A PHASE 1 STUDY TO DETERMINE THE SINGLE DOSE, SAFETY AND PHARMACOKINETICS OF SYM-1219 (SECNIDAZOLE) IN HEALTHY FEMALE VOLUNTEERS

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ABSTRACT

Background: This study evaluated the safety and pharmacokinetics (PK) of a 1 or 2 gram doses of a new granule formulation for SYM-1219, a 5-nitroimidazole being developed for the treatment of women with bacterial vaginosis (BV).

Methods: 28 healthy female subjects (14/group) ages 18-65 years were randomized to receive a single oral dose of either 1 or 2 grams of SYM-1219, mixed into approximately 4 oz. of applesauce. Serial blood samples were collected over 168 hours to determine SYM-1219 plasma concentrations. A noncompartmental analysis was performed and the PK parameters for each treatment group are reported. Safety was evaluated by recording adverse events, vital signs, triplicate ECGs and standard laboratory tests.

Results: All subjects (N=28) completed the study and were evaluable for PK and safety. The PK of SYM-1219 was consistent between individuals, as demonstrated by low %CV estimates. Mean maximum concentrations were 22.6 mcg/mL for the 1 g dose and 45.4 mcg/mL for the 2 g dose and were achieved by approximately 4 hrs in both dose groups. Exposure estimates (AUC_{inf}) were 619 mcg*hr/mL for the 1 g dose and 1331 mcg*hr/mL for the 2 g dose. SYM-1219 was dose proportional when comparing the 1 and 2 g doses.

SYM-1219 was safe and well-tolerated. The most common adverse events were headache and nausea. All adverse events were mild and resolved without sequelae. There were no significant changes in vital signs, ECG or laboratory parameters.

Conclusions: This study characterized the single dose PK and safety of a 1 g and 2 g dose of a new granule formulation of secnidazole, SYM-1219. SYM-1219 was safe and well-tolerated. The consistent PK and resulting exposures, with low variability between subjects, makes this a promising new therapeutic option. Ongoing studies will further evaluate the safety and efficacy of SYM-1219 for the treatment of women with BV.

OBJECTIVES

The objectives of this study were to determine the PK and safety of SYM-1219 granules (1 g and 2 g) sprinkled over 4 ounces of applesauce.

METHODS

This was an open-label, randomized study that evaluated the pharmacokinetics (PK) and safety of single 1 or 2 gram doses of SYM-1219 in 28 healthy female subjects between the ages of 18 and 65 years, inclusive. After eligibility was determined, subjects were randomized in a 1:1 ratio to receive single doses of either 1 g or 2 g of SYM-1219. SYM-1219 was administered sprinkled over approximately 4 oz. of applesauce. The SYM-1219 dose was administered to subjects in both groups after a 10-hour overnight fast. Serial blood samples were obtained for determination of SYM-1219 plasma concentrations to 168 hours post-dose. Urine samples were collected at pre-dose and over 6 to 12-hour intervals to 168 hours post-dose. Safety assessments included ECGs, vital signs, and standard laboratory assessments.

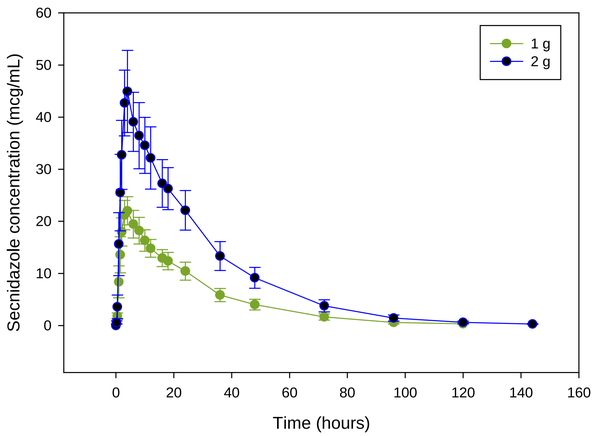
RESULTS

A total of 28 healthy adult female subjects were treated in this study; 14 subjects were treated with a single dose of SYM-1219 1 g and 14 subjects were treated with a single dose of SYM-1219 2 g. The mean plasma concentration-time plot (Figure 1) shows secnidazole plasma levels for both the 1 g and 2 g doses increased and reached the highest concentration at approximately 4 hours after administration of SYM-1219. After 4 hours, the mean concentrations declined and were, on average, no longer measurable (<0.200 µg/mL) at 120 hours for the 1 g dose and 144 hours for the 2 g dose. The mean plasma concentrations for the 2 g dose group were approximately double the mean plasma concentrations for the 1 g dose.

Descriptive statistics for C_{max}, T_{max}, AUC_{0-t}, AUC_{inf}, $t_{½}$, and λz values are presented in Table 1. The dose related parameters (C_{max}, AUC_{0-t}, AUC_{inf}) appeared to exhibit dose proportionality between the two doses. Doubling the dose from 1 g to 2 g resulted in a 2.01-fold increase in C_{max} (22.62 and 45.43mg/mL for the 1 g and 2 g dose, respectively), a 2.17-fold increase in AUC_{0-t} (609.66 and 1322.40 h*mg/mL for the 1 g and 2 g dose, respectively), and a 2.15-fold increase in AUC_{inf} (618.89 and 1331.63 h*mg/mL, for the 1 g and 2 g dose, respectively). C_{max}, AUC_{0-t}, AUC_{inf} all exhibited low intersubject variability with %CVs all below 20% for both the 1 g and 2 g doses. The median time to maximum plasma concentration, T_{max}, was slightly longer (4.00 h vs 3.06 h) for the 2 g dose group as compared to the 1 g dose group. The mean half-lives were similar for both doses, 17.05 h for 1 g dose group and 16.86 h for 2 g dose group.

Over the 168 hour collection period, the %FE values were similar between doses with 13.6% and 15.3% of secnidazole excreted unchanged into the urine for the 1 g and 2 g doses, respectively.

Figure 1: Mean (+SD) Secnidazole Plasma Levels by SYM-1219 Treatment Group



SAFETY

All treatment-emergent adverse events (TEAEs) were mild in intensity and no serious adverse events (SAEs) or deaths were reported.

There were no relevant differences in the reported AEs between the 1 and 2 gram dose group, in particular, no clinically meaningful findings were noted in the physical examinations, vital signs, triplicate ECGs, or clinical laboratory tests in any of the study subjects.

Overall, a total of 15 subjects (53.6%) reported 40 TEAEs. Of these, most TEAEs (33 of 40) were considered treatment related by the investigator. the most frequently reported treatment-related AEs included headache (8 of 28 subjects; 28.6%), nausea (4 of 28 subjects; 14.3%), and abdominal pain upper (3 of 28 subjects; 10.7%). All treatment-related AEs were considered mild by the investigator [two mild adverse events (headache and vaginal discharge/itching) required concomitant medication].

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

Parameter	Statistic	SYM-1219 1 g (N=14)	SYM-1219 2 g (N=14)
Cmax (mcg/mL)	Mean (%CV)	22.62 (12.7)	45.43 (16.8)
T_{max} (h)	Median	3.06	4
	Min, Max	2.00, 6.00	3.00, 4.05
AUC_{0-t} (h*mcg/mL)	Mean (%CV)	609.66 (15.9)	1322.40 (17.4)
AUC_{inf} (h*mcg/mL)	Mean (%CV)	618.89 (15.9)	1331.63 (17.3)
$t_{1/2}$ (h)	Median	16.79	17.13
	Min, Max	14.7, 20.4	11.3, 20.4
%FE	Mean (%CV)	13.6 (17.5)	15.3 (23.2)

CONCLUSIONS

The pharmacokinetics of secnidazole following administration of SYM-1219 was dose proportional when the 1 g and 2 g doses were compared.
The PK parameters for secnidazole exhibited low intersubject variability demonstrating the reproducible performance of the SYM-1219 formulation.
The half-life of secnidazole following SYM-1219 administration was approximately 17 hours and was independent of the dose administered.
There was low excretion of unchanged secnidazole into the urine, representing approximately 13-15% of the administered dose.
Overall, both doses of SYM-1219 were safe and well tolerated.