Abstract

Eravacycline (ERV) is a novel broad-spectrum protein-synthesizing inhibitor being developed for the treatment of serious bacterial infections, including those caused by multi-drug resistant Gram-negative pathogens. This study was undertaken to evaluate the effect of ERV on corrected QT (QTc) intervals and other ECG parameters in healthy subjects.

Methods

Sixty subjects were enrolled into a randomized, double-blind, three-period, placebo- and positive-controlled crossover study and received ERV 1.5 mg/kg IV, placebo (Pbo) or moxifloxacin (Mox) 400 mg IV. Triplet 12-lead ECGs were obtained during 24 h prior to dosing. Triplet ECGs were extracted at 13 timepoints from continuous 12-lead ECG data obtained during 24 h prior to dosing (on treatment). An ECG core laboratory employing a limited number of skilled readers was used for interpretation of the ECGs; the readers were blinded to treatment, treatment sequence, subject and individual QTcF (individual): QTc (time – postdose timepoint) – QTc (time + postdose). Primary analysis: A mixed-effects model with the change in QTcI interval from the predose measurement (ΔQTcI) as the dependent variable and treatment, time, period, sequence, and (treatment) × (sequence) as fixed effects and subject as the random effect. The upper bound of the 1-sided 95% confidence interval (CI) of the QTcI effect to the threshold of 10 ms.

Results

No subject had a QTc interval >480 msec or a QTc change from predose >30 msec at any postdose timepoint following a single dose of 1.5 mg/kg ERV. No subject had a QTcF or QTcI interval >480 msec or change from predose >60 msec following ERV. Changes from predose in P1, G1, and IR interval were made by Treatment. ERV was generally well-tolerated by healthy subjects in this study.

Conclusions

There was no evidence of clinically significant QTc prolongation demonstrated in this study following administration of a single IV dose of 1.5 mg/kg ERV. The maximum time-matched placebo-adjusted change from predose in QTcF, QTcB, and QTcF intervals at each postdose timepoint was less than 10 msec for the upper bound of the 1-sided 95% CI. The plasma ERV concentration versus QTc slope was near zero for all QTc parameters, suggesting that there was no plasma ERV concentration-dependent QTc prolongation following a single dose of 1.5 mg/kg eravacycline IV. The assay sensitivity for detection of QTc prolongation in this study was confirmed by the results of the moxifloxacin positive control arm following an oral single dose administration of moxifloxacin.

Analysis

Population: All subjects who received at least one dose of study drug and for whom adequate ECG data were available

Study design: Randomized, blinded, three-period, placebo- and positive-controlled, three-way crossover

Subjects: Healthy male or female aged 18-55 years

Treatments: ERV 1.5 mg/kg IV, Mox 400 mg PO, Placebo (IV & PO (oral tablet))

EGC collection: Continuous collection on Day 1 of each period using a 12-lead ECG telemetry system or a 12-lead Holter system starting 0.5 h before dosing through 24 h post-dose in each period. In Period 1, continuous collection was also performed on Day 1 (1 day prior to dosing) to obten off-treatment QT data.

EGC reading: Triplet 10-second periods of continuous ECG recordings, extracted from the 5-minute window around each scheduled timepoint and exported to Medpace ECG Core Lab. ECGs were reviewed by a limited number of cardiologists blinded to treatment, subject, and timepoint. For measurement of QT interval, a superimposed global median complex was generated.

Analysis:

All subjects who received at least one dose of study drug and for whom adequate ECG data were available

Conclusions:

• No subject had a QTcI interval >480 msec or a QTc change from predose >30 msec at any postdose timepoint following a single dose of 1.5 mg/kg ERV. No subject had a QTcF or QTcI interval >480 msec or change from predose >60 msec following ERV.
• Changes from predose in P1, G1, and IR interval were made by Treatment. ERV was generally well-tolerated by healthy subjects in this study.
• No SAEs were reported and there were no discontinuations due to AEs. However, a few AEs were reported following ERV and these were all mild or moderate in severity.
• Nausea and vomiting were reported by 22% and 11% of subjects, respectively, but these events were mild and transient in nature.

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