Ibrexafungerp (formerly SCY-078), a Novel IV/Oral Triterpenoid Antifungal Treatment, is Not Embryo/Feto-toxic

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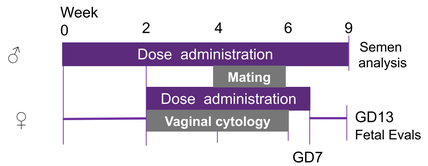
BACKGROUND

A higher prevalence of vaginal colonization and symptomatic vaginitis is seen in pregnant women (Sobel, 2007). FDA has issued a Drug Safety Communication cautioning against the prescribing of oral fluconazole for pregnant women based on reports of abnormalities at birth for women who had taken multiple high doses of oral fluconazole (400-800mg/day). FDA also advised caution in prescribing oral fluconazole based on a Danish study (Nørgaard , 2008) that reported a statistically significant increased risk of miscarriage with the use of oral fluconazole during pregnancy for yeast infections. Additionally, other researchers have reported a potential association between oral fluconazole exposure during pregnancy and abnormalities in the masculinization of male offspring (Mogensen, 2017). Considering these risks, the CDC (CDC, 2015) recommend only the use of topical treatments in the treatment of pregnant women with vulvovaginal yeast infections. Here we present data from a novel, orally-bioavailable triterpenoid glucan synthase inhibitor, Ibrexafungerp, (formerly SCY-078), with proven antifungal activity against *Candida*, *Aspergillus*, and *Pneumocystis* spp., in development for the treatment of multiple fungal infections including Vulvovaginal Candidiasis.

METHODS

A fertility and early embryonic development study was conducted in Han Wistar rats according to the below schedule.



Rats were orally administered ibrexafungerp in 0.5% methylcellulose in reverse osmosis water at doses of 0, 10, 20, 40 or 80 mg/kg/day at a dose volume of 5 mL/kg.

Additionally, standard embryo-fetal development studies were conducted in Wistar rats and Dutch-belted rabbits according to the following schedules.

Rats were orally administered ibrexafungerp in 0.5% methylcellulose in reverse osmosis water at doses of 0, 10, 25, 35 or 50 mg/kg/day; while rabbits were orally administered the same formulations at dose levels of 0, 10, 25 or 50 mg/kg/day.

RESULTS

Fertility and Early Embryonic Development

- Ibrexafungerp showed no effects on mating or fertility of the male or female rats or on ovarian, uterine or litter parameters of female rats evaluated mid-gestation (GD 13) at doses up to 80 mg/kg/day.

Embryo Fetal Development

Rat:

- Ibrexafungerp showed no effects on embryo/fetal survival, fetal skeletal, visceral or external malformations at doses up to 50 mg/kg/day

Rabbit:

- Ibrexafungerp showed no effects on embryo/fetal survival, fetal skeletal, visceral or external malformations. Decreased mean fetal body weights at 50 mg/kg/day at doses up to 25 mg/kg/day

	Dose (mg/kg/day)	C_{max} (ng/mL)	AUC (hr*ng/mL)	Exposure Multiple Relative to Human Efficacy Target
Rat GD 17	50	2630	50900	5X
Rabbit GD 19	25	4200	52100	5X

CONCLUSIONS

The fertility and early embryonic development of male and female Han Wistar rats was unaffected by treatment with ibrexafungerp at doses in excess of the efficacious clinical dose. Male sexual function and maturation of gametes; female estrous cycles, pregnancy rates, and implantation were comparable to those of concurrent vehicle controls. Han Wistar rats and Dutch-belted rabbits administered ibrexafungerp showed no enhanced toxicities relative to those noted in studies conducted with non-pregnant females. There were no increases in embryo-fetal loss, and evaluations of fetal development revealed no ibrexafungerp-related developmental anomalies in rats or rabbits at doses in excess of the efficacious clinical dose.

With proven antifungal activity against many invasive fungal species, ibrexafungerp shows great promise in treating fungal infections. The data presented here show that ibrexafungerp may provide an option for the treatment of fungal infections in women during pregnancy.

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