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

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Introduction

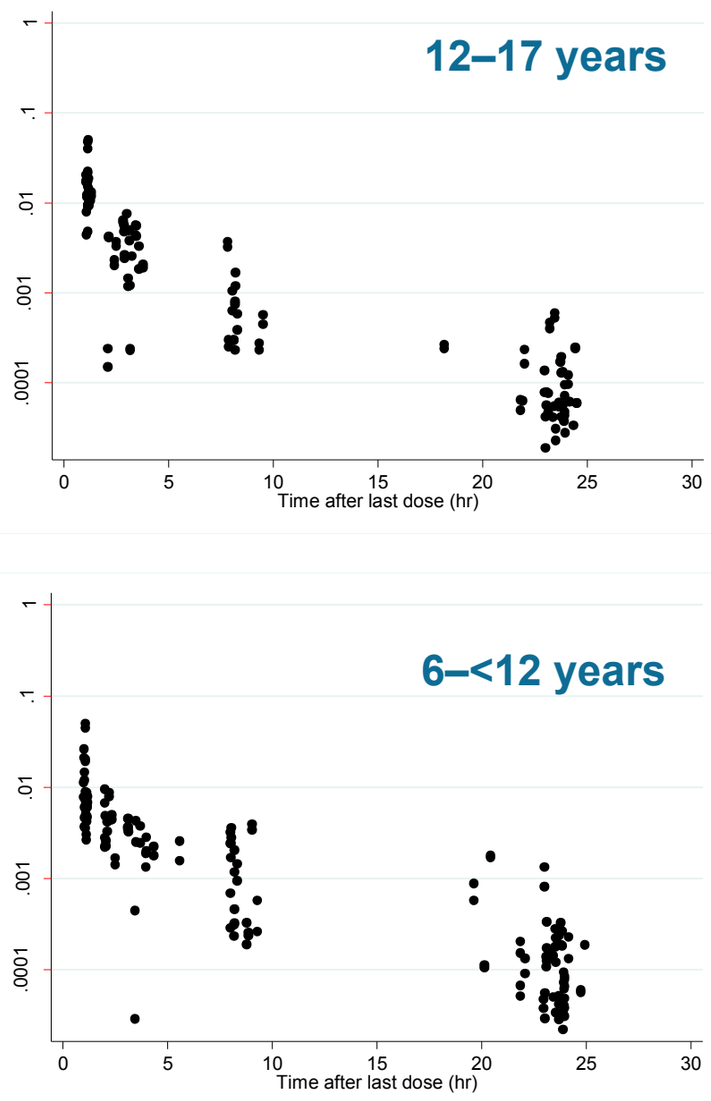
- Solithromycin is a fluoroketolide antibiotic with activity against a wide array of respiratory tract pathogens.
- Solithromycin was demonstrated to be non-inferior to moxifloxacin in the treatment of community-acquired bacterial pneumonia (CABP) in two adult Phase 3 trials.
- Solithromycin is planned 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 infusion, 2–4, 8–10, and 23–24 hours after the first and multi-dose administration.
- 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 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.

Day	Parameter	6–<12 years (n=8)*	12–17 years (n=10)*	Adult Value (n=10)*,†
1	C_{MAX} (µg/mL)	1.9 (0.8–4.7)	1.8 (1.2–8.4)	2.2 (1.6–3.0)
	$AUC_{0\text{-}24}$ (µg*h/mL)	8.3 (3.8–22.1)	7.8 (3.8–30.4)	5.3 (3.9–7.0)
3/4/5	C_{MAX} (µg/mL)	2.8 (1.0–8.1)	2.3 (1.2–7.7)	2.7 (2.2–3.5)
	$AUC_{0\text{-}24}$ (µg*h/mL)	10.6 (2.7–18.4)	12.3 (8.2–19.9)	12.1 (5.8–18.8)

**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.). C_{max}: maximal concentration; $AUC_{0\text{-}24}$: 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.

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