CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214958Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214958

Assessment 1

Drug Product Name	SOTYKTU (deucravacitinib) tablets
Dosage Form	Tablet
Strength	6 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Bristol-Myers Squibb Company (BMS)
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission, eCTD SN 0001	09/10/2021	DS, DP, OPMA, labeling, and Biopharm
Amendment, SN 0002	09/20/2021	DP, labeling
Amendment, SN 0004	11/24/2021	DS, DP, OPMA
Amendment, SN 0005	12/01/2021	DP, labeling
Amendment, SN 0010	02/15/2022	OPMA
Amendment, SN 0014	03/31/2022	OPMA
Amendment, SN 0025	05/06/2022	DP
Amendment, SN 0032	05/27/2022	Biopharm

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sharon Kelly	Lawrence Perez
Drug Product	Zhengfang Ge	Nina Ni
Manufacturing	Yong Wu	Vaikunth Prabhu
Microbiology	Yong Wu	Vaikunth Prabhu
Biopharmaceutics	Assad Noory	Tapash Ghosh
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead (ATL)	Nina Ni	
Laboratory (OTR)	N/A	N/A
Environmental	Zhengfang Ge	Nina Ni

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	It was not used in the primary packaging component

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

Document	Application Number	Description
IND	131993	Conducted clinical studies

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			

CDRH	N/A			
Clinical	N/A			
Other	N/A			

NDA Executive Summary

1. Application/Product Information

NDA Number.	NDA 214958		
Applicant Name	Bristol-Myers Squibb Company (BMS)		
Drug Product Name	SOTYKTU (deucravacitinib) tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	6 mg		
Route of Administration	Oral		
Maximum Daily Dose	6 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the treatment of adult patients with moderate to severe psoriasis		
Drug Product Description	Pink, round, biconvex, film-coated tablet laser printed with “BMS 895” and 6 mg” on one side in black ink with no content on the other side. The recommended dose is 6 mg taken orally once daily, with or without food.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sharon Kelly	Lawrence Perez
	Drug Product/ Labeling	Zhengfang Ge	Nina Ni
	Manufacturing	Yong Wu	Vaikunth Prabhu

	Biopharmaceutics	Assad Noory	Tapash Ghosh
	Microbiology	Yong Wu	Vaikunth Prabhu
	Other (specify):	N/A	N/A
	RBPM	Grafton Adams	
	ATL	Nina Ni	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 36 months

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 214958 for commercialization of SOTYKTU (deucravacitinib) tablets, 6 mg. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate chemistry, manufacturing, and controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: None

Nina Ni

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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:

The Prescribing Information is deemed ADEQUATE with all editorial changes in the prescribing information were implemented in the final labeling in the SharePoint which will be conveyed to the applicant.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME™	**Adequate**
Established name(s)	(deucravacitinib) tablet	**Adequate** Changed tablet to tablets in the updated labeling in the SharePoint.
Route(s) of administration	for oral use	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4) tablets: 6 mg	**Adequate** Deleted "(b) (4)" in the updated labeling in the SharePoint

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)

1.2.2

2 DOSAGE AND ADMINISTRATION

(b) (4)

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)	Do not crush, cut, or chew the tablets.	**Adequate**

1.2.3 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) tablets	**Adequate** - Changed the format to the following: Tablets: 6 mg, pink, round, biconvex, (b) (4), laser printed with… in the updated labeling in the SharePoint
Strength(s) in metric system	6 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	pink, round, biconvex, (b) (4) laser printed with "BMS 895 6 mg" on one side (b) (4) (b) (4) with no content on the other side	**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	

1.2.4 Section 11 (DESCRIPTION)

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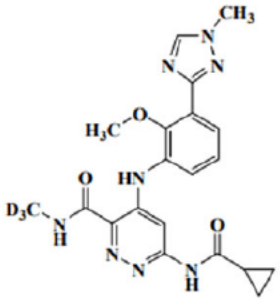
Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	[TRADENAME] tablets	**Adequate** - deucravacitinib was added in the updated labeling in the SharePoint
Dosage form(s) and route(s) of administration	tablets	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	hypromellose acetate succinate, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate. In addition, the film coating Opadry® II Pink contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red and yellow.	**Adequate** - Excipients were arranged in alphabetic order in the updated labeling in the SharePoint.
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	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	(b) (4) inhibitor of tyrosine kinase 2 (TYK2)	**Adequate**

Chemical name, structural formula, molecular weight	Name: 6-cyclopropaneamido-4-{[2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl]amino}-N-(2H3)methylpyridazine-3-carboxamide Molecular formula: $C_{20}H_{19}D_3N_8O_3$ Molecular weight: 425.47 	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Deucravacitinib is a white to yellow powder. The solubility of deucravacitinib is pH dependent. Solubility decreases with increasing pH	**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	

1.2.5 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

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	6 mg	**Adequate**
Available units (e.g., bottles of 100 tablets)	bottle of 30	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	- Pink round, biconvex, filmcoated tablet - Laser printed with "BMS 895"and "6 mg" on one side (b) (4). - NDC number provided	**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	
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	
If the product contains a desiccant, ensure the size and	N/A	

shape differ from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store [TRADENAME™] tablets at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59° to 86°F).	**Adequate** - Added "[see USP Controlled Room Temperature]" in the updated labeling in the SharePoint.
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	Not included	**Adequate** - revised to "bottle of 30 with child resistant closure" in the updated labeling in the SharePoint.

1.2.6 Other Sections of Labeling

N/A

1.2.7 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	Distributed by: Bristol-Myers Squibb Company Princeton, New Jersey 08543 USA	**Adequate**

2.0 PATIENT LABELING

The following Patient Information is generally adequate from CMC perspective. The inactive ingredients should be rearranged in alphabetic order

(b) (4)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	SOTYKTU (deucravacitinib) tablets	**Adequate**
Dosage strength	6 mg	**Adequate**
Route of administration	tablets	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	30 tablets	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Provided	**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 between 15°C and 30°C (59°F and 86°F) [see USP controlled room temperature]	**Adequate**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA Product of Ireland	**Adequate**
Medication Guide (if applicable)	Please see accompanying full prescribing information (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	**Adequate**

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

All editorial changes listed in the above tables of each section of the PI review were updated in the final labeling in the SharePoint which will be conveyed to the applicant.

Overall Assessment and Recommendation:

The NDA is now ready for approval in its present form per CFR 314.125(b)(6).

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):

Nina Ni, Ph. D.
SPQA, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Nina Ni

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BIOPHARMACEUTICS

Product Background:

NDA: 214958-ORIG-1

Drug Product Name / Strength: Deucravacitinib, Tablet, 6 mg

Route of Administration: Oral

Applicant Name: Bristol-Myers Squibb Company

Review recommendation:

The Division of Biopharmaceutics finds the provided biopharmaceutics information adequate and recommends approval of this NDA for **Deucravacitinib, 6 mg immediate release tablet.** The approved dissolution test and dissolution acceptance criterion are shown below.

Approved dissolution method and acceptance criterion

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criterion
2	75	50 mM potassium phosphate pH 6.3 with 0.01% (w/v) Brij®35 at 37°C	1000	Q= (b) (4)% in 30 minutes

Review Summary:

Deucravacitinib (DEUC) is a weak base, and the drug substance may fall under BCS Class 2 due to claimed high permeability and limited solubility at high pH (b) (4). An oral solution, a capsule, and a tablet formulation of DEUC have been developed to support the clinical development program. DEUC (b) (4) was selected for development of the oral solution and capsule formulations used in the Phase 1 first-in-human (FIH), and Phase 2 studies, respectively.

DEUC (b) (4) film coated tablet was used to support Phase 3 studies and is also the proposed commercial formulation. (b) (4)

(b) (4)

(b) (4)

Both the Phase 3 clinical and proposed commercial formulations are 6-mg tablets that use the same core tablet composition and (b) (4). The proposed commercial tablet uses a pink Opadry II film coat compared to the clinical tablet, which uses a (b) (4) (b) (4). These changes to the formulation are considered minimal. The proposed commercial tablets will therefore have similar clinical behavior to the tablets used in Phase 3 studies and they are also adequately bridged by comparative dissolution..

Drug Formulations and Dissolution Testing

The dissolution methods used to support the clinical batch release testing for tablet formulations are listed below in Table 1.2.5-2.

Table 1.2.5-2: Clinical Dissolution Method for Tablet Formulation

Dosage Form	Tablets
Product Identification Number (PIN)	(b) (4)
Apparatus	
Medium/Temperature	
Media Volume	
Speed of Rotation	
Brief Description of the Dissolution Analytical Method	

Source: Refer to Module 3.2.P.2.2.3

The proposed commercial dissolution method for the tablet formulation is listed below in Table 1.2.5-3. The method utilizing potassium phosphate buffer (pH 6.3) with 0.01% Brij® 35 medium, demonstrates robustness, repeatability, and discrimination for tablet quality and performance attributes of a (b) (4) tablet formulation designed to (b) (4) (b) (4) Details can be found in Module 3.2.P.2.2.3.

Table 1.2.5-3: Proposed Commercial Dissolution Method - Tablet Formulation

Dosage Form	Tablets
Product Identification Number (PIN)	986165-K006-034[a] and proposed commercial formulation
Apparatus	Apparatus 2 (Paddle)
Medium/Temperature	50mM pH 6.3 phosphate buffer with 0.01% w/v Brij® 35, @37 °C
Media Volume	1000 mL
Speed of Rotation	75 RPM
Brief Description of the Dissolution Analytical Method	The dissolution test is performed using 1000 mL 50mM pH 6.3 phosphate buffer with 0.01% w/v Brij® 35 at 37 °C, using Apparatus 2 (paddles) method at a rotation speed of 75 rpm. Samples are removed after 10, 20, 30, 45, 60 minutes from test initiation and analyzed for BMS-986165-01 by UV Vis spectrophotometry at 243 nm

Source: Refer to Module 3.2.P.2.2.3.1

[a] PIN 986165-K006-031 was (b) (4) to produce long-term stability batches PIN 986165-K006-034

List of Submissions being reviewed:

ORIGINAL	09/13/2021
IR	05/25/2022

Highlight Key Outstanding Issues from Last Cycle:

None

Concise Description Outstanding Issues Remaining:

None

BCS Designation

The Applicant indicates that Deucravacitinib (DEUC) drug substance is weakly basic (pKa value of 3.4) with high permeability and limited solubility at moderate to high pH. Hence, the drug substance possesses the attributes of a BCS Class 2 compound.

Solubility:

To improve the solubility, deucravacitinib is formulated as (b) (4) (b) (4). The table below contains the solubility of (b) (4) deucravacitinib.

(b) (4)

Permeability:

The Applicant conducted a membrane permeability study (NCPK156) reviewed by OCP.

Reviewer's Assessment: No formal review for BCS designation was conducted by this reviewer; therefore, no comment on BCS designation will be made.

DISSOLUTION

A robust and discriminating dissolution method for Quality Control testing of 6 mg deucravacitinib tablets is developed. The Proposed dissolution test is shown below.

Table 3.2.P.2.2.3.1-1:Dissolution Method for Deucravacitinib Tablet, 6 mg

Apparatus	USP Apparatus 2 (paddles)
Spindle Rotation Speed	75 rpm
Media Volume	1000 mL
Temperature	37°C
Dissolution Medium	50 mM potassium phosphate buffer (pH 6.3) with 0.01 % (w/v) Brij 35
Sampling Time Points	10, 20, 30, 45 and 60 minutes

The table below shows a summary of dissolution method development.

(b) (4)

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(b) (4)

[redacted]

Discriminatory Power:

To evaluate the discriminatory power of the proposed commercial method, tablets were prepared with varying composition ((b) (4) [redacted] . These factors were selected as having potential impact on tablet disintegration and dissolution of an immediate release tablet. The results are shown below.

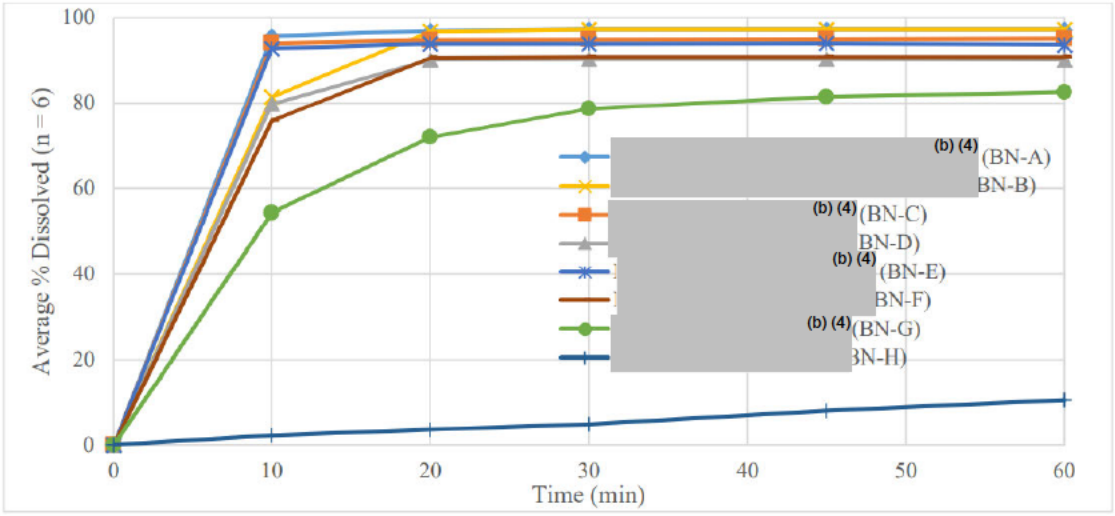
Variations in Formulation Composition, [redacted]:

Table 3.2.P.2.2.3.1-14: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Evaluation of the Impact of [redacted]

Tablet Batch No and Composition Details [redacted]	Average % Dissolved (n = 6) (Range) [% RSD]				
	10 min	20 min	30 min	45 min	60 min
BN-A (Ref Batch): [redacted]	95 [redacted] [0.8]	97 [redacted] [0.8]	97 [redacted] [0.8]	97 [redacted] [0.8]	97 [redacted] [0.7]
BN-B: [redacted]	82 [redacted] [2.2]	97 [redacted] [0.7]	97 [redacted] [0.7]	97 [redacted] [0.7]	97 [redacted] [0.7]
BN-C: [redacted]	94 [redacted] [0.5]	95 [redacted] [0.5]	95 [redacted] [0.4]	95 [redacted] [0.4]	95 [redacted] [0.5]
BN-D: [redacted]	80 [redacted] [3.5]	90 [redacted] [0.7]	90 [redacted] [0.7]	90 [redacted] [0.7]	90 [redacted] [0.8]
BN-E: [redacted]	93 [redacted] [1.1]	94 [redacted] [1.2]	94 [redacted] [1.1]	94 [redacted] [1.2]	94 [redacted] [1.0]
BN-F: [redacted]	76 [redacted] [2.0]	91 [redacted] [0.7]	91 [redacted] [0.7]	91 [redacted] [0.7]	91 [redacted] [0.8]
BN-G: [redacted]	54 [redacted] [16.9]	72 [redacted] [8.4]	79 [redacted] [5.4]	82 [redacted] [4.0]	83 [redacted] [3.4]
BN-H: [redacted]	2 [redacted] [1.7]	4 [redacted] [1.4]	5 [redacted] [1.7]	8 [redacted] [2.7]	10 [redacted] [5.7]

USP Apparatus 2 (Paddles) at 75 rpm, 1000 mL of 50mM phosphate buffer with 0.01% w/w Brij 35 (pH 6.3), 37°C

Figure 3.2.P.2.2.3.1-11: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Variation in Formulation Composition



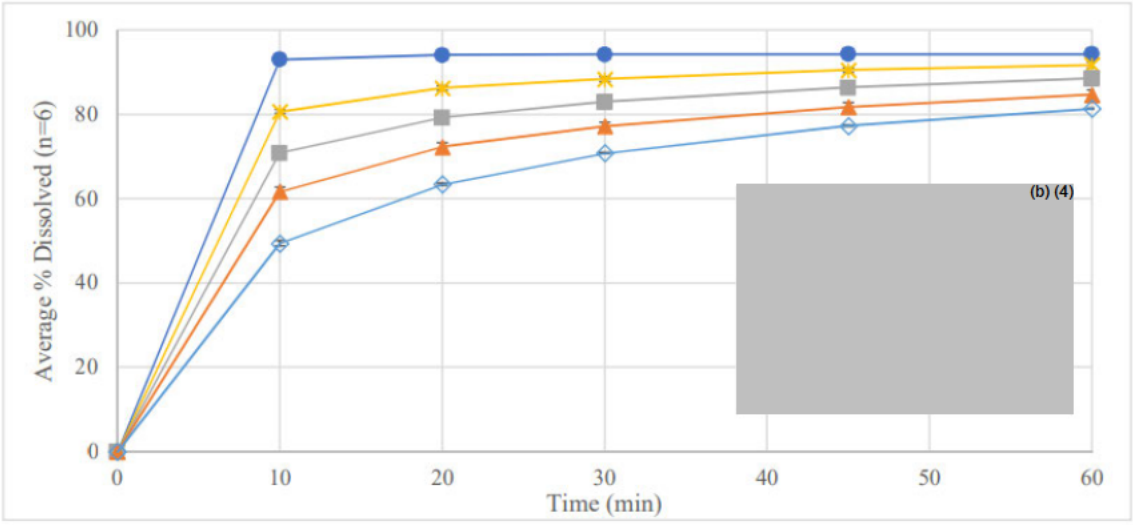
Variation in (b) (4):

Table 3.2.P.2.2.3.1-17: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Variation in (b) (4)

(b) (4)	Average % Dissolved (n = 6) (Range) [% RSD]				
	10 min	20 min	30 min	45 min	60 min
(b) (4)	93 (b) (4) [1.0]	94 (b) (4) [0.9]	94 (b) (4) [1.0]	94 (b) (4) [1.0]	94 (b) (4) [1.0]
	81 [0.6]	86 [0.6]	88 [0.7]	91 [0.7]	92 [0.7]
	71 [1.1]	79 [0.8]	83 [0.8]	86 [0.9]	89 [0.8]
	62 [1.6]	72 [1.4]	77 [1.1]	82 [1.2]	85 [1.2]
	49 [1.3]	63 [0.5]	7 [0.2]	77 [0.3]	81 [0.2]

USPApparatus 2 (Paddles) at 75 rpm, 1000 mL of 50mM phosphate buffer with 0.01% w/w Brij 35 (pH 6.3), 37°C .

Figure 3.2.P.2.2.3.1-14: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Variation in (b) (4)



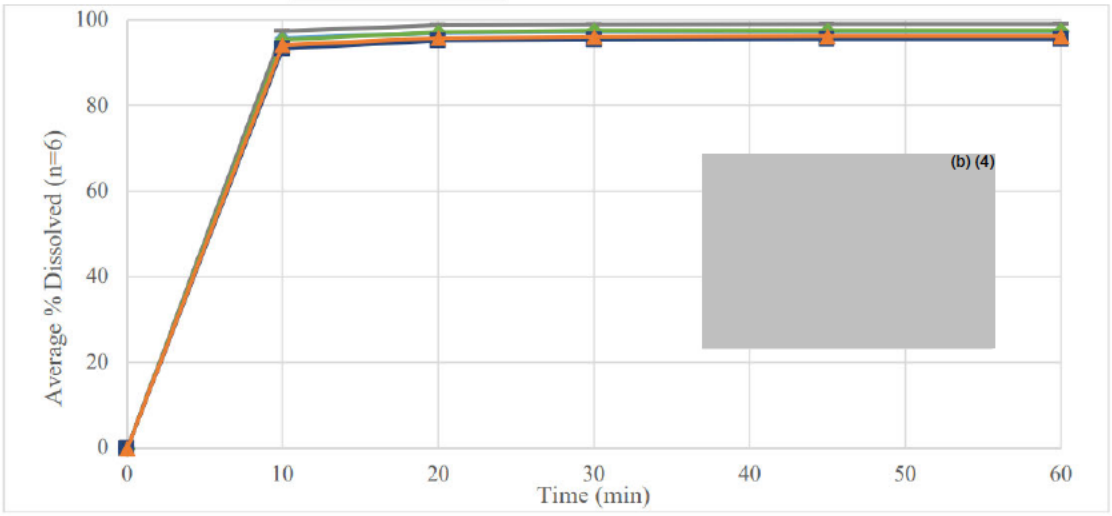
Variation in [redacted]:

Table 3.2.P.2.2.3.1-15: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Variation in [redacted]

[redacted]	Average % Dissolved (n = 6) (Range) [% RSD]				
	10 min	20 min	30 min	45 min	60 min
[redacted]	97 [redacted] [1.5]	99 [redacted] [1.6]	99 [redacted] [1.3]	99 [redacted] [1.4]	99 [redacted] [1.5]
[redacted]	95 [redacted] [2.6]	97 [redacted] [2.5]	97 [redacted] [2.6]	98 [redacted] [2.6]	97 [redacted] [2.6]
[redacted]	93 [redacted] [2.1]	95 [redacted] [2.0]	95 [redacted] [2.0]	95 [redacted] [2.0]	95 [redacted] [2.0]
[redacted]	94 [redacted] [1.6]	96 [redacted] [1.7]	96 [redacted] [1.7]	96 [redacted] [1.7]	96 [redacted] [1.6]

USP Apparatus 2 (Paddles) at 75 rpm, 1000 mL of 50mM phosphate buffer with 0.01% w/w Brij 35 (pH 6.3), 37°C

Figure 3.2.P.2.2.3.1-12: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Variation in [redacted]



(b) (4):

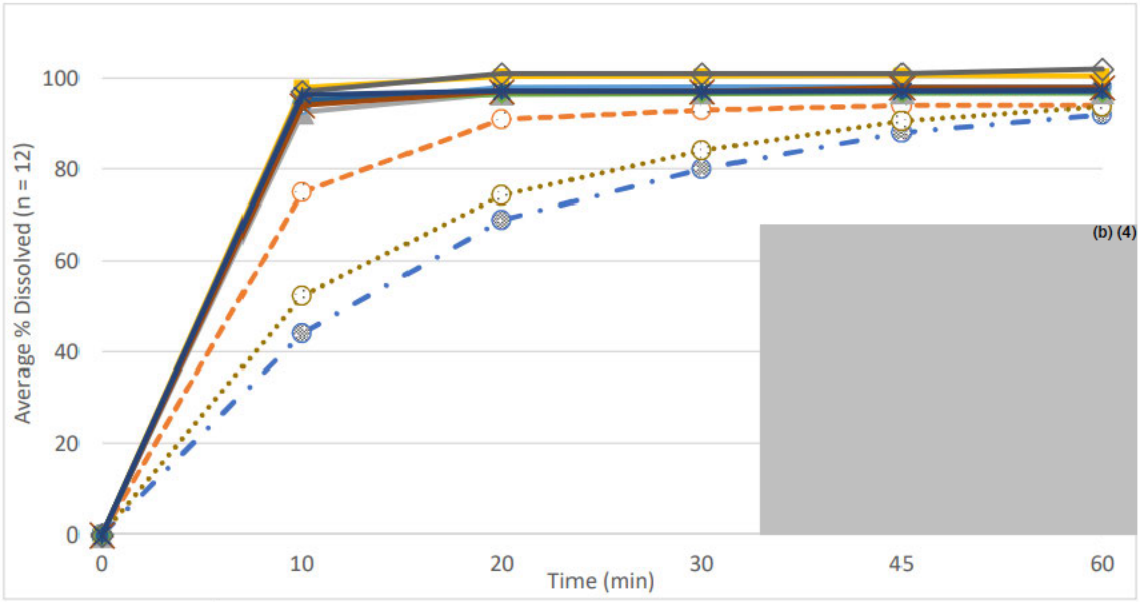
Table 3.2.P.2.2.3.1-16: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Evaluation of the Impact of (b) (4)

(b) (4)	Average % Dissolved (n = 12) (Range) [% RSD]				
	10 min	20 min	30 min	45 min	60 min
(b) (4)	98 (b) (4) [0.7]	100 (b) (4) [1.0]	100 (b) (4) [0.8]	101 (b) (4) (b) (4) [0.9]	101 (b) (4) [1.0]
(b) (4)	44 (b) (4) [2.5]	69 (b) (4) [1.3]	80 (b) (4) [1.2]	88 (b) (4) [1.4]	92 (b) (4) [1.6]
(b) (4)	95 (b) (4) [1.3]	96 (b) (4) [1.3]	97 (b) (4) [1.3]	97 (b) (4) [1.4]	97 (b) (4) [1.4]
(b) (4)	95 (b) (4) [1.9]	97 (b) (4) [1.8]	97 (b) (4) [1.8]	97 (b) (4) [1.8]	97 (b) (4) [1.8]
(b) (4)	96 (b) (4) [1.7]	97 (b) (4) [1.7]	97 (b) (4) [1.8]	97 (b) (4) [1.8]	97 (b) (4) [1.7]
(b) (4)	94 (b) (4) [0.8]	98 (b) (4) [0.8]	98 (b) (4) [0.8]	98 (b) (4) [0.8]	98 (b) (4) [1.2]
(b) (4)	75 (b) (4) [1.2]	91 (b) (4) [0.9]	93 (b) (4) [1.0]	94 (b) (4) [1.0]	94 (b) (4) [1.0]
(b) (4)	94 (b) (4) [0.8]	97 (b) (4) [0.8]	97 (b) (4) [1.0]	98 (b) (4) [0.7]	98 (b) (4) [0.8]
(b) (4)	97 (b) (4) [1.3]	101 (b) (4) [1.0]	101 (b) (4) [1.1]	101 (b) (4) [1.1]	102 (b) (4) [1.0]
(b) (4)	92 (b) (4) [1.5]	97 (b) (4) [1.7]	97 (b) (4) [1.7]	97 (b) (4) [1.8]	97 (b) (4) [1.8]
(b) (4)	52 (b) (4) [3.3]	74 (b) (4) [2.2]	84 (b) (4) [1.9]	91 (b) (4) [1.9]	94 (b) (4) [1.9]

USP Apparatus 2 (Paddles) at 75 rpm, 1000 mL of 50mM phosphate buffer with 0.01% w/w Brij 35 (pH 6.3), 37°C

a (b) (4)

Figure 3.2.P.2.2.3.1-13: Dissolution Profile for Deucravacitinib Tablets, 6 mg - Variation in (b) (4)



Reviewer's Comment: Results of this study indicate that the method has discriminating capability for the removal of (b) (4) from the formulation. Minor differences at the 10-minute timepoint are also observable for tablets with (b) (4). No difference in profile was observable for tablets containing variations in (b) (4). As (b) (4) tablet formulations, the dissolution profiles for batches with varying (b) (4) (b) (4) are consistent with previously observed tablet disintegration data. No difference in dissolution profile was observed for the tablets containing variations in (b) (4) . Results also indicate that the method has discriminating capability for batches with (b) (4) and the proposed method is also able todistinguish between different (b) (4).

Overall, the results indicate that the proposed method has discriminating capability towards some parameters.

Evaluation of Repeatability of the Proposed Method:

Repeatability of the proposed method was assessed from the magnitude of the variability (%RSD) by collecting data from representative batches, ie, greater than or equal to pilot scale batch at clinical and commercial manufacturing sites of the 6 mg tablet strength, shown below.

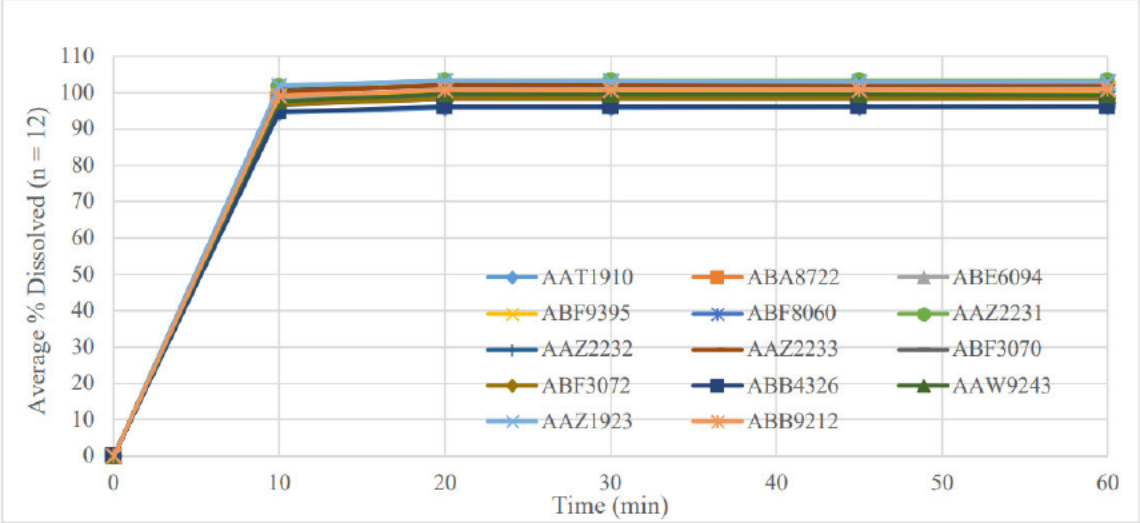
Table 3.2.P.2.2.3.1-18: Evaluation of the Effect of Batch to Batch Variation of Deucravacitinib Tablets 6 mg on Dissolution Profile

Tablet Batch Number	Average % Dissolved (n = 12) (Range) [% RSD]				
	10 min	20 min	30 min	45 min	60 min
AAT1910	94 (b) (4) [1.0]	96 (b) (4) [0.9]	96 (b) (4) [0.9]	96 (b) (4) [1.0]	96 (b) (4) [0.9]
ABA8722	98 (b) (4) [0.8]	99 (b) (4) [0.9]	99 (b) (4) [0.9]	99 (b) (4) [0.9]	99 (b) (4) [0.9]
ABE6094	98 (b) (4) [0.5]	101 (b) (4) [0.9]	101 (b) (4) [0.9]	101 (b) (4) [0.9]	101 (b) (4) [0.9]
ABF9395	99 (b) (4) [0.5]	101 (b) (4) [0.7]	100 (b) (4) [0.7]	100 (b) (4) [0.6]	100 (b) (4) [0.7]
ABF8060	97 (b) (4) [0.9]	99 (b) (4) [0.8]	99 (b) (4) [0.8]	99 (b) (4) [0.8]	99 (b) (4) [0.8]
AAZ2231	102 (b) (4) [0.8]	103 (b) (4) [0.7]	103 (b) (4) [0.7]	103 (b) (4) [0.7]	103 (b) (4) [0.7]
AAZ2232	101 (b) (4) [1.0]	102 (b) (4) [1.1]	102 (b) (4) [1.0]	102 (b) (4) [1.1]	102 (b) (4) [1.0]
AAZ2233	100 (b) (4) [0.8]	102 (b) (4) [0.8]	102 (b) (4) [0.8]	102 (b) (4) [0.9]	102 (b) (4) [0.9]
ABF3070	97 (b) (4) [0.9]	98 (b) (4) [0.9]	98 (b) (4) [1.1]	98 (b) (4) [0.9]	98 (b) (4) [1.0]
ABF3072	97 (b) (4) [2.1]	98 (b) (4) [2.5]	98 (b) (4) [2.5]	98 (b) (4) [2.7]	98 (b) (4) [2.5]
ABB4326	95 (b) (4) [0.7]	96 (b) (4) [0.8]	96 (b) (4) [0.8]	96 (b) (4) [0.8]	96 (b) (4) [0.8]
AAY6331	99 (b) (4) [1.1]	101 (b) (4) [1.6]	101 (b) (4) [1.6]	101 (b) (4) [1.6]	101 (b) (4) [1.6]
AAW9240	97 (b) (4) [0.7]	100 (b) (4) [1.1]	100 (b) (4) [1.1]	100 (b) (4) [1.1]	100 (b) (4) [1.2]
AAW9241	99 (b) (4) [1.3]	101 (b) (4) [1.3]	101 (b) (4) [1.3]	101 (b) (4) [1.2]	101 (b) (4) [1.3]
AAW9243	98 (b) (4) [1.0]	100 (b) (4) [1.2]	99 (b) (4) [1.2]	99 (b) (4) [1.2]	99 (b) (4) [1.3]
AAZ1923[a]	102 (b) (4) [0.5]	103 (b) (4) [0.6]	103 (b) (4) [0.5]	103 (b) (4) [0.6]	103 (b) (4) [0.6]

[a] Tablets from batch AAZ1923 were (b) (4)

USP Apparatus 2 (Paddles) at 75 rpm, 1000 mL of 50 mM phosphate buffer with 0.01% w/w Brij 35 (pH 6.3),37°C

Figure 3.2.P.2.2.3.1-15: Evaluation of the Effect of Batch to Batch Variability for Deucravacitinib Tablets, 6 mg, on Dissolution Profile



The results from this evaluation show only minor effects of batch-to-batch variations and low variability within batch. At the 30-minute time point average % release values ranged from 96-103%, which compares favorably with the tablet assay data range for the same batches (b) (4)). The within batch intermediate precision data generated during method validation, resulted in ≤ 1.0% difference between laboratories.

Dissolution Method and Acceptance Criteria

Proposed dissolution method for stability and quality control of commercial tablets.

Table 3.2.P.2.2.3.1-19: Proposed Stability and Quality Control Dissolution Method for Commercial Tablets

Apparatus	USP Apparatus 2 (paddles)
Spindle Rotation Speed	75 rpm
Media Volume	1000 mL
Temperature	37°C
Dissolution Medium	50 mM potassium phosphate buffer (pH 6.3) with 0.01 % (w/v) Brij 35
Sampling Time Points	10, 20, 30, 45 and 60 minutes

Table 3.2.P.5.4-5: Dissolution Data from Proposed Commercial Method for Deucravacitinib Tablets, 6 mg

Batch Number	% Dissolved: Mean (Range for n=12) [% RSD]				
	10 Minutes	20 Minutes	30 Minutes	45 Minutes	60 Minutes
Commercial Image Batches					
CFFWZ	104 ((b) (4) [0.7]	106 ((b) (4) [0.7]	106 ((b) (4) [0.7]	106 ((b) (4) [0.7]	106 ((b) (4) [0.7]
CGGYD[a]	101 ((b) (4) [1.0]	102 ((b) (4) [1.1]	102 ((b) (4) [0.9]	102 ((b) (4) [1.1]	102 ((b) (4) [1.1]
CGGYG[a]	101 ((b) (4) [1.7]	102 ((b) (4) [1.6]	102 ((b) (4) [1.5]	102 ((b) (4) [1.5]	101 ((b) (4) [1.6]
CGGYK[a]	101 ((b) (4) [1.1]	101 ((b) (4) [1.2]	101 ((b) (4) [1.1]	101 ((b) (4) [1.2]	101 ((b) (4) [1.2]

All of the above batches were used for Stability.

Batch Number	% Dissolved: Mean (Range for n=12) [% RSD]				
	10 Minutes	20 Minutes	30 Minutes	45 Minutes	60 Minutes
AAW9241	99 ((b) (4) [1.3]	101 ((b) (4) [1.3]	101 ((b) (4) [1.3]	101 ((b) (4) [1.2]	101 ((b) (4) [1.3]
AAW9243	98 ((b) (4) [1.0]	100 ((b) (4) [1.2]	99 ((b) (4) [1.2]	99 ((b) (4) [1.2]	99 ((b) (4) [1.3]
AAY6331	99 ((b) (4) [1.1]	101 ((b) (4) [1.6]	101 ((b) (4) [1.6]	101 ((b) (4) [1.6]	101 ((b) (4) [1.6]
ABA8722	98 ((b) (4) [0.8]	99 ((b) (4) [0.9]	99 ((b) (4) [0.9]	99 ((b) (4) [0.9]	99 ((b) (4) [0.9]

Commercial dissolution method, M00004128: 50 mM phosphate buffer (pH 6.3) with 0.01% w/v Brij® 35

[a] Dissolution data were collected in accordance with the proposed commercial specification provided in Section 3.2.P.5.1, *Specification*.

All of the above batches were used in the clinical studies.

Based on the dissolution data from the stability and clinical batches using the proposed regulatory/commercial dissolution method, the proposed dissolution specification: **Q= (b) (4) % in 30 minutes** is justified.

Reviewer's Assessment:

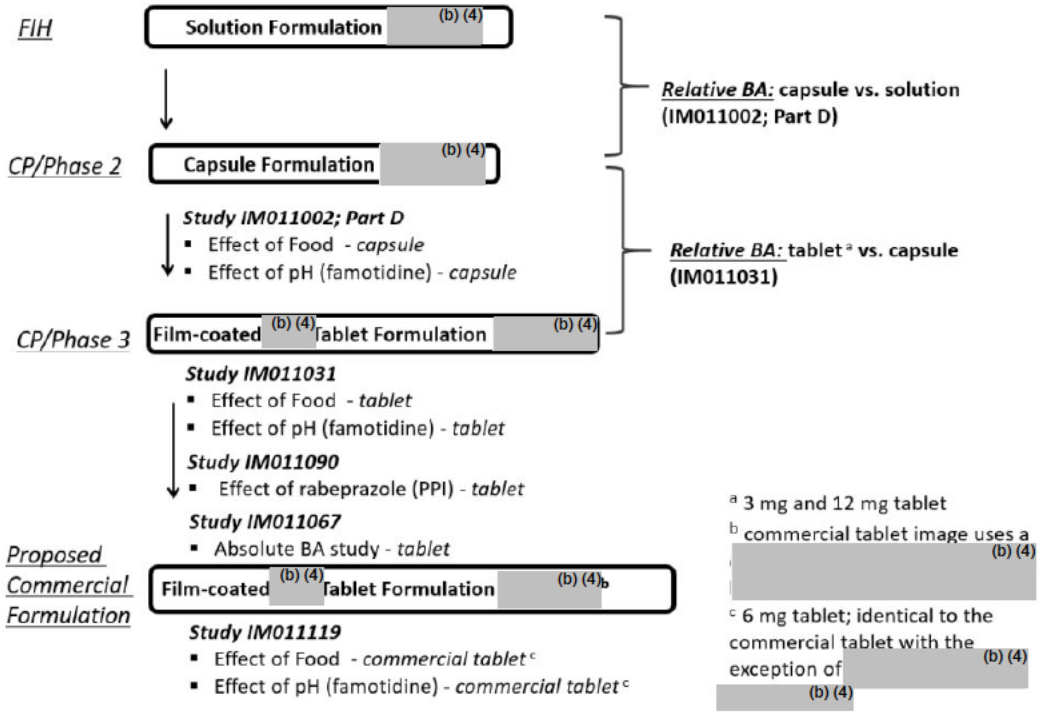
The proposed dissolution method is robust with discriminating capability; it is appropriate for product release and quality control of 6-mg Deucravacitinib film-coated tablets. The applicant could have proposed a thighter acceptance criterion based on the dissolution data; however, as

the division's current practice for IR products is (b)(4)% dissolution in 30 minutes the proposed dissolution acceptance criterion (Q= (b)(4)% at 30 minutes) is adequate.

Bridging of Formulations

The clinical pharmacology/biopharmaceutics studies conducted to bridge across various formulations are summarized below.

Figure 1-1: Biopharmaceutical Studies to Bridge the Deucravacitinib Formulations from Early Clinical Development to the Phase 3 and Proposed Commercial Tablet

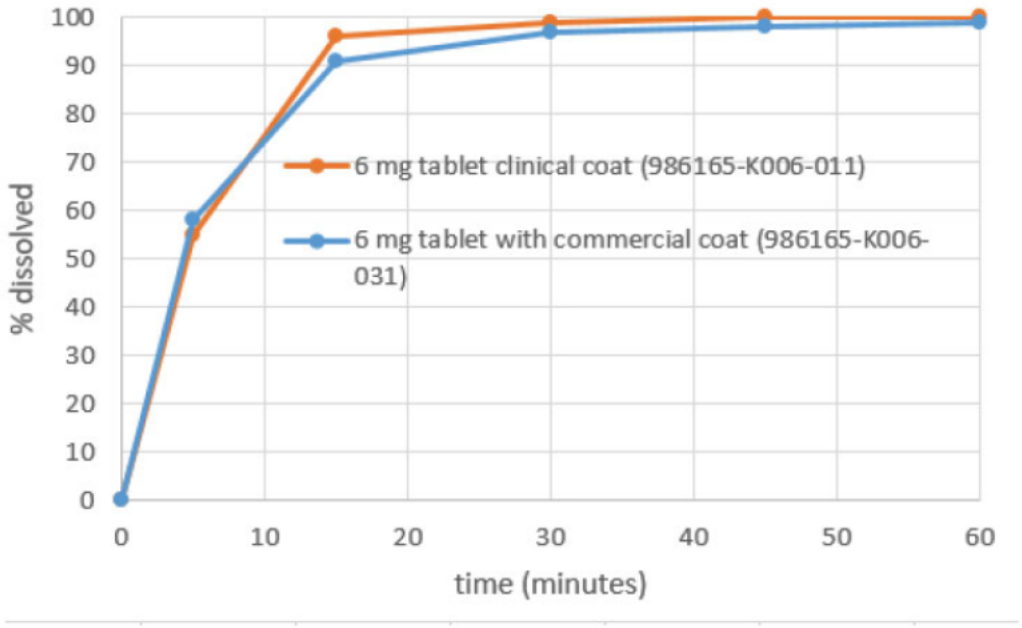


The 6-mg tablets used in the Phase 3 studies and the commercial tablet share the same composition and manufacturing process and only differ in color description and (b) (4) printing. The following figure shows comparative dissolution profile of the clinical batch and the commercial batch.

The proposed commercial formulation is the 6 mg tablet which uses the same core tablet composition and (b) (4) as the 6 mg tablet used in the Phase 3 clinical studies. The proposed commercial tablet uses a pink Opadry II film coat compared to the clinical tablet which uses (b) (4) (b) (4). A comparison of dissolution profiles for

6-mg tablets manufactured using the commercial and clinical film-coat using the clinical release method (provided in Table 1.2.5-2) is presented in Figure 3.2-3.

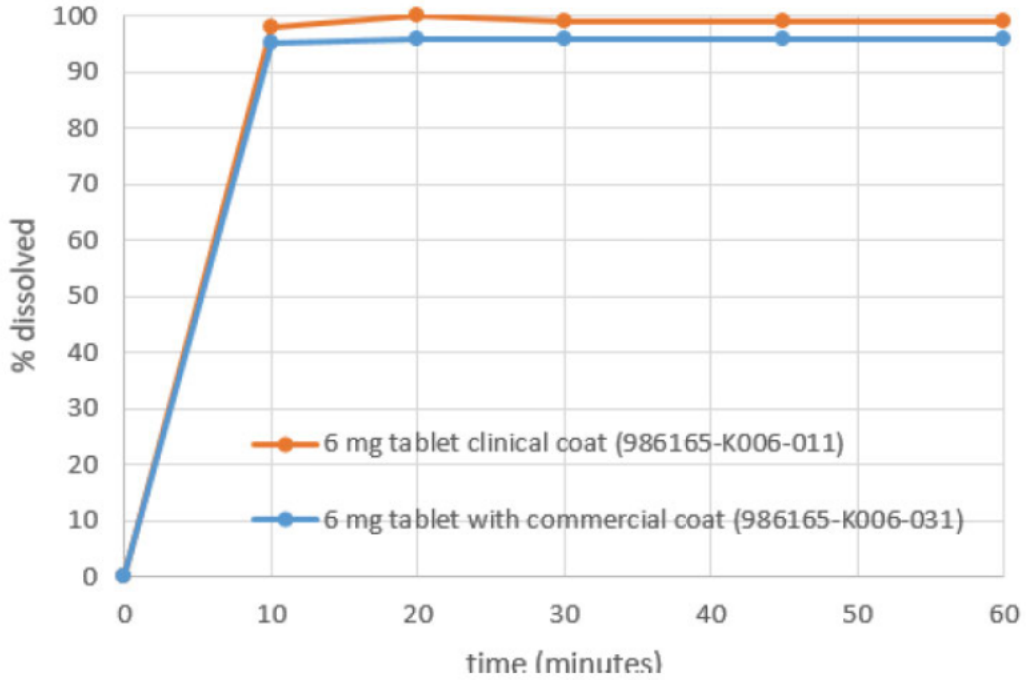
Figure 3.2-3: Dissolution Comparison of 6-mg Tablets with Clinical vs Commercial Film-Coat Using Clinical Dissolution Method



Source: Refer to Module 3.2.P.2.2.3 and Section 1.2.5

A comparison of dissolution profiles for 6-mg tablets manufactured using the commercial and clinical film-coat color using the dissolution method developed for commercial tablet release is presented in Figure 3.2-4. The dissolution data from both methods show fast and comparable dissolution performance with greater than (b)(4)% dissolved at 30 minutes for tablets anufactured using commercial and clinical film coats.

Figure 3.2-4: Dissolution Comparison of 6-mg Tablets with Clinical vs Commercial Film-Coat Using Proposed Commercial Dissolution Method



Source: Refer to Module 3.2.P.2.2.3 and Section 1.2.5

The dissolution results for all 6 mg clinical coat and proposed commercial coat tablet batches ((b) (4)) are presented in Module 3 for the clinical dissolution and for the proposed commercial dissolution methods (Refer to Module 3.2.P.4.5). All batches show similar and rapid dissolution in both methods.

In conclusion, in vitro dissolution data, as well as in vivo relative bioavailability studies, demonstrate that the formulation changes from early studies through the Phase 3 studies utilizing the proposed commercial tablet have minimal impact on the tablet dissolution and plasma DEUC exposures.

Reviewer's Assessment:

The biopharmaceutics program of this NDA adequately bridged oral formulations used in the clinical development program with the proposed commercial tablets. However, it is not clear why the applicant switched from clinical dissolution method to commercial dissolution method.

Links to dissolution data:

\\CDSESUB1\evsprod\nda214958\0001\m2\23-qos\drug-product-23p2pharmdev.pdf

\\CDSESUB1\evsprod\nda214958\0001\m2\27-clin-sum\summary-bio-pharm-bms986165-pso-initial.pdf

\\CDSESUB1\evsprod\nda214958\0001\m3\32-body-data\32p-drug-prod\deucravacitinib-tablets\32p2-pharm-dev\pharmaceutical-development-32p2231-dp-dissolution-method-dev.pdf

Biowaiver Request

Not applicable

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

None

Reviewer's Assessment:

Lifecycle Management Considerations

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:

Assadollah Noory, Ph. D.

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

Tapash Ghosh, Ph. D.

Assadollah Noory

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Date: 5/26/2022 03:51:10PM
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Tapash Ghosh

Digitally signed by Tapash Ghosh
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Nina Ni

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Date: 8/01/2022 02:01:04PM
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