2389

Effect of Rezafungin on QT Interval in Healthy Subjects

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INTRODUCTION

Rezafungin (formerly CD101), a new echinocandin antifungal agent, is being developed to treat candidemia and/or invasive candidiasis.

In addition, rezafungin is being studied as a single agent for prevention of invasive fungal infections caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. among immunosuppressed patients, including those undergoing allogeneic stem cell transplantation and those receiving cytotoxic chemotherapy for hematologic malignancies.

Rezafungin has successfully met safety and efficacy endpoints in Phase 2 for treatment[1] and is advancing to Phase 3 studies for treatment and prophylaxis.

Rezafungin is the first echinocandin to undergo a definitive QT evaluation. Anidulafungin Prescribing Information (PI) indicates QT prolongation as an infrequent (<2%) adverse reaction[2], and the PIs of other echinocandins (caspofungin and micafungin) do not mention QT prolongation. In contrast, the PI of trimethoprim/sulfamethoxazole, used prophylactically to prevent *Pneumocystis* infections, includes postmarketing experience of QT prolongation resulting in ventricular tachycardia and *torsade de pointes*.[3] Similarly, azole antifungals are associated with both direct pharmacodynamic effects on QT prolongation as well as interacting pharmacokinetically with a number of other agents that prolong QT [4-6].

METHODS

This Phase 1, single-center, randomized, double-blind, comparative study evaluated the effects of rezafungin on the QTcF (corrected using Fridericia's formula) interval, heart rate, and other cardiac parameters.

There were three dose groups, IV rezafungin (600 mg or 1400 mg), IV placebo, and oral moxifloxacin (positive control).

Subjects were enrolled in 2 cohorts of 30 subjects, each with 3 active groups plus placebo: IV rezafungin (600 or 1400 mg), IV placebo, and oral moxifloxacin as an unblinded, positive control plus IV placebo (Table 1).

METHODS (cont'd)

Table 1: Summary of Study Design

Cohort	Treatment		
	IV Rezafungin	**IV Placebo**	**Oral Moxifloxacin**
Cohort 1 Dose Groups	Single dose (600 mg) in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)	IV Placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (±5 min)	Single dose (400 mg) administered with approximately 240 mL of water plus IV placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)
n	12	6	12
Cohort 2 Dose Groups	Single dose (1400 mg) divided into a 375 mL infusion over 1.5 h (± 5 min) followed by a 500 mL infusion over 2 h (± 5 min)	IV Placebo in a 375 mL infusion over 1.5 h (±5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 minutes)	Single dose (400 mg) administered with approximately 240 mL of water plus IV placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)
n[a]	12	6	12
Total (N)	**24**	**12**	**24**

IV = intravenous

[a]Subjects were randomized 2:1:2 for the IV rezafungin, IV placebo, and oral moxifloxacin groups.

The 600 mg (therapeutic) and 1400 mg (supratherapeutic) doses were selected to achieve exposures approximating those after multiple doses of the highest dosage regimen assessed in the Phase 2 study (400 mg once weekly) and exposures ~2.5-fold higher, respectively.

The primary endpoint was based on an analysis of change of QTcF from Baseline (ΔQTcF) as a function of rezafungin plasma concentration, to derive the estimated mean placebo-adjusted change of QTcF from Baseline (ΔΔQTcF) for the rezafungin dose groups at the geometric mean C_{max} for each dose level. The outcome was defined by a comparison of the upper bounds of the 2-sided 90% CIs within 10 msec.

RESULTS

60 subjects were enrolled and completed the study. Demographics included: sex (43.3% male) and age (median age: 34.0 years; ranging from 20 to 51 years) approximately evenly distributed by treatment.

The majority of subjects were of Hispanic or Latino ethnicity (75%). Anthropometric measures of height, weight, and BMI were also similar between treatment groups.

RESULTS

A linear regression model best fit the data, as shown in **Figure 1**. From this model, the estimated mean ΔΔQTcF at the C_{max} for both of the rezafungin doses had upper bounds <10 msec.

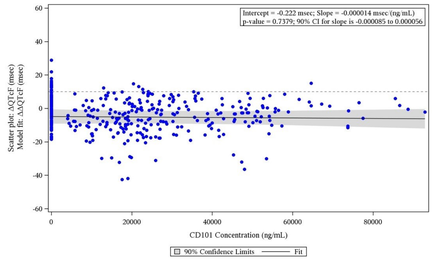

Figure 1. Scatter Plot of Change of QTcF from Baseline (ΔQTcF) for Rezafungin and Placebo Subjects versus Rezafungin Concentration; and Linear Model Slope and 2-sided 90% Confidence Bounds of the Slope Representing Placebo-adjusted Change of QTcF from Baseline (ΔΔQTcF) (msec)

The mean ΔΔQTcF at each time point by dose showed all 2-sided 90% upper bounds to be <10 msec, thus supporting the conclusion of the primary analysis.

Assay sensitivity was established for moxifloxacin. The estimated mean ΔΔQTcF at the geometric mean plasma concentrations for the moxifloxacin dose had a lower bound >5 msec. A linear regression model best fit the data, as shown in **Figure 2**, with a statistically significant slope of 0.004785 ($p < 0.0001$).

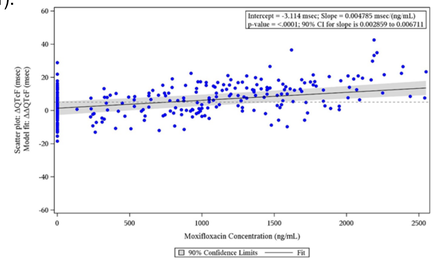

Figure 2. Scatter Plot of ΔQTcF for Moxifloxacin and Placebo versus Moxifloxacin Plasma Concentrations; a Linear Model Slope and 2-sided 90% Confidence Bounds of the Slope Representing ΔΔQTcF (msec)

RESULTS (cont'd)

No clinically significant effects on any of the cardiac parameters tested (RR, QRS, HR) were observed.

Rezafungin was generally well tolerated. All adverse events (AEs) were mild to moderate in severity with no discontinuations due to AEs. All reported TEAEs were mild to moderate in severity. There were no severe TEAEs. The most frequent TEAEs were headache (10 events) and nausea (5 events). Headache occurred more often in the 600 mg rezafungin (2 mild events and 2 moderate events) and the 1400 mg rezafungin (4 moderate events) dose groups compared to the moxifloxacin and placebo groups (1 mild event each). Nausea occurred evenly across the 600 mg rezafungin (2 mild events), 1400 mg rezafungin (1 mild event) and moxifloxacin (2 mild events) groups. Nausea was not reported in the placebo group.

CONCLUSIONS

- Rezafungin, in single IV doses up to 1400 mg, does not prolong the QT interval
- There was no effect of either rezafungin dose on repolarization or QRS duration
- The above findings support the clinical safety and continued development of rezafungin.

REFERENCES

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