CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213931Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	213931		
Applicant Name	Ardelyx, Inc		
Drug Product Name	(b) (4) (tenapanor) tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	10 mg, 20 mg and 30 mg (provided as 10.6, 21.3, and 31.9 mg of tenapanor hydrochloride)		
Route of Administration	Oral		
Maximum Daily Dose	60 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Control of serum phosphorus in adult patients with Chronic Kidney Disease (CKD) on dialysis.		
Drug Product Description	• 10 mg tenapanor supplied as a yellow, oval, biconvex film-coated tablet debossed with "A " on oneside and "T10" on the other side. • 20 mg tenapanor supplied as a brown, oval, biconvex film-coated tablet debossed with "A " on one side and "T20" on the other side. • 30 mg tenapanor supplied as a red, oval, biconvex film-coated tablet debossed with "A " on one side and "T30" on the other side.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F)		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Joseph Leginus OPQ/ONDP/DNDAPI/NDB3	Suong Tran OPQ/ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Dan Berger OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5
	Manufacturing	Nancy Waites OPQ/OPMA/DPMAII/PMB7	Feiyan Jin OPQ/OPMA/DPMAII/PMB7
	Biopharmaceutics	Rebecca Moody OPQ/ONDP/DB/BB3	
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
	ATL	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

The expiry dating period for (b) (4) (tenapanor) tablets shall be 24 months from the date of manufacture when stored in the purposed commercial packaging at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background

The Applicant, Ardelyx, Inc., previously submitted NDA 231931 seeking U.S. marketing approval for tenapanor tablets under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic (FDC) Act. Previously, IBSRELA® (tenapanor, 50 mg tablet), was approved for the treatment of Irritable Bowel Syndrome (IBS-C) in adults under NDA 211801, also submitted by Ardelyx, Inc. NDA 213931 was submitted with a new propriety name and a new indication. Tenapanor for hyperphosphatemia in end stage renal disease (ESRD) has been developed with the same active moiety and dosage form as previously approved for tenapanor IBSRELA® (tenapanor) for IBS-C, and the two products differ only with respect to proposed indication and strength. The previous recommendation was approval from the OPQ perspective, see the Integrated Quality Assessment (IQA) dated 3/31/2021; however, the NDA received an overall Complete Response letter (July 28, 2021) due to clinical deficiencies. The current resubmission includes new information submitted for the tenapor drug substance and a updated quality labeling. For complete reviews of information submitted in the original NDA for all disciplines, see the IQA submitted on 3/31/2021.

2. Drug Substance

The recommendation from Drug Substance for NDA 213931 was Adequate in the previous review cycle (March 31, 2021). The current resubmission includes updated information on the drug substance. This new information for the drug substance has been previously submitted to the Applicant's approved NDA 211801 in two Prior Approval Supplements both of which have been recommended for Approval. Therefore, the recommendation for NDA 213931 Resubmission from the drug substance perspective remains approval.

3. Manufacturing

The OPQ review recommendation for the manufacturing process and facilities remains approval. No new information was submitted for these disciplines and the facilities remain approvable at the time of review.

4. Quality Labeling

With regards to quality aspects of the drug product labeling, the conclusion of the updated OPQ review is that the labeling is approvable with minor recommendations that have been communicated to the Applicant.

5. Other OPQ Disciplines

No new information was submitted for the drug product and biopharmaceutics disciplines, including drug product and these OPQ disciplines continue to recommend approval for this NDA.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Theodore Carver

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Drug Substance Name	Tenapanor Hydrochloride
NDA Number	213931 Resubmission
Assessment Cycle Number	2
DMF Number (If Applicable)	N/A
Applicant Name	Ardelyx, Inc.
DMF Holder	N/A

Assessment Recommendation: *Adequate*.

Document(s) Assessed	Date Received
NDA 213931 Resubmission	4/17/2023

Assessment Summary

CMC information for tenapanor hydrochloride drug substance was previously submitted in the Applicant's NDA 211801 (IBSRELA® [tenapanor] tablet; approved 9/12/2019) for the treatment of Irritable Bowel Syndrome. On 6/26/2020, the Applicant submitted NDA 213931 ((b) (4) [tenapanor] tablet) for a new indication (control of serum phosphorus levels in adult patients with chronic kidney disease) having the same information for the drug substance that had been provided in the approved NDA 211801. The recommendation from Drug Substance (11/16/2020) for NDA 213931 was Adequate. On 7/28/2021, the Applicant received a Complete Response due to Clinical issues. (No CMC issues were included in the Complete Response). The NDA has been resubmitted (4/17/2023) and includes updated information on the drug substance. This new information for the drug substance has been previously submitted to the Applicant's approved NDA 211801 in two Prior Approval Supplements both of which have been recommended for Approval.

Therefore, the recommendation for NDA 213931 Resubmission from a drug substance perspective remains Adequate. A summary of the two approved Supplements submitted to the referenced NDA 211801 is provided below.

Joseph Leginus

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Su (Suong) Tran

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The prescribing information meets all regulatory requirements from a CMC perspective, following edits made during the previous review cycle and a new recommendation to include the street address in section 17.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Xphozah (tenapanor)	Adequate
Established name(s)	Tenapanor	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	10 mg, 20 mg and 30 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	10 mg, 20 mg, 30 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Tenapanor	Adequate, USP salt policy is applied (DS is a dihydrochloride salt)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Dosage strength, shape, color, coating and debossing for 10 mg, 20 mg and 30 mg strengths.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Xphozah (tenapanor)	Adequate
Dosage form(s) and route(s) of administration	10 mg, 20 mg and 30 mg tablets, oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Equivalent of 10, 20, 30 mg of tenapanor (provided as 10.6, 21.3, and 31.9 mg of tenapanor hydrochloride).	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder. Coating: hydroxypropyl methylcellulose, titanium dioxide and triacetin, iron oxide red, yellow and black	Adequate
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	NHE3 inhibitor	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, $C_{50}H_{68}Cl_6N_8O_{10}S_2$, 1217.97.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Practically insoluble in water.	Adequate

*12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2).

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	10 mg, 20 mg, 30 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 14 and 60 tablets (all strengths)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, size, color, debossing, NDC numbers present for all strengths & packaging.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4)	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Desiccant size and shape are distinct from the tablets.	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F and 86°F)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Child-resistant cap.	Adequate.

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Ardelyx, Inc. Waltham, MA 02451 USA	**Adequate with recommended edit.** A recommendation was made to include street address.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

NA

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Bottle (10 mg strength):

3.2 Carton Labeling

NA

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Proprietary name, established name, and dosage form (font size and prominence	Xphozah (tenapanor)	Adequate
Dosage strength	10 mg, 20 mg and 30 mg	Adequate
Route of administration	oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains the Equivalent of 10, 20 or 30 mg of tenapanor (provided as 10.6, 21.3, or 31.9 mg of tenapanor hydrochloride).	Adequate
Net contents (e.g. tablet count)	Bottles of 14 and 60.	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Not present	Adequate following DMEPA recommendations.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F and 86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Distributed by: Ardelyx, Inc. Waltham, MA 02451 USA	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*

It has been confirmed that DMEPA will address the missing lot # and expiration date information (via email on 8/14/2023). With this change, the labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All labeling deficiencies have been addressed. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger August 15, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Theodore Carver August 15, 2023

Dan Berger

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Theodore Carver

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NDA 213931: [redacted] (b) (4) (tenapanor) Tablets

Integrated Quality Review

Recommendation: Approval

Product Name	[redacted] (b) (4) (tenapanor) tablets
Indication	Indicated for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis
Strength	10 mg, 20 mg and 30 mg (provided as 10.6, 21.3, and 31.9 mg of tenapanor hydrochloride)
Dosage Form; Route of Administration	Oral tablets
Rx/OTC Dispensed	Rx
Applicant	Ardelyx, Inc.
Submissions (s) Reviewed	NDA 213931 and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	OPQ/ONDP/DNDAPI/NDB3
Drug Product	Dan Berger	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Feiyan Jin	OPQ/OPMA/DPMAII/PMB7
Biopharmaceutics	Min Sung Suh	OPQ/ONDP/DB/BB3
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

Related/Supporting Documents:

Document	Application Number	Description
NA	NA	NA

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 213931, [redacted] (b) (4) (tenapanor) tablets, is recommended for approval. Based on the stability data submitted to date, the expiry dating period for [redacted] (b) (4) (tenapanor) tablets shall be 24 months from the date of manufacture when stored in the purposed commercial packaging at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

II. Quality Assessment Summary

1. Background: The Applicant, Ardelyx, Inc., has sought U.S. marketing approval for tenapanor tablets under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic (FDC) Act. Previously, IBSRELA® (tenapanor, 50 mg tablet), has been approved, for the treatment of Irritable Bowel Syndrome (IBS-C) in adults, under NDA 211,801 (approved September 2019), but due to the disparate indications, the Applicant has submitted a separate NDA application with a separate propriety name. Tenapanor for hyperphosphatemia in end stage renal disease (ESRD) has been developed with the same active moiety, dosage form as previously approved tenapanor (IBSRELA®) for IBS-C, and the two products differ only with respect to proposed indication and strength. Regarding NDA classification code, given that the proposed drug product: a) is a duplicate of a drug product that is the subject of an approved NDA (IBSRELA® for IBS; NDA 211801), and b) has a new indication or claim with labeling and/or a proprietary name that is distinct from that of the original NDA, this NDA best fits the Type 10 NDA classification code. A complete CMC package has been provided in the NDA without cross-referencing to the prior NDA 211801.

2. Drug Substance (Tenapanor Hydrochloride)**:** The active ingredient tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor. The drug substance is an amorphous solid. CMC information for tenapanor hydrochloride drug substance was been previously submitted in the Applicant's approved NDA 211801 (IBSRELA® [tenapanor] tablet) and found adequate. A Prior Approval Supplement (PAS) has been previously approved for NDA 211801 (4/21/2020) regarding revisions to the drug substance [redacted] (b) (4) manufacturing process [redacted] (b) (4). The revised [redacted] (b) (4) process, as described in the PAS, has been included in the Description of the Manufacturing Process in NDA 213931. The drug substance manufacturing process is well-controlled. The specification includes testing

of all critical quality attributes (CQAs). The stability data support a retest period of (b) (4) months for the drug substance when stored at (b) (4)

3. Drug Product (Tenapanor Tablets)

3.1. Product Design, and Release Specification: Tenapanor tablets (10, 20, and 30 mg), are immediate-release oral tablets containing 10.6 (b) (4) tenapanor hydrochloride (equivalent to 10.0 (b) (4) tenapanor). The (b) (4) (b) (4) product release specification is essentially identical to previously approved 50 mg tablets (NDA 211801). Tablet strengths for NDA 213931 are adequately distinguishable by color, size and debossing. All excipients are compendial and present in quantities within FDA Inactive Ingredients Database levels. The drug substance is susceptible to oxidative and hydrolytic degradation. Drug substance stability is enhanced by use of appropriate excipients. (b) (4) (b) (4) (b) (4). The coatings are similar in composition; the main differences being in iron oxide content. Clinical drug product differs from registration/commercial batches in that the tablets are debossed (versus plain), which is considered a minor change. The product release specification involves testing of all the product critical quality attributes (CQAs). The key analytical method - the HPLC method used to assess identity, assay (tenapanor and propyl gallate), impurities and content uniformity- is fully validated. The identified degradation products are limited to qualified levels in alignment with previously approved NDA 211801 specification. The Applicant has performed a risk assessment screening for elemental impurities per ICH Q3D taking into account any potential contributions from the drug substance, excipients, manufacturing equipment and process, and leachables from the container closure system. Based on this assessment, the product as a whole does not exceed the control threshold of 30% for elemental impurities, and hence no additional testing for elemental impurities is required. Calculated based on a maximum daily dose of 60 mg, the acceptance limit (b) (4) is acceptable. Thus, product release specification is adequate to ensure the identity, strength, quality, purity, and potency of the drug product.

3.2. Manufacturing: The drug product manufacturing process involves the following (b) (4) (b) (4)

3.3. Microbiological Aspects: Water activity has been tested in tablets stressed to a water content up to (b) (4)%. Water activity has been found to be ≤ (b) (4). As a water activity of at least 0.6 is required for any known microorganism (>0.9 for bacteria), tenapanor tablets will meet the specification for microbiological attributes. Additionally, the excipients are tested for microbial growth and the tablets are stored in bottles with a desiccant. Thus, commercial batches of tenapanor tablets will not be routinely tested for microbiological growth, consistent with USP <1112> and ICH Q6A decision tree #6.

3.4. Biopharmaceutics Aspects: (b) (4) (tenapanor) tablets are immediate release tablets with non-functional coating. Tenapanor has low permeability (low systemic exposure), is insoluble in pH > 5.0 and is moderately soluble at pH < 4.0. The Applicant classified tenapanor as a BC 4 compound. The Biopharmaceutics review mainly focused on the evaluation and acceptability of the dissolution method and acceptance criterion for quality control of the proposed product and biowaiver request of the intermediate strength 20 mg. It is noted that the proposed dissolution method is the same as described in previously approved NDA 211801 {IBSRELA (tenapanor) tablets, 50 mg}. The Applicant provided complete dissolution data for the clinical and registration batches. Based on the provided dissolution data, the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 minutes (75 rpm speed) for all strengths is acceptable. Overall, the proposed dissolution specification (method and criterion) is adequate.

Biowaiver request for 20 mg strength is granted based on the following considerations:

- Demonstration of bioequivalence for phase 2b/3 versus phase 3/TBM formulation for both 10 mg and 30 mg strengths. Based on communication with the OCP reviewer, it has been confirmed that phase 2b/3 formulation and phase 3/TBM formulation for both 10 mg and 30 mg strengths are bioequivalent.

- All three strengths are compositionally proportional.

- *In vitro* dissolution similarity (proposed dissolution method) of 20 mg registration batches when compared to 10 mg (3147517R) and 30 mg (3164129R) TBM formulation used in TEN-02-106.

3.5. Container Closure System: Drug product packaging consists of an HDPE bottle enclosed with a polypropylene closure and liner with desiccant packs enclosed that meet the USP specifications. The primary packaging and bulk packaging components that contact the drug product are suitable for pharmaceutical or food contact per 21 CFR regulations. The stability data lends additional support to the suitability of the container closure system for providing adequate protection to the drug product over the proposed shelf-life.

3.6. Stability, Storage Conditions and Expiration Date: Based on up to a period of 12 months of stability data at 25°C/60% RH and 30°C/75% RH, and 6-month of stability data at 40°C/75% RH, the expiry dating period for [redacted] (b) (4) (tenapanor) tablets shall be 24 months from the date of manufacture when stored in the purposed commercial packaging at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). The post-approval stability protocol and commitment are acceptable.

III. Assessment of Manufacturing Facilities: All the manufacturing and testing facilities listed in this NDA are deemed acceptable. Specifically, the drug product and drug substance facilities have been approved based on inspection history and manufacturing experience of these facilities.

IV. Environmental Assessment

The Applicant has claimed categorical exclusion, under 21 CFR § 25.15(d) and 21 CFR Part 25.31(b), because the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The claim for a categorical exclusion is acceptable.

V. Product Quality Labeling Recommendations:

The product quality labeling recommendations are included in the latest version of labeling, including the Prescription Information.

VI. Life Cycle Knowledge Information

See Final Risk Assessment on the next page.

Final Risk Assessment

NDA 213931: (b) (4) (tenapanor) Tablets

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay, Stability	• Formulation • Container closure • Impurity exceeding specification • Process parameters • Scale/ equipment/ site	Low (L)	(b) (4)	Acceptable	.
Solid state Polymorphic form)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Moderate (M)		Acceptable	N/A
Content Uniformity	• Formulation • Particle size • Segregation • Raw materials • Process parameters • Scale/ equipment/ site	Moderate (M)		Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
(b) (4)	• Formulation • Process parameters • Scale/equipment/site	Low (L)	(b) (4)	Acceptable	
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment/site • API sources	Moderate (M)		Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low (L)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 213931, (b) (4) (tenapanor) tablets, is recommended for approval. Based on the stability data submitted to date, the expiry dating period for (b) (4) (tenapanor) tablets shall be 24 months from the date of manufacture when stored in the purposed commercial packaging at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead; Division of Cardiology and Nephrology
CDER/OPQ/ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The prescribing information meets all regulatory requirements from a CMC perspective, following edits made to alphabetize the inactive ingredients in Section 11, and to re-phrase the salt equivalency statement.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4) (tenapanor)	Adequate (will be updated to Xphozah)
Established name(s)	Tenapanor	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	10 mg, 20 mg and 30 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	10 mg, 20 mg, 30 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Tenapanor	Adequate, USP salt policy is applied (DS is a dihydrochloride salt)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Dosage strength, shape, color, coating and debossing for 10 mg, 20 mg and 30 mg strengths.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4) (tenapanor)	Adequate
Dosage form(s) and route(s) of administration	10 mg, 20 mg and 30 mg tablets, oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Equivalent of 10, 20, 30 mg of tenapanor (provided as 10.6, 21.3, and 31.9 mg of tenapanor hydrochloride).	Adequate, following edits made.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder. Coating: hydroxypropyl methylcellulose, triacetin and titanium dioxide, iron oxide red, yellow and black	Adequate, following edits made.
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	NHE3 inhibitor	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, $C_{50}H_{68}Cl_6N_8O_{10}S_2$, 1217.97.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Practically insoluble in water.	Adequate

*12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2).

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	10 mg, 20 mg, 30 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 14 and 60 tablets (all strengths)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, size, color, debossing, NDC numbers present for all strengths & packaging.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4)	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Desiccant size and shape are distinct from the tablets.	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at (b) (4) (b) (4) 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Adequate, following edits made.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Child-resistant cap.	Adequate.

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Ardelyx, Inc. (b) (4) (b) (4)	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

NA

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Bottle (30 mg strength):

(b) (4)

3.2 Carton Labeling

NA

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4) (tenapanor)	Adequate (will be updated to Xphozah)
Dosage strength	10 mg, 20 mg and 30 mg	Adequate
Route of administration	oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains the Equivalent of 10, 20 or 30 mg of tenapanor (provided as 10.6, 21.3, or 31.9 mg of tenapanor hydrochloride).	Adequate, the Applicant has agreed to revise the language as requested.
Net contents (e.g. tablet count)	Bottles of 14 and 60.	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present	Adequate, addressed by DMEPA.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Distributed by: Ardelyx, Inc. (b) (4)	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*

In response to an Information Request, the Applicant has agreed to revise the salt statement as requested (via email on March 5, 2021). The labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All labeling deficiencies have been addressed. Edits were made to Section 11 of the Prescribing Information. The Applicant has agreed to revise the container label salt statement in response to an Information Request sent by the Agency. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger March 8, 2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

David Claffey March 8, 2021

Dan Berger

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Date: 3/08/2021 12:45:57PM
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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	213931
Drug Product Name/ Strength	XPHOZAH™, Tenapanor hydrochloride, Immediate Release (IR) Tablets, 10 mg, 20 mg, and 30 mg
Route of Administration	Oral
Applicant Name	Ardelyx, Inc.
Therapeutic Classification/ OND Division	CDER/OCHEN/DCN
IND Number	120566
Proposed Indication	Control of serum phosphorus in adult patients with chronic kidney disease (CKD) on dialysis
Primary Reviewer	Min Sung Suh, Ph.D.
Secondary Reviewer	Poonam Delvadia, Ph.D.
Recommendation	Adequate

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant submitted a 505 (b)(1) for approval of XPHOZAH™, Tenapanor hydrochloride, Immediate Release (IR) Tablets, 10 mg, 20 mg, and 30 mg, indicating control of serum phosphorus levels in adult patients with Chronic Kidney Disease (CKD) on dialysis. It is noted that previously, IBSRELA (Tenapanor hydrochloride, 50 mg tablet), was approved for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults under NDA 211801 (approved on 09/12/2019). As of 03/09/2021; IBSRELA is discontinued.

XPHOZAH™ is administered as an IR tablet with a non-functional film coating, and the active ingredient, Tenapanor hydrochloride (HCl) is a locally acting and essentially non-absorbed small molecule that inhibits the sodium-hydrogen exchanger isoform (NHE3) transporter in the gastrointestinal (GI) tract to reduce intestinal phosphate absorption (reducing phosphate permeability via paracellular pathway). The recommended dose is 30 mg twice daily (down-titrated), prior to breakfast or the first meal of the day and just prior to dinner. The dose can be adjusted to 20 mg or 10 mg twice daily as needed to maintain serum phosphorus at target levels or manage GI tolerability. Tenapanor HCl is non-absorbed following repeated twice daily oral administration. Plasma concentrations of Tenapanor were below the limit of quantitation (less than 0.5 ng/mL) in the majority of samples from subjects following single and repeated oral administration of Tenapanor hydrochloride, 30 mg twice daily. Therefore,

standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (C_{max}), and half-life ($t_{1/2}$) could not be determined.
The Biopharmaceutics review focused on the evaluation and acceptability of the dissolution method and acceptance criterion for quality control of the proposed product and biowaiver request of the intermediate strength 20 mg.

Dissolution Method and Acceptance Criterion:
The Applicant provided dissolution method development/validation reports, dissolution data of the batches used during clinical development as well as the registration batches in this submission. It is noted that the proposed dissolution method is the same as that of NDA 211801 previously approved on 09/12/2019 for IBSRELA (Tenapanor HCl tablets, 50 mg). The Applicant also provided comparative dissolution data from method development studies and batches used in pivotal clinical studies. Dissolution parameters and variations in CMAs, CFVs, and CPPs were evaluated to support discriminating ability of the proposed method. The provided dissolution data demonstrated the limited discriminating ability of the proposed dissolution method towards critical attributes. The overall information/data and additional controls support the proposed dissolution method.

To support and consider adequacy of the proposed dissolution acceptance criteria, detailed information and complete dissolution data for clinical and registration batches were requested via the Information Request (IR) dated 12/01/2020. In the response to the IR dated 12/15/2020, the Applicant provided complete dissolution data of the clinical and registration batches. Based on the provided dissolution data, the proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in 30 minutes for all strengths is acceptable. Overall, the proposed dissolution specification (method and criterion) is adequate. The dissolution method and acceptance criterion for all strengths of Tenapanor HCl, tablets are shown in Table 1.

Table 1. Approved dissolution specification for finished product batch release and stability testing of Tenapanor HCl, Tablets (10 mg, 20 mg, and 30mg)

Apparatus	USP II (Paddle)
Speed	75 rpm
Medium	900 mL, 69.4 mM Citrate Buffer, pH 4.0
Temperature	37 °C
Acceptance criterion	NLT (b)(4)% (Q) in 30 minutes

Biowaiver Request:
Based on the in vivo PD and plasma PK (metabolite) results in the bioequivalence study (TEN-02-106) evaluating phase 2b/3 and phase 3/TBM formulation at 10 mg and 30 mg strengths, compositional proportionality across

all strengths, and in vitro dissolution similarity, the biowaiver request for 20 mg strength is granted.

List submissions being assessed (table):

Document(s) Assessed	Date Received
Original review (Seq. 0001)	06/29/2020
IR response (Seq. 0011)	12/15/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Tenapanor HCl is designed to have low permeability (low systemic exposure). Tenapanor is insoluble in pH > 5.0 and is moderately soluble at pH < 4.0. The Applicant identified that Tenapanor can be classified as a BCS class 4 compound.

Solubility:

The solubility of Tenapanor HCl in aqueous media is shown in Table 2.

Table 2. Solubility of Tenapanor HCl

Buffer /Medium	Tenapanor HCl Lot 17LVO4SD.HQ00004	
	Final pH	Solubility (mg/mL)
Water	2.7	9.804
0.1N HCl, pH 1.0	1.0	8.267
0.013 N HCl, pH 2.0	1.6	40.852
Citrate Buffer, pH 3.0	2.7	0.567
Citrate Buffer, pH 4.0	3.5	0.896
Citrate Buffer, pH 5.0	4.6	0.000847
Citrate Buffer, pH 6.0	5.6	0.0000713
50mM Na_2PO_4, pH 7.0	6.6	0.0000317
Simulated Gastric Fluid (SGF)	1.0	5.122
Simulated Intestinal Fluid (SIF)	5.2	0.00198
Fed State SIF (FeSSIF) pH 5.0	4.7	0.226
Fasted SIF (FaSSIF), pH 6.5	4.5	0.285

Permeability:

Tenapanor is locally acting and designed to be minimally absorbed. The Applicant provided human ADME study and nonclinical PK data indicating that fecal excretion is the major elimination route of Tenapanor (approximately 80%).

B.2 FORMULATION

The Applicant proposed three strengths (10 mg, 20 mg, and 30 mg) IR, film-coated tablets, and the proposed strengths are consisted of the same formulation as IBSRELA, Tenapanor HCl 50 mg tablets under NDA 211801. The lower and higher strengths were evaluated in phase 1 (TEN-02-106: BE study performed on 10 mg and 30 mg strength evaluating different formulation (TBM vs phase 3 formulation)), 2b/3 (TEN-02-201 study evaluated phase 3 formulation of both 10mg and 30mg strength,), and 3 (TEN-02-301 study evaluated TBM formulation of 10mg strength) clinical trials. The formulation compositions of Tenapanor tablets used in Phase 2b/3 (TEN-02-201) and Phase 3 (TEN-02-301) including TBM tablets are shown in Table 3 and 4, respectively.

Table 3. Composition of Tenapanor tablets, 3 mg, 10 mg, 15 mg, and 30 mg used in TEN-02-201 study

Components	Quantity (mg per unit)				Function	Standard
	TEN-02-201 Study Tablets Phase 2b					
Strength (mg)	3	10	15	30		
Tablet Core						
Tenapanor Hydrochloride	(b) (4)	10.6[a]	(b) (4)	31.9[a]	Active	In-house
Microcrystalline Cellulose					(b) (4)	USP-NF
Colloidal Silicon Dioxide						USP-NF
Low-substituted Hydroxypropyl Cellulose						USP-NF
Propyl Gallate						USP-NF
Stearic Acid						USP-NF
Tartaric Acid						USP-NF
Total Core Weight						
Tablet Film Coat						
						(b) (4)

Table 4. Composition of Phase 3 (TEN-02-301) and TBM Tenapanor Tablets, (10 mg, 20 mg, and 30 mg)

Component	Amount per Tablet (mg)			Function	Quality Standard
	10 mg	20 mg	30 mg		
Tenapanor Hydrochloride	10.6[a]	21.3[b]	31.9[c]	Drug Substance	In-house
Microcrystalline Cellulose[d]	(b) (4)				USP-NF
Low-substituted Hydroxypropyl Cellulose					USP-NF
Colloidal Silicon Dioxide					USP-NF
Tartaric Acid[e]					USP-NF
Propyl Gallate					USP-NF
Stearic Acid[f]					USP-NF
Core Weight					*N/A*
Coating					
(b) (4)					

The Applicant conducted a bioequivalence (BE) study on both 10 mg and 30 mg strength to establish comparability between Tenapanor tablets used in Phase 2b/3 (Phase 3 formulation) and Phase 3 (TBM formulation) studies. Please see the detailed assessment below in the section of Biowaiver.

B.3 DISSOLUTION METHOD

The Applicant provided dissolution method development and validation reports to support discriminating ability of the proposed dissolution method (USP II, 75 rpm, 900 mL, 69.4 mM Citrate Buffer, pH 4.0). The proposed dissolution accetpance criterion is NLT (b) (4)%(Q) in 30 min for all strengths. It is noted that the proposed method was previously presented for Tenapanor tablets, 50 mg (IBSRELA) under NDA 211801 approved 09/12/2019 and was found adequate for IBSRELA tablets.

The method development with respect to dissolution parameters and discriminating ability of the proposed method is presented below.

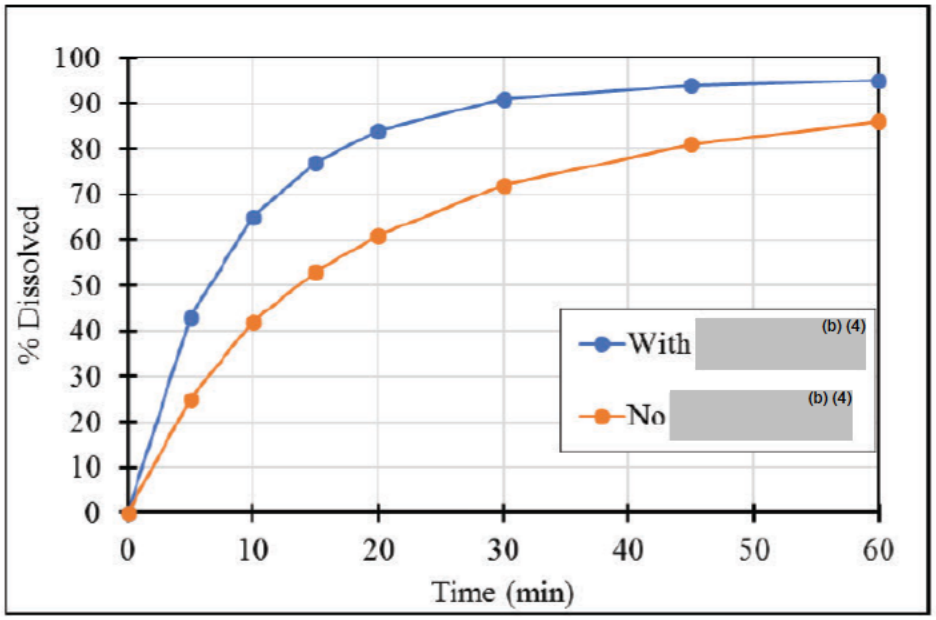
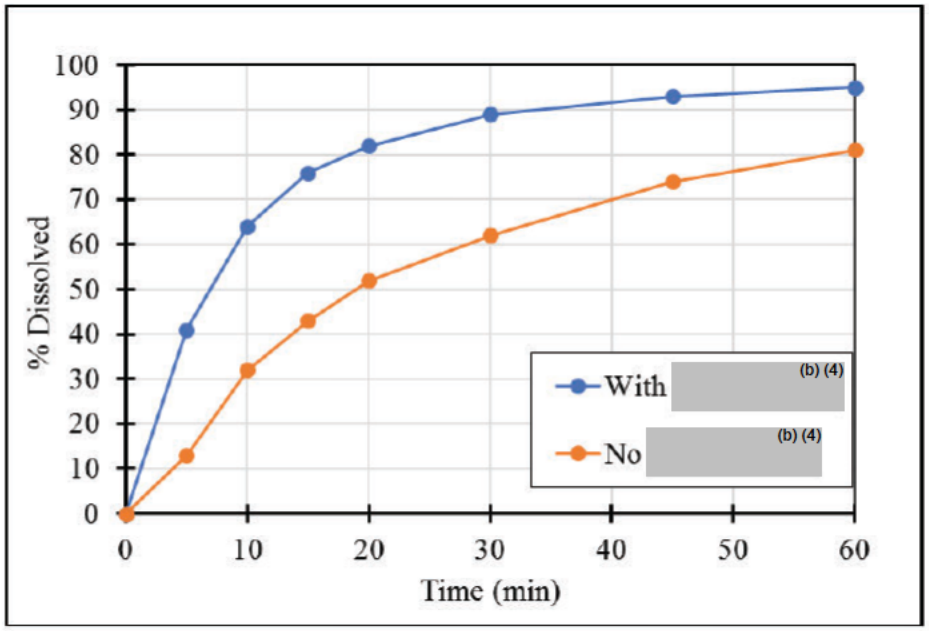
Dissolution method parameters

(b) (4)

Evaluation of discriminatory power

Formulation composition change: Comparative dissolution study was conducted using development batches without the (b) (4), to support discriminating ability of the proposed method. The dissolution profiles of both strengths without the (b) (4) showed that the batches are not equivalent to the control tablets containing the (b) (4) (Figure 4).

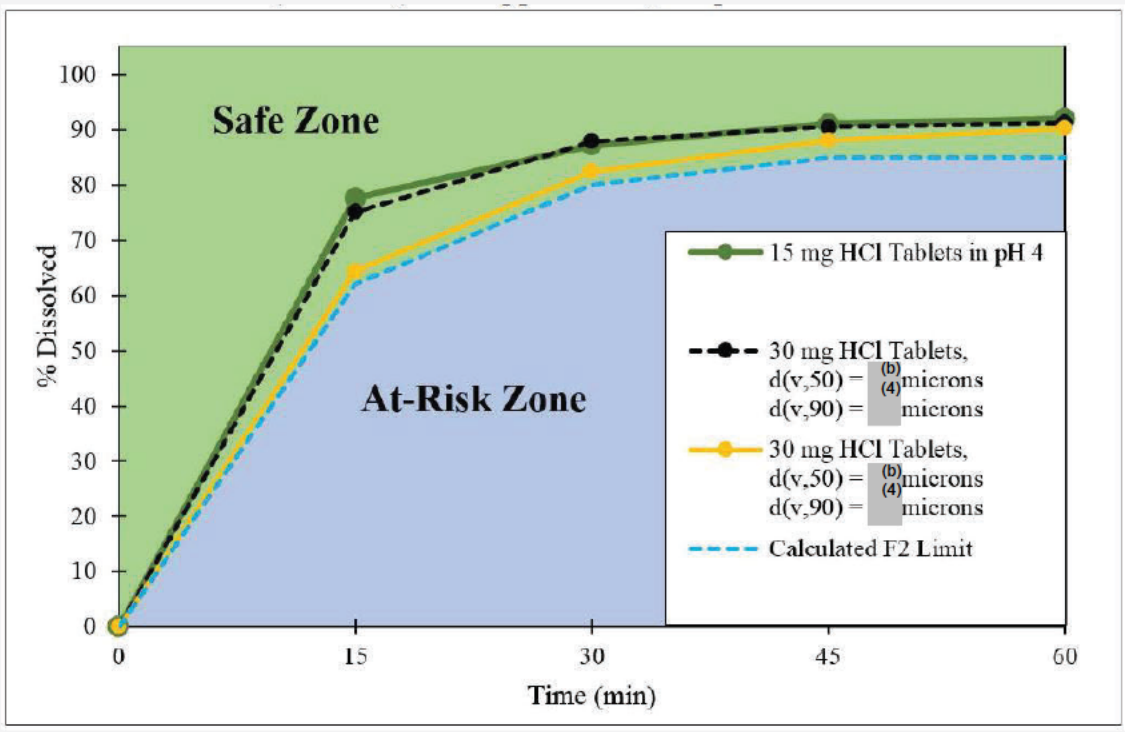
Figure 4. Dissolution profiles of Tenapanor tablets, 10 mg and 30 mg with and without (b) (4)

10 mg	
30 mg	

Drug substance particle size distribution: The effect of drug substance particle size distribution (PSD) on dissolution was investigated using risk assessment approach relating in vitro dissolution profiles and in vivo pharmacodynamic data for 14 mg Tenapanor free base tablets (b) (4)) and 15 mg Tenapanor HCl tablets (b) (4). It is noted that the Applicant has used (b) (4) for clinical trials (phase 1 in vivo BE study, phase 2b/3, phase 3 clinical trials) and is proposed for commercial manufacturing. The dissolution data indicated that the dissolution of

Tenapanor tablets, 30 mg manufactured with smaller PSD (d(v,50)= (b) (4) µm, d(v,90)= (b) (4) µm) is faster than that manufactured with larger PSD (d(v,50)= (b) (4) µm, d(v,90)= (b) (4) µm) but the difference is insignificant (Figure 5).

Figure 5. Dissolution rate-based risk assessment for potential impact of Tenapanor particle size on pharmacodynamic performance using dissolution profiles of Tenapanor tablets, 30 mg produced with a range of Tenapanor particle sizes tested in pH 4.0 citrate buffer (69.4 mM)



No significant difference in dissolution profiles (generated in the proposed QC medium) between tablets with smaller or larger PSD was observed since the dissolution profile of the batch with larger PSD was above the calculated f2 limit profile.

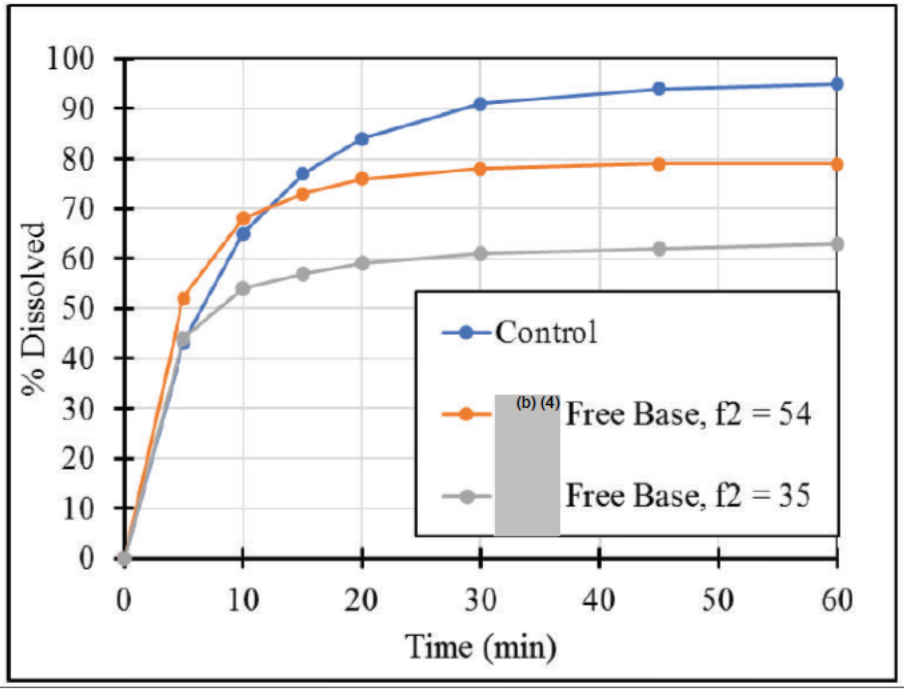
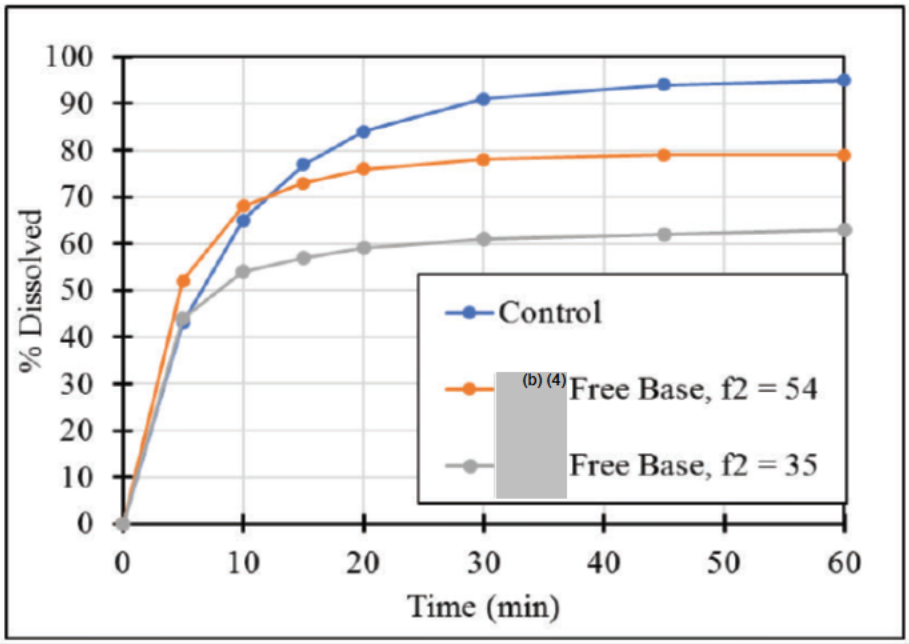
The Applicant also performed the same approach by generating dissolution profiles (b) (4) The assessment showed that the dissolution of 30 mg-tablets manufactured with larger PSD (d(v,50)= (b) (4) µm, d(v,90)= (b) (4) µm) falls into the At-Risk Zone (i.e., below the f2 limit profile) compared to that manufactured with smaller PSD (d(v,50)= (b) (4) µm, d(v,90)= (b) (4) µm) as shown in Figure 6.

Figure 6. Dissolution rate-based risk assessment for potential impact of Tenapanor particle size on pharmacodynamic performance using

dissolution profiles of Tenapanor tablets, 30 mg produced with a range of Tenapanor particle sizes tested (b) (4)

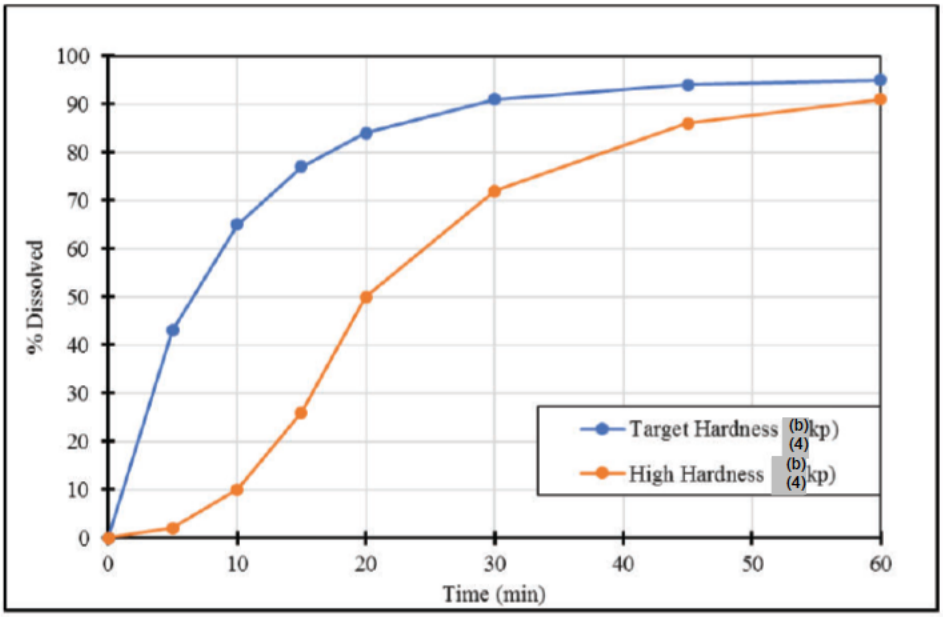
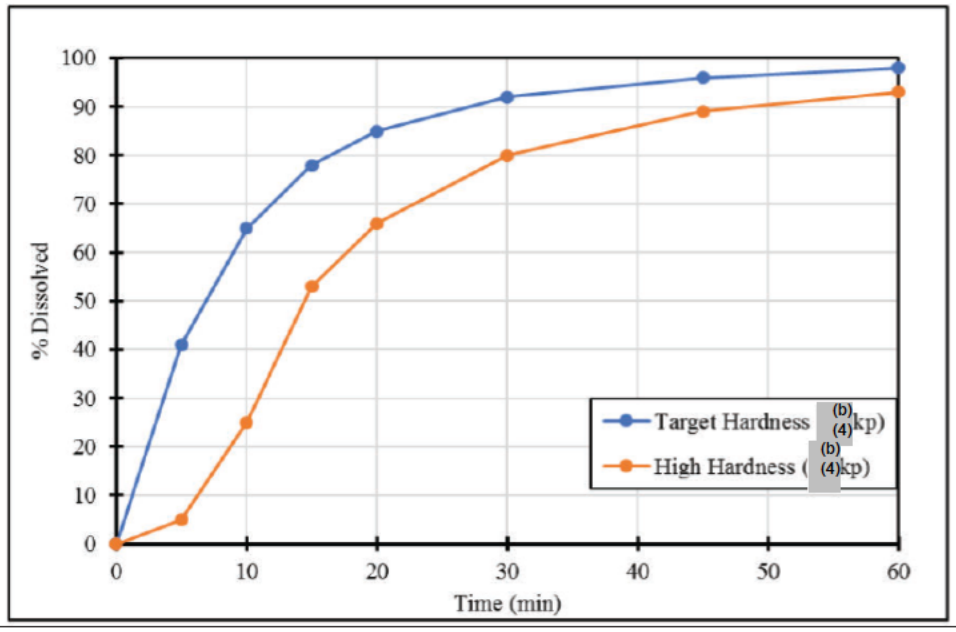
Drug substance physical form: To investigate the ability of the proposed method discriminating the presence of free base content in formulation, comparative dissolution studies were investigated using Tenapanor tablets (10 mg and 30 mg) manufacture with different amount of Tenapanor free base (b) (4) (b) (4). The results showed that the dissolution of the tablets with Tenapanor free base is dissimilar to the control tablets with (b) (4) free base, and incomplete dissolution was observed for the tablets with (b) (4) free base content (Figure 7).

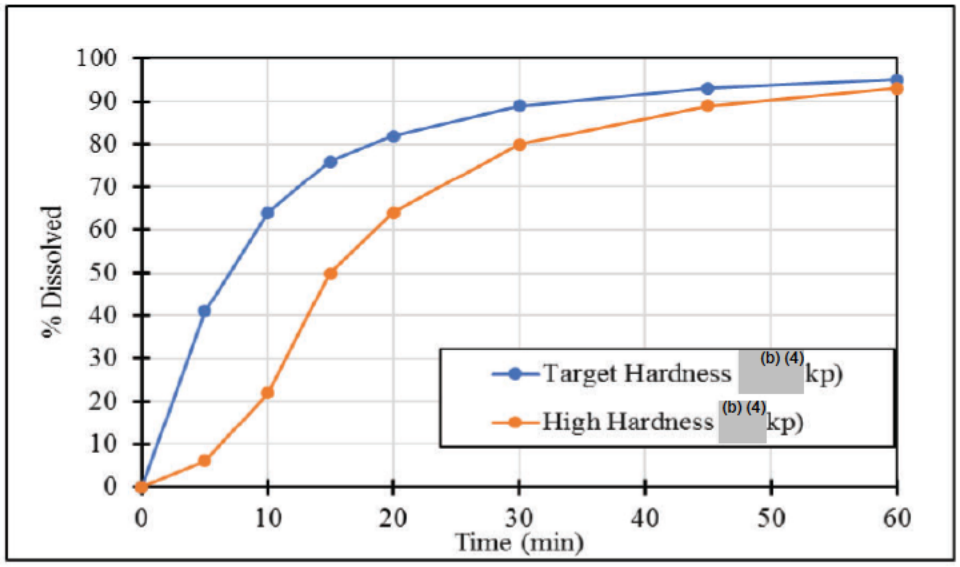
Figure 7. Dissolution of Tenapanor tablets manufacture with (b) (4) free base spiked in place of Tenapanor HCl

10 mg	
30 mg	

Tablet hardness: The effect of tablet harness on dissolution was investigated to support discriminatory power of the proposed method. The dissolution profiles of the tablets (b) (4) target vs. high hardness showed significant differences in the dissolution profiles for all strengths (10 mg, 20 mg, and 30 mg) as shown in Figure 8.

Figure 8. Dissolution profiles of Tenapanor tablets (b) (4) target hardness and high hardness (outside the upper hardness limit)

10 mg	
20 mg	

30 mg	

***Assessment:* {Adequate}**

It is noted that dissolution testing of Tenapanor tablets used in clinical studies (TEN-02-106, TEN-02-201, and TEN-02-301) and registration batches was performed using the proposed dissolution method. The Applicant conducted the method development studies on 10mg and 30mg strengths.

Dissolution Method: Dissolution parameters such as medium and agitation speed, were evaluated and optimized in order to achieve a robust method. The method development report indicated that complete dissolution of Tenapanor tablets (~ (b) (4)% in 30 min) was achieved under the proposed method conditions (USP II, 75 rpm, 900 mL of citrate buffer pH 4). (b) (4) (b) (4) (b) (4) Based on the provided data, the dissolution method (USP II, 75 rpm, 900 mL, 69.4 mM Citrate Buffer, pH 4.0) proposed for quality control of the product is optimal.

Discriminating Ability of the Proposed Dissolution Method:

The discriminatory power and robustness of the proposed method were evaluated by dissolution data of the batches with variations, such as CMAs (PSD and solid state), CFVs (b) (4)) and CPPs (hardness). It is noted that the Applicant used (b) (4)

(b) (4) for clinical trials (phase 1 in vivo BE study, phase 2b/3, phase 3 clinical trials) and is proposed for commercial manufacturing.

However, in reviewer's opinion, the (b) (4) and the study evaluating the impact of (b) (4) drug substance content does not represent meaningful changes for evaluating discriminating ability of the method. Further, the proposed quality control dissolution method does not discriminate the smaller [d(v,50)= (b) (4) µm, d(v,90)= (b) (4) µm] and larger [d(v,50)= (b) (4) µm, d(v,90)= (b) (4) µm] API PSD evaluated as the dissolution profile with larger PSD is above the profile representing the f2 limit indicating dissolution similarity. The comparative dissolution profiles of the batches of all strengths with hardness variations indicated discriminating ability based on dissolution profile dissimilarity (f2 < 50). Only 10mg strength batch with higher hardness was rejected by the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 min. The above data indicated limited discriminating ability of the proposed dissolution method.

Given the provided data in the method development, the limited discriminating ability of the method, and the clinical performance of the API (locally acting and minimally absorbed in GI tract), the proposed method is found adequate for quality control of Tenapanor tablets (all strengths) based on the following:

1) API PSD is controlled and included as specification (d(v,0.5) of ≤ (b) (4) µm; d(v,0.9) of (b) (4) µm) which from biopharmaceutics perspective are supported by API PSD of drug substance batches used for manufacturing products used in clinical trial batches (API PSD specification is found adequate by drug substance reviewer);

2) The impact of the presence of (b) (4) drug substance on in vivo performance is unknown, (b) (4) test is included for API quality control, and there is evidence of physical stability of the amorphous solid for all three strengths of the product at elevated temperature and humidity for 6 months and 16 months which is found adequate by drug product reviewer.[1]

(b) (4)

B.4 DISSOLUTION ACCEPTANCE CRITERION

The proposed dissolution acceptance criterion for quality control of XPHOZAH™, Tenapanor hydrochloride, Immediate Release (IR) Tablets, 10 mg, 20 mg, and 30 mg is NLT (b) (4)% (Q) after 30 minutes.

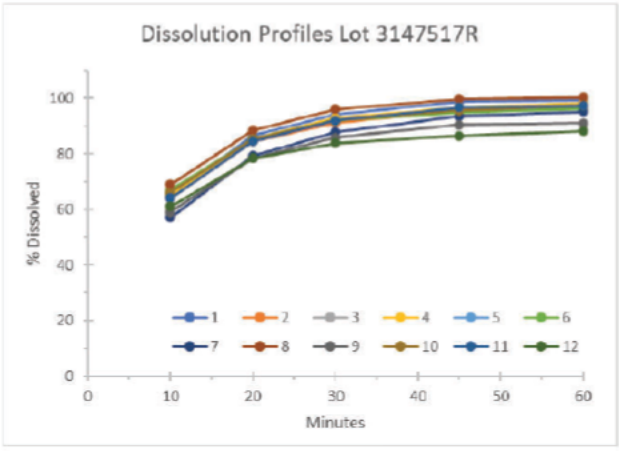
[1] \\CDSESUB1\evsprod\nda213931\0001\m3\32-body-data\32p-drug-prod\tenapanor-tablets\32p2-pharm-dev\drug-product.pdf

Dissolution data of batches used in clinical studies as well as of the proposed commercial drug products (TBM)/registration batches are shown in Figure 9, 10 and 11. Further details on the dissolution data are shown in the link below.[2]

Figure 9. Dissolution data for Tenapanor Tablets, 10 mg used in clinical studies (TEN-02-106 and TEN-02-301) and of registration batches (TBM).

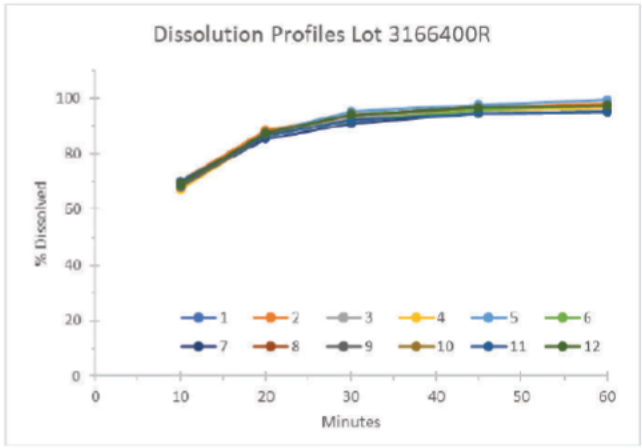
Lot 3147517R (TEN-02-106 and TEN-02-301)

Lot 3147517R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	64	84	91	95	96
Min	(b) (4)				
Max					
% RSD	5.4	3.9	3.8	3.7	3.5

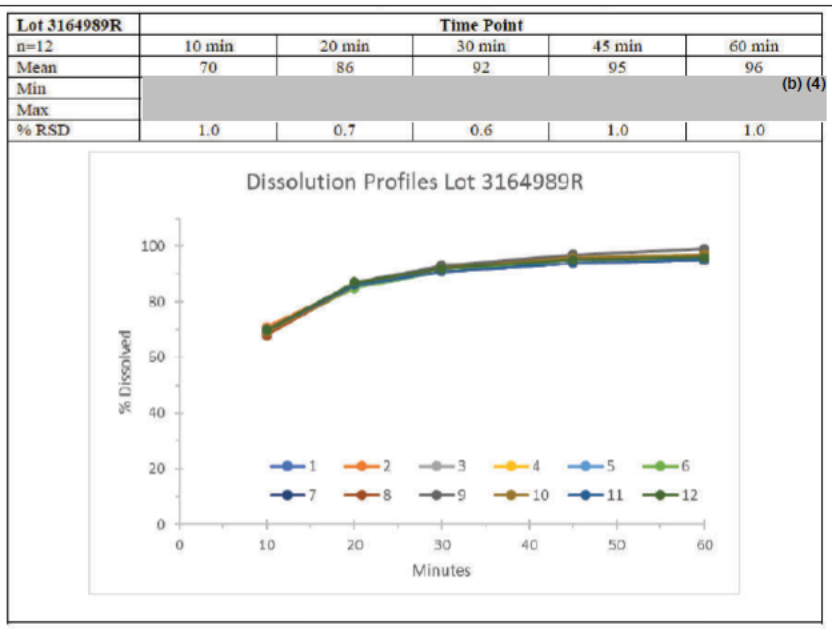
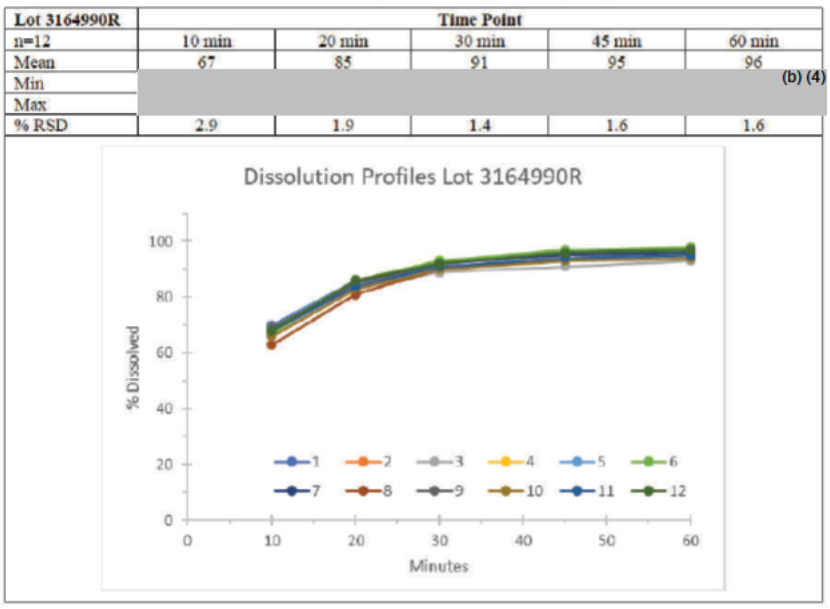


Lot 3166400R (TEN-02-301)

Lot 3166400R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	69	87	93	96	97
Min	(b) (4)				
Max					
% RSD	1.4	0.9	1.3	1.0	1.3



[2] \\CDSESUB1\evsprod\nda213931\0011\m1\us\qua-info-amend-dissoluction-data.pdf

Lot 3164989R (TBM)	
Lot 3164990R (TBM)	

Lot 3164989R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	70	86	92	95	96
Min	(b) (4)				
Max					
% RSD	1.0	0.7	0.6	1.0	1.0

Lot 3164990R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	67	85	91	95	96
Min	(b) (4)				
Max					
% RSD	2.9	1.9	1.4	1.6	1.6

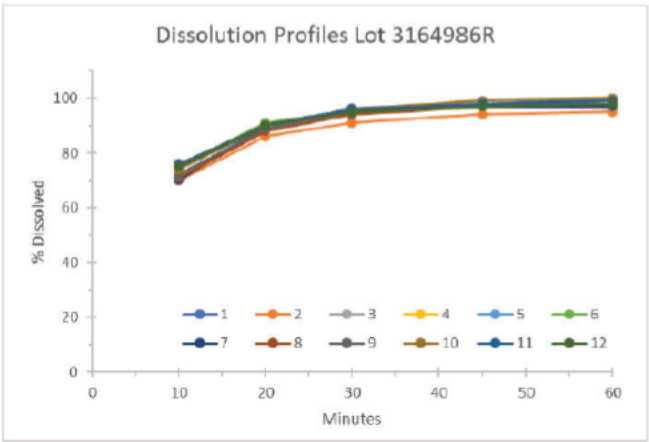
Lot 3164991R (TBM)	

Lot 3164991R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	70	88	94	97	98
Min	(b) (4)				
Max					
% RSD	1.5	1.0	1.1	1.3	1.3

Figure 10. Dissolution data for Tenapanor Tablets, 20 mg of registration batches (TBM).

Lot 3164986R (TBM)	

Lot 3164986R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	73	89	95	97	98
Min	(b) (4)				
Max					
% RSD	3.5	1.4	1.3	1.2	1.3



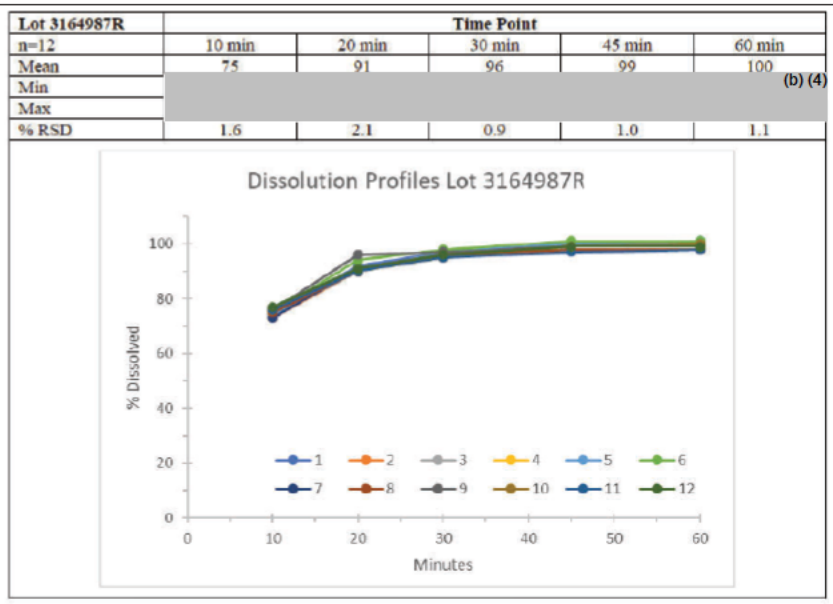
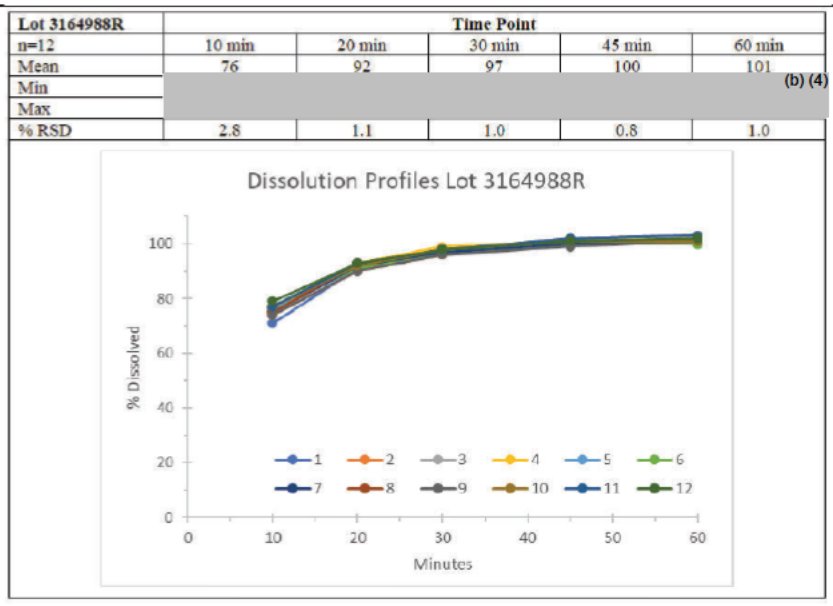
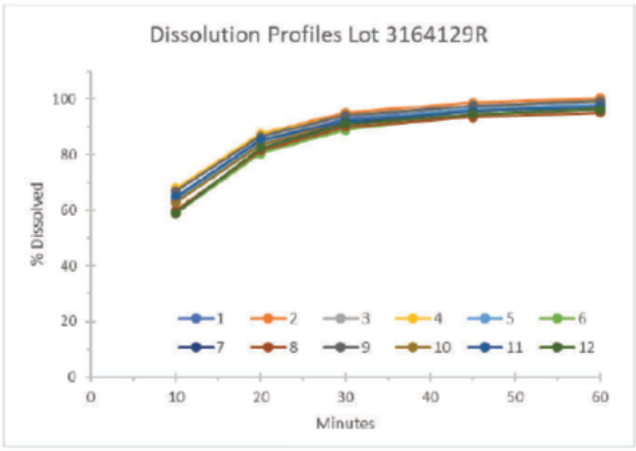
Lot 3164987R (TBM)	
Lot 3164988R (TBM)	

Figure 11. Dissolution data for Tenapanor Tablets, 30 mg used in clinical studies (TEN-02-106 and TEN-02-201) and of registration batches (TBM).

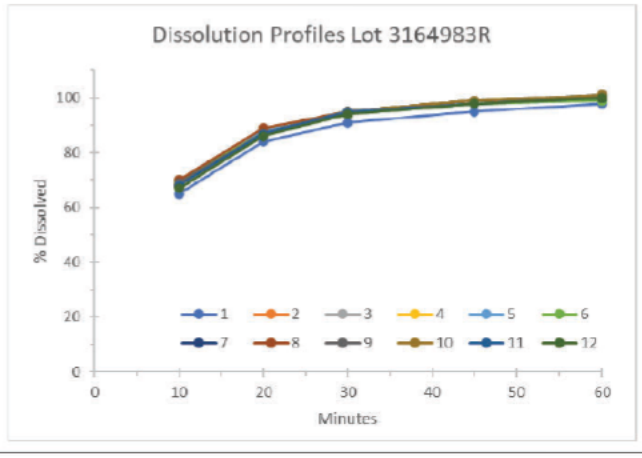
Lot 3164129R (TEN-02-106)	

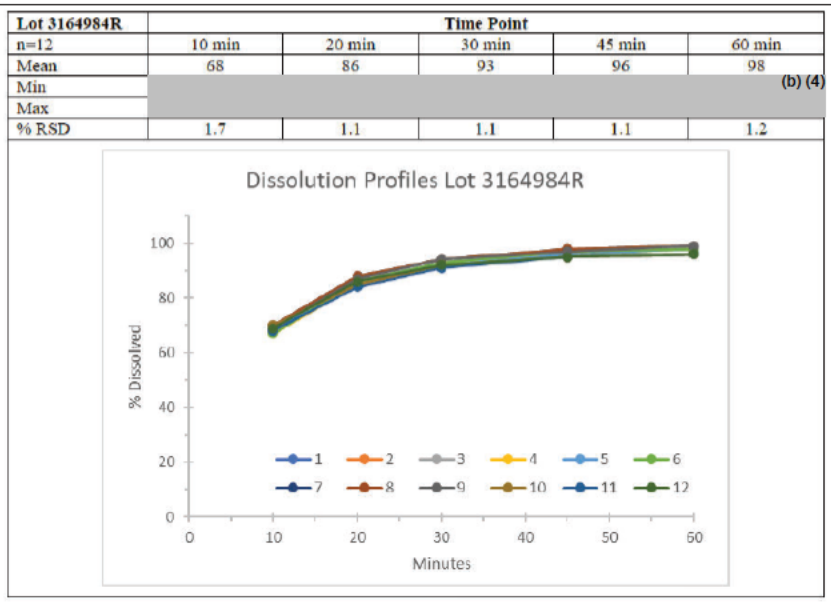
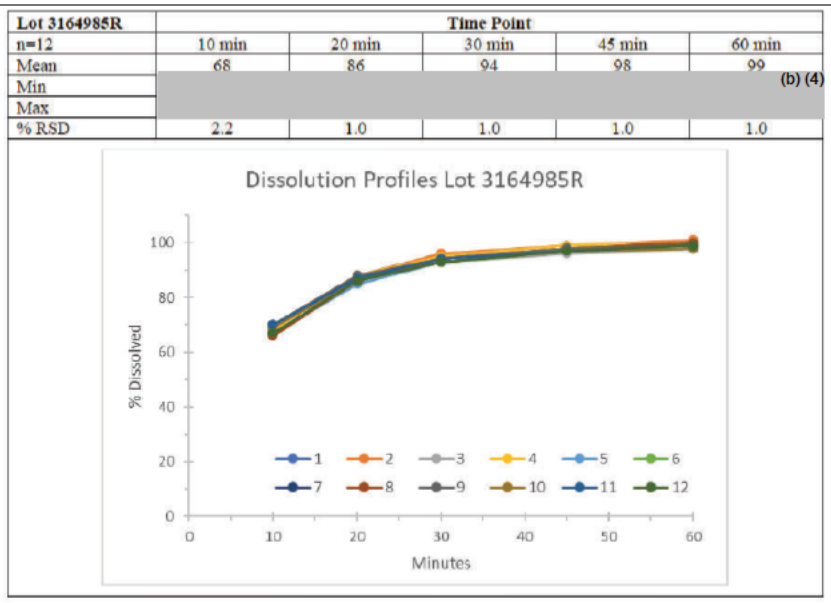
Lot 3164129R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	64	84	92	96	98
Min	(b) (4)				
Max					
% RSD	4.8	2.7	2.0	1.7	1.6



Lot 3164983R (TBM)	

Lot 3164983R	Time Point				
n=12	10 min	20 min	30 min	45 min	60 min
Mean	68	87	94	98	100
Min	(b) (4)				
Max					
% RSD	1.7	1.4	1.1	1.0	0.9



Lot 3164984R (TBM)	
Lot 3164985R (TBM)	

Assessment: {*Adequate*}

To support the proposed dissolution acceptance criterion, complete dissolution profiles and detailed information for the clinical and registration (TBM) batches as well as batches used in method development studies were requested via the IR dated 12/01/2020. In the Applicant's response to the IR date 12/15/2020, the Applicant provided complete dissolution profiles and information for the batches. Based on the dissolution data of the clinical and registration batches, the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 min is adequate given that Tenapanor is locally-acting and minimally absorbed in GI tract.

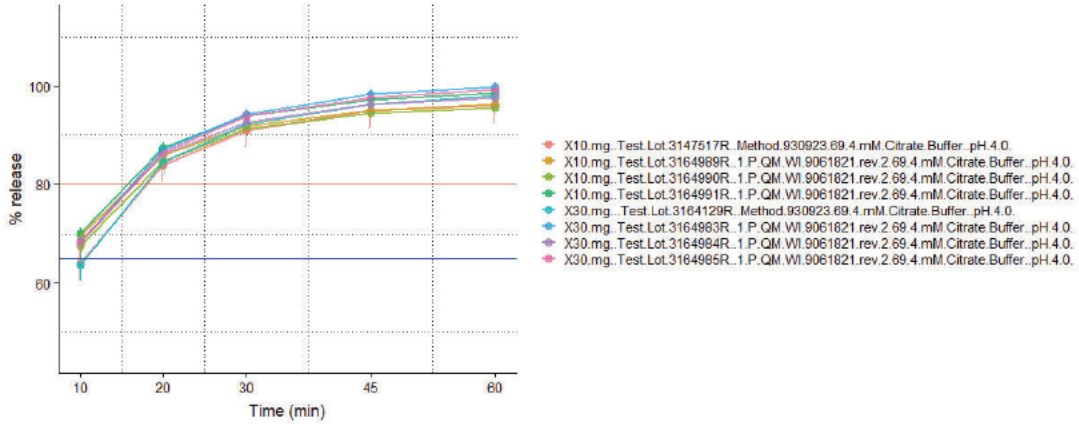
B.5 BRIDGING OF FORMULATIONS

It is noted that the tablets representative of TBM formulation used in the clinical studies (Phase 3 TEN-02-301; and Phase 1 in vivo BE study TEN-02-106; 10mg - 3147517R, 3166400R; 30mg - 3164129R) are plain faced; whereas, the TBM/registration batch tablets (10mg - 3164989R, 3164990R, 3164991R; 30mg - 3164983R, 3164984R, 3164985R) are debossed.

Assessment: ***{*****Adequate*****}***

Comparative dissolution profiles (using the proposed QC method) of batches used in the above clinical trials (plain faced) and TBM/registration (debossed) batches indicate similarity (Figure 12) and supports the inclusion of debossing for TBM/commercial product.

Figure 12. Dissolution profiles of Tenapanor 10 mg and 30 mg tablets used in TEN-02-301 and TEN-02-106 vs TBM/registration 10 mg and 30 mg tablets.



B.6 BIOWAIVER REQUEST

The Applicant has requested biowaiver for 20 mg strength tablets and is relying on the in vivo BE study (TEN-02-106) based on PD end point conducted using 10 mg and 30 mg strength.[3] It is noted that 20mg dose was evaluated in phase 3 TEN-02-301 study using 2 units of 10 mg strength.

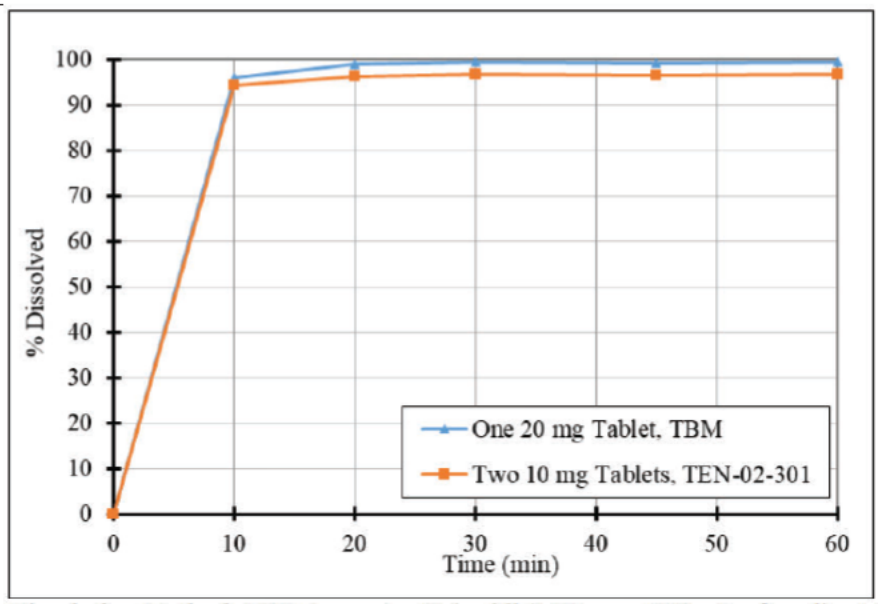
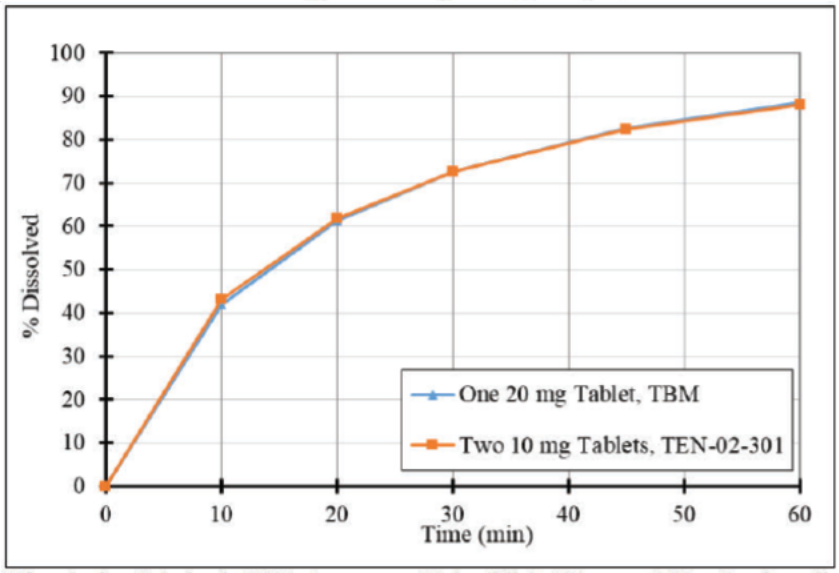
The composition of Tenapanor tablets (10 mg and 30 mg) used in Phase 2b/3 (TEN-02-201) clinical study is dissimilar to the formulations used in Phase 3 (TEN-02-301; representative of TBM formulation) clinical study due to the difference in drug load and quantitative differences in multiple inactive ingredients (Table 3 and

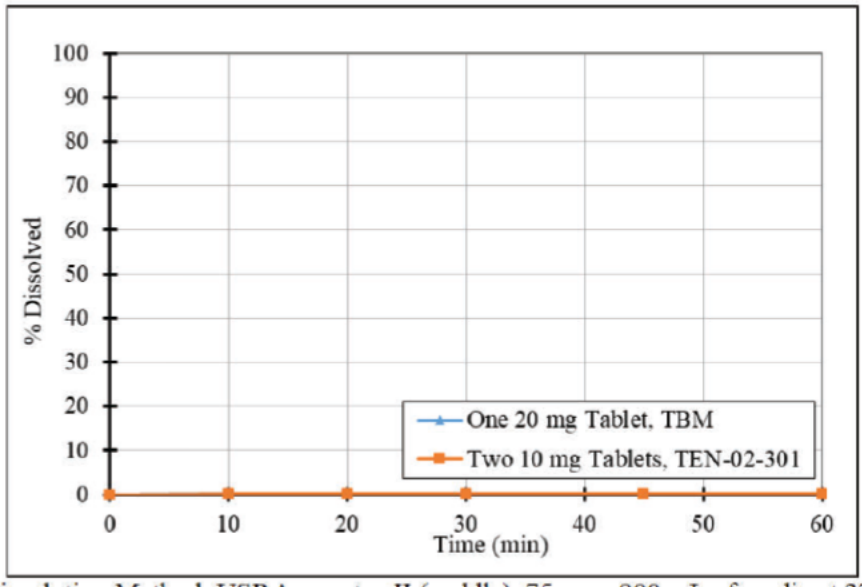
[3] \\CDSESUB1\evsprod\nda213931\0001\m1\us\waiver-req.pdf

4). Also, the tablets used in the first pivotal Phase 3 clinical study (TEN-02-201; 10 mg and 30 mg) were manufactured [redacted]; while, the TBM formulation tablets used in second pivotal phase 3 clinical study (TEN-02-301; 10 mg) and registration batches were manufactured at the proposed commercial manufacturing site, [redacted]. The bridge between these two formulations and manufacturing site is based on in vivo BE study (PD endpoint study based on sodium, phosphorus and creatinine levels in urine; TEN-02-106) evaluating 10mg and 30mg strength. The Applicant conducted dissolution studies at multimedia (pH 1.0, 4.5, and 6.8) to further support comparability between the Phase 2b/3 and Phase 3 clinical study tablets (10 mg and 30 mg). The evaluation (primary and secondary PD endpoints) from the BE study (TEN-02-106) comparing the 10 mg tablets used in TEN-02-201 (phase 2b/3 formulation) vs TEN-02-301 (TBM formulation)) and the 30 mg tablets used in TEN-02-201 (phase 3 formulation) vs TBM tablets indicated that there is no in vivo difference between the phase 3 and TBM tablets. The Applicant included in vitro bridging study results of TBM tablets (20 mg strength) and 2 units of TBM 10 mg tablets since the comparability of the tablets used in clinical studies and TBM tablets (10 mg and 30 mg) was found adequate based on the in vivo BE study evaluating urine sodium/phosphorus/creatine PD endpoints and plasma PK profiles of Tenapanor metabolite, AZ13792925). The TBM 20 mg tablets are compositionally proportional to the TBM 10 mg and 30 mg tablets (Table 4).

The TBM tablets across strengths (exhibit/registration batches) are operated and controlled at a single manufacturing site [redacted]. Dissolution comparison studies at multimedia (pH 1.0, 4.5, and 6.8) using TBM 20 mg and 2 units of TBM 10 mg tablets showed that the dissolution profiles of the tablets (1x20 mg vs 2x10 mg) are similar under different pH conditions as show in Figure 13.

Figure 13. Dissolution profiles of TBM Tenapanor tablets 20 mg and 2 x 10 mg of TBM (TEN-02-301 20 mg dose) in multimedia.

pH 1.0 (0.1N HCl)	 Dissolution Method: USP Apparatus II (paddle), 75 rpm, 900 mL of media at 37°C
pH 4.5 (50 mM Citrate buffer)	 Dissolution Method: USP Apparatus II (paddle), 75 rpm, 900 mL of media at 37

pH 6.8 (50 mM Potassium phosphate buffer)	 Dissolution Method: USP Apparatus II (paddle), 75 rpm, 900 mL of media at 37°C

Assessment: ***{*****Adequate*****}***

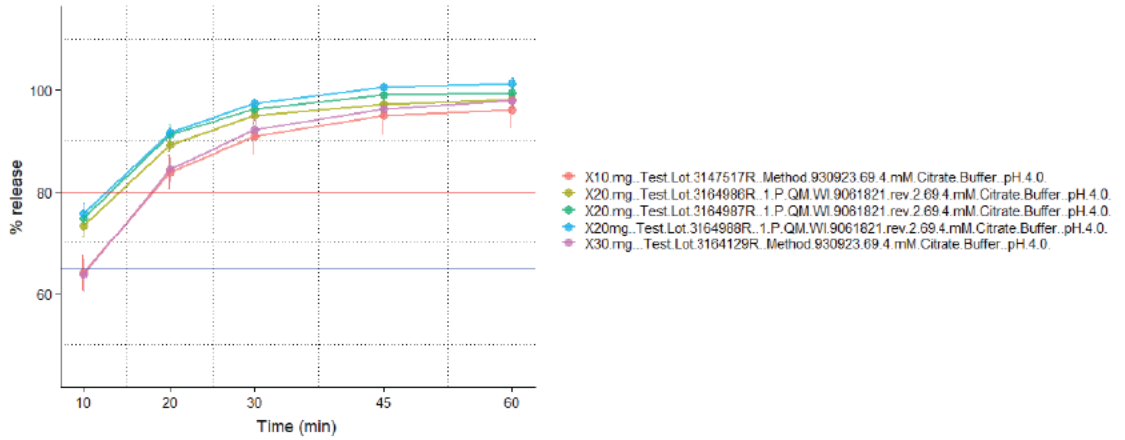
Biowavier request for 20 mg strength is granted based on the following:

1) Demonstration of bioequivalence for phase 2b/3 versus phase 3/TBM formulation for both 10 mg and 30 mg strengths. On communication with the OCP reviewer, it was confirmed that phase 2b/3 formulation and phase 3/TBM formulation for both 10 mg and 30 mg strengths were bioequivalent.

2) All three strengths are compositionally proportional.

3) In vitro dissolution similarity (proposed dissolution method) of 20 mg registration batches when compared to 10 mg (3147517R) and 30 mg (3164129R) TBM formulation used in TEN-02-106 (Figure 14). It is noted that all batches in Figure 14 meet the dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 min.

Figure 14. Dissolution profiles of Tenapanor 10 mg and 30 mg tablets used in TEN-02-301 and TEN-02-106 vs TBM/registration 20 mg tablets.



Overall, the provided clinical performance based on outcome of the BE study and in vitro dissolution results support a biowaiver for TBM 20 mg formulation, and hence the biowaiver is found adequate.

R. REGIONAL INFORMATION

Comparability Protocols: N/A

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

Min Sung Suh

Digitally signed by Min Sung Suh
Date: 3/15/2021 04:11:17PM
GUID: 5d418e82002882e44eb53342e324cad8

Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 3/15/2021 04:26:03PM
GUID: 5388edae000671a12787e2fcf4cde1bb

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

/s/

MOHAN K SAPRU
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