Published in final edited form as:

J Clin Pharmacol. 2019 May ; 59(5): 654–667. doi:10.1002/jcph.1358.

Pharmacokinetics, Safety, and Tolerability of Single-Dose Intravenous Moxifloxacin in Pediatric Patients: Dose Optimization in a Phase 1 Study

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Abstract

The pharmacokinetics, safety, and tolerability of a single dose of moxifloxacin were characterized in 31 pediatric patients already receiving antibiotics for a suspected or proven infection in an open-label phase 1 study.A dosing strategy for each age cohort (Cohort 1: ≥6 years to ≤14 years; Cohort 2: ≥2 years to <6 years; Cohort 3:>3 month to <2 years) was developed using physiology-based pharmacokinetic modeling combined with a stepwise dosing scheme to obtain a similar exposure to adults receiving 400 mg of moxifloxacin. Doses, adjusted to body weight and age, were gradually escalated from 5 mg/kg in Cohort 1 to 10 mg/kg in Cohort 3 based on interim analysis of the pharmacokinetic and safety data. Plasma and urine samples before and after the 60-minute infusion were collected for the analysis of moxifloxacin and its metabolites using a validated high-pressure liquid chromatography assay with tandem mass spectrometry. Moxifloxacin and metabolite concentrations in plasma were within the ranges observed in adults;however,clearance of all analytes was lower in pediatric patients compared with adults.Population pharmacokinetic

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Declaration of Conflicting Interests

H.S., S.W., J.L., and K.M.V. are employees of Bayer AG. The Institutions employing J.S.B., J.E.S., L.P.J., and A.C.A. received funds from Bayer, Leverkusen, Germany, to support research staff and clinical costs of the study.

Presented in part as a poster at the Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, March 18–22, 2014, Atlanta, GA, USA.

analyses using the achieved exposure levels in the 3 age cohorts (with known body weight and clearance) predicted similar efficacy and safety profiles to adults. Moxifloxacin was well tolerated in all pediatric age cohorts.Adverse events related to moxifloxacin were mild or moderate in intensity and showed no correlation with increased weight-adjusted doses. Our findings guided the selection of age-appropriate clinical doses for a subsequent phase 3 clinical trial in pediatric patients with complicated intra-abdominal infections.

Keywords

dose finding; fluoroquinolone; moxifloxacin; pediatrics; pharmacokinetics/pharmacodynamics; phase 1 study

Moxifloxacin is an 8-methoxy-fluoroquinolone antimicrobial with a broad spectrum of activity against most causative organisms implicated in frequently diagnosed community-acquired pneumonia (CAP; eg, *Streptococcus pneumoniae*), complicated skin and skin structure infections (eg, *Staphylococcus aureus*), and complicated intra-abdominal infections (cIAIs; eg, *Escherichia coli*), as well as activity against *Pseudomonas aeruginosa*.[1-3] It also has improved activity against gram-positive cocci; aerobic, anaerobic, and intracellular bacteria; and other "atypical organisms" compared with third-generation fluoroquinolone agents.[4] The pharmacokinetic (PK) and pharmacodynamic (PD) properties of moxifloxacin have been extensively investigated in adults; moxifloxacin has an almost complete oral bioavailability (90%).[5] It is well absorbed from the gastrointestinal tract.[6,7] Mean protein binding of moxifloxacin in plasma is 39%, and the volume of distribution at steady state is 2.1 L/kg following IV infusion, indicating good tissue penetration.[5] Moxifloxacin is eliminated from plasma with a terminal half-life of approximately 12 hours.[5,8,9] Approximately 45% of the dose is excreted as unchanged drug, 25% in feces and 20% in urine.[5] Moxifloxacin undergoes phase 2 metabolism resulting in the formation of 2 inactive metabolites, a sulfate metabolite (M1, recovered from urine and feces) and a glucuronide (M2, excreted into urine), which have no antibacterial activity.[5] Following multiple dosing, steady state is reached within 3 days.[10] In accordance with its elimination profile, dose adjustment in patients with renal or hepatic impairment is not required.[11-13] The efficacy and safety of moxifloxacin have also been established in several large randomized, multicenter, international phase 3 clinical trials in adult patients with CAP, cIAIs, and complicated skin and skin structure infections, and it is recommended as an effective option in clinical practice guidelines for these indications.[14-17]

Currently, the use of systemic fluoroquinolones is very limited in pediatric patients due to lack of evidence for efficacy, as well as concerns for safety, although several clinical conditions exist in which an oral fluoroquinolone is considered to be an acceptable alternative to standard parenteral or oral therapy in situations of multidrug resistance or antibiotic allergy.[18] Ciprofloxacin suspension plus metronidazole, for example, is recommended for pediatric patients with cIAIs when severe allergic reactions occur to betalactam antibiotics, or for children whose oral step-down therapy requires coverage for *P aeruginosa* or other gram-negative pathogens for which an alternative oral therapy option does not exist.[17,18] Oral levofloxacin is recommended for treatment of children

aged 6 months or older with CAP caused by highly penicillin-resistant *S pneumoniae.*[19] Moxifloxacin currently is not approved in children for any indication.[20] Knowledge on the pharmacokinetics in pediatric patients is scarce and restricted to special populations,[21] where interpretation of the data is difficult due to the inherent complexity of the studies (eg, individualized combination therapy to treat the infection). However, given its well-defined PK properties and favorable efficacy and safety profiles in adults, moxifloxacin has been a candidate for the treatment of pediatric populations with similar indications as for adults, including cIAIs, CAP, and complicated skin and skin structure infections.

Dose selection in children requires careful consideration of the benefit-risk profile and disease severity, as well as the pharmacokinetics and pharmacodynamics of the antibiotic. A drug's PK properties may differ between children and adults due to the developmental differences in various organ functions responsible for drug metabolism and elimination, as well as potential differences in general distribution characteristics.[22] The goal of pediatric dosing strategies for drugs already approved in adults is to achieve the same drug exposure as that documented to be associated with efficacy and safety in adults.[23] PK modeling plays a supporting role in the initial dose selection for pediatric patients, with approaches including scaling down of adult PK data or physiology-based modeling to estimate PK parameters. Initial dosing in children thus requires consideration of various factors such as relative bioavailability, age and weight of study participants, therapeutic index, and even PK data from other populations.[24] Indeed, current guidelines[25-27] recommend that the initial administered dose should be a fraction of the adult recommended dose, based on allometric scaling, the above mentioned factors, and any additional experience with pediatric populations.[24,28]

For fluoroquinolones, the area under the plasma concentration versus time curve from zero to infinity ($AUC_{0-\infty}$)/minimum inhibitory concentration and maximum drug concentration in plasma after single dose administration (C_{max})/minimum inhibitory concentration ratios are the PK/PD parameters that best correlate with microbiologic and clinical outcomes in adults.[23,29] Therefore, to determine appropriate doses of moxifloxacin for children, the drug exposure parameters AUC and C_{max} were chosen as surrogates for efficacy and safety.

The objectives of this open-label phase 1 study were to (1) describe the pharmacokinetics of moxifloxacin administered as a single intravenous dose in children of different ages, (2) establish doses for various pediatric age groups that would provide similar exposure as that achieved for adults treated with the approved therapeutic dose of 400 mg once daily, and (3) assess the safety and tolerability of moxifloxacin in children with particular regard to cardiovascular and musculoskeletal safety.

Methods

Study Design and Patient Population

The study protocol was approved by the ethics committee of each participating site. Written informed consent was obtained from all patients' parents or guardians, and assent was obtained if age appropriate before enrollment into the trial. The study was conducted according to the provisions of legal guidelines and the Declaration of Helsinki. The

pharmacokinetics, safety, and tolerability of moxifloxacin in children were investigated in a multicenter, nonrandomized, open-label, noncontrolled study (NCT01049022). Males and females, aged from 3 months to 14 years, who were already receiving antibiotics for a suspected or proven infection (Table 1) were eligible for the study. Moxifloxacin was given as a single, 60-minute intravenous infusion to patients in 3 age cohorts: Cohort 1 included children aged ≥6 years to ≤14 years (school children), Cohort 2 included children aged ≥2 years to <6 years (preschool children), and Cohort 3 included children aged >3 months to <2 years (infants and toddlers).

Patients were not eligible for enrollment if they had a body weight >45 kg, known or suspected allergy to quinolone antibiotics, history of myasthenia gravis, renal or hepatic disease, history of tendon disorder, abnormal musculoskeletal evaluation, severe life-threatening condition, history of cardiac arrhythmia, clinically relevant findings on electrocardiogram (ECG), or were taking any of the following medications: antiseizure medications within 30 days of moxifloxacin dosing, antiarrhythmic agents, any medication that prolongs the ECG QT interval, or other fluoroquinolone antibiotics.[20]

Treatments

The dosing regimens of moxifloxacin for each age group were established based on physiology-based pharmacokinetic (PBPK) modeling. The PBPK model was scaled from an adult to a pediatric model following a previously established generic workflow by the same group[30] and incorporated the description of gastrointestinal metabolism, enterohepatic recycling, and binding to charcoal.[31,32]

The current approved dose of moxifloxacin in adults is 400 mg once daily,[20] corresponding to approximately 4 to 8 mg/kg over a body weight range of 50 to 100 kg. The following pediatric dose recommendations were calculated based on PBPK modeling to achieve exposure comparable to that of adults, without exceeding critical C_{max} limits for safety, for the following 3 age cohorts: 5 to 6 mg/kg for school children (≥6 to ≤ 14 years), 7 to 8 mg/kg for preschool children (≥2 to <6 years), and 9 to 10 mg/kg for infants and toddlers (>3 months to <2 years).

Patients received moxifloxacin as a single intravenous infusion administered over 60 minutes. The stepwise protocol stipulated that children included initially in Cohort 1 would receive moxifloxacin at a dose of the lower bound of the calculated dose recommendations (5 mg/kg; see above). Following evaluation of initial safety and PK results at this dose and comparison of drug exposures with those reported in adults, the dose was adjusted for children subsequently enrolled into Cohort 1. Before proceeding to the next age cohort, the complete data for each cohort were revisited to allow for dose adaptations if required.

Blood and Urine Sampling

Blood samples (0.5 mL/sample) were collected for measurements of moxifloxacin and its major metabolites M1 and M2 at a number of time points: prior to infusion and at 1, 1.5, 4, 8, 12, and 24 hours after dosing. Additional sampling at 36 and 48 hours was optional. Samples were obtained by capillary blood sampling, venipuncture, through a saline/heparin lock or through a central line. Plasma was separated by centrifugation at 2500 to 3000 rpm

for 10 minutes within 1 hour of sampling, transferred into a polypropylene cryovial, and stored at −15°C before analysis.

Collection periods for urine were pre dose, 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, and 12 to 24 hours after dosing with an optional additional sample at 24 to 36 hours. The total volume of urine for each sample interval was recorded. For each interval, the entire urine collection was combined and thoroughly mixed, and a 2- to 4-mL aliquot was transferred to a polypropylene cryovial. Samples were stored at −15°C within 1 hour of collection. No urine could be collected for Cohort 3 due to the technical feasibility of collecting urine from infants in diapers and ethical considerations that prevented bladder catheterization of infants for purposes of a PK study.

Safety and Tolerability

The safety and tolerability of moxifloxacin were monitored by assessment of adverse events, laboratory assessments (blood chemistry), measurements of vital signs (blood pressure, heart rate, and respiratory rate) and 12-lead ECG recordings. Musculoskeletal safety adverse events and ECG QT intervals were carefully assessed and investigated. In particular, joint appearance, structure, function (ie, both active and passive range of motion), pain/tenderness, and signs of inflammation were examined by a fully trained study physician, rheumatologist, or physical therapist. Patients were followed for 12 months to assess musculoskeletal safety.

Drug and Metabolite Assays

Plasma and urine concentrations of moxifloxacin and its metabolites M1 and M2 were determined after protein precipitation followed by separation employing a validated high-pressure liquid chromatography assay with tandem mass spectrometry. Study samples were analyzed concurrently with calibrators and quality control samples. Mean precision for quality control samples was ≤4.4%, ≤5.5%, and ≤4.3%, and mean accuracy was 98.6 to 101.3%, 98.9 to 105.3%, and 97.0 to 100.7% for moxifloxacin, M1, and M2, respectively. The lower limit of quantification was 10 μg/L for the parent drug and 11 μ-g/L for M1 and M2. All assays were fully validated according to US Food and Drug Administration guidelines.[33]

Pharmacokinetic and Statistical Analysis

Noncompartmental PK parameters were calculated for moxifloxacin, M1, and M2 from concentration data using the model-independent method and WinNonlin (Version 4.1.a; Certara USA Inc.) in conjunction with an Automation Extension (Bayer AG). C_{max} and time to peak concentration values were taken directly from the plasma concentration time profiles. AUCs were calculated using the log-linear trapezoidal rule. Terminal half-lives were obtained by linear regression analysis of the last data points after log-transformation of the data. The clearance of the drug was calculated as (dose/AUC). The apparent volume of distribution at steady state was determined according to the equation $Vss = [CL \times MRT(\text{iv})]$, where MRT is the mean residence time following intravenous infusion calculated as $[(AUMC/AUC) - T/2]$ where T is infusion time and AUMC is the area under the first moment of the concentration-time curve determined by integrating the product of time and

concentration from 0 to infinity. Amounts excreted into urine were based on concentrations of drug in urine and urine volumes collected in the interval following drug administration.

Physiology-Based Pharmacokinetic Modeling

PBPK modeling was used to predict the initial doses for children to be tested in this study and to guide dosing based on the available safety and PK data at each study milestone (ie, interim analysis within a cohort and analysis of the completed cohort before starting the subsequent age cohort).

The development of the pediatric PBPK model for moxifloxacin followed the same generic workflow as previously described for rivaroxaban.[30] As the first step, an adult PBPK model for moxifloxacin after intravenous and oral administration was developed using physicochemical and PK data obtained in clinical studies in adults. In the second step, the adult PBPK model was scaled to children using prior knowledge about the age-dependency of physiologic processes relevant for the absorption, distribution, metabolism, and excretion. PK-Sim, Version 4.2 (Bayer Technology Services, Leverkusen, Germany) was used as the PBPK software platform, together with its underlying databases that contain relevant age-dependent physiologic and anatomic information.

Population Pharmacokinetic Analysis

Population pharmacokinetic (popPK) modeling was performed in order to characterize moxifloxacin pharmacokinetics in children and to quantify the influence of potential covariates.

To build the popPK model, clinical data from this phase 1 study were combined with data from a subset of patients with cIAIs (n = 155) from the phase 3 pediatric clinical trial (NCT01069900). The results of the phase 3 study are reported elsewhere.[34,35] Briefly, pediatric and adolescent patients with cIAIs received moxifloxacin as a 60-minute intravenous infusion for at least 3 days, followed by oral administration for a total treatment duration of 5 to 14 days at the discretion of the treating physician. Two sets of blood samples were collected from each patient in using a sparse sampling protocol. The first sample set was taken on treatment day 3 following infusion of moxifloxacin, and the second sample set was obtained on treatment day 5 irrespective of the route of administration. Plasma concentration of moxifloxacin was assessed as described above and PK parameters were calculated.[35]

The popPK analysis was conducted via nonlinear mixed-effects modeling using NONMEM (ICON Development Solutions, Version 7.2) with the Navigator workbench (Mango Solutions, Version 9.1.5146) on a Red Hat Enterprise Linux 6.3 environment. The covariates tested were body weight, body surface area, serum creatinine, estimated glomerular filtration rate, study, sex, and age. The outcomes of the popPK model were then used to predict individual PK parameters (AUC and C_{max}) at steady state in order to evaluate the proposed age- and body weight-dependent dosing regimen. AUC and C_{max} determined in adults were used as the evaluation criterion for the pediatric data. Estimated drug exposures were plotted together with the predicted target range for AUC to determine if moxifloxacin exposure was within the predefined antimicrobial range seen in adults after administration

of moxifloxacin 400 mg. Predicted maximum concentrations were plotted together with the predicted range for C_{max} to determine if concentrations were within the target safety range predicted from adult studies.[29] Based on general PK/PD considerations for fluoroquinolones (eg, AUC/minimum inhibitory concentration as a predictor of antimicrobial efficacy in clinical practice) comparability was concluded if the pediatric PK data (either predicted or estimated) fell within the adult range (Figure 1).[29] Details of the popPK model development, validation, and application for the evaluation of clinical study results will be described in a separate paper.

Results

Patient Demographics

A total of 31 patients aged from 0.4 to 13.4 years (mean 5.3 ± 3.7 years) participated in the study. The majority of patients were male (77%) and of Caucasian race (68%); body weight ranged between 6.6 kg and 43.4 kg. Demographics for each age cohort are shown in Table 1.

Target Moxifloxacin Exposure in Pediatric Patients

To facilitate dose estimation for pediatric patients, plasma exposures obtained in adults in previous phase 1 studies after intravenous and oral administration of moxifloxacin 400 mg were plotted (Figure 1). The target range for area under the curves from 0 to 24 hours ($AUC_{[0-24]}$) at steady state was determined to be between 20 mg • h/L and 60 mg • h/L and target maximum plasma concentrations (C_{max}) at steady state were identified as 2 to 6 mg/L (Figure 1).

Pharmacokinetics of Moxifloxacin

The geometric mean plasma concentration (and geometric standard deviation) vs time profile curves of moxifloxacin are illustrated in Figure 2, A, B, and C, per cohorts, and the results from the noncompartmental pharmacokinetic analysis are shown in Table 2. For the starting doses of 5 mg/kg (Cohort 1 [n = 7]), 7 mg/kg (Cohort 2 [n = 7]), and 9 mg/kg (Cohort 3 [n = 6]) initial PK data showed that the geometric mean AUC values achieved were just below or in the lower portion of the target interval. The dose of moxifloxacin for subsequent patients was therefore increased to 6 mg/kg in Cohort 1, 8 mg/kg in Cohort 2, and 10 mg/kg in Cohort 3 (Table 2).

Geometric mean C_{max} values were within the predicted clinical safety target range and were between 3.2 mg/L and 6.5 mg/L. Patients in the younger age groups (Cohort 2 and 3) tended to have higher C_{max} values compared with those in the oldest age group (Cohort 1) corresponding to the higher doses of moxifloxacin received. Two patients in Cohort 2 had unusually high C_{max} values (11.4 mg/L and 11.2 mg/L); however, these were deemed to be questionable because the blood samples were collected through the moxifloxacin infusion line. These values were included in the calculations of PK parameters and figures; however, they should be interpreted with caution. Importantly, neither of these patients had any adverse events.

Median time to peak concentration was approximately 1 hour for all cohorts and doses. Mean elimination half-life was approximately 6 to 8 hours in older children (Cohort 1) and 6 to 7 hours in younger children (Cohorts 2 and 3). Mean geometric clearance (coefficient of variance) of moxifloxacin was lower in younger patients compared with the oldest age group (Table 2).

The amount of drug excreted into urine ranged from 14.8% to 22.6% of the single dose in the first 36 hours after moxifloxacin infusion. There was no notable difference in urine excretion between age groups or doses.

Pharmacokinetics of Metabolites

Plasma concentrations of metabolites M1, a sulfate conjugate, and M2, a glucuronide, were determined for all 31 patients. Concentration (geometric means with geometric standard deviation) vs time profiles for both metabolites are displayed in Figure 3, A and B, and data of noncompartmental PK analyses are shown in Table 3.

Geometric mean AUC values of M2 (the major metabolite) were 30% to 69% of the parent drug AUC values. M2 concentrations and relative AUC ratios were highest in the youngest cohort. Geometric mean C_{max} values of M2 across cohorts ranged from 0.67 to 2.10 mg/L and mean elimination half-life of M2 ranged from 5.2 to 7.0 hours.

The relative AUC ratios for metabolite M1 compared with the parent drug ranged from 2.9% to 8.9%. Concentrations and relative ratios of M1 tended to be higher in the younger age groups. Mean elimination half-life of M1 ranged from 4.7 to 7.0 hours.

The mean amount of M2 excreted into urine was between 9.2% and 16.0%, with higher excretion of M2 in preschool children (Cohort 2) compared with the oldest children (Cohort 1). The amount of M1 excreted into urine within 36 hours following dosing ranged from 1.8% to 4.8%, with slightly higher M1 excretion in Cohort 2 compared with Cohort 1. No urine was collected for the youngest age cohort.

Association Between Dose Selection and Target Plasma Exposure

PopPK modeling was used to estimate exposure level at steady state with the selected and applied doses of intravenous moxifloxacin. For popPK modeling, a total of 190 plasma concentration measurements were taken from 31 patients in this study who received a single intravenous dose of moxifloxacin. Additionally, 1238 plasma concentration measurements were obtained from 155 patients in the phase 3 study who received once- or twice-daily intravenous/oral moxifloxacin treatment for 5 to 14 days.[34,35]

The individual estimated drug exposures at steady state for the phase 1 patients plotted together with the predicted target range for AUC and C_{max} are shown in Figure 4, A and B, respectively. The estimated AUC values were slightly lower than predicted but still within a range in which antimicrobial efficacy can be expected for susceptible pathogens. Some data were below the predefined lower limit; however, they were still within the range observed for an adult population,[31] and no differential pattern was observed between age groups.

The majority of the estimated C_{max} values were within the predefined range indicating clinical safety; however, some values for younger patients were higher than predicted. None of the values were outside of the range seen in adult patients.

Safety and Tolerability of Moxifloxacin

A total of 50% (6 of 12), 50% (6 of 12), and 71% (5 of 7) of patients in Cohorts 1, 2, and 3, respectively, had at least 1 treatment-emergent adverse event (TEAE). All patients received the full dose with no modifications in dose or any discontinuation. One patient had a brief 5-minute interruption during drug administration due to a TEAE (ie, emesis) but continued the infusion and received the full dose.

The incidences of TEAEs considered to be related to the study drug by the investigator were 50% for Cohort 1, 17% for Cohort 2, and 14% for Cohort 3. All drug-related TEAEs were mild or moderate in intensity. The most common drug-related TEAEs by the Medical Dictionary for Regulatory Activities (version 16.1) preferred term reported in Cohort 1 were frequent bowel movements, erythema and infusion site erythema, venipuncture site pain, pruritus and venipuncture site pruritus, burning sensation, cough, papular rash, and flushing (each in 8%). In Cohort 2, vomiting (17%) was the most frequent drug-related TEAE. There was no increase in the incidence of study drug-related TEAEs with higher doses of moxifloxacin or with younger age. Only 1 patient in Cohort 3 experienced TEAEs (anemia and oxygen saturation decreased), which were classified as severe but not related to moxifloxacin. Two patients in Cohort 3 had serious adverse events that were not considered to be related to moxifloxacin treatment: 1 patient had prolonged pneumonia, which emerged prior to moxifloxacin infusion and required prolonged intubation and hospitalization, and 1 patient required hospitalization for evaluation and treatment of preexisting histiocytosis 5 days after moxifloxacin dosing.

There were no moxifloxacin-related adverse joint (or neuropathic) findings assessed in any patient. One case of tilted patella reported at the 1-year follow-up visit was ascribed by the investigator to rapid growth (aged 8.7 years; Cohort 1).

No absolute QT interval or corrected QT interval based on the Bazett's (QTcB) and Fridericia's (QTcF) formulae exceeding 500 milliseconds was observed in any of the cohorts at any time during the study (Table 4). Only 1 patient in Cohort 1 had QTc prolongation (ie, ΔQTcB, 63 milliseconds; and AQTcF, 62 milliseconds) at 1.5 hours after dosing. No cases of QTc prolongation–related morbidity or mortality (ie, clinical cardiac signs or symptoms) were observed, and there was no correlation between age and extent of QTc prolongation.

No clinically relevant changes were seen in laboratory parameters, vital signs, or other ECG parameters (RR, PR, and QRS intervals). Values for serum levels of alanine transaminase and aspartate transaminase (AST) outside of respective normal ranges were noted in a very low number of subjects in Cohort 2. Thus, in 1 patient, alanine transaminase increased from 26 U/L at baseline to 46 U/L (normal range, 10-25 U/L) following moxifloxacin administration, and AST values above the upper limit of normal were recorded for 2 patients. In 1 of these patients, the AST level was elevated at baseline (134 U/L; normal range, 15-50 U/L) and decreased to 78 U/L after moxifloxacin administration. In the other

patient, the AST elevation was marginal (63 U/L compared with a normal range of 20-60 U/L).

Discussion

Dose selection for pediatric patients is challenging because scaling adult doses to children requires careful consideration of age-dependent demographic and ontogenic effects.[22] In this study, doses were determined using a PBPK model in combination with a stepwise dosing scheme. After assessment of PK parameters and safety of an initial dose, weight-adjusted doses were increased in all 3 age cohorts. AUC values remained relatively low within the target range, even with higher weight-adjusted doses of moxifloxacin. In contrast, C_{max} values approached the upper threshold value of 6 mg/L defined by PK/PD pooled analysis, but fell within the overall range seen for adults,[29] demonstrating the value of PBPK modeling to predict pediatric clinical dosing.[30] The results also showed that the age- and body weight–adjusted, single intravenous dose of moxifloxacin in children aged 3 months to 14 years was well tolerated, further supporting the utility of dosing based on exposure predictions scaled from adults.[29] The PK parameters established in this study also informed selection of dosing regimens in a subsequent phase 3 randomized, controlled clinical trial of moxifloxacin in pediatric patients with cIAIs.[34,35]

The popPK model confirmed the age-dependent dosing scheme predicted by PBPK modeling. Previously, AUC has been identified as a PD driver of moxifloxacin efficacy.[23,29] The target range of this parameter (ie, 20-60 mg • h/L) for pediatric patients included in PBPK modeling was based on results of PK studies and subsequent popPK analysis for adult patients who received moxifloxacin 400 mg once daily.[30] Estimated AUC and C_{max} values for the 3 age-based cohorts were within or close to the predefined limits for efficacy and safety and showed that dose predictions were accurate. If peak concentrations outside the target range pose a safety risk, twice-daily administration offers a suitable alternative approach to achieve adequate exposure while avoiding excessively high peak concentrations, thus improving the balance of benefit–side effect risk in certain pediatric patients. Adolescents ≥ 12 years of age with a body weight ≥45 kg exhibit similar PK characteristics to adults, and data from phase 2 to 3 clinical studies of moxifloxacin document comparable safety and efficacy of 400 mg once-daily dosing in adult patients with a body weight similar to adolescents. Dosing equivalent to the recommended adult dose is suitable for adolescents ≥12 years of age of body weight ≥45 kg, while for adolescents aged 14 years and younger children weighing <45 kg, a pediatric dosage twice daily has been documented to be safe and effective.[35] Using this approach, the following doses were proposed to achieve AUC >20 mg • h/L, while not exceeding the C_{max} safety threshold across the pediatric age range: 6 mg/kg twice daily for infants and toddlers (>3 months to <2 years); 5 mg/kg twice daily for preschool children (≥2 years to <6 years); 4 mg/kg twice daily for school-aged children (≥6 to <12 years); 4 mg/kg twice daily for adolescents (≥ 12 to <18 years) with a body weight <45 kg, and 400 mg once daily for adolescents (≥12 to <18 years) with a body weight ≥45 kg. This dose yielded comparable systemic exposure to moxifloxacin as seen in adults receiving 400 mg once-daily treatment.[35]

Overall, the PK characteristics of moxifloxacin and its metabolites in children aged from 3 months to 14 years were similar to the PK profile described in adults.[5,8,9] After moxifloxacin infusion, plasma concentrations rose quickly, reaching C_{max} after approximately 1 hour, similar to findings in adults.[5,8,9] Clearance, elimination half-life, and the volume of distribution of moxifloxacin were, however, slightly lower in children compared with adults[5,8,9] and, for all 3 parameters, geometric mean values decreased with cohort age. Growth stage and organ function in children both impact the PK profile of a drug.[22,29] No consistent trend was observed with body weight normalized data for either volume of distribution or clearance, and it was not possible to conclude the role of age and organ function owing to the high variability and low patient numbers in each dose group. Further studies with more patients are necessary to confirm these findings.

As found in adult studies, moxifloxacin glucuronide (M2) was the major metabolite, and sulfate conjugate (M1) was the minor metabolite in plasma. Concentrations of both metabolites were lower than those of the parent drug in all age groups, but greater than that reported for adults following 400-mg intravenous dosing.[5,8,9] All values were, however, still within the range predicted by the PBPK model as well as suggested by preclinical safety studies.[36] Elimination half-lives were similar for moxifloxacin, M1, and M2 suggesting no important differences in the distribution and elimination of the metabolites and the parent drug; similar half-lives for moxifloxacin and the metabolites were observed in all 3 cohorts. It is worth noting that the elimination half-lives of all analytes were considerably shorter in children compared with adults. Amounts of M1 and M2 excreted into urine were similar to that seen in adult populations.[5,8] As both metabolites are pharmacologically inactive and have considerably lower systemic exposure than the parent drug, it is suggested that these will have little effect on tolerability in children.

The safety profile of fluoroquinolones is well described in the literature, although data are scarce in pediatric patients, as their use is limited to a handful of approved indications.[18] Fluoroquinolones have been associated with increased risk of tendinitis, tendon rupture, and potential polyneuropathy leading to disability,[20,37,38] especially in older patients.[39-41] Recently, the US Department of Health and Human Services and Food and Drug Administration requested the addition of a new boxed warning on the potential (although very rare) irreversible changes that may lead to disabilities.[20,37,38] Monitoring joint and nerve functions is therefore a particular focus of safety assessments when dosing children with quinolones, including moxifloxacin. It is known that moxifloxacin prolongs the QT interval on ECG, an effect that is reversible and is concentration and dose dependent[42] and can potentially lead to fatal arrhythmia.[43,44] There is a positive correlation between plasma concentration of moxifloxacin and change in QTc interval.[45] In adults, administration of oral moxifloxacin 400 mg results in a 7.5 to 12.5-millisecond increase in the mean placebo- and baseline-corrected QTc interval and PK analysis of moxifloxacin 400 mg suggested that every 1-mg/mL increase in the plasma concentration is associated with 3.9-millisecond increase in QTc interval.[45] Intravenous treatment of hospitalized patients with moxifloxacin 400 mg transiently prolongs the QT interval by approximately 10 milliseconds.[46] However, a meta-analysis of 64 phase 1 to phase 3 clinical studies highlighted that the treatment of adult outpatients or hospitalized patients with intravenous and/or oral moxifloxacin 400 mg was not associated with increased risk of cardiac adverse events related to QTc prolongation

vs comparator antibiotic treatment.[46] This finding is important because any prolongation of the QT interval resulting in a QTc interval >500 milliseconds or a change of >60 milliseconds from baseline could trigger (potentially fatal) arrhythmias.[47] The current results shown here indicate that moxifloxacin was not associated with an increased risk of QTc prolongation-related morbidity or mortality in pediatric patients.

In the current study, a single dose of moxifloxacin was well tolerated, with less than one-third of patients experiencing one mild or moderate drug-related adverse event and no notable or permanent findings related to safety, including ECG and joint assessments. Follow-up joint assessments at 1 month, 3 months, and 1 year after exposure to moxifloxacin did not reveal relevant findings in any of the 3 age cohorts. While the absence of any safety concerns in this study is encouraging, the findings are not sufficient to alter any current recommendation on the use of fluoroquinolones in pediatric patients.[18] Encouragingly, 1 large long-term, unblinded safety study of levofloxacin treatment in pediatric patients (N = 2233) has reported no clinically detectable changes in the cartilage of weight-bearing joints compared with comparator antibiotics.[48] Additionally, the MOXIPEDIA (Moxifloxacin in Pediatric Subjects With Complicated Intra-abdominal Infection) study, a double-blind, randomized, prospective study enrolling 451 pediatric patients with cIAIs receiving moxifloxacin or comparator treatment, demonstrated similar rates of musculoskeletal adverse events between treatment arms and found no cases of QTc interval prolongation–related morbidity or mortality.[35]

In conclusion, this study demonstrates that moxifloxacin is well tolerated when administered as an age- and weight-adjusted single dose by intravenous infusion over 60 minutes to children aged between 3 months and 14 years. PK parameters were within or close to the predefined ranges for antimicrobial efficacy and safety seen in adults given the standard therapeutic dose of moxifloxacin 400 mg once daily. The use of PK modeling combined with a stepwise dose escalation scheme allowed appropriate doses to be selected for each age group and informed dose selection for subsequent clinical studies. The limited clinical data provided by the present study, however, do not allow proper assessment of the benefit-risk ratio of moxifloxacin treatment in children. The MOXIPEDIA phase 3 randomized, controlled trial of moxifloxacin in children with cIAIs,[34,35] provided more high-quality evidence of the efficacy and safety of this drug.

Acknowledgments

The authors acknowledge all investigators who participated in this study at each clinical site. The authors thank Christa Rotolo, Bayer Healthcare Pharmaceuticals, Whippany, New Jersey, for coordinating and supporting the study; and Ulrike Grossmann, Bayer, Berlin, Germany for her critical review of the data set of this paper. Highfield Communication, Oxford, UK, sponsored by Bayer, Berlin, Germany, provided editorial support in the preparation of this manuscript.

The authors participated in respective phases of the study, including the preparation of the protocol of the study, obtaining the data from pediatric patients, and interpretation of the data. All authors take full responsibility for the data included in this paper. All authors had access to the study data set. All authors participated in writing of the paper, reviewed and approved the final version, and agreed with submission to this journal for publication.

Funding

This study was sponsored and funded by Bayer HealthCare AG, Leverkusen, Germany.

Data Sharing Statement

The data sets generated and/or analyzed during and following the current study can be requested by qualified researchers from the corresponding author on reasonable request via https://www.clinicalstudydatarequest.com, which is in agreement with Bayer's data-sharing policy.

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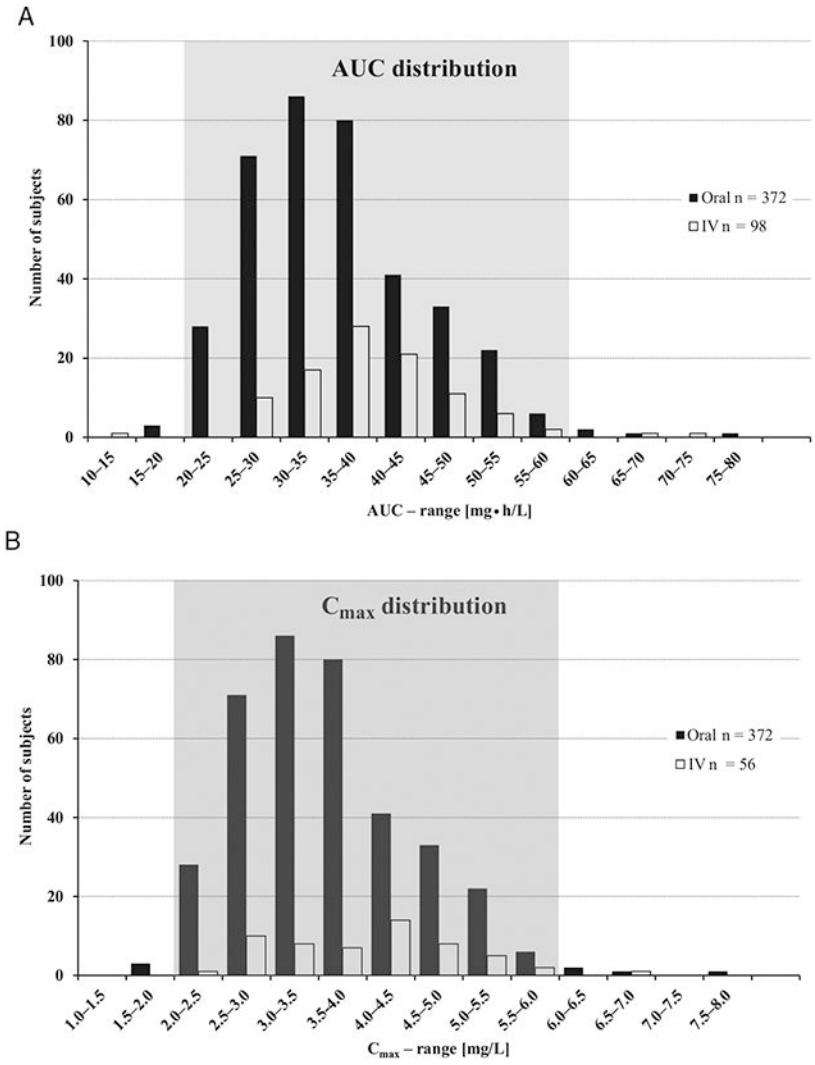

Figure 1.

Distribution of $AUC_{0\text{-}24}$ (A)and C_{max} (B) derived from evaluation of pooled phase 1 study data in adults used to define the target exposure ranges for clinical efficacy based on PK/PD considerations. (Part of the data were reproduced with permission of Springer as published by Stass and Dalhoff.[29]) $AUC_{0\text{-}24}$, area under the curve from 0 to 24 hours at steady state; C_{max}, maximum drug concentration in plasma; IV, intravenous.

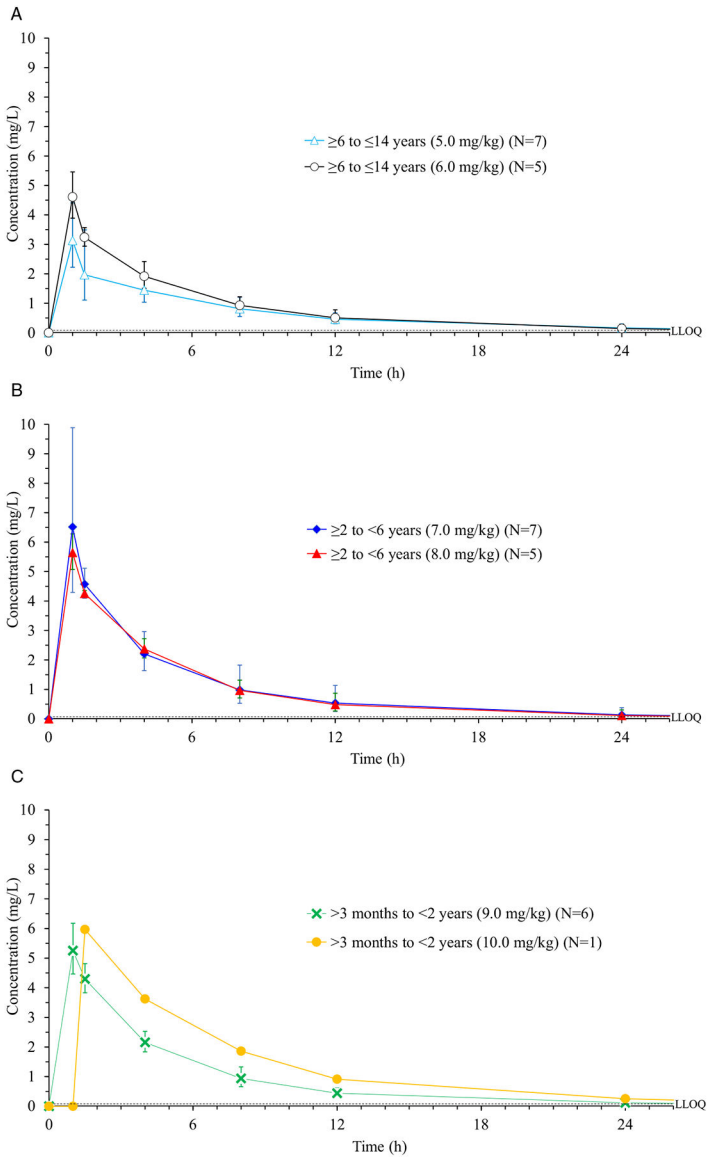

Figure 2.

(A) Time course of moxifloxacin concentration in plasma following the administration of a single intravenous dose in Cohort 1. Data obtained with 5 mg/kg and 6 mg/kg doses are shown separately. (B) Time course of moxifloxacin concentration in plasma following the administration of a single intravenous dose in Cohort 2. Data obtained with 7-mg/kg and 8-mg/kg doses are shown separately. (C) Time course of moxifloxacin concentration in plasma following the administration of a single intravenous dose in Cohort 3. Data obtained with 9-mg/kg and 10-mg/kg doses are shown separately. LLOQ, lower limit of quantification.

Note: Geometric mean (geometric standard deviation) are shown.

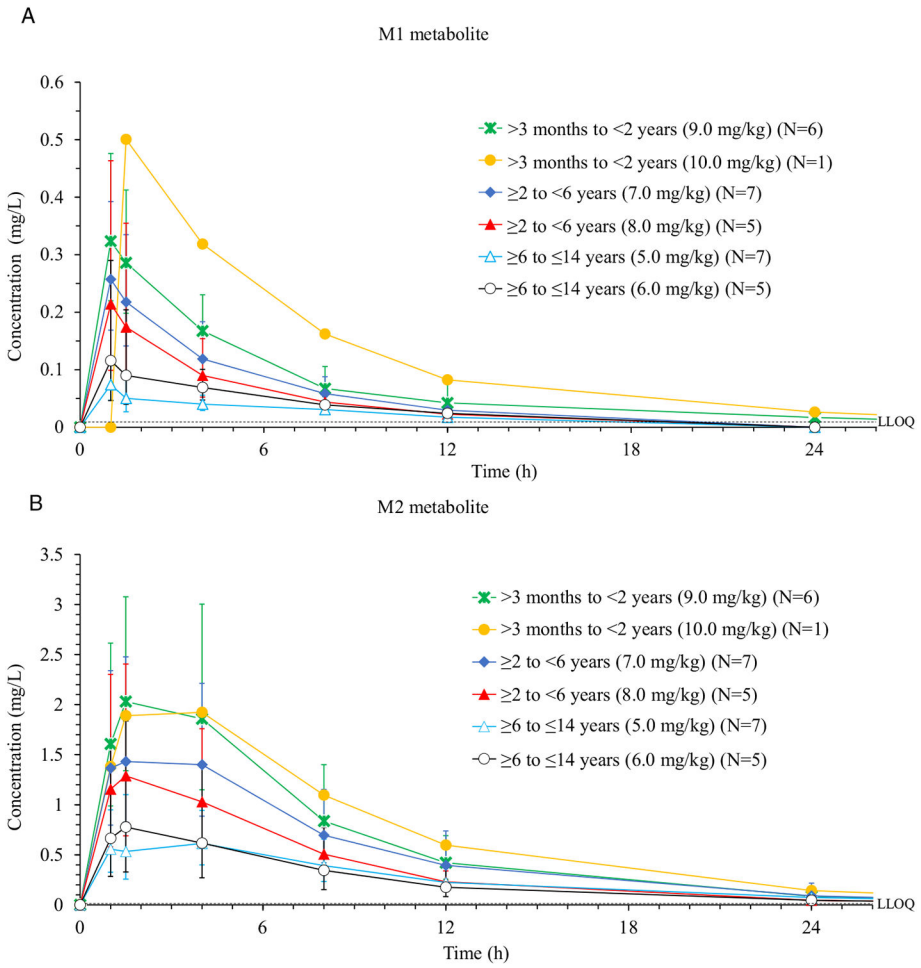

Figure 3.

(A) Time course of metabolite M1 concentration in plasma following the administration of a single intravenous dose of moxifloxacin in 3 age groups. Data obtained with 5 mg/kg and 6 mg/kg doses in Cohort 1, 7 mg/kg and 8 mg/kg in Cohort 2, and 9 mg/kg and 10 mg/kg in Cohort 3 are shown separately. (B) Time course of metabolite M2 concentration in plasma following the administration of a single intravenous dose of moxifloxacin in 3 age groups. Data obtained with 5 mg/kg and 6 mg/kg doses in Cohort 1, 7 mg/kg and 8 mg/kg in Cohort 2, and 9 mg/kg and 10 mg/kg in Cohort 3 are shown separately. LLOQ, lower limit of quantification.

Note: Geometric mean (geometric standard deviation) are shown.

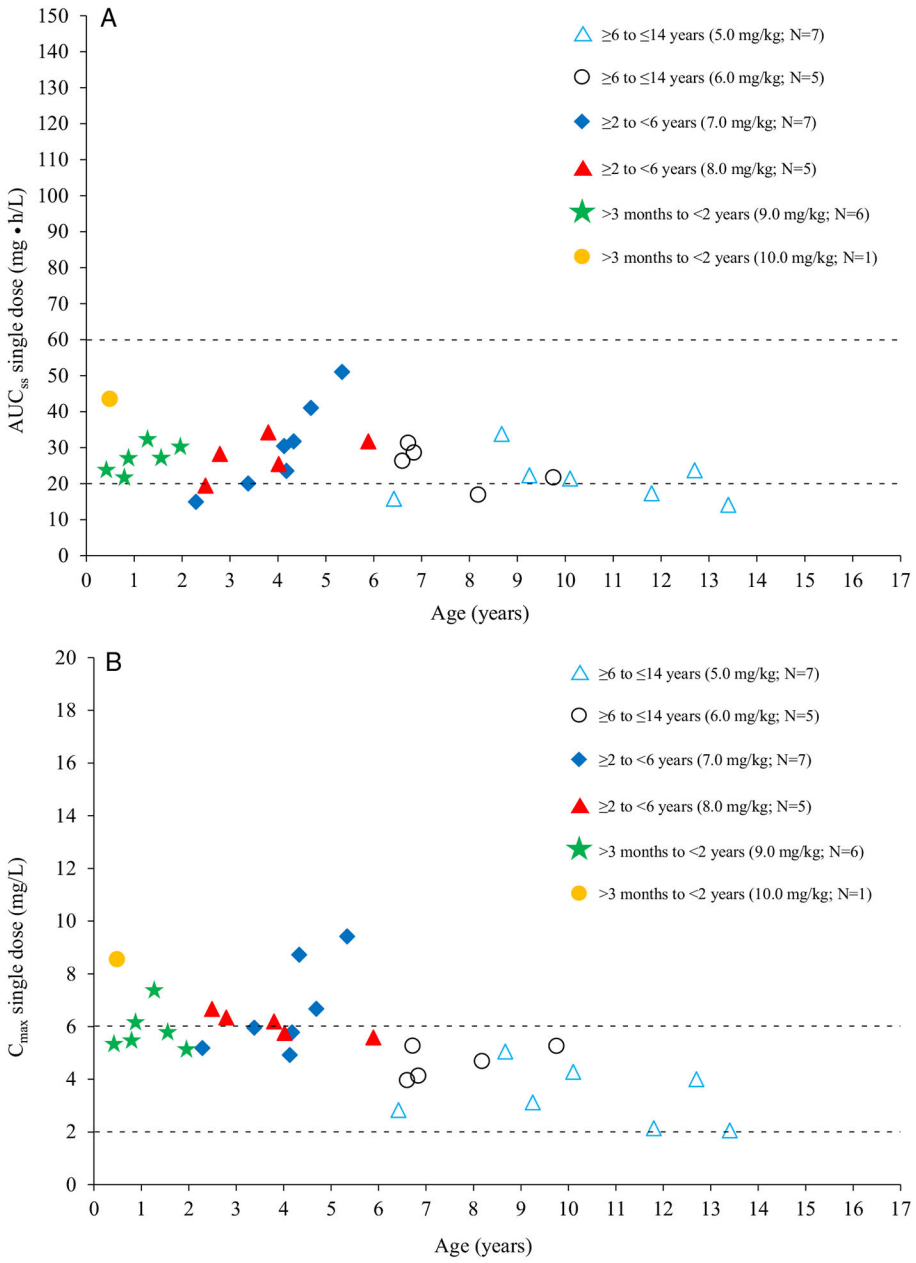

Figure 4.

(A) Predicted AUC at steady state based upon single-dose intravenous administration of moxifloxacin vs age based on final population pharmacokinetic model. Dashed lines: limits of the AUC target range (shown in Figure 1). (B) Predicted C_{max} at steady state based upon single-dose intravenous administration of moxifloxacin vs age based on final population PK model. Dashed lines: limits of the C_{max} target range (shown in Figure 1). AUC, area under the concentration curve; C_{max}, maximum drug concentration in plasma.

Table 1.

Demographic Characteristics of All Patients Who Received a Single Dose of Moxifloxacin

Variable	Cohort 1 ≥6 to ≤14 years (N = 12)	Cohort 2 ≥2 to <6 years (N = 12)	Cohort 3 >3 months to <2 years (N = 7)	Overall (N = 31)
Sex, n (%)				
Male	9 (75)	9 (75)	6 (86)	24 (77)
Female	3 (25)	3 (25)	1 (14)	7 (23)
Race, n (%)				
White	8 (67)	11 (92)	2 (29)	21 (68)
Black	3 (25)		2 (29)	5 (16)
Asian			1 (14)	1 (3)
Hispanic	1 (8)	1 (8)	1 (14)	3 (10)
Uncodable			1 (14)	1 (3)
Age (years)				
Mean (SD)	9.2 (±2.4)	3.9 (±1.1)	1.1 (±0.6)	5.3 (±3.7)
Median (range)	9.0 (6.4-13.4)	4.1 (2.3-5.9)	0.9 (0.4-2.0)	4.3 (0.4-13.4)
Weight (kg)				
Mean (SD)	29.8 (±7.6)	17.1 (±4.5)	10.5 (±2.5)	20.5 (±9.6)
Median (range)	28.7 (19.1-43.4)	16.5 (12.0-25.0)	10.9 (6.6-13.8)	19.1 (6.6-43.4)
Height (cm)				
Mean (SD)	128.5 (±14.2)	101.3 (±7.1)	76.4 (±8.0)	106.2 (±22.8)
Median (range)	130.0 (106.0-150.0)	100.0 (90.5-117.0)	73.0 (68.0-86.5)	104.0 (68.0-150.0)
BMI (kg/m^2)				
Mean (SD)	17.8 (±2.1)	16.5 (±3.0)	17.8 (±2.4)	17.3 (±2.5)
Median (range)	17.4 (14.6-22.3)	15.5 (13.0-23.1)	18.4 (14.3-21.2)	16.9 (13.0-23.1)
Underlying infection types, n (%)				
Respiratory tract	3 (25)	4 (33.3)	1 (14.3)	8 (25.8)
Intra-abdominal	4 (33.3)	1 (8.3)	0	5 (16.1)
Urinary tract	1 (8.3)	0	1 (14.3)	2 (6.5)
Abscess of various locations	3 (25)	0	0	3 (9.7)
Otitis media	0	0	2 (28.6)	2 (6.5)

Variable	Cohort 1 ≥6 to ≤14 years (N = 12)	Cohort 2 ≥2 to <6 years (N = 12)	Cohort 3 >3 months to <2 years (N = 7)	Overall (N = 31)
Infection type not available	0	4 (33.3)	1 (14.3)	5 (16.1)
Various infections	1 (8.3)	3 (25)	2 (28.6)	6 (19.4)

BMI, body mass index; SD, standard deviation.

Table 2.

Noncompartmental Pharmacokinetic Parameters of Moxifloxacin Following Administration of a Single Intravenous Dose in 3 Pediatric Age Groups (Geometric Mean/Geometric CV)[a]

	Cohort 1 ≥6 to ≤14 years (N = 12)		Cohort 2 ≥2 to <6 years (N = 12)		Cohort 3 >3 months to <2 years (N = 7)	
Variable	**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)**
AUC (mg • h/L)	19.73/30.53	24.04/24.11	28.21/42.75	27.18/19.29	25.52/17.26	40.51/–
C_{max} (mg/L)	3.16/33.33	4.61/17.10	6.51/43.54	5.64/10.71	5.31/14.67	5.96/–
$t_{1/2}$ (h)	7.89/34.32	6.16/23.99	5.66/18.79	6.03/24.78	6.82/35.10	5.94/–
CL (L/h)	8.11/40.08	6.24/32.37	4.36/26.19	4.51/21.75	3.68/27.10	2.20/–
CL (L/h/kg)[b]	0.25/30.53	0.25/24.16	0.25/42.78	0.30/19.71	0.35/17.28	0.25/–
V_{ss} (L)	73.86/49.67	45.00/10.55	26.80/20.30	28.46/26.61	23.45/31.35	16.74/–
V_{ss} (L/kg)[b]	2.31/35.51	1.80/12.49	1.52/21.52	1.86/9.62	2.25/16.84	1.88/–
AE_{ur} (%)	14.75/34.47	16.97/26.69	22.58/55.26	17.89/34.90	–	–

AE_{ur}, amount of drug excreted via urine in the first 36 hours; AUC, area under the curve; CL, clearance; C_{max}, maximum drug concentration in plasma after single-dose administration; CV, geometric coefficient of variation; $t_{1/2}$, half-life; Vss, volume of distribution at steady state.

[a]Data obtained with 5 mg/kg and 6 mg/kg doses in Cohort 1, 7 mg/kg and 8 mg/kg in Cohort 2, and 9 mg/kg and 10 mg/kg in Cohort 3 are shown separately.

[b]Values are normalized to body weight.

Table 3.

Noncompartmental Pharmacokinetic Parameters of M1 and M2 Metabolites of Moxifloxacin in Cohorts 1, 2, and 3 (Geometric Mean/Geometric CV)[a]

	Cohort 1 ≥6 to ≤14 years (N = 12)		Cohort 2 ≥2 to <6 years (N = 12)		Cohort 3 >3 months to <2years (N = 7)	
Variable	**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)**
M1 (BAY 31-8061)						
AUC (mg • h/L)	0.57/67.66	0.99/47.59	1.45/35.37	1.11/54.27	2.02/56.78	3.62/–
C_{max} (mg/L)	0.08/43.52	0.12/115.0	0.26/44.12	0.21/90.21	0.32/40.05	0.50/–
$t_{1/2}$ (h)	6.18/80.62	6.72/43.26	4.71/47.04	4.74/41.41	7.04/106.7	6.55/–
AE_{ur} (%)	1.98/83.79	1.81/142.1	3.85/53.41	4.88/48.84	–	–
M2 (BAY 58-8178)						
AUC (mg • h/L)	7.60/43.51	7.00/88.27	15.05/41.66	10.52/47.20	17.59/47.61	20.52/–
C_{max} (mg/L)	0.67/41.21	0.81/98.07	1.59/53.26	1.32/74.63	2.09/48.26	1.92/–
$t_{1/2}$ (h)	7.02/22.14	5.79/25.16	5.26/21.61	5.17/22.22	5.93/32.83	5.70/–
AE_{ur} (%)	12.78/62.22	9.19/90.17	16.03/18.47	14.31/17.43	–	–

AE_{ur}, amount of drug excreted via urine in the first 36 hours; AUC, area under the curve; C_{max}, maximum drug concentration in plasma after single-dose administration; CV, coefficient of variation; $t_{1/2}$, half life.

[a]Data obtained with 5 mg/kg and 6 mg/kg doses in Cohort 1, 7 mg/kg and 8 mg/kg in Cohort 2, and 9 mg/kg and 10 mg/kg in Cohort 3 are shown separately.

Table 4.

Descriptive Statistics and Change From Baseline at T_{max} for QT Corrected According to Bazett's Formula and Fridericia's Formulae

	Cohort 1 ≥6 to ≤14 years			Cohort 2 ≥2 to <6 years			Cohort 3 >3 months to <2 years		
	Baseline	T_{max} MXF, T_{max} M1[a]	T_{max} M2	Baseline	T_{max} MXF, T_{max} M1[a]	T_{max} M2	Baseline	T_{max} MXF, T_{max} M1[a]	T_{max} M2
QTc variable (msec) – Bazett's formula									
n	11	12	12	11	12	12	5	6	7
Mean (SD)	413.7 (11.4)	429.4 (18.1)	426.2 (19.8)	416.0 (27.4)	422.5 (26.7)	420.3 (25.4)	387.9 (29.7)	407.4 (20.0)	399.1 (18.7)
Median	410.5	424.6	417.9	411.6	419.8	415	384.3		
Min, max	401, 438	407, 473	406, 474	385, 479	396, 490	392, 488	356, 425	386, 440	379, 437
Change from baseline									
n		11	11		11	11		4	5
Mean (SD)		14.6 (14.5)	11.9 (21.4)		8.3 (25.3)	4.5 (23.7)		15.6 (17.7)	5.3 (23.3)
Median		17.2	7.1		10.5	4.7		20.4	15.4
Min, max		−8,35	−23,63		−49, 42	−51, 40		−8, 30	−30, 30
QTc variable (msec) – Fridericia's formula									
n	11	12	12	11	12	12	5	6	7
Mean (SD)	386.7 (17.4)	396.8 (20.1)	397.9 (24.2)	369.2 (22.8)	372.6	374.4	341.5 (24.5)	353.0 (17.0)	348.4 (16.1)
Median	390.8	398.2	395.7	364.3	366.9	369.9	384.3		
Min, max	356, 413	360, 435	363, 454	336, 416	344, 442	344, 450	319, 375	329, 378	330, 377
Change from baseline									
n		11	11		11	11		4	5
Mean (SD)		9.6 (14.6)	10.8 (21.7)		5.5 (16.9)	6.9 (17.6)		8.0 (19.1)	2.1 (28.9)
Median		8.0	7.3		6.9	7.5		8.0	3.6
Min, max		−18, 31	−22, 62		−35, 26	−35, 34		−15, 32	−45, 32

MXF, moxifloxacin; SD, standard deviation; T_{max}, time to maximum concentration.

[a]Values of QTc variables for T_{max} MXF and T_{max} M1 were identical and are shown as a single column.