CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213716Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 213716

Integrated Quality Assessment

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval – once labeling deficiencies addressed
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213716
Assessment #1

Drug Product Name	Voclosporin capsules
Dosage Form	capsules
Strength	7.9 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Aurinia Pharmaceuticals Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Presubmission	13-APR-2020	All
Amendment	23-APR-2020	Drug Substance
Original	22-MAY-2020	All
Amendment	16-JUN-2020	Manufacturing
Amendment	18-AUG-2020	Labeling
Amendment	11-SEP-2020	Drug product, biopharmaceutics, manufacturing
Amendment	21-SEP-2020	Labeling
Amendment	24-SEP-2020	Drug product
Amendment	08-OCT-2020	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Duncan	Donna Christner
Drug Product	Zhengfang Ge	Wendy Wilson-Lee
Manufacturing	Ramesh Dandu	Yong Hu
Microbiology	Ramesh Dandu	Yong Hu
Biopharmaceutics	Kamrun Nahar	Haritha Mandula
Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Craig Bertha	
Laboratory (OTR)	N/A	
Environmental	Zhengfang Ge	Wendy Wilson-Lee

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Based on the evaluation of the drug substance, drug product, biopharmaceutics, manufacturing, and facilities, the application is considered to be ready for approval. However, there are labeling deficiencies that need to be addressed by the applicant before approval can be recommended.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Voclosporin is a calcineurin-inhibitor immunosuppressant indicated for the treatment of patients with lupus nephritis (LN)
Duration of Treatment	Chronic
Maximum Daily Dose	47.4 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The voclosporin (a new molecular entity) drug substance CMC information is cross-referenced to DMF 033779. DMF 033779 was reviewed by Katharine Duncan on 07-Oct-2020 (Panorama) in support of this NDA and found adequate. The applicant provides a brief description of the general properties of the drug substance and organic impurities. The applicant provides the specification used by the manufacturer for the release of the drug substance. The analytical methods and validation reports are cross-referenced to DMF 033779. The applicant has set an **API retest period of** (b) (4) **months when stored at** (b) (4) **°C**, which is acceptable. The NDA is recommended for approval from the perspective of drug substance quality.

Drug Product: Adequate

Voclosporin capsules (7.9 mg) for oral administration are for immediate release and are formulated in (b) (4) soft gelatin capsules. The total daily dose is 47.4 mg (23.7 mg BID). All excipients are of compendial grade or are mixtures excipients of compendial grade. (b) (4) (b) (4)

(b) (4) The container closure system consists of aluminum foil/foil blisters. The applicant provided stability data for the drug product to support a **36 months expiration dating period when stored at 20 to 25ºC (68 to 77ºF) with excursions permitted to 15 to 30ºC (59 to 86ºF)**.

Method verification for Method 001651 HPLC for Assay and Degradation Products is still pending from Office of Testing and Research at the current time due to COVID-19 restriction.

Labeling: Inadequate

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved. Refer to the labeling chapter below for details.

Manufacturing: Adequate

Voclosporin is practically insoluble in water.

(b) (4) is the manufacturing facility for the Voclosporin capsule drug product. Firm's profile code CSG (Capsules, Soft Gelatin) is acceptable from the Post approval inspection, and GMP inspections in Feb 2019 and June 2018, respectively. This facility has substantial softgel processing experience based on inspectional history. Based on acceptable profile and compliance coverage site is acceptable for proposed function. The drug substance (DS) manufacturing facility is Lonza AG (FEI: 3002930340). Synthesis at this site (Lonza) consists of (b) (4)

(b) (4)

(b) (4) This site is acceptable based on recently concluded PAI and GMP inspections (b) (4)

(b) (4) Control testing facilities and packing facilities listed are acceptable based on profile and compliance coverage. Final facility recommendation (OMIR) shall be made at the time of quality due date.

(b) (4)

(b) (4)

(b) (4) This review entails evaluation of the study data from their (i) process scale-up, (ii) overall control strategy, (iii) the proposed parameter ranges and in-process controls during manufacture to determine the acceptability of their manufacturing process.

Biopharmaceutics: Adequate

Overall, Voclosporin softgel capsules demonstrated dissolution profiles with high variability at early time points which diminished afterwards. The dissolution method is discriminatory to the formulations (b) (4) (b) (4) (b) (4) Dissolution method may show some significant difference in drug release profiles due to variations in (b) (4) (b) (4). Hence, dissolution method is acceptable. Dissolution data demonstrated complete release of the drug at 45 minutes and dissolution acceptance criterion is set as Q= (b) (4)% in 45 minutes. **The applicant did not attempt to demonstrate clinical relevance of the dissolution method and hence the method is an acceptable quality control test.**

Microbiology (if applicable):

N/A

Final Risk Assessment

DP CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA FMECA RPN #	Comments/Lifecycle considerations
Identification	• Formulation of incorrect API	2	3	1	6	(b) (4)		
Assay	• degradation of API during manufacture or during drug product shelf life • incorrect amt. formulated	2	3	2	12			
Uniformity of dosage units	(b) (4)	3	3	2	18			

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

						(b) (4)		
Dissolution	• Moisture uptake during shelf-life leading to precipitation of API (b) (4)	1	3	4	12			
Degradation Products	• degradation of API during manufacture or during drug product shelf life • API interaction with excipients	2	3	2	12			
Appearance	• gel mass color/air bubbles • capsule leakage due to (b) (4)	2	3	3	18			

						(b) (4)		
Ethanol Content (b) (4) (b) (4)	• Loss during manufacturing • Loss during shelf life due to failure of blister package seal	3	3	3	27		3x3x2=18	(b) (4)
Water Content	• Failure of blister package seal	3	3	3	27		3x3x2=18	See above
Microbial Limits Tests	• Failure of blister package leading to moisture uptake to levels high enough to support microbial growth	3	3	3	27		3x3x2=18	See above

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

See labeling chapter of IQA (p. 125 of 152)

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Craig M. Bertha, CMC Lead for DPACC/DRTM, 21-OCT-2020

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
33779	II	Lonza AG	Voclosporin	**Adequate**	07-OCT-2020	
(b) (4)	II		(b) (4)	**Adequate**	15-SEP-2020	
	II			**Adequate**	31-AUG-2020	
	IV			**Adequate**	09-OCT-2020	
	III			N/A		Sufficient information provided in NDA

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	114577	Voclosporin for LN
(b) (4)		

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other				

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	pending
Established name(s)	**(voclosporin) capsules**	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.	capsules, 7.9 mg	Adequate
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 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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2 DOSAGE AND ADMINISTRATION

(b) (4)

[redacted]

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)	Capsules must be swallowed whole and must not be opened, crushed, or divided.	**Adequate**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

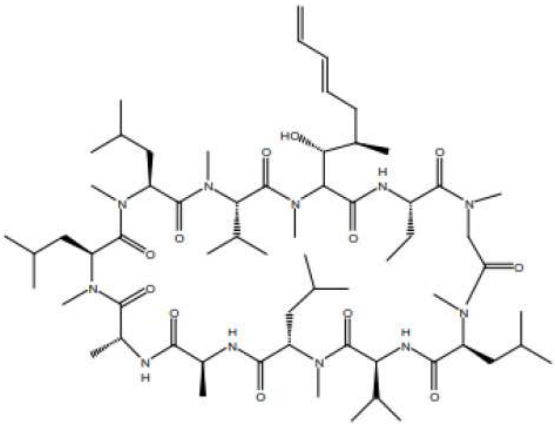
(b) (4) capsules: 7.9 mg (voclosporin) oval, pink/orange in color, imprinted on one side with VCS in white ink.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	capsules	**delete** (b) (4)
Strength(s) in metric system	7.9 mg	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	oval, pink/orange in color, imprinted on one side with VCS in white ink	**Adequate**
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 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	

1.2.3 Section 11 (DESCRIPTION)

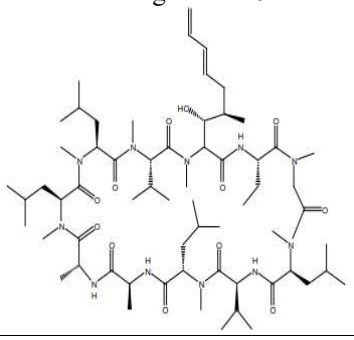
(b) (4) a calcineurin-inhibitor immunosuppressant, is available for administration as soft gelatin capsules containing (b) (4) 7.9 mg of drug substance per capsule. Inactive ingredients include alcohol, Vitamin E polyethylene glycol succinate (NF), polysorbate 40 (NF), and medium-chain triglycerides (NF).

Voclosporin (90 to 95% *trans*-isomer) is the active ingredient in (b) (4) Chemically, voclosporin is named: Cyclo{{(6E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6,8-nonadienoyl}-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}. The chemical structure of voclosporin is:



Voclosporin has an empirical formula of $C_{63}H_{111}N_{11}O_{12}$ and a molecular weight of 1214.6. It appears as white to off-white solid matter. At ambient temperature, voclosporin is freely soluble in acetone, acetonitrile, ethanol, and methanol, and practically insoluble in heptanes (USP). Voclosporin is practically insoluble (less than 0.1 g/L at 20°C) in water and melts above 144°C with decomposition.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	**Not Adequate** - Change (b) (4) "(voclosporin) capsules
Dosage form(s) and route(s) of administration	capsules	**Adequate** Added "(voclosporin) capsules" as above
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	**Not Adequate** - The active ingredient is not a salt, delete (b) (4) in front of "7.9 mg of the drug substance"
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	alcohol, Vitamin E polyethylene glycol succinate (NF), polysorbate 40 (NF), and medium-chain triglycerides (NF)	**Not Adequate** - Add all the inactive ingredients contained in the soft gelatin capsule
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	Not applicable for capsules
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	calcineurin-inhibitor immunosuppressant	**Adequate**

Chemical name, structural formula, molecular weight	Cyclo{{(6E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6,8-nonadienoyl}-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl} The compound has the empirical formula $C_{63}H_{111}N_{11}O_{12}$ and molecular weight 1214.6 	**Not Adequate** - Add "g/mole" after the molecular weight
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	It appears as white to off-white solid matter. At ambient temperature, voclosporin is freely soluble in acetone, acetonitrile, ethanol, and methanol, and practically insoluble in heptanes (USP). Voclosporin is practically insoluble (less than 0.1 g/L at 20°C) in water and melts above 144°C with decomposition.	**Adequate**

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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) packed in cold-formed aluminum blisters, consisting of laminated backing and lidding materials that are thermo-sealed together. Four individual 3 × 5 blister strips are assembled into a cardboard wallet.

(b) (4)

(b) (4) is provided in child-proof packaging to avoid unintentional ingestion of study medication by children.

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4) capsules	**Adequate** - **remove** (b) (4)
Strength(s) in metric system	7.9 mg	**Adequate**
Available units (e.g., bottles of 100 tablets)	Four individual 3X5 blister strips	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Identification is not provided NDC number is provided	**Not Adequate** Add "oval, pink/orange capsules, imprinted on one side with VCS in white ink" Remove (b) (4) see DP review
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 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	**Adequate**
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.)	N/A	**Adequate**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at controlled room temperature 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 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	N/A	

or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	(b) (4) is provided in child-proof packaging to avoid unintentional ingestion of study medication by children	**Adequate**

1.2.5 Other Sections of Labeling

N/A

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: Aurinia Pharmaceuticals Inc. Victoria, BC Canada Distributed by: Aurinia Pharma U.S., Inc. Rockville, MD USA	**Not Adequate** Add street address, and zip code

2.0 PATIENT LABELING

The following dosing guidance is provided

- **capsules must be swallowed whole and must not be opened, crushed, or divided.**

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (blister wallet)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4) (b) (4)	**Not Adequate** The format of the drug product name, dosage form and strength should be displayed as: (b) (4) (voclosporin) capsules 7.9 mg
Dosage strength	7.9 mg	**Adequate**
Route of administration	(b) (4), for oral use	**Not Adequate** Delete (b) (4) in front of "for oral use"
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	On blister pack: 60 capsules (4 blister packs of 15 capsules) On carton: 180 capsules (3 wallets of 60 capsules each)	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Not provided	**Not Adequate** Add lot number and expiration date on container and carton labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	On Labels for Container and Carton: Medication should be stored at controlled room temperature 20°C-25°C (68°F-77°F). Excursions permitted to 15°C- 30°C (59°F-86°F)	**Not Adequate** Add "[see USP Controlled Room Temperature]"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	**Adequate**

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		**Adequate**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	**not applicable for solid oral dose**
Bar code	Provided in carton not in blister wallet	**Not Adequate** **Add bar code in the blister wallet**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	**Adequate**
Medication Guide (if applicable)	(b) (4)	**Adequate**
No text on Ferrule and Cap overseal	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	Keep out of reach of children, are provided in carton label.	**Adequate**

Assessment of Carton and Container Labeling: *Inadequate*

1. The format of the drug product name, dosage form and strength should be displayed as:

(b) (4)

(voclosporin) capsules 7.9 mg

2. Delete [redacted] in front of "for oral use"
3. Add lot number and expiration date on container and carton labels
4. Add "[see USP Controlled Room Temperature]" after the storage condition
5. Add bar code in the blister wallet
6. Remove [redacted]

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

The following changes have been implemented in the PI

For Prescribing Information:

Section 3 Dosage Forms and Strengths

1. Delete [redacted]

Section 11 Description

2. Change the 1st sentence from [redacted] to [redacted] (voclosporin) capsules
3. Add "soft gelatin capsule" in the inactive ingredient list
4. The active ingredient is not a salt, delete [redacted] in front of "7.9 mg of the drug substance"
5. Add all the inactive ingredients contained in the soft gelatin capsule

Section 16: How Supplied

6. Remove [redacted] in the dosage form
7. Add identification "oval, pink/orange capsules, imprinted on one side with VCS in white ink"
8. Remove [redacted]

The following deficiencies in the carton/container labels need to be conveyed to the applicant

9. For Container/Carton Labels:

10. The format of the drug product name, dosage form and strength should be displayed as:

(b) (4)

(voclosporin) capsules 7.9 mg

11. Delete (b) (4) in front of "for oral use"
12. Add lot number and expiration date on container and carton labels
13. Add "[see USP Controlled Room Temperature]" after the storage condition
14. Add bar code in the blister wallet
15. Remove (b) (4)

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

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

Wendy Wilson, Ph. D.
Director/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 10/19/2020 09:17:04AM
GUID: 508da7210002a030e76df4f60ccd142a

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 10/20/2020 09:16:11AM
GUID: 50816dbc000085595ca3284bbca465a8

0BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 213716-ORIG-1

Drug Product Name / Strength: Voclosporin softgel capsule, 7.9 mg

Route of Administration: Oral

Applicant Name: Aurinia Pharmaceuticals Inc.

FDA Received date: 03/12/2020

Review Summary: ADEQUATE
The proposed drug product, Voclosporin softgel capsule, 7.9 mg is an immediate release softgel capsule dosage form which is indicated for the treatment of Lupus Nephritis (LN). The Applicant seeks approval of this NDA via the 505(b)(1) regulatory pathway.

List Submissions being reviewed: Dissolution method and acceptance criterion among formulations.

1. 0001 (1) 03/12/2020 ORIG-1/ Multiple Categories/Subcategories
2. 0015 (15) 09/11/2020 ORIG-1/ Multiple Categories/Subcategories

Highlight Key Outstanding Issues from Last Cycle: None

Solubility: Voclosporin is practically insoluble in water. Aqueous solubility of Voclosporin is given below-

Table 1: Solubility of Voclosporin in aqueous buffer-

Media	Saturation concentration µg/mL	Concentration in 250 mL (mg/250 mL)	Solubility
USP pH buffer 1.2	9.5	2.34	Practically insoluble
USP pH buffer 4.5	4.4	1.1	Practically insoluble
USP pH buffer 6.8	10.8	2.7	Practically insoluble

From the solubility data, it is observed that Voclosporin is sparingly soluble in 250 mL. The label claimed amount of the drug is 7.9 mg. Hence, as per the BCS classification, Voclosporin is a low soluble drug.

As Voclosporin drug substance (DS) is practically insoluble in water, (b) (4) Hence, DS solid state form and particle size do not have impact on drug product (DP) performance.

Voclosporin softgel capsule formulation:

Voclosporin softgel capsule 7.9 mg is the to-be-marketed (TBM) product which is an immediate release capsule. (b) (4) Voclosporin drug substance (DS) is practically insoluble in water, (b) (4) . Hence, DS solid state form and particle size do not have impact on drug product (DP) performance. Refer to the drug product and process review for additional details. The composition of the capsule is given below.

Table 2: Composition of the Voclosporin softgel capsules

Component	Function	Quality Standard	Amount % w/w	Quantity Per Capsule (mg)
(b) (4)				
Voclosporin	Drug Substance	In-house	(b) (4)	7.9
Dehydrated Alcohol	(b) (4)	USP		21.57
Vitamin E Polyethylene Glycol Succinate		NF		(b) (4)
Polysorbate 40		NF		
Medium Chain Triglycerides		NF		
(b) (4)				
Gelatin	(b) (4)	NF		
(b) (4)		In-house[b]		
Purified Water		USP		
Iron Oxide, Yellow		NF		Refer to DMF No (b) (4)
Iron Oxide, Red		NF		
Titanium Dioxide		USP		
(b) (4)		NF		
		In-house		
		In-house		
(b) (4) White (b) (4) (b) (4)	Ink	In-house		(b) (4)
Total Capsule Weight	--	--	--	374.72[b]
(b) (4)				

Voclosporin softgel capsule development history:

(b) (4)

(b) (4)

Bridging study:
N/A. The TBM formulation of Voclosporin softgel capsule, 7.9 mg is used in all the pivotal phase 3 clinical studies. Hence bridging study is not required.

Biowaiver request:
N/A. The applicant is seeking approval of Voclosporin softgel capsule, 7.9 mg, which is used in all pivotal phase 3 studies. Hence biowaiver is not required.

Batches used in clinical trial:

Table 3: Summary of the batches used for the clinical trial and manufacturing process development

Drug Product Batch	Strength (mg)	Site of Manufacture	Theoretical Batch Size (capsules)	Batch Use
3792408[a]	7.9	(b) (4)		Commercial-Scale Demonstration and Confirmation on New Gelatin Evaluation
3705624[b]	7.9			New Gelatin Evaluation
3705628[b]	7.9			New Gelatin Evaluation
3791495[b]	7.9			New Gelatin Evaluation
3705630[b][c]	7.9			New Gelatin Evaluation
3161303	7.9			Phase 3 Clinical Study/ Primary Registration Stability
3137084	7.9			Phase 3 Clinical Study/ Primary Registration Stability
3088814	7.9			Phase 3 Clinical Study/ Primary Registration Stability
14JM-281	7.9			Phase 2 and 3 Clinical/ Supportive Registration Stability
13JM-274	7.9			Phase 2 Clinical/ Supportive Registration Stability
12JM-131	(b) (4)			Supportive Registration Stability
12JM-119				Supportive Registration Stability

(b) (4)

Refer to the Appendix 1 for the link of the list of batches used in clinical trial.

Dissolution method development and parameter selection:

(b) (4)

(b) (4)

Discriminating ability of the dissolution method:
The Applicant demonstrated discriminating ability of the dissolution method by considering several factors, i.e. presence of high level of (b) (4) in raw materials, formulation variables, i.e. different (i.e. low and very low) (b) (4) levels, different amount of (b) (4) and the softgel capsules shell variables, i.e. shell weight and under and over (b) (4)

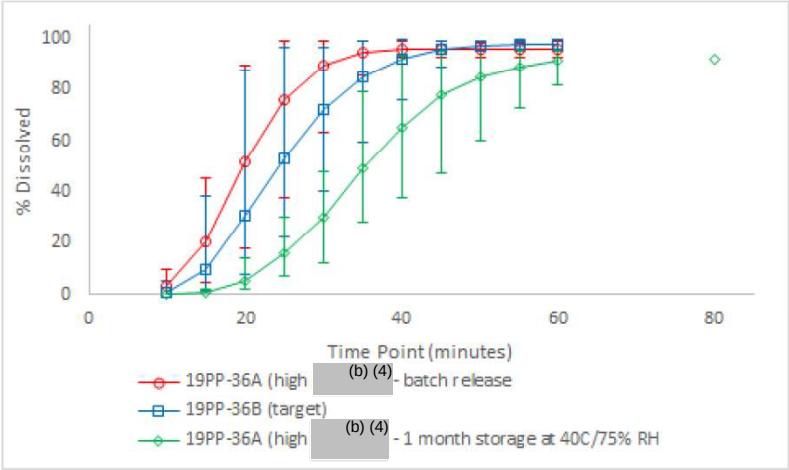
Table 6: Overview of the factors considered in the Voclosporin capsules to determine discriminating ability of the dissolution method

Batch	Sub-lot	Factor Variation Description
19PP-36	19PP-36A	High level of (b) (4) in raw materials[a]
	19PP-36B	Target batch
	19PP-36C	Shell weight variation – low
	19PP-36D	Shel weight variation – high
	19PP-36B1	Under (b) (4)
	19PP-36B2	Over-
19PP-54	19PP-54A	Low (b) (4) level (b) (4)
	19PP-54B	Very low (b) (4) level (b) (4)
19PP-55	19PP-55A	(b) (4)
	19PP-55B	
	19PP-55C	
	19PP-55D	
	19PP-55E	
	19PP-55F	

a Batch 19PP-36A was also evaluated following 1 month of storage at 40°C/75%RH.
Notes: (b) (4)

High level of (b) (4) in raw materials:
The applicant developed a batch, i.e. 19PP-36A with high level of (b) (4) in raw materials. Dissolution data at release of the batch 19PP-36A is similar as the target batch. However, after one-month storage at 40°C/75RH, drug release rate was of the batch 19PP-36A has been decreased compared to fresh batch. This may be due to the formation of cross-linking in the capsule shell due to the presence of high level of (b) (4) in the shell in the accelerated storage condition, i.e. 40°C/75%RH.

Figure 2: Dissolution profile for drug product batch with different levels of (b) (4) in raw materials at batch release and after one month of storage at 40°C/75%RH and target batch

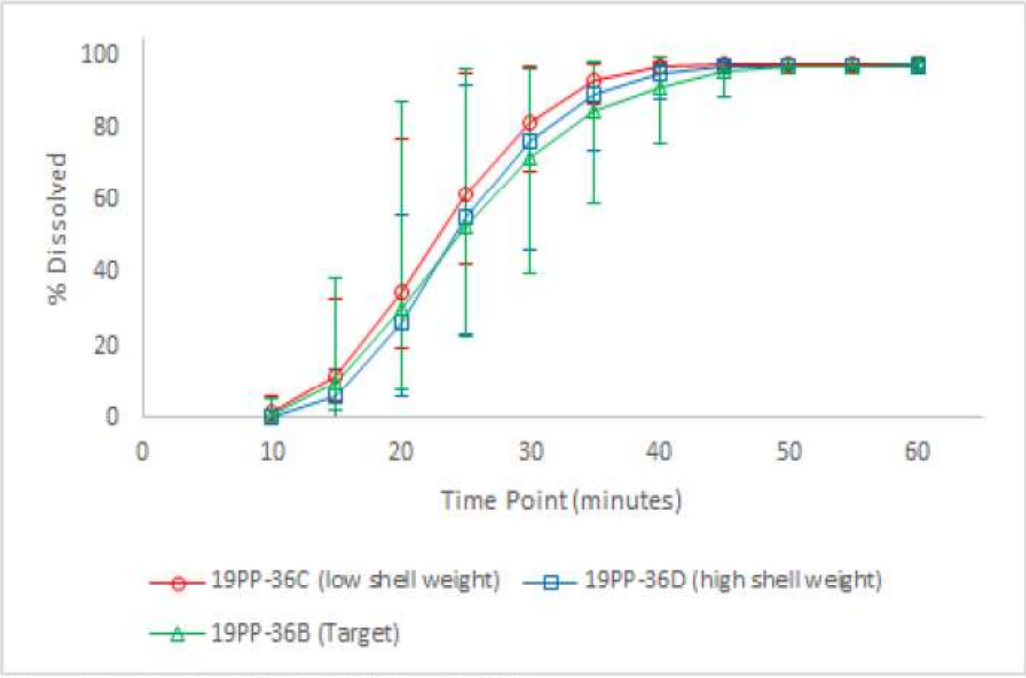


Note: Error bars represent minimum-maximum dissolved. 80-minute time point is an infinity time point (b) (4)

Shell weigh variation:
The applicant developed two batches of formulation with low shell weight (batch# 19PP-36C) and high shell weight (bat# 19PP-36D) and compared drug release with target formulation. Dissolution

data of all these formulations have similar profiles indicating dissolution method is not discriminating to the shell weight variation.

Figure 3: Dissolution profile for drug product batch with different shell weight

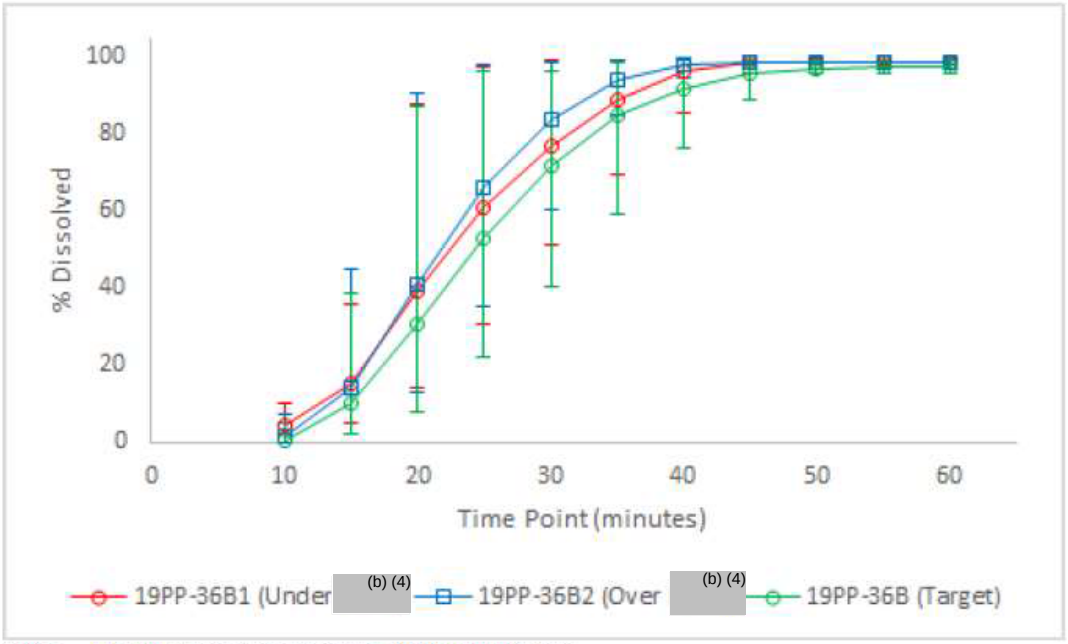


Note: Error bars represent minimum-maximum dissolved.

Variation in shell (b) (4)

Two formulations were developed with variation in capsule shell (b) (4) i.e. batch# 19PP-36B1 with under (b) (4) and batch#19PP-36B2 with over (b) (4) Dissolution data of the two formulation did not result in different release profile compared to the target formulation (batch# 19PP-36B).

Figure 4: Differences in capsule shell (b) (4) Dissolution profile for drug product batch with different shell (b) (4)



Note: Error bars represent minimum-maximum dissolved.

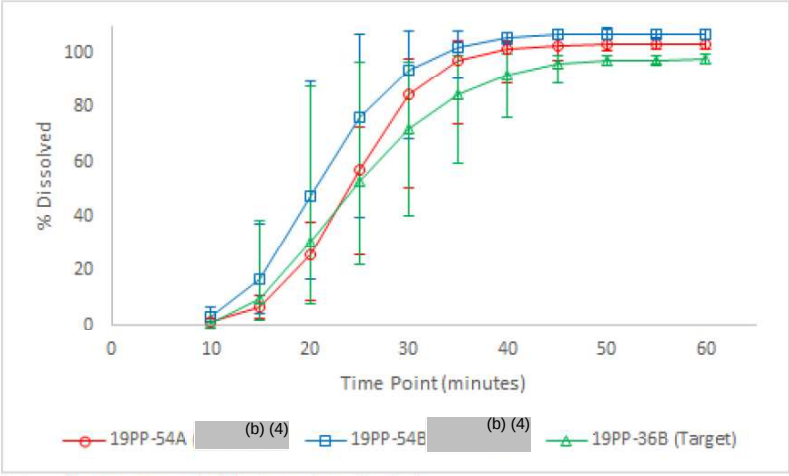
Different levels of (b) (4) in the formulations:

The applicant developed two formulations with low level and very low level of (b) (4) content. Formulation batch# 19PP-54A is the low-level (b) (4) batch with (b) (4) /capsule and batch# 19PP-54B is the very low-level (b) (4) batch with (b) (4) /capsule. The target batch#19PP-36B has (b) (4) mg/capsule of (b) (4) Dissolution data did not demonstrated differences in dissolution due to presence of low level of (b) (4) than the target formulation. On the other hand, formulation with very low level of (b) (4) showed higher drug release compared to the target formulation. A slightly higher drug release from batches 19PP-54A and 19PP-54B is due to the higher drug content (refer to the table below) in those batches.

Table 7: Quantitative composition of low (b) (4) batch#19PP-54A, very low-level (b) (4) batch#19PP-54B and target batch 19PP-36B

(b) (4)

Figure 5: Dissolution profile for drug product batch with different levels of (b) (4)



Note: Error bars represent minimum-maximum dissolved.

Formulation variable by altering amount of (b) (4)

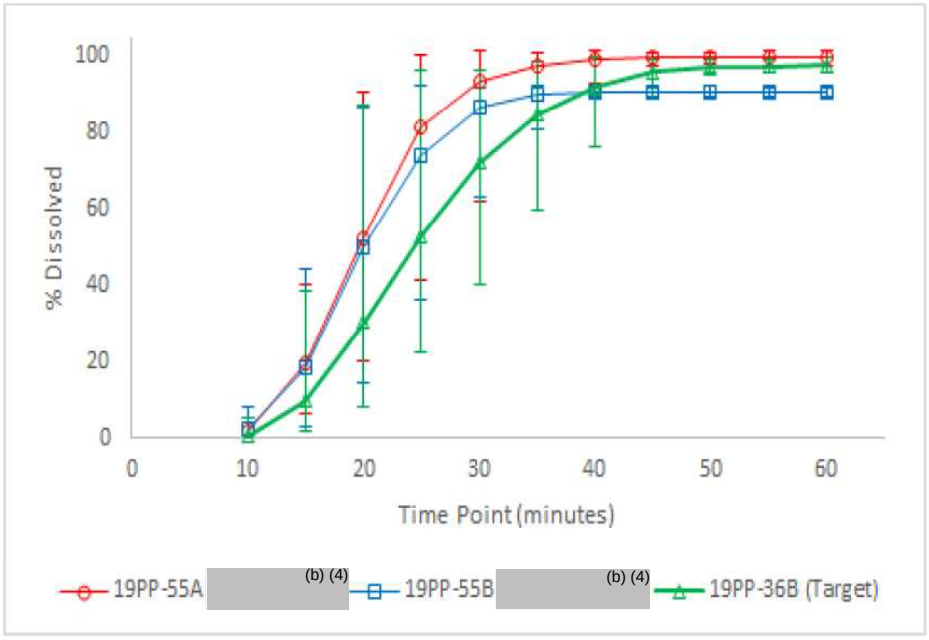
The applicant developed several formulations by altering (b) (4) Voclosporin amount ranges from (b) (4) mg which is in the range of (b) (4) % limit. The final formulation (b) (4) was kept at (b) (4) mg. The composition of different formulations is given below-

Table 8: Quantitative composition of formulation variation batches evaluated in discriminating ability of the dissolution method.

(b) (4)

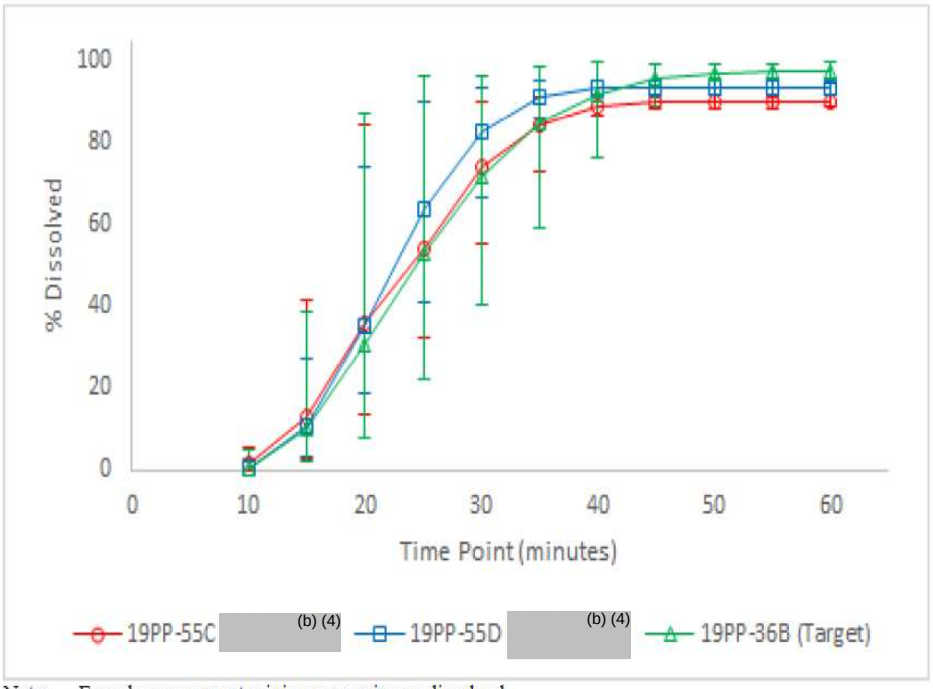
Dissolution data of these aberrant formulations did not demonstrate discriminating ability of the dissolution method.

Figure 6: Dissolution profile for drug product batch with different amount of (b) (4)



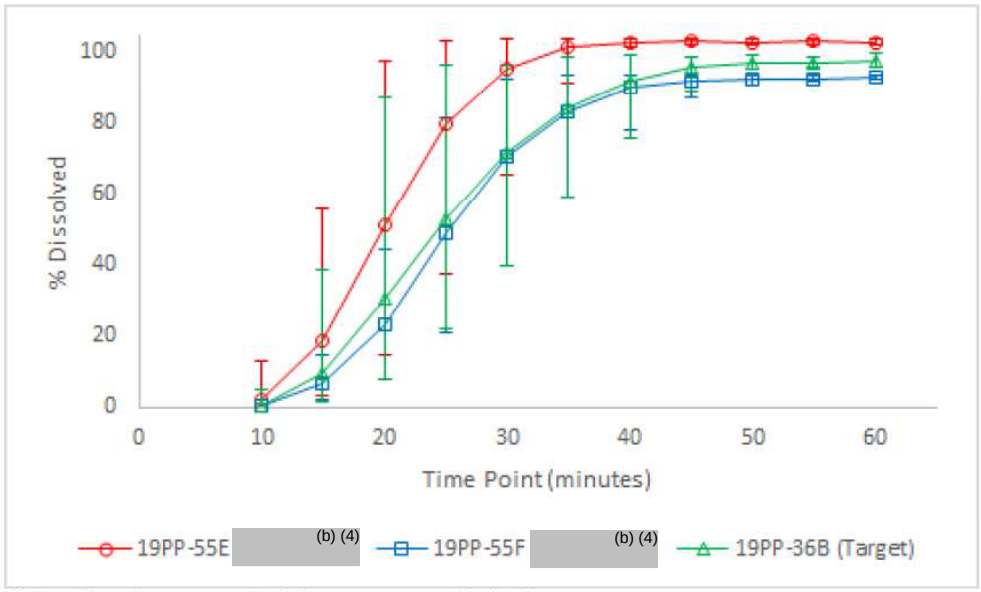
Note: Error bars represent minimum-maximum dissolved.
(b) (4)

Figure 7: Dissolution profile for drug product batch with different amount of (b) (4)



Note: Error bars represent minimum-maximum dissolved.

Figure 8:
Dissolution profile for drug product batch with different amount of (b) (4)



Note: Error bars represent minimum-maximum dissolved (b) (4)

Statistical evaluation of discriminating power assessment:
Discriminating ability of the dissolution method was evaluated using average equivalence approach and evaluation of coefficient of variation (%CV). Two criteria are given below-

- Comparison of time point by when %CV is ≤10% is achieved for control and test batch
  - There is no significant effect if the %CV is ≤10% by at least the same time point for the test and control batches
  - There is a significant effect if the %CV is ≤10% for the control batch is reached prior to the timepoint for the test batch
- Average equivalence statistical test:
  - There is no significant effect if the lower and upper 90% confidence interval limits are within the ±10% average relative difference criterion
  - There is a significant effect if the lower and/or upper 90% confidence interval limits are outside the ±10% average relative difference criterion

In conclusion, Dissolution method demonstrated discriminating ability for the (b) (4) spiked batch aged for one month at 40°C/75%RH and there might be some effect due to the variation in the (b) (4) in the formulations. The reviewer also analyzed the dissolution data and observed that multivariate analysis did not show significant difference in the release of the (b) (4) spiked batch aged batch, and batch with very low (b) (4) However, F2Bootstrap statistical analysis showed significant difference. Although the results of the two methods are inconclusive, the reviewer agrees to the discriminating ability of the dissolution method.

Dissolution acceptance criteria:
The Applicant provided dissolution data of the Voclosporin softgel capsules used in pivotal clinical studies.

Table 9: Dissolution results for Voclosporin softgel capsules, 7.9 mg, batch 13JM-274 at batch release and initial stability time point

		Time Point (minutes)			
Data Source	**Vessel**	**15**	**30**	**45**	**60**
Batch Release	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
Initial Stability Time Point	1				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
Mean	--	22	86	92	92
Minimum	--	(b) (4)			
Maximum	--				
% RSD	--	62.9	11.9	5.8	5.9

Method conditions: proposed commercial QC method (Table 1)
Notes: RSD = relative standard deviation.

Table 10: Dissolution results for Voclosporin softgel capsules, 7.9 mg, batch 14JM-281 at batch release and initial stability time point

		Time Point (minutes)			
Data Source	**Vessel**	**15**	**30**	**45**	**60**
Batch Release	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
Initial Stability Time Point	1				
	2				
	3				
	4				
	5				
	6				
Mean	--	16	77	94	95
Minimum	--	(b) (4)			
Maximum	--				
% RSD	--	54.1	19.1	2.7	2.2

Method conditions: proposed commercial QC method (Table 1)
Notes: RSD = relative standard deviation.

Table 11: Dissolution results for Voclosporin softgel capsules, 7.9 mg, batch 308814 (pivotal phase 3 batch) at batch release and initial stability time point

		Time Point (minutes)			
Data Source	**Vessel**	**15**	**30**	**45**	**60**
Batch Release	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
Initial Stability Time Point	1				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
Mean	--	9	74	95	96
Minimum	--	(b) (4)			
Maximum	--				
% RSD	--	81.5	22.3	3.6	2.2

Method conditions: proposed commercial QC method (Table 1)
Notes: RSD = relative standard deviation.

Table 12: Dissolution results for Voclosporin softgel capsules, 7.9 mg, batch 3137084 (pivotal phase 3 batch) at batch release and initial stability time point

		Time Point (minutes)			
Data Source	**Vessel**	**15**	**30**	**45**	**60**
Batch Release	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
Initial Stability Time Point	1				
	2				
	3				
	4				
	5				
	6				
Mean	--	23	93	98	98
Minimum	--	(b) (4)			
Maximum	--				
% RSD	--	37.7	8.1	2.7	3.3

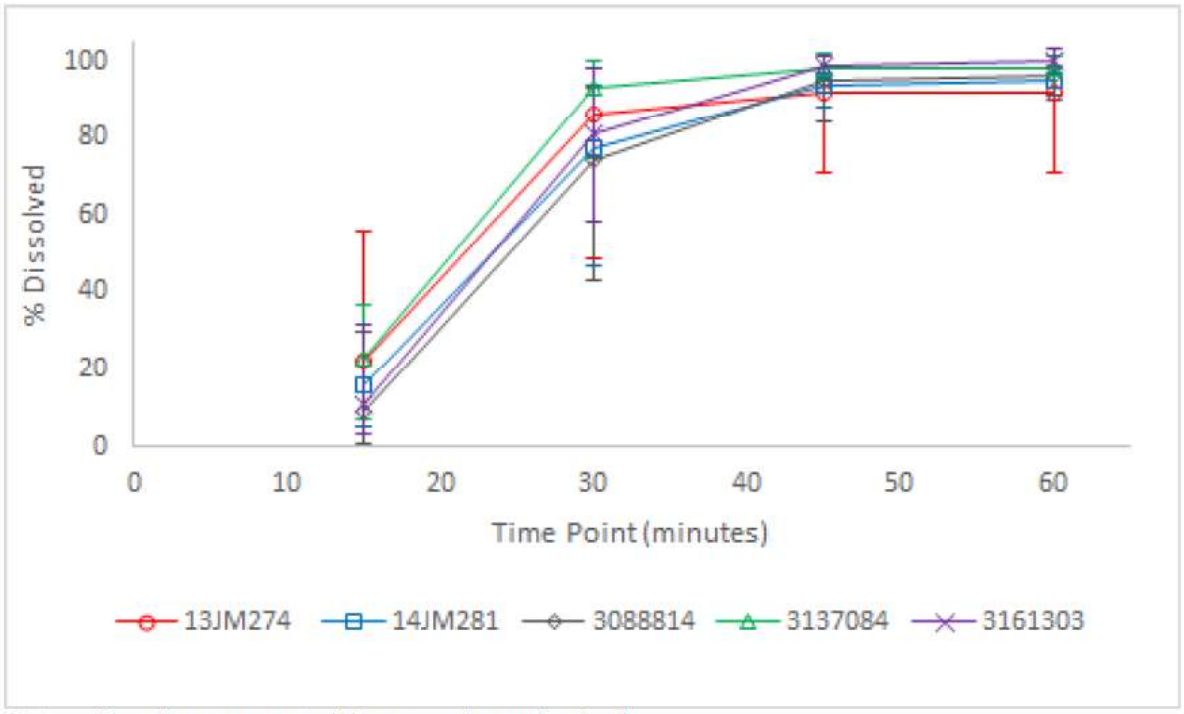
Method conditions: proposed commercial QC method (Table 1)
Notes: RSD = relative standard deviation.

Table 13: Dissolution results for Voclosporin softgel capsules, 7.9 mg, batch 3161303 (pivotal phase 3 batch) at batch release and initial stability time point

		Time Point (minutes)			
Data Source	**Vessel**	**15**	**30**	**45**	**60**
Batch Release	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
Initial Stability Time Point	1				
	2				
	3				
	4				
	5				
	6				
Mean	--	11	81	99	100
Minimum	--	(b) (4)			
Maximum	--				
% RSD	--	73.8	18.9	1.7	1.7

Method conditions: proposed commercial QC method (Table 1)
Notes: RSD = relative standard deviation.

Figure 9: Dissolution profiles for Voclosporin softgel capsules, 7.9 mg batches used in clinical studies



Note: Error bars represent minimum-maximum dissolved.

Dissolution data demonstrated complete release of the drug from Voclosporin softgel capsule, 7.9 mg at 45 minutes. There is a high variability in drug release at early time points up to 35 minutes which diminished afterwards
and is acceptable (CV <10%) at later time points. The Applicant set the dissolution acceptance criterion as Q= (b) (4)% at 45 minutes. Based on the dissolution data of the clinical phase 3 studies batches at release, i.e. batch# 3088814, 3137084 and 3161303, the applicant's proposed dissolution acceptance criterion is acceptable.

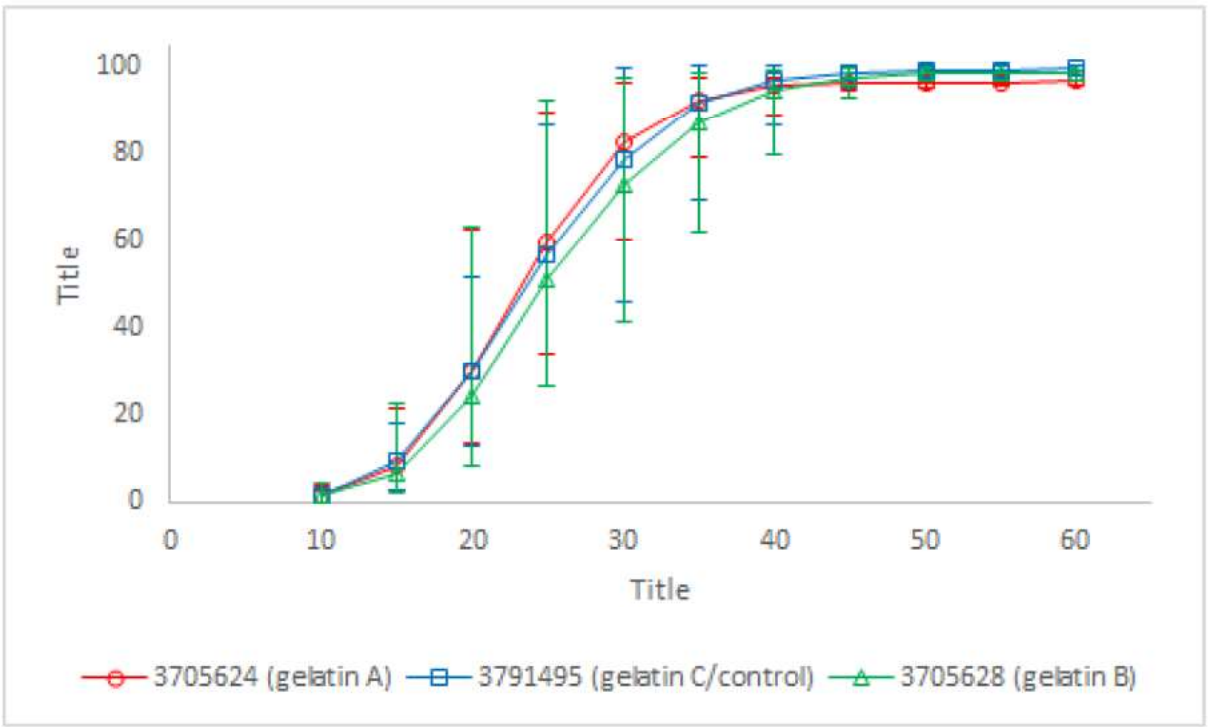
Evaluation of new gelatin source:
The applicant evaluated new sources of gelatin. Gelatin C is the control batch gelatin used in clinical batches and is no longer available. Therefore, the applicant developed a pilot batch of voclosporin (b) (4) and divided it to four sublots. One lot is not used further. Three other sublots were used to produce voclosporin 7.9 mg softgel capsules using two new gelatin sources, i.e. gelatin A and gelatin B and gelatin C (control gelatin). Table below lists the detail information and figure below shows the drug release profile from these formulations.

Table 14: Information of different gelatin sources used to manufacture Voclosporin softgel capsules, 7.9 mg batches

Attribute	Drug Product Batch		
	3705624	3705628	3791495
Description	Gelatin A	Gelatin B	Gelatin C/control
Batch Size (capsules)	[redacted] (b) (4)		
Drug Substance Batch			
Gelatin Origin			
Batch Description	Gelatin to be used for commercial drug product production	Gelatin to be used for commercial drug product production	Control batch[a]

a Gelatin NF used to manufacture voclosporin clinical and registration stability batches

Figure 10: Dissolution profile (n=12) for Voclosporin Softgel Capsules, 7.9 mg batches manufactured with new gelatin sources (batch# 3705624 with gelatin A and batch# 3705628 with gelatin B) and gelatin used for clinical batches (control batch#3791495)

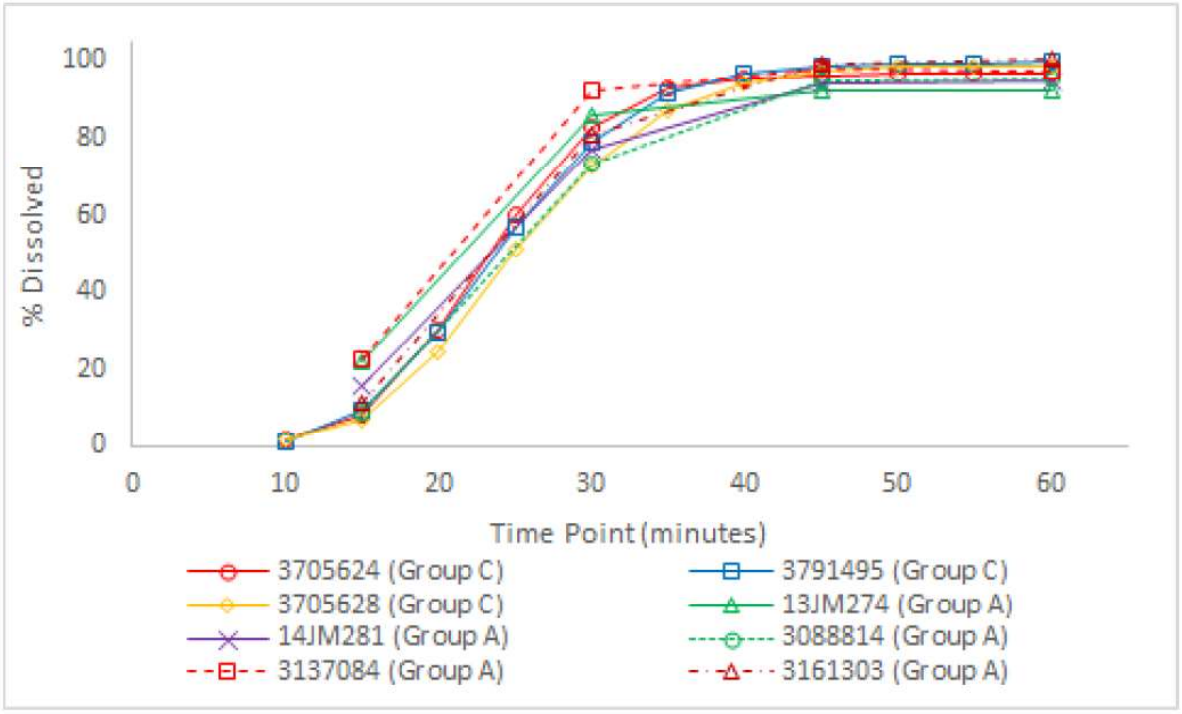


Note: Error bars represent minimum-maximum dissolved.

Dissolution profile similarity-based release rates for drug product batches used in pivotal clinical studies (at release):

Dissolution profiles of the batches with different gelatin sources (batch# 3705624 with gelatin A and batch# 3705628 with gelatin B) has similar drug release profiles as the control batch (batch# 3791495 with gelatin C) and the clinical/primary registration batches, i.e. (batch# 13JM274, 14JM281, 3088814, 3137084 and 3161303)

Figure 11: Comparison of dissolution profiles (n=12) of Voclosporin softgel capsules, 7.9 mg used for clinical batches at release and batches with different gelatin sources at release.



Dissolution profile similarity analysis:
Voclosporin softgel capsules demonstrated drug release profile with high variability that made it difficult to evaluate dissolution profile similarity. For the phase 3 pivotal clinical batches, the variability (%RSD) of the release rate at early time points was >20% and >10% up to 30 minutes. Therefore, model independent approach (f2 similarity factor) analysis is not suitable. Therefore, the applicant used F2Bootstrap analysis and average equivalence analysis to compare dissolution profiles of different batches.

Dissolution profile similarity analysis using F2Bootstrap analysis:
The applicant proposed to use Bootstrap f2 approach to compare dissolution profiles for the group B (aged pivotal clinical batches) to the group C (new gelatin source batches) to demonstrate dissolution profiles similarity. The bootstrap f2 test were conducted assuming the following-

a. Data from 10 to 45 minutes were included per batch for the f2 tests, as 85% dissolution is exceeded beyond 40 minutes (individual results).
b. The simulations were conducted with 50,000 iterations for the 95% lower confidence interval limit (LCL) of the f2 estimate.
c. The f2 result for the 95% LCL must be $\geq$ 50 to demonstrate that the dissolution profiles are similar.

Dissolution profile similarity using average equivalence approach:

The applicant evaluated dissolution profile similarity using average equivalence test per time point via simple effects through ANOVA model. The outcomes of the average equivalence test are interpreted as follows-

a. If both the upper and lower 90% confidence interval (CI) limits are within the similarity criterion of ± 10%, similarity is demonstrated.
b. If only one 90% confidence interval limit is within the similarity criterion of ±10%, the test result is deemed inconclusive
c. If both 90% CI limits are outside the similarity criterion of ±10%, non-similarity is demonstrated.

The results for the average equivalence tests comparison of the group B (aged clinical batches) and Group C dissolution profiles showing that the dissolution profiles at early time points fail to meet similarity, 25- and 30-minutes time points are inconclusive and similar at 35 minutes and subsequent time points.

The bootstrap f2 analysis demonstrated the Group B (aged clinical batches) and Group C has 95% LCL ≤50, indicating that dissolution profiles are not comparable.

Table 15: Bootstrapped f2 test result (10 to 45 minutes) for the comparison of Group B (aged pivotal clinical batches) to Group C (new gelatin source batches)

Simulated Comparison	f_2	f_2 95% LCL	95% LCL ≥50
Group C versus Group B	44.8	32.8	Fails

Table 16: Comparison of dissolution profiles for Group B (aged clinical batches) and Group C using the average equivalence tests

Time Point (minutes)	%Relative Difference Between Group B and Group C	90% Lower Confidence Interval Limit	90% Upper Confidence Interval Limit	Similarity Criterion ±10%
10	-66.483	-80.523	-52.442	Fails
15	-46.598	-68.560	-24.636	Fails
20	-27.902	-47.200	-8.604	Fails
25	-14.678	-26.955	-2.402	Inconclusive
30	-8.73	-15.745	-1.713	Inconclusive
35	-4.925	-8.505	-1.346	Passes
40	-2.961	-4.526	-1.394	Passes
45	-1.82	-2.452	-1.188	Passes
50	-1.537	-2.076	-0.997	Passes
55	-1.346	-1.920	-0.771	Passes
60	-1.374	-1.921	-0.829	Passes

In conclusion, model independent f2 analysis, bootstrap f2 similarity analysis and average equivalence were unsuitable due to the high variability in the dissolution profile.

The reviewer analyzed the dissolution data of the formulations with gelatin A and gelatin B and compared it with gelatin C (control batch) and found that both multivariate analysis (MVA) and F2bootstrap analysis is indicating similarity in dissolution data.

Table 17: Gelatin source change: Group C 3705624 (gelatin A) vs 3791495 (control lot with gelatin C):

MVA

Compare	Time points	Dosage unit	Mahalanobis Distance (MSD)	Upper 90% CI (MSD)	MAX MSD	Similarity limit
X3705624 vs X3791495	11	12	6.24518381385312	8.94336663002619	29.9724663603582	10

In MVA, the similarity can be verified if the upper bound of the confidence interval is smaller or equal to the MAX MSD

Boostrapping result

Compare	Time points	Dosage unit	Lower 90% CI (BCA)	Upper 90% CI (BCA)	Mean from bootstrapping	Original f2
X3705624 vs X3791495	11	12	77,9504160866693	86,3338633190479	72,7442609053731	80,7433477856277

In bootstrapping, the similarity can be verified if the lower bound of the confidence interval is larger or equal to 50

Table 18: Gelatin source change: Group C 3705628 (gelatin B) vs 3791495 (control lot with gelatin C):

MVA

Compare	Time points	Dosage unit	Mahalanobis Distance (MSD)	Upper 90% CI (MSD)	MAX MSD	Similarity limit
X3705628 vs X3791495	11	12	2.6858669178949	5.38395782465182	27.4194649763276	10

In MVA, the similarity can be verified if the upper bound of the confidence interval is smaller or equal to the MAX MSD

Boostrapping result

Compare	Time points	Dosage unit	Lower 90% CI (BCA)	Upper 90% CI (BCA)	Mean from bootstrapping	Original f2
X3705628 vs X3791495	11	12	50.4445459061098	91.6921429589803	68.1734543002393	71.5041156246359

In bootstrapping, the similarity can be verified if the lower bound of the confidence interval is larger or equal to 50

Conclusion:
Overall, Voclosporin softgel capsules demonstrated dissolution profile with high variability at early time points which diminished afterwards. Dissolution method is discriminatory to the formulations with high (b) (4) in the raw material that can induce crosslinking in the capsule shell upon storage in extreme condition. Dissolution method may show some significant difference in drug release profiles due to variations in (b) (4) Hence, dissolution method is acceptable. Dissolution data demonstrated complete release of the drug at 45 minutes and dissolution acceptance criterion is set as Q= (b) (4)% in 45 minutes. **The applicant did not attempt to demonstrate clinical relevance of the dissolution method and hence the method is an acceptable quality control test.**

Dissolution test parameters for quality control test:
The Approved dissolution method and acceptance criterion of Voclosporin softgel capsule, 7.9 mg-

Apparatus	Media and temperature	Media volume (mL)	Speed (rpm)	Acceptance Criterion
USP Apparatus II (paddle)	0.75%Polyoxyl 40 hydrogenated castor oil in sodium acetate buffer, pH 4.5, 37.0°C±0.5°C	900 mL	75	Q = (b) (4)% in 45 minutes

Signature Block

Primary Biopharmaceutics Reviewer Name:

Kamrun Nahar, PhD.

Secondary Biopharmaceutics Reviewer Name:

Haritha Mandula, Ph.D.

Appendix 1

Voclosporin Softgel Capsules dissolution data link:
\\CDSESUB1\evsprod\nda213716\0002\m3\32-body-data\32p-drug-prod\voclosporin-capsule\32p5-contr-drug-prod\32p54-batch-analys\ind-diss-data-regis-batches.xlsx

\\CDSESUB1\evsprod\nda213716\0004\m3\32-body-data\32p-drug-prod\voclosporin-capsule\32p2-pharm-dev\physicochem-biol-prop.pdf

Appendix 2

Information request 1:

(b) (4)

Applicant's response:
\\CDSESUB1\evsprod\nda213716\0015\m1\us\111-information-amendment\response-ir-dated-28aug2020.pdf

Reviewer's assessment:

(b) (4)

Kamrun Nahar

Digitally signed by Kamrun Nahar
Date: 10/16/2020 02:58:41PM
GUID: 57b38236009c032e2a84627cd295a5cd

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 10/16/2020 05:36:36PM
GUID: 508da6fb000282df41459408f32a1ce0

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/

CRAIG M BERTHA
10/21/2020 09:11:26 AM