CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	December 12, 2019
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Ubrelvy (ubrogepant)
Application Type/Number:	NDA 211765
Applicant/sponsor:	Allergan Sales, Inc.
OSE RCM #:	2019-2289

1. BACKGROUND INFORMATION

1.1. Medical Product

Ubrogepant (UBRELVY™, Allergan Sales, Inc.) is a small molecule high-affinity calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP, a potent vasodilator of intracranial blood vessels, has been shown to have a role in migraine pathophysiology (Ashina, Hansen et al. 2019); it is a peptide neurotransmitter that is produced in peripheral sensory neurons and numerous sites throughout the central nervous system. The CGRP receptor is a complex of several proteins, each of which is required for the ligand specificity and function of the receptor (Edvinsson, Haanes et al. 2018). Ubrogepant competes with the binding of CGRP and inhibits the function of CGRP at its receptor. It is a new molecular entity (NME) and is currently not approved or marketed in any country. The proposed indication is the acute treatment of migraine with or without aura. If approved, it will be available in 50 mg- and 100 mg-tablets. The proposed dosing is 50 mg or 100 mg taken orally with or without food; a second dose may be administered at least two hours after the initial dose; the maximum daily dose is 200 mg. Ubrogepant is rapidly absorbed with a Tmax of 0.7 to 1.5 hours post-dose. The α half-life is about 3 hours and the β half-life (terminal phase) is about 5–7 hours. It is extensively and almost exclusively, metabolized by CYP3A4. Co-administration with a strong CYP3A4 inducer may cause a loss of efficacy.[1]

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. Clinical trials mostly included relatively healthy patients without major cardiovascular diseases. A total of 3,624 individuals took at least one dose of ubrogepant during development. Of these, 1,567 received at least one dose of ubrogepant 100 mg (highest dose proposed for marketing). Common adverse events in ubrogepant-treated patients included viral infections, nausea, somnolence, confusion, dizziness, dry mouth, and abdominal pain. Although small, there was a dose-dependent increase in the incidence of nausea and somnolence as compared to placebo. These trials did not identify major, serious toxicities or clear safety signals for theoretical issues related to the use of CGRP receptor antagonists: cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, and liver toxicity. Enhanced pharmacovigilance for myocardial infarction and stroke will be used to address potential safety issues associated with the theoretical cardiovascular risk associated with CGRP antagonism.[2]

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4%.[3] Migraine is a neurological disorder characterized by recurrent headache attacks of moderate to severe pain. The prevalence of

[1] Draft clinical review dated December 10, 2019
[2] Draft clinical review dated December 10, 2019
[3] U.S. Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved October 18, 2019, from https://www.fda.gov/media/90160/download.

migraine is higher among women (18%) and lower among children, adolescents, and individuals over 60 years of age (Lipton, Stewart et al. 2001). Women with migraine who become pregnant may have a greater risk of placenta abruption, preterm delivery, lower gestational age at delivery, hypertension, preeclampsia, and cardiovascular complications (Sanchez, Williams et al. 2010, Wabnitz and Bushnell 2015, Tietjen and Collins 2018, Allais, Chiarle et al. 2019).

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of ubrogepant. Female subjects who were pregnant or lactating were excluded from enrolling in the ubrogepant clinical studies. Despite requirements for contraception, there were a total of 19 pregnancies among ubrogepant-treated women: eight unknown pregnancy outcomes, five full term births of healthy infants, two spontaneous abortions (at ~9 and 12 weeks of gestation, respectively), two elective terminations (reasons not reported), one ectopic pregnancy (ended by therapeutic abortion), and one preterm birth (at ~32 weeks of gestation) without complications other than low birth weight.[4] As per the applicant, in animal studies, no evidence of teratogenicity has been observed in rats or rabbits with UBRELVY.[5]

In the proposed labeling, as of December 28, 2018, the Risk Summary in Section 8.1 Pregnancy states:

*"**Risk Summary**. There are no adequate data on the developmental risk associated with the use of UBRELVY in pregnant women.* (b) (4) *In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively.*
***Clinical Considerations.** Disease-Associated Maternal and/or Embryo/Fetal Risk* (b) (4) *have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.*
Animal Data. (b) (4)

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	

[4] 2.7.4. Summary of Clinical Safety. Allergan Sales, Inc.
(b) (4)

Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☒ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☒ Other, please specify: *Alternative study designs for the electronic database study without chart review would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case-control study*

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.
Because broad-based signal detection is not currently available, other parameters have not been assessed.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by the Division of Neurology Products (DNP) as of October 21, 2019 for PMRs related to pregnancy outcomes:

"Conduct 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."

"Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3769-4 (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, preterm births, and small-for-gestational-age births in women exposed to Ubrelvy during pregnancy compared to an unexposed control population."

REFERENCES

Allais, G., G. Chiarle, S. Sinigaglia, O. Mana and C. Benedetto (2019). "Migraine during pregnancy and in the puerperium." Neurol Sci **40**(Suppl 1): 81-91.
Ashina, M., J. M. Hansen, T. P. Do, A. Melo-Carrillo, R. Burstein and M. A. Moskowitz (2019). "Migraine and the trigeminovascular system-40 years and counting." Lancet Neurol.
Edvinsson, L., K. A. Haanes, K. Warfvinge and D. N. Krause (2018). "CGRP as the target of new migraine therapies - successful translation from bench to clinic." Nat Rev Neurol **14**(6): 338-350.
Lipton, R. B., W. F. Stewart, S. Diamond, M. L. Diamond and M. Reed (2001). "Prevalence and burden of migraine in the United States: data from the American Migraine Study II." Headache **41**(7): 646-657.
Sanchez, S. E., M. A. Williams, P. N. Pacora, C. V. Ananth, C. Qiu, S. K. Aurora and T. K. Sorensen (2010). "Risk of placental abruption in relation to migraines and headaches." BMC Womens Health **10**: 30.
Tietjen, G. E. and S. A. Collins (2018). "Hypercoagulability and Migraine." Headache **58**(1): 173-183.
Wabnitz, A. and C. Bushnell (2015). "Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature." Cephalalgia **35**(2): 132-139.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	December 4, 2019
To:	E. Andrew Papanastasiou, MS, PharmD Senior Regulatory Health Project Manager **Division of Neurology II**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	UBRELVY (ubrogepant)
Dosage form:	tablets, for oral use
Application Type/Number:	NDA 211765
Applicant:	Allergan Sales LLC

1 INTRODUCTION

On December 26, 2018 Allergan Sales LLC submitted for the Agency's review a New Drug Application (NDA) for ubrogepant tablets, for oral use. The proposed indication for ubrogepant tablets is the acute treatment of migraine with or without aura in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on January 28, 2019 for DMPP and OPDP to provide a review of the Applicant's proposed PPI for ubrogepant, tablets for oral use.

2 MATERIAL REVIEWED

- Draft UBRELVY (ubrogepant) PPI received on December 26, 2018 and received by DMPP and OPDP on November 25, 2019.
- Draft UBRELVY (ubrogepant) Prescribing Information (PI) received on December 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 25, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI documents using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 3, 2019

To: Laura Jawidzik, M.D.
Division of Neurology Products (DNP)

E. Andrew Papanastasiou, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for UBRELVY™ (ubrogepant) tablets, for oral use

NDA: 211765

In response to the DNP consult request dated January 28, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for UBRELVY™ (ubrogepant) tablets, for oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (E. Andrew Papanastasiou) on November 25, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 16, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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DHARA SHAH
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Clinical Inspection Summary

Date	10/15/2019
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrew (Emilios) Papanastasiou, Regulatory Project Manager Laura Jawidzik, M.D., Medical Officer Division of Neurology Products
NDA #	211765
Applicant	Allergan Sales, LLC
Drug	Ubrogepant
NME	Yes
Proposed Indication	Acute treatment of migraine with or without aura in adults
Consultation Request Date	2/12/2019
Summary Goal Date	10/25/2019
Action Goal Date	12/26/2019
PDUFA Date	12/26/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Galen, Mehra, Muse, and Sugimoto were inspected as well as the sponsor, Allergan Sales, LLC, in support of this NDA. These inspections covered Protocols UBR-MD-01 and UBR-MD-02. The studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Ubrogepant oral tablets are being developed by Allergan Sales, LLC, under NDA 211765 (IND 113924), for the acute treatment of migraine with or without aura in adults. The sponsor has submitted two Phase 3 studies, UBR-MD-01 and UBR-MD-02, to support the efficacy and safety of ubrogepant in the acute treatment of migraine.

Protocol UBR-MD-01

Title: 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

Subjects: 1672 randomized

Sites: 89 in the United States

Study Initiation and Completion Dates: 7/22/2016 to 12/14/2017

This was a randomized, double-blind, placebo-controlled study in subjects a history of migraine with or without aura for at least one year. Included were males or females, 18 to 75 years of age, migraine onset before age 50, and who had to have experienced between 2 to 8 migraine attacks of moderate to severe pain in each of three months prior to screening.

Following screening, subjects were randomized (1:1:1) to one of three treatment groups:

- Ubrogepant 50 mg
- Ubrogepant 100 mg
- Placebo

Subjects were stratified by their previous response to triptans and their current use of prophylactic concomitant medication for migraine. Subjects had up to 60 days to treat a single qualifying migraine attack. A qualifying migraine attack was a headache severity of moderate or severe, presence of at least one migraine-associated symptom (photophobia, phonophobia, or nausea), headache started less than 4 hours prior, prohibited medication had not been taken, migraine headache is a new headache (not a recurrence), migraine headache is not already resolving on its own.

Two hours after the initial treatment with study drug, subjects who did not adequately respond could take a blinded optional second dose (active treatment or placebo as assigned at randomization), subjects' own rescue medication, or may elect to take no further medication. Subjects returned to the clinic four days after treating their qualifying migraine. A follow-up phone call occurred on day 14 after migraine treatment. The last study visit was the 4-week safety follow-up visit.

Efficacy assessments were based on information recorded by the subject in an electronic diary (e-diary). These assessments included headache severity, migraine associated symptoms, use of rescue medication, use of optional second dose, and recurrence of headache pain.

The *co-primary efficacy endpoints* were:

- Pain freedom at 2 hours after the initial dose. Pain freedom was defined as a reduction in headache severity from moderate/severe at baseline to no pain
- Absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose.

<u>Protocol UBR-MD-02</u>

Title: 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

Subjects: 1686 randomized

Sites: 100 in the United States

Study Initiation and Completion Dates: 8/26/2016 to 2/26/2018

The study design was the same as UBR-MD-01 except that subjects were randomized to ubrogepant 25 mg, ubrogepant 50 mg, or placebo.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, and prior inspectional history.

III. RESULTS

1. **R. Michelle Galen, M.D.**
Deaconness Clinic, Inc.
421 Chestnut Street
Evansville, IN 47713

At this site for Protocol UBR-MD-01 (Site #75), 26 subjects were screened, 23 were randomized, and 22 subjects completed the study. Two of the 22 subjects who completed the study did not have a migraine attack of sufficient severity during the study and did not take investigational product. One subject ((b) (6)) discontinued the study due to pregnancy; she had not taken any investigational product.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

During the inspection, electronic diary data was available for review via a certified CD provided to the site by the sponsor. The co-primary efficacy endpoint data were verified against sponsor data listings, and no discrepancies were identified. There was no evidence of under-reporting of adverse events. No SAEs were reported at this site.

2. **Vishaal Mehra, M.D.**
Artemis Institute for Clinical Research
770 Washington Street, Suite 300
San Diego, CA 92103

At this site for Protocol UBR-MD-02 (Site #64), 45 subjects were screened, 35 were randomized, and 34 subjects completed the study. One of the 34 subjects who completed the study did not have a migraine attack of sufficient severity during the study and did not take investigational product. One subject discontinued the study due to “loss to follow-up.”

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring

documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, concomitant medications, protocol deviations, and primary efficacy endpoint data.

During the inspection, electronic diary data was available for review via the web portal for the clinical investigator. The co-primary efficacy endpoint data were verified against sponsor data listings, and no discrepancies were identified. There was no evidence of under-reporting of adverse events. No SAEs were reported at this site.

In the Clinical Study Report (CSR), the sponsor stated that there were two more subjects in the ITT[1] population than in mITT[2] and safety[3] populations. Per the CSR, Subjects (b) (6) and (b) (6), both randomized to ubrogepant 50 mg at this site, "each took their initial dose and optional second dose of IP but failed to record complete dose dates (i.e., day was missing). …Because the complete date of dosing was not recorded and could not be verified, these two patients were excluded from the safety and mITT populations". The FDA field investigator reviewed the web portal data for these subjects, and no data was available for review, including headache data.

Of note, the sponsor data listing 16.2.6-1.1 (Rating of Headache Severity and Migraine Associated Symptoms), included in the CSR, does not list Subject (b) (6) but does list Subject (b) (6). The listing for Subject (b) (6) does not include a date or time for investigational product administration but only provides a predose assessment of headache severity and associated migraine symptoms.

Reviewer comment: As requested by the review division, it was confirmed that the investigational product administration data (date/time) was missing from the electronic diary data for Subjects (b) (6) and (b) (6). It is unclear why the predose assessment of headache severity data for Subject (b) (6) was not in the electronic diary data since this information, though not used in the efficacy analyses, is included in sponsor data listings.

3. Derek Muse, M.D.
Highland Clinical Research
4460 S. Highland Drive, Suite 120
Salt Lake City, UT 84124

At this site for Protocol UBR-MD-01 (Site #154), 56 subjects were screened, 43 were randomized, and 41 subjects completed the study. Six of the 41 subjects who completed the study did not have a migraine attack of sufficient severity during the study and did not take investigational product. Two subjects discontinued the study due to "loss to follow-up" and withdrawal of consent.

[1] Intent to Treat (ITT) population: all randomized subjects
[2] Modified ITT (mITT) population: all randomized subjects who received at least one dose of investigational product, recorded a baseline migraine headache severity measurement, and had ≥1 postdose migraine headache severity or migraine-associated symptom measurement at or before the 2-hour timepoint
[3] Safety population: all subjects who received ≥1 dose of investigational product

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, concomitant medications, protocol deviations, and primary efficacy endpoint data.

During the inspection, electronic diary data was available for review via a certified CD provided to the site by the sponsor as well as through web-portal access. The co-primary efficacy endpoint data were verified against sponsor data listings, and no discrepancies were identified. There was no evidence of under-reporting of adverse events. No SAEs were reported at this site.

4. **Danny Sugimoto, M.D.**
   Cedar Crosse Research Center
   800 S. Wells Street, Suite M-15
   Chicago, IL 60607

   At this site for Protocol UBR-MD-02 (Site #115), 57 subjects were screened, 30 were randomized, and 24 subjects completed the study. Six of the 24 subjects who completed the study did not have a migraine attack of sufficient severity during the study and did not take investigational product. Six subjects were discontinued due to "loss to follow-up."

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 26 of 30 (87%) randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory indices, concomitant medications, protocol deviations, and primary efficacy endpoint data.

   During the inspection, electronic diary data was available for review via a certified CD provided to the site by the sponsor. The co-primary efficacy endpoint data were verified against sponsor data listings, and no discrepancies were identified. There was no evidence of under-reporting of adverse events. No SAEs were reported at this site.

5. **Allergan Sales, LLC**
   5 Giralda Farms
   Madison, NJ 07940

   This inspection covered the sponsor practices related to Protocols UBR-MD-01 and UBR-MD-02 and focused on the four clinical investigator sites (64, 75, 115, and 154) that had been selected for inspection.

   Records reviewed included, but were not limited to, SOPs, organizational charts, monitoring plan and reports, monitor training records and CVs, vendor contracts, transfer of responsibilities, investigator agreements, financial disclosure forms, blinding/unblinding

procedures, pharmacovigilance procedures and records, protocol deviations, adverse event reporting, and test article accountability.

The FDA field investigator confirmed that the database for Protocol UBR-MD-01 was locked on 1/23/2018 and that the database for Protocol UBR-MD-02 was locked on 3/30/2018. Neither of the databases were unlocked after the initial lock dates.

Clinical monitoring for these protocols was performed by the sponsor. There was no evidence of inadequate monitoring. No clinical sites were terminated due to noncompliance with the protocols. However, two sites were terminated from participation in Protocol UBR-MD-01 for other issues. Site 35 was terminated due to the site being acquired by Novant Health, and the sponsor could not agree to the terms. No further information was available from the FDA field investigator. Three subjects were enrolled at this site and completed the study prior to site termination. Site 43 was terminated due to lack of subject recruitment; no subjects were enrolled at this site.

Eight sites were terminated from participation in Protocol UBR-MD-02 due to lack of subject recruitment (sites 17, 108, 109, 307, 308) or site closure (sites 10 and 159). Subjects enrolled at the sites that closed were able to complete the study prior to site closure.

Complaint Follow-up

There was a complaint regarding Site 150 (Freeman) enrolling subjects in Protocol UBR-MD-02. The complainant alleged that the "Allergan monitor was fired for failure to monitor studies and report noncompliance to protocol". The FDA field investigator reviewed all monitoring reports for Site 150 and did not note any deficiencies. The sponsor stated that no monitors were fired due to inadequate monitoring.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 30, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211765
Product Name and Strength:	Ubrelvy (ubrogepant) tablets, 50 mg, 100 mg
Applicant/Sponsor Name:	Allergan Sales, LLC. (Allergan)
FDA Received Date:	July 16, 2019
OSE RCM #:	2018-2809-2
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 16, 2019 for Ubrelvy. The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Ubrelvy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a,b]

2 DISCUSSION

We previously recommended that the expiration date be expressed as YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. On July 16, 2019, Allergan stated that they intend to use the expiration date format of "MM/YYYY" using only numerical characters for the following reasons:

- "The slash is larger and will provide a higher success rate of detection with vision equipment used to scan the date versus the dash."

[a] Rider, B. Label and Labeling Review for Ubrelvy (NDA 211765). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 11. RCM No.: 2018-2809.
[b] Little, C. Label and Labeling Review Memo for Ubrelvy (NDA 211765). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 14. RCM No.: 2018-2809-1.

- "Marking the month first then the year is the standard format that our packager, (b) (4) uses for Allergan's products such as, Trelsar, Delzicol, and Asacol to name a few. Keeping the format consistent can reduce the risk for downstream errors."

We acknowledge Allergan's rationale for not implementing our recommendation regarding the format of the expiration date and we find the proposed expiration date format acceptable from a medication error perspective.

Allergan implemented all of our other recommendations.

3 CONCLUSION

We have no additional recommendations at this time.

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/s/

COLLEEN L LITTLE
07/30/2019 08:45:24 AM

BRIANA B RIDER
07/30/2019 09:00:07 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 14, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211765
Product Name and Strength:	Ubrelvy (ubrogepant) tablets, 50 mg, 100 mg
Applicant/Sponsor Name:	Allergan Sales, LLC.
FDA Received Date:	May 24, 2019
OSE RCM #:	2018-2809-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
Acting DMEPA Team Leader:	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 24, 2019 for Ubrelvy. The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Ubrelvy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective.

- On the revised 30-count commercial carton labeling, the net quantity statements have been relocated in close proximity to the strength statements, posing risk of numerical confusion.
- The format for expiration date on the container labels and carton labeling should be further clarified.

[a] Rider, B. Label and Labeling Review for Ubrelvy (NDA 211765). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 11. RCM No.: 2018-2809.

We provide recommendations to address these concerns in Section 3 below.

3 RECOMMENDATIONS FOR ALLERGAN SALES, LLC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling (Commercial & Professional Samples)
    i. As currently presented, the format for the expiration date on the container labels and carton labeling is "YYYY-MM." However, it is unclear whether the month (i.e., MM) will be displayed using numerical or alphabetical characters. Please clarify whether you propose to use only numerical characters for the expiration date, or whether you proposed to use alphabetical characters for the month.

B. 30-count Commercial Carton Labeling (50 mg and 100 mg)
    i. The net quantity statement (i.e., 30 tablets) appears in close proximity to the product strength. From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength, such as to the upper left corner of the principal display panel (PDP). Ensure there is adequate spacing between the relocated net quantity statement and other important product information on the PDP (e.g., NDC number, etc.).

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COLLEEN L LITTLE
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BRIANA B RIDER
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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 211765
Submission Number	0001
Submission Date	12/26/2018
Date Consult Received	1/30/2019
Clinical Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT protocol review under IND 113924 dated 05/02/2017 in DARRTS (link);
- UBR-PK-02 study report (SDN 0001; link);
- Investigator's brochure (IND 113924 / SDN 0024; link);
- Proposed label (SDN 0001; link); and
- Highlights of clinical pharmacology and clinical safety (SDN 0001; link).

1 SUMMARY

No significant QTc prolongation effect of ubrogepant (100 mg and 400 mg) was detected in this TQT study (Study UBR-PK-02).

The 400-mg dose provided approximately 2-fold coverage of the maximum therapeutic dose (i.e., two 100 mg doses given 2 hours apart). This dose is not adequate to cover the worst exposure scenario of a 5-fold C_{max} with co-administration of ketoconazole (a strong CYP3A4 inhibitor) or a 3-fold C_{max} with co-administration with verapamil (a moderate CYP3A inhibitor). The USPI proposes contraindication with strong CYP3A4 inhibitors and dose reduction with concomitant use of moderate CYP3A4 inhibitors.

The data from Study UBR-PK-02 was analyzed using central tendency as the primary analysis – see Table 1 for overall results. The moxifloxacin profile over time is adequately demonstrated in Table 3, indicating that assay sensitivity was established. The findings of this analysis are further supported by the available nonclinical data (section 3.1), exposure-response analysis (section 4.5) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ubrogepant (100 mg and 400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Ubrogepant 100 mg	1.5	1.0	(-0.9, 2.9)
Ubrogepant 400 mg	1.5	2.1	(0.2, 4.0)
Moxifloxacin 400 mg*	4	12.3	(10.4, 14.3)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints was 9.7 ms.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 PROPOSED LABEL

The QT-IRT agrees with the proposed language in section 12.2 of the label (SDN 0001).

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 2 times the MRHD, TRADENAME does not prolong the QT interval to any clinically relevant extent. (b) (4)

Reviewer's comment:

A single dose of 400 mg is the maximum tested dose. The maximum tolerated dose has not been established. A single dose of 400 mg provides approximately 2-fold coverage of Cmax after the maximum recommended therapeutic dose (i.e. two 100 mg doses separated by at least 2 hours). Strong and moderate CYP3A4 inhibitors increase Cmax by 5-fold and 3-fold, respectively. Therefore, the selected doses are not adequate to satisfy ICH E14 as they do not cover the supratherapeutic exposure scenario or the maximum tolerated dose.

On the other hand, strong CYP3A4 inhibitors are contraindicated and dose reduction to 50 mg (without a second dose) is recommended for concomitant medication with moderate CYP3A4 inhibitors. Therefore, a single dose of 400 mg provides at least 2-fold coverage of Cmax at the maximum therapeutic dose in the clinical setting. In addition, the concentration-QTc analysis does not suggest a positive exposure-response relationship in the exposure range studied. Therefore, the QT-IRT agrees with reporting a lack of clinically relevant effect within the exposure range.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Ubrogepant is a novel calcitonin gene-related peptide (CGRP) receptor antagonist (RA) being developed for the acute treatment of migraine with or without aura in adults. The proposed therapeutic dose is 50 mg or 100 mg taken orally with or without food. If needed, a second dose may be administered at least 2 hours after the initial dose. The recommended maximum daily dose is 200 mg. The drug product is an oral (b) (4) tablet that has not been marketed in any countries.

Ubrogepant is rapidly absorbed following oral administration with Tmax around 1.5 hours post-dose. Ubrogepant displays near dose-proportional pharmacokinetics within the range 40 to 400 mg. Typical C_{max} after a 100 mg dose is approximately 250-300 ng/mL. The terminal elimination half-life is approximately 5 hours.

Co-administration of ubrogepant with verapamil (a moderate CYP3A4 inhibitor) showed a 3.5-fold increase in ubrogepant $AUC_{0-\infty}$ and a 2.8-fold increase in ubrogepant C_{max}. Co-administration of ubrogepant with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 9.7-fold increase in $AUC_{0-\infty}$ and a 5.3-fold increase in C_{max}. In the proposed label, ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors. The proposed label also suggests dose reduction to 50 mg in the presence of moderate CYP3A4 inhibitors and avoid second dose within 24 hours.

No evidence of QTc prolongation or potential for QTc prolongation has been found in preclinical studies. These results include no significant inhibition of the human ether-à-go-go related gene potassium channel, as well as no effects on cardiovascular (hemodynamic or ECG parameters) following oral administration of single doses of 5 mg/kg and 30 mg/kg on Days 1 and 2, respectively, and daily doses of 75 mg/kg of ubrogepant for 3 consecutive days (Days 3 to 5) in rhesus monkeys. The ratio between the Sponsor's hERG IC50 (63 uM, link) and the therapeutic free ubrogepant is between 89 and 107 (C_{max} 250-300 ng/mL, fu=0.13, nM = 0.5496 ng/mL).

The QT-IRT reviewed UBR-PK-02 protocol and the QT assessment plan under IND 113924 previously (DARRTS 05/02/2017). UBR-PK-02 is a single-dose, placebo- and active-controlled, double-blind (open label for moxifloxacin), 4-period, 12-sequence balanced crossover study in healthy volunteers. The primary endpoint was QTcF. The major issue found in the previous review was that the supratherapeutic dose of 400 mg would not cover the expected highest clinically relevant exposure scenario of a 5.3-fold increase in Cmax with co-administration of ketoconazole. Another issue was that the sponsor proposed separate linear mixed model at each timepoint for the primary analysis. FDA reviewer suggested a single linear mixed model for longitudinal ECG data with correlations across timepoints taken into account. Study design and the primary endpoint remain the same since the previous QT-IRT review. Sixty-seven subjects (79.8%) completed the study; a total of 84 subjects were included in the safety, PK and PD populations.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The results of the reviewer's analysis are similar to the sponsor's results. The minor differences are due to different mixed models used, both concluded no QT prolongation observed in the study. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

The results of the reviewer's analysis are similar to the sponsor's results. Both concluded assay sensitivity observed in the study. Please see section 4.3.1.1 for additional details.

3.2.2 Categorical Analysis

The sponsor concluded that no subject had a QTcB or QTcF >500 ms or an increase >60 ms based on safety ECG data. The sponsor also showed that no QTcF >500 msec or an increase >60 ms in its Holter ECG summary.

FDA reviewer included all Holter ECGs submitted and showed that subject UBR-PK-02. (b) (6) had a postbaseline QTcF>500 ms and an increase >60 ms in Holter ECGs; however, this outlier value is a result of an erroneous measurement. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

Safety population included all 84 subjects who received at least 1 dose of IP.

No deaths or SAEs were reported during the study. Three subjects discontinued from the study prematurely due to an AE – 2 subjects discontinued because of QT prolongation:

- Subject (b) (6) (29-year old white male) experienced a non-serious mild AE of ECG QT prolonged on Day 15. He received 100 mg ubrogepant in Period 1 and placebo in Period 2 (Day 8). On Day 15, just prior to moxifloxacin treatment for Period 3, the subject was noted to have predose QT prolongation (QTcF was 460 msec). This occurred 6 days after the Period 2 treatment with placebo. The subject was treated with 1000 mL of IV sodium chloride for the event, which resolved on Day 16. The subject's QTcF at baseline was 436 msec (abnormal and not clinically significant). The subject was subsequently discontinued from the study.
- Subject (b) (6) (45-year old black female) experienced a non-serious moderate AE of ECG QT prolonged on Day 15. She received placebo in Period 1 and ubrogepant 400 mg in Period 2 (Day 8). On Day 15, prior to moxifloxacin treatment for Period 3, the subject was noted to have predose QT prolongation (QTcF was 443 msec). This occurred 6 days after the Period 2 treatment with ubrogepant 400 mg. The subject was treated with 1000 mL of IV sodium chloride for the event, which resolved the same day (Day 15). The subject's QTcF at baseline was 429 msec (abnormal and not clinically significant). The subject was subsequently discontinued from the study.

Reviewer's comment*: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

3.2.4 Exposure-Response Analysis

The sponsor plotted plasma concentrations of ubrogepant after administration of 100 mg ubrogepant and 400 mg ubrogepant against ΔΔQTcF. No trend in the QTcF interval change from baseline was noted with increasing plasma ubrogepant concentrations.

The results of the reviewer's analysis support the Sponsor's conclusion. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate were observed (i.e., absolute mean change in HR <10 bpm; see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.3 CENTRAL TENDENCY ANALYSIS

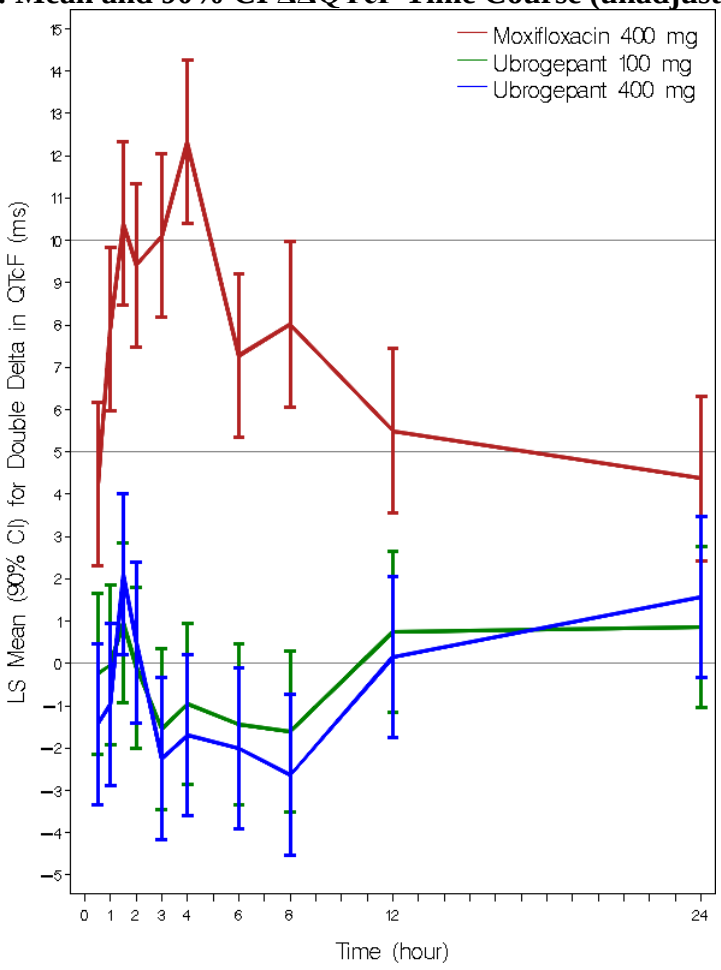
4.3.1 QTc

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, sequence, period, timepoint, and treatment by timepoint as fixed effects and subject as a random effect. Period specific baseline values are also included in the model as a covariate. Due to different statistical models, there are minor differences between the analysis results but both lead to the same conclusions. The following table and figure display the reviewer's analysis results and the time profile of ΔΔQTcF for different treatment groups.

Table 2: Analysis Results of ΔQTcF and ΔΔQTcF

	Ubrogepant 100 mg (N=78)			**Ubrogepant 400 mg (N=76)**		
	ΔQTcF (ms)		**ΔΔQTcF (ms)**	**ΔQTcF (ms)**		**ΔΔQTcF (ms)**
Time (hour)	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**
0.5	-0.8	-0.5	-0.2 (-2.1, 1.7)	-2.0	-0.5	-1.4 (-3.3, 0.5)
1	0.9	0.9	-0.0 (-1.9, 1.9)	-0.1	0.9	-1.0 (-2.9, 0.9)
1.5	0.1	-0.8	1.0 (-0.9, 2.9)	1.3	-0.8	2.1 (0.2, 4.0)
2	-0.2	-0.1	-0.1 (-2.0, 1.8)	0.3	-0.1	0.5 (-1.4, 2.4)
3	-1.1	0.4	-1.6 (-3.4, 0.3)	-1.8	0.4	-2.2 (-4.2, -0.3)
4	-1.3	-0.3	-1.0 (-2.8, 0.9)	-2.0	-0.3	-1.7 (-3.6, 0.2)
6	-10.7	-9.3	-1.5 (-3.4, 0.5)	-11.3	-9.3	-2.0 (-3.9, -0.1)
8	-10.0	-8.4	-1.6 (-3.5, 0.3)	-11.0	-8.4	-2.6 (-4.5, -0.7)
12	-5.7	-6.4	0.7 (-1.2, 2.6)	-6.3	-6.4	0.2 (-1.8, 2.1)
24	-1.4	-2.3	0.9 (-1.0, 2.8)	-0.7	-2.3	1.6 (-0.3, 3.5)

Figure 1: Mean and 90% CI ΔΔQTcF Time Course (unadjusted CIs).



4.3.1.1 Assay Sensitivity

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The largest unadjusted 90% lower confidence interval for placebo corrected mean change from baseline was 10.4 ms. By applying Bonferroni method to all time points to adjust for multiplicity for 4 timepoints, the largest lower confidence interval was 9.7 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected and thus assay sensitivity was demonstrated in the study.

Table 3: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTcF (ms) Moxifloxacin 400 mg (N=72)	**ΔQTcF (ms) Placebo (N=74)**	**ΔΔQTcF (ms) Moxifloxacin 400 mg**		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
0.5	3.7	-0.5	4.2	(2.3, 6.2)	(1.6, 6.9)
1	8.8	0.9	7.9	(6.0, 9.8)	(5.3, 10.5)
1.5	9.6	-0.8	10.4	(8.5, 12.3)	(7.8, 13.0)

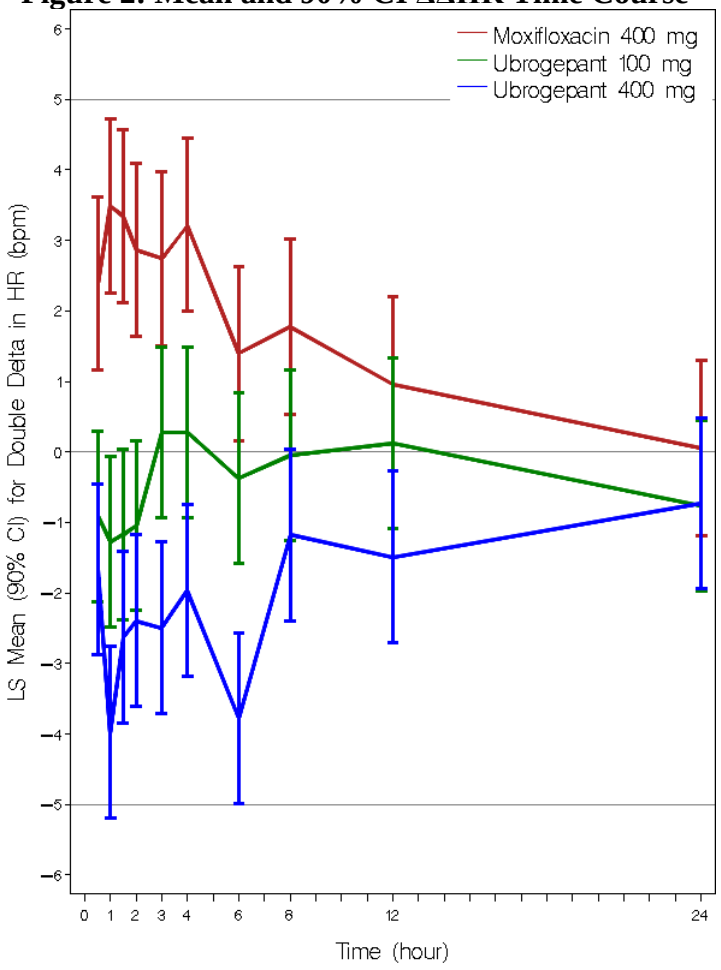
	ΔQTcF (ms) Moxifloxacin 400 mg (N=72)	ΔQTcF (ms) Placebo (N=74)	ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
2	9.3	-0.1	9.4	(7.5, 11.3)	(6.8, 12.1)
3	10.6	0.4	10.1	(8.2, 12.0)	(7.5, 12.7)
4	12.0	-0.3	12.3	(10.4, 14.3)	(9.7, 15.0)
6	-2.0	-9.3	7.3	(5.3, 9.2)	(4.6, 9.9)
8	-0.4	-8.4	8.0	(6.1, 10.0)	(5.4, 10.7)
12	-0.9	-6.4	5.5	(3.6, 7.4)	(2.8, 8.2)
24	2.1	-2.3	4.4	(2.4, 6.3)	(1.7, 7.0)

* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 4 time points around moxifloxacin C_{max}.

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between ubrogepant 100 mg and placebo and ubrogepant 400 mg and placebo were 1.5 bpm and 0.5 bpm, respectively. The sponsor listed descriptive statistics for heart rate at the end of the study.

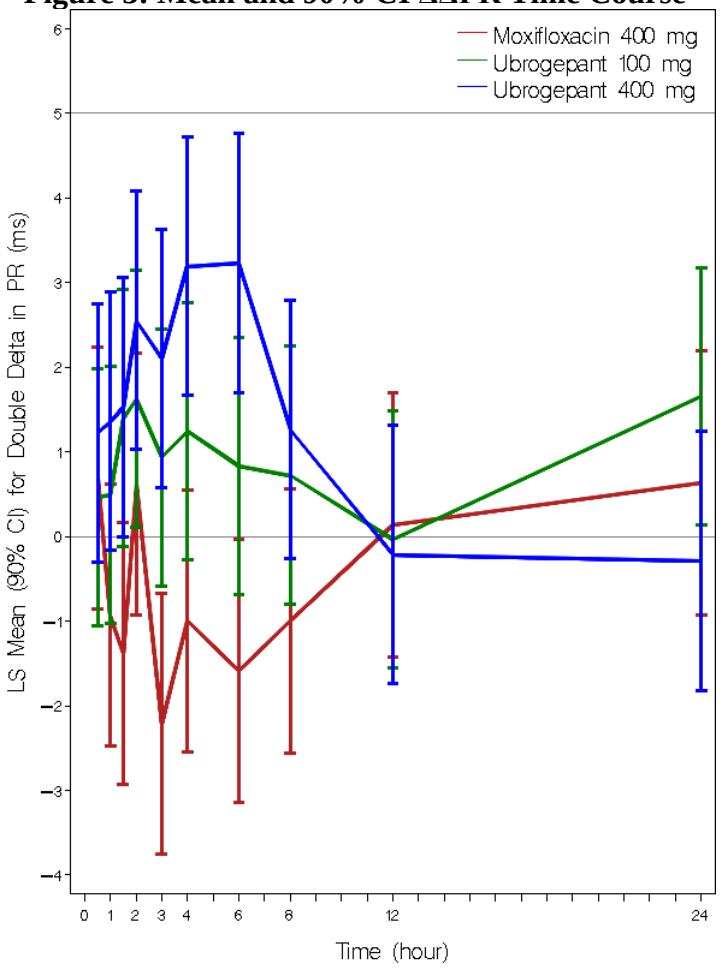
Figure 2: Mean and 90% CI ΔΔHR Time Course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the PR mean differences between ubrogepant 100 mg and placebo and ubrogepant 400 mg and placebo were 3.2 ms and 4.8 ms, respectively. The sponsor listed descriptive statistics for PR at the end of the study.

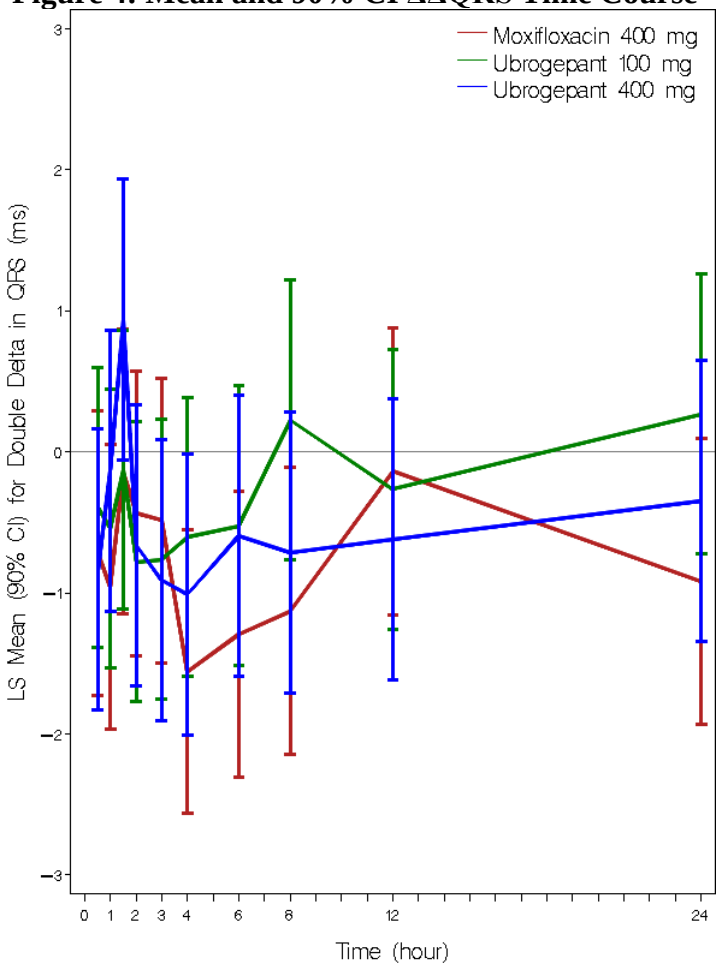
Figure 3: Mean and 90% CI ΔΔPR Time Course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between ubrogepant 100 mg and placebo and ubrogepant 400 mg and placebo were 1.3 ms and 1.9 ms, respectively. The sponsor listed descriptive statistics for QRS at the end of the study.

Figure 4: Mean and 90% CI ΔΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values were between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. Subject UBR-PK-02. (b) (6) had a postbaseline QTcF>500 ms and ΔQTcF >60 ms at 1.5 hours postdose on Day 1. Of the note, the three individual QTcF values are 399, 766, 418 (average QTcF=527.7) and the individual PR value that corresponds to QTcF=766 ms is 0. This indicates that those outliers are likely due to measurement errors as all other postbaseline average QTcF values were less than 450 ms and all other ΔQTcFs were less than 30 ms.

Table 4: Categorical Analysis for QTcF

Treatment Group	Total N		450<QTcF<=480 ms		480<QTcF<=500 ms		QTcF>500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	84	903	6 (7.1%)	21 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	74	740	4 (5.4%)	7 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Treatment Group	Total N		450<QTcF<=480 ms		480<QTcF<=500 ms		QTcF>500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Ubrogepant 100 mg	78	776	3 (3.8%)	6 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ubrogepant 400 mg	76	760	1 (1.3%)	6 (0.8%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.1%)

Table 5 lists the categorical analysis results for ΔQTcF.

Table 5: Categorical Analysis of ΔQTcF

Treatment Group	Total N		30<ΔQTcF<=60 ms		ΔQTcF>60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	74	740	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ubrogepant 100 mg	78	776	1 (1.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Ubrogepant 400 mg	76	760	1 (1.3%)	4 (0.5%)	1 (1.3%)	1 (0.1%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 6. No subjects had PR >220 ms. Two and 6 subjects had post baseline PR between 200 ms and 220 ms in in the ubrogepant 100 mg and ubrogepant 400 mg groups, respectively. One of the 2 subjects and 2 of the 6 subjects had baseline PR between 200 ms and 220 ms also for the two groups, respectively.

Table 6: Categorical Analysis for PR

Treatment Group	Total N		PR<=200 ms		200<PR<=220 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	84	903	82 (97.6%)	888 (98.3%)	2 (2.4%)	15 (1.7%)
Placebo	74	740	71 (95.9%)	733 (99.1%)	3 (4.1%)	7 (0.9%)
Ubrogepant 100 mg	78	776	76 (97.4%)	769 (99.1%)	2 (2.6%)	7 (0.9%)
Ubrogepant 400 mg	76	760	70 (92.1%)	735 (96.7%)	6 (7.9%)	25 (3.3%)

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 7. Four subjects each had post baseline QRS >110 ms for the ubrogepant 100 mg and ubrogepant 400 mg groups. For both groups, 3 of the 4 subjects had baseline QRS >110 ms also.

Table 7: Categorical Analysis for QRS

Treatment Group	Total N		QRS<=110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	84	903	80 (95.2%)	878 (97.2%)	4 (4.8%)	25 (2.8%)
Placebo	74	740	71 (95.9%)	720 (97.3%)	3 (4.1%)	20 (2.7%)

Treatment Group	Total N		QRS<=110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Ubrogepant 100 mg	78	776	74 (94.9%)	760 (97.9%)	4 (5.1%)	16 (2.1%)
Ubrogepant 400 mg	76	760	72 (94.7%)	747 (98.3%)	4 (5.3%)	13 (1.7%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 8.

Table 8: Categorical Analysis for HR

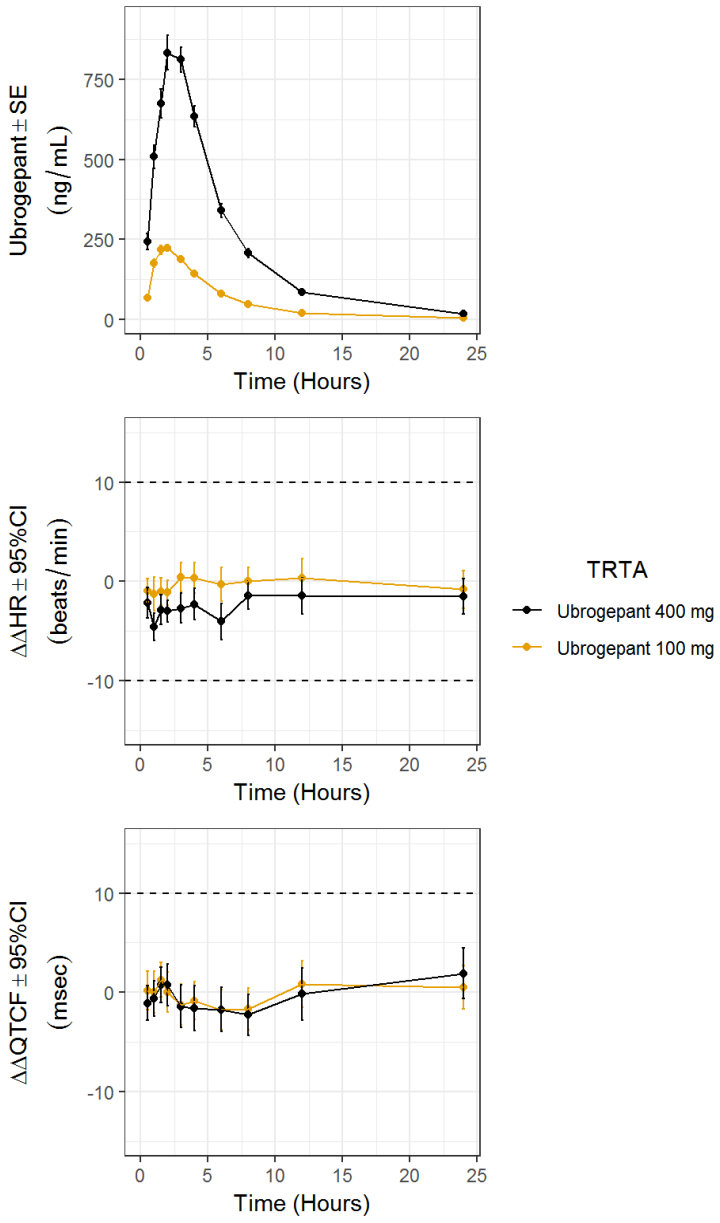
Treatment Group	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	84	83 (98.8%)	1 (1.2%)	81 (96.4%)	3 (3.6%)
Placebo	74	74 (100%)	0 (0.0%)	70 (94.6%)	4 (5.4%)
Ubrogepant 100 mg	78	77 (98.7%)	1 (1.3%)	75 (96.2%)	3 (3.8%)
Ubrogepant 400 mg	76	76 (100%)	0 (0.0%)	72 (94.7%)	4 (5.3%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ubrogepant concentration and ΔQTcF.

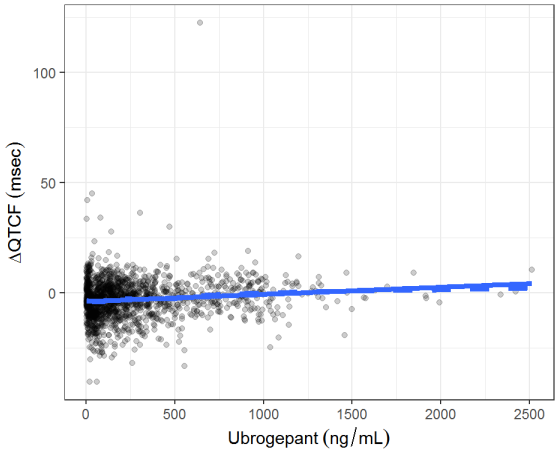
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma ubrogepant concentration and ΔQTcF and 3) presence of non-linear relationship. An evaluation of the time-course of ubrogepant concentration and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.

Figure 5: Time Course of Drug Concentration (top), Heart Rate (middle) and QTcF (bottom)



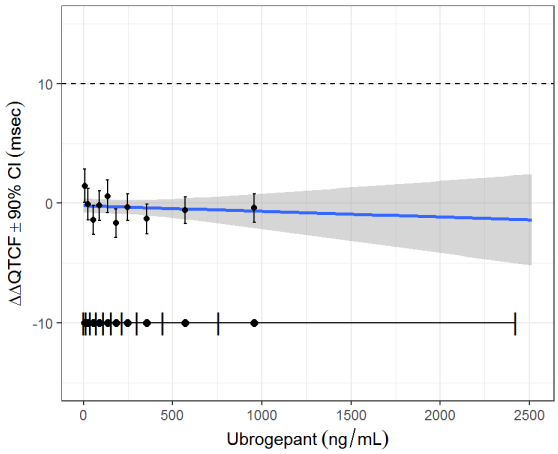
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between ubrogepant concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of Linearity of Concentration-QTc Relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. The model suggests a lack of clinically relevant effect at the 400 mg dose (geometric mean Cmax: 951.6 ng/mL).

Figure 7: Goodness-of-fit Plot for QTc



4.5.1 Assay sensitivity

Assay sensitivity was established using central tendency analysis. Please see section 4.3.1.1 for additional details.

4.6 SAFETY ASSESSMENTS

No additional safety analyses were conducted. See section 3.2.3

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/13/2019

TO: Division of Neurology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211765

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in October 2018 and the analytical inspection was conducted in (b) (4), which falls within the surveillance interval. The inspections were conducted under the following submissions: NDAs (b) (4) (b) (4)

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspections and the rationale described above, inspections are not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Spaulding Clinical Research, LLC.	525 South Silverbrook Drive, West Bend, WI
Analytical	(b) (4)	

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/s/

ANGEL S JOHNSON
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 11, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 211765
Product Name and Strength:	Ubrelvy (ubrogepant) tablets, 50 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Allergan Sales, LLC.
FDA Received Date:	December 26, 2018
OSE RCM #:	2018-2809
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ubrelvy (ubrogepant) tablets, the Division of Neurology Products (DNP) requested that we review the proposed Ubrelvy prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Table 2 below includes the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Allergan Sales, LLC. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling (Commercial & Professional Samples)			
1.	The format for expiration date is not defined.	We are concerned the lack of a clearly defined expiration date will lead to confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-

Table 2. Identified Issues and Recommendations for Allergan Sales, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The "usual dose" statement is missing from the container labels and carton labeling.	The "usual dose" statement is required per 21 CFR 201.55.	Revise the statement "(b) (4) " to read "See package insert for dosing information" or "Usual dosage: see prescribing information" or a similar statement.
Container Labels and Carton Labeling ((b) (4) mg Commercial & Professional Samples)			
1.	The product information presented in (b) (4) font (e.g., net quantity statement, 'Rx only' statement) on the principal display panel (PDP) is difficult to read.	The contrast between the text in (b) (4) font and the (b) (4) colors, is insufficient.	We recommend changing the (b) (4) font color to a darker color to increase the readability of the product information currently presented in (b) (4) font.
Commercial Carton Labeling (50 mg and 100 mg)			
1.	The carton labeling lacks a linear barcode.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	We request you add the product's linear barcode to the carton labeling as required per 21 CFR 201.25(c)(2).
Professional Sample Carton Labeling (b) (4)			

Table 2. Identified Issues and Recommendations for Allergan Sales, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The net quantity statement (i.e., 1 tablet) appears in close proximity to the product strength.	From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.
30-count Commercial Carton Labeling (50 mg and 100 mg)			
1.	The net quantity statement, 'Rx only' statement and NDC number are located on a panel other than the Principal Display Panel (PDP).	This important information may be overlooked.	Relocate the net quantity statement, 'Rx only' statement and NDC number to the PDP (see *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*

4 CONCLUSION

Our evaluation of the proposed Ubrelvy container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to Allergan Sales, LLC. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Ubrelvy that Allergan Sales, LLC. submitted on December 26, 2018.

Table 3. Relevant Product Information for Ubrelvy	
Initial Approval Date	N/A
Active Ingredient	Ubrogepant
Indication	Acute treatment of migraine with or without aura in adults
Route of Administration	Oral
Dosage Form	Tablet
Strength	50 mg, 100 mg
Dose and Frequency	50 mg or 100 mg taken orally with or without food. If needed, a second dose may be administered at least 2 hours after the initial dose. The maximum daily dose is 200 mg.
How Supplied	50 mg and 100 mg strengths are supplied in cartons containing 6, 8, 10, 12, or 30 (b) (4).
Storage	Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).
Container Closure	Unit-dose (b) (4) foil pouch (b) (4) material.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Ubrelvy labels and labeling submitted by Allergan Sales, LLC. and received on December 26, 2018.

- Commercial Container labels (1 ct.)
- Commercial Carton labeling (6, 8, 10, 12, and 30-ct.)
- Professional Sample Container labels (b) (4)
- Professional Sample Carton Labeling (b) (4)
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

14 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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LOLITA G WHITE
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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 6, 2019

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Director
Silvia N. Calderon Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Ubrogepant (MK-1602)
NDA 211,765 (IND 113,924)
Indication: treatment of migraine with or without aura in adults
Dosage: 50 or 100 mg, PO
Sponsor: Allergan

Materials reviewed: NDA 211,765 (submitted 12/26/18)
CSS consult reviews (Bonson, 3/10/16, 4/14/17, and 8/20/18)

I. Background

This memorandum is in response to a consult from the Division of Neurology Products (DNP) regarding the fileability of NDA 211,765 for ubrogepant (MK-1602), which is proposed for the treatment of migraine with or without aura in adults. The product is formulated as 50 and 100 mg tablets for oral administration. Ubrogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. It was previously known as MK-1602 when it was sponsored by Merck.

CSS interacted with the Sponsor throughout the IND stage and provided guidance regarding the assessment of the abuse potential of ubrogepant on 3/10/16, 4/14/17, and 8/20/18.

II. Conclusions

Based on prior reviews of the data provided by the Sponsor under IND #113,924, CSS concluded and communicated to the Sponsor in 2017 and 2018 that there were no abuse potential signals in the 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. Thus, CSS determined that the Sponsor did not need to conduct a human abuse potential study or a human physical dependence study.

III. Recommendations to the Division

- Given that CSS previously determined that there were no abuse-related signals resulting from administration of ubrogepant, CSS does not need be part of the review team for this NDA. Thus, CSS will not be submitting a filing checklist for ubrogepant (NDA 211,765).

- However, CSS requests that the Division consult CSS if the DNP review team identifies any abuse-related concerns associated with the drug through the course of their review of this NDA.

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/s/

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