CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209363Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader, Division Director, and Deputy Office Director Summary Review

Date	*Stamp Date*
From	Shrimant Mishra, MD, MPH, Sumathi Nambiar, MD, MPH, John Farley, MD, MPH
Subject	Combined Cross-Discipline Team Leader, Division Director, and Deputy Office Director Summary Review
NDA#	209363
Applicant	Symbiomix Therapeutics, LLC
Date of Submission	1/17/2017
PDUFA Goal Date	9/20/2017
Proprietary Name / Non-Proprietary Name	Solosec/Secnidazole
Dosage form(s) / Strength(s)	Oral Granules, 2 grams
Applicant Proposed Indication(s)/Population(s)	Treatment of Bacterial Vaginosis
Regulatory Action	*Approval*
Indication(s)/Population(s)	Treatment of Bacterial Vaginosis in adult women

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewer**
Medical Officer Review	Mayurika Ghosh, MD
Statistical Review	Cheryl Dixon, PhD
Pharmacology Toxicology Review	Owen McMaster, PhD
OPQ Review	George Lunn, PhD
Microbiology Review	Avery Goodwin, PhD
Clinical Pharmacology Review	Sonia Pahwa, PhD
OPDP	Puja Shah, PharmD
OSI	John Lee, MD
OMP/DMPP	Aman Sarai, BSN, RN
OSE/DMEPA	Sevan Kolejian, PharmD
OSE/DRISK	Naomi Redd, PharmD
DPMH	Jane Liedtka, MD
QT-IRT	Dhananjay D. Marathe, PhD

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bacterial Vaginosis (BV) is a vaginal infection of high prevalence among post menarchal, premenopausal, sexually active women. The infection causes vaginal discharge and discomfort. While BV has been associated with more serious health consequences including increased risk of HIV acquisition and preterm birth/low birth weight, data are inconclusive regarding whether treatment of BV is associated with improvement in maternal and fetal outcomes. Approved treatment options include oral or topical metronidazole, oral and topical clindamycin, and oral tinidazole.

Secnidazole is a 5-nitroimidazole drug to be taken as a one-time 2 g dose of a packet of granules mixed with applesauce, pudding, or yogurt. Efficacy of secnidazole for the treatment of BV was demonstrated in two randomized, double-blind, placebo-controlled, U.S. based, multicenter clinical trials in a representative population of women. In one trial, two doses of secnidazole were compared to placebo and in the second trial, a 2 g dose of secnidazole was compared to placebo. In both trials, a 2 g secnidazole dose was shown to be efficacious (relative to placebo) in achieving a Clinical Response of normal vaginal discharge, clue cells < 20% on microscopy, and a negative whiff test. In Trial SYM 1219-201, there were 67.7% (42/62) Clinical Responders in the 2 g secnidazole arm compared to 17.7% (11/62) in the placebo arm, treatment difference 50.0% ($p<0.001$). In Trial SYM 1219-301, there were 53.3% (57/107) Clinical Responders in the secnidazole arm compared to 19.3% (11/57) in the placebo arm, treatment difference 38.6% ($p<0.001$). This primary outcome was supported by success on secondary outcomes such as a normal Nugent score and the combined response of normal Nugent Score/Clinical Response. In Trial SYM 1219-301, the benefit of secnidazole on the primary outcome was also shown at two different timepoints. Design of the two trials was generally consistent with Agency guidance. While the Clinical Response rates were lower in the subgroups of Black women and in those with a history of 4 or more BV episodes in the past 12 months; there was a treatment difference in favor of secnidazole in these subgroups.

In addition to safety data from the two randomized controlled trials, safety data were also obtained from an open-label single arm safety trial. The most frequently reported treatment emergent adverse events (TEAEs) are similar to those seen with other drugs in the 5-nitroimidazole class, such as nausea, vomiting, diarrhea, abdominal pain, headache, and dysgeusia (metallic taste). These adverse events (AEs) are also similar to AEs reported for secnidazole used in other countries. Vulvovaginal candidiasis (VVC) was the most commonly reported TEAE. A Warning that VVC may develop with secnidazole treatment and require treatment with an antifungal agent will be included in the Prescribing Information. Secnidazole was administered after mixing in applesauce, pudding, or yogurt in clinical trials and studies, and a food effect study showed no significant exposure differences between the fed and fasted state.

In conclusion, the Applicant has provided substantial evidence to support the safety and efficacy of secnidazole for the treatment of BV in adult women. The safety findings for secnidazole support an acceptable benefit-risk for its use for the treatment of BV. Labeling will include safety findings from the clinical trials and important known class drug effects. A required PREA pediatric study in postmenarchal adolescent girls will be performed as a postmarketing requirement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	BV is a common cause of vaginitis in women of childbearing age. Beyond the morbidity from the clinical entity itself, there are epidemiological associations between BV and other adverse health outcomes such as increased risk of human immunodeficiency virus acquisition and preterm birth. However, data are inconclusive regarding whether treatment of BV is associated with improvement in maternal and fetal outcomes. Based on the National Health and Nutrition Examination Survey, the prevalence of BV was estimated to be 29% in the general population of women aged 14-49 years and 50% among Black women[1]. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms of BV within three months and more than 50 percent experience a recurrence within 12 months.	BV is associated with significant morbidity as well as other serious conditions. The prevalence of BV among women aged 14-49 years is estimated at 29% and the prevalence is estimated to be higher among Black women.
Current Treatment Options	Metronidazole vaginal gel 0.75% and 1.3%, extended release oral metronidazole tablets, tinidazole tablets, clindamycin vaginal cream and clindamycin vaginal suppository are FDA approved for the treatment of BV. Treatment duration ranges from 1 to 7 days	A number of systemic and topical drugs are approved for the treatment of BV. A safe and effective single dose oral therapy for BV may be more convenient and may improve patient compliance.
Benefit	The Applicant performed two clinical trials, SYM 1219-201 and SYM 1219-301, to demonstrate the efficacy of secnidazole in the treatment of BV. The primary endpoint for both trials was the Clinical Response evaluated at the Test of Cure (TOC) visit (Day 21 to 30) in the mITT population. In Trial SYM 1219-201, there were 67.7% (42/62) Clinical Responders in the 2 g secnidazole arm compared to 17.7% (11/62) in the placebo arm, treatment difference 50.0% [95% CI 33.4, 66.7] ($p<0.001$). The pre-specified primary analysis was comparison of the 2 g secnidazole	Efficacy of a single 2 g dose of secnidazole in the treatment of BV was demonstrated in two adequate and well-controlled trials. The treatment effect of secnidazole was greater than placebo across all endpoints. Black women constituted nearly half of trial enrollees. While the Clinical Response rates were lower in the subgroup of Black women, treatment differences favored secnidazole in this subgroup.

1 Koumans EH, Sternberg M, Bruce C, McQuillan G, Kendrick J, Sutton M, Markowitz LE The prevalence of bacterial vaginosis in the United States, 2001-2004 associations with symptoms, sexual behaviors, and reproductive health *Sex Transm Dis.* 2007 Nov;34(11):864-9

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	arm with the placebo arm. In the 1 g secnidazole arm there were 51.6% Clinical Responders. In Trial SYM 1219-301, there were 53.3% (57/107) Clinical Responders in the secnidazole arm compared to 19.3% (11/57) in the placebo arm, treatment difference 34.0% [95% CI 18.7, 49.3] ($p<0.001$). In terms of the secondary endpoints, including normal Nugent Score and Therapeutic Outcome responders, the 2 g secnidazole arm had a greater response than placebo across the endpoints. Black women constituted nearly half of those enrolled in Trials SYM 1219-201 and 301. In this sub-group, overall response rates were lower. The treatment differences between secnidazole and placebo were comparable to the overall trial population in Trial 1219-201 51.8% [95%CI 27.8, 75.8] and lower in Trial 1219-301 25.1% [95% CI 3.1, 47.1]. Findings in the subgroup of patients with a history of 4 or more BV episodes in the past 12 months were similar.	
Risk	During the secnidazole development program, a total of 783 subjects were exposed to the drug, including 589 subjects in the BV trials and 194 in the phase 1 trials; 518 subjects in the BV trials received a dose of 2 g. The safety analysis was primarily conducted in subjects enrolled in the two randomized, placebo controlled BV trials (Trials SYM1219-201 and 301) and a third open label single arm safety trial (Trial SYM 1219-350). The drug exposure data is considered adequate. Four subjects, all who had received the 2 g dose, had treatment emergent serious adverse events, one of which was considered related to study drug (loss of consciousness). There were no deaths in the trials. The most frequent TEAEs probably related to 2 g secnidazole were VVC (9.6%), headache (3.6%), nausea (3.6%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal pruritus (2.0%) in the pooled SYM1219-201 and 301 trials and VVC (8.4%), nausea (5.3%), dysgeusia (3.4%) in trial SYM 1219-350. The risk difference analysis of the AEs showed that nausea, vomiting and diarrhea, and VVC occurred at a higher frequency in the 2gm arm of controlled trials compared to placebo.	No major safety concerns were identified in the clinical trials. The safety profile of the drug is consistent with the known safety profile of 5-nitroimidazoles. A Warning has been included in the product label regarding an association of secnidazole with VVC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Between the controlled trials and the safety trial, 46 subjects in the 2 g secnidazole arm developed VVC. In the controlled studies alone, 19 subjects in the 2g arm developed VVC vs. 4 in the placebo arm. In general, these infections were not severe and most subjects recovered. Adverse events commonly noted in literature with the use of secnidazole outside the U.S. are nausea, dysgeusia, abdominal pain, headache, and vomiting, similar to the TEAEs noted in the BV clinical trials. The trials excluded pregnant patients, but there were 7 pregnancies reported among patients enrolled in the secnidazole trials. No conclusion can be drawn regarding the effects of secnidazole on pregnancy from these patients (3 chose to have elective abortions, 2 had healthy pregnancies, and 2 were lost to follow up).	
Risk Management	No specific serious risks have been identified that necessitate specific risk management strategies at this time.	The safety and efficacy of secnidazole in pediatric patients has not been studied; a study in postmenarchal adolescent girls with BV will be conducted as a postmarketing requirement.

2. Background

The Applicant, Symbiomix Therapeutics, LLC submitted NDA 209363 for the treatment of BV. The initial IND, (#117811), was filed on December 18, 2013. The drug received QIDP designation on November 18, 2014 for the treatment of BV. The product received Fast Track status on August 12, 2015.

Secnidazole is a 5-nitroimidazole class antimicrobial proposed, that is not approved in the United States for any indication. It is marketed outside the U.S. for the treatment of infections such as trichomoniasis, giardiasis, amebiasis, and BV. The proposed dose is a single 2g dose of a packet of granules admixed with yogurt, applesauce, or pudding. Similar to other drugs in this class, such as metronidazole and tinidazole, secnidazole's mechanism of action is primarily through interactions of toxic radical ions (of reduced secnidazole) with microbial DNA, leading to microbial death.

BV is a common condition among postmenarchal, premenopausal, sexually active females associated with the replacement of lactobacilli in the vagina with numerous anaerobic organisms. Symptoms include a foul smelling vaginal discharge and vaginal irritation. Approved therapies used for treatment of BV include metronidazole vaginal gel, metronidazole tablets, tinidazole tablets, clindamycin tablets, and clindamycin vaginal cream/suppositories. Treatment durations range from 1 to 7 days. Sex partners are generally not treated as this has not been proven to be effective in reducing transmission.

3. Product Quality

The Office of Product Quality (OPQ) review team for this NDA included Sithamalli Chandramouli, PhD for drug substance, George Lunn, PhD for drug product, Sateesh Kumar Sathigari, PhD for manufacturing process and product quality microbiology, Banu Zolnik, PhD for biopharmaceutics, and Daniel DeCiero, PhD for facilities.

The drug product consists of white to slightly yellowish granules that are sprinkled on food (e.g., applesauce, yogurt, pudding) and consumed. The granules are supplied in single-dose packets with 4.76 g granules containing 2 g secnidazole. Each packet is supplied in a cardboard box.

Dr. Lunn noted that Critical Quality attributes of the drug product included secnidazole particle size, (b) (4) size as well as the solids concentration (b) (4). For example, lack of tight control of (b) (4) size could lead to variable dissolution profiles. Formulation development is modeled after the (b) (4). The drug product has (b) (4) than previously marketed products though this was accepted by the Agency at an end of phase 2 (EOP2) meeting in 2015. Certificates of analysis have been provided for all excipients, including sugar spheres, povidone, PEG 4000, Eudragit, (b) (4) and talc.

Key analytical methods (such as HPLC method, dissolution method, method of particle size measurement, and method of measuring elemental impurities) were found to be adequately described and validated. Batch analyses of commercial test batches were adequate. The stability testing was found to be adequate and supported the proposed expiration date of 30 months when the drug is stored at 25°C; the container closure system was also found to be adequate.

Three formulations of drug were manufactured, initial formulations at the (b) (4) manufacturing site (formulation #1) and two later formulations at the Catalent manufacturing site (formulations # 2 and # 3). Formulation #1 and #2 were different enough to require a bridging pharmacokinetic (PK) study; please see Clinical Pharmacology (section 5) for further details. The differences between formulations #2 and #3 were thought to be minor and thus did not require a comparative PK study; similarity was assessed through an in vitro dissolution study. The in vitro dissolution study showed no significant difference in dissolution profiles between these two formulations, and, thus, the formulations were considered equivalent.

Information regarding the drug product manufacturing process provided in the NDA has been found acceptable. Based on inspectional history for all manufacturing sites listed in this NDA, it was determined that there were no significant outstanding issues with the facilities involved in the manufacturing of the proposed product.

The product quality review team recommends approval of the NDA. We concur that there are no product quality issues precluding approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer for the NDA was Dr. Owen McMaster.

The nonclinical data package included 7 and 28 day rat and dog studies, genotoxicity studies, embryofetal development studies, and fertility studies.

In the 7-day studies, proximal tubule changes in rats were seen at the expected clinical exposure. Significant morbidity and mortality were noted in dogs at 5 times the expected clinical exposure. In the 28-day studies, effects on body weight, thymus weight, pituitary gland, thyroid/parathyroid weights were noted in rats at subclinical exposures. In both rats and dogs, supraclinical exposures were associated with significant morbidity and mortality. The relevance of these findings to the proposed single dose secnidazole regimen is unclear.

In animal reproduction studies, pregnant rats were dosed orally with secnidazole during organogenesis (gestational days 6-17) at 100, 300 and 1000 mg/kg/day, up to 4 times the clinical dose based on AUC comparisons. Animals showed no evidence of adverse developmental outcomes, but maternal toxicity (including reduced body weight gain) was observed at and above 300 mg/kg/day. In rabbits, no evidence of adverse developmental outcomes was observed when oral doses of secnidazole were administered to dams during

organogenesis (gestational days 7-20) at doses up to 100 mg/kg/day (about 0.1 times the clinical dose, based on AUC comparisons). Secnidazole was associated with maternal toxicity (reduced food consumption and markedly reduced body weight gain) in dams at 100 mg/kg/day.

Other nitroimidazoles, which have similar chemical structures to secnidazole, have been associated with tumors affecting the liver, lungs, mammary, and lymphatic tissues in animals after lifetime exposures. It is unclear if these positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of secnidazole to treat BV. A Warning will be included in the Prescribing Information regarding the potential risk for carcinogenicity.

Secnidazole is genotoxic. Secnidazole was positive in the Bacterial Reverse Mutation Assay, but was negative in the rat micronucleus test and mouse lymphoma test.

Dr. McMaster recommends approval of the NDA. We concur that there are no Pharmacology Toxicology issues precluding approval.

5. Clinical Pharmacology

The Clinical Pharmacology review of this NDA was performed by Dr. Sonia Pahwa.

Secnidazole is absorbed in the gut and, after a 2 g dose, reaches a peak plasma concentration of 45 mcg/mL 1.5 hours after dosing. It is minimally metabolized in the liver and is to a large extent slowly renally excreted as unchanged or glucoronidated secnidazole. However, it should be noted that at least 50% of the metabolism/elimination of a secnidazole dose remains unknown. Because secnidazole is administered as a single dose and has been used clinically, a formal ADME study was deemed unnecessary. Secnidazole has a half-life of 17 hours.

A food effect study was performed in which a secnidazole dose (mixed with applesauce) was given in fed and fasted conditions. No significant differences in Cmax or AUC were noted. Thus, secnidazole can be administered without regard to meals (but must be admixed with the soft food options listed below). Drug exposure was also compared when admixing secnidazole in applesauce, yogurt, or pudding. As no notable differences in the rate and extent of secnidazole exposure were noted, labelling will state that secnidazole could be admixed in any of the three soft food options.

Phase 1 PK studies examined subjects by race (primarily Black vs White) and ethnicity (Hispanic/Latino vs Not Hispanic/Latino) and no significant differences in exposure were noted. Since this is a single dose regimen, studies in renally/hepatically impaired subjects were not performed, consistent with FDA guidance.

Several drug-drug interaction studies were performed and all studies showed no significant drug interactions with secnidazole. Inhibitory and inducer effects were noted on CYP enzymes at concentrations that were not clinically relevant. Secnidazole is minimally

metabolized by the CYP 450 system so it is unlikely to be affected by CYP system inducers/inhibitors. No interaction effects were noted on intestinal transporters. A drug interaction study with aldehyde dehydrogenase showed minimal inhibition at clinically relevant doses. A drug interaction study was performed with a combination oral contraceptive (ethinyl estradiol and norethindrone). Though a 29% decrease in Cmax was noted for ethinyl estradiol, this was not deemed to be clinically relevant.

(b) (4) facility manufactured the initial clinical batches of drug that were used in the early phase 1 studies and also one of the clinical trials (Trial SYM 1219-201). Catalent, Inc. produced the clinical/to-be-marketed batches that were used in the later PK studies as well as in the other clinical studies (Trials SYM 1219-301 and SYM 1219-350). A bioequivalence study was performed and products from both facilities were found to be bioequivalent.

Given that this product is to only be used in females, and given that very few adolescents were enrolled (as well as no geriatric individuals), PK characteristics by age and gender were not evaluated.

A thorough QT study was performed and at the clinical dose, no significant prolongation was observed. At the supratherapeutic dose of 6 g, the largest upper bound of the 90% CI for the mean difference between the 6 g dose and placebo was 11 msec. Given that secnidazole will be administered as a single 2 g dose, this is not expected to be clinically significant.

Dr. Pahwa recommends approval of the NDA. We concur that there are no Clinical Pharmacology issues precluding approval.

6. Clinical Microbiology

The Clinical Microbiology reviewer for this NDA was Dr. Avery Goodwin.

The structure of secnidazole is similar to that of metronidazole and tinidazole, and secnidazole is assumed to have a similar mechanism of action as metronidazole and tinidazole. This mechanism involves diffusion of the inactive prodrug into the bacterium, reduction of the prodrug compound by bacterial enzymes, and then interference with DNA synthesis by the resultant toxic radical anion. Resistance to secnidazole was not tested, though there was some suggestion of cross–resistance between secnidazole and metronidazole in vitro (metronidazole resistance can occur with plasmid transfer of resistant genes, drug efflux, etc.). Dr. Goodwin notes that the in vitro activity of secnidazole was evaluated against some bacterial isolates associated with BV (*Anaerococcus tetradius*, *Atopobium vaginae*, *Finegoldia magna*, *Gardnerella vaginalis*, *Mageeibacillus indolicus*, *Mobiluncus* spp., *Peptoniphilus* spp., *Bacteroides* spp., *Porphyromonas* spp., *Prevotella* spp., and *Megasphaera*-like bacteria). The MIC90 of secnidazole was similar to metronidazole and tinidazole for all bacterial species studied. It should be noted, however, that secnidazole did show slightly reduced activity against *Gardnerella* relative to metronidazole and tinidazole.

Dr. Goodwin recommends approval of the NDA. We concur that there are no Clinical Microbiology issues precluding approval.

7. Clinical/Statistical- Efficacy

The review of efficacy was conducted by the Statistical Reviewer Dr. Cheryl Dixon and the Clinical Reviewer Dr. Mayurika Ghosh.

The efficacy of secnidazole was demonstrated in two clinical trials. Trial SYM 1219-201 was a multicenter, randomized, double-blind, placebo-controlled, dose ranging study that compared two doses of secnidazole (1 g and 2 g) vs placebo in the treatment of nonpregnant adult women with BV. Trial SYM 1219-301 was a multicenter, randomized, double-blind, placebo controlled trial of 2 g secnidazole vs placebo for the treatment of nonpregnant adult females and post menarchal adolescent females with BV.

Trial SYM 1219-201 was conducted at 24 sites in the United States. Subjects were evaluated at three time points: baseline, a post-treatment phone call, and a TOC visit. Subject eligibility was determined at the baseline visit. Females aged 18 years of age and older with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV was defined as having an off-white, thin, homogenous discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. Subjects were to have a Nugent score ≥4; however, the results of the Gram stain for the Nugent score were not known until after randomization. Additionally, subjects with known or suspected other infectious causes of vulvovaginitis (e.g., candidiasis, *T. vaginalis, C. trachomatis, N. gonorrhoeae,* or active *H. simplex)* were to be excluded. Pregnant women were also excluded from enrollment.

Eligible subjects were randomized in a 1:1:1 ratio to receive treatment with one of the following: single oral dose of secnidazole 1 g, single oral dose of secnidazole 2 g, or placebo. Randomization was stratified by the number of BV episodes in the past 12 months (3 or fewer, 4 or more). Subjects were to complete a daily telephone diary on Days 1 through 7 and at the TOC visit. The diary included questions regarding whether the subject was having their menstrual period and to rate their vaginal discharge and vaginal odor at that time. Subjects were also contacted by telephone between Days 8 and 10 to inquire about possible adverse events. The TOC visit was conducted between Days 21 and 30. At the in-clinic visits, a gynecological exam was conducted and vaginal fluid specimens were collected. The primary objective of the trial was to evaluate the safety and efficacy of 1 g and 2 g of SYM-1219 compared to placebo for the treatment of BV. The evaluation of 2 g vs placebo was the prespecified primary analysis.

The primary efficacy endpoint was clinical outcome at TOC. A clinical responder was defined as a subject with normal vaginal discharge, negative whiff test, and clue cells less than 20%. Secondary endpoints were Nugent score and therapeutic outcome at TOC. A Nugent score of 0 to 3 was considered normal and a score of 4 or greater was considered abnormal. A therapeutic responder was a clinical responder with a normal Nugent score. Exploratory efficacy variables were the pH of the vaginal discharge at TOC (< 4.7 normal or ≥ 4.7 abnormal), patient

responses to telephone diary questions on Day 1 to 7 and at TOC, and the Investigator's clinical assessment of the need for additional BV treatment at the TOC visit.

Trial SYM 1219-301 was similar in design save for a few key details that are noted here. The trial was conducted at 21 centers in the United States. Subjects were evaluated at three time points: baseline, the interim visit (Study Day 7 to 14 - not included in SYM 1219-201), and the test of cure (TOC) visit (Study Day 21 to 30). Subject eligibility was determined at the baseline visit. Adult females or post menarchal adolescent girls aged 12 years of age and older (not included in SYM 1219-201) with a clinical diagnosis of BV were eligible to be enrolled.

Eligible subjects were randomized in a 2:1 ratio to receive treatment with either a single 2 g dose of secnidazole or placebo. Randomization was stratified by the number of reported episodes of BV in the past 12 months (3 or fewer vs 4 or more) and by race (Black vs all others – not done in SYM 1219-201). Treatment was self-administered on Day 1. Subjects returned to the clinic between Day 7 and 14 to assess response to treatment and inquire about possible AEs. The TOC visit was conducted between Day 21 and 30 and was to be at least 10 days after the Interim visit. At all visits, a gynecological exam was conducted and vaginal fluid specimens were collected. The primary efficacy endpoint was clinical outcome at TOC. A clinical responder was defined similarly to Trial SYM 1219-201. Secondary efficacy endpoints included clinical outcome at the Interim visit, Nugent score at the Interim visit and TOC, therapeutic outcome at the Interim visit and TOC, and the Investigator's clinical assessment at TOC. Nugent score and therapeutic responders were defined similar to Trial SYM 1219-201. The Investigator's clinical assessment was based on their opinion of the patient's need for additional BV treatment at the TOC visit.

For both trials, the trial populations were as follows. The Intent-to-Treat (ITT) population included all randomized subjects. The modified intent-to-treat (mITT) population included all randomized patients that had a Gram stain Nugent score ≥4 at baseline and were negative for other sexually transmitted infections at baseline. The mITT population was the primary efficacy analysis population. The Safety population included all randomized subjects who received study drug. The per-protocol (PP) population definition differed slightly between the two studies and was used as a supportive efficacy analysis population.

In general, both trials were conducted in accordance with the Agency draft guidance, *Bacterial Vaginosis: Developing Drugs for Treatment, Guidance for Industry*.[2] However, two differences are notable. The draft guidance recommends the TOC Visit at 7 to 14 days after randomization, and the mITT population is defined as subjects with a Nugent score ≥ 7. Though this differs from the two trials conducted, SYM1219-301 included a 7-14 day visit. A sensitivity analysis at the 7-14 day Interim Visit was performed by Dr. Dixon (see Table 3).

In Trial SYM1219-201, 71, 72, and 72 subjects were randomized into the 1g, 2g, and placebo groups respectively. The majority of subjects in the 2 g group were White while in the placebo group, the majority were Black. The baseline mean Nugent score ranged from 8.2 to 8.7

[2] Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510948.pdf

across the three arms. Roughly 30% of subjects in both arms had 4 or more BV episodes in the past 12 months.

The 2 g arm performed significantly better than the placebo group on both the primary and secondary endpoints, including Clinical Outcome, Nugent Score, and Therapeutic Outcome Responder. Notably, Clinical Response aligned closely numerically with Investigator assessment of need for further treatment. Also, the 2 g dose performed better than the 1 g arm in all response categories. Most non-responders were the results of failure on all three failure criterion suggesting true nonresponse.

Table 1:
SYM-1219-201: Summary of Responses at Test of Cure (mITT)

	Secnidazole 1 g (n=64)	**Secnidazole 2 g** (n=62)	**Placebo** (n=62)
Clinical Outcome Responder	33 (51.6) 33.9 (16.8, 51.0) p<0.0001	42 (67.7) 50.0 (33.4, 66.7) p<0.0001	11 (17.7)
Nugent Score (Normal)	15 (23.4) 16.9 (3.3, 30.5) p=0.0068	25 (40.3) 33.8 (18.5, 49.1) p<0.0001	4 (6.5)
Therapeutic Outcome Responder	14 (21.9) 15.4 (2.0, 28.8) p=0.0111	25 (40.3) 33.8 (18.5, 49.1) p<0.0001	4 (6.5)
Investigator's Clinical Assessment (Additional BV treatment not required)	36 (56.3) 32.1 (14.4, 49.9) p=0.0002	45 (72.6) 48.4 (31.4, 65.4) p<0.0001	15 (24.2)

Missing data classified as non-responder or abnormal (2 Secnidazole 1 g, 2 Secnidazole-2 g, and 4 placebo)
Difference (95% CI) for Secnidazole group-placebo
Two-sided p-value based on CMH test adjusted for BV strata vs placebo
Source: FDA Statistical Review, Table 12

In Trial SYM1219-301, 125 and 64 subjects were randomized into the 2 g and placebo groups, respectively. The mITT populations included 107 and 57 subjects, respectively. The majority of subjects in both arms were Black. The median Nugent score was 8 for these groups. Roughly a quarter of subjects in both arms had 4 or more BV episodes in the past 12 months.

Similar to Trial SYM1219-201, the secnidazole 2g arm performed significantly better than placebo on the primary outcome of clinical responder at the Day 21-30 visit; this was supported by findings in the per protocol population as shown in Table 2. The majority of patients classified as nonresponders were classified as such because none of the three success criteria were met (suggesting true nonresponse).

Table 2
SYM-1219-301: Clinical Outcome Responder at TOC (Day 21-30)

	Secnidazole 2 g	**Placebo**	**p-value***	**Difference (95% CI)****
mITT	57/107 (53.3)	11/57 (19.3)	<0.001	34.0 (18.7, 49.3)
PP	43/77 (55.8)	11/37 (29.7)	0.006	26.1 (5.7, 46.5)

*p-value of CMH test adjusted for # of BV episodes and race strata
**Difference is Secnidazole –placebo and 95% confidence interval
Source: FDA Statistical Review, Table 5

The secondary analyses (including Clinical Responder Outcome at the Interim Visit) were all supportive of the primary analysis. All showed a significant effect of the 2g arm over placebo on Nugent Score and Therapeutic Outcome at the Interim and TOC visits as shown in Table 3

Table 3
SYM-1219-301: Analysis of Secondary Endpoints

	Secnidazole 2 g (n=107)	Placebo (n=57)	p-value*	Difference (95% CI)**
Clinical Outcome at Interim Visit				
Responder	62 (57.9)	14 (24.6)	p< 0.001	33.3 (17.4, 49.2)
Non-Responder	35 (32.7)	31 (54.4)		
Missing	10 (9.3)	12 (21.1)		
Nugent Score at TOC				
Normal (0-3)	47 (43.9)	3 (5.3)	p< 0.001	38.6 (26.2, 51.0)
Abnormal (≥4)	52 (48.6)	51 (89.5)		
Missing	8 (7.5)	3 (5.3)		
Nugent Score at Interim Visit				
Normal (0-3)	49 (45.8)	2 (3.5)	p< 0.001	42.3 (30.4, 54.2)
Abnormal (≥4)	48 (44.9)	43 (75.4)		
Missing	10 (9.3)	12 (21.1)		
Therapeutic Outcome at TOC				
Responder	37 (34.6)	2 (3.5)	p< 0.001	31.1 (19.6, 42.6)
Non-Responder	62 (57.9)	52 (91.2)		
Missing	8 (7.5)	3 (5.3)		
Therapeutic Outcome at Interim Visit				
Responder	37 (34.6)	2 (3.5)	p< 0.001	31.1 (19.6, 42.6)
Non-Responder	60 (56.1)	43 (75.4)		
Missing	10 (9.3)	12 (21.1)		
Investigator's Clinical Assessment				
Additional BV treatment not required	68 (63.6)	16 (28.1)	p< 0.001	35.5 (19.3, 51.7)
Additional BV treatment required	32 (29.9)	38 (66.7)		
Missing	7 (6.5)	3 (5.3)		

*p-value of CMH test adjusted for # of BV episodes and race strata
**Difference is Secnidazole –placebo and 95% confidence interval
Source: FDA Statistical Review, Table 8

The main subgroups analyzed were race and number of previous BV episodes. In the subgroup of Black patients, overall response rates were lower. The treatment differences between secnidazole and placebo were comparable to the overall trial population in Trial 1219-201 and lower in Trial 1219-301 as shown in Tables 4 and 5.

Table 4
SYM-1219-201: Clinical Outcome Responder at TOC by Race (mITT)

	Secnidazole 1 g	Secnidazole 2 g	Placebo
White	12/18 (66.7) 29.2 (-4.8, 63.2)	24/32 (75.0) 37.5 (9.4, 65.6)	9/24 (37.5)
Black	21/42 (50.0) 44.1 (24.4, 63.8)	15/26 (57.7) 51.8 (27.8, 75.8)	2/34 (5.9)
Others	0/4	3/4	0/4

Difference of Secinidazole group minus placebo and 95% confidence interval

Table 5
SYM-1219-301: Clinical Outcome Responder at TOC by Race (mITT)

	Secnidazole 2 g (n=107)	Placebo (n=57)	Difference (95% CI)
White	29/46 (63.0)	5/26 (19.2)	43.8 (20.2, 67.4)
Black	27/59 (45.8)	6/29 (20.7)	25.1 (3.1, 47.1)
Others	1/2	0/2	

Findings were similar in the subgroup of patients with 4 or more episodes of BV in the past year.

We concur with the conclusion of the Clinical and Statistical Reviewers that substantial evidence of efficacy of the 2 g secnidazole dose for the treatment of BV in adult women has been provided. The SYM1219- 201 and SYM1219-301 trials enrolled a representative BV population and the trial designs were generally consistent with Agency guidance for BV trials. Benefit was shown on the primary measure of Clinical Response as well as on secondary measures such as Nugent Score and Therapeutic Response (including at the interim visit for Trial SYM1219-301). Although there was significant treatment difference for secnidazole relative to placebo, approximately 40% of subjects did not respond to therapy, highlighting the difficulty in treating this syndrome. Black patients and those patients with a history of 4 or more BV episodes in the past 12 months had lower overall response rates.

Because adequate numbers of adolescent, geriatric, or pregnant patients were not enrolled in the trials, no data are available regarding the efficacy of secnidazole in these subpopulations. No data were submitted regarding treatment for recurrent BV, nor is there sufficient information to assess the frequency of relapse with secnidazole. No comparisons can be made regarding efficacy for treatment of BV relative to currently approved drugs for BV.

8. Safety

The review of safety was conducted by Dr. Mayurika Ghosh.

During the secnidazole development program, a total 783 subjects were exposed to the drug, including 589 subjects in the BV trials and 194 in phase 1 trials; 518 subjects in the BV trials received the proposed treatment dose of 2 g. The safety analysis was primarily conducted in subjects enrolled in the two randomized, placebo controlled BV trials (Trials SYM1219- 201 and SYM 1219-301) and a third open label single arm safety trial (TrialSYM 1219-350).

Additional safety data were available from the use of secnidazole outside the US.

Overall, the secnidazole 2 g and placebo arms were well-matched in terms of ethnicity, age, prior BV episodes, and baseline health.

No deaths occurred during the trials. Four SAEs were reported, all in the 2 g secnidazole arm (syncope, loss of consciousness, wound, and ectopic pregnancy); one event (loss of consciousness) was thought to be related to the drug. In this event, a subject consumed alcohol

after receiving secnidazole. This was followed by nausea and eventually loss of consciousness with an associated fall and nasal fracture. The patient recovered with symptomatic treatment.

Since the treatment regimen is only a single dose, study treatment discontinuation was not a major review concern regarding trial interpretability. Few patients discontinued from the study, all due to VVC.

The most frequent TEAEs probably related to 2 g of secnidazole were VVC (9.6%), headache (3.6%), nausea (3.6%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal pruritus (2.0%) in the pooled SYM1219-201/301 trials and VVC (8.4%), nausea (5.3%), vomiting (2.5%), and dysgeusia (3.4%) in trial SYM 1219-350. The risk difference analysis of the AEs showed that nausea, vomiting and diarrhea, and VVC occurred at a higher frequency in the 2 g arm of the controlled trials compared to placebo. Few TEAEs were severe; the vast majority of TEAEs were mild.

VVC was the most commonly reported TEAE. A total of 46 subjects in the 2 g secnidazole arm developed VVC. In the controlled studies alone, 19 subjects in the 2 g arm developed VVC vs. 4 in the placebo arm. In general, these infections were not severe and most subjects recovered. A Warning has been included in the product label regarding an association of secnidazole with VVC.

In terms of laboratory parameters, no concerning hematologic findings were noted. However, given hematologic changes with other drugs in this class (e.g., transient neutropenia) we will assess this further during post-approval pharmacovigilance safety monitoring.

No Hy's Law cases were detected and clear trends were not noted with regard to liver enzyme elevation. A few cases of transaminase elevation were noted, however causation was difficult to discern due to comorbidities/concomitant medications and elevations were generally modest. Two subjects exposed to 2 g secnidazole in Trial SYM1219-350 had ALT elevation > 10X upper limit of normal. Both cases had confounding factors. One patient with baseline ALT elevation of 271 IU/L, had an ALT value of 472 IU/L at an unscheduled visit. At the end of the study, the ALT value was 259. She was also receiving Effexor and naproxen. The second patient was a 30 year old female with history of diabetes and nonalcoholic fatty liver disease whose baseline values of ALT increased from 23 to 626 U/L, AST from 14 to 435 U/L and ALP from 108 to 196 U/L at the end of the study. She also had associated nausea and vomiting. The total bilirubin was normal. She had a plantar burn wound for which she had received multiple antibacterial drugs. Data following the end of study visit was not available for either of these patients.

In a thorough QT study, at therapeutic concentrations, secnidazole did not prolong the QTc interval to any clinically relevant extent; at 3-fold the therapeutic concentrations, the largest mean ΔQTc was 8 ms with upper bound of two-sided 90% confidence interval of 11 ms.

Though pregnant women were excluded from the clinical trials, seven subjects were found to be pregnant during the course of the studies. However, no conclusion can be drawn regarding the effects of secnidazole on pregnancy from these subjects (3 chose to have elective

abortions, 2 had healthy pregnancies, and 2 were lost to follow up. There are no concerning reports in the published literature or postmarketing reports from other countries regarding potential adverse effects of secnidazole on pregnancy.

Findings from the published literature based on marketing experience in other countries generally identified similar safety findings as the data reviewed in this NDA.

We concur with Dr. Ghosh that there are no safety concerns that preclude approval.

9. Advisory Committee Meeting

The NDA was not discussed at an Advisory Committee meeting as there were as there were no specific questions that needed input from the committee.

10. Pediatrics

Though postmenarchal adolescent girls were not excluded from TrialsSYM 1219-301 and SYM 1219-350, very few adolescents were enrolled. An iPSP has been submitted and agreed to by the Agency, including the Pediatric Review Committtee (PeRC). A study of secnidazole in (b) (4) postmenarchal adolescent girls with BV will be conducted as a postmarketing requirement. This study will primarily focus on safety as efficacy and systemic exposure would be expected to be similar to adult females and extrapolation of efficacy seems appropriate. The title of the study and agreed upon timelines are provided in Section 13 of this review.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspection/review was conducted by Dr. John Lee. Three investigator sites as well as the contract research organization (CRO) conducting the studies were inspected and found to be acceptable. Only one inspection was classified as Voluntary Action Indicated (VAI) for a minor violation for one investigator.

12. Labeling

The Prescribing Information (PI), carton container, and Patient Package insert (PPI) have been reviewed by the Office of Prescription Drug Promotion (OPDP), Division of Medical Policy Programs (DMPP), and the Office of Surveillance and Epidemiology (OSE), and their comments have been incorporated in labeling.

Secnidazole is proposed for the treatment of BV in adult women without regard to pregnancy. Other nitromidazoles are currently contraindicated in the first trimester of pregnancy and the

prescribing information of other nitromidazoles approved for BV currently state that the drug is indicated in non-pregnant women. The review team consulted with the Division of Pediatric and Maternal Health (DPMH) regarding this issue as part of the NDA review. Reproductive toxicology studies in animals for secnidazole were negative. Secnidazole is genotoxic based on the Bacterial Reverse Mutation Assay. Other drugs in the class have been associated with carcinogenicity in animals. Given the lack of adverse findings in animals in reproductive toxicology studies and the lack of human data in pregnancy, the review team and the DPMH consultant concluded that there is insufficient evidence to contraindicate the use of secnidazole in any trimester of pregnancy. Both the genotoxicity finding and a class Warning regarding carcinogenicity will be included in the Prescribing Information.

A Warning regarding risk of VVC has been included in the Prescribing Information. Awareness of this possible adverse reaction can lead to appropriate monitoring and early treatment by both the patient and the practitioner.

The proprietary name of Solosec was reviewed and found to be acceptable.

13. Postmarketing Recommendations

No risk evaluation and mitigation strategies (REMS) are recommended.

The Applicant has agreed to the following postmarketing requirement (PMR) and timelines.

3249-1: Conduct an open label, multicenter, safety study of Solosec (secnidazole) oral granules in healthy post menarchal adolescent girls age 12 years to less than 18 years old with bacterial vaginosis.

Draft Protocol Submission: 12/2017
Final Protocol Submission: 03/2018
Study/Trial Completion: 03/2020
Final Report Submission: 03/2021

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

/s/

SHRIMANT MISHRA
09/12/2017

SUMATHI NAMBIAR
09/12/2017

JOHN J FARLEY
09/12/2017