CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215559Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215559 Resubmission		
Applicant Name	Ipsen Pharmaceuticals Inc.		
Drug Product Name	Sohonos (palovarotene) capsules		
Dosage Form.	Capsule		
Proposed Strength(s)	1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg		
Route of Administration	Oral		
Maximum Daily Dose	20 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the prevention of heterotopic ossification in adults and children (aged 8 years and above for females, and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressiva (FOP)		
Drug Product Description	Opaque white elongated size “0” hard-gelatin capsule containing white to off-white powder to be available in 5 strengths and imprints. Tablets are packaged in 14ct blister card.		
Co-packaged product information	Not applicable		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20 °C to 25 °C with excursions permitted between 15 °C to 30 °C. protect from light.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joesph Leginus	Suong Tran
	Drug Product/ Labeling	Ali Mohamadi	Akm Khairuzzaman

	Manufacturing	Xueli Zhu	Erin Kim
	Biopharmaceutics	Parnali Chatterjee	Haritha Mandula
	Microbiology	NA	NA
	Other (specify):	Caryn McNab	
	RBPM	Nowrin Kakon	
	ATL	Muthukumar Ramaswamy	
Consults	Pharm./Toxicology: Dave Carlson/Lydia Halie		

2. Final Overall Recommendation - Approval

3. Action Letter Information:

Expiration Dating: An expiry dating period of 36 months is granted when the drug product is stored at 20°C to 25°C; excursions permitted to 15°C to 30°C.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality Review team has assessed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 215559 original submission and resubmission and determined that the NDA meets applicable standards to support the quality and purity of the drug product. As such, OPQ recommends approval of this NDA from a quality perspective.

Background. The original submission for NDA 215559 was filed initially on March 31, 2021, withdrawn later, on August 12, 2021, and was resubmitted on April 29, 2022. OPQ review determined that the NDA meets the applicable standards to support the quality, and purity of the drug product. OPQ review team recommends approval of this NDA from a quality perspective. However, the NDA received complete response action on December 23, 2022, due clinical

issues. The applicant resubmitted the NDA on February 16, 2023, with no CMC updates to Module 3 of the NDA submission. Labeling review was completed during previous cycle. The OPQ recommendation for the current cycle is approval based on previous cycle CMC reviews and the acceptable status of the manufacturing facilities listed in the application in Panorama on 7/13/2023.

(b) (4)

[redacted]

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	**-**	**N/A**

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

Muthukumar Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 7/14/2023 10:07:07AM
GUID: 508da7210002a0c0870017f6c83398f4

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/

MUTHUKUMAR RAMASWAMY
07/14/2023 10:34:35 AM
OPQ recommends approval of this application. See also previous OPQ IQA dated 9/26/2022 in DARRTS

NDA Executive Summary

1. Application/Product Information

NDA Number.	215559
Applicant Name	Ipsen Biopharmaceuticals, Inc.
Drug Product Name	SOHONOS (palovarotene) capsules
Dosage Form.	Capsule
Proposed Strength(s)	1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg
Route of Administration	Oral
Maximum Daily Dose	20 mg
Rx/OTC Dispensed	Rx
Proposed Indication	For the prevention of heterotopic ossification in adults and children (aged 8 years and above for females, and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressiva (FOP)
Drug Product Description	Opaque white elongated hard-gelatin capsule. SOHONOS is available in size “0”capsule, containing white to off-white powder. Following table shows capsules’ strengths and imprints.
Co-packaged product information	Not Applicable (N/A)
Device information:	N/A
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

Strength (mg)	Imprint
1	PVO 1
1.5	PVO 1.5
2.5	PVO 2.5
5	PVO 5
10	PVO 10

Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joseph Leginus	Suong (Su) Tran
	Drug Product/ Labeling	Ali Mohamadi	Akm Khairuzzaman
	Manufacturing	Xueli Zhu	Erin Kim
	Biopharmaceutics	Parnali Chatterjee	Haritha Mandula
	Microbiology	None	
	Other (specify):	Caryn McNab (ORA)	
	RBPM	Nowrin Kakon	
	ATL	Akm Khairuzzaman	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiry dating period of 36 months is granted when the drug product is stored at 20°C to 25°C (68° F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. **Conclusion**: The Office of Pharmaceutical Quality Review team has assessed NDA 215559 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that the drug product

purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2. **Background**: The original submission for NDA 215559 was filed on May 30, 2021, and withdrawn later on August 12, 2021. The NDA was resubmitted on April 29, 2022.
3. **Summary of the resolution of deficiencies and the review for each OPQ discipline:**
   I. **Drug substance:** The Palovarotene drug substance is a new chemical entity. It is a poorly soluble achiral compound with a molecular formula of $C_{27}H_{30}N_2O_2$ and a molecular weight of 414.5 g/mol. It is manufactured as a single crystalline form (b) (4) . The review confirmed the identity of the drug substance based on IR, ^{1}H and ^{13}C NMR, MS, UV, elemental analysis and XRPD data. The review also assessed starting material design, manufacturing process, in process controls, characterization, impurities, and physicochemical properties as adequate to support the quality of the drug substance. The drug substance specification includes appropriate tests and acceptance criteria to support the identity, strength, purity, and quality of the drug substance. Related substances are limited at levels recommended in ICH Q3A except for (b) (4) , which is proposed at a limit of ≤ (b) (4) %. This limit has been determined to be reasonable by the Pharm/Tox review team. Solvents used during the manufacturing process are controlled as per the ICH Q3C Guidelines. The risks associated with potential genotoxic impurities in the drug substance were assessed following ICH M7 and were determined to be extremely low. A retest date of (b) (4) months is granted for palovarotene drug substance when stored at (b) (4)

   II. **Drug Product:** The drug product is an immediate release capsule composed of the drug substance and inactive ingredient such as croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The hard gelatin capsule (size 0) is composed of titanium dioxide (b) (4) and gelatin (b) (4) . The formulation contains no phthalates. The drug product was assessed with respect to its critical quality attributes and risks associated with drug product formulation, specification for quality control, stability for shelf-life determination, impurities, packaging, and compatibility with soft food for pediatric patient population. The review assessed the physicochemical risks to the drug product such as possible degradation during manufacturing and product shelf life,

source of impurities in the drug product, and compatibility with soft food. Absence of drug product compatibility data with soft food, and risk of [redacted] (b) (4) impurity were identified during the review cycle. These issues were satisfactorily addressed by the Applicant. Labeling was revised as follows: *"SOHONOS may be swallowed whole, or capsules may be opened, and the contents emptied onto a teaspoon of soft food and taken within 1 hour of opening provided it was maintained at room temperature and not exposed to direct sunlight".* The drug product specification included acceptable tests and acceptance criteria to assure the identity, strength, purity, and quality of all strengths of the drug product. Analytical method validations for all tests are found to be acceptable. The shelf-life of 36 months is supported based on 36 months of long-term, 36 months of intermediate and 6 months of accelerated stability data. Photostability study shows that the drug product is sensitive to light. Therefore, appropriate instruction on container closure has been added. Finally, the in-use stability results show that drug product stays within the specification when blisters are exposed for 10 minutes to fluorescent light for 28 consecutive days.

III. **Quality labeling:** The quality aspects of the labeling were reviewed and found to be adequate.

IV. **Manufacturing:** *Process*: Manufacturing process utilizes [redacted] (b) (4) [redacted] (b) (4) [redacted] The review assessed the critical manufacturing unit operation that can possibly impact the critical quality attributes of the drug product, risk assessment, process parameters, in-process control, sampling, executed master batch records, packaging, and manufacturability (i.e., yield and reconciliation). The reviewer identified absence of certain critical manufacturing information such as reconciliation data for each manufacturing unit operation, in-process controls for [redacted] (b) (4). These issues were satisfactorily resolved during the review cycle. Based on manufacturing knowledge gained with the experimental batch and historical data from the clinical batches, the Applicant has adequately established a viable commercial manufacturing process with acceptable operational targets and ranges for process parameters. *Facilities*: All facilities were found to be acceptable based on previous inspection history.

V. **Biopharmaceutics**: The biopharmaceutics review focused on the acceptability of the in vitro dissolution test method and acceptance criteria. No biowaiver for lower strengths of the drug product was requested as clinical and TBM (to be marketed) drug product batches were administered in various clinical safety/pharmacokinetic studies.

[redacted]

Bridging of clinical and TBM drug products manufactured at different manufacturing sites is supported by pharmacokinetic (PK) data in healthy and FOP patient population that were assessed by the Office of Clinical Pharmacology (OCP). In response to several information requests, the Applicant provided adequate justification for the final test method parameters and acceptance criteria, as well as data to support the discriminating power of the method with respect to variations in manufacturing and drug substance particle size variation. Because the drug is a BCS class II compound, the Applicant Team Lead (ATL) initiated a discussion between the OPQ sub discipline reviewers regarding the acceptability of the drug substance particle size distribution (PSD) limit and its possible impact on bioavailability. Both the biopharmaceutics and drug substances reviewers agreed with the Applicant's proposed PSD limit of D_{90}-NMT (b) (4) µm for the drug substance specification.

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	**-**	**N/A**

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: Palovarotene is a BCS class II drug. Therefore, any change in the drug substance particle size distribution and polymorphism may require appropriate bridging to establish bioequivalence and a prior approval supplement (PAS).

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	SOHONOS (palovarotene) capsules
Route(s) of administration	Adequate	oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral 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.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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)	Adequate	**Adequate per recommendation below**: Take SOHONOS with food preferably at the same time each day. SOHONOS may be swallowed whole, or capsules may be opened, and the contents emptied onto a teaspoon of soft food and taken within 1 hour of opening provided it was maintained at room temperature and not exposed to direct sunlight.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	**Adequate per CMC recommendation below:** SOHONOS capsules can be used with soft foods if you (a) open the capsules and mix the capsule content with a teaspoon of soft food immediately, (b) keep the mixture at room temperature, (c) protect the mixture from direct sunlight, and (d) take the mixture within 1 hour of opening the capsules.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be	N/A	

applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

<table>
<tr><th>Item</th><th>Items in Proposed Labeling
(choose “Adequate”, “Inadequate”, or “N/A”)</th><th>Assessor’s Comments
(If an item is Inadequate, provide more details on the issues, as appropriate)</th></tr>
<tr><td colspan="3">DOSAGE FORMS AND STRENGTHS section</td></tr>
<tr><td>Available dosage form(s)</td><td>Adequate</td><td>Capsule</td></tr>
<tr><td>Strength(s) in metric system</td><td>Adequate</td><td>Adequate per a CMC recommendation below:

SOHONOS is an opaque white elongated hard-gelatin capsule. SOHONOS is available in size “0”capsule, containing white to off-white powder. Table 3 shows capsules’ strengths and imprints.

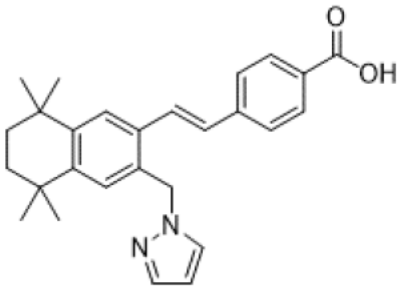
Table 3. SOHONOS capsules’ strengths and imprints.
<table>
<tr><td>Strength (mg)</td><td>Imprint</td></tr>
<tr><td>1</td><td>PVO 1</td></tr>
<tr><td>1.5</td><td>PVO 1.5</td></tr>
<tr><td>2.5</td><td>PVO 2.5</td></tr>
<tr><td>5</td><td>PVO 5</td></tr>
<tr><td>10</td><td>PVO 10</td></tr>
</table>
</td></tr>
<tr><td>If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).</td><td>N/A</td><td></td></tr>
<tr><td>A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable</td><td>Adequate</td><td>See the CMC recommendation above</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”</td><td>N/A</td><td></td></tr>
</table>

For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate," "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	SOHONOS and Palovarotene
Dosage form(s) and route(s) of administration	Adequate	Capsule for oral use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	**Adequate per CMC revision below:** Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Povidone, and Sodium Lauryl Sulfate. The black printing ink consists of black iron oxide, (b) (4) potassium hydroxide, propylene glycol, (b) (4) Shellac, (b) (4)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	retinoic acid receptor gamma (RARγ) selective agonist

Chemical name, structural formula, molecular weight	Adequate	4-[(E)-2-(5,5,8,8-tetramethyl-3-pyrazol-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid with an empirical formula of C27H30N2O2 and has a molecular weight of 414.54 g/mol. 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate," or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

<table>
<tr><th>Item</th><th>Items in Proposed Labeling
(choose “Adequate,” “Inadequate”, or “N/A”)</th><th>Assessor’s Comments
(If an item is Inadequate, provide more details on the issues, as appropriate)</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>Adequate</td><td>Capsule</td></tr>
<tr><td>Strength(s) in metric system</td><td>Adequate</td><td>Adequate per recommendation below:

<table><tr><th>Strength (mg)</th><th>Imprint</th><th>NDC</th></tr><tr><td>1</td><td>PVO 1</td><td>15054-0010-1</td></tr><tr><td>1.5</td><td>PVO 1.5</td><td>15054-0015-1</td></tr><tr><td>2.5</td><td>PVO 2.5</td><td>15054-0025-1</td></tr><tr><td>5</td><td>PVO 5</td><td>15054-0050-1</td></tr><tr><td>10</td><td>PVO 10</td><td>15054-0100-1</td></tr></table></td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>Adequate</td><td>blister strip containing 14 capsules</td></tr>
<tr><td>Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)</td><td>Adequate</td><td>Adequate per recommendation below:

an opaque white elongated hard-gelatin capsule</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”</td><td>N/A</td><td></td></tr>
<tr><td>For injectable drug products for parenteral 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.</td><td>N/A</td><td></td></tr>
</table>

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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	**Adequate per CMC recommendation below:** SOHONOS must be kept in the original carton to protect from light

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

Item	**Items in Proposed Labeling** (choose "Adequate," "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room temperature].
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."*	N/A	
Include information about child-resistant packaging	Adequate	This package is child-resistant

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate," "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Distributed by: Ipsen Biopharmaceuticals, Inc. Cambridge, MA; 02142.

2.0 PATIENT LABELING

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

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate," "Inadequate", or "N/A")	Assessor's Comments about Medication Guide Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	SOHONOSTM [so-ho-nos] (palovarotene capsules)
Special preparation instructions (if applicable)	Adequate	(b) (4) [redacted]
Storage and handling information (if applicable)	Adequate	Store SOHONOS at room temperature 68° to 77°F (20° to 25°C); excursions permitted to 15° to 30°C (59° to 86°F). **Adequate per recommendation below:** SOHONOS must be kept in the original carton to protect from light
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	palovarotene

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Alphabetical listing of inactive ingredients (if applicable)	Adequate	**Adequate per recommendation below:** Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Povidone, and Sodium Lauryl Sulfate. The black printing ink consists of black iron oxide, (b) (4) potassium hydroxide, propylene glycol, (b) (4) Shellac, (b) (4)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: Ipsen Biopharmaceuticals, Inc. Cambridge, MA; 02142. For more information about SOHONOS, call 855-463-5127 or go to www.SOHONOS.com.

3.0 CONTAINER AND CARTON LABELING

(1.5 mg strength is used as an representative of other strengths)

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate," or "N/A")	Assessor's Comments about Container & Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	1, 1.5, 2.5, 5, and 10 mg
Route(s) of administration	Adequate	**Adequate per recommendation below:** For oral use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	14 capsules
"Rx only" displayed on the principal display	Adequate	(b) (4)
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	**Adequate per recommendation:** SOHONOS must be kept in the original carton to protect from light
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Name of manufacturer/distributor /packer	Adequate	(b) (4) Ipsen Biopharmaceuticals, Inc. One Main Street 7th Floor Cambridge, MA, 02142, USA **Adequate per recommendation below (to be consistent with PI):** Use "distributed by" (b) (4)
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others, if space is available.	Adequate	(b) (4) **Adequate per recommendation below:** In the blister label, use prescribing information instead of package insert

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Overall Assessment and Recommendation:

The labeling is adequate from CMC perspective if the Applicant revises the label per recommendations stated in this review and IRs below:

(a) Use "SOHONOS must be kept in the original carton to protect from light". Instead of "protect from light".
(b) Add the inactive ingredients: Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Povidone, and Sodium Lauryl Sulfate.
(c) Add ink composition: The black printing ink consists of black iron oxide, (b) (4) potassium hydroxide, propylene glycol, (b) (4) Shellac, (b) (4)
(d) Add route of administration: "For oral use".
(e) Use "Distributed by" (b) (4)
(f) In the blister label, use "prescribing information" instead of "package insert"

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 9/12/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed): Akm Khairuzzaman, Ph.D., 9/13/2022

Ali Mohamadi

Digitally signed by Ali Mohamadi
Date: 9/14/2022 04:41:25PM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 9/14/2022 04:49:56PM
GUID: 502d1ab500002aef5afaa6f74ddf7e69

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Office of Pharmaceutical Quality

New Drug Application (NDA)

Integrated Quality Assessment Template

CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	Immediate-Release Hard Gelatin Capsule Product
NDA Number	215559
Assessment Cycle Number	ORIG-1-Resub 29
Drug Product Name/ Strength	Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg
Route of Administration	Oral
Applicant Name	Ipsen Biopharmaceuticals, Inc.
Therapeutic Classification/ OND Division	OCHEN/DGE
Proposed Indication	For prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressive (FOP)

Assessment Recommendation: **Adequate**

Assessment Summary:

Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg is an immediate-release capsule product that contains palovarotene, a pH-dependent, low soluble drug substance. The label claim of Sohonos™ (palovarotene capsules) for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia (b) (4) ossificans progressive (FOP) is supported by a pivotal Phase 2 clinical study, PVO-1A-201 in FOP patients. The safety, efficacy, and pharmacokinetics of Sohonos™ (palovarotene capsules) is supported by numerous Phase 2 and Phase 3 clinical studies.

In the original submission, dissolution of each strength of the drug product was initially conducted using a dissolution method that included (b) (4) With changes in the drug product manufacturer, the originally proposed dissolution method was optimized [*USP Apparatus 2 (paddle with spiral sinkers) at 50 rpm in 900 mL 5 mM phosphate buffer, pH 8.0 containing 0.5% SLS at 37°C*].

The newly proposed QC method demonstrated limited discriminating ability with respect to the particle size distribution (PSD) of the drug substance. The 1 mg and 2.5 mg strengths of the TBM registration batches (b) (4) demonstrated >85% dissolution in 30 minutes at release using the proposed QC

method. To mitigate dissolution failures of the drug product, PSD of the drug substance is controlled at D_{90} NMT (b) (4) µm in the drug product and (b) (4) (b) (4) that ensures rapid dissolution (>85% dissolution in 30 minutes) using the QC dissolution method. Based on the totality of the dissolution data, the QC dissolution method was deemed adequate for dissolution testing of the drug product in the original submission.

During review of the original submission, sufficient batch release data was not provided for 1.5 mg, 5 mg and 10 mg strengths of the drug product using the QC dissolution method. The dissolution acceptance criterion '*NLT (b) (4)% (Q) in 30 minutes*' was implemented on an interim basis. Further, high within-batch variability in dissolution data was observed at 30 minutes for each strength of the drug product on stability beyond 12 months. The understanding on the high data variability on stability with respect to the product quality and in vivo performance was not provided in the submission.

The Applicant was requested to provide complete dissolution data for all strengths of the drug product at the time of batch release for process validation batches. Additionally, the Applicant was requested to investigate the root-cause for high variability in dissolution data on stability and provide mitigating solutions for deficiencies conveyed to acknowledge withdrawal of the original NDA submission (dated 08/12/2021).

In the current Resubmission-29, the Applicant provided complete dissolution profile data for each strength of the process validation batches that demonstrate >85% dissolution in 15 minutes. Based on the overall dissolution data of the clinical and process validation batches at release, dissolution acceptance criterion for Sohonos™ (palovarotene capsules) was finalized as '*NLT (b) (4)% (Q) in 30 minutes*'.

Bridging of clinical and TBM drug products manufactured at different manufacturing sites is supported by pharmacokinetic (PK) data in healthy and FOP patient population that is assessed by the Office of Clinical Pharmacology (OCP). No biowaiver for lower strengths of the drug product is requested as clinical and TBM drug product batches were administered in various clinical safety/pharmacokinetic studies.

Taking into consideration the overall dissolution data, the risk of dissolution failures from Biopharmaceutics perspective is considered 'medium'.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Dissolution Method and	Medium	Dissolution data for the batches on stability using	Medium	High within-batch variability in dissolution data observed for some batches of the drug

Acceptance Criterion		QC dissolution method		product at release and on long-term stability for up to 36 months at early sampling time-points of 5 min and/or 10 min, but not at 15 min and 30 min. The Firm was recommended to implement Tier II testing for scenarios when downward trend in dissolution data is observed on stability.

Final Dissolution Method and Acceptance Criterion

Apparatus	Rotation Speed (rpm)	Medium/ml Temperature (°C)	Acceptance Criterion	
			Time (min)	Percent (%)
Apparatus 2 (paddle with 6 spiral stainless-steel sinkers)	50 rpm	900 mL 5 mM phosphate buffer, pH 8.0 containing 0.5% sodium lauryl sulfate at 37°C	30 minutes	NLT(b) (4)%

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original submission NDA 215559 (\\CDSESUB1\evsprod\nda215559\0001\m2\27-clin-sum\summary-biopharm.pdf)	03/31/2021
Final Meeting Minutes IND 120181 (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804e2971)	03/08/2019
Response to Information Request #1 (dated 04/30/2021) (\\CDSESUB1\evsprod\nda215559\0003\m1\us\111-info-amend\20210430-rtq-fda.pdf)	05/05/2021
Response to Information Request #2 (dated 05/05/2021) (\\CDSESUB1\evsprod\nda215559\0004\m1\us\111-info-amend\20210505-rtq-fda.pdf)	05/10/2021
Response to Information Request #3 (dated 05/20/2021) (\\CDSESUB1\evsprod\nda215559\0009\m1\us\111-info-amend\20210520-rtq-fda.pdf)	06/04/2021
Response to Information Request #4 (dated 06/30/2021) (\\CDSESUB1\evsprod\nda215559\0016\m1\us\111-info-amend\response-biopharmaceutic.pdf)	07/09/2021
Response to Information Request #5 (dated 07/14/2021) (\\CDSESUB1\evsprod\nda215559\0019\m1\us\111-info-amend\response-fda-20210714-biopharmaceutic.pdf)	07/19/2021
Request to withdraw the original NDA submission (\\CDSESUB1\evsprod\nda215559\0028\m1\us\12-cover-letter\cover-letter-0028.pdf)	08/12/2021
Resubmission of NDA 215559 (\\CDSESUB1\evsprod\nda215559\0029\m1\us\12-cover-letter\cover-letter-0029.pdf)	04/29/2022
Response to Information Request #6 (dated 05/27/2022) (\\CDSESUB1\evsprod\nda215559\0033\m1\us\111-info-amend\response-fda-220527-ir.pdf)	06/02/2022

Highlight Key Issues from Last Cycle and Their Resolution:

Key Issues in the Original Submission:

1. In the original submission, sufficient batch release data was not provided for 1.5 mg, 5 mg and 10 mg strengths of the drug product using the QC dissolution method. The Applicant was requested to provide complete dissolution data for all strengths of the drug product at the time of batch release for process validation batches.

2. An interim dissolution acceptance criterion '*NLT* (b) (4) *% (Q) in 30 minutes*' was recommended for each strength of the proposed drug product.
3. Further, high within-batch variability in dissolution data was observed at early time-points for each strength of the drug product on stability beyond 12 months.
4. The understanding on the high data variability on stability with respect to the product quality and in vivo performance was not provided in the submission. The Applicant was requested to investigate the root-cause for high variability in dissolution data on stability and provide mitigating solutions for deficiencies conveyed to acknowledge withdrawal of the original NDA submission (dated 08/12/2021).

Resolution of Issues in the Original Submission:

1. In the Resub-29, complete dissolution profile data were provided for each strength of the process validation batches at release. All strengths of the process validation batches demonstrate >85% dissolution in 15 minutes and would meet the recommended acceptance criterion '*NLT* (b) (4) *% (Q) in 30 minutes*'.

2. High within-batch variability in dissolution data is observed at early sampling time-points of 5 min and/or 10 min, but not at 15 min and 30 min for some registration and process validation batches of the drug product at release and on long-term stability for up to 36 months. The Firm was recommended to implement Tier II testing for scenarios when downward trend in dissolution data is observed on stability.

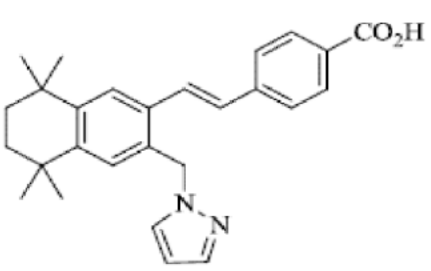
B.1 BCS DESIGNATION

Assessment: BCS II/IV

The current submission does not include an official request for BCS designation for palovarotene drug substance or palovarotene capsule drug product. However, based on the solubility, in vitro permeability (PAMPA) data, and in vivo ADME study, the Applicant classified palovarotene as a BCS Class II drug substance.

Palovarotene ($C_{27}H_{30}N_2O_2$; molecular weight 414.54 g/mole) is a white, (b) (4) crystalline (b) (4) achiral, non-hygroscopic drug substance (see **Figure 1**). Palovarotene is a weakly acidic, low solubility drug substance that demonstrates a pKa= 4.31 and a LogP=6.80.

Figure 1. Chemical structure of palovarotene



Solubility:

Equilibrium solubility of palovarotene was determined in buffer solutions across the physiological pH range 2.0-7.0. The drug substance demonstrates pH-dependent low solubility profile with highest solubility (2.2 mcg/mL) in buffer solution, pH 8.0 (see **Table 1a**).

In fasted state simulated gastric fluid (FaSSGF), pH 1.6, palovarotene demonstrates higher solubility (21.4 mcg/mL) as compared to 0.01N HCl (see **Table 1a** and **Table 1c**). Higher solubility is also observed in fasted state simulated intestinal fluid (FaSSIF, pH 5.0) as compared to 0.01M phosphate acetate, pH 5.0-pH 7.0.

Overall, the highest dose of the drug substance, i.e., 20 mg is not soluble in 250 mL buffer solutions, pH 2.0-7.0 or in bio-relevant buffers (see **Table 1a, Table 1b,** and **Table 1c**). Therefore, palovarotene can be categorized as a low solubility drug substance per BCS.

Table 1a. Equilibrium solubility of palovarotene drug substance in buffer solutions, pH 2.0-7.0

Buffer	Solubility (µg/mL)	USP/Ph.Eur Solubility
0.01M Hydrochloric Acid, pH 2.0	Not detected	Practically insoluble or insoluble
0.01M Potassium Acetate, pH 4.0	Not detected	Practically insoluble or insoluble
0.01M Potassium Acetate, pH 5.0	0.006	Practically insoluble or insoluble
0.01M Potassium Acetate, pH 6.0	0.04	Practically insoluble or insoluble
0.01M Potassium Phosphate Monobasic, pH 7.0	0.2	Practically insoluble or insoluble
0.01M Potassium Phosphate Monobasic, pH 8.0	1.8	Practically insoluble or insoluble

Table 1b. Kinetic solubility of palovarotene drug substance in buffer solutions, pH 2.0-7.0 for up to 6 days

Solvents	Day 1 (µg/mL)	Day 4 (µg/mL)	Day 6 (µg/mL)	Average (µg/mL)
pH 2.0	ND	ND	0.0015	N/A
pH 4.0	ND	ND	0.0013	N/A
pH 5.0	0.009	0.006	0.0018	0.0056
pH 6.0	0.0468	0.0384	0.0035	0.0396
pH 7.0	0.2296	0.1594	0.1899	0.1930
pH 8.0	2.228	1.5404	1.6233	1.7972

ND = not detected, N/A = not applicable

Table 1c. Solubility of palovarotene drug substance in bio-relevant buffers for up to 6 days

Biorelevant buffer	**Solubility** (mcg/mL)
Fasted state simulated gastric fluid (FaSSGF), pH 1.6 for 3 hours	21.4 mcg/mL
Fed state simulated intestinal fluid (FeSSIF), pH 5 for 5 hours	2.4 mcg/mL
Fasted state simulated intestinal fluid (FaSSGF), pH 6.5 for 5 hours	1.5 mcg/mL

Permeability:

In vitro permeability of palovarotene was determined using parallel artificial membrane permeability assay (PAMPA) with fasted and fed state simulated intestinal fluid (FaSSIF and FeSSIF) containing various amounts of sodium taurocholate and lecithin to solubilize palovarotene. Palovarotene demonstrates moderate-high permeability in FaSSIF, pH 6.5 and FeSSIF, pH 5.0. However, no positive controls are provided in the submission.

In vivo disposition of palovarotene was determined in six healthy male subjects (aged 45 to 64 years) that received a single oral dose of two (2) hard gelatin capsules containing a solution of 0.5 mg palovarotene labeled with 25 µCi ^{14}C-palovarotene.

Following oral administration of a total radioactive dose of 54.5 mcCi ^{14}C-palovarotene/1 mg under fed condition, palovarotene is almost completely absorbed with approximately 97.1% of the total radioactive dose recovered in feces over 13 days post-dose that accounted as the major route of elimination. Palovarotene is extensively metabolized into four major metabolites that accounted for 67.2% of the radioactive dose in feces; six unidentified metabolites accounted for the remaining 28.4% dose in feces; with biliary excretion as the major route of elimination.

Urinary excretion was minimal and accounted for approximately 3.2% of the total dose over 13 days. The time-to-reach maximum concentration (Tmax) was achieved in

approximately 4 hours with palovarotene demonstrating a delay in absorption and a biphasic elimination with terminal half-life ($t_{1/2}$) of approximately 8 hours in plasma.

Palovarotene is extensively metabolized into four major metabolites that account for approximately 40% of total systemic exposure for up to 7 days post-dose. Palovarotene demonstrates linear, dose-proportional increase in peak plasma concentration (Cmax) and systemic exposure ($AUC_{0-\infty}$) from 0.02 mg to 10 mg dose range under fed condition.

Taking into consideration the overall ADME data, palovarotene may be classified as a highly permeable drug substance if oxidative and conjugative metabolites are predominantly the major metabolites in systemic circulation.

Dissolution:

The commercial drug product is a hard gelatin capsule containing different (b) (4) depending on the strength) of the drug product.

(b) (4)

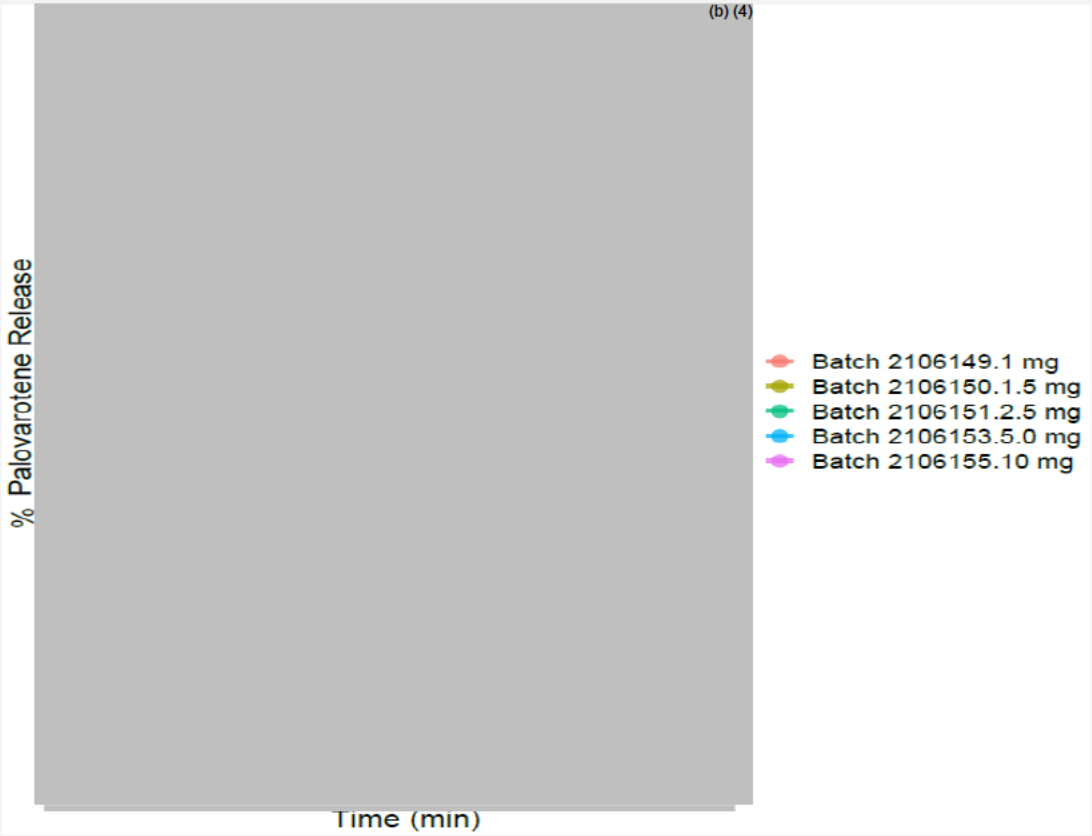
The composition of each strength of the drug product is provided in **Appendix 1** (see Table 1a, Table 1b, and Table 1c).

The dissolution profile data for the clinical and registration batches at release using the proposed QC method were not available in the original submission.

The Applicant was requested to provide complete dissolution data for all strengths of the drug product at the time of batch release for process validation batches in deficiencies conveyed to acknowledge withdrawal of the original NDA submission (dated 08/12/2021).

In the current Resubmission-29, the Applicant provided complete dissolution profile data for each strength of the process validation batches at release that demonstrate >85% dissolution in 15 minutes (see **Figure 2**).

Figure 2. Dissolution profile data for Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg process validation batches at release using QC dissolution method



B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

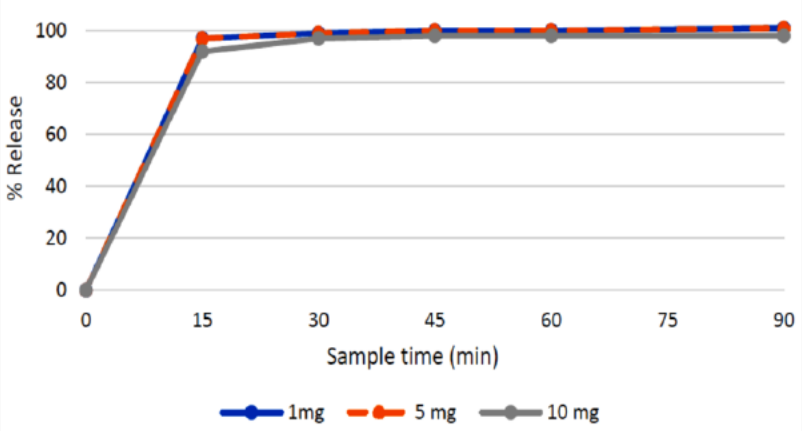
Assessment: *{Dissolution Method: Adequate; Acceptance Criterion: Adequate}*

Dissolution testing was identified as a critical quality attribute that could have an impact on the quality of the drug product. Dissolution testing was incorporated all through the product development process. Additionally, dissolution testing was used at batch release and on stability as a quality control test.

Originally, (b) (4) was proposed as the dissolution method for dissolution testing of the drug product batches administered in the pivotal, Phase II, and Phase III clinical trials and for batches on stability program (see **Table 2**).

Mean dissolution profile data for 1 mg, 5 mg, and 10 mg drug product using the originally proposed dissolution method (b) (4) is rapid (>85% dissolution in 15 minutes) and similar (see **Figure 3)**.

Figure 3. Mean dissolution profile data for 1 mg, 5 mg, and 10 mg drug product using the originally proposed dissolution method (b) (4)



With changes in the NDA holder and drug product manufacturer, the originally proposed dissolution method was optimized (b) (4). The optimized method was implemented as a QC dissolution method in 2019 (see **Table 2**).

Table 2. Originally and newly proposed QC dissolution methods and acceptance criterion for Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg

Originally and Newly Proposed Dissolution Methods and Acceptance Criterion					
	Apparatus	**Rotation Speed (rpm)**	**Medium/ml Temperature (°C)**	**Acceptance Criterion**	
Originally proposed method	(b) (4)				
Newly proposed QC method (2019)	Apparatus 2 (paddle with 6 spiral stainless-steel sinkers)	50 rpm	900 mL 5 mM phosphate buffer, pH 8.0 containing 0.5% sodium lauryl sulfate at 37°C	Time (min)	Percent (%)
				(b) (4) minutes	NLT (b) (4) %

Dissolution Method Development for the Newly Proposed QC Method:

(b) (4)

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(b) (4)

[redacted]

Reproducibility and Robustness of the Proposed QC Dissolution Method:

To support the reproducibility and robustness of the proposed QC method, dissolution data were provided for 1 mg, 5 mg, and 10 mg clinical batches and 2.5 mg process development batch at 9 month long-term stability time-point (see **Figure 5a**). The batch information (batch number, manufacturing date, and dissolution testing date) are provided in **Table 4**. Dissolution data for the process validation batches at release were also provided to support the QC method (see **Figure 5b**).

Table 4. Batch information (batch number, manufacturing date, and dissolution testing date) to support the reproducibility and robustness of the proposed QC method

Test Material Strength	Test Material (b) (4) Information				Test Material Date of Dissolution Testing[a]
	Batch Number	Strength / Batch Size	Date of Manufacture	Use of the (b) (4)	
1 mg	1802030	(b) (4) [redacted]	08 Feb 2018	Clinical Batch Manufacture	23 Feb 2019
1.5 mg	1706094		29 Jun 2017	Clinical Batch Manufacture	28 Feb 2019
2 mg	1142-047		12 Feb 2018	Manufacturing Process Development[b]	26 Feb 2019
2.5 mg					28 Feb 2019

Test Material Strength	Test Material (b) (4) Information				Test Material Date of Dissolution Testing[a]
	Batch Number	Strength / Batch Size (b) (4)	Date of Manufacture	Use of the (b) (4)	
3 mg	1706095		03 Jul 2017	Clinical Batch Manufacture	26 Feb 2019
4 mg					01 Mar 2019
5 mg	1712213		11 Dec 2017	Clinical Batch Manufacture	28 Feb 2019
10 mg	1712217		27 Dec 2017	Clinical Batch Manufacture	25 Feb 2019

a (b) (4)

b

Figure 5a. Dissolution profile data for Sohonos™ (palovarotene capsules), 1mg, 2.5 mg, 5 mg, and 10 mg registration batches at 9-month long-term stability time-point using QC dissolution method

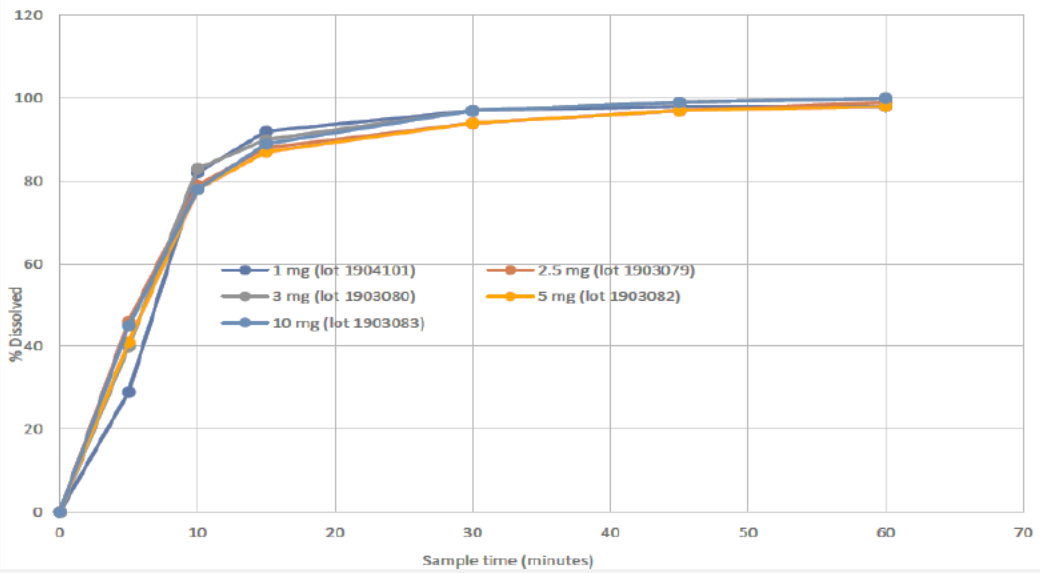
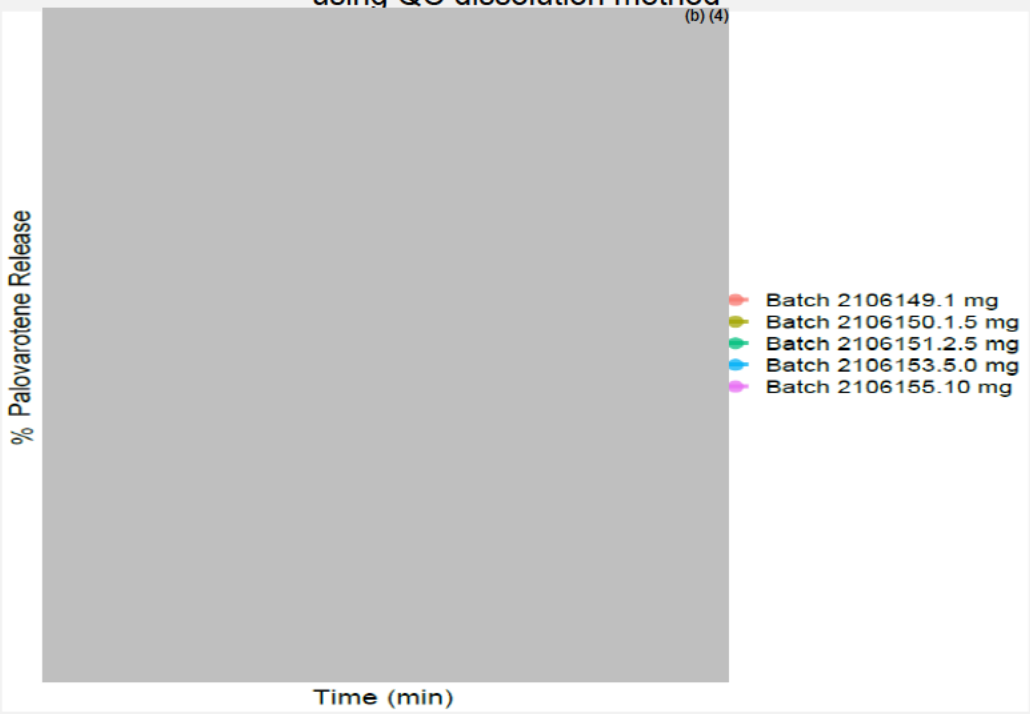


Figure 5b. Dissolution profile data for Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg process validation batches at release using QC dissolution method



The proposed dissolution method was further evaluated with respect to its discriminating ability.

Discriminating Ability of the QC Dissolution Method:

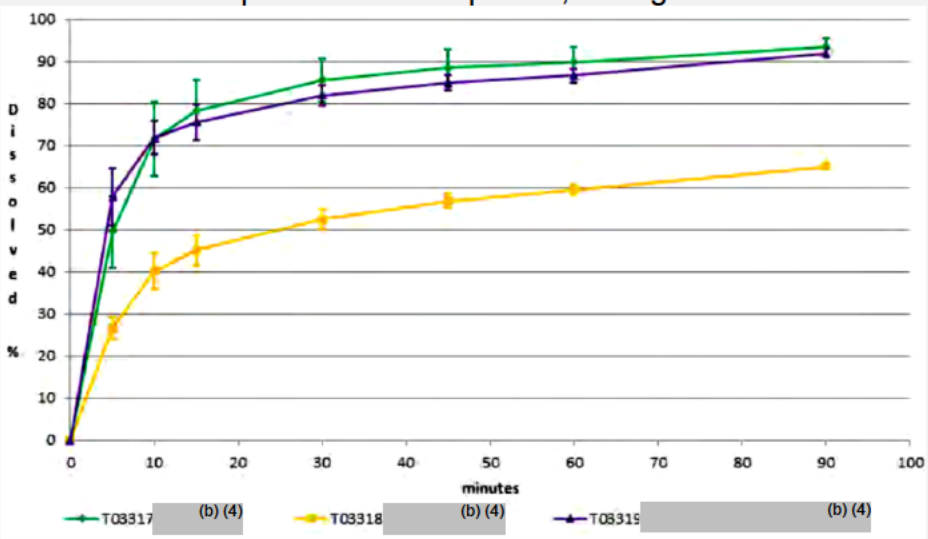
- Effect of disintegrant and drug substance particle size on dissolution:

A number of drug product batches were manufactured to evaluate the effect of (b) (4) on dissolution of the drug product. Dissolution of 10 mg drug product batches (see **Figure 6)** manufactured using (b) (4) drug substance (batch T03317) and (b) (4) (batch T03319) is faster (≥80% in 30 minutes) as compared to the drug product batch, T03318 manufactured using (b) (4) drug substance (50% dissolution in 30 minutes).

Particle size of the (b) (4) and (b) (4) drug substance for the batches is provided below:

Particle size distribution:	Dv 0.1;	(b) (4)
	Dv 0.5;	
	Dv 0.9;	
Specific surface area:		

Figure 6. Effect of (b) (4) on dissolution of palovarotene capsules, 10 mg



Similar discriminating ability of the proposed dissolution method was obtained with 1 mg and 3 mg drug product batches manufactured with (b) (4) drug substance (>80% dissolution in 30 minutes) as compared to batches manufactured with (b) (4) drug substance (65-70% dissolution in 30 minutes). These data demonstrate discriminating ability of the newly proposed dissolution method towards (b) (4) (particle size distribution) of the drug substance in the drug product.

- Effect of (b) (4) on dissolution of the drug product:

Palovarotene hard gelatin capsules are filled using (b) (4) process. (b) (4) can have an impact on the (b) (4) and consequently on the dissolution of a drug product. Three different (b) (4) were evaluated to study the impact on dissolution of each strength of the drug product (see **Figure 7a** and **Figure 7b**).

Figure 7a. Effect of different (b) (4) on dissolution of palovarotene capsules, 1 mg (Left) and 2.5 mg (Right) drug product

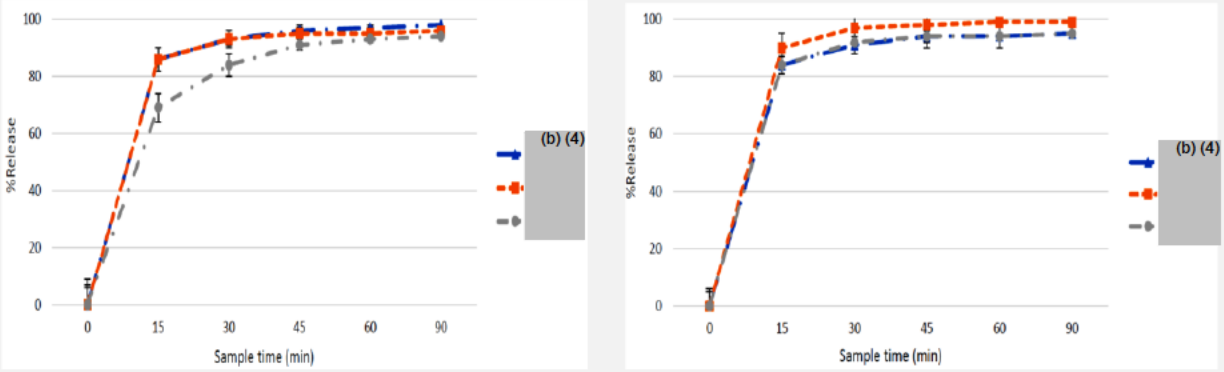
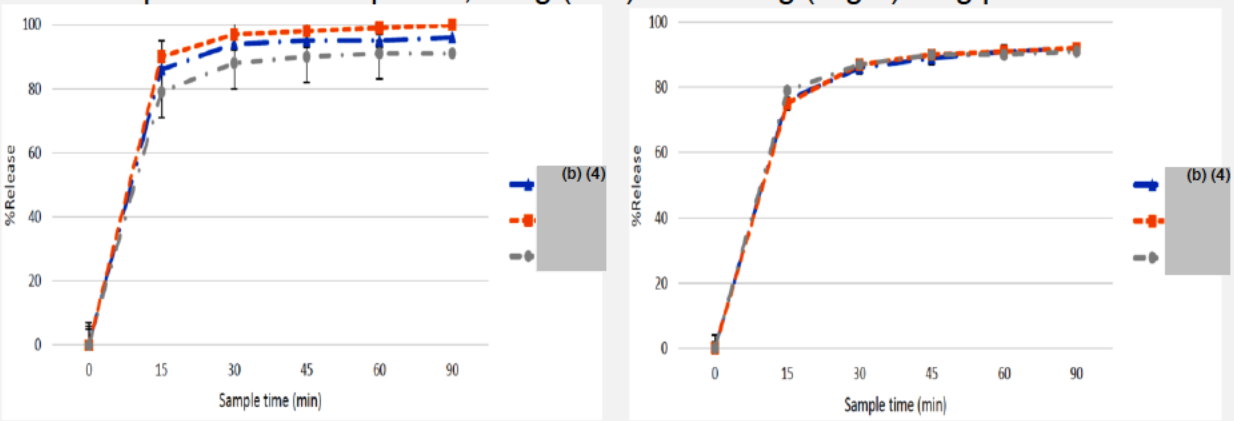


Figure 7b. Effect of different (b) (4) on dissolution of palovarotene capsules, 3 mg (Left) and 10 mg (Right) drug product



A (b) (4) slowed the dissolution of 1 mg drug product such that the dissolution of 1 mg drug product at (b) (4) is significantly faster ($f2$<50) as compared to that of (b) (4) (see **Figure 7a** and **Figure 7b**). However, for 10 mg strength drug product, all (b) (4) evaluated slowed the dissolution as compared to 2.5 mg and 3 mg drug products, but the dissolution profiles are similar and >80% dissolution is reached in 30 minutes within the studied range of (b) (4)

- Effect of (b) (4) on dissolution of the drug product:

Four drug product batches were manufactured at two different (b) (4) levels (b) (4)/10 mg capsule *vs.* (b) (4) 10 mg capsule) and two different (b) (4) to evaluate the impact on dissolution of palovarotene capsules, 10 mg.

Dissolution of palovarotene capsules, 10 mg batch 1142-066A manufactured at normal (Target) [redacted] (b) (4) ([redacted] (b) (4)/10 mg capsule) and normal (Target) [redacted] (b) (4) is similar (≥80% in 30 minutes; *f2*>50) to that of aberrant batches 1142-066B manufactured with [redacted] (b) (4) and [redacted] (b) (4)

As in the case of the effect of [redacted] (b) (4) particle size had minimal effect on the dissolution of each strength of the drug product.

Based on the overall dissolution data, the proposed dissolution method demonstrates discriminating ability with respect to the particle size of the drug substance and to lesser extent, the [redacted] (b) (4) (for 1 mg drug product).

- *Particle size distribution (PSD) of the drug substance:*

Dissolution of the drug product was significantly higher (see **Figure 6**) when the drug substance was [redacted] (b) (4) (>80% dissolution in 30 minutes) as compared to [redacted] (b) (4) drug substance (approximately 50% dissolution in 30 minutes). Therefore, all drug substance batches used in the manufacture of pivotal clinical (Phase 2 and Phase 3) and registration stability batches [redacted] (b) (4) particle size distribution: D_{10}: [redacted] (b) (4) µm; D_{50} [redacted] (b) (4) µm; and D_{90}: [redacted] (b) (4) µm. The proposed PSD specification: D_{90} NMT [redacted] (b) (4) µm is under the purview of drug product reviewers.

Dissolution Acceptance Criterion:

In the original submission, the Applicant proposed '*NLT* [redacted] (b) (4) *% (Q) in* [redacted] (b) (4) *minutes*' as the acceptance criterion for each strength of Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg drug product. An assessment of the dissolution data for the TBM registration and process validation batches at release (see below) support '*NLT* [redacted] (b) (4) *% (Q) in 30 minutes*' using the QC dissolution method.

- ***Dissolution Profile Data for Clinical and Registration Batches at Release**:*

Originally, 2.5 mg, 5 mg, and 10 mg strength drug product manufactured using [redacted] (b) (4) were administered in the pivotal clinical study, PVO-1A-201. The batches administered in the pivotal and other clinical studies are provided in **Appendix 1** (Table 2a).

These clinical batches manufactured using [redacted] (b) (4) demonstrated >85% dissolution in 60 minutes (see **Table 5a**) using the originally proposed dissolution method [[redacted] (b) (4)

Table 5a. Mean dissolution data at release for drug product batches from (b) (4) administered in the pivotal clinical study, PVO-1A-201 using the originally proposed dissolution method

Study Ref. No	Product Lot No	Dosage Form (Capsule) Strength	Dissolution Conditions	No of Dosage Units	Collection Times (minute) Mean% Dissolved (range) (b) (4)	
PVO-1A-201	22101.001	2.5 mg	(b) (4)	6		99.5 (97.7-100.9)
	22103.001	5 mg		6		97.6 (95.3-100.7)
	22104.001	10 mg		6		97.2 (96.1-99.7)

Later, different strengths of the TBM registration batches were manufactured from (b) (4) and administered in the Phase 2 (PVO-1A-202; parts A/B/C) and Phase 3 (PVO-1A-301) studies (see **Appendix 1**; Table 2b) to provide a 'bridge' to the pivotal clinical batches.

Dissolution data at release for batches manufactured using (b) (4) and administered in the Phase 2 clinical study, PVO-1A-202 (parts A/B/C) and other studies demonstrate >85% dissolution in 30 minutes using the originally proposed dissolution method (see **Appendix 1,** Table 3a). No dissolution data was provided for these 10 mg clinical batches at release using the QC dissolution method as the QC method was not implemented until 2019.

Limited dissolution data was provided for 1.0 mg and 2.5 mg strength of the TBM registration batches using the QC dissolution method at release. Comparability of originally and newly proposed QC dissolution methods can be supported by comparing dissolution profile data of the 2.5 mg, 5 mg, and 10 mg clinical batches, and 1 mg and 2.5 mg strength registration batches at release that demonstrate >85% release in 30 minutes using the QC dissolution method (see **Table 5b** and **Table 5c** and **Figure 8a**).

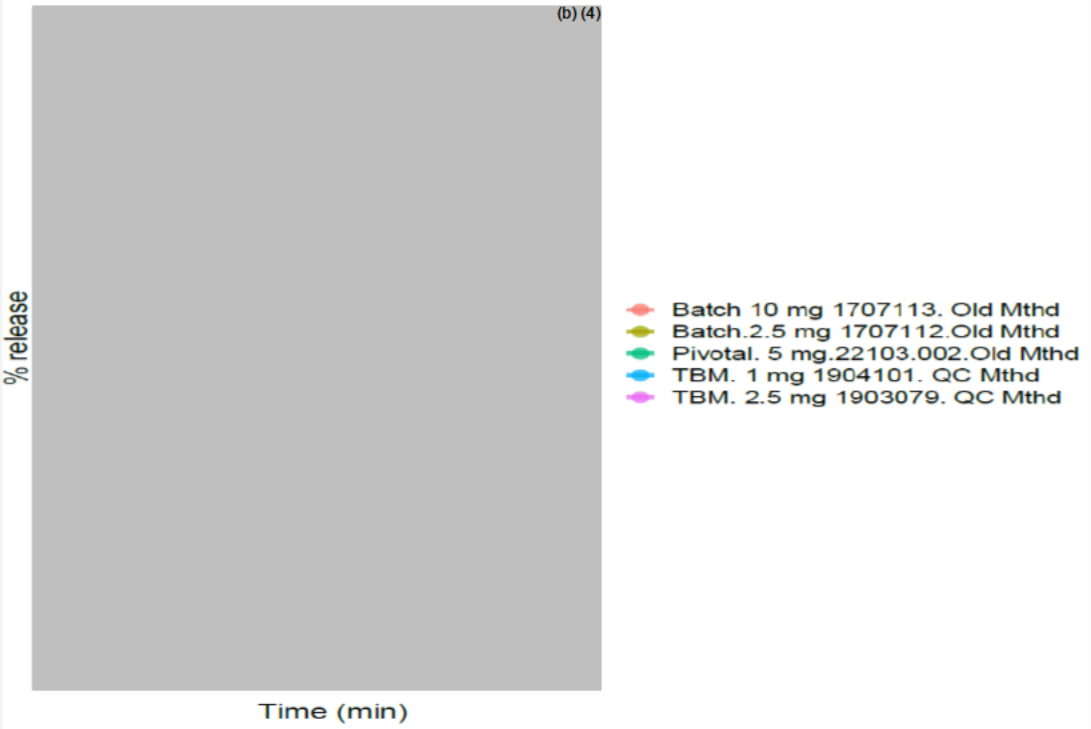
Table 5b. Dissolution profile data for 1 mg strength TBM registration batch Lot 1904101 of palovarotene capsules at batch release using the QC dissolution method

Timepoints	Sample Time (min)	%Release v1	v2	v3	v4	v5	v6	v7	v8	v9	v10	v11	v12	Mean	SD	%RSD
Release	5	(b) (4)												31	23	74
	10													72	13	18
	15													83	9	11
	30													93	5	5
	45													97	3	3
	60													98	2	2

Table 5c. Dissolution profile data for 2.5 mg strength TBM registration batch Lot 1903079 of palovarotene capsules at batch release using the QC dissolution method

Timepoints	Sample Time (min)	%Release												Mean	SD	%RSD
		v1	v2	v3	v4	v5	v6	v7	v8	v9	v10	v11	v12			
Release	5	(b) (4)												43	9	21
	10													80	8	10
	15													89	6	7
	30													95	4	4
	45													97	3	3
	60													98	3	3

Figure 8a. Mean dissolution data for 2.5 mg, 5 mg, and 10 mg clinical batches of drug product using originally proposed dissolution method and 1mg and 2.5 mg TBM drug product using QC dissolution method



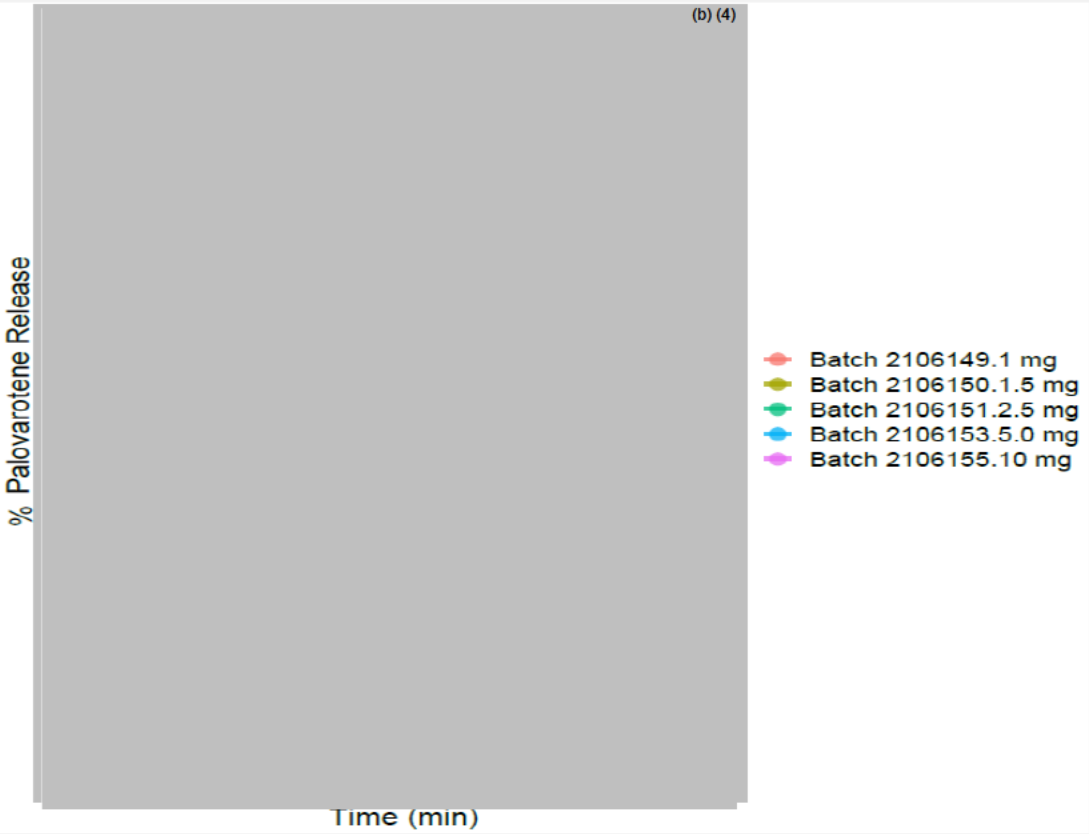
High intra-batch variability in dissolution data (see **Table 5b** and **Table 5c**) is observed at early sampling time-points of 5 minutes and/or 10 minutes due to which neither similarity factor (*f2* value) nor multivariate analysis (such as MDS) can be used to compare two dissolution profiles using 5-minute sampling time-point.

The Applicant was requested to provide complete dissolution data for all strengths of the drug product at the time of batch release for process validation batches in deficiencies conveyed to acknowledge withdrawal of the original NDA submission (dated 08/12/2021).

Dissolution Profile Data for Process Validation Batches at Release:

In a response (dated 04/29/2022), in the current Resubmission-29, the Applicant provided complete dissolution profile data for each strength of the process validation batches at release that demonstrate >85% dissolution in 15 minutes (see **Figure 8b**).

Figure 8b. Dissolution profile data for Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg process validation batches at release using QC dissolution method

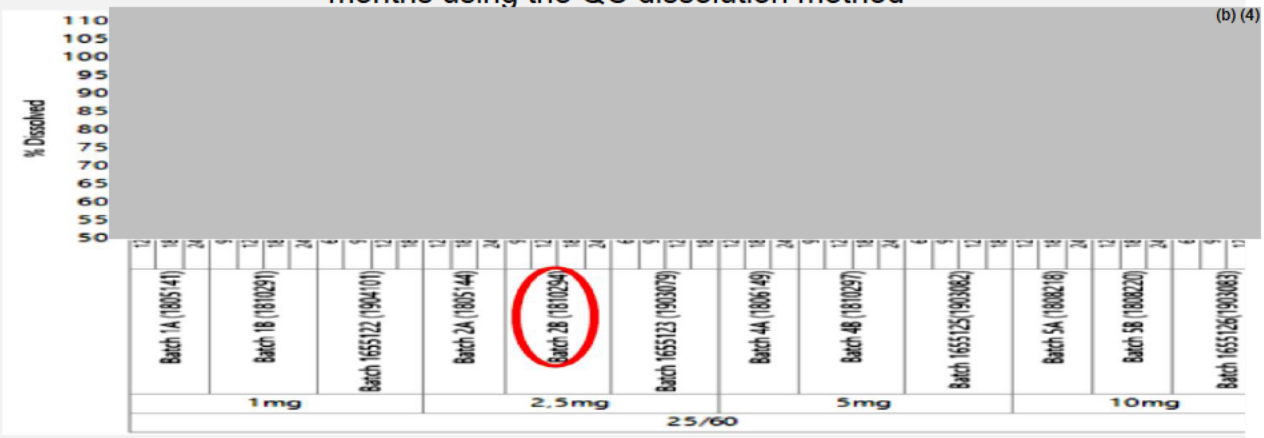


Dissolution Data on Long-Term Stability:

Dissolution data for TBM registration batches of each strength of the drug product on long-term stability for up 24 months demonstrate >85% release in 30 minutes using the QC dissolution method, with high intra-batch and inter-batch variability (refer to **Figure 9a** and **Figure 9b**).

Downward trend (~82% average dissolution at 30 minutes) due to within-batch variability in the dissolution data is observed for one batch of the 2.5 mg (Lot 1810294) TBM registration drug product on long-term stability beyond 12 months; however, the batches would comply with the recommended acceptance criterion of 'NLT (b) (4) %(Q) in 30 minutes' at *Stage 2* testing.

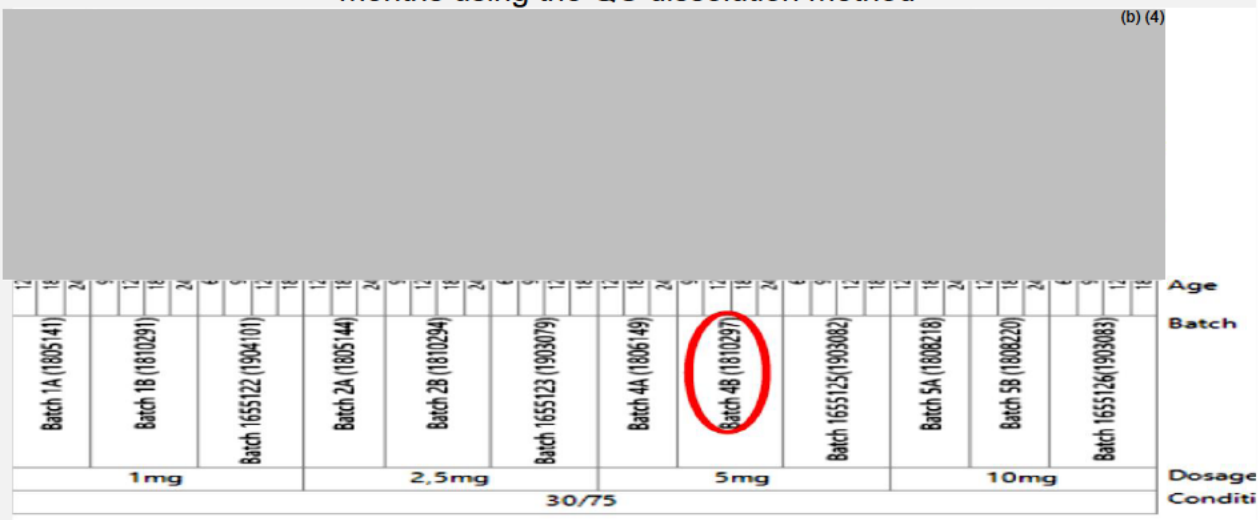
Figure 9a. Dissolution data at 30 minutes for registration stability batches of each strength of palovarotene capsules on long-term stability (25℃/60% RH) for up to 24 months using the QC dissolution method



Similar downward trend (<80% average dissolution at 30 minutes) due to within-batch variability in the dissolution data using the QC dissolution method is observed for the 2.5 mg (Lot 1810294) TBM registration drug product batch on intermediate stability (30℃/75% RH) for up to 24 months, in addition to other strengths of the drug product including 1 mg (Lot 1805141), 5 mg (Lot 1810297), and 10 mg (Lot 1808220) that would be subjected to Stage 2/Stage 3 testing.

As no information is provided for the high dissolution data variability on stability with respect to the product quality and in vivo performance, the Applicant was recommended to investigate the within-batch variability in the dissolution data for all strengths of the drug product and provide mitigating solutions in deficiencies conveyed to acknowledge withdrawal of the original NDA submission (dated 08/12/2021).

Figure 9b. Dissolution data at 30 minutes for registration stability batches of each strength of palovarotene capsules on intermediate stability (30℃/75% RH) for up to 24 months using the QC dissolution method



Overall Assessment of the Dissolution Method and Acceptance Criterion and its Bio-relevance:

Palovarotene is a pH-dependent, low soluble drug substance. The drug product is designed as an immediate-release capsule product.

The newly proposed QC dissolution method [*USP Apparatus 2 (paddle with spiral sinkers) at 50 rpm in 900 mL 5 mM phosphate buffer, pH 8.0 containing 0.5% SLS at 37℃*] demonstrates discriminating ability with respect to the particle size of the drug substance and to lesser extent, the (b) (4) for 1 mg drug product.

Dissolution data for 1 mg and 2.5 mg TBM registration batches (manufactured using (b) (4)) and each strength of the process validation batches demonstrates >85% release in 30 minutes at release using the newly proposed QC method, indicating solubility of the drug substance, and not dissolution of the drug product, may be the rate-limiting step in the absorption of the drug product.

The PSD of the drug substance is controlled at D_{90} NMT(b) (4) µm in the drug product and the drug product (b) (4) that ensure rapid dissolution (>85% dissolution in 15 minutes) using the QC dissolution method. Based on the totality of the dissolution data, the QC dissolution method is adequate for dissolution testing of the drug product at release and on stability.

The Tmax of the drug product in various pharmacokinetic studies is between 3-4 hours. Therefore, acceptance criterion of '*NLT*(b) (4)*% (Q) in 30 minutes*' will ensure complete dissolution and availability of the drug product prior to absorption.

As no dissolution data was provided for 5.0 mg and 10 mg strength of the TBM registration batches at release using the QC dissolution method, the acceptance criterion of '*NLT*(b) (4)*% (Q) in 30 minutes*' was set on an 'interim basis'. The Applicant was requested to provide complete dissolution data for all strengths of the drug product (at least three batches) at the time of batch release from the process validation or commercial batches that was agreed upon to be manufactured to support the revision of dissolution specification, if necessary, in deficiencies conveyed to acknowledge withdrawal of the original NDA submission (dated 08/12/2021).

In the current Resubmission-29, the Applicant provided complete dissolution profile data for each strength of the process validation batches at release that demonstrate >85% dissolution in 15 minutes and would meet the interim set acceptance criterion of '*NLT* (b) (4)*% (Q) in 30 minutes*'. Considering the overall dissolution data for each strength of the process validation batches, the Applicant was recommended to implement '*NLT*(b) (4)*% (Q) in 30 minutes*' as the final acceptance criterion for Sohonos™ (palovarotene capsules), 1mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg.

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B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERION *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: ***{Adequate}***

A number of variant formulations were manufactured to assess the discriminatory ability of the QC dissolution method. However, in vivo performance of the variant formulations was not investigated; therefore, the QC dissolution method is not used to support 'safe space'.

Palovarotene is a low soluble drug substance for which complete dissolution of the proposed drug product prior to absorption will enable availability of the drug product for in vivo performance. The provided dissolution data for the 1.0 mg and 2.5 mg registration batches of the drug product across pivotal clinical study and other Phase 2 studies using originally and newly proposed QC dissolution method was used to support the recommended acceptance criterion of '*NLT* (b) (4) *% (Q) in 30 minutes*' for each strength of the drug product.

Dissolution data for 2.5 mg batches, 22101.001 and 1707112 of the drug product with slightly different composition of the formulations manufactured across different manufacturing sites and administered across pivotal clinical study PVO-1A-201 and Phase 2 clinical study PVO-2A-201, demonstrate >85% dissolution in 30 minutes, using originally and newly proposed QC dissolution method (see **Table 5**).

The geometric mean Cmax for the 2.5 mg batches, 22101.001 and 1707112 are 19 ng/mL and 18.0 ng/mL, respectively, and $AUC_{(0-T)}$ for the batches, 22101.001 and 1707112 are 143 ng*hr/mL and 112.0 ng*hr/mL, respectively, across pivotal clinical study PVO-1A-201 and Phase 2 clinical study PVO-2A-201 in FOP subjects. The batches, 22101.001 and 1707112 achieve almost similar Tmax of 3.9 hr and 3.0 hr, respectively, across pivotal clinical study PVO-1A-201 and Phase 2 clinical study PVO-2A-201 (see **Table 5**).

Table 5. Dissolution data for 2.5 mg registration batches of the drug product across different clinical studies using originally and newly proposed QC dissolution method

Strength	**2.5 mg**		
Batch	22101.001	1707112	1903079
Manufacturing Site	(b) (4)		(b) (4)
Clinical Study in FOP Subjects	PVO-1A-201 Cmax (ng/mL):19.0 (9.24) $AUC_{(0-T)}$ (ng*hr/mL): 143 (84.8) T_{max} (hr): 3.9 (1.5)	PVO-2A-201 Cmax (ng/mL):18.0 (50.2) $AUC_{(0-T)}$ (ng*hr/mL): 112 (29.1) T_{max} (hr): 3.0 (2.47-10.0)	Registration Stability Program
Dissolution Method	Original	Original	QC

			[USP App 2 (paddle) at 50 rpm in 900 ml 0.5% SLS in 5mM phosphate buffer, pH 8.0 at 37°C]
Dissolution Data (minutes) (Percent % Released)	99.5 (b) (4)) at 60	95 (b) (4)) at 15; 97 ((b) (4)) at 30; 97 (b) (4)) at 45; 97 ((b) (4)) at 60	43 (b) (4) t 5; 80 t 10; 89 t 15; 95 at 30; 97 at 45; 98 at 60

Taking into consideration the dissolution data and PK parameters for different strengths of the drug product, acceptance criterion '*NLT (b) (4) % (Q) in 30 minutes*' appears to be clinically relevant as almost similar PK parameters (Cmax and $AUC_{(0-T)}$) of the drug product is observed for the clinical batches across various Phase 1, Phase 2 and Phase 3 clinical studies in FOP patients.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *{Adequate}*

Palovarotene is a low soluble drug substance. Therefore, particle size of the drug substance can have an impact on the dissolution of the drug product. As Sohonos™ (palovarotene capsules) is designed to release the drug product with an immediate-release profile, (b) (4) can alter the release profile of the drug product. The effect of (b) (4) on dissolution of 1.0 mg, 2.5 mg, and 10 mg variant drug product batches was investigated using the proposed QC dissolution method.

Dissolution of variant batches with (b) (4) drug substance and (b) (4) were faster (≥80% in 30 minutes) as compared to the variant batches with (b) (4) drug substance (50-65% dissolution in 30 minutes). For further details regarding the batches, refer to '*Discriminating Ability of the QC Dissolution Method*' under Section B:2 'Dissolution Method and Acceptance Criterion'.

These dissolution data demonstrate that (b) (4) (particle size distribution) of the drug substance is a critical material attribute that can have a rate-limiting influence on the dissolution of the drug product. Further, the data indicate that (b) (4) may not be a critical (b) (4) variable that will have an impact on the dissolution of the drug product.

BB.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

The formulation of the clinical batches of the drug product administered in the pivotal clinical study, PVO-1A-201 were manufactured using (b) (4).

Later, different strengths (1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg) of the TBM drug product were manufactured (b) (4) that

differ with respect to [redacted] and palovarotene. Additionally, two different types of hard gelatin capsule shell [redacted] gelatin source and [redacted] gelatin source) were used along with printed capsule shell in Phase 2 and Phase 3 clinical studies.

As composition of the [redacted] TBM drug product is very similar to the clinical batches (administered in the pivotal clinical study, PVO-1A-201), and the 10 mg (with [redacted]) TBM registration batch and 10 mg clinical batch were administered in the Phase 2 (PVO-1A-202; parts A/B/C) and in the Phase 3 study, PVO-1A-301 that included pharmacokinetic (PK) studies; no bridging using dissolution data is necessary.

Several manufacturing sites [redacted] were identified for the drug product batches administered in the clinical studies and for the commercial drug product. The clinical batches manufactured at [redacted] were dosed in the pivotal clinical study PVO-1A-201. Similarly, clinical batches manufactured at [redacted] the commercial manufacturing site, were dosed in the food-effect study PVO-1A-102, pivotal clinical study PVO-1A-201, and PVO-1A-202 (part B/C). Bridging of manufacturing sites is supported by pharmacokinetic (PK) data in healthy and FOP patient population (see **Table 6**). No bridging using dissolution data is therefore necessary. Refer to Office of Clinical Pharmacology (OCP) review for assessment of the PK data.

Table 6. Pharmacokinetic parameters (Cmax and $AUC_{(0-T)}$) for 2.5 mg drug product across different manufacturing sites, [redacted] and clinical studies

Strength	**2.5 mg**		
Batch	22101.001	1707112	1903079
Manufacturing Site	[redacted]	[redacted]	[redacted]
Clinical Study in FOP Subjects	PVO-1A-201 Cmax (ng/mL):19.0 (9.24) $AUC_{(0-T)}$ (ng*hr/mL): 143 (84.8) T_{max} (hr): 3.9 (1.5)	PVO-2A-201 Cmax (ng/mL):18.0 (50.2) $AUC_{(0-T)}$ (ng*hr/mL): 112 (29.1) T_{max} (hr): 3.0 (2.47-10.0)	Registration Stability Program
Dissolution Method	Original	Original	QC [USP App 2 (paddle) at 50 rpm in 900 ml 0.5% SLS in 5mM phosphate buffer, pH 8.0 at 37°C]
Dissolution Data (minutes) (Percent % Released)	99.5 [redacted]) at 60 min	95 [redacted]) at 15; 97 [redacted] at 30 min; 97 [redacted]) at 45 min; 97 [redacted]) at 60 min	43 [redacted] t 5 min; 80 t 10 min; 89 t 15 min; 95 at 30 min; 97 at 45 min; 98 at 60 min

B. 13 BIOWAIVER REQUEST

Assessment: *{Not Applicable}*

There is no request for biowaiver of lower strengths (1.0 mg, 1.5 mg, 2.5 mg, and 5 mg) of the drug product as 2.5 mg, 5 mg, and 10 mg clinical and TBM drug product batches were administered in the various clinical safety/pharmacokinetic studies, PVO-1A-102, PVO-1A-202, PVO-2A-201, and PVO-1A-301 in FOP subjects. For the assessment of the adequacy of the PK data, refer to OCP review.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *{Not Applicable}*

Post-Approval Commitments

Assessment: *{Not Applicable}*

Lifecycle Management Considerations

Assessment: *{Not Applicable}*

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Parnali Chatterjee, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Haritha Mandula, Ph.D.

APPENDIX I

Table 1a. Composition of the 1 mg, 1.5 mg, and 2.5 mg drug product manufactured (b) (4)

Component	Quality Standard	Function	Theoretical Quantity (mg/unit dose)			% w/w
			1 mg	1.5 mg	2.5 mg	
(b) (4)						
Palovarotene	In house	Active Ingredient	1 mg	1.5 mg	2.5 mg	(b) (4)
Lactose Monohydrate	NF/Ph.Eur./JP	(b) (4)				(b) (4)
Povidone	USP/Ph.Eur./JP					
Croscarmellose Sodium	NF/Ph.Eur./JP					
Sodium Lauryl Sulfate	NF/Ph.Eur./JP					
(b) (4)						(b) (4)
Microcrystalline Cellulose	NF/Ph.Eur./JP					(b) (4)
Magnesium Stearate	NF/Ph.Eur./JP					
Fill Weight						(b) (4)
HARD GELATIN CAPSULE (size 0 elongated)						
Total Weight (capsule fill weight and capsule body/cap weight)			**291 mg**	**383 mg**	**567 mg**	-

a (b) (4)

b

Table 1b. Composition of the 5 mg drug product manufactured (b) (4)

(b) (4)

Component	Quality Standard	Function	Theoretical Quantity (mg/unit dose)	% w/w
			5 mg	
(b) (4)				
Palovarotene	In house	Active Ingredient	5.0 mg	(b) (4)
Lactose Monohydrate	NF/Ph.Eur./JP			(b) (4)
Povidone	USP/Ph.Eur./JP			
Croscarmellose Sodium	NF/Ph.Eur./JP			
Sodium Lauryl Sulfate	NF/Ph.Eur./JP			
(b) (4)				
Microcrystalline Cellulose	NF/Ph.Eur./JP			(b) (4)
Magnesium Stearate	NF/Ph.Eur./JP			
Fill Weight				(b) (4)
HARD GELATIN CAPSULE (size 0 elongated)				
Total Weight (fill weight and capsule body/cap weight)			**567 mg**	-

a (b) (4)

b

Table 1c. Composition of the 10 mg drug product manufactured (b) (4)

(b) (4)

Component	Quality Standard	Function	Theoretical Quantity (mg/unit dose) 10 mg	% w/w
(b) (4)				
Palovarotene	In house	Active Ingredient	10.0 mg	(b) (4)
Lactose Monohydrate	NF/Ph.Eur./JP			(b) (4)
Povidone	USP/Ph.Eur./JP			
Croscarmellose Sodium	NF/Ph.Eur./JP			
Sodium Lauryl Sulfate	NF/Ph.Eur./JP			
				(b) (4)
Microcrystalline Cellulose	NF/Ph.Eur./JP			(b) (4)
Magnesium Stearate	NF/Ph.Eur./JP			
Fill Weight				(b) (4)
HARD GELATIN CAPSULE (size 0 elongated)				
Total Weight (capsule fill weight and capsule body/cap weight)			**567 mg**	-

a (b) (4)

b

Table 2a. Clinical batches (manufactured (b) (4)) administered in the pivotal clinical study, PVO-1A-201 and Phase 2 (PVO-1A-202; parts A/B/C) studies

Strength	Batch No.		Manufacturer	Date of Manufacture	Batch Size		Drug Substance Batch No.	Use (see Table 2 for study designation description)
	Capsule Batch No.	(b) (4) *Batch No. / Strength*			(b) (4)	*Capsules*		
Hard Gelatin Capsule								
2.5 mg	22101.001	N/A	(b) (4)	Feb 2014		(b) (4)	02140020	PVO-1A-201, PVO-1A-202, parts A/B/C
5 mg	22103.001	N/A		Feb 2014			02140020	PVO-1A-101, PVO-1A-201, PVO-1A-202, parts A/B
10 mg	22104.001	N/A		Feb 2014			02140020	PVO-1A-101, PVO-1A-201, PVO-1A-202, parts A/B/C

Table 2b. Clinical batches of the TBM drug product (manufactured using (b) (4)) administered in the Phase 2 (PVO-2A-201 and PVO-1A-202; parts B/C) and Phase 3 (PVO-1A-301) clinical studies

1 mg	1707109	1706094 / (b) (4)	(b) (4)	Jun 2017	(b) (4)	171208	PVO-2A-201
1.5 mg	1707110						PVO-2A-201, PVO-1A-301
2 mg	1707111						PVO-2A-201
2.5 mg	1707112						PVO-1A-202, parts B/C, PVO-1A-301, PVO-2A-201
10 mg	1707113	1706096 / (b) (4)		Jul 2017		171220	PVO-1A-202, part C, PVO-1A-301

Table 3a. Mean dissolution data at release for batches manufactured using (b) (4) and administered in the Phase 2 clinical study, PVO-1A-202 (parts A/B/C) using the originally proposed dissolution method

Study Ref. No	Product Lot No	Dosage Form (Capsule) Strength	Dissolution Conditions	No of Dosage Units	Collection Times (minute) Mean% Dissolved (range) (b) (4)					
PVO-1A-202 B	22101.001	2.5 mg	(b) (4)	6						99.5 (b) (4)
	22103.001	5 mg		6						97.6 (b) (4)
	22104.001	10 mg		6						97.2 (b) (4)
	22103.002	5 mg		6			86	91	94	95 (b) (4)
	1707112	2.5 mg		6			95	97	97	97 (b) (4)
	1707115	5 mg		6			96	98	99	99 (b) (4)

1707112	2.5 mg	6			95	97	98	97 (b) (4)
1707113	10 mg	6			97	99	99	100 (b) (4)
1707114	3 mg	6			90	96	97	98 (b) (4)
1707115	5 mg	6			96	98	99	99 (b) (4)

Parnali Chatterjee

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Haritha Mandula

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Date: 9/02/2022 03:47:50PM
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/s/

AKM KHAIRUZZAMAN
09/26/2022 03:49:41 PM
OPQ Team Recommends an Approval on this NDA

MOHAN K SAPRU
09/26/2022 04:05:48 PM