INTRODUCTION

- Teipiben pivoxil (TBPM-PI) is an orally bioavailable carbapenem currently in clinical development.
- The pharmacokinetic-pharmacodynamic (PK-PD) relationship has been well characterized using mouse neutrophilic thigh and lung models and also hollow fibre infection models.
- From these studies, the PD driver was derived to be AUC/MIC1/tau<1.
- Using this parameter, the magnitude of the PD target is adjusted for the dosing interval.
- Phase I SAD and MAD studies have been completed and the PK data used to develop a population PK (PPK) model.
- The PPK model was used in Monte Carlo simulations to calculate probability of target attainment (PTA)
- PTA analysis against the derived PD target was used to select the clinical dose for Phase III.

METHODS

Population PK model
- A PPK model was developed using PK data from 36 healthy volunteers receiving either a single or multiple doses of TBPM-PI in either the fasted or fed state.
- PMetrics version 1.5.2 was used to model the data.

PK-PD target
- From studies in the mouse neutrophilic thigh model in 11 wild-type strains and ESBL-producing organisms, the PKPD target was derived to be AUC/MIC1/tau<23 for stasis.
- TBPM-PI was dosed 3 times daily (q12h) in the preclinical studies, so the derived PD target must be adjusted for dosing interval to explore alternative dosing regimens.
- For simulations of q12h regimen, the target for PTA calculations was AUC0-24h/MIC1/tau<23 and for a twice daily dosing regimen (q12h) was AUC0-24h/MIC1/tau<34.5.

PTA
- The PPK model was used to simulate 5000 patients and PTA calculated using the target of free AUC0-24h at steady state (AUC0-24h/tau<1).
- As the PPK model was build from healthy volunteer data, further simulations were conducted based on the same PPK model but with inflated variance on clearance to account for higher variability in patient PK.
- A SENTRY surveillance program was conducted to evaluate the MIC distributions of TBPM across 309 clinical isolates of E. coli and K. pneumoniae, and the PTA by MIC was compared to this.

RESULTS

Table 1 Population PK parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>43.65</td>
<td>9.19</td>
<td>21.05</td>
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<tr>
<td>V/F (L)</td>
<td>25.81</td>
<td>16.88</td>
<td>65.40</td>
</tr>
<tr>
<td>Ka (1/h)</td>
<td>4.33</td>
<td>4.12</td>
<td>95.19</td>
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<tr>
<td>Tlag (h)</td>
<td>0.20</td>
<td>0.14</td>
<td>55.22</td>
</tr>
<tr>
<td>KCP (1/h)</td>
<td>13.72</td>
<td>12.11</td>
<td>88.25</td>
</tr>
<tr>
<td>KPC (1/h)</td>
<td>22.98</td>
<td>10.92</td>
<td>47.53</td>
</tr>
</tbody>
</table>

Figure 1. Goodness of fit plot for the final population PK model

Figure 2. Relationship between 3PR94 AUC/MIC1/tau and efficacy against 11 E. coli and K. pneumoniae wild type and ESBL-producing strains, overlaid by a box and whisker plot of predicted human exposure across the SENTRY E. coli and K. pneumoniae MIC distribution.

Figure 3. Simulated PTA of different dose regimens of TRPM-PI and PTA of TBPM-PI with inflated variance, by MIC overlaying the percentage distribution of E. coli and K. pneumoniae isolates.

CONCLUSIONS

- 600mg given every 8 hours has been selected as the Phase III dose for TBPM-PI-HR for a clinical trial in patients with cUTI.
- This dose is well tolerated in healthy volunteers and is predicted to achieve high PTA against the wild-type distribution of common cUTI pathogens.


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