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

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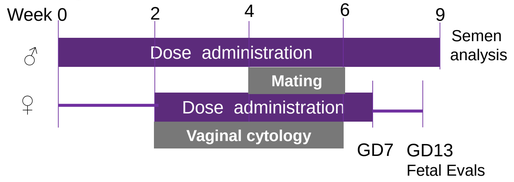
BACKGROUND

The treatment of fungal infections in pregnancy has long been difficult due to the known teratogenicity associated with existing antifungal treatment options. Azole and echinocandin treatments in pregnancy have been shown to be embryo and developmentally toxic in animal studies. Additionally, observations of congenital abnormalities have been reported in infants exposed *in utero*. Here we present data from a novel, orally-bioavailable triterpenoid glucan synthase inhibitor, SCY-078, with proven antifungal activity against *Candida*, *Aspergillus*, and *Pneumocystis* spp., in development for the treatment of multiple severe fungal infections.

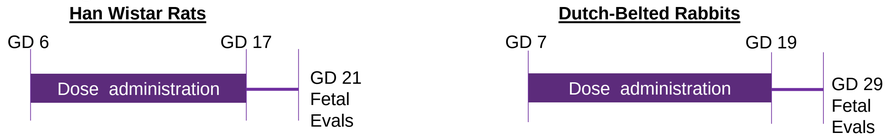
METHODS

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



Rats were orally administered SCY-078 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 SCY-078 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

- 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).
  - Reproductive NOAEL = 80 mg/kg/day

Embryo Fetal Development

Rat:

- Decreased mean maternal body weight gain and mean food consumption at 50 mg/kg/day from GD 6-9.
  - Maternal NOAEL = 35 mg/kg/day
- No effects on embryo/fetal survival, fetal skeletal, visceral or external malformations.
  - Developmental NOAEL = 50 mg/kg/day

Rabbit:

- Decreased mean maternal body weight gain and food consumption at ≥25 mg/kg/day.
  - Maternal NOAEL = 10 mg/kg/day
- No effects on embryo/fetal survival, fetal skeletal, visceral or external malformations. Decreased mean fetal body weights at 50 mg/kg/day.
  - Developmental NOAEL = 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	7X

CONCLUSIONS

The fertility and early embryonic development of male and female Wistar rats was unaffected by treatment with SCY-078 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. Wistar rats and Dutch-belted rabbits administered SCY-078 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 SCY-078-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, SCY-078 shows great promise in treating fungal infections. The data presented here shows that SCY-078 may also provide a greatly needed option for the treatment of fungal infections in women during pregnancy.

For additional information, contact us at info@scynexis.com