OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA#	21085 (S-061: SDN1661, 1669, 1672, 1676, 1683) 21277 (S-057: SDN591, 598, 599, 601, 605, 611)
Date of Original Submission:	September 11, 2015
Brand Name:	Avelox®
Generic Name:	Moxifloxacin hydrochloride
Strength and Formulation:	Tablets: 400 mg tablet (NDA21085) IV injection: 400 mg/250 mL 0.8% saline
Sponsor:	(NDA21277)
Indication:	Bayer HealthCare
Submission Type:	Not applicable Pediatric sNDA; (b) (4) Safety Labeling Supplement for Pediatric Patients with complicated Intra-Abdominal Infections (cIAI)
Clinical Pharmacology Review Team:	Xiaohui (Tracey) Wei, Reviewer Philip M. Colangelo, Team Leader Dhananjay Marathe, Pharmacometrics Reviewer Jeffry Florian, Pharmacometrics Team Leader

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EXECUTIVE SUMMARY

Avelox® (moxifloxacin hydrochloride) was initially approved in adult patients in 1999 for the treatment of a variety of bacterial infections caused by susceptible strains, including the following indications: respiratory tract infections (acute exacerbations of chronic bronchitis, community acquired pneumonia (CAP), acute sinusitis), uncomplicated skin and skin structure infection (uSSSI), (b) (4) complicated skin and skin structure infection (cSSSI, including diabetic foot infections), complicated intra-abdominal infection (cIAI, including polymicrobial infections such as abscesses), and plague (both pneumonic and septicemic). For all of these infections / indications, the approved adult dose regimen is 400 mg once daily (QD) either IV or PO. Moxifloxacin 400 mg film-coated tablet and moxifloxacin 400 mg / 250 mL solution for intravenous infusion are the approved formulations and dose strengths for adult patients.

Moxifloxacin is not approved for any pediatric indications but in practice has been used to treat pediatric patients with various types of infections (e.g. respiratory tract, chronic bronchitis, intra-abdominal, tuberculosis) even though limited safety information is available in pediatric patients. To better understand the safety profile of moxifloxacin in pediatric patients and to explore the potential public health benefit by offering an additional treatment option to pediatric patients, a pediatric written request (PWR) for moxifloxacin was issued by the Agency on December 7, 2009 which outlined two pediatric studies:

- one pharmacokinetic (PK) Phase 1 study in pediatric patients 3 months to ≤14 years;
- one Phase 3 study in pediatric patients 3 months to <18 years with cIAI

In the Phase 1 Study 11826, 31 pediatric patients 3 months to ≤14 years old received a single IV dose of moxifloxacin to investigate the PK, safety, and tolerability. The Phase 3 Study 11643 enrolled 451 pediatric patients 3 months to <18 years of age (mean age of 12 ± 4 years) with cIAI; 301 of which were treated with moxifloxacin, and 150 treated with active comparator (intravenous ertapenem followed by oral amoxicillin/clavulanate). Safety profiles of moxifloxacin in the pediatric population were investigated in both Phase 1 and Phase 3 studies. Special emphasis was placed on cardiac and musculoskeletal adverse events. (b) (4) the Sponsor proposed to include information regarding the trial results (safety (b) (4) in Section 8.4 Pediatric Use in the Avelox labeling, (b) (4) The Clinical Pharmacology review team concurs with this decision, but additional analyses were conducted to determine if the Sponsor achieved moxifloxacin exposures in pediatrics comparable to adults with the doses utilized in the study.

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1.1. Recommendation

(b) (4)

There are no proposed Clinical Pharmacology labeling revisions / recommendations.

1.2. Phase 4 Commitments

There are no Phase 4 commitments.

1.3. Summary of Important Clinical Pharmacology Findings

The pharmacokinetics (PK) of moxifloxacin in pediatric patients was assessed in one Phase 1 PK Study 11826 and one Phase 3 cIAI Study 11643. (b) (4)

The Sponsor previously established a PBPK model for moxifloxacin and its two metabolites, M1 (sulfate) and M2 (glucuronide), in adults and was scaled to children between 7 days and 14 years of age (below 45 kg body weight) and adolescents between 12 and 18 years (above 45 kg body weight) using independent prior information about age-dependencies of anthropometry, physiology and clearance. Based on the PBPK model prediction, an age and body weight dependent dosing scheme was tested in the Phase 1 single dose PK Study 11826 in children ranging in age from 3 months to 14 years. **Table 3** below provides the PK parameters of moxifloxacin stratified by three age groups.

Table 3: Sponsor derived pharmacokinetic parameters for moxifloxacin in pediatric patients after single IV 1-hour infusion in Study 11826 (values are Geo Mean (CV [%]))

Age group	6 to ≤14 years		2 to <6 years		3 months to < 2 years	
Dose	5 mg/kg (N=7)	6 mg/kg (N=5)	7 mg/kg (N=7)	8 mg/kg (N=5)	9 mg/kg (N=6)	10 mg/kg (N=1)
Variable						
AUC (mg*h/L)	19.73 (30.5)	24.04 (4.1)	28.21 (2.8)	27.18 (19.3)	25.52 (17.3)	40.5 (-)
C_{max} (mg/L)	3.16 (33.3)	4.61 (17.1)	6.51 (43.5)	5.64 (10.7)	5.31 (4.7)	5.96 (-)
$t_{1/2}$ (h)	7.89 (34.3)	6.16 (24.0)	5.66 (18.8)	6.03 (24.8)	6.82 (35.1)	5.94 (-)
Ae_{ur} (%)	22.9 (33.2)	25.4 (27.5)	31.3 (32.4)	24.7 (54.4)	-	-

AeUr = amount excreted into urine; AUC = area under the curve; Cmax = maximum drug concentration in plasma after single dose administration; CV = coefficient of variation; $t_{1/2}$ = half life

Source: Sponsor's justification document no. 067b, Table 2-1

The PK data indicate that with increasing doses, the mean AUC and Cmax estimates also increased. Although AUC values remained relatively lower than that seen in adults at the approved dose of 400 mg (adult AUC ~39 mg*h/L), at higher doses in pediatrics mean C_{max} values approached or exceeded the threshold value of 6 mg/L for safety (i.e., QT prolongation).

Table 1 above shows the moxifloxacin dose regimens used by the Sponsor in Study 11643 in pediatric patients with cIAI. Population pharmacokinetic analysis conducted by the Sponsor based on PK data derived from pediatric patients in the Phase 1 and Phase 3 studies confirmed that the proposed pediatric dose regimens as shown in **Table 1** yielded comparable overall systemic exposure to moxifloxacin as that in adults receiving 400 mg QD, with the exception of the C_{max} estimates in pediatric patients who are 12 to <18 years old with body weight ≥45 kg. In these pediatric patients, 47% of the C_{max} values exceeded the 6 mg/L threshold for safety in Study 11643 after 400 mg QD IV administration. Additional simulations performed by the Sponsor showed that a switch from 400 mg QD IV to 200 mg BID IV would result in a higher proportion of subjects with predicted C_{max} estimates below the threshold limit for safety (6 mg/L) while keeping AUC exposure similar to that of adults at 400 mg QD IV. (b) (4)

The review of the Sponsor's population PK analysis by the FDA Clinical Pharmacology review team based on data from the Phase 1 and Phase 3 studies showed that body weight was a significant covariate on moxifloxacin clearance, but age was not identified as a covariate. (b) (4)

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2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What is the proposed dosage, route of administration and therapeutic indication(s)?
Moxifloxacin is not currently approved for the treatment of any pediatric infections / indications.

Moxifloxacin has been tested in a Phase 3 trial (Study 11643) in pediatric patients 3 months to <18 years with cIAI. The sponsor dosed moxifloxacin in pediatric patients with cIAI in this study in an age- and body weight- based manner according to the dose regiments presented in **Table 1** above. Similar exposures were observed in pediatrics to that observed in adults administered 400 mg QD PO or IV. (b) (4) [redacted].

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies (b) (4) [redacted] *?*
It can be assumed for moxifloxacin in the treatment of cIAI that a similar disease progression, similar response to intervention and the same exposure-response relationship as known for adults is also applicable for pediatric patients for most adult infections / indications. (b) (4) [redacted]

Physiologically based pharmacokinetic (PBPK) and population PK modeling and simulation were employed by the Sponsor to assist in the determination of dose regimens in pediatrics leading to comparable exposures as seen in adults. Based on the prediction from PBPK modeling, an age and body weight dependent dosing scheme was tested in the Phase 1 single dose PK Study 11826. Study 11826 included 31 moxifloxacin treated pediatric patients from 3 months to 14 years suffering from various infections. Pediatric patients were stratified by age group and by dose strengths in order to characterize PK and safety, and to determine an age- and body weight-based dosing regimen for pediatric patients in Phase 3. Dosing schedules were calculated from the Phase 1 study results based on PK considerations and carried forward into the Phase 3 Study 11643.

Study 11643 was a prospective, randomized, double-blind, active controlled, multi-center Phase 3 study to evaluate the safety and tolerability of treatment with moxifloxacin administered IV for at least 3 days followed by oral administration, if appropriate, compared to treatment with comparator (intravenous ertapenem followed by oral amoxicillin/clavulanate) in pediatric subjects with cIAI. A sparse pharmacokinetic sampling schedule suitable to derive the PK parameters relevant for PK/PD and safety evaluations were implemented in the Phase 3 trial. Population pharmacokinetic analysis based on PK data from pediatric patients in Phase 1 and Phase 3 studies was conducted by the Sponsor to verify that the pediatric dose regimens tested in Phase 3 study yielded similar systemic exposure to that in adults receiving 400 mg QD moxifloxacin.

An overview of pediatric studies for moxifloxacin is listed in **Table 2.2.1-1**.

Table 2.2.1-1: Overview of Pediatric Studies with Moxifloxacin

Study Number (Phase)	Study Title	Patient Population	Total Pediatric Patients
11826	Safety, tolerability and pharmacokinetics of single dose intravenous moxifloxacin in pediatric patients	Various infections	31 moxifloxacin
11643	A randomized, double-blind, multicenter trial to evaluate the safety and efficacy of sequential (intravenous, oral) moxifloxacin versus comparator in pediatric subjects with complicated intra-abdominal infection	Complicated intra-abdominal infection	301 moxifloxacin 150 ertapenem IV followed by amoxicillin/clavulanate PO (comparator)

2.2.2. What are the PK characteristics of moxifloxacin in pediatric patients?

The PK characteristics of moxifloxacin in pediatric patients were determined from data obtained from Studies 11826 and 11643 and incorporated in a population PK analysis, as discussed below.

Study 11826:

The objectives of this study were to evaluate the pharmacokinetics and safety of IV moxifloxacin after a single IV dose as a 1-hour infusion in children 3 months to 14 years who already received antibiotics for suspected or proven infection. The dosing and PK parameters by age cohorts in this study are shown in **Table 3** above. Results from the Phase 1 study showed that higher doses of moxifloxacin produced C_{max} estimates exceeding the threshold value of 6 mg/L while yielding relatively low AUC estimates. (b) (4) The metabolite profile of moxifloxacin was similar in children as seen in adults, with M-2 being the major metabolite, and M-1 a lesser metabolite.

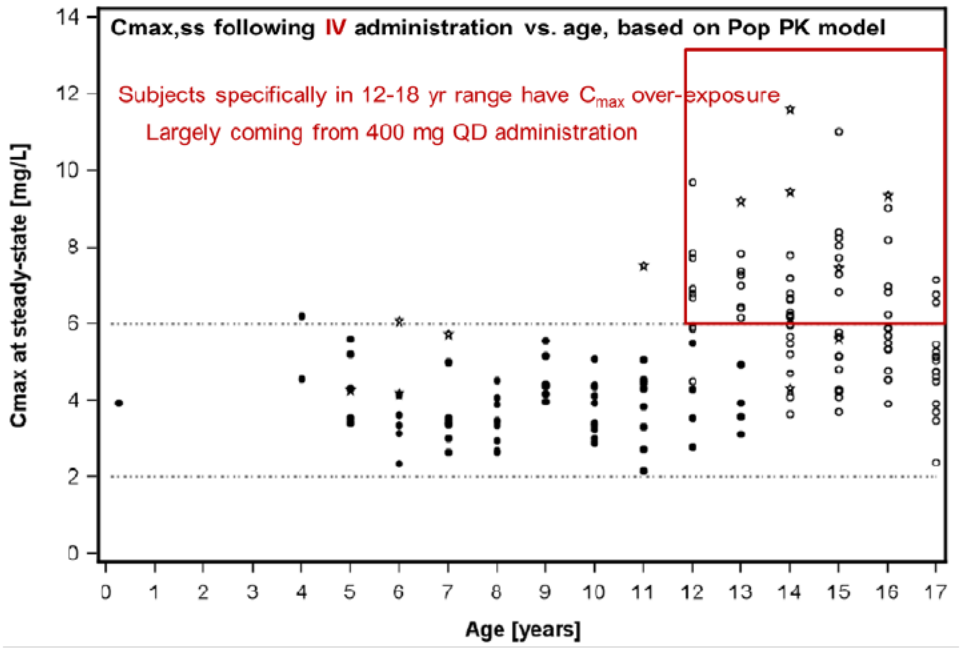
Study 11643:

This study assessed safety and the exploratory efficacy of sequential IV to PO administration of moxifloxacin compared to that of IV ertapenem followed by PO amoxicillin/clavulanate for the treatment of pediatric patients with cIAI. In this study, a total of 301 pediatric subjects with cIAI received moxifloxacin according to an age and weight based dosing as presented in **Table 1**

above. Results from this study showed that the dose regimens employed yielded similar systemic exposure to that in adults receiving 400 mg QD moxifloxacin, except that in adolescent patients 12 to <18 years old with body weight ≥45 kg. As shown in **Figure 2.2.2-1**, 47% of the Cmax estimates in these adolescent patients aged 12 to < 18 years exceeded the 6 mg/L threshold for safety in Study 11643 after 400 mg QD IV administration. (b) (4)

[redacted]

Figure 2.2.2-1: Steady state C_{max} following IV administration in Phase 3 vs. age, based on estimated concentrations from the Sponsor's Pop-PK model



○ MD IV administration 400 mg once daily
● MD IV administration 4 mg/kg - 6 mg/kg twice daily
☆ subjects with at least 1 non-influential outlier concentration included in the analysis
---- Limits of the Cmax target range

Population PK Analysis:

The population PK model of moxifloxacin in pediatric patients was developed by the Sponsor and was used to simulate pediatric moxifloxacin exposure at steady state in order to confirm or refine the moxifloxacin dose regimens in pediatric patients to achieve target ranges of PK parameters. The development and validation of the proposed population PK model are summarized in the Pharmacometrics Review (Appendix-A) and was found to be acceptable by the Pharmacometrics reviewer. Body weight was found to be the only significant covariate on clearance. (b) (4)

[redacted]

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Dosing regimen for pediatric patients:

(b) (4)

[redacted]

[redacted] (b) (4). The predicted pediatric PK exposures (C_{max}, AUC_{0-24h}) with the proposed weight-based only dose regimens are generally similar to that in adults who received the approved dosing regimen of 400 mg QD. However, there are some AUC estimates that are slightly above, and some C_{max} estimates that are lower than adult exposures. [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

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2.3. Analytical Section

2.3.1. What bioanalytical methods are used to determine drug concentrations? Briefly describe the methods and summarize the assay performance.

The applicant used a high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) method of bioanalysis to determine concentrations of moxifloxacin (BAY 12-8039) and its two metabolites (M-1, M-2) in human plasma and urine samples. The assay methods are validated per the FDA Guidance. In **Table 2.3.1-1**, the bioanalytical reports and the corresponding trials are given.

Table 2.3.1-1: Bioanalytical Method Reports Used in Pediatric Clinical Studies Method Validation for Determination of Moxifloxacin and Metabolites in Human Plasma

Study Detection Method	Bioanalytical Report Number (s)	Laboratory Site	Analyte (s)	Metrics
BAY 12-8039/11826 HPLC/MS-MS	BAR_KINC11826-EXT-STY151	(b) (4)	BAY 12-8039, M-1 and M-2	Plasma
	BAR_KINC11826-EXT-STY152		BAY 12-8039, M-1 and M-2	Urine
BAY 12-8039/11643 HPLC/MS-MS	Bioanalysis of BAY 12-8039, M-1 and M-2 in study BAY 12-8039/11643		BAY 12-8039, M-1 and M-2	Plasma

Method Validation for Determination of Moxifloxacin and its Metabolite in Human Plasma via HPLC-MS/MS

Sample preparation, extraction, and chromatographic conditions were kept the same for analysis of moxifloxacin and its metabolites M-1 and M-2 for both pediatric clinical studies (Studies 11826 and 11643). In this method, plasma samples were mixed with the internal standard contained precipitating solution (70% Acetonitrile/30% 10 mM Ammonium Acetate) for extraction of analyte from the plasma matrix. The samples were centrifuged and the supernatant (100 µL) was mixed with 100 µL buffer (solution B 3.7.1). This solution was injected into the HPLC system and analyzed by HPLC-MS/MS. Separation of analytes was achieved on a Synergi Polar RP (100 x 3.0 mm) column using a mobile phase consisting of acetonitrile/10 mM Ammonium Acetate. Analytes were detected by a PE Sciex API-3000 Mass Spectrometer.

The lower limit of quantification (LLOQ) and the nominal calibration range for moxifloxacin and its metabolites M-1 and M-2 in plasma are reported to be:

- LLOQ of 10 µg/mL and a calibration range of 10 – 5547 µg/mL for moxifloxacin
- LLOQ of 11 µg/mL and a calibration range of 11 – 2309 µg/mL for its metabolite M-1
- LLOQ of 11 µg/mL and a calibration range of 11 – 2342 µg/mL for its metabolite M-2

The calibration curves for Moxifloxacin and metabolites M-1 and M-2 were constructed as a function of the weighted ($1/x^2$) linear regression of the theoretical concentration versus response ratio (where response ratio = ratio of analyte peak area to internal standard peak area).

The precision and accuracy of the method were within acceptance criteria for each validation report [**Table 2.3.1-2**], and show that the analytical method used in the clinical studies with pediatric patients was valid for the determination of moxifloxacin and its metabolites in human plasma.

Table 2.3.1-2: Calibration Range, Precision and Accuracy of Moxifloxacin and Metabolites in Human Plasma Determined by High Performance Liquid Chromatography/Mass Spectrometry Assay

Report Parameter	BAY 12-8039	M-1	M-2
Study 11826			
Nominal calibration range (µg/L)	10 ─ 5547	11 ─ 2309	11-2342
LLOQ (µg/L)	10	11	11
Inter-assay precision (CV%)	≤4.0%	≤7.5%	≤4.9%
Inter-assay accuracy (%)	98.0% ─ 102.1%	88.8% ─ 106.6%	96.1% ─ 102.7%
Precision at LLOQ (CV%)	3.3%	2.2%	5.1%
Accuracy at LLOQ (%)	100.9%	100.1%	100.8%
Study 11643 (first set of samples)			
Nominal calibration range (µg/L)	10 ─ 5542	11 ─ 2306	11-2342
LLOQ (µg/L)	10	11	11
Inter-assay precision (CV%)	≤4.2%	≤6.3%	≤4.5%
Inter-assay accuracy (%)	98.6% ─ 101.9%	92.7% ─ 108.5%	96.8% ─ 102.6%
Precision at LLOQ (CV%)	4.6%	7.9%	3.8%
Accuracy at LLOQ (%)	100.9%	104.0%	100.7%

Method Validation for Determination of Moxifloxacin and its Metabolite in Human Urine via HPLC-MS/MS

Concentrations of moxifloxacin (BAY 12-8039) and its two metabolites (M-1, M-2) were determined in human urine samples from Study 11826 using HPLC-MS/MS method.

Urine samples were spiked with the internal standard contained spiking solution (70% Acetonitrile/30% 10 mM Ammonium Acetate). This solution (200 µL) was injected into the HPLC system and analyzed by HPLC-MS/MS. Separation of analytes was achieved on a Synergi Polar RP (100 x 3.0 mm) column using a mobile phase consisting of acetonitrile/10 mM Ammonium Acetate. Analytes were detected by a PE Sciex API-3000 Mass Spectrometer.

The lower limit of quantification (LLOQ) and the nominal calibration range for moxifloxacin and its metabolites M-1 and M-2 in urine are reported to be:

- LLOQ of 10 µg/mL and a calibration range of 510 – 168170 µg/mL for moxifloxacin
- LLOQ of 11 µg/mL and a calibration range of 50 – 10504 µg/mL for its metabolite M-1
- LLOQ of 11 µg/mL and a calibration range of 92 – 22483 µg/mL for its metabolite M-2

The calibration curves for Moxifloxacin and metabolites M-1 and M-2 were constructed as a function of the weighted ($1/x^2$) linear regression of the theoretical concentration versus response ratio (where response ratio = ratio of analyte peak area to internal standard peak area).

The precision and accuracy of the methods were within acceptance criteria for each validation report [**Table 2.3.1-3**], and show that the analytical methods used in this clinical study of pediatric patients was valid for the determination of moxifloxacin and its metabolites in human urine.

Table 2.3.1-3: Calibration Range, Precision and Accuracy of Moxifloxacin and Metabolites in Human Plasma Determined by High Performance Liquid Chromatography/Mass Spectrometry Assay

Report Parameter	BAY 12-8039	M-1	M-2
Study 11826			
Nominal calibration range (µg/L)	510 – 168170	50 – 10504	92-22483
LLOQ (µg/L)	510	50	92
Mean inter-assay precision (CV%)	≤5.1%	≤4.9%	≤4.4%
Mean inter-assay accuracy (%)	96.1% – 102.9%	97.8% – 101.9%	98.7% – 101.1%
Precision at LLOQ (CV%)	2.0%	4.5%	4.2%
Accuracy at LLOQ (%)	102.0%	100.2%	99.7%

2.3.2. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See above section 2.3.1

2.3.3. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See above section 2.3.1

2.3.4. What are the accuracy, precision, and selectivity at these limits?

See above section 2.3.1

2.3.5. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Plasma sample extracts were found to be stable when stored in the autosampler tray at 5°C for at least 72 hours. Freeze-thaw stability results showed that Moxifloxacin, M-1, and M-2 were stable in plasma after 3 freeze-thaw cycles.

Long term frozen stability of the analytes in plasma at -20˚C and -70˚C was assessed at 1-month (38 days). All three analytes were found to be stable at -20˚C and -70˚C in plasma for this period.

Urine sample extracts were found to be stable when stored in the autosampler tray at 5°C for at least 72 hours. Freeze-thaw stability results that Moxifloxacin, M-1, and M-2 were stable in urine after 3 freeze-thaw cycles. Moxifloxacin, M-1, and M-2 were found to be stable in urine when stored at room temperature for 4 hours.

3. APPENDIX-A: PHARMACOMERICS REVIEW

Results of Sponsor's Population PK Analysis and reviewer's comments

The Sponsor performed population pharmacokinetic (pop-PK) analyses in patients to:

1. Characterize the PK and variability of moxifloxacin after IV and PO dosing in pediatric patients aged 3 months to <18 years.
2. Quantify the influence of potential covariates
3. Confirm or refine dosing scheme for moxifloxacin in children to target ranges for PK parameters that are considered safe and efficacious

Data

The dataset for pop-PK analysis of pediatric subjects consisted of 186 subjects with 1562 moxifloxacin plasma concentrations from two studies. Study 11826 contributed 31 subjects, with single dose IV treatment, ranged 5–10 mg/kg body weight, which yielded 190 plasma concentration measurements. Study 11643 contributed 155 subjects; all with multiple dose once or twice daily IV treatment, which yielded 1238 plasma concentration measurements. Depending on the age and weight, some subjects of Study 11643 could be switched to PO treatment by protocol design. This was done in 28 subjects who contributed 134 plasma concentrations. In this study, an age and weight dependent dosing scheme was applied in the range of 4–6 mg/kg body weight twice daily or 400 mg once daily.

Results

The final pop-PK model was a linear three-compartment model with eliminations from the central compartment. Oral dosing used the same structure with a first-order absorption process. Final parameter estimates for the population PK model are summarized in **Table 1** below. All inter-compartmental clearances and volumes of distribution were scaled by body weight using an allometric exponent of 0.75 for clearances and 1 for volume parameters. The allometric exponent for body weight scaling of clearance (CL) was first fixed to 0.75 and later estimated using the data to reduce the extent of model misspecification for lower age groups suggested by the diagnostic plots (eta plot of inter-individual variability on CL). No covariates other than body weight were identified by model fits and diagnostics. Thirty-three outlier concentrations with a range of 17.4 to 294 mg/L were excluded from the model estimation due to their disproportionate influence on fixed effect parameters. The goodness-of-fit (observed vs individual predicted concentrations etc.) plots are provided in **Figure 1**.

(b) (4)

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Table 1: Pharmacokinetic and covariate parameter estimates of the final model

Parameter	Estimate	RSE	Description
Fixed Effects (Theta)			
TKA, 1/h	0.541	27%	Absorption rate constant
TCL, L/h/kg$^{0.589}$	0.807	15%	Weight-scaled clearance from central compartment
TV2, L/kg	0.91	6%	Weight-scaled volume of distribution of central compartment
TQ3, L/h/kg$^{0.75}$	1.72	15%	Weight-scaled inter-compartmental clearance between central and first peripheral compartment
TV3, L/kg	0.727	6%	Weight-scaled volume of distribution of first peripheral compartment
TF	0.858	4%	Absolute bioavailability
TQ4, L/h/kg$^{0.75}$	0.0891	13%	Weight-scaled inter-compartmental clearance between central and second peripheral compartment
TV4, L/kg	0.618	17%	Weight-scaled volume of distribution of second peripheral compartment
POWCL	0.589	7%	Allometric exponent on clearance
POWQ3, POWQ4	0.75 (Fixed)		Allometric exponent on inter-compartmental clearance
POWV2, POWV3, POWV4	1 (Fixed)		Allometric exponent on peripheral compartments
Random Effects (Inter-individual Variability, Omega)			
CL, ω^2 (CV%)	0.104 (33.1%)	18%	Inter-individual variability on CL
V2, ω^2 (CV%)	0.256 (54.0%)	20%	Inter-individual variability on V2
Random Effects (Residual Error, Sigma)			
Study 11826 IV, σ^2 (CV%)	0.0234 (15.3%)	21%	Proportional residual error of moxifloxacin of study 11826, IV administration
Study 11643 IV, σ^2 (CV%)	0.114 (33.8%)	11%	Proportional residual error of moxifloxacin of study 11643, IV administration
Study 11643 PO, σ^2 (CV%)	0.225 (47.4%)	17%	Proportional residual error of moxifloxacin of study 11643, PO administration

Source: Reviewer's analysis of Sponsor's population PK model

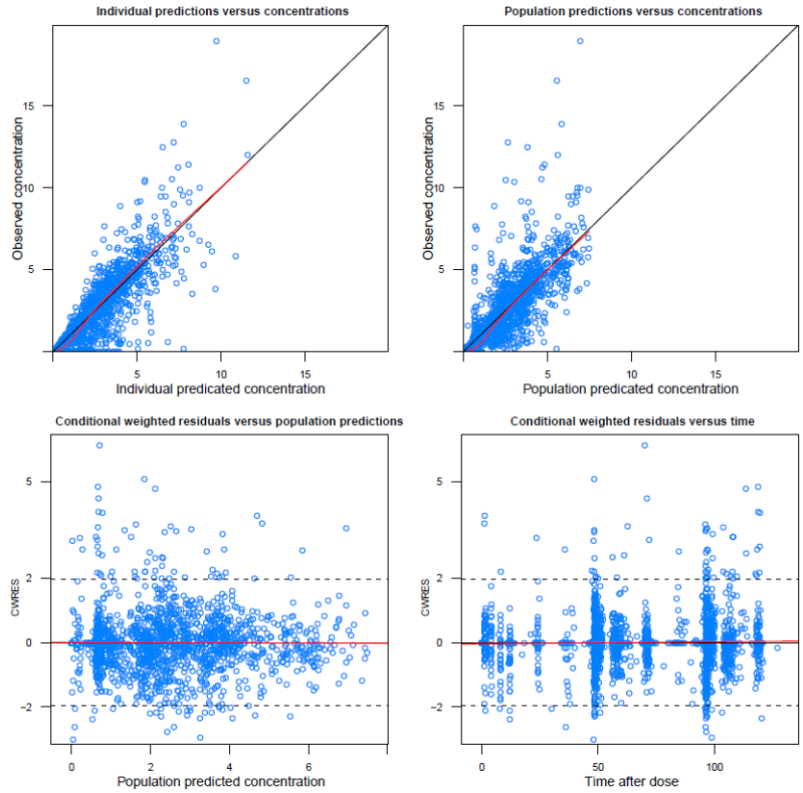

Figure 1: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model (*Source: Reviewer's analysis of Sponsor's population PK model)*

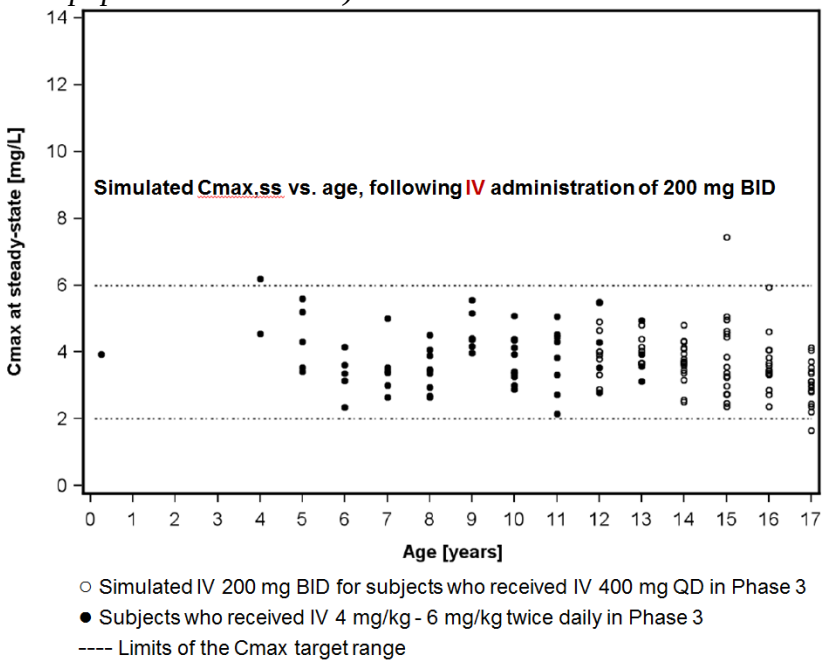

Figure 2: Simulated steady state C_{max} following IV administration of 200 mg BID for subjects administered with IV 400 mg QD in Phase 3 study. The dosing remained the same for subjects who received IV 4-6 mg/kg BID in Phase 3. (*Source: Adapted from Sponsor's pop-PK study report 17806, Figure 2-5)*

Reviewer's comments:

1. *The Sponsor's Pop-PK model provides reasonable description of moxifloxacin concentrations for individual predictions (observed vs. individual predicted concentrations in **Figure 1**). Visual inspection shows that the model reasonably predicts individual data over the range of moxifloxacin concentrations from the included studies.*
2. *Body weight was a significant covariate on clearance. Age was not identified as a covariate.* (b) (4) [redacted].

Listing of analyses datasets, codes and output files

Table 2: Analysis Data Sets

Study Number	**Name**	**Link to EDR**
Pop-PK Analysis:		
Dataset	imp17806-pk-010.xpt	\\cdsesub1\evsprod\NDA021085\0114\m5\datasets\17806\analysis\legacy\datasets\imp17806-pk-010.xpt
Model File	imp17806-modified-final-model-mod.txt	\\CDSESUB1\evsprod\NDA021277\0119\m5\datasets\17806\analysis\legacy\datasets\imp17806-modified-final-model-mod.txt
Simulation output file	imp17806-profilesim.xpt	\\CDSESUB1\evsprod\NDA021277\0119\m5\datasets\17806\analysis\legacy\datasets\imp17806-profilesim.xpt

Table 3: Codes and Output Files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics\Reviews\ Ongoing PM Reviews\ Moxifloxacin_sNDA21085_DDM **
Peds_PK.sas	PK analysis in pediatrics	ER_Analyses\codes
run1.mod	Modified model file	PK_Analyses\codes\run1
sdtab1.csv patab1.csv cotab1.csv catab1.csv	Output files for predicted concentrations, PK parameters, continuous covariates and categorical covariates	PK_Analyses\codes\run1

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/s/

DHANANJAY D MARATHE
02/18/2016

PHILIP M COLANGELO on behalf of XIAOHUI WEI
02/19/2016
Signing on behalf of Xiaohui (Tracey) Wei

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