Solithromycin in Children and Adolescents With Community-acquired Bacterial Pneumonia

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Background: Solithromycin is a new macrolide-ketolide antibiotic with potential effectiveness in pediatric community-acquired bacterial pneumonia (CABP). Our objective was to evaluate its safety and effectiveness in children with CABP.

Methods: This phase 2/3, randomized, open-label, active-control, multicenter study randomly assigned solithromycin (capsules, suspension or intravenous) or an appropriate comparator antibiotic in a 3:1 ratio (planned n = 400) to children 2 months to 17 years of age with CABP. Primary safety endpoints included treatment-emergent adverse events (AEs) and AE-related drug discontinuations. Secondary effectiveness endpoints included clinical improvement following treatment without additional antimicrobial therapy.

Results: Unrelated to safety, the sponsor stopped the trial prior to completion. Before discontinuation, 97 participants were randomly assigned to solithromycin (n = 73) or comparator (n = 24). There were 24 participants (34%, 95% CI, 23%–47%) with a treatment-emergent AE in the solithromycin group and 7 (29%, 95% CI, 13%–51%) in the comparator group. Infusion site pain and elevated liver enzymes were the most common related AEs with solithromycin. Study drug was discontinued due to AEs in 3 subjects (4.3%) in the solithromycin group and 1 (4.2%) in the comparator group. Forty participants (65%, 95% CI, 51%–76%) in the solithromycin group achieved clinical improvement on the last day of treatment versus 17 (81%, 95% CI, 58%–95%) in the comparator group. The proportion achieving clinical cure was 60% (95% CI, 47%–72%) and 68% (95% CI, 43%–87%) for the solithromycin and comparator groups, respectively.

Conclusions: Intravenous and oral solithromycin were generally well-tolerated and associated with clinical improvement in the majority of participants treated for CABP.

Key Words: pneumonia, solithromycin, macrolide, pediatric

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Community-acquired bacterial pneumonia (CABP) is an acute infection of the lung parenchyma among patients not residing in a hospital or long-term care facility. CABP is common world-

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All clinical studies from which data were obtained were conducted in accordance with the ethical standards of the institutional and/or national research committee and the Helsinki Declaration.

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wide and associated with significant morbidity and mortality,[1] often causing fever, chills, rigors, cough, chest pain and dyspnea. In children, numerous bacterial species can cause CABP including *Streptococcus pneumoniae (S. pneumoniae)*, *Mycoplasma pneumoniae (M. pneumoniae), Hemophilus influenzae (H. influenzae)* and *Staphylococcus aureus* (*S. aureus*).[2–5] Of these, *S. pneumoniae* is the most common worldwide cause of CABP in children older than 1 week of age,[6] and in many regions the frequency of macrolide resistance among *S. pneumoniae* isolates approaches 90%.[7–9] However, solithromycin—a new fourth generation macrolide-ketolide antibiotic—has superior antimicrobial activity against macrolide-resistant *S. pneumoniae*[10] and >15 times the potency of other macrolides against common gram-positive, gram-negative and atypical CABP pathogens.[11] Additionally, *M. pneumoniae* has been found to have frequent macrolide resistance in the pediatric population.[12] Solithromycin allows once daily dosing while displaying a low rate of developing resistance.[13] Because of the increasing problem of antibiotic resistance and high worldwide morbidity and mortality of CABP, there is an urgent need to develop novel antibiotics for the treatment of CABP.

Solithromycin has excellent in vitro bactericidal activity against all of these CABP organisms, including methicillin-resistant *S. aureus*,[14,15] due to its ability to bind to 3 distinct sites on the bacterial ribosome.[16] Two large phase 3 clinical trials in adults demonstrated Food and Drug Administration (FDA)-required effectiveness targets of solithromycin in the treatment of CABP.[17,18] In a global trial comparing 5 days of oral solithromycin versus 7 days of oral moxifloxacin for treatment of CABP in adults, solithromycin was noninferior to moxifloxacin in both early clinical response and short-term follow-up.[17] Similarly, intravenous-to-oral solithromycin was noninferior to intravenous-to-oral moxifloxacin in CABP among 863 adults.[18] In these phase 3 trials, serum alanine aminotransferase elevations above the 3-fold upper limit of normal (ULN) occurred at a higher frequency than with other macrolide antibiotics, leading the FDA to mandate expanded safety trial data prior to approval.[19,20] We previously performed 2 phase 1 studies to assess the pharmacokinetics and safety of solithromycin in children 2 months to 17 years of age with suspected or confirmed bacterial infections. We present the results of a planned safety and effectiveness study in children that were collected before a financially-based sponsor-initiated termination of the pediatric development program.

METHODS

Study Design and Procedures

This study was planned as a multicenter global phase 2/3, randomized open-label comparator study to determine the safety and effectiveness of solithromycin in pediatric patients 2 months to 17 years of age with suspected or confirmed CABP. Participants were enrolled to receive solithromycin or a comparator antibiotic selected by the investigator (see below), administered intravenous and/or by mouth (PO) based on weight and age. We used a block randomization schedule generated using a clinical database randomization module. Randomization was stratified by age groups: 2 months to <2 years, 2 to <6 years, 6 to <12 years and 12 to 17 years (inclusive). Clinical assessments were conducted at baseline, during the treatment period, and at days 16 and 28 postrandomization. The study protocol was approved by all site; and included written informed consent/assent as appropriate, and a data and safety monitoring board monitored the study. The planned 400 enrollments were stopped by the sponsor due to discontinuation of their solithromycin development program. The trial was registered with ClinicalTrials.gov (NCT02605122).

Study Participants

Between September 2016 and April 2018, children and adolescents from the age of 2 months to 17 years were eligible if they required hospitalization or urgent care visit for the presence of CABP. CABP diagnosis required each of the following criteria within 72 hours of randomization: (1) history of fever (rectal, temporal, ear or oral temperature ≥38 °C or axillary temperature ≥37.5 °C) or hypothermia (rectal, temporal, ear or oral temperature <35 °C or axillary temperature <34.5 °C), (2) chest radiograph infiltrates consistent with bacterial pneumonia or pneumonia caused by atypical bacterial agents (participants seen in an outpatient setting otherwise meeting CABP criteria and starting on oral therapy did not require a radiograph for inclusion), (3) ≥2 CABP cardiorespiratory signs or symptoms and (4) ≥1 abnormal biomarkers suggestive of CABP. Participants with bacterial meningitis, active tuberculosis, active pregnancy or any other condition deemed by the site investigator to impair study participation were excluded. Participants were excluded if they had previously received >48 hours of antibacterial therapy or were suspected to have a hospital-acquired or ventilator-associated infection.

Study Treatment

Participants were randomized to either solithromycin or an approved comparator antibiotic chosen by the local clinician-investigator and could include amoxicillin, amoxicillin clavulanate, ampicillin, azithromycin, erythromycin or ceftriaxone. Acceptable comparator drugs were selected to include drugs commonly used per standard-of-care in both the United States and at participating international sites. Participants receiving intravenous or oral solithromycin were treated daily for 5 to 7 days. Body-weight adjusted therapeutic solithromycin dosing regimens for each age group and each of the 3 formulations (oral capsule, oral suspension and intravenous infusion) were determined in phase 1 studies in children.[21,22] We used a model informed drug development approach based on population pharmacokinetics modeling and simulation to derive oral and intravenous dosing for children and adolescents to achieve solithromycin exposures consistent with therapeutic exposures seen in adults. Participants starting with oral solithromycin were initiated with a loading dose, while no loading doses were used with intravenous solithromycin. Participant dosing was based on route [intravenous: 8 mg/kg; oral suspension: day 1—20 mg/kg (max 800 mg), days 2–5—10 mg/kg (max 400 mg); capsules: >30 kg: day 1—800 mg, days 2–5—400 mg, >20–30 kg: day 1—600 mg, days 2–5—400 mg, ≤20 kg: day 1–400 mg, days 2–5—200 mg]. Participants randomized to comparator were treated for 5 to 10 days at the discretion of the site investigator. Enteral solithromycin was administered approximately every 24 hours without regard to food. Solithromycin was provided as hard gelatin capsules that contained 200 mg of solithromycin, as a powder for oral suspension, or as a lyophilized powder for intravenous infusion after reconstitution and dilution. The intravenous formulation of solithromycin (solithromycin for injection) was provided as a lyophilized formulation in 50-mL clear glass vials containing 400 mg of solithromycin for single use only. The lyophilized cake was reconstituted with sterile water for injection and then added to sterile 0.9% sodium chloride injection.

Microbiology Assessments

Microbiology assessments performed in accordance with routine standard-of-care were recorded. These included all cultures from cerebrospinal fluid, pleural fluid, blood, urine (catheter or suprapubic tap) and sputum, as well as molecular and serologic tests for *M. pneumoniae* and *C. pneumoniae.*

Safety Measures

The safety of solithromycin versus comparator was assessed using frequency of adverse events (AE). The primary safety endpoints were the proportion of participants experiencing a treatment-emergent AE (TEAE) through day 16 and the proportion of participants discontinuing study drug due to a related AE. SeriousAEs (SAEs) were followed for 28 days postrandomization. New diagnoses or examination/laboratory findings that occurred or preexisting conditions that worsened in frequency or intensity were considered AEs or SAEs. Study-required safety laboratory tests included hemoglobin, hematocrit, white blood cell count with differential, platelet count, blood urea nitrogen, calcium, serum creatinine, potassium, sodium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin and albumin and were collected at baseline, during treatment and at day 16 and 28 postrandomization. An independent data monitoring committee was created and oversaw prespecified rules for safety reporting and stopping rules.

Effectiveness Measures

Planned clinical effectiveness endpoints included clinical improvement on the last day of treatment (end of treatment response). Clinical improvement was defined as improvement of at least 1 of the presenting signs and symptoms of CABP with no deterioration or progression in any presenting sign or symptom, no development of new sign or symptom of CABP, and no requirement for additional or alternative antimicrobial therapy. Effectiveness was also defined by early clinical response at days 2 to 4, and clinical success (ie, cure) at the short-term follow-up visit [16 days (±4 days) postrandomization]. Clinical cure was defined as resolution of all presenting signs and symptoms of CABP (excluding cough), no development of new signs or symptoms of CABP, and no requirement for alternative antimicrobial therapy. While this study was open-label, there was a blinded subinvestigator at each site who was responsible for conducting the clinical outcome (effectiveness) assessments.

Statistical Analyses

All participants who received at least one dose of study drug (solithromycin or active comparator) were included in the safety analysis population; while all randomized participants were included in the effectiveness population. For TEAEs and study drug discontinuation due to a related AE (primary safety endpoints), the frequency and percentage was determined by treatment group for the overall safety population with Clopper-Pearson exact 95% CIs. Additional safety analyses included summaries of treatment-related AEs as well as SAEs. Liver function tests were categorized by multiples of the ULN for each test (>ULN, >3× ULN and >10× ULN). All analyses included summaries for both treatment and active comparator. The planned study was powered to compare safety endpoints between treatment groups. The original sample size of 300 in the solithromycin group was chosen based on the ability to observe an SAE at a frequency higher than 1%. With a safety population of 70 in the solithromycin treatment group, the probability (power) of observing at least one participant with an SAE frequency ≥1% was approximately 51%.

The primary effectiveness endpoint was the presence or absence of clinical improvement on the last day of treatment. Additionally, effectiveness was described similarly as a binary variable representing early clinical improvement on treatment days 2 to 4, and representing clinical cure on day 16 (±4 days) postrandomization. The frequency and percentage of participants achieving each effectiveness endpoint was determined along with 95% Clopper-Pearson (exact) CIs. Summaries were calculated by treatment group for the overall intention-to-treat population. The study was not powered for a statistical comparison of efficacy end points between treatment groups. The statistical analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

Between September 2016 and April 2018, we enrolled 97 participants from 27 sites around the world including from the United States (30 participants across 11 sites), Bulgaria (27 participants across 4 sites), Hungary (23 participants across 7 sites), the Philippines (16 participants across 4 sites) and Spain (1 participant at 1 site). Among the 97 enrolled participants, 68 (93%) of 73 participants in the solithromycin group and 22 (92%) of the 24 participants in the comparator group completed all doses of study drug and the follow-up visit at 16 days (±4 days) after randomization. Withdrawal and early discontinuation from study drug were generally balanced across the treatment arms (Fig. 1). Demographics

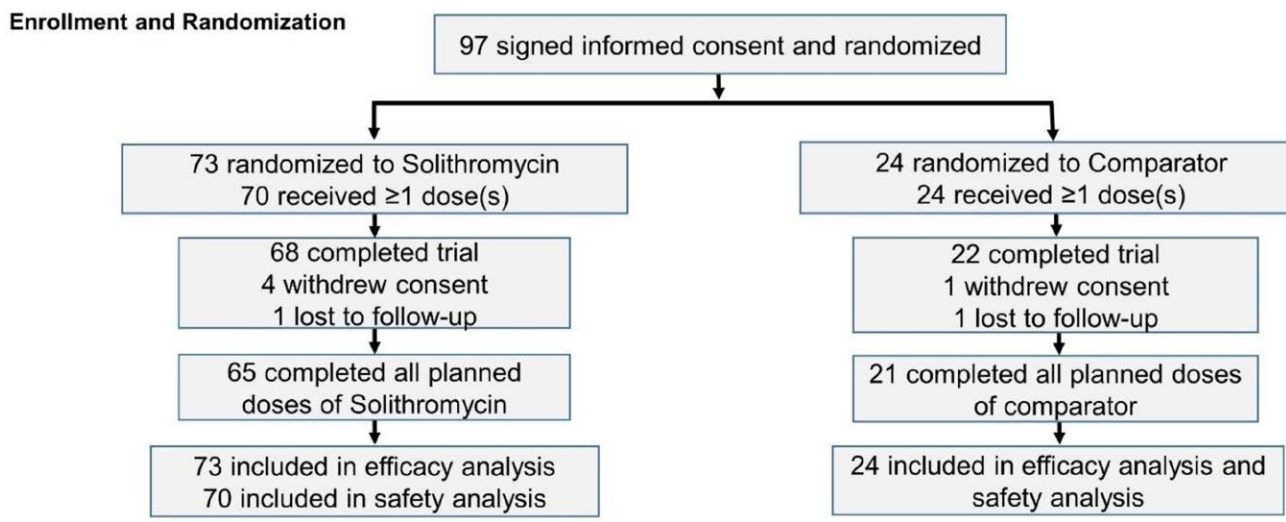

FIGURE 1. Profile of participants.

of the study population were generally similar by treatment arm and are summarized in Table 1. Only 19 (20.2%) participants had an identifiable respiratory pathogen either at baseline or during the treatment period (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E719). The most common pathogens detected were *S. aureus* (4.3%), *Haemophilus* species (3.2%) and *Neisseria* species (3.2%).

Safety

The solithromycin safety profile, measured by the frequency of TEAEs and of AEs deemed related to study drug leading to drug discontinuation, was generally similar to that seen in the comparator group. However, the frequency of total AEs related to study drug was higher in the solithromycin group versus the comparator group (24.3% vs. 8.3%). This difference was driven by increases in hepatic enzymes and infusion site reactions (Table 2). The most commonly observed AEs and abnormalities (excluding infusion site pain) were hepatic enzyme increase and skin and subcutaneous tissue disorders (rash and phlebitis). Of the 41 participants who received solithromycin intravenously, 11 (26.8%) experienced a related infusion site AE.

There were 24 (34.3%) participants with a TEAE in the solithromycin group and 7 (29.2%) in the comparator group. Study drug was discontinued due to AEs in 3 participants (4.3%) in the solithromycin group and 1 participant (4.2%) in the comparator group. Among the 3 participants with solithromycin discontinuation, 2 had infusion site reactions and one had urticaria. There were 2 SAEs, one in each treatment arm. The SAE in the solithromycin group was reported as pneumonia prolonging hospitalization, which was deemed unrelated to study drug, and did not lead to study drug discontinuation. There were no fatal AEs. Overall, 17 (24.3%) participants in the solithromycin group reported an AE related to study treatment, with the highest rate in the 6- to <17-year-old cohort. In the comparator group, 2 (8.3%) participants reported an AE related to study treatment. The solithromycin group experienced more AEs deemed related to study treatment, most of which were related to infusion site pain.

TABLE 1. Participant Population

Population	Solithromycin (n = 70)	Comparator (n = 24)
Age, y, mean (SD)	9.5 (4.7)	9.7 (5.0)
Female sex, n (%)	30 (42.9)	11 (45.8)
Race, n (%)		
Black or African American	11 (15.7)	2 (8.3)
White	47 (67.1)	16 (66.7)
Asian	12 (17.1)	4 (16.7)
Other	0 (0)	2 (8.3)
Hispanic/Latino ethnicity, n (%)	2 (2.9)	2 (8.3)
Medical history at enrollment		
Asthma	12 (17.1)	3 (12.5)
Allergic disease	5 (7.1)	2 (8.3)
Tracheomalacia	1 (1.4)	0 (0)
ADHD	0 (0)	0 (0)
Restrictive lung disease	0 (0)	1 (4.2)
GERD	3 (4.3)	0 (0)
Region of enrollment, n (%)		
Bulgaria	21 (30)	6 (25)
Hungary	19 (27.1)	4 (16.7)
Philippines	12 (17.1)	4 (16.7)
Spain	0 (0)	1 (4.2)
United States	18 (25.7)	9 (37.5)

ADHD indicates attention deficit/hyperactivity disorder; GERD, gastroesophageal reflux disease.

Across all age and treatment groups, the majority of participants did not have postbaseline liver function test changes (change from normal to >ULN) in hepatic enzymes, total bilirubin and direct bilirubin (Table 3). Among solithromycin-treated participants, 2 (3.0%) developed new onset alanine aminotransferase or aspartate aminotransferase elevation >3× ULN while this did not occur among comparator-treated participants. One patient (1.4%) in the solithromycin group (6–<17 years) reported a TEAE of hepatic enzyme increase. The patient did not have a prior medical history of liver disease, and the findings resolved spontaneously without intervention or drug discontinuation.

Clinical Outcomes

Results of the planned effectiveness measures were generally similar between treatment groups. Among the 62 solithromycin-treated participants, 40 (64.5%, 51%–76%) achieved clinical improvement on the last day of treatment versus 17 of the 21 comparator-treated group (81%, 58%–95%). There was substantial overlap in the 95% CI range of clinical improvement for both treatment groups, as shown in Table 4. The proportion of participants achieving early clinical response was 66.7% and 46.7% for the solithromycin and comparator group, respectively. The proportion of participants achieving clinical cure was 60.0% and 68.4% for the solithromycin and comparator groups, respectively.

DISCUSSION

Safety and clinical outcomes following intravenous and oral solithromycin in children 2 months to 17 years of age were evaluated in this Phase 2/3 multicenter, open-label, comparator-controlled trial. Following an FDA advisory board meeting which did not approve the use of 5 or more days of solithromycin in adults for CABP, the decision was made by the sponsor to discontinue the adult drug development program. Early discontinuation of the pediatric trial was then initiated by the sponsor and was not due to any specific safety or effectiveness concerns in the current pediatric trial. This study exhibited a high rate of completion in the solithromycin group, and in this study's limited number of participants, was safe and well-tolerated. In addition, clinical outcomes following solithromycin were comparable to those seen in the standard-of-care comparator group. Because antibiotics with once daily dosing and a short treatment duration are especially desirable in children, solithromycin may be a promising novel treatment for children with CABP, particularly in an era of increasing antibiotic resistance to standard antimicrobial agents.

The safety and tolerability profile of solithromycin in children enrolled in this study is consistent with our prior study findings.[21,22] Specifically, the rate of elevated liver enzymes >3× ULN was 2.4% among the 84 children ages 0 to 17 years enrolled in a prior pediatric solithromycin study[21] and 4.6% among 424 adults with CABP,[17] comparable to the 3.0% rate observed in this study. One patient in the solithromycin group (6–<17 years) reported a TEAE of hepatic enzyme increase. This patient did not have a prior medical history of liver disease, and the findings resolved spontaneously without intervention and without solithromycin discontinuation. The current finding of 3.0% is important given that the shorter treatment duration in the prior pediatric solithromycin study (<5 days) could have limited hepatic toxicity of solithromycin. The rate in this study is lower than the 9.1% observed in adult subjects treated with solithromycin.[18] Numerous factors not explored in this study, including physiologic differences resulting in reduced sensitivity of hepatocytes to solithromycin, variability in systemic exposure to solithromycin, or differences in underlying severity of illness may explain these differences.

TABLE 2. Safety Outcomes

	Solithromycin (n = 70)		Comparator (n = 24)	
Outcomes	n/N (%)	95% CI	n/N (%)	95% CI
Related AEs causing drug discontinuation, n (%)	3/70 (4.3)	(1%–12%)	0/24 (0)[a]	(0%–14%)
Reason for discontinuation, n (%)				
Infusion site reaction[b]	2 (2.9)		0	
Urticaria	1 (1.4)		0	
Other	0		0	
Treatment-emergent AE, n (%)	24/70 (34.3)	(23%, 47%)	7/24 (29.2)	(13%, 51%)
Treatment-emergent AE by system, n (%)[c]				
Anemia	1/70 (1.4)		0	
Bradycardia	0		1/24 (4.2)	
Diarrhea	1/70 (1.4)		4/24 (16.7)	
Abdominal discomfort	1/70 (1.4)		0	
Vomiting	1/70 (1.4)		0	
Fatigue	0		1/24 (4.2)	
Infusion site findings				
Pain	6/70 (8.6)		0	
Pruritis	1/70 (1.4)		0	
Urticaria	1/70 (1.4)		0	
Reaction	1/70 (1.4)		0	
Peripheral edema	1/70 (1.4)		0	
Infection-related findings				
Bacteremia	1/70 (1.4)		0	
Infectious pleural effusion	1/70 (1.4)		0	
Hypokalemia	0		1/24 (4.2)	
Hyperglycemia	1/70 (1.4)		0	
Respiratory				
Nasal congestion	0		1/24 (4.2)	
Epistaxis	1/70 (1.4)		0	
Allergic rhinitis	1/70 (1.4)		0	
Tachypnea	1/70 (1.4)		0	
Skin/subcutaneous				
Pruritis	1/70 (1.4)		0	
Rash (not defined)	1/70 (1.4)		0	
Rash erythematous	1/70 (1.4)		0	
Rash maculopapular	1/70 (1.4)		0	
Urticaria	1/70 (1.4)		0	
Phlebitis	5/70 (7.1)		0	
SAE, n (%)[d]	1/70 (1.4)		1/24 (4.2)	
Viral pneumonia	0		1 (4.2)	
Pneumonia	1 (1.4)		0	
Related AE, n (%)	17/70 (24.3)		2/24 (8.3)	
Diarrhea	0		2 (8.3)	
Epistaxis	1 (1.4)		0	
Hepatic enzyme increase	5 (7.1)		0	
Infusion site reaction	11 (15.7)		0	
Abdominal discomfort	1 (1.4)		0	
Fatal SAE, n (%)	0		0	

[a]One participant in the comparator group had TEAE (viral pneumonia) which led to drug discontinuation but this was deemed not related to study drug.

[b]One participant reported pain/phlebitis, one reported pain, pruritis/urticaria.

[c]Infusion site AEs.

[d]Both SAEs were deemed not related to study drug.

While not powered for comparisons of effectiveness endpoints, the study assessed clinical outcomes following solithromycin and comparator antibiotic treatment at three separate time points using clinically important endpoints of response and cure. Outcomes used for preliminary effectiveness suggested that overall cure rate was lower in this study compared to other recent pediatric CABP trials. However, cure rates do not appear to differ significantly between the solithromycin and comparator arms of the study, though the trial was not powered to conclusively detect differences. Overall, clinical cure rate at 16 days postrandomization was lower for children treated with solithromycin (60%, 95% CI, 47%–72%) when compared to prior pediatric CABP trials of levofloxacin (94%),[23] amoxicillin clavulanate (90%), azithromycin (72%),[24] erythromycin (93%), ceftaroline (88%)[25] or ceftriaxone (89%).[25] However, a stricter definition of clinical cure that was used in this trial, requiring the resolution of all presenting signs and symptoms (except cough) as opposed to the resolution of signs and symptoms associated with active infection, as well differences in the timing of cure assessment, likely explain these differences. Clinical improvement on the last day of treatment (65%) and early clinical response rates (67%) on solithromycin were comparable to clinical cure rates at 16 days postrandomization (60%). These findings may suggest that longer treatment duration would not be needed despite the lower cure rate observed.

This study had limitations including its early termination, which limited the ability to make conclusions about solithromycin's safety and effectiveness. The study was discontinued early due to a company business decision. Study discontinuation was not related

TABLE 3. Summary of Liver Function Tests by Treatment Arm—Safety Population

		Solithromycin, N = 70		Comparator, N = 24	
Outcome		Screening, n/N (%)	Follow-up, n/N (%)	Screening, n/N (%)	Follow-up, n/N (%)
ALT	>ULN	3 (4.6%)	11 (16.4%)	1 (4.3%)	3 (13.6%)
	>3× ULN	0	1 (1.5%)	0	0
	>10× ULN	0	0	0	0
	Evaluable subjects	65	67	23	22
AST	>ULN	11 (16.9%)	13 (19.4%)	3 (13.0%)	4 (18.2%)
	>3× ULN	1 (1.5%)	1 (1.5%)	0	0
	>10× ULN	0	0	0	0
	Evaluable subjects	65	67	23	22
ALT or AST	>ULN	12 (18.5%)	18 (26.9%)	4 (17.4%)	6 (27.3%)
	>3× ULN	1 (1.5%)	2 (3.0%)	0	0
	>10× ULN	0	0	0	0
	Evaluable subjects	65	67	23	22
Direct bilirubin	>ULN	1 (1.7%)	3 (4.5%)	0	1 (4.3%)
	>3× ULN	0	0	0	0
	>10× ULN	0	0	0	0
	Evaluable subjects	60	67	20	23

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 4. Clinical Effectiveness

Outcomes	Solithromycin		Comparator	
All ages	n/N (%)	95% CI	n/N (%)	95% CI
Clinical improvement[a]	40/62 (64.5)	51%–76%	17/21 (81.0)	58%–95%
Early clinical response[b]	34/51 (66.7)	52%–79%	7/15 (46.7)	21%–73%
Clinical cure[c]	36/60 (60.0)	47%–72%	13/19 (68.4)	43%–87%
Two months to 5 y				
Clinical improvement[a]	5/10 (50.0)	19%–81%	2/3 (66.7)	9%–99%
Early clinical response[b]	4/9 (44.4)	14%–79%	1/5 (20.0)	1%–72%
Clinical cure[c]	4/9 (44.4)	14%–79%	3/4 (75.0)	19%–99%
Six–17 y				
Clinical improvement[a]	35/52 (67.3)	53%–80%	15/18 (83.3)	59%–96%
Early clinical response[b]	30/42 (71.4)	55%–84%	6/10 (60.0)	26%–88%
Clinical cure[c]	32/51 (62.7)	48%–76%	10/15 (66.7)	38%–88%

[a]Assessed on last day of treatment (+48 h) and defined as an improvement in at least one CABP presenting sign or symptom with no deterioration in any sign or symptom of CABP, no development of new sign or symptom of CABP, and no requirement for additional or alternative antimicrobial therapy.

[b]Assessed on days 2–4 and defined similarly to clinical improvement.

[c]Assessed on day 16 postrandomization (±4 d) and defined resolution of all presenting CABP signs and symptoms and no requirement for an additional antibiotic.

to safety or tolerability. Some study staff and participants were not blinded to study treatment. In some cases, this can contribute to performance or attrition bias, though we did not see evidence of differential attrition. Overall, the preliminary safety findings in this phase 2/3 study in children with suspected or confirmed CABP support further evaluation of solithromycin in a larger clinical study population of children with CABP, to support new options for treatment in an era of increasing antibiotic resistance.

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