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Pharmacokinetic Simulations of a Fixed-Dose Ethambutol Formulation for
Pediatric Tuberculosis

Prepared For:
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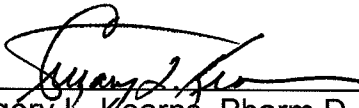
The World Health Organization, Geneva, Switzerland



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Objectives

In July 2008, WHO convened a task force which was charged to evaluate the dosing of drugs currently recommended (by WHO) for use in the treatment of children with tuberculosis. This task force was comprised of experts in pediatrics, pediatric infectious diseases, tropical medicine and pediatric clinical pharmacology. A comprehensive review of four drugs (isoniazid, rifampin, pyrazinamide and ethambutol) was undertaken with respect to age-appropriate guidelines for their dosing and use. The task force considered the importance of adherence and compliance in drug regimens to treat pediatric tuberculosis and identified the need to produce an age-appropriate solid, combination fixed drug-dose formulation. The formulation should possess the necessary characteristics to enable age-appropriate drug dosing in a precise manner that would be suitable for administration by caregivers with minimal sophistication. The work product from this meeting included the development of a dosing “table” for isoniazid, rifampin and pyrazinamide constructed using a weight-based strategy that would encompass a pediatric population of infants and children ranging from 5 to 30 kg total body weight. Predicted exposure estimates resulting from the proposed dosing strategy were simulated for infants, children and adolescents across a range of weights in previous report to WHO (CPMT 08-011).

WHO commissioned this second *in silico* study to explore the possible dose-exposure-response relationship for a fixed-strength formulation of ethambutol administered to pediatric patients of varying body weights. The two primary objectives of this exercise included:

1. Simulate the steady state plasma concentrations of ethambutol based on age-specific estimates of pharmacokinetic (PK) parameters derived from the existing medical literature.
2. Explore exposure-response relationships for ethambutol based on appropriate pharmacodynamic (PD) surrogates previously described in the literature as they may pertain to the treatment of tuberculosis in pediatric patients.

Pharmacokinetic Simulations

Simulations were performed to determine the range of pediatric exposures expected in children following administration of ethambutol contained in a solid formulation at a fixed strength chosen (based on expected ranges of patient weights) to approximate the recommended daily dose of the drug (15 to 25 mg/kg) for the treatment of tuberculosis (Micromedex, 2009). . The simulations were conducted using established pharmacokinetic methods and used pharmacokinetic parameter estimates derived from previously conducted pediatric studies as detailed in the references section. Drug concentrations were simulated according to a once-daily (i.e. every 24 hour) dosing regimen and accumulated to steady-state using a model-dependent approach with first-order absorption and mono-exponential decay. The parameter estimates employed in the simulations along with the resultant average estimates of drug exposure (+/- 90% confidence interval) are provided in the Appendix.

It should be highlighted that several critical and necessary assumptions are nested in these simulations. The most relevant assumptions employed herein are detailed as follows:

1. The pharmacokinetic parameters used in these simulations (derived from primary medical literature) offer a reasonable approximation of those that would be observed in the children receiving the fixed-dosing combination under evaluation.
2. The pharmacokinetic parameters employed herein represent values that approximate those that would be observed after repeated drug administration.
3. The pharmacokinetic parameters used for the simulation of any given drug represent values that approximate those that would be observed with concomitant administration of the other drugs contained in a single formulation (i.e. no accounting for drug-drug interactions).
4. The pediatric weights used in these simulations reflect the range of weights anticipated for children (both male and female) expected to receive the fixed-dosing combination

under evaluation.

5. No dose-dependent (i.e. zero-order, mixed zero-order/first-order) absorption is observed within the range of doses evaluated.
6. There are no appreciable age-dependent differences in the rate and extent of absorption between the age groups evaluated.
7. Systemic drug exposure resulting from dose escalation within any given individual is linear and does not vary with age and/or drug dose.
8. There are no formulation specific (i.e. physicochemical) effects that would independently alter the disposition of the component drugs under evaluation.

Note: in the absence of existent relevant *in vivo* and *in vitro* data, the validity of selected assumptions can neither be confirmed or tested in the context of this *in silico* simulation exercise.

Pharmacokinetic/Pharmacodynamic Surrogates

The singular putative pharmacokinetic surrogate endpoint associated with expected efficacy in the treatment of systemic infections produced by *M. tuberculosis* was extracted from the WHO “Ethambutol Efficacy and Toxicity” report (2006). This reflected attainable post-dose plasma drug concentrations. Pharmacodynamic surrogate endpoints [e.g. maximum plasma concentration to MIC ratio (C_{max}/MIC), area under the plasma concentration vs. time curve to MIC ratio (AUC/MIC) and percent of the dosing interval where concentrations remain above the MIC (%T>MIC)] were determined using the minimum inhibitory concentration that reflects the upper limit of susceptibility against *M. tuberculosis*. Several important caveats must be highlighted: 1) PD surrogate endpoints derived from *in vitro* data represent a static, single-dimension perspective of pathogen sensitivity to a fixed concentration of drug, 2) the discussion of PD surrogates and their potential implications do not consider additivity and/or synergy that

can be achieved *in vivo* with combination therapy and 3) none of these surrogates have been validated as markers of enhanced efficacy and/or toxicity in children suffering from *M. tuberculosis* infections.

Results

Table 2 (Appendix) details the parameter estimates used in the simulations of ethambutol exposure at the dose levels provided in Table 1 (Appendix). It should be emphasized that the number of existing studies describing the pharmacokinetics of ethambutol in children is extremely limited in number and scope (ie., patients studied). Consequently, pharmacokinetic parameter estimates derived from investigations with small numbers of children, some of which used sparse sampling methods, resulted in wide confidence limits and pharmacokinetic estimates with a significant degree of variability.

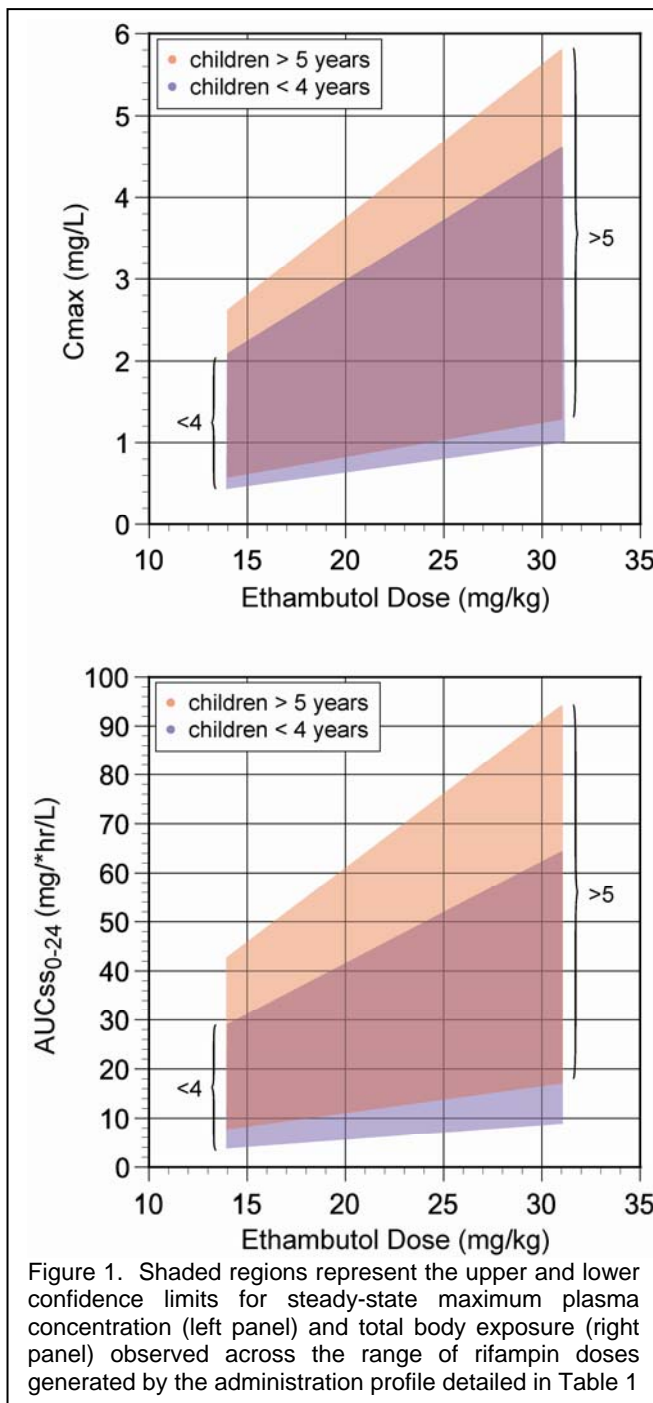


Figure 1. Shaded regions represent the upper and lower confidence limits for steady-state maximum plasma concentration (left panel) and total body exposure (right panel) observed across the range of rifampin doses generated by the administration profile detailed in Table 1

Tables 3 and 4 (Appendix) provide a summary of the average exposure estimates of ethambutol (along with the 90% confidence interval) as well as corresponding values for ethambutol pharmacokinetic and pharmacodynamic surrogates. Across the range of doses from 14 to 31

mg/kg, average estimates of C_{max} range from 1.0 to 2.3 mg/L in children under the age of 4 years and 1.3 to 3.0 mg/L in children 5 years and over (Figure 1, upper). Similarly, average AUC ranges between 12.5 to 27.6 mg*hr/L and 20.7 to 44.4 mg*hr/L for children above and below the age of 5 years, respectively (Figure 1, lower).

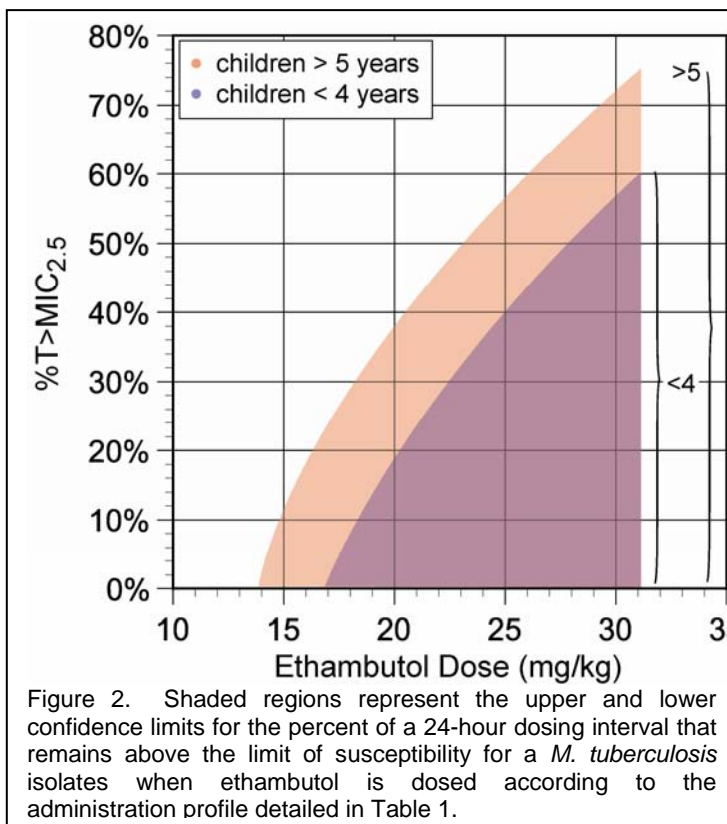


Figure 2. Shaded regions represent the upper and lower confidence limits for the percent of a 24-hour dosing interval that remains above the limit of susceptibility for a *M. tuberculosis* isolates when ethambutol is dosed according to the administration profile detailed in Table 1.

The simulated plasma concentration-vs.-time profiles suggest that a subset

of children can spend as much as 75% of a 24-hour dosing interval above the susceptibility limit

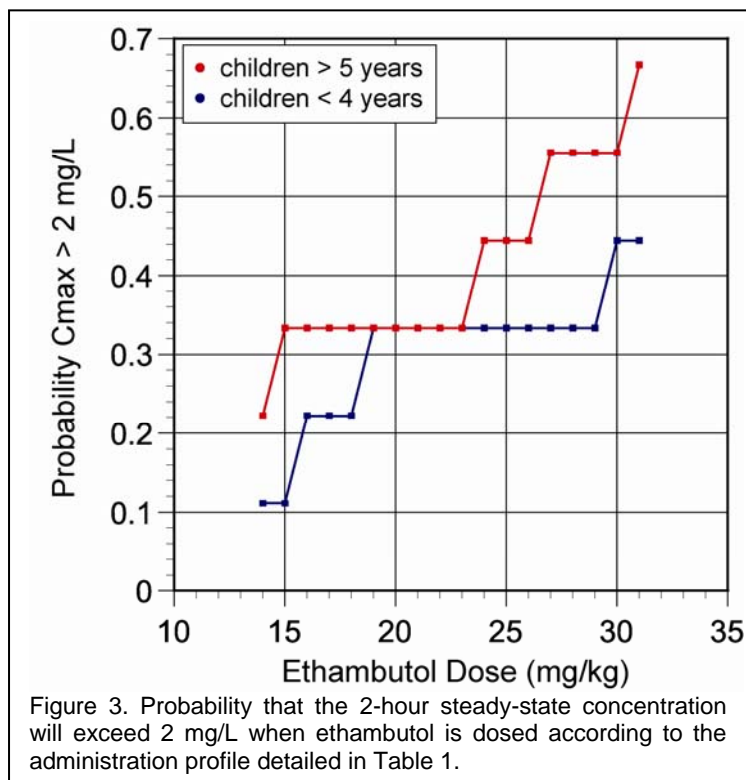


Figure 3. Probability that the 2-hour steady-state concentration will exceed 2 mg/L when ethambutol is dosed according to the administration profile detailed in Table 1.

for *M. tuberculosis* (2.5 mcg/mL) at the doses defined in Table 1. However, a proportion of children may never experience plasma concentrations above the susceptibility breakpoint irrespective of dose between 14 to 31 mg/kg (Figure 2).

As depicted in Figure 3, the probability of achieving plasma concentrations 2 hours post-dose

that equal or exceed 2 mg/L (described as desirable) increases in direct proportion with increasing dose between 14-31 mg/kg (Figure 3). Notably, the probability remains below 70% in older children and below 50% in younger children at the highest doses simulated. However, as denoted above, this surrogate remains to be validated in children.

Summary/Conclusions

Consequent to modest developmental differences in ethambutol elimination and marked inter-individual variation in apparent distribution volume (likely contributed to, in part, by a variable absorption profile), the degree of systemic exposure attained with the administration of ethambutol doses ranging from 14 to 31 mg/kg is predicted to vary by 6-8 fold at any given dose level. Consequently, one is unable to predict with certainty the dose level at which children will attain putative pharmacokinetic or pharmacodynamic targets. It should be noted that the MIC evaluated herein represents the upper limit of susceptibility and thus reflects the most conservative estimate of PK/PD adequacy. Moreover, the un-validated nature of these surrogates coupled with the role of ethambutol as an ancillary agent intended to mitigate resistance can serve to limit the overall relevance of these efficacy markers.

Recommendations / Future Directions

The results from these initial simulations should be further considered by WHO professional staff, the WHO subcommittee tasked to evaluate pediatric TB therapy (a group containing experts in antimycobacterial treatment, pediatric infectious disease and pediatric clinical pharmacology and pharmacy) and the WHO Expert Committee on Essential Medicines. After this review, the simulations can be re-visited as necessary (e.g., performance of additional simulations, use of refined PK parameter estimates based on more current data) and/or modifications to the proposed dosing table can be made.

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Table 1. Proposed dosing strategies for a single-dose, fixed-strength formulation containing ethambutol at the dosage strength delineated.

Product: Ethambutol (250 mg)		
Weight	Dosage	Dose (mg/kg)
5 kg	½ pill	25.0
6 kg	½ pill	20.8
7 kg	½ pill	17.9
8 kg	½ pill	15.6
9 kg	½ pill	13.9
8 kg	1 pill	31.3
9 kg	1 pill	27.8
10 kg	1 pill	25.0
11 kg	1 pill	22.7
12 kg	1 pill	20.8
13 kg	1 pill	19.2
14 kg	1 pill	17.9
15 kg	1 pill	16.7
16 kg	1 ½ pills	23.4
17 kg	1 ½ pills	22.1
18 kg	1 ½ pills	20.8
19 kg	1 ½ pills	19.7
20 kg	1 ½ pills	18.8
21 kg	1 ½ pills	17.9
21 kg	2 pills	23.8
22 kg	2 pills	22.7
23 kg	2 pills	21.7
24 kg	2 pills	20.8
25 kg	2 pills	20.0
26 kg	2 pills	19.2
27 kg	2 pills	18.5
28 kg	2 pills	17.9
29 kg	2 pills	17.2
30 kg	2 pills	16.7

Table 2. Ethambutol parameter estimates used in the simulations.

	Children (< 4 yr)	Children (≥ 5 yr)
Tau (hr)	24	24
bioavailability (%)	nested in Vd/F	nested in Vd/F
Volume/F (L/kg)	6-20	6-20
ka (1/hr)	0.68	0.68
kel (1/hr)	0.11	0.069
lag time (hr)	0	0
MIC (mcg/mL)	2.5	2.5

Tau- dosing interval, F- bioavailability, Vd, distribution volume, ka- absorption rate constant, kel- terminal elimination rate constant, MIC- minimum inhibitory concentration

Table 3. Ethambutol PK/PD estimates calculated for children < 4 yr

Dose mg/kg	C _{max} (mcg/mL)	AUC _{ss0-24} (mcg*hr/mL)	C ₂ >2mcg/mL	AUC/MIC _{2.5}	%T>MIC _{2.5}	C _{max} /MIC _{2.5}
14	1.0 [0.4, 2.1]	12.48 [4.05, 28.96]	No] [No, Yes]	4.99 [1.62, 11.59]	0% [0%, 0%]	0.42 [0.18, 0.83]
15	1.1 [0.5, 2.2]	13.37 [4.34, 31.03]	No [No, Yes]	5.35 [1.73, 12.41]	0% [0%, 0%]	0.45 [0.19, 0.89]
16	1.2 [0.5, 2.4]	14.26 [4.63, 33.10]	No [No, Yes]	5.70 [1.85, 13.24]	0% [0%, 0%]	0.48 [0.20, 0.95]
17	1.3 [0.5, 2.5]	15.15 [4.92, 35.17]	No [No, Yes]	6.06 [1.97, 14.07]	0% [0%, 1%]	0.51 [0.22, 1.01]
18	1.3 [0.6, 2.7]	16.04 [5.20, 37.24]	No [No, Yes]	6.42 [2.08, 14.90]	1% [0%, 7%]	0.54 [0.23, 1.07]
19	1.4 [0.6, 2.8]	16.93 [5.49, 39.31]	No [No, Yes]	6.77 [2.20, 15.72]	1% [0%, 13%]	0.57 [0.24, 1.13]
20	1.5 [0.6, 3.0]	17.83 [5.78, 41.38]	No [No, Yes]	7.13 [2.31, 16.55]	2% [0%, 19%]	0.60 [0.26, 1.19]
21	1.6 [0.7, 3.1]	18.72 [6.07, 43.45]	No [No, Yes]	7.49 [2.43, 17.38]	3% [0%, 24%]	0.63 [0.27, 1.25]
22	1.6 [0.7, 3.3]	19.61 [6.36, 45.52]	No [No, Yes]	7.84 [2.54, 18.21]	5% [0%, 28%]	0.66 [0.28, 1.31]
23	1.7 [0.7, 3.4]	20.50 [6.65, 47.58]	No [No, Yes]	8.20 [2.66, 19.03]	6% [0%, 33%]	0.69 [0.29, 1.37]
24	1.8 [0.8, 3.6]	21.39 [6.94, 49.65]	No [No, Yes]	8.56 [2.78, 19.86]	7% [0%, 37%]	0.72 [0.31, 1.42]
25	1.9 [0.8, 3.7]	22.28 [7.23, 51.72]	No [No, Yes]	8.91 [2.89, 20.69]	8% [0%, 41%]	0.75 [0.32, 1.48]
26	1.9 [0.8, 3.9]	23.17 [7.52, 53.79]	No [No, Yes]	9.27 [3.01, 21.52]	9% [0%, 44%]	0.78 [0.33, 1.54]
27	2.0 [0.9, 4.0]	24.06 [7.81, 55.86]	No [No, Yes]	9.63 [3.12, 22.34]	11% [0%, 48%]	0.81 [0.34, 1.60]
28	2.1 [0.9, 4.2]	24.96 [8.10, 57.93]	No [No, Yes]	9.98 [3.24, 23.17]	12% [0%, 51%]	0.84 [0.36, 1.66]
29	2.2 [0.9, 4.3]	25.85 [8.39, 60.00]	No [No, Yes]	10.34 [3.35, 24.00]	13% [0%, 54%]	0.87 [0.37, 1.72]
30	2.2 [1.0, 4.5]	26.74 [8.67, 62.07]	No [No, Yes]	10.70 [3.47, 24.83]	14% [0%, 57%]	0.90 [0.38, 1.78]
31	2.3 [1.0, 4.6]	27.63 [8.96, 64.14]	No [No, Yes]	11.05 [3.59, 25.65]	15% [0%, 60%]	0.93 [0.40, 1.84]

Data presented as average [90% CI]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 4. Ethambutol PK/PD estimates calculated for children ≥ 5 yr

Dose mg/kg	C _{max} (mcg/mL)	AUC _{ss0-24} (mcg*hr/mL)	C ₂ >2mcg/mL	AUC/MIC _{2.5}	%T>MIC _{2.5}	C _{max} /MIC _{2.5}
14	1.3 [0.6, 2.6]	20.07 [7.82, 42.50]	No [No, Yes]	8.03 [3.13, 17.00]	0% [0%, 4%]	0.54 [0.24, 1.05]
15	1.4 [0.6, 2.8]	21.51 [8.38, 45.53]	No [No, Yes]	8.60 [3.35, 18.21]	1% [0%, 11%]	0.58 [0.25, 1.12]
16	1.5 [0.7, 3.0]	22.94 [8.93, 48.57]	No [No, Yes]	9.18 [3.57, 19.43]	2% [0%, 17%]	0.61 [0.27, 1.20]
17	1.6 [0.7, 3.2]	24.37 [9.49, 51.60]	No [No, Yes]	9.75 [3.80, 20.64]	3% [0%, 22%]	0.65 [0.29, 1.27]
18	1.7 [0.8, 3.4]	25.81 [10.05, 54.64]	No [No, Yes]	10.32 [4.02, 21.86]	4% [0%, 28%]	0.69 [0.30, 1.35]
19	1.8 [0.8, 3.6]	27.24 [10.61, 57.67]	No [No, Yes]	10.90 [4.24, 23.07]	6% [0%, 32%]	0.73 [0.32, 1.42]
20	1.9 [0.8, 3.7]	28.67 [11.17, 60.71]	No [No, Yes]	11.47 [4.47, 24.28]	7% [0%, 37%]	0.77 [0.34, 1.50]
21	2.0 [0.9, 3.9]	30.11 [11.73, 63.75]	No [No, Yes]	12.04 [4.69, 25.50]	8% [0%, 41%]	0.81 [0.35, 1.57]
22	2.1 [0.9, 4.1]	31.54 [12.28, 66.78]	No [No, Yes]	12.62 [4.91, 26.71]	9% [0%, 45%]	0.84 [0.37, 1.65]
23	2.2 [1.0, 4.3]	32.98 [12.84, 69.82]	No [No, Yes]	13.19 [5.14, 27.93]	10% [0%, 49%]	0.88 [0.39, 1.72]
24	2.3 [1.0, 4.5]	34.41 [13.40, 72.85]	No [No, Yes]	13.76 [5.36, 29.14]	11% [0%, 53%]	0.92 [0.40, 1.79]
25	2.4 [1.1, 4.7]	35.84 [13.96, 75.89]	No [No, Yes]	14.34 [5.58, 30.36]	12% [0%, 56%]	0.96 [0.42, 1.87]
26	2.5 [1.1, 4.9]	37.28 [14.52, 78.92]	No [No, Yes]	14.91 [5.81, 31.57]	13% [0%, 60%]	1.00 [0.44, 1.94]
27	2.6 [1.1, 5.0]	38.71 [15.08, 81.96]	Yes [No, Yes]	15.48 [6.03, 32.78]	14% [0%, 63%]	1.04 [0.45, 2.02]
28	2.7 [1.2, 5.2]	40.14 [15.63, 84.99]	Yes [No, Yes]	16.06 [6.25, 34.00]	15% [0%, 66%]	1.07 [0.47, 2.09]
29	2.8 [1.2, 5.4]	41.58 [16.19, 88.03]	Yes [No, Yes]	16.63 [6.48, 35.21]	16% [0%, 69%]	1.11 [0.49, 2.17]
30	2.9 [1.3, 5.6]	43.01 [16.75, 91.07]	Yes [No, Yes]	17.20 [6.70, 36.43]	17% [0%, 72%]	1.15 [0.50, 2.24]
31	3.0 [1.3, 5.8]	44.44 [17.31, 94.10]	Yes [No, Yes]	17.78 [6.92, 37.64]	18% [0%, 75%]	1.19 [0.52, 2.32]

Data presented as average [90% CI]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio