CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

SUMMARY REVIEW

Summary Review

Date	December 23, 2019
From	Heather Fitter, MD Nick Kozauer, MD Billy Dunn, MD
Subject	Summary Review
NDA #	211765
Applicant	Allergan Sales, LLC
Date of Submission	December 26, 2018
PDUFA Goal Date	December 26, 2019
Proprietary Name	Ubrelvy
Established or Proper Names	Ubrogepant
Dosage Form(s)	50, 100 mg tablets
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Recommended 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

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Ubrogepant is a new molecular entity (NME) developed for the acute treatment of migraine with and without aura in adults. This is the first oral calcitonin gene-related peptide (CGRP) antagonist to be reviewed in an FDA marketing application.

There are many FDA-approved drugs for the acute treatment of migraine with and without aura in adults, including triptans (5-$HT_{1B/1D}$ receptor agonists), lasmiditan (5-HT_{1F} receptor agonist), dihydroergotamine (DHE), and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter of which can be used alone or in combination with a triptan. In addition, there are over-the-counter products marketed for migraine. The use of many of the marketed prescription medications described above for the acute treatment of migraine is restricted in patients with cardiovascular (CV) disease. Although lasmiditan is not restricted in patients with CV disease, there is a restriction regarding driving, specifically that patients should avoid driving for 8 hours after dosing. There are currently 3 injectable monoclonal antibodies that target the CGRP system and that are indicated for the preventive treatment of migraine in patients with chronic migraine and episodic migraine. These products do not appear to be associated with increased CV risk.

The efficacy of ubrogepant was demonstrated in two adequate and well-controlled studies. The studies used well-validated and clinically meaningful co-primary endpoints to establish efficacy: the proportion of patients who were pain-free and the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. One study evaluated the efficacy and safety of 50 mg and 100 mg doses of ubrogepant compared to placebo, and the other study evaluated the efficacy and safety of 25 mg and 50 mg doses of ubrogepant compared to placebo. The 50 mg and 100 mg ubrogepant doses were effective and demonstrated statistically significant superior results on both co-primary endpoints compared to placebo. The 25 mg dose demonstrated statistically significant superiority to placebo for pain-freedom at 2 hours, but not on MBS-freedom at 2 hours. The dose-response for ubrogepant was relatively flat in both studies suggesting similar efficacy for both doses. The treatment effect size for pain freedom at 2 hours post-dose was approximately 7-9% greater than placebo over the range of the two doses tested (ubrogepant responder rate of approximately 19-22%). The treatment effect size for MBS-freedom at 2 hours was approximately 10-12% greater than placebo over the range of two doses (ubrogepant responder rate of approximately 38-39%).

The development program was not designed in a manner that could definitively establish the efficacy of a second dose taken at least 2 hours after the initial dose; however, there are no safety issues that would preclude taking a second dose, so labeling will allow for this option (similar to

most other drugs for the acute treatment of migraine).

The safety profile of ubrogepant was characterized in two controlled efficacy studies, and a long-term open-label study with repeat dosing. Additionally, a dedicated hepatic safety study was conducted because of the occurrence of serious hepatotoxicity with previous oral CGRP antagonists that are no longer in development. No serious toxicities were identified in these trials. Common adverse events in clinical trials that occurred in at least 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 CV disease. The data provided with this application, including ex-vivo coronary artery vasoconstriction studies, do not support the need for CV restrictions with the use of ubrogepant; however, these data are too limited to definitively establish the CV safety of ubrogepant.

The risk/benefit profile of ubrogepant is acceptable and supports approval for the acute treatment of migraine with and without aura in adults. There is no evidence to suggest that ubrogepant is more effective than other FDA-approved drugs for the acute treatment of migraine; however, ubrogepant is the first oral CGRP antagonist to be approved, and may offer a needed treatment alternative to some patients. Labeling will clearly convey the generally favorable safety profile demonstrated in this application which includes a dose-dependent increase in the incidence of nausea and somnolence as compared with placebo.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the second highest cause of disability in the Global Burden of Disease Study in 2016. The prevalence of migraine is approximately 9% in males and 20% in females in	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>the U.S., thus resulting in a major impact to public health.</td><td></td></tr>
<tr><td>Current Treatment Options</td><td>• There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamines (DHE), lasmiditan, and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter which can be used alone or in combination with a triptan. Triptans and DHE are contraindicated in patients with cardiovascular (CV) disease and NSAIDS have labeling that warns patients of the risk of CV events with the use of these products. Lasmiditan includes a restriction on driving for 8 hours following a dose, and does not allow for a second dose within 24 hours. In addition, there are several over-the-counter drugs marketed for migraine.</td><td>Several classes of drugs are indicated for the acute treatment of migraine with and without aura in adults. However, many patients still do not respond adequately to these therapies.

An oral medication in a new class for the acute treatment of migraine could be an important treatment option for some patients.</td></tr>
<tr><td>Benefit</td><td>• The efficacy of ubrogepant was demonstrated in two adequate and well-controlled clinical studies (Studies MD-01 and MD-02). The studies used well-validated and clinically meaningful endpoints to establish efficacy, the proportion of patients that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. Results are summarized in the table below; comparisons between the ubrogepant (50 mg and 100 mg) groups and placebo are highly statistically significant.
<table>
<tr><th></th><th>PF at 2 hours (%)</th><th>Placebo corrected PF (%)</th><th>MBS free at 2 hours (%)</th><th>Placebo corrected MBS free (%)</th></tr>
<tr><td>Study MD-01*</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>11.8</td><td></td><td>27.8</td><td></td></tr>
<tr><td>Ubrogepant 50 mg</td><td>19.2</td><td>7.4</td><td>38.6</td><td>10.8</td></tr>
<tr><td>Ubrogepant 100 mg</td><td>21.2</td><td>9.4</td><td>37.7</td><td>9.9</td></tr>
<tr><td>Study MD-02*</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>14.3</td><td></td><td>27.4</td><td></td></tr>
<tr><td>Ubrogepant 25 mg</td><td>20.7</td><td>6.4</td><td>34.1**</td><td>6.7</td></tr>
<tr><td>Ubrogepant 50 mg</td><td>21.8</td><td>7.5</td><td>38.9</td><td>11.5</td></tr>
</table></td><td>Ubrogepant is effective for the acute treatment of a migraine with and without aura in adults.

The recommended doses of ubrogepant for marketing will be 50 mg and 100 mg. Although efficacy of a second dose was not clearly demonstrated, there are no safety issues that would preclude taking a second dose, so labeling should allow for this option.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	*all comparisons statistically significant unless otherwise specified. **not statistically significantly superior to placebo • There was a relatively flat dose-response relationship demonstrated for PF at 2 hours post-dose and MBS-freedom at 2 hours post-dose in both studies. There was no dose-response for the MBS-freedom endpoint at 2 hours for Study MD-01 as both doses had a similar treatment effect. In Study MD-02, the 50 mg dose demonstrated a treatment effect that was statistically significant as compared to placebo on both endpoints; however, the 25 mg dose failed to demonstrate a statistically significant effect on MBS-freedom at 2 hours post-dose. • Both pivotal clinical studies planned to evaluate the efficacy of a second dose which could be administered from 2-48 hours post the initial dose. However, due to shortcomings of the second dose analyses, these data are not informative and the efficacy of a second dose has not been established.	
Risk and Risk Management	• The most common treatment emergent adverse events (TEAEs) in the pooled Phase 3 controlled clinical trials of ubrogepant-treated patients included nausea, somnolence, and dry mouth, all occurring at relatively low incidence rates. • In patients that opted to take a second dose, there was an increase in the incidence of dizziness, somnolence, and nausea/vomiting. • There were no patients in the controlled trials that experienced a serious adverse events (SAEs) within 48 hours of dosing. • The rate of adverse dropouts was low and there was no clear pattern or adverse event (AE) that led to withdrawal during the controlled trials. • Clinical trials included generally younger, healthy patients and effectively excluded patients with major CV disease. • In vitro studies using human distal coronary, middle meningeal, and cerebral arteries showed that ubrogepant inhibited CGRP-induced vasodilatation, but did not induce vasoconstriction.	There were no significant safety findings that would preclude approval of ubrogepant. Adequate labeling and enhanced pharmacovigilance will address the identified safety issues. The data submitted with this application do not support the need to include CV restrictions in labeling. However, these data are also insufficient to definitively establish the CV safety of ubrogepant. Because the risk of adverse outcomes in pregnancy has not been characterized, and because ubrogepant will be used in women of childbearing potential, a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Based on either the proposed mechanism of action or previous safety issues seen with CGRPs, safety issues of concern for ubrogepant were CV, cerebrovascular, peripheral vascular, gastrointestinal, and hepatotoxicity. No clear safety signals were detected upon review of these issues. • A thorough QT study showed no significant QT prolongation at supratherapeutic doses and no clinically meaningful effect on mean PR or QRS intervals. • No serious safety issues related to the use of ubrogepant were identified during this review. Other uncertainties • The risk of adverse outcomes in pregnancy has not been characterized. • Safety and efficacy in pediatric migraine patients has not been established.	pregnancy registry and a pregnancy outcomes study will be postmarketing requirements. Since safety and efficacy of ubrogepant in pediatric migraine patients has not been established, studies to evaluate ubrogepant in pediatric migraine patients will be required under the Pediatric Research Equity Act (PREA). There should be enhanced pharmacovigilance with periodic evaluation of CV events, cerebrovascular events, and hepatotoxicity.

2. Background

This review discusses the data presented by Allergan Sales LLC (the applicant) in support of a new drug application (NDA) for ubrogepant tablets for the acute treatment of migraine with and without aura in adults. Ubrogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist intended for oral administration.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a range of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 to 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura. Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders (ICHD).

Many products are FDA-approved for the acute treatment of migraine in adults. These products include a number of different triptans, dihydroergotamine, nonsteroidal anti-inflammatory drugs (NSAIDs) used alone or in combination with a triptan, and a 5-HT_{1F} agonist, lasmiditan, which was recently approved. In addition, there are many over-the-counter medications that are labeled for the acute treatment of migraine. However, not all migraineurs respond well to the available therapies, the use of which can also be limited by safety concerns (e.g., restrictions for the use of triptans, ergotamines, and NSAIDs in patients with cardiovascular (CV) disease). Recently, three monoclonal antibodies targeting the CGRP system have been approved for the preventive treatment of both chronic and episodic migraine; erenumab (Aimovig) targeting the CGRP receptor, and fremanezumab (Ajovy) and galcanezumab (Emgality) targeting the CGRP peptide.

Ubrogepant is the first marketing application for a small molecule targeting CGRP. Previously, development of other small molecules in this class, referred to as “gepants”, has been limited by the finding of serious hepatotoxicity. Therefore, the Division had multiple interactions with the applicant to discuss the need to thoroughly evaluate this signal in the ubrogepant development program. The Division stated that this plan should include an evaluation of patients with daily or near daily use of this medication over the course of several months with close monitoring for potential hepatotoxicity. To address this concern, the applicant conducted a study in healthy volunteers in which patients alternated receiving ubrogepant for two days on and two day off for two months with follow-up in the third month off ubrogepant. In addition, to characterize any CV risk of this product, considering CGRP is thought to be involved in reactive vasodilatation in the face of ischemia, the Division stated that patients with CV disease should be included in studies to investigate the safety of ubrogepant in this population. The Division acknowledged that assay sensitivity would be expected to be low due to the infrequent number of cardiac events that would likely be observed in the clinical trials; however, the approved CGRP-monoclonal antibodies have not

demonstrated an increase in CV risk.

The applicant provides data from two placebo-controlled efficacy trials, Studies MD-01 and MD-02, in patients with migraine with and without aura to support the efficacy of ubrogepant for the proposed indication. Three doses of ubrogepant were evaluated between these studies: 25, 50, and 100 mg; however, the applicant proposes only the 50 mg and 100 mg doses for marketing.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson-Lee (refer to her review for the entire OPQ list of participants in the review of this application). Ubrogepant's drug product is an immediate-release tablet containing 50 mg and 100 mg dose strengths. The drug substance is a free base (b) (4). Dr. Wilson-Lee states that control strategy for impurities is acceptable and that mutagenic impurities have been assessed appropriately. The only specified impurity in the drug substance specification is (b) (4) with a qualified limit of (b) (4)%. She reports that based on the stability data provided, a drug substance retest date of (b) (4)-months is acceptable.

Dr. Wilson-Lee describes the drug product as a white to off-white capsule biconvex tablet. She states that the applicant provided release results for six batches of the 50 mg strength and three batches of the 100 mg strength, all of which met the proposed specifications. Upon review, no significant quality issues were identified. The primary container closure system for the drug product is a unit-dose (b) (4) foil pouch (b) (4) material. A 24-month expiry for the drug product is supported when stored at controlled room temperature based on the long-term stability data provided.

The overall manufacturing inspection recommendation is approval. There are no significant outstanding manufacturing or facility risks and all manufacturing facilities for this application are in good standing.

The comparative in vitro dissolution profile and in vivo bioequivalence (BE) data provided in the NDA are adequate to qualify chemistry, manufacturing, and control (CMC) changes that were introduced to the ubrogepant tablets after the conduct of the Phase 3 clinical trials.

The OPQ review team has determined that ubrogepant meets all applicable standards regarding identity, strength, quality, and purity. OPQ recommends approval of this application from a quality perspective.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for this application was Dr. Ed Nesti, with Dr. Lois Freed performing the secondary review. A standard battery of nonclinical studies was conducted. Refer to Dr. Nesti's review of this NDA for a detailed discussion of these studies. The following are among the key conclusions from these studies:

- Ubrogepant was negative in an in vitro hERG assay.
- In the 6-month rat and 9-month monkey toxicology studies, there were minimal or no adverse findings. The safety margins based on plasma AUC at the highest doses tested were approximately 30- and 60-fold in rat and monkey relative to the maximum recommended human dose (MRHD).
- Ubrogepant was negative in the genetic toxicology assessments (Ames test, in vitro chromosomal aberration, and in vivo rat bone marrow micronucleus assays). Ubrogepant was negative in mouse and rat carcinogenicity studies. Dr. Nesti notes that the safety margin, based on plasma exposure (AUC), did not achieve the 25-fold predicted by the sponsor.
- There were no ubrogepant-related findings in the fertility and early embryonic development study in rat, and the safety margin based on the highest dose tested was approximately 30-fold that in humans at the MRHD, based on plasma AUC.
- In the rat embryofetal development study (EFD) there were no ubrogepant-related findings, and the safety margin at the highest dose tested was approximately 45-fold the MRHD, based on plasma AUC. Two EFD studies were conducted in rabbit EFD testing the same doses. In the second study, the high dose group had to be sacrificed due to blood in the cage, abortion, and a decrease in body weight. The NOAEL in dams was 45 mg/kg with a safety margin of approximately 3-fold the MRHD, based on the plasma AUC. The fetal NOAEL was approximately 8-fold the MRHD, based on plasma AUC. In the prenatal and postnatal developmental study in rat, the NOAEL was 25 mg/kg based on reductions in maternal mean body weight gain and decreases in pup body weight at the mid and high doses. The safety margin at the NOAEL was approximately 15-fold the MRHD, based on plasma AUC.

In addition, the applicant conducted in vitro assays to assess the potential of ubrogepant to induce coronary artery vasoconstriction. Drs. Nesti and Freed report that in the in vitro study using human distal coronary, middle meningeal, and cerebral arteries ubrogepant inhibited CGRP-induced vasodilatation, but did not induce vasoconstriction at concentrations up to 100 µM.

Investigative hepatotoxicity assays were conducted comparing ubrogepant to two other CGRP receptor antagonists for which development was discontinued due to hepatotoxicity. The results indicated that ubrogepant inhibited bile acid transporters and HepG2 oxygen consumption in a concentration-dependent manner, suggesting the potential to induce mitochondrial toxicity. The applicant predicted up to a 10-fold safety margin at a human dose of 100 mg for the in vitro findings, which would be up to 5-fold at the MHRD (200 mg/day).

Drs. Nesti and Freed conclude that the nonclinical data are adequate to support approval of this NDA.

5. Clinical Pharmacology

The primary reviewers for the Office of Clinical Pharmacology (OCP) review were Drs. Bilal AbuAsal and Atul Bhattaram. Dr. Sreedharan Sabarinath was the team leader. The OCP review states that the clinical pharmacology information included in this NDA supports

approval of the 50 mg and 100 mg dose, with an option to take a second dose at least two hours after the first dose (i.e., a maximum daily dose of 200 mg).

The clinical trial formulation differed from the to-be-marketed formulation; therefore, the applicant conducted a pharmacokinetic (PK) bridging study of these formulations. Drs. AbuAsal and Bhattaram state that results of this study establish BE between these two formulations. The Office of Study Integrity and Surveillance (OSIS) determined that no site inspection was needed for the site of the PK bridging study since this site was recently inspected and received a No Action Indicated (NAI) classification.

Mechanism of Action
Drs. AbuAsal and Bhattaram state that ubrogepant is an oral CGRP receptor antagonist. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology. CGRP levels in the cranial circulation are thought to be increased during a migraine attack and CGRP itself has been shown to trigger migraine-like headache.

Absorption
Ubrogepant is rapidly absorbed following oral administration with peak plasma concentrations observed by around 1.5 hours post dose. Ubrogepant displays dose-proportional PK within the dose range of 1 to 400 mg. When ubrogepant was administered with a high-fat meal, the time to maximum ubrogepant plasma concentration was delayed by about 2 hours and resulted in a 22% reduction in C_{max} with no change in AUC. Since the efficacy trials were conducted without regard to food, and only approximately 10-13% of patients reported taking ubrogepant within 2 hours of a high-fat meal, the information available does not allow for a definitive conclusion regarding the impact of meals on efficacy. The OCP review does not recommend dosing adjustments with regard to food (a recommendation that would also be impractical for an acute treatment for migraine).

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

Metabolism and Elimination
Ubrogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (ubrogepant), and 2 glucuronide conjugate metabolites were the most prevalent circulating components in human plasma. The glucuronide metabolites are not expected to contribute to the pharmacological activity of ubrogepant.

The elimination half-life of ubrogepant is approximately 5-7 hours. Ubrogepant is excreted mostly via the biliary/fecal route, while the renal route is a minor route of elimination.

Special Populations/Intrinsic Factors
Clinical studies demonstrated that patients with severe hepatic impairment require a dose adjustment. Because of a two-fold increase in ubrogepant systemic exposure in patients with severe hepatic impairment, such patients should be advised to use only 50 mg ubrogepant and, if required, a second 50 mg dose 2 hours after initial dosing. No dose adjustment is required for patients with mild and moderate hepatic impairment.

A study to evaluate the impact of renal impairment on the PK of ubrogepant was not conducted. Instead, a population PK approach (Report UBR-MS-01) was used to assess the impact of renal impairment on the exposure of ubrogepant. Renal function, as measured by creatinine clearance, did not have a statistically significant effect on the clearance in patients with mild and moderate renal impairment. Based on this observation, no dose adjustment is necessary for patients with mild and moderate renal impairment (creatinine clearance greater than 30 mL/min). Patients with severe renal impairment or end stage renal disease (ESRD) were not included in any of the studies with ubrogepant. As a cautionary measure, Drs. AbuAsal and Bhattaram only recommend the use of a 50 mg dose of ubrogepant in patients with severe renal impairment. If required, an optional 50 mg second dose is allowed 2 hours after the initial dose in these patients. Ubrogepant should be avoided in patients with ESRD (creatinine clearance less than 15 mL/min).

The PK characteristics of ubrogepant are similar in elderly men and women (65-80 years of age), relative to younger patients. C_{max} was most similar, while the $AUC_{0\text{-}inf}$ was slightly higher in the elderly than in young males. A PopPK analysis evaluating the impact of body weight, race, age, and sex, demonstrated that these factors did not have a significant impact on ubrogepant systemic exposure; therefore, no related dose-adjustment is needed.

Dosing

Drs. AbuAsal and Bhattaram's recommended dose for the acute treatment of a migraine is 50 mg or 100 mg, with an option to take a second dose at least 2 hours after the initial dose. The maximum daily dose should not exceed 200 mg.

Drug-Drug Interactions

Ubrogepant is a significant substrate of BCRP; therefore, BCRP inhibitors may increase exposure of ubrogepant and the OCP review recommends that concomitant use should be avoided.

Drs. AbuAsal and Bhattaram recommend that ubrogepant be contraindicated with concomitant use of strong CYP3A4 inhibitors. Dose adjustments should be made for moderate CYP3A4 inhibitors (50 mg dose for the first dose and avoid a second dose within 24 hours) and weak CYP3A4 inhibitors (50 mg dose may be used, and a second 50 mg dose may be used 2 hours after the initial dose). Use of ubrogepant with strong CYP3A4 inducers should be avoided because loss of efficacy is expected, yet with moderate and weak CYP3A4 inducers the 100 mg dose should be used for the first dose, and if required a second 100 mg dose can be administered 2 hours after the initial dose.

Ubrogepant is a P-gp substrate and concomitant administration with P-gp inhibitors can increase the exposure of ubrogepant. Drs AbuAsal and Bhattaram estimate that the expected maximal increase in exposure due to P-gp only inhibition would result in less than 2-fold. Therefore, OCP recommends that the 50 mg dose of ubrogepant be used with concomitant use of P-gp only inhibitors. If required, a second dose of 50 mg may be taken 2 hours after the initial dose.

No clinically significant PK interactions were observed when ubrogepant was co-administered with oral contraceptives, acetaminophen, naproxen, sumatriptan, or proton pump inhibitors.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Laura Jawidzik conducted the clinical efficacy review for this application. Dr. Joanne Liu conducted the biometrics review and Dr. Kun Jin was the biometrics team leader.

The applicant conducted two placebo-controlled efficacy trials (Table 1) in adult migraine patients with and without aura: Study UBR-MD-01 (Study MD-01) and Study UBR-MD-02 (Study MD-02).

Table 1: Clinical Efficacy Studies

	Population	Treatment Duration	Doses	Location
Study MD-01	Migraine with and without aura	Single attack; optional second dose	50 mg or 100 mg	U.S.
Study MD-02	Migraine with and without aura	Single attack; optional second dose	25 mg or 50 mg	U.S.

Study MD-01

Study MD-01 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of ubrogepant for the acute treatment of a single migraine attack in 89 sites in the United States. Patients were randomized in a 1:1:1 ratio to either 50 mg ubrogepant, 100 mg ubrogepant, or placebo. Patients had the option of taking a second dose of investigational product (IP) or their own rescue medication at least 2 hours following the initial dose of IP, if needed. At randomization, patients were provided a blinded dose of study drug (active drug or placebo) to use for the treatment of a qualifying migraine (defined below). Patients that completed the double-blind portion of the trial had the option to continue into the open-label extension trial.

Patients eligible for enrollment into Study MD-01 were adults 18-75 years of age with at least a one-year history of migraine with or without aura. Patients had to be diagnosed with migraine before the age of 50 years and have a history of 3-8 migraines/month with moderate to severe headache pain in each of the 3 months before screening. Patients with uncontrolled hypertension or clinically significant CV or cerebrovascular disease were excluded. Patients with a myocardial infarction, transient ischemic attack, or stroke within 6 months prior to screening were excluded.

The co-primary endpoints used to establish efficacy were the proportion of patients who were headache pain-free at 2 hours, and the proportion of patients who were most bothersome

symptom (MBS)-free at 2 hours, following the initial dose. Pain freedom was defined as the absence of migraine pain at 2 hours following the treatment of a qualifying migraine attack (defined below). The MBS for a qualifying migraine attack was defined as either nausea, phonophobia, or photophobia, and was to be determined prospectively by the patient at the time of a qualifying migraine attack but before administration of study drug. The statistical analysis plan specified that both co-primary endpoints would have to be statistically significant in favor of ubrogepant in order to consider the study supportive of a treatment effect. The applicant included the following secondary endpoints, and included a plan to control for multiple comparisons: pain-relief at 2 hours, sustained pain-relief from 2-24 hours, sustained pain-freedom from 2-24 hours, absence of photophobia at 2 hours, absence of phonophobia at 2 hours, and absence of nausea at 2 hours.

The primary and secondary efficacy endpoints were analyzed using a logistic regression model. The applicant controlled the overall Type 1 error rate for multiple comparisons across two ubrogepant doses versus placebo for the primary and secondary endpoints. The secondary endpoints for a given dose could only be analyzed in a manner that preserved Type I error control if the analysis of both co-primary endpoints for that dose were statistically significant, relative to placebo.

The mITT population was defined by the applicant as all patients who received at least 1 dose of IP, recorded a baseline migraine severity measurement, and had at least 1 post-dose migraine severity or migraine associated symptom measurement at or before the 2 hour timepoint. Patients were told to only treat a qualifying migraine, which was defined as a migraine of moderate-severe intensity, associated with at least one migraine associated symptom (nausea, photophobia, and phonophobia), that started less than 4 hours prior to dosing. All efficacy analyses were conducted on the mITT population. Missing data was imputed using the last observation carried forward (LOCF) approach. Although this approach is not currently endorsed for a study evaluating an acute treatment for migraine, at the time in development when this plan was pre-specified by the applicant, the LOCF approach was considered acceptable. Additional sensitivity analyses were conducted using methods currently deemed acceptable, such as imputing missing data as non-responders, and where missing data were assumed to occur at random. The results of both sensitivity analyses were consistent with those observed for the primary analysis.

Study MD-02

Study MD-02 was identical in design to Study MD-01, except the ubrogepant doses studied in MD-02 were 25 mg and 50 mg. Study MD-02 was a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study conducted at 100 sites in the United States. Patients were randomized in a 1:1:1 ratio to either ubrogepant 25 mg or 50 mg, or placebo.

Results

Studies MD-01 and MD-02

The median age of the patients in both trials was 38-41 years. Eighty-six to 91% of subjects were female, and 79 to 86% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups in both trials. The median duration of migraine history was 16-17 years, the median of the average number of migraine/month over the past 3 months was 4, and approximately 18-27% of patients experienced migraine both with and without aura.

Co-primary endpoints

Table 2 presents the results of the primary efficacy analyses for Studies MD-01 and MD-02.

Table 2: Study MD-01 and MD-02- Co-primary Endpoint Efficacy Results (source: modified from Dr. Liu's review Table 6 and Table 24)

	Study MD-01			**Study MD-02**		
	Placebo	**Ubrogepant**		**Placebo**	**Ubrogepant**	
		50 mg	**100 mg**		**25 mg**	**50 mg**
Pain recorded as moderate to severe at time of dosing (n)	456	422	448	456	435	464
Pain Free at 2 hours (n)	54	81	95	65	90	101
%	11.8	19.2	21.2	14.3	20.7	21.8
p-value		0.0017	0.0001		0.0143	0.0065
MBS recorded at time of dosing (n)	454	420	448	456	435	464
MBS Free at 2 hours (n)	126	162	169	125	148	180
%	27.8	38.6	37.7	27.4	34.1	38.9
p-value		0.0003	0.0008		0.0355*	0.0005

*this p-value is not statistically significant since for this analysis a p-value must be less than 0.025 to be considered statistically significant

Drs. Jawidzik and Liu both conclude that treatment with ubrogepant resulted in statistically significant increases in the proportion of patients reporting pain freedom at 2 hours post-dose and MBS freedom at 2 hours post-dose as compared to placebo for the 50 mg and 100 mg dose in Study MD-01. In Study MD-02, the 50 mg ubrogepant dose was also statistically superior to placebo on both co-primary endpoints; however, although the 25 mg dose reached statistical significance on pain freedom at 2 hours, this was not the case for MBS-freedom at 2 hours.

Missing data for the pain freedom endpoint at 2 hours ranged from approximately 4-7% for Study MD-01 and 6-8% for Study MD-02. Alternate sensitivity analyses to evaluate missing data, including a semi-worst case scenario (missing data from placebo group were excluded and missing data from the drug group were assigned as treatment failures), an analysis where missing data was imputed as non-responders, and an analysis where missing data were considered as missing at random, were performed; all three analyses yielded results consistent with the primary analysis.

Secondary endpoints

Regarding the analyses of the secondary endpoints in Study MD-01, ubrogepant 100 mg demonstrated a statistically significant improvement over placebo on pain-relief at 2 hours, SPR from 2-24 hours, SPF at 2-24 hours, and absence of photophobia at 2 hours. Ubrogepant 50 mg demonstrated a statistically significant improvement over placebo for pain-relief at 2 hours and SPR 2-24, only. In Study MD-02, ubrogepent 50 mg demonstrated a statistically significant improvement over placebo on pain-relief at 2 hours, SPR from 2-24 hours, SPF from 2-24 hours, absence of photophobia at 2 hours, and absence of phonophobia at 2 hours. According to Dr. Liu's review, the analyses of the results of the ubrogepant 25 mg dose did not demonstrate statistically significant effects on any of the secondary endpoints because of a lack of Type I error control, given the lack of statistical significance of the analysis of this dose on the co-primary endpoint of MBS-freedom at 2-hours post-dose; therefore, any of the results for the 25 mg dose in Table 3, below, could only be considered nominally significant. Refer to Table 3, below, for the results of the analyses of the secondary efficacy endpoints from both controlled efficacy trials (note that this table, modified from the statistical review, includes those results that were statistically significant, and notes where the results were not statistically significant). There was no increase in the incidence of nausea at 2 hours post-dose for any of the ubrogepant doses as compared to placebo in either trial.

Table 3: Study MD-01 and MD-02 Results for Secondary Endpoints (source: modified from Dr. Liu's review Table 19 and Table 37)

	Study MD-01			Study MD-02		
	Placebo N=456	**50 mg N=423**	**100 mg N=448**	**Placebo N=456**	**25 mg N=435**	**50 mg N=464**
Pain Relief at 2 hours						
Responders, n (%)	224 (49.1)	256 (60.7)	275 (61.4)	220(48.2)	263 (60.5)	291 (63)
Difference from placebo (%)		11.6	12.3		12.3	14.8
p-value		0.0002	0.0002		NS	<0.0001
SPR 2-24 hours						
Responders, n (%)	93 (20.8)	150 (36.3)	165 (38.0)	93 (21)	138 (32.5)	165 (36.7)
Difference from placebo (%)		15.5	17.2		11.5	15.7
p-value		<0.0001	<0.0001		NS	<0.0001
SPF 2-24 hours						
Responders, n (%)	39 (8.6)	53 (12.7)	68 (15.4)	37 (8.2)	55 (12.7)	66 (14.4)
Difference from placebo (%)		4.1	6.8		4.5	6.2
p-value		NS	0.0018		NS	0.0051
Absence of Photophobia at 2 hrs						
Responders, n (%)	143 (31.4)	172 (40.7)	205 (45.8)	162 (35.5)	171 (39.3)	203 (43.8)
Difference from placebo (%)		9.3	14.4		3.8	8.3
p-value		NS	<0.0001		NS	0.0042
Absence of Phonophobia at 2 hrs						
Responders, n (%)	215 (47.1)	245 (57.9)	244 (54.5)	211 (46.3)	233 (53.6)	251 (54.1)
Difference from placebo (%)		10.8	7.4		7.3	7.8
p-value		NS	NS		NS	0.0220

NS=not significant

Use of Rescue Medication

Table 4 and Table 5, present the results of the use of rescue medication within 24 hours (defined as either an optional second dose of study drug, or patient's own acute treatment) in Studies MD-01 and MD-02, respectively.

Table 4: Study MD-01- Use of Rescue Medication (source: modified from Dr. Jawidzik's review Table 15)

	Placebo N=456	50mg N=423	100mg 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%
p-value		<0.001*	<0.001*

*nominally significant

Table 5: Study MD-02- Use of Rescue Medication (source: modified from Dr. Jawidzik's review Table 28)

	Placebo N=456	25mg N=435	50mg 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%
p-value		0.005*	0.0001*

*nominally significant

Although the results of these analyses can only be considered nominally significant as they were not controlled for Type 1 error, these results are consistent with the findings of the co-primary endpoints.

Second Dose Efficacy

The applicant allowed for the use of a second dose of IP if patients decided to take a second dose within 24 hours; however, the results of these analyses lacked even nominal significance and were not controlled for Type I error. Additionally, there were several additional factors that further limit the interpretability of any observed trends in these analyses, including:

- Not all patients who took a second dose of migraine medication decided to take study drug. Therefore, selection bias likely affected the results of the analysis since patients in the second dose group were more likely to have had a good response from the first dose and therefore were more likely to be responders with the use of second dose.

- There is a large amount of missing data for the 2-hour timepoint for pain free in each treatment group even considering only the patients that chose to take study drug were included.

- The number of patients in these groups were small and therefore the analysis was underpowered to identify a treatment difference between groups.

Based on these shortcomings, efficacy of a second dose has not been established.

Efficacy by Subgroups
Dr. Liu performed analyses of the treatment effect across subgroups for both Studies MD-01 and MD-02, and concludes that the efficacy trends observed in the primary efficacy analyses appeared to be similar across all subgroups (age, gender, and race); however, no definitive conclusions can be made based on the small sample sizes for these respective comparisons.

Efficacy Conclusions
The applicant has provided substantial evidence of effectiveness of ubrogepant based on the results from two adequate and well-controlled investigations. Both studies were conducted in patients with migraine with and without aura and both demonstrated significant increases in the proportion of patients who were pain-free at 2 hours post-dose and MBS-free at 2 hours post-dose in the ubrogepant 50 mg and 100 mg groups, as compared to placebo. There was a shallow dose-response relationship. The analyses of the trials' secondary endpoints were generally supportive of the primary efficacy analyses. The 50 mg and 100 mg doses are effective and should be described in labeling. In addition, labeling should include an option to take a second dose within 24 hours, a recommendation common to most approved acute treatments for migraine.

Dr. Jawidzik also recommends the approval of the 25 mg dose, noting that the treatment effects on the co-primary endpoints between the 25 and 50 mg doses in Study MD-02 were similar. However, the analysis of the 25 mg dose co-primary endpoint MBS-free at 2 hours lacked statistical significance. Additionally, beyond the lack of Type I error control in the analyses of the secondary endpoints for the 25 mg dose, these results were generally numerically inferior compared to the 50 mg dose. Further, as discussed in Section 8 of this review, the safety profile of ubrogepant is relatively benign at all doses proposed for marketing. Therefore, these data ultimately do not support the utility of the 25 mg dose, given the potential for reduced efficacy in the absence of any significant safety signal at the 50 and 100 mg doses, and the 25 mg dose will not be described in labeling.

8. Safety

Dr. Laura Jawidzik conducted the clinical safety review of this application.

As discussed by Dr. Jawidzik, the overall exposure to ubrogepant exceeds the minimum number of patients recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. She reports that 3,624 patients were exposed to at least one dose of ubrogepant, of which 2,581 were exposed in the controlled clinical trials and 1,567 received at least one dose of ubrogepant 100 mg, the highest dose proposed for marketing. When considering exposure to both doses of ubrogepant proposed for marketing (50 and 100 mg) 421 patients treated at least 2 migraines per month for at least 6 months and 281 treated at least 2 migraines per month for 12 months.

Dr. Jawidzik notes that this development program allowed patients up to the age of 75 to enroll, although only a small proportion of patients were 65 years of age and over (3%). Given that there have been safety concerns regarding the theoretical risk of CGRP antagonism since

CGRP is considered a potent vasodilator, CV safety has been identified as a safety concern of special interest in this application. In addition, hepatotoxicity was also identified as a safety concern of special interest due to the occurrence of serious hepatotoxicity that occurred during the development of other small molecule CGRP antagonists. Regarding her evaluation of these safety issues, Dr. Jawidzik notes that the migraine studies excluded patients with hepatic disease, unstable angina, myocardial infarction, TIA, and stroke, within 6 months of the study. She suggests that this may limit the generalizability of the safety data to the larger population when considering that postmarketing use will be much less restrictive.

There were no obvious demographic imbalances between active treatment and placebo when considering, gender, age, race, ethnicity, or weight.

Deaths

There was one death in the ubrogepant safety database. A 35 year-old male that participated in a Phase 1 study died in a motor vehicle accident (MVA). This subject received ketoconazole for 5 days and a single dose of ubrogepant on the second day of ketoconazole dosing. The accident occurred 14 days after the last dose of ketoconazole. The half-life of ubrogepant is 5-7 hours; therefore, this medication should have been cleared long before the MVA. Dr. Jawidzik concludes that it was unlikely that this event was related to the use of ubrogepant, a reasonable assessment.

Serious Adverse Events (SAEs)

Dr. Jawidzik notes that there were few overall SAEs. There were only seven patients that reported an SAE within 30 days of dosing and no patients in the controlled clinical trials that experienced an SAE within 48 hours of dosing of IP. Of the seven patients described above reporting SAEs within 30 days of IP dosing, all patients were assigned to ubrogepant. One patient reported 7 SAEs, while the others experienced one each. The single patient that reported multiple SAEs was involved in a serious bicycle accident. This accident occurred 14 days after the last dose of ubrogepant. In the long-term extension study, there were 30 SAEs reported by 21 patients. One patient experienced 6 SAEs, notably, acute respiratory failure, acute cholecystitis and cholelithiasis, diabetic ketoacidosis, pneumonia, and sepsis. One patient experienced 3 episodes of acute pancreatitis. Most SAEs occurred in just 1 patient. The gastrointestinal, general and administration site, hepatobiliary disorder, injury, poisoning and procedural complications system organ classes (SOCs) had more than 1 SAE.

Of these SAEs, Dr. Jawidzik identified only one event in the controlled trials in which she states that a relationship to ubrogepant cannot be ruled out. She notes that all SAEs reported were confounded by other factors and selected cases are discussed in detail in her review. The case that she feels may have a relationship to ubrogepant is that of a patient that experienced a partial focal seizure with secondary generalization occurring 5 hours after taking study drug. However, this case was confounded by the fact that the patient was also on alprazolam 1 mg three times a day, and reportedly only took 1 mg on the day prior to the seizure and no alprazolam on the day of the seizure. Therefore, acknowledging Dr. Jawidzik's assessment the contribution of ubrogepant in this case cannot be ruled out, it is also likely that this seizure may have been a benzodiazepine withdrawal seizure.

As stated, SAEs were collected and included in the applicant's analysis when they occurred within 48 hours of dosing. Dr. Jawidzik notes that a 48-year-old female who was participating in the double-blind period of Study MD-01 experienced right lower quadrant pain. This event occurred 33 days after the last dose of ubrogepant 100 mg. A CT scan showed possible appendicitis. Her liver enzymes rose to ALT 580 (greater than 10x ULN) and AST 965 (greater than 28x ULN) and her lipase rose to 2908. Her total bilirubin remained normal. She underwent a laparoscopic appendectomy due to her diagnosis of 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. Dr. Jawidzik concludes that it is unlikely that this event was related to ubrogepant because she had an alternative diagnosis that could lead to elevated liver enzymes, and the event also occurred well after 5 half-lives since the last dose of ubrogepant.

Two patients had acute kidney injury (AKI), but continued in the long-term extension trial with resolution of the AKI and Dr. Jawidzik does not believe that these cases are related to the use of ubrogepant.

One patient in the open-label extension trial experienced a small bowel obstruction and discontinued from the study. The last dose of ubrogepant was 4 weeks prior to this event and the patient was being treated at the time for Clostridium difficile infection. Dr. Jawidzik does not consider this SAE as to be related to ubrogepant since the drug was taken over 5 half-lives from the drug.

One patient in the open-label extension trial experienced colitis approximately 3 weeks after her last dose of 100 mg ubrogepant. An abdominal CT of the abdomen and pelvis demonstrated colonic wall thickening, fatty infiltration of the liver, and mild hepatic steatosis. Bloody diarrhea and colonic wall thickening can be seen in ischemic colitis; therefore, this case is described since ischemic colitis is a class-related concern considering the proposed mechanism of action of CGRP, but due to the fact that this case occurred 3 weeks after dosing, Dr. Jawidzik concludes that a relationship to ubrogepant is unlikely.

Discontinuations

Dr. Jawidzik identified 7 patients that withdrew IP due to an adverse event. No AEs reported occurred in only one patient with the exception of 2 AEs of rash that occurred in the placebo group. In the open-label experience, the only withdrawal reported due to an AE that occurred in more than one patients was nausea which occurred in 3 patients. Dr. Jawidzik also notes that dose interruption was reported in 9 patients experiencing 11 AEs, but the only event that occurred in more than 1 patient was abnormal weight gain (2).

Treatment Emergent Adverse Events (TEAEs)

Table 6, modified from Dr. Jawidzik's review, summarizes the most common TEAEs from the controlled trials.

Table 6: Study MD-01 and MD-02- Pooled TEAEs after the first dose in the DBTP with an incidence of at Least 1% and At Least 1% Greater than Placebo (modified from Dr. Jawidzik's review Table 57)

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

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

Table 6 demonstrates a dose-response for somnolence. Nausea and dry mouth demonstrate similar incidences between placebo and 50 mg, but an increased incidence for the 100 mg dose. At the 25 mg dose, nausea and dizziness are higher in the 25 mg group as compared to the 50 mg group, and actually lower for dry mouth than in placebo. The TEAE profile of ubrogepant from the long-term extension trial is similar to that described in the controlled trials except the long-term extension trial also includes an increased incidence of dizziness and abdominal pain, which was also noted in placebo-controlled healthy volunteer studies.

Dr. Jawidzik notes that her analysis of safety with the optional second dose of IP suggests that there is an increase in the rate of dizziness, somnolence, and nausea/vomiting in the patients who opted to take a second dose.

Laboratory Findings

Dr. Jawidzik did not find clinically meaningful differences in the controlled trials between ubrogepant and placebo mean changes from baseline compared to placebo for all laboratory measures.

Since the evaluation of possible hepatotoxicity was a critical part of the safety review, Dr. Jawidzik's review contains a detailed discussion of this issue. The applicant evaluated several databases to address this concern, namely, the safety database from the controlled clinical trials, the open-label safety study, a 32-patient study in healthy volunteers who received 150 mg daily for 28 days (Study P004), and an 8-week study in healthy volunteers in which patients received ubrogepant 100 mg for two days on, two days off for 8 weeks (Study 3110-105-002). Based on Table 7 and Table 8 below, it does appear that at the 100 mg dose, there was a higher incidence of patients with elevated transaminases, but this finding is not observed for total bilirubin values. There were no Hy's law cases reported. In the 8-week hepatic safety study described above, there were no differences in elevations of transaminase between placebo patients and those that received 100 mg ubrogepant (refer to Table 9). Overall, Dr. Jawidzik concludes that there is no clinically meaningful signal for hepatic injury in this safety database.

Table 7: Study MD-01 and MD-02-Pooled Analysis of Elevated ALT, AST or Total Bilirubin (source: Dr. Jawidzik's review Table 60)

	Placebo N=984 n(%)	25mg N=478 n(%)	50mg N=954 n(%)	100mg 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
Total Bilirubin				
≥1.5xULN	3 (0.3)	2 (0.4)	3 (0.3)	2 (0.4)
≥ 2xULN	0	1 (0.2)	2 (0.2)	0

Table 8: Study MD004- Post Baseline AST, ALT, Total Bilirubin (source: Dr. Jawidzik's review Table 61)

	50mg N=404 n(%)	100mg 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
Total Bilirubin			
≥ 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

Table 9: Study 3110-105-002-Post Baseline Elevations in AST, ALT and Total Bilirubin (source: Dr. Jawidzik's review Table 86)

	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
Total Bilirubin (mg/dl)		
≥1.5xULN	2 (0.8)	0
≥ 2xULN	0	0

Despite findings in the in vitro investigative hepatotoxicity assays, as described in the nonclinical section of this review, no evidence of hepatotoxicity was demonstrated in the clinical studies.

Vital Signs

Dr. Jawidzik notes that treatment with ubrogepant did not appear to result in clinically meaningful changes in vital signs with respect to analyses of mean values, as well as outliers in both the controlled efficacy trials and in the Phase 1 studies in regard to the doses proposed for marketing. Dr. Jawidzik reports that in a multiple ascending dose safety study, when either ubrogepant 50 mg, 100 mg, 400 mg, or placebo was taken for 10 consecutive days, there were notable trends of an increase in mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline with the 400 mg dose. There were no notable changes in orthostatic blood pressure.

Electrocardiogram (ECG)

Dr. Jawidzik found no clinically significant changes from baseline in mean heart rate (HR), PR interval, QRS, or QTcF, as compared to placebo in the controlled clinical trials.

Dr. Jawidzik reports that the applicant conducted a thorough QT (TQT) study (UBR-PK-02) which was reviewed by the Interdisciplinary Review Team for QT Studies (QT-IRT). They found no significant QTc prolongation effect with the use of 100 mg and 400 mg of ubrogepant. The QT-IRT notes that the 400 mg dose provided approximately a 2-fold coverage of the maximum therapeutic dose (two 100 mg doses given 2 hours apart). They also note that strong and moderate CYP3A4 inhibitors increase C_{max} by 5-fold and 3-fold.

The QT-IRT concludes that the selected doses are not adequate to satisfy ICH E14 as they did not cover the supratherapeutic exposure or the maximum tolerated dose; however, the

applicant has proposed labeling to handle this scenario by proposing to contraindicate the use of ubrogepant with strong CYP3A4 inhibitors and to impose a dose reduction with the use of concomitant moderate CYP3A4 inhibitors. The QT-IRT reviewed the applicant's proposed language in section 12.2 of the label and agrees that the suggested labeling adequately mitigates these concerns.

Cardiovascular Risk

Dr. Jawidzik did not identify any potential CV or cerebrovascular safety concerns in regard to toxicity associated with the use of ubrogepant, noting that her review is limited in this respect, 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 CV, cerebrovascular, and peripheral vascular disease was low.

Please also refer to the nonclinical discussion in this review, which discusses the lack of nonclinical evidence of vasoconstrictive effects of ubrogepant, athough there was evidence that ubrogepant inhibited CGRP-induced vasodilatation.

Dr. Jawidzik concludes that the current database does not support an increased CV risk with ubrogepant and that labeling should not include CV restrictions. However, these data are also insufficient to definitively establish the CV safety of ubrogepant, and enhanced pharmacovigilance in the postmarket setting will be required.

Gastrointestinal Toxicity

Nausea and dry mouth were increased in a generally dose-dependent fashion with the use of ubrogepant. 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.

Medication Overuse Headache

Although the theoretical potential for medication overuse headache (MOH) exists for ubrogepant, as it is intended for the acute treatment of migraine, no data exists for this class or any related class of drugs to support inclusion of an MOH warning in labeling. Drugs targeting the CGRP pathway that result in consistent daily exposures (although dosed monthly or every 3 months) are also approved for the preventive treatment of migraine. Therefore, currently, there is no empirical basis to restrict the number of acceptable monthly doses, although we will note in labeling that the available safety data only address dosing up to 8 attacks/month.

Suicidality and Depression

Dr. Jawidzik has evaluated the risks of suicidality and depression using AE terms and using results of the Columbia Suicide Severity Rating Scale (C-SSRS) in Studies MD-01, MD-02, and MD-04, and concludes that there does not appear to be a signal for suicidal ideation or behavior among patients treated with ubrogepant.

Safety Conclusions
The safety profile of ubrogepant is acceptable for the acute treatment of migraine with and without aura in adults. There are no safety issues that preclude approval.

Most notable in this application is the low number of SAEs overall, specifically in the controlled clinical trials (none reported within 48 hours of dosing). None of the reported SAEs clearly seem related to ubrogepant use.

Ubrogepant was also found to cause AEs such as nausea, somnolence, and dry mouth. The use of a second dose of ubrogepant was associated with an increase incidence of dizziness and abdominal pain. The risks of ubrogepant can be accurately conveyed with labeling.

Labeling will limit the use of ubrogepant to the treatment of no more than 8 migraines per month, consistent with the approach used in the development program.

A pregnancy registry and pregnancy outcome studies will be required.

There should be enhanced pharmacovigilance of CV events, cerebrovascular events, and hepatotoxicity.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because it was clear that the applicant had provided substantial evidence of effectiveness from two adequate and well-controlled studies, using clinical trial designs similar to those of trials for previously approved drugs for the acute treatment of migraine. Moreover, the safety profile was deemed acceptable for the treatment of migraine, without controversial issues.

10. Pediatrics

Ubrogepant was discussed at a Pediatric Review Committee (PeRC) meeting on November 19, 2019. Agreement was reached with the applicant's plan for requesting a partial waiver of clinical trials in patients 0 to less than 6 years of age (on the basis that such studies are highly impracticable) and a post-approval deferral of such trials in patients 6 to 17 years of age. Please refer to Section 14 of this memo for the required pediatric postmarketing studies.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the team leader. Dr. Alfaro states that four clinical sites were inspected in support of this NDA, specifically for Studies MD-01 and MD-02. In addition, the inspection covered the applicant practices related to MD-01 and MD-02 and focused on the four clinical sites selected for inspection. Dr. Alfaro confirmed that the databases for the two efficacy studies were locked appropriately and neither database was unlocked after the initial lock. There was no

evidence of inadequate monitoring by the applicant. There was a complaint regarding Site 150 enrolling patients in Study MD-02. The complainant alleged that the "Allergan monitor was fired for failure to monitor sites and report noncompliance to protocol". However, the FDA inspector did not note any deficiencies of monitoring for this site and also did not find evidence that a monitor was fired due to inadequate monitoring.

Controlled Substance Staff (CSS)
Dr. Katherine Bonson from CSS concluded that there were no abuse potential signals seen in nonclinical 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; therefore, a human abuse potential study or a human physical dependence study was not required.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Briana Rider was the primary reviewer and Dr. Lolita White was Team Leader for the DMEPA review. DMEPA concludes that the final agreed-upon PI, container labels, and carton labeling are acceptable.

Dr. Morris reviewed the proposed proprietary name, Ubrelvy, and concluded that this name is acceptable.

12. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRISK) has determined that a REMS is not necessary for ubrogepant.

Pharmacovigilance
There should be enhanced pharmacovigilance postmarketing with periodic evaluation of CV events and cerebrovascular events.

Postmarketing Requirements (PMRs)

PMR-1 A juvenile animal toxicology study in one species.

PMR-2 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA to evaluate two doses of Ubrelvy (high dose and low dose) compared to placebo during a single migraine attack in pediatric patients ages 6 to less than 18 years. This study will include an open-label pharmacokinetic cohort in order to select appropriate doses for patients 6-11 years old in the efficacy portion of the study. This efficacy study must be designed to show superiority of Ubrelvy over placebo and is to be submitted as a special protocol assessment (SPA).

PMR-3 An open-label, long-term safety study under PREA in pediatric patients ages 6 to 17 years, for up to one year.

PMR-4 A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Ubrelvy during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Ubrelvy before or during pregnancy, and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR-5 A pregnancy outcomes study using a different study design than provided for in PMR-4 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Ubrelvy during pregnancy compared to an unexposed control population.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER on behalf of HEATHER D FITTER
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