CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220442Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	220442		
Applicant Name	Shionogi Inc.		
Drug Product Name	XOCOVA (ensitrelvir) tablet		
Dosage Form.	Tablet		
Proposed Strength(s)	125 mg		
Route of Administration	Oral		
Maximum Daily Dose	375 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Post-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.		
Drug Product Description	The proposed drug product is a white to light yellow-white, round tablet containing 125 mg of ensitrelvir, debossed with the Shionogi trademark () above the identifier code “711” on one side and with a “125” on the other side. The drug product is packaged in a child-resistant blister pack containing 7 tablets.		
Co-packaged product information	n/a		
Device information:	n/a		
Storage Temperature/ Conditions	20º to 25ºC (68º to 77ºC) with excursions permitted to 15º to 30ºC (59º to 86ºC)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sivakoteswara Mandadapu	Katherine Windsor
	Drug Product	Hitesh Agarwal	Molly Escarcega

	Labeling	Hitesh Agarwal	David Claffey
	Manufacturing	Yogesh Chachare	Hang Guo
	Biopharmaceutics	Payal Agarwal	Elsbeth Chikhale
	Microbiology	n/a	
	Other (specify):	n/a	
	RBPM	Megan Nguyen	
	ATL	Molly Escarcega	
Consults	n/a		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 36 months at 20° to 25°C (68° to 77°F)

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL for NDA 220442 for the commercialization of ensitrelvir tablets, 125 mg. The proposed drug product is white to light yellow-white, round tablets containing 125 mg of ensitrelvir, debossed with the Shionogi trademark () above the identifier code “711” on one side and with a “125” on the other side. The drug product is packaged in a child-resistant single cavity blister containing 7 tablets per blister pack.

The Applicant provided adequate drug substance, drug product, biopharmaceutics, and manufacturing information and data to support an approval recommendation from the product quality perspective. The drug substance is ensitrelvir fumaric acid, which is a co-crystal and is manufactured through (b) (4) The application included sufficient stability data to support the proposed (b) (4) month retest period for ensitrelvir fumaric acid drug substance. The drug product manufacturing process utilizes typical pharmaceutical unit operations associated with the dosage form: (b) (4)

(b) (4). The manufacturing process is designed and developed adequately, and the risk of API uniformity in finished product is low; the overall control strategy is sufficient to ensure consistent production of finished product capable of meeting the acceptance criteria. The dissolution method and acceptance criteria are acceptable. 36 months of long-term stability data and six months of accelerated stability data are provided for the drug product primary stability batches to support the proposed 36-month shelf-life.

The manufacturing inspection recommendation is approval for all facilities associated with this application. All facilities have relevant experience in executing responsibilities listed in this application for the specific facilities.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes
Comments:
Comparability protocol to register additional primary packaging component materials (container closure system) as an annual reportable change

Additional Lifecycle Comments: N/A

93 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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	220442
Assessment Cycle Number	1
Drug Product Name	Xocova (Ensitrelvir) Tablets 125 mg

Assessment Recommendation: Choose an item.

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

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0002, 0040, 0049 and 0073	06-16-2025	

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

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	XOCOVA® (ensitrelvir) tablets, for oral use
Route(s) of administration	Adequate	Oral use
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	2026
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	
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	API is not a salt

[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>

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

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."[7]	N/A	Tablet is not scored
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*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

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	N/A	No special preparation instructions needed for this oral drug product

[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>
[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

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 stability of the reconstituted or diluted product).		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	(b) (4)
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 the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
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*

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

APPREAS THIS WAY IN ORIGINAL

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

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	Tablets
Strength(s) in metric system	Adequate	125 mg
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 of drug-x hydrochloride). No equivalency statement.	Adequate	API is not a salt.
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	No Scoring
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*

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

1.2.3 Section 11 (DESCRIPTION)[14]

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	
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)].	N/A	API is not a salt. Revised to remove API equivalency statement: (b) (4)
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)].	N/A	
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	

[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).

[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.

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 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	
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	XOCOVA is a 1:1 co-crystal of ensitrelvir and fumaric acid
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	

[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.

[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)

Assessment: *Adequate*

API is a co-crystal and not a salt. Applicant was asked to revise the equivalency statement for (b) (4) that is equivalent to 125 mg of ensitrelvir. Description was revised to remove the equivalency information.

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

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	Tablets
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	125 mg tablet
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	7 tablets blister pack
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	Supplied as a white to light yellow-white, round, debossed with Shionogi trademark above identification code 711 on one side and 125 on the other side
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	No tablet Scoring
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	N/A	

[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)
bulk package and imaging bulk package (see USP <659>).		
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)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Store XOCOVA in the original package at 20°C to 25°C (68°F to 77°F)
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."*[21]	N/A	

[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)

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)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	Applicant confirmed in response to an IR dated 21st November, 2025 that the commercial CCS meets the consumer product safety commission regulations per 16 CFR 1700. However, no information about child resistance packaging for blister in provided in packaging insert. Carton label contains information "This package is child-resistant."

Assessment: *Adequate*

1.2.5 Other Sections of Labeling

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

[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

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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	Store XOCOVA at room temperature between 68°F and 77°F (20°C to 25°C)
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.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	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]

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)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[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.

3.2 Carton Labeling

(b) (4)

[redacted]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	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	Adequate	Yes	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
and prominence) [§ 201.10(g)(2)].			
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	Statement provided "For oral use"
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>].	N/A	Choose an item.	API is not a salt.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	Statement provided "7 tablets"
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type	N/A	Choose an item.	

[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)

[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 Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
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>).			
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	Choose an item.	
For parenteral injectable dosage forms, include 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	Choose an item.	
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	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor	Adequate	Yes	

[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 Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
/packer [§ 201.1(a), 201.1(h)(5)].			
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes	Statement provided "Recommended Dosage and Alerts: Find out about medications that should not be taken with XOCOVA. See Prescribing Information."
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
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	Choose an item.	
And others if space is available.	N/A	Choose an item.	

[31] USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*

API is a co-crystal and not a salt. Applicant was asked to revise the equivalency statement for [redacted] (b) (4) that is equivalent to 125 mg of ensitrelvir. Description was revised to remove the equivalency information. The carton labels and container labeling were also asked to revise to add tablets after "(entsitrelvir)" and the updated carton and container labels comply with all regulatory requirements from a CMC perspective.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.

Primary Drug Product Assessor
Hitesh K. Agarwal, Ph.D., Pharmaceutical Scientist, Division of Pharmaceutical Quality Assessment III, OPQA1, OPQ

Secondary Assessor
David Claffey, Ph.D., Supervisory Pharmaceutical, Division of Pharmaceutical Quality Assessment III, OPQA1, OPQ

Hitesh Agarwal

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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Ensitrelvir Tablets, 125 mg
NDA Number	220442
Assessment Cycle Number	1
Drug Product Name/ Strength	Xocova™(ensitrelvir) Tablets, 125 mg (proposed)
Route of Administration	Oral
Applicant Name	SHIONOGI Inc.
Therapeutic Classification/ OND Division	Division of Antivirals/Office of Infectious Diseases
RLD/RS Number	N/A
Proposed Indication	For the post-exposure prophylaxis of COVID-19 following contact with an individual who has COVID-19

Assessment Recommendation: **Adequate**

Executive Summary: This 505(b)(1) New Drug Application (NDA 220442) seeks approval of Ensitrelvir 125 mg Tablets (proposed trade name: Xocova) for the prevention of COVID-19 in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19. Ensitrelvir is a novel, oral, once-daily SARS-CoV-2 main protease (Mpro) inhibitor developed by Shionogi & Co., Ltd. that exerts antiviral activity by blocking viral replication.

This Biopharmaceutics review is focused on the 1) Evaluation and acceptability of the proposed dissolution method and acceptance criterion for the proposed test product, and the 2) Evaluation of the need for bridging.

In Vitro Dissolution Method and Acceptance Criterion:
Based on the totality of data/information provided, the following dissolution testing method and acceptance criterion are found acceptable for the QC of the proposed drug product at batch release and for stability testing.

Dissolution Method and Acceptance Criterion found Adequate for Ensitrelvir Tablets, 125 mg

Strengths	Apparatus	Dissolution medium	Dissolution volume	Rotation speed	Acceptance criterion
125 mg	USP Apparatus 2	0.1 N HCl with 0.1% SLS	900 mL	50 rpm	Q = (b)(4)% in 20 minutes

Bridging of formulations and other drug product changes made throughout the clinical development:

The Applicant developed an oral suspension formulation for initial Phase 1 studies, then transitioned to tablet formulations (125 mg and 250 mg (b) (4)) for subsequent clinical development and commercialization. The Applicant conducted in vivo bridging study between the suspension and the tablets via a cross-cohort PK study 2102T1211. In addition, the Applicant conducted in vitro comparative dissolution testing to bridge the drug product strengths (125 mg vs. 250 mg, shapes (round/ (b) (4) and manufacturing sites (Shionogi, Nipro (b) (4)).

BIOPHARMACEUTICS OVERALL RECOMMENDATION

From the Biopharmaceutics perspective, NDA-220442-ORIG-1 for the proposed Ensitrelvir Tablets, 125 mg, is **Adequate** and recommended for **Approval.**

Biopharmaceutics risk:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Solubility	Medium	Ensitrelivir is a low soluble drug substance, however, the drug substance is manufactured as a co-crystal form (b) (4)	Low	(b) (4)
Polymorphism	Medium	Co-crystals can exist in different polymorphic forms that may have significantly different dissolution rates and bioavailability	Low	The co-crystal formed is not hygroscopic and exists in a stable crystal form. No crystalline polymorphism has been observed.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
NDA original	03/31/2025
IR Response #1	09/08/2025
IR Response # 2	12/18/2025

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues: N/A

B.1 BCS DESIGNATION

Assessment:
There is no official BCS designation request for the proposed drug product.

Solubility: Ensitrelvir fumaric acid exists as a 1:1 co-crystal of ensitrelvir and fumaric acid. Ensitrelvir fumaric acid is a white powder and is practically insoluble in water and buffer solutions at pH 1 to 7. The Applicant is using ensitrelvir as **ensitrelvir fumaric acid** (ensitrelvir fumaric acid co-crystal) as the preferred crystal form selected for the manufacturing of the proposed drug product. The solubility of **ensitrelvir fumaric acid** (co-crystal) across the physiological pH range is shown in Table 1.

Table 1. Solubility profile of Ensitrelvir Fumaric Acid (co-crystal) in the physiological pH conditions at 37 °C

Items	Properties
Solubility (water)	0.02364 mg/mL
Solubility (pH 1.2 hydrochloric acid solution)	0.0686 mg/mL
Solubility (pH 6.8 phosphate buffer)	0.0180 µg/mL
Partition Coefficient	log P = 1.06
Crystallinity/Polymorphism	Ensitrelvir fumaric acid is a co-crystal composed of ensitrelvir and fumaric acid (coformer). Ensitrelvir fumaric acid (ensitrelvir-fumaric acid co-crystal) is produced as a non-solvate form.

Permeability: No data provided

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

(b) (4)

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The Applicant justified the use of 0.1% SLS by emphasizing that the validated method was specifically developed to achieve sink conditions using mild conditions (50 rpm paddle speed). The Applicant stated that the proposed dissolution method demonstrated discriminating ability between the co-crystal form (ensitrelvir fumaric acid) and free form (ensitrelvir) as shown in Figure 1. In addition, the proposed dissolution method was able to demonstrate discriminating ability for changes in various critical quality attributes (discussed in upcoming section). Based on these considerations, the Applicant proposed to retain SLS concentration at 0.1 %. The adequacy of the 0.1% SLS concentration in the dissolution medium was further discussed with the Biopharmaceutics Supervisor, who concurred with this selection based on the scientific rationale and supporting data presented.

Discriminating Ability of the Proposed Dissolution Method

The Applicant conducted a comprehensive discriminating ability study to evaluate whether the proposed dissolution method (USP Apparatus 2, 50 rpm, 900 mL pH 1.2 HCl with 0.1% SLS) could adequately detect meaningful quality changes arising from variations in drug substance physicochemical parameters, formulation attributes, and manufacturing process parameters. Multiple variant batches of 125 mg tablets were manufactured, and the dissolution profiles were compared against the target clinical batch S21035.

The proposed dissolution method successfully demonstrated discriminating ability towards:

- Drug substance solid form (co-crystal vs. free form): Variant batch showed slower dissolution for a drug product batch containing the free form, with only ~73% released at 30 minutes compared to ~99% for a drug product batch containing the co-crystal (Figure 3)

- [redacted] type ([redacted]): Variant drug product batch demonstrating measurable differences in dissolution profiles (Figure 4)
- [redacted] amount ([redacted]) - showing substantially slower dissolution for a drug product batch containing a reduced level of [redacted] (Figure 5)

However, the proposed dissolution method was not able to demonstrate discriminating ability towards the drug substance particle size distribution (PSD ranging from [redacted]), manufacturing method [redacted]), and tablet thickness variations ([redacted]) (Figures 6 to 8).

Based on the totality of information submitted and demonstration of acceptable discriminating ability towards several critical formulation attributes, the proposed dissolution method is found adequate for quality control purposes of the proposed drug product Ensitrelvir Tablets, 125 mg.

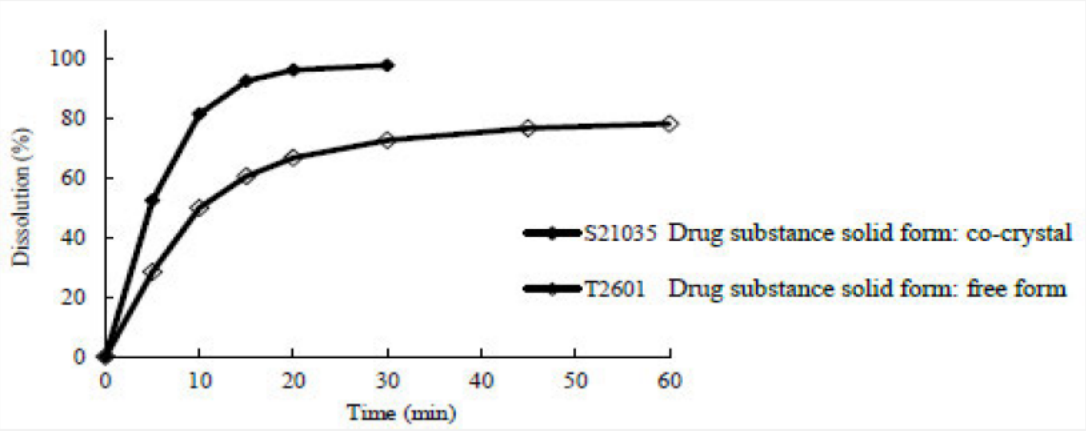

Figure 3. Dissolution Profiles of 125 mg Tablets with Different Solid Forms of Drug Substance using the proposed dissolution method

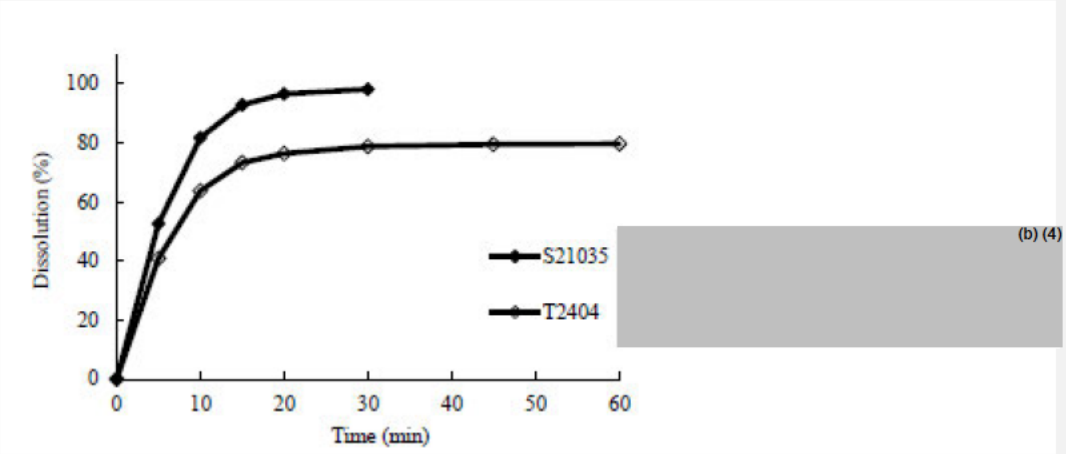

Figure 4. Dissolution Profiles of 125 mg Tablets with Disintegrant Type Change using the proposed dissolution method

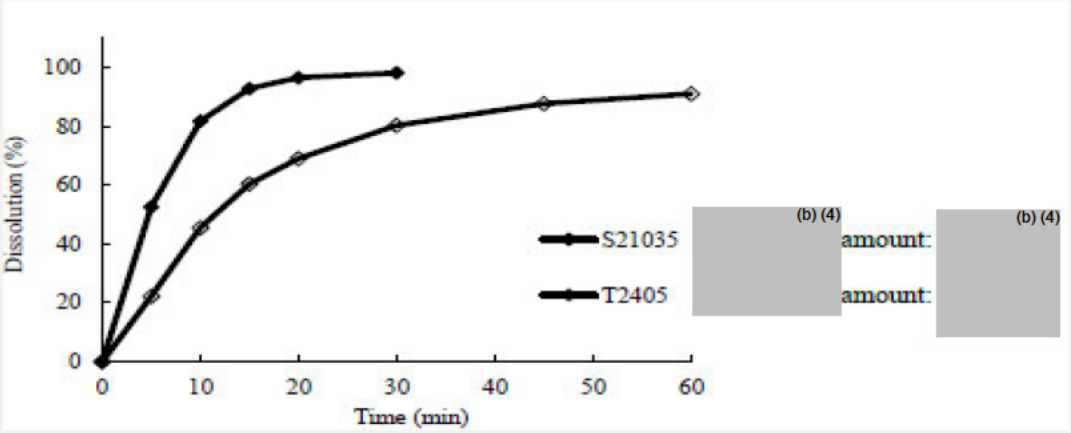

Figure 5. Dissolution Profiles of 125 mg Tablets with (b) (4) Amount Change using the proposed dissolution method

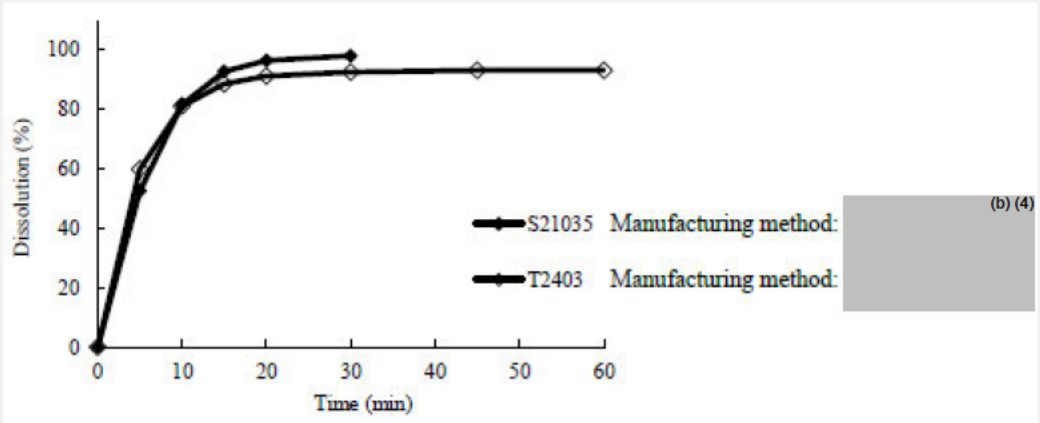

Figure 6. Dissolution Profiles of 125 mg Tablets with Different Manufacturing Method using the proposed dissolution method

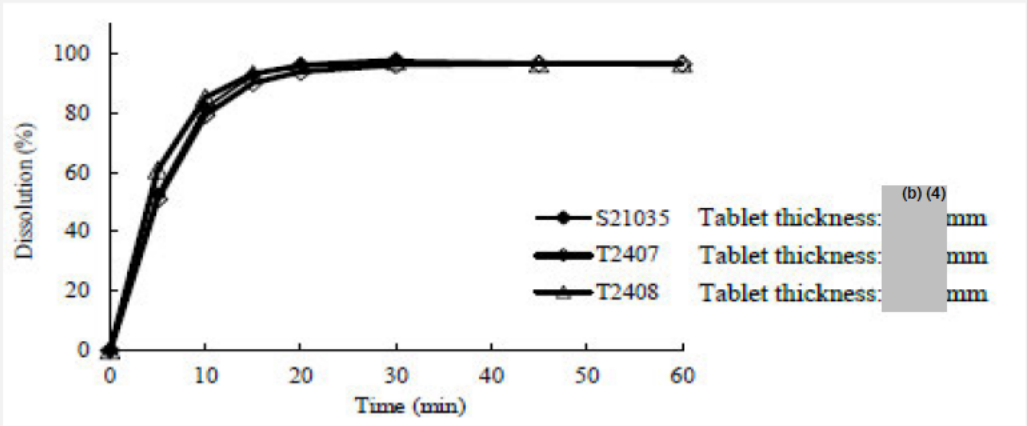

Figure 7. Dissolution Profiles of 125 mg Tablets with Different Tablet Thickness using the proposed dissolution method

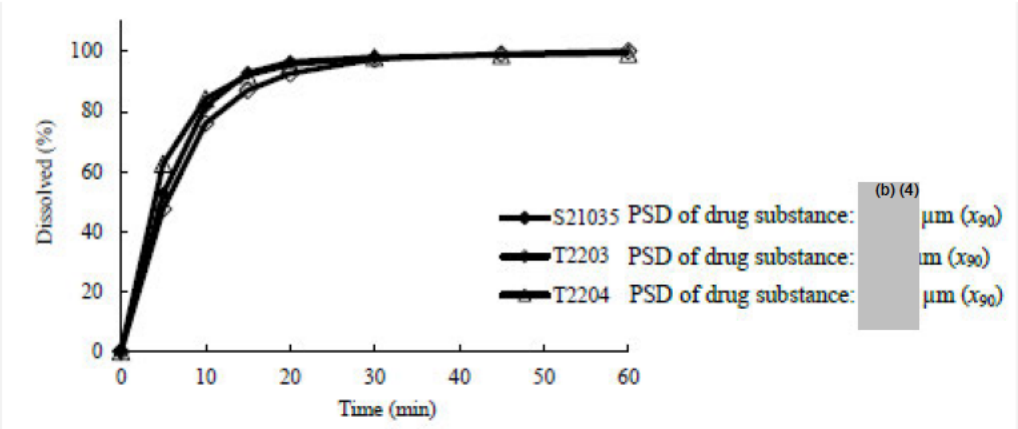

Figure 8. Dissolution Profiles of 125 mg Tablets with Different Drug Substance PSD using the proposed dissolution method

Dissolution Acceptance criterion

The initial dissolution acceptance criterion of Q = (b) (4), for Ensitrelvir Tablets, 125 mg was set by the Applicant to ensure that sufficient in-vitro dissolution can be achieved while still obtaining adequate discriminating ability. However, based on the submitted dissolution data for the registration batches of Ensitrelvir Tablets 125 mg, the initially proposed dissolution acceptance criteria of Q = (b) (4) was too permissive and not acceptable. The mean percentage drug release for all the batches tested: S21035, S21048, and S21046 is (b) (4) (Table 5). Therefore, through Biopharmaceutics IR #2, the Applicant was recommended to implement a dissolution acceptance criterion of Q = (b) (4), for the proposed drug product Ensitrelvir Tablets, 125 mg. The Applicant acknowledged FDA's recommendations and revised the dissolution acceptance criterion to Q = (b) (4)% in 20 min for Ensitrelvir Tablets, 125 mg at batch release and for stability studies in all relevant sections of the NDA (e.g., batch release and stability specifications, analytical method etc.) accordingly.

Table 5. Summary of In Vitro Dissolution Studies of Ensitrelvir Tablets, 125 mg

Batch No. (Used in Clinical Study)	Tablet Strength (mg)	Dissolution Method Conditions	No. of Dosage Units	Collection Times (minutes) Mean Percentage Drug Dissolved (range)					Location in CTD
S21035 (2102T1211 2130T1215 2305T1218)	125	Dissolution Apparatus 2 (USP) Rotation speed: 50 rpm Medium: Hydrochloric solution (pH 1 (containing 0.1% b(w/v) sodium lauryl sulfate Temperature: 37 °C ± 0.5 °C Volume: 900 mL	(b) (4)	5	10	15	20	30	CTD Section 3.2.P.2.2 Table 15
				52.6	81.7	92.8	96.5	98.1	
				(b) (4)					
S21037 (2102T1211)	250			5	10	15	20	30	
				39.0	72.5	86.6	92.8	95.9	
				(b) (4)					
S21048 (2128T1214 Study ACTIV-2d/A5407)	125			5	10		20	30	Batch details and single point batch release data presented in CTD Section 3.2.P.5.4
				54	83	Not tested	96	98	
				(b) (4)					
S21056 (2127T1213 2108T1221)	125			5	10		20	30	
				57	83	Not tested	94	95	
				(b) (4)					
S21057 (2108T1221)	250	Same as above apart from 0 (% (w/v) sodium lauryl sulfate[a]		5	10		20	30	Not applicable
				47	78	Not tested	92	95	
				(b) (4)					

CTD = common technical document; No. = number; rpm = revolutions per minute; USP = United States Pharmacopeia; w/v = weight by volume
a Dissolution method used during early product development for 250-mg tablets.

N/A

B.11 EXTENDED-RELEASE DOSAGE FORMS –*Extended-Release Claim*

Assessment:
N/A

B.12 BRIDGING

Assessment: ADEQUATE

Schematic of bridging:

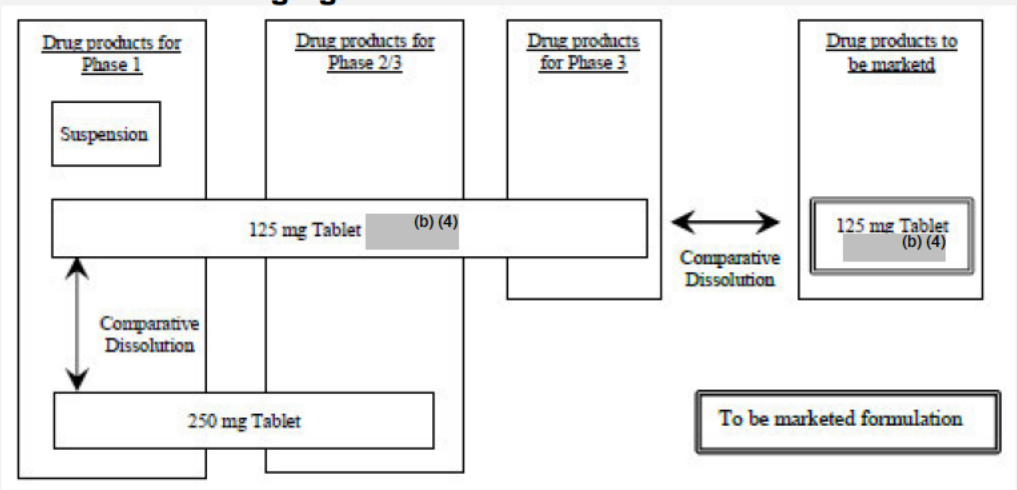

Figure 9. Drug Product Changes During Development of the Proposed Ensitrelvir Tablets

The initial drug product used by the Applicant in early Phase 1 clinical studies was an **oral suspension formulation (**Figure 9**)**. The suspension formulations of the drug substance, ensitrelvir fumaric acid, (b) (4) (b) (4). Ensitrelvir Oral Suspension was used in the single ascending dose (SAD) part of the first-in-human Phase 1 study. Consequently, the Applicant developed tablet formulations using (b) (4) for the clinical studies.

The 125 mg tablet formulation is the proposed commercial formulation and was used in the Phase 1, Phase 2/3 and Phase 3 clinical studies. The Phase 1 and Phase 2/3 clinical studies also used Ensitrelvir Tablets in 250 mg strength. The composition of the tablet formulation was consistent during development and a (b) (4) was employed to produce 125 mg and 250 mg strength tablets for use in clinical studies.

The Applicant conducted a cross-cohort pharmacokinetic comparison study (Study 2102T1211) between the **oral suspension and 250-mg tablets** in healthy adults receiving ensitrelvir 750 mg on Day 1 followed by 250 mg on Days 2 to 6 under fasted conditions. The adequacy of the data will be reviewed by the OCP. In addition, all pivotal efficacy and safety data were generated with the

tablet formulations, therefore this NDA is not relying on clinical data obtained from the oral suspension.

The **strength bridging between 125 mg and 250 mg** tablets is well-supported by comparative dissolution data showing similar rapid release profiles and clinical PK data demonstrating dose proportionality. The dissolution methods used for batch release of the two clinical study tablet strengths differed only in the use of (b) (4) (b) (4) for the 250 mg tablet. (b) (4)

Table 6. Comparative dissolution data of 125 mg and 250 mg Ensitrelvir Tablets

Time (min)		125 mg Tablets (Batch S21035)	250 mg Tablets (Batch S21037)
5	Actual Value	(b) (4)	(b) (4)
	Min. – Max.		
	Mean	52.6	39.0
	%RSD	11	6.1
10	Actual Value	(b) (4)	(b) (4)
	Min. – Max.		
	Mean	81.7	72.5
	%RSD	2.8	3.2
15	Actual Value	(b) (4)	(b) (4)
	Min. – Max.		
	Mean	92.8	86.6
	%RSD	1.2	1.5
20	Actual Value	(b) (4)	(b) (4)
	Min. – Max.		
	Mean	96.5	92.8
	%RSD	1.0	1.1
30	Actual Value	(b) (4)	(b) (4)
	Min. – Max.		
	Mean	98.1	95.9
	%RSD	1.1	1.1

It was therefore concluded that the clinical performance of the 250 mg Tablets is expected to be similar to that of the 125 mg Tablets based on the similar dissolution profiles.

Bridging of Drug Product Shape and Manufacturing Site

A comparative dissolution profile study was performed between 125 mg tablets manufactured at Shionogi Pharma Co., Ltd. (Settsu Plant) with the original **round** (b) (4) **tablet** shape and (b) (4) with **round** (b) (4) **tablet shape**. The dissolution test conditions used are provided in Table 4 and are the same as those proposed for routine drug product quality control.

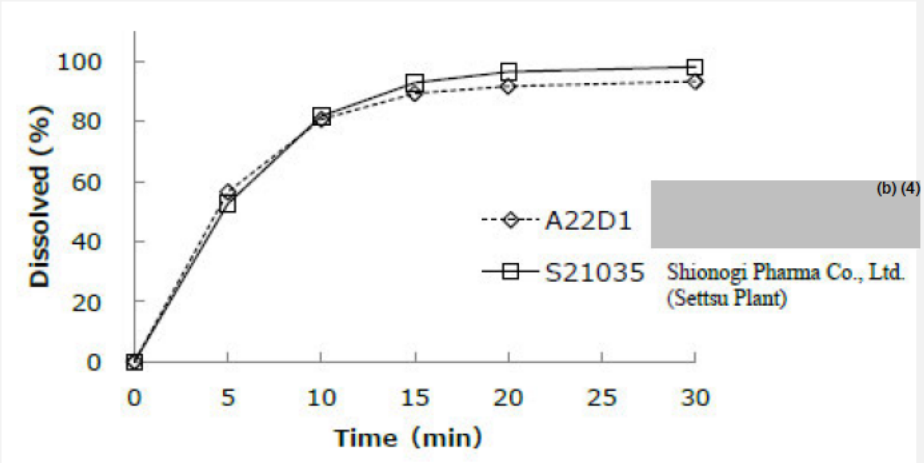

Figure 10. Dissolution profile Comparison of Ensitrelvir Tablets, 125 mg with different shapes and manufactured at two different sites

Manufacturing site Bridging[1]: Ensitrelvir Tablets 125 mg have been manufactured at

- Shionogi Pharma (Japan) - Primary development and initial manufacturing site
- (b) (4)
- (b) (4)

Dissolution profile comparison using 125 mg (b) (4) tablets (n=12) was used by the Applicant to bridge manufacturing site changes of the proposed drug product. As shown in Figures 10 and 11, dissolution profiles of proposed drug product batches manufactured as all three sites achieved more than > (b) (4)% dissolution at 15 minutes, indicating rapid, complete, and similar dissolution profiles.

[1] \\CDSESUB1\EVSPROD\nda220442\0000\m2\23-qos\drug-product-ensitrelvir-all.pdf

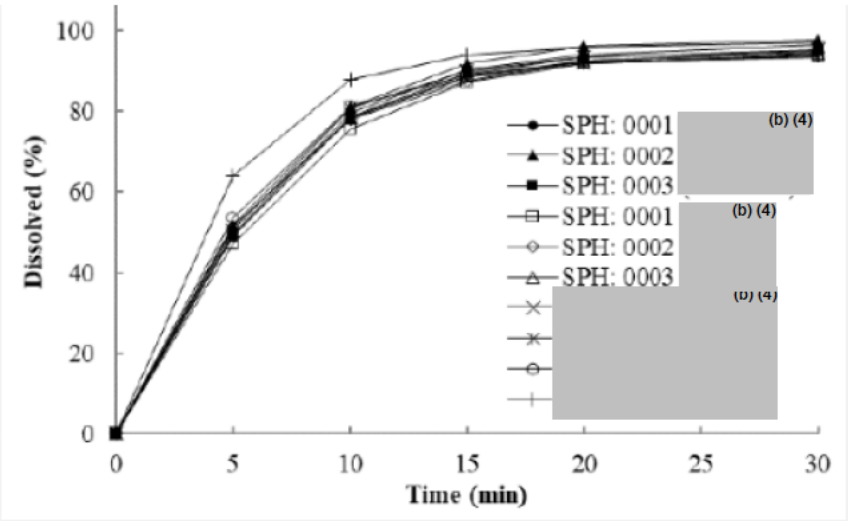

Figure 11. Dissolution Profile Comparison of Ensitrelvir Tablets,125 mg

In addition, a small change in tablet profile (same shape, with reduced thickness) prior to commercialization was made by the Applicant. The Applicant conducted in vitro dissolution comparison studies to support the change across these respective formulations.

Conclusion: The Applicant conducted comparative in vitro dissolution testing to adequately bridge the drug product formulation, shape, and manufacturing site changes.

OVERALL BIOPHARMACEUTICS RECOMMENDATION: From a Biopharmaceutics perspective, NDA 220442 for Ensitrelvir Tablets, 125 mg, is adequate and recommended for **Approval.**

B. 13 BIOWAIVER REQUEST

Assessment: N/A
A biowaiver request is not submitted nor required.

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: N/A

BIOPHARMACEUTICS LIST OF DEFICIENCIES

N/A

Primary Biopharmaceutics Assessor's Name and Date: Payal Agarwal, Ph.D. 02/18/2026
Secondary Assessor Name and Date: Elsbeth Chikhale, Ph.D. 02/18/2026

Payal Agarwal

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