**Background & Objective**

**Background**  
WCK 771, a novel broad-spectrum florofloquinolone with enhanced activity against MRSA and quinolone-resistant staphylococci, is being developed by Wockhardt as a parenteral anti-MRSA agent.

**Objective**  
The aim of this analysis was to reconcile a 2-fold lower steady-state exposure in subjects from the United States in comparison to subjects in India given the same dose, and determine if any dose adjustments would be required for either population due to differences in body weight.

**Methods**

**Modeling Population**  
Plasma concentration-time data were obtained from 54 Indian patients in various Phase I clinical trials given either single dose (range 600-1200 mg) or multiple dose (range 600-1200 mg BID or TID for 5 days), as well as 30 Caucasian subjects in a single US trial (600, 800, 1000 mg BID for 5 days). For individuals given multiple doses, trough samples as well as rich samples were available for all individuals for analysis.

**Model Development**  
The data was modeled using Phoenix NLME (Nonlinear Mixed Effects v1.3) with the FOCE-ELS algorithm.

**Results**

**Final Model**  
The WCK771 concentrations were analyzed using a 2-compartment IV-infusion model. The absorption of WCK771 after intravenous dosing was described using a zero-order infusion process where the duration of infusion (D1) was estimated. The systemic clearance (CL), the distribution clearance (Q), the volumes of distribution of the central compartment (Vc) and peripheral compartment (Vp) were also estimated.

**Exposure Differences**  
A significant portion of the 2-fold differences in AUC and Cmax between the Indian and US studies for the same dose was explained by allometrically scaling CL and V by body weight. Hence, differences were attributed to the difference in the body weights of the subjects.

**Table 1: Pharmacokinetic Parameters from final population PK model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>BSV (% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Infusion (h)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CL (L/h/70kg)</td>
<td>5.40</td>
<td>19.1%</td>
</tr>
<tr>
<td>Vc (L/70kg)</td>
<td>37.12</td>
<td>29.1%</td>
</tr>
<tr>
<td>Q (L/h/70kg)</td>
<td>0.63</td>
<td>42.3%</td>
</tr>
<tr>
<td>Vp (L/70kg)</td>
<td>7.15</td>
<td>55.3%</td>
</tr>
<tr>
<td>Residual Error (Proportional)</td>
<td>16.5%</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

Simulations showed that the typical steady-state concentrations of WCK771 after multiple-doses of 600 and 800 mg stay above the MIC of 1 mg/L for WCK771 for light and heavy patients. Therefore, no weight based dosage adjustments are required for WCK 771.

**References**


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