CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: **APPROVAL**

NDA 211765
Review #01

Drug Name/Dosage Form	Ubrogepant Tablets
Strength	50 mg, 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Allergan Sales LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original (SD 1)	26-DEC-2018	*Amendment (SD 15)*	24-MAY-2019
Amendment (SD 3)	23-JAN-2019	*Amendment (SD 16)*	07-JUN-2019
Amendment (SD 6)	13-MAR-2019	*Amendment (SD 17)*	20-JUN-2019
Amendment (SD 11)	12-APR-2019	*Amendment (SD 22)*	16-JUL-2019
Amendment (SD 13)	14-MAY-2019	*Amendment (SD 23)*	03-SEP-2019

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rajan Pragani	Suong Tran	ONDP
Drug Product	Andrei Ponta	Wendy Wilson-Lee	
Labeling			
Environmental	Raanan Bloom	Scott Furness	
Manufacturing	Qin Liang	Erin Kim	OPF
Biopharmaceutics	Gerlie Gieser	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		n/a	n/a	Sufficient information in NDA.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)
IND	113924	Ubrogepant (AGN-241688, MK-1602) for treatment of migraine
		(b) (4)

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 211765 for ubrogepant tablets, 50 mg and 100 mg.

II. Summary of Quality Assessments

A. Product Overview

Allergan seeks approval of ubrogepant for the acute treatment of migraines with or without aura in adults. The ubrogepant drug product was developed as an immediate release, tablet containing 25 mg, 50 mg, and 100 mg dose strengths. However, based on the clinical results, only the 50 mg and 100 mg strengths are proposed for marketing. (b) (4) , the drug product is formulated (b) (4) . No other drug product degradants are identified. The drug substance is hygroscopic and has several known polymorphs and solvates. Attributes such as (b) (4) are critical. OPQ provided development guidance as part of a Type C CMC-only meeting in May 2018. Topics of discussion included regulatory starting materials, control strategy for impurities, dissolution method parameters, testing for polymorphism, drug product stability data package, and the organization of the NDA. Additional guidance on potentially mutagenic impurities was provided as part of the pre-NDA meeting in September 2018.

Proposed Indication(s) including Intended Patient Population	*Treatment of migraines with and without aura in adults*
Duration of Treatment	*Acute*
Maximum Daily Dose	*200 mg*
Alternative Methods of Administration	*None*

B. Quality Assessment Overview

Upon review of the information, no significant quality issues were identified. The drug substance is a free base (b) (4) and has been assigned the USAN name ubrogepant. The chemical structure of the drug substance was adequately confirmed, including by x-ray crystallography (b) (4)

(b) (4)

(b) (4) The agency agreed to the starting material designations in the Type C meeting. Sufficient manufacturing information was provided, (b) (4) .

The control strategy for impurities (including residual solvents) is acceptable. Mutagenic impurities have been assessed appropriately. For the (b) (4) impurity discussed at the pre-NDA meeting, information was provided in the NDA to justify (b) (4) as a non-mutagenic impurity, which was found acceptable by the nonclinical reviewer. The only specified impurity in the drug substance specification is (b) (4)t), with a qualified limit of (b) (4)% as per the nonclinical assessment. **Based on the stability data provided for the registration batches, a drug substance retest date of (b) (4) months ((b) (4)) is acceptable.**

The drug product is a white to off-white, capsule shaped biconvex tablet with "U" debossed (b) (4) "50" or "100" (b) (4). The two strengths are (b) (4), with the lower strength having a total mass of 500 mg and the higher strength having a mass of 1000 mg. The drug product contains the drug substance and the following USP/NF excipients: polyvinylpyrrolidone/vinyl acetate copolymer, Vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate.

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. The primary container closure system for the drug product is a unit-dose (b) (4) (b) (4) foil pouch (b) (4). **The drug product has been granted 24-month expiry when stored at controlled room temperature based on the long-term stability data provided.**

The proposed commercial drug product manufacturing includes (b) (4) . The commercial scale batch size is identical to that of exhibit batches. The batch sizes used in primary and process evaluation campaign are representative of commercial manufacture. (b) (4).

The development of the ubrogepant tablet formulation and manufacturing process was based on product and process understanding through structured experimentation, including design of experiments (DOE), univariate and multivariate studies, and the application of established scientific principles. Quality by Design (QbD) principles including risk assessment and risk mitigation were used to ensure all desired quality attributes were addressed. The identified critical quality attributes (CQAs) of the product were employed as benchmark parameters

during product development as well as formulation and process optimization studies. The key process unit operations including (b) (4) are selected for manufacturing ubrogepant tablets. (b) (4) Adequate controls ensure microbiological quality of the drug product at release and over the shelf life.

The selection of the manufacturing process appears to be reasonable for conducting a robust manufacturing process. Various process optimization studies were conducted to understand the operating range and to define process parameters. During these studies, the (b) (4) operations were optimized. Systematic risk assessment approach was used throughout the development and optimization phase to identify potentially low to medium risk formulation and process variables. The material attributes and process parameters identified as potentially medium to high risks during the initial risk assessment were investigated. The development studies identified appropriate controls to be implemented to reduce the risk to an acceptable level.

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks for the facilities. The manufacturing facilities for NDA 211765 are in good standing. No pre-approval inspections were requested. **The overall manufacturing inspection recommendation is approve.**

The proposed dissolution method and revised acceptance criterion are approved for the routine quality control (QC) of the 50 mg and 100 mg strengths of ubrogepant immediate release tablets at batch release and during stability testing. Based on the data provided for the 50 mg tablets, the approved dissolution method demonstrated Level C in vitro – in vivo (IVIVC) with respect to ubrogepant Cmax and AUC_{0-4h}.

Ubrogepant is a (b) (4) drug substance that exhibits low solubility per BCS criteria; (b) (4) . The ubrogepant tablet lots used in the pivotal Phase 3 clinical trials and the pivotal BE study exhibited very rapid dissolution when tested using the proposed QC dissolution method.

Altogether, **the comparative *in vitro* dissolution profile and *in vivo* BE data provided in the NDA are adequate to qualify the CMC changes** (in API supplier, (b) (4) tablet manufacturers, batch size, as well as debossing of the tablets) that were introduced to the ubrogepant (b) (4) tablets after the conduct of the pivotal Phase 3 clinical trials.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable. Modeled and available information indicates a low potential for ubrogepant interaction with estrogen and androgen receptors. No embryo-fetal toxicity was observed over a range of dose

concentrations. Modeled aquatic toxicity results show a large margin between exposure and effects. The Fish Plasma Model output indicates that additional studies may be required. However, based on the expected low exposure concentrations (EIC = (b) (4) ppb), low environmental risk is expected due to approval of this application.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation Raw Materials Container Closure Process/Equipment/Scale Site	Low	(b) (4)	Acceptable	-
Physical Stability		Medium		Acceptable	Changes to critical excipients and manufacturing process should be assessed for impact on drug substance solid state in final drug product
Content Uniformity		Medium		Acceptable	-
Microbial Limits		Low		Acceptable	-
Dissolution		Medium		Acceptable	-
(b) (4)		Low		Acceptable	-

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

TRADENAME™ (ubrogepant) Tablets for oral use
Initial U.S. Approval: 20XX

INDICATIONS AND USAGE
TRADENAME is a calcitonin gene-related peptide receptor antagonist indicated for the acute treatment of migraine with or without aura in adults. (1)

DOSAGE AND ADMINISTRATION
• Recommended dose: 50 mg or 100 mg taken orally (b) (4)
(b) (4)
• If needed, a second dose may be administered at least 2 hours after the initial dose. (2)
• The maximum daily dose is 200 mg. (2)

DOSAGE FORMS AND STRENGTHS
Tablets: 50 mg and 100 mg (3)

CONTRAINDICATIONS
• Concomitant use with strong CYP3A4 inhibitors. (4)

ADVERSE REACTIONS
(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
(b) (4)
• Strong CYP3A4 Inducers: Concomitant use will result in reduction of ubrogepant exposure. (7.2)
(b) (4)

USE IN SPECIFIC POPULATIONS
(b) (4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 0X/20XX

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	(ubrogepant) Tablets for oral use
Dosage form, route of administration	Tablets, oral
Controlled drug substance symbol	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 50 mg and 100 mg

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

The recommended dose of TRADENAME is 50 mg or 100 mg taken orally with or without food.

If needed, a second dose may be taken at least 2 hours after the initial dose. The maximum daily dose is 200 mg. The safety of (b) (4) more than (b) (4) in a 30-day period has not been established.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	None

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

TRADENAME 50 mg: (b) (4) as white to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) "50" (b) (4)

TRADENAME 100 mg: (b) (4) as white to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) "100" (b) (4)

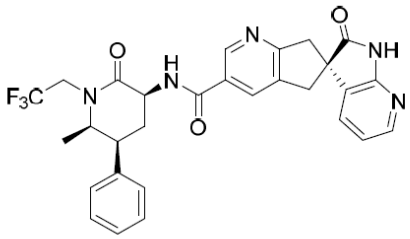
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	Tablets: 50 mg and 100 mg
Active moiety expression of strength with equivalence statement	Ubrogepant Reviewer's Note: Applicant will be asked to include active moiety expression of strength
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) "50" (b) (4). White to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) "100" (b) (4)

Is the information accurate? ☒ Yes ☐ No

4. *Section 11 Description*

11 DESCRIPTION

The active ingredient of TRADENAME is ubrogepant, a (b) (4) calcitonin gene-related peptide (CGRP) receptor antagonist. The chemical name of ubrogepant is (b) (4) (b) (4) and has the following structural formula:



The molecular formula is $C_{29}H_{26}F_3N_5O_3$ and molecular weight is 549.6. Ubrogepant is a white to off-white powder. It is freely soluble in ethanol, methanol, acetone, acetonitrile and practically insoluble in water.

TRADENAME is available as tablets for oral administration containing 50 mg and 100 mg ubrogepant. The inactive ingredients include polyvinylpyrrolidone vinyl acetate copolymer, vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide, and sodium stearyl fumarate.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Tradename (ubrogepant) tablets
Dosage form and route of administration	Tablets: 50 mg and 100 mg
Active moiety expression of strength with equivalence statement (if applicable)	Ubrogepant
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The drug product contains the following USP/NF excipients: polyvinylpyrrolidone/vinyl acetate copolymer (b) (4), Vitamin E polyethylene glycol succinate, mannitol, microcrystalline cellulose, sodium chloride, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate Reviewer's Note: Applicant will be asked to reorder the excipients so that they are in alphabetical order.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	selective calcitonin gene-related peptide (CGRP) receptor antagonist
Chemical name, structural formula, molecular weight	$C_{29}H_{26}F_3N_5O_3$ – 549.6 g/mol
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	White to white off powder that is practically insoluble in water but freely soluble in ethanol,methanol, acetone, and acetonitrile.

Is the information accurate? ☒ Yes ☐ No

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRADENAME 50 mg is supplied as white to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) (b) (4) "50" (b) (4) in unit-dose (b) (4):

- (b) (4) of 6 (b) (4) NDC: 0023-6498-06
- of 8 NDC: 0023-6498-08
- of 10 (b) (4) NDC: 0023-6498-10
- of 12 NDC: 0023-6498-12
- of 30 NDC: 0023-6498-30

TRADENAME 100 mg is supplied as white to off-white capsule-shaped, biconvex tablets debossed with "U" (b) (4) "100" (b) (4) in unit-dose (b) (4):

- (b) (4) of 6 (b) (4) NDC: 0023-6501-06
- of 8 NDC: 0023-6501-08
- of 10 (b) (4) NDC: 0023-6501-10
- of 12 NDC: 0023-6501-12
- of 30 NDC: 0023-6501-30

16.2 Storage and Handling

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) [See *USP Controlled Room Temperature*].

Distributed by: Allergan USA, Inc.
Madison, NJ 07940

Allergan

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Tablets: 50 mg and 100 mg
Available units (e.g., bottles of 100 tablets)	50 mg: unit-dose (b) (4) 100 mg: unit-dose (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) "50" (b) (4) . White to off-white, capsule-shaped, biconvex tablets debossed with "U" (b) (4) "100" (b) (4)
Special handling (e.g., protect from light)	Not Applicable
Storage conditions	USP controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Allergan

Reviewer's Assessment of Package Insert: *Adequate*

Prescribing Information complies with all regulatory requirements from a CMC perspective.

However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations. The labeling is adequate assuming Applicant accepts edits.

II. Labels:

1. (b) (4) ***and Carton Labels***

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

Item	Information provided in the bottle label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	UBRELVY (ubrogepant) tablets
Dosage strength	Complies
Net contents	Complies
"Rx only" displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies
Lot number and expiration date (21 CFR 201.17)	Complies
Storage conditions	Complies
Bar code (21CFR 201.25)	Complies
Name of manufacturer/distributor	Complies
And others, if space is available	Not Applicable

Reviewer's Assessment of Labels: *Adequate*

The carton/container label complies with regulatory requirements from a CMC perspective, with the exception of the proprietary name. It bears the "Rx only" statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

Revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations. The carton/container labeling is adequate assuming Applicant accepts edits.

List of Suggested Edits Communicated to Applicant:

1. *Include the active moiety in Section 3 (Dosage forms and strengths).*
2. *Ensure that the excipients are listed in alphabetical order in the PI.*

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta, Ph.D. 7-Aug-2019

Andrei Ponta

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Wendy Wilson- Lee

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NDA 211765

MEMORANDUM OF QUALITY AMMENDMENTS

Application Number: NDA 211765
Product Name: UBRELVY (ubrogepant) tablets / 50 mg and 100 mg
Sponsor/Applicant Name: Allergan

Subject: Drug Substance and Drug Product Degradation Product Specifications

1.0 BACKGROUND:

The drug substance and drug product release and stability acceptance criteria for individual, unspecified impurities are in line with ICH Q3B (NMT (b) (4)% and NMT (b) (4)%, respectively). The proposed acceptance criteria for (b) (4) were NMT (b) (4)% for the drug substance and NMT (b) (4)% for the drug product. The Applicant indicated that the (b) (4) limits were supported by nonclinical studies; however, the nonclinical team indicated the was insufficient data to support the qualification of the impurity. Thus, the impurity must be controlled per ICH guidelines.

2.0 QUALITY AMMENDMENT SUMMARY:

List Submissions being reviewed:

Documents Reviewed	Date received	Document Type
SD#:0026	24-Oct-2019	Quality Response to Information Request
SD#:0029	18-Nov-2019	Quality Response to Information Request

In the response to an information request dated 24-Oct-2019, the Applicant agreed to the Agency's suggestion to tighten the (b) (4) release and stability limit to NMT (b) (4)% for the drug substance.

In the response to an information request dated 18-Nov-2019, the Applicant agreed to the Agency's suggestion to tighten the (b) (4) release and stability limit to NMT (b) (4)% for the drug product.

3.0 OUTCOME

The Applicant has agreed to tighten the drug substance and drug product (b) (4) specification per the Agency's recommendation (NMT (b) (4)% for the drug substance and NMT (b) (4)% for the drug product). Module 3.2.S.4.1, 3.2.S.4.5, 3.2.P.5.1, 3.2.P.5.6 and 2.3.P have been updated to reflect the tightened specifications.

The tightening of the specification does not impact the drug substance or drug product expiry as the (b) (4) did not increase on stability. This is acceptable.

Andrei Ponta

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Wendy Wilson- Lee

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QUALITY ASSESSMENT

ENVIRONMENTAL REVIEW

IQA Review Guide Reference

1. Regional Information

1.12.14: Environmental Analysis

Application: NDA 211765
Drug product: Ubrogepant
Indication: Acute treatment of migraine with or without aura in adults.
MW: 549.554 g/mol
Proposed doses: 50 mg or 100 mg

Mechanism of action: potent, selective calcitonin gene-related peptide (CGRP) receptor antagonist. Calcitonin gene-related peptide (CGRP) is a neuropeptide present in the peripheral and central nervous system. CGRP is released from sensory nerve endings during a migraine attack, particularly the nerve endings of sensory trigeminal ganglion neurons. Ubrogepant is a small molecule, high affinity (K_i = 0.07nM) CGRP receptor antagonist that blocks the binding of the ligand and antagonizes CGRP receptor function.

Claim of Categorical Exclusion: The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of no extraordinary circumstances under 21 CFR 25.21. Minimal supporting information is provided. An estimated environmental concentration is provided (see below). No environmental effects data are provided.

Environmental Exposure: Using a production estimate of (b) (4) kg ubrogepant/yr as a worst-case estimate, (which represents the maximum active ingredient production for sale within 5 years of initial marketing) the total amount of API introduced into the aquatic environment at discharge from WWTPs (EIC: expected introductory concentration) as a result of the use of this product is estimated at EIC = (b) (4) ppb:

Application Review: In evaluation of the claim for categorical exclusion, in addition to the provided information, the following models were used:

I. Model Predictions

1. Fish Plasma Model

Production volume = (b) (4) kg/year
EIC= (b) (4) ppb = (b) (4) µg/L = (b) (4) nM
Log P = (b) (4) (measured)
P_{bw} : (b) (4)
Human therapeutic concentration
oral dose 50mg (single dose): Cmax= 125.531 ng/mL (study UBR-MD-02)
oral dose 100mg (single dose): Cmax= 263.311 ng/mL (study UBR-MD-01)
FssPC = EIC * Pbw = (b) (4) ng/mL
ER = FssPC/Cmax: (b) (4)

Based on fish plasma model result (ER=(b) (4)), fish chronic studies may be needed for ubrogepant *(ER < 1,000).*

2. Aquatic Toxicity predictions (Danish QSAR DB)

Aquatic toxicity predictions for ubrogepant are not reported in the Danish QSAR toolbox database. Data for top 4 analogues were retrieved

- Fathead minnow: 96h LC50 range estimate (b) (4) µg/L
- Daphnia magnia: 48h EC50 range estimate (b) (4) µg/L
- Pseudokirchneriellas. 72h EC50 range estimate (b) (4) µg/L

- Pseudokirchneriella predicted to be most sensitive organism
- **The EIC ((b) (4) µg/L) is approximately 90-fold lower than the lowest predicted acute toxicity value (b) (4) from analogues.**

3. ECOSAR

- QSAR predictions for acute and chronic effects
- Functional groups used in predictions: amides

3.1 Acute Toxicity

Predicted acute toxicity values for fish (LC50_96h): (b) (4) mg/L

- ✓ Predicted acute toxicity values for Daphnid (LC50_48h) (b) (4) mg/L.
- ✓ Predicted acute toxicity values for green algae (EC50_96h) (b) (4) mg/L.
- ✓ **EIC is > 100,000 times lower than predicted acute toxicity value for most sensitive organism (green algae; EC50_96h = (b) (4) mg/L).**

3.2 Chronic Toxicity

- ✓ Predicted chronic toxicity values for fish (b) mg/L
- ✓ Predicted chronic toxicity values for Daphnid (b) (4) mg/L
- ✓ Predicted chronic toxicity values for green algae (b) (4) mg/L.
- ✓ Predicted chronic toxicity values for mysid (seawater): (b) (4) mg/L.
- ✓ **EIC is > 10,000 times lower than predicted chronic value for fish**.

4. QSARs for estrogen and androgen receptor activity

- Predictions for Estrogen receptor activity **NOT** reported in Mansouri et al., 2016 (CERAPP)
- **INACTIVE** in binding, agonist and antagonist ER models (OCHEM model)
- **INACTIVE** in binding, agonist, antagonist AR models (OCHEM model)

II. Animal Studies

According to data submitted to the Agency, no evidence of teratogenicity has been observed in rats or rabbits. Oral administration of ubrogepant (1.5, 5, 25, 125 mg/kg/day) to pregnant rats during the period of organogenesis resulted in no embryo-fetal toxicity. In a similar study in rabbits, maternal toxicity was observed at 75 mg/kg/day; however, there was no embryo-fetal toxicity at this dose level.

Reviewer's Assessment: Adequate

Modeled and available information indicates a low potential for ubrogepant interaction with estrogen and androgen receptors. No embryo-fetal toxicity was observed over a range of dose concentrations. Modeled aquatic toxicity results show a large margin between exposure and effects. The Fish Plasma Model output indicates that additional studies may be required. However, based on the expected low exposure concentrations (EIC = (b) (4) ppb), low environmental risk is expected due to approval of this application.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.

Primary Environmental Reviewer Name and Date: Raanan A. Bloom, Ph.D.

Secondary Reviewer Name and Date: Scott Furness, Ph.D.

Raanan Bloom

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Michael Furness

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BIOPHARMACEUTICS

Product Background:

NDA: 211765

Drug Product Name / Strength: Ubrogepant Tablets/ 50 mg, 100 mg

Route of Administration: Oral

Proposed Indication and Dosage: For the acute treatment of migraine with or without aura in adults, 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.
Maximum daily dose: 200 mg

Applicant Name: Allergan Sales, LLC
Primary Reviewer: Gerlie Gieser, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

Review Recommendation: *APPROVAL*

Review Summary:

Dissolution Method and Acceptance Criterion

The proposed dissolution method and revised acceptance criterion (as tabulated below) are approved for the routine quality control (QC) of the 25 mg, 50 mg, and 100 mg strengths of ubrogepant immediate release tablets at batch release and during stability testing. Based on the data provided for the 50 mg tablets, the approved dissolution method demonstrated Level C in vitro – in vivo (IVIVC) with respect to ubrogepant Cmax and $AUC_{0\text{-}4h}$.

Note that ubrogepant is a (b) (4) drug substance that exhibits low solubility per BCS criteria; (b) (4) Note also that the ubrogepant tablet lots used in the pivotal Phase 3 clinical trials and the pivotal BE study exhibited very rapid dissolution when tested using the proposed QC dissolution method.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddle)	75 rpm	Simulated Gastric Fluid (without enzyme): 0.05% HCl/34 mM NaCl, pH 1.8 37 ± 0.5°C	900 mL	NLT (b) (4) (Q) of the label claim dissolved in 15 min

Bridging to the To-Be-Marketed Drug Product

Altogether, the comparative *in vitro* dissolution profile and *in vivo* BE data provided in the NDA are adequate to qualify the CMC changes (in API supplier, (b) (4) and/or tablet manufacturers, batch size, as well as debossing of the tablets) that were

introduced to the ubrogepant (b) (4) tablets after the conduct of the pivotal Phase 3 clinical trials.

List of Submissions reviewed:
SDN-1, 12/26/2019 (Original NDA Submission)
SDN-3, 1/23/2019 (CMC Amendment)
SDN-4, 2/1/2019 (Response to Clinical Pharmacology Information Request (Formulations)
SDN-6, 3/13/2019 (Response to Early Biopharmaceutics Information Request)
SDN-11, 4/12/2019 (Response to Quality Information Request)
SDN-13, 5/14/2019 (Response to Biopharmaceutics Information Request)

Concise Description Outstanding Issues Remaining:
None

BCS Designation

The Applicant considers ubrogepant as a BCS IV (low solubility/low permeability) drug substance.

Reviewer's Assessment:

Solubility: *Low* (b) (4)
The (b) (4) drug substance (b) (4) exhibits low solubility per BCS criteria. (b) (4) . For details, refer to the pH-solubility profile data of the (b) (4) drug substances in Table 22 of the Applicant's 4/12/2019 Response to the Quality Information Request dated 4/1/2019, and Table 1 of the dissolution method development report PD-TRPT-00757.

Permeability: *Low* (b) (4)
The (b) (4) drug substance permeability across LLCPK1 cells is 15 x 10^{-6} cm/sec.

Dissolution: *Rapid to Very Rapid Dissolution*
The (b) (4) tablets exhibit rapid to very rapid dissolution in 900 mL volumes of various pH buffers (b) (4) in Simulated Gastric Fluid (b) (4) see Figure 1 of Report PD-TRPT-00757.

Dissolution Method and Acceptance Criteria

The proposed dissolution method parameters and the sampling time point for Q of (b) (4)% dissolved are shown below:

Table 10 Dissolution Parameters

Apparatus	USP apparatus II (paddles)
Rotation speed	75 rpm
Dissolution medium	0.05% HCl/34 mM NaCl
Dissolution volume	900 mL
Temperature	37.0°C ± 0.5°C
Sampling intervals	(b) (4) minutes

Reviewer's Assessment:

Dissolution Method *- ADEQUATE*

Justification of Dissolution Method Conditions

(b) (4)

Discriminating Power and Level C IVIVC

The proposed dissolution method was demonstrated to be capable of detecting changes/differences in the levels of the (b) (4), tablet hardness, and (b) (4) (b) (4) as well as (b) (4) Particle Size Distribution; refer to Figures 1 to 4.

Additionally, using 50 mg (b) (4) tablets manufactured with low (b) (4), medium, and high (b) (4) and evaluated for PK in Phase 1 Study MK-1602 P010, the Applicant reported Level C IVIVC potential for the proposed QC dissolution method. The dissolution method's 'Level C' IVIVC potential was demonstrated with respect to Cmax and AUC_{0-4h}; see Figure 5. Note however that a 'Level A' IVIVC (defined as a point-by-point relationship between *in vitro* and *in vivo* input rates) is preferred for more comprehensive regulatory applications/purposes.

Figure 1

I **Figure 4** (b) (4) **egrant Level on Dissolution of Ubrogepant tablets** s

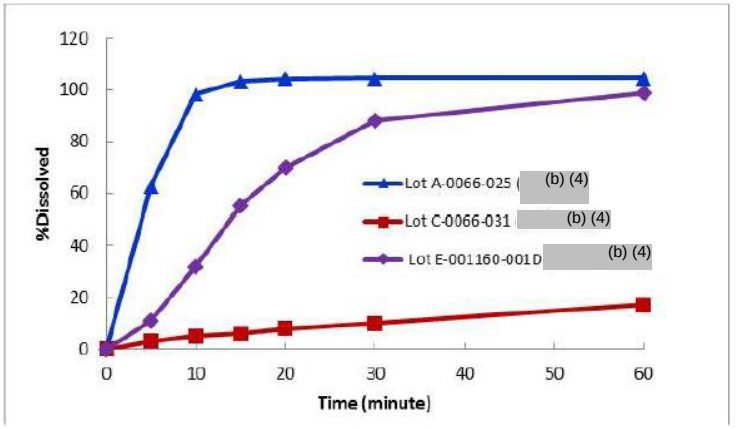


Figure 2

Ef **Figure 5** (b) (4) **Forces on Dissolution of Ubrogepant tablets** ets

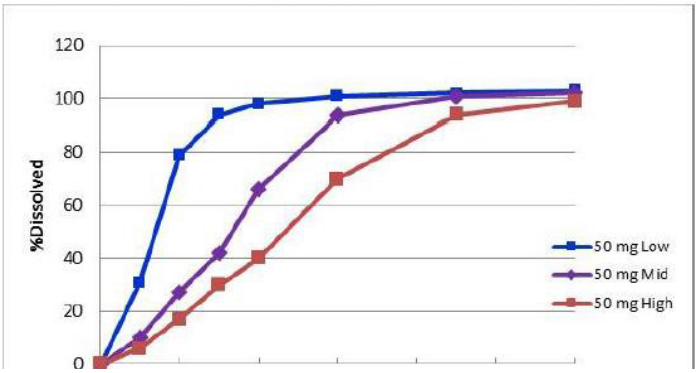
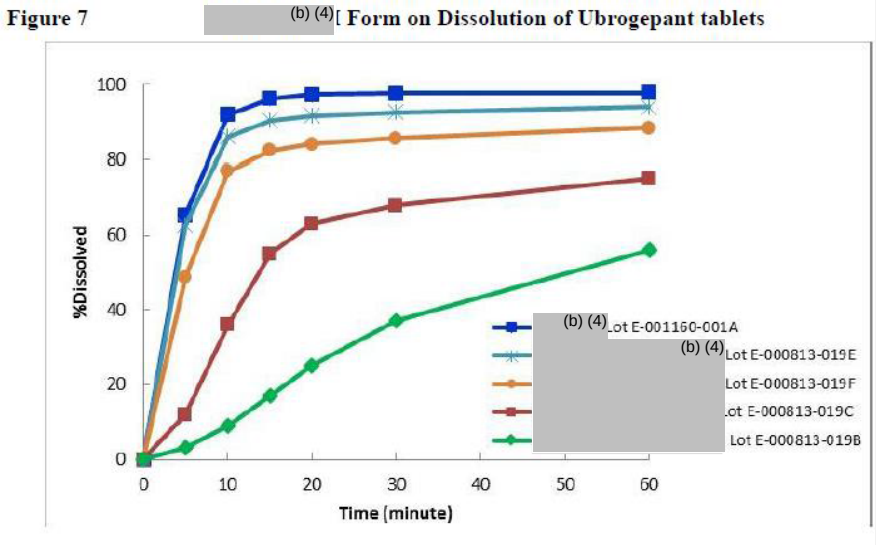


Table 5 Comparison of the in vitro release (%Dissolved at 10, 15 and 20 minutes) and the in vivo responses (Cmax) of Ubrogepant tablets manufactured with different hardness (b) (4) (b) (4) (b) (4)

Formulation (b) (4)	%Dissolved			Human PK
	10 minutes	15 minutes	20 minutes	Mean Cmax (nM)
50 mg Low	(b) (4)			326.804
50 mg Mid				236.786
50 mg High				208.822
Correlation Coefficient R^2	0.9939	0.9974	0.9457	--

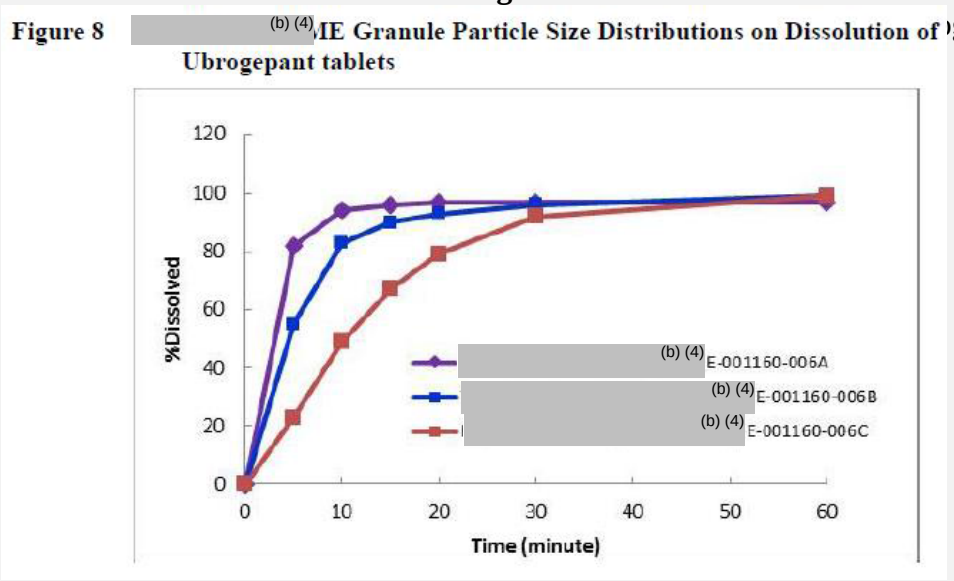
Reviewer Note: These 50 mg Pre-Market Formulation (PMF)-like (b) (4) Low, Mid, High hardness tablets had the same formulation composition as the Phase 3 tablets (but were manufactured by Merck using (b) (4) , and was) used in Phase 1 Clinical Study P010 and other earlier clinical studies.

Figure 3



Reviewer Note: Based on Figure 3, the proposed QC dissolution method may be able to detect potential (b) (4) at levels (b) (4)% in the tablets. (b) (4) .

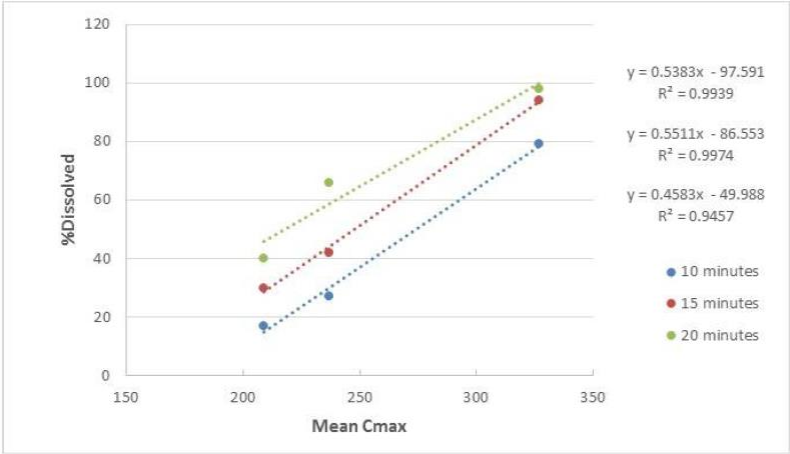
Figure 4



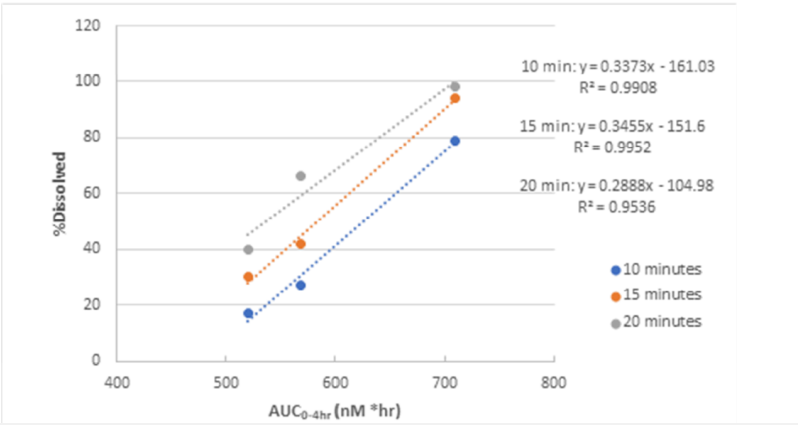
Reviewer Note: (b) (4) particle size distribution could potentially impact dissolution rate of the proposed drug product.

Figure 5

Level C IVIVC: Ubrogepant Cmax versus Dissolution at 10, 15, and 20 min



Level C IVIVC: Ubrogepant $AUC_{0\text{-}4h}$ versus Dissolution at 10, 15, and 20 min



Reviewer Note: The composition of the pre-market formulation (PMF)-like (b) (4) tablets (manufactured with variations in tablet hardness) used in the IVIVC study is the same as the "(b) (4) tablets" used in Phase 3 studies.

Analytical Method Validation

The dissolution method was reported to be (1) robust in terms of presence/absence of medium deaeration, and the studied concentration ranges of HCl (0.05% ± 0.005%) and NaCl (34 ± (b) (4) mM) in the dissolution medium, and (2) compatible with PVDF, Nylon, and PTFE filters. The standard & sample solutions were reported to be stable at room temperature for up to at least 14 – 15 days. Note that the Drug Product Reviewer (Dr. Andrei Ponta) confirmed the acceptability of the analytical method validation of the isocratic HPLC method with UV detection at 282 nm for quantification of drug in the dissolution samples.

Dissolution Acceptance Criteria *– REVISED DISSOLUTION ACCEPTANCE CRITERIA ACCEPTABLE*

The originally proposed dissolution acceptance criterion was Q = (b) (4)% at (b) (4)min, based on "the dissolution data of acceptable clinical batches, stability samples under long-term and accelerated conditions, tablets produced during manufacturing process development and the ICH Q6A guideline, decision trees #7". The Applicant stated that following ICH Q6A, an acceptance criterion of NLT(b) (4)% (Q) a (b) (4)minutes was selected to pass clinically acceptable batches while discriminating against tablets manufactured with meaningful changes to the formulation composition or manufacturing process that would produce slower dissolution profiles.

This Reviewer recommended a dissolution acceptance criterion of 'Q = (b) (4)% at 15 min' based on: (1) the dissolution profile data of the pivotal Phase 3 clinical trial and the pivotal BE lots, and (2) ability to reject batches with unacceptable quality attributes including those with intentionally manufactured with substantially higher than target levels of (b) (4) material, tablet hardness, or (b) (4) particle size distributions, as well as those manufactured with substantially lower than target levels of (b) (4). Additionally, this Reviewer recommended a dissolution specification time point of 15 min (instead of the Applicant's proposed specification of (b) (4)min) for the Q of (b) (4)% considering the following factors: (1) The proposed drug product is for the treatment of migraine for which a rapid onset of action is desired (consistent with the drug's observed median Tmax of ~ 1.5 hours [max: 4 hours]), (2) The Level C IVIVC of tablets with varying tablet hardness showed a better correlation with dissolution at 15 min (b) (4) for both ubrogepant Cmax and $AUC_{0-4h,}$ (3) The pivotal Phase 3 clinical trial lots exhibited (b) (4)% dissolution in the proposed QC dissolution medium as early as 15 min, and (2) per the proposed package insert (and as confirmed by the CDER QT-IRT), ubrogepant tablets do not possess QT prolongation potential.

Dissolution on Stability

The Applicant reported that there were no stability trends and the dissolution remained relatively unchanged from the initial timepoint through the study durations for all studied storage conditions. All dissolution results met the proposed acceptance criterion (Q = (b) (4)% at (b) (4)min) at each stability time point. The Applicant also reported that the ages of the Phase 3 clinical and Pivotal BE tablets were 9 – 67 months (50 mg), 9 -12 months (100 mg), and 45 – 63 months (25 mg).

Based on the dissolution profile data for the 50 mg and 100 mg lots that were used in both the Pivotal BE and primary registration (stability) studies, the proposed drug product lots were able to conform to this Reviewer's recommended dissolution acceptance criterion (Q = (b) (4)% at 15 min). Specifically, the individual units of 50 mg Lot 501704D and 100 mg Lot 10017031A had dissolution data at 15 min of at least 92% and at least 93%, respectively, during 12 months of long-term (25°C/60%RH) and intermediate storage (30°C/75%RH)/stability testing over 12 months, as well as during 6 months of accelerated (40°C/75%RH) stability testing.

In the 5/14/2019 Response to the Biopharmaceutics Information Request dated 5/7/2019, the Applicant revised the finished product QC specifications and other pertinent NDA documents to reflect agreement with the FDA's recommendation to (b) (4) the dissolution acceptance criterion to "Q = (b) (4)% at 15 min".

Bridging of Formulations

Reviewer's Assessment: *ADEQUATE*

Various formulations (containing either (b) (4)) produced using different manufacturing process types were evaluated during different stages of clinical development of ubrogepant tablets; see Tables 4-1 and 4-15 of 2.7.1 Biopharmaceutics Summary. Note that the ubrogepant formulation/dosage form evaluated in the pivotal Phase 3 clinical trials and proposed for marketing is referred to as the "(b) (4) tablet". Based on efficacy data, the Applicant proposes to market the 50 mg and 100 mg strengths (but not the 25 mg strength) of this (b) (4) tablet. However, this Reviewer's bridging and other Biopharmaceutics evaluation of the NDA also included the 25 mg strength for the following reasons: (b) (4) (2) the efficacy profile of the 25 mg dose/strength is acceptable to the FDA Clinical/Statistical Reviewers, and (3) (b) (4) .

The 50 mg strength of the oral (b) (4) tablets (manufactured by Merck (b) (4) was evaluated for efficacy/safety and PK in two pivotal Phase 3 trials (UBR-MD-01 and UBR-MD-02). In addition, the 25 mg strength was evaluated for PK, efficacy and safety in Study UBR-MD-02; see Table 17 of SDN-4 which shows (b) (4) the compositions of the 25 mg and 50 mg tablets used in Phase 3. Note that the proposed 100 mg strength was not included in the Phase 3 clinical trials; however, in "Pivotal BE" Study 3110-103-002, the proposed commercial 100 mg strength (b) (4) tablet was evaluated for bioequivalence to two 50 mg (b) (4) tablets (used in Phase 3 studies) in terms of PK, (b) (4) with comparable *in vitro* dissolution profile as the 50 mg strength. (b) (4) .

In Vivo PK Bridging Data

The Applicant conducted an ***in vivo* BE** (with food-effect) study (Study 3110-103-002) because they consider ubrogepant as a BCS-IV drug substance and also to (1) support the addition of the 100 mg strength, and (2) qualify the proposed cumulative CMC changes to the 50 mg strength that were introduced after conducting the Phase 3 clinical trials and for the manufacture of the primary registration (stability) lots, i.e., with respect to the (b) (4) and tablet manufacturing site [Merck/PA (USA) → Allergan/Forest Laboratories (Ireland),

using the same process steps and equipment type], the API supplier [Merck (USA) → (b) (4)], as well as the small scale down in the batch sizes of the (b) (4) and 50 mg (b) (4) tablets [(b) (4) kg vs. (b) (4) kg]. Note that the Clinical Pharmacology Reviewer confirmed the adequacy/acceptability of the *in vivo* BE study results.

Note that Allergan/Forest Laboratories manufactured the primary (registration) batches of all three strengths of the (b) (4) tablets (as well as the (b) (4) that went into the manufacture of the finished product), in addition to the 25 mg strength that was evaluated in Phase 3 Study UBR-MD-02 (i.e., using the (b) (4) manufactured previously [for both 25 mg and 50 mg clinical trial materials and early development studies] by Merck). Refer to Table 54 of SDN-4 for a comparison of the formulation composition and manufacturers of the (b) (4) (b) (4) and different strength tablets used in Phase 3 clinical trials and those proposed for marketing. Note that for the 25 mg strength tablet, there is a difference between the tablets used in the pivotal clinical trial versus those used in the primary/stability studies (b) (4) in terms of the manufacturers of (b) (4), i.e., Merck (NJ) and Merck (PA) versus (b) (4)) and Forest Laboratories (Ireland).

Additionally, except for the presence/absence of markings, the appearance (color/shape) of the clinical lots, registration/stability lots and the final commercial image tablets (all three strengths) are the same. Whereas the tablets used in Phase 3/Pivotal BE clinical and the primary registration (stability) studies were unmarked, the final commercial image tablets will be debossed on one side with the logo (b) (4) "U50", or "U100" depending on the strength.

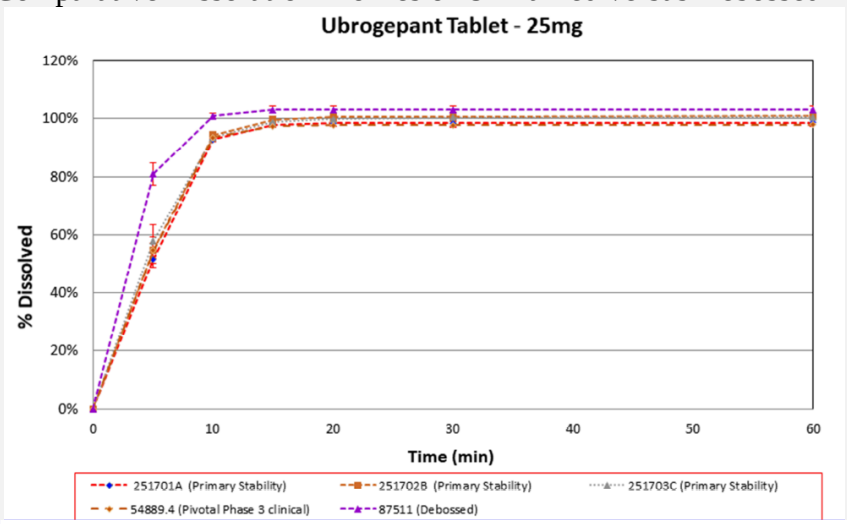
In Vitro Bridging Data

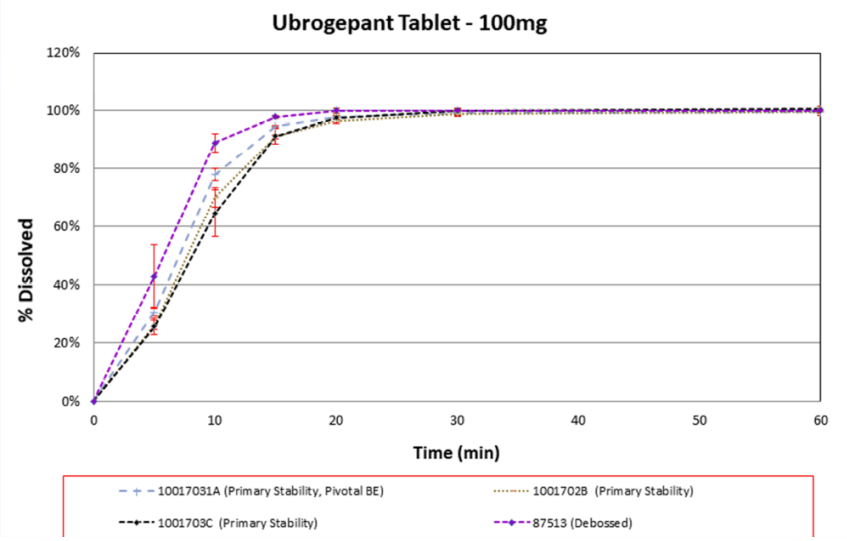
Figures 1 to 3 of the Applicant's 4/12/2019 Response to the Quality Information Request dated 4/1/2019) show that the debossed and unmarked tablets of all three strengths are very rapidly dissolving (i.e., at least (b) (4)% dissolved within 15 min) in the proposed dissolution medium; see Figure 6. Additionally, ubrogepant tablets exhibit rapid to very rapid dissolution, regardless of media pH. Thus, altogether these data indicate that the post-clinical trial addition of the tablet marking (and additionally, the post-clinical trial change in the API and (b) (4) suppliers (b) (4)) did not impact the very rapid dissolution profiles of all three strengths of the proposed drug product in the proposed QC dissolution medium (simulated gastric fluid).

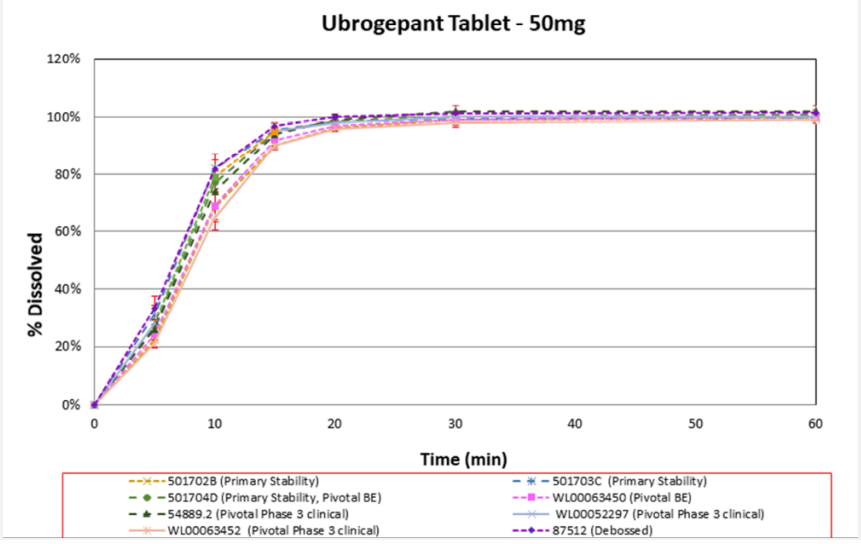
The clinical trial lots were provided as bulk products whereas the supporting stability lots were tested in (b) (4) packaging configurations and the primary/registration lots and the final to-be-marketed tablets were/will be packaged in (b) (4). Based on the stability data provided, there was no evidence of storage temperature- and time-dependent changes in the very rapid dissolution profiles of the primary registration and supporting stability (clinical) batches regardless of packaging configuration over up to 24/60 months of long-

term/intermediate, over 12 months of refrigerated and over 6 months of accelerated storage.

Figure 6. Comparative Dissolution Profiles of Unmarked versus Debossed Tablets







Note that PK data are available in case bridging to the earlier clinical development formulations/dosage forms is needed.

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

A biowaiver request was not submitted nor required because all three strengths of ubrogepant tablets manufactured using the proposed commercial drug product *formulation* and manufacturing *process* were evaluated for PK. Additionally, the two lower (25 mg and 50 mg) strengths were evaluated for efficacy and safety including in the two pivotal Phase 3 clinical trials.

List of Deficiencies:

None

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 12/16/2019 02:35:22PM
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Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 12/16/2019 02:40:30PM
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/s/

DAHLIA A WALTERS
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