Pharmacokinetics and Safety of Intravenous Solithromycin in Children ≥6 Years of Age

Introduction

Solithromycin is a fluoroketolide antibiotic with activity against a wide array of respiratory tract pathogens.

Solithromycin was demonstrated to be non-inferior to moxifloxacin in the treatment of community-acquired bacterial pneumonia (CABP) in two adult Phase 3 trials.

Solithromycin is planned to be available in oral and intravenous (i.v.) formulations.

We sought to characterize the pharmacokinetics (PK) and safety of i.v. solithromycin in children ≥6 years of age.

Methods

We performed a phase 1, multi-dose, open-label, multi-center study (ClinicalTrials.Gov #NCT02268279) to determine the PK of intravenous solithromycin in children ≥6 years with suspected or confirmed bacterial infections.

Children and adolescents were administered solithromycin as an add-on therapy for up to 5 days according to the following age-based dosing regimens: 6–<12 years, 7 mg/kg daily; 12–<17 years, 6 mg/kg daily (up to 400 mg).

We collected PK samples at end of administration in children ≥6 years.

PK samples were analyzed by a central laboratory using a validated LC/MS/MS method.

A noncompartmental PK analysis was performed in Phoenix WinNonLin (ver. 6.3, Pharsight Corporation). We calculated the maximal solithromycin concentration (Cmax) and area under the concentration (Cmax) and area under the concentration versus time curve from 0 to 24 hours (AUC0-24) on Day 1 and Days 3–5.

Estimates of solithromycin exposure in children and adolescents were compared to i.v. adult PK estimates from Phase 1 studies.

Results

Figure 1. Dose-corrected solithromycin concentration versus time following intravenous administration in children ≥6 years.

- Eight children (median [range] age 7 years [6–10]; weight 26 kg [11–36]) and 10 adolescents (median [range] age 14.5 years [12–17]; weight 53 kg [29–69]) completed the study.
- The median (range) daily dose was 7.0 mg/kg (7.0–7.1) and 5.9 mg/kg (5.8–6.0) in children and adolescents, respectively.
- Solithromycin concentrations versus time are shown in Figure 1. A comparison of solithromycin exposure for children and adolescents enrolled in this study and historical healthy adult data is shown in Table 1.
- The most common drug-related adverse events were infusion site pain/reaction (4 [22.2%]), diarrhea (3 [16.7%]), and headache (1 [6.3%]). The incidence of infusion-related adverse events in the adult phase 3 study was 31.3%. There were no drug-related alterations in liver transaminases.

Table 1. Observed median (range) solithromycin exposure estimates.

<table>
<thead>
<tr>
<th>Day</th>
<th>Parameter</th>
<th>6–&lt;12 years (n=8)*</th>
<th>12–17 years (n=10)*</th>
<th>Adult Value (n=10)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cmax (µg/mL)</td>
<td>1.9 (0.8–4.7)</td>
<td>1.8 (1.2–8.4)</td>
<td>2.2 (1.6–3.0)</td>
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<tr>
<td></td>
<td>AUC0-24 (µg*h/mL)</td>
<td>8.3 (3.8–22.1)</td>
<td>7.8 (3.8–30.4)</td>
<td>5.3 (3.9–7.0)</td>
</tr>
<tr>
<td>3/4/5</td>
<td>Cmax (µg/mL)</td>
<td>2.8 (1.0–8.1)</td>
<td>2.3 (1.2–7.7)</td>
<td>2.7 (2.2–3.5)</td>
</tr>
<tr>
<td></td>
<td>AUC0-24 (µg*h/mL)</td>
<td>10.6 (2.7–18.4)</td>
<td>12.3 (8.2–19.9)</td>
<td>12.1 (5.8–18.8)</td>
</tr>
</tbody>
</table>

*Not all participants contributed data because of samples observed below the quantification limit or partial data. **Adult data taken from phase 1 studies (400 mg administered i.v.). Cmax: maximal concentration; AUC0-24: area under the concentration versus time curve from 0 to 24 hours.

Conclusions

Intravenous solithromycin exposure and safety in a small cohort of children and adolescents was comparable to that reported in adults.

ACKNOWLEDGEMENTS: This research was sponsored by the U.S. Biomedical Advanced Research and Development Authority (HHSO100201300009C), who has a contract with Cempra Pharmaceuticals, Inc. to perform the study.