CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217900Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 217900
Assessment 1

Drug Product Name	LEQSELVI (deuruxolitinib), Tablet 8 mg
Dosage Form	Tablet
Strength	8 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries, Inc
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original, SD#1	Jul 28, 2023	DS, DP, Biopharma, OPMA, labeling
SD#2	Sep 13, 2023	DP
SD#4	Sep 21, 2023	OPMA
SD#8	Dec 08, 2023	OPMA
SD#10	Dec 12, 2023	DP
SD#17	Feb 9, 2024	OPMA
SD#20	Feb 15, 2024	Biopharma
SD#26	Mar 08, 2024	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sam Bain, PhD	Lawrence Perez, PhD
Drug Product	Hitesh Shroff, PhD	Nina Ni, PhD
Manufacturing	Jing Fang, PhD	Baoqing Ma, PhD
Microbiology	Wei Yang, PhD	Jean Tang, PhD
Biopharmaceutics	Rajesh Savkur, PhD	Tapash Ghosh, PhD
Other (specify) Labeling	Hitesh Shroff, PhD	Julia Pinto, PhD

Regulatory Business Process Manager	Rajani Ranga	
Application Technical Lead	Baoqing Ma, PhD	
Laboratory (OTR)	N/A	N/A
Environmental	Hitesh Shroff, PhD	Baoqing Ma, PhD

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

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

Document	Application Number	Description
IND	131423	Conducted clinical studies

2. CONSULTS

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

NDA Executive Summary

- **Application/Product Information**

NDA Number	217900
Applicant Name	Sun Pharmaceutical Industries, Inc
Drug Product Name	LEQSELVI (deuruxolitinib), Tablet 8 mg
Dosage Form	Tablet
Proposed Strength(s)	8 mg
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	16 mg
Rx/OTC Dispensed	Rx
Proposed Indication	for the treatment of adults with moderate to severe alopecia areata
Drug Product Description	Sun Pharmaceutical Industries, Inc. submitted a new NDA217900 for LEQSELVI® (deuruxolitinib), Tablet 8 mg via 505 (b)(1) regulatory pathway for the treatment of adults with moderate to severe alopecia areata. This NDA is based on the IND 131423 and has been granted for Fast-Track (2017) and Breakthrough Therapy (2000) Designation. Deuruxolitinib Tablet 8 mg and 12 mg strengths have been developed and studied in clinical trial, however, only 8 mg strength is included within this application for marketing. The drug substance (DS), deuruxolitinib phosphate, is a deuterated version of ruxolitinib phosphate. It is a white to off-white crystalline solid and highly aqueous solubility at low pH and good to poor solubility in a range of common organic solvents. It belongs to BCS Class I based on the Biopharmaceutical Classification System (BCS). It is not hygroscopic with a melting

	point of 196°C. Deuruxolitinib phosphate is packaged (b) (4) (b) (4) The re-test period is (b) (4) months. Deuruxolitinib phosphate is formulated as a film-coated immediate release tablet. The deuruxolitinib (b) (4) The product has been manufactured at a contract manufacturer, Halo Pharmaceutical, Inc. Six batches for each strength including three primary registration batches have been manufactured for preclinical and clinical use. Their COAs have been provided. Deuruxolitinib Tablet 8 mg is intended to be packaged in 45 cc white, wide-mouth, square HDPE bottle, along with one 1-gram silica gel desiccant canister and closed with 24 mm white, child-resistant closures with (b) (4) foil liners. The applicant provided 18 months long-term stability data at 25°C/60%RH, 12 months intermediate stability data at 30°C/65%RH and 6 months accelerated data at 40°C/75%RH for three primary registration batches (0000107543, 0000107544 and 0000107545) for 8 mg strength and three primary registration batches (0000107546, 0000107547 and 0000107548) for 12 mg strength manufactured from (b) (4) drug substance source, and 3 months long-term and accelerated stability data for one batch (0000133703) for 8 mg strength and one batch (0000133705) for 12 mg strength manufactured from (b) (4) drug substance source. The proposed expiry period for the drug product is 30 months when stored at 20–25 °C.

Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	at 20°C to 25°C (68°F to 77°F) and excursions permitted to 15°C to 30°C (59°F to 86°F).		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sam Bain, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Hitesh Shroff, PhD	Baoqing Ma, PhD
	Manufacturing	Wei Yang, PhD	Jean Tang, PhD
	Biopharmaceutics	Rajesh Savkur, PhD	Tapash Ghosh, PhD
	Other (specify) Labeling	Hitesh Shroff, PhD	Julia Pinto, PhD
	RBPM	Rajani Ranga	
	ATL	Baoqing Ma, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application is recommended for approval with the expiration dating periods of 30 months when packaged in the proposed container closure and stored at 20–25 °C.

The CMC-recommended PI labeling as well as container and carton labels revisions have been communicated to the applicant. The applicant has accepted all CMC-recommended revision and will submit the finalized PI labeling as well as container and carton labels to the application prior to the action date. Therefore, no additional labeling memorandum is needed for the approval of this application from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, Deuruxolitinib phosphate, and drug product, Deuruxolitinib Tablet 8 mg.

- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

- The CMC revisions on labels/labeling have been communicated to the applicant and the recommended CMC revisions have been accepted by the applicant.

- The applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 30 months when stored at 20–25 °C.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Baoqing Ma, PhD
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

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Important: Do Not Change the Header or Footer

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	217900
Assessment Cycle Number	1
Drug Product Name	Leqselvi (deuruxolitinib) tablets

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	SDN 001
Patient Information	Choose an item.	SDN 001
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	SDN 001
Carton Labeling	N/A	

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001	July 18, 2023	Labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	The drug approval year, 2024, is added at the time of the final approval.
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Adequate	The FDA salt policy is adhered to. 8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: *Adequate*

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg	Adequate	The following equivalency statement is included in Sec. 11 DESCRIPTION.

[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
of drug-x hydrochloride). No equivalency statement.		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	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 parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	The equivalency statement should be revised as shown below. 8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).
[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	The equivalency statement is in Sec. 11 DESCRIPTION
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	Revise the statement as shown below: LEQSELVI is available as purple, round, immediate tablets debossed with "C" on one side and "8" on the other side.

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	The following statement regarding storage is included in Sec. 16 Storage and Handling Store in the original bottle in order to protect from moisture.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	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.*	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Avoid statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

The following comments regarding the PI are conveyed to the applicant.

- Revise the equivalency statement in the Sec. 11 DESCRIPTION as shown below.
  8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)

- Revise the identification of the dosage statement in Sec. 16 HOW SUPPLIED/STORAGE AND HANDLING as shown below:
  LEQSELVI is available as purple, round, immediate tablets debossed with "C" on one side and "8" on the other side.

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 review 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.

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

2.0 PATIENT LABELING

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	Adequate	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Assessment: *Adequate*

APPEARS THIS WAY ON ORIGINAL

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(Copy/paste or refer to a representative example of a proposed container label)

3.2 Carton Labeling

The drug product is provided in a bottle. A carton is not used a secondary container closure system. Therefore, a carton label is not provided.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	The equivalency statement should be revised as shown below. 8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

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

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	
For parenteral injectable dosage forms, include quantities of all inactive	N/A	

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Add the following statement: Dispense a Medication Guide to each patient
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the	N/A	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
labeling requirement is fulfilled.		
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.[31]	N/A	
And others if space is available.	N/A	

Assessment of Carton Labels and Container Labeling: *Adequate*

The drug product is provided in a bottle. A carton is not used a secondary container closure system. Therefore, a carton label is not provided.

The following comments regarding the container labels will be conveyed to the NDA applicant.

- The equivalency statement should be revised as shown below:
  8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)

- Add the following statement:
  Dispense a Medication Guide to each patient

[31] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The PI and the container labels are satisfactory from the CMC perspective. The drug product is supplied in bottles. No secondary carton container is used therefore, carton labels were not provided.

This NDA is recommended for "Approval" from the CMC labeling perspective.

The following edit in the PI are made and conveyed to the applicant.

- Revise the equivalency statement in Sec. 11 DESCRIPTION as shown below.
  8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)

- Revise the identification of the dosage statement in Sec. 16 HOW SUPPLIED/STORAGE AND HANDLING as shown below:
  LEQSELVI is available as purple, round, immediate tablets debossed with "C" on one side and "8" on the other side.

The following comments regarding the container labels should be conveyed to the NDA applicant.

- The equivalency statement should be revised as shown below:
  8 mg deuruxolitinib (equivalent to 10.50 mg of deuruxolitinib phosphate)

- Add the following statement:
  Dispense a Medication Guide to each patient

Primary Labeling Assessor Name and Date:

Hitesh Shroff
OPQ, ONDP, DNDP II, Branch IV

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

Julia Pinto
OPQ, ONDP, DNDP II, Branch III

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-217900-ORIG-1
Submission History	7/28/2023 (Seq 0001): Original submission 2/15/2024 (Seq 0020): Response to Biopharmaceutics IR#1
Drug Product Name/ Strength	LEQSELVI – Deuruxolitinib (CTP-543) Tablets, 8 mg
Route of Administration	Oral
Applicant Name	Sun Pharmaceuticals Industries, Inc.
Therapeutic Classification/ OND Division	DDD
Proposed Indication	Deuruxolitinib, a selective Janus Kinase (JAK) JAK1 and JAK2 inhibitor, is indicated for the treatment of adults with moderate to severe alopecia areta.
IND Number	IND 131423
Primary Reviewer	Rajesh Savkur, Ph.D.
SPQA	Tapash Ghosh, Ph.D./Okpo Eradiri, Ph.D.
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of LEQSELVI – Deuruxolitinib (CTP-543) tablets, 8 mg. The proposed drug product is a selective Janus Kinase (JAK) JAK1 and JAK2 inhibitor, that is indicated for the treatment of adults with moderate to severe alopecia areta. NDA-217900-ORIG-1 was initially submitted to the Division of Dermatology and Dentistry on 7/28/2023 under section 505(b)(1). Pivotal Phase 3 studies demonstrated efficacy with the 8 mg and 12 mg strengths of the drug product administered twice-daily. However, due to long-term safety concerns of the 12 mg twice-daily dosing regimen, approval of only the 8 mg strength as a twice-daily dose is being sought in this submission. The recommended dosage of LEQSELVI for the treatment of moderate to severe alopecia areata is 8 mg orally twice daily, with or without food.

***Assessment Summary*:**
The Biopharmaceutics assessment focuses on evaluating (i) the *in vitro* dissolution method development, the dissolution data and the dissolution acceptance criterion, and (ii) the bridging data between the clinical and commercial/to-be-marketed drug products, the manufacturing sites, batch sizes and (iii) waiver of bioequivalence between the clinical and TBM formulations.

- **In Vitro Dissolution Method and Acceptance Criterion:**
  The proposed drug product is an immediate release product wherein the deuruxolitinib API is a high-solubility drug substance. (b) (4)

(b) (4)

(b) (4)

. Based on the information submitted, the following dissolution method and acceptance criterion are agreed for the QC test of Deuruxolitinib tablets, 8 mg, at batch release and through stability (Table 1).

Table 1: Approved dissolution method and acceptance criterion for Deuruxolitinib tablets, 8 mg

Approved dissolution method				Approved dissolution acceptance criterion
Source	**Apparatus**	**Media/ Volume**	**Agitation speed/ Temperature**	
2018 FDA Guidance	USP apparatus 1	Medium: 0.1 N HCl Volume: 500 mL	Speed: 100 rpm Temp: 37±0.5 °C	30 min: NLT (b) (4)% (Q)

From a Biopharmaceutics perspective, the initial risk is very low and further risk mitigation is not needed (Table 2).

Table 2: Risk Assessment

Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Very Low	• The drug product is an immediate release product. • The deuruxolitinib API is a high-solubility drug substance. • (b) (4) .	Very Low	• Further risk mitigation is not needed.

- **Product Bridging:**

Bridging of drug product formulations across product development: The composition of the 8 mg strength used in the Phases 1–3 clinical studies differs from the 8 mg to-be-marketed (TBM) formulation.

- The Phase 1 formulation contains (b) (4)
- The Phase 3 formulation contains (b) (4)
- The TBM formulation contains Microcrystalline cellulose ((b) (4) w/w), Lactose monohydrate (b) (4) w/w), Povidone (b) (4) w/w), Low-substituted hydroxypropyl cellulose (b) (4) w/w), magnesium stearate ((b) (4) w/w) and (b) (4) w/w).

(b) (4)

The Applicant did not conduct any BE studies

to bridge the 8 mg formulation used in the Phase 3 clinical studies to the 8 mg TBM/Commercial formulation. Instead, the Applicant proposed to establish a bridge between the 8 mg Phase 3 formulation and the 8 mg TBM formulation. A bridge between the 8 mg clinical formulations and the 8 mg TBM/Commercial formulation has been satisfactorily established using comparative *in vitro* dissolution data and a single-dose pivotal BE study.

Bridging of manufacturing sites and batch sizes:

- Two sites have been used to manufacture the batches used in the Phases 1–3 clinical studies ((b) (4)). The TBM batches are manufactured at Halo Pharmaceutical, Inc.
- The sizes of the batches used in the Phases 1–3 and for stability range from (b) (4) kg. The size of the proposed commercial batch is (b) (4) kg.

Based the information submitted in support of the bridging across the formulations, the overall bridging of the products across the three manufacturing sites is found acceptable. In addition, based on the totality of the information submitted in support of the bridging across the formulations, the overall bridging of the products across the batch sizes is deemed acceptable.

- **Biowaiver request:**
  The Applicant initially proposed and developed two strengths of the drug product – 8 mg and 12 mg. Pivotal Phase 3 studies demonstrated efficacy on both 8 mg and 12 mg twice daily administration. However, based on safety concerns, approval of only the 8 mg twice daily dose is being sought in this submission. Based on the totality of the information submitted in support of the bridging across the formulations, manufacturing sites and batch sizes, the data in support of a waiver for demonstration of *in vivo* bioequivalence between the clinical and TBM formulations for the 8 mg strength in accordance with 21 CFR 320.22(d)(2) is found acceptable. An additional *in vivo* study is not required. The efficacy studies for the 8 mg strength will be assessed by the Clinical/Clinical Pharmacology Reviewer.

The list of submissions assessed in the NDA are shown below in Table 3.

Table 3: List of Submissions Being Assessed

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	7/28/2023	Original Submission
NDA	0020	2/15/2024	Quality/Response to Biopharmaceutics IR #1

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

OVERALL BIOPHARMACEUTICS RECOMMENDATION:
From a Biopharmaceutics perspective, NDA 217900-ORIG-1 for LEQSELVI (Deuruxolitinib) tablets, 8 mg, is **adequate** and is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

B.1. BCS DESIGNATION:

Assessment: Not Applicable

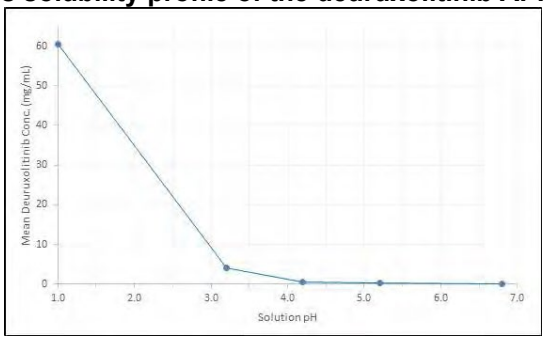
Solubility:

The active pharmaceutical ingredient (API), deuruxolitinib, is a white to off-white crystalline solid that is exhibits a high aqueous solubility at low pH and good to poor solubility in a range of organic solvents. The aqueous solubility profile of the deuruxolitinib drug substance across the physiological pH range (as shown below in Table 4 and Figure 1) indicates a pH-dependent solubility ranging from 60.5 mg/mL (pH 1.0) to 0.124 mg/mL (pH 6.8).

Table 4: Aqueous solubility data of the deuruxolitinib API (37 °C; 48 hours)

Buffer/pH	Solubility (mg/mL)	Volume (mL) required to dissolve highest dose (8 mg)
1.0	60.5	0.13
3.2	4.05	1.97
4.2	0.612	13.07
5.2	0.165	48.48
6.8	0.124	64.51
SGF	43.1	0.19
SIF	0.287	27.87

Figure 1: Aqueous solubility profile of the deuruxolitinib API (37 °C; 48 hours)



Permeability:

The apical-to-basolateral apparent permeability (P_{app}) of the deuruxolitinib drug substance at concentrations of 4.07 µM (1% of a 32 mg dose in 250 mL [407 µM free base]), 40.7 µM (10%) and 175 µM (43%) was greater than the high-permeability reference compound, minoxidil, in the Caco-2 cell monolayer test system (Table 5A). The test could not be performed with 407 µM (100%) concentration due to tolerability issues with the Caco-2 cell testing system.

Table 5A: Average unidirectional (A-to-B) permeability of deuruxolitinib and reference compounds

Nominal Deuruxolitinib Dosing Concentration (µM)[a]		4.07	40.7	175
Deuruxolitinib phosphate	Papp (10^{-6} cm/s)	37.0 ± 0.744	40.6 ± 2.13	44.8 ± 2.32
	Recovery (%)	101 ± 3.01	89.3 ± 3.83	96.3 ± 2.48
Minoxidil (10 µM)	Papp (10^{-6} cm/s)	5.08 ± 0.332	4.56 ± 0.459	4.96 ± 0.169
	Recovery (%)	110 ± 0.736	103 ± 4.71	107 ± 6.01
Atenolol (100 µM)	Papp (10^{-6} cm/s)	0.153 ± 0.0128	0.179 ± 0.0149	0.190 ± 0.0239
	Recovery (%)	111 ± 1.62	109 ± 3.92	107 ± 1.77

The three deuruxolitinib dosing levels evaluated for bidirectional (A-to-B and B-to-A) permeability were 4.07 µM (1% of a 32 mg dose in 250 mL [407 µM free base]), 40.7 µM (10%) and 102 µM (25%). The efflux ratio was between 1.35 and 0.763 over the tested concentration range (Table 5B).

Table 5B: Average bidirectional permeability of deuruxolitinib

Direction	Parameter	Nominal Dosing Concentration (µM)[a]		
		4.07	40.7	102
A-to-B	Papp (10^{-6} cm/s)	35.5 ± 0.547	45.9 ± 2.06	42.2 ± 3.37
	Recovery (%)	95.7 ± 3.19	97.8 ± 3.33	97.8 ± 4.39
B-to-A	Papp (10^{-6} cm/s)	47.9 ± 0.824	40.9 ± 2.46	32.2 ± 1.56
	Recovery (%)	90.5 ± 4.23	94.2 ± 3.98	87.0 ± 3.14
Efflux Ratio		1.35	0.891	0.763

In addition to the Caco-2 permeability studies, a human absorption and metabolism study (Study# CP543.1004) was conducted by dosing radiolabeled deuruxolitinib to healthy volunteers. Following the administration of a single oral-Deuruxolitinib in healthy adult male subjects, an average of 90% of the administered radioactivity was recovered, of which approximately 70% was recovered in urine, predominantly as metabolites, and approximately 20% was recovered in feces, predominantly as metabolites. Unchanged deuruxolitinib represented less than 2% of the radioactivity in excreta.

***Reviewer's assessment*:**

Based on the solubility profile of the deuruxolitinib API across the physiological pH range of 1.0 to 6.8, at the highest dose strength of 8 mg and the lowest solubility of 0.124 mg/mL (at pH 6.8 pH 6.8; Table 4), the volume of solvent required to dissolve the API is 64.51 mL. It is to be noted that dissolution development and *in vivo* PK studies were conducted on the 12 mg strength of the drug product. For a dose strength of 12 mg and the lowest solubility of 0.124 mg/mL, the volume of solvent required to dissolve the API is 96.77 mL. Thus, the deuruxolitinib API can be considered to be a high-solubility compound. Based on the results of the Caco-2 permeability and human absorption-metabolism studies, the deuruxolitinib API can be considered to be a high-permeability compound.

Based on the BCS classification system, the Applicant has classified the deuruxolitinib API as a BCS Class 1 compound. However, the Applicant has not requested a formal claim for the BCS designation. Hence, the permeability and BCS class of the deuruxolitinib API have not been assessed.

B.2. DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

Assessment: Adequate

B.2.1. In vitro dissolution method:

During the early stage of the drug product development, dissolution media and volume were established based on the drug substance solubility and immediate release nature of the dosage form. As part of the dissolution method development, the following dissolution parameters were investigated:

- Apparatus:
  - USP apparatus 1
  - (b) (4)
- Dissolution media:
  - (b) (4)
  - 0.1 N HCl
- Media volume:
  - 500 mL
  - (b) (4)
- Rotation speed:
  - (b) (4) 100 rpm
- Temperature:
  - 37±0.5 °C

The details are provided in the Dissolution method development report (page 1). The dissolution method adopted by the Applicant for QC of the drug product at release and through the stability program is in accordance with the method in the (August 2018) FDA *Guidance for Industry* on "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" and is stated below in Table 6:

Table 6: Proposed dissolution method for QC of the drug product

Media	0.1N HCl in water
Media volume	500 mL
Apparatus	USP 1 (baskets)
Rotation speed	100 rpm
Temperature	37.0 °C
Sampling time points	5, 10, 20, 30 minutes[a]

[a] A single sampling point at 30 minutes is proposed for routine commercial testing

***Reviewer's assessment*:**

Based on the solubility profile of the deuruxolitinib API across the physiological pH range of 1.0 to 6.8, at the highest dose strength of 8 mg and the lowest solubility of 0.124 mg/mL (at pH 6.8 pH 6.8; Table 4), the volume of solvent required to dissolve the API is 64.51 mL. It is to be noted that dissolution development and *in vivo* PK studies were conducted on the 12 mg strength of the drug product. For a dose strength of 12 mg and the lowest solubility of 0.124 mg/mL, the volume of solvent required to dissolve the API is 96.77 mL. Thus, the deuruxolitinib API can be considered to be a high-solubility compound. Phase 1 studies of a single dose of the 12 mg strength of the product (Study# CP543.1009) indicated a median T_{max} of 0.5–0.88 hours which is in accordance with the immediate release nature of the dosage form. Thus, the proposed acceptance method

which is in accordance with the method in the (August 2018) FDA *Guidance for Industry* on "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" is found acceptable. Based on the deuruxolitinib API being highly soluble across the physiological pH range of 1.0 to 6.8 and the dissolution method being in accordance with the *Guidance*, the risk from a Biopharmaceutics perspective is very low and demonstration of discriminating ability of the method is not critical and is not deemed necessary.

B.2.2. Dissolution Data and Acceptance Criterion:

Based on the dissolution method, the acceptance criterion proposed by the Applicant for QC of the product at release and through the stability program is "Q = (b) (4)% at 30 minutes". The dissolution method and acceptance criterion proposed by the Applicant for QC of the drug product is shown below in Table 7.

Table 7: Dissolution method and acceptance criterion proposed by the Applicant and agreed by the FDA

Dissolution method Proposed (seq 0001) and agreed by FDA				**Dissolution acceptance criterion** Proposed (seq 0001) and agreed by FDA
Source	**Apparatus**	**Media/ Volume**	**Agitation speed/ Temperature**	30 min: NLT (b) (4)% (Q)
2018 FDA Guidance	USP apparatus 1	Medium: 0.1 N HCl Volume: 500 mL	Speed: 100 rpm Temp: 37±0.5 °C	

***Reviewer's assessment*:**

The proposed drug product an immediate release product (with a median T_{max} of 0.5–0.88 hours) containing a high-solubility drug substance. (b) (4)

(b) (4)

Based on the totality of the submitted information, the dissolution method and acceptance criterion as shown above in Table 7 are found acceptable.

The link to the dissolution data of the clinical and TBM batches of the 8 mg and 12 mg strengths is provided in Appendix 1.

B.2.3. Dissolution data during Stability:

Stability studies were conducted on the four registration batches of the 8 mg strength as shown below in Table 8 using the proposed dissolution method/acceptance criterion. Primary stability data was generated under long term (25 °C/60% RH), accelerated (40 °C /75% RH) and intermediate storage conditions (30 °C/65% RH).

Table 8: Details of batches of the 8 mg strength placed on stability

Strength	Batch No.	Manufacturing Date	Theoretical Batch Size	Drug Substance Batch No. (Manufacturer)	Purpose/Use	Stability Data Included
8 mg	0000107543	August 2021	(b) (4)	2102992 (b) (4)	Primary stability, Phase 3[a] clinical	25 °C/60% RH: 18 months 30 °C/65% RH: 12 months 40 °C/75% RH: 6 months
	0000107544	August 2021		2103050	Primary stability, photostability	
	0000107545	August 2021		2103084	Primary stability	
	0000133703	November 2022		2200216 (b) (4)	Stability	25 °C/60% RH: 3 months 40 °C/75% RH: 3 months

***Reviewer's Assessment*:**
The dissolution method and acceptance criterion as shown above in Table 7 have been proposed for the QC of the drug product at release and through the stability period. Assessment of the stability data is under the purview of the CMC/DP Reviewer.

B.3. CLINICAL RELEVANCE OF DISSOLUTION METHOD AND ACCEPTANCE CRITERION (e.g., *IVIVR/IVIVC, In silico modeling, small scale in vivo*):
Assessment: Adequate

***Reviewer's assessment*:**
The Applicant has not performed an IVIVR/IVIVC nor any modeling studies. The dissolution method proposed by Applicant is to ensure batch-to-batch consistency, and this is acceptable. Based on the Phase 1 PK study on the 12 mg strength of the product (Study# CP543.1009), the median T_{max} of the product ranges from 0.5–0.88 hours. The short T_{max} for the immediate-release drug product is supported by the dissolution data wherein >90% of the product is dissolved at the 30-minute time-point under physiologically-relevant dissolution conditions (b) (4) (b) (4). The rapid dissolution of the drug product is supported by (b) (4) acceptance criterion of "Q = (b) (4) % in 30 minutes". With the deuruxolitinib API being a high-solubility API in an immediate release dosage form, the risk from a Biopharmaceutics perspective is minimal, and demonstration of discriminatory ability is not critical.

B.12. BRIDGING OF PRODUCTS:
Assessment: Adequate

***Bridging of Formulations*:** Phase 1 PK studies (Study# CP543.1001 Part B and Study# CP543.1002) were conducted on the 8 mg uncoated formulation (Table 9A).

Table 9A: Composition of the uncoated 8 mg batch used in Ph 1 PK studies

Component	Amount per Unit[a]	Function
	8 mg Strength	
Deuruxolitinib phosphate	10.49 (5.25%)	Active
(b) (4)		
Total	(b) (4) (100.0%)	-

The composition of the film-coated 8 mg and 12 mg Phase 3 clinical and TBM batches is shown below in Tables 9B and 9C, respectively. It is to be noted that the composition of the 8 mg strength

uncoated formulation (Table 9A) used in the Phase 1 PK studies differs from the 8 mg Phase 3 and the to-be-marketed (TBM) film-coated formulations (Tables 9B and 9C).

Table 9B: Composition of the film-coated 8 mg (Ph 3) and 12 mg (Ph 1 and Ph 3) batches

Component	Amount per Unit[a]			Function
	4 mg Strength	8 mg Strength	12 mg Strength	
Deuruxolitinib phosphate	5.25 (2.63%)	10.50 (5.25%)	15.75 (7.88%)	Active
(b) (4)				

Table 9C: Composition of the film-coated 8 mg TBM and 12 mg proposed TBM batches

Ingredients	8 mg		12 mg		Pharmaceutical Function	Quality Standards
	mg per tablet	% w/w	mg per tablet	% w/w		
Active Ingredient						
Deuruxolitinib phosphate	10.50[a]	8.75	15.75[a]	8.75	Active	Specification
Inactive Ingredients						
Microcrystalline cellulose	(b) (4)					
Lactose monohydrate						
Povidone						
Low-substituted hydroxypropyl cellulose						
Colloidal silicon dioxide						
Magnesium stearate						
Total (Tablet Core)						
				(b) (4)	Film coat	Specification
Total (Coated Tablet)	**123.6**	(b) (4)	**185.4**	(b) (4)	**N/A**	**N/A**

In addition to the differences in the weight of the tablet, the compositional differences include:

- qualitative changes in the composition –
  - The Phase 1 formulation contains (b) (4)
  - The Phase 3 formulation contains (b) (4)

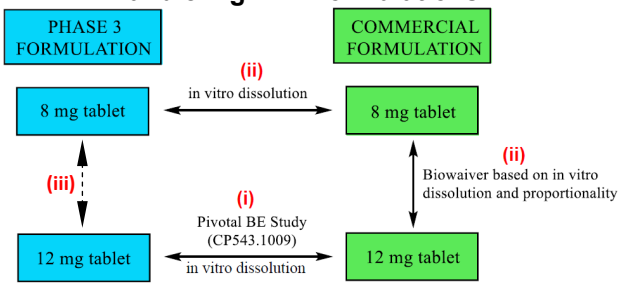
- The TBM formulation contains Microcrystalline cellulose (b) (4) Lactose monohydrate (b) (4) Povidone (b) (4) Low-substituted hydroxypropyl cellulose (b) (4), Colloidal silicon dioxide (b) (4), magnesium stearate (b) (4) and (b) (4) (film-coat).

- quantitative changes in the composition –
  - The Phase 1 formulation contains (b) (4)
  - The Phase 3 formulation contains (b) (4)
  - The TBM formulation contains Microcrystalline cellulose ((b) (4) w/w), Lactose monohydrate ((b) (4) w/w), Povidone (b) (4) w/w), Low-substituted hydroxypropyl cellulose (b) (4) w/w), magnesium stearate (b) (4) w/w) and (b) (4)

(b) (4)

The Applicant did not conduct any BE studies to bridge the 8 mg Phase 3 formulation to the 8 mg TBM/Commercial formulation. Instead, the Applicant proposed to establish a bridge between the 8 mg Phase 3 formulation (Table 9B) and the 8 mg TBM formulation (Table 9C) as shown below in Figure 2.

Figure 2: Bridging strategy between the 8 mg Ph 3 and 8 mg TBM formulations



The bridging strategy, as summarized below under "Summary of bridging strategy", is based upon:

- Differences between the Phase 3 and TBM composition of 8 mg tablets being (b) (4) (Tables 9B and 9C).
- Side-by-side comparison of 8 mg and 12 mg tablets TBM formulations (Table 9C) demonstrating compositional proportionality between the two strengths, and the two strengths being manufactured (b) (4)

- The deuruxolitinib API is a high-solubility API (Table 4) in an immediate release dosage form (Study# CP543.1009) wherein the risk from a Biopharmaceutics perspective is minimal and demonstration of discriminatory ability is not critical.
- Dissolution similarity between all batches of both strengths as evidenced by ≥85% dissolution at the 10-minute time-point in the *Guidance*-recommended method without the need for an *f*2 calculation (Tables 10B–10D).
- All the batches of both strengths complying with the (b) (4) acceptance criterion of "Q = (b) (4)% in 30 minutes" (Tables 10B–10D).

Summary of bridging strategy (Figure 2):

(i) Establish a bridge between the 12 mg Phases 1–3 film-coated formulation (Table 9B) and the 12 mg TBM/Commercial formulation (Table 9C) based on –
- Single-dose pivotal BE study (Study# CP543.1009).
- Comparative *in vitro* dissolution data.

(ii) Establish a bridge between the 8 mg Phase 3 film-coated formulation and the 8 mg TBM/Commercial formulation based on –
- Compositional proportionality between the TBM formulations of the 12 mg and 8 mg strengths (Table 9C), and the two strengths being manufactured (b) (4)
- Comparative *in vitro* dissolution data of the 12 mg and 8 mg TBM formulations.
- Comparative *in vitro* dissolution data of the 8 mg Phase 3 and 8 mg TBM formulations.

The PK parameters of the Phase 1 single-dose pivotal BE study comparing the 12 mg Phases 1–3/CLIN film-coated formulation (B# 200198) and the 12 mg Commercial/TBM formulation (B# 107550/B# 0000107547; see Appendix 2) are shown below in Table 10A and the comparative dissolution data is shown below in Table 10B.

Table 10A: PK parameters of the BE assessment comparing the 12 mg Ph1–3 (CLIN) and 12 mg commercial (TBM) formulations

Comparison	Parameter	Units	Test N	Reference N	Test Mean	Reference Mean	GMR (Test/Reference)	90% Confidence Interval
CTP-543 12mg TBM VS. CTP-543 12mg CLIN	C_{max}	ng/mL	20	20	275	299	92.01	(82.12, 103.10)
CTP-543 12mg TBM VS. CTP-543 12mg CLIN	AUC_{last}	h*ng/mL	20	20	1200	1260	95.27	(90.36, 100.45)
CTP-543 12mg TBM VS. CTP-543 12mg CLIN	AUC_{inf}	h*ng/mL	20	20	1200	1260	95.35	(90.44, 100.53)

Table 10B: Comparative in vitro dissolution data of the 12 mg Ph1–3 (CLIN) and 12 mg commercial (TBM) formulations

Batch details	Phase studies	Manufacturing site	Batch size	Mean % Dissolved (min)			
				5	10	20	30
CTP-543 12 mg TBM (B# 107550/ B# 0000107547)	–	Halo Pharmaceutical, Inc.	(b) (4)	91.3	100.3	100.7	100.7
CTP-543 12 mg CLIN (B# 200198)	Ph1, Ph2 & Ph3	(b) (4)		91.7	97.7	98.5	98.5

The comparative dissolution data for the 12 mg Commercial/TBM formulation (B# 0000107547) and five batches of the 8 mg Commercial/TBM formulation (B#s 0000107543, 0000107544, 0000107545, 0000133703 and 0000137584) is shown below in Table 10C.

Table 10C: Comparative in vitro dissolution data of the 12 mg commercial (TBM) and 8 mg TBM formulations

Batch details	Manufacturing site	Batch size	Mean % Dissolved (min)			
			5	10	20	30
CTP-543 12 mg TBM (B# 0000107547)	Halo Pharmaceutical, Inc.	(b) (4)	91.3	100.3	100.7	100.7
CTP-543 8 mg TBM (B# 0000107543)	Halo Pharmaceutical, Inc.		51.8	100.0	100.2	100.2
CTP-543 8 mg TBM (B# 0000107544)	Halo Pharmaceutical, Inc.		98.3	101.3	101.3	101.7
CTP-543 8 mg TBM (B# 0000107545)	Halo Pharmaceutical, Inc.		94.7	101.2	103.3	103.5
CTP-543 8 mg TBM (B# 0000133703)	Halo Pharmaceutical, Inc.		93.3	101.3	101.5	101.5
CTP-543 8 mg TBM (B# 0000137584)	Halo Pharmaceutical, Inc.		76.2	97.7	98.0	98.0

The comparative dissolution data for four batches of the 8 mg Phases 1–3 formulations (B#s 16D082, M10487, 190076 and 200197) is shown below in Table 10D.

Table 10D: In vitro dissolution data of the and 8 mg Ph1–3 formulations

Batch details	Phase studies	Manufacturing site	Batch size	Mean % Dissolved (min)			
				5	10	20	30
CTP-543 8 mg CLIN (B# 16D082)	Ph1		(b) (4)	95.2	96.8	96.7	96.5
CTP-543 8 mg CLIN (B# M10487)	Ph2			81.2	93.7	97.5	98.0
CTP-543 8 mg CLIN (B# 190076)	Ph1 & Ph2			88.0	95.0	96.0	96.0
CTP-543 8 mg CLIN (B# 200197)	Ph2 & Ph3			94.8	97.5	97.7	97.5

***Reviewer's Assessment*:**

(i) Establishing a bridge between the 12 mg Phases 1–3 film-coated formulation (Table 9B) and the 12 mg TBM/Commercial formulation (Table 9C) based on –

- *Phase 1 single-dose pivotal BE study (Study# CP543.1009)*: The PK parameters of the Phase 1 single-dose pivotal BE study (Table 10A) comparing the 12 mg Phases 1–3/CLIN film-coated formulation (B# 200198) and the 12 mg Commercial/TBM formulation (B# 107550/B# 0000107547) indicate that the two batches are BE to each other (90% CI values for C_{max}, AUC_{last} and AUC_{inf} are between the range of 80%–125%). The *in vivo* bioavailability study will be further evaluated by the Clinical Pharmacology Reviewer.

- *Comparative in vitro dissolution data*: The comparative dissolution data of the two batches (Table 10B) indicates similarity in their dissolution profiles (≥85% dissolution of both batches at the 10-minute time-point in the *Guidance* method without the need for an *f2* calculation). Furthermore, both products comply with the acceptance criterion of "Q = (b) (4)% in 30 minutes".

Thus, based on the submitted data, this Reviewer concludes that a bridge between the 12 mg Phases 1–3 film-coated formulation and the 12 mg TBM/Commercial formulation has been satisfactorily established.

(ii) Establishing a bridge between the 8 mg Phases 1–3 film-coated formulations and the 8 mg TBM/Commercial formulation based on –

- *Compositional proportionality between the TBM formulations of the 12 mg and 8 mg strengths, and being manufactured* [redacted] (b) (4) Based on the information submitted in Table 9C, the 12 mg and the 8 mg strengths are compositionally proportional. Furthermore, the two strengths are manufactured [redacted] (b) (4)

- *Comparative in vitro dissolution data of the 12 mg and 8 mg TBM formulations*: The comparative dissolution data of the 12 mg TBM formulation (B# 0000107547) to the four batches of 8 mg TBM formulations (Table 10C) indicates similarity in their dissolution profiles (≥85% dissolution of all batches at the 10-minute time-point in the *Guidance* method without the need for an *f*2 calculation). Furthermore, all the products comply with the acceptance criterion of "Q = [redacted] (b) (4)% in 30 minutes".

- *Comparative in vitro dissolution data of the 8 mg clinical and 8 mg TBM formulations*: The comparative dissolution data of the four batches of 8 mg strength TBM formulation (Table 10C) to the four batches of 8 mg clinical formulation (Table 10D) indicates similarity in their dissolution profiles (≥85% dissolution of all batches at the 10-minute time-point in the *Guidance* method without the need for an *f*2 calculation). Furthermore, all the products comply with the acceptance criterion of "Q = [redacted] (b) (4)% in 30 minutes".

(iii) It is noted that the 8 mg and 12 mg batches used for the Phase 3 studies differ in the concentration of [redacted] (b) (4) and are not compositionally proportional (Table 9B). However, based on the high aqueous solubility and *in vitro* permeability of the API, similarity in the *in vitro* dissolution profiles of the 12 mg and 8 mg strengths (≥85% dissolution of all batches at the 10-minute time-point in the *Guidance* method without the need for an *f*2 calculation and all the batches of the 8 mg and 12 mg strengths complying with the *in vitro* dissolution acceptance criterion of "Q = [redacted] (b) (4)% in 30 minutes" [Tables 10B and 10D]), rapid *in vivo* absorption and dose proportionality between 12 mg and 8 mg strengths (Refer to the Clinical Pharmacology Reviewer's assessment for additional details), this Reviewer concludes that the risk from a Biopharmaceutics perspective is low, and the 8 mg Phase 3 formulation can be considered to be bridged to the 12 mg Phase 3 formulation.

Thus, based on the totality of the submitted data, this Reviewer concludes that a bridge between the 8 mg clinical film-coated formulation and the 8 mg TBM/Commercial formulation has been satisfactorily established, and an additional *in vivo* BE study is not required.

***Bridging of Manufacturing sites and batch sizes*:** Two sites have been used to manufacture the batches used in the Phases 1–3 clinical studies ([redacted]). The TBM batches are manufactured at Halo Pharmaceutical, Inc. The sizes of the batches used in the Phases 1–3 and for stability range from [redacted] kg. The size of the proposed commercial batch is [redacted] kg (Table 11).

Table 11: Details of manufacturing site and size of batches

Manufacturer	[redacted]	[redacted]	Halo Pharmaceutical, Inc. [redacted]
Batch size	[redacted]	[redacted]	[redacted]
Use	Phases 1 & 2	Phases 1–3	Primary stability and Commercial

***Reviewer's Assessment*:**
Based on the totality of the information submitted in support of the bridging across the formulations, this Reviewer finds the overall bridging of the products across the three manufacturing sites to be acceptable.

The sizes of the clinical and the primary stability batches range from [redacted] kg. Based on the totality of the information submitted in support of the bridging across the formulations, this Reviewer finds the overall bridging of the products across the different sizes of the clinical and the primary stability batches to be acceptable. The size of the proposed commercial batch is [redacted] kg, and is within 10× the size of the primary stability batches ([redacted] kg). The documentation recommended to support the Level 1 change in batch size (as per the SUPAC-IR Guidance) is a dissolution documentation in the application/compendial media. The comparative dissolution data of the proposed commercial batch to the four primary stability batches and the proposed commercial batch of 8 mg strength TBM formulation (Table 10C) indicates similarity in their dissolution profiles (≥85% dissolution of all batches at the 10-minute time-point in the *Guidance* method). Furthermore, all the batches comply with the acceptance criterion of "Q = [redacted]% in 30 minutes". Based on the totality of the information submitted in support of the bridging across the formulations, this Reviewer finds the overall bridging of the products across the batch sizes to be acceptable.

B.13. BIOWAIVER REQUEST:

Assessment: Adequate

The Applicant initially proposed and developed two strengths of the drug product – 8 mg and 12 mg. Pivotal Phase 3 studies demonstrated efficacy on both 8 mg and 12 mg twice daily administration. However, based on safety concerns, approval of only the 8 mg twice daily dose is being sought in this submission.

A waiver for demonstration of bioequivalence between the clinical and TBM formulations has been requested for the 8 mg strength based on the following:

- The *in vivo* PK profile of the 12 mg strength commercial formulation is bioequivalent to the 12 mg Phase 3 clinical formulation (the 90% CI values for C_{max}, AUC_{last} and AUC_{inf} are within the acceptance criterion range of 80%–125% [Table 10A]).

- The *in vitro* dissolution profile of the 12 mg strength commercial formulation is similar to the 12 mg Phase 3 clinical formulation (>85% dissolution of both products at the 10-minute time-point in the *Guidance*-recommended method without the need for an *f*2 calculation, and both products complying with the (b) (4) acceptance criterion of "Q = (b) (4)% in 30 minutes" [Table 10B]).
- The 8 mg and 12 mg strengths of the TBM formulations are in the same dosage form, compositionally proportional and manufactured (b) (4) (Table 9C).
- The *in vitro* dissolution profiles of the Phases 1–3 and TBM formulations of the 8 mg strength are similar to the TBM formulation of the 12 mg strength (>85% dissolution of all the products at the 10-minute time-point in the *Guidance*-recommended method without the need for an *f*2 calculation, and all products complying with the (b) (4) acceptance criterion of "Q = (b) (4)% in 30 minutes" [Tables 10C and 10C]).

The bridging approach in support of the biowaiver request is shown in Figure 2.

***Reviewer's Assessment*:**
Based on the totality of the information submitted in support of the bridging across the formulations, manufacturing sites and batch sizes, this Reviewer finds the data in support of a waiver for demonstration of *in vivo* bioequivalence between the clinical and TBM formulations for the 8 mg strength in accordance with 21 CFR 320.22(d)(2) to be acceptable. An additional *in vivo* study is not required. The efficacy studies for the 8 mg strength will be assessed by the Clinical/Clinical Pharmacology Reviewer.

R. REGIONAL INFORMATION:
Life Cycle Management Considerations and Risk Mitigation Strategies
***Reviewer's Assessment*:**
The proposed drug product is an immediate release product wherein the deuruxolitinib API is a high-solubility drug substance. (b) (4) (b) (4) (b) (4) (b) (4) From a Biopharmaceutics perspective, the risk is very low and further risk mitigation is not needed.

BIOPHARMACEUTICS PENDING DEFICIENCIES:
None

APPENDIX 1

Data Tables and Figures

The dissolution data for the clinical and TBM batches of the 8 mg and 12 mg strengths of the drug product in the proposed method [USP apparatus 1; 500 mL of 0.1 N HCl; 100 rpm; 37 ± 0.5 °C] is provided in the link to dissolution data.

APPENDIX 2

(b) (4)

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