Background: WCK 771 (IV) and WCK 2349 (PO) are L-arginine salt and LA-lasine acid prodrug, respectively, of levofloxacin (active moiety), a benzodiazepine quinolone. These agents are being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP) caused by methicillin-resistant Staphylococcus aureus (MRSA). These studies were conducted to evaluate the tolerability and pharmacokinetics of multiple ascending doses of WCK 2349 and WCK 771 in healthy volunteers in US.

Material/methods: These were two separate trials wherein sequential cohorts (n=10 active, 2 placebo) received multiple twice daily doses (5 days) of WCK 771 (800, 1000, or 1200 mg) or placebo, and WCK 2349 (800, 1000, or 1200 mg) or placebo. Blood and urine sampling was done to assess levofloxacin pharmacokinetics. Safety and tolerability assessments were performed throughout dosing and during follow-up visit.

Results: The mean AUC(0-24) and C(max) on Day 1 were 72.70 h•μg/mL, 157.43 h•μg/mL, and 75.79 (15.78) μg/mL respectively for 600 mg; 81.77 h•μg/mL, 178.54 h•μg/mL, and 71.26 (15.49) μg/mL respectively for 800 mg; and 111.49 h•μg/mL, 264.00 h•μg/mL, and 80.80 (17.26) μg/mL respectively for 1200 mg.

Conclusions: WCK 771 and WCK 2349 administered in multiple escalating doses were well tolerated by the healthy subjects in US. Mean total and peak exposures of levofloxacin increased with an increase in dose from 600 to 1000 mg after WCK 2349 but the values remained relatively unchanged from 1000 to 1200 mg. Mean total and peak exposures of levofloxacin increased with an increase in dose from 600 mg to 1200 mg after WCK 2349 was administered.

METHODS

Two separate randomized, double-blind, clinical trials were conducted wherein sequential cohorts (n=10 active, 2 placebo) received multiple twice daily doses (5 days) of WCK 771 (800, 1000, or 1200 mg) or placebo and WCK 2349 (800, 1000, or 1200 mg) or placebo. In both the studies the study drug was administered twice daily at 12-hour intervals.

Blood and urine samples to assess levofloxacin pharmacokinetics were collected at various time points on Days 1, 2, 3, and 5 (blood) and Days 1 and 5 (urine). Safety and tolerability assessments were performed throughout dosing and during follow-up visit.

INTRODUCTION & PURPOSE

WCK 771 (IV) and WCK 2349 (PO) are L-arginine salt and LA-lasine acid prodrug, respectively, of levofloxacin (active moiety), a benzodiazepine quinolone. These agents are being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP) caused by gram-positive bacteria, including MRSA.

Multiple Ascending Dose (MAD) studies were conducted to evaluate the safety, tolerability and pharmacokinetics of WCK 2349 and WCK 771 in healthy adult volunteers in US.

RESULTS

- Equal number of male and female subjects enrolled in both studies. Subject demographics summarized in Table 1.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCK 771</td>
<td>40 (25)</td>
<td>38 (35-45)</td>
</tr>
<tr>
<td>WCK 2349</td>
<td>40 (25)</td>
<td>38 (35-45)</td>
</tr>
</tbody>
</table>

- After administration of WCK 771 and WCK 2349 twice daily on Day 1 and Day 5, mean AUC and C(max) of levofloxacin increased as the dose increased.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(0-24) (mmol/L • h/L)</th>
<th>C(max) (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCK 771</td>
<td>284.68 ± 247.60</td>
<td>22.36 ± 17.26</td>
</tr>
<tr>
<td>WCK 2349</td>
<td>287.90 ± 250.61</td>
<td>22.25 ± 17.26</td>
</tr>
</tbody>
</table>

- Plasma concentration-time profiles of levofloxacin versus time by treatment on Day 5 for WCK 771 and WCK 2349 is presented in Figure 4 and 5 respectively.

CONCLUSIONS

- There were no deaths or Serious Adverse Events (SAEs) during the studies. Adverse events (AEs) were generally mild or moderate in severity. No clinically significant abnormalities were observed in vital sign measurements, 12-lead ECG results, or phototoxicity assessments.

- After administration of WCK 771 and WCK 2349 administered in multiple escalating doses were well tolerated by the healthy subjects in US. Mean total and peak exposures of levofloxacin increased from 800 to 1000 mg after WCK 2349 but the values remained relatively unchanged from 1000 to 1200 mg.

- Mean total and peak exposures of levofloxacin increased with an increase in dose from 600 mg to 1200 mg after WCK 2349 was administered.

- Multiple Ascending Dose (MAD) studies were conducted to evaluate the safety, tolerability and pharmacokinetics of WCK 2349 and WCK 771 in healthy adult volunteers in US.

- Safety and Pharmacokinetics of Multiple Ascending Doses of WCK 771 and WCK 2349

R. Chugh, F. Lakdavala, A. Bhatia
Wockhardt Ltd., Mumbai, India

Poster presented at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 9th-12th April, 2016, Amsterdam.