Pharmacometrics Review

NDA:	20634/S043; 20635/S-046; and 21721/S-011
Submission Date	20 Dec 2006 (SE5 043)
Type of Submission	Supplemental NDA-Post Exposure Prophylaxis for Inhalational Anthrax in Pediatric Patients
Generic Name	Levofloxacin
Brand Name	LEVAQUIN
Dosage Form	Tablets, Injection, and Oral Solution
Sponsor	Johnson & Johnson PRD, LLC
Primary PM Reviewer	Fang Li, Ph.D.
Secondary PM Reviewer	Christoffer W. Tornoe, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
PDUFA Date:	June 16, 2007

1 Executive Summary

Treatment of inhalational anthrax (post exposure) in adults with levofloxacin 500 mg q.d. was approved by FDA in November, 2004. However, the approval of levofloxacin for the same indication in pediatrics was not granted at the same time. After completing more clinical studies in patients aged 6 months to 16 years per a Pediatric Written Request issued by FDA, the sponsor submitted this application with aim to seek approval of levofloxacin for the treatment of inhalational anthrax (post-exposure) in pediatrics.

For this indication, the sponsor (b) (4) submitted pediatric PK data, which include data in three (3) Phase I studies and one (1) Phase III study for treatment of community-acquired pneumonia (CAP). In addition, the sponsor conducted a population PK analysis employing PK data from both pediatrics and adults. (b) (4)

After reviewing the submitted data and analysis, the Pharmacometrics Group in the Office of Clinical Pharmacology has the following findings:

- The submitted data were well documented and adequate for safety evaluation and dosing recommendation.
- The population PK analysis was not adequately performed. (b) (4)

New analyses were conducted using pediatric and adult Phase I PK data. Pediatric clearance was found dependent on both body weight and age in the youngest patients due to immature renal function.

Based on the results of the analyses, the pediatric dosage regimen for inhalational anthrax (post-exposure) matching the adult exposure following 500 mg q.d. is:

≥ 6 months and ≤50 kg:	8 mg/kg b.i.d. (not to exceed 250 mg/dose)
>50 kg:	500 mg q.d.

2 Key Questions

2.1 What evidence of effectiveness for Anthrax exists for levofloxacin?

The effectiveness of levofloxacin for the treatment of inhalational anthrax was based on monkey data (Levofloxacin Package Insert). A placebo-controlled study in rhesus monkey exposed to an inhaled mean dose of 49 LD_{50} (~2.7 x 10^6) spores (range 17-118 LD_{50}) of *B. anthracis* (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 µg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 µg/mL. Mean steady state trough concentration at 24 hour post-dose ranged from 0.107 to 0.164 µg/mL. Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) (p =0.0011, 2 sided Fisher's Exact Test).

2.2 What pediatric dosing regimen of levofloxacin will match adult exposure?

The approved adult dose of 500 mg q.d. for treating inhalational anthrax achieved plasma levofloxacin concentrations exceeding rhesus monkey plasma levofloxacin concentrations at almost all sampling times. As per the approved labeling for levofloxacin, multiple levofloxacin dosing of 500 mg q.d. in adults achieved a mean (± SD) AUC of 54.6 ± 11.1 (µg·h/ml) and C_{max} of 6.4 ± 0.8 (µg/mL). The adult plasma levofloxacin concentration-time profile exceeded MIC for the entire 24-hour dose interval. In contrast, the rhesus monkey levofloxacin concentration-time profile following an oral dosing regimen of 15 mg/kg initially, then 4 mg/kg at 12 hours after the initial dose, was estimated to exceed the MIC for about 20 hours of the 24-hour interval (Previous FDA review on Levaquin® for inhalational anthrax, Francis R. Pelsor May 2004).

The objective of pediatric dosing is to achieve exposures that match those observed in adults after multiple dosing of 500 mg of levofloxacin. Such exposure is expected to achieve at least equal efficacy as observed in the animal study. FDA analysis (see reviewer's analysis section) demonstrated that a 7.5 mg/kg b.i.d. for pediatric patients greater than 6 months of age will achieve same exposure as observed in adults taking 500 mg q.d. of levofloxacin.

For practical reasons, it is acceptable to round the pediatric dose up from 7.5 mg/kg to 8 mg/kg since the maximal additional total dose is 15 mg (i.e. (8-7.5) mg/kg * 250 mg/8 mg/kg = 15 mg) which is less than a 10% increase in the total dose.

2.3 Is there adequate safety data in pediatrics?

The maximum dose of levofloxacin studied in pediatrics is 10 mg/kg b.i.d. in a Phase III study (LOFBIV-PCAP-003) for Community-Acquired Pneumonia (CAP), which was found safe. The proposed dose (7.5 mg/kg b.i.d.) in this review is predicted to give rise to an AUC and C_{max} below what has previously been observed and should therefore be safe.

3 Recommendations

3.1 Dosage and Administration in Pediatrics

For pediatric patients ≥6 months and ≤50 kg: 8 mg/kg every 12 hours for 60 days, not exceeding 250 mg/dose or 500 mg/day;

For pediatric patients >50 kg: 500 mg every 24 hours for 60 days.

Summary of Recommended Levofloxacin Dosage Regimens for Treatment of Inhalational Anthrax (Post Exposure).

	IV	**PO (Tablets)**	**PO (Solution)**
Adults	500 mg q.d.	500 mg q.d.	500 mg q.d.
Pediatrics ≥ 6 months and ≤ 50 kg	8 mg/kg b.i.d. (not to exceed 250 mg/dose)	8 mg/kg b.i.d. (not to exceed 250 mg/dose)	8 mg/kg b.i.d. (not to exceed 250 mg/dose)
Pediatrics >50 kg	500 mg q.d.	500 mg q.d.	500 mg q.d.

4 Background

Levofloxacin intravenous, tablet, and oral solution formulations have been approved in the U.S. since 1996 for the treatment of mild-severe infections. Approved indications include acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, nosocomial pneumonia, community-acquired pneumonia, complicated skin and skin structure infections, uncomplicated skin and skin structure infections, chronic bacterial prostatitis, complicated and uncomplicated urinary tract infections, and acute pyelonephritis. Most recently (November 2004), levofloxacin (500 mg q.d.) was approved for the treatment of inhalational anthrax (post-exposure) in adults.

The purpose of the present application is to seek approval for LEVAQUIN® for the treatment of inhalational anthrax (post-exposure) in pediatrics.

To support the dosage of levofloxacin in pediatrics that is sought to achieve exposures matching those of adults, the sponsor submitted PK studies in children from 6 months to 16 years old. PK data following single (7 mg/kg, Phase I) and multiple doses (10 mg/kg, Phase III) of intravenous infusions, oral tablets, as well as oral solution, were collected. In addition, the sponsor conducted a population pharmacokinetics analysis based on 8 Phase I studies (5 in adults and 3 in pediatrics) and 1 pediatric Phase III study for treatment of community acquired pneumonia (CAP). The sponsor concluded that pediatric clearance normalized by body weight was constant in young children up to 5.5 years of age, after which it showed a mono-exponential decline of approximately 5% per decade of age (Sponsor's Population PK analysis Report. Doc. NO. EDMS-USRA-10174272:3.0). (b) (4)

The mentioned Phase I PK studies (Levofloxacin 7 mg/kg) have been previously reviewed by the Office of Clinical Pharmacology under the submission for treatment of inhalational anthrax (NDA 20-634 (S-035), NDA 20-635 (S-035); NDA 21-721 (S-003), Reviewer: Francis R. Pelsor). In addition to the currently submitted Phase III data, the provided PK studies fulfilled the pediatric written request issued by FDA, and were found adequate for pediatric dosing recommendation.

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5 Reviewer's Comments on Sponsor's Analysis

The reviewer's identified deficiencies of the sponsor's population PK analysis (see appendix) include:

- The sponsor used allometric models with the exponents fixed to 0.75 for clearance and 1.0 for volume of distribution, instead of exploring these parameters based on the available data for levofloxacin. While the fixed values are correct for many drugs, our analysis of Phase I PK data suggests that the exponent is 0.43 for clearance and 0.82 for volume of distribution. The fixed exponents are one of the reasons for observing a downward trend in the clearance residuals for patients above 5 years of age.

- Since levofloxacin is predominantly cleared via the kidneys, dosing purely based on weight is not appropriate in the youngest patients due to renal function not being fully matured until 2-3 years of age.

- The plasma levofloxacin concentrations collected in the Phase III pediatric study (LOFBIV-PCAP-003) provided valuable information with regards to the safety and the achieved exposure to levofloxacin in pediatrics receiving the maximal tested pediatric dose of 10 mg/kg b.i.d. However, the PK data was unable to provide information about key PK parameters of interest (e.g. CL and V_d) and the posthoc estimates from the NONMEM analysis were all close to the population prediction due to shrinkage towards the mean (see Figure 1). The Phase III data might have been adequate to use for the analysis had the population PK clearance model been more plausible and relied on a mechanistic understanding of the modeled system.

- The sponsor's proposed structural clearance model including a switch at 5 years of age based on weight-normalized clearance plots (see Figure 20 in appendix). The sponsor's clearance model did not adequately account for the above mentioned factors and can therefore not be used to determine pediatric dosing across all ages.

New analysis was performed based on the submitted data and alternative pediatric dosing is explored. The identified deficiencies of sponsor's analysis will be addressed in the reviewer's analysis.

6 Reviewer's Analysis

6.1 Objective of the analysis

The objective of this analysis is to determine the levofloxacin pediatric dosing regimen that will match exposure in adults taking levofloxacin 500 mg q.d., i.e. the approved adult dose for treatment of inhalational anthrax (post-exposure).

6.2 Background

The clinical pharmacokinetic profile of levofloxacin has been well documented from numerous studies conducted in healthy adults, patients, and special populations (Sponsor's Summary of Clinical Pharmacology Studies, Doc. No. EDMS-USRA-10172150:4.0). Levofloxacin is rapidly and completely absorbed in adults (> 18 years) after oral administration with peak concentrations usually achieved one to two hours after oral doing. The absolute oral bioavailability of levofloxacin tablets is approximately 99%.

Levofloxacin pharmacokinetics is linear and predictable for single and multiple oral or intravenous dosing regimens in adults. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosing regimen. The mean (SD) peak and trough plasma concentrations attained following multiple once-daily oral dosing regimens were 5.7 (1.4) and 0.5 (0.2) µg/mL after the 500 mg doses and 8.6 (1.9) and 1.1 (0.4) µg/mL after the 750 mg doses, respectively. Dose linearity, with respect to peak and total drug exposure (C_{max} and AUC), was observed for doses ranging from 50 to 1500 mg.

The mean volume of distribution of levofloxacin ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin is mainly bound to serum albumin in humans and is independent of drug concentration.

Levofloxacin undergoes limited metabolism in adults and is primarily excreted as unchanged drug in urine. Approximately 87% of the dose is excreted unchanged in urine within 48 hours after dosing. Mean terminal plasma elimination half-life in adults generally ranges from 6 to 8 hours following single or multiple dosing of levofloxacin when administered orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144-226 mL/min and 96-142 mL/min, respectively. Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min).

6.3 Data

The submitted levofloxacin pharmacokinetic (PK) and demographic data from five Phase I studies (three in pediatrics and two in adults) were used for the analysis.

The sparse samples taken in the Phase III study in pediatrics for treatment of community-acquired pneumonia (CAP) were not included in the reviewer's analysis, since the data did not support calculating clearance by non-compartment methods or by population PK methods due to shrinkage towards the population mean (see Figure 1). The Phase III data might have been possible to use for the reviewer's analysis if a new population PK model had been developed but due to time constraints and the fact that an adequate number of young (i.e. below 1 year) pediatric patients with rich PK sampling is available from the phase I trials, it was decided not to use the Phase III data for this analysis.

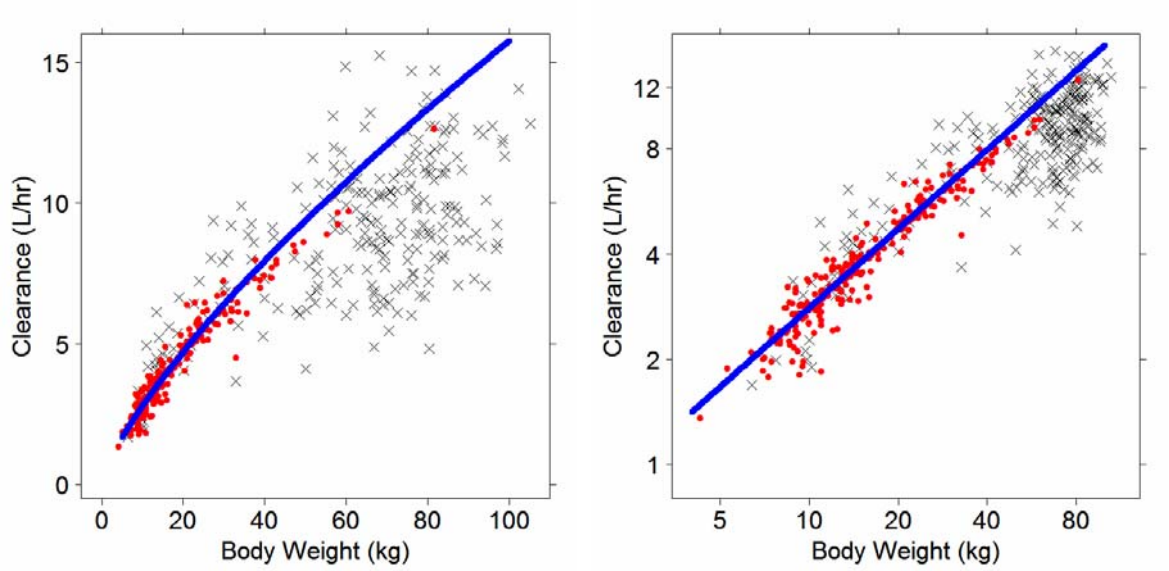


Figure 1: Sponsor's NONMEM clearance estimates vs body weight on normal (Left) and double-log scale (Right). The blue line is the population predictions, the red dots are the phase III CAP patients and the remaining subjects are shown as black crosses.

6.3.1 Pediatric Studies

LOFBIV-PHI-057

This was an open-label single intravenous dose (7 mg/kg) study to evaluate the safety and pharmacokinetics of levofloxacin in infants and children aged 6 months to 12 years. Each subject received a single intravenous levofloxacin dose of 7 mg/kg (not to exceed 500 mg) at a constant infusion rate over a one-hour period. Pharmacokinetic profiles were evaluated in 19 subjects (10M/9F) with sufficient PK samples.

LOFBIV-PHI-058

This was an open-label, single-dose study to evaluate the safety and pharmacokinetics of levofloxacin in children aged 8 to 16 Years. Subjects were enrolled into one of four cohorts stratified by age (12-16 years inclusive in Cohorts1 and 2; 8 to 11 years inclusive in Cohorts 3 and 10-12 years in Cohort4). Subjects in Cohorts 1, 3, and 4 were administered a single i.v. dose of

levofloxacin, 7 mg/kg (not to exceed 500 mg), at a constant infusion rate over a 60-minute period. Subjects in Cohort 2 were administered a single oral dose of levofloxacin as a 250-mg tablet (not to exceed 7 mg/kg). A total of 31 subjects (12M/19F) were included in the study.

To simplify analysis, only subjects receiving IV infusions were included in the present analysis.

LOFBIV-PHI-115
This was an open-label single dose study to evaluate the safety and pharmacokinetics of levofloxacin oral suspension formulation in infants and children aged 6 months to 16 years. Levofloxacin was administered as a single oral 7 mg/kg dose (not to exceed 500 mg) using a 50 mg/mL suspension formulation. A total of 40 subjects (17M/23F) were included for pharmacokinetic analysis.

6.3.2 Adult Studies

LOFBO-PHIO-097
This study compared the bioavailability of levofloxacin from a 500 mg clinical tablet, a 500 mg market-image tablet, and a 500 mg market-image intravenous solution, each administered as a single 500 mg dose in the fasted state to healthy male subjects. Twenty four subjects were enrolled and twenty three (23) were included in the pharmacokinetic analysis.

LOFBO-PHI-108
This was an open label, single-center, randomized, complete three-way crossovers study. Bioavailability of levofloxacin was comparatively assessed from an oral dose of one 750 mg market-image tablet, an oral dose of one 250 mg marketed tablet and one 500 mg marketed tablet, and a 750 mg intravenous dose of marketed solution for injection, each administered as a single 750 mg dose in the fasted state to healthy subjects. Twenty-four healthy subjects (21M/3F) were enrolled in the study.

6.4 Methods

Levofloxacin undergoes limited metabolism in humans and is primarily (~87%) excreted as unchanged drug in the urine. Therefore, the elimination of levofloxacin is dependent on the renal function. The clearance of the drug in pediatrics is expected to be influenced by body weight and furthermore age for younger patients due to immature renal function.

The relationships between associated PK parameters (CL and V_d) and body weight and age were explored.

Pediatric clearance (CL) and volume of distribution (V_d), calculated by non-compartmental methods (NCA), were obtained from reports submitted by the sponsor.

Adult CL and V_d were calculated from the concentration-time profiles provided by the sponsor, employing non-compartment methods (WinNolin 5.1, Pharsight, Mountain View, CA).

SAS 9.1 Proc NLIN procedure was used to investigate the relationship between CL, V_d and body weight (WT) and age.

The calculated pediatric and adult Phase I PK parameters (CL and V_d) using NCA are plotted against those estimated by NONMEM by the sponsor (see Figure 2). For patients with intensive PK sampling, no significant disparities were observed among those parameters, suggesting that similar conclusion about pediatric doing could be reached using NCA or NONMEM PK parameter estimates.

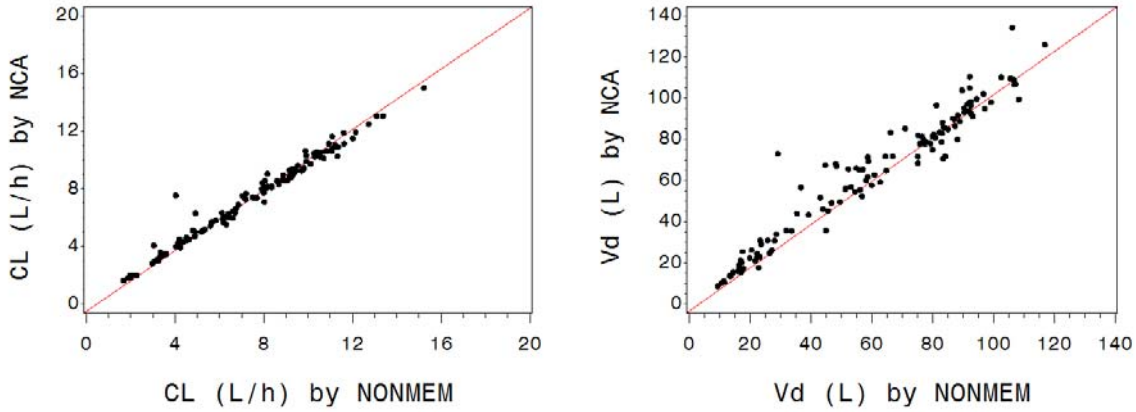


Figure 2: Correlation of PK parameters by NONMEM and NCA.

6.5 Results & Discussion

6.5.1 Clearance models

The initial model (Model 1 in Table 1) for clearance explored an allometric function between CL and body weight (WT). The residual plots for Model 1 (see Figure 3) exhibited a clear negative trend at low body weight, suggesting that body weight is not the only factor influencing CL for patients with low body weight.

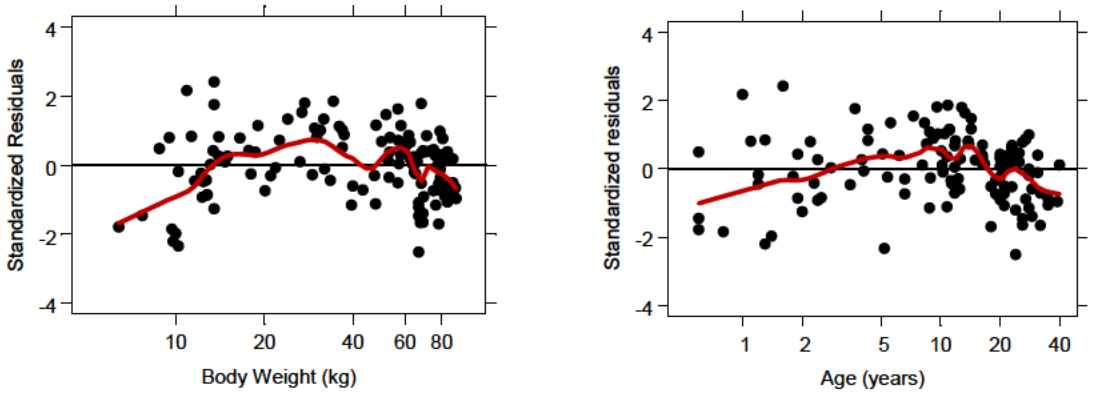


Figure 3: CL standardized residual plot for body weight only model (Model 1). The solid red line is a local smoothing line and the solid black dots are the standardized residuals (raw residuals divided by the corresponding standard errors) for each individual.

As suggested by developmental pharmacology, renal function of pediatrics is not fully developed until 2- 3 years of age (Figure 4) (see references). Therefore, a renal function maturation factor, Age/(Age+A_{50}), was added to the clearance model (Model 2 in Table 1) to account for such effects. The A_{50} estimate using the levofloxacin data, i.e. the age required for achieving 50% of full renal maturation, is 0.32 years (~4 months).

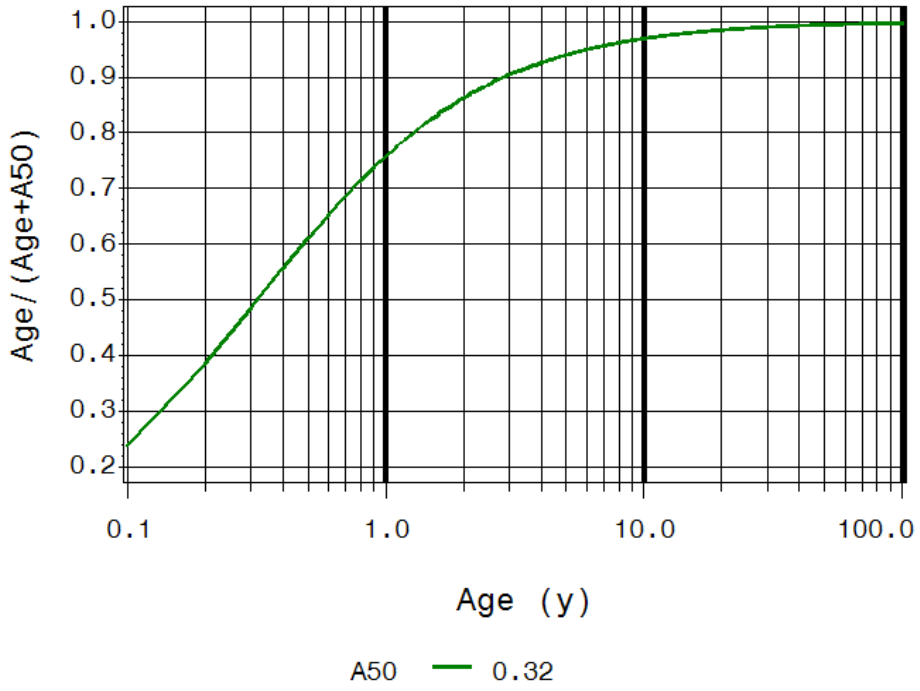


Figure 4: Estimated renal function maturation curve vs. age.

For a one year old child, the renal function is 75% matured whereas a child aged 6 months old has 60% matured renal function.

As demonstrated in Figure 5, after including both age and weight in the clearance model (Model 2 in Table 1), there was no apparent trend in the residuals at low body weight and age.

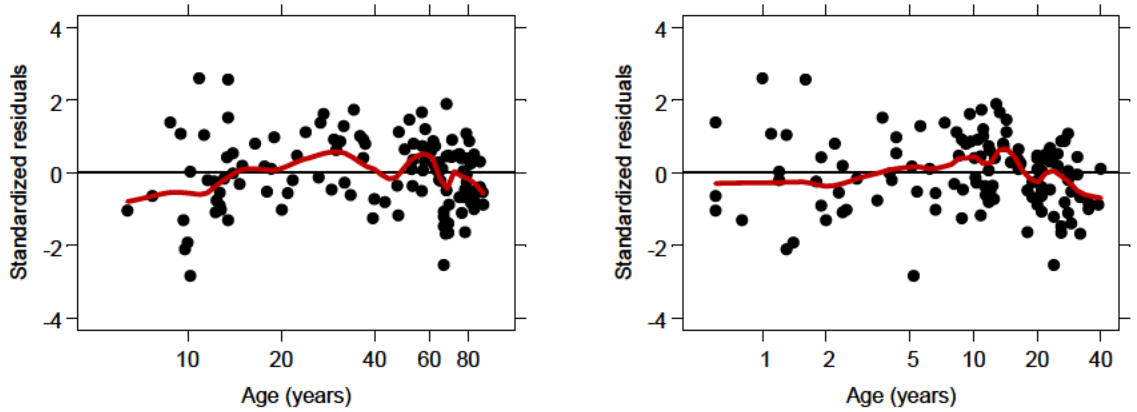


Figure 5: CL standardized residual plot for body weight and age model (Model 2). The solid red line is a local smoothing line and the solid black dots are the standardized residuals for each individual.

The model predicted clearance (solid red line) and the NCA-calculated clearance (black dots) vs. body weight are plotted in Figure 6. A summary of the tested clearance models are summarized in Table 1. The final model (Model 2) was chosen based on physiological knowledge and visual inspection of residual plots.

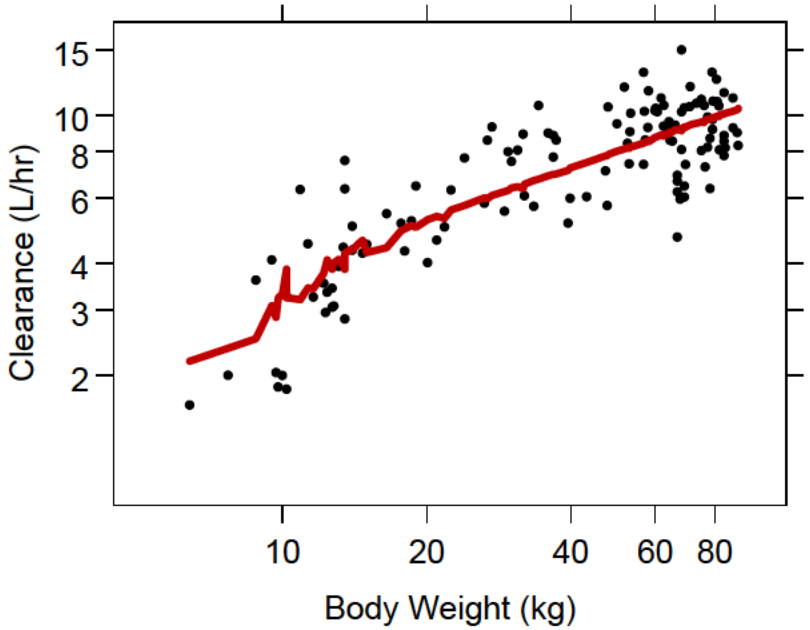


Figure 6: Plot of individual NCA-calculated (black dots) and model predicted (solid red line) clearance (CL) vs. body weight.

Table 1: Tested clearance models.

Model	Description	Parameter	Estimate (SE)	Between subject variability (CV%)	Residual sum of squares
1	$CL = \alpha \cdot WT^{\beta} \exp(\eta)$	α β	1.01 (0.12) mL/min/kg 0.53 (0.03)	26.6%	8.52
2 FINAL	$CL = \alpha \cdot WT^{\beta} \cdot age/(age+a50) \cdot \exp(\eta)$	α β a_{50}	1.50 (0.34) mL/min/kg 0.43 (0.06) 0.32 (0.18) years	26.2%	8.17

6.5.2 Volume of distribution models

Visual inspection of V_d vs. body weight (see Figure 7) suggested there might exist a linear relationship. A linear model (Model 3 in Table 2) and an allometric model (Model 4 in Table 2) were explored.

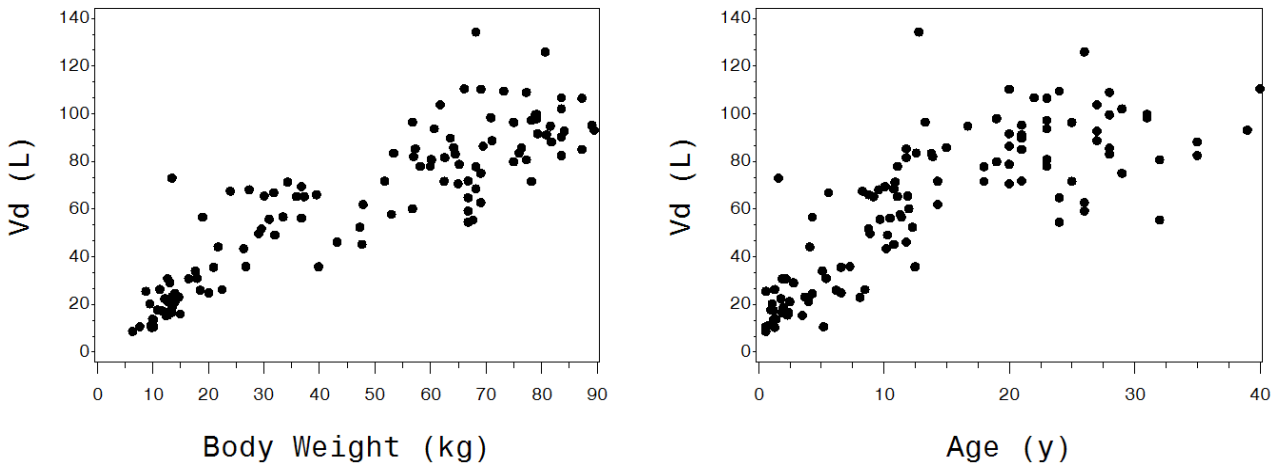


Figure 7: Scatter plot of volume of distribution (V_d) vs. body weight and age.

Table 2: Tested volume of distribution models.

Model	Description	Parameter	Estimate (SE)	Between subject variability (CV%)	Residual sum of squares
3	$V_d = \alpha\ WT\exp(\eta)$	α	1.41 (0.04) L/kg	29.6%	10.6
4 FINAL	$V_d = \alpha \cdot WT^{\beta}\exp(\eta)$	α	2.71 (0.32) L/kg	26.4%	8.3
		β	0.82 (0.03)		

The linear model was found inadequate to characterize the relationship between V_d and body weight (WT) due to a downward trend (over prediction) in the residuals at high body weight (see Figure 8).

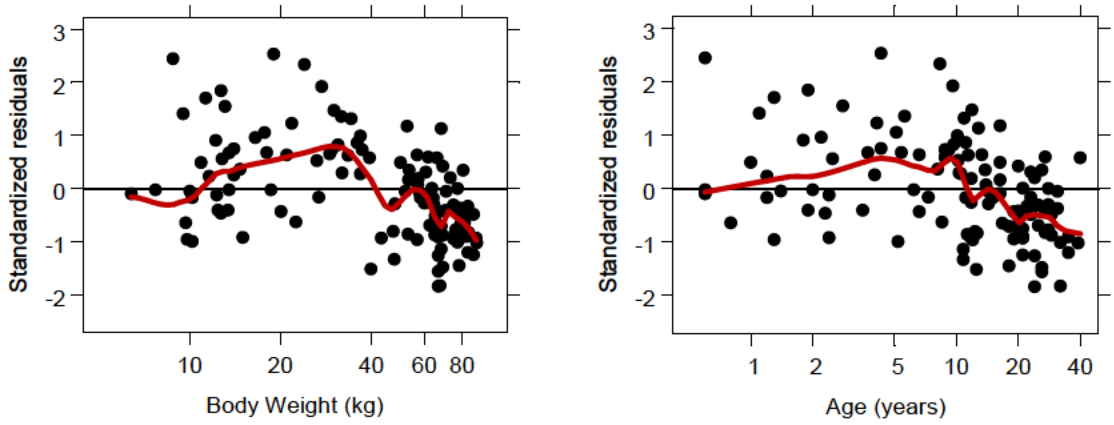


Figure 8: V_d residual plot for linear model (Model 3). The solid red line is a local smoothing line and the solid black dots are the standardized residuals for each individual.

No clear pattern is observed in the residual plot for Model 4 (see Figure 9). This model was therefore the final model.

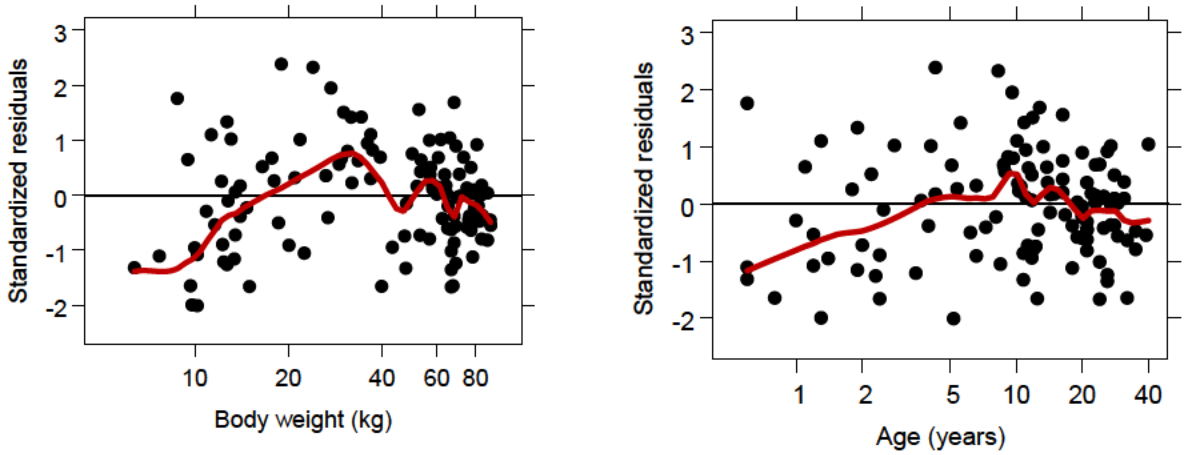


Figure 9: V_d Residual plot for linear model (Model 4). The solid red line is a smooth line using a spline routine and the solid black dots are the residuals for each individual.

Model based V_d and NCA-calculated V_d are plotted against body weight (see Figure 10). The predictions were found to be adequate.

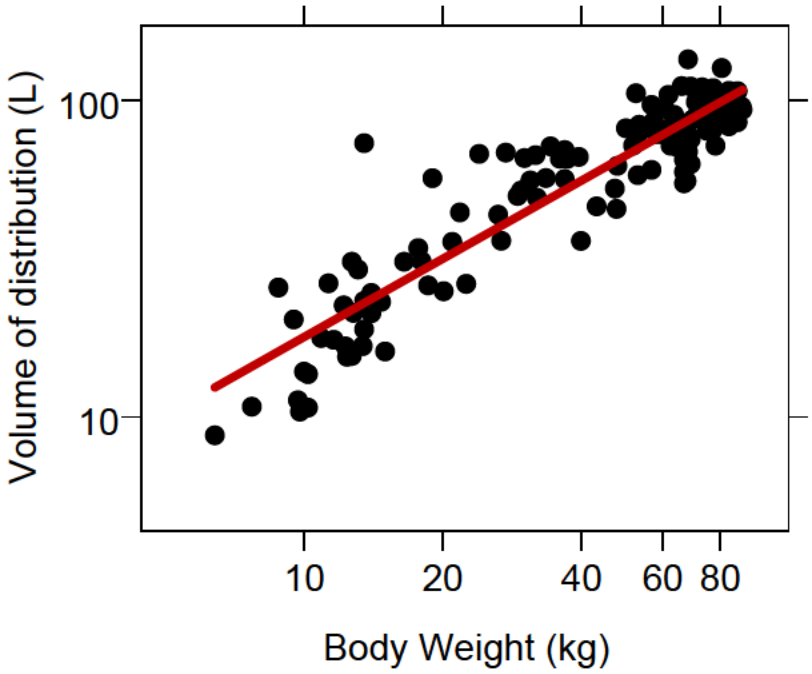


Figure 10: Plot of NCA-calculated (black dots) and model predicted (solid red line) volume of distribution (V_d) vs. body weight.

6.5.3 Dose Calculations

6.5.3.1 Adult AUC Targeting

As indicated in the levaquin® package insert, the steady-state levofloxacin $AUC_{0\text{-}24}$ (Mean ± SD) after multiple IV dosing of 500 mg q.d. is 54.6 ± 11.1 μg.h/mL. To match such exposure in pediatric population, the proposed dosing was calculated using the formula below:

Target dose (mg) = CL (pediatric patients L/h) · $AUC_{0\text{-}24}$(adults) (mg·h/L)
= $1.5 \cdot WT^{0.43} \cdot Age/(Age+0.32) \cdot 54.6$ (1)

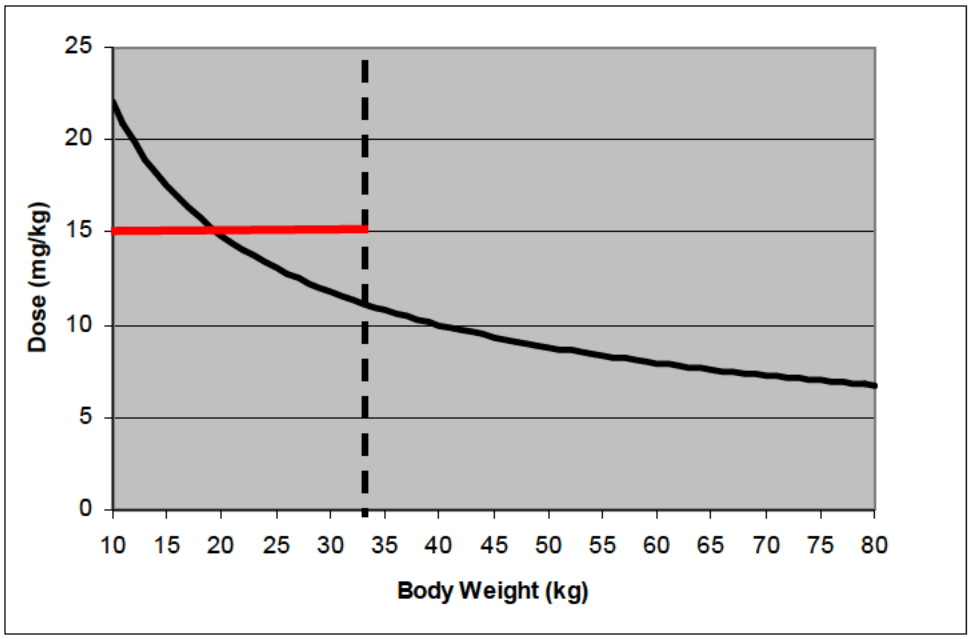
When age > 2 years, the renal function is close to being fully developed and the renal maturation factor Age/Age+0.32 approaches 1. Formula (1) can then be simplified into:

Target dose (mg) = $1.5 \cdot WT^{0.43}$ (L/h) ·54.6 (mg·h/L) (2)

For patients older than 2 years, a plot of formula (2) using either mg/kg dose (top) or mg dose (bottom) against body weight is shown in Figure 11. For patients between 10-70 kg, a dose ranging 7-22 mg/kg is needed to match adult exposure.

In order to simplify the pediatric dosing and still reasonably match adult exposure, a dose of 15 mg/kg with a cap of 500 mg was chosen for pediatric patients to be adequate to match adult exposure. Under the propopsed dose of 15 mg/kg, pediatric patients weighing more than 33 kg will be given adult dose of 500 mg (see Figure 11).

(b) (4) a dose of 15 mg/kg q.d. is proposed since a higher dose (10 mg/kg b.i.d.) previously has been tested in phase III study and found safe and effective but 40% over exposed.



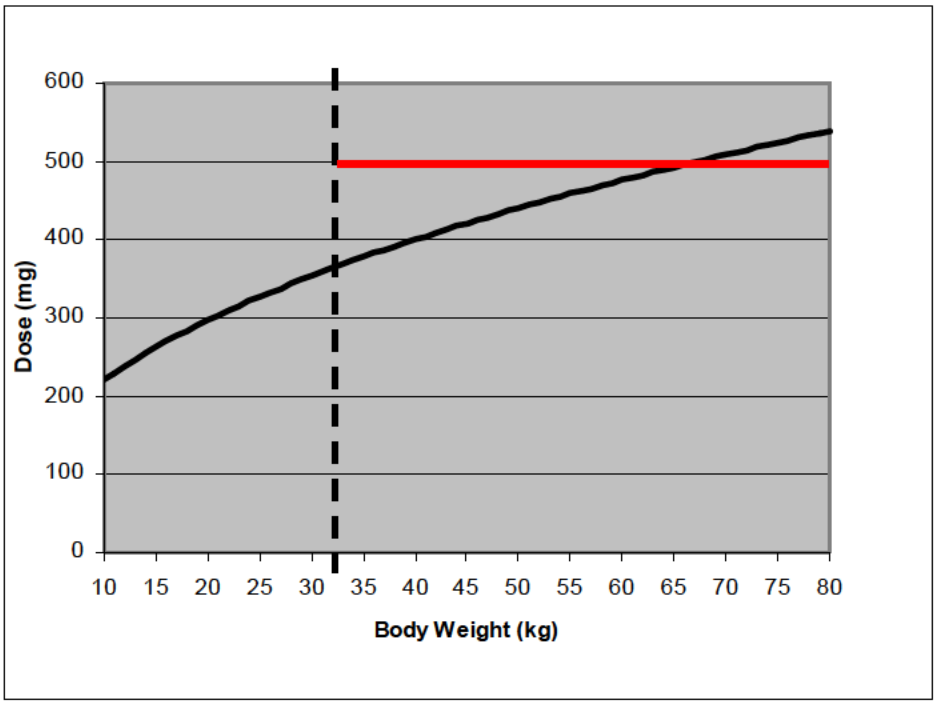


Figure 11: Plot of target dose in unit of mg/kg (top) and mg (bottom) vs. body weight (kg) for pediatrics above 2 years of age. Pediatrics below 33 kg will receive 15 mg/kg and patients above 33 kg get the adult dose of 500 mg symbolized by the solid red lines.

The exposure of the reviewer's dosing regimens was predicted using subjects (Pediatrics and Adults) in the five Phase I studies included in the reviewer's analysis. The steady state AUC_{ss} was calculated using the formula

$$AUC_{ss0\text{-}24} = Dose_{24}/CL \qquad (3)$$

The predicted steady state $AUC_{0\text{-}24}$ after taking the 15 mg/kg q.d. vs. body weight and age is plotted in Figure 12. The predicted pediatric AUC was found to match that observed in adults taking 500 mg q.d. in all dosing groups.

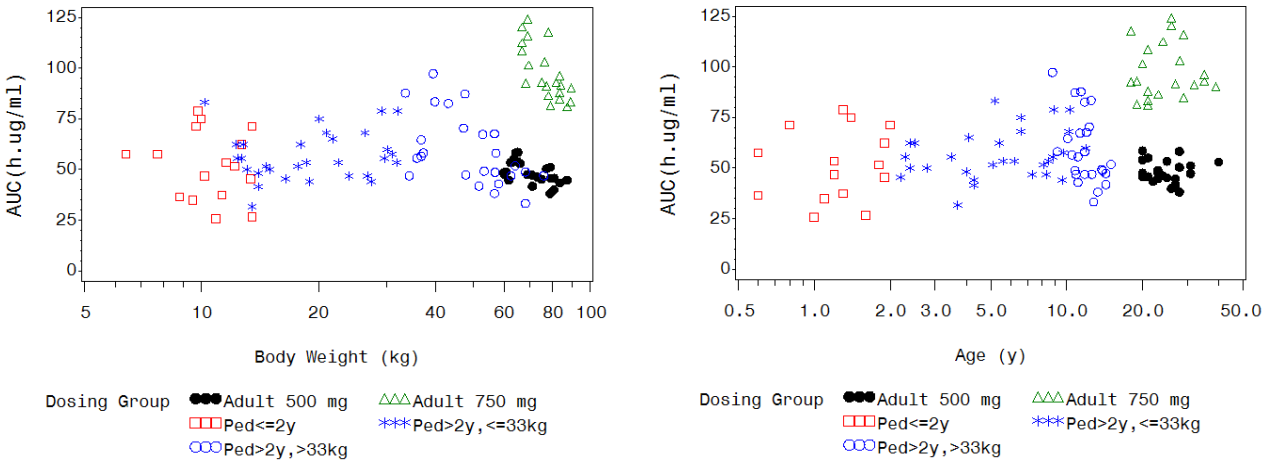


Figure 12: Predicted steady state AUC following 15 mg/kg levofloxacin (not exceeding 500 mg) vs. Body Weight and Age.

6.5.3.2 Adult C_{max} Targeting

The next objective is to match C_{max}. From a safety perspective, it is desirable that the values of C_{max} in pediatrics do not exceed those observed in adults while the values of C_{min} are maintained above the MIC to ensure efficacy. A prediction of steady-state C_{max} and C_{min} in pediatrics taking the FDA proposed dose is made by using the formula:

$$C_{max,\,ss} = Dose/(V_d \times (1 - e^{-k}e^{\tau})) \qquad (4)$$

$$C_{min,\,ss} = C_{max,\,ss} \times e^{-k\tau} \qquad (5)$$

where τ is the dosing interval, and $k_e = CL/V_d$.

A plot (see Figure 13) of formula (4) suggests that the C_{max} after 15 mg/kg q.d. with a cap to 500 mg q.d. would fail to match the C_{max} observed in adults taking 500 mg q.d. (black dots) and some are even close to the maximum observed adult C_{max} after 750 mg q.d. (green dots), despite matching the adult $AUC_{0\text{-}24}$.

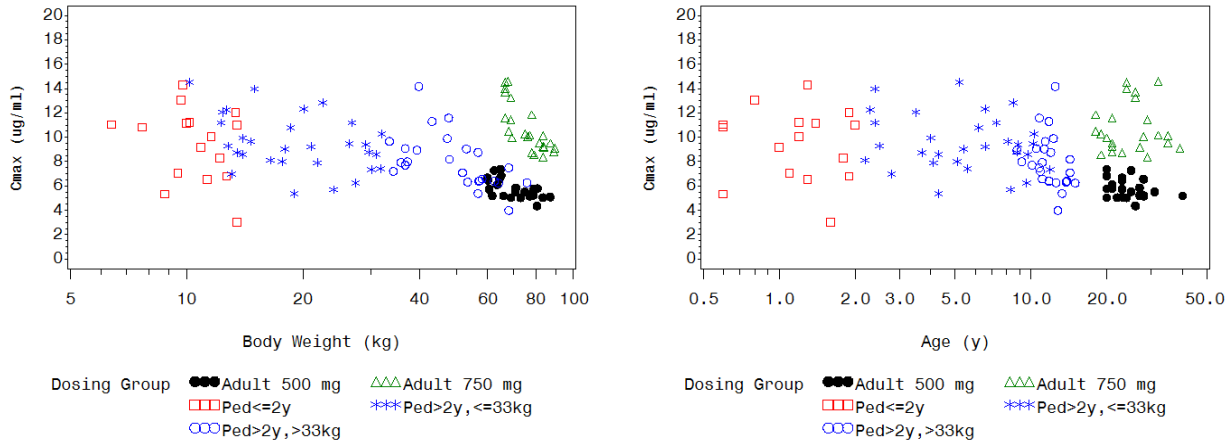


Figure 13: Predicted steady state C_{max} following 15 mg/kg q.d. levofloxacin (not exceeding 500 mg) vs. Body Weight and Age.

To solve this problem, we changed our dosing strategy by keeping the total daily dose but switching from q.d. to b.i.d. dosing. A plot (see Figure 14) of this dosing strategy suggests that steady-steady C_{max} in all pediatrics dosing group will match that in adults taking a dose of 500 mg q.d.

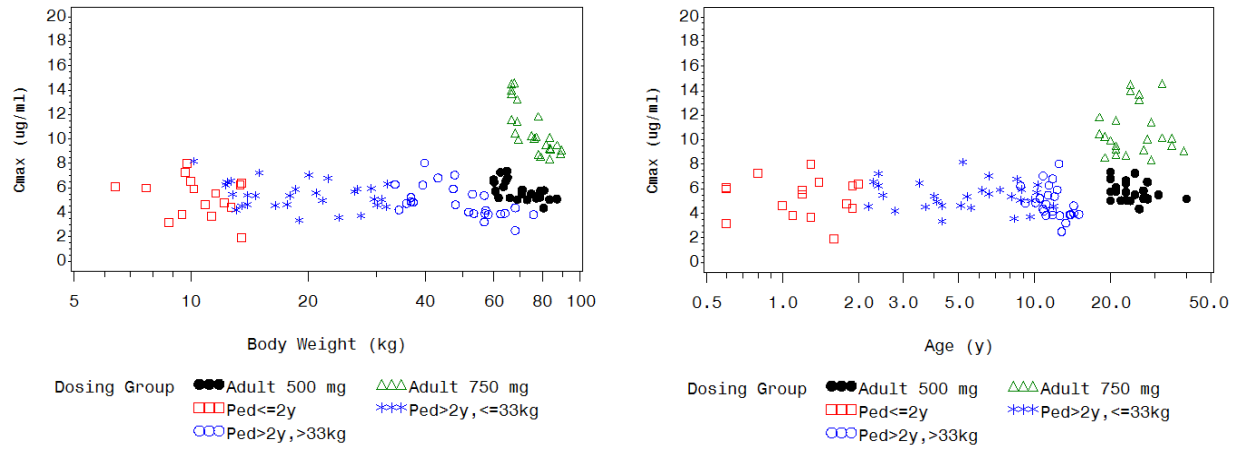


Figure 14: Predicted steady state C_{max} following 7.5 mg/kg b.i.d levofloxacin (not exceeding 250 mg) vs. body weight and age.

For pediatrics weighing more than 50 kg, q.d. dosing of 500 mg is acceptable, as indicated by the plot of steady state C_{max} vs. body weight and age in Figure 15 (see black crosses).

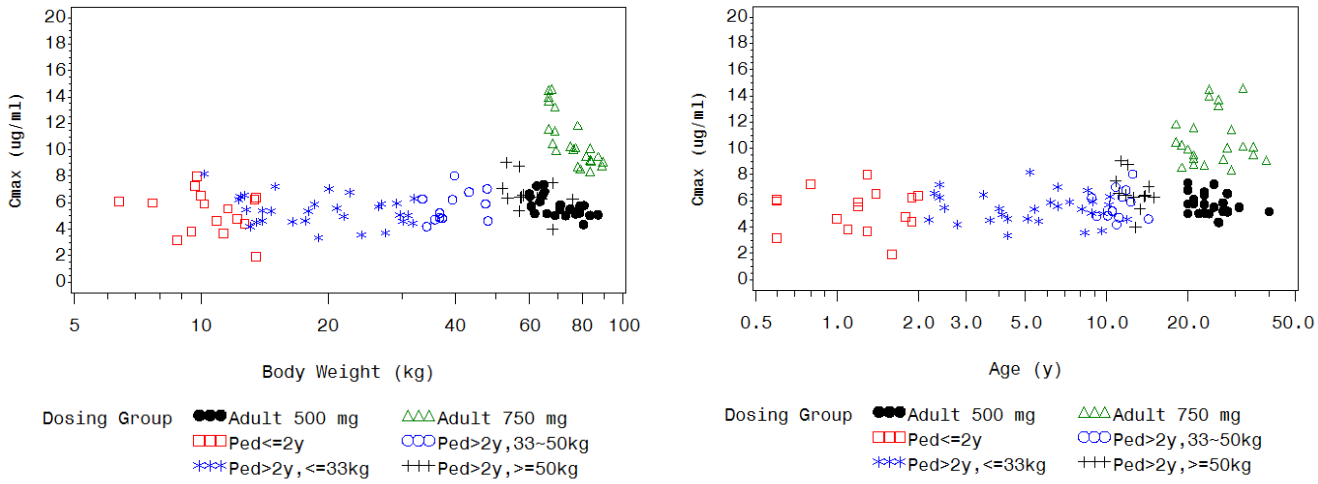


Figure 15: Predicted steady state C_{max} vs. body weight and age following 7.5 mg/kg b.i.d levofloxacin (not exceeding 250 mg) in pediatrics less than 50 kg and 500 mg q.d. in patients 50 kg and above.

It is predictable that the switch from q.d. dosing to b.i.d dosing will increase the steady state trough concentrations and reduce the difference between the peak and trough concentrations. A plot of the predicted steady state trough concentration (C_{min}) of levofloxacin (Figure 16) suggested that the b.i.d dosing will achieve C_{min} values much higher than those observed in adults with 500 mg q.d of levofloxacin, making the minimum plasma concentrations much higher than the MIC.

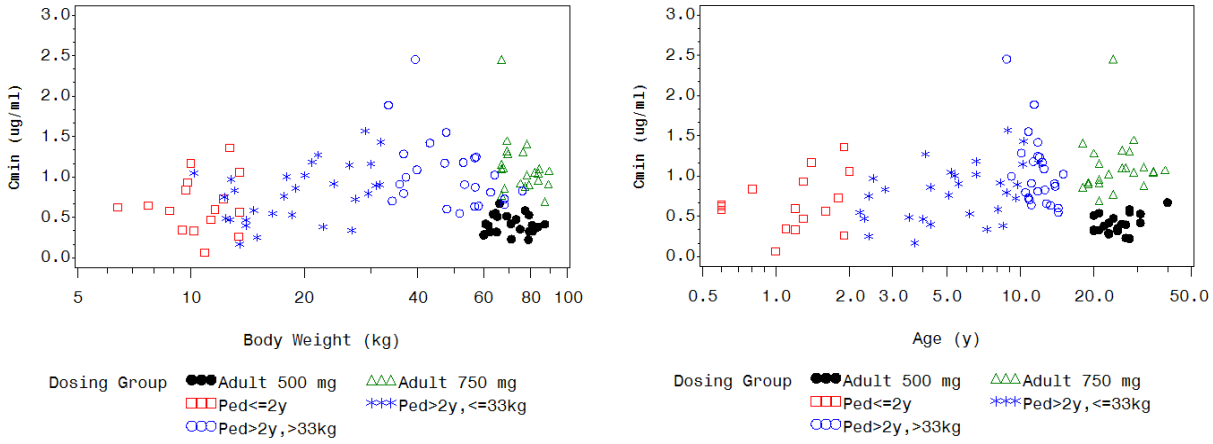


Figure 16: Predicted steady state C_{min} following 7.5 mg/kg b.i.d levofloxacin (not exceeding 250 mg) vs. body weight and age.

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For children aged less than 6 months, according to the maturation rate plot (see Figure 4), the pediatric dose for children aged less than 6 months of age should be reduced by a factor of 0.65, i.e. 5 mg/kg b.i.d. (7.5 mg/kg b.i.d x 0.65).

For practical reasons, it is acceptable to round the pediatric dose up from 7.5 mg/kg to 8.0 mg/kg since the maximal additional total dose is 15 mg (i.e. 8-7.5 mg/kg * 250 mg/8 mg/kg = 15 mg) which is less than a 10% increase in the total dose (see Appendix 8.4).

A summary of the proposed pediatric dosing is as follows:

For pediatric patients >6 months and ≤50 kg: 8 mg/kg every 12 hours for 60 days, not exceeding 250 mg/dose or 500 mg/day;

For pediatric patients >50 kg: 500 mg every 24 hours for 60 days.

6.6 Conclusions

- (b) (4)

- For a drug predominantly cleared via kidney, factors for dosing consideration should include immature rental function in kids younger than 2-3 years old.

- Using intensive PK data in Phase I studies, a new clearance model including age-associated renal maturation function was developed and used for pediatric dosing recommendation.

- In summary, the FDA proposed pediatric dosing regimen of levofloxacin for inhalational anthrax is as follows:

	IV	PO (Tablets)	PO (Solution)
Adults	500 mg q.d.	500 mg q.d.	500 mg q.d.
Pediatrics ≥ 6 months and ≤50 kg	8 mg/kg b.i.d. (not to exceed 250 mg/dose)	8 mg/kg b.i.d. (not to exceed 250 mg/dose)	8 mg/kg b.i.d. (not to exceed 250 mg/dose)
Pediatrics >50 kg	500 mg q.d.	500 mg q.d.	500 mg q.d.

- For practical reasons, it is acceptable to round the pediatric dose up from 7.5 mg/kg to 8.0 mg/kg since the maximal additional total dose is 15 mg (i.e. 8-7.5 mg/kg * 250 mg/8 mg/kg = 15 mg) which is less than a 10% increase in the total dose (see Appendix 8.4).

7 References

Rebecca L. Milsap, Malcolm r. Hill, and Stanley J. Szefler: Pharmacokinetic Considerations in Children. In Book Applied Pharmacokinetics Principles of Therapeutic Drug Monitoring, third edition

Christoffer W. Tornoe, Jeffrey J. Tworzyanski, Menfo A. Imoisili et al. Optimising piperacillin/tazobactam dosing in paediatrics, International Journal of Antimicrobial Agents 30 (2007) 320-324.

8 Appendices

8.1 Sponsor's PK Analysis in the Phase III Study (LOFBIV-PCAP-003):

Using available pharmacokinetic data obtained in studies conducted in pediatric patients and in adults, pharmacokinetic modeling and simulations were performed to find a dosing regimen that would produce systemic exposure in children that had been shown to be effective in adults. The selected regimens (10 mg/kg b.i.d. in patients <5 years of age and 10 mg/kg q.d. in patients >5 years of age) were tested in Study LOFBIVPCAP-003, a study designed to assess the efficacy of levofloxacin in the treatment of community-acquired pneumonia (CAP) in children 6 months to 16 years of age. Steady-state plasma concentrations of levofloxacin in children <5 years of age, who received 10 mg/kg b.i.d., were comparable to concentrations in children >5 years of age who received 10 mg/kg q.d. (Table 14).

Table 14: Mean ± SD Plasma Concentrations (μg/mL) at Steady-State in Pediatric Subjects with Community-Acquired Pneumonia
(Study LOFBIV-PCAP-003: Pharmacokinetic Analysis Set (PK Evaluable Subjects Subset)

	Dosing Regimen / Age Group			
Time Interval	**10 mg/kg bid**	**10 mg/kg qd**		
After Dosing (h)	0.5 to < 5 yrs	5 to < 10 yrs	10 to 16 yrs	5 to 16 yrs
0 to < 1	3.83 ± 3.75 (n=5)	5.53 ± 4.18 (n=6)	5.70 ± 4.69 (n=2)	5.57 ± 3.96 (n=8)
1 to < 2	6.14 ± 2.80 (n=20)	5.45 ± 2.16 (n=8)	7.42 ± 2.78 (n=2)	5.85 ± 2.27 (n=10)
2 to < 4	4.36 ± 2.44 (n=52)	4.02 ± 2.02 (n=8)	2.38 ± 3.26 (n=4)	3.47 ± 2.48 (n=12)
8 to < 12	1.75 ± 1.89 (n=81)	0.600 ± 0.738 (n=3)	NA -	0.600 ± 0.738 (n=3)
12 to < 24	1.21 ± 2.37 (n=72)	0.642 ± 1.13 (n=106)	1.06 ± 1.51[a] (n=46)	0.769 ± 1.26[a] (n=152)

bql = below quantitation limit (0.0500 μg/mL), NA = Not applicable
[a] One extreme high outlier excluded

Mean plasma concentrations 1 to 2 hours after dosing, the expected time of peak concentration, for the <5 years and >5 years age groups were 6.14 and 5.85 μg/mL, respectively. For the q.d. dosing regimen (>5 years) mean plasma concentrations were somewhat lower in the 5 to 10 year old subgroup compared to the 10 to 16 year old subgroup (5.45 and 7.45 μg/mL, respectively).

Although the data were limited and highly variable due to the sparse sampling PK design, the results of this study showed that both the 10 mg/kg b.i.d. and q.d.

regimens produced steady state maximal plasma concentrations that were somewhat higher than those seen in other studies in which levofloxacin was administered at a 7 mg/kg dose. Observed maximal levels, although efficacious (on the basis of the clinical efficacy outcome of the study), were some what less than those predicted by simulations that were performed in an effort to design dosing regimens that would produce plasma concentrations similar to those seen in adult studies in which subjects received 500 mg daily doses. They were, however, similar to those observed in adults receiving i.v and tablet formulations (5.36 and 6.18 µg/mL, respectively) from Study LOFBO-PHIO-097, (NDA 20 634, originally submitted 21 December 1995, volume 1.053, page 06 00396). AUC values were not estimated due to limitations in the data.

8.2 Sponsor's Population PK Analysis

Population Pharmacokinetic Analysis of Levofloxacin in Pediatric Subjects
(Document number: EDMS-USRA-10174272:3.0)
A two-compartment disposition model with linear elimination and sequential zero- and first order absorption processes with lag-time is suitable to describe the pharmacokinetic behavior of levofloxacin after intravenous and oral administration to pediatrics and adults.

Pharmacokinetic parameters related to drug disposition were scaled by body weight according to an allometric function.

Clearance normalized by body weight was constant in young children up to 5.5 years of age after which it showed a mono-exponential decline of approximately 5% per decade of age. Similarly, volume of distribution of the peripheral compartment when normalized by body weight declined mono-exponentially with age after 0.5 years of age. The magnitude of the decline is about 17% per decade of age.

While the extent of absorption was the same for suspension and tablet formulations. Levofloxacin exhibited a faster absorption profile when given as a suspension as compared to the tablet formulations.

Levofloxacin clearance adjusted by body weight and age was not related to creatinine clearance over the range of 16.1 – 249 mL/min. This phenomenon is probably due to the high correlation between body weight and age with creatinine clearance.

Simulations showed the dose regimen used in the Phase 3 study was adequate to achieve the targeted AUC24.

8.2.1 Objectives of the Analysis

The pharmacokinetics (PK) of levofloxacin have been studied in pediatrics. However, the development of a population PK model, based on data from adults and pediatrics, provides an opportunity to better understand the disposition of levofloxacin and to evaluate the interindividual differences in pharmacokinetics across a more general population, allowing the relationship between subject covariates and pharmacokinetic parameters to be quantified.

The objectives of this analysis were:
(1) to develop a population PK model to describe plasma concentrations of levofloxacin following intravenous (i.v.) and oral (tablet and suspension) administration, and
(2) to identify patient demographics and other covariates influencing the pharmacokinetics of levofloxacin in a pediatric population.

8.2.2 Data Included in the Analysis

The population PK analysis was performed using data from 8 Phase 1 studies (3 studies in pediatrics: LOFBIV-PHI-057, LOFBIV-PHI-058 and LOFBO-PHI-115 and 5 studies in adults: LOFBO-PHI-108, LOFBO-PHI-111, LOFBO-PHIO-097, LOFBO-PHI-116, and N93-024) and 1 pediatric Phase 3 study (LOFBIV-PCAP-003) using the NONMEM software. In these studies, patients received either i.v. (7 mg/kg for Phase 1 and 10 mg/kg Phase 3) or oral levofloxacin (500 mg to 1500 mg single doses). In total, 3830 plasma concentrations from 536 subjects were used for the population PK analysis (1047 concentrations in 381 pediatric subjects and 2783 concentrations in 155 adults).

8.2.3 Model Development

Nonlinear mixed effects modeling of the pooled data was conducted using NONMEM. Several different structural models were tested to evaluate their fit to the dataset. Structural models were explored to evaluate their fit to the dataset. Inter-individual variability was explored for each of the PK parameters in the model. Observation and model predictions were log-transformed and additive error model on the log domain was used to account for the residual variability. Two separate additive error terms were used to account for the differences is sampling schemes between Phase 1 Phase 3 studies. Using the base structural model, the relationships between subject covariates and PK parameters were explored to explain inter-individual differences. The final model, including all significant subject covariates, was then examined for potential biases and modifications to refine the model were made.

8.2.4 Key Results

An open, two-compartment disposition model with linear elimination from the central compartment was used to describe the plasma pharmacokinetics of levofloxacin. Pharmacokinetic parameters related to drug disposition were scaled by body weight according to an allometric function. Levofloxacin absorption was modeled as a zero-order input into the depot compartment, followed by a first-

order absorption from depot compartment into central compartment, after a lag-time. Between-subject variability was assumed to be log-normally distributed and was estimated for CL (total systemic clearance), V_2 (volume of central compartment), V_3 (volume of peripheral compartment), K_A (rate of first-order absorption from depot), F_{ABS} (bioavailability of oral formulations), D_1 (duration of zero order input into depot) and A_{LAG} (absorption lag time from depot). Inter-occasion variability was identified for K_A, F_{ABS}, D_1 and A_{LAG}. All measured concentrations and individual model predictions were converted into natural logarithms (transform-both sides approach) and the magnitude of residual random error in the log domain was modeled using an additive error model. Separate residual variability models were used to account for intra-individual random error in Phase 1 and sparse Phase 3 studies.

8.2.5 Effects of Covariates on Levofloxacin Clearance

Besides body weight that was used to allometrically scale pharmacokinetic parameters related to drug disposition, the other demographic factors controlling levofloxacin PK were: age which influenced CL and V_3. The relationship between age and levofloxacin clearance was well described by a function in which the clearance was constant in younger children (up to 5.5 years of age) and then declined mono-exponentially in older children.

The expression for the typical value of levofloxacin systemic was:

If Age<5.5 yr, CL (L/h) = 6.39•(BWT/30)^0.75

If Age>5.5 yr, CL (L/h) = 6.39•exp(-0.00899)(Age-5.51)) •(BWT/30)^0.75*

where, Age and BWT represent age (years) and body weight (Kg).

Creatinine clearance exhibited a high positive correlation with body weight (R^2=0.680) and with age (R^2=0.627), Since both age and body weight were incorporated into the population PK model in the initial stages of model building, it is likely that much of the inter-subject variability due to creatinine clearance was accounted for by inclusion of these covariates. Thus, creatinine clearance does not directly influence the model after adjusting pharmacokinetic parameters by body weight and age.

Similarly, volume of distribution of the peripheral compartment followed a mono-exponential decline from the age of 0.5 years onwards.

The expression for the typical value of V_3 in subjects older than 6 months was

V_{3j} (L) = 19.4•exp(-0.0189)(Age-0.5)) •(BWT/30)*

Expressions for the typical value of V2 and Q, which were allometrically related to bodyweight, were as follows:

V_{2j} (L) = 25.8• (BWT/30)

Q_j *(L/h) = 11.0• (BWT/30)^0.75*

Oral absorption from tablet and suspension formulations was modeled as sequential zero-order input into the depot compartment, followed by a first-order absorption from the depot compartment into the systemic circulation, after a lag time. Absorption lag time from the depot compartment was found to be 20% faster for the suspension formulation (0.132 h) compared to the tablet (0.169 h). Similarly, duration of zero order input into the depot was 74% lower for suspension (0.0976 h) relative to the tablet formulation (.0375 h). The rate of first order absorption from the depot was the same for the oral formulations (2.14 h-1), and the extent of absorption was also equivalent for both oral formulations and almost complete (95.3%).

Creatinine clearance exhibited a high positive correlation with body weight (R^2=0.680) and with age (R^2=0.627) Since both age and body weight were incorporated into the population PK model in the initial stages of model building, it is likely that much of the inter-subject variability due to creatinine clearance was accounted for by inclusion of these covariates.

Thus, creatinine clearance does not directly influence the PK model.

Table 17: Model Parameters for Levofloxacin After Intravenous and Oral Administration of Tablet and Suspension Formulations

Pharmacokinetic Parameter	Typical value*	Variability	
		Between subjects (IIV, %)*	Within subjects (IOV, %)*
CL (L/h) [(a)]	6.39 (2.7)	22.0 (11.1)	-
CL-age Decline exponent	0.00899 (8.4)	-	-
CL-age breakpoint (yr)	5.51 (26.1)	-	-
V_2 (L) [(b)]	25.8 (12.2)	24.0 (25.4)	-
V_3 (L) [(b)]	19.4 (12.2)	31.9 (47.0)	-
V_3-age Decline exponent	0.0189 (34.6)	-	-
V_3-age breakpoint (yr)	0.5[(e)]	-	-
Q (L/h) [(a)]	11.0 (50.5)	-	-
K_A (h^{-1})	2.14 (15.0)	60.6 (31.6)	52.8 (32.6)
F_{abs} (%)[(c)]	95.3 (1.3)	90.6 (34.1)	62.2 (43.7)
D_1 (h) (Tablet)	0.375 (8.0)	79.9 (20.5) [(d)]	74.2 (26.3)
D_1 (h) (Suspension)	0.0976 (20.1)	79.9 (20.5) [(d)]	74.2 (26.3)
A_{LAG} (h) (Tablet)	0.169 (7.9)	62.2 (18.3) [(d)]	24.0 (78.9)
A_{LAG} (h) (Suspension)	0.132 (16.7)	62.2 (18.3) [(d)]	24.0 (78.9)

* Results expressed as parameter (RSE: relative standard error of parameter estimate, %).
[a)] Clearance terms are normalized for a bodyweight of 30 kg. The normalization coefficient is equal to $(BWT/30)^{0.75}$, where BWT is bodyweight (kg).
[b)] Volume of distribution terms are normalized for a bodyweight of 30 kg. The normalization coefficient is equal to (BWT/30)1.0, where BWT is bodyweight (kg).
[c)] Expressed as standard deviation in the logit domain.
[d)] Correlation between D_1 and A_{LAG} implemented
[e)] Parameter fixed – not estimated
Residual variability, expressed as percentage:
Full PK profiles: 12.1 (RSE = 5.98 %)
Isolated measurements of Phase 3 studies: 93.9 (RSE =16.9 %)

Population pharmacokinetic model parameters are shown in Table 17. Good precision estimates of the majority of fixed and random effects were obtained. The precision in the estimation of fixed effects parameters was less than 30%, except for the V_3-age Decline exponent and Inter-compartmental clearance precision estimates. Large inter-subject variability was noted for absorption parameters though neither weight nor age-related differences in absorption were noted in the covariate analysis. This suggests that absorption was not markedly different between adults and pediatrics. Although a separate residual variability model was used to account for within subject variability in Phase 3 studies, residual variability was still estimated to be high.

8.2.6 Simulations

The population PK model was used to simulate the dosing regimens used in the Phase 3 studies, to compare the resulting range of systemic exposures in specific pediatric age groups of interest with those in adults. Stochastic simulations were performed to estimate the parameters of systemic exposure (AUC24 and C_{max}) provided by the dosing regimens used in the Phase 3 studies (Studies LOFBIV-PCAP-003 and LOFBO-OTMD-001). An AUC24 of 50 µg.h/mL was targeted; this value corresponds to the systemic exposure seen in the adult population receiving a daily dose of at least 500 mg. Results of these simulations, along with parameters reported in previous adult studies1, are presented in Table 18.

Table 18: Simulated Systemic Exposure Parameters in Children Relative to Those Observed in Adults

	6 months to <5 yr	5 to <10 yr	10 to 16 yr	Adults	
Parameter	10 mg/kg bid[a]	10 mg/kg qd[b]	10 mg/kg qd[b]	500 mg qd[c]	750 mg qd[d]
AUC_{24} (µg.h/mL)	75.6 (56.8-102)[g]	46.2 (34.8-62.1)[g]	52.0 (38.5-70.0)[g]	54.6 (11.1)[e,f]	91.0 (18.0)[e,f]
C_{max} (µg/mL)	9.75 (7.71-12.3)[g]	8.95 (6.91-11.6)[g]	9.05 (6.70-11.8)[g]	6.40 (0.80)[e,f]	8.60 (1.86)[e,f]

[a] 10500 pediatrics simulated for 10 mg/kg bid dosing regimen
[b] 10500 pediatrics simulated for 10 mg/kg qd dosing regimen
[c] Recommended adult dose for the treatment of community-acquired pneumonia
[d] Recommended adult dose for the treatment of complicated skin and skin structure infections
[e] Observed data in healthy adults, as reported on the Levaquin package insert
[f] Results are presented as mean (SD) values
[g] Results are presented as median (10^{th} Percentile – 90^{th} Percentile)

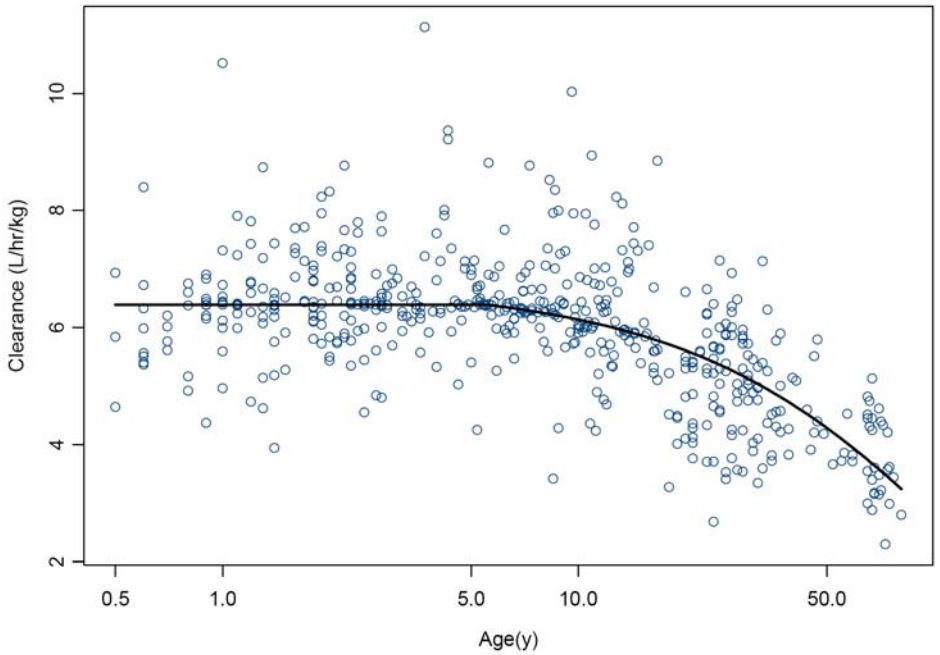

Figure 20: Plot of the Clearance vs. Age. Solid Line Represents Estimated Clearance Function and Individual Points are Posthoc Estimates of Clearance.

(Sponsor's Attachment 22 in population PK in Pediatric Subjects Report, page 127)

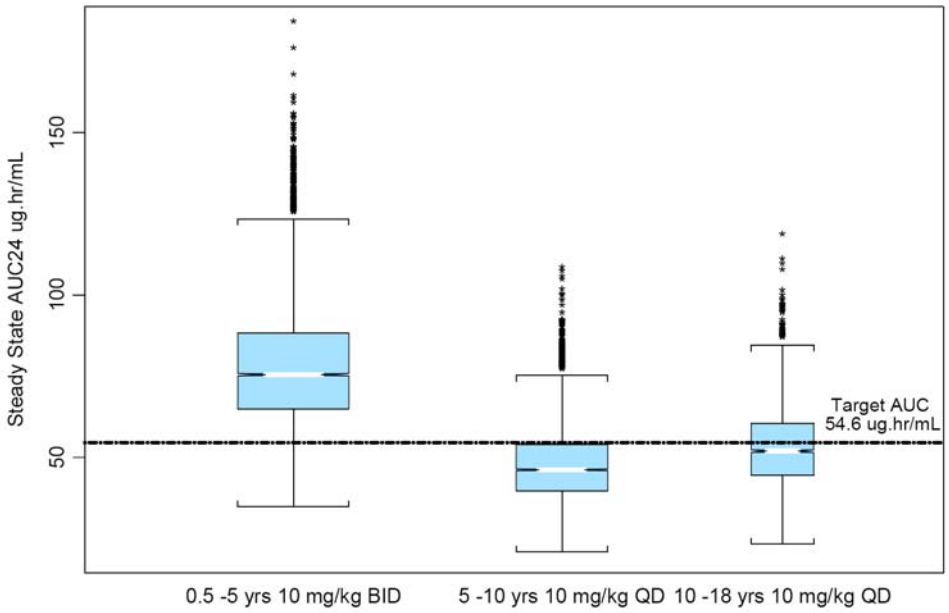

Figure 21: Box represents interquartile range and whiskers correspond to the 95% confidence interval.

(Sponsor's Attachment 24 in population PK in Pediatric Subjects Report, page 129)

8.3 Additional FDA Population PK Analysis

In order to evaluate the ability to predict the exposure and concentration-time profiles following 10 mg/kg in the phase III pediatric CAP study, a population PK model was developed using the clearance and volume of distribution models described in Sections 6.5.1 and 6.5.2 using the same data as described in Section 6.3.

Figure 22 illustrates the goodness-of-fit of the individual model predictions and the observed data used to build the population PK model. The model predictions are very close to the observed data illustrated by the close proximity of the dots to the red line of unity.

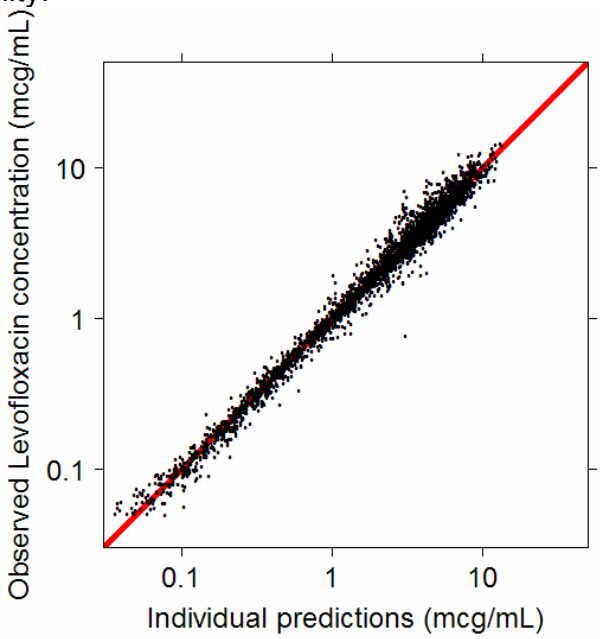

Figure 22 Observed levofloxacin concentration vs. individual predicted concentrations. The red line is the line of unity.

In Figure 23, the population predicted concentration-time profiles are shown following 7 mg/kg q.d. (red), 10 mg/kg b.i.d./q.d. (blue), 7.5 mg/kg b.i.d. (orange) for a median body weight pediatric patient in the Phase III pediatric CAP study below 5 years (left, 11 kg) and above 5 years (right, 23 kg) of age compared to the adult reference of 500 mg q.d..

Finally, the concentration-time profiles following 10 mg/kg IV and POS for pediatrics below 5 year (b.i.d dosing) and above 5 years (q.d. dosing) were predicted to evaluate whether they correspond to what was observed in the Phase III CAP study (which weren't used for the model development). In Figure 24 , the typical pediatric patient's concentration-time profiles (red line) for the median body weight pediatric patient (11 kg for pediatric patients below 5 years and 23 kg for pediatric patients above 5 years) together with the observed concentrations in the Phase III CAP study (black dots).

The model captures the C_{max} (around 10 mcg/mL) and C_{trough} (around 0.6 and 0.1 mcg/mL for b.i.d. and q.d. dosing) reasonably well. This finding is similar to sponsor's predictions of a mean C_{max} of 9.75 and 8.95 mcg/mL following 10 mg/kg b.i.d. and q.d., respectively, compared to the mean C_{max} in adults of 6.4 mcg/mL following 500 mg q.d. Similar plots are shown in Figure 25, showing the typical minimum (blue), median (orange), and maximal (red) body weight pediatric patient's concentration-time profiles.

The conclusions from the additional PK analysis are:

- The exposures (AUC, C_{max}, and C_{trough}) following 10 mg/kg b.i.d. and q.d. in pediatrics are predictable without using the phase III CAP data for population PK model building.

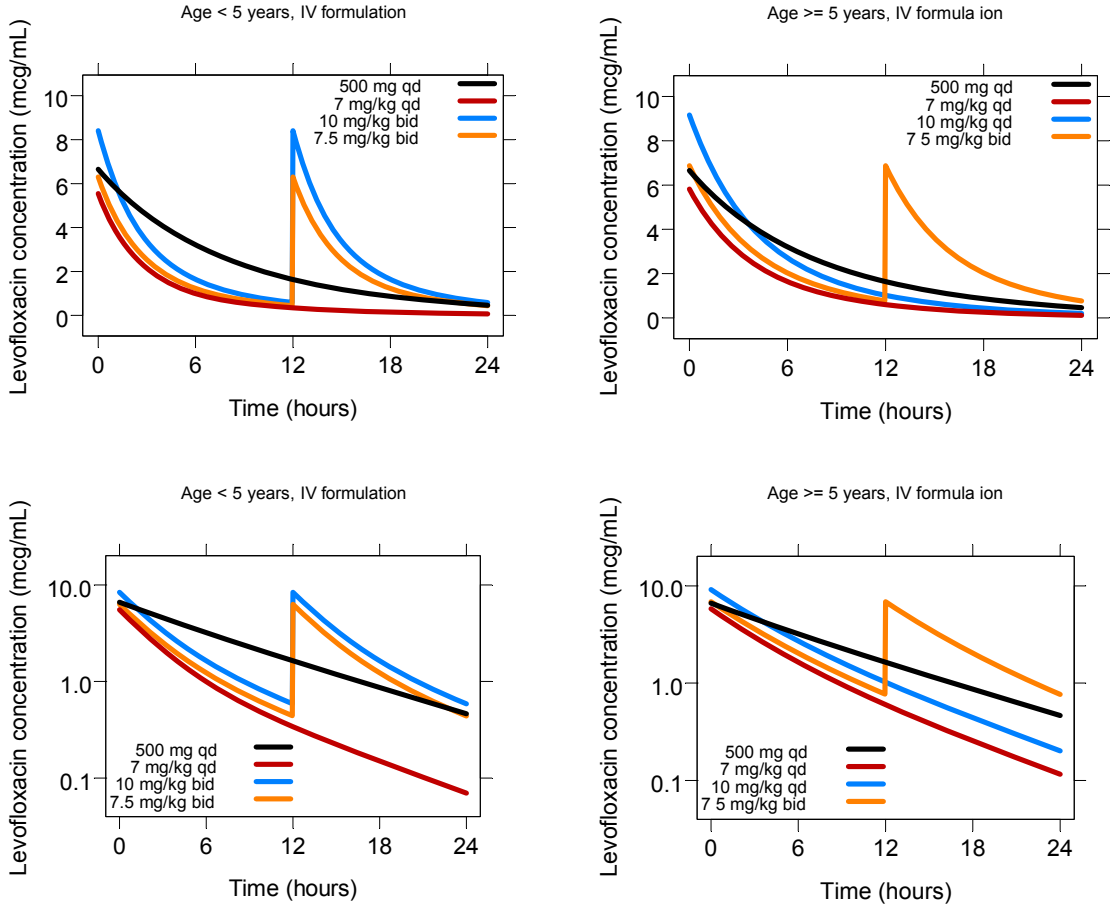

Figure 23 Population IV concentration-time predictions of 7 mg/kg q.d. (red), 10 mg/kg b.i.d/q.d. (blue), 7.5 mg/kg b.i.d. (orange) for the median body weight pediatric patient in the Phase III pediatric CAP study for pediatric patients below 5 years (left, 11 kg) and above 5 years (right, 23 kg) of age compared to the adult reference of 500 mg q.d. on the normal (top) and log (bottom) scale.

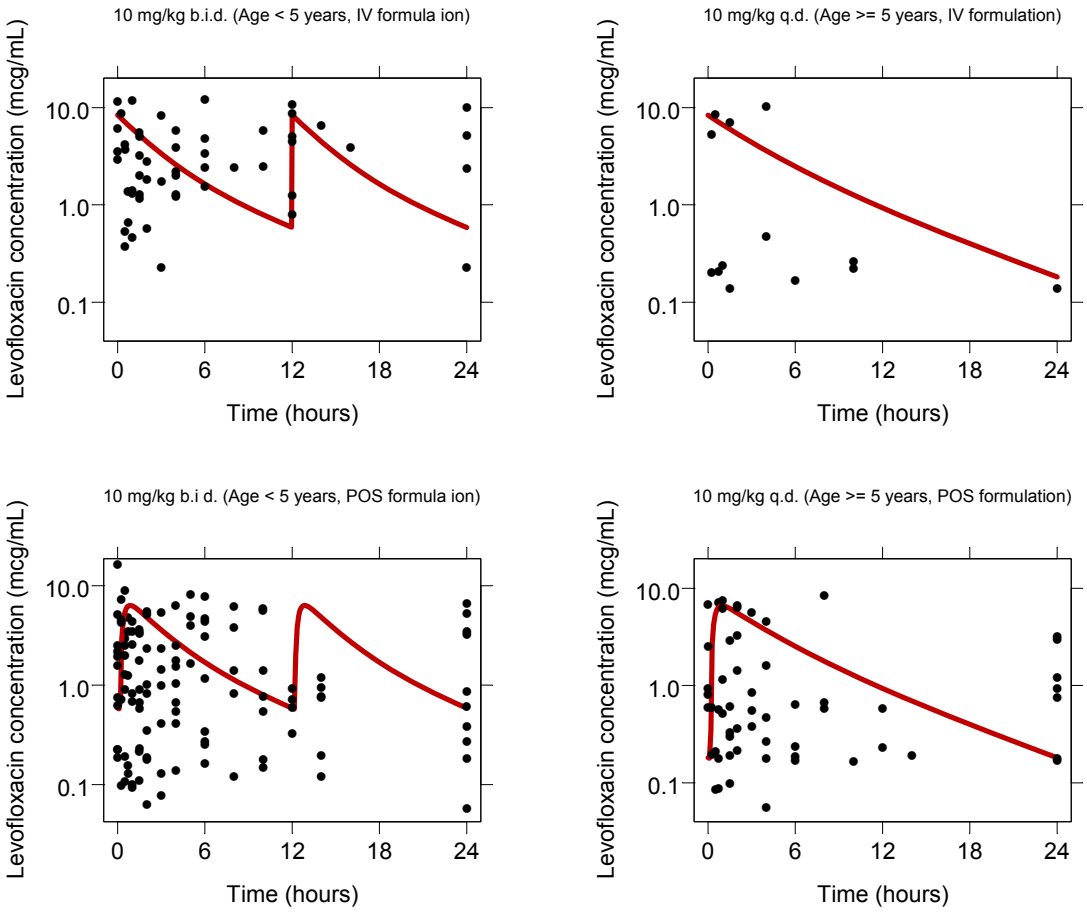

Figure 24 Population predictions for the median body weight pediatric patient in the Phase III pediatric CAP study for pediatric patients below 5 years (left, 11 kg) and above 5 years (right, 23 kg) of age.

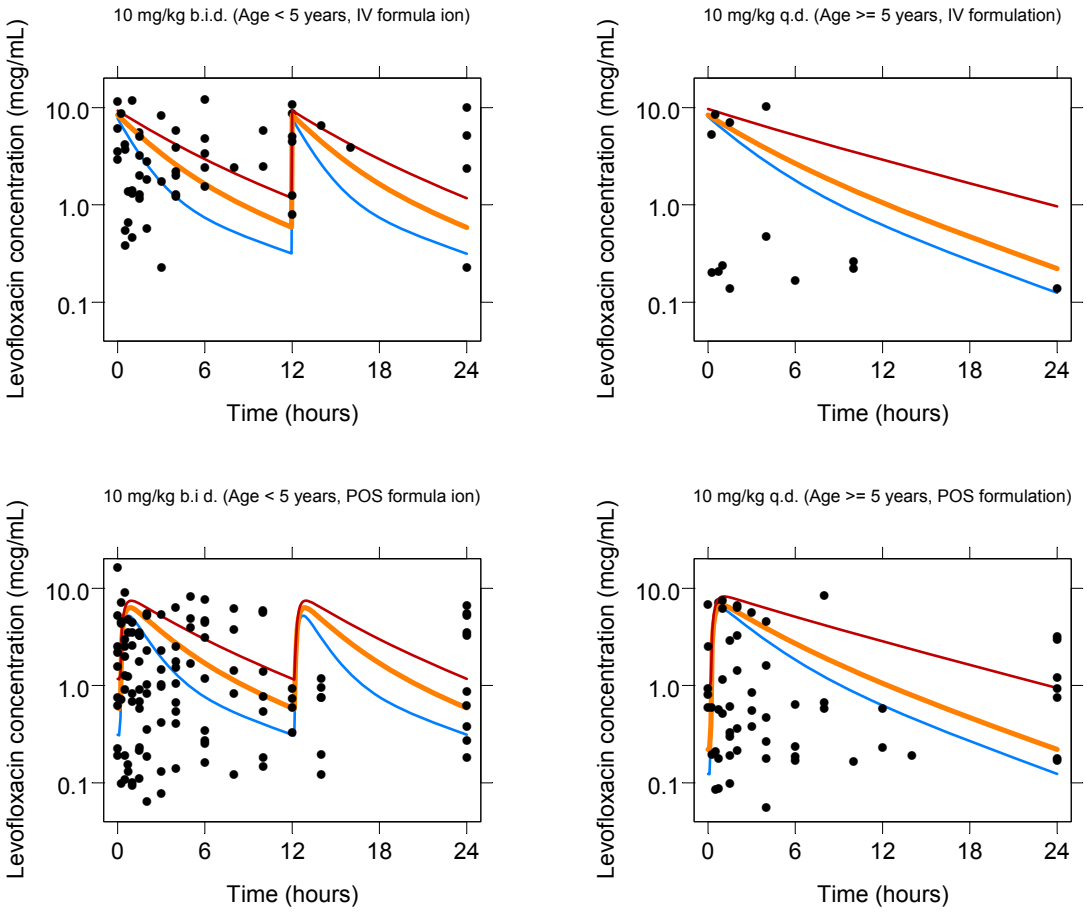

Figure 25 Population predictions for the minimum (blue), medium (orange), and maximal (red) body weight pediatric patient in the Phase III pediatric CAP study in pediatric patients below 5 years (left, 4.3, 11, and 23 kg) and above 5 years (right, 14, 25, and 82 kg) of age.

8.4 Comparison of Pediatric Exposure following 7.5 and 8 mg/kg

For practical reasons, it is acceptable to round the pediatric dose up from 7.5 mg/kg to 8 mg/kg since the maximal additional total dose is 15 mg (i.e. 8-7.5 mg/kg * 250 mg/8 mg/kg = 15 mg) which is less than a 10% increase in the total dose. The differences in steady-state AUC, C_{max}, and C_{min} between 7.5 and 8 mg/kg b.i.d. is illustrated in Figure 26.

The mean AUC increases from 57 to 59 mcg*hr/mL, C_{max} from 5.7 to 5.9 mcg/mL, and C_{min} from 0.75 to 0.79 mcg/mL when increasing the dose from 7.5 mg/kg to 8 mg/kg b.i.d. which all are close to those following 500 mg q.d. in adults.

The pediatric exposure following 8 mg/kg b.i.d. was found to reasonably match the adult exposure following 500 mg q.d.

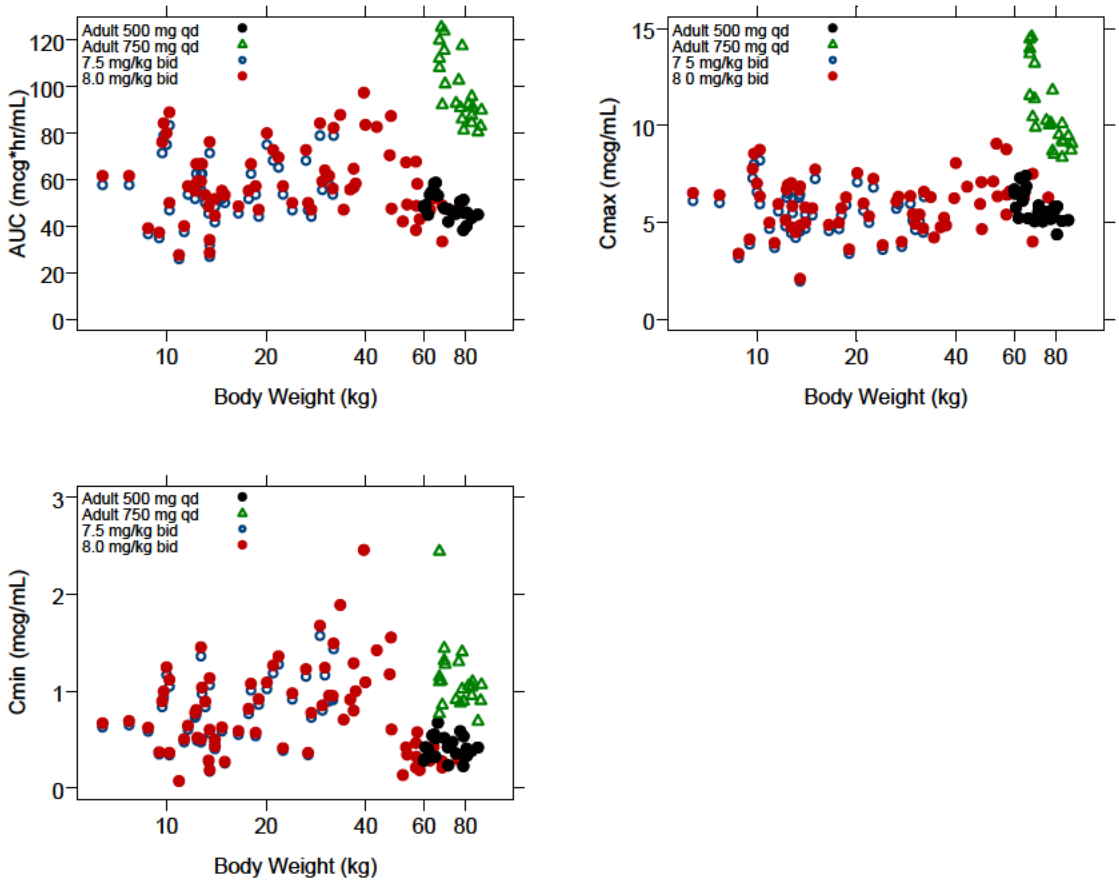

Figure 26 Predicted steady-state AUC (top left), Cmax (top right), and Cmin (bottom left) vs. body weight following 7.5 mg/kg b.i.d. (open blue circle) and 8 mg/kg b.i.d. (solid red dot) along with adults receiving 500 mg q.d. (black solid dot) and 750 mg q.d. (open green triangle).

8.5 Draft Label 4-16-2008

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