172
06/03/17

asm microbe 2017
JUNE 1–5 • NEW ORLEANS

Lack of an Effect of SCY-078 a Novel Antifungal Agent on QTc Interval in Healthy Subjects

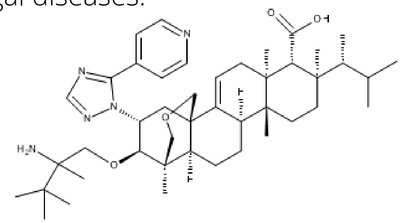
SCYNEXIS, Inc.
Tel. 201-884-5485
info@scynexis.com

G. Murphy[1], B. Darpo[2], T. Marbury[3], M. Hyman[4] and **D. Angulo**[5]

[1]Riverside Consulting, LLC, Wilmington, DE; [2]iCardiac Technologies, Rochester, NY; [3]Orlando Clinical Research Center, Orlando, FL; [4]BCH Research Solutions, LLC, West Chester, PA; [5]SCYNEXIS, Inc, Jersey City, NJ.

INTRODUCTION

- 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.



- *In vitro* SCY-078 inhibited IKr (hERG current) with an IC50 value of 1200 nM. *In vivo* no QT/QTc interval prolongation was seen in dogs up to plasma concentrations of ≈ 30000 nM (≈ 21900 ng/mL) after IV administration.

- The proarrhythmic potential of SCY-078 was evaluated in this Phase 1 study using exposure response analysis of the relationship between SCY-078 plasma concentrations and the heart rate corrected QT interval.

- The primary ECG endpoint was change-from-baseline QTc corrected for heart rate by the Fridericia method (ΔQTcF).

METHODS: STUDY DESIGN

In this Phase 1, IV dose escalation study in healthy male and female subjects, 12-lead ECGs were recorded at baseline and serially post-dosing, paired with PK samples. ECG parameters were measured with the High Precision QTc technique.

The Panel A rising doses of SCY-078 for were 30 mg, 125 mg (n=5) and 375 mg (n=6) infused over 1 hour. The Panel B rising doses of SCY-078 for were 60 mg, 250 mg (n=5) infused over 1 hour and 375 mg (n=2) infused over 2 hours. Six subjects received placebo in Panels A and B. Each subject received up to 3 rising doses separated by a minimum 10-day washout interval.

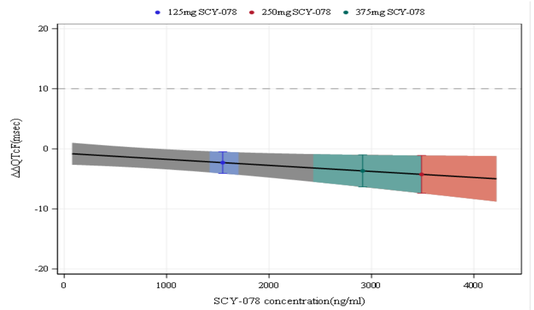
For each Holter recording, up to ten (10) ECG replicates were extracted at the following predefined timepoints: 90, 75, and 60 min Predose, 0.5, 1, 1.5 (for 1-hour Infusion only), 2, 2.5 (for 2-hour Infusion only), 3, 4, 6, 8, 12 and 24 hours postdose. ECG intervals were measured blindly by the core laboratory and the ECG database was locked before any statistical analysis was undertaken.

CONCLUSION

Exposure-response analysis demonstrated that SCY-078 does not have a clinically meaningful effect on the QTcF interval within the range of observed plasma concentrations up to ~4000 ng/mL.

RESULTS

Predicted Mean (90% CI) ΔΔQTcF Interval at Geometric Mean Peak SCY-078*



* The solid black line with gray shaded area denotes the model-predicted mean (90% CI) ΔΔQTcF. Blue, red, and green shaded areas denote the predicted mean (90% CI) ΔΔQTcF at the geometric mean (90% CI) Cmax of SCY-078 on doses 125 mg, 250 mg, and 375 mg, respectively.

- The slope of the relationship between SCY-078 and the placebo-corrected, change-from-baseline QTcF (ΔΔQTcF) was very shallow and not statistically significant.

- SCY-078 did not have a clinically relevant effect on heart rate, PR interval or QRS interval.

Predicted ΔΔQTcF at the geometric mean peak SCY-078 plasma concentration

Treatment	Geometric Mean (90% CI*) of C_{max} (ng/mL)	Predicted ΔΔQTcF (msec)	90% CI of ΔΔQTcF (msec)
125 mg SCY-078 (1 hour infusion)	1547.55 (1405.62;1703.8)	-2.29	(-4.11;-0.47)
250 mg SCY-078 (1 hour infusion)	3489.07 (2767.37;4398.97)	-4.25	(-7.41;-1.09)
375 mg SCY-078 (1 and 2 hour infusions)	2914.19 (2418.89;3510.91)	-3.67	(-6.35;-0.99)

* The 90% CI of the geometric mean was calculated in the logarithmic domain and presented after back-transformation to the original concentration domain.