Pharmacokinetic and Tissue Distribution of Eravacycline following Intravenous Administration in Rabbits

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Materials and Methods

Eravacycline (2-fluoro-2-phenyl-3,4-dihydro-2H-pyran-6-carboxylic acid) is a novel synthetic tetracycline antibiotic in preclinical and early clinical development. Its mechanism of action involves binding to the translocated 30S ribosomal subunit to block protein synthesis. The drug has a bactericidal activity against a wide spectrum of bacteria, including multidrug-resistant strains. Its pharmacokinetics were studied in NZW rabbits at 1, 2, 4, 8 & 10 mg/kg IV QD with a 5-10 min infusion (n = 6) for 5 days. Plasma samples were collected at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, and 192 hours. Studies were performed at 0.5, 1, 2, and 4 mg/kg as an IV infusion over 6 days with serial plasma sampling on days 1-6, 1-2, 3, 4, 5, and 6. The plasma pharmacokinetic profile was calculated using non-compartmental methods. The peak drug concentration (Cmax) and time of peak drug concentration were obtained directly from the observed data. The terminal elimination rate constant (β) was obtained from a log-linear regression of the plasma concentration-time data. Absolute bioavailability (F) was obtained from the equation AUC = F x CL x AUC. The volume of distribution (Vd) was calculated as Vd = CL / kel.

Results

Pharmacokinetic analysis - The pharmacokinetic profiles for eravacycline were compared from the drug concentration-time data using non-compartmental methods. The peak drug concentration (Cmax) and time of peak drug concentration were obtained directly from the observed data. The terminal elimination rate constant (β) was obtained from a log-linear regression of the plasma concentration-time data. Absolute bioavailability (F) was obtained from the equation AUC = F x CL x AUC. The volume of distribution (Vd) was calculated as Vd = CL / kel.

Plasma Pharmacokinetics of Eravacycline after Intravenous Single Dose Administration at 1, 2, 4, & 10 mg/kg IV to NZW Rabbits

Plasma pharmacokinetic parameters for eravacycline at 1, 2, 4, & 10 mg/kg IV to NZW Rabbits are presented in the table below:

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Cmax (ng/mL)</th>
<th>T1/2 (h)</th>
<th>AUC (hr·ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.16 ± 0.025</td>
<td>1.12 ± 0.32</td>
<td>5,375 ± 549</td>
</tr>
<tr>
<td>2</td>
<td>0.18 ± 0.019</td>
<td>1.12 ± 0.32</td>
<td>12,563 ± 1,790</td>
</tr>
<tr>
<td>4</td>
<td>0.18 ± 0.019</td>
<td>1.12 ± 0.32</td>
<td>45,614 ± 7,887</td>
</tr>
<tr>
<td>10</td>
<td>0.18 ± 0.019</td>
<td>1.12 ± 0.32</td>
<td>150,000 ± 25,000</td>
</tr>
</tbody>
</table>

Eravacycline Plasma AUC vs Dose Correlation

The plasma AUC vs dose relationship and to bridge that relationship to human dosing as a foundation for potential investigation in emerging worldwide, including the two main acquired tetracycline-specific resistance mechanisms: drug efflux pumps and ribosomal protection. Eravacycline is two- to fourfold more potent than tigecycline versus Gram-positive cocci and two- to eightfold more potent against some of the most life-threatening multidrug resistant pathogens that are rapidly emerging worldwide. These include:

- Infections, particularly of pneumonia, intra-abdominal infections, and vascular catheter-related infections that are caused by multidrug-resistant bacteria.
- Pathogens that are rapidly emerging worldwide, including:
  - Drug-resistant Neisseria meningitidis.
  - Carbapenem-resistant Enterobacteriaceae (CRE) and Pseudomonas aeruginosa.
  - Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.
  - Carbapenem-resistant Acinetobacter baumannii.
  - Methicillin-resistant Staphylococcus aureus (MRSA).
  - Vancomycin-resistant Enterococcus (VRE).

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Conclusion/Summary

- Within the single-dose eravacycline PK study, the mean AUCs ranged from 5,375 ng·h/mL to 150,000 ng·h/mL, across doses of 1 to 10 mg/kg. AUCs correlated well within the dosing range (r=0.7).
- Within the multiple-dose eravacycline PK study, the mean AUCs ranged from 2,020 ng·h/mL to 28,888 ng·h/mL, across the range of dosages from 0.5 mg/kg to 4 mg/kg.
- Assuming an MIC of 1 µg/mL, for any one of MDR Enterobacteriaceae, these data would suggest that eravacycline’s AUC/MIC ratios at 1 or 2 mg/kg Q12 of 3.3 to 6.7 that would predict potent activity in plasma and in most tissue sites.
- For patients harboring proteins in infections caused by susceptible bacteria in sites not yet currently studied in clinical trials, these data provide key information about the distribution of eravacycline that would enable probability of success or predict the need for dose escalation to each target tissue exposed.

Abstract

Background: Eravacycline is a novel synthetic tetracycline antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including multidrug-resistant strains. Previous studies have demonstrated that eravacycline has excellent pharmacokinetics and pharmacodynamics in preclinical and clinical settings. This study aimed to evaluate the pharmacokinetic and tissue distribution of eravacycline following intravenous administration in NZW rabbits.

Methods: Rabbits were administered a single dose of eravacycline (1, 2, 4, 8, & 10 mg/kg IV) and tissue samples were collected at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours. Tissue concentrations were determined using liquid chromatography-mass spectrometry. Pharmacokinetic parameters were estimated using non-compartmental methods.

Results: The plasma pharmacokinetic profile of eravacycline was determined in NZW rabbits. The mean peak plasma concentration (Cmax) and time to peak concentration (Tmax) were obtained from the observed data. The terminal elimination rate constant (β) was obtained from a log-linear regression of the plasma concentration-time data. Absolute bioavailability (F) was obtained from the equation AUC = F x CL x AUC. The volume of distribution (Vd) was calculated as Vd = CL / kel.

Conclusions: Eravacycline displays excellent pharmacokinetic characteristics in NZW rabbits and has potential for clinical development against multidrug-resistant bacteria.