Ibrexafungerp, a Novel Oral Antifungal, Demonstrates No Reproductive or Developmental Harm in Preclinical Models

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INTRODUCTION

The treatment of fungal infections during pregnancy is difficult due to teratogenicity associated with existing anti-fungal treatment options. Vulvovaginal candidiasis (VVC), also known as yeast infection, is especially common during pregnancy. Fluconazole, the oral standard of care for the treatment of VVC, has been shown to be embryo/feto toxic in animal studies, and these results correlate to several reports of similar patterns of congenital abnormalities and spontaneous abortions observed following treatment in the clinical setting. Ibrexafungerp is a novel triterpenoid glucan synthase inhibitor, with proven anti-fungal activity against *Candida*, *Aspergillus*, and *Pneumocystis* spp., in development for the treatment of fungal infections, including VVC.

AIM

The aim of this poster is to guide the reader through the preclinical study designs and the evaluation of ibrexafungerp exposure on the fertility, gestation, and parturition of adults as well as any potential effects of ibrexafungerp on the development of offspring indirectly exposed *in utero* and/or during lactation.

RESULTS

Fertility and Early Embryonic Development

No effects on mating or fertility of the male or female rats on ovarian, uterine or litter parameters of female rats evaluated mid-gestation (Day 13/21)

- Reproductive no-adverse-effect-level = 80 mg/kg/day, the highest dose evaluated

Pre- and Post-natal Development

No maternal toxicity

- Maternal no-adverse-effect-level = 50 mg/kg/day, the highest dose evaluated

No effect on offspring survival, growth, behavior, or reproductive performance

- Developmental no-adverse-effect-level = 50 mg/kg/day, the highest dose evaluated

Embryo Fetal Development

Rat:

- Decreased mean maternal body weight gain and mean food consumption at 50 mg/kg/day from GD 6-9/21.
  - Maternal no-adverse-effect-level = 35 mg/kg/day
- No effects on embryo/fetal survival, fetal skeletal, visceral or external malformations.
  - Developmental no-adverse-effect-level = 50 mg/kg/day, the highest dose evaluated

Rabbit:

- Decreased mean maternal body weight gain and food consumption at ≥25 mg/kg/day.
  - Maternal no-adverse-effect-level = 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 no-adverse-effect-level = 25 mg/kg/day

Pharmacokinetic Parameters as Measured During Gestation and at the End of the Dosing Period Relative to Human Efficacy Target

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

CONCLUSIONS

With proven anti-fungal activity against a broad spectrum of pathogenic fungi, ibrexafungerp shows great promise in treating fungal infections. The lack of reproductive harm in these animal studies provide support for ibrexafungerp as an alternative treatment of fungal infections in women of child-bearing age.

CONTACT INFORMATION

For additional information contact SCYNEXIS at info@scynexis.com

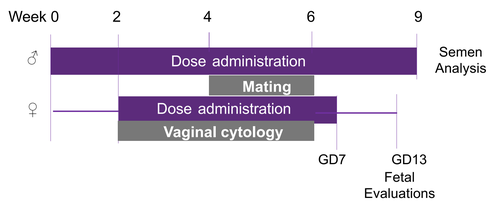
METHODS

A full developmental and reproductive toxicity package for ibrexafungerp was recently concluded, as required for approval and labeling of prescription medications. These preclinical studies included investigation of the effects of ibrexafungerp on a) fertility and libido of adult male and female animals during treatment; b) conception, implantation and development of embryos; c) development of fetuses, parturition, survival and lactation; d) the development of offspring from birth through sexual maturation; and e) the ability of those offspring to mate and conceive a second-generation post exposure.

Fertility and Early Embryonic Development

These studies assess pre-breeding and mating exposures for both sexes and exposure to pregnant females until implantation to provide information on effects on breeding, fertility, preimplantation, implantation, and early embryonic development to mid-gestation (after maternal exposure prior to implantation).

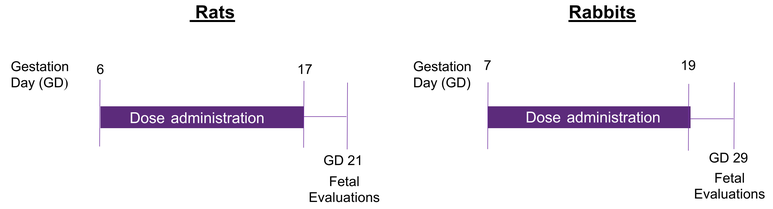
A fertility and early embryonic development study was conducted in Wistar rats with daily oral doses of 0, 10, 20, 40 or 80 mg/kg/day ibrexafungerp according to the below schedule.



Embryo-fetal Development

Gestation in a rat is 21 days and in a rabbit is 29 days. These studies are designed to indirectly expose developing offspring during the entire period of major organogenesis to provide information on effect on *in utero* survival and morphological growth and development, including teratogenicity.

Standard embryo-fetal development studies were conducted in Wistar rats and Dutch-belted rabbits with daily oral dose of ibrexafungerp of 0, 10, 25, 35, or 50 mg/kg/day for rats and 0, 10, 25 or 50 mg/kg/day for rabbits according to the below schedule.



Pre- and Post-natal Development

These studies are designed to assess exposure of the offspring from the onset of the fetal period through weaning to provide information on maternal parturition, lactation and on F_1 late intrauterine and postnatal growth and development through reproductive maturity and production of the F_2 generation.

A pre- and post-natal development study was conducted in Wistar rats with daily oral dose administration of 0, 10, 20, 35, or 50 mg/kg/day ibrexafungerp according to the below schedule.