CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 214900
Assessment # 1

Drug Product Name	BREXAFEMME™ (ibrexafungerp tablets)
Dosage Form	Tablets
Strength	150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	SCYNEXIS, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0000	October 1, 2020	All
0003	October 30, 2020	Drug Product
0007	November 25, 2020	Drug Product
0011	January 25, 2021	Drug Substance, Process
0013	February 12, 2021	Process
0014	February 22, 2021	Drug Substance, Facilities
0016	March 4, 2021	Labeling
0017	March 12, 2021	Biopharmaceutics
0020	March 30, 2021	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Ali Al Hakim
Drug Product	Molly Lee	Thomas Oliver
Manufacturing	Jiao Yang	Steven Frisbee
Microbiology	Jiao Yang	Steven Frisbee
Biopharmaceutics	Mathew John	Elsbeth Chikhale
Environmental Analysis	Refer to Drug Product Review	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: None

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
N/A						

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

Document	Application Number	Description
IND	107521	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (acceptance criteria for impurities)	*Refer to Drug Substance review*	Dr. James Wild
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, ibrexafungerp tablets. The manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on February 25, 2021. Therefore, this NDA is recommended for **approval** by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Ibrexafungerp is a novel broad-spectrum antifungal agent intended for the treatment of vulvovaginal candidiasis. Ibrexafungerp is an orally active, semi-synthetic triterpenoid derivative of the natural product, enfumafungin. Ibrexafungerp belongs to a structurally distinct class of glucan synthase inhibitors (GSI) that inhibit the synthesis of the fungal cell wall polymer β-(1,3)-D-glucan. The inhibition of β-(1,3)-D-glucan synthesis is a proven antifungal target.

Ibrexafungerp has been formulated as an immediate-release, film-coated tablet, each containing (b) (4) mg of ibrexafungerp citrate, which is equivalent to 150 mg ibrexafungerp free base. BREXAFEMME™ (ibrexafungerp tablets) are (b) (4) oval shaped tablets, which will be provided for commercial use in a unit dose blister package containing four tablets.

Ibrexafungerp tablets received Qualified Infectious Disease Product (QIDP) and Fast Track (FT) designations on April 18, 2018 (for the treatment of vulvovaginal candidiasis).

Proposed Indication(s) including Intended Patient Population	Treatment of vulvovaginal candidiasis (VVC), also known as vaginal yeast infection in (b) (4) adult women.
Duration of Treatment	One-day treatment. The recommended dosage of BREXAFEMME™ tablets is 300 mg (two tablets of 150 mg) twice a

	day for one day, for a total treatment dosage of 600 mg. BREXAFEMME™ tablets may be taken with or without food.
Maximum Daily Dose	600 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The CMC information for the ibrexafungerp citrate drug substance has been provided in Module 3 of the NDA. Ibrexafungerp, a semi-synthetic triterpenoid derivative is an optically active molecule containing 12 chiral centers. The ibrexafungerp citrate drug substance is a white to off-white yellow solid, manufactured (b) (4) The drug substance manufacturing process described in this NDA (b) (4) he overall information regarding the drug substance manufacturing process, starting materials and controls provided in the NDA was found acceptable by the Drug Substance Reviewer. Similarly, information regarding the drug substance characterization, structure elucidation, and the impurity profile was found acceptable. The drug substance specification includes all relevant quality attributes such as appearance, identification, assay, impurities, polymorphic form, citrate content, water content, optical rotation, and residual solvents. In addition, a test with appropriate acceptance criteria for particle size distribution was added at the FDA recommendation during the NDA review.

The ibrexafungerp citrate drug substance is (b) (4) Based on the review of the stability data, the retest period of (b) (4) months proposed by the Applicant for the ibrexafungerp citrate drug substance stored at (b) (4) in the proposed container closure system, was found acceptable. For further details refer to the Drug Substance Review, below.

Drug Product: Adequate

The drug product is an immediate release tablet designed as a one-day treatment of vulvovaginal candidiasis in adolescent and adult women. Ibrexafungerp tablets are formulated as purple, oval, biconvex shaped tablets, with 150 debossed on one side and SCYX debossed on the other side. Each tablet contains (b) (4) mg of ibrexafungerp citrate, which is equivalent to 150 mg ibrexafungerp free base. The tablet manufacturing (b) (4)

The commercial drug product will be packaged in a blister pack consisting of 4 tablets. The PVC/PVDC film coating is sealed with aluminum foil and heat sealed onto a child-resistant (b) (4). Overall information provided for the container closure system was found acceptable by the Drug Product Reviewer.

The stability information submitted for the drug product in the NDA includes 12 months long term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) stability data for three registration batches. All stability testing results conform to the acceptance criteria set in the proposed drug product specification. There are no trends observed for the measured values of the tests performed, (b) (4). There are no significant levels of degradation products observed for the three registration batches at release or on stability. Therefore, the proposed 24 months expiry for this product is granted and controlled room temperature storage recommendation has been found acceptable.

The drug product specification includes all relevant quality attributes such as: description, identification, assay, degradation products, dissolution, (b) (4) uniformity of dosage units, microbial limits, and BHA identification and assay. The PXRD patterns for the drug substance and drug product stability samples from the long-term (25°C/60% RH) stability studies were provided to demonstrate that the (b) (4) of the low solubility ibrexafungerp citrate does not change during drug product manufacturing and storage. Initially, the BHA assay limit was set only on release. At the FDA recommendation, the BHA assay limit was also set as part of the stability/regulatory specification. With this revision, the drug product specification has been found adequate.

The Applicant is claiming a categorical exclusion from the requirement to prepare an Environmental Assessment based on 21 CFR 25.31(b) and the claim was found acceptable.

For further details refer to the Drug Product Review and Addendum, below.

Labeling: Adequate

The proposed prescribing information (PI), container labels, and the carton labeling were found to include generally the necessary information. Several revisions and additions have been recommended in the applicable to the product quality sections of the PI (Sections 3, 11 and 16), also for the container/blister label and carton labeling (for details refer to the Labeling Review, below).

Labeling recommendations have been communicated to OND PM. The labeling review by the NDA review team is currently pending.

Manufacturing: Adequate

(b) (4)

All manufacturing facilities have been found acceptable by OPMA and are commended for approval (for details refer to the Manufacturing Integrated Assessment, below).

Biopharmaceutics: Adequate

The biopharmaceutics review focused on the assessment of the proposed dissolution test (analytical procedure and acceptance criterion), to be used for release and stability testing of ibrexafungerp tablets. The dissolution method and the proposed acceptance criterion as outlined below were found acceptable:

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	50 RPM	0.1 N HCl	900 mL/ 37.0 ± 0.5 °C	Q= (b) (4) % at (b) (4) minutes

In addition, bridging of formulations was also part of the biopharmaceutics assessment. The drug product used in Phase 1, 2 and 3 clinical studies was manufactured by (b) (4) however, the commercial manufacturing will be conducted at (b) (4) In addition to the change in the drug product manufacturing site, the clinical and commercial drug product differ in the coating, size and shape of the tablets. The overall information, including the comparative dissolution data and PK information, was found to be supportive of the changes in the manufacturing site, coating, shape, and tablet size between the commercial drug product and the clinical drug product and, thus, the bridging between the clinical and the commercial drug product was found adequate. For further details refer to the Biopharmaceutics Review, below.

Microbiology: Adequate

The drug product (ibrexafungerp tablets) is an oral dosage form; therefore, a separate microbiology review was not needed. The microbiological controls proposed for the drug product were found adequate by the Process Reviewer (refer to the Manufacturing Integrated Assessment, below).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference
NDA 214900

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**BREXAFEMME™**	
Established name(s)	(ibrexafungerp (b) (4) tablets	Revise to remove (b) (4) (ibrexafungerp) tablets
Route(s) of administration	Tablets, for oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Revise to- Tablets: 150 mg of ibrexafungerp (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	n/a	No special preparation instructions needed for this oral dosage form

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	150 mg	Revised to: 150 mg per tablet to match DMEPA's comments for container and carton label
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Per OPPQ, equivalency statement should be present in Section 11
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	Revised to include debossing: BREXAFEMME tablets are purple, oval, bicovex shaped, (b) (4) tablets debossed with 150 on one side and SCYX on the other side containing 150 mg of ibrexafungerp. (b) (4)

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	The tablet is not scored	n/a
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BREXAFEMME, available as an oral tablet, contains ibrexafungerp citrate, a triterpenoid antifungal agent.	Adequate
Dosage form(s) and route(s) of administration	tablet for oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	(b) (4)	Revised to remove (b) (4) 150 mg of ibrexafungerp equivalent to 189.5 mg of ibrexafungerp citrate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Revised to put inactive ingredients in alphabetical order per USP<1091> and remove (b) (4) In addition to the active ingredient, the tablet formulation contains butylated hydroxyanisole, crospovidone, colloidal silicon dioxide, magnesium stearate (b) (4) mannitol and (b) (4) microcrystalline cellulose. The tablet film-coating contains FD&C Blue #2, FD&C Red #40, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, talc and titanium dioxide.

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	n/a	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Statement of being sterile (if applicable)	n/a	
Pharmacological/ therapeutic class	a triterpenoid antifungal agent	Adequate- defer to review team
Chemical name, structural formula, molecular weight	(b) (4)	After evaluating the USAN file for ibrexafungerp citrate, the following changes were recommended: • Revised chemical name to match USAN #2. This chemical name provides the 1:1 ibrexafungerp:citrate composition information as well as lists the chemical name of the citrate salt • Change empirical formula to match USAN file to separate out citrate formula from ibrexafungerp formula • Molecular weight matches USAN file, recommendation to add in grams per mole for molecular weight Revised to: Ibrexafungerp is designated chemically as (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-15-[[(2R)-2-amino-2,3,3-trimethylbutoxy]-1,6a,8,10a-tetramethyl-8-[(2R)-3-methylbutan-2-yl]-14-[5-(pyridine-4-yl)-1H-1,2,4-

		triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-2H,4H-1,4a-propanophenanthro[1,2-c]pyran-7-carboxylic acid compound with 2-hydroxypropane-1,2,3-tricarboxylic acid (1:1) with an empirical formula of $C_{44}H_{67}N_5O4 \bullet C_6H_8O_7$ and a molecular weight of 922.18 grams per mole. The chemical structure is:
If radioactive, statement of important nuclear characteristics.	n/a	
Other important chemical or physical properties (such as pKa or pH)	None provided	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	tablets	Adequate
Strength(s) in metric system	150 mg ibrexafungerp (equivalent to (b) (4) mg of ibrexafungerp citrate)	Corrected equivalency amount
Available units (e.g., bottles of 100 tablets)	polyvinyl/polyvinylidene chloride blister packs, four (4) tablets per pack	Adequate Could be revised to: child-resistant blister packages comprised of a polyvinylchloride film with foil and paper backing, four tablets per pack
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Changed description to match specification purple, film-coated tablets are oval, biconvex shaped and debossed with 150 on one side and SCYX on the other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored	
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	

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

Item	Information Provided in the NDA	Assessor's Comments

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.)	(b) (4)	Remove this statement for consistency with container and carton labeling. (b) (4)
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	n/a	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store BREXAFEMME tablets at 68°F to 77°F	Add in Celsius (°C) range and the USP controlled temperature statement: Revised to: Store BREXAFEMME tablets at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).
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	n/a	

statements such as “latex-free.”		
Include information about child-resistant packaging	not present	Added child-resistant to packaging information

1.2.4 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 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.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: **SCYNEXIS, Inc.** Jersey City, NJ (b) (4) [redacted]	Adequate Recommend to remove (b) (4) [redacted]

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
Ingredients section modified to match Section 11
Storage conditions modified to match Section 16
Removed Opadry trademark information

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

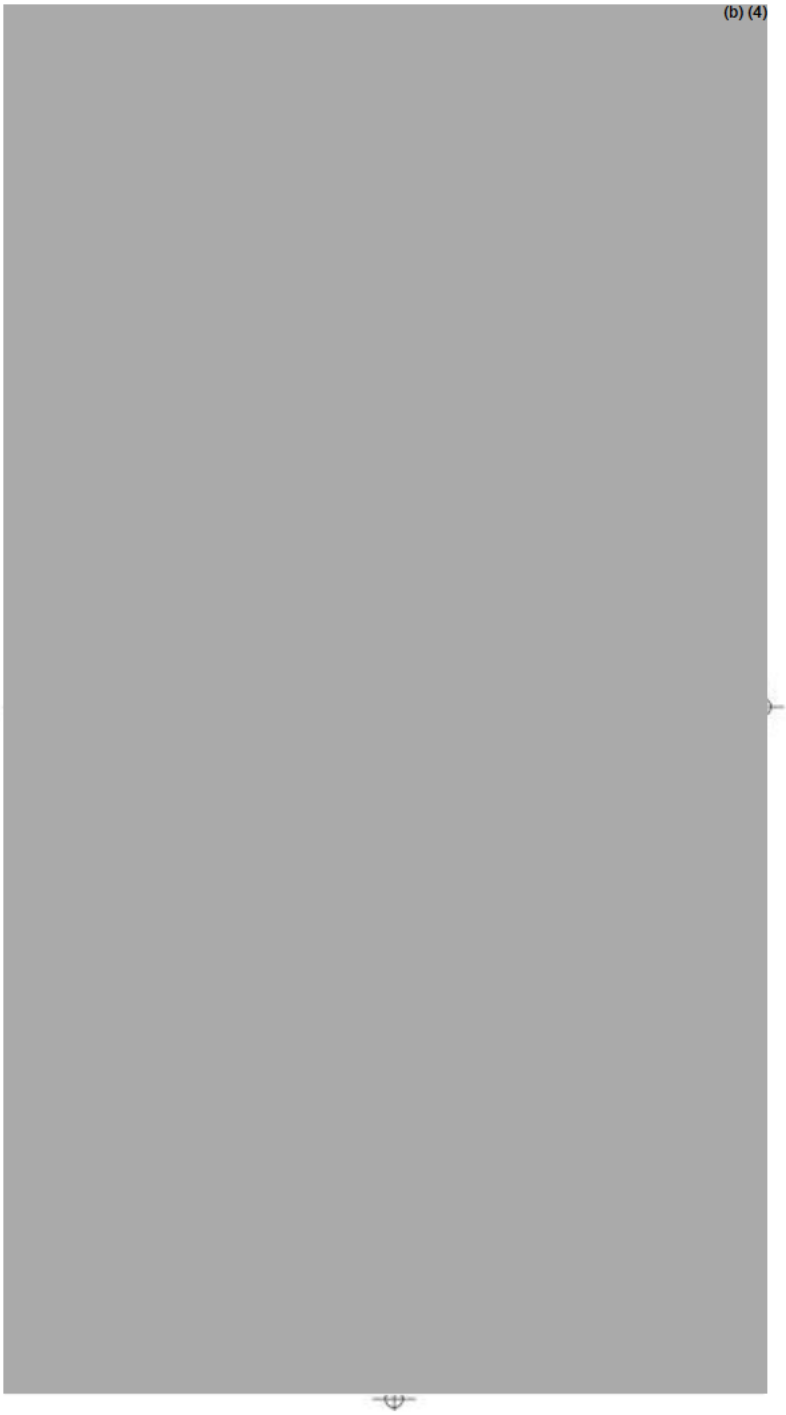
3.0 CARTON AND CONTAINER LABELING

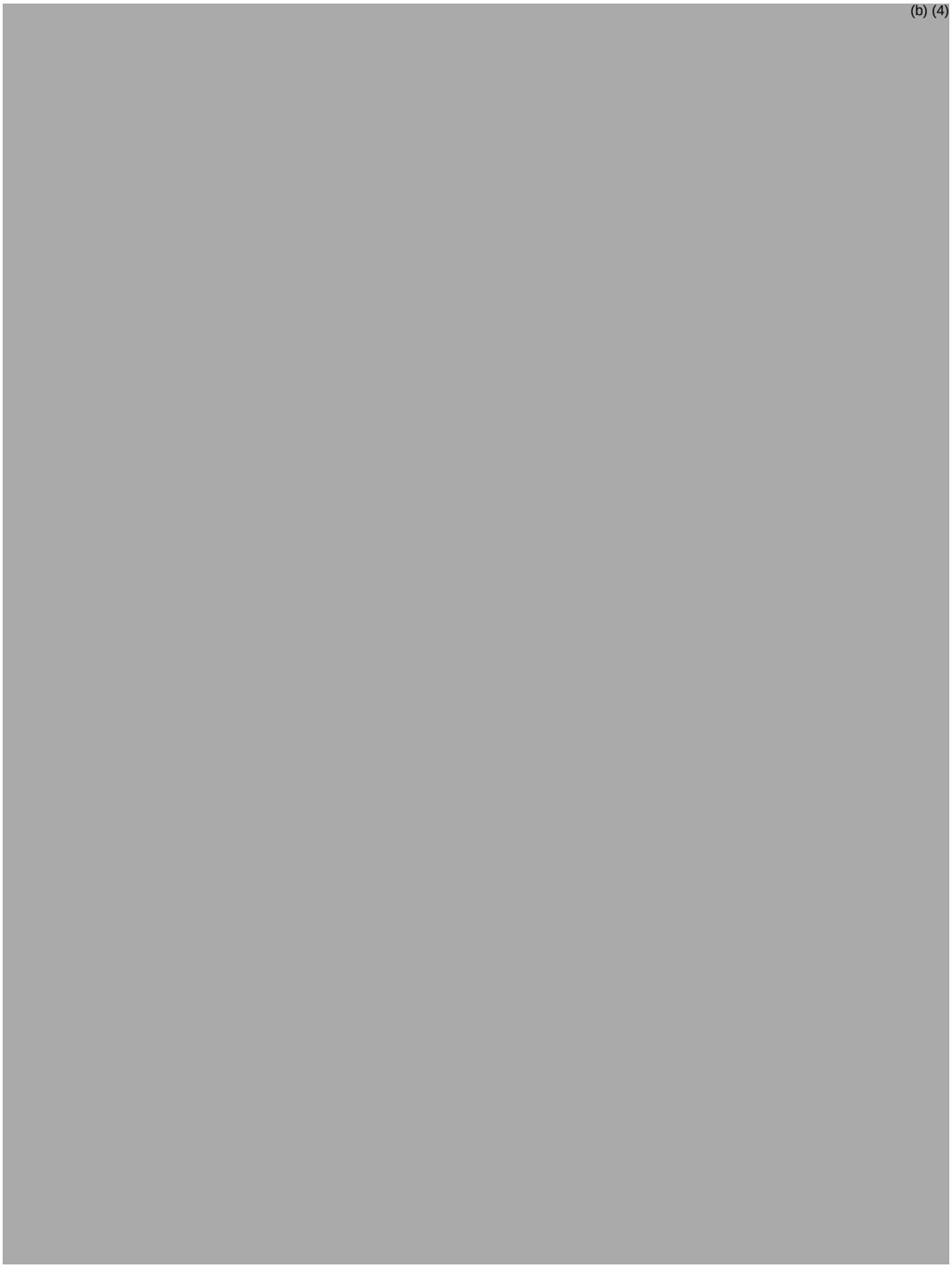
3.1 Container Label

See 3.2

3.2 Carton Labeling

Carton and container label were updated in Seq. #001, dated 3/4/2021 following recommendations from OPQ and DMEPA




(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	BREXAFEMME™ Ibrexafungerp, 150 mg per tablet	Per DMEPA's labeling recommendations to the applicant, in Seq. #0016, the name on the carton was changed from (b) (4) [redacted] to "BREXAFEMME™ Ibrexafungerp, 150 mg per tablet" (b) (4) [redacted] Applicant will be notified to change this section on carton and container to: "BREXAFEMME™ Ibrexafungerp tablet, 150 mg per tablet"
Dosage strength	150 mg	In Seq. # 0016, applicant revised to "150 mg per tablet" per DMEPA's recommendation
Route of administration	For oral use only Taken orally	Adequate

If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not present in original submission	Per the FDA Guidance: Naming of Drug Products Containing Salt Drug Substances and recommendation conveyed to the applicant, the applicant added *Each tablet contains 189.5 mg ibrexafungerp citrate equivalent to 150 mg ibrexafungerp.* to the carton and container in Seq. # 0016 and is therefore in compliance with the salt naming guidance
Net contents (e.g. tablet count)	4 tablets	Adequate
"Rx only" displayed on the principal display	present	Adequate
NDC number	NDC 75788-115-04	Adequate
Lot number and expiration date	Present on back	Adequate

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Add in Centigrade range and see insert* per OPPQ In Seq. #0016, the applicant revised to the following: Container: Store at 25°C (77°F), see insert. Carton: Store BREXAFEMME tablets at room temperature 20°C to 25°C (68°F to 77°F). (b) (4)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	n/a	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Bar code	Present on back	Adequate

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Front: SCYNEXIS Back: Manufactured for and distributed by: SCYNEXIS, Inc., Jersey City, NJ 07302	Adequate
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal	n/a	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	
And others, if space is available	n/a	

Assessment of Carton and Container Labeling: ***Recommendation to change name on Carton and Container will be communicated to applicant.***

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

ITEMS FOR ADDITIONAL ASSESSMENT

Following recommendations sent to the applicant, the carton and container labeling were revised in Seq. #0016, dated 3/4/2021, which incorporated recommended changes from OPQ and DMEPA. Following this revision, the name of the product on the carton and container was changed to "BREXAFEMME™ Ibrexafungerp, 150 mg per tablet". The established name should read ibrexafungerp tablet, and therefore the applicant will be notified to change this section of the carton and container label to "BREXAFEMME™ Ibrexafungerp tablet, 150 mg per tablet" Beyond this recommended change, the labels are adequate.

Overall Assessment and Recommendation:

Recommendations from the product quality perspective were incorporated into the prescribing information and patient information to be sent to the applicant.

Primary Drug Product Assessor Name and Date:
Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, 3/19/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Thomas Oliver, Ph.D., ONDP Division of New Drug Products I, 3/19/2021

Molly Lee

Digitally signed by Molly Lee
Date: 3/19/2021 04:24:34PM
GUID: 5e2b04c70029e7c7580982b0a5cb16be

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 3/22/2021 06:55:05AM
GUID: 508da71f00029ed4697700cee3d31ca0

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U.S. FOOD & DRUG ADMINISTRATION

BIOPHARMACEUTICS REVIEW

NDA Number	NDA 214900
Drug Product Name/ Strength	Ibrexafungerp [redacted] (b) (4) Tablets, 150 mg.
Route of Administration	Oral
Sponsor Name	Scynexis
Therapeutic Classification / OND Division	DAI
Proposed Indication	For treatment of vulvovaginal candidiasis.
Submission Date(s)	10/01/2020
Primary Assessors	Mathew John, Ph.D.
Secondary Assessors	Elsbeth Chikhale, Ph.D.
Recommendation	**Adequate.**

Background:

This is the Biopharmaceutics assessment of NDA 214900 for Ibrexafungerp [redacted] (b) (4) Tablets, 150 mg. The Applicant seeks approval for Ibrexafungerp [redacted] (b) (4) Tablets, 150 mg under section 505(b)(1) of the Federal Food Drug and Cosmetics Act for the treatment of vulvovaginal candidiasis.

Bridging of Formulations:

Drug Product development started in [redacted] (b) (4) for Phase 1, 2 and 3 clinical studies and transferred to [redacted] (b) (4) for commercial manufacturing. The Applicant has submitted the comparative dissolution data of the batches used in Phase 2 and Phase 3 clinical studies (manufactured at [redacted] (b) (4) and registration batches (manufactured at [redacted] (b) (4). The Applicant has also submitted the primary and secondary efficacy results of the Phase 2 and Phase 3 studies which will be evaluated by the Clinical Division.

Summary:

Based on the provided information and data, the following dissolution method and acceptance criterion are found acceptable for Quality Control batch release and stability testing of Ibrexafungerp [redacted] (b) (4) Tablets, 150 mg.

Table 1: Acceptable Dissolution Method and Acceptance Criterion for Ibrexafungerp [redacted] (b) (4) Tablets, 150 mg.

USP Apparatus	Rotation Speed	Medium	Volume /Temperature	Acceptance Criterion
II (Paddle)	**50 rpm**	**0.1 N HCl**	**900 mL / 37 ± 0.5 °C**	**NLT [redacted] (b) (4) % (Q) at 30 minutes.**

Recommendation:

From a Biopharmaceutics perspective, NDA 214900 (Ibrexafungerp (b) (4) Tablets, 150 mg.) is adequate and recommended for **Approval**.

BIOPHARMACEUTICS ASSESSMENT

B.1 BCS DESIGNATION

The Applicant did not request a BCS designation for the proposed drug product. Ibrexafungerp (b) (4) has a pH dependent low solubility. The Applicant considers the proposed drug product to be consistent with BCS class IV, based on the drug substance solubility and permeability information.

B.2 DISSOLUTION METHOD

Assessment: ***Adequate***

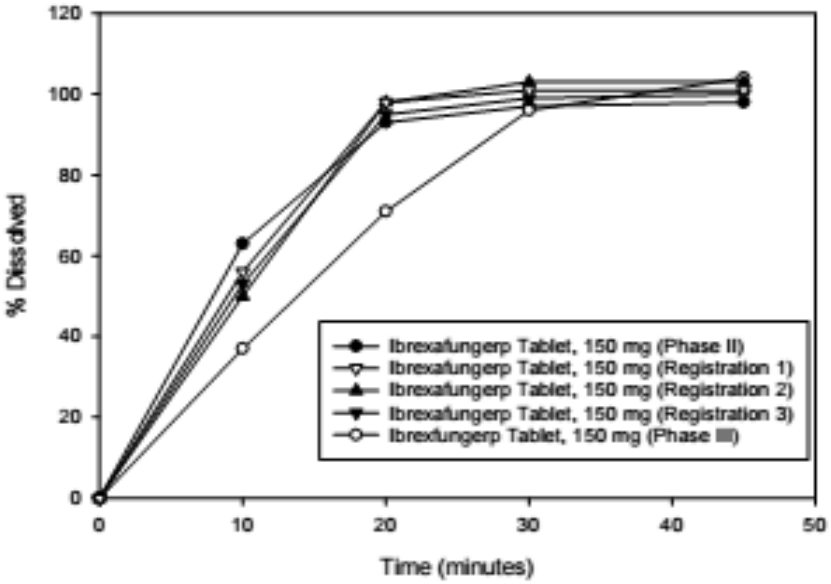
The proposed quality control dissolution method for Ibrexafungerp (b) (4) Tablets, 150 mg uses USP Apparatus II (paddle) at 50 rpm in 900 mL of 0.1N HCl at 37 ± 0.5 °C. The dissolution method development report was submitted in IND 107521/SDN-171 (dated 04/28/2020) which was evaluated and found adequate as per the Biopharmaceutics review in DAARTS[1] (dated 07/27/2020).

B3. DISSOLUTION ACCEPTANCE CRITERION

The Applicant proposed a dissolution acceptance criterion of NLT (b) (4) % (Q) at 30 minutes. Figure 1 shows the dissolution profiles of the clinical and registration batches as follows:

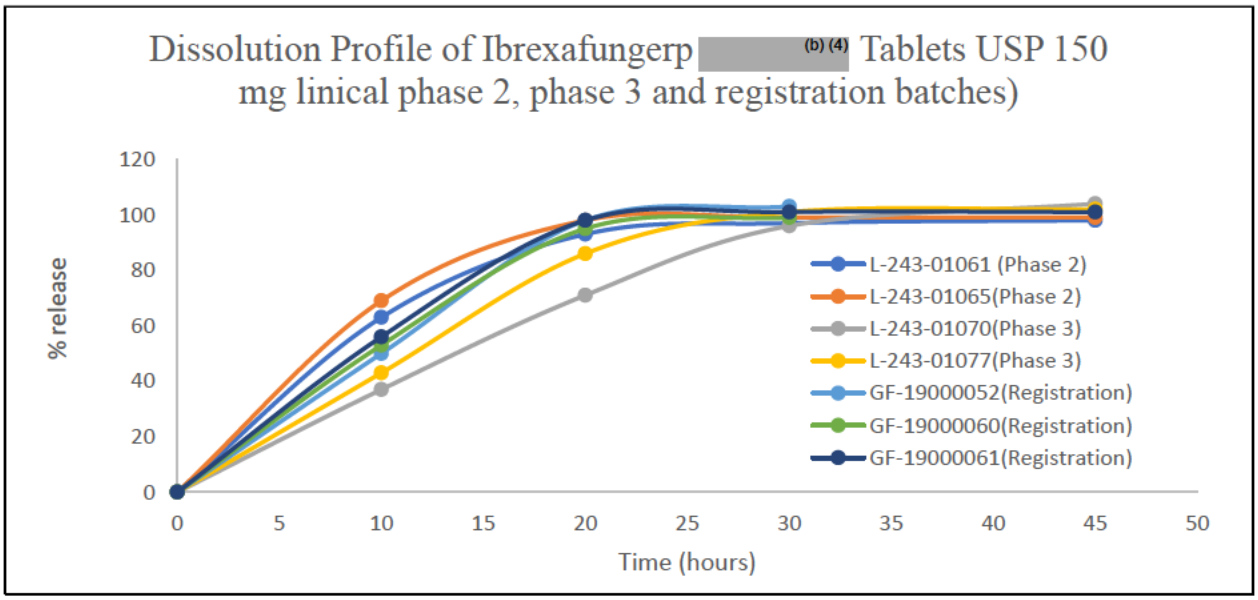
[1] DAARTS REV-QUALBIOPHARM-21 (Primary Review_07/27/2020)

Figure 1: Comparative dissolution profiles of Ibrexafungerp Tablet 150 mg used in clinical phase 2 (batch L-243-01061) and phase 3 study (batch L-24301070) which were manufactured at [redacted] (b) (4) (uncoated, round) and registrational batches (coated, oval, batch # s GF-19000052, GF-19000060 and GF-19000061) which were manufactured at the proposed commercial site, [redacted] (b) (4) in 900 mL 0.1N HCl using USP Apparatus II at 50 rpm and 37°C.



The in-vitro dissolution profiles of batch # L-243-01070 which was used for clinical Phase 3 study SCY-078-303 was slower at the initial time points of 10 and 20 minutes compared to the batch used for Phase 2 study and the registrational batches. In the batch analysis report the Applicant mentioned that drug product batches L-243-01070 and L-243-01077 were used in clinical Phase 3 studies SCY-078-303 and SCY-078-306. In the Pharmaceutical Development Report (PDR) the Applicant mentioned that lot numbers 201822705 and 201822707 were used in SCY-078-303 and SCY-078-306. An Information Request (IR) was send to the Applicant to clarify how the two lot numbers relate to the batch numbers (see IR # 1 in Appendix 1). In their response the Applicant explained that Lot # 201822705 is from batch # L-243-01070 and 188 patients were dozed with batch # L-243-01070 in Phase 3 clinical study SCY-078-303. The Applicant also explained that Lot # 201822707 is from batch # L-243-01077 and 188 patients were dozed with batch # L-243-01077 in Phase 3 clinical study SCY-078-306. The Applicant provided additional dissolution data for batch L-243-01077, which were left out in Figure 1. Since a significant number of patients (n = 188) were dozed with batch L-243-01070 as well as batch L-243-01077, in each of the pivotal clinical studies, [redacted] (b) (4) A more comprehensive Figure with additional dissolution data for a Phase 2 and Phase 3 batch is shown in Figure 2 below.

Figure 2: Dissolution Profile of Ibrexafungerp [redacted] tablets USP 150 mg (Phase 2 and 3 Clinical and Registration Batches)



Although most of the clinical and registration batches (except for batch L243-01070) support a dissolution acceptance criterion of Q= [redacted] minutes, this would fail the one slower dissolving clinical batch L243-01070. Because batch L243-01070 is a pivotal clinical batch, used in a significant number of patients, a dissolution acceptance criterion of Q= [redacted]% at 30 minutes (which batch L243-01070 would meet), is found acceptable.

BRIDGING OF FORMULATIONS

Drug Product development started in [redacted] for Phase 1, 2 and 3 clinical studies and transferred to [redacted] for commercial drug product manufacturing. In addition to the change in the drug product manufacturing site, the clinical and commercial drug product differ in the coating, size and shape of the tablets, as shown in Table 2 below.

Table 2: Comparison of Clinical and Commercial Formulation of Ibrexafungerp (b) (4) Tablets, 150 mg:

Component	mg/Tablet		Function
Active Ingredient	**150 mg Strength[2]**	**150 mg Strength (commercial)[3]**	
Ibrexafungerp citrate[1]	189.49	189.49	Active ingredient
(b) (4) microcrystalline cellulose (b) (4)	(b) (4)		
Mannitol			
Crospovidone			
Colloidal silicon dioxide			
Butylated hydroxyanisole			
Magnesium stearate (b) (4) (b) (4)			
Total Core Tablet Weight			
(b) (4)			

[1] Ibrexafungerp citrate 189.49 mg is equivalent to 150 mg of Ibrexafungerp free base.
[2] 11 mm round
[3] 15.5 x 8 mm oval
(b) (4)
[5] QS: Quantity Sufficient

To support the difference in drug product manufacturing site, coating, shape, and tablet size between the clinical and commercial drug products, the similarity factors of the clinical and registration batches shown in Figure 2 above, were calculated as follows, using registration batch GF-19000052 as representative of the other registration batches:

Table 3: Similarity factor (f2) calculations between clinical and registration batches

Batch #s compared	F2 values calculated
L-243-01061 (Phase2) vs GF-19000052 (Registration)	57.0
L-243-01065 (Phase2) vs GF-19000052 (Registration)	52.4
L-243-01077 (Phase 3) vs GF-19000052 (Registration)	59.8
L-243-01070 (Phase 3) vs GF-19000052 (Registration)	40.6

The in-vitro dissolution profile of batch # L-243-01070, with f2<50 indicating dissimilarity, is slower at the initial time points of 10 and 20 minutes compared to the batches used for the Phase 2 and the other Phase 3 clinical study and the registrational stability batches. The Applicant claims that the slower dissolution of this batch at 10 and 20 minutes is due to the higher hardness (b) (4) compared to Phase 2 clinical batch L-243-01061 (b) (4) and increased disintegration time (b) (4) compared to Phase 2 clinical batch L-243-01061 (b) (4) as shown in Table 4.

[2] \\CDSESUB1\evsprod\nda214900\0001\m3\32-body-data\32p-drug-prod\ibrexafungerp-(b) (4)-tablet-common\32p2-pharm-dev\pharmaceutical-development.pdf

Table 4: Comparative summary of in-process and dissolution characteristics of Ibrexafungerp (b) (4) Tablets 150 mg

Batch Number		L243-01061[1]	L243-01070[2]
Disintegration time in water at 37°C		(b) (4)	
Friability (%)			
Hardness (kP)			
	Time (Minutes)	% Dissolved (N=6)[3]	
	10	63	37
	20	93	71
(Q = (b) (4)%)	30	97	96
	45	98	104

[1] Phase 2 Study; [2] Phase 3 Study; [3] 900 mL (b) (4) N HCl using USP Apparatus II at 50 rpm and 37°C

As shown in Table 2, the clinical and commercial formulations have the same active and inactive ingredients in the same amounts except for the presence of (b) (4) mg of the nonfunctional film coating agent in the commercial formulation. In addition, the size and shape of the clinical drug product (11 mm round) differs from the commercial drug product (15.5 × 8 mm oval).

Based on the calculated similarity factors of > 50, between the Phase 2 batches (L-243-01061 and L-243-01065), Phase 3 batch # L-243-01077 vs. the registration batch (GF-19000052, see Table 3), the dissolution profiles for these clinical batches are considered similar to the registration batch. However; the Phase 3 clinical batch # L-243-01070 is not similar to the registration batch. The slower dissolution for the Phase 3 clinical batch # L-243-01070 at the initial time points of 10 and 20 minutes is not expected to affect the in-vivo performance of the proposed drug product as the T_{max} reported for the proposed dose of 150 mg is between 4-6 hours[3]. In addition, the slower dissolution of batch # L-243-01070 is not believed to be due to the change in manufacturing site, shape, tablet size or coating, because the other Phase 3 batch (L-243-01077) and the two Phase 2 batches have the same changes in manufacturing site, shape, tablet size and coating, and have similar dissolution profiles as the commercial tablets. The slower dissolution of batch # L-243-01070 is believed to be due to difference in tablet hardness (see Table 4). Therefore, based on the totality of the comparative dissolution data and PK information, the changes in manufacturing site, coating, shape, and tablet size between the commercial drug product and the clinical drug product is supported by the comparative dissolution data and provided information, and is found acceptable. Therefore, the bridging between the clinical drug product and the commercial drug product is adequate from a Biopharmaceutics perspective.

[3] \\CDSESUB1\evsprod\ind107521\0095\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\scy-078-001\scy-078-001-synopsis.pdf

Appendix 1

Biopharmaceutics Information Request dated 03/10/2021

Per Table 1 in 3.2.P.5.4, drug product batches L243-01070 and L243-01077 were used in SCY-078-303 and SCY-078-306. In Table 18 of the Pharmaceutical Development Report (3.2.P.2), you indicated that drug product lot numbers 201822705 and 201822707 were used in SCY-078-303 and SCY-078-306.

- Clarify how the two lot numbers (201822705 and 201822707) relate to the two batch numbers (L-243-01070 and L-243-01077).
- Clarify how many patients in each clinical study (SCY-078-303 as well as SCY-078-306) were dosed with drug product lot number 201822705 and how many were dosed with drug product lot number 201822707.
- Provide the full dissolution profiles for drug product lot number 201822705 and for drug product lot number 201822707, using the proposed dissolution method (900 mL of 0.1 N HCl, Apparatus II (Paddle) at 50 rpm). Include the age of the drug product batches at the time of dissolution testing and the storage conditions.

Provide your response by COB 03/12/2021.

Applicant's Response (dated 03/12/2021) and Assessment of the Response:

In their response the Applicant clarified that they listed the blinded clinical trial lot # s by mistake in place of the batch numbers in Table 18 of PDR.[4]. The Applicant also clarified that Lot # 201822705 is from Phase 3 batch L-243-01070 and is the only batch used in SCY-078-303 in 188 patients. The Applicant also clarified that Lot # 201822707 is from Phase 3 batch L-243-01077 and is the only batch used in SCY-078-306 dozed in 188 patients. The Applicant has also provided the comparative dissolution data of Lot # s 201822705 and 201822707 which correspond to batch # L-243-01070 and L-243-01077 respectively. Based on the data and additional information provided by the Applicant, the Applicant's response is adequate and acceptable.

[4] \\CDSESUB1\evsprod\nda214900\0017\m1\us\coverletter.pdf

Mathew John

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Elsbeth Chikhale

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/s/

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