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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Table of Contents

1 EXECUTIVE SUMMARY 3

2 INTRODUCTION 4

2.1 OVERVIEW 4
2.2 DATA SOURCES 6

3 STATISTICAL EVALUATION 6

3.1 DATA AND ANALYSIS QUALITY 6
3.2 EVALUATION OF EFFICACY 6
3.2.1 Study SYM-1219-301 6
3.2.1.1 Study Design and Endpoints 6
3.2.1.2 Statistical Methodologies 7
3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics 8
3.2.1.4 Results and Conclusions 9
3.2.2 Study SYM-1219-201 12
3.2.2.1 Study Design and Endpoints 12
3.2.2.2 Statistical Methodologies 13
3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics 14
3.2.2.4 Results and Conclusions 15
3.2.3 Study SYM-1219-350 17
3.2.3.1 Study Design and Endpoints 17
3.2.3.2 Statistical Methodologies 18
3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics 18
3.2.3.4 Results and Conclusions 19
3.3 EVALUATION OF SAFETY 20

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 21

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION 21
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 22

5 SUMMARY AND CONCLUSIONS 23

5.1 STATISTICAL ISSUES 23
5.2 COLLECTIVE EVIDENCE 24
5.3 CONCLUSIONS AND RECOMMENDATIONS 25
5.4 LABELING RECOMMENDATIONS 26

1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking the approval of SYM-1219 (secnidazole) oral granules for the indication of the treatment of bacterial vaginosis (BV). SYM-1219 will be provided as a single 2 gram packet of granules that may be sprinkled onto soft food (applesauce, yogurt or pudding) to consume without chewing or crunching the granules. Secnidazole is approved outside the United States for the treatment of amebiasis, giardiasis, trichomoniasis, urethritis, and BV. The duration of treatment with SYM-1219 is a single 2 gram dose. With the approval of SYM-1219, the Applicant is hoping to provide a single dose oral formulation that will provide an alternative to currently approved products that involve multi-day treatment regimens or intravaginal formulations.

The evidence of efficacy of SYM-1219 2 gram is based on a Phase 3 trial SYM-1219-301 and a Phase 2 trial SYM-1219-201. SYM-1219-301 was a randomized, multicenter, double-blind study designed to evaluate the safety and efficacy of a single dose of SYM-1219 2 gram compared to placebo in treating female subjects with BV. SYM-1219-201 was a multicenter, randomized, double-blind, dose ranging efficacy and safety study of SYM-1219 (single dose of 1 gram and single dose of 2 gram) compared to placebo for the treatment of BV. The endpoints assessed in both trials were similar. The primary efficacy endpoint was clinical outcome at test of cure (TOC, Day 21 to 30). A clinical outcome responder was defined as a subject with normal vaginal discharge, a negative Whiff test, and clue cells < 20%. Secondary efficacy endpoints included Nugent score and therapeutic outcome. Nugent score was considered normal if the Nugent score was between 0 and 3. A therapeutic outcome responder was defined as a clinical outcome responder with a normal Nugent score. For SYM-1219-301, the primary analysis was a Cochran-Mantel Haenszel (CMH) chi-square test to compare the responder rates between the two treatment groups with stratification by the number of BV episodes in the previous 12 months (3 or fewer vs 4 or more) and race (black vs others) strata. For SYM-1219-201, the primary analysis was a CMH chi-square test to compare the responder rates between the SYM-1219 2 gram treatment group and placebo with stratification by the number of BV episodes in the previous 12 months strata. A comparison of the SYM-1219 1 gram treatment group and placebo was secondary. For this review, the difference in the responder rates between treatment groups (SYM-1219 minus placebo) was also calculated along with the corresponding two-sided 95% confidence interval about the difference based on the normal approximation to the binomial.

In SYM-1219-301, 189 subjects were randomized to treatment in a 2:1 ratio and approximately 85% of the subjects completed the study. The primary analysis population consisted of 107 SYM-1219 2 gram subjects and 57 placebo subjects who had a Gram stain Nugent score ≥4 at baseline and were negative for other sexually transmitted infections at baseline. The clinical outcome responder rate at TOC was statistically significantly higher for those subjects treated with SYM-1219 2 gram compared to placebo. Clinical outcome responder rate at TOC was 53.3% for SYM-1219 2 gram and 19.3% for placebo. The difference in clinical outcome responder rates between treatment groups was 34.0% with a 95% confidence interval of (18.7%, 49.3%). The proportion of subjects with a normal Nugent score at TOC was statistically significantly greater for SYM-1219 2 gram compared to placebo (43.9% vs. 5.3%, respectively). The difference in the proportion of subjects with a normal Nugent score at TOC was 38.6% with

a 95% confidence interval of (26.2%, 51.0%). Therapeutic outcome responder rate at TOC was statistically significantly greater for SYM-1219 2 gram compared to placebo (34.6% vs. 3.5%, respectively). The difference in therapeutic outcome responder rates was 31.1% with a 95% confidence interval of (19.6%, 42.6%).

In SYM-1219-201, 215 subjects were randomized to treatment in a 1:1:1 ratio and approximately 88% of the subjects completed the study. The primary analysis population consisted of 64 SYM-1219 1 gram subjects, 62 SYM-1219 2 gram subjects, and 62 placebo subjects who had a Gram stain Nugent score ≥4 at baseline and were negative for other sexually transmitted infections at baseline. Clinical outcome responder rates, the proportion of subjects with a normal Nugent score, and therapeutic outcome responder rates at TOC were significantly higher for both doses of SYM-1219 compared to placebo. Additionally, the SYM-1219 2 gram group had numerically higher response rates than the SYM-1219 1 gram group.

Based on the results of the Phase 3 trial, the trial met its stated objective in that the clinical outcome responder rate was significantly higher with treatment with SYM-1219 2 gram compared to placebo. Similar results were shown for the secondary endpoints of Nugent score and therapeutic outcome. Confirmatory evidence was provided by the Phase 2 dose response trial which also showed significantly higher clinical outcome responder rates, proportion of subjects with a normal Nugent score, and therapeutic outcome responder rates at TOC for treatment with SYM-1219 2 g as compared to placebo. Therefore, there is adequate evidence of efficacy to support the indication of the treatment of BV for SYM-1219 2 gram.

2 INTRODUCTION

2.1 Overview

This is an NDA submission for SYM-1219, secnidazole oral granules 2 gram. The indication being sought by the Applicant is the treatment of bacterial vaginosis (BV). Secnidazole is commercially available outside the United States for the treatment of amebiasis, giardiasis, trichomoniasis, urethritis, and BV. The most commonly administered dose of secnidazole is a single 2 gram dose which is the dose of this proposed formulation.

The development program for SYM-1219 consisted of 5 Phase 1 studies in healthy subjects, and one Phase 2 and two Phase 3 trials in subjects with BV. Primary support of the efficacy of SYM-1219 is based on the Phase 3 trial, SYM-1219-301 and the Phase 2 dose ranging study, SYM-1219-201. SYM-1219-301was a randomized, multicenter, double- blind study designed to evaluate the safety and efficacy of a single dose of SYM-1219 2 grams compared to placebo in treating female subjects with BV. SYM-1219-201 evaluated the safety and efficacy of two single dose levels of SYM-1219 (1 gram and 2 gram) compared to placebo. Additional safety data is provided by the Phase 3 trial, SYM-1219-350. SYM-1219-350 was a non-comparative study designed to evaluate the safety of a single dose of SYM-1219 2 grams in women and postmenarchal adolescent girls with BV. The focus of this review will be the Phase 3 efficacy trial and the Phase 2 trial. The Phase 3 safety trial will be briefly summarized.

Table 1
Listing of Studies Included in Review

Protocol	Phase and Design	Dosing Regimen/ Duration of Treatment	# of Subjects per Arm	Study Population
SYM-1219-301	Phase 3 multi-center, randomized, double-blind, placebo-controlled	Single dose SYM-1219 2 g or placebo for 1 day	125 SYM-1219 2 g 64 placebo	Female patients diagnosed with BV
SYM-1219-201	Phase 2 multi-center, randomized, double-blind, dose ranging	Single dose SYM-1219 1 g or 2 g or placebo for 1 day	72 SYM-1219 2 g 71 SYM-1219 1 g 72 placebo	Female patients diagnosed with BV
SYM-1219-350	Phase 2 multi-center, uncontrolled safety study	Single dose SYM-1219 2 g for 1 day	321 SYM-1219 2 g	Female patients diagnosed with BV

During the development program, the design of the Phase 2 and Phase 3 trials were discussed and agreed upon based on guidance given at the time. This guidance is generally consistent with the July 2016 draft guidance "Bacterial Vaginosis: Developing Drugs for Treatment" that was issued during the Applicant's preparation of the NDA submission. At the End of Phase 2 meeting held March 18, 2015, the preliminary results of the Phase 2 trial and the proposed Phase 3 clinical program were discussed. At this meeting, the Medical Division agreed that the Phase 2 trial could be used as one of the two pivotal trials needed to support the efficacy of SYM-1219. Therefore, only a single Phase 3 trial for efficacy would be needed. It was also agreed that the Phase 3 safety study would provide the additional safety data needed to ensure an overall safety database for the single 2 gram dose of SYM-1219 of at least 600 subjects.

In October 2015, a revised statistical analysis plan (SAP) for SYM-1219-301 was submitted. The main revision in the SAP was to change the definition of clinical responder with respect to the vaginal discharge portion of the endpoint. Vaginal discharge was assessed on the case report form (CRF) as "normal", "abnormal (consistent with BV)", and "abnormal (other)". Therefore, the Applicant wanted to indicate that a clinical responder would include a subject with either "normal" or "abnormal (other)" vaginal discharge. Only a vaginal discharge of "abnormal (consistent with BV)" would be considered in the definition as a non-responder. The Medical Division did not agree with this change and maintained that the original definition of clinical response with respect to a return to a normal vaginal discharge should be kept for the primary analysis as this was consistent with advice given in response to questions posed in the pre-IND meeting background package and maintained during the review of the Phase 2 and Phase 3 protocols. It was indicated that clinical response using the distinctions in discharge could be assessed as a sensitivity analysis. This advice was provided to the Applicant in correspondences dated November 12, 2015 and February 2, 2016.

SYM-1219 was granted Qualified Infectious Disease Product (QIDP) and Fast Track status. Therefore, the NDA has been granted a priority review. SYM-1219 was granted QIDP on the basis that BV can be considered "a serious infection within the meaning of the Generating Incentives Now Act because it increases the risk of HIV and pre-term birth". However, the trials conducted to support approval of this NDA submission do not address either of these issues.

2.2 Data Sources

The data analyzed in this review comes from the Phase 2 and Phase 3 trials submitted as the evidence to support the efficacy and safety of SYM-1219. The final SYM-1219-301, SYM-1219-201, and SYM-1219-350 Study Reports, and datasets for the three studies provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\CDSESUB1\evsprod\NDA209363\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets submitted were of acceptable quality. Minimal programming was necessary to reproduce the results presented by the Applicant.

Reviewer's Comment: *Unless otherwise indicated, tables presented in this review are based on analyses conducted by this reviewer using the analysis datasets submitted by the Applicant and confirm the results of those presented by the Applicant in the SYM-1219-301, SYM-1219-201, and SYM-1219-350 Study Reports.*

3.2 Evaluation of Efficacy

3.2.1 Study SYM-1219-301

3.2.1.1 Study Design and Endpoints

SYM-1219-301 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of a single dose SYM-1219 compared to placebo for the treatment of BV. The study was conducted at 21 investigational centers in the United States. Subjects were evaluated at 3 time points: baseline, the interim visit (Study Day 7 to 14), and the test of cure (TOC) visit (Study Day 21 to 30). Subject eligibility was determined at the baseline visit. Adult females or postmenarchal adolescent girls aged 12 years of age and older with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV is defined as having an off-white, thin, homogenous vaginal discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. Subjects were to have a Nugent score ≥ 4. However, the results of the Gram stain for the Nugent score were not known until after randomization. Additionally, subjects with a known or suspected other infectious cause of vulvovaginitis (e.g. candidiasis, *T. vaginalis, C. trachomatis, N. gonorrhoeae,* or Herpes simplex*)* were to be excluded. Pregnant women were also excluded from enrollment. Eligible subjects were randomized in a 2:1 ratio to

receive treatment with either a single 2 g dose of SYM-1219 or placebo. Randomization was stratified by the number of reported episodes of BV in the past 12 months (3 or fewer vs 4 or more) and by race (black vs all others). Treatment was self-administered on Day 1. Subjects returned to the clinic between Day 7 and 14 to assess response to treatment and inquire about possible adverse events. The TOC visit was conducted between Day 21 and 30 and was to be at least 10 days after the Interim visit. At all visits, a gynecological exam was conducted and vaginal fluid specimens were collected.

The primary objective of the study was to evaluate the safety and efficacy of a single dose of SYM-1219 containing 2 grams of secnidazole compared to placebo for the treatment of women and postmenarchal adolescent girls with BV. The primary efficacy endpoint was clinical outcome at TOC. A clinical outcome responder was defined as a patient with a normal vaginal discharge, a negative whiff test, and clue cells < 20%. Secondary efficacy endpoints included clinical outcome at the Interim visit, Nugent score at the Interim visit and TOC, therapeutic outcome at the Interim visit and TOC, and the Investigator's clinical assessment at TOC. A Nugent score of 0-3 was considered normal and a score of 4 or more was considered abnormal. A therapeutic outcome responder was defined as a clinical outcome responder with a normal Nugent score. The Investigator's clinical assessment was based on their opinion of the subject's need for additional BV treatment at the TOC visit.

3.2.1.2 Statistical Methodologies

The primary analysis of clinical outcome was based on a Cochran-Mantel-Haenszel chi-square test to compare the clinical outcome responder rates between the 2 treatment groups adjusted for the BV episodes and race strata. For this review, the difference in responder rates between the two treatment groups (SYM-1219 – placebo) was also calculated and the two-sided 95% confidence interval about the difference was estimated based on the normal approximation to the binomial distribution. The secondary endpoints were analyzed similarly. Missing data for assessing the primary and secondary efficacy endpoints were imputed as a non-responder for clinical and therapeutic outcomes and as abnormal for Nugent score. Per the protocol, no imputation was done for the Investigator's Clinical Assessment.

Four data sets were used in the analyses. The Intent-to-Treat (ITT) population included all randomized subjects. The modified intent-to-treat (mITT) population included all randomized patents that had a Gram stain Nugent score ≥4 at baseline and were negative for other sexually transmitted infections at baseline. The mITT population was the primary efficacy analysis population. The per-protocol (PP) population is a subset of the mITT population including subjects who met the following: received the study medication, met inclusion and exclusion criteria, had an Interim visit between Days 7-14 and a TOC visit between Days 21-30 which was at least 10 days after the Interim visit, and had no protocol violations. The PP population was used as a supportive efficacy analysis population. The Safety population included all randomized subjects who received study drug.

Sample size was based on assuming a 2-sided alpha of 5%, 80% power, a 2:1 randomization, a clinical outcome responder rate of 50% in the SMT-1219 group, and a clinical outcome responder rate of 25% in the placebo group. Thus, a total sample size of 132 subjects was

needed. It was assumed that approximately 25% would be ineligible for the mITT population. Therefore, 120 subjects were to be randomized to the SYM-1219 group and 60 subjects were to be randomized to the placebo group.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 189 subjects were randomized into the study: 125 to the SYM-1219 2 gram group and 64 to the placebo group. Approximately 85% of the randomized subjects completed the study. The most common reasons for discontinuation from the study were lost to follow-up, or positive for other vulvovaginal/sexually transmitted infections. Reasons for discontinuation from the study are reported in Table 2.

Table 2
SYM-1219-301
Patient Disposition

	SYM-1219 2 gram	Placebo
Randomized	125	64
Completed Study	109 (87.2)	52 (81.3)
Discontinued Study	16 (12.8)	12 (18.8)
Subject's request	3	2
Perceived lack of therapeutic effect	0	3
Positive for other sexually transmitted infection	5	4
Non-compliance with study protocol	1	0
Use of concomitant therapy	0	1
Lost to Follow-up	7	2

All subjects received the treatment to which they were randomized. Therefore, the ITT and the Safety Population are the same. Twenty-five subjects were excluded from the mITT population due to not having a baseline Nugent score ≥4 (10 SYM-1219 and 2 placebo) or due to being positive at baseline for a sexually transmitted infection (8 SYM-1219 and 5 placebo). An additional 50 subjects (30 SYM-1219 and 20 placebo) were excluded from the PP population due to protocol violations, primarily due to missed visits or the use of prohibited concomitant medications.

Table 3
SYM-1219-301
Analysis Populations

	SYM-1219 2 gram	Placebo
Randomized	125	64
ITT/Safety Population	125	64
mITT Population	107	57
PP Population	77	37

Table 4 summarizes the demographic and baseline characteristics of the mITT population. There were no significant differences between treatment groups. Overall, 54% of the study population was black and 44% was white. The mean age of the patients was 31 years. The median baseline Nugent score was 8. The median number of BV episodes in the past 12 months was 2 and 77% of the study population was in the 3 or fewer BV episodes strata.

Table 4
SYM-1219-301
Demographic and Baseline Characteristics (mITT)

	Treatment Group	
	SYM-1219 2 gram	**Placebo**
# Patients	107	57
Age mean (SD)	32.2 (8.7)	29.6 (7.6)
min, max	18, 54	18, 46
Race		
White	46 (43.0)	26 (45.6)
Black	59 (55.1)	29 (50.9)
Asian	0	1 (1.8)
Other	2 (1.9)	1 (1.8)
Nugent Score		
mean (SD)	8.1 (1.8)	8.6 (1.3)
median	8	8
min, max	4, 10	5, 10
Number of BV episodes in the past 12 months		
mean (SD)	2.9 (2.4)	2.9 (2.6)
median	2	2
min, max	1, 12	1,12
Race Strata		
Black	59 (55.1)	29 (50.9)
All others	48 (44.9)	28 (49.1)
BV Episodes Strata		
3 or fewer episodes	83 (77.6)	43 (75.4)
4 or more episodes	24 (22.4)	14 (24.6)

3.2.1.4 Results and Conclusions

Clinical Outcome Responder rates at TOC (Day 21-30) are presented in Table 5 for the mITT and PP populations. In the mITT population, significantly more SYM-1219 subjects were considered a clinical outcome responder at TOC compared to placebo subjects (53.3% vs. 19.3%, CMH $p<0.001$). The results for the PP populations are supportive of those seen for the mITT population.

Table 5
SYM-1219-301
Clinical Outcome Responder at TOC (Day 21-30)

	SYM-1219 2 gram	Placebo	p-value*	Difference (95% CI)**
mITT	57/107 (53.3)	11/57 (19.3)	<0.001	34.0 (18.7, 49.3)
PP	43/77 (55.8)	11/37 (29.7)	0.006	26.1 (5.7, 46.5)

*p-value of CMH test adjusted for # of BV episodes and race strata
**Difference is SYM-1219 –placebo and 95% confidence interval

Reviewer's Comment: *The remainder of the efficacy discussion of Study SYM-1219-301 will focus on the mITT population.*

Table 6 summarizes clinical outcome at TOC for the mITT population including the reason for clinical non-responder. Subjects were non-responders primarily because none of the three criteria needed for clinical cure were resolved although slightly more of the placebo non-responders compared to SYM-1219 non-responders were failures due to this reason.

Table 6
SYM-1219-301
Clinical Outcome at TOC (mITT)

	SYM-1219 2 gram (n=107)	Placebo (n=57)
Clinical Responder	57 (53.3)	11 (19.3)
Clinical Non-responder	50 (46.7)	46 (80.7)
All 3 criteria not met	26 (24.3)	32 (56.1)
2 of 3 criteria not met	2 (1.9)	4 (7.0)
1 of 3 criteria not met	14 (13.1)	7 (12.2)
Missing	8 (7.5)	3 (5.3)

Table 7 summarizes the results for the individual components of clinical outcome at TOC for the mITT population. The results for vaginal discharge indicate that the majority of the subjects who had an abnormal discharge at TOC had a discharge that was consistent with BV.

Table 7
SYM-1219-301
Individual Components of Clinical Outcome at TOC (mITT)

	SYM-1219 2 gram (n=107)	**Placebo** (n=57)
Vaginal Discharge		
Normal	66 (61.7)	15 (26.3)
Abnormal (consistent with BV)	26 (24.3)	36 (63.2)
Abnormal (Other)	7 (6.5)	3 (5.3)
Missing	8 (7.5)	3 (5.3)
Clue Cells		
< 20%	67 (62.6)	19 (33.3)
≥ 20%	32 (29.9)	35 (61.4)
Missing	8 (7.5)	3 (5.3)
Whiff Test		
Negative	68 (63.5)	17 (29.8)
Positive	31 (29.0)	37 (64.9)
Missing	8 (7.5)	3 (5.3)

The results for clinical outcome at the Interim visit, Nugent score at the Interim and TOC visits, therapeutic outcome at the Interim and TOC visits, and the Investigator's Clinical Assessment at TOC for the mITT population are summarized in Table 8. For each of the secondary endpoints, a statistically significant greater proportion of subjects were responders (clinical, Nugent score, or therapeutic depending on endpoint) in the SYM-1219 2 gram group as compared to the placebo group. Significantly more subjects in the SYM-1219 2 gram group did not require additional BV treatment at TOC as compared to placebo. It should be noted that the percentage of subjects not requiring additional BV treatment are different than those presented in the Study Report because the Applicant excluded subjects with missing data from the denominator used to calculate the rates. The same is true for the percentage of subjects requiring additional BV treatment.

It should also be noted that there was a larger amount of missing data at the Interim visit than the TOC visit, especially in the placebo group. Three of the 10 SYM-1219 2 gram subjects and 10 of the 12 placebo subjects with missing data at the Interim visit returned for the TOC visit. At the TOC visit, all of these subjects but 1 SYM-1219 2 gram subject was considered a non-responder. Therefore, it is more than likely that these subjects were actually non-responders at the Interim visit as well.

Table 8
SYM-1219-301
Analysis of Secondary Endpoints

	SYM-1219 2 gram (n=107)	Placebo (n=57)	p-value*	Difference (95% CI)**
Clinical Outcome at Interim Visit				
Responder	62 (57.9)	14 (24.6)	p< 0.001	33.3 (17.4, 49.2)
Non-Responder	35 (32.7)	31 (54.4)		
Missing	10 (9.3)	12 (21.1)		
Nugent Score at TOC				
Normal (0-3)	47 (43.9)	3 (5.3)	p< 0.001	38.6 (26.2, 51.0)
Abnormal (≥4)	52 (48.6)	51 (89.5)		
Missing	8 (7.5)	3 (5.3)		
Nugent Score at Interim Visit				
Normal (0-3)	49 (45.8)	2 (3.5)	p< 0.001	42.3 (30.4, 54.2)
Abnormal (≥4)	48 (44.9)	43 (75.4)		
Missing	10 (9.3)	12 (21.1)		
Therapeutic Outcome at TOC				
Responder	37 (34.6)	2 (3.5)	p< 0.001	31.1 (19.6, 42.6)
Non-Responder	62 (57.9)	52 (91.2)		
Missing	8 (7.5)	3 (5.3)		
Therapeutic Outcome at Interim Visit				
Responder	37 (34.6)	2 (3.5)	p< 0.001	31.1 (19.6, 42.6)
Non-Responder	60 (56.1)	43 (75.4)		
Missing	10 (9.3)	12 (21.1)		
Investigator's Clinical Assessment				
Additional BV treatment not required	68 (63.6)	16 (28.1)	p< 0.001	35.5 (19.3, 51.7)
Additional BV treatment required	32 (29.9)	38 (66.7)		
Missing	7 (6.5)	3 (5.3)		

*p-value of CMH test adjusted for # of BV episodes and race strata
**Difference is SYM-1219 –placebo and 95% confidence interval

3.2.2 Study SYM-1219-201

3.2.2.1 Study Design and Endpoints

SYM-1219-201 was a Phase 2, multicenter, randomized, double-blind, efficacy and safety study of SYM-1219 (single dose of 1 gram and single dose of 2 gram) compared with placebo for the treatment of BV. The study was conducted at 24 investigational centers in the United States. Subjects were evaluated at 3 time points: baseline, a post-treatment phone call, and a TOC visit. Subject eligibility was determined at the baseline visit. Females aged 18 years of age and older with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV is defined as having an off-white, thin, homogenous discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. Subjects were to have a Nugent score ≥4. However, the results of the Gram stain for the Nugent score were not known until after randomization. Additionally, subjects with a known or suspected other infectious cause of vulvovaginitis (e.g. candidiasis, *T. vaginalis, C. trachomatis, N. gonorrhoeae,* or active *H. simplex)* were to be excluded. Pregnant women were also excluded from enrollment. Eligible subjects were randomized in a 1:1:1 ratio

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

The primary objective of the study was to evaluate the safety and efficacy of 1 gram and 2 gram of SYM-1219 compared to placebo for the treatment of BV. The primary efficacy endpoint was clinical outcome at TOC. A clinical outcome responder was defined as a subject with normal vaginal discharge, negative Whiff test, and clue cells less than 20%. Secondary endpoints were Nugent score and therapeutic outcome at TOC. A Nugent score of 0 to 3 was considered normal and a score of 4 or greater was considered abnormal. A therapeutic outcome responder was a clinical outcome responder with a normal Nugent score. Exploratory efficacy variables were the pH of the vaginal discharge at TOC (< 4.7 normal or ≥4.6 abnormal), patient responses to telephone diary questions on Day 1 to 7 and at TOC, and the Investigator's clinical assessment of the need for additional BV treatment at the TOC visit.

3.2.2.2 Statistical Methodologies

The primary analysis of clinical outcome was based on a Cochran-Mantel-Haenszel chi-square test to compare the clinical outcome responder rates between each SYM-1219 treatment group and placebo adjusted for the number of previous BV episodes strata. For this review, the difference in responder rates between the treatment groups (each SYM-1219 group- placebo) was also calculated and the two-sided 95% confidence interval about the difference was estimated based on the normal approximation to the binomial distribution. The secondary endpoints were analyzed similarly. Missing data for assessing the primary and secondary efficacy endpoints were imputed as a non-responder for clinical and therapeutic outcomes and as abnormal for Nugent score. The primary comparison was between the SYM-1219 2 gram group and placebo. The comparison between the SYM-1219 1 gram group and placebo was considered a secondary comparison; therefore, no adjustment for multiple comparisons was made.

Four data sets were used in the analyses. The Intent-to-Treat (ITT) population included all randomized subjects. The modified intent-to-treat (mITT) population included all randomized patents that had a Gram stain Nugent score ≥4 at baseline and were negative for other sexually transmitted infections at baseline. The mITT population was the primary efficacy analysis population. The per-protocol (PP) population is a subset of the mITT population including subjects who had no major protocol violations and met the following: consumed all of the study drug, responded 'no' at the phone interview to the questions: "Have you used any vaginal products during the first week of the study?" and "Have you had vaginal intercourse during the first week of the study?", had a TOC visit between Days 21-30 as scheduled, TOC visit data was complete for clinical vaginal assessments (vaginal discharge, KOH Whiff test and Clue Cells)

and Nugent score, any sexually transmitted infection assessments done at the TOC/EOS visit were negative, did not take a prohibited concomitant medication, and had no significant post-baseline medical condition or procedure that could impact efficacy. The PP population was used as a supportive efficacy analysis population. The Safety population included all randomized subjects who received study drug.

Assuming a clinical outcome responder rate of 40% in the SYM-1219 groups and 15% in the placebo group, a sample size of 52 subjects per group would provide approximately 80% power to detect a statistically significant difference between an SYM-1219 group and placebo at a 5% two-sided alpha level using a Cochran-Mantel-Haenszel test. To allow for 25% ineligibility for the mITT population, a sample size of 70 subjects per group (210 total) was planned for randomization.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 215 subjects were randomized into the study: 71 to the SYM-1219 1 gram group, 72 to the SYM-1219 2 gram group, and 72 to the placebo group. Approximately 88% of the randomized subjects completed the study. The most common reasons for discontinuation were lost to follow-up and positive for other vulvovaginal infections. Reasons for discontinuation are reported in Table 9.

Table 9
SYM-1219-201
Patient Disposition

	SYM-1219 1 gram	**SYM-1219 2 gram**	**Placebo**
Randomized	71	72	72
Completed Study	67 (94.4)	63 (87.5)	60 (83.3)
Discontinued Study	4 (5.6)	9 (12.5)	12 (16.7)
Subject's request	0	0	1
Perceived lack of therapeutic effect	0	1	2
Positive for *N. gonorrhoeae* or *C. trachomatis*	2	6	4
Lost to Follow-up	2	2	4
Other	0	0	1

All subjects received the treatment to which they were randomized and were included in the ITT population and Safety population. Twenty-seven subjects were excluded from the mITT population (7 SYM-1219 1 gram, 10 SYM-1219 2 gram, and 10 placebo). Subjects were excluded for not having a baseline Nugent score ≥4 (5 SYM-1219 1 gram, 4 SYM-1219 2 gram, and 4 placebo) or for being positive at baseline for either *N. gonorrhoeae* or *C. trachomatis* (2 SYM-1219 1 gram, 6 SYM-1219 2 gram, and 5 placebo). Thirty-six patients (9 SYM-1219 1 gram, 15 SYM-1219 2 gram, and 12 placebo) were further excluded from the PP population due to protocol violations, primarily due to not having a TOC visit assessed between Days 21 and 30.

Table 10
SYM-1219-201
Analysis Populations

	SYM-1219 1 gram	SYM-1219 2 gram	Placebo
ITT population	71	72	72
Safety Population	71	72	72
MITT Population	64	62	62
PP Population	55	47	50

Table 11 summarizes the demographic and baseline characteristics of the mITT population. There were no significant differences between treatment groups. Overall, 54% of the study population was black and 39% was white. However, there were a higher proportion of white subjects in the SYM-1219 2 gram group compared to the SYM1219 1 gram and placebo groups. The mean age of the patients was 33 years. The median baseline Nugent score was 8. The median number of BV episodes in the past 12 months was 3 and 68% of the study population was in the 3 or fewer BV episodes strata.

Table 11
SYM-1219-201
Demographic and Baseline Characteristics (mITT)

	SYM-1219 1 gram	SYM-1219 2 gram	Placebo
# Patients	64	62	62
Age mean (SD)	32.8 (7.7)	33.1 (9.3)	32.5 (7.7)
min, max	19, 49	19, 54	19, 49
Race			
White	18 (28.1)	32 (51.6)	24 (38.7)
Black	42 (65.6)	26 (41.9)	34 (54.8)
Other	4 (6.3)	4 (6.5)	4 (6.5)
Nugent Score			
mean (SD)	8.7 (1.4)	8.2 (1.7)	8.6 (1.3)
median	9	8	8
min, max	5, 10	4, 10	4, 10
Number of BV episodes in the past 12 months			
mean SD)	3.5 (2.9)	3.2 (2.9)	3.1 (2.1)
median	3	2	3
min, max	1, 13	1, 12	1, 12
BV Strata			
3 or fewer episodes	44 (68.8)	41 (66.1)	43 (69.4)
4 or more episodes	20 (31.3)	21 (33.9)	19 (30.6)

3.2.2.4 Results and Conclusions

Table 12 summarizes the results for clinical outcome, Nugent score, therapeutic outcome, and the Investigator's clinical assessment at TOC for the mITT population. Clinical responder rates, the proportion of subjects with a normal Nugent score, therapeutic responder rates, and

proportion of subjects assessed by the Investigator as not needing additional BV treatment at TOC were significantly higher for both doses of SYM-1219 compared to placebo. Additionally, the SYM-1219 2 gram group had numerically higher response rates than the SYM-1219 1 gram group. It should be noted that the percentage of subjects not requiring additional BV treatment are different than those presented in the Study Report because the Applicant excluded subjects with missing data from the denominator used to calculate the rates.

Table 12
SYM-1219-201
Summary of Responses at Test of Cure (mITT)

	SYM-1219 1 gram (n=64)	**SYM-1219 2 gram** (n=62)	**Placebo** (n=62)
Clinical Outcome Responder	33 (51.6) 33.9 (16.8, 51.0) p<0.0001	42 (67.7) 50.0 (33.4, 66.7) p<0.0001	11 (17.7)
Nugent Score (Normal)	15 (23.4) 16.9 (3.3, 30.5) p=0.0068	25 (40.3) 33.8 (18.5, 49.1) p<0.0001	4 (6.5)
Therapeutic Outcome Responder	14 (21.9) 15.4 (2.0, 28.8) p=0.0111	25 (40.3) 33.8 (18.5, 49.1) p<0.0001	4 (6.5)
Investigator's Clinical Assessment (Additional BV treatment not required)	36 (56.3) 32.1 (14.4, 49.9) p=0.0002	45 (72.6) 48.4 (31.4, 65.4) p<0.0001	15 (24.2)

Missing data classified as non-responder or abnormal (2 SYM-1219 1 gram, 2 SYM1219-2 gram, and 4 placebo)
Difference (95% CI) for SYM-1219 group-placebo
Two-sided p-value based on CMH test adjusted for BV strata vs placebo

Table 13 summarizes clinical outcome at TOC for the mITT population including the reason for clinical non-responder. Subjects were non-responders primarily because none of the three criteria needed for clinical cure were resolved.

Table 13
SYM-1219-201
Clinical Outcome at TOC (mITT)

	SYM-1219 1 gram (n=64)	**SYM-1219 2 gram** (n=62)	**Placebo** (n=62)
Clinical Responder	33 (51.6)	42 (67.7)	11 (17.7)
Clinical Non-responder	31 (48.4)	20 (32.3)	51 (82.3)
All 3 criteria not met	21 (32.8)	17 (27.4)	40 (64.5)
2 of 3 criteria not met	5 (7.8)	1 (1.6)	3 (4.8)
1 of 3 criteria not met	3 (4.7)	0	4 (6.5)
Missing	2 (3.1)	2 (3.2)	4 (6.5)

Table 14 summarizes the results for the individual components of clinical outcome at TOC for the mITT population.

Table 14
SYM-1219-201
Individual Components of Clinical Outcome at TOC (mITT)

	SYM-1219 1 gram (n=64)	SYM-1219 2 gram (n=62)	Placebo (n=62)
Vaginal Discharge			
Normal	38 (59.4)	42 (67.7)	14 (22.6)
Abnormal	24 (37.5)	18 (29.0)	44 (71.0)
Missing	2 (3.1)	2 (3.2)	4 (6.5)
Clue Cells			
< 20%	37 (57.8)	43 (69.4)	13 (21.0)
≥ 20%	25 (39.1)	17 (27.4)	45 (72.6)
Missing	2 (3.1)	2 (3.2)	4 (6.5)
Whiff Test			
Negative	35 (54.7)	42 (67.7)	17 (27.4)
Positive	27 (42.2)	18 (29.0)	41 (66.1)
Missing	2 (3.1)	2 (3.2)	4 (6.5)

3.2.3 Study SYM-1219-350

3.2.3.1 Study Design and Endpoints

SYM-1219-350 was a Phase 3, multicenter, open-label non-comparative safety study of SYM-1219 (single 2 gram dose) for the treatment of women and post menarchal adolescent girls with BV. The study was conducted at 34 investigational centers in the United States. Subjects were evaluated at 3 time points: baseline, a post-treatment phone call, and an end of study (EOS) visit. Subject eligibility was determined at the baseline visit. Adult females and post menarchal adolescent girls aged 12 years of age and older with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV is defined as having an off-white, thin, homogenous discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. Subjects with a known or suspected other infectious cause of vulvovaginitis (e.g. candidiasis, *T. vaginalis, C. trachomatis, N. gonorrhoeae,* or active *H. simplex)* were to be excluded. Pregnant women were also excluded from enrollment. Eligible subjects received treatment with a single oral dose of SYM-1219 2 gram. Subjects were contacted by telephone between Days 8 and 10 to inquire about possible adverse events and any concomitant medication use. The EOS visit was conducted between Days 21 and 30. A pelvic exam was conducted and vaginal fluid specimens were collected at the baseline visit and at the EOS visit only if the subject reported any vulvovaginal signs/symptoms/adverse events or at the Investigator's discretion.

The primary objective of the study was to evaluate the safety of SYM-1219 2 grams for the treatment of BV. Safety evaluations were based on the incidence, intensity, and type of adverse events, and changes in the subject's physical examination findings, vital signs and clinical safety laboratory findings. Efficacy was limited to the Investigator's clinical assessment at EOS which

was based on the Investigator's opinion of whether the patient required additional treatment for the BV infection. A post hoc analysis of clinical outcome was conducted by the Applicant for those subjects that had an EOS pelvic examination (vaginal assessment).

3.2.3.2 Statistical Methodologies

The results of the study are summarized using descriptive statistics (frequency percentages or change from baseline). The Safety population consisted of all enrolled subjects who received the study drug.

No formal sample size calculation was made. A total of 325 subjects was chosen to provide observational safety data only.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 325 patients were enrolled. Four patients did not consume study mediation and were excluded from the Safety population. Therefore, the Safety population consists of 321 patients. Approximately 88% of the patients completed the study. The most common reasons for discontinuation from the study were lost to follow-up and positive for other vulvovaginal infections. Reasons for discontinuation are reported in Table 15.

Table 15
SYM-1219-350
Patient Disposition (Safety Population)

	SYM-1219 2 gram
Received Treatment	321
Completed Study	283 (88.2)
Discontinued Study	38 (11.8)
Safety reasons	1
Subject's request	2
Perceived lack of therapeutic effect	3
Positive for *N. gonorrhoeae* or *C. trachomatis*	17
Use of concomitant therapy	1
Lost to Follow-up	13
Other	1

Table 16 summarizes the demographic and baseline characteristics of the Safety population. Overall, 46% of the study population was black and 51% was white. The mean age of the patients was 32 years. The median number of BV episodes in the past 12 months was 2 and 79% of the study population reported 3 or fewer BV episodes.

Table 16
SYM-1219-350
Demographic and Baseline Characteristics (Safety)

	SYM-1219 2 gram
# Patients	321
Age mean (SD)	31.5 (8.5)
min, max	15, 53
Race	
White	165 (51.4)
Black	148 (46.1)
Other	8 (2.5)
Number of BV episodes in the past 12 months	
mean (SD)	2.8 (2.5)
median	2
min, max	1, 25
BV Strata	
3 or fewer episodes	254 (79.1)
4 or more episodes	67 (20.9)

3.2.3.4 Results and Conclusions

The Investigator's Clinical assessment at EOS is summarized in Table 17. The proportion of subjects assessed as not requiring additional BV treatment was 69.2%. It should be noted that this percentage is different from that presented in the Study Report because the Applicant excluded the 15 subjects with missing data from the denominator.

Table 17
SYM-1219-350
Investigator's Clinical Assessment at End of Study (Safety)

	SYM-1219 2 gram (n=321)
Additional BV treatment needed	84 (26.2)
No additional BV treatment needed	222 (69.2)
Missing	15 (4.7)

A post hoc analysis of clinical outcome was conducted by the Applicant based on the vaginal assessment of discharge, clue cells, and Whiff test at the EOS visit. As previously, mentioned a pelvic examination was not required at EOS unless the subject reported any vulvovaginal signs/symptoms/ adverse events or at the Investigator's discretion. Table 18 summarizes the assessment of clinical outcome at EOS.

Table 18
SYM-1219-350
Assessment of Clinical Outcome at End of Study (Safety)

	SYM-1219 2 gram (n=321)
Responder	159 (49.5)
Non-responder	116 (36.1)
Pelvic exam not required	30 (9.3)
Missing	16 (5.0)

3.3 Evaluation of Safety

For Study SYM-1219-301, the Safety population consisted of 125 SYM-1219 2 gram subjects and 64 placebo subjects. Overall, 34.4% (43/125) SYM-1219 2 gram treated subjects and 21.9% (14/64) placebo treated subjects experienced a treatment emergent adverse event (TEAE). The TEAEs were primarily mild or moderate in severity. Five subjects in the SYM-1219 2 gram group reported 7 severe TEAEs of which 2 were also considered serious. No severe or serious adverse events were reported in the placebo group. The most commonly reported adverse event was vulvovaginal candidiasis (VVC) or vulvovaginal mycotic infection which occurred in 17 (13.6%) SYM-1219 2 gram treated subjects and 3 (4.7%) placebo treated subjects. The occurrence of VVC following treatment for BV is not uncommon. There were no discontinuations due to adverse events or deaths during the study.

For Study SYM-1219-201, the Safety population consisted of 71 SYM-1219 1 gram subjects, 72 SYM-1219 2 gram subjects, and 72 placebo subjects. Overall, 12.7% SYM-1219 1 gram subjects, 19.4% SYM-1219 2 gram subjects, and 9.7% placebo subjects experienced a TEAE. The most commonly reported TEAEs were related to infections and infestations. VVC or vulvovaginal mycotic infection occurred in 1 SYM-1219 1 gram subject, 2 SYM-1219 2 gram subjects, and 1 placebo subject. All of the TEAEs were mild to moderate in severity. One subject in the placebo group discontinued the study due to an adverse event (vulvovaginal mycotic infection). There were no serious TEAEs or deaths during the study.

For Study SYM-1219-350, the Safety population consisted of 321 patients who received SYM-1219 2 gram. Overall, 29.6% of the SYM-1219 2 gram subjects experienced a TEAE. The most commonly reported adverse event was VVC or vulvovaginal mycotic infection which occurred in 27 (8.4%) SYM-1219 2 gram treated subjects. The majority of the TEAEs were mild or moderate in severity. Four subjects reported 8 severe TEAEs of which 2 were also considered serious. Two subjects discontinued the study due to an AE (both due to vaginal yeast infection). There were no deaths during the study.

For a detailed review of the safety data, please see the Medical Officer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 19 summarizes the results by race for clinical outcome at TOC in the mITT population of Study SYM-1219-301. The results for the strata were consistent to those seen for the overall population in that clinical outcome responder rates for SYM-1219 2 gram were higher than for placebo. However, the treatment effect for Black subjects (25.1%) was smaller than the treatment effect for White subjects (43.8%). Also, the clinical outcome responder rate for Black subjects treated with SYM-1219 2 gram was numerically lower than the rate for White subjects treated with SYM-1219 2 gram. The results for the Others race subgroup should be interpreted with caution given the small sample sizes. Since all subjects were female, the mean age was 31 years and no subjects were older than 65 years, analyses by gender and age were not conducted. Analyses by geographic region were not conducted since all clinical sites were in the United States.

Table 19
SYM-1219-301
Clinical Outcome Responder at TOC by Race (mITT)

	SYM-1219 2 gram (n=107)	**Placebo** (n=57)	**Difference (95% CI)**
White	29/46 (63.0)	5/26 (19.2)	43.8 (20.2, 67.4)
Black	27/59 (45.8)	6/29 (20.7)	25.1 (3.1, 47.1)
Others	1/2	0/2	

Table 20 summarizes the results by race for clinical outcome at TOC in the mITT population of Study SYM-1219-201. The results for the strata were consistent to those seen for the overall population in that clinical outcome responder rates for the SYM-1219 treated groups were higher than for placebo. The treatment effect observed for Black subjects was larger than the treatment effect for White subjects but there was an extremely low clinical outcome responder rate observed for Black subjects who received placebo. The clinical outcome responder rate for Black subjects was numerically lower than the rate for White subjects for all treatment groups. The results for the Others Race subgroup should be interpreted with caution given the small sample sizes. Since all subjects were female and the mean age was 33 years and no subjects were older than 65 years, analyses by gender and age were not conducted. Analyses by geographic region were not conducted since all clinical sites were in the United States.

Table 20
SYM-1219-201
Clinical Outcome Responder at TOC by Race (mITT)

	SYM-1219 1 gram	SYM-1219 2 gram	Placebo
White	12/18 (66.7) 29.2 (-4.8, 63.2)	24/32 (75.0) 37.5 (9.4, 65.6)	9/24 (37.5)
Black	21/42 (50.0) 44.1 (24.4, 63.8)	15/26 (57.7) 51.8 (27.8, 75.8)	2/34 (5.9)
Others	0/4	3/4	0/4

Difference of SYM-1219 group minus placebo and 95% confidence interval

4.2 Other Special/Subgroup Populations

In Study SYM-1219-301, randomization was stratified by the number of BV episodes in the previous 12 months and race. Table 21 summarizes the results by the number of BV episodes in the previous 12 months strata for clinical outcome at TOC in the mITT population. The results for subjects with 3 or few episodes are consistent with that seen for the overall mITT population. However, the treatment effect for subjects with 4 or more episodes was small (7.8%) and highly variable due to small number of subjects in this stratum. Additionally, the clinical outcome responder rates for subjects with 4 or more episodes treated with SYM-1219 were numerically lower as compared to subjects with 3 or fewer episodes treated with SYM-1219.

Table 21
SYM-1219-301
Clinical Outcome Responder at TOC by Number of BV Episodes (mITT)

	SYM-1219 2 gram (n=107)	Placebo (n=57)	Difference (95% CI)
3 or fewer	50/83 (60.2)	8/43 (18.6)	41.6 (24.1, 59.1)
4 or more	7/24 (29.2)	3/14 (21.4)	7.8 (-26.0, 41.6)

In Study SYM-1219-201, randomization was stratified by the number of BV episodes in the previous 12 months. Table 22 summarizes the results by the number of BV episodes in the previous 12 months strata for clinical outcome at TOC in the mITT population. The results are consistent with that seen for the overall mITT population. The treatment effect observed is similar for the two strata. However, clinical outcome responder rates for subjects with 4 or more episodes were numerically lower as compared to subjects with 3 or fewer episodes for both SYM-1219 treatment groups as well as placebo.

Table 22
SYM-1219-201
Clinical Outcome Responder at TOC by Number of BV Episodes (mITT)

	SYM-1219 1 gram	SYM-1219 2 gram	Placebo
3 or fewer	26/44 (59.1) 35.8 (14.2, 57.4))	30/41 (73.2) 49.9 (29.0, 70.8)	10/43 (23.3)
4 or more	7/20 (35.0) 29.7 (1.4, 58.0)	12/21 (57.1) 51.8 (23.3, 80.3)	1/19 (5.3)

Difference of SYM-1219 group minus placebo and 95% confidence interval

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

On the CRF for Study SYM-1219-301, Investigators were requested to assess vaginal discharge at the Interim and TOC visits as "Normal", "Abnormal (consistent with BV)", or "Abnormal (Other)". The definition of clinical outcome responder recommended by the Medical Division requires a return to normal vaginal discharge in addition to clue cells < 20% and a negative Whiff test. The Applicant proposed an alternative definition to clinical outcome responder to include either normal vaginal discharge or abnormal (other) and used this definition in a sensitivity analysis of the primary endpoint. As seen in Table 7, there were relatively few subjects whose discharge was classified as "Abnormal (other)" at the TOC visit. Of these subjects, only 1 SYM-1219 2 gram subject would be considered a clinical non-responder under the alternative definition. Thus under the alternative definition, 63 (58.9%) SYM-1291 2 gram subjects and 14 (24.6%) placebo subjects were clinical outcome responders. The difference between treatment groups of 34.3% and 95% confidence interval of (18.4%, 50.2%) are consistent with those observed for the primary analysis (Table 5). The Applicant indicates that this alternative definition is consistent with the definition of clinical cure in the July 2016 draft BV guidance. While the definition of clinical cure in the current draft guidance states "resolution of the abnormal discharge", this was intended to be inferred as a "return to normal discharge". Therefore, the definition of clinical outcome responder used for the primary analysis is the preferred definition.

Randomization ratios were different in the two controlled trials i.e., 1:1:1 in SYM-1219-201 and 2:1 in SYM-1219-301. Therefore, crude pooling of the trial results would typically not be recommended when comparisons between treatment arms are to be made as "Simpson's Paradox" may be a concern. The Applicant's proposed labeling includes a table of adverse events occurring in ≥ 2% of patients received SYM-1219 2 gram for these 2 studies pooled and also presents the corresponding placebo rate pooled. The overall incidence of subjects experiencing at least one adverse event was relatively low in the studies, not more than 35% which was observed for SYM-1219 2 gram subjects in SYM-1219-301. Although, there was a slightly larger incidence of adverse event reported in SYM-1219-301 as compared to SYM-1219-201. For the adverse events reported in the Applicant's proposed label Table 1, adjusted incidence proportions taking into account study were calculated and are presented in Table 23. In this situation, there is minimal difference in the adjusted proportions and crude pooling proportions and no sign of Simpson's Paradox. Therefore, the results as presented with the crude

pooling for the adverse events reported in the Applicant's proposed label Table 1 will be acceptable.

Table 23
Crude vs Adjusted Pooling of SYM-1219-201 and SYM-1212-301 of Selected Adverse Events (Safety Population)

	SYM-1219-201		SYM-1219-301		Pooled			
					Crude		Adjusted	
Adverse event	SYM-1219 2 g (n=72)	Placebo (n=72)	SYM-1219 2 g (n=125)	Placebo (n=64)	SYM-1219 2 g (n=197)	Placebo (n=136)	SYM-1219 2 g	Placebo
Any AE	14 (19.4)	7 (9.7)	43 (34.4)	14 (21.9)	28.9	15.4	27.9	16.6
Vulvovaginal candidiasis	2 (2.8)	1 (1.4)	17 (13.6)	3 (4.7)	9.6	2.9	8.9	3.3
Headache	1 (1.4)	0 (0)	6 (4.8)	2 (3.1)	3.6	1.5	3.3	1.8
Nausea	1 (1.4)	0 (0)	6 (4.8)	1 (1.6)	3.6	0.7	3.3	0.9
Diarrhea	0 (0)	0 (0)	5 (4.0)	1 (1.6)	2.5	0.7	2.3	0.9
Abdominal pain	0 (0)	0 (0)	4 (3.2)	2 (3.1)	2.0	1.5	1.8	1.8
Vulvovaginal pruritus	1 (1.4)	0 (0)	3 (2.4)	2 (3.1)	2.0	1.5	2.0	1.8

5.2 Collective Evidence

Two studies were conducted to evaluate the efficacy of SYM-1219 2 gram, a Phase 3 confirmatory trial (SYM-1219-301) versus placebo and a Phase 2 dose ranging study (SYM-1219-201) also compared to placebo. The study populations, the endpoints assessed, timing of TOC and the control of the two studies were similar. SYM-1219-201 did not require an Interim visit at the clinic to assess clinical outcome, Nugent score, and therapeutic outcome. Given the differences in the randomization (1:1:1 in SYM-1219-201 and 2:1 in SYM-1219-301) and the need for confirmatory evidence, the efficacy results have not been presented in an integrated fashion.

The efficacy data at the TOC visit for the proposed SYM-1219 2 gram dose and placebo from the studies are presented side-by-side in Table 24. In both studies, treatment with SYM-1219 2 gram led to a statistically significantly greater proportion of clinical outcome responders at TOC than treatment with placebo. Significant differences are also seen for the secondary endpoints of Nugent score and therapeutic outcome at TOC.

Table 24
SYM-1219-201 and SYM-1219-301
Summary of Responses at Test of Cure (mITT)

	SYM-1219-201		SYM-1219-301	
	SYM-1219 2 gram (n=62)	**Placebo** (n=62)	**SYM-1219 2 gram** (n=107)	**Placebo** (n=57)
Clinical Outcome Responder	42 (67.7)	11 (17.7)	57/107 (53.3)	11/57 (19.3)
	50.0 (33.4, 66.7)		34.0 (18.7, 49.3)	
	p<0.0001		p<0.001	
Nugent score (normal)	25 (40.3)	4 (6.5)	47 (43.9)	3 (5.3)
	33.8 (18.5, 49.1)		38.6 (26.2, 51.0)	
	p<0.0001		p< 0.001	
Therapeutic Outcome Responder	25 (40.3)	4 (6.5)	37 (34.6)	2 (3.5)
	33.8 (18.5, 49.1)		31.1 (19.6, 42.6)	
	p<0.0001		p< 0.001	

Difference of SYM-1219 minus placebo and 95% confidence interval
p-value for CMH test adjusted for BV strata in Study SYM-1219-201 and for BV strata and race strata in Study SYM-1219-301

Subgroup analyses were conducted by race and the number of previous episodes of BV strata. Overall the results for the individual strata were consistent with the overall population in that clinical outcome responder rates for the SYM-1219 2 gram group were higher than for placebo. However, Black subjects tended to have lower clinical outcome responder rates compared to White subjects. In SYM-1219-301, the treatment effect for Black subjects was smaller than that observed for White subjects. Subjects with 4 or more previous episodes of BV tended to have lower clinical outcome responder rates compared to subjects who had 3 or fewer previous episodes. In SYM-1219-201, the treatment effect observed for these two strata was similar. However, in SYM-1219-301, the treatment effect for subjects with 4 or more previous episodes of BV was very small although highly variable due to the small sample size in this stratum.

The safety study, SYM-1219-350, provided limited efficacy information. The Investigator's clinical assessment at EOS was similar to that observed in the two controlled studies. The proportion of subjects who received SYM-1219 2 gram assessed as not requiring additional BV treatment was 69.2% in SYM-1219-350, 72.6% in SYM-1219-201, and 63.6% in SYM-1219-301. The clinical outcome responder rate, 58.8% when considering subjects who did not require a pelvic exam at EOS since they were not experiencing any vulvovaginal sign/symptoms as a responder, is also similar to that observed in the two controlled trials.

5.3 Conclusions and Recommendations

Based on the results of the Phase 3 trial, a single dose of SYM-1219 2 gram was shown to be more effective than placebo in producing clinical outcome responders at the TOC visit. Secondary endpoints of normal Nugent score and therapeutic outcome responder at the TOC visit were also significantly better for SYM-1219 2 gram than placebo. Additionally, the Phase 2 dose ranging study showed similar results of a single dose of SYM-1219 2 gram compared to placebo. Therefore, there is adequate evidence of efficacy to support the indication of the treatment of BV for SYM-1219 2 gram.

5.4 Labeling Recommendations

The following labeling changes are recommended in Section 14 Clinical Studies.

- All discussions of (b) (4) should be removed.
- For Table 2 of the labeling, it is recommended that results for clinical outcome, Nugent score, and therapeutic outcome at TOC be presented. Differences in response rates and 95% confidence intervals should also be presented. (Similar to Table 24 above) Note in the Applicant's proposed labeling for Study 2 (SYM-1219-301), (b) (4) .
- Table 3 of the labeling should be replaced with the results for clinical outcome, Nugent score and therapeutic outcome at the Interim visit for Study SYM-1219-301.

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/s/

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06/15/2017

KAREN M HIGGINS
06/15/2017
I concur.

TSAE YUN D LIN
06/15/2017