asm microbe 2019
JUNE 20 – 24 ● SAN FRANCISCO, CA

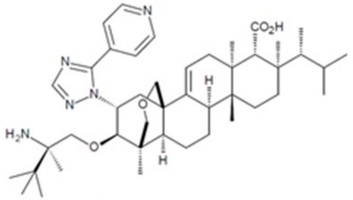
Preclinical Safety Evaluation of the Novel Antifungal Ibrexafungerp (formerly SCY-078) Supports Long-Term Dosing

AAR-635

Christina M. Carruthers, Stephen A. Barat, and David Angulo
SCYNEXIS, Inc., Jersey City, NJ.

BACKGROUND

Ibrexafungerp (formerly SCY-078) is the first representative of orally-bioavailable glucan synthase inhibitors referred to as "fungerps" currently in development for mucocutaneous and invasive fungal infections.



Ibrexafungerp has broad antifungal activity against *Candida, Aspergillus* and *Pneumocystis* spp. The treatment of patients with chronic and invasive fungal infections may require long-term therapy; therefore, understanding the safety profile following chronic dose administration of ibrexafungerp is necessary.

METHODS

Preclinical studies have been conducted with ibrexafungerp, in which genetic toxicity, end organ toxicity from chronic daily oral dosing (in rats up to 6 months and in dogs up to 9 months) and developmental and reproductive toxicity in rats and/or rabbits from conception to sexual development of the offspring were evaluated.

RESULTS

Repeat-Dose General Toxicology:

Following repeat-dose oral administration in rats (6-months) and dogs (9-months), Ibrexafungerp was well-tolerated in both species, with end organ toxicity consisting primarily of findings related to phospholipidosis, with no-observed-adverse-effect-levels (NOAEL) determined.

Chronic Oral Toxicology Studies in Rats and Dogs

Species	Doses (mg/kg)	NOAEL (mg/kg)	Exposure (uM*hr) at NOAEL	Animal:Human Exposure Multiple*
Rat	20, 40, 80	40	110	7
Dog	30, 60, 100	100	50	3

*Animal:Human exposure multiple calculated relative to a target exposure of 15.4 uM*hr based on results from in vivo efficacy models in mice.

Reproductive and Developmental Toxicology:

The developmental and reproductive safety profile was fully evaluated in a fertility and early embryonic development study (seg I) in rats, in embryo-fetal development studies (seg II) in rats and rabbits, and in a peri-/post-natal development study (seg III) in rats. The collective results showed no evidence of developmental or reproductive toxicity in rats or rabbits at exposures equivalent to 5-fold the targeted efficacious exposure.

Genetic Toxicology:

The genotoxic potential of ibrexafungerp was also fully evaluated *in vitro* in the bacterial mutagenicity assay and Chinese hamster ovary chromosomal aberration assay, and *in vivo* in the rat micronucleus assay. Ibrexafungerp was determined to not be genotoxic.

CONCLUSIONS

Collectively, the results of the preclinical safety assessment program indicate that ibrexafungerp has a very favorable profile which is supportive of its use in the treatment of patients with various fungal infections, including those suffering from invasive fungal diseases which may require long-term dosing.

For additional information contact SCYNEXIS at *info@scynexis.com.*