CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215500Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215500		
Applicant Name	USWM LLC		
Drug Product Name	IWILFIN (eflornithine)		
Dosage Form.	Tablet		
Proposed Strength(s)	192 mg		
Route of Administration	Oral		
Maximum Daily Dose	1536 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	IWILFIN (eflornithine) is indicated to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy.		
Drug Product Description	Round, white to off white tablets imprinted with EFL on one side and 192 on the other side.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Rajan Pragani	Haripada Sarker
	Drug Product/ Labeling	Xiao Hong Chen	Xing Wang
	Manufacturing	Jiao Yang	Nathan Davis

	Biopharmaceutics	Mei Ou	Mei Ou
	Microbiology	Jiao Yang	Nathan Davis
	Other (specify):	N/A	
	RBPM	Janell Artis	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - *Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 215500 for IWILFIN™ (eflornithine) tablets, for oral use.

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items 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		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
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	Adequate	

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items 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, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	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	N/A	

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	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items 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 (Tablets: 10 mg of drug-x hydrochloride).	Adequate	The active is in a salt form. Per USP salt policy, the strength is expressed as a free base form. The salt equivalency statement is included in section 11.
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 parental 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.	N/A	

Section 11 (DESCRIPTION)

Item	Items 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)	Adequate	
Dosage form(s) and route(s) of administration	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)"	Adequate	The active is in a salt form. Per USP salt policy, the strength is expressed as a free base form. The salt equivalency statement is included in section 11.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items 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)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items 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)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). 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."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items 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)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The applicant should use the USP storage condition. The applicant currently stated store at 25C. It should be changed to read: store at 20C to 25C. The IR was conveyed and the applicant agreed and made the change as we requested.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

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 parenteral, 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.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items 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)
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	The distributor's (which is the applicant itself) name and address are provided.

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	N/A	
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 differs from the dosage form.	N/A	
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	Inadequate	The applicant will be asked to include the information.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

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

3.0 CONTAINER AND CARTON LABELING

The representative container and carton labels are shown below. The applicant should revise the storage conditions to be consistent with the USP recommended storage condition which reads: Store at room temperature, 20ºC to 25°C (68ºF to77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

IR: For the Prescribing Information and container carton labels, revise the storage conditions to be consistent with the USP recommended storage condition: Change from "Store at room temperature, 25°C (77°F)" to "Store at room temperature, 20ºC to 25°C (68ºF to77°F)".

USWM Response:
USWM has revised the storage conditions to be consistent with the USP recommended storage condition of "Store at room temperature, 20°C to 25°C (68°F to77°F)". The following versions of draft labeling that have been updated are included in the submission:

- Updated Bottle Label
- Updated Carton Label
- Bottle Label Comparison of previously submitted version vs the updated version
- Carton Label Comparison of previously submitted version vs the updated version

Assessment: Adequate

3.1 Container Labels

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

(b) (4)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	The active ingredient is a salt, The equivalency statement is included.
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***Adequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

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 as deficiencies in this section.

Overall Assessment and Recommendation: Adequate

For Patient Labeling, the applicant should include Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.

Primary Labeling Assessor Name and Date: Xiao Hong Chen, 4/13/2023

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

Xiao Chen

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Xing Wang

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 215500 [505(b)(2)]
Drug Product Name/Strength: Iwilfin™ (Eflornithine Hydrochloride) Tablets, 192 mg (free base) (250 mg as monohydrochloride monohydrate)
Route of Administration: Oral
Applicant Name: USWM, LLC (dba US WorldMeds)
Proposed Indication: To reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy.
Submission: 10/11/2022 (presubmission-1), 10/27/2022 (presubmission-2), 11/21/2022 (final submission of this NDA), 12/16/2022 (Response to the Biopharmaceutics Information Request)
Primary/Secondary Reviewer: Mei Ou, Ph.D.

REVIEW SUMMARY

The Applicant is seeking the approval of the proposed drug product, Iwilfin™ Eflornithine Hydrochloride (DFMO HCl) Tablets, 192 mg (free base) (250 mg as Eflornithine HCl monohydrate). The proposed drug product is the immediate-release, 7/16" white to off-white, round, biconvex tablets with "EFL" debossed on one side and "192" on the reverse side. The recommended dose is orally taken one to four tablets twice a day, based on body surface area (BSA, m^2), for two years. Iwilfin™ can be taken with or without food. For patients who are unable to, or prefer not to, swallow whole tablets, Iwilfin™ may be chewed, or can be crushed then dissolved in/mixed with two tablespoons of liquid or soft food (b) (4)

This 505(b)(2) NDA relies on FDA's previous findings of clinical safety and efficacy, and nonclinical safety of the listed drug (LD) product, Ornidyl® (*Eflornithine HCl Injection, 200 mg/mL, NDA 019879 approved on 11/28/1990, discontinued not related to safety or efficacy concerns*). The proposed drug product has same drug substance (eflornithine hydrochloride) with the LD, but differs in indication, formulation/composition, dosage forms and strengths, administration and supplied/storage and handling.

The Applicant conducted the following clinical studies to support this NDA: *(i)* a phase 1 food-effect study USWM-FEI-1001; *(ii)* a phase 2 comparative bioavailability and pharmacokinetics (PK), safety and efficacy study NMTRC003b, including the change of drug substance supplier from (b) (4) (study NMTRC003, a predecessor study to study NMTRC003b) to ScinoPharm (study NMTRC003b); *(iii)* a phase 2 safety, efficacy and PK study NMTRC0014[1].

[1] \\CDSESUB1\EVSPROD\nda215500\0005\m2\25-clin-over\clinical-overview.pdf

The Biopharmaceutics review focuses on the evaluation of *(i)* the proposed in vitro dissolution method and acceptance criterion as a quality control (QC) test for the drug product for batch release and stability testing, and *(ii)* bridging.

In Vitro Dissolution Testing: The proposed dissolution method and acceptance criterion are acceptable as a QC test for the proposed drug product, listed as below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium	500 mL of 0.1 N HCl
Temperature	37°C
Acceptance Criterion	Q(b) (4)% in 30 minutes

Bridging:
(1) Scientific bridging throughout the drug product development appears to be established based on the following reasons:

(a) There are no formulation composition changes from the first prototype batches to the primary registration/to-be-marketed drug product batches. The formulation, manufacturing process and dosage strengths used in the pivotal clinical studies are identical to those of the proposed commercial drug product.

(b) The drug product batches contain different drug substance sources (i.e., (b) (4) and ScinoPharm), and different scale up batches from the mini-lab scale prototype tablets (b) (4), lab-scale critical material attribute DoE tablets (b) (4)), to registration batches (b) (4)), showed very rapid and similar dissolution in multi-pH media and QC medium. The drug substance sources changes, manufacturing process and batch scale up appear not impacting the drug product dissolution behavior. Note that the in vivo pharmacokinetics (PK) data information of drug product clinical batches containing different drug substance sources is under purview of the Office of Clinical Pharmacology (OCP).

(2) Scientific bridging between the proposed drug product and the LD is pending on the PK data/information under the purview of OCP.

RECOMMENDATION:
From the Biopharmaceutics perspective, NDA 215500-ORIG-1 for the proposed drug product, Iwilfin™ (Eflornithine Hydrochloride) Tablets, 192 mg, is recommended for **approval**.

BIOPHARMACEUTICS REVIEW

1. Regulatory history

Biopharmaceutics commented about the *(i)* in vitro dissolution method development, and *(ii)* bridging strategy for the drug product batches containing drug substance from different sources ([(b) (4)], DMF [(b) (4)] vs. ScinoPharm DMF [(b) (4)]) in the Type B meetings of IND 144875 (CMC meeting minutes dated 11/10/2020[2], pre-NDA meeting minutes dated 11/22/2020[3], Biopharmaceutics Review for IND 144875 dated 10/16/2020[4]).

2. Drug substance solubility and permeability

The drug substance (eflornithine hydrochloride monohydrate) has high solubility [Table 1 below, solubility ~ 340 mg/mL > 1000 mg (highest dose) / 250 mL (4 mg/mL)] and low permeability (absolute bioavailability is 54-58%)[5]. It appears eflornithine hydrochloride monohydrate is a BCS Class 3 compound.

Table 1: Eflornithine solubility
(*from M.3.2.P.2.1*)

Media	Solubility
Water	340 mg/mL
pH 1.3	Freely soluble
pH 3.7	Freely soluble
pH 8.5	Freely soluble

	Solubility (mg/mL)	
pH	[(b) (4)] Lot 5202	ScinoPharm - Lot 76000AA072
1.0	369	344
4.5	373	335
6.8	340	337

3. In vitro dissolution

The proposed dissolution method and acceptance criterion for the proposed drug product as a QC test are listed as below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium	500 mL of 0.1 N HCl
Temperature	37°C
Acceptance Criterion	Q= [(b) (4)]% in 30 minutes

[2] \\CDSESUB1\EVSPROD\nda215500\0001\m1\us\16-meetings\minutes-type-b-cmc-2020-11-10.pdf
[3] \\CDSESUB1\EVSPROD\nda215500\0001\m1\us\16-meetings\minutes-prenda-meeting-2021-11-22.pdf
[4] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805a0970
[5] \\CDSESUB1\EVSPROD\nda215500\0001\m3\32-body-data\32p-drug-prod\eflornithine-192-mg-tablets-oral-corerx-pharmaceuticals-inc\32p2-pharm-dev\pharmaceutical-development-components.pdf

Dissolution Method: One batch of the proposed drug product containing drug substance from (b) (4) ("reference" batch 20112, represent clinical product from 2015 to 2020) and two batches of the proposed drug product containing drug substance from ScinoPharm ("test" batches 20332 and 20333, represent clinical product in 2021) were used for the dissolution method development (*M.3.2.P.2, report VV-QUAL-08661*[6]). The three batches drug product have same composition.

From the report, the multi-pH media (i.e., 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, n=12) were evaluated, while the dissolution method parameters were kept the same, as *USP Apparatus II paddle, 50 rpm, 500 mL of medium, 37°C*. The comparative dissolution profile data in multi-pH media are presented as below (Table 2, Figure 1 to 3)[7]. From the results, the proposed drug product showed very rapid and similar dissolution in multi-pH media by using USP Apparatus II paddle, 50 rpm, 500 mL of medium.

Table 2: Mean In Vitro Dissolution Results of Eflornithine Tablets, Two Drug Substances Sources
(*from M.3.2.P.2.2*)

		% Eflornithine Label Claim Dissolved, Mean, n = 12 (Relative Standard Deviation)					
Lot No.[1]	Medium[2]	5 min	10 min	15 min	20 min	30 min	45 min
20112 (b) (4)	0.1 N HCl	86 (5.6)	89 (4.1)	91 (3.7)	92 (3.1)	95 (2.7)	97 (2.2)
20332 (SPT)	0.1 N HCl	79 (5.0)	83 (3.3)	86 (2.9)	89 (2.2)	92 (2.0)	96 (1.8)
20333 (SPT)	0.1 N HCl	80 (3.5)	86 (3.4)	88 (3.6)	90 (3.1)	93 (2.6)	97 (2.1)
20112 (b) (4)	pH 4.5	83 (4.9)	88 (4.1)	90 (3.7)	93 (4.4)	96 (4.2)	98 (3.0)
20332 (SPT)	pH 4.5	82 (4.7)	88 (3.6)	91 (3.5)	92 (3.2)	95 (2.8)	98 (2.2)
20333 (SPT)	pH 4.5	82 (4.5)	87 (3.7)	89 (3.4)	92 (3.0)	94 (2.4)	98 (1.7)
20112 (b) (4)	pH 6.8	77 (4.3)	82 (2.3)	85 (2.1)	87 (1.8)	90 (1.3)	94 (2.3)
20332 (SPT)	pH 6.8	78 (5.9)	82 (5.4)	85 (4.5)	87 (4.4)	91 (3.9)	94 (3.2)
20333 (SPT)	pH 6.8	77 (4.5)	84 (6.2)	87 (5.6)	89 (5.4)	91 (4.3)	95 (3.4)

[1] (b) (4) drug substance. SPT = ScinoPharm drug substance.
[2] pH 1.1 = 0.1 N HCl, pH 4.5 = 50 mM sodium acetate buffer, pH 6.8 = 50 mM phosphate buffer

[6] \\CDSESUB1\EVSPROD\nda215500\0001\m3\32-body-data\32p-drug-prod\eflornithine-192-mg-tablets-oral-corerx-pharmaceuticals-inc\32p2-pharm-dev\pharmaceutical-development-drug-product-vv-qual-08661.pdf
[7] \\CDSESUB1\EVSPROD\nda215500\0001\m3\32-body-data\32p-drug-prod\eflornithine-192-mg-tablets-oral-corerx-pharmaceuticals-inc\32p2-pharm-dev\pharmaceutical-development-drug-product.pdf

Figure 1: Dissolution Profiles for Eflornithine Tablets in **0.1 N HCl** [redacted], SPT = ScinoPharm)
(*from M.3.2.P.2.2*)

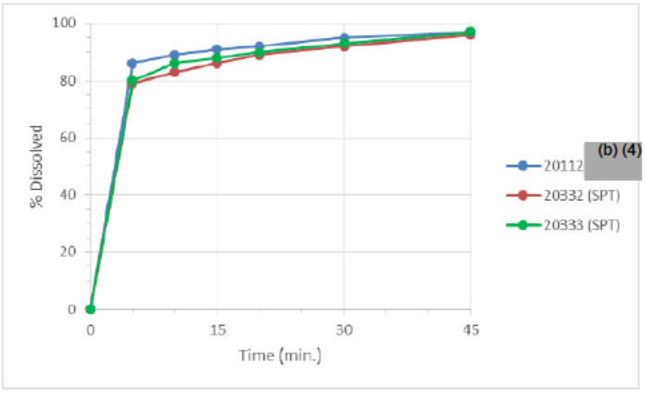


Figure 2: Dissolution Profiles for Eflornithine Tablets in **pH 4.5 Acetate Buffer** (50 mM) [redacted] SPT = ScinoPharm)
(*from M.3.2.P.2.2*)

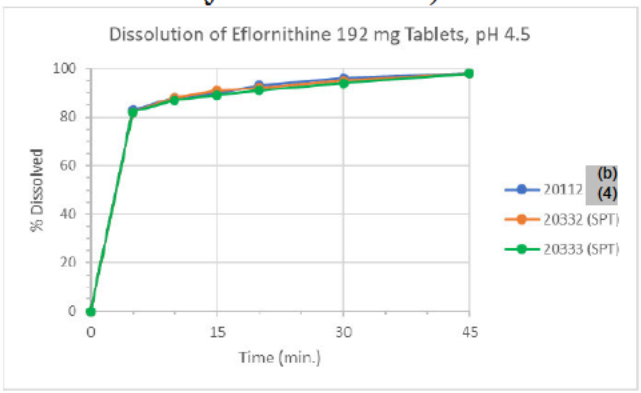
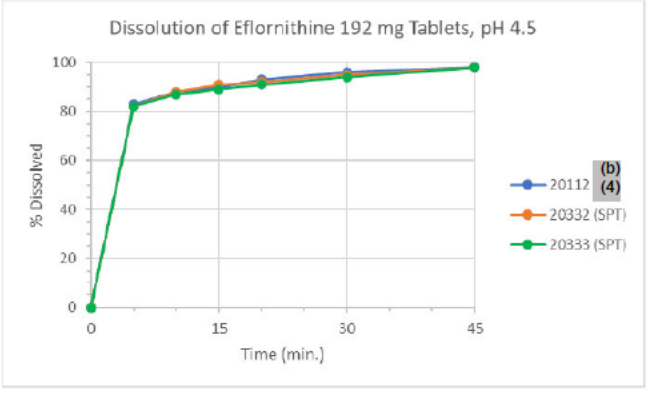


Figure 3: Dissolution Profiles for Eflornithine Tablets in **pH 6.8 Phosphate Buffer** (50 mM) [redacted], SPT = ScinoPharm)
(*from M.3.2.P.2.2*)



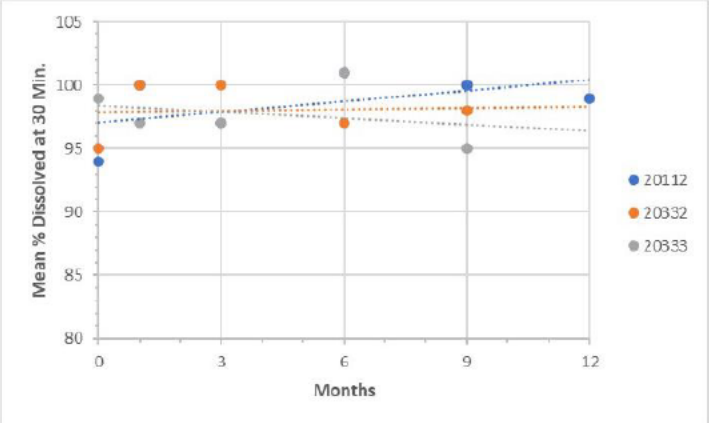
Dissolution Data: The information of registration batches is presented in Table 3 below.

Table 3: Batch Information of Eflornithine Tablets
(*from M.3.2.P.5.4*)

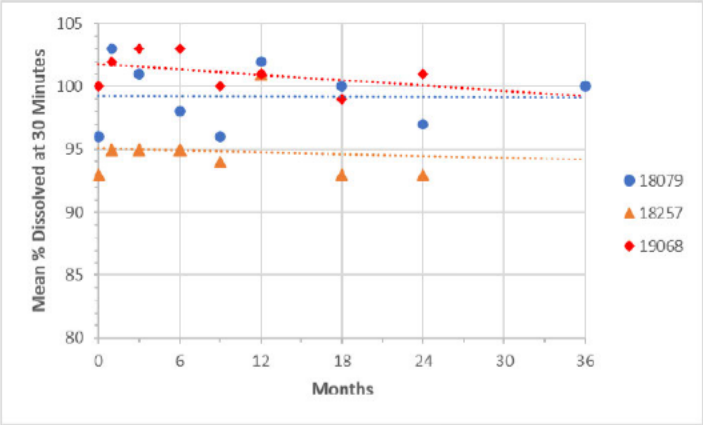
Batch Number	Manufacturing Date	Manufacturing (b) (4) Site	API Source	Batch Size (Theoretical)	Use of Batch
18079	05Apr2018	CoreRx	(b) (4)	(b) (4)	Registration #1 Supportive
18257	18Oct2018	CoreRx			Registration #2 Supportive
19068	22Apr2019	CoreRx			Registration #3 Supportive
20112	13Apr2020	CoreRx			Registration #4 Supportive
20332	16Nov2020	CoreRx	ScinoPharm		Registration #5 Primary
20333	05Dec2020	CoreRx	ScinoPharm		Registration #6 Primary
21202	27Jul2021	CoreRx	ScinoPharm		Registration #7 Primary

Note that (b) (4) was initially used as the dissolution medium (*dissolution method TM-0138*) in stability testing for batch 20112 (up to 12 months), batches 20332 and 20333 (up to 9 months), batches 18257 and 19068 (up to 24 months) and batch 18079 (up to 36 months). Single time point dissolution data (at 30 minutes) showed that the above registration batches containing drug substances from (b) (4) and SinoPharm had complete dissolution (b) (4) up to 36 months in long-term stability condition (Figure 4 below)[8].

Figure 4: Mean % Dissolved at 30 Minutes for Primary Registration Stability Batches Stored at 25°C/60%RH (TM-0138, (b) (4)
(*from M.3.2.P.8.1*)



[8] \\CDSESUB1\EVSPROD\nda215500\0001\m3\32-body-data\32p-drug-prod\eflornithine-192-mg-tablets-oral-corerx-pharmaceuticals-inc\32p8-stab\stability-summary.pdf



0.1 N HCl was replaced [(b) (4)] and used as dissolution QC medium (*dissolution method TM-0712*) in stability testing for batch 20112 (since 18 months), batches 20332 and 20333 (since 6 months), batches 18079, 18257, 19068 (up to 38 months). Single time point dissolution data (at 30 minutes) showed these registration batches containing drug substances from [(b) (4)] and SinoPharm had complete dissolution in 0.1 N HCl from 6 months to 38 months in long-term stability condition (Table 4 below). *Note that the zero-month data is "surrogate" data, obtained by analyzing tablets stored at 5°C/amb after 16 months (batch 20112) and 9 months (batches 20332, 20333) and assuming no change in the dissolution rate had occurred since the manufacturing dates.*

Table 4: Mean % Dissolved at 30 Minutes for Primary Registration Stability Batches (TM-0712, 0.1 N HCl dissolution medium) (*from M.3.2.P.8.1*)

Batch No.	Stability Station	Mean % Dissolved at 30 Minutes						
		0 mos.	3 mos.	6 mos.	9 mos.	12 mos.	18 mos.	24 mos.
20112	25°C/60%RH	98 [1]					97	97
20332		95 [1]		92	95	97		
20333		97 [1]		91	94	98		
20332	40°C/75%RH	95 [1]		96				
20333		97 [1]		95				
21202	[(b) (4)]	98	93	96	97			

[1] "Surrogate" zero-month data obtained from samples stored at 5°C for 16 mos. (20112) or 9 mos. (20332, 20333)

Batch No.	Stability Condition	Mean % Dissolved at 30 Min.	
		TM-0712	TM-0138
18079	25°C/60%RH (38 mos.), unscheduled	98	101
18257	25°C/60%RH (36 mos.), scheduled	91	Not tested
18257	25°C/60%RH (33 mos.), unscheduled	87	94
19068	25°C/60%RH (24 mos.), unscheduled	97	101
19068	25°C/60%RH (36 mos.), scheduled	92	Not tested

Reviewer's assessment:
Considering the drug substance has high solubility, the drug product is an immediate release tablets, the change of drug substance source does not impact the drug product dissolution behavior, the overall dissolution method development and dissolution data support the acceptability of the proposed dissolution method (USP Apparatus II Paddle, 50 rpm, 500 mL of 0.1 N HCl, 37°C) and acceptance criterion (Q= (b) (4) % in 30 minutes) as a QC test for the proposed drug product.

Alternative administration method: The Applicant proposed an alternative administration for patients who are unable to, or prefer not to, swallow whole tablets, then the tablets may be chewed, or can be crushed then dissolved in/mixed with two tablespoons of liquid or soft food (b) (4) Per the Applicant, the in vivo PK data of whole tablets under fasted and fed conditions and crushed tablets mixed into pudding under fasted conditions were collected in the phase 1 clinical study USWM-FE-1001[9]. Note the PK data will be under purview of OCP.

The comparative in vitro dissolution testing between the whole and crushed tablets in multi-pH media (i.e., 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) by using dissolution method of USP Apparatus II Paddle, 50 rpm, 500 mL of medium was also provided[10]. As results summarized in the following Table 5 and Figures 5-7, the whole and crushed tablets showed very rapid and similar dissolution in multi-media. Note that the stability of the crushed tablets and the determination of the compatibility of crushed tablets in soft food is under CMC purview.

Table 5: Comparative Dissolution Results for Whole and Crushed Eflornithine Tablets (Primary Registration Batch 20332)
(*from M.3.2.P.2.2*)

		Mean % Eflornithine Dissolved, n = 12 (Relative Standard Deviation)					
Medium[1]	**Tablet Type**	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**
0.1 N HCl	Whole	97 (1.2)	99 (1.0)	99 (1.0)	99 (1.0)	100 (1.0)	100 (1.0)
	Crushed	94 (4.8)	95 (3.6)	96 (3.3)	96 (2.9)	97 (2.6)	99 (2.1)
pH 4.5	Whole	91 (2.8)	96 (1.7)	98 (1.6)	99 (1.2)	100 (1.3)	101 (1.4)
	Crushed	99 (3.5)	100 (2.8)	100 (2.5)	100 (2.1)	100 (2.0)	101 (1.7)
pH 6.8	Whole	81 (3.6)	87 (3.9)	89 (3.0)	91 (2.7)	94 (2.2)	96 (2.0)
	Crushed	89 (9.0)	91 (7.1)	93 (6.1)	95 (5.5)	96 (4.8)	97 (3.8)

[1] pH 4.5 = 50 mM sodium acetate buffer, pH 6.8 = 50 mM phosphate buffer

[9] \\CDSESUB1\EVSPROD\nda215500\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\uswm-fe1-1001\uswm-fe1-1001-synopsis.pdf
[10] \\CDSESUB1\EVSPROD\nda215500\0001\m3\32-body-data\32p-drug-prod\eflornithine-192-mg-tablets-oral-corerx-pharmaceuticals-inc\32p2-pharm-dev\pharmaceutical-development-compatibility.pdf

Figure 5: Dissolution Profiles for Whole and Crushed Eflornithine Tablets in 0.1 N HCl, n = 12 vessels each (*from M.3.2.P.2.2*)

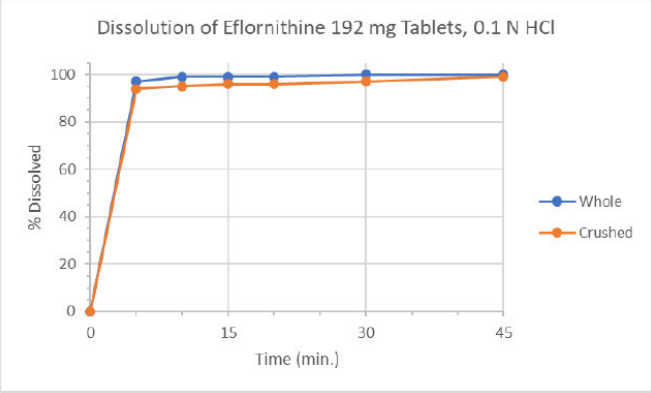


Figure 6: Dissolution Profiles for Whole and Crushed Eflornithine Tablets in pH 4.5 Acetate Buffer (50 mM), n = 12 vessels each (*from M.3.2.P.2.2*)

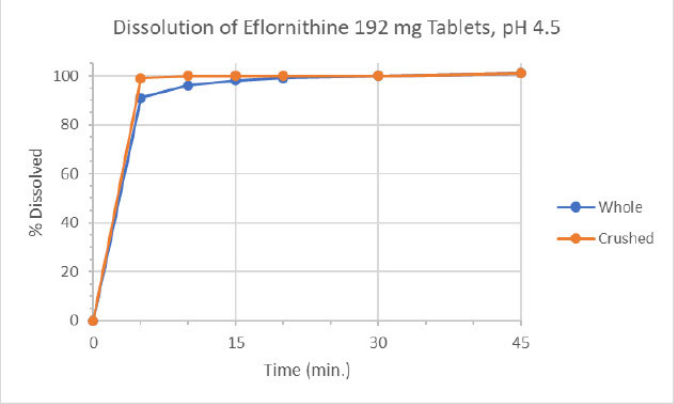
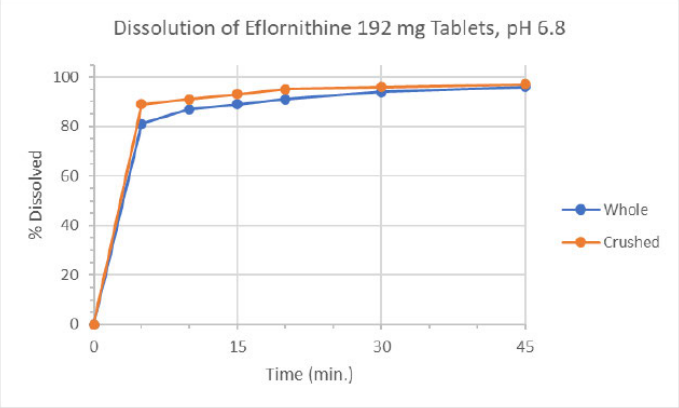


Figure 7: Dissolution Profiles for Whole and Crushed Eflornithine 192 mg Tablets in pH 6.8 Phosphate Buffer (50 mM), n = 12 vessels each (*from M.3.2.P.2.2*)



4. Bridging:

Per the Applicant, the drug substance source was changed during the pivotal phase 2 clinical studies from NMTRC003 to NMTRC003b. The drug substance used in clinical

development (2015-2020, study NMTRC003, a predecessor study to study NMTRC003b) was supplied by [redacted] DMF [redacted]). The drug substance used in clinical studies NMTRC003b and NMTRC0014 (in 2021) and for commercial drug product batches (in 2022) was supplied by ScinoPharm (Taiwan, DMF [redacted]).

Biopharmaceutics information request (IR) asking for the clarification and batch information was conveyed on 12/07/2022[11]. The Applicant provided the acceptable response on 12/16/2022[12] and the Application Orientation Meeting (AOM, slides 44 to 46). The clarification information is presented in Table 6 below.

Table 6: Comparison of Eflornithine 192 mg Tablets Used in Clinical Program and CMC Registration Package
(*from 12/16/2022 submission and AOM slide 46*)

Drug Product	**Investigational from CPP**	**Investigational from KCP**	**To-be-marketed from USWM**
API source	ScinoPharm[1] DMF [redacted]	[redacted] DMF [redacted]	ScinoPharm DMF [redacted]
DP manufacturer	[redacted][2]	CoreRx	CoreRx (no formulation or process change vs. KCP)
Product Utilization in Relevant Clinical Studies	NMTRC003 (predecessor study to NMTRC003b) PK sub-study in NMTRC003b	NMTRC003b USWM-FE-1001 (Food effect) NMTRC014 (until 2022)	NMTRC014 (starting 2022) Proposed Commercial Product
CMC Registration Package Contribution	N/A	1 Primary Supportive Registration Batch Multiple Supporting CTM Batches	2 Primary Registration Batches 1 supporting development batch, serves as third Primary Registration batch
Bridging Information Discussed in 2.7.1	Study 3b Cross-over PK sub-study Report location: 5.3.5.1 Study 3b CSR, Appendix 16.5		--
	--	In Vitro Biowaiver Dissolution Comparison of tablets of both DS in three media (pH 1, 4.5, 6.8), performed in accordance with FDA Guidance (Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System) Report location: 3.2.P.2.2	

[1] USWM's understanding based on public records as discussed in NDA eSeq007 IR response.

[2] USWM's understanding based on public records as discussed in NDA eSeq007 IR response.

[11] \\CDSESUB1\EVSPROD\nda215500\0007\m1\us\112-other-correspondence\fda-information-request-cmc-2022-12-07.pdf

[12] \\CDSESUB1\EVSPROD\nda215500\0007\m1\us\111-information-amendment\quality-information-amendment-resp-to-fda-cmc-ir-2022-12-07.pdf

The Applicant provided the following data/information to support the bridging of the drug substance changes: *(i)* physicochemical characteristics data (i.e., x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), moisture content, bulk and tap density, microscopy, assay and related compound, drug substance particle size distribution (DS PSD), solubility, appearance, identification, assay, related substances, content uniformity, etc.), which is under purview of CMC chemists; *(ii)* comparative in vitro dissolution data profiles of drug product batches containing drug substance from (b) (4) and ScinoPharm; *(iii)* in vivo PK data of drug product batches containing drug substance from (b) (4) and ScinoPharm in clinical study NMTRC003b (i.e., Table 9 in M.2.7.1), which is under purview of OCP.

The clinical batches and registration/to-be-marketed batches have same formulation and composition, as presented in Table 7 below.

Table 7: Formulation Composition for Clinical Batches and Registration Batches of Eflornithine 192 mg Tablets
(*from M.2.7.1, Table 2*)

Item No.	Ingredient	Concentration % w/w	Target Unit Weight (mg/Tablet)	Quality Standards
1	DFMO HCl Monohydrate[a]	(b) (4)	250	DMF (b) (4) (b) (4) DMF (b) (4) (ScinoPharm)
2	Silicified Microcrystalline Cellulose		220	USP, NF, EP
3	Pre-Gelatinized Maize Starch (b) (4)		25	USP, NF, EP
4	Colloidal Silicon Dioxide, (b) (4)		2.5	USP, NF, EP
5	Magnesium Stearate		2.5	USP, NF, EP
Total		100	500	

Source: 3.2.P.1
[a] 250 mg of DFMO HCl monohydrate is equivalent to 192 mg of DFMO free base

Registration batches information is presented in Table 8 below. One registration batch of drug product (batch 20112) containing drug substances from (b) (4) and two registration batches of drug product (batches 20332 and 20333) containing drug substance from SinoPharm showed very rapid and similar dissolution in QC and multi-pH media (presented in Table 2, Figures 1-3 above).

Table 8: Batch Information of Eflornithine 192 mg Tablets
(*from M.3.2.P.5.4, Table 1*)

Batch Number	Manufacturing Date	Manufacturing and Testing Site	API Source	Batch Size (Theoretical)	Use of Batch
18079	05Apr2018	(b) (4)	(b) (4)	(b) (4)	Registration #1 Supportive
18257	18Oct2018				Registration #2 Supportive
19068	22Apr2019				Registration #3 Supportive
20112	13Apr2020				Registration #4 Supportive
20332	16Nov2020		ScinoPharm		Registration #5 Primary
20333	05Dec2020		ScinoPharm		Registration #6 Primary
21202	27Jul2021		ScinoPharm		Registration #7 Primary

Batch Number of Drug Substance	Drug Substance Manufacturer	Batch Number of Drug Product
1202	(b) (4)	15005
5003		15057 15062 16008 16084 17051
4207		18079 18257 19068 19070
5202		20112
70600AA072 70600AA079	ScinoPharm	20332
70600AA076	ScinoPharm	20333
70600AA072 70600AA079 70600AA076	ScinoPharm	21202

The single time point (at 30 minutes, n=6) supportive dissolution data of batches 15005, 15057, 15062, 16008, 16084, and 17051 by using the dissolution method of *USP Apparatus II Paddle, 50 rpm,* (b) (4)*, 37°C*, are provided and presented in Table 9 below.

Table 9: Dissolution Results for Clinical Batches of Eflornithine 192 mg Tablets in (b) (4), 30-Minute Sampling Time
(*from M.1.11.1, Table 4, in 12/16/2022 submission*)

Dissolution Results (n = 6)	15005	15057	15062	16008	16084	17051
Mean, % Dissolved (30 min)	97%	96%	99%	97%	102%	97%
RSD	2.3%	2.3%	1.8%	1.3%	1.5%	1.5%

All clinical and registration/to-be-marketed batches were manufactured using the same manufacturing process. All the commercial batches (b) (4) were manufactured using the final commercial formulation and the final manufacturing process and provided the stability data for the NDA.

The batch size was scaled up during drug development, as *(i)* mini-lab scale prototype tablets (b) (4)), *(ii)* lab-scale critical material attribute DoE studies (b) (4)), (iii) registration batches ((b) (4).

There are no formulation composition changes from the first prototype batches to the primary registration batches (as the composition presented in Table 10 below). The formulation, manufacturing process, and dosage strengths used in the pivotal clinical studies (NMTRC003b and NMTRC014) are identical to those for the proposed commercial drug product.

Note that the drug product batches showed pH independent and very rapid then similar dissolution (b) (4) and the QC medium (0.1 N HCl), so that (b) (4) is considered acceptable for dissolution testing during the initial pharmaceutical development. Other physicochemical comparison (i.e., assay, related compound, content uniformity, degradation products) is under CMC chemists' purview.

The comparative dissolution data of mini-lab scale products are presented in Table 11 below by using the dissolution method of *USP Apparatus II (Paddle), 50 rpm, 500 mL of* (b) (4) The comparative dissolution data of DoE batches are presented in Tables 12-14 below by using the proposed dissolution QC method of *USP Apparatus II (Paddle), 50 rpm, 500 mL of 0.1 N HCl.*

From the results showed below, the mini-lab scale tablets and DoE tablets all showed very rapid and similar dissolution (b) (4) and 0.1 N HCl. Overall, itt appears the drug substance sources (b) (4) and ScinoPharm), manufacturing process and batch scale up do not impact the drug product dissolution behavior.

Table 10: Formulation and Batch Information for Mini Lab-Scale Tablets
(from M.3.2.P.2, Table 10)

				Batch 177-20001	Batch 177-20005
Item No.	**Ingredient**	**Concentration % w/w**	**Amount/ Tablet (mg)**	**Amount/ Batch (g)**	**Amount/ Batch (g)**
1	(b) (4)				
2					
3					
4					
5					

Table 11: Dissolution Results for Mini Lab-Scale Tablets
(from M.3.2.P.2, Table 13)

Dissolution, USP Apparatus 2, 50 rpm, 500 mL (b) (4) 37°C		
Time, minutes	**% Dissolved (RSD, n = 6)**	
	177-20001 (b) (4)	**177-20005 (ScinoPharm 70600AA076)**
10	103 (3.6)	93 (3.5)
15	104 (3.3)	95 (3.5)
30	105 (3.2)	97 (3.5)

Table 12: Dissolution Results for Tablets from DoE Tablets - DoE 1 (ScinoPharm API)
(from M.3.2.P.2, Table 39)

Tablet Batch No. (b) (4) Target Hardness)	**Description (N=6 for each batch)**	**% Dissolved**			
		10 Min. Average [%RSD]	**15 Min. Average [%RSD]**	**20 Min. Average [%RSD]**	**30 Min. Average [%RSD]**
21001	(b) (4)	99.8 [2.9]	100.5 [2.6]	101.2 [2.2]	102.0 [2.2]
21008		95.8 [4.0]	99.7 [4.0]	102.0 [3.8]	104.4 [3.4]
21010		96.8 [4.3]	99.0 [3.4]	100.5 [3.1]	102.2 [2.7]
21012		96.3 [2.4]	97.8 [2.0]	99.3 [1.8]	101.0 [1.4]
21014		90.5 [3.7]	93.0 [3.2]	94.8 [2.9]	97.3 [2.5]

Table 13: Dissolution Results for Tablets from DoE Tablets - DoE 2 (b) (4) API)
(from M.3.2.P.2, Table 40)

Tablet Batch#: (b) (4) Target Hardness	Description (N=6 for each batch)	% Dissolved			
		10 Min. Average [%RSD]	15 Min. Average [%RSD]	20 Min. Average [%RSD]	30 Min. Average [%RSD]
21002	(b) (4)	97.5 [1.1]	98.2 [1.2]	98.5 [1.2]	99.5[0.8]
21007		98.2 [3.2]	99.2 [3.2]	99.7 [2.7]	100.8 [2.7]
21009		95.3 [2.6]	96.5 [2.4]	97.3 [2.3]	98.5 [1.7]
21011		89.3 [4.5]	91.8 [3.6]	93.8 [3.0]	96.2 [2.2]
21013		94.2 [2.3]	95.8 [2.8]	97.0 [2.6]	99.0 [2.6]

Table 14: Dissolution Results (30 min) for DoE 1 and DoE 2
(from M.3.2.P.2, Table 42)

	% Dissolved, 30-minute (n = 6)			
	DoE 1, ScinoPharm API		DoE 2, (b) (4) API	
Batch Description (Batch Nos.)	Mean	RSD	Mean	RSD
(b) (4) (21001, 21002)	102.0	2.2	99.5	0.8
(b) (4) 21008, 21007)	104.4	3.4	100.8	2.7
(b) (4) 21010, 21009)	102.2	2.7	98.5	1.7
(b) (4) (21012, 21011)	101.0	1.4	96.2	2.2
(b) (4) 21014, 21013)	97.3	2.5	99.0	2.6

Overall, considering *(i)* there are no formulation composition changes from the first prototype batches to the primary registration/to-be-marketed drug product batches; *(ii)* the manufacturing process and dosage strengths used in the pivotal clinical studies are identical to those of the proposed commercial drug product batches; *(iii)* the drug substance sources, manufacturing process and batch scale up do not impact the drug product dissolution behavior, therefore, scientific bridging throughout the pharmaceutical development appears to be established, pending on the in vivo PK purview under OCP.

Scientific bridging between the proposed drug product and the LD is pending on the in vivo PK data/information under the purview of OCP.

APPENDIX
Biopharmaceutics Information Request and Applicant's Responses

Biopharmaceutics IR (conveyed on 12/7/22):
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(1) From information provided in M.2.5 and M.2.7.1, clarify if (i) Cancer Prevention Pharmaceuticals (CPP) is the original API source (b) (4) with DMF (b) (4), (ii) KC Pharma (KCP) is the second API source ScinoPharm with DMF (b) (4).

(2) Provide batch information of the drug product (batch # 15005, 15057, 15062, 16008, 16084, 17051) used in clinical study NMTRC003b (Appendix 6.1 in M.2.7.1), e.g., composition, drug substance source, drug product manufacturing site, manufacturing date, etc.

(3) Provide side-by-side comparison (composition, API source, drug product manufacturing site, manufacturing date, etc.) of the six clinical batches (batch # 15005, 15057, 15062, 16008, 16084, 17051 used in clinical study NMTRC003b, Appendix 6.1 in M.2.7.1) vs. the registration batches (batch # 20112 containing drug substance from (b) (4) and batch # 20332, 20333, 21202 containing drug substance from ScinoPharm).

(4) Provide complete dissolution data profiles (n=12) of the six clinical batches above in multi-media (i.e., 0.1 N HCl, pH 4.5 and pH 6.8) if available.

Applicant's responses to the IR (submitted on 12/16/2022):
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