A PHASE 1, OPEN-LABEL STUDY TO DETERMINE THE EFFECT OF SYM-1219 ON THE PHARMACOKINETICS OF ETHINYL ESTRADIOL (EE2) AND NORETHINDRONE (NET) IN HEALTHY FEMALE VOLUNTEERS

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ABSTRACT

Background: This study evaluated the effect of a single 2 g dose of SYM-1219 (secnidazole), a new granule formulation of a 5-nitroimidazole in development to treat women with bacterial vaginosis, on the pharmacokinetics (PK) of ethinyl estradiol (EE2) and norethindrone (NET).

Methods: Fifty-four (54) healthy female subjects, ages 18-45, received EE2/NET alone and in combination, where SYM-1219+ EE2/NET were co-administered on Day 1 (Group B1; N=27) or SYM-1219 was administered on Day 1 and EE2/NET on Day 2 (Group B2; N=27). Serial blood samples were drawn to measure plasma concentrations of EE2/NET. A noncompartmental analysis was performed and the PK parameters of EE2 and NET for each treatment group are reported. Safety was evaluated by recording of adverse events, vital signs, ECGs and standard laboratory tests.

Results: Fifty-one (N=26 for B1 and N=25 for B2) subjects completed the study. EE2 Cmax was reduced by 29% for Group B1; no change in EE2 AUC was seen. EE2 PK was not altered for Group B2. NET Cmax and AUC increased (13%) slightly for Group B1. NET Cmax increased by 16% for Group B2; no change was seen for NET AUC.

SYM-1219 was safe and well-tolerated when taken alone or in combination with EE2/NET. 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 PK of EE2 and NET with SYM-1219 co-administration. Minor, not clinically relevant reductions in EE2 exposure were seen when SYM-1219 and EE2/NET were co-administered on the same day. No change in EE2 exposure was seen when the SYM-1219 and EE2/NET doses were staggered by one day. No reductions in drug exposure were evident for NET for either treatment group. These PK data demonstrate that contraceptive efficacy for EE2/NET would not be altered by SYM-1219 administration.

OBJECTIVE

This objective of this study was to evaluate the effect of a single 2 g dose of SYM-1219 (secnidazole) on the pharmacokinetics (PK) and safety of ethinyl estradiol (EE2) and norethindrone (NET) and a single 2 gram dose of SYM-1219.

METHODS

This was an open-label, randomized study designed to evaluate the effect of a single, 2 g dose of SYM-1219 on the PK of single doses of EE2 and NET in fifty-four (54) healthy female volunteers. The study consisted of 2 treatment periods. Period 1: Subjects received a single dose of EE2/NET on Day 1. Blood was obtained at predetermined times over a 24-hour period to assess EE2/NET PK. Period 2: Group B1 received EE2/NET followed by SYM-1219 on Day 1 and remained confined in the in-patient unit for 24 hours post-dose. Blood was obtained over a 24-hour period starting on Day 1 to determine SYM-1219 and EE2/NET plasma PK. Group B2 received SYM-1219 2 g on Day 1 and then received EE2/NET on Day 2. Blood was obtained over a 24-hour period starting on Day 2 to determine EE2/NET plasma PK only. Safety assessments included ECGs, vital signs, and standard laboratory assessments.

RESULTS

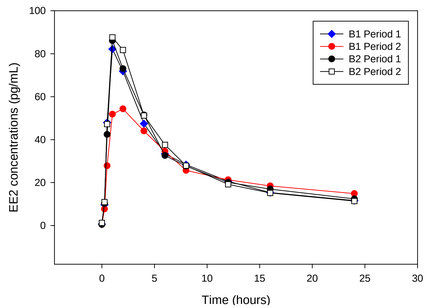
Fifty-four (54) subjects were enrolled in the study and 51 subjects completed the study as planned.

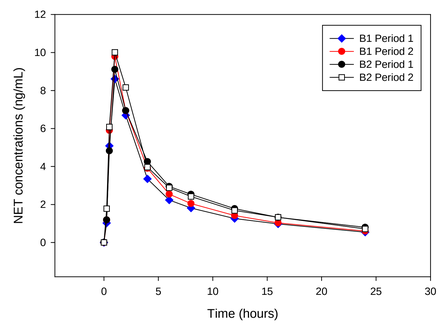
The effect of SYM-1219 on the pharmacokinetics on EE2 and NET was evaluated when SYM-1219 was administered immediately after EE2/NET and one day before administration of EE2/NET. The EE2 C_{max} was statistically significantly reduced when SYM-1219 was taken immediately after administration of EE2/NET; however, this reduction was not considered clinically relevant. There was no effect on the AUC_{0-t} and AUC_{inf} of EE2 when SYM-1219 was taken immediately after administration of EE2/NET. When SYM-1219 was administered 1 day before EE2/NET administration, there was no effect on C_{max} or AUC of EE2.

Small increases (13-16%) were observed in NET C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ with administration of EE2/NET followed by SYM-1219 compared with EE2/NET administered alone. The upper value of 90% CIs for C_{max} (127.63%), AUC_{0-t} (125.92%) and AUC_{inf} (127.04%) were all slightly above the 125% upper confidence limit. When the administration of SYM-1219 and EE2/NET were separated by a day, only the C_{max} 90% CI (upper value 131.32%) was above 125%. NET AUC_{0-t} and AUC_{inf} were 11% and 9% higher but 90% CIs were within 80-125% indicating no effect on extent of absorption. The changes observed for the NET PK parameters are not considered clinically relevant.

SYM-1219 pharmacokinetic parameters observed in this study were consistent with previously reported data from subjects who received a single 2 g dose.

Figure 1: Mean EE2 and NET Concentrations by Group and Period





SAFETY

All reported treatment emergent AEs (TEAEs) were considered mild in severity; no severe or moderate TEAEs were reported. All subjects in Period 1 received EE2/NET. In general, fewer treatment-related TEAEs were observed in Period 1 (EE2/NET alone) as compared to Period 2 when the EE2/NET was administered with SYM-1219 within one day from each other. There were no clinically relevant changes in vital signs, lab parameters, or ECGs in either study period.

Similar to the overall rate of TEAEs, a higher rate of treatment-related TEAEs was reported during Period 2 (Group B1, 37.0%; B2; 52.0%) compared to Period 1 (Group B1, 7.4%; B2; 22.2%). The most frequently reported treatment-related AEs nausea and headache.

A total of 3 subjects (5.6%) reported AEs leading to study discontinuation (2 subjects discontinued due to vomiting, 1 subject due to dysuria). All TEAEs leading to study discontinuation were mild, non-serious, and all resolved with no further action required.

Table 1: Plasma PK Parameters and 90% CI for EE2

Parameter	Treatment	Period	Mean (%CV)	Mean ratio (90% C.I.)
C_{max} (pg/mL)	Group B1	Period 2	59.88 (42.19)	71.07 (63.09, 80.05)
		Period 1	80.63 (26.84)	
	Group B2	Period 2	92.60 (34.77)	104.96 (98.28, 112.09)
		Period 1	89.12 (36.36)	
AUC_{0-t} (pg*hr/mL)	Group B1	Period 2	615.55 (31.20)	94.26 (89.78, 98.95)
		Period 1	643.67 (23.85)	
	Group B2	Period 2	668.63 (26.22)	99.04 (95.20, 103.04)
		Period 1	680.48 (28.91)	
AUC_{inf} (pg*hr/mL)	Group B1	Period 2	954.35 (28.75)	105.37 (97.84, 113.48)
		Period 1	911.11 (29.39)	
	Group B2	Period 2	937.42 (33.60)	93.32 (87.41, 99.63)
		Period 1	994.55 (28.91)	

Table 2: Plasma PK Parameters and 90% CI for NET

Parameter	Treatment	Period	Mean (%CV)	Mean ratio (90% C.I.)
C_{max} (ng/mL)	Group B1	Period 2	10.07 (43.62)	113.18 (100.37, 127.63)
		Period 1	9.18 (56.07)	
	Group B2	Period 2	10.69 (48.34)	116.46 (103.27, 131.32)
		Period 1	9.63 (56.25)	
AUC_{0-t} (ng*hr/mL)	Group B1	Period 2	53.45 (45.15)	115.52 (105.99, 125.92)
		Period 1	49.37 (70.06)	
	Group B2	Period 2	61.16 (66.70)	110.78 (103.97, 118.03)
		Period 1	61.35 (92.70)	
AUC_{inf} (ng*hr/mL)	Group B1	Period 2	62.39 (47.98)	116.27 (106.41, 127.04)
		Period 1	57.79 (74.72)	
	Group B2	Period 2	71.53 (72.42)	108.75 (101.78, 116.19)
		Period 1	74.98 (108.73)	

Group B1 = EE2/NET on Day 1 of Period 1, then EE2/NET followed by SYM-1219 2 g on Day 1 of Period 2. Group B2 = EE2/NET on Day 1 of Period 1, then SYM-1219 2 g on Day 1 and EE2/NET on Day 2 of Period 2.

CONCLUSIONS

- Minor, but not clinically relevant reductions in EE2 exposure were seen when SYM-1219 and EE2/NET were co-administered on the same day.
- No change in EE2 exposure was seen when the SYM-1219 and EE2/NET doses were staggered by one day.
- No reductions in drug exposure were evident for NET for either treatment group.
- These data demonstrate that contraceptive efficacy for EE2/NET would not be altered by SYM-1219 administration.