

Two Phase I, Open-Label, Single-Dose, Randomized, Crossover Studies to Assess the Pharmacokinetics, Safety, and Tolerability of Orally Administered Granules of Secnidazole (2 g) in Healthy Female Volunteers Under Different Administration Conditions

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Abstract

Bacterial vaginosis (BV) is the most common vaginal infection in reproductive-age women and a significant risk factor for sexually transmitted diseases and pregnancy complications. Standard 5- to 7-day antimicrobial treatments for BV are associated with high rates of recurrence and adverse events. SYM-1219 is a novel granule formulation containing 2 g of secnidazole, developed as an oral, single-dose BV treatment. Two phase I, open-label, single-center, randomized, crossover trials (studies 102 and 103) assessed the pharmacokinetics and safety of SYM-1219 single doses (≥ 7 -day washout between doses) in healthy, nonpregnant women aged 18 to 65 years inclusive. Study 102 compared SYM-1219 in applesauce in fasted vs fed states. Study 103 compared SYM-1219 (fasted) in pudding and yogurt vs applesauce. Studies 102 and 103 each dosed 24 subjects (mean [standard deviation] ages, 36 [1.8] and 40 [11.6] years, respectively). In both studies the 90% confidence intervals for all treatment comparisons of maximum plasma concentration, area under the concentration-time curve from 0 to last measurable concentration and to infinity, geometric mean ratios were within 80% to 125%, demonstrating bioequivalence. In both studies median fasted time to maximum plasma concentration was 4 hours (6 hours fed in study 102), and mean half-life ranged from 17 to 19 hours. Treatment-emergent adverse events occurred in 70.8% and 83.3% subjects in studies 102 and 103, respectively, most commonly headache (41.7% and 50.0%) and gastrointestinal treatment-emergent adverse events. The pharmacokinetics of SYM-1219 were similar in fed and fasted states and when administered in different foods.

Keywords

bacterial vaginosis, treatment, secnidazole, pharmacokinetics, adverse events

Bacterial vaginosis (BV) is the most common vaginal infection in women aged 14 to 49 years, affecting an estimated 29% of reproductive-age women in the United States.^{1–3} In addition to causing distressing symptoms that may impact quality of life,⁴ BV is associated with an increased risk of pregnancy complications such as preterm birth and sexually transmitted diseases including human immunodeficiency virus.^{3,5–7} A disturbance of the vaginal microbiome, BV is characterized by replacement of the normally dominant *Lactobacillus* spp, which produce hydrogen peroxide in the healthy vagina, with a variable assortment of anaerobic and facultative bacteria, including *Gardnerella*, *Atopobium*, *Prevotella*, and other microorganisms.^{6,8} The major

symptoms of BV are a homogeneous, thin, grayish discharge coating the vaginal walls with a malodor

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usually described as “fishy.”^{4,6,9} The traditional diagnostic “Amsel criteria” for BV include a vaginal fluid pH of >4.5; a fishy odor confirmed with a “whiff test” when vaginal discharge is mixed with 10% potassium hydroxide on a slide; and the presence of clue cells (epithelial cells coated with bacteria) in secretions viewed under a microscope.^{6,9} Alternatively, the Nugent assay,¹⁰ which relies on a more objective observation of Gram-stained vaginal secretions, is increasingly being used for BV diagnosis.⁶

Treatment of BV is recommended for women with symptoms,⁹ although a majority of women with BV are asymptomatic.^{2,3} The most commonly used and widely recommended therapies include antimicrobial treatment with metronidazole, an agent of the 5-nitroimidazole class, and clindamycin, which are available as either oral or gel formulations.^{9,11,12} Other treatments include tinidazole, another 5-nitroimidazole, and use of probiotics and prebiotics, among various alternative active and preventive therapeutic strategies.^{11,13} Four-week cure rates with standard BV therapy are approximately 40% to 80%.^{14–18} However, major unmet medical needs remain in BV treatment, including 6-month and 12-month recurrence rates of 28% and 58%, respectively, with metronidazole.^{19,20} Additionally, gastrointestinal adverse events (AEs) occur in up to half of patients taking oral metronidazole treatment, including high rates of nausea, abdominal pain, and a “metallic” taste.^{16,21,22} Given the standard treatment regimens of 7 days for both metronidazole and clindamycin, their associated AEs, and the need for alcohol restriction during metronidazole treatment, these therapies may be associated with poor adherence, increased rates of treatment failure, and BV recurrence.¹³ Although study data on patient compliance with BV treatment are scant, 1 study in 71 patients with BV found that half were noncompliant with metronidazole treatment.²³

SYM-1219 is a granule formulation containing 2 g of secnidazole, a next-generation antimicrobial agent in the 5-nitroimidazole class, that has been developed as an oral, single-dose treatment for BV. Although it has been recognized that the efficacy of secnidazole for treatment of BV as well as giardiasis, amoebiasis, and trichomoniasis is similar to that of other 5-nitroimidazoles, and secnidazole has been widely used in many countries, there are no approved formulations in the United States.²⁴ SYM-1219 represents a novel formulation that may facilitate administration because it enables oral intake by sprinkling the granules on food rather than as a pill, capsule, or tablet that requires swallowing whole. Secnidazole is rapidly and completely absorbed following oral administration and demonstrates a longer terminal elimination half-life of approximately 17 to 29 hours vs other drugs

in its class.^{24,25} It is metabolized by oxidation in the liver to a hydroxyethyl metabolite without any effects, neither induction nor inhibition, on cytochrome P450 enzymes^{24–26}; elimination is mainly through the urinary route, with approximately 50% excreted by 96 hours. A previous pharmacokinetic (PK) study has been conducted using different formulations of secnidazole, and bioequivalence was demonstrated for capsule and tablet formulations.²⁷

In patients with BV, single-dose treatment with secnidazole has been shown to be at least as effective as 7-day treatment with metronidazole, with a similar tolerability profile.^{24,28} A more recent randomized, placebo-controlled phase 2 dose-ranging study of SYM-1219 showed that single doses of 1 g and 2 g had favorable safety and tolerability profiles and that both doses resulted in significantly ($P < .05$) higher cure rates than placebo among women with BV.²⁹ In particular, the 2-g dose resulted in cure rates vs placebo of 67.7% vs 17.7% ($P < .001$) for clinical cure (normalization of discharge, amine odor, and clue cells), 40.3% vs 6.5% ($P < .001$) for microbiologic cure (Nugent score 0 to 3), and 40.3% vs 6.5% ($P < .001$) for therapeutic cure (meeting both clinical and microbiologic criteria).²⁹ A phase 3 study further confirmed the significant efficacy of SYM-1219 vs placebo for curing BV ($P < .001$), with low rates of AEs.³⁰ In addition, the PK of SYM-1219 was not affected by concomitant use of hormonal contraceptives, ethinyl estradiol, and norethindrone, commonly prescribed for reproductive-age women.³¹

The 2 phase 1 studies reported here were conducted to evaluate various dosing conditions and the effect on the PK of SYM-1219 containing 2 g of secnidazole in healthy female volunteers. Study SYM-1219-102, or study 102, assessed the PK and safety of SYM-1219 under fed and fasted conditions. Study SYM-1219-103 (study 103) evaluated the PK and safety of SYM-1219 administered under fasted conditions on 3 different foods, yogurt, pudding, and applesauce. The results of these studies will be used to inform patient labeling and provide dosing instructions for patients.

Methods

Study Objectives and Design

The main objectives of study 102 were (1) to compare in healthy women the PK of SYM-1219 administered in applesauce under fed and fasted conditions and (2) to evaluate the safety of single doses of SYM-1219 administered in applesauce. The 3 main objectives of study 103 were to compare in healthy women (1) the PK of SYM-1219 administered in (granules sprinkled over) pudding vs applesauce (the reference treatment) and (2) the PK of SYM-1219 administered in yogurt vs applesauce, and (3) to evaluate the safety of

a single dose of SYM-1219 administered in pudding, yogurt, or applesauce under fasting conditions in healthy women.

Both study 102 and study 103 were designed and conducted in accordance with the ethical principles of the Good Clinical Practice guidelines of the International Conference on Harmonisation, the ethical requirements referred to in the European Union directive 2001/20/EC, and the ethical principles set forth in the Declaration of Helsinki. The protocols for both studies were reviewed and approved by the Chesapeake Institutional Review Board/Chesapeake Research Review, Inc. All study procedures were explained to subjects, and all subjects were required to sign an informed consent form before participating in the study.

Both studies were phase 1, single-center, open-label, single-dose, randomized, crossover studies conducted to assess PK, safety, and tolerability of SYM-1219 containing 2 g of secnidazole (Solosec™) in healthy women. Study 102 was performed at Spaulding Clinical Research (West Bend, Wisconsin), and study 103 at Celerion (Tempe, Arizona). SYM-1219 granules in both studies were provided by Catalent Pharma Solutions (Somerset, New Jersey). Each study began with 30-day screening periods to determine eligibility and included comparative SYM-1219 treatments/treatment periods and a washout period in between treatments. In both studies eligible subjects were admitted to the clinical research unit on day -1 of period 1 and remained in the unit until all PK sampling and assessments were concluded on day 5 of the last study period. Blood samples were collected to determine secnidazole plasma concentrations following each SYM-1219 treatment, and safety assessments, including vital signs, were performed at specified time points during each treatment period and at study conclusion in both studies.

Study 102 Design. In study 102, all doses of SYM-1219 were sprinkled over a single serving (4 oz) of commercially available, unsweetened applesauce (Mott's Applesauce). All subjects received each of the treatments described below in crossover fashion according to the randomization schedule:

- Treatment A: 1 dose of SYM-1219 under fasted conditions
- Treatment B: 1 dose of SYM-1219 under fed conditions

Treatments were administered with a minimum 7-day washout period after the previous dose. The fasted treatments were administered after an overnight fast of ≥ 10 hours. The fed treatment was administered after an overnight fast of ≥ 10 hours followed by a high-fat, high-calorie breakfast served to subjects at 30 minutes before dosing. The breakfast consisted of 2 eggs

fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash browns, and 8 oz of whole milk, containing approximately 150 protein calories, 250 carbohydrate calories, and 500–600 fat calories. Each fed and fasted dose of SYM-1219 was followed by 240 mL of water, with no food allowed for 4 hours following administration, and water restricted for 2 hours following dosing (other than fluids consumed during breakfast for fed treatment).

During each treatment period, blood samples were collected for determination of secnidazole plasma concentrations at the following time points: before dosing (within 30 minutes of dosing) and then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 72, and 96 hours postdose. Blood samples (6 mL) were collected into lavender-top Vacutainer® collection tubes containing K₂EDTA as the anticoagulant and stored at -20°C. Urine samples were also collected at 6- to 12-hour intervals following dosing for exploratory purposes but were not analyzed as part of this study.

Study 103 Design. In study 103, subjects were administered each of the following treatments with SYM-1219 sprinkled over foods as described below in randomized, crossover fashion:

- Treatment A: SYM-1219 added to a single serving of approximately 4 oz of chocolate pudding (Snack Pack Pudding Chocolate 3.25-oz cups)
- Treatment B: SYM-1219 added to a single serving of approximately 6 oz of low-fat vanilla yogurt (Dannon Light & Fit Vanilla Nonfat Yogurt 6-oz cup)
- Treatment C: SYM-1219 added to a single serving of approximately 4-oz of unsweetened applesauce (reference treatment; Mott's Applesauce Original 4.0-oz container)

The foods used in this study were selected based on variations in properties such as water content and pH (pudding, 5.8, yogurt, 4.5; applesauce, 3.2) to provide a range of conditions, and on research data (unpublished) indicating that patients preferred these foods for use with drug consumption. Treatments were administered with a minimum 7-day washout after the previous dose. All treatments in study 103 were administered following an overnight fast of ≥ 10 hours. Each dose was to be consumed within 5 minutes of the scheduled dosing time, followed by 240 mL of water and no additional food allowed for 4 hours after administration.

During each treatment period, blood samples were collected for PK analysis at the following time points: before dosing (within 30 minutes of dosing) and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose. Blood samples (4 mL) were collected

into lavender-top Vacutainer® collection tubes containing K₂EDTA as the anticoagulant and stored at -20°C.

Study Population

Both studies enrolled healthy female volunteers (n = 25 in study 102, n = 24 in study 103) aged 18 to 65 years inclusive and employed otherwise similar inclusion/exclusion criteria. Women of childbearing potential were required to be nonpregnant, as determined via negative pregnancy test results at screening and check-in (day -1) and to be using adequate birth control, as determined by the investigator. Other eligibility criteria for both studies included body mass index between 18 and 32 kg/m² inclusive; subject was nonsmoking (for the 6 months previous to screening); agreed to abstain from alcohol for 48 hours and coffee for 24 hours before each study dose and until the end of sample collection in each study period, and from intake of grapefruit and grapefruit-containing products from 72 hours before the initial study dose until the end of the study; no abnormalities in 12-lead electrocardiogram; in generally good health based on prestudy medical history, physical examination, and routine laboratory tests; and no clinically significant disease. Key exclusion criteria for both studies were pregnancy; a history of drug or alcohol abuse within 12 months of study screening; a supine systolic blood pressure of >150 mm Hg or <85 mm Hg, a supine diastolic blood pressure >95 mm Hg or <40 mm Hg, or a pulse rate >100 or <40 beats per minute at screening or check-in (day -1); and positive screening for human immunodeficiency virus, hepatitis B surface antigen, or anti-hepatitis C virus antibody.

Assessments

Pharmacokinetic Parameters. Both studies assessed the following PK parameters: area under the plasma concentration-time curve (AUC) from time 0 to last measurable concentration (AUC_{0-t}), calculated using the linear trapezoidal method; AUC from time 0 extrapolated to infinity (AUC_{0-inf}), calculated as $AUC_{0-inf} = AUC_{0-t} + (C_{last}/\lambda_z)$ where C_{last} is the last observed/measured concentration and λ_z represents the fraction of drug eliminated per unit time; the maximum observed plasma concentration (C_{max}); the time to reach C_{max} (T_{max}); and the terminal elimination half-life ($t_{1/2}$), calculated as $t_{1/2} = \ln(2)/\lambda_z$.

Safety Assessments. Both studies monitored all AEs reported during the treatment (ie, treatment-emergent AEs [TEAEs]) and assessed them for relatedness to treatment with the study drug (treatment-related AEs; possible, probable, or not related), their severity (mild, moderate, or severe), and whether they were serious (se-

rious AEs [SAEs]). In both studies, all AEs were coded using the most current available version of the Medical Dictionary for Regulatory Activities (version 17.1 for study 102, version 18.0 for study 103).

Physical examination and laboratory testing were conducted at screening, day -1 (clinic admission), and day 5 (before discharge). Vital signs were obtained at screening, day -1, before each dose, and at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours after dosing (after blood sample collection if measured at the same time). In study 102, 12-lead electrocardiograms (ECGs) were obtained at screening, day -1, before each dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 48, 72, and 96 hours postdose (when coincident with plasma collections, the ECG was obtained 5 minutes before the time point and plasma collection performed on the time point). In study 103, 12-lead ECGs were performed at screening and on day 5 in period 3 or at early termination from the study.

Bioanalytical Methods and Statistical Analysis. Study 102 was designed to test the hypothesis that the PK characteristics of SYM-1219 are the same in the fed and fasted states. Therefore, for this analysis, and using the criterion that the 90%CI of the test-to-reference ratio was between 80% and 125%, it was determined that a sample size of at least 18 subjects would provide at least 90% power to demonstrate bioequivalence between the test and reference formulations assuming intrasubject coefficient of variation (CV) ≤ 15% and a true ratio of geometric means of 1.

Similarly in study 103, which evaluated bioequivalence of SYM-1219 sprinkled on pudding or yogurt compared with applesauce, at least 90% power to demonstrate bioequivalence between the test and reference formulations would require 18 evaluable subjects assuming intrasubject CV ≤ 15% and a true ratio of geometric means of 95% to 105%. Enrollment of 24 subjects was deemed adequate to ensure that 18 subjects would complete the study.

Studies 102 and 103 used similar methods for bioanalysis, which were conducted by Celerion (Lincoln, Nebraska). Secnidazole was extracted from the plasma samples using acetonitrile protein precipitation and analyzed by liquid chromatography with mass spectrophotometric detection. The standard curve ranges were 0.200 to 50 μg/mL, and the lower limit of quantitation was 0.200 ng/mL. Metronidazole was the internal standard. The chromatography stationary phase was performed on an Agilent Technologies (Santa Clara, California) Zorbax 300-SCX column, 50 × 3.0 mm, 5 μm, maintained at ambient temperature. The mobile phase consisted of 50:50:1 acetonitrile: 5 mmol/L ammonium formate:formic acid with a flow rate of 1.0 mL/min. The m/z ion utilized for quantitation was 186.23. The interday variability was ≤ 5.3%,

and the intraday variability was $\leq 6.2\%$. The method was validated to bioanalytical standards including low-, middle-, and high-concentration quality-control samples.

Both studies generated statistical analyses using SAS (Cary, North Carolina) and calculated PK parameters using WinNonlin version 6.3 or later (Pharsight, Inc, Mountain View, California). Plasma PK parameters calculated for secnidazole were summarized by treatment using descriptive statistics (number of observations, mean, geometric mean, standard deviation [SD], CV, median, minimum, and maximum). Mean and individual plots were presented on linear and semilogarithmic scales.

To compare treatments, a mixed-effects model was used in both studies that was fitted on the natural logarithm (log)-transformed secnidazole PK parameters, ie, C_{\max} , AUC_{0-t} , and AUC_{0-inf} , with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect. Least-squares (LS) means, differences between LS means, and corresponding 90% CIs were determined for each parameter. Geometric LS means, geometric mean ratios (GMR), and 90% CIs were obtained by exponentiation and presented. Bioequivalence of treatments in both studies was defined as containment of the corresponding CIs for secnidazole C_{\max} , AUC_{0-t} , and AUC_{0-inf} completely within the interval of 80% to 125%; absence of a food effect on the PK of SYM-1219 granules in study 102 was determined on the same basis. The T_{\max} was presented and compared using descriptive statistics represented by the statistical significance of the Wilcoxon-signed rank test and the 90% CI for the median difference between the treatments.

Results

Study Population Disposition and Characteristics

Of the 25 subjects randomized in study 102, 24 received study medication; 1 randomized subject withdrew from the study before receiving any treatment, and another subject discontinued early (withdrew consent) and was not included in the PK analysis group ($n = 23$). In study 103, a total of 24 subjects were randomized, and all 24 completed the study and were included in the safety analysis. However, the predose concentration value for 1 subject was more than 5% of C_{\max} (7.9%); therefore, the PK values for this subject were excluded from the PK statistical analysis. The demographic and baseline characteristics of the subjects in each study are shown in Table 1.

Pharmacokinetic Parameters

Study 102. In study 102, similar secnidazole plasma concentrations were evident for SYM-1219

Table 1. Demographics and Baseline Characteristics of Study Population^{a,b}

	Study 102 (n = 24)	Study 103 (n = 24)
Age (y)		
Mean (SD)	36 (1.8)	40 (11.6)
Median (min, max)	33 (22, 61)	37.0 (18, 65)
Childbearing potential, n (%)		
Yes	17 (70.8)	10 (41.7)
No	7 (29.2)	14 (58.3)
Ethnicity, n (%)		
Hispanic or Latino	6 (25.0)	20 (83.3)
Not Hispanic or Latino	18 (75.0)	4 (16.7)
Race, n (%)		
American Indian or Alaskan native	1 (4.2)	0
Asian	0	1 (4)
Black	9 (37.5)	1 (4)
Native Hawaiian or other Pacific Islander	0	0
White	14 (58.3)	22 (91.7)
Weight, kg		
Mean (SD)	64.2 (10.4)	66.4 (8.2)
Median (min, max)	62.6 (44.5, 91.0)	67.5 (45.4, 80.8)
Height, cm		
Mean (SD)	163.1 (7.6)	160.2 (5.3)
Median (min, max)	162.6 (44.5, 91.0)	160.0 (150, 169)
BMI (kg/m ²)		
Mean (SD)	24 (2.9)	25.9 (3.2)
Median (min, max)	24 (19, 30)	26.4 (18.3, 32.0)

BMI, body mass index; max, maximum; min, minimum.

^aSafety population in study 102; safety and pharmacokinetic population in study 103.

^bSubjects may appear in more than 1 category.

when administered under fed or fasting conditions (Figure 1). Although measurable predose concentrations were observed in 3 subjects (1 during treatment A and 2 during treatment B), these concentrations were low ($\leq 0.25 \mu\text{g/mL}$) and did not impact the PK analysis. Median T_{\max} was 4 hours for SYM-1219 under fasted conditions but was significantly longer (6 hours) for the SYM-1219 fed group ($P < .001$), showing an effect of food on this parameter. However, mean \pm SD $t_{1/2}$ was similar for the SYM-1219 fasted (17.53 ± 2.8 hours) and fed (16.9 ± 2.5 hours) treatments.

Mean/geometric mean values for C_{\max} , AUC_{0-t} , and AUC_{0-inf} for both treatments in study 102, as well as the results of the statistical evaluations that compare their bioequivalence, are presented in Table 2. As shown, low intersubject variability was observed for C_{\max} , AUC_{0-t} , and AUC_{0-inf} , with CV below 23.5% for all treatment

Table 2. Secnidazole Plasma PK Parameters of Bioequivalence and Comparison (n = 23): Study 102

Treatment	Mean (%CV)	Geometric LS Mean (SE) ^a	Comparison	% Ratio: 100/Test/Reference	
				Geometric LS Mean % Ratio (SE) ^a	90%CI ^a
C_{max} (μg/mL)					
SYM-1219 Fasted (A)	41.21 (13.32)	40.91 (1.121)	Test (B)/Reference (A)	97.36 (1.905)	94.21–100.62
SYM-1219 Fed (B)	40.13 (12.14)	39.83 (1.092)			
AUC_{0-t} (μg·h/mL)					
SYM-1219 Fasted (A)	1224.06 (17.74)	1211.14 (42.253)	Test (B)/Reference (A)	98.10 (2.617)	93.79–102.60
SYM-1219 Fed (B)	1214.36 (22.45)	1188.09 (41.448)			
AUC_{0-inf} (μg·h/mL)					
SYM-1219 Fasted (A)	1261.47 (18.75)	1246.95 (45.789)	Test (B)/Reference (A)	97.77 (2.659)	93.40–102.35
SYM-1219 Fed (B)	1248.15 (23.36)	1219.16 (44.769)			

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last measurable concentration; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; LS, least squares; PK, pharmacokinetic; SE, standard error.

^aFrom an analysis of variance model for the log-transformed results with fixed effects of treatment, sequence, period, and random effect of subject within sequence.

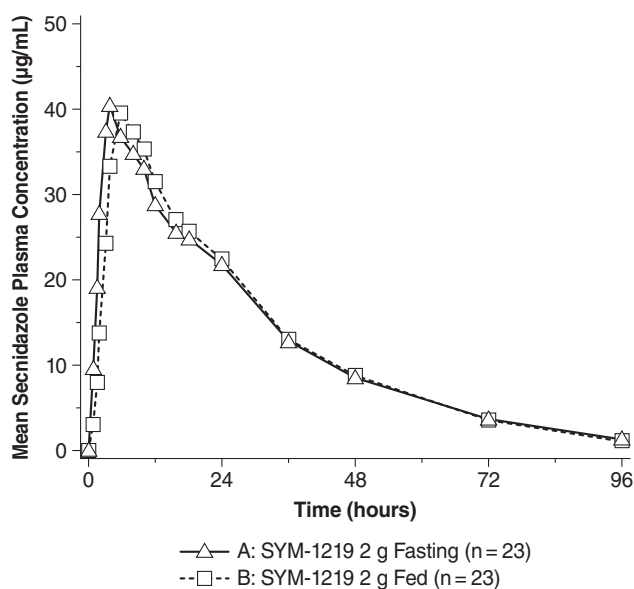


Figure 1. Arithmetic mean secnidazole plasma concentration-time profiles by SYM-1219 treatment group: fasting vs fed; linear scale. Study 102 pharmacokinetic population.

groups. In addition, the 90% CIs for C_{max}, AUC_{0-t}, and AUC_{0-inf} for each treatment comparison were all within the 80% to 125% equivalence limits, thus demonstrating bioequivalence between the treatments.

Study 103. In Study 103, secnidazole plasma concentrations following 1 dose of SYM-1219 in (granules sprinkled over) pudding (treatment A), yogurt (treatment B), and applesauce (treatment C, reference) increased gradually and peaked at 4 hours postdose for all treatments in the PK analysis population (n = 23).

The secnidazole plasma concentrations were measurable in all subjects by 0.5 hour postdose and were still measurable in all subjects at 96 hours postdose with all treatments. Mean secnidazole plasma concentration-time profiles for treatments A, B, and C overlapped through most of the sampling interval, indicating similar total exposure to secnidazole following SYM-1219 administration in pudding, yogurt, and applesauce, respectively (Figure 2).

A summary of the secnidazole plasma PK parameters following treatments A, B, and C is presented in Table 3. Overall, the PK profiles of all treatments were well characterized. The mean t_{1/2} was <20% of the sampling interval following all treatments, with values ranging from 17.6 hours to 18.5 hours across treatments. Both extent of secnidazole exposure, as assessed with geometric mean AUC_{0-t} and AUC_{0-inf}, and peak exposure, as measured by geometric mean C_{max}, were similar following all treatments. The median T_{max} was 4 hours in all treatments with low variability observed among subjects.

The statistical comparisons of the 2 test treatments of SYM-1219, in pudding (treatment A) and in yogurt (treatment B), vs the reference treatment in applesauce (treatment C) are shown in Table 4. Extent of exposure to secnidazole, as measured by the geometric LS means of AUC_{0-t} and AUC_{0-inf}, and peak exposure, as assessed with the geometric LS mean of C_{max}, were similar between treatments A (pudding), B (yogurt), and C (applesauce), with a maximum of 4% difference in geometric LS means. The 90% CIs around the GMRs derived from the analysis of the ln-transformed parameters, ie, AUC_{0-t}, AUC_{0-inf}, and C_{max}, were all

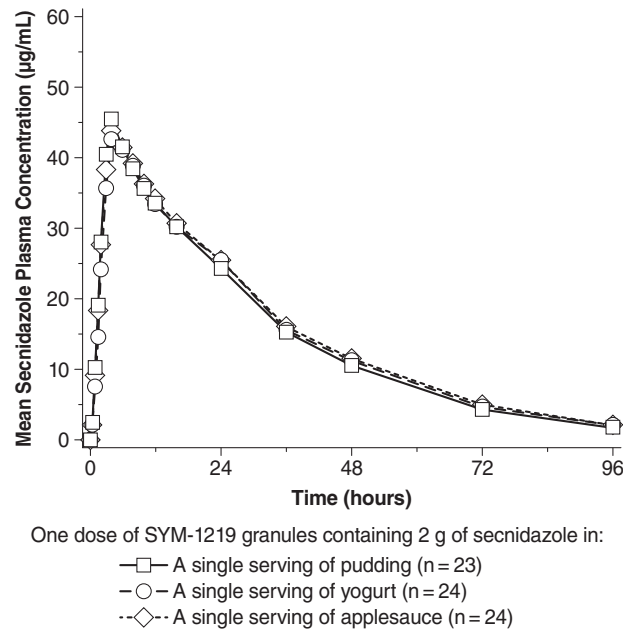


Figure 2. Arithmetic mean secnidazole plasma concentration-time profiles following administration of SYM-1219 in pudding (treatment A, test), yogurt (treatment B, test), and applesauce (treatment C, reference); linear scale. Study 103 pharmacokinetic population, n = 23.

completely within the 80% to 125% CI, thus demonstrating bioequivalence between the treatments.

Safety Assessments

All 24 subjects randomized to treatment in each of studies 102 and 103 received at least 1 dose of study

medication (all 24 subjects in study 103 received all 3 treatments) and were included in the safety analyses. The total number (%) of subjects reporting TEAEs were 17 (70.8%) in study 102 and 20 (83%) in study 103. Overall, the majority of patients with TEAEs had experienced a (possibly or probably) treatment-related AE in both study 102 (n = 16; 66.7%) and study 103 (n = 19; 79.2%). No severe TEAEs, SAEs, or TEAEs leading to discontinuation occurred in either study 102 or 103. No deaths occurred in either study. Summaries of TEAE incidence and the most common types of TEAEs in both studies are presented by treatment in Table 5.

Headache was the most common AE reported in both study 102 (41.7%) and study 103 (50.0%) (Table 5). In study 103, headache incidence was particularly high for the reference treatment C (applesauce, 33.3%). Although somnolence was also common in study 103 (33.3%), this TEAE was reported by only 1 subject in study 102 (4.2%). Gastrointestinal system TEAEs were particularly common in both studies (37.5% of subjects in study 102, 54.2% of subjects in study 103), including nausea, which occurred in 12.5% of subjects in study 102 and 16.7% in study 103. However, incidence of other types of gastrointestinal AEs varied markedly between the studies. Dysgeusia was reported by 20.8% of subjects in study 102 but none in study 103, and constipation was reported by 41.7% of subjects in study 103 but not reported in study 102. The incidence of constipation in study 103 was particularly high for treatment B (yogurt, 25.0%) vs treatments A (pudding, 8.3%) and C (applesauce, 16.7%). No clinically significant changes

Table 3. Summary of Secnidazole Plasma PK Parameters Following Administration of SYM-1219 in Pudding (Treatment A, Test), Yogurt (Treatment B, Test), and Applesauce (Treatment C, Reference): Study 103, PK Population, n = 24

PK Parameters	Treatment A (Pudding; n = 23)	Treatment B (Yogurt; n = 24)	Treatment C (Applesauce; n = 24)
AUC_{0-t} (µg·h/mL)			
Arithmetic mean (SD)	1396 (284.1)	1420 (285.0)	1456 (310.6)
Geometric mean (%CV)	1370 (19.6)	1390 (19.9)	1430 (20.8)
AUC_{0-inf} (µg·h/mL)			
Arithmetic mean (SD)	1447 (331.0)	1478 (335.0)	1523 (372.2)
Geometric mean (%CV)	1410 (21.9)	1410 (21.9)	1480 (23.6)
C_{max} (µg/mL)^a	45.4 (10.8)	43.1 (11.7)	43.9 (10.3)
Arithmetic mean (SD)	45.6 (5.1)	43.4 (5.4)	44.1 (4.6)
Geometric mean (%CV)	45.4 (10.8)	43.1 (11.7)	43.9 (10.3)
T_{max} (h)^a	4.00 (3.99, 6.01)	4.00 (4.00, 8.00)	4.00 (3.02, 6.14)
t_{1/2} (h)^b	17.6 ± 4.41	18.1 ± 4.73	18.5 ± 4.85

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last measurable concentration; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration; t_{1/2}, half-life.

Note: The predose concentration value for 1 subject was more than 5% of C_{max} (7.9%); therefore, the concentrations of this subject were not included in the statistical analysis.

^aPresented as median (minimum, maximum).

^bPresented as mean ± SD.

Table 4. Statistical Comparisons of Secnidazole Plasma PK Parameters Following Administration of SYM-1219 in Pudding (Treatment A–Test) and Yogurt (Treatment B–Test) Versus Applesauce (Treatment C–Reference) (PK Population, n = 23): Study 103

Parameter	Treatment A (Pudding–Test; n = 23)	Treatment C (Applesauce–Reference; n = 24)	GMR, % ^a	90%CI
AUC _{0-t} (μg·h/mL)	1381	1427	96.8	93.51–100.22
AUC _{0-inf} (μg·h/mL)	1428	1483	96.3	92.82–99.92
C _{max} (μg/mL)	45.3	43.9	103.3	100.33–106.24
	Treatment B (Yogurt–Test; n = 24)	Treatment C (Applesauce–Reference; n = 24)	GMR, % ^a	90%CI
AUC _{0-t} (μg·h/mL)	1393	1427	97.7	94.39–101.05
AUC _{0-inf} (μg·h/mL)	1444	1483	97.4	93.90–100.96
C _{max} (μg/mL)	43.1	43.9	98.2	95.50–101.03

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last measurable concentration; AUC_{0-inf}, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; LS, least squares; PK, pharmacokinetic.

Note: Parameters were ln-transformed prior to analysis. Geometric LS means were calculated by exponentiating the LS means from the mixed-effects model.

^a%GMR = 100 × (test/reference).

Table 5. Frequency of TEAEs and Most Common TEAEs: Studies 102 and 103

	Study 102 Treatments A and B			Study 103 Treatments A, B, and C			
	SYM-1219 Fasted (A) (n = 23)	SYM-1219 Fed (B) (n = 23)	Overall (n = 24)	SYM-1219 in Pudding (A) ^a (n = 24)	SYM-1219 in Yogurt (B) ^a (n = 24)	SYM-1219 in Applesauce (C) ^b (n = 24)	Overall (n = 24)
Summary, n (%)							
≥ 1 TEAEs	9 (39.1)	6 (26.1)	17 (70.8)	10 (41.7)	17 (70.8)	14 (58.3)	20 (83.3)
≥ 1 TRAEs	9 (39.1)	5 (21.7)	16 (66.7)	9 (37.5)	15 (62.5)	14 (58.3)	19 (79.2)
≥ 1 Severe TEAEs	0	0	0	0	0	0	0
≥ 1 SAEs	0	0	0	0	0	0	0
≥ 1 TEAEs leading to discontinuation	0	0	0	0	0	0	0
Common TEAEs (≥ 10% subjects overall in either study), n (%)							
Headache	5 (21.7)	0	10 (41.7)	2 (8.3)	5 (20.8)	8 (33.3)	12 (50.0)
Somnolence	0	0	1 (4.2)	4 (16.7)	4 (16.7)	6 (25.0)	8 (33.3)
Dysgeusia	3 (13.0)	1 (4.3)	5 (20.8)	0	0	0	0
Nausea	2 (8.7)	1 (4.3)	3 (12.5)	1 (4.2)	3 (12.5)	2 (8.3)	4 (16.7)
Constipation	0	0	0	2 (8.3)	6 (25.0)	4 (16.7)	10 (41.7)
Abdominal pain	0	0	0	1 (4.2)	1 (4.2)	1 (4.2)	3 (12.5)
Abdominal pain lower	0	0	0	1 (4.2)	1 (4.2)	1 (4.2)	3 (12.5)

AEs, adverse events; SAEs, serious AEs; TEAEs, treatment-emergent AEs; TRAEs, treatment-related AEs.

Note: Subjects who experienced multiple TEAEs of a given type are counted only once for that type. The same subject may appear in different categories. If the same TEAE was reported in each of the 3 treatment periods by the same subject (for each study), the TEAE was reported only once for that subject.

^aTest treatment.

^bReference treatment.

in laboratory, vital sign, and physical examination findings were observed in either study.

Discussion

The 2 phase 1, open-label, crossover-design PK and safety studies reported here together provide data on the bioequivalence and safety of SYM-1219, as assessed under fed and fasted conditions and when administered in 3 different kinds of soft food un-

der fasted conditions, in healthy female volunteers. In general, the PK, safety, and tolerability of SYM-1219 remained consistent across these different test conditions.

In study 102, although T_{max} was extended for SYM-1219 under fed conditions to 6 hours vs 4 hours under fasted conditions, the delay did not affect overall drug exposure and bioequivalence. Intersubject variabilities for the exposure PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}, as expressed with CV, were

less than 23% for both treatment groups, demonstrating consistency of these parameters under both fed and fasted conditions. In addition, the 90% CIs of the GMRs of C_{\max} , AUC_{0-t} , and AUC_{0-inf} were all within the predetermined interval of 80% to 125% that was required to demonstrate bioequivalence for SYM-1219 under fasted and fed conditions. Similarly, in study 103, the statistical comparisons of the test treatments of SYM-1219 administered in (granules sprinkled over) pudding and yogurt, each vs the reference treatment of SYM-1219 administered in (granules sprinkled over) applesauce, yielded 90% CIs for the GMRs of C_{\max} , AUC_{0-t} , and AUC_{0-inf} , all within the 80% to 125% interval, demonstrating bioequivalence.

The PK values obtained in studies 102 and 103 were also consistent across the 2 studies. Both studies reported a mean $t_{1/2}$ of approximately 18 hours, a mean T_{\max} of 4 hours under fasted conditions, mean C_{\max} of 40 to 44 $\mu\text{g/mL}$, and AUC values in the range of 1200 to 1400 $\mu\text{g}\cdot\text{h/mL}$. This similarity of findings across the studies may be related to consistency of the formulation as well as the close similarity of population and methods used in both. However, the PK values observed in studies 102 and 103 are similar to previously reported PK values for different formulations of secnidazole administered orally at 2 g in healthy female volunteers.³²

Overall, the data from these 2 studies indicate a consistency of bioavailability, $t_{1/2}$, and other PK parameters of SYM-1219 across food and fasting states and administration in different foods. Three single SYM-1219 doses administered in a crossover design were also well tolerated in both studies under the different treatment conditions assessed. The most common TEAEs in both studies were headache and gastrointestinal problems, all of which were mild to moderate in severity, with no SAEs or TEAEs leading to discontinuation in either study.

These data suggest several practical advantages for clinical use of SYM-1219. The $t_{1/2}$ of approximately 17 hours demonstrated in these studies across the different test conditions is of particular note because, combined with the demonstrated efficacy of SYM-1219 in phase 2 and 3 clinical trials,^{29,30} it suggests that this formulation provides the potential of a patient-friendly, 1-dose antimicrobial treatment regimen for BV. Multiple studies have reported statistically significant, inverse correlations between patient adherence to medication and frequency of dosing.³³⁻³⁵ SYM-1219 formulation characteristics optimized for patient flexibility are further demonstrated by the bioequivalence of SYM-1219 in yogurt, pudding, and applesauce, suggesting that patients can take it without regard to food and without risk of dose dumping (rapid drug release in a short period of time), which may occur with some

formulations.³⁶ The T_{\max} values, which were slightly extended to 6 hours in fed dosing vs 4 hours for fasted administration, suggest a small food effect on absorption time. The shift in T_{\max} is likely a result of a slight delay in gastric emptying following ingestion of a meal with high fat content and not a clinically relevant drug-food interaction.³⁷ In addition, the slight change in the absorption time does not impact bioequivalence because SYM-1219 demonstrated consistency in exposure across the different test dosing conditions in both trials, indicating reliable drug delivery that was also well tolerated as indicated by the safety results.

These consistent PK data also confirm that the subjects received the correct doses of drug via the process of emptying the packets of granules and sprinkling the granules on the foods provided for consumption, as instructed on the packets. Although study doses were prepared by clinical research personnel, it may be expected that when self-administered by patients, following the administration instructions will achieve similar correct doses. It is worth noting in this context that difficulties with swallowing pills may represent an underrecognized problem. Studies in the United States, the United Kingdom, and Germany have consistently reported that approximately 40% to 60% of people surveyed had trouble swallowing pills, often resulting in the opening of capsules or crushing tablets to facilitate swallowing, which may potentially reduce the administered dose.³⁸⁻⁴⁰ In particular, a nationwide survey of adults in the United States ($n = 679$; 513 aged 18 to 64 years, 166 aged ≥ 65 years), conducted by Harris Interactive®, found that 40% of respondents overall and 51% of women (27% of men) had trouble swallowing medications in pill form.³⁸ Of the respondents with difficulty swallowing pills, 14% reported having delayed taking doses of medication, 8% having skipped doses, and 4% having discontinued taking their medication.³⁸ Therefore, given that half of US women may have trouble taking pills, the flexibility of taking medication as granules with food rather than in pill form offered by SYM-1219 may be of considerable benefit for patients and clinicians. The consistency of SYM-1219 PK parameters across the varied foods tested further suggests that its administration with soft foods other than the ones used in this study would similarly have no effect on drug metabolism, exposure, and elimination.

In conclusion, the PK of SYM-1219 granules containing 2 g of secnidazole in healthy female volunteers were bioequivalent when administered under a range of conditions, including fasted and fed, and in either pudding or yogurt vs applesauce. SYM-1219 administered under different conditions in each of these crossover studies was well tolerated, with no occurrence of severe TEAEs, SAEs, or TEAEs leading to discontinuation.

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Declaration of Conflicting Interests

Helen S. Pentikis is a consultant and equity holder of Symbiomix Therapeutics, LLC. Nikki Adetoro is an employee and equity holder of Symbiomix Therapeutics, LLC.

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