mg N=954 n(%)	100 mg N=478 n(%)
>450 to 480	11 (1.1)	8 (1.7)	8 (0.9)	5 (1.0)
>480 to 500	0	0	0	0
>500	0	0	0	0
Change of 30 to 60	8 (0.8)	9 (1.9)	12 (1.3)	6 (1.3)
Change >60	0	0	0	0

Adapted from ISS table 10-1a.7.1 and from the IR response dated June 26, 2019 eCTD 0018

Table 78 Group 2: Max QTcF Post-Baseline and Max Increase from Baseline

QTcF (msec)	Usual Care N=417 n(%)	50 mg N=404 n(%)	100 mg N=409 n(%)
>500	0	0	0
Change of 30 to 60	23 (6.0)	26 (6.7)	37 (9.3)
Change >60	1 (0.3)	0	0

Adapted from the CSR Table 14.3-6.1 for study MD-04 and from the IR response dated June 26, 2019 eCTD 0018

ECG-Related AEs

Table 79 Group 1a: ECG-Related AEs

Preferred Term	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%	100 mg N=485 n(%
Bundle branch block (right)	0	0	1 (0.1)	0
Cardiac flutter	0	0	2 (0.2)	0
Nodal rhythm	0	0	0	1 (0.2)
Tachycardia/heart rate increased	2 (0.2)	1 (0.2)	6 (0.6)	4 (0.8)

Reviewer created table from ISS dataset ADAE for Group 1a where TRTEMFL=Y and AEDBODSYS= Cardiac Disorders or Investigations

8.4.9. QT

The applicant conducted a thorough QT (TQT) study which was reviewed by the Interdisciplinary Review Team for QT Studies (QT-IRT). The QT-IRT reviewed the TQT study UBR-PK-02. They found no significant QTc prolongation effect with the use of 100 mg and 400mg of ubrogepant. The QT review team notes that the doses are not adequate to cover the worst-case scenario of a 5-fold Cmax with co-administration of ketoconazole (strong CYP3A4 inhibitor) or a 3-fold Cmax with co-administration of verapamil (moderate CYP3A4 inhibitor). The applicant has not satisfied ICH E14 as they did not cover the supratherapeutic exposure or the maximum tolerated dose. The applicant has proposed labeling to handle this scenario. The applicant has proposed to contraindicate the use of ubrogepant with strong CYP3A4 inhibitors and has proposed dose reduction with the use of concomitant moderate CYP3A4 inhibitors. The QT-IRT teams agreed with the applicant's proposed language in section 12.2 of the label.

8.4.10. Immunogenicity

N/A

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease

CGRP is a potent vasodilator. For this reason, there is a theoretical cardiovascular safety risk potentially associated with antagonism of the CGRP receptor. This concern is centered around a potential lack of compensatory vasodilatation in the context of ischemia. Plasma CGRP levels have been found to be increased during myocardial infarction and it is thought that these increased levels of CGRP may act as a defense mechanism (Mair et al. 1990).

Migraine has an association with increased risk of vascular disease especially in patients with migraine with aura (Scher et al. 2005). There is some evidence that migraine patients are at increased risk of cardiovascular events (e.g., ischemic heart disease, myocardial infarction) and increased risk of stroke. These epidemiological findings combined with the theoretical risk of CGRP antagonism have made cardiovascular and cerebrovascular safety issues of concern warranting a closer evaluation.

Reviewer's comment: During the review of prior CGRP receptor antagonists, the inclusion of a warning for the theoretical cardiovascular safety risk in patients with major cardiovascular disease was considered by the Division. A consult from the Division of Cardiovascular and Renal Products (DCRP) was obtained to assess whether the available nonclinical literature supported inclusion of this warning in the label. DCRP concluded that there is consensus that CGRP is a potent microvascular vasodilator, but that CGRP is one of multiple redundant control mechanisms regulating blood flow. They concluded that in animal models, loss of vasodilatation from CGRP antagonism does not result in tissue threatening ischemia.

At that time, a meeting with the Medical Policy and Program Review Council (MPPRC) was requested to discuss whether the animal data was compelling enough to include a warning in section 5 describing the theoretical risk of CGRP receptor antagonism in patients with major cardiovascular disease. The animal data was presented to the MPPRC as were details about the mechanism of CGRP. The Council unanimously felt that the animal data was not compelling enough to include a warning in section 5 of the label.

Although the theoretical risk was not included in product labeling because of lack of evidence in animal models, I think careful examination of CV safety in humans is still warranted. The clinical trials in migraine patients generally include younger, healthier patients without major cardiovascular disease

Some patients in the controlled trials for ubrogepant had cardiovascular risk factors such as diabetes, hypertension, cigarette use, hyperlipidemia, or obesity (Table 80). However, the overall prevalence of pre-existing major cardiovascular disease in the entire database was very low. I summarized some of the major cardiovascular, cerebrovascular, and peripheral vascular disease reported in the ISS medical and surgical history for Group 1a (Table 81).

Table 80 Group 1a: Baseline Cardiac Risk Factors

	Placebo N=984 n (%)	25 mg N=478 n (%)	50 mg N=954 n (%)	100 mg N=485 n (%)
Diabetes	46 (4.7)	24 (5.0)	54 (5.7)	27 (5.6)
History of hypertension	125 (12.7)	47 (9.8)	126 (13.2)	55 (11.3)
Current cigarette use	99 (10.1)	51 (10.7)	90 (9.4)	40 (8.2)
Hyperlipidemia	61 (5.4)	29 (4.8)	44 (4.0)	29 (4.7)
BMI>30 kg/m²	402 (40.9)	196 (41.0)	437 (45.8)	204 (42.1)

This table was provided by the applicant in an IR dated May 20, 2019, eCTD 0014

Table 81 Group 1a: Summary of Major Cardiovascular, Cerebrovascular, or Peripheral Arterial Disease Medical History

	Placebo N=984 n (%)	25 mg N=478 n (%)	50 mg N=954 n (%)	100 mg N=485 n (%)
Angina pectoris	1 (0.1)	1 (0.2)	2 (0.2)	1 (0.2)
Aortic arteriosclerosis/ Arteriosclerosis	1 (0.1)	0	2 (0.2)	1 (0.2)
Cardiac failure	0	1 (0.2)	2 (0.2)	0
Coronary artery disease/occlusion	2 (0.2)	1 (0.2)	5 (0.5)	0
Myocardial infarction	1 (0.1)	1 (0.2)	2 (0.2)	0
Coronary artery stent insertion/vascular stent insertion	1 (0.1)	2 (0.4)	2 (0.2)	0
Cerebral infarction/ cerebrovascular accident	2 (0.2)	1 (0.2)	1 (0.1)	0
Peripheral vascular disorder	0	0	1 (0.1)	1 (0.2)
Transient ischemic attack	1 (0.1)	1 (0.2)	4 (0.4)	2 (0.4)

Summarized from ISS table 3-1a.2.1 (Medical and surgical history)

(b) (6)

(b) (6) The NCEP classification is used to determine the 10-year risk of developing atherosclerotic cardiovascular disease (ASCVD) defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke.

Category 1 (high risk): >20% 10-year CV risk
Category 2 (moderate risk): 10% to 20% 10 year-CV risk
Category 3 (low risk): <10% 10-year CV risk

Table 82 Group 1a: Cardiovascular Risk as per the NCEP Classification

	Placebo N=984 n (%)	25 mg N=478 n (%)	50 mg N=954 n (%)	100 mg N=485 n (%)
Category 1 (high)	28 (2.8)	13 (2.7)	30 (3.1)	14 (2.9)
Category 2 (moderate)	72 (7.3)	38 (7.9)	70 (7.3)	46 (9.5)
Category 3 (low)	884 (89.8)	427 (89.3)	854 (89.5)	425 (87.6)

This table was adapted from the ISS table 3-1a.1.1.

Reviewer's comment: (b) (6) *The risk factor algorithm utilized by the applicant is used to predict a 10-year risk of developing atherosclerotic disease. The theoretical safety concern with CGRPs is in patients with concurrent cardiovascular disease, not in those who MIGHT develop CV disease over the next ten years. The percentage of patients included in the studies with actual cardiovascular disease was very low likely due to the inclusion/exclusion criteria. The percentage of patients included in the study with moderate to high risk of developing cardiovascular disease in 10 years was low as well.*

I assessed the database for potential cardiovascular, cerebrovascular, and peripheral vascular effects of ubrogepant. In the double-blind treatment period (Table 83) and the open-label safety study (Table 84), the incidence rates for AEs related to cardiovascular, cerebrovascular, or peripheral vascular disorders was low.

Table 83 Group 1a: Summary of Preferred Terms for Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease AEs

Preferred Term	Placebo N=984	25 mg N=478	50 mg N=954	100 mg N=485
Aphasia	0	0	1 (0.1)	0
Blood pressure diastolic increased	0	0	1 (0.1)	1 (0.2)
Blood pressure increased	2 (0.2)	0	1 (0.1)	1 (0.2)
Bundle branch block right	0	0	1 (0.1)	0
Cardiac flutter	0	0	1 (0.1)	0

Flushing/hot flush	1 (0.1)	0	4 (0.4)	0
Heart rate increased/tachycardia	2 (0.2)	1 (0.2)	4 (0.4)	1 (0.2)
Hypertension	0	1 (0.2)	1 (0.1)	0
Nodal rhythm	0	0	0	1 (0.2)
Palpitations	1 (0.1)	0	4 (0.4)	2 (0.4)
Pericardial effusion	0	0	1 (0.1)	0
Peripheral coldness	0	0	0	2 (0.4)
Peripheral pulse decreased	0	0	1 (0.1)	0
Syncope	0	2 (0.4)	0	0

Reviewer created table from dataset ADAE for studies MD-01 and MD-02

Table 84 Group 2: Summary of Preferred Terms for Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease AEs

Preferred Term	50 mg N=404	100 mg N=409
Angina	2 (0.5)	2 (0.5)
Arrhythmia	0	1 (0.2)
AV block first degree	1 (0.2)	0
Cardiac failure congestive	1 (0.2)	0
Cardiac flutter	1 (0.2)	0
Extrasystoles	0	1 (0.2)
Flushing/hot flush	2 (0.5)	2 (0.5)
Hypertension/hypertensive crisis	10 (2.5)	7 (1.7)
Hypotension	2 (0.5)	2 (0.5)
Mitral valve incompetence/prolapse	0	2 (0.5)
Palpitations	3 (0.7)	2 (0.5)
Pericarditis	0	1 (0.2)
Peripheral coldness	1 (0.2)	0
Presyncope/syncope	1 (0.2)	7 (1.7)
Sinus bradycardia	1 (0.2)	0
Sinus tachycardia/tachycardia	0	3 (0.7)
Ventricular extrasystoles	0	1 (0.2)
Wolff-Parkinson-White Syndrome	0	1 (0.2)

Reviewer created table from 120-day safety update inclusive of study MD-04

A deficiency in the release of CGRP has been implicated in the lack of vasodilatation observed in Raynaud's phenomenon, and administration of CGRP has been shown to have a beneficial effect (Bunker et al. 1993, and Russell et al. 2014). There were 14 patients in Group 1 and 2 combined with a medical history of Raynaud's phenomenon. None of them were noted to have worsening of their disease. However, in the double-blind period, there were two patients who experienced 'peripheral coldness' in the hands and feet and in the open-label period, there was one patient who experienced 29 episodes of cold hands with each dose of ubrogepant 50 mg in the open-label study. None of these three patients had an a priori diagnosis of Raynaud's disease or syndrome.

Reviewer's comment: [redacted] (b) (4) *, it may be worth monitoring in the postmarketing setting when more patients with Raynaud's phenomenon may be exposed to ubrogepant or develop a Raynaud's-like phenomenon.*

Hypertension

There is some suggestion that CGRP has a role in the development of hypertension (Russell et al. 2014) although that understanding is not clear. It may be that CGRP release is enhanced early in the development of hypertension as a compensatory or protective effect.

In Group 1a, there was no imbalance between placebo-treated and ubrogepant-treated patients in the incidence of adverse events related to hypertension. In Group 1a there were 2 (0.2%) placebo-treated patients, 1 (0.2%) patient treated with 25 mg of ubrogepant, 3 (0.3%) patients treated with 50 mg of ubrogepant and 2 (0.4%) patients treated with 100 mg of ubrogepant who experienced treatment-emergent adverse events related to hypertension within 30 days of taking ubrogepant. In the Group 2 (open-label study), the overall rate of hypertension related TEAEs were low. There were 13 (3.2%) of patients treated with 50mg of ubrogepant, 11 (2.7%) of patients treated with 100 mg of ubrogepant, and 19 (4.6%) of patients in the usual care arm who experienced hypertension-related TEAEs. There was one patient in the open-label study who was taking 50 mg of ubrogepant when she experienced hypertensive crisis. This case is discussed in section 8.4.2 Serious Adverse Events and is unlikely to be secondary to the use of ubrogepant.

8.5.2. Hepatotoxic Effects

No cases of Hy's law were identified in the two phase 3 pivotal studies, or the two hepatic safety studies. In Study MD-04, the long-term open-label study, there was one patient that had an ALT≥3xULN with a TBili ≥2x ULN. This case did not meet criteria for Hy's Law as the patient had an alternative diagnosis for his elevated ALT and TBili. The patient had acute cholelithiasis and cholecystitis at the time of the elevated LFTs. Liver enzymes normalized following

emergent cholecystectomy. In study MD-01, there was one patient with an AST and ALT >10x ULN; however, the bilirubin remained normal. Please see section 8.4.2 Serious Adverse Events for a summary of these patients' narratives.

Because of hepatoxic effects seen in other CGRP antagonists that are no longer in development, the applicant was asked to conduct a dedicated hepatic safety study. Please see section 8.7.1 for a summary of the results of the 8-week hepatic safety study, 3110-105-002.

8.5.3. Gastrointestinal Effects

Nonclinical data suggest that CGRP has protective effects against gastric injury. Mechanisms of gastric protection include inhibition of gastric secretion of somatostatin, stimulation of gastric mucin synthesis, and mucosal hyperemia via direct vasodilation. Endogenous CGRP has been shown to reduce gastric acid secretion. Theoretically concerns with CGRP antagonists include increased risk of gastric ulcer, bowel ischemia, and obstruction as CGRP has known roles in blood flow, inflammation, motility, and secretion into the colon.

In the gastrointestinal SOC, there was no imbalance compared to placebo in the incidence of GI related AEs with the exception of the 100 mg dose. This increase was primarily driven by the PT nausea which is higher in the 100 mg dose group. The rates were 7.6%, 7.5%, 6.4%, 12.2% in placebo, 25 mg, 50 mg, and 100 mg respectively. There were no GI SAEs in Group 1, but there was an imbalance compared to placebo in the incidence of abdominal pain in Group 1 with a risk difference of about 1%. The rates were 0.9%, 1.2%, 0.6%, and 1.8% in placebo, 25 mg, 50 mg, and 100 mg respectively (see Table 50). However, this difference was no longer noted in the analysis of Group 1a, when the phase 2 studies were removed from the analysis. In Group 2, there was one patient for whom the drug was withdrawn secondary to colitis (type not specified). Please see section 8.4.2 Serious Adverse Events for the summary of this patient's narrative.

8.5.4. Suicidality Assessment

The applicant utilized the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess patients for suicidality in the pivotal studies (MD-01 and MD-02) and in the long-term safety study (MD-04). See Appendix 13.4 for details regarding the scale. There does not appear to be a signal for suicidal ideation or suicidal behavior.

In Group 1 there were a total of four patients who expressed suicidal ideation during the double-blind treatment period: 1 patient who received placebo, 2 patients who received ubrogepant 50 mg, and 1 patient who received ubrogepant 100 mg. The most severe level of ideation expressed by three of these patients was Level 1 (wish to be dead). There was one

patient treated with ubrogepant 50 mg who most severe suicidal ideation was Level 3 (active suicidal ideation with any methods without intent to act (i.e., no plan). In Group 1 there was no suicidal behavior.

In Group 2 there were a total of ten patients who expressed suicidal ideation during open-label period: 5 (1.2%) in the usual care arm, 3 (0.7%) patients who received ubrogepant 50 mg, and 2 (0.5%) patients who received ubrogepant 100 mg. The highest level of ideation expressed was Level 4 (active suicidal ideation with some intent to act, without specific plan), by one patient in the usual care arm. In Group 2 no suicidal behavior was reported during the study.

8.6. Safety Analyses by Demographic Subgroups

The database for ubrogepant overall has very few SAEs and AEs. Analysis of SAEs by demographic subgroup was not possible as there were too few. I have presented the rates of AEs by sex, age, and race in the ISS from the 120-day safety update. This analysis represents 2194 patients who received at least a single dose of ubrogepant 25 mg, 50 mg, or 100 mg in studies MD-01, MD-02, and MD-04. Of these 2194, 42.7% reported at least one AE at any time. The rates of AEs by sex, age and race roughly reflects the rates of AEs in ISS. Some of the race categories have too few patients to make any meaningful comparisons or conclusions.

Table 85 Rates of AEs by Sex, Age, and Race in Patients Exposed to Ubrogepant

	Sex		Age		Race					
	M N=232 n(%)	F N=1962 n(%)	< age 40 N=1038 n(%)	≥ age 40 N=1156 n(%)	White N=1812 n(%)	Black N=322 n(%)	Asian N=23 n(%)	Multiple/ Other N=18 n(%)	American Indian/ Alaskan Native N=12 n(%)	Native Hawaiian N=7 n(%)
# of patients experiencing AEs	87 (37.5)	850 (43.3)	416 (40.1)	521 (45.1)	798 (44.0)	118 (36.6)	9 (39.1)	4 (22.2)	4 (33.3)	4 (57.1)

*Reviewer created table using ISS dataset from 120-day update ADAE, and ADSL as denominator inclusive of studies MD-01, MD-02, and MD-04. This table is at the patient level. Some patients may have experienced more than one AE but are only represented once in each category.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Study 3110-105-002: 8-week Hepatic Safety Study

The applicant was asked to conduct a safety study to assess the hepatotoxicity of ubrogepant in patients taking the drug daily or near daily. Prior small molecule CGRP receptor antagonists that were in development had demonstrated hepatotoxicity in the setting of daily use of the product (Yao et al 2013).

The applicant conducted study 3110-105-002 in a total of 516 healthy adults. The study was a multi-center, double-blind, placebo-controlled, parallel-group study. Subjects were randomized 1:1 to receive either placebo or ubrogepant 100 mg for 8 weeks (56 days). Randomization was stratified by sex. Exposure to study treatment was assessed using PK sample collection. After the double-blind period was completed, there was a 1-month (28-day) safety follow-up period. The two treatment groups were as follows:

Treatment Group 1: 2 placebo tablets taken once daily for the entire DBTP
Treatment Group 2: 2 consecutive days of 100 mg (2 x 50 mg tablets) followed by two consecutive days of placebo (2 tablets) for the entire DBTP

Liver function tests were performed at days 1, 5, 14, 21, 28, 33, 42, 49, and 56. PK sampling was done at days 1, 5, 9, 14, 17, 21, 25, 33, 37, 42, 45, 49, and 53.

A total of 516 subjects received at least 1 dose of IP. Of those patients, 468 (90.7%) completed the entire treatment phase. There were almost equal numbers of placebo patients (N=26) and ubrogepant-treated patients (N=22) who did not complete the treatment phase.

Treatment-emergent hepatic adverse events were low, and similar in both treatment groups (Table 86). There were no clinically meaningful mean changes from baseline in AST, ALT, Tbili, or alk phos (data not shown). There were no cases of Hy's law.

Table 86 Study 3110-105-002: Hepatic TEAEs

Preferred Term	Placebo N=260 n(%)	100 mg N=256 n(%)
AST increased	4 (1.5)	0
ALT increased	3 (1.2)	2 (0.8)

This table was created by the reviewer using dataset ADAE for study 3110-105-002

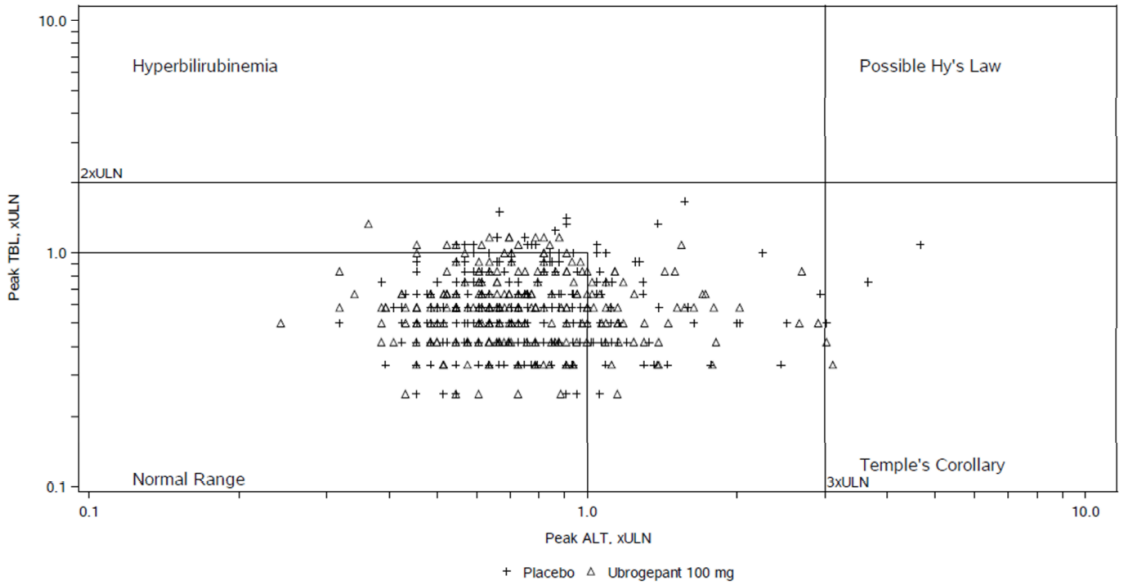
More placebo-treated patients than ubrogepant-treated patients had post-baseline elevations in AST, ALT, or Tbili (Table 87). A graphical representation (eDISH plot) of the post-baseline elevations in ALT, and Tbili can be seen in Figure 8.

Table 87 Study 3110-105-002: Post Baseline Elevations in AST, ALT, and TBili

	Placebo N=260 n(%)	100 mg N=256 n(%)
AST		
≥3x ULN	4 (1.5)	0
≥5x ULN	3 (1.2)	0
≥10x ULN	1 (0.4)	0
ALT		
≥3x ULN	3 (1.2)	2 (0.8)
≥5x ULN	0	0
≥10x ULN	0	0
TBili (mg/dl)		
≥1.5xULN	2 (0.8)	0
≥ 2xULN	0	0

This table was adapted from the outputs provided by the JumpStart team

Figure 8 Study 3110-105-002: eDISH Plot for Post Baseline Measurements



This table was provided by the applicant in an IR dated July 2, 2019, eCTD 0014

Reviewer's comment: There was no evidence of hepatotoxicity from the use of ubrogepant 100 mg for 50% of the days over a two-month period.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Overall there were very few malignancies in the database. Eight malignancies were detected during the open-label study. Three of these occurred in patients in the 'usual care' arm and the other five occurred in the ubrogepant 100 mg arm. The malignancies reported in ubrogepant-treated patients are as follows: basal cell carcinoma (3), fibrous histiocytoma, and malignant melanoma in situ. There were too few malignancies to make any conclusions about the carcinogenicity of ubrogepant. At this time, I do not detect a signal for the development of malignancy with the use of ubrogepant.

8.8.2. Human Reproduction and Pregnancy

Despite requirements for contraception, the ubrogepant development program had some pregnancies. The data are insufficient to support conclusions on the effect of ubrogepant on reproduction and pregnancy.

Pregnant and lactating women were excluded from ubrogepant studies. According to the applicant, ubrogepant is transferred in to the milk in rats in concentrations comparable to that achieved in plasma.

There were a total of 28 pregnancies during the development of ubrogepant. Nineteen occurred in patients receiving ubrogepant, three in patients receiving placebo, and 6 in patients in the 'usual care' arm of the open-label study, MD-04.

Table 88 Summary of Pregnancy and Outcomes in Patients Exposed to Ubrogepant

Birth Outcome	Maternal Exposure
Full term birth without complications	5
Preterm birth without complications	1
Elective termination due to ectopic pregnancy	1
Elective termination	2

Spontaneous abortion	2
Follow up pending/pregnancy on going	1
Lost to follow up	7
Total	19

Reviewer created table, adapted from appendix 10.1 from the SCS

8.8.3. Pediatrics and Assessment of Effects on Growth

This section is not applicable to this review. Pediatric patients were not exposed to ubrogepant. Patients under age 18 were excluded from all studies.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no cases of overdose reported in the clinical studies. The highest doses of ubrogepant received were single and multiple doses of 400mg in PK study and in the TQT study. There were no SAEs reported in those studies.

A consult to the controlled substance staff (CSS) was placed when the NDA was received. Dr. Katherine Bonson provided the following conclusions in her memo dated February 7, 2019: there were no abuse potential signals seen in preclinical studies (receptor binding, general behavior, self-administration, drug discrimination, and physical dependence) or in the abuse-related adverse events reported in the clinical studies conducted. CSS determined that the applicant did not need to conduct a human abuse potential study or a human physical dependence study. CSS determined that they did not need to be part of the review team for this NDA.

In accordance with the Guidance for Industry, "Assessment of Abuse Potential of Drugs," the applicant queried the database for the following abuse-related terms: affective disorder, aggression, confusional state, disorientation, dizziness, drug tolerance, drug withdrawal syndrome, euphoric mood, feeling abnormal, feeling drunk, feeling of relaxation, hallucination, inappropriate affect, mood altered, psychotic disorder, somnolence, substance abuse, substance dependence, substance use, substance-induced mood disorder, substance-induced psychotic disorder, and abnormal thinking. No signal for abuse-related potential was found (Table 89) in the pooled data from the four single attack studies or in the long-term safety study (Table 90).

Table 89 Group 1: Adverse Events Associated with Abuse Potential

Preferred Terms	Placebo N=1125	50 mg N=1089	100 mg N=614

	n(%)	n(%)	n(%)
Dizziness	19 (1.7)	20 (1.8)	17 (2.8)
Somnolence	13 (1.2)	12 (1.1)	17 (2.8)
Confusional state	0	1 (0.1)	2 (0.3)
Disorientation	1 (0.1)	0	1 (0.2)
Euphoric mood	0	2 (0.2)	0
Feeling abnormal	0	4 (0.4)	0
Mood altered	1 (0.1)	0	0

This table was adapted from the SCS, table 7-9

Table 90 Group 2: Adverse Events Associated with Abuse Potential

Preferred Terms	Usual Care N=417 n(%)	50 mg N=404 n(%)	100 mg N=409 n(%)
Dizziness	6 (1.4)	5 (1.2)	12 (2.9)
Somnolence	1 (0.2)	6 (1.5)	5 (1.2)
Confusional state	0	0	1 (0.2)
Feeling abnormal	0	1 (0.2)	0
Substance-induced mood disorder	0	1 (0.2)	0

This table was adapted from the SCS, table 7-10.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

This section is not applicable. Ubrogepant is not marketed in any country at the time of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

The applicant attempted to include a population representative of the U.S. migraine population. The demographics of the patients included seem to adequately represent the U.S. population. However, the inclusion and exclusion criteria effectively selected for a relatively healthy population. The migraine studies excluded patients with cardiovascular disease, major psychiatric disorders, and major neurological disorders (including epilepsy). This may limit the generalizability of the safety data to the larger U.S. population when considering that postmarketing use will be much less restrictive. The applicant attempted to include the over 65 population in this study. However, patients in this age bracket in the general population will be expected to have higher rates of cardiovascular disease than those who were included in the pivotal studies.

8.9.3. Additional Safety Issues from Other Disciplines

At the time of this writing, I am not aware of other additional safety issues from other disciplines.

8.10. Integrated Assessment of Safety

The following safety issues were examined in this review based on the theoretical concerns associated with CGRP antagonism: cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal. Close attention was also paid to hepatoxicity given the prior history with small molecular CGRP receptor antagonists that were previously in development. The safety of ubrogepant has been evaluated in two large double-blind placebo-controlled studies and a large open-label study. In addition, the applicant also conducted a dedicated safety study to evaluate the safety of ubrogepant in patients using ubrogepant on a very frequent basis. My review of these trials has not revealed a clear relationship to any serious safety issues related to the use of ubrogepant.

The review focusing on cardiovascular and cerebrovascular disorders did not reveal any potential safety concerns in regard to toxicity associated with the use of ubrogepant. However, this review is extremely limited as the population studied was primarily young, and healthy. The applicant included some patients over the age of 65 in the studies; however, the overall presence of cardiovascular, cerebrovascular, and peripheral vascular disease was quite low.

Another safety concern for the review was gastrointestinal toxicity. The primary finding was an increase in nausea and dry mouth with the use of ubrogepant. Both AEs increased in a dose dependent fashion. The incidence of nausea increased in patients who took a second dose of ubrogepant as well. Three patients withdrew from the open-label study due to nausea. There was one patient who experienced colitis possibly ischemic and one patient who experienced a small bowel obstruction. Neither case was clearly related to the use of ubrogepant. However, given the biological plausibility of the role of CGRP antagonism in bowel motility, it is something that may need monitoring in the postmarketing setting.

Another safety concern addressed in this review is the concern for hepatotoxicity. There were no cases of Hy's law identified during the review in the two phase 3 pivotal studies or the two hepatic safety studies. In the long-term open-label study there was one patient who had an ALT≥ 3 x ULN and a TBili ≥ 2 x ULN. However, this patient did not meet Hy's law criteria as the patient had an alternative cause for the elevated ALT and TBili namely acute cholecystitis. The applicant conducted a dedicated safety study in healthy volunteers to evaluate hepatotoxicity in frequent users of ubrogepant 100 mg. There was no evidence of hepatoxicity from the use of ubrogepant 100 mg over a two-month period.

There are still many uncertainties that remain with the use of ubrogepant that may arise in the

postmarketing period and will need to be monitored carefully. Theoretical concerns related to the cardiovascular risk of ubrogepant remain. Patients with major cardiovascular disease were effectively excluded from clinical studies. The theoretical risk of CGRP antagonism lies with the potential loss of compensatory vasodilatation in the setting of ischemia. There is no data yet on the consequence of chronic CGRP antagonism in patients with cardiovascular disease. Other drugs that have been approved in this class (i.e., the three monoclonal antibodies) for the preventive treatment of migraine, despite not being labeled with cardiovascular risk language, are conducting enhanced pharmacovigilance in the postmarketing setting for myocardial infarction, and stroke. I recommend that this should be done for ubrogepant as well.

Another concern for ubrogepant that is unique to medications that are used for the acute treatment of migraine is the development of medication overuse (MO). This phenomenon is described in product labeling for all triptans and NSAIDs that are approved for the acute treatment of migraine. If used daily and consistently, CGRP receptor antagonists may be useful for the preventive treatment of migraine. However, thus far there is no data to support or refute whether the use of short-acting CGRP receptor antagonists can contribute to the development of medication overuse headache when used on an intermittent basis; therefore, I recommend that this class labeling be included in the ubrogepant label. My concern is that the way drugs are used for the acute treatment of migraine is important for the development of MO rather than the mechanism by which the drug acts as this phenomenon is seen in drugs that act across a variety of mechanisms.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting is not anticipated for this product.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The final label was not available at the time of this review. After reviewing the applicant's submitted application, I have the following recommendations for labeling:

Section 2: I recommend approval of the 25 mg dose as well as the 50 mg and 100 mg doses. I recommend stating that the safety of treating more than 8 migraines per month in a 30-day period has not been established.

Section 6: I recommend inclusion of the following table and footnote:

Table 91 Suggested Adverse Event Table for the FDA-Approved Label

	Placebo N=984 n(%)	25 mg N=478 n(%)	50 mg N=954 n(%)	100 mg N=485 n(%)	Risk Difference		
					25 mg	50 mg	100 mg
Nausea	2	3	2	4	1	0	2
Somnolence* **	1	2	2	3	1	1	2
Dizziness**	1	2	1	1	1	0	0
Dry mouth	1	0	0	2	0	0	1

*Somnolence includes the following PTs: somnolence, sedation, fatigue
** There was an increased incidence of dizziness and somnolence seen in those patients who opted to take a second dose of ubrogepant.

Section 14: (b) (4) I recommend including a graph of the co-primary endpoints. (b) (4)

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A.

12. Postmarketing Requirements and Commitments

PMRs

1. Deferred pediatric studies required under the Pediatric Research Equity Act
2. Pregnancy registry and outcomes study

Enhanced Pharmacovigilance

1. Myocardial infarction
2. Stroke

13. Appendices

13.1. References

Bigal M, and R Lipton. Migraine at All Ages. Current Pain and Headache Reports. 2006 June; 10(3): 207-213.

Bunker CB, Reavley C, O'Shaughnessy DJ, and PM Dowd. Calcitonin Gene-Related Peptide Treatment of Severe Peripheral Vascular Insufficiency in Raynaud's Phenomenon. Lancet. 1993, 342: 80-83.

Hansen J, Hauge A, Olesen J, and M Ashina. Calcitonin Gene-Related Peptide Triggers Migraine-Like Attacks in Patients with Migraine with Aura. Cephalalgia. 2010 Oct; 30(10): 1179-1186.

Lipton R, Stewart W, Diamond S, Diamond M, and M Reed. Prevalence and Burden of Migraine in the United States: Data from the American Migraine Study II. Headache. 2001 Jul-Aug; 41(7):646-657.

Lipton R, Bigal M, Diamond M, Freitag F, Reed M, and W Stewart. Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy. Neurology. 2007 Jan 30; 68(5):343-349.

Mair J, Lechleitner P, Langle T, Wiedermann C, Dienstl F, and A Saria. Plasma CGRP in Acute Myocardial Infarction. Lancet. 1990 Jan 20; 335 (8682): 168.

Marmura MJ, Silberstein SD, and TJ Schwedt. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. Headache. 2015 Jan; 55(1): 3-20.

Russell F, King R, Smillie S, Kodji X, and S Brain. Calcitonin Gene-Related Peptide: Physiology and Pathophysiology. Physiol Rev. 2014 Oct; 94(4): 1099-1142.

Scher A, Terwindt G, Picavet H, Verschuren W, Ferrari M, and L Launer. Cardiovascular Risk Factors and Migraine: The Genetic Epidemiology of Migraine (GEM) Population-Based Study. Neurology. 2005 Feb 22; 64(4): 614-620.

Yao G, Tingmin Y, Han X, Mao X, and B Li. Therapeutic Effects and Safety of Olcegepant and Telcagepant for Migraine: A Meta-Analysis. Neural Regen Res. 2013 Apr 5; 8(10): 938-947.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): MD-01, MD-02

Was a list of clinical investigators provided?:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 189 (total for the two studies)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): six		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: six Proprietary interest in the product tested held by investigator: one Significant equity interest held by investigator in Sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Levels of Evidence

Level A: established as effective; requires at least two Class I studies
Level B: probably effective; requires at least one Class I study, or two Class II studies
Level C: possibly effective; at least one Class II study, or two Class III studies

13.4. Columbia-Suicide Severity Rating Scale

0: No suicidal ideation or behavior
1: Wish to be dead
2: Non-specific active suicidal thoughts
3: Active suicidal ideation with any methods without intent to act (no plan)
4: Active suicidal ideation with some intent to act, without specific plan
5: Active suicidal ideation with specific plan and intent
6: Preparatory acts or behavior
7: Aborted attempt
8: Interrupted attempt
9: Actual attempt (non-fatal)
10: Completed suicide

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/s/

LAURA A JAWIDZIK
12/19/2019 05:50:56 PM

HEATHER D FITTER
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