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A Phase 1, Open-Label, Single-Dose, Randomized, 3-Way Crossover Study to Assess the Pharmacokinetics and Safety of SYM-1219 Containing 2 g of Secnidazole Administered Orally as Granules in Pudding, Yogurt, or Applesauce to Healthy Female Volunteers

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PURPOSE

Background: Symbiomix Therapeutics, LLC (Symbiomix) is developing SYM-1219 containing secnidazole, a new chemical entity in the US, as an oral, antimicrobial drug in the 5-nitroimidazole class. SYM-1219 is intended to be used to treat women with BV. SYM-1219 has the potential to lead to improved clinical outcomes and provide a potentially more effective treatment alternative. SYM-1219's *in vitro* antimicrobial spectrum and potency provide coverage of most of the bacterial species implicated in BV. Several published clinical studies demonstrate clinical and/or microbiologic evidence of activity of secnidazole in the treatment of BV (Gillis & Wiseman 1996). Finally, the SYM-1219 single-dose regimen will allow for the entire treatment course to be completed with the first and only drug dose. This "one and done" dosing strategy offers improved patient adherence and holds the promise of improved patient outcomes with a lower incidence of undertreated BV infections, given that the entire treatment regimen is completed with just 1 dose. This dosing regimen is in distinct contrast to the currently used treatment regimens requiring extended dosing that is known to impact patient adherence (Bartley et al 2004, Cockburn et al 1987).

Purpose: The present study was designed to assess the bioequivalence between SYM-1219 granules containing 2 g of secnidazole administered under fasting conditions in 3 different foods: pudding, yogurt or applesauce. Analysis of plasma concentrations characterized the single-dose pharmacokinetics of secnidazole from the SYM-1219 formulation. Secnidazole bioequivalence was based on the criteria of area under the plasma concentration-time curve (AUC) and C_{max} to determine the extent and rate of drug absorption, respectively. If bioequivalence is demonstrated for the 2 comparisons of interest (pudding versus applesauce and yogurt versus applesauce), then patients would be able to choose between these 3 foods based on personal preference for administration of SYM-1219 granules.

Methods: This was an open-label, randomized, 3-way crossover study of SYM-1219 granules, containing 2 g of secnidazole, conducted in healthy female volunteers (N=24). Following an overnight fast, SYM-1219 was administered in pudding, yogurt or applesauce. Subjects underwent screening procedures up to 30 days before the initial dose of study drug; eligible subjects were then randomized to receive treatment according to a pre-specified randomization scheme: SYM-1219 granules containing 2 g of secnidazole in pudding (test treatment), yogurt (test treatment), or applesauce (reference treatment) followed by 240 mL of water. Subjects were kept in the clinical research unit from Day-1 through Day 5 of each study period for assessments and observation. On Day 1 of each study period, after fasting overnight for at least 10 hours, subjects received the assigned treatment. No additional food was allowed for 4 hours after study drug administration. There was a washout period of at least 7 days prior to the start of the next study period for all subjects. Serial blood samples were collected over 96 hours to determine secnidazole plasma concentrations. A noncompartmental analysis was performed and the PK parameters for each treatment group are reported. Bioequivalence was determined based on the 90% confidence interval criteria for Cmax, AUClast, and AUCinf. Safety assessments and vital signs (seated blood pressure and heart rate) were performed at specified time points during each treatment period and at the conclusion of the study.

Results: All 24 subjects enrolled completed the study. The PK data for secnidazole following single-dose administration of SYM-1219 granules was similar for all 3 treatments and statistical analyses demonstrated bioequivalence between SYM-1219 granules in pudding or yogurt and SYM-1219 granules in applesauce. A summary of the PK parameters by treatment and 90% confidence intervals is presented in Table 1. There were no deaths, serious adverse events (SAEs), or subject discontinuations due to AEs in this study, and a majority of adverse events were mild in severity. Overall, a total of 86 treatment emergent AEs (TEAEs) were experienced by 20/24 subjects (83%) in this study (10/24 subjects after receiving pudding, 17/24 subjects after receiving yogurt, and 14/24 subjects after receiving applesauce). The TEAEs reported by >10% of subjects overall were headache, constipation, somnolence, nausea, abdominal pain, and lower abdominal pain. There were no clinically significant abnormalities in clinical laboratory, vital sign, electrocardiogram, or physical examination findings.

METHODS

This was an open-label, randomized, 3-way crossover study of SYM-1219 (containing 2 g of secnidazole) administered as granules in pudding, yogurt, or applesauce to healthy female subjects. A total of 24 female subjects were enrolled to ensure that 18 subjects completed the study.

Subjects underwent screening procedures to determine eligibility up to 30 days before the initial dose of study drug. Subjects determined to be eligible for the study were enrolled and randomly assigned to receive 3 treatments in a crossover fashion according to the randomization schedule. Subjects were admitted to the clinical research unit on Day –1 of each period and remained confined in the clinical research unit until PK sampling and all assessments were completed on Day 5 of each period.

On Day 1 of each period, subjects received 1 of 3 treatments according to the randomization scheme. Subjects fasted overnight for at least 10 hours, before receiving the study drug SYM-1219 granules containing 2 g of secnidazole in 1 of the 3 foods (pudding, yogurt, or applesauce) followed by 240 mL of water. No additional food was allowed for 4 hours after study drug administration.

Water was allowed in all treatment groups as desired for up to 2 hours predose but restricted until 2 hours postdose, except for that consumed in conjunction with the dose.

All subjects received a single oral dose of SYM-1219 granules containing 2 g of secnidazole in each treatment period in 1 of the 3 foods consumed within 5 minutes from the time of mixing of the granules into the food, followed by 240 mL of water. Subjects received all 3 treatments administered in a crossover fashion per the randomization schedule

Three (3) doses of SYM-1219 were administered as follows:

- Treatment A: One (1) dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of chocolate pudding (approximately 4 oz.)
- Treatment B: One (1) dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of low-fat, vanilla yogurt (approximately 6 oz.)
- Treatment C: One (1) dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of unsweetened applesauce (approximately 4 oz.)

During each treatment period, serial blood samples were collected over 96 hours for the determination of secnidazole plasma concentrations following administration of SYM-1219. There was a minimum of a 7-day washout period between each dose of SYM-1219.

Noncompartmental PK parameters, C_{max}, t_{max}, AUC_{0-t}, AUC_{inf}, and $T_{1/2}$, were calculated from the plasma secnidazole concentration-time data using Phoenix® WinNonlin® Version 6.3.

Safety assessments were performed at specified time points during each treatment period and at the conclusion of the study. Vital signs (seated blood pressure and heart rate) were obtained in each period.

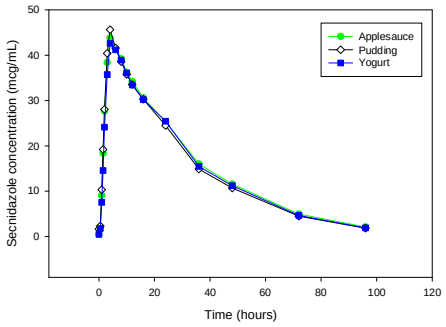
Actual sample times were used in the calculations. For the calculation of the PK parameters, plasma concentrations below the limit of quantitation (BLQ) prior to the first quantifiable concentration were set to 0.00 and plasma concentrations BLQ after the first quantifiable concentration were treated as missing.

RESULTS

The PK data for secnidazole following single-dose administration of SYM-1219 granules in either pudding or yogurt was comparable to that of SYM-1219 granules administered in applesauce. The statistical analysis demonstrated bioequivalence between SYM-1219 granules in pudding or yogurt and SYM-1219 granules in applesauce. The 90% confidence intervals for secnidazole AUC_{0-inf}, AUC_{0-t}, and C_{max} were contained within the 80.00 - 125.00% bioequivalence limits.

There were no deaths, SAEs, or subject discontinuations due to AEs in this study. Overall, the majority of TEAEs were mild in severity and considered possibly drug related by the PI. There were no clinically significant abnormalities in clinical laboratory, vital sign, ECG, or physical examination findings.

Figure 1: Mean Plasma Secnidazole Concentration-Time Profiles Following Administration in Pudding, Yogurt, and Applesauce



CONCLUSIONS

The pharmacokinetics of secnidazole following oral administration of SYM-1219 granules in pudding or yogurt are bioequivalent to that of SYM-1219 granules administered in applesauce.

Based on the results of this study, SYM-1219 granules containing 2 g of secnidazole can be administered in either pudding, yogurt, or applesauce.

A single oral dose of SYM-1219 granules containing 2 g of secnidazole administered in pudding, yogurt, or applesauce was safe and generally well tolerated in healthy female volunteers.

Table 1: Summary of Plasma Secnidazole Pharmacokinetic Parameters Following Treatment A - Pudding (Test), Treatment B – Yogurt and Treatment C - Applesauce (Reference)

Pharmacokinetic Parameters	Treatment A (Pudding) (N=23)	Treatment B (Yogurt) (N=24)	Treatment C (Applesauce) (N=24)
AUC_{0-t} (mcg*hr/mL)[a]	1370 (19.6)	1390 (19.9)	1430 (20.8)
AUC_{inf} (mcg*hr/mL)[a]	1410 (21.9)	1440 (22.2)	1480 (23.6)
C_{max} (mcg/mL)[a]	45.4 (10.8)	43.1 (11.7)	43.9 (10.3)
t_{max} (hr)[c]	4.00 (3.99, 6.01)	4.00 (4.00, 8.00)	4.00 (3.02, 6.14)
$T_{1/2}$ (hr)[b]	17.6 ± 4.41	18.1 ± 4.73	18.5 ± 4.85

Treatment A = One dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of pudding (test)
Treatment B = One dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of yogurt (test)
Treatment C = One dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of applesauce (reference)

[a] Presented as geom. mean (geom. CV%)
[b] Presented as mean ± SD
[c] Presented as median (minimum, maximum)

Table 2: Summary of Statistical Comparisons of Plasma Secnidazole Pharmacokinetic Parameters Following SYM-1219 Administration in Pudding and Yogurt Relative to Applesauce

Parameters	Treatment A vs Treatment C GMR (%) and 90% CI	Treatment A vs Treatment C GMR (%) and 90% CI
AUC_{0-t} (mcg*hr/mL)	96.80 (93.51 - 100.22)	97.66 (94.39 - 101.05)
AUC_{inf} (mcg*hr/mL)	96.31 (92.82 - 99.92)	97.37 (93.90 - 100.96)
C_{max} (mcg/mL)	103.25 (100.33 - 106.24)	98.22 (95.50 - 101.03)

Treatment A = One dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of pudding (test)
Treatment B = One dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of yogurt (test)
Treatment C = One dose of SYM-1219 granules containing 2 g of secnidazole in a single serving of applesauce (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares (LS) means were calculated by exponentiating the LS means from the mixed-effects model
% Geometric mean ratio (GMR) = 100 × (test/reference)

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