A PHASE 1 STUDY TO DETERMINE THE EFFECT OF FOOD ON THE PHARMACOKINETICS OF A SINGLE DOSE OF SYM-1219 (SECNIDAZOLE) IN HEALTHY FEMALE VOLUNTEERS

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INTRODUCTION

Background: This study evaluated the safety and pharmacokinetics (PK) of SYM-1219, a granule formulation containing 2 g of secnidazole, administered to healthy females under fed (commercial formulation) and fasted conditions (commercial and development formulation). The SYM-1219 2 g oral formulation of secnidazole, a 5-nitroimidazole, is being developed for the treatment of women with bacterial vaginosis (BV). The food effect comparison data for the commercial formulation are presented.

Methods: 24 healthy females ages 18-65 years were randomized to receive SYM-1219 under fasted conditions (reference) or with a high fat meal (test), mixed into 4 oz of applesauce. Serial blood samples were collected over 96 hours to determine secnidazole plasma concentrations. A noncompartmental analysis was performed and the resulting PK parameters were evaluated for bioequivalence by using a 90% confidence interval (CI) approach. Safety was evaluated by recording adverse events, vital signs, physical exams, ECGs and laboratory tests.

Results: 23 of the 24 randomized subjects completed the study and were evaluable for PK. The PK of secnidazole from the SYM-1219 formulation was not affected by concomitant food administration. Mean maximum concentrations (C_{max}) were 41.2 mcg/mL for the fasted treatment and 40.1 mcg/mL for the fed treatment. Exposure estimates (AUC_{inf}) were 1261.5 mcg*hr/mL for the fasted treatment and 1248.2 mcg*hr/mL for the fed treatment. A slight delay in secnidazole T_{max} was evident when SYM-1219 was administered with food (4 hrs fasted or 6 hrs fed). The 90% CI for the fed:fasted comparison were 89.7-95.7% for C_{max}, 87.7-95.9% for AUC_{last}, and 86.8-95.1% for AUC_{inf} and demonstrate bioequivalence of the fed and fasted treatments.

SYM-1219 was safe and well-tolerated in all 24 subjects. Common adverse events were headache and nausea. There were no clinically significant changes in vital signs, ECG or laboratory parameters.

Conclusions: The concomitant administration of SYM-1219 with a high fat meal does not impact the bioavailability of secnidazole from the formulation. The 90% CI for C_{max}, AUC_{last}, and AUC_{inf} are contained within the 80% to 125% intervals for bioequivalence. Based on these data, SYM-1219 can be dosed without regard to food.

OBJECTIVES

- To compare the pharmacokinetics of SYM-1219 granules containing 2 g of secnidazole administered in applesauce under fed and fasted conditions in healthy female volunteers
- To evaluate the safety of single doses of SYM-1219 granules containing 2 g of secnidazole administered in applesauce in healthy female volunteers

METHODS

This was an open-label, randomized study that evaluated the pharmacokinetics (PK) and safety of single doses of SYM-1219 containing 2 g of secnidazole administered fasted or with a high fat meal in 24 healthy female subjects between the ages of 18 and 65 years, inclusive. After eligibility was determined, subjects were randomized to receive single doses of SYM-1219 containing 2 g of secnidazole under fasted conditions or with a high fat meal in a crossover design. SYM-1219 was administered sprinkled over approximately 4 oz of applesauce. The SYM-1219 dose was administered after a 10-hour overnight fast. Subjects in the fed treatment received SYM-1219 after consuming a high fat meal consisting of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash browns, 8 ounces of whole milk; this meal contained approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories.

Serial blood samples were obtained for determination of SYM-1219 plasma concentrations to 96 hours post-dose. Safety assessments included ECGs, vital signs, and standard laboratory assessments.

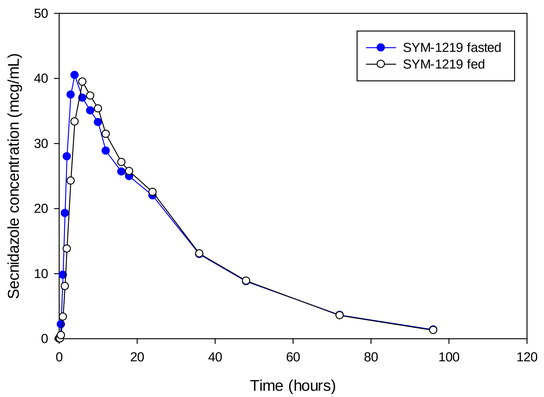
RESULTS

A total of 23 healthy adult female subjects received both the fed and fasted treatments in this study. The mean plasma concentration-time plot (Figure 1) shows secnidazole plasma levels for both treatments increased and reached the highest concentration at approximately 4 hours after administration of SYM-1219.

The PK of secnidazole following administration of SYM-1219 was comparable for both treatments and is consistent with previously reported exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole C_{max}, and AUC exhibited low intersubject variability as the %CV estimates were less than 23% for all treatment groups, demonstrating the reproducible performance of the formulation under both fasted and fed conditions. The time to maximum plasma concentrations, T_{max}, was approximately 4 hours for the fasted treatment. A slight delay in T_{max} was evident, however, for the fed treatment; the median value was 6.00 hours under fed conditions. This slight delay in T_{max} following administration of SYM-1219 under fed conditions did not have an impact on the overall bioavailability of secnidazole for this treatment group. The mean secnidazole half-life ranged from 16.9 to 17.5 hours across all treatment groups and is consistent with previously reported estimates.

The 90% confidence interval statistical evaluation of the fed and fasted treatments demonstrated bioequivalence for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The administration of SYM-1219 with a high fat meal did not have an impact on the pharmacokinetics of secnidazole, indicating that SYM-1219 can be administered without regard to meals.

Figure 1: Mean Secnidazole Plasma Levels by SYM-1219 Treatment



SAFETY

Overall, the SYM-1219 granules containing 2 g of secnidazole were well tolerated in both treatment groups. No subjects reported SAEs or discontinued prematurely from the study due to treatment-emergent adverse events. Most observed adverse events were mild and resolved. No clinically significant changes were observed in vital signs, or laboratory parameters. Not unexpectedly, a higher incidence of headaches was observed in the fasted group (5 of 24 subjects; 21.7%) compared to the fed group (0%). A small increase in heart rate at most post-dose time points was likely due to changes in posture, increased activity and circadian variation rather than being a direct effect of secnidazole. Mean changes in QTcF were negative (ΔQTcF<0) at most post-dose time points. The categorical analysis of QTcF similarly led to the conclusion that secnidazole likely had no pharmacologic effect on QTcF. Finally, the statistical analysis of the frequent ECG sampling and triplicate ECG recordings showed no clinically relevant findings on any ECG intervals.

Table 1: Plasma Pharmacokinetics of Secnidazole After a Single Oral Dose of SYM-1219 Administered to Healthy Female Subjects

Parameter	Statistic	SYM-1219 2 g Fasted (N=23)	SYM-1219 2 g Fed (N=23)
Cmax (mcg/mL)	Mean (%CV)	41.21 (13.32)	40.13 (12.14)
T_{max} (h)	Median	4.0	6.0
	Min, Max	3.0,6.0	4.0,8.0
AUC_{0-t} (h*mcg/mL)	Mean (%CV)	1224.06 (17.74)	1214.36 (22.45)
AUC_{inf} (h*mcg/mL)	Mean (%CV)	1261.47 (18.75)	1248.15 (23.36)
$t_{1/2}$ (h)	Median	17.53	16.92
	Min, Max	12.6, 24.6	12.6,21.6

CONCLUSIONS

The SYM-1219 fasted and fed comparisons for C_{max}, AUC_{0-t}, and AUC_{inf} demonstrated that the administration of SYM-1219 with a high fat meal did not have an impact on the pharmacokinetics of secnidazole and indicated that SYM-1219 can be administered without regard to meals.

Overall, SYM-1219 was well tolerated. Most adverse events were considered mild and no subjects reported SAEs or discontinued prematurely due to adverse events

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