

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209363Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # **209363** SUPPL # n/a HFD # 520/Division of Anti-Infective Products

Trade Name **Solosec Oral Granules**

Generic Name **Secnidazole**

Applicant Name **Symbiomix Therapeutics, LLC**

Approval Date, If Known **September 15, 2017**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

c) Did the applicant request exclusivity?

YES **X** NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

**New Chemical Entity (NCE) – 5 years;
Generating Antibiotic Incentives Now (GAIN)-Qualified Infectious Disease Product (QIDP) – 5 year extension**

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO **X**

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO **X**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO **X**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to

clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!
IND #	!
YES ☐	! NO ☐
	! Explain:

Investigation #2	!
IND #	!
YES ☐	! NO ☐
	! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
YES ☐	!
Explain:	! NO ☐
	! Explain:

Investigation #2	!
------------------	---

YES ☐

Explain:

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☐

If yes, explain:

=====

Name of person completing form: **Maureen Dillon-Parker**

Title: **Chief, Project Management Staff, Division of Anti-Infective Products**

Signature/Date: *{see electronic signature/date}*

Name of Division Director signing form: **Sumathi Nambiar, MD, MPH**

Title: **Director, Division of Anti-Infective Products**

Signature/Date: *{see electronic signature/date}*

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN P DILLON PARKER
09/15/2017

DMITRI IARIKOV
09/15/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209363	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a (an action package is not required for SE8 or SE9 supplements)
Proprietary Name: SOLOSEC Established/Proper Name: secnidazole Dosage Form: Oral Granules, 2g		Applicant: Symbiomix Therapeutics, LLC Agent for Applicant (if applicable): Salamandra, LLC
RPM: Maureen Dillon-Parker		Division: Anti-Infective Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity (notify CDER OND IO) Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>09/17/17</u>		☒ AP ☐ TA ☐ CR
Previous actions (specify type and date for each action taken)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? n/a Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ **Priority**
 Chemical classification (new NDAs only): **Type 1/NME -Antibacterial (bacterial vaginosis)**
(confirm chemical classification at time of approval)

X Fast Track

- ☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation

- ☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

X Qualified Infectious Disease Product (QIDP)

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes n/a
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Approval/September 15, 2017
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	X Included FDA Revised Version 08/21/17
Original applicant-proposed labeling	X Included Original 01/17/17 Revised Original 04/11/17
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide X Patient Package Insert X Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	X Included
Original applicant-proposed labeling	X Included (dated 01/17/17)
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	X Included
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	11/09/15 (under IND) 04/14/17 04/13/17
❖ Labeling reviews (indicate dates of reviews)	RPM: X None DMEPA: 04/13/17; 05/09/17; 06/07/17 DMPP/PLT (DRISK): 07/05/17 OPDP: 06/29/17 & 07/03/17 SEALD: X None CSS: X None Product Quality X None Other: -Pediatric and Maternal Health 08/25/17 - CMC Labeling CTD 08/10/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	09/05/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	X Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	X Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes X No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No n/a n/a ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC 08/09/17 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	X N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	n/a
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	n/a
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	n/a
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Enclosed
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	n/a
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	X N/A
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	X No mtg
EOP2 meeting (<i>indicate date of mtg</i>)	03/18/15
Mid-cycle Communication (<i>indicate date of mtg</i>)	05/02/17
Late-cycle Meeting (<i>indicate date of mtg</i>)	07/18/17
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	n/a
❖ Advisory Committee Meeting(s)	X No AC meeting
Date(s) of Meeting(s)	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	Combined /CDTL/OD/DD Review; See CDTL review
Division Director Summary Review (<i>indicate date for each review</i>)	Combined /CDTL/OD/DD Review; See CDTL review
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	09/12/17
PMR/PMC Development Templates (<i>indicate total number</i>)	09/08/17 (1)

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	X No separate review
• Clinical review(s) (indicate date for each review)	07/17/17
• Social scientist review(s) (if OTC drug) (indicate date for each review)	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	Page 141/Clinical Review 07/17/17 n/a
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	05/04/17 QT/IRT
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	X N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) - REMS Memo(s) and letter(s) (indicate date(s)) - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	n/a n/a 06/15/17
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☐ None requested 07/28/17
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	X No separate review
Clinical Microbiology Review(s) (indicate date for each review)	08/08/17
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	X No separate review
Statistical Team Leader Review(s) (indicate date for each review)	X No separate review
Statistical Review(s) (indicate date for each review)	6/15/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	X No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	X No separate review
Clinical Pharmacology review(s) (indicate date for each review)	06/16/17
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	X None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	X No separate review – comments included in P/T review
• Supervisory Review(s) (indicate date for each review)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	08/29/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	X None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	X No carc
❖ ECAC/CAC report/memo of meeting	X None Included in P/T review, page n/a
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	X None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	X None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	X None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	Drug Substance 06/30/17 Drug Product 07/05/17 Quality Biopharm 07/20/17 Process 07/24/17 Facilities 09/05/17 Integrated QA Review 09/08/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	See Page 21 of Quality Assessment Drug Product review
☐ Review & FONSI (indicate date of review)	n/a
☐ Review & Environmental Impact Statement (indicate date of each review)	n/a
❖ Facilities Review/Inspection	
X Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	9/8/17 X Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

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/s/

MAUREEN P DILLON PARKER
09/15/2017

PeRC Meeting Minutes
August 9, 2017

PeRC Members Attending:

John Alexander
Gettie Audain
Meshaun Payne
Donna Snyder
Lily Mulugeta
Wiley Chambers
Greg Reaman
Jinging Ye
Raquel Tapia
Gilbert Burkhart
Dionna Greene
Hari Cheryl Sachs
Thomas Smith
Daiva Shetty
Ikram Elyam
Jackie Yancy
Rosemary Addy
Julia Pinto
Belinda Hayes
Barb Buch
Adrienne Hornatko-Munoz

Agenda

9:00	NON-RESPONSIVE				
9:20					
9:40					
9:55					
10:15					
10:35	NDA 209363	Solosec (secnidazole) Granules Deferral/Plan (with Agreed iPSP)	DAIP	Maureen Dillon Parker	Treatment of Bacterial Vaginosis
	NON-RESPONSIVE				
10:45					

NON-RESPONSIVE

Solosec (secnidazole) Granules Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Proposed Indication: Treatment of Bacterial Vaginosis
- This product triggers PREA as a new active ingredient and has a PDUFA date of September 17, 2017.
- The division stated the sponsor stated there was insufficient enrollment of adolescents in the Phase 3 trial, but did not provide explanation as to why there were difficulties in enrollment.
- The division stated the adult studies are completed and ready for approval.
- *PeRC Recommendations:*
 - o The PeRC concurred with granting the request for a full waiver in males and pre-menarchal adolescent females because studies are impossible or highly impractical and to the deferral in post-menarchal adolescent females ages 12 to less than 18 years of age for safety.
 - o The PeRC recommended that the sponsor should be able to submit their protocol and final submission within the next 6 months.

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/s/

MESHAUN L PAYNE
08/23/2017



NDA 209363

MID-CYCLE COMMUNICATION

Symbiomix Therapeutics, LLC
c/o Salamandra LLC
Attention: Kaylee White, RAC
Associate Director for Regulatory Affairs
4800 Hampden Lane, Suite 900
Bethesda, MD 20814-2998

Dear Ms. White:

Please refer to your New Drug Application (NDA) dated January 17, 2017, received January 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Secnidazole Granules, 2g.

We also refer to the teleconference between representatives of your firm and the FDA on May 2, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any question, call Maureen Dillon-Parker, Chief, Regulatory Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MID-CYCLE COMMUNICATION

Meeting Date and Time: May 2, 2017 at 11:30 AM

Application Number: NDA 209363

Product Name: Secnidazole Granules, 2g

Indication: Treatment of Bacterial Vaginosis

Applicant Name: Symbiomix Therapeutics, LLC

Meeting Chair: Shrimant Mishra, M.D.

Meeting Recorder: Maureen Dillon-Parker

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

Edward Cox, M.D., M.P.H.	Director
John J. Farley, M.D., M.P.H.	Deputy Director

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H.	Director
Joseph G. Toerner, M.D., M.P.H.	Deputy Director for Safety
Shrimant Mishra, M.D.	Cross Discipline Team Leader
Dmitri Iarikov, MD, Ph.D.	Deputy Director (Acting)
Mayurika Ghosh, M.D.	Clinical Reviewer
Avery Goodwin, Ph.D.	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
Abimbola O. Adebawale, Ph.D.	Associate Director of Labeling
Maureen P. Dillon-Parker	Chief, Project Management Staff

Division of Clinical Pharmacology IV (DCP IV)

Sonia Pahwa, Ph.D.	Clinical Pharmacology Reviewer
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Division of Biometrics IV (DBIV)

Cheryl Dixon, Ph.D.	Biostatistics Reviewer
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Office of Pharmaceutical Quality(OPQ)

Dorota M. Matecka, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Lead
Banu S. Zolnik, Ph.D.	Biopharmaceutical Quality Reviewer

Office of Surveillance and Epidemiology (OSE)

Janet Higgins	Regulatory Project Manager
Sevan Kolejian, Pharm.D.	DMEPA Reviewer
Adebola Ajao, Ph.D.	DEPI Reviewer

APPLICANT ATTENDEES - Symbiomix Therapeutics

Thomas Beck, MD	Chief Medical Officer, Head Research/Development
Helen Pentikis, PhD	Chief Scientific Officer
Nikki Adetoro	VP Clinical Operations and Project Management
David Palling, PhD	Head of Manufacturing
Robert Jacks	President and Chief Financial Officer
David Stern	Chief Executive Officer
Sharon Rowland	PhD, RAC, VP Regulatory Affairs
Kaylee White	RAC, Regulatory Consultant

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical

We have reviewed the label for Secnidal (secnidazole) approved in Brazil, submitted on April 13, 2017 and note that use of secnidazole is contraindicated during the first trimester of pregnancy. Secnidazole is classified as pregnancy risk D (first trimester) and C (second and third trimester) in that label. We also note similar contraindications for metronidazole. Your proposed draft label for secnidazole does not have this contraindication for use in pregnancy. We will be issuing an information request (IR) for you to provide information and rationale for this contraindication in the other labels.

We also note that the proposed draft label under lactation states

(b) (4)

. Please discuss the rationale for this statement; is this

(b) (4)

Also, we recommend discontinuation of breastfeeding until after the drug has cleared from plasma (approximately 4-5 times the half-life of the drug) which would be 6 days. We will be issuing an IR for you to discuss the rationale for (b) (4).

3.0 INFORMATION REQUESTS

Chemistry, Manufacturing, and Controls (CMC):

The response is pending for April 26, 2017, Information Request (IR).

Clinical

An IR will be issued as discussed regarding the contraindication issue. The division requested that the sponsor provide a timeframe for response.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late cycle meeting date is July 18, 2017, at 3:00 PM at FDA White Oak campus.

7.0 MEETING DISCUSSION POINTS

- The sponsor inquired if there were any known issues with manufacturing facilities. The sponsor was concerned about the timing of the inspections and whether a delay would impact the NDA action. The CMC team commented that the manufacturing facilities are under assessment as part of the NDA review and there were no comments or information requests at this time.
- With regard to carton and container labeling, the sponsor inquired as to when they may receive comments on the labels as there is a long lead time for preparing these. The labeling team commented that they plan to have comments to the sponsor within a few weeks.

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/s/

SUMATHI NAMBIAR
05/19/2017



NDA 209363

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Symbiomix Therapeutics, LLC
1101 E. 33rd Street, Suite E306
Baltimore, MD 21281

ATTENTION: Sharon Rowland, PhD, RAC
Vice President, Regulatory Affairs

Dear Dr. Rowland:

Please refer to your New Drug Application (NDA) dated and received January 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Secnidazole Oral Granules, 2 grams per packet.

We also refer to your correspondence, dated and received on January 30, 2017, requesting review of your proposed proprietary name, Solosec.

We have completed our review of the proposed proprietary name, Solosec and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 30, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Maureen Dillon Parker, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
04/14/2017



NDA 209363

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Symbiomix Therapeutics, LLC
Attention: Sharon Rowland, PhD, RAC
Vice President, Regulatory Affairs
1101 E. 33rd Street
Suite E306
Baltimore, MD 21218

Dear Dr. Rowland:

Please refer to your New Drug Application (NDA) dated January 17, 2017, received January 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Secnidazole Granules, 2g.

We also refer to your amendments dated February 06, 17, and 27, and March 02, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 17, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 16, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

In addition, the planned date for our internal mid-cycle review meeting is April 19, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following issues and have the following comments and requests for information:

1. According to 21 CFR 201.57(c)(13)(i)(B), you should include a statement such as ‘Secnidazole exposure-response relationships and the time course of pharmacodynamic response is unknown’ in subsection 12.2 of the label.
2. Provide a study report to support the statement ‘(b) (4)’ in subsection 12.3 of the label.
3. Section 5, WARNINGS AND PRECAUTIONS, is listed in FULL PRESCRIBING INFORMATION. Please revise the labeling to also include it in the ‘FPI: Contents’ and in ‘HIGHLIGHTS’.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 17, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Maureen Dillon-Parker, Chief/Regulatory Project Manager, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
03/28/2017



NDA 209363

PRIORITY REVIEW DESIGNATION

Symbiomix Therapeutics, LLC
Attention: Sharon Rowland, PhD, RAC
Vice President, Regulatory Affairs
1101 East 33rd Street
Suite E306
Baltimore, MD 21218

Dear Dr. Rowland:

Please refer to your New Drug Application (NDA) dated January 17, 2017, received January 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Secnidazole Granules, 2g.

We also refer to your submission(s) dated February 06, 17, and 27, and March 02, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 17, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 16, 2017.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before April 1, 2017.

If you have any questions, call Maureen Dillon-Parker, Chief, Regulatory Project Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
03/13/2017



NDA 209363

NDA ACKNOWLEDGMENT

Symbiomix Therapeutics, LLC
Attention: Sharon Rowland, PhD, RAC
Vice President, Regulatory Affairs
1101 E. 33rd Street, Suite E306
Baltimore, MD 21218

Dear Dr. Rowland:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Secnidazole Granules, 2 g

Date of Application: January 17, 2017

Date of Receipt: January 17, 2017

Our Reference Number: NDA 209363

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 18, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 209363** submitted on January 17, 2017, and that it contains the **FDA Form 3674** that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
03/08/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117,811

MEETING MINUTES

Symbiomix Therapeutics, LLC
Attention: Caryn Peterson
Regulatory Consultant
105 Lock Street, Suite 409
Newark, NJ 07102

Dear Ms. Peterson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SYM-1219 (secnidazole), (b) (4) 2 gram, granules.

We also refer to the Type B End-of-Phase 2 meeting held between representatives of your firm and the FDA on March 18, 2015. The purpose of the meeting was to discuss the development program for SYM-1219 for the treatment of bacterial vaginosis (BV).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2
Meeting Date and Time: March 18, 2015/11:00 am -12:00 pm
Meeting Location: 10903 New Hampshire Avenue
White Oak, Building 22, Room 1421
Silver Spring, MD 20993
Application Number: IND 117,811
Product Name: SYM-1219 (secnidazole) (b) (4) 2 gram Granules
Indication: Treatment of bacterial vaginosis (BV)
Sponsor Name: Symbiomix Therapeutics, LLC
Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Maureen Dillon-Parker

FDA ATTENDEES - Division of Anti-Infective Products (Division)

Maureen Dillon-Parker, Chief, Project Management Staff
Cheryl Dixon, PhD, Statistical Reviewer
Salaheldin Hamed, PhD, Biopharmaceutical Reviewer
Karen Higgins, ScD, Statistical Team Leader
Dmitri Iarikov, MD, PhD, Acting Clinical Team Leader
Seong Jang, PhD, Clinical Pharmacology Reviewer
Katherine Laessig, MD, Deputy Director
Owen McMaster, PhD, Non-clinical Reviewer
Shrimant Mishra, MD, Clinical Reviewer
Sumathi Nambiar, MD, MPH, Director
Wendelyn Schmidt, PhD, Non-clinical Team Leader
Kerry Snow, MS, Clinical Microbiology Team Leader
Joseph Toerner, MD, MPH, Acting Deputy Director for Safety
ChunChun Zhang, PhD, Chemistry, Manufacturing and Controls Reviewer

SPONSOR ATTENDEES – Symbiomix Therapeutics, LLC

Zainab (Nikki) Adetoro, Senior Director, Clinical Operations and Project Management
Joseph Amprey, M.D., Ph.D., Chief Business Officer
Thomas Beck, MD, Clinical Development Advisor
Carol J. Braun, MD, Chief Medical Officer
Robert Casper, Sr. Director Clinical Operations
(b) (4) Consultant Biostatistician
Robert Jacks, President/Chief Financial Officer
(b) (4) Clinical Consultant*
David Palling, PhD, Chief Manufacturing Officer
Ruth Penn, MD, Senior Director of Clinical Research and Development
Helen Pentikis, PhD, Chief Scientific Officer
Caryn Peterson, Regulatory Consultant
Sharon Rowland, Ph.D., Regulatory

(b) (4) ., Microbiology Consultant*
*by phone

BACKGROUND

This product is an oral antimicrobial drug in the 5-nitroimidazole class and is being developed for the treatment of bacterial vaginosis (BV). The Sponsor met with the agency on two prior occasions; a pre-IND meeting on August 20, 2013, and a meeting to discuss the clinical pharmacology program on January 21, 2015. Additionally, this product, for this indication, received Qualified Infectious Disease Product (QIDP) designation on November 18, 2014.

The Division provided the Sponsor with preliminary comments to the questions outlined in their February 16, 2015 meeting package via email on March 13, 2015 in preparation for this meeting. The Sponsor provided, on March 17, 2015, follow-up comments to Questions #2 and #3, and a request to further discuss Questions #14, #15, #17, and #12. A complete copy of the documentation is attached.

DISCUSSION

Timing of Test of Cure Visit

- The Sponsor requested clarification on the Division's request to assess clinical and microbiological cure at both Days 14 and 28. Specifically, the Sponsor requested the rationale for using Day 14 as the primary endpoint assessment and Test-of-Cure visit, and clarification on why two assessments would be necessary.
- The Division explained that currently the bacterial vaginosis (BV) guidance is being revised and the time point for measuring efficacy is under discussion. Since secnidazole is a single-dose product its efficacy assessment on Day 14 may be more appropriate as compared to a later assessment. However, optimal timing for efficacy assessment in BV is not certain at this point and it would be important and informative to compare efficacy results obtained at earlier and later time points. A later time point would be important to evaluate for relapses of BV. The Division suggested that the visits be separated by approximately 2 weeks.
- The Sponsor stated that there is always the issue of compliance, should a patient not return for the second visit. The Division agreed that this might be an issue. The Sponsor also noted that the window for visits allows for menstruation to occur and thus it is possible that a subject's two visits could become very close together.
- The Sponsor asked if they could have an earlier time point between Days 7-14, and a later time point between Days 21-30 noting that the Phase 2 study has the later visit as the primary endpoint. This would alleviate the need for a phone call at Day 8-10.
- The Division re-iterated that it is important to have a 2-week interval between an earlier and later assessment and that both assessments should include clinical and microbiological evaluations.
- The Sponsor indicated that they would consider the earlier time point as the primary endpoint but need some time to discuss it further.
- The Division agreed to provide the Sponsor with publications that discuss appropriate endpoints for BV and the Sponsor agreed to get back with the Division regarding the proposal of 2 visits 2-weeks apart.

Nugent Score

- With regard to increasing the baseline Nugent score from ≥ 4 to ≥ 7 , the Division commented that a new guidance on BV that has been under development suggests a baseline Nugent score of ≥ 7 . It was also noted that the majority of patients in the secnidazole Phase 2 study had a score of ≥ 7 and that the treatment effect in patients with a Nugent score of 4 to 6 was less prominent. The Sponsor stated that they would prefer to keep the number at ≥ 4 but they will consider increasing it to ≥ 7 .

Safety Database

- Regarding the Safety Study [SYM-1219-350], the Sponsor commented that they are not planning to assess Nugent score at the end-of-treatment because this is a safety study.
- In the safety study, the patients will not be seen at the earlier time point.
- It was agreed that a safety database of approximately 600+ patients is acceptable.

Exclusion of Pregnant Subjects

- In response to the Division question on the rationale for excluding pregnant subjects, the Sponsor explained that they would like to exclude pregnant subjects until the repro-tox studies have been completed. The Sponsor stated that the in-life portion of the Segment III study will not be completed prior to the anticipated start of the Phase 3 trial.
- The Division asked whether it would be possible to enroll pregnant subjects in the safety study. The Division commented that one of the reasons for granting QIDP designation for secnidazole was the correlation between BV and pre-term births and that it would be helpful to have this information from a clinical standpoint.
- The Sponsor responded that a Phase 3 safety study will also likely be completed prior to the completion of repro-tox studies. The safety trial will use the same sites as the pivotal trial and start enrollment immediately after enrollment for the pivotal trial is completed.
- The Sponsor stated that they acknowledge the importance of collecting safety data in pregnant patients (b) (4).

Screening for Sexually Transmitted Diseases (STDs) at Baseline

- The Sponsor confirmed that all subjects will be screened at baseline for STDs. Subjects with herpes will not be enrolled.

General Comments

- The Sponsor continues to investigate the dissolution of secnidazole in yogurt and once they have data they will discuss this issue again with the Division.
- The Division reminded the Sponsor that if they want to include yogurt in the labeling, additional bioavailability (BA) studies are necessary. The Division stated that the BA study conducted to evaluate the effect of a high fat food admixed with applesauce does not address the issue for yogurt. If the Sponsor conducts dissolution testing with low fat and regular yogurt and if no

changes in dissolution are observed, then the Sponsor may not have to conduct any further BA studies with yogurt.

- With regard to Question #2, there is agreement with the approach due to the SUPAC guidance. Whether they meet the general dissolution guidelines needs to be confirmed.
- With regard to Question #3, the dosage terminology for loose granules in (b) (4) will require review by the CMC policy group. The Division will send an inquiry to the group and follow-up with the Sponsor once more information becomes available.
- The Sponsor commented that they will also be providing written responses to Questions #2 and #3.
- The Sponsor was reminded that stability data will be needed on three batches and that the (b) (4) should have no compaction, they should remain as loose granules so that they can be poured onto a specified food type.
- The Sponsor was reminded that their initial Pediatric Study Plan (iPSP) will need to be submitted within 60-days of the meeting.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Evaluate increasing the baseline Nugent score to ≥ 7	Sponsor	Respond when decision is made.
Provide literature on Nugent score to Sponsor.	Division	As soon as possible
Sponsor agreed to inform the Division of the decision regarding 2 visits, 2-weeks apart.	Sponsor	As soon as available
Written responses to Questions #2 and #3	Sponsor	As soon as available.
Provide additional clarification on terminology of loose granules in (b) (4)	Division/CMC	As soon as CMC has additional information.
Submit iPSP	Sponsor	May 17, 2015
Issue Meeting Minutes	Division	April 17, 2015

ATTACHMENTS

- Division Preliminary comments with Sponsor comments to preliminary comments.
- Sponsor slides (2) presented at meeting

Scheduled for March 18, 2015

8.1 CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

Symbiomix has developed a granule formulation of SYM-1219 which includes talc. This formulation is intended as a single dose therapy. The amount of talc to be included in the final marketed formulation is (b) (4) mg per dose.

Although the amount of talc in the SYM-1219 (b) (4) of which Syngene is aware, it is within the limits of talc used in food products. A review of the safety and toxicology information on talc indicates that this (b) (4) talc in the SYM-1219 drug product intended as a single-use does not pose any safety concerns in humans. ***Does the FDA agree?***

Symbiomix has developed a 2 gram, granule formulation of SYM-1219 which requires administration of approximately 4.76 g of material to deliver the 2 g dose. The final formulation contains (b) (4) mg of talc per dose. Talc is used (b) (4)

The amount of talc that we propose in our formulation (b) (4) currently available formulations based on a search of the FDA website that reports the levels of inactive ingredients, including talc, in approved drug products. Values for the maximum potency per dose of talc range from less than 1 mg (soft gelatin capsules) to 220.4 mg (capsules) (<http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm>). The level cited for enteric coated granules for oral administration, (b) (4) is 215.2 mg per dose.

Following a thorough review of the literature and regulatory websites, we believe that the level of talc used in our formulation is safe for human use. Talc is classified as GRAS by FDA <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm261481.htm>.

Quoting from the SCOGS Opinion, “A major food use of talc is in the coating of rice.”

Assuming package label statements are ignored and coated rice is not washed prior to cooking and no other losses occur, maximum per capita intake of talc from this source appears to be 0.5g per day”. Talc is also used in the coating of chewing gum sticks, although the quantity used is not disclosed publicly (Google: key words: “talc” and “chewing gum”: Dec 4, 2014). Talc meeting the specification in the USP may be safely used in amounts consistent with good manufacturing practice to color drugs, generally (21CFR73.1550).

A review of the safety of talc has recently been published by a Cosmetic Ingredient Review expert panel (Bergfeld and Belsito, Expert Report, 2013). Although there are limited studies evaluating the safety of talc via the oral route of administration, several key study results demonstrate the safety of talc. These include the following:

- Single dose toxicity studies in rats have provided oral LD50 values of 920 mg/kg (one study) or >5000 mg/kg (two studies).
- In repeat dose studies, no toxicologically significant results were noted in a 5-month study in which rats were fed a diet containing 100 mg/day of talc.
- Orally administered talc was not a developmental toxicant in mice, rats, hamsters or rabbits.
- ADME studies in several rodent species show that talc is minimally absorbed from the GI tract (less than 2% radioactivity found outside the GI tract and feces).
- Talc was not genotoxic in several in-vitro and in-vivo assays.
- There were no remarkable results found in studies examining the cellular effects of talc, such as cytotoxicity, cell viability or induction of apoptosis.

Therefore, based on the aforementioned information, we conclude that the (b) (4) mg of talc in our single dose, 2 gram formulation SYM-1219 will not be a safety concern in humans.

DIVISION RESPONSE- Question 1: The Division agrees.

Question 2

Symbiomix has switched manufacturing sites during clinical development of SYM-1219. The

early formulations (Phase 1 and Phase 2 pivotal registration trial) for SYM-1219 were manufactured at (b) (4) and the Phase 3 and commercial batches are being manufactured at Catalent Pharma Solutions (Somerset, NJ). Due to the need for some process improvements, two clinical trial product batches, with (b) (4), have been manufactured at Catalent. The first Catalent batch (Batch 14JM-342) was compared to the (b) (4) batch (Batch 21301.002) in a clinical study and the two formulations were found to be bioequivalent. The second Catalent batch (Batch 15JM-024) that will be used in the pivotal Phase 3 trial contains (b) (4) compared to Batch 14JM-342 that represents a change of (b) (4) mg ((b) (4) % relative to the overall weight of the unit dosage form). As this change is considered minor by SUPAC Guidelines, and assuming there is no change in the dissolution between Catalent batches 14JM-342 and 15JM-024 (data pending). Symbiomix believes that an additional bioequivalence study to compare the two Catalent batches will not be required. **Does the FDA agree?**

Company's Position/Question 2

During development of the formulation, Symbiomix has moved manufacturing from (b) (4) to Catalent Pharma Solutions (Somerset, NJ). The (b) (4) product (batch 21301.002), the drug product used in the Phase 2 clinical study (SYM-1219-201), and the first Catalent clinical trial product (batch 14JM-342) contained (b) (4), respectively; see Table 1). Because of the manufacturing site change, a clinical bioequivalence study (Study SYM-1219-102) was conducted to compare the (b) (4) batch to the Catalent batch (14JM-342).

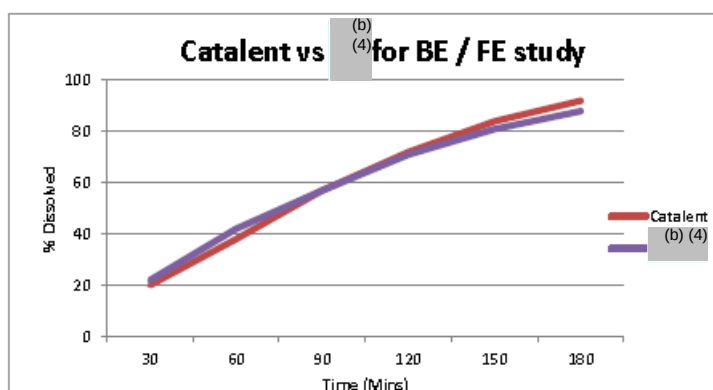
The clinical bioequivalence study (Study SYM-1219-102) was conducted to compare the (b) (4) and Catalent (Batch 14JM-342) formulations. This study had two objectives which included comparison of the (b) (4) and Catalent formulations under fasted conditions and comparison of the Catalent formulation under fed and fasted conditions. The pharmacokinetic analysis of the (b) (4) and Catalent 14JM-342 formulations (preliminary data analysis) is presented within this document in the Clinical Pharmacology Section 9.3.1; the statistical analysis results (preliminary data) are presented in Table 1. The results of the clinical study demonstrate that the (b) (4) and Catalent formulations are bioequivalent based on pharmacokinetic analysis. These clinical data are consistent with the fact that the dissolution profiles of the (b) (4) and Catalent 14JM-342 batches were equivalent ($f_2 = 77$; see Figure 2 below).

Table 1 Statistical analysis results for the pharmacokinetic comparison of the (b) (4) and

Catalent (14JM-342) formulations (Study SYM-1219-102)

Parameter	Mean ratio	90% Confidence Interval
Cmax	95.15	(92.082, 98.322)
AUC0-t	93.52	(89.385, 97.844)
AUC0-inf	92.94	(88.783, 97.290)

Figure 2 Dissolution profiles for (b) (4) and Catalent formulations



Following the conduct of the clinical bioequivalence study mentioned above, process improvements were implemented at Catalent and a new batch (Catalent batch 15JM-024) was prepared that will be used in the Phase 3 clinical program. Compared to the first Catalent product used in the clinical bioequivalence study (Batch 14JM-342), the Catalent Phase 3 product (Catalent batch 15JM-024) contains an (b) (4) that represents a change of (b) (4), relative to the overall weight of the unit dosage form. In accordance with SUPAC guidelines, this (b) (4) in Batch 15JM-024 is considered minor.

We, therefore, believe that dissolution data between the two Catalent batches will be sufficient to demonstrate equivalence such that a clinical bioequivalence study will not be required. (Dissolution data comparing the two Catalent batches pending.)

As previously described, Symbiomix has performed several process improvements to the SYM- 1219 formulation which have resulted in a different amount Symbiomix has evaluated the SYM-1219 formulations via a dissolution approach and via a clinical bioequivalency study. The Phase 1 and Phase 2 formulations and the Catalent Batch 14JM-342 are bioequivalent and also equivalent based on the f2 comparability test (Figure 2). The (b) (4) in the Phase 3 Catalent formulation (Batch 15JM-024) represents a minor change as described in the SUPAC guidelines. Therefore, we believe that a clinical

bioequivalence study will not be required to link the Catalent Phase 3 material (Batch 15JM-024) to the Catalent batch used in the clinical bioequivalent study (Batch 14JM-342) and the (b) (4) formulation (Batch 21301.002) used in Study SYM-1219-201 (Study SYM-1219-201 is intended to be a pivotal registration study).

A summary of the (b) (4) in the Phase 3 formulation as compared to the Phase 1 and 2 formulation.

A summary of the (b) (4) in the relevant clinical batches is provided in Table 2 below.

Table 2 (b) (4) in SYM-1219 clinical batches

Batch #	Clinical Use	(b) (4)
(b) (4) 21301.002	Phase 1, 2	
Catalent: 14JM-342	BE	
Catalent: 15JM-024	Phase 3	

DIVISION RESPONSE – Question 2: Based on the provided information, FDA agrees with your approach. However, a final decision cannot be made at this time, because the supportive information is still pending.

SYMBIOMIX RESPONSE: We have completed the dissolution studies of the two Catalent batches (14JM-342 and 15JM-024) and the data show comparability based on the f2 value of 70. Please see the attached graph of the data in Attachment 1.

Question 3

Symbiomix proposes that the drug dosage form term to identify SYM-1219 Final Drug Product be “Granules” in accordance with CDER specifications. *Does the Agency agree?*

Company’s Position/Question 3

SYM-1219 granules have (b) (4)

(b) (4). Several existing FDA and USP dosage form descriptions have been considered; we believe that none of the definitions adequately describe our product. (b) (4)

(b) (4) In the absence of additional modifying terms for granules, Symbiomix believes the simple term, “granules”, is the best

descriptor for the SYM-1219 product.

DIVISION RESPONSE- Question 3: There is a lack of clarity regarding several important points to consider in order to determine if the term “granules” applies with adequate certainty. On page 6 of the briefing document you describe the drug product as follows: “SYM-1219 is provided as granules to be sprinkled on soft food (e.g., applesauce, pudding, yogurt) for oral administration as a single 2 g dose”. On page 8 of the briefing document, you indicate that this 2 g dose requires approximately 4.76 g of formulated granule material (including of note, (b) (4) per dose). If the so-called granules are encapsulated or compressed so as to bring a certain mass of granules together into a single unit, the appropriate dosage form term could be capsule or tablet.

SYMBIOMIX RESPONSE: The batch formula for SYM-1219 granules is provided in Table 6 (pg. 31 of the briefing document). As shown in Table 6, the final product is a granule formulation of a particle size range of (b) (4) µm, what we believe to be consistent with CDER dosage form terminology of “a small particle or grain”. Within the (b) (4) they are individual granules, they are neither encapsulated nor compressed, so as to bring to a single unit. (b) (4)
(b) (4).

Further, in several places in the briefing document you refer to a (b) (4) as containing the granules. Is this (b) (4) the to-be-marketed presentation? If so, then the (b) (4) (material, size, drawing or picture, etc.) and the instruction for its use need to be defined better and clarified before we can determine if “granules” is the appropriate dosage form terminology to use in this case. If the (b) (4) is not the to-be-marketed formulation, then a complete description of what is intended should be provided.

SYMBIOMIX RESPONSE: SYM-1219 will be packaged and marketed as granules in a (b) (4). The instructions for use are attached. A 2 g dose of secnidazole formulated as SYM-1219 requires administration of (b) (4) g of granules that contain drug and excipients including a (b) (4). The (b) (4) measures 2.25” x 2.75”. A picture of a (b) (4) is below.

8.2 MICROBIOLOGY

Question 4

The FDA Guidance document for antibacterial drug products (FDA Guidance (Draft). Microbiologic Data for Systemic Antibacterial Drug Products - Development, Analysis and Presentation, 2009) specifies that for any organism that will be included in the product labeling, the Sponsor should submit susceptibility data for 100 isolates per species that are less than 36 months old at the time of NDA submission. This requirement can be readily met for most organisms and indications, however, it can be difficult to source this number of recent BV clinical isolates of *Mobiluncus* spp. The number of sites culturing BV specimens, especially for *Mobiluncus*, is quite limited and the relative availability of isolates meeting these two requirements is generally dependent upon the recent conduct of clinical research at sites that both culture vaginal specimens for *Mobiluncus* and archive isolates. Therefore, given the anticipated difficulty in sourcing isolates of *Mobiluncus* spp. the Sponsor proposes the testing of at least 60 isolates, rather than 100 isolates. **Does the FDA agree?**

Company's Position/Question 4

In the specific situation of *Mobiluncus* spp. in BV, the Sponsor is skeptical that it will be able to source 100 clinical isolates that are less than 36 months old for a secnidazole susceptibility study.

However, given the previous profiling of metronidazole activity against *Mobiluncus* spp. and the structural relationship and similarity of the mechanism of action and activity profile of these two agents, we believe that a study of lesser scope will be adequate to define the general activity of secnidazole against this organism. Therefore, we propose the evaluation of secnidazole against at least 60 isolates that meet the specified criteria.

DIVISION RESPONSE – Question 4: The Division agrees

Question 5

Similar to the situation described in Question 4 above, we also anticipate difficulty in sourcing 100 vaginal isolates each of *G. vaginalis*, *B. fragilis* and *Prevotella* spp. for susceptibility studies that will be less than 36 months old at the time of the NDA submission. Therefore, we propose a modified study design whereby at least 75 of 100 isolates are less than 36 months old, and no isolate is greater than 60 months old. **Does the FDA agree?**

Company's Position/Question 5

The Sponsor recognizes the potential difficulty associated with sourcing 100 vaginal clinical isolates each of *G. vaginalis*, *B. fragilis* and *Prevotella* spp. for susceptibility studies with the requirement of all being less than 36 months old at the time of the NDA submission. The Sponsor recognizes the objective of establishing activity against recent clinical isolates and will make a good faith effort to meet the requirements. However, it is possible that a sufficient number of age-qualified, vaginal isolates may not be available despite our best efforts. Therefore, given the similarity of the activity of metronidazole and secnidazole, we propose the allowance of at least 25 isolates in each test group (of 100) that are greater than 36 months old but less than 60 months old. The Sponsor feels that even with this modification, the susceptibility data for secnidazole and the historical data for metronidazole will be sufficient to characterize the activity of secnidazole against these species.

DIVISION RESPONSE – Question 5: The Division agrees.

Question 6

Secnidazole, a 5-nitroimidazole, is a structural homolog of metronidazole that has enhanced pharmacokinetic properties relative to metronidazole. Mechanistic studies have been extensive but have typically employed metronidazole as the class-representative agent. Secnidazole specific mechanism-of-action and–resistance studies have not been conducted. However, since the mechanism-of-action and–resistance of secnidazole are assumed to be the same as metronidazole, no other secnidazole-specific studies are planned for the NDA submission. **Does the FDA agree?**

Company's Position/Question 6

The modest change in secnidazole structure relative to metronidazole may be expected to modify various physiochemical and biochemical characteristics, such as pharmacokinetic properties (BrJ Vener Dis (editorial). 1978 Apr;54(2):69-71). This structural change does not affect the essential antibacterial (and antiprotozoal) action which is a function of the nitro

group associated with the imidazole ring, a structural feature present in both secnidazole and metronidazole. The agents demonstrate a similar activity profile and isolates resistant to metronidazole have elevated MIC values for secnidazole. Therefore, the Sponsor assumes that the mechanism-of-action and –resistance of secnidazole is the same as metronidazole and no other secnidazole-specific studies are required.

DIVISION RESPONSE – Question 6: The Division agrees.

Question 7

Per the FDA Guidance (FDA Guidance (Draft). Microbiologic Data for Systemic Antibacterial Drug Products - Development, Analysis and Presentation, 2009), the Sponsor will conduct a Tier II multi-center quality control study to define quality control ranges for reference isolates employed in the reference anaerobe agar dilution method. In addition, since there exists no reference method for the testing of *G. vaginalis*, the Sponsor will conduct a Tier I quality control study for a standard strain of *G. vaginalis* to define a quality control range for purposes of quality-controlling the susceptibility studies with this organism. **Does the FDA agree?**

Company's Position/Question 7

The fully-powered Tier II study will meet CLSI requirements for definition of anaerobe quality control ranges. The Tier I study of *G. vaginalis* will provide a means to quality-control MIC assays of *G. vaginalis*, an organism for which a reference method does not exist.

DIVISION RESPONSE: Question 7: The Division agrees. Labeling for this product will not include susceptibility testing interpretive criteria. Studies typically associated with these criteria will not be required in this submission.

Question 8

Since the current development program targets only the BV indication, the Sponsor does not intend to conduct studies of intracellular concentration, fixed combinations, post-antibiotic effect, post-antibiotic leukocyte effect, sub-MIC effects, effects on endotoxin, effects on virulence factors, interactions with the host immune system, etc. and activity of metabolites.

Does the FDA agree?

Company's Position/Question 8

The Sponsor's position is that due to the unknown relevance of in vitro study outcome to BV, studies of intracellular concentration, fixed combinations, post-antibiotic effect, post-antibiotic leukocyte effect, sub-MIC effects, effects on endotoxin, effects on virulence factors,

interactions with the host immune system, etc. are not required for the NDA. Furthermore, the metabolites of secnidazole exist at less than 1% of the total dose. Given the small amounts of metabolites present, the Sponsor does not feel that it is necessary to synthesize these molecules and assess their in vitro antibacterial activity as they would not be expected to significantly impact the antibacterial effect.

DIVISION RESPONSE: Question 8: The Division agrees

Question 9

As is the standard practice in clinical trials for patients with BV, the Sponsor has no plans to culture vaginal discharge and perform susceptibility testing with vaginal discharge isolates from the secnidazole Phase 3 trials. **Does the FDA agree?**

Company's Position/Question 9

The Sponsor seeks confirmation that this plan will be acceptable to FDA.

DIVISION RESPONSE – Question 9: The Division agrees: Vaginal swabs should be sent to a reference laboratory to be Gram stained. Specimens should be evaluated based on the standardized Nugent scoring system.

Question 10

Symbiomix believes that the data from the proposed microbiology program will be sufficient to support an NDA submission for secnidazole as a single dose therapy to treat women with BV. **Does the FDA agree?**

Company's Position/Question 10

Table 3 summarizes the studies conducted or ongoing for the microbiology program for secnidazole, organized by topic for the microbiology section of the NDA. The table includes relevant supporting literature information. The combined data from the literature and Symbiomix-sponsored studies will provide the basis for the microbiology information in the product labeling.

DIVISION RESPONSE – Question 10: The Division agrees.

Table 3 The Microbiology Studies Conducted, Ongoing or Planned to Generate Data To Be Submitted to the Microbiology Section of the SYM-1219 NDA for the Treatment of Women with Bacterial Vaginosis

Study Title	Reference or Report No	Objectives	Status
Antibacterial Spectrum and Potency			
<i>In vitro</i> study of secnidazole, the S and R enantiomers, and metronidazole against anaerobic isolates from bacterial vaginosis specimens and other clinical sources	SYM1219 MICRORPT4003	To assess the <i>in vitro</i> activity of secnidazole against 120 strains of anaerobic bacteria predominantly from patients with BV or other pelvic infections	Completed
Study to investigate the activity of LifeQual's racemate secnidazole and enantiomers (Peak 1 & Peak 2) against clinical isolates of anaerobic bacteria	SYM1219 MICRORPT4001	To assess the <i>in vitro</i> activity of secnidazole against clinical isolates of <i>B. fragilis</i> , <i>G. vaginalis</i> , and <i>C. difficile</i>	Completed
Secnidazole: antibacterial activity against strict anaerobes	Dubreuil L., 2005	To assess the <i>in vitro</i> activity of secnidazole against 372 clinical isolates of strict anaerobes	Published
<i>In vitro</i> activity of secnidazole against <i>Atopobium vaginae</i> , an anaerobic pathogen involved in bacterial vaginosis	DeBacker E., 2009	To assess the <i>in vitro</i> activity of secnidazole against 16 strains isolates of <i>A. vaginae</i>	Published
<i>In vitro</i> activity of secnidazole and metronidazole against vaginal isolates of <i>Lactobacillus gasseri</i> , <i>L. criEptus</i> , <i>L. jensenii</i> , and <i>L. iners</i>	SYM1219 MICRORPT4005	To assess the <i>in vitro</i> activity of secnidazole against 40 isolates of lactobacilli from patients enrolled in clinical studies of BV	Completed
Secnidazole vs <i>Candida albicans</i> and non- <i>albicans</i> Species	SYM1219 MICRORPT4004	To assess the <i>in vitro</i> activity of secnidazole against 10 isolates each of <i>C. albicans</i> and non- <i>albicans</i> species	Completed
<i>In vitro</i> activity of secnidazole against <i>Mobiluncus</i> Species		To assess the <i>in vitro</i> activity of secnidazole against > 60 clinical isolates of <i>Mobiluncus</i> spp	Proposed
<i>In vitro</i> activity of secnidazole against <i>Gardnerella vaginae</i>		To assess the <i>in vitro</i> activity of secnidazole against 100 clinical	Proposed

Study Title	Reference or Report No.	Objectives	Status
Mechanism(s) of Action			
<i>In vitro</i> activity of secnidazole against <i>Bacteroides fragilis</i> and <i>Prevotella</i> spp		isolates of <i>G. vaginalis</i> To assess the <i>in vitro</i> activity of secnidazole against 100 clinical isolates each of <i>B. fragilis</i> and <i>Prevotella</i> spp	Proposed
<i>In vitro</i> activity of secnidazole against hydrogen peroxide-producing and non-producing <i>Lactobacillus</i> spp		To assess the <i>in vitro</i> activity of secnidazole against 50 clinical isolates each of hydrogen peroxide-producing and non-producing <i>Lactobacillus</i> spp	Proposed
Mechanism(s) of Resistance			
Nitroimidazole drugs-actions and resistance mechanisms I Mechanisms of action	Eckwards DI, 1993	Review of 5-nitroimidazole mechanisms of action	Published
Chromosomal breakage in the <i>B. fragilis</i> Group induced by metronidazole treatment	Diniz CG, 2000	To examine DNA integrity and metronidazole levels in both metronidazole-susceptible and -resistant isolates of <i>B. distasonis</i>	Published
Structural basis of 5-nitroimidazole antibiotic resistance: the crystal structure of NimA from <i>Deinococcus radiodurans</i>	Leiros HKS, 2004	Reaction mechanism examined in which the 2-electron reduction of 5-nitroimidazole prevents accumulation of the toxic nitro radical suggesting that Nim proteins form a new class of reductases that confer resistance against 5-nitroimidazoles	Published
Mechanism(s) of Resistance			
Genetics of 5-nitroimidazole resistance in <i>Bacteroides</i> Species	Reysset G, 1996	Identification of nim genes as a resistance mechanism in <i>Bacteroides</i> species	Published
Structural basis of 5-nitroimidazole antibiotic resistance: the crystal structure of NimA from <i>Deinococcus radiodurans</i>	Leiros HKS, 2004	Co-crystallization of <i>D. radiodurans</i> nimA polypeptide with metronidazole and pyruvate results in a proposed mechanism in which a 2-electron	Published

Study Title	Reference or Report No.	Objectives	Status
		reduction of metronidazole leads to the formation of non-toxic compounds	
Metronidazole is still the drug of choice for treatment of anaerobic infections	Lofmark S, 2010	Review other proposed mechanisms of resistance to 5-nitroimidazoles including drug efflux and decreased activity of ferredoxin	Published
<i>Susceptibility Test Methods and Detection of Resistant Organisms</i>			
Impact of non-standard test parameters on agar dilution susceptibility testing of secnidazole against anaerobic CLSI ATCC quality control organisms	SYM1219.MICRO.012.RPT4006	To assess the effects of pH, medium lot, etc. on secnidazole results in the reference agar dilution MIC assay	Completed
Tier I MIC quality control study for secnidazole and <i>Gardnerella vaginalis</i>		To define a Tier I quality control range for a standard strain of <i>G. vaginalis</i> that can be used to quality control multi-isolate MIC assays since standard methods do not exist	Proposed
Tier II, multi-center, quality control study of secnidazole and anaerobic bacteria using the reference agar dilution method		To define MIC quality control ranges for secnidazole and ATCC reference strains of anaerobic bacteria	Proposed
<i>Intracellular Antimicrobial Concentration Assessment</i>			
No studies will be included			
<i>Antibacterial Interactions and Fixed Combination Studies</i>			
No studies will be included			
<i>Other Effects of Antibacterial Drug Product</i>			
No studies will be included			
<i>Activity in Animal Models of Human Disease</i>			
No studies will be included			
<i>In Vitro Studies Conducted During the Phase II and Phase III Clinical Trials</i>			
Vaginal specimens will not be cultured for BV pathogens and therefore no data on clinical trial isolates will be presented			

Study Title	Reference or Report No.	Objectives	Status
<i>Proposed Interpretive Breakpoints</i>			
The Sponsor will not propose interpretive breakpoints for secnidazole in BV			
<i>Organisms to Include in Labeling</i>			
On the basis of the susceptibility data submitted in the NDA, Symbiomix will request the listing of the following pathogens in Section 12.4 of the product labeling as being associated with bacterial vaginosis: <i>Gardnerella vaginalis</i> <i>Mobiluncus</i> spp. <i>Bacteroides</i> spp. <i>Prevotella</i> spp. Symbiomix will also request inclusion of a statement regarding (b) (4)			

8.3 CLINICAL PHARMACOLOGY

Question 11

Symbiomix originally requested that this clinical pharmacology question be addressed at the Clinical Pharmacology Meeting that was held on January 21, 2015. At that meeting we agreed with the Division that the question below would be addressed at this EOP2 meeting. As requested by the Division, we verified that all of the in vitro metabolism reports have been submitted for review.

Symbiomix has conducted in vitro CYP metabolism studies to evaluate the inhibition, metabolism, and induction properties of secnidazole. In addition, the effect of secnidazole on transporters has been evaluated. These data have shown that secnidazole is a weak inhibitor of CYP3A4 and CYP2C19. In addition, at concentrations approximately 10-fold greater than clinical concentrations from a 2 gram dose, secnidazole appears to be an inducer of CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, and CYP2C19. Secnidazole does not have an impact on any of the transporters tested. Since secnidazole is planned to be administered as a single dose regimen for the treatment of BV, Symbiomix believes the in vitro characterization of secnidazole is sufficient and therefore, no in vivo studies are needed. **Does the FDA agree?**

Company's Position/Question 11

The single dose regimen for SYM-1219 2 g provides mean maximum concentrations of secnidazole of approximately 45 µg/mL that are achieved by 4 hours. At 96 hours post dose, secnidazole concentrations have declined to approximately 1.4 µg/mL. The formulation characteristics for SYM-1219 do not provide prolonged and sustained concentrations of secnidazole and concentrations decline to low levels within a few days of the single dose administration. These data are consistent with the pharmacokinetic information that is published in the literature for secnidazole.

In vitro transporter studies showed no effect of secnidazole. The in vitro metabolism data show minimal impact of secnidazole CYP metabolizing enzymes. In CYP inhibition experiments, secnidazole was a weak inhibitor of CYP3A4 and CYP2C19; the calculated R values did not exceed the 1.1 cutoff value indicating that clinical drug interaction studies are not needed.

The induction experiments demonstrated that some CYPs (CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, and CYP2C19) could be induced by secnidazole at very high concentrations, greater than 10-fold the observed maximum clinical concentrations. The relative induction score (RIS) experiments produced equivocal data; mRNA levels were increased at high concentrations of secnidazole (>5000 µM), whereas the RIS and R3 calculations predicted induction by secnidazole at lower levels (14 µM to 85 µM). Although the in vitro data show some propensity towards induction with secnidazole, clinical induction studies are conducted with repeated administration of the inducing drug and this experimental design is not clinically meaningful for SYM-1219 due to the single dose regimen.

In conclusion, based on the results of the in vitro experiments and the single dose, therapeutic regimen for SYM-1219, clinical drug interaction studies for inhibition, induction, and transporters are not warranted. Therefore, the current in vitro characterization of secnidazole and its impact on metabolizing enzymes is adequate and will provide sufficient metabolism information for patient labeling.

DIVISION RESPONSE – Question 11: We agree that in vitro characterization of secnidazole is sufficient and therefore, no in vivo drug-drug interaction studies are needed.

Question 12

Symbiomix has conducted in vitro and nonclinical cardiac safety studies as well as collected triplicate ECGs in subjects enrolled in two clinical pharmacology studies. None of the laboratory, nonclinical or clinical data indicates any QTc interval or other clinically relevant ECG abnormalities. Symbiomix believes these data are adequate to describe the cardiac safety of the single dose SYM-1219 2 gram regimen, and therefore, a formal TQT study is not required. **Does the FDA agree?**

Company's Position/Question 12

The pre-clinical and clinical studies completed to date suggest that secnidazole does not have cardiovascular effects on either hemodynamic performance or the conduction system. Preclinical studies included a hERG channel study and a dog ECG pharmacology study.

In clinical studies conducted thus far, an ECG safety data base has been produced in over 100 subjects, which indicates no evidence of an unfavorable effect of SYM-1219 on treatment emergent adverse events (TEAEs). In Study SYM-1219-101 Part A, 28 subjects were randomly assigned to receive single doses of either SYM-1219 1 gram (n=14) or 2 gram (n=14) sprinkled over approximately 4 ounces of applesauce. Triplicate ECGs were performed Pre-dose on Day 1 and then at 14 post-dose time points: 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72, 120, and 168 hours. The change from Day 1, Pre-dose was calculated for each ECG interval and reported as mean, standard deviation, minimum, median, and maximum. A p-value was calculated for change at each time point versus the null hypothesis of no change using a t-test. The statistical analysis showed that mean QTcF did not exceed 440 msec at any post-dose time point. Changes from Day 1, Pre-dose were mostly small and mostly negative. The largest change in either direction in the 1 gram dose group from Day 1, Pre-dose was -7 ± 5.9 (p<0.001) msec at 8 hours post-dose and in the 2 gram dose group was -8 ± 6.8 (p<0.001)

msec also at 8 hours post-dose.

No clinically important or statistically significant increases in QTcF were observed in either dose group. Pre- and post-dose ECGs were also performed in the 52 subjects who received a single SYM-1219 2 gram dose who were enrolled in Part B of Study SYM-1219-101. At Screening the mean QTcF in Group B1 was 407 ± 18.4 and in Group B2 was 410 ± 15.9 msec. At Period 2, Day 8 the mean change from Screening in Group B1 was -3 ± 10.8 msec and in Group B2 was -1 ± 12.6 msec.

Triplicate ECGs were also obtained in the 24 subjects enrolled in Study SYM-1219-102; the data from this study are currently being analyzed.

In addition to the lack of a demonstrable effect on QTcF to date, the single dose regimen for SYM-1219 will not result in any drug accumulation over time and therefore therapeutically relevant dosing and concentrations have been evaluated for cardiac safety in Studies SYM-1219-101 and SYM-1219-102 in these study subjects. Symbiomix believes that the available nonclinical and clinical data demonstrate no cardiotoxicity with the single dose SYM-1219 administration regimen, and, therefore, a formal TQT study is not required.

DIVISION RESPONSE – Question 12: We will determine the need for a TQT study after we evaluate the data from Study SYM-1219-102.

In addition, we note that secnidazole granules will be given to the patients with applesauce in the proposed Phase 3 studies. We also note that your clinical development program does not include a relative bioavailability (BA) study to address the effect of admixing secnidazole granules with yogurt. As discussed in the previous meeting held between FDA and Symbiomix on January 21, 2015, we expressed concern over the relatively slow and/or incomplete in vitro dissolution of secnidazole granules when admixed with yogurt.

Agreement was reached at the meeting for you to conduct a clinical study to compare the relative BA of secnidazole granules when admixed separately with yogurt (test) compared to when secnidazole granules are admixed with applesauce (reference). The purpose of this study is to provide information/data for the relative BA of secnidazole granules if you intend to include applesauce, pudding, or yogurt to be admixed separately with secnidazole granules in the future labeling of secnidazole granules. In lieu of this BA

study, you would need to randomize BV patients in your Phase 3 trials to receive secnidazole granules when admixed with applesauce, pudding, or yogurt to evaluate the efficacy and safety with each of these soft foods. Please address this issue by clarifying if you intend to conduct the aforementioned relative BA study and provide the proposed protocol for our review.

8.4 CLINICAL

Question 13

Symbiomix conducted Study SYM-1219-201, a Phase 2, double blind, randomized, placebo controlled study to evaluate SYM-1219 1 g and 2 g doses compared to placebo in 215 women with bacterial vaginosis at multiple sites in the United States. Eligible study subjects were first stratified based on the number of BV episodes in the past 12 months (≤ 3 or 4 or more) and then randomized 1:1:1 to receive a single dose of SYM-1219 1 gram, SYM-1219 2 grams or placebo. Patients were assessed at the End of Study/Test of Cure (EOS/TOC) visit once between Study Days 21-30 for clinical outcome. The primary endpoint was the proportion of patients who had a Clinical Outcome Response defined by a normal vaginal discharge, a negative KOH whiff test and Clue cells < 20% on saline wet mount. Secondary endpoints were the proportion of patients with a Nugent score of between 0-3 and the proportion of patients with a Therapeutic Outcome (Clinical Outcome Responders and Nugent score between 0-3) at the EOS/TOC visit. The prespecified primary analysis compared the SYM-1219 2 gram group to the placebo group. There were no notable safety issues during the study with either dose.

Symbiomix believes the robust results from this adequately controlled, well-designed study supports the efficacy and safety of SYM-1219 2 grams for the treatment of women with bacterial vaginosis. Symbiomix further believes this study could serve as one of the two pivotal trials for an NDA for this indication. **Does the FDA agree?**

Company's Position/Question 13

Study SYM-1219-201 was a randomized, prospective, double-blind placebo controlled study in 215 women with bacterial vaginosis. Patients were randomized 1:1:1 to receive single doses of SYM-1219 2 grams, SYM-1219 1 gram or matching placebo. Standard criteria were used to establish study eligibility and, notably, diagnose bacterial vaginosis. The primary and two secondary study endpoints were chosen after consultation with the FDA during the pre-IND process. The primary and secondary endpoints in both the mITT and PP Populations

overwhelmingly demonstrated the efficacy of the single 2 gram dose of SYM-1219 when compared to placebo (Section 9.4.1.3). Statistical significance was also shown when comparing the 1 gram SYM-1219 dose to placebo. However, when comparing the data between the 1 g and 2 g dose groups, the data showed better outcomes for the patients who received the 2 gram SYM- 1219 dose. As there were no notable safety issues during the study with either dose, Symbiomix plans to submit this study as one of its two pivotal efficacy and safety trials to support an NDA for a single, 2 gram SYM-1219 dose for the treatment of women with BV.

DIVISION RESPONSE – Question 13: The initial review of the information provided for study SYM-1219-201 indicates that the study may serve as one of the two pivotal studies to support the NDA. However, the final decision will be made upon review of the full submission of the study results.

Question 14

Symbiomix plans to conduct one Phase 3, double blind, randomized, placebo controlled study in women with bacterial vaginosis, Study SYM-1219-301. Approximately 180 patients determined to be eligible for enrollment after study screening will be randomized 2:1 to receive either SYM- 1219 2 grams or placebo as a single dose. The randomization will be stratified by BV episode history (≤ 3 or ≥ 4 episodes in the past 12 months, including the current episode) and by race (blacks vs. non-blacks). Patients will be assessed for their clinical response once between Study Days 21-30. The primary study endpoint will be Clinical Outcome as determined by a normal vaginal discharge, a negative KOH whiff test and Clue cells $< 20\%$ on saline wet mount. The secondary endpoints will include the proportion of subjects who achieve a Nugent score between 0-3 and the proportion of subjects who achieve Therapeutic Cure, as determined by patients who achieved both a Clinical Outcome Response together with a Nugent score between 0-3. **Does the FDA agree that this Phase 3 study as designed could serve as the second pivotal study for the NDA for SYM-1219 for this indication?**

Company's Position/Question 14

This planned study will be a randomized, prospective, double-blind placebo controlled study in approximately 180 women and post-menarchal adolescent girls with bacterial vaginosis randomized to receive either a single 2 gram dose of SYM-1219 or placebo, respectively. The patient selection criteria as related to the diagnosis of BV will be identical to those used in the SYM-1219-201 study. The primary and secondary endpoints will be identical to those used in Study SYM-1219-201; these endpoints were chosen based on discussions with the FDA at the

pre-IND meeting held in September 2013. Symbiomix believes that, as designed, the data from this study will serve as one of the two pivotal studies to demonstrate the efficacy and safety of a single, 2 gram dose of SYM-1219 to treat women with BV.

DIVISION RESPONSE – Question 14: The Division’s thinking regarding the design of trials for the treatment of bacterial vaginosis (BV) is currently evolving. There is still some uncertainty as to the most appropriate timing of the test of cure visit. We suggest assessing efficacy at two separate time points separated by sufficient duration, e.g. at Day 14 and Day 28. The earlier time point could serve as the primary endpoint. For example, clinical and microbiologic cure could be assessed at Day 14 as well as Day 28 with Day 14 serving as the TOC visit. Of note, the primary and secondary endpoints as proposed in the protocol synopsis are acceptable. The phone call at Day 8-10 should remain to assess for adverse events.

Additionally, note the following comments:

- While perhaps not necessary for the proposed trial, you may want to consider changing the requirement of a Nugent score ≥ 4 at baseline to a Nugent score of ≥ 7 at baseline in the definition of BV.
- The proposed definition for the Modified Intent-To-Treat (mITT) population requires that all inclusion/exclusion criteria are met. The mITT population should follow the ITT principle of including all randomized subjects as close as possible with the possible exception of excluding those who fail to satisfy major entry criteria that were measured prior to randomization but the results not known at the time of randomization. For bacterial vaginosis (BV) trials, the mITT population is typically defined as all randomized subjects excluding those who have a baseline Nugent score < 4 or are positive for other vulvovaginal infections (*Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*) which may interfere with the efficacy assessment for BV. These exclusions from the mITT population are acceptable since they were measured prior to randomization but the results were not known until afterward. The requirement to meet all inclusion/exclusion criteria is acceptable for defining the Per-Protocol (PP) population.
- The PP population should be analyzed according to the treatment that the patient was randomized. To ensure this, “receipt of incorrect therapy as assigned” can be included as an exclusion criterion from the PP population.

SYMBIOMIX RESPONSE: Thank you for your comments. We will discuss further at the meeting.

Question 15

Symbiomix plans to conduct Study, SYM-1219-350 (Appendix 3), an open label, safety study of a single 2 gram dose of SYM-1219 in approximately 325 women diagnosed with BV to achieve an overall safety database for an NDA for this indication in over 600 healthy female volunteers, women and post-menarchal adolescents who received at least one, 2 gram dose of SYM-1219. Study SYM-1219-350 will enroll women diagnosed with BV using the Amsel criteria (abnormal vaginal discharge, positive KOH Whiff test, Clue cells $\geq$ 20% on saline wet mount and pH $\geq$ 4.7). Patients will take a single 2 gram dose of SYM-1219 in approximately 4 ounces of applesauce either unsupervised at the clinical site or may take the study drug after they leave the clinical site anytime on Study Day 1. The site will contact the study patients to assess for adverse events once during Study Days 8-10, and patients will return to the clinical for one visit during Days 21-30 to be assessed for safety using standard clinical and laboratory procedures and to have the Investigator indicate either satisfactory clinical resolution of the patient's condition or the necessity for additional BV treatment.

The safety data in these women will be supported by safety data from 85 women who received a single 1 gram dose of SYM-1219 during the SYM-1219 development program, as well as the extensive prior human experience information in the published medical literature. All of the available safety data, including the safety data from the completed clinical studies of SYM-1219, are quite unremarkable. **Does FDA agree that the planned safety study and the overall, planned safety database will be adequate to support an NDA filing?**

Company's Position/Question 15

Symbiomix plans to submit pivotal, safety data in over 600 women and post-menarchal girls who have received 2 gram doses of SYM-1219, including 325 women with BV from a planned, open label safety study, SYM-1219-350 (Appendix 3). Table 24 provides a summary overview of all clinical studies where safety data were obtained to support an NDA filing for this indication. To date, the safety data from the three completed clinical studies (SYM-1219-101, SYM-1219-102 and SYM-1219-201, summarized in Section 9.4.1) where over 160 healthy female volunteers and women with bacterial vaginosis received single 2 gram doses of SYM-1219 has been quite unremarkable.

Additional supportive safety data will include safety data in 85 women who received single 1

gram dose of SYM-1219 as part of the development program. Safety data from the extensive prior human experience as published in the medical literature will also be used to support the safety of the 2 gram single dose of SYM-1219.

Symbiomix believes that this safety database as described above will be sufficient to adequately describe the safety of this single dose, 2 gram SYM-1219 treatment regimen for women diagnosed with bacterial vaginosis.

DIVISION RESPONSE – Question 15: This is acceptable. Please note that some of the advice given above regarding trial design could apply to the open label trial as well.

Question 16

In Study SYM-1219-201, patients prepared and took the study medication at the clinical site under supervision of the study staff. For the upcoming pivotal Phase 3 study, SYM-1219-301, Symbiomix plans to instruct the patients to prepare and administer the study medication at the clinical site without the assistance or supervision of the study staff to insure medication adherence for this study. **Does the FDA agree that dosing SYM-1219 in this manner would support out-patient dosing of SYM-1219 in the product label (i.e., dosing not observed by a health care professional)?**

Company's Position/Question 16

Symbiomix believes that providing the study patients instruction and then asking the patients to self-administer their assigned study medication without supervision but within the confines of the clinical study unit provides sufficient autonomy to the patients so that the SYM-1219 product label would not require supervised administration of SYM-1219 upon product approval.

DIVISION RESPONSE – Question 16: It is important to administer the medication in an environment as close to real life usage as is possible within the confines of a clinical trial. It is acceptable for patients to administer the dose unsupervised at the clinical site; however, please provide more information about what type of instructions (verbal or written) will be provided for the patients.

Symbiomix Response: Final dosing instructions for the Phase 3 studies are attached (Attachment 2).

Question 17

Symbiomix has begun the process of drafting a Target Product Profile (TPP) for SYM-1219 for the treatment of women with BV. (Appendix 4). In the process of developing this Target

Product Profile (TPP), Symbiomix has reviewed product labels from other approved 5- nitroimidazole drugs. It appears that these non-metronidazole product labels contain nonclinical and clinical data that were specifically generated for metronidazole. In the eventual label for SYM-1219 (secnidazole), Symbiomix plans to include data that are generated directly with SYM-1219 or directly applicable to SYM-1219 (secnidazole) from the published literature (e.g., mechanism of action, mechanisms of resistance). **Does the FDA agree?**

Company's Position/Question 17

Symbiomix is developing its TPP for SYM-1219 and noted that other 5-nitroimidazole (nonmetronidazole) drugs include data that were generated from the evaluation of metronidazole.

Based on these labels, it is not clear if the FDA has certain, required "class labeling" for this group of compounds. Given the completeness of Symbiomix's nonclinical and clinical program for the development of SYM-1219 as a single dose therapy to treat women with BV, Symbiomix plans to include data in its TPP and eventual product label that have either been generated during our SYM-1219 development program or are from literature data that can be directly related to SYM-1219 administration.

DIVISION RESPONSE – Question 17: A reasonable principle in thinking about future labeling for secnidazole is to include pertinent information (safety, pharmacology, etc.) for single dose usage of secnidazole as well as information that may be relevant to the safe use of secnidazole based on single dose use of other nitroimidazoles.

Additional Comments

- Please clarify your rationale for excluding pregnant subjects from secnidazole clinical trials. Bacterial vaginosis has been linked to preterm birth, so secnidazole may benefit this patient population.
- Please clarify whether all subjects will be screened for STDs at baseline. Exclusion criterion 4 for both Phase 3 trials states that subjects who are suspected clinically (or confirmed diagnostically) of having other STDs will be excluded but the protocols do not clearly state that all subjects will undergo STD screening with diagnostic tests. We recommend STD baseline screening of all subjects.

DIVISION REGULATORY COMMENTS

Please note under FDASIA the new requirement to submit your initial Pediatric Study Plan within 60-days of this meeting (EOP2). See the following link for additional information.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

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/s/

SUMATHI NAMBIAR

04/15/2015

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 209363

LATE-CYCLE MEETING MINUTES

Symbiomix Therapeutics, LLC
c/o Salamandra LLC
Attention: Kaylee White, RAC
Associate Director for Regulatory Affairs
4800 Hampden Lane, Suite 900
Bethesda, MD 20814-2998

Dear Ms. White:

Please refer to your New Drug Application (NDA) dated January 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for secnidazole granules, 2 g.

We also refer to the Late-Cycle Meeting (LCM) held between representatives of your firm and the FDA on July 18, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Maureen Dillon-Parker, Chief, Regulatory Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Shrimant Mishra, MD, MPH
Cross-Discipline Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 18, 2017, 1:00 pm ET
Meeting Location: White Oak, Building 22, Room 1313

Application Number: NDA 209363
Product Name: Solosec (secnidazole) Granules 2g
Applicant Name: Symbiomix Therapeutics LLC

Meeting Chair: Shrimant Mishra, MD, MPH
Meeting Recorder: Maureen Dillon-Parker

FDA ATTENDEES [*via phone]

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, MD, MPH Director
Joseph G. Toerner, MD, MPH Deputy Director for Safety
Shrimant Mishra, MD, Cross-Discipline Team Leader
Dmitri Iarikov, MD, PhD, Deputy Director (Acting)
Mayurika Ghosh, MD, Clinical Reviewer
Avery Goodwin, PhD, Clinical Microbiology Reviewer
Owen McMaster, PhD, Nonclinical Reviewer
Terry Miller, PhD, Nonclinical Team Leader
Abimbola O. Adebowale, PhD, Associate Director of Labeling
Maureen Dillon-Parker, Chief, Project Management Staff

Division of Clinical Pharmacology IV

Sonia Pahwa, PhD, Clinical Pharmacology Reviewer
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader

Division of Biometrics IV

Cheryl Dixon, PhD, Biostatistics Reviewer

Office of Pharmaceutical Quality (OPQ)

Banu S. Zolnik, PhD, Biopharmaceutics Reviewer

Office of Surveillance and Epidemiology (OSE)

Sevan H. Kolejian, PharmD, Safety Evaluator, DMEPA
Naomi Reed, PharmD, DRISK Team Leader*
Aman Sarai, PharmD, Reviewer, DMPP*
Timothy Jancel, PharmD, Reviewer, Division of Pharmacovigilance II*

APPLICANT ATTENDEES – Symbiomix Therapeutics

Nikki Adetoro, Vice President, Clinical Operations and Project Management
Joseph Amprey, Head of Medical Affairs/CBO
Thomas Beck, MD, Chief Medical Officer, Head Research/Development
Robert Jacks, President and Chief Financial Officer
David Palling, PhD, Head of Manufacturing
Helen Pentikis, PhD, Chief Scientific Officer
David Stern, Chief Executive Officer
Kaylee White, RAC, Regulatory Consultant, Salamandra LLC

BACKGROUND

NDA 209363 was submitted on January 17, 2017, for Solosec (secnidazole) Granules 2g, for the treatment of Bacterial Vaginosis. The PDUFA goal date for this application is September 17, 2017.

FDA issued a Background Package in preparation for this meeting on June 28, 2017.

DISCUSSION

1. Introductory Comments

Following introductions, the following paragraph was communicated to the Sponsor.

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

There were no other introductory comments.

2. Postmarketing Requirements/Postmarketing Commitments (PMR/PMC)

Discussion: The FDA conveyed that the following study will be required as a PMR:

Trial SYM-1219-104, an open label, safety study in healthy postmenarchal adolescent girls with bacterial vaginosis (ages 12 to <18 years).

3. Major Labeling Issues

Discussion: The Sponsor asked FDA to clarify what type of information they (FDA) are expecting in response to the preliminary comment requesting proposed wording for the carcinogenicity section of the labeling.

The FDA clarified that section 13.1 *'must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results'* according to current labeling regulations. Information available from the World Health Organization indicates that carcinogenicity studies have been conducted with secnidazole but these data may not be cited in the label (per the WHO document). The document indicates that adenomas and carcinomas were increased in secnidazole-treated animals compared to controls. FDA asked the Sponsor whether they had additional information on the study or if they are aware of other studies. The Sponsor had no knowledge of any reports of carcinogenicity studies.

The Sponsor agreed to provide to the FDA with proposed wording for consideration for labeling.

4. Review Plans

Discussion:

The Sponsor requested feedback on the carton/container labeling information as soon as possible. Additionally, they (Sponsor) requested feedback on the (b) (4) protocol sent to the CMC team.

The CMC team agreed to follow-up and let the sponsor know if comments will be forthcoming or not.

5. Wrap-up /Action Items

- Revised draft labeling will be communicated by the end of July. Labeling discussions will be held as needed.
- Agreement on timeline for PREA PMR will be reached at the time of labeling discussions.
- Issue minutes within 30 days.

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/s/

SUMATHI NAMBIAR

08/14/2017

Signed on behalf of Dr. Shrimant Mishra.



NDA 209363

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Symbiomix Therapeutics, LLC
c/o Salamandra LLC
Attention: Kaylee White, RAC
Associate Director for Regulatory Affairs
4800 Hampden Lane, Suite 900
Bethesda, MD 20814-2998

Dear Ms. White:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for secnidazole granules, 2 g.

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 18, 2017. Attached is our background package, including our agenda, for this meeting.

For each foreign visitor, complete and email maureen.dillonparker@fda.hhs.gov the enclosed Foreign Visitor Data Request Form, at least **two weeks** prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

If you have any questions, call Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES: Late-Cycle Meeting Background Package
FDA Foreign Visitor Request Form

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: July 18, 2017 1:00 PM to 2:00 PM EDT

Meeting Location: White Oak Campus, Building 22, Room 1313

Application Number: NDA 209363

Product Name: Secnidazole Granules 2 g

Indication: Treatment of Bacterial Vaginosis

Applicant Name: Symbiomix Therapeutics LLC

FDA ATTENDEES (tentative)

Office of Antimicrobial Products (OAP)

John J. Farley, M.D., M.P.H. Deputy Director

Katherine Schumann, MS, Associate Director for Regulatory Affairs

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H. Director

Joseph G. Toerner, M.D., M.P.H. Deputy Director for Safety

Shrimant Mishra, M.D., Cross Discipline Team Leader

Dmitri Iarikov, MD, Ph.D., Deputy Director (Acting)

Mayurika Ghosh, M.D., Clinical Reviewer

Avery Goodwin, Ph.D., Clinical Microbiology Reviewer

Owen McMaster, Ph.D., Nonclinical Reviewer

Terry Miller, Ph.D., Nonclinical Team Leader

Abimbola O. Adebawale, Ph.D., Associate Director of Labeling

Maureen Dillon-Parker, Chief, Project Management Staff

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Philip Colangelo, PharmD, Ph.D., Clinical Pharmacology Team Leader

Division of Biometrics IV

Cheryl Dixon, Ph.D., Biostatistics Reviewer

Karen Higgins, ScD, Biostatistics Team Leader

Office of Pharmaceutical Quality (OPQ)

George Lunn, Ph.D., OPQ Reviewer

Dorota M. Matecka, Ph.D., OPQ Team Leader

Banu S. Zolnik, Ph.D., Biopharmaceutical Quality Reviewer

Elsbeth G. Chikhale, Ph.D., Biopharmaceutical Quality Team Leader

Office of Surveillance and Epidemiology (OSE)

Janet Higgins, Regulatory Project Manager

Division of Medication Error Prevention and Analysis (DMEPA)

Sevan H. Kolejian, PharmD, Safety Evaluator

Otto L. Townsend, PharmD, Safety Team Leader

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

3. Advisory Committee Meeting

An Advisory Committee meeting is not planned.

4. REMS or other Risk Management Actions

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

- No issues have been identified to date.

3. Discussion of Minor Review Issues

- No issues have been identified to date.

4. Additional Applicant Data

- No issues have been identified to date.

5. Information Requests

- No issues have been identified to date.

6. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

The required secnidazole pediatric development program will include the following trial:

Trial SYM-1219-104, an open label, safety study in healthy postmenarchal adolescent girls with bacterial vaginosis (ages 12 to <18 years).

7. Major labeling issues – 5 minutes

For Section 13 of labeling: Publicly available information indicate that long term carcinogenicity studies have been conducted with secnidazole and that adenomas and carcinomas are increased in secnidazole-treated animals compared to controls. Please review these materials and provide wording for the proposed prescribing information. See http://apps.who.int/iris/bitstream/10665/61289/1/PDP_EC_WP_86.8.pdf

8. Review Plans

The team plans to complete reviews to meet the PDUFA goal date of September 20, 2017.

9. Wrap-up and Action Items – 5 minutes

- Revised draft labeling will be communicated by the end of July. Labeling discussions will be held as needed.
- Agreement on timeline for PREA PMR will be reached at the time of labeling discussions.



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FOREIGN VISITORS DATA REQUEST FORM

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VISITOR'S FULL NAME	First	Middle	Last
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PLACE OF BIRTH (CITY AND COUNTRY)			
PASSPORT NUMBER			
ISSUING COUNTRY			
ISSUANCE DATE			
EXPIRATION DATE (MM/DD/YYYY)			
VISITOR'S ORGANIZATION/EMPLOYER			
MEETING START (DATE/TIME)	July 18, 2017 @ 1:00 PM		
MEETING ENDING (DATE/TIME)	July 18, 2017 @ 2:00 PM		
PURPOSE OF MEETING	NDA Late Cycle Meeting		
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO 22 / Room 1313		
BUILDING ENTRANCE	White Oak 22		
FDA LABORATORIES T O BE VISITED	None		
HOSTING FDA CENTER	CDER / OAP /DAIP		
HOSTING OFFICIAL	Name: Maureen Dillon-Parker		
	Title: Chief Project Management Staff		
	Office/Bldg.: OAP/DAIP/WO22		
	Email: Maureen.dillonparker@fda.hhs.gov	Phone: 301-796-0706	
ESCORT INFORMATION (If different from Hosting Official)	Name:		
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Important: Type or Print Clearly. Illegible handwriting may delay or prevent proper vetting of the foreign visitor.

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/s/

SUMATHI NAMBIAR
06/28/2017