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Eravacycline Does Not Prolong Corrected QT Intervals in a Thorough QT Study Conducted in Healthy Subjects

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Abstract

Objectives: Eravacycline (ERV) is a novel broad-spectrum tetracycline being developed for the treatment of serious bacterial infections, including those caused by multidrug-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, blinded, three-period, placebo- and positive-controlled crossover study and received ERV 1.5 mg/kg IV, placebo (Pbo) or moxifloxacin (Mox) 400 mg po. Triplicate ECGs were extracted at 13 timepoints from continuous 12-lead ECG data obtained during 24 h prior to dosing in Period 1(off-treatment) and during each period starting 0.5 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 timepoint. QT intervals were determined and corrected by the individual (QTcI, using data from the off-treatment ECGs to calculate individual correction factors), Bazett's (QTcB), and Fridericia's (QTcF) methods. Time-matched pre-dose adjusted changes in QTc between either ERV or Mox and Pbo were calculated. Plasma samples were collected for pharmacokinetic determination. Safety assessments, including adverse events were collected throughout the study.

Results: Fifty-three subjects completed all three periods. The upper bound of the 1 sided 95% CI of the time matched mean difference between ERV and Pbo for QTcI did not exceed 10 msec at any post-dose timepoint. The largest difference in time-matched pre-dose adjusted change in QTcI for ERV from Pbo was 3.56 msec (90% CI 1.37, 5.75) at 3 h post-dose. Following Mox, the maximum time matched mean difference from Pbo was 12.12 msec (90%CI 9.81, 14.42), and the lower bound did not contain zero at any timepoint. Changes in either QTcB or QTcF were similar. No subject had a QTcI interval > 480 msec or a QTcI change from pre-dose >30 msec at any post-dose timepoint following ERV. Changes from pre-dose in PR, QRS and RR intervals following ERV were small and similar to placebo. The plasma ERV concentration-versus QTc slope was near zero for all QTc parameters.No serious adverse events were reported and no subject was discontinued from the study due to adverse events. The most frequent adverse events reported following ERV treatment were nausea, vomiting, and headache reported in 12/54 (22.2%), 6/54 (11.1%) and 6/54 (11.1%) of subjects, respectively.

Conclusion: There was no evidence of clinically significant QTc prolongation or any other changes in ECG parameters demonstrated in this study following ERV. The assay sensitivity for detection of QTc prolongation in this study was confirmed by the results of the Mox positive control arm. ERV was generally well tolerated by healthy subjects in this study.

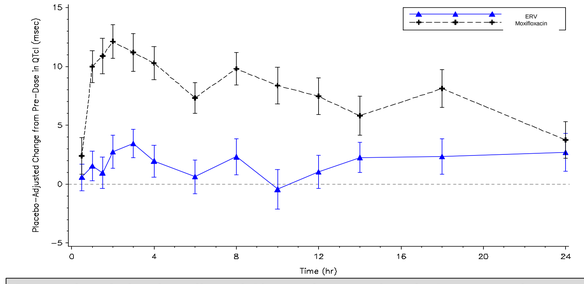
Methods

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 (0.9% NaCl) and PO (oral tablet)
ECG 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 hours before dosing through 24 hours post-dose in each period. In Period 1, continuous collection was also performed on Day -1 (day prior to dosing) to obtain off-treatment QT data
ECG reading:	Triplicate 10-second periods of continuous ECG recordings were 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 Population:	All subjects who received at least one dose of study drug and for whom adequate ECG data were available

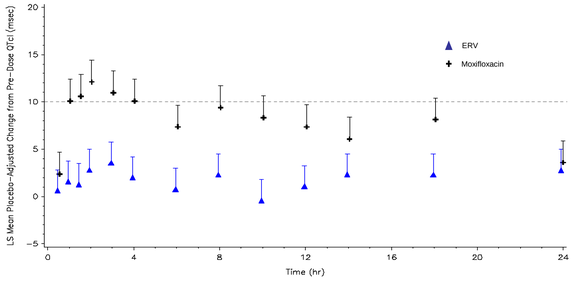
QTcI (Individual):	QT/(RR)$^{\beta}$, where β was the subject-specific fixed correction factor computed from a log-linear model $log_e\ (QT) = \alpha + \beta \times log_e\ (RR) + \varepsilon$ using information obtained from 8 hours of data during off-treatment 12-hour continuous ECG assessment at Period 1 Day -1.
QTcB (Bazett's):	QT/(RR)$^{1/2}$
QTcF (Fridericia's):	QT/(RR)$^{1/3}$
ΔQTc :	QTc (time = postdose timepoint) – QTc (time = predose)
ΔΔQTc:	Placebo-adjusted change from predose = ΔQTc (treatment) – ΔQTc (placebo)
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 time by treatment interaction as fixed effects and subject as the random effect. The upper bound of the 1-sided 95% CI and the point estimate were obtained for the differences in time-matched QTc between eravacycline and placebo. The inference was made by comparing the upper bound of the 1-sided 95% confidence Interval (CI) of the QTcI effect to the threshold of 10 msec.

Results

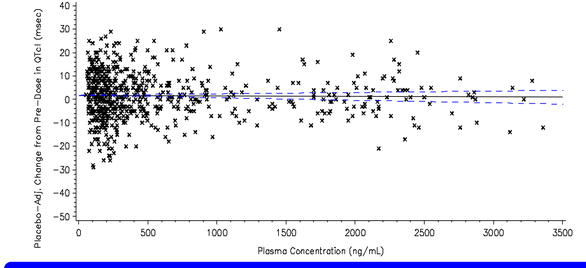
Plot of Mean (+/- SE) Placebo-adjusted Change from Predose in QTcI Over Time by Treatment – QT Evaluable Population



Plot of Least-Squares Mean and 1-Sided 95% CI for Placebo-Adjusted Change From Predose in QTcI Over Time by Treatment – QT Evaluable Population



Scatterplot of Placebo-adjusted Change from Predose in QTcI Intervals Versus Plasma ERV Concentration – QT Evaluable Population



- No subject had a QTcI interval >480 msec or a QTcI 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 QTcB interval >480 msec or change from predose >60 msec following ERV.
- Changes from predose in PR, QRS, and RR intervals following a single dose of 1.5 mg/kg ERV were generally small and similar to placebo.
- No SAEs were reported and there were no discontinuations due to AEs.
- 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.

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 QTcI, QTcF, and QTcB 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.
- Administration of a single IV dose of 1.5 mg/kg ERV was generally safe and well-tolerated in the healthy subjects in this study.

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