Effect of SCY-078 on the Pharmacokinetics of Tacrolimus: Results from a Phase 1 Clinical Drug-Drug Interaction Trial

27th ECCMID Vienna, Austria 22 – 25 April 2017

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INTRODUCTION & PURPOSE

- SCY-078 is an oral and intravenous semi-synthetic triterpenoid antifungal glucan synthase inhibitor, in development for the treatment of invasive and mucocutaneous fungal diseases.
- Tacrolimus is an immunosuppressive drug often used in solid organ transplants patients. These patients often develop invasive fungal infections (IFIs).
- Azoles, commonly used antifungal and the only orally available class of antifungals, are inhibitors of CYP3A Azoles can cause a marked (2 to 4 fold) increase in tacrolimus blood levels requiring dose adjustment of tacrolimus to prevent toxicities.
- SCY-078 is neither an inducer nor a time-dependent inhibitor of CYP3A. SCY-078 is not an inhibitor of CYP2C8 or other CYP isozymes where the inhibitory potency of SCY-078 is even lower based on a clinical study of SCY-078 on a probe CYP2C8 substrate rosiglitazone. Thus, it has a low risk for interaction with tacrolimus and may provide a safer alternative for the treatment and prophylaxis of IFIs in the transplant population.

METHODS: STUDY DESIGN

A Phase 1, open-label, study was conducted in 24 healthy adult male subjects to assess the effects of multiple doses of SCY-078 on the pharmacokinetics of tacrolimus. The study had 2 sequential periods, as follows:

PERIOD 1

Single 2-mg dose of Tacrolimus on Day 1

15 DAY WASHOUT

PERIOD 2

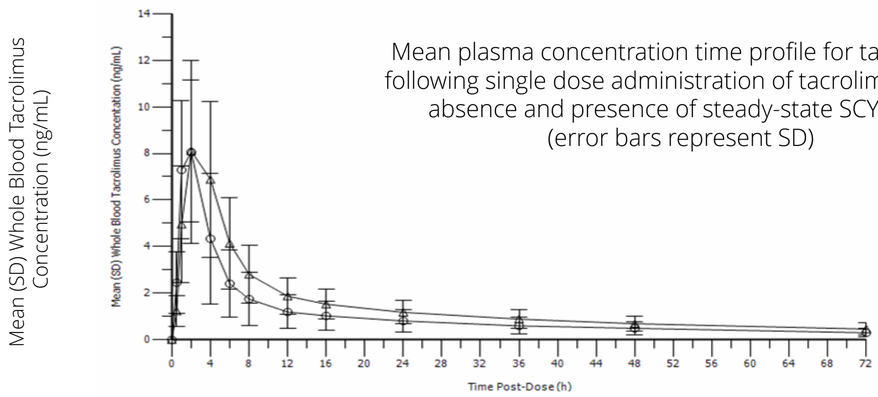
Loading dose of oral 1250-mg SCY-078

Oral 750-mg SCY-078 QD for 7 additional days

Single 2-mg dose of Tacrolimus on Day 3
(Predicted to be at steady-state exposure for SCY-078)

- Safety was monitored throughout the study by repeated clinical and laboratory evaluations.
- Whole blood (tacrolimus) and plasma (SCY-078) samples were obtained at selected time points

RESULTS



Mean plasma concentration time profile for tacrolimus following single dose administration of tacrolimus in the absence and presence of steady-state SCY-078. (error bars represent SD)

PK Tacrolimus Co-administered with SCY-078 vs. Tacrolimus Alone

Treatment	AUC 0-inf (ng•h/mL)[a]	AUC 0-24hr (ng•h/mL)[a]	Cmax (ng/mL)[a]	Tmax (h)[b]
Test (Tacrolimus + SCY-078)	116.9 (94.53, 144.7)	63.22 (52.08, 76.73)	8.29 (6.93, 9.93)	2.0 (1.0-4.0)
Reference (Tacrolimus Alone)	82.50 (66.68, 102.1)	46.16 (38.03, 56.03)	8.03 (6.71, 9.61)	2.0 (1.0-4.0)
GMR[d]	1.42 (1.25, 1.61)	1.37 (1.21, 1.56)	1.03 (0.89, 1.20)	

[a] LS geometric Mean and its 95% CI were calculated based on linear mixed effects model: (log PK Result)= treatment + subject
[b] Median (Min - Max).
[c] GMR = Geometric Means Ratio, GMR Test/Reference (90% CI).

CONCLUSION

The concurrent co-administration of tacrolimus and SCY-078 had no effect on the maximum blood levels of tacrolimus (no change in Cmax) with only mild effect in tacrolimus' overall exposure (1.4 fold increase in AUC). This results indicate a low risk for a clinically meaningful interaction and support the co-administration of SCY-078 and tacrolimus, when indicated.

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