CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	19-537
Date of Submission	August 4, 2003
Brand name	Cipro®
Generic name	Ciprofloxacin HCl
Applicant	Bayer
Type of submission	Pediatric Supplemental NDA
Primary Reviewer	Dakshina M. Chilukuri, Ph.D.
Pharmacometrics Reviewer	Jenny J. Zheng, Ph. D.
Team Leader	Philip Colangelo, Pharm.D, Ph.D.
Date of Review	March 24, 2004

Executive Summary

Bayer was issued a Written Request (WR) in October 2001 to satisfy the pediatric exclusivity requirements. As part of the WR, an efficacy and safety study was conducted in pediatric patients from 1 to 17 years of age with complicated urinary tract infections (cUTI) and/or acute pyelonephritis. In addition, a pharmacokinetic substudy of ciprofloxacin in these pediatric patients with cUTI and/or acute pyelonephritis was also conducted. The proposed indication is treatment of cUTI and/or acute pyelonephritis.

A population PK (POPPK) analysis was conducted using data from a total of 6 pediatric studies. These 6 studies included the efficacy study conducted to satisfy the WR requirement along with 5 other studies performed in pediatric patients with varied disease diagnoses. These studies included a variety of infections such as urinary tract infection, lower respiratory tract infection, skin and soft tissue infection, severe sepsis, acute invasive diarrhea and cystic fibrosis. The POPPK analysis was conducted with the following objectives:

- To estimate typical population pharmacokinetic parameters for ciprofloxacin in pediatric patients.
- To identify covariate, demographic and clinical factors that are significant predictors of variability in ciprofloxacin pharmacokinetic parameters.
- To provide a dosing recommendation for pediatric patients.

Plasma ciprofloxacin concentration-time data were available in 357 pediatric patients. The age of these patients ranged from 0.27 to 16.9 years. The body weight of these patients ranged from 4.2 to 73.5 kg. One hundred and five patients were male and 252 patients were female. Twenty-eight out of 357 patients had a history of cystic fibrosis and 207 out of 357 patients were being treated for complicated urinary tract infection / acute pyelonephritis. Population pharmacokinetic analyses were performed with the NONMEM software using the First-Order Conditional Estimation (FOCE) method.

The pharmacokinetics of oral ciprofloxacin was described by a two-compartment model with first order absorption and absorption lag time. The POPPK analysis identified cystic fibrosis, body weight and creatinine clearance as the significant covariates for the

apparent clearance (CL/F) of ciprofloxacin. In addition, the effect of cystic fibrosis on the absorption rate constant (k_a) was also found to be a significant covariate.

The predicted exposure of ciprofloxacin derived from the population PK analysis compared to the exposure observed in adults is given in Table 1.

Table 1. Predicted ciprofloxacin exposure derived from the population PK analysis compared to the exposure observed in adults

Creatinine Clearance (mL/min)	Pediatric dose	Predicted AUC (µg-h/mL)	Adult dose	Observed AUC (µg-h/mL)
>50	15 mg/kg BID (po)	11.8	500 mg BID (po)	13.7
>50	9 mg/kg BID (iv)	12.1	400 mg BID (iv)	12.7

The population based estimates for ciprofloxacin half-life ($T_{1/2}$) ranged from approximately 4 to 5 hours in pediatric patients and was similar to that reported in adults (approximately 4 hours).

Based on the results of the efficacy study, the dosing regimen proposed for the treatment of cUTI and/or acute pyelonephritis is: (a) oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day) or (b) intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) or intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) followed by oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day).

Reviewer's Comments (Not to be sent to the sponsor):

1. The POPPK analysis identified three significant covariates, namely, body weight, creatinine clearance and presence of cystic fibrosis in patients. The effect of cystic fibrosis on the absorption rate constant was also found to be a significant factor.

2. The applicant used body weight as a covariate with an allometric exponent of 0.75 for clearance parameters based on literature. Instead of this, the applicant should have estimated the allometric exponent, which would have ensured correct estimation of the effect of body weight on clearance.

3. The applicant used a base model comprising of body weight as a covariate. Several covariates such as age were tested using this base model. This approach is not optimal, since age and body weight are inter-related and so using a base model with body weight fails to distinguish the effect of age on clearance. Instead, the applicant should have tested the effect of age on the base model without body weight.

Phase IV Commitments

No Phase IV studies are requested.

Recommendations:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in the sNDA for ciprofloxacin in pediatric patients and has found it to be acceptable. The following dosing recommendation for ciprofloxacin in pediatric patients for use in complicated UTI infections and/or acute pyelonephritis, as used in the pivotal Phase III trial of Complicated Urinary Tract Infection (Study 100169), is proposed:

(a) oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day) or (b) intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) or intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) followed by oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day).

Dakshina M. Chilukuri, Ph.D. _____
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Philip Colangelo, Pharm.D., Ph.D., _____
cc: NDA 19-537, HFD-590, HFD-880 and CDR (Biopharm)

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APPENDIX I:

Proposed Labeling for Ciprofloxacin
With
Clinical Pharmacology / Biopharmaceutics Revisions

Version: 03/2003

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APPENDIX II:

POPULATION PHARMACOKINETIC ANALYSIS

TITLE: Population pharmacokinetic modeling of ciprofloxacin in pediatric patients.

OBJECTIVE:

- To estimate typical population pharmacokinetic parameters for ciprofloxacin in pediatric patients.
- To identify covariate, demographic and clinical factors that are significant predictors of variability in ciprofloxacin pharmacokinetic parameters.
- To provide a dosing recommendation for pediatric patients

STUDY DESIGN:

The data from 6 studies in pediatric subjects were pooled and used in this analysis.

Study #	Design	Patient population	Age	Dose regimen
536	Open, single dose and multiple-dose study	16 pediatric patients with various infections (UTI, lower respiratory tract infection, skin and soft tissue infection)	4 months – 12 years	10 mg/kg oral ciprofloxacin administered TID for 5-7 days
553	Non-controlled, multiple dose study	20 pediatric patients with severe sepsis	3 months – 5 years	10 mg/kg IV ciprofloxacin administered BID for 7 – 14 days
573	Double-blind, double-dummy, single-center study	86 pediatric patients with invasive diarrhea	6 months – 12 years	10 mg/kg oral ciprofloxacin administered BID for 3 days given in combination with ceftriaxone im injection at a dose of 50 mg/kg once-daily
1172	Open-label, randomized controlled trial	10 pediatric patients with cystic fibrosis for 2-3 weeks	5 - 17 years	Patients received ceftazidime 300 mg/kg/day, amikacin 36 mg/kg/day intravenously and amikacin 2×250 mg per inhalation. During this maintenance period, these patients received IV ciprofloxacin at a dose

				of 10 mg/kg BID on day-1 and received oral ciprofloxacin at a dose of 15 mg/kg/day BID on day-2
1359	Multiple dose study	18 pediatric patients with cystic fibrosis with acute pulmonary exacerbation	5 - 17 years	IV ciprofloxacin at doses of 10 mg/kg BID for 3 days and oral ciprofloxacin at a dose of 20 mg/kg TID for 3 days
100169	Randomized study to compare ciprofloxacin vs. comparative regimens in the treatment of UTI or pyelonephritis	207 pediatric patients with complicated UTI or pyelonephritis	1 – 17 years	Stratum I: Oral ciprofloxacin at doses of 5 – 20 mg/kg BID for 7 – 21 days Stratum II: IV ciprofloxacin at doses 6 – 10 mg/kg TID or IV ciprofloxacin at doses of 6 – 10 mg/kg TID followed by oral ciprofloxacin at doses of 5 – 20 mg/kg BID for 7 – 21 days.

DATA:
Patient demographics:

Table 8-1: Summary of patient demographics

Protocol number	Age, years Median (range)	Body weight, kg Median (range)	Number of males	Number of females
536	2.63 (0.33 – 7.08)	12.65 (6.4 – 23.8)	6	10
553	1.00 (0.27 – 4.75)	10.85 (4.2 – 23.2)	6	14
573	2.01 (0.52 – 11.96)	11.12 (6.5 – 37.7)	48	38
1172	9.50 (6.00 – 16.00)	27.85 (14.9 – 42.0)	5	5
1359	12.21 (5.17 – 16.92)	30.15 (18.5 – 63.7)	7	11
100169	5.00 (1.00 – 16.00)	19.70 (7.15 – 73.5)	33	174
Total	4.00 (0.27 – 16.92)	17.00 (4.2 – 73.5)	105	252

Sampling:
A total of 1462 plasma ciprofloxacin concentrations were available from 357 patients.

Table 8-2: Number of pediatric patients and ciprofloxacin concentrations in five age subgroups

Age range	Number of patients	Number of ciprofloxacin concentrations
Between 0.25 year (inclusive) and 1 year	41	281
Between 1 year (inclusive) and 2 years	56	274
Between 2 years (inclusive) and 6 years	123	270
Between 6 years (inclusive) and 12 years	111	384
Between 12 years (inclusive) and 17 years	26	253
Total	357	1462

Assay Methodology:

Study 100169:

All assay results tabulated in this report were obtained with an HPLC procedure that involves protein precipitation and enhanced fluorescence detection after post-column UV reaction. The procedure contains a detailed description of the procedure and relevant assay validation data. The calibration range of ciprofloxacin was from 0.05 to 7.5 µg/mL. According to the method report, the intra-day precision (% CV) ranged from 0.7 to 5.9% and the inter-day precision (% CV) ranged from 2.0 to 4.3% for all the QC samples and lower quantitation limit calibration standard. The corresponding intra-day accuracy ranged from 94.6 to 102.5 % and inter-day accuracy ranged from 98.0 to 100.0%. Ciprofloxacin is stable in serum up to 15 month at –20 °C.

Formulation of Ciprofloxacin Suspension:

For this clinical investigation, ciprofloxacin oral suspension 5% (5 g ciprofloxacin/100 mL) strength was used. The drug product is (b) (4) suspension made of 2 components that are mixed together prior to dispensing. The individual components are microcapsules containing ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hydroxypropylmethylcellulose, magnesium stearate, and Polysorbate 20 and a suspension fluid made of medium chain triglyceride, sucrose (b) (4), lecithin, and strawberry flavor.

Assumptions:

- In Study 553, the rate of infusion was not available for some patients on non-pharmacokinetic assessment days. In these patients, it was assumed that the rate of infusion corresponded to the duration of infusion recommended in the study protocol (60-minute infusion).

- In Study 573, information on the application time of ciprofloxacin was not available. Therefore, it was assumed that the dosing interval was 12 hours.

- In Study 573, the date of blood sample collection and the time after dosing were available for each patient. Clock times of blood sample collection were not available. Consequently, the blood sample could have been collected either after the first or second dose of ciprofloxacin on the sampling day. However, it is unlikely that the

samples were collected after the second dose as this would indicate that the samples were taken in the evening or late night in most cases. Therefore, it was assumed that sampling took place after the first dose of ciprofloxacin on the day of sampling.

- In Study 1359, information on the time of administration of ciprofloxacin was not available. Therefore, it was assumed that the dosing interval specified in the protocol was adhered to and that oral administration of ciprofloxacin was started immediately after completion of the last intravenous dosing interval.

- In Study 100169, the duration of infusion was not reported in 22/45 patients who received ciprofloxacin by intravenous infusion. In these patients, the duration of infusion was assumed to be 1 hour (as specified in the package insert).

- In Study 100169, the following information was collected: date and time of plasma sample collection (for determination of ciprofloxacin concentration), the date and time of the two doses administered prior to the collection of the plasma sample and date of start of ciprofloxacin treatment. The dosing interval for ciprofloxacin administration on the initial days of treatment was assumed to be 12 hours (as stated in the protocol). For example, if the plasma sample (for the determination of ciprofloxacin concentration) was collected on Day 5, the times of administration of ciprofloxacin on the morning of Day 5 and the evening of Day 4 were available. The dosing interval for ciprofloxacin on Days 1, 2 and 3 was assumed to be 12 hours.

METHODS:
The NONMEM software (version V, Level 1.1) with NM-TRAN and PREDPP were used for population non-linear mixed-effects modeling. Analyses were performed on a personal computer with the Compaq Visual Fortran Compiler (Standard Edition version 6.5) and Windows NT 4.0 operating system. S-PLUS 2000 and Sigmaplot 2000 software packages were used in the generation of various plots.

A one-compartment linear model with first-order absorption was initially evaluated for fitting the ciprofloxacin plasma concentration data. More complex models were to be fit to the data based on inspection of diagnostic plots and parameter estimates. The first-order conditional estimation (FOCE) method with η- ε interaction was employed in all population pharmacokinetic models. Population and individual estimates of pharmacokinetic parameters were obtained from this conditional estimation method.

Initially, the model building strategy involved construction of a base model. In pediatric patients, pharmacokinetic parameters such as clearance and volume of distribution are known to be related to indices of body mass (e.g., body weight, body surface area). Recent articles in the literature advocate the use of principles of allometry (with specific reference to body weight) in population pharmacokinetic analyses, especially those that involve pediatric patients. According to principles of allometry, exponent values of 0.75 (for most physiologic process parameters) and 1.00 (for most volume-related parameters) have also been shown to accurately describe clearance and volume parameters over a wide range of body weights. Therefore, in the current population pharmacokinetic

analysis, following identification of an appropriate structural model, body weight was to be used as a covariate with an allometric exponent of 0.75 for clearance parameters (e.g., total clearance and inter-compartmental clearance for two compartment models). In addition, body weight was to be used as a covariate with an allometric exponent of 1.00 for volume parameters (eg, central and peripheral volumes of distribution). Such a model was to be considered the base model. The resulting model parameterization was consistent with prior physiologic knowledge and allowed the estimation of model parameters that were easily interpretable across a large range of body weights.

A preliminary graphical screen of potential covariates was conducted to identify any highly correlated covariate factors (such as age and height). In such cases, the most clinically useful covariate was selected to be included in the model building process. Exploratory analysis of the relationship between patient covariates, clinical and demographic factors and individual pharmacokinetic parameters was performed graphically. The exploratory analysis helped in the construction of parameter- covariate relationships, which were tested by explicit incorporation into the population mixed-effects pharmacokinetic model.

Covariate models were built by stepwise forward inclusion procedure. Covariates were added one-at-a-time to the base model. The covariate that resulted in the greatest statistically significant decrease in the value of the objective function was added to the base model. The entire procedure was repeated until no further statistically significant decrease in the value of objective function occurred. Along with typical goodness of fit diagnostic plots, the likelihood ratio test[1] was used to discriminate among alternative nested models, based on an alpha level that was set *a priori* to 0.999 ($p<0.001$). When comparing alternative models, differences in the value of objective function, which is proportional to minus twice the maximum logarithm of the likelihood of the data, are approximately chi-squared distributed with n degrees of freedom (n is the difference in the number of parameters between the full and the reduced model). This approximation has been shown to be accurate for the FOCE method.

Exponential error models were used to describe the inter-individual variance on pharmacokinetic parameters (Equation 6-1). Modeling was initially performed with the assumption of no covariance between inter-individual random effects but a block covariance matrix was subsequently explored.

Equation 6-1

$$P_i = \hat{P}\exp(\eta^{Pi})$$

Where:
P_i is the true parameter value for individual *i*
$\hat{P}$ is the typical population value of the parameter
η^{Pi} are individual-specific interindividual random effects for individual *i* and parameter *P* and are assumed to be independently and identically distributed: $\eta \sim N(0, \omega^2)$

In the population pharmacokinetic analysis, the residual error model was initially described by a combination additive and proportional error model (Equation 6-2).

Equation 6-2

$$C_{ij} = \hat{C}_{ij}(1+\varepsilon_{pij}) + \varepsilon_{aij}$$

Where:
C_{ij} is the *j*th measured observation (plasma concentration) in individual *i*
$\hat{C}_{ij}$ is the *j*th model predicted value (plasma concentration) in individual *i*
ε_{pij} and ε_{aij} are proportional and additive residual random errors, respectively, for individual *i* and measurement *j* and are assumed to be independently and identically distributed: $\varepsilon \sim N(0, \sigma^2)$

Methods for Model Evaluation:
The robustness of the final model was evaluated by (a) parametric bootstrap method, (b) leverage analysis followed by cross-validation and (c) outlier analysis.

Parametric bootstrap
In the parametric bootstrap procedure, the final model and the estimates for population parameters were used to perform Monte-Carlo simulations of plasma ciprofloxacin concentrations for all patients who were included in the population pharmacokinetic analysis. These simulations included both inter-individual and intra-individual (residual) variability components. The final model was then fit individually to each of the simulated dataset and all population parameters were estimated. This procedure was repeated using the SIMULATION, SUBPROBLEM feature in NONMEM and results from 1000 successful runs were obtained. Values for median, 2.5th and 97.5th percentiles (denoting the 95% confidence interval) for all the population parameters were calculated.

Leverage analysis and cross-validation
Leverage analysis was performed by randomly removing ten percent of the patients without replacement. The steps involved in this procedure are outlined below.

1. Ten percent of the patients were randomly removed (without replacement) from the complete data set to form a smaller set that contained all data from the remaining ninety percent of the patients.
2. The final model was applied to the smaller dataset and the population pharmacokinetic parameters were estimated.

3. The population pharmacokinetic parameters were then used to predict plasma concentrations in the ten percent of the patients who were randomly removed in Step 1.
4. Steps 1 through 3 were repeated 10 times with subsets of patients randomly removed without replacement each time.

For each population pharmacokinetic parameter, the average of the ten leverage analysis runs and the standard deviation was obtained. After completion of leverage analysis, prediction error and absolute prediction error were calculated with predictions made in Step 3 (referred to as cross-validation). Prediction error (PE) was calculated as *ln* (predicted) minus *ln* (observed). Absolute prediction error was calculated by obtaining the absolute value of prediction error.

Outlier analysis

In the outlier analysis, the final model was evaluated by deletion of outliers concentrations with weighted residuals less than 0.5 or greater than 5).

Results:

At the conclusion of the pharmacokinetic (structural) model identification process, a two compartment pharmacokinetic model with absorption lag time and first order absorption was identified as the best pharmacokinetic (structural) model and was chosen for further model building. Diagnostic plot for this pharmacokinetic (structural) model is shown in Figure 12-2.

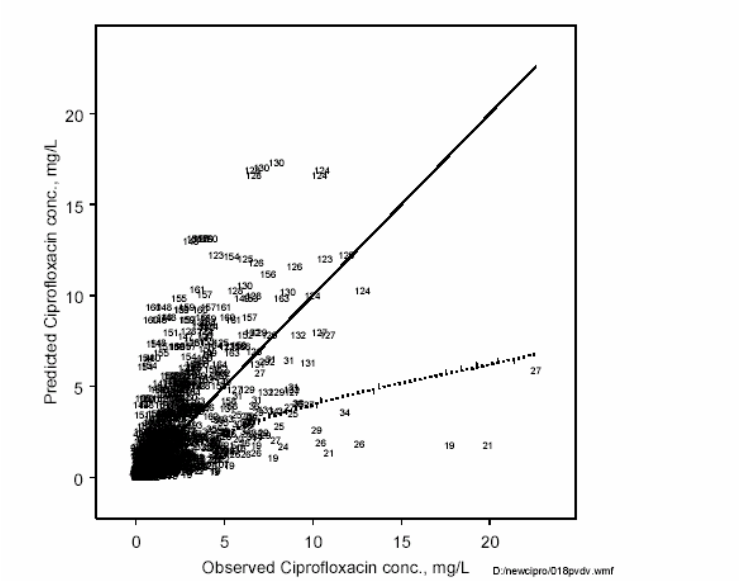
Table 8-8: Pharmacokinetic (structural) model

Run	Model description	VOF
018	2 compartment model. Parameters estimated: CL, V2, V3, Q, KA, F1 and ALAG1. Inter-individual variance estimated for CL , V2, V3, Q, F1 and KA. Covariance between inter-individual random effects in CL, V2, V3 and Q estimated. Residual variance model stratified by route of administration with shared additive component.	-464.847

VOF: Value of objective function

Figure 12-2: Population Mean Prediction vs. Observed Plasma Ciprofloxacin Concentration (Structural Pharmacokinetic Model Run 018)

Population mean predictions versus observed plasma ciprofloxacin concentrations are indicated by individual ID numbers and a loess (local regression method) smooth of the data (dotted line). The line of identity (solid) is included as a reference.



The structural model identified in Run 018 was used in the construction of the base PK model, which is presented below:

Table 8-9: Base model description

Run	Model description	VOF
029	TVCL = THETA(1)*((WT/70)**0.75) CL = TVCL*EXP(ETA(1)) TVV2 = THETA(2)*((WT/70)**1.00) V2 = TVV2*EXP(ETA(2)) TVV3 = THETA(3)*((WT/70)**1.00) V3 = TVV3*EXP(ETA(3)) TVQ = THETA(4)*((WT/70)**0.75) Q = TVQ*EXP(ETA(4)) TVKA = THETA(5) KA = TVKA*EXP(ETA(6)) TVF1 = THETA(6) F1 = TVF1*EXP(ETA(5)) ALAG1= THETA(7) S2 = V2 ; Residual variance model FLAG=0 IF (ROUT.EQ.1) FLAG=1 Y1= F+F*EPS(1)+EPS(2) ; residual variance for oral Y2= F+F*EPS(3)+EPS(2) ; residual variance for i.v. Y = (Y1*FLAG)+(Y2*(1-FLAG))	-655.521

VOF: Value of objective function

Table 8-10: Inter-individual variance for pharmacokinetic parameters

Parameter	Inter-individual Variance Estimates (Exponential Error Model)	
	Structural model (Run 018)	Base model (Run 029)
Clearance (CL)	0.501	0.130
Central volume of distribution (V2)	0.609	0.108
Peripheral volume of distribution (V3)	0.651	0.107
Inter-compartmental clearance (Q)	0.719	0.192
Bioavailability (F1)	0.0435	0.0344
Absorption rate constant (KA)	0.327	0.264

Stepwise Covariate model building:
Covariate models were built by stepwise forward inclusion procedure. In order to identify clinically meaningful covariates and to minimize the chances of obtaining a statistically significant covariate by random chances, the total number of covariate models was limited by pre-defined comparisons based on prior knowledge and clinical interest in factors that might affect the pharmacokinetics of ciprofloxacin in the pediatric population. The influence of age, gender, cystic fibrosis, creatinine clearance (estimated from serum creatinine) and complicated urinary tract infection / pyelonephritis on ciprofloxacin clearance was evaluated. The effect of age, gender and cystic fibrosis on the central and peripheral volumes of distribution was determined and the influence of cystic fibrosis on absorption rate constant was also determined. The results of the first step of the stepwise forward inclusion procedure are shown in Table 8-11.

Table 8-11: Results of the first step of the stepwise forward inclusion procedure.

Run number	Model Description	VOF	Δ VOF
029	Base model	-665.521	
034	Effect of age on CL	-672.433	-16.912
035	Effect of gender on CL	-657.271	-1.75
036	Effect of cystic fibrosis on CL	-680.488	**-24.967**
037	Effect of creatinine clearance on CL	-670.852	-17.331
038	Effect of cUTI on CL	-662.653	-7.132
039	Effect of age on V2	-656.992	-1.471
040	Effect of gender on V2	-655.741	-0.22
041	Effect of cystic fibrosis on V2	-661.668	-6.147
042	Effect of age on V3	-655.512	0.009
043	Effect of gender on V3	-656.612	-1.091
044	Effect of cystic fibrosis on V3	Minimization terminated	
045	Effect of cystic fibrosis on KA	-661.722	-6.201

VOF: Value of objective function
Δ VOF: VOF (full model) – VOF (reduced model); the reduced model being the base model
CL: clearance, V2: central compartment, V3: peripheral compartment and KA: absorption rate constant, cUTI: complicated urinary tract infection / pyelonephritis

Inclusion of cystic fibrosis as a covariate for clearance resulted in the maximum decrease (24.967 points) in the value of objective function (Table 8-11). Inclusion of this covariate also resulted in a decrease in the estimate of inter-individual variance for ciprofloxacin clearance from 0.130 to 0.083 (Table 8-12). The base model with the addition of cystic fibrosis as a covariate for clearance (Run 036) will be referred to as Model 1 in the rest of this report.

Table 8-12: Inter-individual variance for PK parameters (Base model and Model 1).

Parameter	Inter-individual Variance Estimates (Exponential Error Model)	
	Base model (Run 029)	Model 1 (Run 036)
Clearance (CL)	0.130	0.083
Central volume of distribution (V2)	0.108	0.118
Peripheral volume of distribution (V3)	0.107	0.0967
Inter-compartmental clearance (Q)	0.192	0.162
Bioavailability (F1)	0.0344	0.0497
Absorption rate constant (KA)	0.264	0.324

The stepwise forward inclusion procedure was continued with Model 1 serving as the next base model. The results of the second step of the stepwise forward inclusion procedure are presented in Table 8-13.

Table 8-13: Results of the second step of the stepwise forward inclusion procedure.

Run number	Model Description	VOF	Δ VOF
036	Model 1 (Base model + CL ~ cystic fibrosis)	-680.488	
101	Effect of age on CL	-685.901	-5.413
102	Effect of gender on CL	-681.995	-1.507
103	Effect of creatinine clearance on CL	-694.974	-14.486
104	Effect of cUTI on CL	-681.084	-0.596
105	Effect of age on V2	-680.576	-0.088
106	Effect of gender on V2	-681.046	-0.558
107	Effect of cystic fibrosis on V2	-680.536	-0.048
108	Effect of age on V3	-680.850	-0.362
109	Effect of gender on V3	-681.469	-0.981
110	Effect of cystic fibrosis on V3	-682.307	-1.819
111	Effect of cystic fibrosis on KA	-695.531	**-15.043**

VOF: Value of objective function

Δ VOF: VOF (full model) – VOF (reduced model); the reduced model being Model 1

CL: clearance, V2: central compartment, V3: peripheral compartment and KA: absorption rate constant, cUTI: complicated urinary tract infection / pyelonephritis

Inclusion of cystic fibrosis as a covariate for absorption rate constant resulted in the maximum decrease (15.043 points) in the value of objective function. This resulted in a decrease in the estimate of inter-individual variance for absorption rate constant from 0.324 to 0.218 (Table 8-14). Model 1 with the addition of cystic fibrosis as a covariate for absorption rate constant (Run 111) will be referred to as Model 2 in the rest of this report.

Table 8-14: Inter-individual variance for PK parameters (Model 1 and Model 2).

Parameter	Inter-individual Variance Estimates (Exponential Error Model)	
	Model 1 (Run 036)	Model 2 (Run 111)
Clearance (CL)	0.083	0.0771
Central volume of distribution (V2)	0.118	0.116
Peripheral volume of distribution (V3)	0.0967	0.0906
Inter-compartmental clearance (Q)	0.162	0.150
Bioavailability (F1)	0.0497	0.0503
Absorption rate constant (KA)	0.324	0.218

The stepwise forward inclusion procedure was continued with Model 2 serving as the base model. The results of the third step of the stepwise forward inclusion procedure are presented in Table 8-15.

Table 8-15: Results of the third step of the stepwise forward inclusion procedure.

Run number	Model Description	VOF	Δ VOF
111	Model 2 (Base model + CL ~ cystic fibrosis + KA ~ cystic fibrosis)	-695.531	
201	Effect of age on CL	-699.909	-4.378
202	Effect of gender on CL	-697.432	-1.901
203	Effect of creatinine clearance on CL	-708.282	**-12.751**
204	Effect of cUTI on CL	-696.814	-1.283
205	Effect of age on V2	-695.552	-0.021
206	Effect of gender on V2	-696.078	-0.547
207	Effect of cystic fibrosis on V2	-695.825	-0.294
208	Effect of age on V3	-695.697	-0.166
209	Effect of gender on V3	-696.488	-0.957
210	Effect of cystic fibrosis on V3	-697.073	-1.542

VOF: Value of objective function
Δ VOF: VOF (full model) – VOF (reduced model); the reduced model being Model 2
CL: clearance, V2: central compartment, V3: peripheral compartment and KA: absorption rate constant, cUTI: complicated urinary tract infection / pyelonephritis

Inclusion of creatinine clearance as a covariate for clearance resulted in the maximum decrease (12.751 points) in the value of objective function. This resulted in a marginal decrease in the estimate of inter-individual variance for clearance (from 0.0771 to 0.0678, Table 8-16). Model 2 with the addition of creatinine clearance as a covariate for clearance (Run 203) will be referred to as Model 3 in the rest of this report.

Table 8-16: Inter-individual variance for PK parameters (Model 2 and Model 3).

Parameter	Inter-individual Variance Estimates (Exponential Error Model)	
	Model 2 (Run 111)	Model 3 (Run 203)
Clearance (CL)	0.0771	0.0678
Central volume of distribution (V2)	0.116	0.104
Peripheral volume of distribution (V3)	0.0906	0.0926
Inter-compartmental clearance (Q)	0.150	0.148
Bioavailability (F1)	0.0503	0.0461
Absorption rate constant (KA)	0.218	0.215

The fourth step of the stepwise forward inclusion procedure did not identify any additional covariates. Therefore, Model 3 was declared as the final model and Run 203 was rerun with the covariance step.

The pharmacokinetic model fit was evaluated based on parameter estimates, standard errors of the estimates and diagnostic plots. The parameter estimates, asymptotic standard errors (SE), relative standard error (calculated as SE/estimate) expressed as percentage (%RSE) and the symmetric 95% confidence intervals for the fixed and random effect parameters are presented in Table 8-17. Symmetric 95% confidence intervals were calculated as point estimate ± 1.96 × SE.

Table 8-17: Ciprofloxacin population pharmacokinetic parameters in pediatric patients (see Table 12-2 for covariate-parameter relationships)

	Estimate	Standard error (SE)	%RSE	95 % confidence interval
THETA(1) - $\theta_{CL,NREN}$, L/h	19.6	3.34	17.0	[13.1 , 26.1]
THETA(2) - θ_{V2}, L	58.4	4.91	8.4	[48.8 , 68.0]
THETA(3) - θ_{V3}, L	92.8	5.42	5.8	[82.2 , 103.4]
THETA(4) - θ_{Q}, L/h	37.2	3.89	10.5	[29.6 , 44.8]
THETA(5) - θ_{KA}, 1/h	0.878	0.114	13.0	[0.655 , 1.101]
THETA(6) - θ_{F1}, %	0.568	0.0292	5.1	[0.511 , 0.625]
THETA(7) - θ_{ALAG}, h	0.323	0.0126	3.9	[0.298 , 0.348]
THETA(8) - $\theta_{CL,NREN\sim CF}$	0.73	0.183	25.1	[0.371 , 1.089]
THETA(9) - $\theta_{KA\sim CF}$	-0.459	0.0967	21.1	[-0.649 , -0.269]
THETA(10) - $\theta_{CL,REN\sim CLCR}$	1.26	0.452	35.9	[0.37 , 2.15]
OMEGA(1,1) - ω^2_{CL}	0.0678	0.0194	28.6	[0.03 , 0.106]
OMEGA(2,2) - ω^2_{V2}	0.104	0.0432	41.5	[0.019 , 0.189]
OMEGA(3,3) - ω^2_{V3}	0.0926	0.0213	23.0	[0.051 , 0.134]
OMEGA(4,4) - ω^2_{Q}	0.148	0.0646	43.6	[0.021 , 0.275]
OMEGA(5,5) - ω^2_{F1}	0.0461	0.0143	31.0	[0.018 , 0.074]
OMEGA(6,6) - ω^2_{KA}	0.215	0.0551	25.6	[0.107 , 0.323]
OMEGA(2,1) - $COV_{V2,CL}$	0.0566	0.0209	36.9	[0.016 , 0.098]
OMEGA(3,1) - $COV_{V3,CL}$	0.00382	0.0128	335.1	[-0.0213 , 0.0289]
OMEGA(3,2) - $COV_{V3,V2}$	0.0579	0.0212	36.6	[0.016 , 0.099]
OMEGA(4,1) – $COV_{Q,CL}$	0.0264	0.0282	106.8	[-0.029 , 0.082]
OMEGA(4,2) - $COV_{Q,V2}$	0.108	0.043	39.8	[0.024 , 0.192]
OMEGA(4,3) - $COV_{Q,V3}$	0.100	0.0447	44.7	[0.012 , 0.188]
SIGMA(1,1) - $\sigma^2_{PROP, ORAL}$	0.175	0.0156	8.9	[0.144 , 0.206]
SIGMA(2,2) - σ^2_{ADD}	0.0011	0.00103	93.6	[-0.00092 , 0.00312]
SIGMA(3,3) - $\sigma^2_{PROP, IV}$	0.0763	0.0118	15.5	[0.0532 , 0.0994]

The final model parameter estimates were relatively precise. Further, the parameters appeared reasonable when compared to data reported in the literature. Inter-individual variability in pharmacokinetic parameters was calculated as the square root of inter-individual variance ($\omega 2$) and was expressed as percent coefficient of variation (%CV). Inter-individual variability ranged from 21.5 %CV (bioavailability) to 46.4 %CV (absorption rate constant). The arithmetic mean of the different ηs used in the population

pharmacokinetic model was not statistically significantly different from zero as indicated by the ETABAR test in NONMEM (Table 12-2).

The combination proportional/additive residual variance model structure was stratified by route of administration, with a shared additive term. The estimate of the proportional residual variance for the oral data was 0.175 (~42 % CV), which may indicate some misspecification of the oral absorption model, a greater degree of process error or lack of information / non-compliance associated with some oral dosing studies. The estimate of the proportional term for the intravenous variance model was 0.0763 (~28 % CV). The estimate of the shared additive residual variance component was quite small, 0.0011 (SD = 0.03 mg/L). Although the shared additive residual variance component was small, it added stability to the model. Exclusion of the additive residual variance component resulted in minimization problems. The symmetric confidence intervals for all of the random variance terms are probably not accurate, but can still be used to judge relative precision of these parameter estimates.

For the final model, typical diagnostic plots such as population predicted versus observed ciprofloxacin concentration, individual predicted versus observed ciprofloxacin concentration and weighted residual vs. predicted concentrations are shown in Figures 12-8, 12-9 and 12-10, respectively. As seen in the population predicted versus observed ciprofloxacin concentration plot, the model is predictive but for the three outliers observed at higher concentrations (>15 mg/L). The residuals plot shows that the weighted residuals fall around the unity line and the smoothed line.

Figure 12-8: Population Mean Prediction versus Observed Plasma Ciprofloxacin concentration (Final Model, Run 203)

Population mean predictions versus observed plasma ciprofloxacin concentrations are indicated by individual ID numbers and a loess (local regression method) smooth of the data (dotted line). The line of identity (solid) is included as a reference.

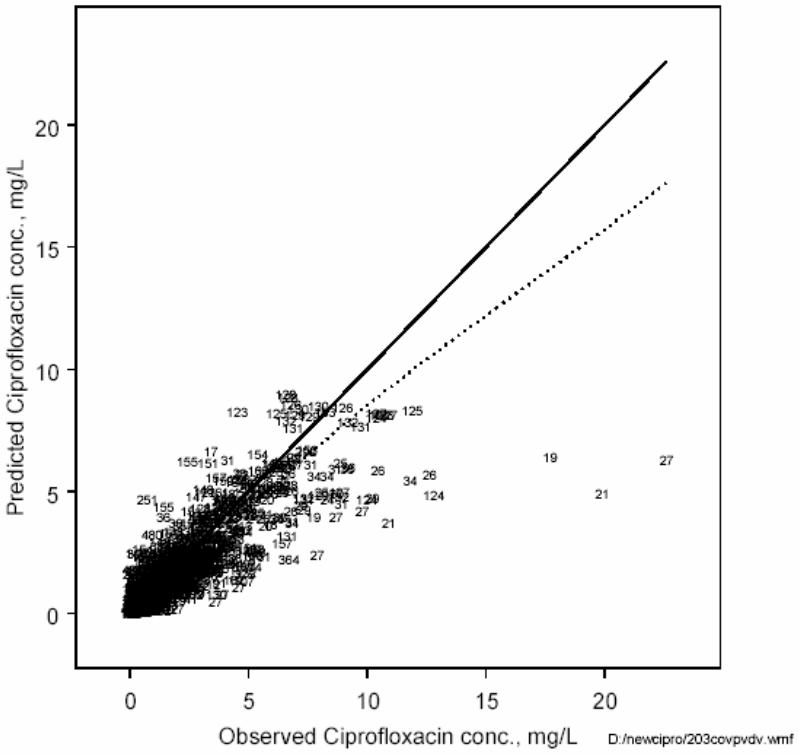


Figure 12-9: Individual Prediction versus Observed Plasma Ciprofloxacin Concentration (Final Model, Run 203)

Individual predictions versus observed plasma ciprofloxacin concentrations are indicated by individual ID numbers and a loess (local regression method) smooth of the data (dotted line). The line of identity (solid) is included as a reference.

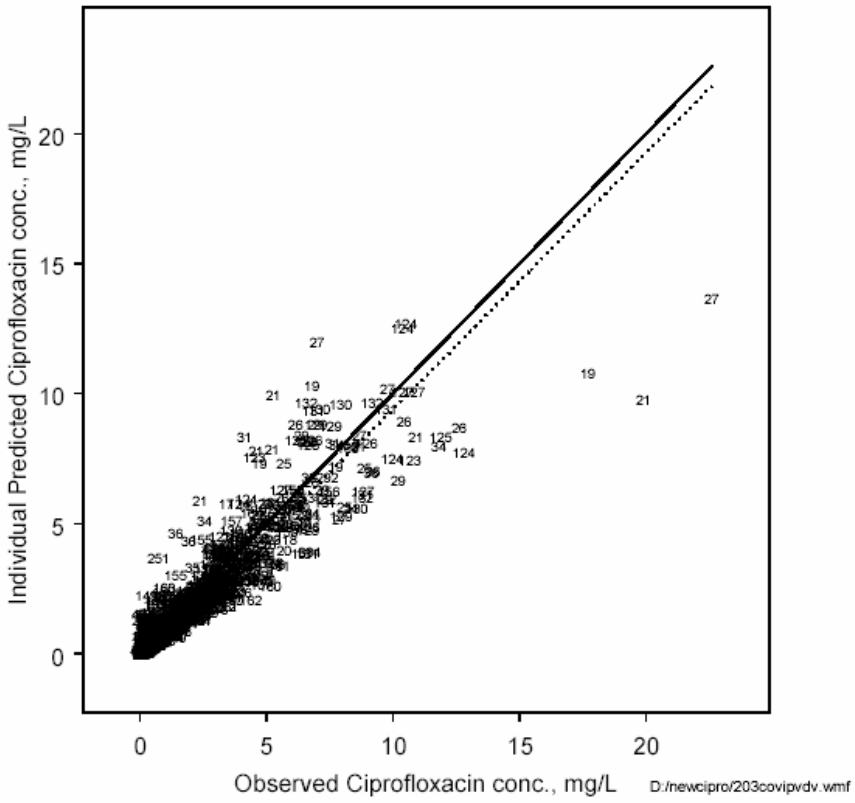
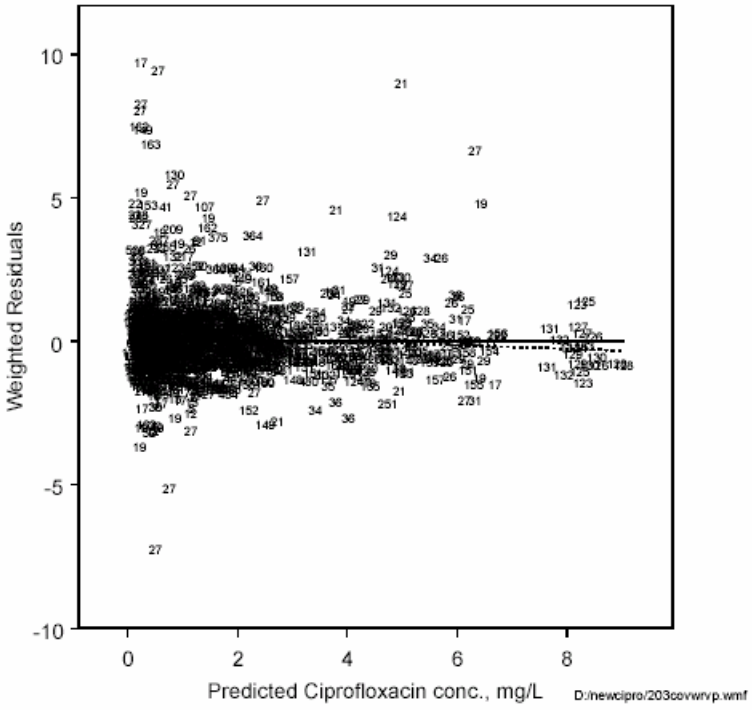


Figure 12-10: Weighted Residuals versus Predicted Ciprofloxacin Plasma Concentration (Final Model, Run 203)

Weighted residuals versus population mean predicted ciprofloxacin plasma concentrations are indicated by individual ID numbers and a loess (local regression method) smooth of the data (dotted line). A line at y = 0 (solid) is included as a reference.



Equation 1-1: Final model

$$CL_i = \left(CL_{NREN,i} + CL_{REN,i}\right) \cdot \exp^{\eta_{CLi}}$$

$$CL_{NREN,i} = \theta_1 \cdot \left(\frac{WT_i}{70}\right)^{0.75} \cdot \left(1 + \theta_8 \cdot CF_i\right)$$

$$CL_{REN,i} = \theta_{10} \cdot CL_{creatinine,i}$$

$$V2_i = \theta_2 \cdot \left(\frac{WT_i}{70}\right)^{1} \cdot \exp^{\eta_{V2i}}$$

$$V3_i = \theta_3 \cdot \left(\frac{WT_i}{70}\right)^{1} \cdot \exp^{\eta_{V3i}}$$

$$Q_i = \theta_4 \cdot \left(\frac{WT_i}{70}\right)^{0.75} \cdot \exp^{\eta_{Qi}}$$

$$Ka_i = \theta_5 \cdot \left(1 + \theta_9 \cdot CF_i\right) \cdot \exp^{\eta_{Kai}}$$

$$F1_i = \theta_6 \cdot \exp^{\eta_{F1i}}$$

$$ALAG1_i = \theta_7$$

Where, pharmacokinetic model parameters are clearance (CL), central volume of distribution (V2), peripheral volume of distribution (V3), inter-compartmental clearance (Q), absorption rate constant (Ka), absorption lag-time (ALAG1) and oral bioavailability fraction (F1); the subscript *i* indicates an individual-specific parameter or variable, θ are fixed-effects parameters and η are inter-individual random effects. The continuous covariate body weight (WT) was normalized to a reference value (70-kg). Creatinine clearance ($CL_{creatinine}$) was estimated by Schwartz method and is expressed in L/h. Cystic fibrosis patients were assigned a value of 1 for the variable CF and non-cystic fibrosis patients were assigned a value of 0 for the same variable. The residual error model, stratified by route of administration, is shown in Equation 1-2.

Model Evaluation

Consistency of Model Parameters

In general, the population pharmacokinetic parameters were consistent with prior knowledge about the pharmacokinetics and disposition of ciprofloxacin. For non-cystic fibrosis patients, the population pharmacokinetic model derived equation for ciprofloxacin clearance is shown in Equation 8-1.

Equation 8-1

$$CL = (19.6 \times (WT / 70)^{0.75}) + (1.26 \times CL_{creatinine})$$

Substituting a typical body weight of 70 kg for adults, and a creatinine clearance value of 7.8 L/h (130 mL/min), the typical value for ciprofloxacin clearance in adults is predicted to be 29.4 L/h. In a previous pharmacokinetic study (D90-012-01) in healthy adults, the geometric mean ciprofloxacin clearance following intravenous administration was determined to be 32.5 L/h, which is in agreement with the clearance value predicted based on the final population pharmacokinetic model of this study.

Using Equation 8-1, the clearance component associated with creatinine clearance is estimated to be 9.83 L/h for a typical adult with creatinine clearance of 7.8 L/h (130 mL/min). The clearance component not associated with creatinine clearance (.non renal clearance. component) is estimated to be 19.6 L/h for a typical adult weighing 70 kg. Thus, according to the final model parameter estimates, the ratio of renal clearance to total clearance is approximately 33%. This value is different than the reported value in the literature indicating that renal clearance accounts for 50% of total clearance in adults. The fact that the current population pharmacokinetic model did not precisely determine the relative contribution of ciprofloxacin renal and nonrenal components may be attributed to sparse sampling in a large number of pediatric patients in this study. It should be noted that 82 % of pediatric patients provided one ciprofloxacin concentration for the current analysis.

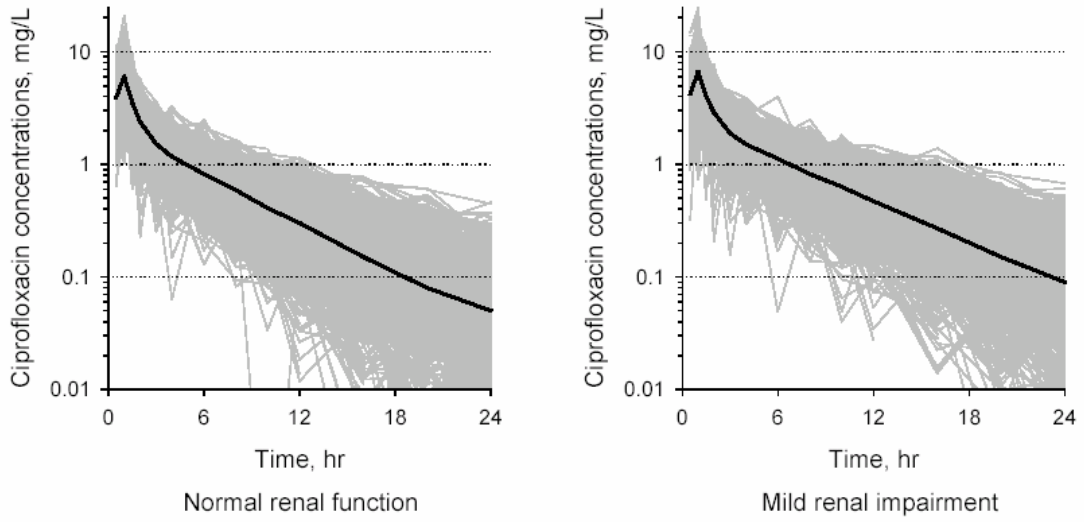
In the current dataset, 295 (83%) out of 357 patients had a creatinine clearance value greater than 4.8 L/h/1.73m2 (80 mL/min/1.73m^2). Fifty-eight (16%) patients had a creatinine clearance value between 3.0 L/h/1.73m^2 (50 mL/min/1.73m^2) and 4.8 L/h/1.73m^2 (80 mL/min/1.73m2). The estimated creatinine clearance value was less than 3 L/h/1.73m^2 in 4 (1%) patients. Since a vast majority of the pediatric patients exhibited creatinine clearance greater than 50 mL/min/1.73m^2, the clinical usefulness of the final population pharmacokinetic model is restricted to pediatric patients with mild renal impairment (by convention creatinine clearance above 50 mL/min/1.73m^2) and normal renal function. The final model was used to estimate (by means of simulation) the change in ciprofloxacin exposure in pediatric patients with mild renal impairment. Simulations were performed for a typical 12-year old (body weight = 41 kg, height = 150 cm) pediatric subject. The first set of simulations was performed using a creatinine clearance value of 5.94 L/h (which is equivalent to 7.8 L/h/1.73m^2 or 130 mL/min/1.73m^2 for the 12-year old subject). Plasma ciprofloxacin concentrations were simulated in 1000

typical 12-year pediatric subjects each receiving 370-mg of ciprofloxacin by a 1-hour intravenous infusion.

Note that the ciprofloxacin dose used for simulation was 9-mg/kg rounded to the nearest 10-mg. The second set of simulation was performed using a creatinine clearance value of 2.30 L/h (which is equivalent to 3.0 L/h/1.73m^2 or 50 mL/min/1.73m^2). As before, plasma ciprofloxacin concentrations were simulated in 1000 typical 12-year old pediatric subjects each receiving 370-mg of ciprofloxacin by a 1-hour intravenous infusion. The individual and median simulated plasma concentrations for subjects with creatinine clearance value of 130 mL/min/1.73m^2 and for subjects with creatinine clearance value of 50 mL/min/1.73m^2 are shown in Figure 12-12.

Figure 12-12: Simulated plasma ciprofloxacin concentration profile in a pediatric patient population with normal renal function (creatinine clearance 130 mL/min/1.73m^2) and a pediatric patient population with mild renal impairment (creatinine clearance 50 mL/min/1.73m^2).

The solid black line in the figure represents median simulated concentration.



The individual simulated ciprofloxacin concentrations were analyzed in WinNonlin (version 3.3 Pharsight Corporation) and the summary statistics for derived pharmacokinetic parameters are shown in Table 8-18.

Table 8-18: Ciprofloxacin pharmacokinetic parameters (Mean (%CV) and Median) derived from simulated plasma concentrations (Dose: 370 mg 1 hour intravenous infusion).

Parameter	Creatinine clearance = 130 mL/min/1.73m2	Creatinine clearance = 50 mL/min/1.73m2
C_{max}, mg/L	6.63 (38 %)	7.20 (39 %)
	6.19	6.66
AUC0-inf, mg×hr/L	18.51 (27 %)	23.97 (28 %)
	17.95	23.23
Half-life, hr	4.34 (60 %)	4.83 (40 %)
	3.96	4.50

From Table 8-18, it can be seen that the average ciprofloxacin simulated C_{max}, $AUC_{0\text{-}inf}$ and half-life values are comparable in the two groups. The average $AUC_{0\text{-}inf}$ was 18.51-mg×hr/L for the 130 mL/min/1.73m^2 creatinine clearance group and was 23.97-mg×hr/L for the 50 mL/min/1.73m^2 creatinine clearance of group. Therefore, when compared to pediatric subjects with normal renal function (130 mL/min/1.73m^2), based on the final population pharmacokinetic model, approximately 30% increase in exposure should be expected in subjects with creatinine clearance of 50 mL/min/1.73m^2. This prediction is somewhat consistent with ciprofloxacin pharmacokinetic data observed in adults with normal renal function and mild renal impairment. In adults, a 50% increase has been reported in ciprofloxacin $AUC_{0\text{-}inf}$ in subjects with mild renal impairment (when compared to normal subjects) and no substantial increase was observed in ciprofloxacin C_{max} and half-life.

Parametric Bootstrap

Following parametric bootstrap, median, 2.5th and 97.5th percentile (n = 1000) for all parameters in the final model were calculated and are presented in Table 8-19. For easy comparison, the parameter estimates and symmetric 95% confidence intervals from Table 8-17 are also reproduced in Table 8-19.

The median (and mean, data not shown) population parameter estimates obtained from the parametric bootstrap procedure were generally comparable to the original parameter estimates indicating little bias in the parameters. Further, in most cases, the 2.5th and 97.5th percentiles (denoting the 95% confidence interval) indicated good precision in parameter estimates.

Table 8-19: Results of parametric bootstrap

	Parametric bootstrap		Reproduced from Table 8-17	
	Median	[2.5th , 97.5th percentile]	Estimate	95 % confidence interval
THETA(1) - $\theta_{CL,NREN}$, L/h	19.8	[15.1 , 25.0]	19.6	[13.1 , 26.1]
THETA(2) - θ_{V2}, L	60.3	[53.2 , 67.7]	58.4	[48.8 , 68.0]
THETA(3) - θ_{V3}, L	95.2	[84.6 , 105.3]	92.8	[82.2 , 103.4]
THETA(4) - θ_{Q}, L/h	38.5	[32.3 , 44.7]	37.2	[29.6 , 44.8]
THETA(5) - θ_{KA}, 1/h	0.857	[0.662 , 1.137]	0.878	[0.655 , 1.101]
THETA(6) - θ_{F1}, %	0.542	[0.498 , 0.584]	0.568	[0.511 , 0.625]
THETA(7) - θ_{ALAG}, h	0.318	[0.270 , 0.358]	0.323	[0.298 , 0.348]
THETA(8) - $\theta_{CL,NREN\sim CF}$	0.70	[0.448 , 1.038]	0.73	[0.371 , 1.089]
THETA(9) - $\theta_{KA\sim CF}$	-0.448	[-0.601 , -0.251]	-0.459	[-0.649 , -0.269]
THETA(10) - $\theta_{CL,REN\sim CLCR}$	1.43	[0.69 , 2.11]	1.26	[0.37 , 2.15]
OMEGA(1,1) - ω^2_{CL}	0.064	[0.04 , 0.091]	0.0678	[0.03 , 0.106]
OMEGA(2,2) - ω^2_{V2}	0.102	[0.052 , 0.174]	0.104	[0.019 , 0.189]
OMEGA(3,3) - ω^2_{V3}	0.085	[0.038 , 0.146]	0.0926	[0.051 , 0.134]
OMEGA(4,4) - ω^2_{Q}	0.159	[0.062 , 0.307]	0.148	[0.021 , 0.275]
OMEGA(5,5) - ω^2_{F1}	0.043	[0.013 , 0.080]	0.0461	[0.018 , 0.074]
OMEGA(6,6) - ω^2_{KA}	0.172	[0.074 , 0.302]	0.215	[0.107 , 0.323]
OMEGA(2,1) - $cov_{V2,CL}$	0.055	[0.023 , 0.094]	0.0566	[0.016 , 0.098]
OMEGA(3,1) - $cov_{V3,CL}$	0.0058	[-0.0210 , 0.0336]	0.00382	[-0.0213 , 0.0289]
OMEGA(3,2) - $cov_{V3,V2}$	0.053	[0.015 , 0.100]	0.0579	[0.016 , 0.099]
OMEGA(4,1) - $cov_{Q,CL}$	0.025	[-0.016 , 0.071]	0.0264	[-0.029 , 0.082]
OMEGA(4,2) - $cov_{Q,V2}$	0.092	[0.037 , 0.165]	0.108	[0.024 , 0.192]
OMEGA(4,3) - $cov_{Q,V3}$	0.099	[0.037 , 0.177]	0.100	[0.012 , 0.188]
SIGMA(1,1) - $\sigma^2_{PROP, ORAL}$	0.177	[0.154 , 0.205]	0.175	[0.144 , 0.206]
SIGMA(2,2) - σ^2_{ADD}	0.0011	[0.0005 , 0.0020]	0.0011	[-0.00092 , 0.00312]
SIGMA(3,3) - $\sigma^2_{PROP, IV}$	0.076	[0.067 , 0.087]	0.0763	[0.0532 , 0.0994]

Leverage Analysis and Cross-validation

The robustness of the final model was assessed by leverage analysis and cross-validation. For all parameters in the final model, the average of the ten leverage analysis runs and the standard deviation is presented in Table 8-20. Graphical representations of the result of the leverage analysis (for all θ, diagonal ω2 and σ2) are shown in Figure 12-13 to Figure 12-31. The average values, especially for the fixed effect parameters (θ), were comparable to the final model parameter estimates indicating that the final model was fairly robust.

Table 8-20: Results of leverage analysis

	Leverage analysis – Average (SD)	Final model estimate (reproduced from Table 8-17)
THETA(1) - $\theta_{CL,NREN}$, L/h	19.7 (1.2)	19.6
THETA(2) - θ_{V2}, L	58.4 (1.2)	58.4
THETA(3) - θ_{V3}, L	92.7 (3.0)	92.8
THETA(4) - θ_{Q}, L/h	37.4 (1.5)	37.2
THETA(5) - θ_{KA}, 1/h	0.892 (0.025)	0.878
THETA(6) - θ_{F1}, %	0.567 (0.011)	0.568
THETA(7) - θ_{ALAG}, h	0.329 (0.008)	0.323
THETA(8) - $\theta_{CL,NREN\sim CF}$	0.744 (0.077)	0.73
THETA(9) - $\theta_{KA\sim CF}$	-0.464 (0.03)	-0.459
THETA(10) - $\theta_{CL,REN\sim CLCR}$	1.25 (0.196)	1.26
OMEGA(1,1) - ω^2_{CL}	0.065 (0.012)	0.0678
OMEGA(2,2) - ω^2_{V2}	0.108 (0.009)	0.104
OMEGA(3,3) - ω^2_{V3}	0.092 (0.008)	0.0926
OMEGA(4,4) - ω^2_{Q}	0.151 (0.028)	0.148
OMEGA(5,5) - ω^2_{F1}	0.047 (0.009)	0.0461
OMEGA(6,6) - ω^2_{KA}	0.217 (0.029)	0.215
OMEGA(2,1) - $cov_{V2,CL}$	0.056 (0.011)	0.0566
OMEGA(3,1) - $cov_{V3,CL}$	0.0033 (0.0044)	0.00382
OMEGA(3,2) - $cov_{V3,V2}$	0.058 (0.006)	0.0579
OMEGA(4,1) - $cov_{Q,CL}$	0.021 (0.015)	0.0264
OMEGA(4,2) - $cov_{Q,V2}$	0.102 (0.014)	0.108
OMEGA(4,3) - $cov_{Q,V3}$	0.1 (0.313)	0.100
SIGMA(1,1) - $\sigma^2_{PROP,\ ORAL}$	0.175 (0.006)	0.175
SIGMA(2,2) - σ^2_{ADD}	0.00116 (0.00036)	0.0011
SIGMA(3,3) - $\sigma^2_{PROP,\ IV}$	0.076 (0.004)	0.0763

Discussion and Conclusions

The purpose of this study was to develop a population pharmacokinetic model for ciprofloxacin in pediatric patients. Data from six pediatric studies covering the entire pediatric age range (3 months to 17 years) were used in this study. An allometrically scaled (based on body weight) two-compartment model with absorption lag time and first order absorption adequately fit the plasma concentration data. Cystic fibrosis was a covariate that significantly influenced ciprofloxacin clearance and absorption rate constant; cystic fibrosis patients exhibited higher ciprofloxacin clearance and smaller absorption rate constant when compared to non-cystic fibrosis patients. In addition, ciprofloxacin clearance was influenced by creatinine clearance.

The pharmacokinetics and disposition of antimicrobial agents have been reported to be different in cystic fibrosis patients when compared to healthy subjects and other patient populations. According to the final model of this study, pediatric cystic fibrosis patients exhibit higher ciprofloxacin clearance when compared to non-cystic fibrosis patients. Based on the final model, ciprofloxacin clearance in a typical 12-year old cystic fibrosis patient is predicted to be 45% higher when compared to the clearance in a typical 12-year

old non-cystic fibrosis patient, which is consistent with reports of increased ciprofloxacin clearance in adults with cystic fibrosis.

The dosing recommendations made in Section 9 of this report strictly relate to (non-cystic fibrosis) pediatric patients with complicated urinary tract infection. It should be noted that, in general practice, pediatric cystic fibrosis patients receive daily doses of ciprofloxacin that are higher than those recommended in this report for complicated urinary tract infection. These higher doses are supported by the increased ciprofloxacin clearance predicted for this population and are also justified by the minimum inhibitory concentration values for microorganisms in cystic fibrosis patients.

In population analyses, especially those involving pediatric data, age is almost always used as a continuous variable to describe the variability in clearance. When used in population pharmacokinetic models, age is thought to reflect other physiological variables (such as renal function and metabolism) that *gradually* change with age in pediatric patients. In the primary analyses reported herein, age was used as a continuous covariate. However, in order to fulfill the requirements of the Written Request Letter, secondary analyses were performed in which age was used as a categorical covariate. In these secondary analyses, patients were divided into two groups (3 months to 2 years of age and over 2 years of age) and the relative change in ciprofloxacin clearance was determined. The age cutoff of 2 years is supported by the fact that major physiological changes that have the potential to affect drug disposition are mostly complete by 2 years of age. This is also consistent with the general classification of pediatric patients in regulatory guidance documents (infants: 1 month to 2 years and children: 2 to 12 years).

In the secondary analyses, when age was used as a categorical covariate for ciprofloxacin clearance, the decrease in the value of objective function did not reach statistical significance in any step of the stepwise forward inclusion procedure. Therefore, irrespective of the use of age as a categorical or a continuous covariate, this demographic information would not have entered the final population pharmacokinetic model.

A highly statistically significant difference in ciprofloxacin absorption rate constant in pediatric patients with cystic fibrosis is consistent with reports in the literature regarding malabsorption of drugs and nutritional supplements in this population. The gastrointestinal pH is different in pediatric cystic fibrosis patients and is generally considered to be the reason for altered pharmacokinetic profile of drugs in cystic fibrosis patients.

In adults, renal clearance accounts for approximately 50% of total ciprofloxacin clearance and ciprofloxacin pharmacokinetics are sufficiently altered in subjects with moderate renal impairment (creatinine clearance value less than 50 mL/min or 3 L/h) and severe renal impairment to warrant dose adjustment. In the current dataset, 295 out of 357 patients had creatinine clearance values greater than 4.8 L/h/1.73 m^2 (80 mL/min/1.73 m^2). Fifty-eight patients had creatinine clearance between 3.0 L/h/1.73 m^2 (50 mL/min/1.73 m^2) and 4.8 L/h/1.73m^2 (80 mL/min/1.73 m^2). The estimated creatinine clearance value was less than 3 L/h/1.73 m^2 in 4 patients. Therefore, the utility of the final model is restricted to creatinine clearance values above 3.0 L/h/1.73 m^2 (50

mL/min/1.73 m^2) i.e., mild renal impairment and normal renal function. Consequently, the final model cannot be used to predict ciprofloxacin concentrations in pediatric patients with moderate or severe renal impairment; in such situations, the dose adjustment indicated for adults with moderate and severe renal impairment may be considered. The final model and simulations presented previously suggest that ciprofloxacin dose need not be adjusted for pediatric patients with mild renal impairment.

One of the objectives of this study was to develop dosing recommendation for pediatric patients. Ciprofloxacin dose for pediatric patients in the age range 3 months to 17 years was determined based on the population pharmacokinetic model for clearance and target AUC value.

The applicant has proposed three options for determining ciprofloxacin dosing regimen for pediatric patients.

Option A: (b) (4)

Option B: (b) (4)

Option C: Ciprofloxacin dosing regimen employed in Study 100169 may be used. In this study, ciprofloxacin was administered according to one of the following schedules: (a) oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day) or (b) intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) OR intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) followed by oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day).

In conclusion, a population pharmacokinetic model was developed for ciprofloxacin in pediatric patients. Covariates that influence the pharmacokinetics of ciprofloxacin were identified. As demonstrated by model evaluation procedures, the final population pharmacokinetic model resulted in robust parameter estimates and accurate predictive performance.

Reviewer's Comments:

1. The POPPK analysis identified three significant covariates, namely, body weight, creatinine clearance and presence of cystic fibrosis in patients. The effect of cystic fibrosis on the absorption rate constant was also found to be a significant factor.

2. The applicant used body weight as a covariate with an allometric exponent of 0.75 for clearance parameters based on literature. Instead of this, the applicant should have estimated the allometric exponent, which would have ensured correct estimation of the effect of body weight on clearance.

3. The applicant used a base model comprising of body weight as a covariate. Several covariates such as age were tested using this base model. This approach is not optimal, since age and body weight are inter-related and so using a base model with body weight fails to distinguish the effect of age on clearance. Instead, the applicant should have tested the effect of age on the base model without body weight.

APPENDIX III:

PEDIATRIC STUDY DECISION TREE

1. **Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression? Would you expect a similar response to intervention?**

Yes. Pediatric patients are similar to adults with regard to disease progression in cUTI and acute pyelonephritis. A similar response to intervention is expected.

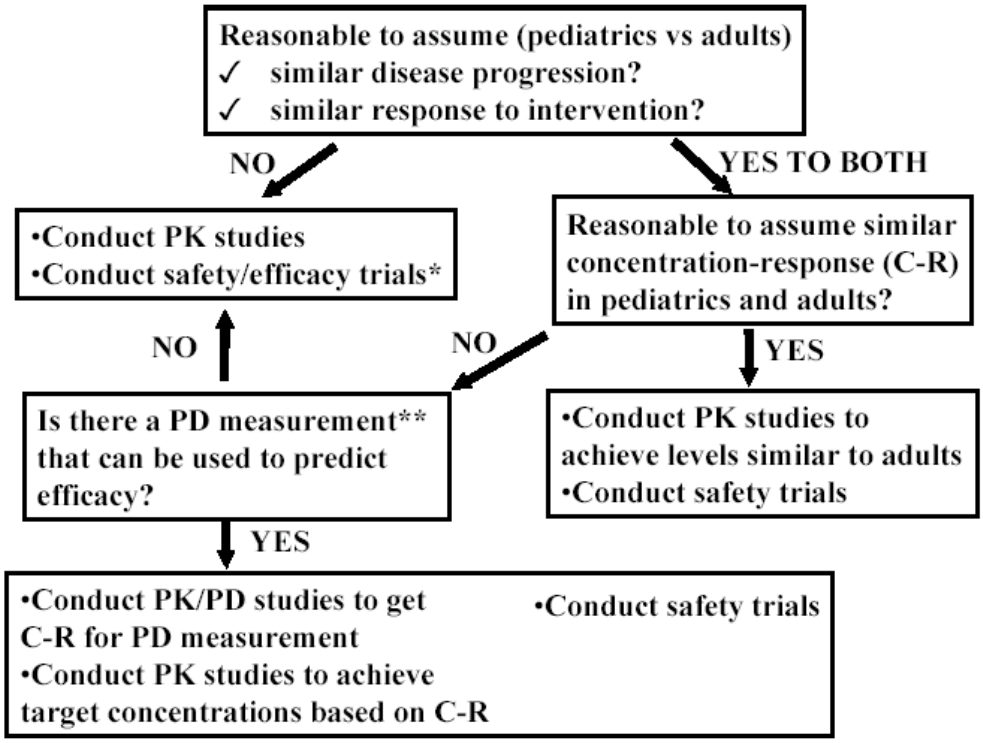
2. **Is it reasonable to assume similar concentration-response (C-R) in pediatrics and adults?**

Yes. Based on the similarity in disease progression in adults and pediatric patients and also based on the minimum inhibitory concentration (MIC) levels for the organisms causing the infection being similar, achieving similar exposure in adults and pediatric patients should be predictive of the efficacy of ciprofloxacin.

3. **Has the sponsor conducted PK studies to achieve levels similar to adults and has the applicant conducted safety trials?**

Yes. The sponsor has conducted a population PK analysis using data generated in 6 studies in pediatric patients with a variety of infection diagnoses. In addition, the sponsor has conducted an efficacy trial to determine the efficacy of ciprofloxacin in the treatment of cUTI and acute pyelonephritis in pediatric patients. Also, the sponsor has conducted a long-term observational safety study to determine the safety profile of ciprofloxacin in pediatric patients.

Pediatric Study Decision Tree



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/s/

Dakshina Chilukuri
3/24/04 02:55:37 PM
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Phil Colangelo
3/25/04 02:45:50 PM
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