CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213498Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 213498
Review # 1

Drug Product Name	PONVORY (ponesimod)
Dosage Form	Tablets
Strength	2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Janssen Pharmaceuticals
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Pratibha Bhat	Yong Hu
Microbiology	N/A	N/A
Biopharmaceutics	Bryan Ericksen	Ta-Chen Wu
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-001, Original NDA	3/18/2020	All
SD-013, Response to IR	7/17/2020	Manufacturing, Biopharmaceutics
SD-017, Response to IR	8/28/2020	Drug Product, Manufacturing
SD-020, Response to IR	9/25/2020	Drug Product
SD-022, Response to IR	10/29/2020	Drug Product
SD-013, Response to IR	11/12/2020	Drug Product

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	III		(b) (4)	--	N/A [1]	
	III			--	N/A	
	III			--	N/A	
	III			--	N/A	
	IV			--	N/A	

[1] N/A: Adequate information in NDA.

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

Document	Application Number	Description
IND	101722	Development of ponesimod for treatment of MS
IND		(b) (4)

2. CONSULTS

None

Reference ID: 4716100

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **APPROVAL** of NDA 2134489 for PONVORY (ponesimod) tablets.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant seeks approval of PONVORY (ponesimod) tablets for treatment of multiple sclerosis. Ponesimod, a [redacted] (b) (4) derivative, is an orally active, selective modulator of the sphingosine 1-phosphate receptor 1 (S1P1). Ponesimod is a new molecular entity; however, there are other approved drugs in this pharmacological class.

The proposed drug products are immediate-release, film-coated tablets containing 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg or 20 mg ponesimod and conventional compendial excipients. The proposed maintenance dose for ponesimod is 20 mg/day. The lower strengths are intended for a 2-week dose titration.

Due to the potential toxicity of ponesimod and the requirement for slow dose titration, the initial risk assessment was based on classification of ponesimod as a "High Risk" drug. Assay/stability, content uniformity, and physical/solid state stability were identified as moderate risk critical quality attributes (CQAs). Dissolution was identified as a high risk CQA.

Proposed indication(s) including intended patient population	Treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Duration of treatment	Chronic
Maximum daily dose	20 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Ponesimod is a new molecular entity with a molecular formula of $C_{21}H_{26}N_2O_4$ ($C_{23}H_{25}ClN_2O_4S$), for a total molecular weight of 460.97 Daltons. Ponesimod

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contains one chiral center [redacted] The [redacted] drug substance is a white to light yellowish powder, the molecule possesses and the melting point ranges from [redacted] °C to [redacted] °C [redacted] It is moderately lipophilic, weakly basic, practically insoluble in aqueous media, and exhibits polymorphism. [redacted] was chosen for development as it is the [redacted] form.

The drug substance is manufactured through [redacted]

Four specified impurities are listed in the drug substance specification. Acceptance criteria for the specified impurities do not exceed the [redacted] %. Impurity [redacted] is also a drug product degradant and is the result of the [redacted] No impurities found in the drug substance were identified as potentially genotoxic in accordance with the classification scheme outlined in ICH M7.

The retest period is [redacted] **months for drug substance stored below** [redacted] **°C** in the proposed container closure system.

Drug Product: Adequate

Ponesimod is supplied as round, biconvex, immediate-release film-coated tablets for oral use at the dosage strengths of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg. The tablets are differentiated by a combination of size, color, and debossing. The excipients used in the core tablets are compendial grade and commonly used in the formulation of oral dosage forms. The [redacted] are proprietary mixtures consisting of compendial grade excipients. The maximum daily exposures for all excipients are considered qualified based on their respective previous use levels in the FDA approved oral drug products.

Except for film-coat color and debossing, the registration and the proposed commercial formulations are identical to the pivotal Phase 3 clinical batches and were manufacturing using the [redacted] of the drug substance. One Phase 3 clinical batch of 20 mg tablets was manufactured by [redacted] The remaining Phase 3 batches, and registration stability batches, were manufactured by the proposed commercial manufacturer, [redacted].

The proposed specification is aligned with ICH Q6A Guideline and appropriate USP chapters. Acceptance criteria for specified and unspecified impurities are consistent with ICH Q3B recommendations. Based on supporting data provided and a risk assessment per ICH Q3D, the applicant has justified omission of the following tests: elemental impurities, [redacted] and elemental analyses. The applicant has also validated the non-compendial analytical methods used for testing the ponesimod tablets in accordance with the ICH Q2(R1) Guideline.

Thus, the specification is deemed adequate to control the identity, strength, quality, purity, and potency of ponesimod tablets through the proposed shelf-life.

Ponesimod tablets are available in two different packaging configurations. The starter pack (b) (4) blisters) contains the 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, and 10 mg tablets, which are intended for a two-week titration period. The 20 mg tablets are packaged in 30-count HDPE bottles with child resistant closures and desiccant. The container closure systems and the components meet the appropriate USP monograph and regulatory requirements applicable to solid oral dosage forms. The available stability data show that the container closure systems are suitable for protecting the ponesimod tablets through the proposed shelf-life.

The applicant used a bracketing approach for stability studies. The data provided include up to 24 months of data under long-term (25°C/60%R.H.) and intermediate (30°C/75%R.H.) storage conditions, and up to 6 months of data for the accelerated (40°C/75%R.H.) storage condition. The only change noted was a slight decrease in (b) (4) Based on the data provided, a **shelf-life of 36 months for tablets stored at controlled room temperature (20°C to 25°C) is granted for both the (b) (4) blister starter pack and the 20 mg tablets packaged in HDPE bottles.**

Labeling: Adequate

Product quality related aspects of the package Insert, patient labeling, and container labels are acceptable.

Manufacturing: Adequate

(b) (4)

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All the facilities listed in the application are acceptable. The drug product and drug substance manufacturing, packaging and testing facilities are approved based on the firm's inspection history and manufacturing experience. There are also no major GMP issue raised based on the review of the submitted batches.

Biopharmaceutics: Adequate

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, 2) formulation bridging throughout product development, 3) the need for biowaiver for the proposed ER drug product.

(1) Dissolution Method and Acceptance Criterion:
The applicant developed and proposed (b) (4) method for the proposed drug product: USP Apparatus 2 (Paddle) at 75 rpm in pH 4.5 phosphate buffer 900 mL with 0.2% CTAB, 37 ± 0.5 ºC. The testing condition/parameters, including type and amount of added surfactant were adequately selected and justified. The proposed dissolution method was shown to be discriminating toward particle size/distribution, but not (b) (4) parameters, (b) (4), or stressed storage conditions. The proposed acceptance criterion of Q= (b) (4)% in 30 minutes is deemed acceptable, considering the totality of the drug release data, physicochemical properties, and PK property (including Tmax being 2-4 hours, not considered as critical, clinically).

(2) Formulation Bridging:
A capsule formulation was initially developed for early Phase 1 studies. The proposed tablet formulation of various dosage strengths was later developed for use

in later clinical trials (Phase 1, 2 and 3) and for commercialization. Therefore, no bridging of formulations is necessary between the capsule and tablet formulations.

Changes in color coating and debossing were made for the tablets, which is considered as Level-1 changes in SUPAC-IR Guidance and do not require comparative dissolution testing for the bridging.

(3) Biowaiver:
No request for biowaiver is necessary because different formulations and all strengths were used through clinical development.

FDA-Approved dissolution method and acceptance criterion for quality control and stability testing of the proposed Ponvory™ (ponesimod) Tablets:

USP Apparatus	Speed (RPM)	Medium/Temperature	Volume (mL)	Acceptance criterion
2 (Paddle)	75	pH 4.5 phosphate buffer with 0.2% CTAB / 37 ± 0.5 ºC	900 mL	Q= (b) (4)% in 30 minutes

Environmental: Adequate

The applicant submitted a claim for categorical exclusion under 21 CFR 25.31(b). Approval of the application will increase use of the active moiety; however, the maximum expected environmental concentration ($EIC_{aquatic}$) is less than (b) (4) part per billion and no extraordinary circumstances exist. Per Raanan Bloom, CDER Environmental Assessment Team, based on the low import volume (approximately (b) (4) kg/year) and lack of estrogenic activity the claim may be accepted.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, Stability	Formulation, container closure, moisture, process parameters	**Low (release)** **Moderate (stability)**	(b) (4)	**Adequate**	
Content uniformity	API physical properties, formulation, process parameters, equipment, scale	**Moderate**		**Adequate**	
Physical stability (solid state)	API physical properties, formulation, process parameters, equipment, scale	**Moderate**		**Adequate**	
Dissolution – BCS Class II & IV	Formulation, API properties, container closure, moisture, process parameters	**High**		**Adequate**	
Microbial limits	Formulation, container closure, moisture, process parameters	**Low**		**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

CMC Lead
Office of New Drug Products
Division of New Drug Products II

12/11/2020

Reference ID: 4716100

Martha Heimann

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

The PI currently does not have the actual tradename ("Ponvory"). This will be edited during the labeling negotiation.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Tradename	adequate
Established name(s)	ponesimod	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.	(b) (4) tablets: 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
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.	n/a	n/a

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)	n/a	n/a

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Reference ID: 4716100

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Film-coated tablets	adequate
Strength(s) in metric system	2, 3, 4, 5, 6, 7, 8, 9, 10, 20 mg	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	color, size and debossing for each strength described	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
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.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Tradename (ponesimod)	adequate
Dosage form(s) and route(s) of administration	tablets for oral administration	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	adequate
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	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	sphingosine 1-phosphate receptor modulator	adequate
Chemical name, structural formula, molecular weight	Yes	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	white to light yellowish powder that is practically insoluble or insoluble in water	adequate

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Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	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	n/a

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	Starter pack: 2, 3, 4, 5, 6, 7, 8, 9, 10 mg Bottle: 20 mg	adequate
Available units (e.g., bottles of 100 tablets)	Starter pack: 14 Bottles: 30	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Color, size, and debossing for each strength of the tablets are listed. NDC number provided for the two packaging configurations.	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
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.	n/a	n/a

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.)	Store in the original package. Do not discard desiccant. Protect from moisture.	The drug product is (b) (4) and the desiccant should be kept in the bottle.
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.”	A warning (b) (4)	adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF)	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.”	n/a	n/a
Include information about child-resistant packaging	Child Resistant Starter Pack. Bottle of 30 tablets with child-resistant closure.	adequate

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they 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: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560	adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Medication Guide is adequate from the CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Ponvory (ponesimod) tablets	adequate
Dosage strength	20 mg	adequate
Route of administration	Not specified	Adequate for tablets
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	30	adequate
"Rx only" displayed on the principal display	Yes	adequate
NDC number	NDC 50458-720-30	adequate
Lot number and expiration date	Yes	adequate
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 from 15°C to 30°C (59°C to 86°F) [see USP Controlled Room Temperature]. Store in the original package. Do not discard desiccant. Protect from moisture. This package is child-resistant.	adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A

Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Janssen Pharmaceuticals, Inc. Titusville, NJ 08560	adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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BIOPHARMACEUTICS

NDA: NDA-213498-ORIG-1
Drug Product Name / Strength: Ponvory™ (ponesimod) Tablets / 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg
Route of Administration: Oral
Indication: Relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Applicant: Janssen Research and Development, LLC
Submission Dates: 03/18/2020; 07/17/2020
Primary Reviewer: Bryan Ericksen, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

BACKGROUND:
The Applicant is seeking approval of Ponvory™ (ponesimod) Tablets (immediate-release; film-coated), 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg, indicating for relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. A 14-day titration scheme was proposed to start with one 2 mg oral tablet taken once-daily until reaching target maintenance dose 20 mg, once-daily.

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, 2) formulation bridging throughout product development, 3) the need for biowaiver for the proposed ER drug product. Summary of the key findings are presented below.

REVIEW SUMMARY: Adequate

(1) Dissolution Method and Acceptance Criterion:
The Applicant developed and proposed (b) (4) method for the proposed drug product: USP Apparatus 2 (Paddle) at 75 rpm in pH 4.5 phosphate buffer 900 mL with 0.2% CTAB, 37 ± 0.5 ºC. The testing condition/parameters, including type and amount of added surfactant. were adequately selected and justified. The proposed dissolution method was shown to discriminating toward particle size/distribution, but not (b) (4) parameters, (b) (4), or stressed storage conditions. The proposed acceptance criterion of Q= (b) (4)% in 30 minutes is deemed acceptable, considering the totality of the drug release data, physicochemical properties, and PK property (including Tmax being 2-4 hours, not considered as critical, clinically).

(2) Formulation Bridging:
A capsule formulation was initially developed for early Phase 1 studies. The proposed tablet formulation of various dosage strengths was later developed for use in later clinical trials (Phase 1, 2 and 3) and for commercialization. Therefore, no bridging of formulations is necessary between the capsule and tablet formulations.

Changes in color coating and debossment were made for the tablets, which is considered as Level-1 changes in SUPAC-IR Guidance and do not require comparative dissolution testing for the bridging.

(3) Biowaiver:
No request for biowaiver is necessary because different formulations and all strengths were used through clinical development.

RECOMMENDATION:
Form a Biopharmaceutics perspective, NDA 213498 for Ponvory™ (ponesimod) Tablets, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg, is deemed adequate and recommended for APPROVAL.

FDA-Approved dissolution method and acceptance criterion for quality control and stability testing of the proposed Ponvory™ (ponesimod) Tablets

USP Apparatus	Speed (RPM)	Medium/Temperature	Volume (mL)	Acceptance criterion
2 (Paddle)	75	pH 4.5 phosphate buffer with 0.2% CTAB / 37 ± 0.5 ºC	900 mL	Q= (b) (4)% in 30 minutes

BIOPHARMACEUTICS ASSESSMENT:

List Submissions being reviewed (table):

03/18/2020	NDA 213498/Sequence 0001/Original Submission
07/17/2020	NDA 213498/Sequence 0013/Response to Information Request

I. *BCS Designation*

No BCS designation was requested. The provided aqueous solubility, in vitro permeability, and absolute bioavailablity data indicate that ponesimod can be considered as a BCS Class 4 drug substance, i.e., low solubility and low permeability, per the FDA's BCS Guidance (2017).

Solubility:

Ponesimod is poorly soluble since the highest anticipated dose strength of 20 mg (also the target maintenance dose taken once-daily) is not soluble in 250 mL of aqueous media over the pH range of 1-7.5 (Table 1). The following solubility data were submitted in module 3.2.P.2.2.3:

Table 1. Drug substance solubility in aqueous media of different pH values at 37 ºC

Medium	Solubility (g/100 mL)	pH of Solution
0.1N HCl	0.0144	1.14
0.01N HCl	0.0023	2.11
0.001N HCl	0.0013	3.09
0.05M pH 4.5 Phosphate buffer	0.0009	4.65
0.05M pH 6.6 Phosphate buffer	0.0008	6.60
0.05M pH 6.8 Phosphate buffer	0.0010	6.79
0.05M pH 7.5 Phosphate buffer	0.0012	7.51
Water	0.0011	-

Permeability:

The Applicant claimed that permeability of ponesimod is (b) (4) in a Caco-2 cell monolayer (b) (4) according to absolute bioavailability, human mass balance study (^{14}C-dose) , PK dose-linearity in SAD study, and lacking in food effects. (b) (4) The time to reach maximum plasma concentration (Tmax) of ponesimod is reported to be 2-4 hours post-dose.

The permeability of ponesimod was investigated in in vitro bidirectional study using the Caco-2 cell monolayer model, including low and high permeability markers (atenolol and propranolol). The apparent permeation rates of ponesimod ($Papp_{AB}$ = 7.16~12.7 x 10^{-6} cm/sec in

concentrations studied) in this model fell in between $Papp_{,AB}$= 0.47 x 10^{-6} cm/sec and 22.0 x 10^{-6} cm/sec for atenolol and propranolol, respectively, and was concluded by the Applicant that ponesimod is a drug substance with (b) (4) permeability without evidence (b) (4) The Caco-2 cell model was validated with regards to cell integrity and functional expression of MDR-1 (with digoxin as substrate).

Dissolution:

The proposed dissolution method employed 0.2% detergent in order to achieve greater than (b) (4)% dissolution in 30 minutes. The use of detergent is characteristic of a low solubility active pharmaceutical ingredient (API).

II. *Dissolution Method and Acceptance Criteria*

The development of the dissolution method was detailed in Module 3.2.P.2.2.3 (\\cdsesub1\evsprod\nda213498\0001\m3\32-body-data\32p-drug-prod\active-tablet\32p2-pharm-dev\pharmaceutical-development-properties.pdf).

Table 2. Parameters of the proposed dissolution method

Parameter	Value
Dissolution Apparatus:	Paddle (USP type 2, Ph. Eur., JP)
Dissolution Medium Temperature:	37.0 °C ± 0.5 °C
Dissolution Medium Volume:	900 mL
Dissolution Medium:	pH 4.5 phosphate buffer containing 0.2% (b) (4) CTAB
Rotation Speed:	75 rpm
Sample Filter:	(b) (4) or equivalent
Analytical Finish:	HPLC with (b) (4) nm

Apparatus

The USP Apparatus 2 was chosen because it is the preferred apparatus for tablet formulations.

Volume

A standard medium volume, 900 mL, was selected.

Dissolution Medium

To select the dissolution medium, solubility studies were done in various media and pH values, including water (see aqueous solubility in Table 2).

(b) (4)

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(b) (4)

[redacted]

Discriminating Ability of the Dissolution Method

The discriminating capabilities were investigated with different drug product batches, drug substance particle sizes and drug product compositions, and applying changes in process parameters.

Particle Size

The target particle size is given by the drug substance specification in module 3.2.S.4.1, as shown in table 4:

Table 4. Particle size distribution

Particle size distribution[1]	
- D_v50	(b) (4) µm
- D_v90	µm

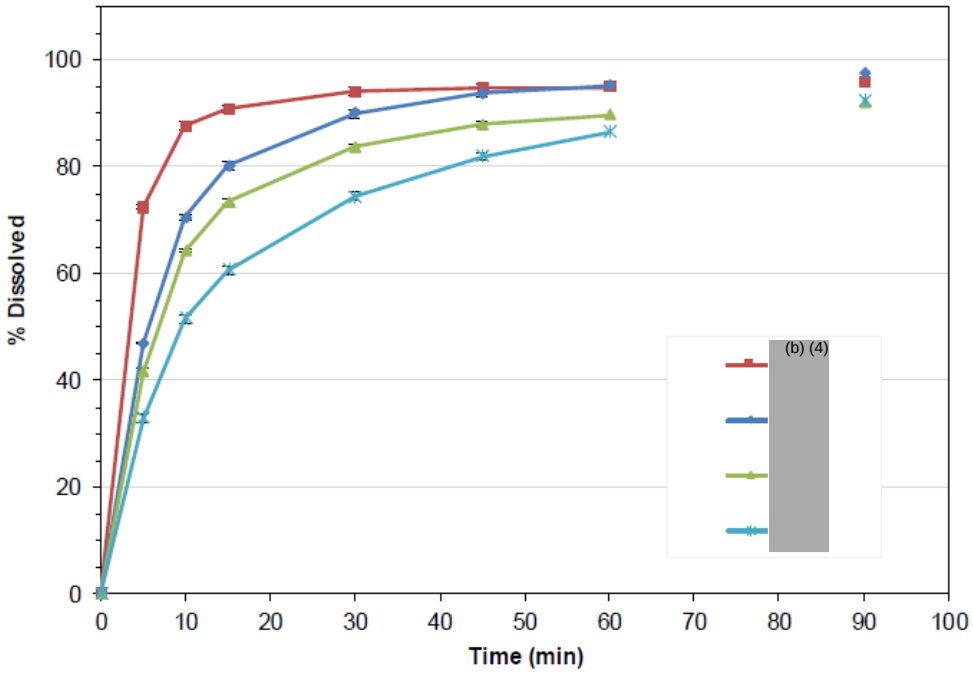
Four batches (20 mg) with different particle sizes were analyzed, as shown in Table 5 below.

Table 5. Information about batches used to demonstrate discriminating capability for particle size

DP Batch (20 mg)	DS Batch	Label	Particle Size (µm) d_v10	d_v50	d_v90
7405 (b) (4)	LTT4MA1005 (L16364A1-Trial-2)				
8419 (b) (4)	LTT4AA1001 (b) (4)				
8420 (b) (4)	LTT4AA1001 (b) (4)				
7406 (b) (4)	LTT4AA1005				

Dissolution results using these batches are shown below.

Figure 4. Mean dissolution profiles of batches produced with drug substance of different particle sizes (n=3)



The (b) (4) particle size would not have passed the acceptance criterion of Q= (b) (4)% in 30 minutes. Therefore, the discriminating ability of the method has been demonstrated with respect to particle size. Note that this particle size is excluded by the particle size specification.

(b) (4) **Parameters**

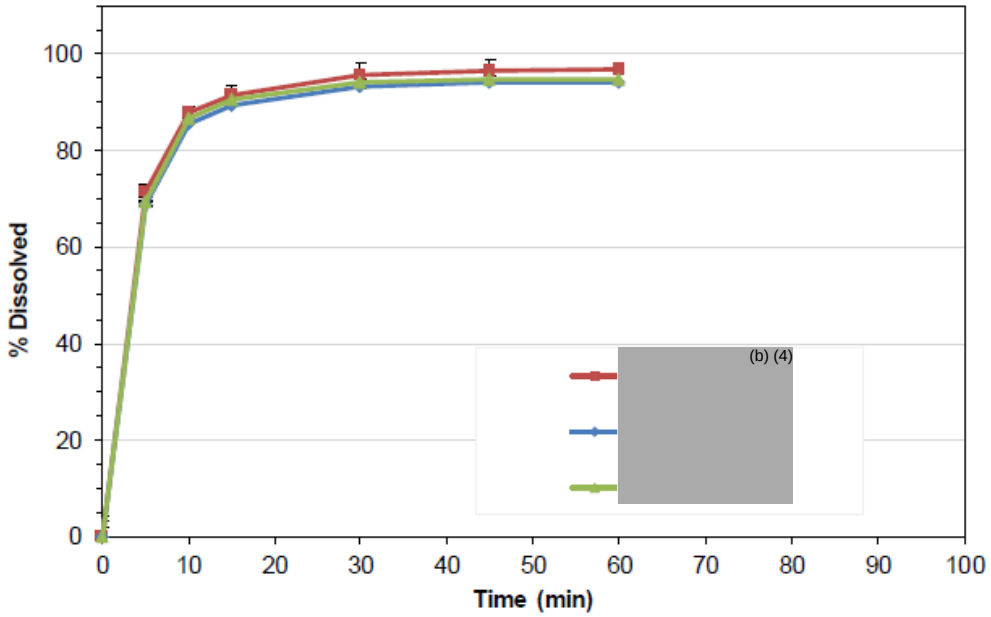
Batches that varied with respect to (b) (4) were tested; however, dissolution profiles of the varied batches were highly similar. Therefore, the dissolution method is not discriminatory with respect to (b) (4) parameters, as shown Table 6 and Figure 5 below.

Table 6. Batches used to demonstrate discriminating capability for (b) (4) parameters

DP Batch (5-mg)	(b) (4)
8328	(b) (4)
8326	
8331	

DP = drug product;

Figure 5. Average dissolution profiles of ponesimod 5 mg tablet produced with different levels of (b) (4)



(b) (4)

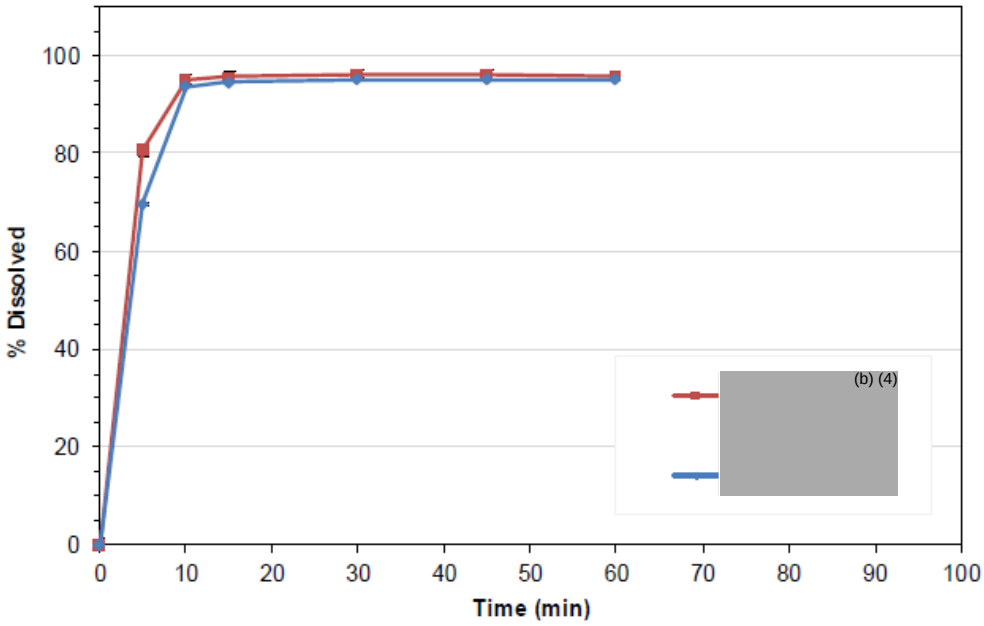
Batches (10 mg) that varied with respect to (b) (4) were tested; however, dissolution profiles of the varied batches were highly similar. Therefore, the dissolution method is not discriminatory with respect to (b) (4), as shown in Table 7 and Figure 6 below.

Table 7. Batches used to demonstrate discriminating capability for (b) (4)

DP Batch (10-mg)	(b) (4)
7103	(b) (4)
7103	

DP = drug product;

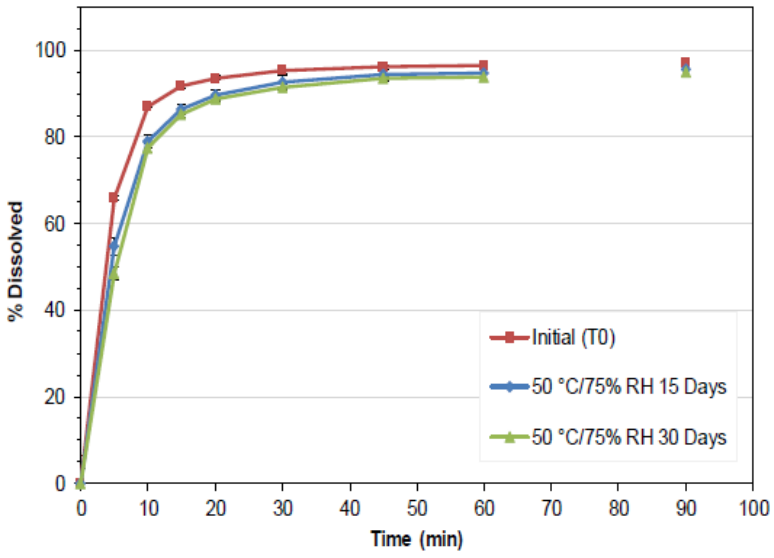
Figure 6. Average dissolution profiles of ponesimod 10 mg tablets produced with a different [redacted] (b) (4)



Drug Product Stability Changes

Storage conditions of batches that were exposed to high temperature and humidity were tested; however, dissolution profiles of the varied batches were similar and would have passed the acceptance criterion of Q= [redacted] (b) (4)% in 30 minutes. Therefore, the dissolution method is not discriminatory with respect to drug product stability, as shown in Figure 7 below.

Figure 7. Average dissolution profiles of ponesimod of batch 7409 (20 mg) exposed to open dish for 15 days and 30 days at accelerated condition 50 ºC/75% RH (n=3) and initial (T_0) (n=6)



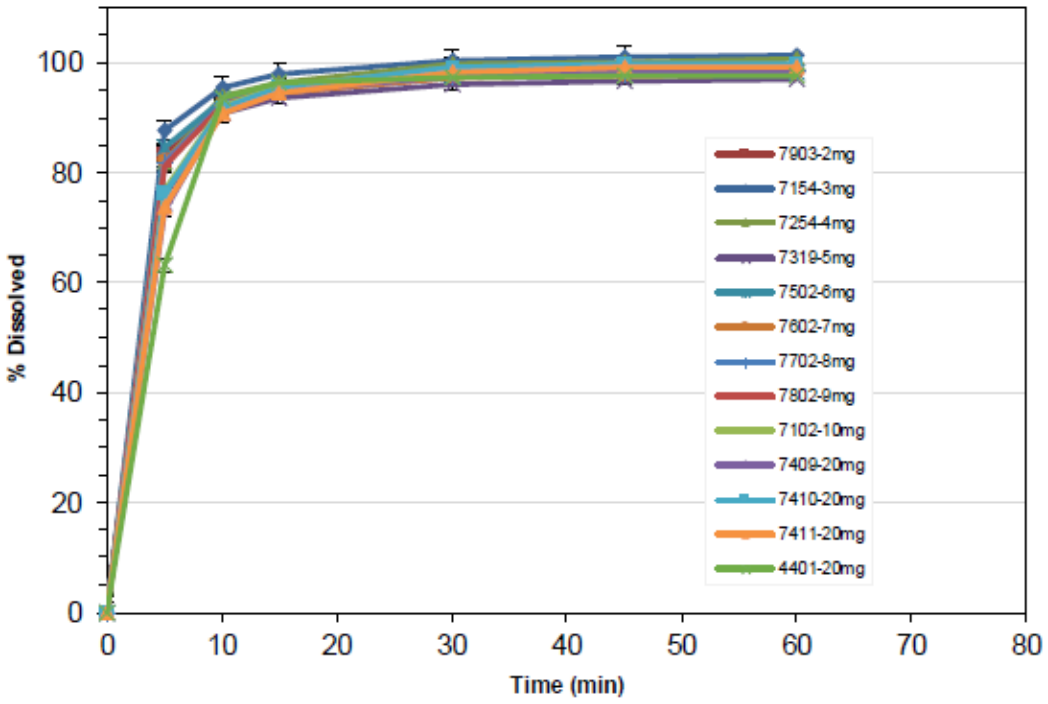
Stability Drug Release Data

The Applicant included full profile stability data for accelerated, long-term, and intermediate storage conditions. All stability data met the acceptance criterion of Q= (b) (4)% in 30 minutes, and no trends were noted.

Acceptance Criterion

The Applicant proposed Q= (b) (4)% in 30 minutes as the dissolution acceptance criterion for QC of batch release and stability testing. As illustrated in Figure 8, similar dissolution profile data across all strengths (2~20 mg) of the exhibit batches, including primary registration stability and clinical batches (n=12), using the proposed dissolution method, submitted in response to an Information Request (***Appendix 1***) conform to the proposed specifications (See \\cdsesub1\evsprod\nda213498\0013\m3\32-body-data\32p-drug-prod\active-tablet\32p2-pharm-dev\pharmaceutical-development-dissolution-data.pdf). Considering the totality of the drug release data, physicochemical properties, and PK property (including Tmax being 2~4 hours, not considered as critical, clinically, or for timely disease control), this Reviewer determines that the proposed acceptance criterion is acceptable.

Figure 8. Mean dissolution profile data of ponesimod batches (2~20 mg strengths) using the proposed dissolution method (n=12)



III. *Formulations Bridging*

For the initial safety and dose finding clinical trials (Phase 1 and 2), a capsule formulation (b) (4) was used. A tablet formulation (preferred for commercialization) of different dosage strengths (1, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 20 and 40 mg) was developed subsequently for use in later clinical trials (Phase 1, 2 and 3) and for commercialization (2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg strength). Therefore, no bridging of formulations is necessary between the capsule and tablet formulations.

The initial tablets, including those used in the human bioavailability trial (AC-058-108), had a brown coating for all dosage strengths and did not have a debossing. For later open label clinical trials and for the commercial tablets, different coating colors were applied for different dosage strengths and a debossment was applied on both sides of the tablets. These changes in appearance are not considered to significantly affect the drug release from the proposed drug product, as per Level-1 changes in SUPAC guidance. Therefore, comparative dissolution testing is not necessary for bridging this change in formulation.

IV. *Biowaiver*

No request for biowaiver is necessary because different formulations and all strengths were used throughout the clinical development. Of note, it was reported that drug exposure (Cmax and AUC) increased approximately dose-proportionally following ponesimod oral dosing in the 1-75 mg dose range studied.

APPENDIX 1

Information Request (dated May 29, 2020):

Complete dissolution data (all raw data, range, mean, % CV, date of dissolution testing) for n=12 units for three exhibit batches of the 20 mg strength, including the biobatch, and one batch of each other strength. Submit data in Module 3.2.P.2, and submit all dissolution data in Excel format

The Applicant's Response to Information Request (IR) (dated 07/17/2020):

\\cdsesub1\evsprod\nda213498\0013\m3\32-body-data\32p-drug-prod\active-tablet\32p2-pharm-dev\pharmaceutical-development-dissolution-data.pdfThe Applicant submitted the dissolution data requested. Since all batches complied with stage 1 acceptance criteria according to USP <711>, n=6 data were obtained. Therefore, the test results of the 1-month stability time point at 25 ºC/60% RH have also been included in the dissolution tables to obtain n=12. No stability trend was observed at the 1-month time point.

Bryan Ericksen

Digitally signed by Bryan Ericksen
Date: 12/04/2020 12:30:29PM
GUID: 59285fba002134adea4d6f405770a2b2

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 12/04/2020 12:31:56PM
GUID: 508da6df000269e151ff37cd8f4e13a1

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/

MARTHA R HEIMANN
12/11/2020 06:56:13 PM