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

Helen S. Pentikis**, Nikki Adetoro*, and Carol J. Braun**, *Symbiomix Therapeutics and ^SAJE Consulting, Baltimore, Maryland

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 SYM-1219 2 g oral formulation was randomized to receive the concomitant administration of SYM-1219 with a high fat meal (70% to 125% intervals for bioequivalence). Based on these data, SYM-1219 administered without regard to meals.

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 obtained for 96 hours to determine secnidazole plasma concentrations. This 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 (Cmax) were 41.2 mcg/mL for the fasted treatment and 40.1 mcg/mL for the fed treatment. Exposure estimates (AUCinf) were 1261.5 mcg*h/mL for the fasted treatment and 1248.2 mcg*h/mL for the fed treatment. For all 24 subjects, mean secnidazole half-life ranged from 16.9 to 17.5 hours across all treatment groups and is consistent with previously reported estimates.

Conclusions: The concomitant 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.

METHODS

This was an open-label, randomized study that evaluated the pharmacokinetics (PK) and safety of single doses of SYM-1219 contained in 2 g of secnidazole administered to 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 80% to 125% intervals for bioequivalence. The SYM-1219 2 g formulation of secnidazole, a 5-nitroimidazole, is being developed for the treatment of women with bacterial vaginosis (BV). The SYM-1219 formulation was randomized to receive the concomitant administration of SYM-1219 with a high fat meal (70% to 125% intervals for bioequivalence). Based on these data, SYM-1219 administered without regard to meals.

The 90% confidence interval statistical evaluation of the fed and fasted treatments demonstrated bioequivalence for Cmax, AUC0-t, and AUC0-inf. 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 Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation.

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 Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation. Secnidazole Cmax and AUC exhibited low intersubject variability as the exposure estimates for secnidazole from the SYM-1219 formulation.

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. No unexpected, a higher incidence of headache was observed in the fasted group (0% vs. 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, or variation rather than a direct effect of SYM-1219 on QTcF. Finally, the statistical analysis of the frequent ECG sampling and triplicate ECG recordings showed no clinically relevant findings on any ECG intervals.

CONCLUSIONS

The SYM-1219 fasted and fed comparisons for Cmax, AUC0-t, and AUC0-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.