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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Mayurika Ghosh, MD
NDA 209363
SYM 1219 (secnidazole)

CLINICAL REVIEW

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Division/Office	Division of Anti-infectives (DAIP)
Reviewer Name(s)	Mayurika Ghosh, MD
Review Completion Date	May 5, 2017, revised May 26, 2017
Established Name	SYM-1219 (Secnidazole)
(Proposed) Trade Name	Solosec
Applicant	Symbiomix Therapeutics LLC
Formulation(s)	Oral granules
Dosing Regimen	2 gms orally once
Applicant Proposed Indication(s)/Population(s)	Bacterial Vaginosis (BV)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Bacterial Vaginosis in adults

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Product Information

SYM-1219 (secnidazole) is an oral, antimicrobial drug in the 5-nitroimidazole class representing a new chemical entity (NCE) in the United States (US), for the treatment of women with Bacterial Vaginosis (BV).

Generic Name: Secnidazole

Proposed Trade Name: The Applicant has proposed a trade name of Solosec on January 30, 2017.

Drug Class: 5-nitroimidazole

Proposed indication, age group: Treatment of Bacterial Vaginosis, Adults

Proposed dosing regimen, route of administration, dosage form: Secnidazole Oral Granules, (SYM-1219), 2g provided as a granule formulation for sprinkling on (b) (4) for oral administration. The granules will be administered orally as a single dose with soft foods such as applesauce, yogurt or pudding.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on clinical efficacy and safety data submitted by the Applicant there is adequate evidence to recommend the approval of secnidazole as a safe and efficacious treatment for non pregnant women with bacterial vaginosis (BV).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

BV is the most common cause of vaginitis, occurring in 29 percent of the general population of women aged 14 to 49 years and 50 percent in African-American women. Although 50 to 75 percent of women with BV are asymptomatic, symptomatic patients present with an off-white, thin, and homogeneous "fishy smelling" discharge. Women with symptomatic BV infection are treated with metronidazole, clindamycin or tinidazole. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms within three months and more than 50 percent experience a recurrence within 12 months. There are prospective cohort studies demonstrating a possible association between BV and both HIV acquisition and preterm delivery. SYM-1219 (secnidazole) is an antimicrobial drug in the 5-nitroimidazole class developed as a single dose of oral granules sprinkled onto soft food (applesauce, yogurt or pudding) for the treatment of adult women with BV. Secnidazole was granted Qualified Infectious Disease Product designation on the basis of its possible association with HIV acquisition and preterm delivery. Secnidazole demonstrated superiority to placebo for the treatment of BV in two randomized controlled trials (SYM 1219-201 and SYM 1219-301). The primary endpoint for both trials was the clinical outcome evaluated at the test of cure (TOC) visit (Day 21 to 30) in the modified intent to treat (mITT) population. In trial SYM 1219-201, there were 67.7% (42/62) clinical outcome responders in the 2 gm secnidazole arm compared to 17.7% (11/62) in placebo ($p < 0.001$). In trial SYM 1219-301, there were 53.3% (57/107) clinical outcome responders compared to 19.3% (11/57) in placebo arm ($p < 0.001$). In terms of secondary endpoints, a greater percentage of patients receiving SYM-1219 2 g achieved normal Nugent score and therapeutic response compared to placebo in the two trials at the TOC visit, which was statistically significant. In trial SYM 1219-301, about 58% (62/107) of the subjects were clinical outcome responders at the interim visit in the secnidazole arm versus 24.6% (14/57) in the placebo arm in the mITT population ($p < 0.001$), and 68% of subjects (68/100) in the 2gm secnidazole arm needed no additional BV treatment compared to 29.6% (16/54) of subjects in the placebo arm. Overall, the results from the clinical trials provide substantial evidence of efficacy of SYM-1219 2 g as treatment of patients with BV. A single oral dose therapy in treating BV would be convenient and would be expected to improve patient compliance compared to the current treatment options. Secnidazole has a tolerable safety profile. Vaginal fungal infections were the most commonly reported Treatment emergent adverse event (TEAEs). The Adverse events (AEs) of nausea, vomiting, diarrhea, dysgeusia, headache, diarrhea fungal superinfections were seen more frequently in the secnidazole arm compared to placebo, however these AEs are all seen with other nitroimidazoles like metronidazole and tinidazole. Approval of secnidazole for use in the treatment of adult patients with BV infection is fully supported by the available evidence of efficacy and safety.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Bacterial vaginosis (BV) is a common cause of vaginitis in women of childbearing age which could progress to a serious condition. There are epidemiological associations between BV and other adverse health outcomes such as human immunodeficiency virus acquisition and preterm birth. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms within three months and more than 50 percent experience a recurrence within 12 months.	This is a disease which could progress to a serious condition for which an approved therapy that met regulatory evidentiary and safety standards would be of significant benefit to patients and clinicians.
Current Treatment Options	The Center for Disease Control(CDC) recommended therapies for BV include topical or oral metronidazole, topical or oral clindamycin, or oral tinidazole. Of these, 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. These treatments are generally given from 2-7 days. Only the clinical studies with tinidazole were conducted using the primary endpoint of	A single oral dose therapy with a tolerable safety profile and effective in treating BV

Dimension	Evidence and Uncertainties	Conclusions and Reasons																				
	therapeutic cure (based on both resolution of 4 out of 4 Amsel’s criteria and a Nugent score of <4).	would be convenient and therefore improve patient compliance compared to the current treatment options.																				
Benefit	The Applicant performed two clinical trials SYM 1219-201 and SYM 1219-301with secnidazole to demonstrate efficacy in the treatment of bacterial vaginosis. The primary endpoint for both trials was the Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30) in the mITT population. The results of the primary and secondary endpoint are summarized below. Table 1-Efficacy of Secnidazole for Treatment of Bacterial Vaginosis in Two Randomized, Double-Blind, Placebo-Controlled Trials in the Modified-Intent-to-Treat Population at 21-30 Days <table><tr><th></th><th colspan="2">SYM 1219-201</th><th colspan="2">SYM 1219-301</th></tr><tr><th></th><th>Secnidazole 2 gm (N=62) n (%)</th><th>Placebo (N=62) n (%)</th><th>Secnidazole 2 gm (N=107) n (%)</th><th>Placebo (N=57) n (%)</th></tr><tr><td>Primary endpoint</td><td></td><td></td><td></td><td></td></tr><tr><td>Clinical Responder</td><td>42 (67.7)</td><td>11 (17.7) p<0.001</td><td>57 (53.3)</td><td>11 (19.3) p<0.001</td></tr></table>		SYM 1219-201		SYM 1219-301			Secnidazole 2 gm (N=62) n (%)	Placebo (N=62) n (%)	Secnidazole 2 gm (N=107) n (%)	Placebo (N=57) n (%)	Primary endpoint					Clinical Responder	42 (67.7)	11 (17.7) p<0.001	57 (53.3)	11 (19.3) p<0.001	The trials were adequate and well-controlled with robust endpoints conducted in a representative patient population. The treatment effect of secnidazole was greater than placebo across all endpoints. The evidentiary standard has been met with
	SYM 1219-201		SYM 1219-301																			
	Secnidazole 2 gm (N=62) n (%)	Placebo (N=62) n (%)	Secnidazole 2 gm (N=107) n (%)	Placebo (N=57) n (%)																		
Primary endpoint																						
Clinical Responder	42 (67.7)	11 (17.7) p<0.001	57 (53.3)	11 (19.3) p<0.001																		

Dimension	Evidence and Uncertainties					Conclusions and Reasons
	Secondary endpoints					regards to treatment of BV by secnidazole. A single dose regimen in the treatment armamentarium would significantly benefit patient.
	Nugent Score Cure	25 (40.3)	4 (6.5) p<0.001	47 (43.9)	3 (5.3) p<0.001	
	Therapeutic responders	25 (40.3)	4 (6.5) p<0.001	37(34.6)	2(3.5) p<0.001	
	Clinical responder(interim visit)			62(58)	14(24.6) p<0.001	
	Investigator’s Clinical Assessment(No additional BV treatment needed)			68/100(68)	16/54(29.6) p<0.001	
		SYM 1219-201		SYM 1219-301		
		Secnidazole 2 gm (N=62) n (%)	Placebo (N=62) n (%)	Secnidazole 2 gm (N=107) n (%)	Placebo (N=57) n (%)	
	Primary endpoint					
	Clinical Responder	42 (67.7)	11 (17.7) p<0.001	57 (53.3)	11 (19.3) p<0.001	
	Secondary endpoints					
	Nugent Score Cure	25 (40.3)	4 (6.5) p<0.001	47 (43.9)	3 (5.3) p<0.001	

Dimension	Evidence and Uncertainties					Conclusions and Reasons
	Therapeutic responders	25 (40.3)	4 (6.5) p<0.001	37(34.6)	2(3.5) p<0.001	
	Clinical responder(interim visit)			62(58)	14(24.6) p<0.001	
	Investigator’s Clinical Assessment(No additional BV treatment needed)			68/100(68)	16/54(29.6) p<0.001	
	In trial SYM 1219-201, there were 67.7% (42/62) Clinical outcome responders in the 2 gm secnidazole arm compared to 17.7%(11/62) in placebo(there were 51.6% clinical outcome responders in the 1 gm secnidazole arm)(p<0.001).In trial SYM 1219-301, there were 53.3%(57/107) Clinical outcome responders compared to 19.3%(11/57) in placebo arm(p<0.001). In terms of the secondary endpoints, the 2 gm secnidazole had a greater response than placebo across the endpoints. Although, the percentage of pooled Clinical Outcome Responders was fewer in Blacks than all others (49.4% and 67.9%, respectively), a greater percentage of Black patients treated with SYM-1219 2 g compared to placebo were Clinical outcome responders (49.4% and 12.7%, respectively), had normal Nugent score (40.0% and 4.8%, respectively), and were Therapeutic outcome responders (32.9% and 4.8%, respectively) .					
Risk	• The safety database included patients from two randomized, placebo controlled BV trials(SYM 1219-201 and SYM 1219-301)and an open label safety trial(SYM 1219-350). The drug exposure data is considered adequate. There were only 4 out of 725 subjects with treatment emergent serious adverse events, including one ectopic pregnancy.					No major safety trends have been identified in the trials. The safety

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There were no deaths in the trials. The incidence of TEAEs were greater in the SYM 1219 2 gm arm compared to placebo; 28.9% compared to 15.4% respectively in trial SYM 1219-201/301. There was a 29.6% incidence of TEAEs in trial SYM 1219-350. The frequency of TEAEs (treatment related) were also higher in the SYM 1219 2gm arm(16%) than the placebo(5.9%) groups. Vaginal fungal infections were the most commonly reported TEAEs. The AEs of nausea, vomiting, diarrhea, dysgeusia, headache, diarrhea fungal superinfections which were seen more frequently in the secnidazole arm compared to placebo are all seen with other nitroimidazoles like metronidazole and tinidazole. AEs commonly noted in literature from outside U.S use of secnidazole were nausea, dysgeusia, abdominal pain, headache, and vomiting, similar to the AEs noted in the BV clinical trials.	profile of the drug is consistent with the known safety profile of nitroimidazoles.
<u>Risk Management</u>	• Vulvo-vaginal yeast infections are an expected adverse reaction of an antimicrobial product which causes a disruption of the normal microbial flora. • The safety and efficacy of secnidazole in pediatric patients have not been studied. The Applicant has requested a deferral for an open label, safety study in healthy postmenarchal adolescent girls with bacterial vaginosis. • The trials did not include pregnant patients but there were 7 pregnancies reported. Three subjects had elective abortions, including one subject who had removal of an ectopic pregnancy. Three subjects were lost to follow up, including one subject who elected to have an abortion. There were 2 healthy pregnancies reported. These data cannot definitely establish or exclude any secnidazole-associated risk during pregnancy. Imidazole class drugs, such as metronidazole, have been associated with tumorigenic effects in nonclinical studies and can cross the placenta and enter the fetal circulation. However, the available data with secnidazole use in pregnant women are limited and insufficient to inform a drug-associated risk of major birth defects and miscarriages, particularly given what is known about the use of other imidazole class drugs in	Labeling indicates that approval is only for adults. The Division agreed with the Applicants proposed pediatric plan. The safety finding of Vulvovaginal fungal infection may lead to inclusion in the

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pregnancy as well as the intrinsic properties of imidazoles. (b) (4)	Warnings and Precautions section of the label.

2 Therapeutic Context

2.1. Analysis of Condition

BV is the most common cause of vaginitis in women of childbearing age. Bacterial vaginosis is most often associated with an overgrowth of specific bacterial species, including *Gardnerella vaginalis*, *Mobiluncus* species, *Bacteroides* species, and a variety of other transient microflora, with a concomitant comparative decrease in *Lactobacillus* species(1). In the United States, the National Health and Nutrition Examination Survey (NHANES) data estimates the prevalence of BV to be 29 percent in the general population of women aged 14 to 49 years and 50 percent in African-American women(2). Sexual activity is a risk factor for bacterial vaginosis and the presence of other sexually transmitted infections appear to be associated with an increased prevalence of BV. Fifty to 75 percent of women with BV are asymptomatic. Symptomatic patients present with an off-white, thin, and homogeneous "fishy smelling" discharge. The diagnosis of BV is based on the presence of at least three of the following four Amsel criteria:

- Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls
- Vaginal pH greater than 4.5
- Positive whiff-amine test, defined as the presence of a fishy odor when 10 percent potassium hydroxide (KOH) is added to a sample of vaginal discharge
- Clue cells on saline wet mount, comprising at least 20 percent of epithelial cells

Gram's stain of vaginal discharge is the gold standard for diagnosis of BV. The Gram-stained smear is evaluated using Nugent criteria(3). The scoring system is as follows:

Table 2-Nugent Scoring System for Gram Stain of Vaginal Smears

<i>Lactobacillus</i>	Score	<i>Gardnerella</i> <i>Bacteroides</i>	Score	Curved Gram variable rods	Score	Total Score
≥ 30	0	0	0	0	0	0
5-30	1	<1	1	< 1	1	3
1-4	2	1-4	2	1-4	1	5
< 1	3	5-	3	5-	2	8
0	4	≥ 3	4	≥ 30	2	1

A Nugent score of at least 7 is indicative of BV. A score of 4-6 is considered intermediate and a score of 0-3 is considered normal.

There are epidemiological associations between BV and other adverse health outcomes, such as sexually transmitted infections including human immunodeficiency virus, herpes simplex

virus type 2 (HSV-2), gonorrhea, chlamydia, and trichomonas, postoperative infections, preterm birth, and other gynecological infections. Women with symptomatic BV infection are generally treated with metronidazole, tinidazole, or clindamycin. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms within three months and more than 50 percent experience a recurrence within 12 months.

Medical reviewer comment: The Applicant submitted a request for Qualified Infectious Disease Product (QIDP) designation for secnidazole for the treatment of bacterial vaginosis on March 20, 2013. The request was denied on January 21, 2014 since there was not adequate information at that time to conclude that bacterial vaginosis is a serious or life-threatening infection. The epidemiological associations between BV and sexually transmitted infections were thought to be subject to confounding. There was also no established benefit of antibacterial drug treatment of bacterial vaginosis in the prevention of obstetrical complications, particularly preterm birth. Further, a placebo controlled trial in this condition was considered acceptable when the likelihood of disease progression was low. On September 15, 2014, the Applicant resubmitted the QIDP designation request for SYM 1219 (secnidazole) for the treatment of BV providing further evidence from prospective cohort studies demonstrating a possible association between BV and both HIV acquisition and preterm delivery. Although clinical trials failed to demonstrate a consistent benefit of treatment of BV in the prevention of preterm delivery and even though HIV acquisition or preterm delivery did not represent direct progression of a primary infection, the Division concluded that for a subgroup of women, it is reasonable to conclude that BV increased the likelihood of progression from a less severe condition to a more serious one. QIDP designation request was therefore granted on November 18, 2014(4,5).

2.2. Analysis of Current Treatment Options

The following treatments are currently available for the treatment of BV.

The CDC recommended therapies for BV include topical or oral metronidazole, topical or oral clindamycin, or oral tinidazole(6).

Table 3-CDC Recommended Treatments for BV - 2015 Treatment Guidelines

Recommended Treatments	Alternative Treatments	Additional Treatments
Metronidazole 500 mg orally twice a day for 7 days,	Tinidazole 2 g orally daily for 2 days,	Metronidazole extended release (ER) 750 mg once daily for 7 days
OR	OR	
Metronidazole gel 0.75% one full applicator (5g) intravaginally once a day for 5 days,	Tinidazole 1 g orally once daily for 5 days	
OR	OR	
Clindamycin cream 2% one full applicator (5g) intravaginally at bedtime for 7 days	Clindamycin 300 mg orally twice daily for 7 days OR	
	OR	
	Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days	

Of the CDC recommended therapies, metronidazole vaginal gel 0.75%, extended release oral metronidazole tablets, tinidazole tablets, clindamycin vaginal cream and clindamycin vaginal suppository are FDA approved for the treatment of BV. Additionally, metronidazole vaginal gel 1.3% is also approved for the treatment of BV. Other oral preparations of metronidazole and oral clindamycin are not FDA approved for this indication but are marketed for other indications.

The therapeutic cure rates reported in the clinical study conducted with tinidazole were based on resolution of 4 out of 4 Amsel's criteria and a Nugent score of <4. The cure rates for previous clinical studies with other products approved for bacterial vaginosis were based on resolution of either 2 or 3 out of 4 Amsel's criteria. At the time of approval for these earlier products, there was no requirement for a Nugent score on Gram stain, resulting in higher reported rates of cure for bacterial vaginosis compared to tinidazole.

The safety and tolerability issues with treatments for BV are summarized in the table below.

Table 4-Safety issues with treatment available for BV

Product (s) Name	Important Safety and Tolerability Issues
Metronidazole(oral)	Metallic taste, nausea (in 10 percent of patients), transient neutropenia (7.5 percent), a disulfiram-like effect with alcohol, prolongation of International Normalized Ratio in patients taking vitamin K antagonists (eg, warfarin), and peripheral neuropathy
Metronidazole vaginal gel	Vulvovaginal candidiasis, headache, vulvovaginal pruritus, nausea, diarrhea, and dysmenorrhea.
Clindamycin vaginal cream	Vaginosis fungal (14%), headache (7%), back pain (5%), constipation (2%), and urinary tract infection (2%), possible C. difficile diarrhea.

Clindamycin (oral)	Abdominal pain, pseudomembranous colitis, esophagitis, nausea, vomiting, and diarrhea, esophageal ulcer, metallic taste, hypersensitivity reactions, jaundice, abnormal liver function tests.
Tinidazole (oral)	Seizures, neuropathy, leucopenia, vaginal candidiasis, metallic/bitter taste, nausea, weakness/fatigue/malaise, dyspepsia/cramps/epigastric discomfort, vomiting, anorexia, headache, dizziness and constipation.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

SYM 1219 (secnidazole) is a new molecular entity (NME) and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The presubmission regulatory history and milestones related to the current NDA submission are summarized as follows:

March 20, 2013: Qualified Infectious Disease Product (QIDP) designation was requested.

September 25, 2013: A Pre-IND meeting was held with the Agency. The DAIP advised that the primary analysis population in the BV trials be a modified intent-to-treat (mITT) population defined by excluding those with a Nugent score < 4 or positive for other vulvovaginal infections based on baseline tests.

December 18, 2013: IND 117811 was submitted for secnidazole .

January 21, 2014: QIDP request was denied.

May 28, 2014: The Applicant started enrollment for their phase 2 trial(SYM1219-201) and completed this on October 4, 2014.

September 15, 2014: QIDP designation request was resubmitted.

November 18, 2014: QIDP designation request was granted.

January 21, 2015: In this meeting, DAIP agreed with the Applicant that a study conducted in healthy volunteers comparing the relative bioavailability (BA) of secnidazole granules when admixed separately with applesauce, pudding, and yogurt was acceptable to determine which of these could be included in the Phase 3 study.

March 18, 2015: In this End of Phase 2 meeting, DAIP advised the Applicant on their phase 3 clinical developmental program. The Division discussed the timing of the efficacy assessments to be concordant with the FDA Draft guidance on BV. The Division suggested increasing the baseline Nugent score from >4 to >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 Applicant acknowledged the importance of collecting safety data in pregnant patients (b) (4)

The Applicant also planned to conduct an open label safety study (Trial SYM 1219-350).

May 4, 2015- The Applicant started enrollment for the phase 3 efficacy and safety trial (SYM 1219-301) and completed this on September 24, 2015.

May 11, 2015- Initial Pediatric Study plan submitted.

June 23, 2015: A Fast Track designation request was submitted.

August 12, 2015: Fast Track designation request was granted.

November 12, 2015: The Division advised the Applicant regarding the revised Statistical analysis plan for the phase 3 trial. The definition of clinical responder with respect to the vaginal discharge was to include either normal vaginal discharge or “abnormal discharge that is not consistent with BV”. The Division recommended that a clinical responder require a return to normal physiological discharge i.e. a subject with abnormal discharge that is not consistent with BV would not be considered a clinical responder. The alternate definition proposed for clinical responder could be used to conduct a sensitivity analysis.

May 4, 2016: Pre-NDA meeting- The Division agreed that the overall clinical program was acceptable for NDA filing. The Applicant was asked to submit the case report forms for all pregnancies reported in the trial as well as a 10% random sample with the NDA. The Applicant agreed to use the original definition of clinical responder.

January 14, 2016: The Agency accepted the Applicant’s Agreed Initial Pediatric Study Plan (IPSP) for the treatment of BV. Under the approved plan, the Applicant is requesting deferral of a pediatric open-label safety study in post-menarchal adolescent girls. Although the two studies, SYM-1219-301 and SYM-1219-350 provided for enrollment of post-menarchal adolescent girls, the enrollment was insufficient, resulting in a deferral request. The agreed IPSP provides for a waiver from conducting a pediatric study in the following pediatric populations because BV is not associated with these populations: boys of all pediatric age ranges, and girls in the following age ranges: birth to one month, 1 month to 2 years, 2 years to 12 years, and premenarchal adolescents 12 to <18 years.

3.3. Foreign Regulatory Actions and Marketing History

Secnidazole was originally approved in France in 1979 and is commercially available in a number of other countries like Bangladesh, Bosnia & Herzegovina, Brazil, China, Colombia, Congo, Costa Rica, Dominican Republic, Ecuador, El Salvador, France, Georgia, Guatemala, India, Luxembourg, Oman, Nicaragua, Mexico, Pakistan, Panama, Peru, Philippines, Portugal, Turkey, Venezuela, and Vietnam for multiple indications including trichomoniasis, bacterial vaginosis, giardiasis, and amoebiasis.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Clinical trials in this program were conducted in adherence with the principles of Good Clinical Practices (GCP), including directions set forth in relevant regulatory guidance (for example, ICH E6) and in keeping with study-subject protection as outlined in the Declaration of Helsinki (1964).

A request for site inspections was submitted to the Division of Scientific Investigations for the following U. S. sites due to high subject enrollments:

SYM 1219-201, SYM 1219-301, SYM 1219-350- Site 4, Principal investigator(PI)- Chavoustie, Steven E, number of subjects(N)= 11/18/22 Florida

SYM 1219-201, SYM 1219-301, SYM 1219-350-Site 5, PI- Eder, Scott E, N=11/15/3 New Jersey

SYM 1219-201, SYM 1219-301, SYM 1219-350- Site 12, PI- Morgan, Franklin G, N= 34/20/20 Virginia

The site inspections are ongoing at the time of this review.

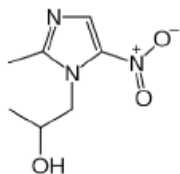
4.2. Product Quality

The proposed drug product is secnidazole 2gm orally , provided as a granule formulation for sprinkling on (b) (4) for oral administration. The granules will be administered with soft foods such as applesauce, yogurt or pudding. It is supplied in single-dose packets. Each packet provides 4.76 g of granules containing 2 g secnidazole. SYM 1219 (secnidazole) used in the clinical drug development program is the same as the 'to be marketed' product.

The chemical name is 1-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-2-ol

The following figure represents the structure of secnidazole:

Figure 1-Structure of secnidazole



Source: page 1 of Quality overall summary
Secnidazole belongs to the 5-nitroimidazole drug class.

Refer to Chemistry Manufacturing and Controls review for details.

4.3. Clinical Microbiology

Refer to the Clinical Microbiology review for details.

4.4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology Toxicology review for details. The safety pharmacology of SYM-1219 was evaluated in a respiratory safety pharmacology study in rats, a cardiovascular safety study in beagle dogs, a CNS safety study in rats, and in in vitro hERG channel assay. SYM-1219 inhibited hERG current by (Mean $\pm$ SEM; n = 4) $2.9 \pm 0.9\%$ at 10 μ M and $3.0 \pm 1.2\%$ at 300 μ M versus $1.6 \pm 0.7\%$ (n = 3) in control, but these changes were not statistically significant ($P < 0.05$) when compared to vehicle control values. The IC₅₀ for the inhibitory effect of SYM-1219 on hERG potassium current was estimated to be greater than 300 μ M.

SYM-1219 was evaluated in single and repeat dose studies in rats and dogs, genotoxicity, reproductive toxicity studies in rats and rabbits, and in phototoxicity study in rats. A 28 day study in rats did not have overt effects except mild histological changes in the adrenal gland, pituitary gland, and spleen. No significant safety concerns were identified based on cardiovascular, respiratory, and CNS evaluations. In terms of the genotoxicity studies, for the bacterial reverse mutation assay, SYM-1219 was concluded to be positive with tester strains TA100, TA1535 and WP2 uvrA in the presence and absence of S9 activation and tester strain TA98 in the presence of S9 activation; this is similar to metronidazole.

4.5. Clinical Pharmacology

Several clinical pharmacology studies have been conducted to describe the rate and extent of secnidazole bioavailability from the SYM-1219 formulation, the effect of administration with a meal or soft foods, and the impact of high doses of secnidazole on cardiac safety. The Applicant initiated the development program by assessing the single dose PK of SYM-1219 containing 1 g or 2 g of secnidazole sprinkled onto applesauce and by evaluating the potential for a drug

interaction between SYM-1219 and Ethinyl Estradiol(EE2) and Norethindrone(NET) in healthy female volunteers (Study SYM-1219-101). A food effect and bioequivalence study (Study SYM-1219-102) to evaluate the effect of a standard, high fat meal on the PK of SYM-1219 containing 2 g of secnidazole and to compare drug produced by 2 manufacturing sites for SYM-1219 has been completed. A PK study (Study SYM-1219-103) compared the bioavailability of SYM-1219 containing 2 g of secnidazole administered in different mediums (applesauce, pudding, and yogurt). In addition, a PK study to determine a supratherapeutic dose (Study SYM-1219-104) and a thorough QT study (Study SYM-1219-105) was also conducted.

4.5.1. Mechanism of Action

The mechanism of action and resistance of secnidazole are expected to be similar that of metronidazole since antibacterial activity is a function of the nitro group associated with the imidazole ring, which both molecules possess. The drug enters the cell as an inactive prodrug by simple diffusion, and the nitro group is then reduced by ferredoxin to a short lived toxic radical anion form that exerts the primary antimicrobial activity.

4.5.2. Pharmacodynamics

No pharmacodynamic studies were conducted. Refer to Clinical microbiology review, section 4.3.

4.5.3. Pharmacokinetics

Refer to the Clinical pharmacology review for details. The pharmacokinetics of SYM-1219 were evaluated as part of the 7-day and 28-day toxicology studies in rats and dogs, and in pregnant rats and rabbits. In addition, in vitro experiments were conducted to evaluate the inhibition and induction potential of SYM-1219 in human microsomes and hepatocytes. In vitro transporter studies were conducted.

Within a dose group, the PK of secnidazole is consistent and exhibits low variability. Following a 2-g dose, maximum secnidazole concentrations of approximately 45 mcg/mL are achieved within approximately 1.5 hours after dosing. The apparent volume of distribution (V/F) is low and protein binding is low (<5%). More than 50% of the absorbed dose is still evident in plasma at approximately 30 hours after dosing. Secnidazole is slowly metabolized in human liver microsomes (HLM) with generally $\leq 1\%$ conversion to metabolites after 90 min incubations at 1.5 mg/mL protein. Secnidazole does not significantly inhibit CYP enzymes. Secnidazole is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. In Study SYM-1219-101, the secnidazole half life was determined to be approximately 17 hours and was independent of the dose administered. The kidney and bile duct represent 2 equilibrated pathways of elimination. The urinary excretion of secnidazole (unconjugated) following single dose administration of SYM-1219 was low: only 13-15% of the administered dose was excreted unchanged into the urine.

4.6. Devices and Companion Diagnostic Issues

Not applicable because no device or companion is being marketed for the study drug.

4.7. Consumer Study Reviews

None performed.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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The following table summarizes the trials conducted to support the indication of BV.

Table 5-Clinical Trials for Secnidazole

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints/Objectives	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
SYM-1219-201	A Phase 2, Multi-Center, Parallel groups, Placebo-, controlled, double blind trial	Granules, 1 gram or 2 grams single dose, oral, sprinkled on applesauce	The primary endpoint was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). A Clinical Outcome Responder was defined as a patient with all of the following: 1) Normal vaginal discharge 2) Negative 10% KOH Whiff test 3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline. The following secondary endpoints were evaluated at the TOC/EOS visit (Day 21 to 30):	Single dose/ days 21-30	215	Women at least 18 years of age with BV	24 centers in the U.S.

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			•Nugent Score: A score of 0 to 3 was considered normal; a score of 4 and above was considered abnormal. •Therapeutic Outcome: A Therapeutic Outcome Responder was defined as a Clinical Outcome Responder with a normal Nugent score (between 0-3). Safety endpoints: Adverse events (AEs), Vital signs, Physical examination, Pelvic Examinations, Laboratory assessments				
SYM-1219-301	A Phase 3, Multi-Center, Parallel groups, Placebo-controlled, double-blind trial	Granules, 2 grams single dose, oral, sprinkled on applesauce	The primary endpoint was similar to trial SYM 1219-201 which was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). The following secondary endpoints were evaluated at the Interim visit (Study Day 7-14) and the TOC/EOS visit (Study Day 21 to 30): •Nugent Score: A score of	Single dose/ days 21-30	189	Women and postmenarchal adolescent girls with BV	21 centers in the U.S.

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			0 to 3 was considered normal; a score of 4 and above was considered abnormal. •Therapeutic Outcome: A Therapeutic Outcome Responder was defined as a Clinical Outcome Responder with a normal Nugent score (between 0-3). •Clinical Outcome (Interim Visit only) •Investigator's Clinical Assessment: Investigator's opinion of the need for additional BV treatment (Yes or No) (at the TOC/EOS Visit only). Safety endpoints: Adverse events (AEs), Vital signs, Physical examination, Pelvic Examinations, Laboratory assessments				
Studies to Support Safety							
SYM-1219-350	Multi-Center, Open-label, Single Arm Safety Study	Granules, 2 grams single dose, oral, sprinkled on	Safety endpoints: Adverse events (AEs), Vital signs, Physical examination,	Single dose/ days 21-30	325	Women and postmenarchal	34 centers in the United States

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		applesauce	Pelvic Examinations, Laboratory assessments			adolescent girls with BV	
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							
SYM-1219-101	Single Center, Open-label Part A: Parallel groups Part B: Parallel groups	Granules, 1 or 2 grams single dose, oral, sprinkled on applesauce	Assess PK and safety 1 or 2 gram dose(Part A) and effect on PK of EE2 and NET (Part B)	Single dose	Part A: 28 Part B: 54	Healthy Females	Single center in U.S.
SYM-1219-102	Single Center, 3 way Cross-over, open label, Bioavailability trial	Granules, 2 grams single dose, oral, sprinkled on applesauce	Assess PK and safety of 2 gram dose in applesauce fed and fasted	Single dose	25	Healthy Females	Single center in U.S.
SYM-1219-103	Single Center, 3 way Cross-over, open label	Granules, 2 grams single dose, oral, sprinkled on applesauce, yogurt or pudding	Compare Bioequivalence and safety of 2 gram dose in applesauce, pudding, and yogurt	Single dose	24	Healthy Females	Single center in U.S.
SYM-1219-104	Single Center, Single blind, placebo controlled, two part study	Granules, 4 or 6 grams single dose, oral, sprinkled on applesauce	Assess PK and safety of 4 and 6 gram dose in applesauce	Single dose	Part A: 8 Part B: 8	Healthy Females and Males	Single center in U.S.
SYM-1219-105	Single Center, Cross-Over, Placebo-controlled, Positive controlled, Double-Blind trial	Granules, 2 or 6 grams single dose,	QT/QTc Study	Single dose	52	Healthy Females and Males	Single center in U.S.

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		oral, sprinkled on applesauce, placebo, moxifloxacin					
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5.2. Review Strategy

The Clinical Review is divided into two general parts: the review of efficacy and the review of safety. Both are conducted by the Medical Reviewer. Statistical analysis of efficacy is conducted by the statistical reviewer. A phase 2 trial (Trial SYM-1219-201) and a phase 3 trial (Trial SYM-1219-301) were conducted by the applicant to evaluate the safety and efficacy of secnidazole in BV. The efficacy assessment will be based on the independent results of these two trials. An additional open label phase 3 safety trial (Trial SYM-1219-350) was conducted and the results will be presented side by side along with the pooled randomized double blinded placebo controlled trials Trial SYM-1219-201 and Trial SYM-1219-301 to evaluate the safety of secnidazole. A pooled safety assessment of the healthy volunteer trials (Study SYM-1219-101, Study SYM-1219-102, Study SYM-1219-103, Study SYM-1219-104 and Study SYM-1219-105) will also be conducted to add to the safety evaluation.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial SYM-1219-201

6.1.1. Study Design

Overview and Objective

Trial SYM-1219-201 was a phase 2, multi-center, prospective, randomized, double-blind, placebo-controlled study to evaluate the effectiveness and safety of 1 gm and 2 gms of SYM-1219 for the treatment of women with bacterial vaginosis.

Trial Design

Date of first enrollment: May 28, 2014

Date of completion: October 6, 2014

Study center(s): 24 research centers in the US

Number of patients: A total of 215 patients were enrolled.

Test product: SYM-1219 1 gram, oral granules, SYM-1219 2 grams, oral granules.

Reference therapy: Placebo

Duration of treatment: single dose

The secnidazole active formulation contained active secnidazole and excipients of sugar spheres, povidone, polyethylene glycol 4000, ethyl acrylate, methyl acrylate copolymer, talc, and (b) (4). The matching placebo contained the same ingredients as the active formulation with the exception of secnidazole and the addition of (b) (4).

Inclusion Criteria

1. Able to give written informed consent.
2. Females at least 18 years of age and not menopausal, as determined by the Investigator (menopausal was defined as no menstrual periods for at least 12 continuous months, or in those who were surgically unable to have menstrual periods, were not menopausal based on clinical symptomatology).
3. Good general health as confirmed by a medical history and physical examination
4. Able to participate in the study as an outpatient, make required visits to the study center, and comply with all study requirements.
5. Had a negative urine pregnancy test result prior to study treatment initiation. In addition, female patients of childbearing potential must have been using an acceptable form of birth control as determined by the Investigator. Note: NuvaRing® or any other vaginal ring products were not permitted.
6. Agreed to abstain from alcohol for 3 days following study treatment.
7. Had a clinical diagnosis of bacterial vaginosis, defined as having all of the following criteria:
 - a. Off-white (milky or gray), thin, homogeneous vaginal discharge
 - b. Vaginal pH $\geq$ 4.7
 - c. Presence of Clue cells $\geq$ 20% of the total epithelial cells on microscopic examination of the vaginal saline wet mount
 - d. A positive 10% potassium hydroxide (KOH) Whiff test.
8. Had a Gram-stain slide Nugent Score $\geq$ 4 at the Baseline visit (Day 1)
9. Agreed to abstain from vaginal intercourse for at least 7 days following study treatment.
10. Agreed not to have any vaginal penetration or use any vaginal products for at least 7 days following treatment.
11. Agreed not to use vaginal douches or similar products for the duration of the study.

Medical Officer comment: The inclusion criteria state that the subjects had a Gram-stain slide Nugent Score $\geq$ 4 at the baseline visit. The FDA Draft Guidance for Industry- Bacterial Vaginosis: Developing Drugs for Treatment, July 2016 recommends that to enhance the reliability for the diagnosis of BV at enrollment, the Gram stain of the vaginal specimen should have a Nugent score of greater than or equal to 7. The Applicant however has analyzed the primary and secondary endpoints by baseline Nugent Score (4-6, 7-10) in the mITT population.

Exclusion Criteria

1. Pregnant, lactating, or planning to become pregnant during the study.
2. Menstruating or had vaginal bleeding at the Baseline visit (Day 1).
3. Were suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms, including candidiasis, Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae, or Herpes simplex (Note: Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis [by Polymerase Chain Reaction, PCR] results

were not available at the time of randomization).

4. Had active genital lesions, including active Herpes simplex lesions, or other vaginal or vulvar conditions which could confound the interpretation of the clinical response, as determined by the Investigator (patients with genital warts that were not being treated may have been enrolled).
5. Had received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days prior to the Baseline visit (Day 1).
6. Were using NuvaRing® or any other vaginal ring products.
7. Had consumed any alcohol within 12 hours prior to treatment with study medication.
8. Had a history of drug or alcohol abuse within the past 12 months, as determined by the Investigator.
9. Had participated in any investigational trial within 30 days or six half-lives of the test drug's biologic activity, whichever was longer, before the Baseline visit (Day 1).
10. Was participating in any investigational, observational or non-interventional study (either currently or during the study).
11. Had a known allergy to nitroimidazoles (e.g., metronidazole, tinidazole, nimorazole, secnidazole, etc.).
12. Had a history of an abnormal Pap smear which required cervical biopsy or cervical cauterization within 6 months of the Baseline visit (Day 1).
13. Had any history of cervical carcinoma or other carcinomas of the vagina or vulva.
14. Had donated or received one or more pints of blood within 30 days of the Baseline visit (Day 1).
15. Had any condition that interfered with their ability to understand or comply with the requirements of the study.

Randomization: Patients determined to be eligible based on the clinical assessments at the Baseline visit (Day 1) were randomized in a 1:1:1 ratio and received a single dose of SYM 1219 1 gm orally or SYM 1219 2 gm orally or placebo on Day 1 under fasted conditions (i.e., no food 2 hours prior to or 1 hour after dosing). Study drug was orally administered as a single dose with 4 ounces of unsweetened applesauce (Mott's® applesauce, a spoon, and an 8 ounce bottle of water were included in the treatment kits). Treatment compliance was ensured by visual inspection of the patient's mouth.

The randomization was stratified by the number of reported episodes of BV in the past 12 months (including the current episode): 3 or fewer episodes versus 4 or more episodes. Patients were asked to complete a daily telephone questionnaire (whether the subject was having their menstrual period and to rate the vaginal discharge and odor on a 5 point scale) on Days 1 through 7 and at the Test of Cure (TOC)/End of Study (EOS) visit. Patients were also contacted by telephone once on Day 8 to 10 to inquire about possible adverse events (AEs). A TOC visit was conducted between Day 21 and 30 or at EOS, if the final visit was not conducted between Day 21 and 30.

Blinding: The total volume of each single dose of study drug was the same in order to maintain blinding. Study drug supplies were packaged in a manner supporting the blinding of the study.

Prior and Concomitant Therapy:

All prescription and non-prescription medication and therapies (including vitamins, herbal medicines, or other non-traditional medicines), taken from 30 days prior to the single dose of study drug through the end of the study, were recorded in the eCRF.

The following medications and products were prohibited during study participation, as described below:

- Systemic antimicrobial therapies for the duration of the study, with the exception of oral antifungal therapy (e.g., oral fluconazole) to treat intercurrent conditions (e.g., candidiasis);
- Topical antimicrobial/antifungal/immunomodulatory therapies in the genital area (vagina, vulva, and surrounding soft tissue), including treatments for external genital warts;
- Warfarin;
- Systemic corticosteroids (intranasal and inhaled steroids were permitted).

The following Table shows the Schedule of Assessment of the Trial.

Table 6-Schedule of Assessments in Trial SYM 1219-201

Assessment	Baseline Visit	Patient Telephone Interview	Test of Cure (TOC)/EOS Assessment
	Day 1	Day 8-10	Day 21-30
Informed consent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X		X
Height/weight	X		
Urine pregnancy test ¹	X		X
Physical examination	X		X
Pelvic examination	X		X
External genitalia and vaginal exam	X		X
Vaginal discharge assessment	X		X
Vaginal wet mount for Clue cell assessment	X		X
Gram stain of vaginal fluid	X ²		X
10% KOH Whiff test	X		X
pH of vaginal fluid	X		X
STI Assessments	X ²		X ³
OSOM [®] Trichomonas Rapid Test	X ⁴		
Bimanual pelvic examination	X ⁵		X ⁵
Labs: Hematology, chemistry, and urinalysis	X ²		X
IWRS Randomization	X		

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Drug dosing	X		
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Patient daily telephone diary completion ⁶	X		X
Telephone interview of patient		X	
Investigator's Clinical Assessment			X

EOS = End of Study; IWRS = Interactive Web Response System; KOH = potassium hydroxide; STI = sexually transmitted infection; TOC = Test of Cure

1. Performed by site personnel (not sent to central laboratory).
2. Results were not available at the time of randomization.
3. Only as indicated as determined by the Investigator.
4. It was recommended that the vaginal sample for the OSOM[®] Trichomonas Rapid Test be obtained early in the collection process to ensure adequate sample for this evaluation.
5. A bimanual pelvic examination was performed after the vaginal discharge assessment and all of the vaginal samples were collected.
6. The telephone patient diary was completed starting predose on Day 1, daily on Days 2 through 7 and at the TOC/EOS visit.

Source: Page 24 of Clinical Study Report

During the telephone interview, the interviewer determined if the patient needed an interim clinic visit. If an interim visit was needed, the visit was scheduled, and the patient underwent a symptom-directed assessment. If an interim visit was not needed, the date and time of the TOC visit was confirmed with the patient (Day 21 to 30). If a patient required early termination (including for a positive STI result from samples obtained at the Baseline visit [Day 1]), or if the TOC visit was not conducted between Day 21 and 30, the patient was scheduled for an EOS visit with all procedures performed.

Definitions: Adverse event (AE): An AE was therefore any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of study drug, whether or not related to study drug.

A suspected adverse reaction was any AE for which there was a reasonable possibility that the drug caused the AE.

An AE or suspected adverse reaction was considered “unexpected” if it was not listed in the Investigator Brochure (IB) or was not listed at the specificity or severity that had been observed; or, if an IB was not required or available, was not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

An AE or suspected adverse reaction was considered “serious” if, in the view of either the Investigator or Sponsor, it resulted in any of the following outcomes:

- Death.
- Life-threatening.
- In-patient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity or substantial disruption of the ability to

conduct normal life functions.

- Congenital anomaly/birth defect in the offspring of a patient.
- An important medical event. An important medical event was an event that may not have resulted in death, was life-threatening, or required hospitalization but may have been considered serious when, based upon appropriate medical judgment, it may have jeopardized the patient or the patient may have required medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Study Endpoints

The primary endpoint was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). A Clinical Outcome Responder was defined as a patient with all of the following:

- 1) Normal vaginal discharge
- 2) Negative 10% KOH Whiff test
- 3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline.

The FDA Draft Guidance for Industry- Bacterial Vaginosis: Developing Drugs for Treatment, July 2016 recommended the primary efficacy endpoint as clinical cure characterized as: resolution of the abnormal vaginal discharge, negative whiff test, and the presence of clue cells at less than 20 percent of the total epithelial cells on microscopic examination of the saline wet mount.

The following secondary endpoints were evaluated at the TOC/EOS visit (Day 21 to 30):

- Nugent Score: A score of 0 to 3 was considered normal; a score of 4 and above was considered abnormal.
- Therapeutic Outcome: A Therapeutic Outcome Responder was defined as a Clinical Outcome Responder with a normal Nugent score (between 0-3).

Medical Officer comment: The primary and secondary endpoints were consistent with the FDA guidance for BV and previous discussions with the Agency. Refer to Regulatory background section 3.2.

Exploratory endpoints

- The pH of vaginal discharge at the TOC/EOS visit (<4.7 normal or ≥4.7 abnormal).
- Patient responses to telephone diary questions obtained on Days 1 to 7 and at the

TOC/EOS visit.

- Investigator's Clinical Assessment: Investigator's opinion of the need for additional BV treatment (Yes or No) at the TOC/EOS visit.

Safety endpoints:

- Adverse events (AEs): Included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation
- Vital signs: Blood pressure, temperature and pulse
- Physical examinations
- Pelvic Examinations: External genitalia, vagina, and bimanual exam
- Laboratory assessments: Included serum chemistry, hematology, and urinalysis.

Statistical Analysis Plan

Refer to detailed Statistical review by Dr. Cheryl Dixon. The trial populations were as follows:

- Intent-to-Treat (ITT): The ITT population included all randomized patients.
- Modified Intent-To-Treat (mITT): The mITT population included all randomized patients who met all inclusion/exclusion criteria.
- Per-Protocol (PP): The PP population was composed of patients in the mITT population who had no major protocol violations.
- Safety: The Safety population was composed of all randomized patients who received the study drug.

Medical Officer comment: Exclusions from the mITT population of subjects with baseline Nugent score < 4 or positive for other vulvovaginal infections (Trichomonas vaginalis, Chlamydia trachomatis, or Neisseria gonorrhoeae) were acceptable since they were measured prior to randomization and the results were not known until later.

The mITT population was the primary efficacy population. The primary and secondary analyses were also conducted on the PP population. All tests were performed at a 0.05 level of significance (two-sided).

Assuming a Clinical Outcome Responder rate of 40% in the active groups, and 15% in the placebo group, a sample size of 52 patients per group was to provide approximately 80% power to detect a statistically significant difference between an active group and placebo at a 0.05 level of significance (two-sided) using a Cochran-Mantel-Haenszel (CMH) test.

The primary endpoint was compared between each active treatment group and the placebo group using a Cochran- Mantel-Haenszel (CMH) statistical test adjusted for BV strata. The primary comparison was between the 2 gram active treatment group and the placebo group in the mITT population. The comparison between the 1 gram active treatment group and the placebo group was considered a secondary comparison. Since there was only one primary comparison, no adjustment for multiple comparisons was indicated. For each treatment group, an exact 95% binomial confidence interval (CI) was calculated for the Clinical Outcome Responder rate.

Secondary efficacy endpoints were analyzed at the TOC/EOS visit using the stratified CMH test. The primary and secondary endpoints were also analyzed by BV strata and by baseline Nugent Score (4-6, 7-10) in the mITT population.

Patients with any missing data required for assessment of primary and secondary efficacy endpoints at TOC/EOS due to treatment failure or early discontinuation were imputed as a non-responder for clinical and therapeutic outcomes and abnormal for Nugent Score.

Protocol Amendments

The original protocol was dated April 16, 2014. Two revisions were made to the original protocol dated May 4, 2014 and Amendment #1 dated May 20, 2014. Patients who were found to have a normal Nugent Score from the sample obtained at the Baseline visit (Day 1) remained in the study and completed all study visits for safety data to be collected. Several exclusion criteria were added. One amendment to the SAP was made on October 29, 2014 to clarify that exploratory endpoints were to be summarized using descriptive statistics and a post hoc summary was added to present the primary analysis by race for the mITT population.

Data Quality and Integrity: Sponsor's Assurance

The Applicant states that the study was organized, performed, and reported in compliance with the Applicant's Standard Operating Procedures or those of its designee, protocol, working practice documents, and GCP guidelines. The Investigator was responsible for all data entered via the electronic data capture (eDC) system eCRFs and confirmed the accuracy of the data. The study centers were visited as frequently as documented in the Study Monitoring Plan to review the eCRFs for completeness and accuracy. Quality control and data validation procedures were applied to ensure the validity and accuracy of the clinical database.

Medical Officer comment: Trial SYM-1219-201 was designed as an adequate and well-controlled trial. The design followed guidance from the Medical Division with respect to the patient population, timing of TOC, and the primary and secondary efficacy endpoints. The study was powered to detect a significant difference between a SYM-1219 arm and placebo. Given the results of the trial, the Division agreed that SYM-1219-201 should be able to serve as one of the two pivotal trials needed for approval to support the indication of treatment of BV for SYM-

1219.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the trial was conducted in the compliance with Good Clinical Practices (GCPs).

Financial Disclosure

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the SYM 1219-201 trial as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f). See Appendix 13.2 for detailed review.

Patient Disposition

The following table depicts the number of subjects in the pre specified analysis populations.

Table 7-Number of Subjects in the prespecified analysis populations in SYM 1219-201

Category	N(SYM-1219 2G)	N(SYM-1219 1G)	N(PLACEBO)	N (Total)
ITT	72	71	72	215
MITT	62	64	62	188
PP	47	55	50	152
SAFETY	72	71	72	215

A total of 215 subjects were randomized in the trial SYM 1219-201. There were 215 subjects in the safety population as well. The primary analysis population which was the MITT population had a total of 188 subjects.

The following table shows the disposition of the subjects by treatment arm in the ITT population.

Table 8-Disposition of the subjects by treatment arm (ITT population) in SYM1219-201

	SYM- 1219 2G N=72 n(%)	SYM- 1219 1G N=71 n(%)	PLACEBO N=72 n(%)	Total N=215 n(%)
DSTERM				
COMPLETED	63(87.5)	67(94.4)	60(83.3)	190(88.4)
Reasons for discontinuation				
OTHER	0(0)	0(0)	1(1.4)	1(0.5)
PATIENT LOST TO FOLLOW-UP	2(2.8)	2(2.8)	4(5.6)	8(3.7)
PATIENTS REQUEST	0(0)	0(0)	1(1.4)	1(0.5)
PERCEIVED LACK OF THERAPEUTIC EFFECT	1(1.4)	0(0)	2(2.8)	3(1.4)
POSITIVE FOR STIS FROM SAMPLE OBTAINED AT BASELINE VISIT (DAY 1)	6(8.3)	2(2.8)	4(5.6)	12(5.6)

Of the 215 patients in the ITT population, 190 (88.4%) completed the trial. Among the 25 (11.6%) patients who discontinued treatment prematurely, the most common reason for discontinuation was detection of sexually transmitted infections (STIs) in baseline vaginal samples (12/215; 5.6%) and lost-to-follow-up (8/215; 3.7%). Nine subjects (12.5%) discontinued the treatment prematurely in the SYM 1219-2gm arm while a greater number of subjects (12/16.7%) discontinued prematurely from the placebo arm.

Medical Reviewer Comment: The subject with "other" reason for discontinuation was due to a vulvovaginal mycotic infection. See section 8.4.3

Protocol Violations/Deviations

The following Table shows the reasons for exclusion from the mITT and PP populations.

Table 9-Reasons for exclusion from mITT and PP populations in SYM 1219-201

		N(SYM -1219 2G)	N(SYM -1219 1G)	N(PLACEBO)	N Rows (Total)
	DVTERM				
Reason for exclusion from mITT population	Did not have baseline Nugent Score >= 4	4	5	4	13
	Had clinically significant baseline lab finding	0	0	1	1
	Had STI at baseline	6	2	5	13
	Total	10	7	10	27
Reason for exclusion from PP population					

	Took prohibited concomitant medication	8	4	3	15
	Did not consume all study drug	2	0	0	2
	Did not have TOC/EOS visit between Days 21-30	10	8	15	33
	Did not respond NO to Phone Interview Q3 and Q4 ¹	7	3	4	14
	Had Positive STI assessment at TOC/EOS	2	1	2	5
	Had significant post-baseline medical condition or procedure	1	0	0	1
	Not in mITT population	10	7	10	27
	Total	40	23	34	97

¹Q3: Did patient use any vaginal products during the first week of the study? Q4: Did patient have any vaginal intercourse during the first week of the study?

Medical Officer Comment: Major protocol deviations excluded the patients from the PP population prior to study unblinding.

Table of Demographic Characteristics

The following table shows the demographics and baseline characteristics in the mITT population.

Table 10-Demographics and Baseline Characteristics by Treatment (mITT population) in trial SYM 1219-201

Characteristics	Statistics	SYM-1219 2G N=62	SYM-1219 1G N=64	PLACEBO N=62
Age Cat 65 [n (%)]	<65	62 (100.00%)	64 (100.00%)	62 (100.00%)
	Min:Age	19.00	19.00	19.00
	Max:Age	54.00	49.00	49.00
	Mean:Age	33.15	32.84	32.45
	Std Dev:Age	9.27	7.70	7.73
Sex [n (%)]	F	62 (100.00%)	64 (100.00%)	62 (100.00%)

Race [n (%)]	AMERICAN INDIAN OR ALASKA NATIVE	1 (1.61%)	1 (1.56%)	0 (0.00%)
	ASIAN	1 (1.61%)	1 (1.56%)	2 (3.23%)
	BLACK OR AFRICAN AMERICAN	26 (41.94%)	42 (65.63%)	34 (54.84%)
	WHITE	32 (51.61%)	18 (28.13%)	24 (38.71%)
Ethnicity[n(%)]	HISPANIC OR LATINO	7 (11.29%)	7 (10.94%)	8 (12.90%)
	NOT HISPANIC OR LATINO	55 (88.71%)	57 (89.06%)	54 (87.10%)
BV Strata[n(%)]	3 or fewer episodes in the past 12 months	41 (66.1%)	44 (68.8%)	43 (69.4%)
	4 or more episodes in the past 12 months	21 (33.9%)	20 (31.3%)	19 (30.6%)
Number of BV episodes in past 12 months	Min:TOTBVEP	1 (0.5%)	1 (0.5%)	1 (0.5%)
	Max:TOTBVEP	12.00	13.00	12.00
	Mean:TOTBVEP	3.24	3.48	3.06
	Std Dev:TOTBVEP	2.95	2.89	2.12
Baseline Nugent Score	Min:BLNUGSCR	4 (1.9%)	5 (2.3%)	4 (1.9%)
	Max:BLNUGSCR	10.00	10.00	10.00
	Mean:BLNUGSCR	8.18	8.66	8.60
	Std Dev:BLNUGSCR	1.73	1.43	1.27

Medical Officer Comment: The treatment groups were similar with respect to demographic and baseline disease characteristics in trial SYM1219-201. There were slightly higher number of white population 51.6%(32/62) in the 2gm secnidazole group compared of 38.7%(24/62)in the placebo group. The placebo group had a higher number of black population 54.8%(34/62) compared to 41.9%(26/62)in the secnidazole 2gm arm. More than half (102/188; 54.3%) of the patients were Black/African American. The mean age of the patients in this study was 33 ± 8.2 years, with a range of 19 to 54 years. There were 16 patients (16/188; 8.5%) with baseline Nugent Scores of 4-6 and 172 patients (172/188; 91.5%) with baseline Nugent Scores of 7-10. In addition to the above analysis, the race for the following subjects were reported as "Other": Subject SYM-1219-201-01-002- Haitian, Subject SYM-1219-201-07-002-White, African – American, Subject SYM-1219-201-09-003- White and Asian, Subject SYM-1219-201-09-008- White, African-American, Subject SYM-1219-201-16-001-Hispanic, Subject SYM-1219-201-18-001-Middle Eastern.

In the United States, the National Health and Nutrition Examination Survey (NHANES) data estimates the prevalence of BV to be 29 percent in the general population of women aged 14 to 49 years and 50 percent in African-American women, therefore the demographics suggest that this population was representative of those typically affected by BV.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Concomitant medications were taken by 60.5% of the study population, with ibuprofen (8.8%), norethisterone and ethinylestradiol (7.4%), and cetirizine (5.6%) being the most commonly used.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 215 randomized patients (100%) received study drug. Subjects 08/004 and 21/004 in the secnidazole 2gm group did not consume the full dose of the study drug due to spillage of part of the drug and nausea respectively.

Efficacy Results – Primary Endpoint

The primary endpoint was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). The primary efficacy analysis was the comparison of Clinical Outcome Responder rates evaluated at the TOC/EOS visit (Between Days 21 and 30) for the mITT population.

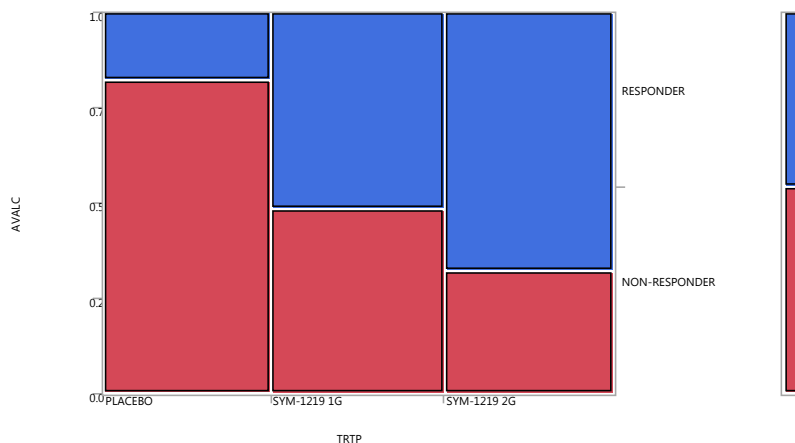
The following table and figure shows the primary endpoint analysis.

Table 11-Clinical Outcome Responder Rates, by Treatment (mITT Population) in SYM 1219-201

		TRTP			
AVALC		SYM-1219 2G N=62 n(%)	SYM-1219 1G N =64 n(%)	PLACEBO N=62 n(%)	All N=188
RESPONDER	n	42	33	11	86
	Column %	67.7%	51.6%	17.7%	45.7%
NON-RESPONDER	n	20	31	51	102
	Column %	32.3%	48.4%	82.3%	54.3%

Figure 2-Mosaic Plot of Clinical Outcome Responder Rates, by Treatment (mITT Population) in SYM 1219-201

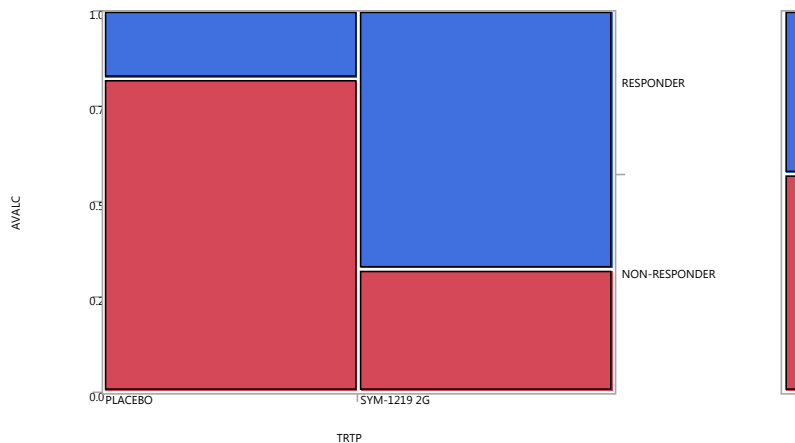
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CMH Test Stratified by BV STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	33.8922	2	<.0001*	188

Pairwise comparison between secnidazole 2gm versus placebo:

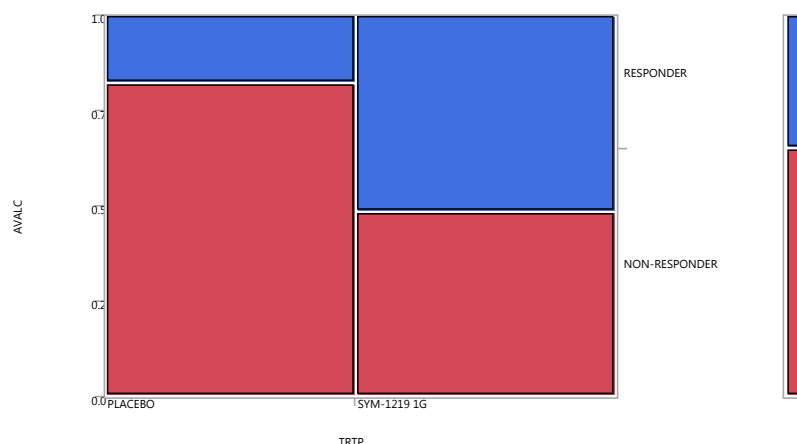
Figure 3-Clinical outcome responder rate by treatment (mITT population) SYM 1219 2gm versus placebo (SYM 1219-201)



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	32.4769	1	<.0001*	124

Pairwise comparison between secnidazole 1gm versus placebo:

Figure 4-Clinical outcome responder rate by treatment (mITT population) SYM 1219 1gm versus placebo (SYM 1219-201)



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	16.4041	1	<.0001*	126

The Clinical responder rate was 67.7% (N=42) in the 2 gm secnidazole arm compared to 17.7%(N=11) in the placebo arm. The Clinical responder rate in the 1 gm secnidazole arm was 51.6% (N=33) compared to 17.7%(N=11) in the placebo arm. The Clinical Responder Rates in both doses of SYM-1219 were statistically superior to placebo (p<0.001). The 95% Exact Binomial Confidence Interval (CI) for the responder rate reported by the Applicant was 38.7, 64.2 in the 1 gm secnidazole arm, 54.7, 79.1 in the 2gm secnidazole arm and 9.2, 29.5 in the placebo arm.

The primary endpoint analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and the p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata was <0.001.

Similar results were seen in the PP population. The Clinical responder rate in the 2 gm secnidazole arm was 72.3% (N=34) compared to 52.7%(N=29) in the secnidazole 1 gm arm and 20% (N=10) in the placebo arm (see table below).

Table 12-Clinical Outcome Responder Rates, by Treatment (PP Population) in trial SYM 1219-201

		TRTP			
AVALC		SYM-1219 2G N=47 n(%)	SYM-1219 1G N=55 n(%)	PLACEBO N=50 n(%)	All N=152
RESPONDER	N	34	29	10	73

		TRTP			
AVALC		SYM-1219 2G N=47 n(%)	SYM-1219 1G N=55 n(%)	PLACEBO N=50 n(%)	All N=152
	Column %	72.3%	52.7%	20.0%	48.0%
NON-RESPONDER	N	13	26	40	79
	Column %	27.7%	47.3%	80.0%	52.0%

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	28.924	<.0001*
Pearson	27.352	<.0001*

Data Quality and Integrity – Reviewers’ Assessment

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format.

Efficacy Results – Secondary and other relevant endpoints

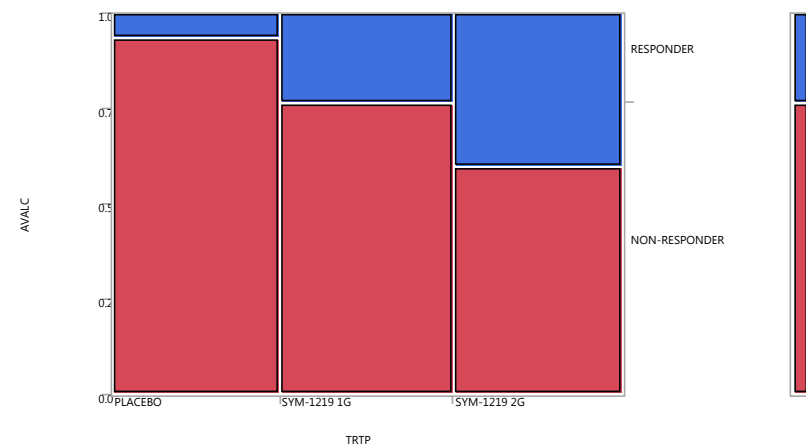
One of the secondary endpoints evaluated at the TOC/EOS visit (Day 21 to 30) was the Nugent score. A score of 0 to 3 was considered normal; a score of 4 and above was considered abnormal. The following tables and figures show the analysis of the secondary endpoint of the Nugent score.

Table 13-Nugent score at Test of Cure visit by Treatment arm (mITT population) in trial SYM 1219-201

		TRTP			
AVALC		SYM-1219 2G N=62 n(%)	SYM-1219 1G N=64 n(%)	PLACEBO N=62 n(%)	All N=188
RESPONDER ¹	N	25	15	4	44
	Column %	40.3%	23.4%	6.5%	23.4%
NON-RESPONDER ²	N	37	49	58	144
	Column %	59.7%	76.6%	93.5%	76.6%
N(no of subjects)		60	62	58	
Mean(SD)score		4.7(3.63)	5.9(3.42)	8.3(2.32)	
Min, Max		0,10	0,10	0,10	

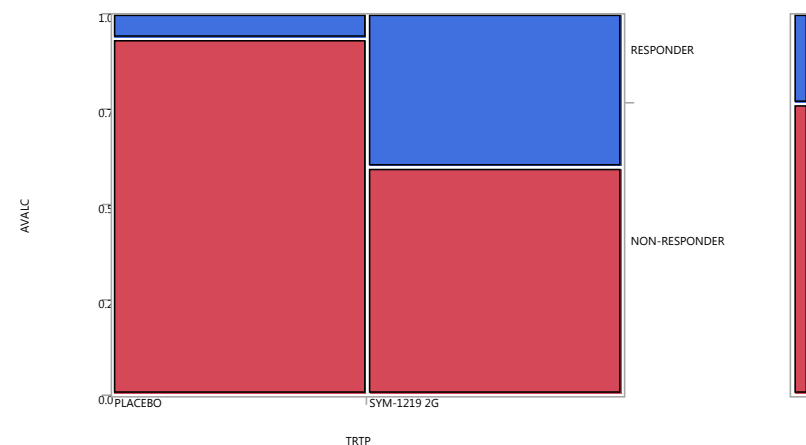
¹ Responder was subjects with Nugent score 0-3(normal). ²Nonresponder was subjects with Nugent score ≥4 (abnormal).

Figure 5-Mosaic plot of Nugent scores at Test of cure visit by Treatment arm (mITT population) in trial SYM 1219-201



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	20.5286	2	<.0001*	188

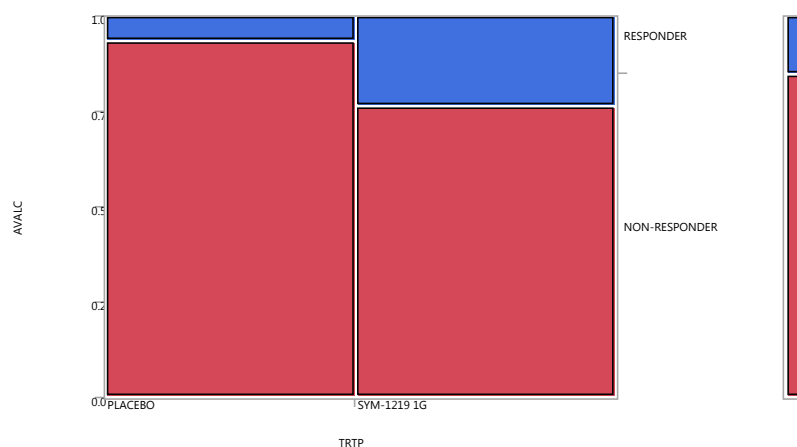
Figure 6-Pairwise comparison between SYM 1219 2gm and placebo of Nugent score at Test of cure(mITT population) in trial SYM 1219-201



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CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	20.0751	1	<.0001*	124

Figure 7-Pairwise comparison between SYM 1219 1gm and placebo of Nugent score at Test of cure visit(mITT population)in trial SYM 1219-201.



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	7.3272	1	0.0068*	126

The 2 gram secnidazole treatment group had numerically higher response rates than the 1 gram secnidazole group. About 40.3% of subjects (25/62) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 23.4%(15/64) in the secnidazole 1 gm arm and 6.5%(4/62) in the placebo arm. Pairwise comparisons of secnidazole 2gm with placebo and secnidazole 1 gm versus placebo showed that 1 gm and 2 gms secnidazole was statistically superior to placebo.

The Nugent score analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and the p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV

strata was <0.001 for secnidazole 2gms and 0.007 for secnidazole 1gm.

Similar results were obtained in the PP population. About 47%(22/47) subjects in the 2gm secnidazole group had normal Nugent score compared to 21.8%(12/55) in the 1gm secnidazole group and 6%(3/50) in the placebo group.

Table 14-Nugent score at test of cure visit by treatment arm (PP population) in trial SYM 1219-201

		TRTP			
AVALC		SYM-1219 2G N=47	SYM-1219 1G N=55	PLACEBO N=50	All N=152
RESPONDER ¹	N	22	12	3	37
	Column %	46.8%	21.8%	6.0%	24.3%
NON-RESPONDER ²	N	25	43	47	115
	Column %	53.2%	78.2%	94.0%	75.7%

¹ Responder was subjects with Nugent score 0-3(normal). ²Nonresponder was subjects with Nugent score>4 (abnormal).

The Nugent score analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and the p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata was <0.001 for secnidazole 2gms and 0.020 for secnidazole 1gm(PP population).

The other secondary endpoint evaluated at the TOC/EOS visit (Day 21 to 30) was the Therapeutic Outcome. A Therapeutic Outcome Responder was defined as a Clinical Outcome Responder with a normal Nugent score (between 0-3). The following tables and figures show the analysis of the secondary endpoint of Therapeutic outcome.

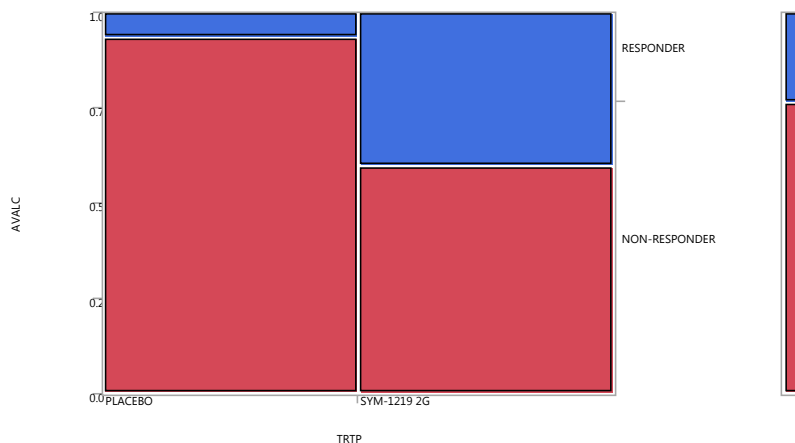
Table 15-Therapeutic outcome responder rate by treatment arm(mITT population) in trial SYM 1219-201

		TRTP			
AVALC		SYM-1219 2G N=62 n(%)	SYM-1219 1G N=64 n(%)	PLACEBO N=62 n(%)	All N=188
RESPONDER	N	25	14	4	43
	Column %	40.3%	21.9%	6.5%	22.9%
NON-RESPONDER	N	37	50	58	145
	Column %	59.7%	78.1%	93.5%	77.1%

Pairwise comparison between secnidazole 2gm versus placebo:

Figure 8-Therapeutic outcome responder rate (mITT population) 2gm SYM 1219 versus placebo in trial SYM 1219-201

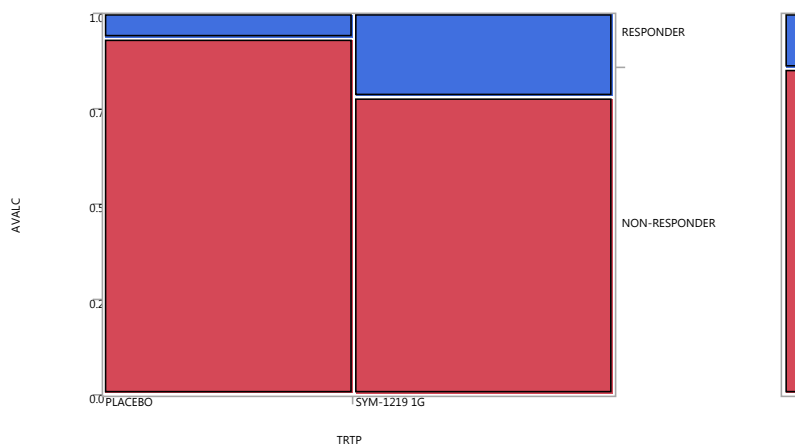
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CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	20.0751	1	<.0001*	124

Pairwise comparison between secnidazole 1gm versus placebo:

Figure 9-Therapeutic outcome responder rate (mITT population) 1gm SYM 1219 versus placebo in trial SYM 1219-201



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	6.4462	1	0.0111*	126

The 2 gram secnidazole treatment group had numerically higher response rates than the 1 gram

secnidazole group. About 40.3% of subjects (25/62) in the secnidazole 2 gm arm were therapeutic responders at end of treatment compared to 21.9%(14/64) in the secnidazole 1 gm arm and 6.5%(4/62) in the placebo arm. Pairwise comparisons of secnidazole 2gm with placebo and secnidazole 1 gm versus placebo showed that 1 gm and 2 gms secnidazole was statistically superior to placebo.

The Therapeutic outcome responder analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and the p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata was <0.001 for secnidazole 2gms and 0.011 for secnidazole 1gm.

Similar results were obtained in the PP population. About 47% of subjects were therapeutic outcome responders(22/47) in the 2gm secnidazole arm compared to 22%(12/55) in the 1 gm secnidazole arm and 6%(3/50) in the placebo arm. The Therapeutic outcome responder analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and the p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata was <0.001 for secnidazole 2gms and 0.020 for secnidazole 1gm.

Table 16-Therapeutic outcome responder rates by treatment arm (PP population) in trial SYM 1219-201

		TRTP			
AVALC		SYM-1219 2G N=47 n(%)	SYM-1219 1G N=55 n(%)	PLACEBO N=50 n(%)	All
RESPONDER	N	22	12	3	37
	Column %	46.8%	21.8%	6.0%	24.3%
NON-RESPONDER	N	25	43	47	115
	Column %	53.2%	78.2%	94.0%	75.7%

Dose/Dose Response

Refer to section 7.1.4.

Durability of Response

Refer to section 7.1.5

Persistence of Effect

Refer to section 7.1.5

Additional Analyses Conducted on the Individual Trial

The following Tables show the exploratory analysis which were conducted by the Applicant.

Table 17-Vaginal pH at TOC/EOS by Treatment Arm (mITT Population) in trial SYM 1219-201

	SYM-1219 2G N=62 n(%)	SYM-1219 1G N=64 n(%)	PLACEBO N=62 n(%)
Vaginal pH<4.7(normal)	33 (53.2%)	26 (40.6%)	13(21.0%)
Vaginal pH≥4.7	27 (43.5%)	36 (56.3%)	45 (72.6%)

Table 18- Investigator's Clinical Assessment at TOC/EOS by Treatment Arm (mITT Population) in trial SYM 1219-201

DSICA	SYM-1219 2G N=62 n(%)	SYM-1219 1G N=64 n(%)	PLACEBO N=62 n(%)
N (No additional BV treatment needed)	45 (72.6%)	36 (56.3%)	15 (24.2%)
Y (Additional BV treatment needed)	15 (24.2%)	26 (40.6%)	43 (69.4%)

Table 19-Telephone Diary Responses by Treatment Arm at EOS (mITT Population) in trial SYM 1219-201

PARAM	AVALC	SYM-1219 2G N=62 n(%)	SYM-1219 1G N=64 n(%)	PLACEBO N=62 n(%)
Menstrual Period	N	60 (96.8%)	59 (92.2%)	60 (96.8%)
	Y	2 (3.2%)	5 (7.8%)	2 (3.2%)
Menstrual Period, Confirmed	N	0 (0.0%)	4 (6.3%)	0 (0.0%)
	Y	2 (3.2%)	1 (1.6%)	2 (3.2%)
Vaginal Discharge	MILDLY ABNORMAL	12 (19.4%)	19 (29.7%)	15 (24.2%)
	MODERATELY ABNORMAL	5 (8.1%)	12 (18.8%)	11 (17.7%)
	NORMAL, NOT AN ISSUE	39 (62.9%)	29 (45.3%)	26 (41.9%)
	SEVERELY ABNORMAL	3 (4.8%)	2 (3.1%)	4 (6.5%)
	VERY SEVERELY ABNORMAL	1 (1.6%)	0 (0.0%)	3 (4.8%)

Vaginal Odor	MILDLY ABNORMAL	9 (14.5%)	11 (17.2%)	14 (22.6%)
	MODERATELY ABNORMAL	9 (14.5%)	12 (18.8%)	12 (19.4%)
	NORMAL, NOT AN ISSUE	41 (66.1%)	36 (56.3%)	22 (35.5%)
	SEVERELY ABNORMAL	0 (0.0%)	3 (4.7%)	8 (12.9%)
	VERY SEVERELY ABNORMAL	0 (0.0%)	0 (0.0%)	3 (4.8%)

Table 20-Telephone Diary Responses(Vaginal discharge) by Clinical Outcome and Treatment Arm at EOS (mITT Population) in trial SYM 1219-201

Vaginal discharge in Clinical outcome responders	SYM-1219 2G N=42 n(%)	SYM-1219 1G N=33 n(%)	PLACEBO N=11 n(%)
Mildly abnormal	7 (16.7%)	6 (18.2%)	1 (9.1%)
Moderately abnormal	0 (0.0%)	3 (9.1%)	0 (0.0%)
Normal, not an issue	33 (78.6%)	22 (66.7%)	10 (90.9%)
Severely abnormal	1 (2.4%)	1 (3.0%)	0 (0.0%)
Very severely abnormal	0	0	0

In the mITT population, about 53% of subjects in the 2gm secnidazole arm had normal vaginal pH at the end of treatment compared to 41% in the secnidazole 1 gm arm and 21% in the placebo arm. No additional BV treatment was needed by Investigator assessment at end of treatment in over 72% of subjects in the 2 gm secnidazole arm compared to 24% in the placebo arm. Telephone diary responses showed that vaginal discharge was normal at end of treatment in 63% of subjects in the secnidazole 2 gm arm versus 42% in the placebo arm. Similarly vaginal odor was normal at end of treatment in 66% of subjects in the 2 gms secnidazole arm compared to 35.5% in the placebo arm. However the proportion of patients who reported normal vaginal discharge increased over the study period but this did not correspond closely with clinical outcome response in the secnidazole arm.

Medical Reviewer Comment: Overall, there were 67.7% (42/62) Clinical outcome responders in the 2 gm secnidazole arm compared to 17.7%(11/62) in placebo (there were 51.6% clinical outcome responders in the 1 gm secnidazole arm). This difference was statistically significant with p value versus placebo from CMH test adjusted for BV (<3 or >3 episodes in the past 12 months) was <0.001. The 95% CI for the responder rate was 54.7, 79.1 in the 2gm secnidazole arm and 9.2, 29.5 in the placebo arm. In terms of the secondary endpoints, the 2 gm secnidazole had a greater response than placebo across the endpoints. In trial SYM 1219-201, about 40.3% of subjects (25/62) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 6.5%(4/62) in the placebo arm in the mITT population(p<0.001). About 40.3% of subjects (25/62) in the secnidazole 2 gm arm were therapeutic responders at end of treatment compared to 6.5%(4/62) in the placebo arm in the mITT population(p<0.001).

6.2. Trial SYM-1219-301

6.2.1. Study Design

Overview and Objective

Trial SYM-1219-301 was a phase 3, multi-center, prospective, randomized, double-blind, placebo-controlled study to evaluate the effectiveness and safety of SYM-1219 2 Grams for the treatment of women and postmenarchal adolescent girls with bacterial vaginosis.

Trial Design

Date of first enrollment: 04 May 2015

Date of completion: 24 Sep 2015

Study center(s): 21 research centers in the US

Number of patients: A total of 189 patients were enrolled.

Test product: SYM-1219 2 grams, oral granules.

Reference therapy: Placebo

Duration of treatment: single dose

Randomization: Patients determined to be eligible at the Baseline visit (Study Day 1) were randomized in a 2:1 ratio to receive a single dose of 2 gms of SYM-1219 and placebo to be self-administered on Day 1 (without regard to meals). The randomization was stratified by the number of reported episodes of bacterial vaginosis (BV) in the past 12 months (including the current episode): 3 or fewer episodes versus 4 or more episodes, and by race (Black versus all others).

Follow up visits: Patients returned to the site once between Days 7-14 for an Interim Visit. A “test of cure” (TOC) Visit was conducted on Day 21 to 30 or at End of Study (EOS) if the final visit was not conducted between Days 21-30 and at least 10 days after the Interim Visit.

Blinding: The total volume of each single dose of study drug was the same as well as the packaging to maintain blinding.

Inclusion criteria: Adult females or postmenarchal adolescent girls ≥ 12 years of age. The rest of the inclusion criteria were similar to trial SYM 1219-201(Refer to section 6.1.1 for details).

Medical Officer comment: The inclusion criteria in trial SYM 1219-301 also state that the subjects had a Gram-stain slide Nugent Score ≥ 4 at the baseline visit. The FDA Draft Guidance for Industry- Bacterial Vaginosis: Developing Drugs for Treatment, July 2016 recommends that to enhance the reliability for the diagnosis of BV at enrollment, the Gram stain of the vaginal specimen should have a Nugent score of greater than or equal to 7. The Applicant however has analyzed the primary and secondary endpoints by baseline Nugent Score (4-6, 7-10) in the mITT population.

Exclusion criteria: Being postmenopausal was listed as an exclusion criterion. The rest of the criteria were similar to trial SYM 1219-201(Refer to section 6.1.1 for details).

Withdrawal/Discontinuation from the trial: Except for pregnancy, the reasons were similar to trial SYM 1219-201(Refer to section 6.1.1 for details).

Prior and Concomitant Therapy: Similar to trial SYM 1219-201(Refer to section 6.1.1 for details).

Study drug was orally administered as a single dose with 4 ounces of unsweetened applesauce (Mott's applesauce, a spoon, and an 8 ounce bottle of water were included in the treatment kits). Treatment compliance was ensured by inspecting used packets and applesauce containers. The following Table shows the Schedule of Assessment of the Trial.

Table 21-Schedule of Assessments in Trial SYM 1219-301

Assessment	Baseline Visit	Interim Visit	Test of Cure (TOC) / EOS Assessment
	Day 1	Day 7-14	Day 21-30
Informed consent/assent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X	X	X
Height/weight	X		
Urine pregnancy test ¹	X	X	X
Physical examination	X	X ⁵	X
Pelvic examination	X	X	X
External genitalia and vaginal exam	X	X	X
Vaginal discharge assessment	X	X	X
Vaginal wet mount for Clue cell assessment	X	X	X
Gram stain of vaginal fluid	X ²	X	X
10% KOH Whiff test	X	X	X
pH of vaginal fluid	X		
STI Assessments	X ²	X ³	X ³

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OSOM® Trichomonas Rapid Test	X ⁴		
Bimanual pelvic examination ⁶	X	X	X
Labs: Hematology, chemistry, and urinalysis	X ²		X
IWRS Randomization	X		
Drug dosing	X		
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Patient interview ⁷		X	
Investigator's Clinical Assessment			X

1. Performed by site personnel (not sent to central laboratory).
2. Results were available at the time of randomization.
3. Only as indicated as determined by the Investigator.
4. It was recommended that the vaginal sample for the OSOM® Trichomonas Rapid Test be obtained early in the collection process to ensure adequate sample for this evaluation.
5. A targeted physical examination at the Interim Visit was only needed per the Investigator's discretion if a reported AE required further evaluation.
6. A bimanual pelvic examination was required for all patients at baseline and was performed after the vaginal discharge assessment and all vaginal samples had been collected. At the Investigator's discretion, a bimanual pelvic examination may have been performed at the TOC/EOS Assessment after the vaginal discharge assessment and all of the vaginal samples were collected.
7. Patient interview: queried the patient regarding intercourse and use of vaginal products during first week of study.

Source: Page 22 of the Clinical Study Report.

The vaginal discharge assessment was marked as normal or abnormal (abnormal consistent with BV or abnormal other) at baseline, interim visit and at TOC.. At the TOC/EOS visit, the investigator answered if additional treatment for BV was required. If the answer was yes, the patient was offered a prescription for a post-study treatment by the Investigator.

All AEs were recorded in the patients source documents and eCRFs. Definitions of AEs were similar to trial SYM 1219-201 (Refer to section 6.1.1 for details). Treatment-emergent AEs were defined as any AE that occurred after administration of the first dose of study drug and through the TOC/EOS visit, any event that was considered study treatment-related, regardless of the start date of the event, or any event that was present at baseline but worsened in intensity or was subsequently considered treatment-related by the Investigator.

Study Endpoints

The primary endpoint was similar to trial SYM 1219-201 which was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). A Clinical Outcome Responder was defined as a patient with all of the following:

- 1) Normal vaginal discharge
- 2) Negative 10% KOH Whiff test
- 3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal

wet mount using saline.

The following secondary endpoints were evaluated at the Interim visit (Study Day 7-14) and the TOC/EOS visit (Study Day 21 to 30):

- Nugent Score: A score of 0 to 3 was considered normal; a score of 4 and above was considered abnormal.
- Therapeutic Outcome: A Therapeutic Outcome Responder was defined as a Clinical Outcome Responder with a normal Nugent score (between 0-3).
- Clinical Outcome (Interim Visit only)
- Investigator's Clinical Assessment: Investigator's opinion of the need for additional BV treatment (Yes or No) (at the TOC/EOS Visit only).

Medical Officer comment: The primary and secondary endpoints were consistent with the FDA guidance for BV and previous discussions with the Agency. Additional secondary endpoints of Clinical outcome at the interim visit and Investigator's clinical assessment were added in this trial.

Safety endpoints

- Adverse events (AEs): Included TEAEs, serious adverse events (SAEs), treatment-related AEs, severe AEs, and AEs leading to study discontinuation
- Vital signs: Blood pressure, temperature and pulse
- Physical examinations
- Pelvic Examinations: External genitalia and vagina
- Laboratory assessments: Included serum chemistry, hematology, and urinalysis.

Statistical Analysis Plan

Refer to detailed Statistical review by Dr. Cheryl Dixon. The trial populations were as follows:

- Intent-to-Treat (ITT): The ITT population included all randomized patients.
- Modified Intent-To-Treat (mITT): The mITT population included all randomized patients who met all inclusion/exclusion criteria.
- Per-Protocol (PP): The PP population was composed of patients in the mITT population who received the study medication, met inclusion and exclusion criteria, had an Interim Visit between Days 7-14 and a TOC/EOS Visit between Days 21-30, at least 10 days after the Interim Visit, and who had no major protocol violations.
- Safety: The Safety population was composed of all randomized patients who received the study drug.

The mITT population was the primary efficacy population. The primary and secondary analyses were also conducted on the PP population. All tests were performed at a 0.05 level of significance (two-sided).

Handling of missing data: Patients with any missing data required for assessment of primary and secondary efficacy endpoints at Interim Visit and TOC/EOS Visit due to treatment failure or early discontinuation were imputed as a non-responder for clinical and therapeutic outcomes, and abnormal for Nugent Score; no imputation was done for the Investigator's Clinical Assessment.

The primary efficacy endpoint was compared between the SYM-1219 and placebo treatment groups using a Cochran-Mantel-Haenszel (CMH) test adjusted for BV and race strata. For each treatment group, an exact 95% binomial confidence interval was calculated for the Clinical Outcome Responder rate.

The primary and secondary endpoints were also separately analyzed at the Interim and TOC/EOS visits by BV strata, race strata, and baseline Nugent Score (4-6, 7-10) in the mITT population.

Sample size determination: Assuming a Clinical Outcome Responder rate of 50% in the active group and 25% in the placebo group, a sample size of 132 patients randomized in a 2:1 ratio was to provide 80% power to detect a statistically significant difference between the active group and placebo at a 0.05 level of significance (two-sided). Assuming 75% of patients would meet the mITT criteria, 120 patients were randomized to the active group and 60 patients were randomized to the placebo group.

Protocol Amendments

Prior to database lock, an amendment to the original SAP (June 8, 2015) was issued, dated October 19, 2015 to propose an alternate definition of the outcome endpoints. The study assessed vaginal discharge as normal, abnormal (consistent with BV), and abnormal (other). Therefore, a Clinical Outcome Responder could include a vaginal discharge assessment of normal or abnormal (other). A vaginal discharge of abnormal (consistent with BV) will be considered a non-responder. The amendment to the SAP was finalized before any data review or unblinding.

Medical Reviewer Comments: The Division of Anti-infectives (DAIP) advised the Applicant that a responder be classified as only those who have a normal discharge rather than allow for

responders to include subjects with an abnormal discharge not consistent with BV. It was not clear how well such distinctions in discharge could be made and it would be difficult classifying someone with an abnormal discharge consistent with another clinical entity (for example, newly acquired vulvovaginal candidiasis as a result of treatment) as a responder. The Applicant therefore used the original definition of the clinical responder (return to normal vaginal discharge) in the primary endpoint analysis and submitted additional analysis using the alternate definition of the clinical responder.

Data Quality and Integrity: Sponsor's Assurance

Refer to section 6.1.1.

Medical Reviewer comment: Both SYM1219-201 and SYM 1219-301 are considered as pivotal trials in this NDA application. There were some differences between the trials with respect to dose administration in relation to meals, inclusion criteria (inclusion of adolescents in trial SYM1219-301), randomization scheme, stratification, per protocol population, addition of interim visit and secondary endpoints in trial in trial SYM 1219-301.

Given the different randomization allocations, i.e 1:1:1 in trial SYM 1219-201 and 2:1 in trial SYM 1219-301, the TEAEs of the individual trials and a study size adjusted AE incidence proportion was calculated since the crude pooling of the two trials could be misleading(see section 8.1). However, the efficacy was evaluated in each of these individual trials these differences are not considered significant.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the trial was conducted in the compliance with Good Clinical Practices (GCPs).

Financial Disclosure

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the SYM 1219-301 trial as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f). See Appendix 13.2 for detailed review.

Patient Disposition

The following table depicts the number of subjects in the pre specified analysis populations.

Table 22-Number of Subjects in the prespecified analysis populations in SYM 1219-301

	TRT01P		
	SYM-1219 2G N	PLACEBO N	Total N
ITT	125	64	189
MITT	107	57	164
PER PROTOCOL	77	37	114
SAFETY	125	64	189

A total of 189 subjects were randomized in the trial SYM 1219-301. There were 189 subjects in the safety population as well. The primary analysis population which was the mITT population had a total of 164 subjects.

The following table shows the disposition of the subjects by treatment arm in the ITT population.

Table 23-Disposition of the subjects by treatment arm (ITT population) in SYM1219-301

DSTERM	SYM-1219 2G N=125 n(%)	PLACEBO N=64 n(%)	All N=189 n(%)
COMPLETED	109(87.2)	52(81.3)	161(85.2)
Reasons for discontinuation	16(12.8)	12(18.8)	28(14.8)
NON-COMPLIANCE WITH STUDY PROTOCOL AS DETERMINED BY THE INVESTIGATOR	1	0	1
PATIENT LOST TO FOLLOW- UP	7(5.6)	2(3.1)	9(4.8)
PATIENTS REQUEST	3	2	5
PATIENTS USE OF OR NEED FOR CONCOMITANT THERAPY LIABLE TO INTERFERE WITH THE INTERPRETATION OF STUDY ENDPOINTS	0	1	1
PERCEIVED LACK OF THERAPEUTIC EFFECT	0	3	3
POSITIVE FOR STIS FROM SAMPLE OBTAINED AT BASELINE VISIT (DAY 1)	5(4.0)	4(6.3)	9(4.8)

Of the 189 subjects in the ITT population, 161 (85.2%) completed the study. Among the 28 (14.8%) subjects who discontinued the study prematurely, the most common reason for discontinuation was detection of sexually transmitted infections (STIs) in baseline vaginal samples (9/189; 4.8%) and lost-to-follow-up (9/189; 4.8%).

Protocol Violations/Deviations

The following Table shows the reasons for exclusion from the mITT and PP populations.

Table 24-Reasons for exclusion from mITT and PP populations in SYM 1219-301

	DVTERM	N(SYM-1219 2G)	N(PLACEBO)	N
Reason for exclusion from mITT population	Did not meet Inclusion/Exclusion criteria at randomization	1	0	1
	Had STI at baseline	8	5	13
	Did not have baseline Nugent Score ≥ 4	10	2	12
Reason for exclusion from PP population	Did not have Interim visit between Days 7-14	24	17	41
	Did not have TOC/EOS visit between Days 21-30, and at least 10 days after the Interim visit	28	24	52
	TOC/EOS visit data was incomplete for key vaginal assessments	9	3	12
	Took prohibited concomitant medication	7	1	8
	Did not consume all study drug	2	0	2
	Not in mITT population	18	7	25

Medical Officer Comment: Major protocol deviations excluded the patients from the PP population prior to study unblinding. There were slightly higher number of excluded subjects in the 2gm secnidazole arm compared to placebo. The Applicant identified one patient (#12-018) as being enrolled in SYM-1219-201 in violation of the protocol. This violation was identified after database lock and study unblinding and, therefore, the subject was not excluded from the analyses of this study. These protocol violations should not affect the analysis of the primary endpoint in the mITT population.

Table of Demographic Characteristics

The following table shows the demographics and baseline characteristics in the mITT population.

Table 25-Demographics and Baseline Characteristics by Treatment (mITT population) in trial SYM 1219-301

Characteristics	Statistics	SYM-1219 2G N=107	PLACEBO N=57
Age Cat 65 [n (%)]	<65	107 (100.00%)	57 (100.00%)
	Min:Age	18.00	18.00
	Max:Age	54.00	46.00
	Mean:Age	32.21	29.65
	Std Dev:Age	8.72	7.63
Sex [n (%)]	F	107 (100.00%)	57 (100.00%)
Race [n (%)]	ASIAN	0 (0.00%)	1 (1.75%)
	BLACK OR AFRICAN AMERICAN	59 (55.14%)	29 (50.88%)
	WHITE	46 (42.99%)	26 (45.61%)
Ethnicity [n(%)]	HISPANIC OR LATINO	20 (18.69%)	9 (15.79%)
	NOT HISPANIC OR LATINO	87 (81.31%)	48 (84.21%)
Race Strata [n(%)]	ALL OTHERS	48 (44.9%)	28 (49.1%)
	BLACK	59 (55.1%)	29 (50.9%)
BV Strata [n(%)]	3 or fewer episodes in the past 12 months	83 (77.6%)	43 (75.4%)
	4 or more episodes in the past 12 months	24 (22.4%)	14 (24.6%)
Number of BV episodes in the past 12 months	Min:TOTBVEP	1 (0.5%)	1 (0.5%)
	Max:TOTBVEP	12.00	12.00
	Mean:TOTBVEP	2.90	2.86
	Std Dev:TOTBVEP	2.42	2.55
Nugent Score Category, [n (%)]	Nugent Score 4-6	18 (16.8%)	4 (7.0%)
	Nugent Score 7-10	89 (83.2%)	53 (93.0%)

Nugent Score	Min:BLNUGSCR	4 (2.1%)	5 (2.6%)
	Max:BLNUGSCR	10.00	10.00
	Mean:BLNUGSCR	8.06	8.60
	Std Dev:BLNUGSCR	1.76	1.29

Medical Officer Comment: The treatment groups were similar with respect to demographic and baseline disease characteristics in trial SYM1219-301. The mean age of the patients in this study was 31 ± 8.4 years, with a range of 18 to 54 years. More than half (88/164; 53.7 %) of the patients were Black/African American. The proportion of patients across the BV and race strata was similar across the treatment groups. There were 22(13.4%) subjects with a 4-6 Nugent score and 142(86.6%) subjects with a Nugent score of 7-10 at baseline. In addition to the above analysis, the race for the following subjects were reported as "Other": Subject SYM-1219-301-21-003-White and African-American, Subject SYM-1219-301-32-002-Multiracial, Subject SYM-1219-301-41-002- White and American Indian or Alaskan native.

In the United States, the National Health and Nutrition Examination Survey (NHANES) data estimates the prevalence of BV to be 29 percent in the general population of women aged 14 to 49 years and 50 percent in African-American women, therefore the demographics suggest that this population was representative of those typically affected by BV. Approximately 30 percent of patients with an initial response to therapy have a recurrence of symptoms within three months and more than 50 percent experience a recurrence within 12 months. In this trial, as expected approximately 25% of patients had 4 or more episodes in the past year.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Concomitant medications were taken by 68.8% of the study population, multivitamin (9.0%), ibuprofen (9.0%), fluconazole (9.0%), and salbutamol (5.8%) being the most commonly used.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 189 randomized patients (100%) received study drug. Patient 04/014 and 05/003 did not consume the full dose of the study drug due to nausea and vomiting.

Efficacy Results - Primary Endpoint

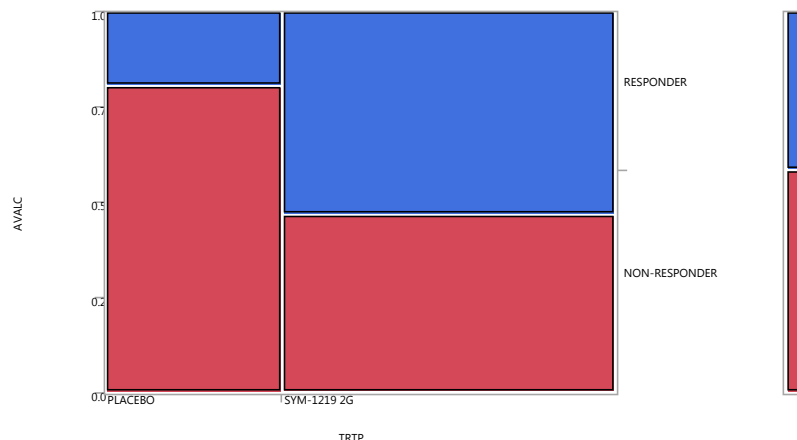
The primary endpoint was Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30). The primary efficacy analysis was the comparison of Clinical Outcome Responder rates evaluated at the TOC/EOS visit (Between Days 21 and 30) for the mITT population.

The following table and figure shows the primary endpoint analysis.

Table 26-Clinical Outcome Responder Rates at TOC by Treatment (mITT Population) in SYM 1219-301

	TRTP					
	SYM-1219 2G N=107 n(%)		PLACEBO N=57 n(%)		All N=164	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	57	53.3%	11	19.3%	68	41.5%
NON-RESPONDER	50	46.7%	46	80.7%	96	58.5%

Figure 10-Mosaic Plot of Clinical Outcome Responder Rates, by Treatment (mITT Population) in SYM 1219-301



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	17.5851	1	<.0001*	164

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	17.9956	1	<.0001*

The Clinical responder rate was 53.3% (N=57) in the 2 gm secnidazole arm compared to 19.3% (N=11) in the placebo arm. The Clinical Responder Rates for SYM-1219 was statistically superior to placebo ($p < 0.001$). The 95% Exact Binomial Confidence Interval (CI) for the responder rate reported by the Applicant was 43.4, 63.0 in the 2gm secnidazole arm and 10.0, 31.9 in the placebo arm.

The primary endpoint analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and by race (black or all others). The p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata and race was <0.001.

In the PP population, the Clinical responder rate in the 2 gm secnidazole arm was 55.8% (N=43) compared to 29.7% (N=11) in the placebo arm (see table below). The 2 gm secnidazole group was statistically superior to the placebo with a p value of 0.006.

Table 27-Clinical Outcome Responder Rates at TOC by Treatment (PP Population) in trial SYM 1219-301

	TRTP					
	SYM-1219 2G N=77 n(%)		PLACEBO N=37 n(%)		All N=114	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	43	55.8%	11	29.7%	54	47.4%
NON-RESPONDER	34	44.2%	26	70.3%	60	52.6%

CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	7.4069	1	0.0065*	114

Data Quality and Integrity - Reviewers' Assessment

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format.

Efficacy Results - Secondary and other relevant endpoints

Nugent score

One of the secondary endpoints evaluated at the Interim visit (Study Day 7-14) and at the TOC/EOS visit (Day 21 to 30) was the Nugent score. A score of 0 to 3 was considered normal; a score of 4 and above was considered abnormal. The following tables and figures show the analysis of the secondary endpoint of the Nugent score.

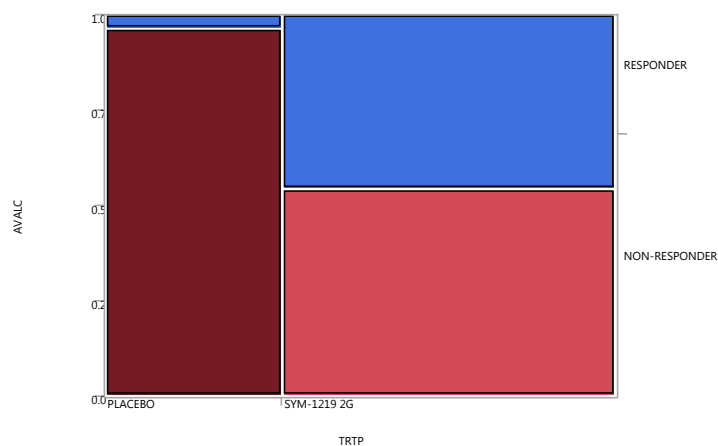
Table 28-Nugent score at Interim and Test of Cure visit by Treatment arm (mITT population) in trial SYM 1219-301

Interim visit	TRTP					
	SYM-1219 2G N=107 n(%)		PLACEBO N=57 n(%)		All N=164	
	N	Column %	N	Column %	N	Column %

	TRTP					
Interim visit	SYM-1219 2G N=107 n(%)		PLACEBO N=57 n(%)		All N=164	
	N	Column %	N	Column %	N	Column %
RESPONDER ¹	49	45.8%	2	3.5%	51	31.1%
NON-RESPONDER ²	58	54.2%	55	96.5%	113	68.9%
N(no of subjects)	97		45			
Mean(SD)score	3.5(3.11)		8.2(2.11)			
Min, Max	0,10		0,10			
TOC visit	N	Column %	N	Column %	N	Column %
RESPONDER ¹	47	43.9%	3	5.3%	50	30.5%
NON-RESPONDER ²	60	56.1%	54	94.7%	114	69.5%
N(no of subjects)	99		54			
Mean(SD)score	4.1(3.23)		7.9(2.23)			
Min, Max	0,10		0,10			

¹ Responder was subjects with Nugent score 0-3(normal). ²Nonresponder was subjects with Nugent score ≥ 4 (abnormal).

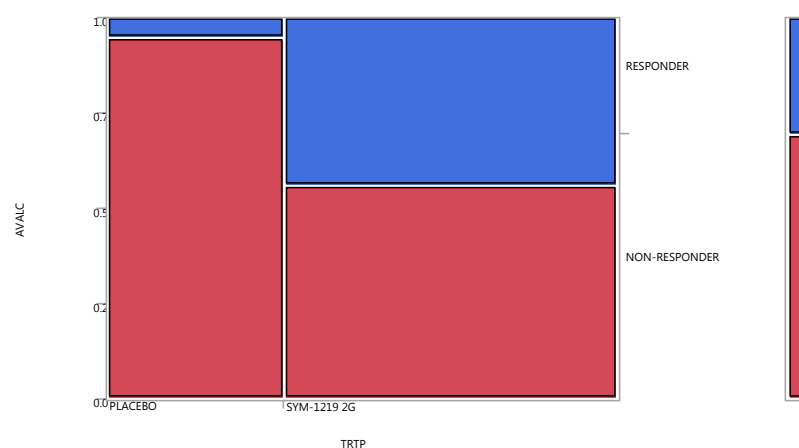
Figure 11-Mosaic plot of Nugent scores at Interim visit by Treatment arm (mITT population) in trial SYM 1219-301



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	30.6645	1	<.0001*	164

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	32.4826	1	<.0001*

Figure 12-Mosaic plot of Nugent scores at TOC visit by Treatment arm (mITT population) in trial SYM 1219-301



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	26.1025	1	<.0001*	164

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	26.2431	1	<.0001*

The 2 gram secnidazole treatment group had numerically higher response rates than the placebo group both at the Interim and TOC visit. About 43.9% of subjects (47/107) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 5.3%(3/57) in the placebo arm. At the interim visit, 45.8% of subjects (49/107) in the secnidazole group had normal Nugent score compared to 3.5%(2/57) in the placebo arm. The secnidazole 2 gram treatment group was statistically superior to placebo ($p < 0.001$) for the percentage of patients with normal Nugent scores at the TOC/EOS and Interim visit. The Nugent score analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and race(black or all others). The p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata and race was <0.001 for secnidazole.

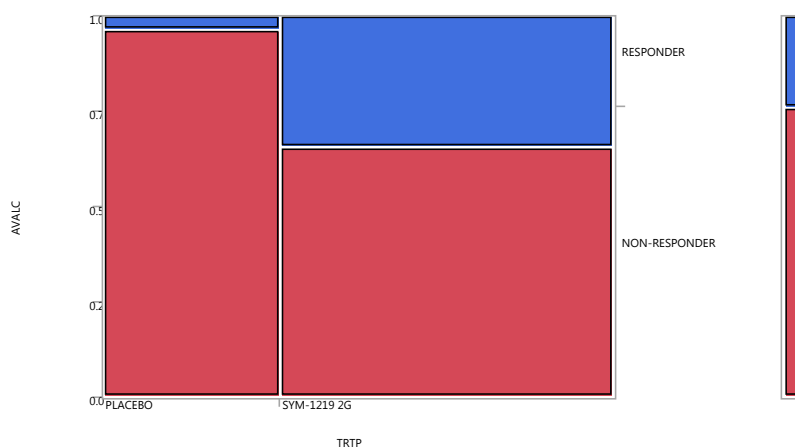
Therapeutic outcome

A Therapeutic Outcome Responder was defined as a Clinical Outcome Responder with a normal Nugent score (between 0-3). The following tables and figures show the analysis of the secondary endpoint of Therapeutic outcome.

Table 29-Therapeutic outcome responder rate by treatment arm (mITT population) in trial SYM 1219-301

TOC visit	TRTP				
	SYM-1219 2G N=107 n(%)		PLACEBO N=57 n(%)		All N=164
	N	Column %	N	Column %	N
RESPONDER	37	34.6%	2	3.5%	39
NON-RESPONDER	70	65.4%	55	96.5%	125
Interim visit					
RESPONDER	37	34.6%	2	3.5%	39
NON-RESPONDER	70	65.4%	55	96.5%	125

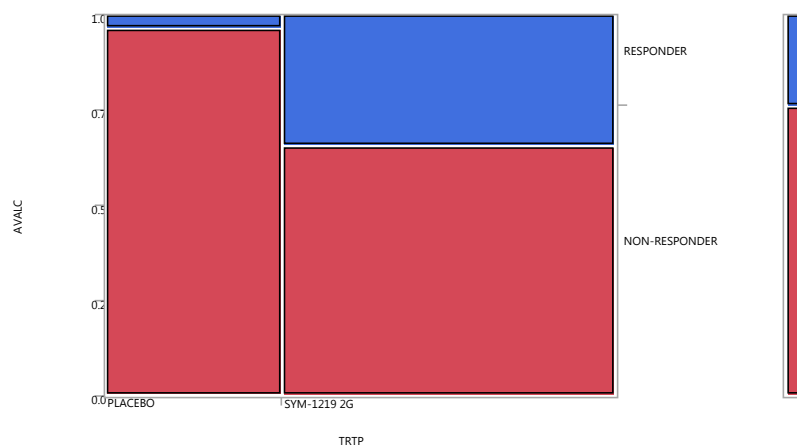
Figure 13-Therapeutic outcome responder rate at the TOC visit (mITT population) 2gm SYM 1219 versus placebo in trial SYM 1219-301



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	19.8037	1	<.0001*	164

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	19.8777	1	<.0001*

Figure 14-Therapeutic outcome responder rate at the Interim visit (mITT population) 2gm SYM 1219 versus placebo in trial SYM 1219-301



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	19.5207	1	<.0001*	164

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	20.5706	1	<.0001*

In the mITT population, the Therapeutic Outcome Responder Rate in the secnidazole 2 gram treatment group was statistically superior to placebo ($p < 0.001$) at the TOC/EOS and Interim visit. About 34.6% of subjects (37/107) in the secnidazole 2 gm arm were therapeutic responders at end of treatment and at interim visit compared to 3.5% (2/57) in the placebo arm.

The Therapeutic outcome responder analysis was stratified by BV strata (<3 or >3 episodes in the past 12 months) and race. The p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata and race was <0.001 for 2 gm secnidazole. The Applicant reports the 95% CI to be 25.6, 44.4 in the 2 gm secnidazole arm and 0.4, 12.1 in the placebo arm.

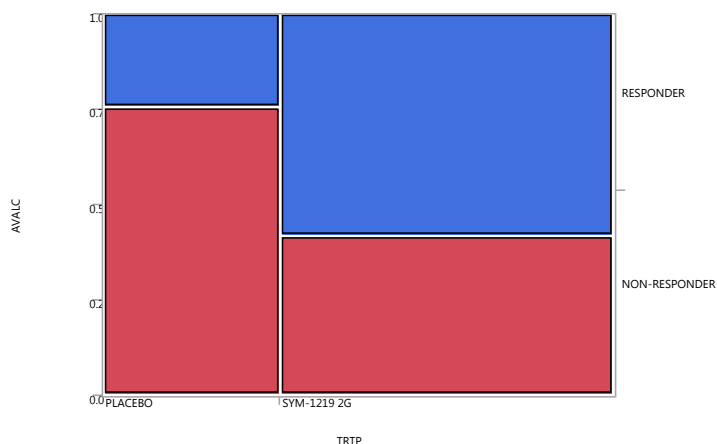
Clinical outcome responders at Interim visit

The following tables and figures show the analysis of the secondary endpoint of clinical outcome responders at the interim visit.

Table 30-Clinical Outcome Responder Rates at the Interim visit by Treatment (mITT Population)in trial SYM 1219-301

	TRTP					
	SYM-1219 2G N=107 n(%)		PLACEBO N=57 n(%)		All N=164	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	62	57.9%	14	24.6%	76	46.3%
NON-RESPONDER	45	42.1%	43	75.4%	88	53.7%

Figure 15-Clinical outcome responders at Interim visit for SYM 1219 2 gm versus placebo(mITT population) in trial SYM 1219-301



CMH Test Stratified by STRATA	ChiSquare	DF	Prob>Chisq	N
General Assoc. of Categories	16.5956	1	<.0001*	164

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	17.6769	1	<.0001*

In the mITT population, about 58%(62/107) of the subjects were clinical outcome responders at the interim visit in the secnidazole arm versus 24.6%(14/57) in the placebo arm. The clinical outcome responder analysis at interim visit was stratified by BV strata(<3 or >3 episodes in the past 12 months) and race. The p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata and race was <0.001 for 2 gm secnidazole . The Applicant reports the 95% CI to be 48.0, 67.4 in the 2 gm secnidazole arm and 14.1, 37.8 in the placebo arm.

Investigator's Clinical Assessment at the TOC visit

The following table shows the Investigator's clinical assessment (whether additional treatment for BV was needed) at TOC visit.

Table 31-Investigator's Clinical Assessment at TOC/EOS by Treatment (mITT population) in trial SYM 1219-301

	TRT01P					
	SYM-1219 2G N=107 n(%)		PLACEBO N=57 n(%)		All N=164	
DSICA	N	Column %	N	Column %	N	Column %
Y	32	32.0%	38	70.4%	70	45.5%
N	68	68.0%	16	29.6%	84	54.5%
Missing	7		3			

In 68% of subjects(68/100) in the 2gm secnidazole arm, no additional BV treatment was needed compared to 29.6%(16/54) of subjects in the placebo arm. The p-value versus placebo from CMH test adjusted for BV (<3 or >3 episodes in the past 12 months) and race (black or all others) strata was <0.001.

Similar results were reported by the Applicant for the analysis of the secondary endpoint in the PP population.

Dose/Dose Response

Not applicable as a single 2 gm dose of secnidazole was evaluated compared to placebo.

Durability of Response

Refer to section 7.1.5

Persistence of Effect

Refer to section 7.1.5

Additional Analyses Conducted on the Individual Trial

Subgroup analysis

Subgroup analysis were conducted for BV strata(3 or fewer, or 4 or more episodes of BV in the past 12 months), race[Black versus all others (primarily White)] and Nugent score(Scores of 7-10 and 4-6 subgroup). The following tables show the subgroup analysis.

BV strata

Table 32-Clinical Outcome Responder Rates by Time Point, BV Strata and Treatment (mITT population) in trial SYM 1219-301

TOC visit 3 or fewer episodes in the past 12 months	TRTP					
	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	50	60.2%	8	18.6%	58	46.0%
NON-RESPONDER	33	39.8%	35	81.4%	68	54.0%
All	83	100.00%	43	100.00%	126	100.00%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		20.5990	1	<.0001*		
TOC visit 4 or more episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
	N	Column %	N	Column %	N	Column %
RESPONDER	7	29.2%	3	21.4%	10	26.3%
NON-RESPONDER	17	70.8%	11	78.6%	28	73.7%
All	24	100.0%	14	100.0%	38	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		0.2545	1	0.6139		
Interim visit 3 or fewer episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
	N	Column %	N	Column %	N	Column %
RESPONDER	48	57.8%	9	20.9%	57	45.2%
NON-RESPONDER	35	42.2%	34	79.1%	69	54.8%
All	83	100.0%	43	100.0%	126	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		16.4417	1	<.0001*		
Interim visit 4 or more episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
	N	Column %	N	Column %	N	Column %
RESPONDER	14	58.3%	5	35.7%	19	50.0%
NON-RESPONDER	10	41.7%	9	64.3%	19	50.0%
All	24	100.0%	14	100.0%	38	100.0%

CMH Test Stratified by RACEGR1	ChiSquare	DF	Prob>Chisq
General Assoc. of Categories	1.8374	1	0.1753

Table 33-Nugent Score by Time Point, BV Strata and Treatment(mITT population) in trial SYM 1219-301

	TRTP					
TOC/EOS Visit 3 or fewer episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER ¹	40	48.2%	3	7.0%	43	34.1%
NON-RESPONDER ²	43	51.8%	40	93.0%	83	65.9%
All	83	100.0%	43	100.0%	126	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		21.6771	1	<.0001*		
TOC visit 4 or more episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER ¹	7	29.2%	0	0.0%	7	18.4%
NON-RESPONDER ²	17	70.8%	14	100.0%	31	81.6%
All	24	100.0%	14	100.0%	38	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		4.7998	1	0.0285*		

¹ Nugent Score 0-3 (Normal), ² Nugent Score $\geq$ 4 (Abnormal)

Table 34-Therapeutic Outcome Responder Rates by Time Point, BV Strata and Treatment (mITTpopulation) in trial SYM 1219-301

	TRTP					
TOC/EOS Visit 3 or fewer episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	33	39.8%	2	4.7%	35	27.8%
NON-RESPONDER	50	60.2%	41	95.3%	91	72.2%
All	83	100.0%	43	100.0%	126	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		17.9116	1	<.0001*		

TOC visit 4 or more episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	4	16.7%	0	0.0%	4	10.5%
NON-RESPONDER	20	83.3%	14	100.0%	34	89.5%
All	24	100.0%	14	100.0%	38	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		2.6667	1	0.1025		
Interim Visit 3 or fewer episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	31	37.3%	1	2.3%	32	25.4%
NON-RESPONDER	52	62.7%	42	97.7%	94	74.6%
All	83	100.0%	43	100.0%	126	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		19.0229	1	<.0001*		
Interim visit 4 or more episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	6	25.0%	1	7.1%	7	18.4%
NON-RESPONDER	18	75.0%	13	92.9%	31	81.6%
All	24	100.0%	14	100.0%	38	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		1.8366	1	0.1754		

Table 35-Investigator's Clinical Assessment at TOC/EOS by BV Strata and Treatment (mITT population) in trial SYM 1219-301

	TRT01P					
3 or fewer episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
DSICA	N	Column %	N	Column %	N	Column %
Y	20	26.0%	28	70.0%	48	41.0%
N	57	74.0%	12	30.0%	69	59.0%
All	77	100.0%	40	100.0%	117	100.0%
CMH Test Stratified by RACEN		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		20.1369	1	<.0001*		
4 or more episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
DSICA	N	Column %	N	Column %	N	Column %
Y	12	52.2%	10	71.4%	22	59.5%

	TRT01P					
3 or fewer episodes in the past 12 months	SYM-1219 2G		PLACEBO		All	
DSICA	N	Column %	N	Column %	N	Column %
N	11	47.8%	4	28.6%	15	40.5%
All	23	100.0%	14	100.0%	37	100.0%
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		1 2286	1	0.2677		

Y- Additional BV treatment needed, N- No additional BV treatment needed

The efficacy results in the 3 or fewer baseline BV strata were consistent with the efficacy analyses for the full mITT population. At the TOC visit, in the 3 or fewer BV episodes group, there were 60.2% clinical outcome responders in the 2gm secnidazole arm compared to 18.6% in the placebo arm. The responder rates however, were generally lower in patients with 4 or more episodes. In the 4 or more episodes group, statistical significance was not achieved for the Clinical Outcome Responder rate, Therapeutic Outcome rates, or Investigator's Clinical Assessments.

Race strata

Table 36-Clinical Outcome Responder Rates by Time Point, Race Strata and Treatment (mITT population) in trial SYM 1219-301

	TRTP					
TOC/EOS Visit Black Race	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	27	45.8%	6	20.7%	33	37.5%
NON-RESPONDER	32	54.2%	23	79.3%	55	62.5%
All	59	100.0%	29	100.0%	88	100.0%
All Others	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	30	62.5%	5	17.9%	35	46.1%
NON-RESPONDER	18	37.5%	23	82.1%	41	53.9%
All	48	100.0%	28	100.0%	76	100.0%
Interim Visit Black Race	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	29	49.2%	5	17.2%	34	38.6%
NON-RESPONDER	30	50.8%	24	82.8%	54	61.4%
All	59	100.0%	29	100.0%	88	100.0%
All Others	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	33	68.8%	9	32.1%	42	55.3%
NON-RESPONDER	15	31.3%	19	67.9%	34	44.7%

	TRTP					
TOC/EOS Visit Black Race	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
All	48	100.0%	28	100.0%	76	100.0%

Table 37-Nugent Score by Time Point, Race Strata and Treatment (mITT population) in trial SYM 1219-301

	TRTP					
TOC/EOS Visit Black Race	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER ¹	24	40.7%	1	3.4%	25	28.4%
NON-RESPONDER ²	35	59.3%	28	96.6%	63	71.6%
All	59	100.0%	29	100.0%	88	100.0%
All Others	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER ¹	23	47.9%	2	7.1%	25	32.9%
NON-RESPONDER ²	25	52.1%	26	92.9%	51	67.1%
All	48	100.0%	28	100.0%	76	100.0%

¹ Nugent Score 0-3 (Normal), ² Nugent Score $\geq$ 4 (Abnormal)

Table 38-Therapeutic Outcome Responder Rates by Time Point, Race Strata and Treatment (mITT population) in trial SYM 1219-301

	TRTP					
TOC/EOS Visit Black Race	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	18	30.5%	1	3.4%	19	21.6%
NON-RESPONDER	41	69.5%	28	96.6%	69	78.4%
All	59	100.0%	29	100.0%	88	100.0%
All Others	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	19	39.6%	1	3.6%	20	26.3%
NON-RESPONDER	29	60.4%	27	96.4%	56	73.7%
All	48	100.0%	28	100.0%	76	100.0%
Interim Visit Black Race	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	16	27.1%	0	0.0%	16	18.2%
NON-RESPONDER	43	72.9%	29	100.0%	72	81.8%
All	59	100.0%	29	100.0%	88	100.0%

All Others	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	21	43.8%	2	7.1%	23	30.3%
NON-RESPONDER	27	56.3%	26	92.9%	53	69.7%
All	48	100.0%	28	100.0%	76	100.0%

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Table 39-Investigator's Clinical Assessment at TOC/EOS by Race Strata and Treatment (mITT population) in trial SYM 1219-301

Race Strata	TRT01P					
Black race	SYM-1219 2G		PLACEBO		All	
DSICA	N	Column %	N	Column %	N	Column %
Y	20	37.0%	18	66.7%	38	46.9%
N	34	63.0%	9	33.3%	43	53.1%
All	54	100.0%	27	100.0%	81	100.0%
All Others	SYM-1219 2G		PLACEBO		All	
DSICA	N	Column %	N	Column %	N	Column %
Y	12	26.1%	20	74.1%	32	43.8%
N	34	73.9%	7	25.9%	41	56.2%
All	46	100.0%	27	100.0%	73	100.0%

Y- Additional BV treatment needed, N- No additional BV treatment needed

The efficacy results of the baseline race strata were consistent with the efficacy analyses for the full mITT population with statistical superiority demonstrated ($p < 0.05$) for the SYM-1219 2 gram treatment group in both race strata for all efficacy outcome measures at both the interim and EOS timepoints.

However, the response rates for the Black patients were numerically lower than response rates for all others. There were 45.8% Black clinical outcome responders compared to 62.5% all

others in the 2 gm secnidazole arm at the TOC visit. Similarly at the interim visit, there were 49.2% Black clinical outcome responders compared to 68.8% All others in the secnidazole arm.

Nugent score strata

Table 40-Clinical Outcome Responder Rates by Time Point, Baseline Nugent Score and Treatment (mITT population) in trial SYM 1219-301

TOC/EOS Visit Baseline Nugent Score of 4-6	TRTP					
	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	9	50.0%	1	25.0%	10	45.5%
NON-RESPONDER	9	50.0%	3	75.0%	12	54.5%
All	18	100.0%	4	100.0%	22	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		0.7143	1	0.3980		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		0.6516	1	0.4196		
TOC visit Baseline Nugent Score of 7-10	SYM-1219 2G		PLACEBO		All	
	N	Column %	N	Column %	N	Column %
RESPONDER	48	53.9%	10	18.9%	58	40.8%
NON-RESPONDER	41	46.1%	43	81.1%	84	59.2%
All	89	100.0%	53	100.0%	142	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		16.1156	1	<.0001*		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		17.5033	1	<.0001*		
Interim Visit Baseline Nugent Score of 4-6	SYM-1219 2G		PLACEBO		All	
	N	Column %	N	Column %	N	Column %
RESPONDER	13	72.2%	1	25.0%	14	63.6%
NON-RESPONDER	5	27.8%	3	75.0%	8	36.4%
All	18	100.0%	4	100.0%	22	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		3.0000	1	0.0833		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		2.5341	1	0.1114		

Interim visit Baseline Nugent Score of 7-10	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	49	55.1%	13	24.5%	62	43.7%
NON-RESPONDER	40	44.9%	40	75.5%	80	56.3%
All	89	100.0%	53	100.0%	142	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		12.6897	1	0.0004*		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		13.7645	1	0.0002*		

Table 41-Nugent Score by Time Point, Baseline Nugent Score and Treatment (mITT population) in trial SYM 1219-301

TOC/EOS Visit Baseline Nugent Score of 4-6	TRTP					
	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER ¹	7	38.9%	0	0.0%	7	31.8%
NON-RESPONDER ²	11	61.1%	4	100.0%	15	68.2%
All	18	100.0%	4	100.0%	22	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		2.2727	1	0.1317		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		1.9784	1	0.1596		
Baseline Nugent Score of 7-10	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER ¹	40	44.9%	3	5.7%	43	30.3%
NON-RESPONDER ²	49	55.1%	50	94.3%	99	69.7%
All	89	100.0%	53	100.0%	142	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		23.5159	1	<.0001*		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		24.4793	1	<.0001*		

¹ Nugent Score 0-3 (Normal), ² Nugent Score $\geq$ 4 (Abnormal)

The efficacy results for patients with baseline Nugent Score of 7-10 were consistent with the efficacy analyses for the full mITT population with statistical significance demonstrated

($p < 0.05$) for the SYM-1219 2 gram treatment group. In the Nugent score baseline 7-10 group, there were 53.9% clinical outcome responders in the secnidazole arm compared to 18.9% in the placebo arm at the TOC visit. Statistical significance was not demonstrated in the Nugent score 4-6 group however, the number of subjects in this group were small to draw conclusions.

Efficacy Outcomes Utilizing An Alternate Definition of Responder

An additional analysis were conducted utilizing an alternate definition of responder. A Clinical Outcome Responder could include a vaginal discharge assessment of normal or abnormal (other- that is not consistent with BV). A vaginal discharge of abnormal (consistent with BV) was considered a non-responder. The following table shows the Clinical outcome responder rates using the alternate definition.

Table 42-Clinical Outcome Responder Rates (Alternate Definition) by Time Point and Treatment (mITT population) in trial SYM 1219-301

TOC visit	TRTP					
	SYM-1219 2G		PLACEBO		All	
AVALC	N	Column %	N	Column %	N	Column %
RESPONDER	63	58.9%	14	24.6%	77	47.0%
NON-RESPONDER	44	41.1%	43	75.4%	87	53.0%
All	107	100.0%	57	100.0%	164	100.0%
CMH Test Stratified by STRATA		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		17.3785	1	<.0001*		
CMH Test Stratified by RACEGR1		ChiSquare	DF	Prob>Chisq		
General Assoc. of Categories		17.8649	1	<.0001*		

There were 60% clinical outcome responders in the secnidazole arm compared to 25% in the placebo arm at the TOC visit. The CMH tests stratified by BV strata and race was < 0.001 .

Medical Reviewer Comment: There were 53.3%(57/107) Clinical outcome responders compared to 19.3%(11/57) in placebo arm($p < 0.001$). In terms of the secondary endpoints, the 2 gm secnidazole had a greater response than placebo across the endpoints. About 43.9% of subjects (47/107) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 5.3%(3/57) in the placebo arm in the mITT population($p < 0.001$). About 34.6% of subjects (37/107) in the secnidazole 2 gm arm were therapeutic responders at end of treatment and at interim visit compared to 3.5%(2/57) in the placebo arm in the mITT population($p < 0.001$). About 58%(62/107) of the subjects were clinical outcome responders at the interim visit in the secnidazole arm versus 24.6%(14/57) in the placebo arm in the mITT population ($p < 0.001$) and 68% of subjects (68/100) in the 2gm secnidazole arm, needed no additional BV treatment compared to 29.6%(16/54) of subjects in the placebo arm. The efficacy results in the 3 or fewer baseline BV strata were consistent with the efficacy analyses for the full mITT population. At the TOC visit, in the 3 or fewer BV episodes group, there were 60.2% clinical outcome responders in the 2gm secnidazole arm compared to 18.6% in the placebo arm. The responder rates however,

were generally lower in patients with 4 or more episodes. Although, the percentage of Clinical Outcome Responders was fewer in Blacks than all others (49.4% and 67.9%, respectively), a greater percentage of patients treated with SYM-1219 2 g compared to placebo were Clinical outcome responders (49.4% and 12.7%, respectively), had normal Nugent score (40.0% and 4.8%, respectively), were Therapeutic outcome responders (32.9% and 4.8%, respectively) in Blacks. The results showed that the clinical outcome response with 2 gm secnidazole at days 7 - 14 was statistically significant over placebo and the degree of effect within 14 days of treatment remained consistent at days 21-30. There were no significant differences in the treatment effect between the MITT and PP populations.

6.3. Trial SYM 1219-350

6.3.1. Study Design

Overview and Objective

Trial SYM 1219-350 was a phase 3, multi-center, prospective, open-label study to evaluate the safety of a single dose of oral granule SYM-1219 containing 2 Grams secnidazole, for the treatment of women and postmenarchal adolescent girls with bacterial vaginosis. Refer to section 8.7 for details of the trial design. Although this was primarily an open label safety trial, some post hoc efficacy analysis was conducted. A pelvic examination (including examination of the internal and external genitalia), vaginal discharge assessment and testing were performed at the Baseline visit (Study Day 1) and at the EOS visit if the patient reported any vulvovaginal signs/symptoms/adverse events, at the Investigator's discretion, or at any time during the study if the patient's clinical response was perceived to be inadequate or as dictated by patient symptoms. This summary was performed defining a Clinical Outcome Responder in two ways; defined as a patient who had all three of the following clinical assessments: normal vaginal discharge, negative KOH Whiff test, and Clue cells <20% or by an alternate definition that classified a responder as a patient who had all three of the following clinical assessments: normal vaginal discharge or abnormal vaginal discharge that is not consistent with BV, negative KOH Whiff test, and Clue cells <20%. This was performed in the sub-group of subjects with both baseline and EOS vaginal assessment data (N=275).

Study Endpoints

Refer to section 8.7

Statistical Analysis Plan

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Refer to section 8.7

Protocol Amendments

Refer to section 8.7

Data Quality and Integrity: Sponsor's Assurance

The Applicant states that the study was organized, performed, and reported in compliance with the Applicant's Standard Operating Procedures or those of its designee, protocol, working practice documents, and GCP guidelines. The Investigator was responsible for all data entered via the electronic data capture (eDC) system eCRFs and confirmed the accuracy of the data. The study centers were visited as frequently as documented in the Study Monitoring Plan to review the eCRFs for completeness and accuracy. Quality control and data validation procedures were applied to ensure the validity and accuracy of the clinical database.

6.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the trial was conducted in the compliance with Good Clinical Practices (GCPs).

Financial Disclosure

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the SYM 1219-350 trial as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f). See Appendix 13.2 for detailed review.

Patient Disposition

There were 321 subjects in the safety population. The following table shows the disposition of the subjects by treatment arm in the safety population.

Table 43-Patient disposition in the safety population in trial SYM 1219-350

Disposition	SYM 1219 2 gm N=321	
	n	% of Total
Completed	283	88.16%
Reason for discontinuation		

OTHER	1	0.31%
PATIENT LOST TO FOLLOW-UP	13	4.05%
PATIENTS REQUEST	2	0.62%
PATIENTS USE OF OR NEED FOR CONCOMITANT THERAPY LIABLE TO INTERFERE WITH THE INTERPRETATION OF STUDY ENDPOINTS	1	0.31%
PERCEIVED LACK OF THERAPEUTIC EFFECT	3	0.93%
POSITIVE FOR SEXUALLY TRANSMITTED INFECTION(S) (STIS) FROM SAMPLES OBTAINED AT BASELINE VISIT (DAY 1)	17	5.30%
SAFETY REASONS (EG ADVERSE EVENT)	1	0.31%

Of the 321 patients in the Safety population, 283 (88.2%) completed the study. Among the 38 (11.8%) patients who discontinued the study prematurely, the most common reason for discontinuation was detection of sexually transmitted infections (STIs) in baseline vaginal samples (17/283; 5.3%) and lost-to-follow-up (13/283; 4.0%).

Medical Reviewer Comment: The subject with "other" reason for discontinuation was due to a vulvovaginal mycotic infection. See section 8.4.3

Protocol Violations/Deviations

The most common protocol deviations were associated with out-of-window visits, labs not done, and other protocol assessments that were missed/not done. The Applicant reports that one patient (#25/503, #30/509) was enrolled into the study twice, in violation of the protocol. However, this violation was identified well after database lock and the data was presented as if collected from unique patients.

Table of Demographic Characteristics

The following table shows the demographics and baseline characteristics of the safety population.

Table 44-Demographics and Baseline Characteristics (Safety Population) in trial SYM 1219-350

Characteristics	Statistics	SYM-1219 2G N=321
Age Cat 65 [n (%)]	<65	321 (100.00%)
	Min:Age	15
	Max:Age	53

	Mean:Age	31.53
	Std Dev:Age	8.48
Sex [n (%)]	F	321 (100.00%)
Race [n (%)]	AMERICAN INDIAN OR ALASKA NATIVE	2 (0.62%)
	ASIAN	2 (0.62%)
	BLACK OR AFRICAN AMERICAN	148 (46.11%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.31%)
	WHITE	165 (51.40%)
Ethnicity [n(%)]	HISPANIC OR LATINO	72 (22.43%)
	NOT HISPANIC OR LATINO	249 (77.57%)
BV category [n(%)]	3 or fewer episodes in the past 12 months	254 (79.1%)
	4 or more episodes in the past 12 months	67 (20.9%)

The mean age of the patients in this study was 31.5 years, with a range of 15 to 53 years. The majority of the study population was either White (164/321; 51.4%) or Black/African American (148/321; 46.1%). Most patients (79.1%) reported 3 or fewer episodes of BV in the past 12 months. About 6.2% of subjects(20/321) had a baseline STI.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medications were taken by 63.6% of the study population. Progesterone/estrogen fixed combinations (19.6%) and ibuprofen/naproxen (9.3%) were the most commonly used concomitant medication. Four patients were excluded from the Safety Population because they did not consume any study medication (one patient participated in a previous trial).

Efficacy Results

The Applicant conducted post-hoc efficacy analysis where the Clinical Outcome was evaluated based on the vaginal assessment at the EOS visit: Since the vaginal assessment was not required and was done at the Investigator's discretion, the responder rates are based on patients with assessments. A Clinical Outcome Responder was defined as a patient with all of the following:

- 1) Normal vaginal discharge.
- 2) Negative 10% KOH Whiff test.
- 3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the

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vaginal wet mount using saline.

The Clinical Outcome Responder rates in the sub-group of subjects with both baseline and EOS vaginal assessment data (N=275) was 57.8%(159/275). The Clinical outcome responder rates using an alternate definition (defined as a patient who had all three of the following clinical assessments: normal vaginal discharge or abnormal vaginal discharge that is not consistent with BV, negative KOH Whiff test, and Clue cells <20%) was 63.3% (174/275).

In the Investigator's Clinical Assessment at the EOS visit, about 72.5% (222/306) subjects did not require additional BV treatment.

Medical Reviewer comment: Since trial SYM 1219-350 is open-label, the above efficacy analysis will be considered exploratory in nature.

Data Quality and Integrity - Reviewers' Assessment

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format.

Dose/Dose Response

Not applicable as a single 2 gm secnidazole was evaluated.

Durability of Response

Refer to section 7.1.5

Persistence of Effect

Refer to section 7.1.5

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The Applicant performed two trials, a phase 2 trial SYM 1219-201 and a phase 3 trial SYM 1219-301 to demonstrate efficacy. Trial SYM-1219-201 was a randomized, double-blind study where both 1 gm and 2 gms of SYM-1219 was compared to placebo for the treatment of women ≥ 18 years with bacterial vaginosis. Trial SYM-1219-301 was a randomized, double-blind study where 2 Grams SYM 1219 was compared to placebo for the treatment of women and postmenarchal adolescent girls with bacterial vaginosis. The primary endpoint for both trials was the Clinical

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Outcome evaluated at the TOC/EOS visit (Day 21 to 30) in the mITT population. A Clinical Outcome Responder was defined as a patient with all of the following:

- 1) Normal vaginal discharge
- 2) Negative 10% KOH Whiff test
- 3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline.

In trial SYM 1219-201, there were 67.7% (42/62) Clinical outcome responders in the 2 gm secnidazole arm compared to 17.7%(11/62) in placebo(there were 51.6% clinical outcome responders in the 1 gm secnidazole arm).In trial SYM 1219-301, there were 53.3%(57/107) Clinical outcome responders compared to 19.3%(11/57) in placebo arm. This difference was statistically significant with p value versus placebo from CMH test adjusted for BV (<3 or >3 episodes in the past 12 months) in trial SYM 1219-201 and trial SYM 1219-301 and for race (black or all others) in trial SYM 1219-301 was <0.001. In trial SYM 1219-201, the 95% CI for the responder rate was 54.7, 79.1 in the 2gm secnidazole arm and 9.2, 29.5 in the placebo arm. For trial SYM 1219-301, the 95% CI for the responder rate was 43.4, 63.0 in the 2gm secnidazole arm and 10.0,31.9 in the placebo arm.

7.1.2. Secondary and Other Endpoints

In trial SYM 1219-201, the secondary endpoints at the TOC/EOS visit (Day 21 to 30) in the mITT population were the Nugent score and the Therapeutic outcome (Clinical outcome responder with a normal Nugent score). In trial SYM 1219-301, the secondary endpoints in the mITT population at the Interim visit (Study Day 7-14) and the TOC/EOS visit (Study Day 21 to 30) were the Nugent score, Therapeutic outcome, Clinical outcome (Interim Visit only) and the Investigator's clinical assessment(TOC/EOS Visit).

- In trial SYM 1219-201, about 40.3% of subjects (25/62) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 6.5%(4/62) in the placebo arm in the mITT population. The mean Nugent score at the TOC was 4.7 in the secnidazole arm compared to 8.3 in the placebo arm. In trial SYM 1219-301, about 43.9% of subjects (47/107) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 5.3%(3/57) in the placebo arm in the mITT population. The mean Nugent score at TOC was 4.1 in the secnidazole arm compared to 7.9 in the placebo arm. At the interim visit, 45.8% of subjects (49/107) in the secnidazole group had normal Nugent score compared to 3.5%(2/57) in the placebo arm. The secnidazole 2 gram treatment group was statistically superior to placebo (p<0.001) for the percentage of patients with normal Nugent scores at the TOC/EOS in both trials and Interim visit in trial SYM 1219-301. The Nugent score analysis was stratified by BV strata(<3 or >3 episodes in the past 12 months) and race(black or all others). The p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata and race was <0.001 for secnidazole.

- In trial SYM 1219-201, about 40.3% of subjects (25/62) in the secnidazole 2 gm arm were therapeutic responders at end of treatment compared to 6.5%(4/62) in the placebo arm in the mITT population. In trial SYM 1219-301, about 34.6% of subjects (37/107) in the secnidazole 2 gm arm were therapeutic responders at end of treatment and at interim visit compared to 3.5%(2/57) in the placebo arm in the mITT population. The p-value versus placebo from Cochran-Mantel-Haenszel (CMH) test adjusted for BV strata and race was <0.001 for 2 gm secnidazole .
- In trial SYM 1219-301, about 58%(62/107) of the subjects were clinical outcome responders at the interim visit in the secnidazole arm versus 24.6%(14/57) in the placebo arm in the mITT population. The p-value versus placebo from CMH test adjusted for BV strata and race was <0.001 for 2 gm secnidazole . The 95% CI to be 48.0, 67.4 in the 2 gm secnidazole arm and 14.1, 37.8 in the placebo arm.
- In trial SYM 1219-301, 68% of subjects(68/100) in the 2gm secnidazole arm, needed no additional BV treatment compared to 29.6%(16/54) of subjects in the placebo arm. The p-value versus placebo from CMH test adjusted for BV and race strata was <0.001.
- In trial SYM 1219-201, about 53% of subjects in the 2gm secnidazole arm had normal vaginal pH at the end of treatment compared to and 21% in the placebo arm. No additional BV treatment was needed by Investigator assessment at end of treatment in over 72% of subjects in the 2 gm secnidazole arm compared to 24% in the placebo arm. Telephone diary responses showed that vaginal discharge was normal at end of treatment in 63% of subjects in the secnidazole 2 gm arm versus 42% in the placebo arm. Similarly vaginal odor was normal at end of treatment in 66% of subjects in the 2 gms secnidazole arm compared to 35.5% in the placebo arm. These analysis were exploratory in nature and conducted in the mITT population.
- In trial SYM 1219-301, an additional analysis was conducted utilizing an alternate definition of responder. A Clinical Outcome Responder could include a vaginal discharge assessment of normal or abnormal (other- that is not consistent with BV). A vaginal discharge of abnormal (consistent with BV) was considered a non-responder. There were 60%(63/107) clinical outcome responders in the secnidazole arm compared to 25%(14/57) in the placebo arm at the TOC visit in the mITT population. The CMH tests stratified by BV strata and race was <0.001.

Medical Reviewer comment:

(b) (4)

The DAIP had advised the Applicant that a responder be classified as only those who have a normal discharge

(b) (4)

This reviewer recommend that the labeling claim be based on the original definition of clinical responder.

7.1.3. Subpopulations

The following table shows the analyses of primary and key secondary endpoints in the subpopulations by number of BV episodes in the preceding 12 months (3 or fewer and 4 or more), race and baseline Nugent score in the pooled mITT population at the TOC/EOS visit.

Table 45-Primary and key secondary endpoints by BV strata, race, baseline Nugent score by treatment in pooled mITT population(SYM 1219-201 and 301)

	SYM-1219 2G		PLACEBO		All	
3 or fewer BV episodes in the past 12 months						
AVALC Clinical Outcome ResponderRate	N	Column %	N	Column %	N	Column %
RESPONDER	80	64.5%	18	20.9%	98	46.7%
NON-RESPONDER	44	35.5%	68	79.1%	112	53.3%
All	124	100.0%	86	100.0%	210	100.0%
AVALC Nugent Score	N	Column %	N	Column %	N	Column %
RESPONDER	58	46.8%	7	8.1%	65	31.0%
NON-RESPONDER	66	53.2%	79	91.9%	145	69.0%
All	124	100.0%	86	100.0%	210	100.0%
AVALC Therapeutic Outcome Responder Rate	N	Column %	N	Column %	N	Column %
RESPONDER	51	41.1%	6	7.0%	57	27.1%
NON-RESPONDER	73	58.9%	80	93.0%	153	72.9%
All	124	100.0%	86	100.0%	210	100.0%
4 or more BV episodes in the past 12 months						
AVALC Clinical Outcome ResponderRate	N	Column %	N	Column %	N	Column %
RESPONDER	19	42.2%	4	12.1%	23	29.5%
NON-RESPONDER	26	57.8%	29	87.9%	55	70.5%
All	45	100.0%	33	100.0%	78	100.0%
AVALC Nugent Score	N	Column %	N	Column %	N	Column %
RESPONDER	14	31.1%	0	0.0%	14	17.9%
NON-RESPONDER	31	68.9%	33	100.0%	64	82.1%
All	45	100.0%	33	100.0%	78	100.0%
AVALC Therapeutic Outcome Responder Rate	N	Column %	N	Column %	N	Column %
RESPONDER	11	24.4%	0	0.0%	11	14.1%
NON-RESPONDER	34	75.6%	33	100.0%	67	85.9%
All	45	100.0%	33	100.0%	78	100.0%
Black Race						

AVALC Clinical Outcome ResponderRate	N	Column %	N	Column %	N	Column %
RESPONDER	42	49.4%	8	12.7%	50	33.8%
NON-RESPONDER	43	50.6%	55	87.3%	98	66.2%
All	85	100.0%	63	100.0%	148	100.0%
AVALC Nugent Score	N	Column %	N	Column %	N	Column %
RESPONDER	34	40.0%	3	4.8%	37	25.0%
NON-RESPONDER	51	60.0%	60	95.2%	111	75.0%
All	85	100.0%	63	100.0%	148	100.0%
AVALC Therapeutic Outcome Responder Rate	N	Column %	N	Column %	N	Column %
RESPONDER	28	32.9%	3	4.8%	31	20.9%
NON-RESPONDER	57	67.1%	60	95.2%	117	79.1%
All	85	100.0%	63	100.0%	148	100.0%
All Others						
AVALC Clinical Outcome ResponderRate	N	Column %	N	Column %	N	Column %
RESPONDER	57	67.9%	14	25.0%	71	50.7%
NON-RESPONDER	27	32.1%	42	75.0%	69	49.3%
All	84	100.0%	56	100.0%	140	100.0%
AVALC Nugent Score	N	Column %	N	Column %	N	Column %
RESPONDER	38	45.2%	4	7.1%	42	30.0%
NON-RESPONDER	46	54.8%	52	92.9%	98	70.0%
All	84	100.0%	56	100.0%	140	100.0%
AVALC Therapeutic Outcome Responder Rate	N	Column %	N	Column %	N	Column %
RESPONDER	34	40.5%	3	5.4%	37	26.4%
NON-RESPONDER	50	59.5%	53	94.6%	103	73.6%
All	84	100.0%	56	100.0%	140	100.0%
Baseline Nugent Score of 7-10						
AVALC Clinical Outcome ResponderRate	N	Column %	N	Column %	N	Column %
RESPONDER	82	57.7%	19	16.8%	101	39.6%
NON-RESPONDER	60	42.3%	94	83.2%	154	60.4%
All	142	100.0%	113	100.0%	255	100.0%
AVALC Nugent score	N	Column %	N	Column %	N	Column %
RESPONDER	60	42.3%	6	5.3%	66	25.9%
NON-RESPONDER	82	57.7%	107	94.7%	189	74.1%
All	142	100.0%	113	100.0%	255	100.0%

AVALC Therapeutic Outcome Responder Rate	N	Column %	N	Column %	N	Column %
RESPONDER	54	38.0%	5	4.4%	59	23.1%
NON-RESPONDER	88	62.0%	108	95.6%	196	76.9%
All	142	100.0%	113	100.0%	255	100.0%
Baseline Nugent Score of 4-6						
AVALC Clinical Outcome ResponderRate	N	Column %	N	Column %	N	Column %
RESPONDER	17	63.0%	3	50.0%	20	60.6%
NON-RESPONDER	10	37.0%	3	50.0%	13	39.4%
All	27	100.0%	6	100.0%	33	100.0%
AVALC Nugent score	N	Column %	N	Column %	N	Column %
RESPONDER	12	44.4%	1	16.7%	13	39.4%
NON-RESPONDER	15	55.6%	5	83.3%	20	60.6%
All	27	100.0%	6	100.0%	33	100.0%
AVALC Therapeutic Outcome Responder Rate	N	Column %	N	Column %	N	Column %
RESPONDER	8	29.6%	1	16.7%	9	27.3%
NON-RESPONDER	19	70.4%	5	83.3%	24	72.7%
All	27	100.0%	6	100.0%	33	100.0%

- In the subpopulation with 3 or fewer BV episodes in the past 12 months, there were a greater percentage of subjects in the secnidazole 2 gm arm compared with placebo who were Clinical Outcome Responders (64.5% and 20.9%, respectively), subjects with normal Nugent score (46.8% and 8.1%, respectively) and Therapeutic Outcome Responders (41.1% and 7.0%, respectively). In the subpopulation with 4 or more BV episodes in the past 12 months, response was generally lower in both treatment groups but response on all endpoints was greater with SYM-1219 2 g than with placebo treatment, i.e., Clinical Outcome Responder: 42.2% and 12.1% respectively; normal Nugent score: 31.1% and 0, respectively and Therapeutic Outcome Responder: 24.4% and 0, respectively. The p value on all these cases were <0.05.
- In the subpopulation of patients who were Blacks, a greater percentage of patients treated with SYM-1219 2 g compared to placebo were Clinical Outcome Responders (49.4% and 12.7%, respectively), had normal Nugent score (40.0% and 4.8%, respectively), were Therapeutic Outcome Responders (32.9% and 4.8%, respectively). Results were similar in the subpopulation of patients with race other than Black(Clinical Outcome Responder: 67.9% and 25.0% in SYM-1219 2 g and placebo, respectively).
- However, among patients treated with SYM-1219 2 g across subpopulations by race, the percentage of Clinical Outcome Responders was fewer in Blacks than all others (49.4% and 67.9%, respectively).

- In the subpopulation with baseline Nugent score of 7-10, a greater percentage of patients treated with SYM-1219 2 g compared to placebo were Clinical Outcome Responders (57.7% and 16.8%, respectively), had normal Nugent score (42.3% and 5.3%, respectively) and were Therapeutic Outcome Responders (38.0% and 4.4%, respectively).
- There were fewer subjects in the baseline Nugent score 4-6 group (N=33) and the differences between the secnidazole arm and placebo arm was smaller. For example, in the subpopulation with baseline Nugent score of 4-6, 63.0% and 50.0% of patients in the SYM-1219 2 g and placebo treatment groups, respectively, were Clinical Outcome Responders with a p value of 0.68.

Medical Reviewer Comment: In the subpopulation with 4 or more BV episodes in the past 12 months, although the response was generally lower in both treatment groups, the response on all endpoints was greater with SYM-1219 2 g than with placebo treatment. Similarly, even though the percentage of Clinical Outcome Responders was fewer in Blacks than all others (49.4% and 67.9%, respectively), a greater percentage of patients treated with SYM-1219 2 g compared to placebo were Clinical outcome responders (49.4% and 12.7%, respectively) in Blacks. The treatment differences between the secnidazole arm and placebo arm was smaller in the subpopulation with baseline Nugent score of 4-6, however the overall sample size in these subpopulation analysis were small to draw any definite conclusions.

The following table shows the pooled demographic and baseline characteristics of subjects in the mITT population in the SYM 1219-201 and SYM 1219-301 trials.

Table 46-Pooled demographic and baseline characteristics of subjects in the mITT population in the SYM 1219-201 and SYM 1219-301 trials.

Characteristics	Statistics	SYM-1219 1G	SYM-1219 2G	PLACEBO	Subjects(Total)
Age Cat 65 [n (%)]	<65	64 (100.0%)	169 (100.00%)	119 (100.00%)	352 (87.13%)
Sex [n (%)]	F	64 (100.00%)	169 (100.00%)	119 (100.00%)	352 (87.13%)
Race [n (%)]	AMERICAN INDIAN OR ALASKA NATIVE	1 (1.56%)	1 (0.59%)	0 (0%)	2 (0.50%)
	ASIAN	1 (1.56%)	1 (0.59%)	3 (2.52%)	5 (1.24%)
	BLACK OR AFRICAN AMERICAN	42 (65.63%)	85 (50.30%)	63 (52.94%)	190 (47.03%)
	WHITE	18 (28.13%)	78 (46.15%)	50 (42.02%)	146 (36.14%)

Ethnicity	HISPANIC OR LATINO	7 (10.9%)	27 (16.0%)	17 (14.3%)	51 (12.6%)
	NOT HISPANIC OR LATINO	57 (89.1%)	142 (84.0%)	102 (85.7%)	301 (74.5%)
BV Strata	3 or fewer episodes in the past 12 month	44 (68.8%)	124 (73.4%)	86 (72.3%)	254 (62.9%)
	4 or more episode in the past 12 months	20 (31.3%)	45 (26.6%)	33 (27.7%)	98 (24.3%)
Baseline Nugent category	4 - 6	5 (7.8%)	27 (16.0%)	6 (5.0%)	38 (9.4%)
	7 - 10	59 (92.2%)	142 (84.0%)	113 (95.0%)	314 (77.7%)

All patients were women in their reproductive age group (ages 18-54) and about 50% were Blacks in the secnidazole 2gm and placebo arm.

The mean baseline Nugent score in each treatment group across the two studies was ≥ 8 . In the pooled mITT population, , 92.2%, 84.0%, and 95.0% of patients in the SYM-1219 1g, 2g, and placebo groups, respectively, had a baseline Nugent score of 7-10.

7.1.4. Dose and Dose-Response

Study SYM-1219-201 evaluated two dose levels of SYM-1219 (1 g and 2 g) compared to placebo. The efficacy across the endpoints was greater with the SYM-1219 2 g dose level than with SYM-1219 1 g compared with placebo. The greater efficacy seen with SYM-1219 2 g was consistent with the higher exposure seen in the pharmacokinetics study in healthy volunteers (Study SYM-1219-101). Refer to the Clinical pharmacology review for details of the study. There were 67.7% Clinical outcome responders in the 2gm secnidazole group compared to 51.6% in the 1 gm secnidazole group and 17.7% in the placebo. There were 40.3% of subjects with normal Nugent score in the 2 gm secnidazole group compared to 23.4% in the 1 gm secnidazole group and 6.5% in the placebo group. Similarly, there were 40.3% Therapeutic outcome responders in the 2 gm secnidazole group compared to 21.9% in the 1 gm secnidazole group and 6.5% in the placebo group.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Secnidazole is being proposed to be used for an acute infection as a single dose, thus duration and durability of efficacy effects is not relevant in this submission.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

See discussion in section 7.3

7.2.2. Other Relevant Benefits

See discussion in section 7.3

7.3. Integrated Assessment of Effectiveness

The Applicant performed two clinical trials SYM 1219-201(Phase2) and SYM 1219-301(Phase3) with secnidazole to demonstrate efficacy in the treatment of bacterial vaginosis. The primary analysis of efficacy included analysis of each trial individually. The Applicant presented a comparison of efficacy from both trials as protocols were mostly identical in patient selection criteria, design, conduct, monitoring, and planned analyses, and the demographic and baseline disease characteristics of the patient populations enrolled in each trial were comparable. The Applicant also conducted a pooled analysis in the subpopulation. The main goal of the pooled analyses was to provide a larger sample of patients to improve the treatment difference in the subpopulation of patients and to increase power to identify factors that might affect differences between the treatments (i.e., demographics, comorbidities, etc.). Pooling of the results of the two pivotal trials in the overall population, despite their similarity in design and results, is generally inappropriate, since each trial should provide independent evidence of efficacy of secnidazole in treating BV and the applicant is still required to demonstrate the efficacy and safety of secnidazole in each trial separately. This reviewer also presents the efficacy analysis from each trial separately. The primary endpoint for both trials was the Clinical Outcome evaluated at the TOC/EOS visit (Day 21 to 30) in the mITT population.

In trial SYM 1219-201, there were 67.7% (42/62) Clinical outcome responders in the 2 gm secnidazole arm compared to 17.7%(11/62) in placebo(there were 51.6% clinical outcome responders in the 1 gm secnidazole arm)($p<0.001$). In trial SYM 1219-301, there were 53.3%(57/107) Clinical outcome responders compared to 19.3%(11/57) in placebo arm($p<0.001$). In terms of the secondary endpoints, the 2 gm secnidazole had a greater response than placebo across the endpoints. In trial SYM 1219-201, about 40.3% of subjects (25/62) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 6.5%(4/62) in the placebo arm in the mITT population($p<0.001$). In trial SYM 1219-301, about 43.9% of subjects (47/107) in the secnidazole 2 gm arm had normal Nugent score at end of treatment compared to 5.3%(3/57) in the placebo arm in the mITT population($p<0.001$). In trial SYM 1219-201, about 40.3% of subjects (25/62) in the secnidazole 2 gm arm were therapeutic responders at end of treatment compared to 6.5%(4/62) in the placebo arm in the mITT population($p<0.001$). In trial SYM 1219-301, about 34.6% of subjects (37/107) in the secnidazole 2 gm arm were therapeutic responders at end of treatment and at interim visit

compared to 3.5%(2/57) in the placebo arm in the mITT population($p<0.001$). In trial SYM 1219-301, about 58%(62/107) of the subjects were clinical outcome responders at the interim visit in the secnidazole arm versus 24.6%(14/57) in the placebo arm in the mITT population ($p<0.001$) and 68% of subjects (68/100) in the 2gm secnidazole arm, needed no additional BV treatment compared to 29.6%(16/54) of subjects in the placebo arm. When an additional analysis was conducted utilizing an alternate definition of responder[i.e. a Clinical outcome responder could include a vaginal discharge assessment of normal or abnormal (other- that is not consistent with BV)],there were 60%(63/107) clinical outcome responders in the secnidazole arm compared to 25%(14/57) in the placebo arm at the TOC visit($p<0.001$). Therefore no matter what definition of Clinical outcome responder was used, secnidazole appeared to have a statistically significant effect over placebo in the clinical cure of bacterial vaginosis. The Applicant has thus provided a substantial evidence of effectiveness based on the results of the conducted trials.

Although, among patients treated with SYM-1219 2 g across subpopulations by race, the percentage of Clinical Outcome Responders was fewer in Blacks than all others (49.4% and 67.9%, respectively), a greater percentage of patients treated with SYM-1219 2 g compared to placebo were Clinical outcome responders (49.4% and 12.7%, respectively), had normal Nugent score (40.0% and 4.8%, respectively), were Therapeutic outcome responders (32.9% and 4.8%, respectively) in Blacks. Therefore the results should be overall generalizable. No definite conclusions can be drawn from the lower treatment difference in the subpopulation with baseline Nugent score 4-6, given the small sample size.

Additionally, the results in trial SYM 1219-301 showed that the clinical outcome response with 2 gm secnidazole at days 7 -14 was statistically significant over placebo and the degree of effect within 14 days of treatment remained consistent at days 21-30.

The results from the pivotal trials are clinically meaningful in this patient population. It has been suggested that BV is more prevalent in HIV (human immunodeficiency virus) infected women and in women infected with HSV-2(herpes simplex virus) than uninfected hosts (7,8).

(b) (4)

The efficacy results from the trials are consistent with those seen with tinidazole, which is currently approved for the treatment of BV. The duration of follow up in the study was 30 days post dose therefore recurrences of BV were not captured in the trial.

Assuming a tolerable safety profile, an advantage of secnidazole is the one time convenient dosing regimen over the existing treatments for BV which would improve treatment compliance in this patient population.

In terms of labeling, this reviewer recommends presenting the primary endpoint data based on the original definition of a Clinical outcome responder, i.e a responder be classified as only those who have a normal discharge

(b) (4)

(b) (4)

The following table shows the efficacy analysis of secnidazole for the treatment of BV in the two randomized, double-blind, placebo-controlled trials(SYM 1219-201 and SYM 1219-301).

Table 47-Efficacy of Secnidazole for Treatment of Bacterial Vaginosis in Two Randomized, Double-Blind, Placebo-Controlled Trials in the Modified-Intent-to-Treat Population at 21-30 Days

	SYM 1219-201		SYM 1219-301	
	Secnidazole 2 gm (N=62) n (%)	Placebo (N=62) n (%)	Secnidazole 2 gm (N=107) n (%)	Placebo (N=57) n (%)
Primary endpoint				
Clinical Responder	42 (67.7)	11 (17.7) p<0.001	57 (53.3)	11 (19.3) p<0.001
Secondary endpoints				
Nugent Score Cure	25 (40.3)	4 (6.5) p<0.001	47 (43.9)	3 (5.3) p<0.001
Therapeutic responders	25 (40.3)	4 (6.5) p<0.001	37(34.6)	2(3.5) p<0.001
Clinical responder(interim visit)			62(58)	14(24.6) p<0.001
Investigator's Clinical Assessment(No additional BV treatment needed)			68/100(68)	16/54(29.6) p<0.001

8 Review of Safety

8.1. Safety Review Approach

This safety review focuses on the pooled data from the safety population enrolled in a phase 2 trial (Trial SYM 1219-201) and a phase 3 trial(Trial SYM 1219-301) both of which were randomized, placebo controlled trials supporting this application. The safety review also includes an additional open label phase 3 safety trial (Trial SYM-1219-350) and the results will be presented side by side along with the randomized, double blinded, placebo controlled

pooled trials, Trial SYM-1219-201 and Trial SYM-1219-301 to evaluate the safety of secnidazole. Given the open label nature of Trial SYM 1219-350, pooling of the results with the two pivotal trials will be considered exploratory in nature. A safety assessment of the healthy volunteer phase 1 trials (Study SYM-1219-101, Study SYM-1219-102, Study SYM-1219-103, Study SYM-1219-104 and Study SYM-1219-105) will also be conducted to add to the safety evaluation.

Given the different randomization allocations, i.e 1:1:1 in trial SYM 1219-201 and 2:1 in trial SYM 1219-301, crude pooling of the two trials (pooling data together as if they came from a single study) could be misleading since it can result in an overall baseline risk that is different among treatment groups(9). Therefore, a study size adjusted AE incidence proportion is calculated and presented in section 8.4.5. In addition the TEAEs of the individual trials (SYM 1219-201 and SYM 1219-301) are also presented in section 8.4.5.

Since the drug is in the 5-nitroimidazole class with a spectrum of microbiologic activity similar to metronidazole, safety review will also be focused to evaluate adverse reactions known to occur with this class of drugs.

For the integrated safety analysis, MAED version 1.5, JMP version 11.0 and JReview 11.0 analytical software were utilized.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Applicant pooled the safety results from the two controlled trials (Trial SYM 1219-201 and Trial SYM 1219-301) and presented them beside the results from the open label safety trial (SYM 1219-350). This strategy was agreed upon by the Agency at the pre-NDA meeting. Overall, there were 783 subjects exposed to SYM 1219 (secnidazole), 589 subjects in the BV trials and 194 subjects in the healthy volunteer trials. A total of 518 subjects were exposed to 2 gm of secnidazole in the BV trials (197 subjects in the controlled trials and 321 in the open label safety trial). The table below summarizes the overall extent of exposure to SYM 1219 in the developmental program.

Table 48-SYM 1219 exposed subjects during the developmental program (safety database)

Study Identifier	SYM-1219 1G	SYM-1219 2G	SYM- 1219 4 G	SYM- 1219 6 G	PLACEBO	Total (Individuals exposed to the study drug for the indication under review) N=783
Controlled Trials for BV						

SYM-1219-201(Phase2)	71	72			72	
SYM-1219-301(Phase3)	0	125			64	
Total	71	197			136	
Open label Trial for BV						
SYM-1219-350(Phase3)		321				
Total	71	518				589
Healthy Volunteer Trials(Phase1)						
SYM-1219-101	14	68				82
SYM-1219-102		24				24
SYM-1219-103		24				24
SYM-1219-104			6	6	4	12
SYM-1219-105 ¹		50		50		52
Total					140	194

Subjects received both dose levels in a crossover design for a cumulative dose of 8 g

One patient (Subject 12/020) received SYM-1219 2 g in Study SYM-1219-201 and subsequently enrolled into Study SYM-1219-301 where she received SYM-1219 2 g. This patient is counted twice as having received SYM-1219 2 g in the table.

8.2.2. Relevant characteristics of the safety population:

The safety population included all enrolled patients who received the study drug. The BV population was generally in good health and baseline STIs were excluded. All patients were female with a median age in the early thirties. About 50% of the population were Blacks. Hispanics represented upto 15% in the pooled SYM 1219-201/301 Trials. The mean Body weight and Blood Pressure showed that the subjects in the treatment arms were comparable. Few patients were hypertensive. Mean body weight was approximately 170 lbs. Overall, the treatment groups were balanced by number of BV episodes. Approximately 75% of patients in the three BV studies had 3 or fewer episodes of BV in the past 12 months. The table below shows the demographics and other characteristics of the safety population in the pooled trials and the open label safety trial.

Table 49-Demographics and other characteristics of the safety population in the BV trials.

	Pooled SYM 1219-201/301 Trials	Trial SYM 1219-350
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	SYM-1219 2G N=197 n(%)	SYM-1219 1G N=71 n(%)	PLACEBO N=136 n(%)	SYM-1219 2G N=321 n(%)
F(sex)	197 (100.0%)	71 (100.0%)	136 (100.0%)	321 (100.00%)
Ethnicity				
Hispanic or latino	29 (14.7%)	7 (9.9%)	20 (14.7%)	72 (22.4%)
Not hispanic or latino	168 (85.3%)	64 (90.1%)	116 (85.3%)	249 (77.57%)
Race				
American indian or alaska native	1 (0.5%)	1 (1.4%)	0 (0.0%)	2 (0.62%)
Asian	2 (1.0%)	1 (1.4%)	3 (2.2%)	2 (0.62%)
Black or african american	95 (48.2%)	46 (64.8%)	72 (52.9%)	148 (46.11%)
Native hawaiian or other pacific islander	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.31%)
White	95 (48.2%)	21 (29.6%)	57 (41.9%)	165 (51.40%)
BV Strata				
3 or fewer episodes in the past 12 month	145 (73.6%)	49 (69.0%)	100 (73.5%)	254 (79.1%)
4 or more episode in the past 12 months	52 (26.4%)	22 (31.0%)	36 (26.5%)	67 (20.9%)
Mean: Age	32	33	31	31.53
Std Dev:Age	8.81	7.98	7.87	8.48
Mean: Number of BV Episodes in Past 12 Months	3	3	2	2
Std Dev:Number of BV Episodes in Past 12 Months	2.7	2.88	2.44	2.5
Mean: Body Weight(lbs)	171	176	174	169
Std Dev: Body Weight(lbs)	45.54	48.83	50.88	44.04
Mean: Systolic Blood Pressure	115	117	116	115
Std Dev: Systolic Blood Pressure	13.52	11.36	13.07	10.82
Mean: Diastolic Blood Pressure	73	74	74	73
Std Dev: Diastolic Blood Pressure	9.96	9.22	9.32	9.08

8.2.3. Adequacy of the safety database:

Overall, the safety database provided adequate number of exposed subjects at the proposed dose and frequency (one time use) for secnidazole. Most of the baseline demographic characteristics were comparable among the treatment arms. The prevalence of BV is about 50% in African American women and Blacks were well represented in the safety population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

A data fitness assessment was performed on February 13, 2017 in collaboration with the Office of Computational Science (OCS). In the BV trials, unscheduled visits in the SDTM (0.3% - 0.8%) laboratory dataset were not included in the ADaM dataset. Some of the unscheduled visits not included in ADaM had results outside of the reference ranges. Other than this, the submission was well organized.

Case report forms were reviewed to assess consistency of the data submitted. The Applicant initially did not submit the CRFs for all pregnancies that were reported in the trials, but did so upon an information request. The reported terms for Adverse Events(AEs) matched the MedDRA dictionary terms used during the trial.

Of note, clinical inspection of three study sites were requested from OSI and the results of the inspections are pending at the time of this review.

8.3.2. Categorization of Adverse Events

The Applicant defined AEs as follows:

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Adverse event (AE): An AE was therefore any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of study drug, whether or not related to study drug.

A suspected adverse reaction was any AE for which there was a reasonable possibility that the drug caused the AE.

An AE or suspected adverse reaction was considered “unexpected” if it was not listed in the Investigator Brochure (IB) or was not listed at the specificity or severity that had been observed; or, if an IB was not required or available, was not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

An AE or suspected adverse reaction was considered “serious” if, in the view of either the Investigator or Sponsor, it resulted in any of the following outcomes:

- Death.
- Life-threatening.
- In-patient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of a patient.
- An important medical event. An important medical event was an event that may not have resulted in death, was life-threatening, or required hospitalization but may have been considered serious when, based upon appropriate medical judgment, it may have jeopardized the patient or the patient may have required medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

For each AE, the Investigator evaluated and reported the onset (date), resolution (date), intensity, causality, action taken, outcome, and whether or not it caused the patient to discontinue the study.

Treatment-emergent AEs were defined as any AE that occurred after administration of the first dose of study drug and through the TOC/EOS visit, any event that was considered study treatment-related, regardless of the start date of the event, or any event that was present at baseline but worsened in intensity or was subsequently considered treatment-related by the Investigator.

AEs were reported by System Organ Class (SOC), as specified by the MedDRA version 17.1 for study SYM-1219-201 and version 18.0 for studies SYM-1219-301 and SYM-1219-350. MedDRA Version 18.0 was used for the pooled safety analysis. Safety variables measured in the trials consisted of serum chemistries, hematology, urinalysis, vital signs, and incidence of clinical AEs. The schedule of tests and observations for each trial is described in sections 6.1.1, 6.2.1 and 8.7. The BV trials collected and assessed serum chemistries, hematology, urinalysis, and vital signs at baseline (predose) and at the TOC/EOS visit (between Days 21 and 30). AEs were assessed by means of telephone contact and clinic visit. The Applicant also conducted safety analysis in subpopulations by race and number of BV episodes in the past 12 months.

8.3.3. Routine Clinical Tests

The schedule of tests and observations for each trial is described in sections 6.1.1, 6.2.1 and 8.7 which provide the timing of safety laboratory collection in the safety population and appear adequate.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported during the conduct of the SYM 1219-201, SYM 1219-301 and SYM 1219-350 trials.

8.4.2. Serious Adverse Events

About 1% of the subjects had a serious adverse event in the pooled SYM 1219-201/301 trials. A total of 4 subjects experienced a treatment emergent SAE in the BV trials, which were syncope, ectopic pregnancy, loss of consciousness, and wound. All SAEs occurred in the 2 gm secnidazole arm. The loss of consciousness was considered to be possibly related to the study drug. None of the SAEs led to study discontinuation.

The Table below shows the incidence of Treatment emergent serious adverse events (SAE) by SOC and PT.

Table 50-Incidence of Treatment emergent SAE by SOC and PT in the Pooled SYM 1219-201/301 trials and the SYM 1219-350 trial

	Pooled SYM 1219-201/301 Trials	Trial SYM 1219-350
Body System or Organ Class(SOC) Preferred Term (PT)	SYM-1219 2G N=197	SYM-1219 2G N=321
Number of subjects with at least 1 serious TEAE	2(1%)	2(0.6%)
Nervous system disorders		
Syncope	1 (0.5%)	
Loss of consciousness		1 (0.3%)
Pregnancy, puerperium and perinatal conditions		
Ectopic pregnancy	1 (0.5%)	
Injury, poisoning and procedural complications		
Wound		1 (0.3%)

Narratives of the SAEs were reviewed and their synopsis is presented below.

- A 47 year old female received 2 gm secnidazole then 27 days later developed syncope due to dehydration. She was hospitalized and treated with intravenous fluids. She recovered the following day.

Medical Reviewer Comment: The SAE seem unlikely to be related to the study drug given the late onset of the reaction.

- A 33 year old female who had a negative pregnancy test at baseline, was found to have urine pregnancy test positive 22 days after taking 2 gm secnidazole. She was diagnosed with a right tubal pregnancy on ultrasound which was surgically removed.
- A 40 year old female who consumed few sips of alcohol after receiving secnidazole, then became nauseated on study day 1 followed by loss of consciousness, a fall and small bilateral nasal fracture. She was treated with intravenous fluids, antiemetics and recovered. The event was thought to be possibly related to the study drug.

Medical Reviewer Comment: This reviewer concurs that the event could be related to the study drug. The nausea could lead to a vasovagal reaction and syncope. The Applicant has conducted in vitro drug-alcohol interaction studies where secnidazole showed no effect on ethanol metabolism, specifically aldehyde dehydrogenase activity. Also, given the minimal amount of alcohol consumed, it seems unlikely that this case represents a drug-alcohol interaction phenomenon, which is seen with metronidazole.

- A 30 yr old female who developed an infected foot wound following a burn, 20 days after receiving secnidazole. Patient was treated with antibiotics and recovered.

Medical Reviewer Comment: The SAE seem unlikely to be related to the study drug given the late onset and nature of the reaction.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment-emergent AEs that led to discontinuation of study treatment were reported in only 1 subject in the pooled SYM1219-201/301 trials (1/404). The AE of vulvovaginal mycotic infection was noted in the placebo arm. There were 2 subjects(0.6%) in the SYM 1219-350 trial with vulvovaginal mycotic infection which led to study discontinuation.

The Table below shows the SOC and the PTs for the AEs which lead to treatment discontinuation in the pooled SYM1219-201/301 trials and the SYM 1219-350 trial.

Table 51-Adverse Events which led to study discontinuation

	Pooled SYM 1219-201/301 Trials	Trial SYM 1219-350
Body System or Organ Class (SOC)Preferred Term (PT)	PLACEBO N=136	SYM-1219 2G N=321

Infections and infestations		
Vulvovaginal mycotic infection	1 (0.7%)	2 (0.6%)

One subject in SYM 1219-350 developed mild vulvovaginal mycotic infection possibly related to secnidazole after 8 days. The event resolved. Another subject(24/502) developed moderate vulvovaginal infection after 9 days which was resolving. The subject was also on ciprofloxacin for urinary tract infection and the event was likely not related.

8.4.4. Significant Adverse Events

Serious TEAE are described in sections 8.4.2. The TEAE leading to treatment discontinuation are described in section 8.4.3 of the review. Refer to Section 8.4.5 for Common Adverse Events.

The following Table represents the TEAE probably or possibly related to the study drug.

Table 52-TEAE probably or possibly related to the study drug in the BV trials

	Pooled SYM 1219-201/301 Trials			Trial SYM 1219-350	
Dictionary Derived Term	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	Dictionary Derived Term	SYM-1219 2G N=321
PROBABLY RELATED				PROBABLY RELATED	
Nausea	5 (2.5%)	0 (0.0%)	1 (0.7%)	Nausea	9 (2.8%)
Vomiting	2 (1.0%)	0 (0.0%)	0 (0.0%)	Dysgeusia	8 (2.5%)
Vulvovaginal mycotic infection	2 (1.0%)	0 (0.0%)	1 (0.7%)	Vulvovaginal mycotic infection	6 (1.9%)
Abdominal pain	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vomiting	3 (0.9%)
Chromaturia	1 (0.5%)	0 (0.0%)	0 (0.0%)	Diarrhoea	2 (0.6%)
Diarrhoea	1 (0.5%)	0 (0.0%)	0 (0.0%)	Dizziness	2 (0.6%)
Dry mouth	1 (0.5%)	0 (0.0%)	0 (0.0%)	Headache	2 (0.6%)
Dysgeusia	1 (0.5%)	0 (0.0%)	0 (0.0%)	Abdominal discomfort	1 (0.3%)
Headache	1 (0.5%)	0 (0.0%)	0 (0.0%)	Abdominal pain upper	1 (0.3%)
POSSIBLY RELATED				Bacterial vaginosis	1 (0.3%)
Vulvovaginal mycotic infection	5 (2.5%)	0 (0.0%)	2 (1.5%)	Gastritis	1 (0.3%)
Headache	4 (2.0%)	1 (1.4%)	2 (1.5%)	Musculoskeletal chest pain	1 (0.3%)
Diarrhoea	4 (2.0%)	0 (0.0%)	1 (0.7%)	Rash	1 (0.3%)
Nausea	3 (1.5%)	0 (0.0%)	0 (0.0%)	POSSIBLY	

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				RELATED	
Vulvovaginal pruritus	3 (1.5%)	0 (0.0%)	0 (0.0%)	Vulvovaginal mycotic infection	8 (2.5%)
Constipation	2 (1.0%)	0 (0.0%)	0 (0.0%)	Nausea	5 (1.6%)
Abdominal pain	2 (1.0%)	0 (0.0%)	1 (0.7%)	Headache	3 (0.9%)
Acne	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vulvovaginal candidiasis	3 (0.9%)
Alanine aminotransferase increased	1 (0.5%)	0 (0.0%)	1 (0.7%)	Abdominal pain	2 (0.6%)
Aspartate aminotransferase increased	1 (0.5%)	0 (0.0%)	0 (0.0%)	Dysgeusia	2 (0.6%)
Back pain	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vomiting	2 (0.6%)
Blister	1 (0.5%)	0 (0.0%)	0 (0.0%)	Abdominal pain upper	1 (0.3%)
Chromaturia	1 (0.5%)	0 (0.0%)	0 (0.0%)	Blood alkaline phosphatase increased	1 (0.3%)
Decreased appetite	1 (0.5%)	0 (0.0%)	0 (0.0%)	Dehydration	1 (0.3%)
Dizziness	1 (0.5%)	0 (0.0%)	0 (0.0%)	Diarrhoea	1 (0.3%)
Dysgeusia	1 (0.5%)	0 (0.0%)	0 (0.0%)	Loss of consciousness	1 (0.3%)
Dyspepsia	1 (0.5%)	0 (0.0%)	0 (0.0%)	Migraine	1 (0.3%)
Fatigue	1 (0.5%)	0 (0.0%)	0 (0.0%)	Somnolence	1 (0.3%)
Menstruation irregular	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vulvovaginal discomfort	1 (0.3%)
Oral candidiasis	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vulvovaginal dryness	1 (0.3%)
Oropharyngeal pain	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vulvovaginal pain	1 (0.3%)
Pelvic pain	1 (0.5%)	0 (0.0%)	0 (0.0%)	Vulvovaginal swelling	1 (0.3%)
Somnolence	1 (0.5%)	0 (0.0%)	0 (0.0%)		
Vaginal haemorrhage	1 (0.5%)	0 (0.0%)	0 (0.0%)		
Vomiting	1 (0.5%)	0 (0.0%)	0 (0.0%)		
Vulvovaginal candidiasis	1 (0.5%)	0 (0.0%)	0 (0.0%)		
Vulvovaginal erythema	1 (0.5%)	0 (0.0%)	0 (0.0%)		

The most frequent TEAEs probably related to 2 gms of secnidazole were nausea (2.5%), vomiting(1%), vulvovaginal mycotic infection(1%) in the pooled SYM1219-201/301 trials and nausea(2.8%), dysgeusia(2.5%) and vulvovaginal mycotic infection(1.9%) in trial SYM 1219-350.

There were also 2.5% vulvovaginal mycotic infection possibly related to 2 gms secnidazole in the pooled SYM 1219 trials as well as the open label BV trial.

The overall severity of TEAEs, measured as the percentage of patients with mild, moderate, and severe TEAEs is presented for each treatment group in the Table below. Most TEAEs experienced during the study were of mild severity as reported by 21.3%, 7% and 14.7% of subjects in the SYM 1219 2 gms, SYM 1219 1gm and placebo groups respectively in the pooled SYM 1219-201/301 trials. In the SYM 1219-350 trial, most TEAEs were also mild in intensity, experienced by 23.7% subjects. Severe TEAEs occurred in 5 subjects in the pooled SYM 1219-201/301 trials and 4 subjects in the SYM 1219-350 trial. The only severe AEs occurring in more than 1 subject each were diarrhea, syncope, and nausea (2 subjects each).

Table 53-TEAEs by severity (Safety population)

	Pooled SYM 1219-201/301 Trials			Trial SYM 1219-350	
Severity Intensity Dictionary Derived Term	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	Severity Intensity Dictionary Derived Term	SYM-1219 2G N=321
MILD	42 (21.3%)	5 (7.0%)	20 (14.7%)	MILD	76 (23.7%)
MODERATE	21 (10.7%)	4 (5.6%)	2 (1.5%)	MODERATE	29 (9.0%)
SEVERE	5 (2.5%)	0 (0.0%)	0 (0.0%)	SEVERE	4 (1.2%)
Dehydration	1 (0.5%)			Facial bones fracture	1 (0.3%)
Diarrhoea	2 (1.0%)			Loss of consciousness	1 (0.3%)
Ectopic pregnancy	1 (0.5%)			Nausea	2 (0.6%)
Syncope	2 (1.0%)			Vomiting	1 (0.3%)
Vulvovaginal mycotic infection	1 (0.5%)			Vulvovaginal pain	1 (0.3%)
				Vulvovaginal swelling	1 (0.3%)
				Wound	1 (0.3%)

One subject may have more than one TEAE.

Vulvo-vaginal fungal infection

In the pooled SYM 1219-201/301 trials, there were 11 subjects(5.6%) with vaginal mycotic infection in the secnidazole 2gm arm compared to 3 subjects(2.2%) in the placebo arm. There were 8 subjects(4.1%) with vaginal candidiasis in the 2gm secnidazole arm compared to 1 subject(0.7%) in the placebo arm. There was 1 subject with vaginal candidiasis(1.4%) in the 1 gm secnidazole arm. Out of the 19 subjects with vaginal fungal infection(vaginal mycotic infection and vaginal candidiasis), only 1 event was severe in nature. None of these events were serious and only 1 subject in the placebo arm discontinued treatment. One subject did not recover and another subject had an unknown outcome in the 2 gms secnidazole group. In trial SYM 1219-350, there were 18 subjects(5.6%) with vaginal mycotic infection and 9

subjects(2.8%) with vaginal candidiasis with 2 gm secnidazole administration. Out of the 27 subjects with vaginal fungal infection, there was 1 subject who had a serious event but was unrelated to the study drug. The rest of the events were mild or moderate in nature. Two subjects discontinued study treatment. One subject did not recover and another subject had an unknown outcome. In all the BV trials, the median day of fungal infection onset was 15 days following treatment, ranging from 5 to 36 days.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The table below enumerates the TEAEs occurring in $\geq 1\%$ of patients in the pooled SYM 1219-201/301 trials and compares them with the TEAEs in the open label SYM 1219-350 trial. The incidence of TEAEs were greater in the SYM 1219 2 gm arm compared to SYM 1219 1 gm or placebo; 28.9% compared to 12.7% and 15.4% respectively in trial SYM 1219-201/301. There was a 29.6% incidence of TEAEs in trial SYM 1219-350. The most frequent TEAEs were in the Infections and Infestations SOC followed by the Gastrointestinal disorder SOC and Nervous system disorder SOC. The most common TEAEs in the SYM 1219 2 gm arm in the pooled SYM 1219-201/301 or the SYM 1219-350 trial were vulvovaginal mycotic infection, nausea, vulvovaginal candidiasis, headache, urinary tract infection, dysgeusia, diarrhea, and vomiting. In the pooled SYM 1219-201/301 trials, the TEAEs of vulvovaginal mycotic infection, nausea, vulvovaginal candidiasis, headache, and diarrhea occurred more frequently(>2%) in the SYM-1219 2 g group than in the placebo or SYM-1219 1 g group.

Table 54-Treatment emergent Adverse Events Occurring in >1% Patients in the Pooled SYM 1219-201/301 trials compared with the TEAEs in the SYM 1219-350 trial.

	Pooled SYM-1219-201/301 trials			Trial SYM 1219-350
	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	SYM-1219 2G N=321
Number of patients with ≥ 1 TEAE	57 (28.9%)	9 (12.7%)	21 (15.4%)	95 (29.6%)
Dictionary Derived Term				
Vulvovaginal mycotic infection	11 (5.6%)	0 (0.0%)	3 (2.2%)	18 (5.6%)
Vulvovaginal candidiasis	8 (4.1%)	1 (1.4%)	1 (0.7%)	9 (2.8%)
Headache	7 (3.6%)	1 (1.4%)	2 (1.5%)	7 (2.2%)
Nausea	7 (3.6%)	0 (0.0%)	1 (0.7%)	17 (5.3%)
Abdominal pain	4 (2.0%)	0 (0.0%)	2 (1.5%)	3 (0.9%)
Diarrhoea	5 (2.5%)	0 (0.0%)	1 (0.7%)	5 (1.6%)
Vulvovaginal pruritus	4 (2.0%)	0 (0.0%)	2 (1.5%)	0
Urinary tract infection	2 (1.0%)	0 (0.0%)	2 (1.5%)	10 (3.1%)
Vomiting	3 (1.5%)	0 (0.0%)	0 (0.0%)	8 (2.5%)
Dizziness	3 (1.5%)	0 (0.0%)	0 (0.0%)	3 (0.9%)

Vulvovaginal discomfort	0 (0.0%)	1 (1.4%)	2 (1.5%)	1 (0.3%)
Constipation	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Fungal infection	0 (0.0%)	1 (1.4%)	1 (0.7%)	0
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	2 (1.5%)	2 (0.6%)
Dehydration	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Dysgeusia	2 (1.0%)	0 (0.0%)	0 (0.0%)	11 (3.4%)
Syncope	2 (1.0%)	0 (0.0%)	0 (0.0%)	0
Chromaturia	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Vaginal haemorrhage	2 (1.0%)	0 (0.0%)	0 (0.0%)	0
Oropharyngeal pain	2 (1.0%)	0 (0.0%)	0 (0.0%)	0
Lymphadenopathy	0 (0.0%)	1 (1.4%)	0 (0.0%)	0
Candida infection	0 (0.0%)	1 (1.4%)	0 (0.0%)	0
Pyelonephritis	0 (0.0%)	1 (1.4%)	0 (0.0%)	0
Desmoid tumour	0 (0.0%)	1 (1.4%)	0 (0.0%)	0
Nephrolithiasis	0 (0.0%)	1 (1.4%)	0 (0.0%)	0

The table below shows the treatment related AEs which occurred in $\geq 1\%$ of patients. Approximately 16% of patients in the SYM-1219 2 g treatment groups experienced at least 1 AE that was related to the study drug compared with 1.4% receiving SYM-1219 1 g and 5.9% receiving placebo. The most frequent TEAEs related to the study drug ($>2\%$) in the pooled SYM-1219-201/301 safety population and trial SYM-1219-350 were vulvovaginal mycotic infection, nausea, headache, diarrhea and dysgeusia. The frequency of TEAEs (treatment related) were higher in the SYM 1219 2gm arm than the SYM 1219 1 gm or placebo groups.

Table 55-Treatment emergent Adverse Events (treatment related) Occurring in $>1\%$ Patients in the Pooled SYM 1219-201/301 trials compared with the TEAEs in the SYM 1219-350 trial.

	Pooled SYM-1219-201/301			Trial SYM 1219-350
	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	SYM-1219 2G N=321
Number of patients with ≥ 1 TEAE	32 (16.2%)	1 (1.4%)	8 (5.9%)	53 (16.5%)
Dictionary Derived Term				
Vulvovaginal mycotic infection	7 (3.6%)	0 (0.0%)	3 (2.2%)	14 (4.4%)
Nausea	7 (3.6%)	0 (0.0%)	1 (0.7%)	14 (4.4%)
Headache	5 (2.5%)	1 (1.4%)	2 (1.5%)	5 (1.6%)
Diarrhoea	5 (2.5%)	0 (0.0%)	1 (0.7%)	3 (0.9%)
Vomiting	3 (1.5%)	0 (0.0%)	0 (0.0%)	5 (1.6%)
Abdominal pain	3 (1.5%)	0 (0.0%)	1 (0.7%)	2 (0.6%)
Vulvovaginal pruritus	3 (1.5%)	0 (0.0%)	0 (0.0%)	
Chromaturia	2 (1.0%)	0 (0.0%)	0 (0.0%)	

Constipation	2 (1.0%)	0 (0.0%)	0 (0.0%)	
Dysgeusia	2 (1.0%)	0 (0.0%)	0 (0.0%)	10 (3.1%)
Vulvovaginal candidiasis	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (0.9%)
Alanine aminotransferase increased	1 (0.5%)	0 (0.0%)	1 (0.7%)	
Aspartate aminotransferase increased	1 (0.5%)	0 (0.0%)	0 (0.0%)	

The safety databases for trials SYM 1219-201 and SYM 1219-301 were explored by conducting standardized MedDRA queries.

This search identified a greater number of subjects with adverse events in the narrow SMQ of Gastrointestinal nonspecific inflammation and dysfunctional conditions in the SYM 1219 2 gm arm compared to placebo (14 subjects with 26 events versus 4 subjects with 4 events). There was also a greater number of subjects with AEs in the narrow SMQ of oropharyngeal disorders in the SYM 1219 2 gm arm compared to placebo (4 subjects vs 0 subjects) and in the narrow SMQ of noninfectious diarrhea in the SYM 1219 2 gm compared to placebo (5 subjects versus 1 subject). There were 13 subjects in the SYM 1219 2gm arm with AEs in the Nervous system disorders SOC compared to 2 subjects in the placebo group(1 subject in SYM 1219 1 gm arm). There were greater number of subjects with AE in the SYM 1219 2 gm arm compared to placebo in the Gastrointestinal disorders SOC (15 vs 4), Infection and Infestations SOC[25 vs 11(4 subjects in the SYM 1219 1 gm arm)] and Reproductive system and breast disorders SOC(8 vs 3; 1 subject in the SYM 1219 1 gm arm).

The following Figures show the risk difference per hundred of adverse events by SOC in the randomized placebo controlled BV trial safety pool (n=404). Adverse events that were observed more frequently in the SYM 1219 2gm versus placebo arm were in the nervous system disorder SOC(6.6% vs 1.5%), Gastrointestinal disorders SOC(7.6% vs 2.9%), Infections and infestations SOC(12.7% vs 8.1%) and reproductive system and breast disorders SOC(4.1% vs 2.2%). Adverse events that were observed more frequently in the SYM 1219 1gm versus placebo arm were in the Blood and lymphatic system disorders SOC (1 subject with lymphadenopathy).

Figure 16-Risk difference per hundred of adverse events by SOC in descending order in the SYM 1219-201/301 safety pool (SYM 1219 2 gm versus placebo)

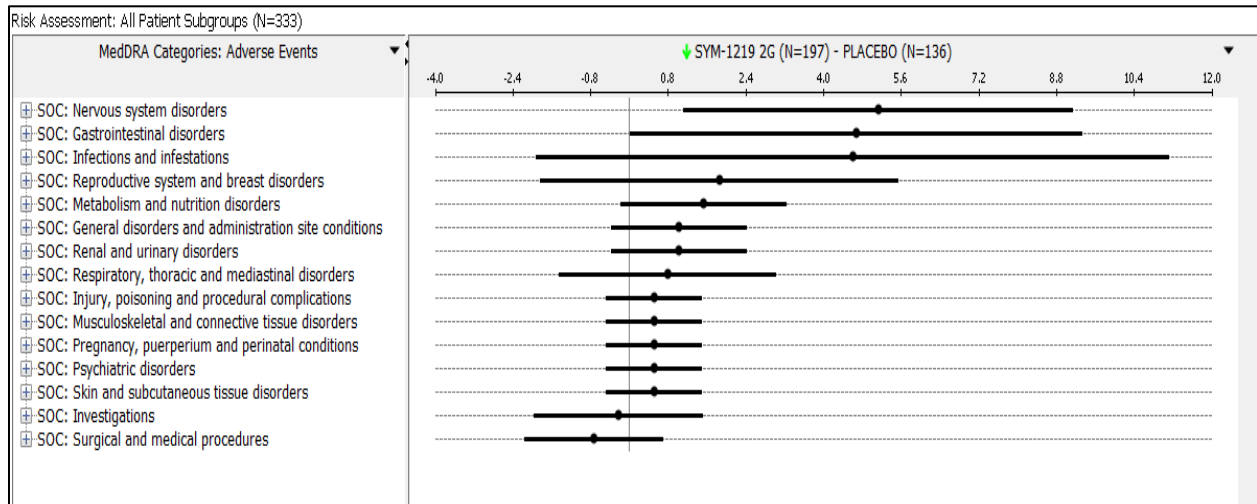
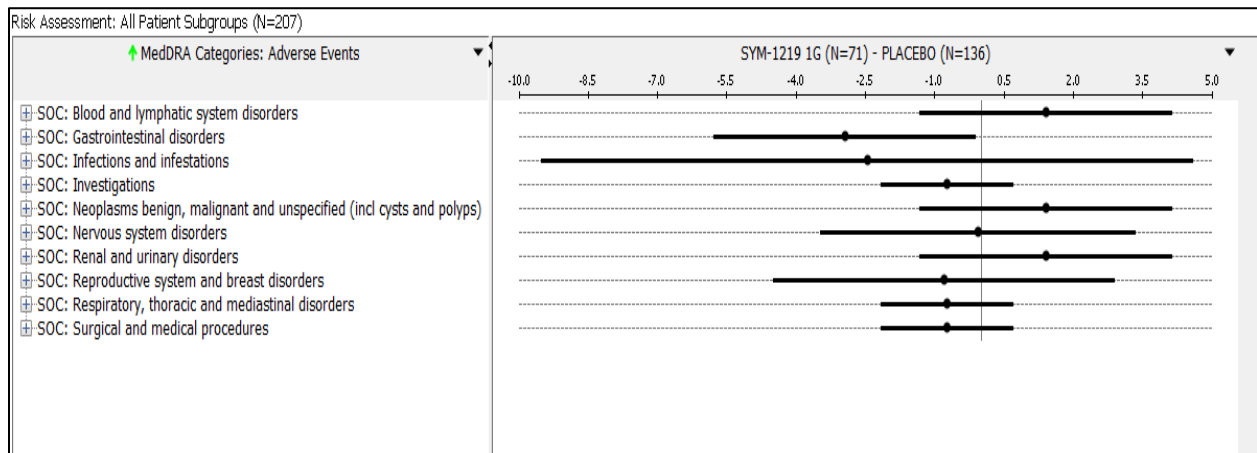


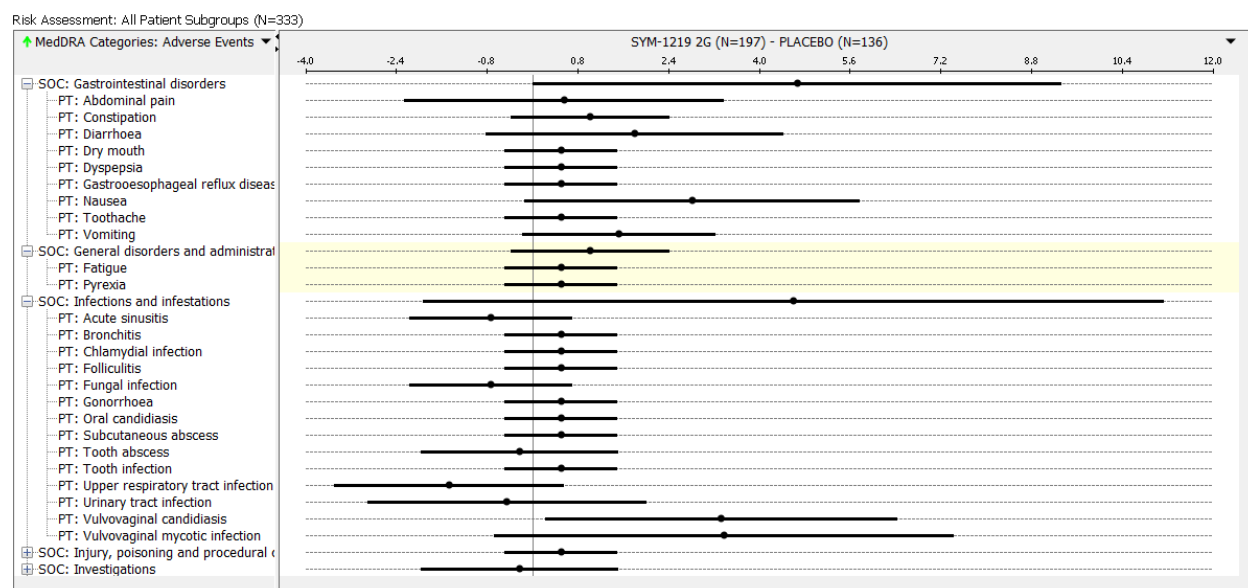
Figure 17-Risk difference per hundred of adverse events by SOC in descending order in the SYM 1219-201/301 safety pool (SYM 1219 1 gm versus placebo)



The following figure shows that nausea, vomiting and diarrhea, vulvovaginal candidiasis and vulvovaginal mycotic infections occurred at a higher frequency in the SYM 1219 2gm arm compared to placebo.

Figure 18-Risk difference per hundred of adverse events by SOC and PT in descending order in the SYM 1219-201/301 safety pool (SYM 1219 2 gm versus placebo)

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The vulvo-vaginal fungal infections are discussed in section 8.4.4.

Medical reviewer comment: Vaginal yeast infections are an expected adverse reaction of an antimicrobial product which causes a disruption of the normal microbial flora.

The AE of vomiting in 3 subjects on 2 gm secnidazole were mild to moderate in nature, occurred on study day 1 and the subjects recovered. The 5 subjects with diarrhea on the 2 gm secnidazole arm reported diarrhea as moderate to severe in nature, occurring on study days 1-5 and treatment related.

There were 2 subjects with bad taste and metallic taste in the mouth post dose 2 gm secnidazole which were treatment related.

Medical reviewer comment: Nausea, vomiting, diarrhea, dysgeusia(bad/metallic taste in the mouth), headache, fungal superinfections are all seen with other nitroimidazoles like metronidazole and tinidazole.

Exploratory analysis

This reviewer conducted an exploratory analysis where the safety databases for trials SYM 1219-201, SYM 1219-301 and SYM 1219-350 were pooled and explored by conducting standardized MedDRA queries. Since trial SYM 1219-350 was open label with 2 gm of SYM 1219, this analysis was considered to be exploratory in nature. This search identified a greater number of subjects with adverse events in the narrow SMQ of Gastrointestinal nonspecific inflammation and dysfunctional conditions in the SYM 1219 2 gm arm compared to placebo (45

subjects versus 4 subjects). There was also a greater number of subjects with AEs in the narrow SMQ of Taste and smell disorders in the SYM 1219 2 gm arm compared to placebo (13 subjects vs 0 subjects) and in the narrow SMQ of noninfectious diarrhea in the SYM 1219 2 gm compared to placebo (10 subjects versus 1 subject). There were greater number of subjects with AE in the SYM 1219 2 gm arm compared to placebo in the Gastrointestinal disorders SOC (47 vs 4), Nervous system disorders SOC(37 vs 2) and Infections and Infestations SOC (70 vs 11).

There were 3 subjects in trial SYM 1219-350 with hypersensitivity reactions (Subjects 350-04-522, 350-05-502, 350-24-502). Among these subjects, one subject had a facial contact dermatitis which was not related. Another subject had an allergic reaction to ciprofloxacin. Subject 350-05-502 had a mild rash on the neck and behind the ears at day 10 which was thought to be probably related to the drug. The patient recovered.

The subjects with dysgeusia in trial SYM 1219-350 complained of mild metallic taste in the mouth(one subject with bad taste) which resolved and occurred at days 1-2 of study.

The study size adjusted AE incidence proportion for trials SYM 1219-201 and 301 is calculated and presented below.

Table 56-Study size adjusted AE incidence proportion for trials SYM 1219-201 and 301(TEAEs >2%)

Adverse Reaction	Integrated SYM 1219-201 and SYM 1219-301	
	SYM 1219 2gm	Placebo
N	197	136
Any, %	27.9	16.6
Vaginal candidiasis (%)	8.9	3.3
Headache (%)	3.3	1.8
Nausea (%)	3.3	0.9
Diarrhea (%)	2.3	0.9
Vulvovaginal pruritus(%)	2.0	1.8

Medical Reviewer comment: The AEs were similar to those seen with crude pooling of the trials except abdominal pain which was reported in 1.8% of patients with 2 gm SYM 1219.

The TEAEs observed in trial SYM 1219-201 are presented in table below.

Table 57-Treatment emergent adverse events occurring in trial SYM 1219-201.

	SYM-1219 1G N=71	SYM-1219 2G N=72	PLACEBO N=72
Subjects with 1 or more TEAE	9 (12.7%)	14 (19.4%)	7 (9.7%)
Dictionary Derived Term			
Vulvovaginal mycotic infection	0 (0.0%)	2 (2.8%)	1 (1.4%)
Fungal infection	1 (1.4%)	0 (0.0%)	1 (1.4%)
Headache	1 (1.4%)	1 (1.4%)	0 (0.0%)
Tooth abscess	0 (0.0%)	1 (1.4%)	1 (1.4%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	2 (2.8%)
Acute sinusitis	0 (0.0%)	0 (0.0%)	1 (1.4%)
Alanine aminotransferase increased	0 (0.0%)	1 (1.4%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	1 (1.4%)	0 (0.0%)
Candida infection	1 (1.4%)	0 (0.0%)	0 (0.0%)
Chlamydial infection	0 (0.0%)	1 (1.4%)	0 (0.0%)
Chromaturia	0 (0.0%)	1 (1.4%)	0 (0.0%)
Desmoid tumour	1 (1.4%)	0 (0.0%)	0 (0.0%)
Dizziness	0 (0.0%)	1 (1.4%)	0 (0.0%)
Dysgeusia	0 (0.0%)	1 (1.4%)	0 (0.0%)
Gonorrhoea	0 (0.0%)	1 (1.4%)	0 (0.0%)
Lymphadenopathy	1 (1.4%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (1.4%)	0 (0.0%)
Nephrolithiasis	1 (1.4%)	0 (0.0%)	0 (0.0%)
Oropharyngeal pain	0 (0.0%)	1 (1.4%)	0 (0.0%)
Pyelonephritis	1 (1.4%)	0 (0.0%)	0 (0.0%)
Thermal burn	0 (0.0%)	1 (1.4%)	0 (0.0%)
Tooth extraction	0 (0.0%)	0 (0.0%)	1 (1.4%)
Tooth infection	0 (0.0%)	1 (1.4%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	1 (1.4%)	0 (0.0%)
Vaginal discharge	0 (0.0%)	1 (1.4%)	0 (0.0%)
Vaginal odour	0 (0.0%)	1 (1.4%)	0 (0.0%)
Vulvovaginal candidiasis	1 (1.4%)	0 (0.0%)	0 (0.0%)
Vulvovaginal discomfort	1 (1.4%)	0 (0.0%)	0 (0.0%)
Vulvovaginal pruritus	0 (0.0%)	1 (1.4%)	0 (0.0%)

There were 19.4% of TEAEs in the 2 gm secnidazole arm compared to 9.7% in the placebo arm. Vulvovaginal mycotic infections(2.8%) were the most common TEAE with 2 gm secnidazole.

The TEAEs observed in >1% patients in trial SYM 1219-301 are presented in table below.

Table 58-Treatment emergent adverse events occurring in > 1% of patients trial SYM 1219-301.

	SYM-1219 2G N=125	PLACEBO N=64
Subjects with 1 or more TEAE	43 (34.4%)	14 (21.9%)
Dictionary Derived Term		
Vulvovaginal mycotic infection	9 (7.2%)	2 (3.1%)
Vulvovaginal candidiasis	8 (6.4%)	1 (1.6%)
Headache	6 (4.8%)	2 (3.1%)
Nausea	6 (4.8%)	1 (1.6%)
Abdominal pain	4 (3.2%)	2 (3.1%)
Diarrhoea	5 (4.0%)	1 (1.6%)
Vulvovaginal pruritus	3 (2.4%)	2 (3.1%)
Urinary tract infection	1 (0.8%)	2 (3.1%)
Vomiting	3 (2.4%)	0 (0.0%)
Constipation	2 (1.6%)	0 (0.0%)
Dehydration	2 (1.6%)	0 (0.0%)
Dizziness	2 (1.6%)	0 (0.0%)
Syncope	2 (1.6%)	0 (0.0%)
Vaginal haemorrhage	2 (1.6%)	0 (0.0%)
Vulvovaginal discomfort	0 (0.0%)	2 (3.1%)
Alanine aminotransferase increased	0 (0.0%)	1 (1.6%)
Metrorrhagia	0 (0.0%)	1 (1.6%)
Sinus congestion	0 (0.0%)	1 (1.6%)

There were 34.4% of TEAEs in the 2 gm secnidazole arm compared to 21.9% in the placebo arm. Vulvovaginal mycotic infections(7.2%) and vaginal candidiasis (6.4%) were the most common TEAEs with 2 gm secnidazole.

8.4.6. Laboratory Findings

Hematology

Subjects in the pooled trials SYM 1219-201/301 had low normal blood counts. About 12.4% of subjects had abnormal baseline leucocytes and hemoglobin. The Table below shows the percentage of subjects with abnormal baseline values of the hematology parameters.

Table 59- Percentage of subjects with abnormal baseline values of hematology parameters in trial SYM 1219-201/301(Safety population)

Parameter	Baseline Reference Range Indicator	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	Overall Subjects N=404
Hematocrit (%)	(missing)	2 (1.0%)	0 (0.0%)	2 (1.5%)	4 (1.0%)
	ABNORMAL	13 (6.6%)	9 (12.7%)	10 (7.4%)	32 (7.9%)
	NORMAL	182 (92.4%)	62 (87.3%)	124 (91.2%)	368 (91.1%)
Hemoglobin (g/dL)	(missing)	2 (1.0%)	0 (0.0%)	2 (1.5%)	4 (1.0%)
	ABNORMAL	23 (11.7%)	13 (18.3%)	14 (10.3%)	50 (12.4%)
	NORMAL	172 (87.3%)	58 (81.7%)	120 (88.2%)	350 (86.6%)
Leukocytes (10 ⁹ /L)	(missing)	2 (1.0%)	0 (0.0%)	2 (1.5%)	4 (1.0%)
	ABNORMAL	28 (14.2%)	8 (11.3%)	14 (10.3%)	50 (12.4%)
	NORMAL	167 (84.8%)	63 (88.7%)	120 (88.2%)	350 (86.6%)
Neutrophils (10 ⁹ /L)	(missing)	2 (1.0%)	1 (1.4%)	2 (1.5%)	5 (1.2%)
	ABNORMAL	16 (8.1%)	8 (11.3%)	10 (7.4%)	34 (8.4%)
	NORMAL	179 (90.9%)	63 (88.7%)	124 (91.2%)	366 (90.6%)
Platelets (10 ⁹ /L)	(missing)	3 (1.5%)	0 (0.0%)	2 (1.5%)	5 (1.2%)
	ABNORMAL	12 (6.1%)	2 (2.8%)	6 (4.4%)	20 (5.0%)
	NORMAL	182 (92.4%)	69 (97.2%)	128 (94.1%)	379 (93.8%)

Analysis of the shift tables showed that 6.9% of subjects had normal to abnormal leucocytes, and 5.2% of subjects with normal to abnormal hemoglobin from baseline to end of study. The following table shows the shift table analysis of hematology parameters from baseline to end of study. There were no trends or safety concerns noted in the treatment groups.

Table 60-Shift table of hematology parameters from baseline to end of study in trial SYM 1219-201/301 (safety population).

Parameter	Shift 1	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	Overall Subjects N=404
Hematocrit (%)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	404 (100.0%)
	ABNORMAL -> ABNORMAL	6 (3.0%)	8 (11.3%)	6 (4.4%)	20 (5.0%)
	ABNORMAL -> NORMAL	6 (3.0%)	1 (1.4%)	4 (2.9%)	11 (2.7%)
	NORMAL -> ABNORMAL	15 (7.6%)	4 (5.6%)	5 (3.7%)	24 (5.9%)
	NORMAL -> NORMAL	154 (78.2%)	56 (78.9%)	107 (78.7%)	317 (78.5%)

Hemoglobin (g/dL)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	404 (100.0%)
	ABNORMAL -> ABNORMAL	12 (6.1%)	9 (12.7%)	1 (8.1%)	32 (7.9%)
	ABNORMAL -> NORMAL	10 (5.1%)	4 (5.6%)	3 (2.2%)	17 (4.2%)
	NORMAL -> ABNORMAL	12 (6.1%)	4 (5.6%)	5 (3.7%)	21 (5.2%)
	NORMAL -> NORMAL	147 (74.6%)	52 (73.2%)	103 (75.7%)	302 (74.8%)
Leukocytes (10 ⁹ /L)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	404 (100.0%)
	ABNORMAL -> ABNORMAL	14 (7.1%)	4 (5.6%)	6 (4.4%)	24 (5.9%)
	ABNORMAL -> NORMAL	13 (6.6%)	4 (5.6%)	6 (4.4%)	23 (5.7%)
	NORMAL -> ABNORMAL	10 (5.1%)	4 (5.6%)	14 (10.3%)	28 (6.9%)
	NORMAL -> NORMAL	144 (73.1%)	57 (80.3%)	96 (70.6%)	297 (73.5%)
Neutrophils (10 ⁹ /L)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	404 (100.0%)
	ABNORMAL -> ABNORMAL	5 (2.5%)	3 (4.2%)	4 (2.9%)	12 (3.0%)
	ABNORMAL -> NORMAL	10 (5.1%)	5 (7.0%)	5 (3.7%)	20 (5.0%)
	NORMAL -> ABNORMAL	9 (4.6%)	3 (4.2%)	4 (2.9%)	16 (4.0%)
	NORMAL -> NORMAL	156 (79.2%)	57 (80.3%)	109 (80.1%)	322 (79.7%)
Platelets (10 ⁹ /L)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	404 (100.0%)
	ABNORMAL -> ABNORMAL	7 (3.6%)	2 (2.8%)	2 (1.5%)	11 (2.7%)
	ABNORMAL -> NORMAL	3 (1.5%)	0 (0.0%)	4 (2.9%)	7 (1.7%)
	NORMAL -> ABNORMAL	4 (2.0%)	2 (2.8%)	1 (0.7%)	7 (1.7%)
	NORMAL -> NORMAL	166 (84.3%)	64 (90.1%)	115 (84.6%)	345 (85.4%)

Hematology laboratory results (including mean hematology values), box plots, scatter plots did not reveal any significant trends.

Medical Reviewer Comment: Although there was a higher percentage of shift from normal to abnormal in hematocrit values (7.6% vs 3.7%) and hemoglobin values (6.1% vs 3.7%) in the 2 gm secnidazole group compared to placebo, there was a similar trend in hemoglobin values shifting from abnormal to normal (5.1% vs 2.2%) in the 2 gm secnidazole group compared to placebo.

One subject in the placebo group (21-016) had baseline leukocytosis to 147.3x10⁹/L which increased to 162.4x10⁹/L due to chronic myeloid leukemia.

There was a low incidence of shift from normal to abnormal hematology values from baseline to end of study in trial SYM 1219-350(See table below).

Table 61-Shift table of hematology parameters from baseline to end of study in trial SYM 1219-350 (safety population).

Parameter	Shift 1	SYM-1219 2G N=321
Eosinophils (10 ⁹ /L)	(missing)	321 (100.0%)
	ABNORMAL -> NORMAL	1 (0.3%)
	NORMAL -> ABNORMAL	2 (0.6%)
	NORMAL -> NORMAL	297 (92.5%)
Hematocrit (%)	(missing)	321 (100.0%)
	ABNORMAL -> ABNORMAL	19 (5.9%)
	ABNORMAL -> NORMAL	9 (2.8%)
	NORMAL -> ABNORMAL	9 (2.8%)
	NORMAL -> NORMAL	263 (81.9%)
Hemoglobin (g/dL)	(missing)	321 (100.0%)
	ABNORMAL -> ABNORMAL	28 (8.7%)
	ABNORMAL -> NORMAL	10 (3.1%)
	NORMAL -> ABNORMAL	10 (3.1%)
	NORMAL -> NORMAL	252 (78.5%)
Leukocytes (10 ⁹ /L)	(missing)	321 (100.0%)
	ABNORMAL -> ABNORMAL	13 (4.0%)
	ABNORMAL -> NORMAL	17 (5.3%)
	NORMAL -> ABNORMAL	26 (8.1%)
	NORMAL -> NORMAL	244 (76.0%)
Neutrophils (10 ⁹ /L)	(missing)	321 (100.0%)
	ABNORMAL -> ABNORMAL	6 (1.9%)
	ABNORMAL -> NORMAL	11 (3.4%)
	NORMAL -> ABNORMAL	13 (4.0%)
	NORMAL -> NORMAL	270 (84.1%)
Platelets (10 ⁹ /L)	(missing)	320 (99.7%)
	ABNORMAL -> ABNORMAL	7 (2.2%)
	ABNORMAL -> NORMAL	3 (0.9%)
	NORMAL -> ABNORMAL	7 (2.2%)
	NORMAL -> NORMAL	280 (87.2%)

Serum Chemistries

Baseline values for each parameter (serum sodium, potassium, calcium, blood urea nitrogen, creatinine, glucose) were mostly normal and the mean change from baseline to end of study (box plots, scatter plots) did not reveal any trends or safety concerns in the pooled trials SYM

1219-201/301 or trial SYM 1219-350.

Liver Labs

There was a slightly higher number of subjects in the 2gm SYM 1219 arm compared to placebo with shift in total bilirubin (7.6% vs 4.4%) and aspartate aminotransferase(AST)(6.6% vs 4.4%) from normal to abnormal in the pooled SYM 1219-201/301 trials, however no significant trends were observed. There were no Hy's law cases in the BV trials. The table below shows the shift analysis in the liver labs in the BV trials.

Table 62-Shift table of liver laboratory parameters from baseline to end of study in pooled trials SYM 1219-201/301 and trial SYM 1219-350 (safety population).

		Trial SYM 1219-201/301			Trial SYM 1219-350
Parameter	Shift 1	SYM-1219 2G N=197	SYM-1219 1G N=71	PLACEBO N=136	SYM-1219 2G N=321
Alanine Aminotransferase (U/L)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	321 (100.0%)
	ABNORMAL -> ABNORMAL	4 (2.0%)	4 (5.6%)	3 (2.2%)	17 (5.3%)
	ABNORMAL -> NORMAL	8 (4.1%)	4 (5.6%)	7 (5.1%)	13 (4.0%)
	NORMAL -> ABNORMAL	11 (5.6%)	1 (1.4%)	7 (5.1%)	10 (3.1%)
	NORMAL -> NORMAL	159 (80.7%)	59 (83.1%)	108 (79.4%)	260 (81.0%)
Alkaline Phosphatase (U/L)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	321 (100.0%)
	ABNORMAL -> ABNORMAL	12 (6.1%)	4 (5.6%)	18 (13.2%)	37 (11.5%)
	ABNORMAL -> NORMAL	7 (3.6%)	6 (8.5%)	2 (1.5%)	15 (4.7%)
	NORMAL -> ABNORMAL	4 (2.0%)	2 (2.8%)	3 (2.2%)	10 (3.1%)
	NORMAL -> NORMAL	159 (80.7%)	57 (80.3%)	102 (75.0%)	238 (74.1%)
Aspartate Aminotransferase (U/L)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	321 (100.0%)
	ABNORMAL -> ABNORMAL	4 (2.0%)	1 (1.4%)	2 (1.5%)	12 (3.7%)
	ABNORMAL -> NORMAL	9 (4.6%)	4 (5.6%)	10 (7.4%)	22 (6.9%)
	NORMAL -> ABNORMAL	13 (6.6%)	3 (4.2%)	6 (4.4%)	18 (5.6%)
	NORMAL -> NORMAL	156 (79.2%)	60 (84.5%)	107 (78.7%)	248 (77.3%)
Bilirubin (mg/dL)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	321 (100.0%)

	ABNORMAL -> ABNORMAL	12 (6.1%)	4 (5.6%)	8 (5.9%)	14 (4.4%)
	ABNORMAL -> NORMAL	23 (11.7%)	5 (7.0%)	18 (13.2%)	25 (7.8%)
	NORMAL -> ABNORMAL	15 (7.6%)	4 (5.6%)	6 (4.4%)	19 (5.9%)
	NORMAL -> NORMAL	132 (67.0%)	56 (78.9%)	93 (68.4%)	242 (75.4%)
Direct Bilirubin (mg/dL)	(missing)	197 (100.0%)	71 (100.0%)	136 (100.0%)	321 (100.0%)
	ABNORMAL -> ABNORMAL	8 (4.1%)	0 (0.0%)	2 (1.5%)	8 (2.5%)
	ABNORMAL -> NORMAL	6 (3.0%)	1 (1.4%)	4 (2.9%)	6 (1.9%)
	NORMAL -> ABNORMAL	2 (1.0%)	0 (0.0%)	1 (0.7%)	3 (0.9%)
	NORMAL -> NORMAL	166 (84.3%)	68 (95.8%)	118 (86.8%)	283 (88.2%)

The following analysis lists the number and percent of subjects where the post-baseline lab results for Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) and Total Bilirubin (TB) were greater than or equal to 2 times, 3 times, 5 times, 10 times and 20 times the upper limit of normal (ULN).

Table 63-Liver labs greater than upper limit of normal in the BV trials (safety population)

	Pooled Trials SYM 1219-201/301			Trial SYM 1219-350
Liver Lab Test	SYM-1219 2G	SYM-1219 1G	Placebo	SYM-1219 2G
	N = 197	N = 71	N = 136	N=321
ALT ≥ ULN	Subject Count(%)	Subject Count(%)	Subject Count(%)	Subject Count(%)
2x ULN	2(1)	0	2(1.5)	6(1.87)
3x ULN	1(0.5)	0	1(0.7)	2(0.6)
5x ULN	1(0.5)	0	0	2(0.6)
10x ULN	0	0	0	2(0.6)
20x ULN	0	0	0	0
AST ≥ ULN	Subject Count(%)	Subject Count(%)	Subject Count(%)	Subject Count(%)
2x ULN	0	0	2(1.5)	3(0.9)
3x ULN	0	0	0	2(0.6)
5x ULN	0	0	0	2(0.6)
10x ULN	0	0	0	1(0.3)
20x ULN	0	0	0	0
ALP ≥ ULN	Subject Count(%)	Subject Count(%)	Subject Count(%)	Subject Count(%)

2x ULN	1(0.5)	0	0	1(0.3)
3x ULN	0	0	0	0
5x ULN	0	0	0	0
10x ULN	0	0	0	0
20x ULN	0	0	0	0
TB ≥ ULN	Subject Count(%)	Subject Count(%)	Subject Count(%)	Subject Count(%)
1.5x ULN	1(0.5)	0	1(0.7)	3(0.9)
2x ULN	0	0	0	0
3x ULN	0	0	0	0

Subject scores may be counted more than once in that they will be counted in all conditions (i.e., 2x, 3x, 5x...) that apply.

The following subjects had notable abnormal LFTs post baseline.

In trial SYM 1219-201, subject 201-09-008 a 39 yr old female in the SYM 1219 2gm arm with a history of gallstones, had asymptomatic elevated ALT from 27 at baseline to 182 U/L and AST from 19 to 67 U/L at EOS. The total bilirubin and ALP were normal. She was on ibuprofen concomitantly. The AE was possibly related to the study drug. She did not return for follow up testing.

In trial SYM 1219-301, subject 301-38-004, a 25 yr old female in the placebo arm with history of Asthma and depression on duloxetine, had mild asymptomatic increase of ALT from 16 at baseline to 61 at EOS which resolved.

In trial SYM 1219-350, subject 350-30-508, a 30 yr old female with history of Diabetes and nonalcoholic fatty liver disease had elevated ALT from baseline 23 to 626 U/L, AST from 14 to 435 U/L and ALP from 108 to 196 U/L with nausea and vomiting. The total bilirubin was normal. She had a plantar burn wound for which she received trimethoprim/sulfamethoxazole, ciprofloxacin, followed by vancomycin, piperacillin/tazobactam, ceftazidime and doxycycline. The AE was reported as not treatment related. The AE was reported as not recovered.

Medical Reviewer Comment: She had multiple comorbidities, underlying infection, and concomitant medications which could contribute to the elevation in transaminases.

Another subject 350-23-506, a 25 yr old female had asymptomatic increase in ALP from 95 at baseline to 113 U/L at EOS. The AE was thought to be treatment related but the outcome was unknown. The rest of the LFTs were within normal limits.

There was a subject 301-09-005 in trial SYM 1219-301, a 32 yr old female in the placebo arm who had history of high LFTS, had baseline ALT 154 and AST of 80 U/L. She had an unscheduled interim visit but LFTS were noted to be ALT of 120 and AST of 52. AT EOS< Alt was 137 and AST 70 U/L. The subject was asymptomatic. This patient was captured in the SDTM data but not in the Analysis dataset.

8.4.7. Vital Signs

In the BV trials, vital signs, including temperature, pulse rate, systolic blood pressure (SBP), and

diastolic blood pressure (DBP) and weight were monitored for clinically significant changes. No meaningful differences were reported in either mean baseline or mean change from baseline values between treatment groups.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms were not performed in the BV trials. The Applicant reported that the in vitro, nonclinical cardiac toxicity studies and safety ECGs in the clinical pharmacology studies did not show relevant ECG abnormalities. The Applicant completed a QTc study SYM 1219-105 during the developmental program.

8.4.9. QT

The Applicant initially asked for a Thorough QT(TQT) study waiver given the low variability in drug exposure of secnidazole, lack of metabolism by the cytochrome P450 system, lack of clinically relevant ECG abnormalities in the clinical pharmacological studies and lack of cardiac toxicity in the nonclinical studies. The FDA Interdisciplinary Review Team (IRT) for QT studies recommended that the Applicant perform a TQT study to rule out the risk of small QTc prolongation for secnidazole since even though it was acceptable to evaluate the QT effect of a product using the concentration-QTc analysis based on a small trial, the mean exposure of the highest dose in the small trial should be multiple-fold the maximum therapeutic exposure if the study has no positive control for assay sensitivity. The Applicant performed the TQT trial SYM 1219-105 to demonstrate that 2 g of secnidazole does not have an effect on the QTc interval exceeding > 10 ms compared to placebo. The Applicant reports that the QTc analysis and PK/QTc analysis demonstrate that SYM-1219 does not have a clinically relevant effect on the QTc interval and correspond to a negative TQT study. The QT IRT team was consulted to review the study results. According to the Agency's analysis, there was a positive relationship of the QTc interval with secnidazole concentrations. At the therapeutic concentrations, secnidazole did not prolong the QTc interval to any clinically relevant extent, but at 3-fold the therapeutic concentrations, the largest mean $\Delta\Delta\text{QTc}$ was 8 ms with upper bound of two-sided 90% confidence interval of 11 ms.

Medical Reviewer Comment: The pharmacodynamics section of the proposed label will be updated to reflect the above findings.

8.4.10. Immunogenicity

Immunogenicity safety issues were not reported in the BV trials. Clinical hypersensitivity reactions are discussed in section 8.4.5 of the review.

8.5. Analysis of Submission-Specific Safety Issues

Vaginal fungal infections were the most commonly reported TEAEs. Refer to sections 8.4.4 and 8.4.5 for a detailed review. The AEs of nausea, vomiting, diarrhea, dysgeusia(bad/metallic taste

in the mouth), headache, fungal superinfections which were seen more frequently in the secnidazole arm compared to placebo are all seen with other nitroimidazoles like metronidazole and tinidazole.

8.5.1. Vulvo-vaginal fungal infection

Refer to sections 8.4.4 and 8.4.5.

8.6. Safety Analyses by Demographic Subgroups

Race

The randomized, double blinded BV trials SYM 1219-201 and SYM 1219-301 were pooled and safety evaluation conducted in the subpopulation by race. The following Figures show the risk difference per hundred of adverse events by SOC in blacks and all other races in the randomized placebo controlled BV trial safety pool. Adverse events that were observed more frequently in the SYM 1219 2gm versus placebo arm in blacks were in the Gastrointestinal disorder SOC(9.5% vs 1.4%) which were nausea, vomiting diarrhea, Infections and Infestations SOC(13.7% vs 8.3%) which were vaginal candidiasis and mycotic infection. Adverse events that were observed more frequently in the SYM 1219 2gm versus placebo arm in all other races were in the Nervous system disorders SOC(6.9% vs 0%) which were headache, dizziness and Infections and Infestations SOC(11.8% vs 7.8%) which were vaginal candidiasis and mycotic infection.

Figure 19-Risk difference per hundred of adverse events by SOC in descending order in the SYM 1219-201/301 safety pool (SYM 1219 2 gm versus placebo) in Blacks

Risk Assessment: BLACK (N=167)

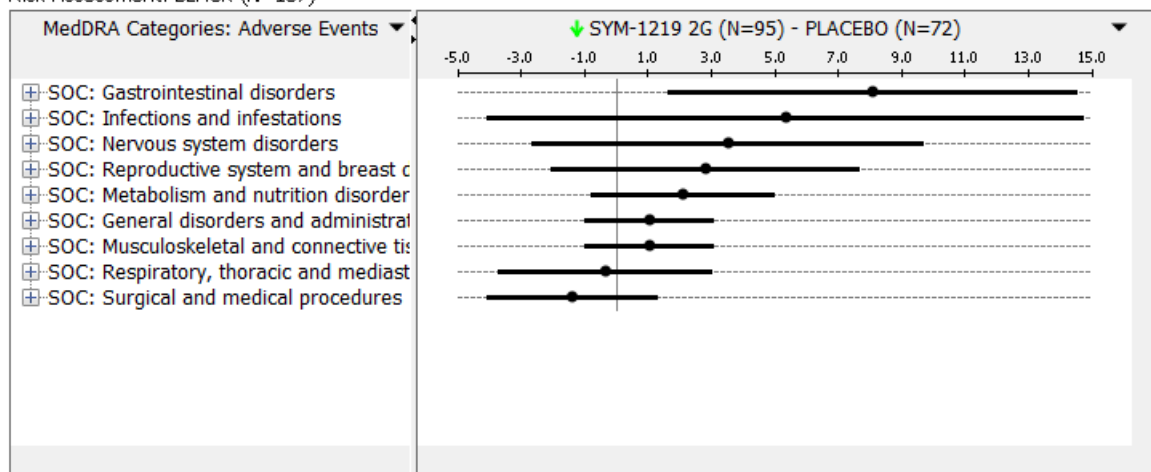
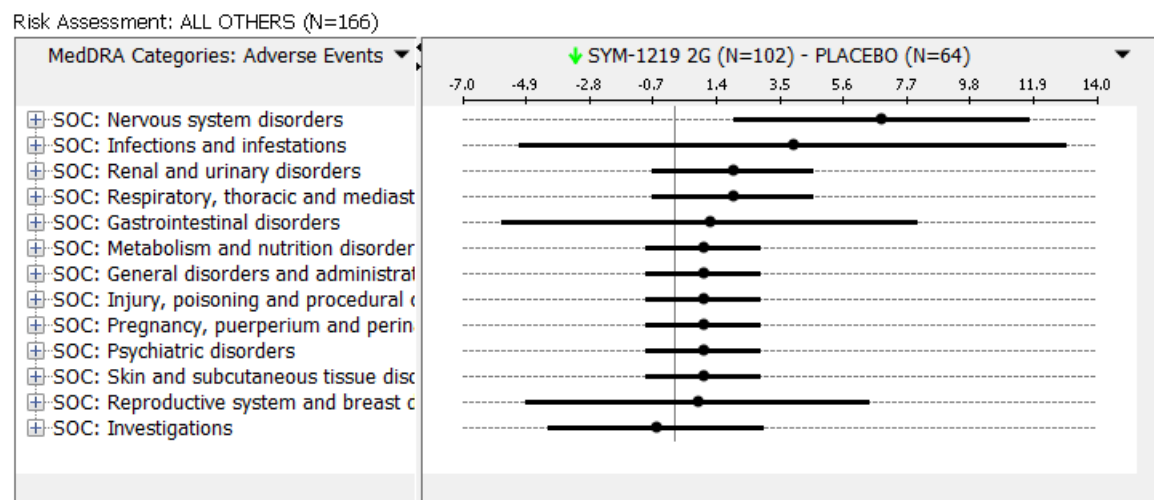


Figure 20-Risk difference per hundred of adverse events by SOC in descending order in the SYM 1219-201/301 safety pool (SYM 1219 2 gm versus placebo) in All other races



The Table below shows the AEs occurring in > 2% of patients receiving SYM-1219 in either blacks or all other races in the pooled SYM-1219-201/301 studies. In both subpopulations by race, the frequency of AEs was higher in the SYM-1219 2 g group compared to placebo.

Medical Reviewer Comment: The overall incidence of AEs in subjects receiving SYM-1219 2 g was slightly higher in non-Blacks compared with Blacks (31.4% and 26.3%). The incidence of nausea, vomiting and diarrhea in the 2gm SYM 1219 arm was slightly higher in blacks. The frequency of vaginal fungal infection(combined vaginal mycotic infection and candidiasis) in the SYM-1219 2 g groups was slightly higher in Black than non-Black patients (11/95 (11.6%) and 8/102 (7.8%), respectively) however the small number of subjects in the subpopulation analysis limits drawing any conclusion.

Table 64-Adverse Events Occurring in > 2% of Patients Receiving SYM-1219 by Race – Pooled SYM-1219-201/301, Safety Population

Blacks				All Other Race			
Dictionary Derived Term	SYM-1219 2G N=95	SYM-1219 1G N=46	PLACEBO N=72	Dictionary Derived Term	SYM-1219 2G N=102	SYM-1219 1G N=25	PLACEBO N=64
Abdominal pain	3 (3.2%)	0 (0.0%)	1 (1.4%)	Chromaturia	2 (2.0%)	0 (0.0%)	0 (0.0%)
Candida infection	0 (0.0%)	1 (2.2%)	0 (0.0%)	Vulvovaginal discomfort	0 (0.0%)	1 (4.0%)	1 (1.6%)

				t			
Desmoid tumour	0 (0.0%)	1 (2.2%)	0 (0.0%)	Dizziness	3 (2.9%)	0 (0.0%)	0 (0.0%)
Diarrhoea	3 (3.2%)	0 (0.0%)	0 (0.0%)	Diarrhoea	2 (2.0%)	0 (0.0%)	1 (1.6%)
Dysgeusia	2 (2.1%)	0 (0.0%)	0 (0.0%)				
Fungal infection	0 (0.0%)	1 (2.2%)	1 (1.4%)	Nephrolithiasis	0 (0.0%)	1 (4.0%)	0 (0.0%)
Headache	3 (3.2%)	1 (2.2%)	2 (2.8%)	Headache	4 (3.9%)	0 (0.0%)	0 (0.0%)
Lymphadenopathy	0 (0.0%)	1 (2.2%)	0 (0.0%)	Syncope	2 (2.0%)	0 (0.0%)	0 (0.0%)
Nausea	5 (5.3%)	0 (0.0%)	0 (0.0%)	Nausea	2 (2.0%)	0 (0.0%)	1 (1.6%)
Pyelonephritis	0 (0.0%)	1 (2.2%)	0 (0.0%)	Urinary tract infection	1 (1.0%)	0 (0.0%)	2 (3.1%)
Vomiting	3 (3.2%)	0 (0.0%)	0 (0.0%)	Oropharyngeal pain	2 (2.0%)	0 (0.0%)	0 (0.0%)
Vulvovaginal candidiasis	3 (3.2%)	1 (2.2%)	1 (1.4%)	Vulvovaginal candidiasis	5 (4.9%)	0 (0.0%)	0 (0.0%)
Vulvovaginal mycotic infection	8 (8.4%)	0 (0.0%)	3 (4.2%)	Vulvovaginal mycotic infection	3 (2.9%)	0 (0.0%)	0 (0.0%)
Vulvovaginal pruritus	2 (2.1%)	0 (0.0%)	1 (1.4%)	Vulvovaginal pruritus	2 (2.0%)	0 (0.0%)	1 (1.6%)

Ethnicity

An analysis of the AEs occurring in > 2% of patients receiving SYM-1219 in either hispanics vs nonhispanics in the pooled SYM-1219-201/301 studies showed there were no increased risk with SYM 1219 2gm by ethnicity. There were no hispanics who received SYM 1219 1 gm in the pooled trials. There were 15% AEs in the placebo arm in both hispanics and non-hispanics and a 41.4% incidence(12/29) of AE in hispanics compared to 26.8%(45/168) of AEs in non hispanics in the SEM 1219 2 gm arm. The number of subjects were small to draw any definite conclusions.

BV strata

The following table shows the AEs occurring in >2% of patients by number of BV episodes in the pooled SYM 1219-201/301 trials.

Table 65-Adverse Events Occurring in > 2% of Patients Receiving SYM-1219 by Number of BV Episodes–Pooled SYM-1219-201/301, Safety Population

	BV episodes 3 or fewer in past 12 months				BV episodes 4 or more in past 12 months		
Dictionary Derived Term	SYM-1219 2G N=145	SYM-1219 1G N=49	PLACEBO N=100	Dictionary Derived Term	SYM-1219 2G N=52	SYM-1219 1G N=22	PLACEBO N=36
n(%)	40(27.6%)	4(8.2%)	17(17%)	n(%)	17(32.69%)	5 (22.73%)	4 (11.11%)
Dizziness	3 (2.1%)	0 (0.0%)	0 (0.0%)	Abdominal pain	2 (3.8%)	0 (0.0%)	1 (2.8%)
Headache	6 (4.1%)	0 (0.0%)	1 (1.0%)	Headache	1 (1.9%)	1 (4.5%)	1 (2.8%)
Nausea	4 (2.8%)	0 (0.0%)	1 (1.0%)	Nausea	3 (5.8%)	0 (0.0%)	0 (0.0%)
Vulvovaginal candidiasis	8 (5.5%)	0 (0.0%)	1 (1.0%)	Vulvovaginal candidiasis	0 (0.0%)	1 (4.5%)	0 (0.0%)
Vulvovaginal mycotic infection	7 (4.8%)	0 (0.0%)	2 (2.0%)	Vulvovaginal mycotic infection	4 (7.7%)	0 (0.0%)	1 (2.8%)
Vulvovaginal pruritus	3 (2.1%)	0 (0.0%)	2 (2.0%)	Dysgeusia	2 (3.8%)	0 (0.0%)	0 (0.0%)
				Lymphadenopathy	0 (0.0%)	1 (4.5%)	0 (0.0%)
				Diarrhoea	4 (7.7%)	0 (0.0%)	0 (0.0%)
				Pyelonephritis	0 (0.0%)	1 (4.5%)	0 (0.0%)
				Sinus congestion	0 (0.0%)	0 (0.0%)	1 (2.8%)
				Acute sinusitis	0 (0.0%)	0 (0.0%)	1 (2.8%)
				Candida infection	0 (0.0%)	1 (4.5%)	0 (0.0%)

The frequency of AEs in the SYM- 1219 2 gm groups was higher in the subpopulation of BV episodes > 4 (32.7%) than in BV episodes <3 (27.6%). The frequency of AEs was higher in the SYM-1219 2 g group compared to placebo in this subpopulation overall. Although the incidence of vulvovaginal candidiasis was higher in BV episodes <3 than >4, in the SYM 1219 2gm arm, the combined vulvovaginal mycotic infection and vulvovaginal candidiasis frequency, in the SYM-1219 2 g groups was generally similar in the subpopulations by BV episodes, i.e., 15/145 (10.3%) in BV episodes 3 and 4/52 (7.7%) in BV episodes 4).

8.7. Specific Safety Studies/Clinical Trials

Trial SYM 1219-350

Objective: Trial SYM 1219-350 was conducted as a safety study to evaluate SYM 1219. This was a phase 3, multi-center, prospective, open-label study to evaluate the safety of a single dose of oral granule SYM-1219 containing 2 Grams secnidazole, for the treatment of women and postmenarchal adolescent girls with bacterial vaginosis.

A total of 325 patients were enrolled at 34 research centers in the United States. The safety population comprised of 321 subjects.

Inclusion criteria: Adult females or postmenarchal adolescent girls ≥ 12 years of age. Rest of the inclusion criteria was similar to trial SYM 1219-201. Refer to section 6.1.1.

Exclusion criteria: Menopausal subjects. Rest of the criteria was similar to trial SYM 1219-201. Refer to section 6.1.1.

Patients determined to be eligible at the Baseline visit (Study Day 1) received a single dose of SYM-1219 granules containing 2 grams of secnidazole in 4 ounces of unsweetened applesauce, which was self administered on Day 1. Patients were contacted by telephone once between Days 8 to 10 to inquire about possible adverse events. A final End of Study (EOS) visit occurred on Day 21 to 30 to assess the patient for safety. During the telephone interview, the interviewer determined if the patient had an interim clinic visit. If an interim visit was needed then the visit was scheduled and the patient underwent a symptom-directed assessment. If an interim visit was not needed, the date and time of the EOS visit was confirmed with the patient (Study Day 21-30).

Safety evaluations were based on the incidence, intensity, and type of AEs, and changes in the patient's physical examination and pelvic examination findings, vital signs, and clinical safety laboratory results. The following table represents the Schedule of Assessments in trial SYM 1219-350.

Table 66-Schedule of Assessments in Trial SYM 1219-350

Assessment	Baseline Visit	Patient Telephone Interview	EOS Visit
	Day 1	Days 8-10	Days 21-30
Informed consent/assent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X		X
Height/weight	X		

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Urine pregnancy test ¹	X		X
Physical examination	X		X
Pelvic examination	X		X ⁶
External genitalia and vaginal exam	X		X ⁶
Vaginal discharge assessment	X		X ⁶
Vaginal wet mount for Clue cells	X		X ⁶
10% KOH Whiff test	X		X ⁶
pH of vaginal fluid	X		
STI Assessments	X ²		X ³
OSOM [®] Trichomonas Rapid Test	X ⁴		
Bimanual pelvic examination	X ⁵		X ⁶
Labs: Hematology, chemistry, and urinalysis	X ²		X
Drug dosing	X		
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Telephone interview of patient		X	
Investigator Clinical Assessment			X

1. Performed by site personnel (not sent to central laboratory).
2. Results were not available at the time of study dosing.
3. Only as indicated as determined by the Investigator.
 4. It was recommended that the vaginal sample for the OSOM[®] Trichomonas Rapid Test be obtained early in the collection process to ensure an adequate sample for this evaluation.
5. At the Baseline visit, a bimanual pelvic examination was required and must have been done after vaginal discharge assessment and collection of all vaginal samples.
 6. At the EOS visit, a pelvic examination (including assessment of vaginal discharge, performing a wet mount to assess for Clue cells and a 10% KOH Whiff test) must have been performed if the patient reports any vulvovaginal signs/symptoms/adverse events. In addition, pelvic examination may have been done at the Investigator's discretion in patients with no vulvovaginal signs/symptoms/adverse events. A bimanual exam was only needed in either case at the Investigator's discretion. If a bimanual pelvic exam was performed, it must have also included assessment of the vaginal discharge and collection of all vaginal samples.

Source: Page 21 of Clinical Study report.

Study medication was orally administered as a single dose with 4 ounces of unsweetened applesauce (Mott's applesauce, a spoon, and an 8 ounce bottle of water were included in the treatment kits). The study medication was mixed and administered by the study patient on Day 1, without regard to meals. Treatment compliance was ensured by inspecting the packages. Treatment discontinuation/withdrawal from study criteria were similar to SYM 1219-201(except pregnancy was not listed).

Prior/concomitant therapy was similar to trials SYM 1219-201 and SYM 1219-301. Refer to section 6.1.1.

Definitions of AEs were similar to trials SYM 1219-201 and SYM 1219-301. Refer to section 6.1.1. For each AE, the Investigator evaluated and reported the onset (date), resolution (date), intensity, causality, action taken, outcome, and whether or not it caused the patient to discontinue the study.

Data quality assurance: The Applicant states that the trial was conducted according to GCP guidelines.

Statistical Analysis Plan: The original SAP was dated July 31, 2015. Minor modifications were

made. The safety population included all enrolled patients who received the study drug.

The safety endpoints were:

- Adverse events (AEs): Included TEAEs, serious adverse events (SAEs), treatment related AEs, severe AEs, and AEs leading to study discontinuation
- Vital signs: Blood pressure, temperature and pulse
- Physical examinations
- Pelvic Examinations: External genitalia and vagina
- Laboratory assessments: Included serum chemistry, hematology, and urinalysis.

For laboratory results and vital sign parameters, changes from baseline to the EOS Visit were summarized. Additionally, shifts from baseline to the EOS Visit in laboratory parameters and physical examinations were summarized.

Results of the SYM 1219-350 trial are presented in section 8.4 of this review.

Healthy Volunteer Trials

SYM 1219-101 was an open label parallel group trial in healthy females(N=28 in part A, N=54 in Part B) to assess the pharmacokinetics(PK) and safety of 1 gm or 2 gm secnidazole(Part A) and effect of secnidazole on PK of ethinyl estradiol (EE2) and norethindrone (NET) (Part B). SYM 1219-102 was a 3 way cross-over, open label, bioavailability trial in healthy females (N=25) to assess PK and safety of 2 gram dose in applesauce(fed and fasted). SYM 1219-103 was also a 3 way cross-over, open label bioequivalence trial in healthy females (N=24) to compare bioequivalence and safety of 2 gram dose in applesauce, pudding, and yogurt. SYM 1219-104 was a single blind, placebo controlled trial in healthy females(N=8) and males(N=8) to assess the PK and safety of 4 gm and 6 gm of secnidazole. SYM 1219-105 was a placebo controlled, positive controlled, double blind QT/QTc trial in healthy females and males(N=52) with 2 gm and 6 gm of secnidazole.

Since these trials were different in terms of dose, comparator and design, the results were not pooled and are presented individually. The Table below shows the demographics of the healthy volunteer studies.

Table 67-Demographics in the Healthy volunteer trials (All randomized population)

	SYM-1219-101 N=82	SYM-1219-102 N=25	SYM-1219-103 N=24	SYM-1219-104 N=16	SYM-1219-105 N=52
Age (years)					
Mean (SD)	33.6(9.3)	35.6(10.6)	40(11.6)	51(9.2)	45(11.6)
Median	33	32	37	54	46
Min, Max	19,61	22, 61	18, 65	35,65	20, 65
Sex, n(%)					
Female	82(100%)	25(100%)	24(100%)	8(50%)	22(42.3%)
Male				8(50%)	30(57.7%)
Race, n(%)					

(missing)	2 (2.4%)				
Black or african american	32 (39.0%)	9 (36.0%)	1 (4.2%)	3 (18.8%)	7 (13.5%)
White	48 (58.5%)	15 (60.0%)	22 (91.7%)	13 (81.3%)	45 (86.5%)
Asian			1 (4.2%)		
American indian or alaska native		1(4.0%)			
Ethnicity, n(%)					
Hispanic or latino	9 (11%)	6 (24.0%)	20 (83.3%)	14 (87.5%)	50 (96.2%)
Not hispanic or latino	73 (89.0%)	19 (76.0%)	4 (16.7%)	2 (12.5%)	2 (3.9%)

Medical Reviewer comment: The safety population in the healthy volunteer trials was similar to the all randomized population, except one subject in trial SYM 1219-102 who withdrew from the study prior to receiving study drug. Trials SYM 1219-103, 104 and 105 had a high percentage(>80%) of hispanic subjects.

Refer to section 8.2.1 for overall exposure to the study drug in the healthy volunteer trials. A total of 166 subjects received the 2 gm secnidazole dose.

The following table shows more than 4.2% of the combined AEs from all the treatment arms in each of the healthy volunteer trials.

Table 68-Adverse events >4.2% from all treatment arms in each healthy volunteer trial

	SYM 1219-101	SYM 1219-102	SYM 1219-103	SYM 1219-104	SYM 1219-105
Dictionary Derived Term	Treatments Part A and B N=82	Treatment N=25	Treatment N=24	Treatment N=16	Treatment N=52
Headache	20 (24.39%)	10 (40.00%)	12 (50.00%)	2 (12.50%)	7 (13.46%)
Nausea	22 (26.83%)	3 (12.00%)	4 (16.67%)		3 (5.77%)
Vomiting	7 (8.54%)				
Dysgeusia	6 (7.32%)	5 (20.00%)			
Dizziness	4 (4.88%)		2 (8.33%)		4 (7.69%)
Abdominal pain upper	5 (6.10%)				
Fatigue		2 (8.00%)			
Medical device site reaction		2 (8.00%)			
Paranasal sinus discomfort		2 (8.00%)			
Phlebotomy		2 (8.00%)			
Rash		2 (8.00%)			

Abdominal pain			3 (12.50%)		
Abdominal pain lower			3 (12.50%)		
Back pain			2 (8.33%)		
Constipation			12 (50.00%)		
Contusion			2 (8.33%)		
Upper respiratory tract infection				1(6.25%)	
Somnolence			8 (33.33%)		
Haematoma					3 (5.77%)
Cough					3 (5.77%)

SYM 1219-102 had 24 subjects in the safety population.

Headache(upto 50% in trial SYM 1219-103), nausea, dysgeusia, constipation and somnolence were the most frequent AEs noted from the healthy volunteer trials. Most of the AEs were treatment related(except in SYM 1219-104) and none were serious. No vaginal fungal infection were noted in the healthy volunteer trials. The headaches were all mild in intensity except 6 subjects with moderate intensity headaches in trial SYM 1219-103 and 1 subject in trial SYM 1219-102, however they all recovered. Nausea was mild in nature and all subjects recovered.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Secnidazole is given as a single dose and not administered chronically. Therefore carcinogenicity studies were not conducted. There was a 28 yr old female subject with history of desmoid tumor in the abdomen who developed pelvic pain in the SYM 1219-1 gm arm in trial SYM 1219-201 at study day 19, which was thought to be unrelated to the study drug.

8.8.2. Human Reproduction and Pregnancy

One of the exclusion criteria of the BV trials was subjects who were pregnant, lactating, or planning to become pregnant during the trial. The following are narratives of subjects who had a positive pregnancy test or self- reported pregnancy during the developmental program.

- Subject 201-16-003: A 34 yr old female, who had a negative urine pregnancy test at baseline had a positive urine pregnancy test on day 22. She received 1 gm secnidazole. She had an elective abortion on day 30. The subject was classified as a clinical outcome, therapeutic outcome and Nugent score responder.
- Subject 201-17-001: A 37 yr old female who had a negative baseline urine pregnancy test self-reported a positive pregnancy test via a home kit on day 10 of study. The subject was lost to follow up and did not complete EOS visit. The subject was classified as a non responder.

- Subject 301-30-019: A 33 year old female with history of left ectopic pregnancy, who had a negative pregnancy test at baseline, was found to have urine pregnancy test positive 22 days after taking 2 gm secnidazole. She was diagnosed with a right tubal pregnancy on ultrasound which was surgically removed. The ectopic pregnancy was classified as a serious adverse event but thought to be unrelated to the study drug. This subject was excluded from the PP and mITT population.
- Subject 350-03-509: A 30 yr old female, who had a negative pregnancy test at baseline received 2gm secnidazole, was discontinued from the study on day 7 due to a STI (chlamydial infection). The pregnancy test was negative at day 7. The subject then self-reported of a positive pregnancy test and delivered a live healthy baby by C-section at 9 months. The subject was classified as a clinical responder.
- Subject 350-30-509: A 25 yr old female, who had a negative urine pregnancy test at baseline, received 2 gm secnidazole then had a positive urine pregnancy test on day 21. The subject was lost to follow up. The subject was a clinical responder at the EOS.
- Subject 350-29-501: A 24 yr old female who had a negative pregnancy test at baseline, received 2 gm secnidazole then had a positive pregnancy test on day 22. The patient delivered a healthy full term baby. The subject was a nonresponder.
- Subject 350-24-504: A 23 yr old female who had a negative pregnancy test at baseline, received 2 gm secnidazole then self-reported pregnancy and elected to have an abortion on day 32. The subject was lost to follow up did not complete an EOS visit.

Medical reviewer comment: In summary, there were 7 pregnancies in the developmental program. Three subjects had an elective abortion, including one subject who had removal of an ectopic pregnancy. Three subjects were lost to follow up, including one subject who elected to have an abortion. There were 2 healthy pregnancies reported. No exposures in lactating women were reported. The Applicant does not have an ongoing or closed pregnancy registry. The Agency at the End of Phase 2 meeting and Pre-NDA meeting asked the Applicant to discuss (b) (4).

The Applicant states that there are no pregnancy reports in the pharmacovigilance database generated from use of secnidazole outside US. The Applicant performed a review of the available published literature regarding secnidazole in pregnant and lactating women. There were 2 studies in which pregnant women were administered secnidazole to treat bacterial vaginosis (BV) or shigellosis. No conclusion can be drawn regarding the effect of secnidazole in pregnant women based on the studies (limited sample size), particularly on the rate of major birth defects or miscarriages associated with secnidazole. There are no clinical studies on the use of secnidazole in lactating women.

In animal reproduction studies in rats and rabbits, no embryotoxicity or teratogenicity was observed when secnidazole was administered orally by gavage at doses of up to 1000 mg/kg/day (5 times the clinical dose based on body surface area comparisons), during the period of major organogenesis. Reduced pup weights were observed in rats in the presence of maternal toxicity (reduced body weight gain) at 1000 mg/kg/day (Refer to the review by the nonclinical reviewer, Dr. McMaster). As noted earlier, the carcinogenicity data revealed

that secnidazole was positive in several tester strains in the bacterial reverse mutation assay. In addition, imidazole class drugs, such as metronidazole, have been associated with tumorigenic effects in nonclinical studies and can cross the placenta and enter the fetal circulation.

A review of the Brazilian label for Secnidol (secnidazole) submitted by the Applicant, finds 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. The label for Secnol (secnidazole) in France recommends that secnidazole not be used while pregnant or breastfeeding and to consult the physician to determine if the dose should be continued. Of note, secnidazole is used outside the US for other indications which require more than a single dose. The U.S label for metronidazole lists the drug as pregnancy category B.

In view of the above data and noting the fact that secnidazole is a single dose administration, this reviewer suggests cautioning the healthcare provider in the label to weigh the risks and benefits of secnidazole treatment during pregnancy, particularly during the first trimester. It will also be prudent to avoid breastfeeding after secnidazole administration for a duration of 5 times the half life (17 hrs) i.e 4 days.

8.8.3. Pediatrics and Assessment of Effects on Growth

The initial pediatric study plan was agreed to by the Agency on January 14, 2016. Trials SYM 1219-301 and 350 were conducted in adult females and postmenarchal adolescent girls >12 years but enrollment was insufficient. The Applicant plans to implement an open label, safety study in healthy postmenarchal adolescent girls with bacterial vaginosis, for which a deferral has been requested.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

With a single dose, no withdrawal or rebound effects have been observed; no such effects are anticipated. No known overdoses occurred in the BV trials. A supratherapeutic dose of 6 gm secnidazole was administered to 6 subjects in SYM-1219-104 trial and 50 subjects in trial SYM-1219-105 who also reported nausea, headache and dizziness.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Secnidazole is marketed outside the U.S. and the Applicant has summarized the safety results of secnidazole monotherapy and when used in combination with other drugs from the literature between 1975 and 2016. The following table shows the AEs noted with monotherapy.

Table 69-Adverse events with secnidazole monotherapy outside the U.S (literature)

Reference	Infection	Treatment	Safety Observations
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	treated		
Videau 1978	Urogenital trichomoniasis	Secnidazole 2 g PO x 1 (n = 140) Secnidazole 2.5 g po x 1 (n = 110)	Nausea was only AE reported (4%)
Qureshi 1994	Amoebiasis	Secnidazole 2 g PO x 1 (n= 25)	Secnidazole overall well tolerated; minor AEs included nausea (3 subjects), and 1 subject each with bitter taste in mouth, vertigo, and leg cramps.
Rastegar-Lari 1996	Giardiasis	Secnidazole 30 mg/kg PO x 1 (n = 27) Metronidazole 20 mg/kg PO TID x 10 d (n=25)	Overall AE incidence was 7% vs 20% for secnidazole vs metronidazole; AEs included nausea, anorexia, abdominal pain. All were mild or moderate. No lab abnormalities.
Cimerman 1997	Giardiasis	Secnidazole 30 mg/kg POx 1 (n = 129) Tinidazole 50 mg/kg POx 1 (n = 138)	Incidence of drug-related AEs was 8% vs 16% for secnidazole vs tinidazole, respectively. Common related AEs included bitter/metallic taste (2% vs 8%), vomiting (2% vs 3%), nausea (<1% vs 4%), cephalgia and abdominal pain (2% vs 1%).
Bhatia 1998	Amoebic liver abscess	Secnidazole 500 mg PO TID x 5 d (n= 17) Metronidazole 400 mg Po TID x 7 d (n= 15)	Common AEs for secnidazole vs metronidazole were anorexia (12% vs 28.5%), metallic taste (29% vs 14%), and epigastric pain/tenderness (6% vs 7%).
Salles 1999	Amoebiasis (pediatric)	Secnidazole 30 mg/kg po x 1 (n = 156) Tinidazole (dose unknown) POx 2 d (n= 147)	Overall AE incidence 8% vs 10% for secnidazole and tinidazole, respectively. AEs seen in both treatments at a similar low incidence were bitter taste, nausea, vomiting, headache, abdominal pain.
DiPrisco 2000	Giardiasis	Secnidazole 30 mg/kg PO x 1 (n = 70)	Overall AE incidence was 9%; no specific AEs reported.

Padilla 2000	Amoebic colitis	Secnidazole 30 mg/kg PO x 1 (n = 127) Quinfamide 4.3 mg/kg PO x 1 (n = 112)	Common AEs for secnidazole vs quinfamide were nausea (17% vs <1%), abdominal pain (14% vs 4%), and metallic taste (14% vs 0%).
Escobedo 2003	Giardiasis	Secnidazole 30 mg/kg PO x 1 (n = 73) Mebendazole 200 mg TID x 3 d (n = 73)	Overall AE incidence was 14% vs 32% for secnidazole vs mebendazole; AEs included nausea (10% each), abdominal pain (8% vs 27%), bitter taste (8% vs 0%), and vomiting (5% vs 4%).
Nunez 2005	Bacterial vaginosis	Secnidazole 1 g PO x 1 (n = 44) Secnidazole 2 g PO x 1 (n = 32)	Overall AE incidence 35.5%. Metallic taste most common AE. Low incidence of GI events and headache.
Bohbot 2010	Bacterial vaginosis	Secnidazole 2g PO x 1 (n = 290) Metronidazole 500 mg BID PO x 7 d (n=287)	Overall AE incidence 39% with secnidazole; related AEs 22.4%. Most AEs Grade 1. Headache 3.5% with secnidazole vs 1.4% for metronidazole.
Almirall 2011	Giardiasis	Secnidazole 2 g PO x 1 (n = 62) Mebendazole 200 mg TID x 3 d (n=64)	Overall AE rate 32% vs 23% for secnidazole and metronidazole, respectively. AEs included bitter taste (24% vs 3%), abdominal pain (23% vs 19%), dizziness (10% vs 0%), nausea (6% vs 8%), diarrhea (5% vs 3%). AEs were mild and transient.
Teles 2011	Giardiasis	Secnidazole 2 g PO x 1 (n = 50) M. crispata 2 g PO x 1 (n = 46)	Overall AE incidence was 40% vs 50% for secnidazole vs M. crispata. Specific AEs were, respectively, metallic taste (34% vs 0%), abdominal pain (0% vs 30%), nausea (26% vs 28%). All were mild and transient.
Moraes 2012	Trichomonas vaginalis	Secnidazole 2 g PO x 1 (n = 30) Mentha crispata	Overall AE incidence 70% vs 20% for secnidazole vs M. crispata. All AEs Grade 1 and non-serious. Most common AE was

		24 mg PO x 1 (n = 30)	metallic taste (50% vs 0%, respectively). Other AEs with secnidazole included nausea (16.6%) and unpleasant odor in the urine {3.3%}.
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Source: Adapted from Applicant's Table 22 in the Integrated summary of safety.

Secnidazole was administered as a single dose of either 2 g or 30 mg/kg as tablets, capsules, or granules. There was a median 14% incidence of AEs in the secnidazole group. AEs commonly noted were nausea, dysgeusia, abdominal pain, headache, and vomiting.

Medical reviewer comment: The AEs were similar to the AEs noted in the BV clinical trials. An independent literature review by this reviewer did not identify any additional articles which described safety of secnidazole.

Some of the outside U.S labels report rare occurrences of vertigo, paresthesia, ataxia, peripheral neuropathy. The BV trials conducted by the Applicant did not identify such AEs.

8.9.2. Expectations on Safety in the Postmarket Setting

The small numbers in the subpopulation analysis of safety (e.g race, ethnicity) may not allow detection of some safety signals in the postmarketing setting. There is also no data for safety if a repeat dose of secnidazole is used off label. Given, secnidazole's structural similarity to other imidazoles, i.e metronidazole, safety signals like liver function test abnormalities, leucopenia may be apparent in the postmarketing setting when a larger population is studied.

8.10. Additional Safety Issues From Other Disciplines

There were no safety concerns raised by product quality, microbiology, clinical pharmacology and pharmacology-toxicology disciplines.

8.11. Integrated Assessment of Safety

Secnidazole 2gm, given as a single oral dose had an overall favorable safety profile. The safety database provided adequate number of exposed subjects at the proposed dose. A total of 518 subjects were exposed to 2 gm of secnidazole in the BV trials (197 subjects in the controlled trials and 321 in the open label safety trial). The safety population comprised of females of generally good health with BV and with a median age in their early thirties. About 50% of the population were Blacks.

No deaths were reported during the conduct of the BV trials (SYM 1219-201, SYM 1219-301 and SYM 1219-350). A total of 4 subjects experienced a treatment emergent serious AE in the secnidazole 2 gm arm, in the BV trials, which were syncope, ectopic pregnancy, loss of consciousness, and wound. However none led to study discontinuation and only the subject with loss of consciousness preceded by nausea could be related to the study drug. The

frequency of study discontinuation due to an AE was low. There was 1 subject in the pooled controlled BV trials in the placebo arm and 2 subjects who received secnidazole in SYM 1219-350 with vulvovaginal mycotic infection who discontinued the trial.

The incidence of TEAEs were greater in the SYM 1219 2 gm arm compared to SYM 1219 1 gm or placebo; 28.9% compared to 12.7% and 15.4% respectively in trial SYM 1219-201/301. There was a 29.6% incidence of TEAEs in trial SYM 1219-350. The frequency of TEAEs (treatment related) were also higher in the SYM 1219 2gm arm(16%) than the SYM 1219 1 gm(1.4%) or placebo(5.9%) groups. The most frequent TEAEs probably related to 2 gms of secnidazole were nausea (2.5%), vomiting(1%), vulvovaginal mycotic infection(1%) in the pooled SYM1219-201/301 trials and nausea(2.8%), dysgeusia(2.5%) and vulvovaginal mycotic infection(1.9%) in trial SYM 1219-350. The risk difference per hundred analysis of the AEs showed that nausea, vomiting and diarrhea, vulvovaginal candidiasis and vulvovaginal mycotic infections occurred at a higher frequency in the SYM 1219 2gm arm compared to placebo.

In the pooled SYM 1219-201/301 trials, there were 11 subjects(5.6%) with vaginal mycotic infection in the secnidazole 2gm arm compared to 3 subjects(2.2%) in the placebo arm. There were 8 subjects(4.1%) with vaginal candidiasis in the 2gm secnidazole arm compared to 1 subject(0.7%) in the placebo arm. In trial SYM 1219-350, there were 18 subjects(5.6%) with vaginal mycotic infection and 9 subjects(2.8%) with vaginal candidiasis with 2 gm secnidazole administration. None of these events were serious and mostly mild to moderate in nature.

The overall incidence of AEs in subjects receiving SYM-1219 2 g was slightly higher in non-Blacks compared with Blacks (31.4% and 26.3%). The incidence of nausea, vomiting and diarrhea in the 2gm SYM 1219 arm was slightly higher in blacks. The frequency of vaginal fungal infection(combined vulvo-vaginal mycotic infection and candidiasis) in the SYM-1219 2 g groups was slightly higher in Black than non-Black patients (11/95 (11.6%) and 8/102 (7.8%), respectively) however the small number of subjects in the subpopulation analysis limits drawing any conclusion.

Vulvo-vaginal fungal infections were the most commonly reported TEAEs. Vaginal yeast infections are an expected adverse reaction of an antimicrobial product which causes a disruption of the normal microbial flora. The AEs of nausea, vomiting, diarrhea, dysgeusia(bad/metallic taste in the mouth), headache, diarrhea fungal superinfections which were seen more frequently in the secnidazole arm compared to placebo are all seen with other nitroimidazoles like metronidazole and tinidazole. AEs commonly noted in literature from outside U.S use of secnidazole were nausea, dysgeusia, abdominal pain, headache, and vomiting, similar to the AEs noted in the BV clinical trials. Even though secnidazole has structural similarity with metronidazole which is known for its interaction with alcohol, the in vitro studies with secnidazole showed no effect on ethanol metabolism. Imidazole class drugs, such as metronidazole, have been associated with tumorigenic effects in nonclinical studies and

in view of the carcinogenicity data of secnidazole (positive bacterial reverse mutation assay) a cautionary statement can be provided in the label for the healthcare provider to weigh the risks and benefits of secnidazole treatment during pregnancy, particularly during the first trimester. Breastfeeding should be avoided for 4 days to minimize exposure to the drug.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held to discuss this application.

10 Labeling Recommendations

Discussions on labeling in the Division are ongoing at the time of this review.

Medical reviewer comment: This reviewer recommends adding vaginal fungal infections(vaginal candidiasis and mycotic infection) to the Warnings and Precautions section of the label. This reviewer also recommends presenting the primary endpoint data based on the original definition of a Clinical outcome responder, i.e a responder be classified as only those who have a normal discharge

(b) (4)

[REDACTED]

In view of the reproductive toxicity studies, carcinogenicity studies, published literature, pregnancy outcomes in the pivotal and safety trials, outside U.S label recommendations, toxicities relating to other imidazoles, and noting the fact that secnidazole is a single dose administration, this reviewer suggests cautioning the healthcare provider in the label to weigh the risks and benefits of secnidazole treatment during pregnancy, particularly during the first trimester. It will also be prudent to avoid breastfeeding after secnidazole administration for a duration of 5 times the half life(17 hrs) i.e 4 days.

11 Risk Evaluation and Mitigation Strategies (REMS)

This reviewer does not recommend REMS for this product.

12 Postmarketing Requirements and Commitments

The Applicant has submitted a deferral request for an open label, safety study in healthy postmenarchal adolescent girls with bacterial vaginosis.

13 Appendices

13.1. References

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13.2. Financial Disclosure

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the SYM 1219-201, SYM 1219-301 and SYM 1219-350 trials as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

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SYM 1219 (secnidazole)

Medical Reviewer comment: The Applicant has adequately disclosed financial interests/arrangements with the clinical investigators.

Covered Clinical Study (Name and/or Number): Trial SYM 1219-201, Trial SYM 1219-301 and Trial SYM 1219-350

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Principal investigators(PI) and sub-investigators- 129(24 PI) in trial SYM 1219-201, 115(22 PI) in trial SYM 1219-301, 200(39 PI) in trial SYM 1219-350		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	NA	No ☐ (Request explanation from Applicant)

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/s/

MAYURIKA GHOSH
07/17/2017