Comparison of azithromycin pharmacokinetics following single oral doses of extended-release and immediate-release formulations in children with acute otitis media

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Azithromycin extended-release (ER) oral suspension was developed to improve the gastrointestinal tolerability profile without substantially compromising the systemic exposure. A 30 mg/kg single dose of azithromycin immediate-release (IR) oral suspension has been used in children to treat acute otitis media (AOM). This study was conducted to compare the pharmacokinetics of 60 mg/kg azithromycin ER single dose with 30 mg/kg azithromycin IR single dose in AOM children aged 6 months to 6 years (n = 19 per treatment). Serum samples were collected at 1, 2, 3, 4, 8, 24, 48 and 72 hours after dosing. Area under the curve from time zero to 72 hours post-dosing (AUC$_{0-72}$) was calculated based on non-compartmental method. One-way analysis of variance (ANOVA) was used to compare exposure parameters (e.g., AUC$_{0-72}$ and peak concentration) as well as concentrations at each time point. The adjusted geometric mean ER/IR AUC$_{0-72}$ ratio [90% confidence interval (CI)] was 157.98% (98.87%, 252.44%), which met the pre-defined criterion on the lower boundary of the 90% CI of ≥80%. As expected, due to the slower release profile of ER, the concentrations of ER during the first 3 hours were lower than that of IR. After 3 hours post-dosing, the lower boundary of the 90% CI for the ER/IR concentration ratios were higher than 100%. These results indicated that a 60 mg/kg azithromycin ER single dose provides similar or greater systemic exposure in children compared with the 30 mg/kg azithromycin IR single dose.
INTRODUCTION

A single dose regimen of azithromycin extended-release (ER) oral suspension (Zmax®) has been developed to deliver systemic exposure that is comparable to the cumulative exposure observed with the currently approved multiple oral dose regimens of the immediate-release (IR) formulation (5, 16). The ER formulation releases the drug more slowly and in the lower gastrointestinal (GI) tract than conventional IR formulations, thereby reducing GI side effects such as nausea and vomiting. Since the ER formulation partially bypasses the absorption window (upper GI tract), the oral bioavailability of azithromycin ER was compromised to a certain extent. Therefore, higher numeric dose was selected for the ER formation to ensure sufficient azithromycin systemic exposure could be achieved. The 2 g azithromycin ER single dose regimen has been approved worldwide for the treatment of acute bacterial sinusitis and community acquired pneumonia (CAP) in adults.

The pharmacokinetics of azithromycin ER have been characterized in pediatric patients aged 3 months to 16 years following a 60 mg/kg (maximum of 2 g) azithromycin ER single dose (16). Although there was large inter-subject variability in systemic exposure (AUC and C\text{max}) across the age groups studied, individual azithromycin AUC and C\text{max} values in pediatric subjects were comparable to or higher than those in adults following a 2 g single dose of azithromycin ER.

Acute otitis media (AOM) is an important health problem in children. The currently approved azithromycin IR oral suspension for AOM is 30 mg/kg total dose given as a single dose, or given over 3 or 5 days (7, 11, 13, 15). It has been demonstrated that the 30 mg/kg azithromycin IR single dose regimen was as effective as the 10-day regimen of high dose amoxicillin-clavulanate (90/6.4 mg/kg/day, given in divided doses q12h) for the treatment of AOM in children, whereas rates of AEs were lower and compliance was improved with the single dose regimen (2).
Nonetheless, the azithromycin pharmacokinetics of 30 mg/kg IR single dose have not been well characterized in children previously. To assess if the 60 mg/kg ER single dose is as effective as the approved 30 mg/kg IR single dose for the treatment of AOM in children, this study was conducted to characterize and compare the pharmacokinetic profiles of these two regimens in AOM children to evaluate if azithromycin systemic exposure from a 60 mg/kg ER single dose is similar to or greater than the 30 mg/kg IR single dose. Additionally, the safety and clinical response of azithromycin were evaluated in AOM children following a single dose of either 60 mg/kg ER or 30 mg/kg IR.

METHODS

Study design

This was an open-label, randomized, single dose, parallel group pharmacokinetic study in 38 children with AOM. Subjects were screened within 48 hours of dosing. Subjects who satisfied all inclusion/exclusion criteria were randomized in 1:1 ratio to receive azithromycin single oral dose of either 30 mg/kg IR formulation or 60 mg/kg ER formulation. Subjects were confined to the clinical research unit until the 8-hour postdose pharmacokinetic sample was collected on day 1 and returned on days 2-4 for pharmacokinetic blood sampling. Clinical response was assessed by the investigator at the test-of-cure (TOC) visit (7-10 days after dosing). Exclusive of the screening period, total participation in the study for each subject was approximately 10 days. The study was conducted in compliance with the Declaration of Helsinki and with International Conference on Harmonization Good Clinical Practice guidelines. The study protocol and informed consent documentation were reviewed and approved by the Independent Ethics Committees at the investigational center participating in the study. Written informed consent was obtained prior to the subject entering the study.
Patients

Male or female children aged 6 months to 6 years old, inclusive, with clinical signs/symptoms of AOM in at least one ear were included in the study. The clinical signs/symptoms of AOM were defined as follows: (i) Purulent otorrhea of ≤24 hours duration, OR (ii) at least 2 otoscopic signs of middle ear effusion [i.e., decreased or absent tympanic membrane mobility by pneumatic otoscopy, yellow or white discoloration of tympanic membrane, and opacification of tympanic membrane (other than scarring)], AND (iii) at least 1 indicator of acute inflammation to support the diagnosis of AOM (i.e., ear pain, including unaccustomed tugging or rubbing, marked redness of tympanic membrane, and distinct fullness or bulging of tympanic membrane).

Subjects were excluded if they had known or suspected hypersensitivity, or intolerance to azithromycin or other macrolides or to any penicillin, beta-lactam antibiotic or beta lactamase inhibitor. Subjects were excluded if they were unable to take oral medications or any condition possibly affecting drug absorption. Subjects were excluded if they had used prescription or nonprescription drugs and dietary supplements, or consumed grapefruit (including grapefruit containing products) within 7 days or 5 half-lives (whichever was longer) prior to the study dosing. As an exception, analgesics such as ibuprofen, acetaminophen could have been used. Other antibiotics without drug-drug interaction with azithromycin were also allowed, such as amoxicillin and cephalosporins. Subjects were excluded if they had any medical condition that could have interfered with the evaluation of the study drug and/or would have made the subject unsuitable for enrollment (e.g., tympanostomy tubes in place, otitis externa, evidence of chronic middle ear disease, or perforations of the tympanic membrane in the affected ear for >24 hours prior to study entry). Subjects were also excluded if they had any other condition which, in the opinion of the investigator, made the subject unsuitable for enrollment.
Study treatment

Each subject received his/her single oral dose of 60 mg/kg ER or 30 mg/kg IR on an empty stomach (1 hour before or 2 hours after a meal). The concentration for azithromycin ER suspension was 27 mg/mL and the concentration for azithromycin IR suspension was 20 mg/mL. Subjects were observed for 1 hour after study drug administration. Any subject who vomited within 1 hour of administration was to receive alternative therapy. Study drug was not to be re-administered to any subject who vomited.

Pharmacokinetic sampling and analysis

Blood samples (approximately 0.75 mL per sample to provide a minimum of 0.3 mL serum) were to be collected at 1, 2, 3, 4, 8, 24, 48 and 72 hours post-dose for pharmacokinetic analysis. The serum samples were stored frozen at −20°C or lower prior to analysis.

Bioanalytical Systems Ltd (Kenilworth, Warwickshire, UK) analyzed serum samples for azithromycin concentration using a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) method. The serum samples (50 µL) were extracted using a liquid-liquid extraction procedure and employed [D-3] azithromycin as the internal standard. The mass spectrometer was operated in the positive ionization mode and monitored the transition ions m/z 749.5→591.1 and 752.6→594.1 for azithromycin and [D-3] azithromycin, respectively. The dynamic range for the assay was 10.0 to 500 ng/mL. The accuracy (% difference from nominal) of the quality control samples used during sample analysis ranged from -1.6% to 3.5% with a precision (as measured by % relative standard deviation) of ≤2.9%.

Non-compartmental pharmacokinetic analysis was performed using an internally validated system eNCA v2.2.1. The peak concentration (C\text{max}) and the time to C\text{max} (T\text{max}) were estimated directly from the concentration-time profiles. The area under the curve from time zero to 8 hours post-dosing...
(AUC\textsubscript{0-8}), AUC\textsubscript{0-24} and AUC\textsubscript{0-72} were estimated using the linear/log trapezoidal approximation. Since no pre-dose samples were obtained in order to spare the children an extra blood draw, pre-dose concentrations were assigned a value of zero for AUC calculations. Samples above the limit of quantification were diluted appropriately within the range for assay. Samples below the lower limit of quantification were set to 0 ng/mL for analysis. Actual sample collection times were used for the pharmacokinetic analysis.

**Safety assessment**

Adverse events (AEs) were monitored throughout the study. Safety laboratory tests were performed at screening (and day 2 for subjects who were discontinued from the study), and vital signs and physical examinations were performed at screening, prior to dosing on day 1 and at the TOC visit (on days 7 to 10).

**Clinical response assessment**

At the TOC visit (between days 7 and 10), or when subjects discontinued the study prematurely (if applicable), the investigator assessed the subject’s response to therapy according to the following criteria: Cure: clinical signs and symptoms related to the acute illness had resolved, or clinical improvement is such that no additional therapy was necessary. Failure: one or more of the following: (i). signs and symptoms related to the acute illness had persisted or worsened and additional therapy was necessary; (ii). new clinical signs and symptoms of acute illness had developed and additional therapy was necessary.

Any worsening of existing signs and symptoms, or new signs and symptoms, were also documented as AEs.

**Statistical analysis**
A sample size of 36 subjects (18 subjects per treatment group) was required to provide 90% power that the lower boundary of the 90% confidence interval (CI) for the ER/IR $AUC_{0-72}$ ratio was $\geq 80\%$. This estimate was based on the assumption that the true ratio between $AUC_{0-72}$, ER (60 mg/kg) and $AUC_{0-72}$, IR (30 mg/kg) was 1.20 and also assumed inter-subject standard deviations of 0.4 for natural log $AUC_{0-72}$ based on historical data (5, 16).

One-way analysis of variance (ANOVA) was used to compare natural log transformed $AUC_{0-8}$, $AUC_{0-24}$, $AUC_{0-72}$ and $C_{\text{max}}$ as well as concentrations at each time point. The 30 mg/kg IR was the reference treatment and the 60 mg/kg ER was the test treatment. The adjusted mean differences (test-reference) between treatments and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CIs for the ratios.

The criterion for primary comparisons ($AUC_{0-72}$) between treatments was pre-defined as maintaining at least a lower 90% CI boundary of 80% to demonstrate that the exposure of ER formulation was similar or greater than that of the IR formulation. Other secondary comparisons between treatments were also evaluated using the same criteria.

No formal inferential statistics were applied to the safety and clinical response data, and these data were listed for descriptive purpose.

RESULTS

Subject disposition and demography

Thirty-eight (38) children with AOM were enrolled at a single study center in Costa Rica (19 in each treatment group) and 36 of them completed the study. One subject in each treatment group discontinued from the study: in the IR group, one subject was inadvertently given a low dose due to a miscalculation based on weight; while in the ER group, one subject vomited while receiving
study drug. The two subjects who were discontinued from the study had safety laboratory tests performed on day 2, but were excluded for pharmacokinetic analysis.

All subjects were Hispanic. As shown in Table 1, demographic data were similar between the two treatment groups although the mean age was slightly higher in the IR group (34.5 months) compared with the ER group (24.3 months).

Concomitant treatments

Seven (7) subjects in the 30 mg/kg azithromycin IR group and four subjects in the 60 mg/kg azithromycin ER group received concomitant medications during the study, and the most commonly taken concomitant treatment was paracetamol (acetaminophen). Two (2) subjects in the IR group and one subject in the ER group received concomitant antibiotic therapy (i.e., ceftriaxone).

Comparison of azithromycin pharmacokinetics between ER and IR

Mean azithromycin serum concentration-time profiles for 60 mg/kg ER and 30 mg/kg IR single doses are presented in Figure 1, and the corresponding pharmacokinetic parameters are summarized in Table 2. As expected, the IR single dose regimen had a higher peak concentration and a faster $T_{\text{max}}$ compared with the ER single dose regimen since the ER formulation was designed to slow down the absorption rate. As shown in Table 2, for $\text{AUC}_{0-72}$, the ER/IR ratio of the adjusted geometric means was 157.98% with the 90% CI of 98.87% - 252.44%. The lower boundary of the 90% CI was greater than the pre-defined criterion of $\geq 80\%$. In addition, the ER/IR ratio for the adjusted means of $\text{AUC}_{0-8}$ was 120.09% with the 90% CI of 74.92%-192.51%, and for $\text{AUC}_{0-24}$, the ER/IR ratio for the adjusted means was 145.76% with the 90% CI of 93.74-226.64% (Table 2). For $C_{\text{max}}$, the ER/IR ratio for the adjusted means was 91.63% with the 90% CI of 56.21% - 149.38%.
Results of comparisons of the concentration data between treatments at each serial time point are summarized in Table 3. The lower boundaries of the 90% CIs for ER/IR concentration ratios at the first 3 time points ($C_1$, $C_2$ and $C_3$) fell below 80%. The lower boundaries of the 90% CIs for ER/IR concentration ratios at all remaining time points ($C_4$, $C_8$, $C_{24}$, $C_{48}$ and $C_{72}$) were greater than 100%.

**Safety assessment**

There were no serious AEs. All AEs were mild or moderate in severity and all resolved by the end of the study. In the IR group, five out of 19 subjects reported 5 treatment-emergent AEs: treatment failure (2), anorexia (1), diarrhea (1) and vomiting (1). Among them, treatment failure and anorexia were assessed as treatment-related by the investigator. In the ER group, four out of 19 subjects reported 4 treatment-emergent AEs: nausea (1) and vomiting (3). Among them, one vomiting event was assessed as treatment-related by the investigator.

The most commonly reported AE was vomiting (4 events). The vomiting event in the ER group, which was assessed as treatment related, led to the discontinuation from the study. This event started approximately 5 minutes after dosing and resolved approximately 19 hours after dosing, which was assessed as mild in severity. The other two vomiting events in subjects from the ER group occurred at a later time point with a very short duration: 9 and 35 hours after dosing, respectively. The vomiting in the subject from the IR group also occurred at a later time point with a very short duration: 16 hours after dosing. All the three vomiting events were attributed to disease under study. It is thought that nausea and vomiting occur shortly after oral dosing of macrolides including azithromycin are primarily local in origin and possibly due to the drug’s action on the motilin receptors in the upper GI tract (12, 14).
There were no clinically significant laboratory tests or vital sign results other than the signs and symptoms from AOM.

**Clinical response assessment**

Sixteen (88.9%) subjects in IR group and 18 (100%) subjects in the ER group had clinical response assessed as Cure. Two (11.1%) subjects in the IR group had clinical response assessed as Failure.

**DISCUSSION**

For azithromycin, \(\text{AUC}_{0-24}/\text{MIC}\) (minimum inhibitory concentration) is considered the pharmacokinetic/pharmacodynamic parameter that best predicts efficacy (1, 6). It has been demonstrated that higher AUC values, achieved by ‘front-loading’ (ie, giving the entire course of therapy as one dose), could result in improved bacteriologic efficacy based on preclinical infection models (8). It should be noted that single dose regimen maximizes patient compliance, therefore eliminating noncompliance as a reason for treatment failure. Also, because of the benefit conferred by delivering the entire dose up front - at a time when the bacterial burden is the greatest - single dose therapy has the potential to minimize the emergence and spread of bacterial resistance in the community. To assess the utility of the azithromycin ER formulation for AOM, this study compared the systemic exposure of the 60 mg/kg single dose of ER to the approved 30 mg/kg single dose of IR in children with AOM.

In this study, the pharmacokinetic parameter \(\text{AUC}_{0-72}\) was the primary endpoint for comparison between ER and IR formulations since azithromycin has a long elimination half-life (approximately 60 hours) (10). Per FDA guidance on bioavailability and bioequivalence studies for orally administered drug products, it is acceptable for drugs with a long elimination half-life that demonstrate low intra-subject variability in distribution and clearance to use an AUC truncated at 72 hours (\(\text{AUC}_{0-72}\)) in place of \(\text{AUC}_{0-\infty}\) (9). The 72-hour sample collection is
considered adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. The criterion for \( \text{AUC}_{0-72} \) between treatments was pre-defined as maintaining at least a lower 90% CI boundary of 80% to demonstrate that the ER formulation is similar to or greater than the IR formulation, which was consistent with the industry accepted lower boundary of bioequivalence range (80 – 125%). The ER/IR \( \text{AUC}_{0-72} \) ratio for the adjusted means (90% CI) was 157.98% (98.87%, 252.44%), which met the pre-defined criterion, thus the exposure from a 60 mg/kg ER dose was considered similar to or greater than that from a 30 mg/kg IR dose.

Although the concentrations of ER during the first 3 hours were lower than those of IR, the exposures over the first 8 hours (\( \text{AUC}_{0-8} \)) were comparable between these two treatments (Table 2). By 24 hours after dosing, the exposure (\( \text{AUC}_{0-24} \)) of ER treatment was similar or higher than that of IR treatment (Table 2). It indicated that slight delay in drug release of the ER formulation has minimal impact on the total azithromycin exposure during the early state of treatment. The azithromycin pharmacokinetic profiles in 7 subjects had a double peak: 3 from the ER group and 4 from the IR group. The reason of the double peaks is unknown. It was also observed from other azithromycin pharmacokinetic studies (data on file).

Azithromycin was safe and well tolerated following single dose administration of either formulation (60 mg/kg ER or 30 mg/kg IR) in children with AOM. Due to the small sample size, comparisons cannot be made between the ER and IR formulations regarding safety.

The observed clinical cure rates for the 2 treatments appeared to be similar as all 18 completed AOM subjects had clinical response assessed as cure in the ER group compared to 16 out of 18 completed subjects in the IR group. It is noted that this study was not designed to demonstrate
clinical non-inferiority between these two treatments and other antibiotic therapy was permitted during the study if clinically indicated. Previously, the efficacy and safety of the 60 mg/kg azithromycin ER single dose regimen in children with AOM had been evaluated in a randomized, double-blinded, double-dummy study in comparison with a 10-day regimen of high dose amoxicillin-clavulanate (90/6.4 mg/kg/day, given in divided doses q12h), particularly in children with or at risk for recurrent middle ear infection (4). In the bacteriologic eligible population (clinically eligible subjects with a key AOM pathogen isolated at baseline), the cure rates for azithromycin ER arm (n = 258) and amox/clav arm (n = 239) were 80.2% and 84.5% respectively; an age-adjusted difference was -3.9% with 95% CI (-10.4%, 2.6%). Unfortunately, the lower boundary of the 95% CI (-10.4%) marginally missed the study-defined non-inferiority criterion of -10%. Vomiting on day 1 had a greater impact on the efficacy rate in the bacteriologic eligible population for azithromycin ER-treated subjects than for amox/clav-treated subjects. Specifically, 4 subjects in the azithromycin ER arm vomited within 30 minutes of dosing on day 1 and were withdrawn from the study, in comparison with 2 subjects in the amox/clav arm, and these subjects were assessed as clinical failures at the TOC visit. In the bacteriologic per protocol population (bacteriologic eligible subjects with a TOC visit), the cure rates for azithromycin ER arm (n = 239) and amox/clav arm (n = 217) were 85.8% and 89.9%, respectively; the age-adjusted difference was -3.4% with 95% CI (-9.1%, 2.4%). The most common treatment-related AE for ER group were vomiting (10.7%), diarrhea and loose stools (9.3% each), and rash (5.1%). The most common treatment-related AEs for amox/clav group were diarrhea (17.7%), loose stools (12.8%), vomiting (8.2%), rash (7.7%), and dermatitis (5.1%). The AE profile of azithromycin ER was favorable compared with amox/clav, particularly with respect to diarrhea. Although azithromycin ER subjects had a higher
incidence of immediate vomiting after dosing, the incidence of longer-term vomiting was higher for amox/clav subjects.

Subsequently, more effort was made to address the tolerability issue (early vomiting) with azithromycin ER. It has been demonstrated that this could be effectively managed by using a more dilute (less viscous) concentration (27 mg/mL vs. the original 60 mg/mL suspension) and a standardized dosing technique (3). The more dilute suspension (27 mg/mL) of the azithromycin ER formulation was used in this study.

In summary, this study demonstrated that the 60 mg/kg azithromycin ER single dose provides similar or greater systemic exposure in children with AOM compared with the 30 mg/kg azithromycin IR single dose.

ACKNOWLEDGEMENT

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azithromycin adult suspension (ADULT-AZM) in children with acute otitis media (AOM).

47th Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, USA: Abstract G-981


Table 1. Baseline demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>60 mg/kg ER N=19</th>
<th>30 mg/kg IR N=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>11/8</td>
<td>12/7</td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.3 (20.6)</td>
<td>34.5 (21.1)</td>
</tr>
<tr>
<td>Range</td>
<td>6-76</td>
<td>9-78</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13.1 (6.1)</td>
<td>14.0 (5.1)</td>
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<tr>
<td>Range</td>
<td>6.7-31.2</td>
<td>7.0-28.3</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>17.8 (3.0)</td>
<td>16.7 (2.0)</td>
</tr>
<tr>
<td>Range</td>
<td>9.2-22.4</td>
<td>12.6-20.7</td>
</tr>
</tbody>
</table>

ER = azithromycin extended release, IR = azithromycin immediate release, SD = standard deviation.
Table 2. Statistical summary of the pharmacokinetic parameters of azithromycin in AOM children following a single oral dose of 60 mg/kg ER or 30 mg/kg IR

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric mean (CV%)</th>
<th>Geometric Mean Ratio (ER/IR, %) (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 mg/kg ER N = 18</td>
<td>30 mg/kg IR N = 18</td>
</tr>
<tr>
<td>AUC$_{0.8}$ (ng·h/mL)</td>
<td>2576 (53)</td>
<td>2145 (60)</td>
</tr>
<tr>
<td>AUC$_{0.24}$ (ng·h/mL)</td>
<td>5765 (49)</td>
<td>3955 (58)</td>
</tr>
<tr>
<td>AUC$_{0.72}$ (ng·h/mL)</td>
<td>9848 (52)</td>
<td>6234 (60)</td>
</tr>
<tr>
<td>C$_{max}$ (ng/mL)</td>
<td>611 (62)</td>
<td>667 (67)</td>
</tr>
<tr>
<td>T$_{max}$ (h)$^*$</td>
<td>3.0 (2.0-8.0)</td>
<td>2.0 (1.00-4.05)</td>
</tr>
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</table>

CV% = coefficient of variation in percentage, ER = azithromycin extended release formulation, IR = azithromycin immediate release formulation, AUC = area under the curve, C$_{max}$ = maximum concentration, T$_{max}$ = time to reach maximum concentration.

$^*$Median (range) for T$_{max}$
Table 3. Statistical summary of azithromycin concentration comparisons at each time point in AOM children following a single oral dose of 60 mg/kg ER or 30 mg/kg IR

<table>
<thead>
<tr>
<th>Concentration (ng/mL)</th>
<th>Adjusted Geometric Mean</th>
<th>Geomean Ratio (ER/IR, %)</th>
<th>90% CI for ER/IR Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 mg/kg ER N = 18</td>
<td>30 mg/kg IR N = 18</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>100</td>
<td>153</td>
<td>65.44 (23.56, 181.77)</td>
</tr>
<tr>
<td>C2</td>
<td>293</td>
<td>580</td>
<td>50.57 (25.24, 101.30)</td>
</tr>
<tr>
<td>C3</td>
<td>382</td>
<td>382</td>
<td>100.07 (57.91, 172.92)</td>
</tr>
<tr>
<td>C4</td>
<td>442</td>
<td>268</td>
<td>164.93 (103.78, 262.12)</td>
</tr>
<tr>
<td>C8</td>
<td>245</td>
<td>140</td>
<td>174.41 (110.07, 276.36)</td>
</tr>
<tr>
<td>C24</td>
<td>142</td>
<td>82</td>
<td>173.01 (111.45, 268.55)</td>
</tr>
<tr>
<td>C48</td>
<td>95</td>
<td>50</td>
<td>189.35 (129.76, 276.30)</td>
</tr>
<tr>
<td>C72</td>
<td>56</td>
<td>31</td>
<td>183.14 (124.61, 269.14)</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1. Mean serum azithromycin concentration–time profiles in AOM children following a single oral dose of 60 mg/kg ER or 30 mg/kg IR (top panel: 8-hour profile, bottom panel: 72-hour profile)
Figure 1. Mean serum azithromycin concentration–time profiles in AOM children following a single oral dose of 60 mg/kg ER or 30 mg/kg IR (top panel: 8-hour profile, bottom panel: 72-hour profile)

The symbol represents arithmetic mean and the error bar represents standard deviation.