



## Pharmacokinetics and penetration of moxifloxacin into infected diabetic foot tissue in a large diabetic patient cohort

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Title:

**Pharmacokinetics and penetration of moxifloxacin into infected diabetic foot tissue in a large diabetic patient cohort**

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43

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45 and skin structure infection

46

## Abstract

### Objectives:

Physiological changes occurring in patients with diabetes may affect pharmacokinetics and penetration of antimicrobial agents into peripheral tissue. We examined the pharmacokinetics and the penetration of moxifloxacin into perinecrotic tissue of diabetic foot lesions in patients with diabetic foot infections (DFI).

### Patients and methods:

Adult patients suffering from type 2 diabetes mellitus and hospitalized for DFI (Texas classification of at least B2) were treated with 400 mg moxifloxacin intravenously (IV) or orally (PO) once daily. Pharmacokinetics of moxifloxacin and its concentration 3 hours after administration in samples of perinecrotic tissue resected from infected diabetic foot wounds were determined at steady state (day 4 to 8).

### Results:

A total of 53 patients with diabetes mellitus type 2 (mean age of  $69.4 \pm 10.8$  years) were included in the study, of whom 28 received PO and 25 IV moxifloxacin therapy for a median of 8 days. In the PO and IV subgroups mean  $C_{\max}$  in plasma was 2.69 mg/L and 4.77 mg/L at a median of 2.0 h ( $T_{\max}$  range of 1.0-8.0 h) and 1h after administration, respectively. An  $AUC_{0-24h}$  with a mean of 29.36 mg/L (PO) and 27.09 mg·h/L (IV) was achieved. Mean moxifloxacin concentrations in perinecrotic tissue of infected diabetic foot wounds following PO or IV administration were  $1.79 \pm 0.82$  µg/g and  $2.20 \pm 1.54$  µg/g, thus exceeding the  $MIC_{90}$  for *Staphylococcus aureus* (0.25 mg/L) 7-fold and 8.5-fold and the  $MIC_{90}$  for *E. coli* (0.06 mg/L) 29-fold and 36-fold, respectively. The mean tissue-to-plasma ratios of moxifloxacin concentration 3 h after administration were  $1.01 \pm 0.57$  (PO) and  $1.09 \pm 0.69$  (IV), respectively. Significant differences between the routes of administration were observed

for  $T_{\max}$  and  $C_{\max}$ , ( $p < 0.01$ ), but not for other clinically relevant parameters ( $AUC_{0-24}$ ,  
moxifloxacin DFI tissue concentration).

Conclusions:

The plasma concentration time curve of moxifloxacin in diabetic patients is similar to that of  
healthy volunteers. We also observed a good penetration of moxifloxacin into inflamed DFI  
tissue, which taken together with the possibility of sequential therapy IV / PO designate  
moxifloxacin 400 mg once daily as a therapeutic option in the treatment of DFI caused by  
susceptible organisms.

85

86 Foot complications are among the most common sequelae of diabetes mellitus and the most  
87 important cause for hospitalization of diabetic patients [1]. Up to one in five patients with  
88 diabetes will develop a foot ulcer during the course of disease and about 60% of these will be  
89 clinically infected [2]. Diabetic foot infections (DFI) may lead to amputation of the involved  
90 limb and are actually responsible for 85% of diabetes-related lower-extremity amputations.

91

92 Though DFI are a complex problem and require multidisciplinary management [1], a prompt  
93 and appropriate antibacterial therapy plays a key role and may contribute to the prevention of  
94 amputations [1-3]. Complicated skin and skin structure infections (cSSSIs), including diabetic  
95 foot infections, are often polymicrobial, requiring broad-spectrum combination therapy.

96

97 For an effective therapy, the antimicrobial agent has to reach an adequate concentration in the  
98 involved peripheral tissue [1, 4, 5]. However, this goal may not be reached in this patient  
99 population and for this site of infection. Physiological changes resulting from the underlying  
100 diabetic conditions such as acidotic metabolic status, reduced blood flow and altered  
101 microenvironment may interfere with the distribution of antibiotics in plasma and tissue.  
102 Local inflammatory processes and fibrotic boundaries in the diabetic foot can additionally  
103 impair tissue penetration at the site of infection [4, 5].

104

105 As the fluoroquinolone moxifloxacin is a broad-spectrum antibiotic with high *in vitro* activity  
106 against gram-positive and gram-negative aerobes and anaerobes including the pathogens  
107 commonly found in DFI [6], it may be potentially useful for initial empirical therapy.  
108 Moxifloxacin's once daily dose regimen with the possibility of sequential IV/PO therapy  
109 offers an advantage to the other current antibiotic regimens used in the treatment of DFI.  
110 Sequential therapy of moxifloxacin is approved for the treatment of adults with complicated

skin and skin-structure infections (cSSSIs), including DFI, though its efficacy in osteomyelitis has not been investigated yet.

An earlier pharmacokinetic study in five diabetic patients with peripheral arterial occlusive disease and soft tissue infections has shown that after a single 400-mg dose of moxifloxacin, effective concentrations are attained in the interstitia of healthy and inflamed subcutaneous adipose tissue of the thigh and in plasma [7].

The present study was set up to investigate the penetration of moxifloxacin into perinecrotic tissue of infected diabetic foot lesions in a large patient cohort and to evaluate its pharmacokinetic profile in a pharmacological risk population of diabetic patients.

## **Patients and methods**

The study population of this prospective, open, multicenter study consisted of male and female patients with type 2 diabetes mellitus hospitalized for DFI graded with a Wagner score of 2 or 3 (equivalent to Texas Diabetic Wound classification of at least B2) and requiring antibacterial therapy.

The following main exclusion criteria were applied: Patients below 18 years of age, with hypersensitivity against quinolones, severe liver dysfunction (Child Pugh class C), heart failure with reduced left ventricular ejection fraction (NYHA III-IV), arrhythmia requiring medical treatment, signs of severe arterial occlusive disease of the lower limbs (Fontaine stages III-IV) or chronic renal insufficiency requiring dialysis.

Written informed consent was obtained from all patients, and the study protocol was approved by the responsible Ethics Committees.

137

138 All patients were monitored for adverse events.

139

#### 140 **Sampling and analytical method**

141 Between days 4 and 8 after start of moxifloxacin treatment the plasma levels were determined  
142 (steady-state). The venous blood samples were taken immediately before (baseline) and at 1,  
143 2, 3, 4, 6, 8, 10, 12, and 24 hours after start of 1h-infusion of 400 mg moxifloxacin (following  
144 once daily IV administration) or after once daily administration of moxifloxacin 400 mg PO.  
145 Blood samples (2.7 mL) were collected in EDTA containing tubes and immediately  
146 centrifuged at 4°C and 2,000 x g for 5 min. Then, plasma was separated, snap frozen at -20°C  
147 and stored at -80°C until analysis.

148 The concentration of moxifloxacin was determined by means of high performance liquid  
149 chromatography (HPLC).

150 Plasma aliquots of 100 µl were spiked with 10 of aqueous ofloxacin (final concentration 200  
151 µg/L) as internal standard and, in case of the calibrators, appropriate concentrations (100 –  
152 1600 µg/L) of moxifloxacin. Then, 20 µl of 50% TFA was added, the mixture was vortexed  
153 and centrifuged at 6000xg for 4 min. Of the supernatant 80 µl was added to 21 µl of 5.0 M  
154 NH<sub>4</sub>OAc, and 20 µl of the mixture subjected to HPLC/fluorescence analysis. The  
155 chromatographic system consisted of a guarded YMC Pro C<sub>18</sub> 120/5 column, 150 x 2 mm i.d.  
156 maintained at 20°C, and a gradient mobile phase comprising of components A (MeOH/1.0 M  
157 NH<sub>4</sub>OAc/H<sub>2</sub>O 10:5:85 v/v/v) and B (40:5:55) pumped at a rate of 250 µl/min, with 22%  
158 initial B changed to stages of 25%, and 32% after 1 and 2 min, respectively. Detection was  
159 performed by the emission at 504 nm at an excitation wavelength of 296 nm. The retention  
160 times were 4.5 and 12.5 min for ofloxacin and moxifloxacin, respectively. The assay was  
161 validated intra- and inter-daily according to standard procedures with precisions (CV) and  
162 accuracies (RE) better than ± 15%; the lower limit of quantification (LLOQ) was calculated



50 µg/L allowing for a deviation of CV and RE < ±20%. Recoveries ranged between 85 and 90% based on spiking solution.

Specimens of at least 100 mg of perinecrotic wound tissue of infected diabetic foot lesions were collected during second wound debridement between days 4 and 8 of antimicrobial treatment and approximately three hours after administration of moxifloxacin. The tissue samples were gently blotted with absorbent paper to remove excrescent blood, snap frozen in liquid nitrogen and stored at -80°C until analysis. Moxifloxacin concentration was determined in the homogenized tissue samples by high-performance liquid chromatography with fluorescence detection as described in detail previously [8].

#### **Pharmacokinetic calculations and statistics**

Pharmacokinetic parameters were calculated by noncompartmental analysis with Kinetika 4.4 software (Thermo Scientific, Dreieich, Germany). The maximum observed plasma concentrations ( $C_{\max}$ ) and time to reach  $C_{\max}$  ( $T_{\max}$ ) after moxifloxacin administration were determined from the concentration-time curves. The area under the plasma concentration-time curve from time 0 until the last quantifiable plasma concentration ( $AUC_{0-24h}$ ) was calculated by using the linear trapezoidal rule. DFI tissue/plasma ratio was estimated using corresponding concentration of moxifloxacin in plasma (three hours after administration of moxifloxacin).

All data were analyzed descriptively. Calculations were performed using the SPSS software release 15.0 (SPSS GmbH, Munich, Germany). For all variables, arithmetic mean values, standard deviations, ranges and the 95% confidence intervals (CI 95%) were calculated, with the exception of  $T_{\max}$ , for which only median and minimum-maximum ranges are given.

Relationships were evaluated using nonparametric Spearman-Rho correlation coefficient.

A two-sided *P* value of <0.05 was considered the level of significance.

## Results

Fifty three patients with DFI were enrolled into the study at nine centres in Germany. At study entry, the patients had a mean age of  $69.4 \pm 10.8$  years, a mean body weight of  $82.9 \pm 17.9$  kg and a mean body mass index (BMI) of  $28.2 \pm 4.5$  kg/m<sup>2</sup>. Mean C-reactive protein (CRP) was  $76.9 \pm 80.4$  mg/L, mean leukocyte count was  $11.0 \pm 3.5$  Gpt/L and average serum creatinine was  $121.6 \pm 97.5$  µmol/L.

Moxifloxacin 400 mg once daily was administered PO to 28 patients and IV to 25 patients for a median of 8 days (range: 4-19). Patients' assignment to IV or PO administration of moxifloxacin followed clinical considerations. As shown in Table 1, both cohorts were similar in their demographic characteristics and laboratory variables at baseline.

In one patient of the IV cohort the amount of tissue collected was too small to measure tissue concentration.

Study drug treatment was well tolerated. No serious adverse events were observed and none of the patients had to be excluded due to adverse events.

The most frequent treatment-emergent adverse event was diarrhea, occurring in 6 patients (10.5%).

The reduction of body temperature by 2.8 degrees C ( $p < 0.01$ ) and C-reactive protein by 1.4 mg/L ( $p > 0.05$ ) at the end of the therapy can indicate an antiinfective effect of moxifloxacin.

Steady-state concentrations of moxifloxacin in plasma (median for both cohorts: day 6) are shown in Figures 1 and 2 and summed-up in Table 2. Significant differences between the routes of administration (IV vs PO) were only observed for  $C_{\max}$  and  $T_{\max}$  in plasma ( $p < 0.01$ ), but not for other relevant pharmacokinetic parameters.

215

216 Mean moxifloxacin concentrations at steady state (median for both cohorts: day 6) in  
217 perinecrotic tissue of infected diabetic foot wounds are shown in Table 3. The mean tissue  
218 concentrations for PO or IV administration did not differ significantly ( $p>0.05$ ). The  
219 concentrations of moxifloxacin achieved in DFI tissue correlated more strongly with the  
220  $AUC_{0-24}$  ( $r=0.659$ ;  $p<0.01$ ) than with the corresponding (3h) plasma values ( $r=0.492$ ,  $p<0.01$ ).

221

222 Mean tissue concentration of moxifloxacin exceeded the *in vitro*  $MIC_{90}$  for *Staphylococcus*  
223 *aureus* (0.25 mg/L) [6, 9, 10] 7-fold and 8-fold and the  $MIC_{90}$  for *E. coli* (0.06 mg/L) [6] 29-  
224 fold and 36-fold, respectively.

225

226 Based on these *in vitro*  $MIC_{90}$  for *Staphylococcus aureus* and *E. coli* fluoroquinolone-relevant  
227 PK/PD-parameters of moxifloxacin were calculated (see Table 4). Taking into account the  
228 predictive PK/PD parameters for moxifloxacin a therapeutic success can be expected in both  
229 administration routes.

230

## 231 Discussion

232 For diabetic foot infection as well as for necrotizing fasciitis the lowest clinical cure rates of  
233 skin and skin-structure infections are reported [11]. Of the fluoroquinolones licensed,  
234 moxifloxacin is the only one demonstrating activity against anaerobe pathogens. This activity,  
235 along with its rapid bactericidal effect and its high *in vitro* activity against gram-positive and  
236 gram-negative bacteria, make moxifloxacin especially attractive as a potential single-drug  
237 regimen for initial antibacterial therapy of mostly polymicrobial DFI, except for methicillin-  
238 resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* [9].

239 Similar to other fluoroquinolones, moxifloxacin penetrates well into peripheral compartments  
240 and achieves high concentrations in many tissues, including skin and soft tissue [2, 15].

However, the present study is the first to investigate moxifloxacin penetration into perinecrotic tissue (i.e. the transition zone between healthy and necrotic tissue) of patients with an inflamed DFI.

To the best of our knowledge, it is also the largest pharmacokinetic study of antibiotic penetration into tissue of infected diabetic feet.

We observed significant differences between the routes of administration (IV vs PO) only for  $C_{\max}$  and  $T_{\max}$ , but not for  $AUC_{0-24h}$ . In general, the plasma pharmacokinetics of moxifloxacin including total exposition were similar to those in healthy volunteers and patients after multiple doses, with the exception of  $T_{\max}$  which was higher and more variable in our patient population [13]. Physiological changes occurring in patients with diabetes, e.g. diabetic gastroenteropathy with delayed gastric emptying and intestinal transit times or diabetic nephropathy can be a reason for the extended time to reach  $C_{\max}$  ( $T_{\max}$ ) in our study [4, 5, 12]. High variability of pharmacokinetic parameters in patients with diabetes was also seen in further studies with other antibiotics, e.g. linezolid or daptomycin [5, 12].

It is recognized that effective concentrations of antibiotics must be achieved in tissues for successful clinical outcomes of antimicrobial therapy. The fast decline of the plasma concentrations after the end of infusion in our study indicates a rapid distribution of moxifloxacin,  $V_{ss}$  was very high in agreement with previous reports [7, 13]. Plasma protein binding, which as long been considered one of the important physicochemical characteristics of antibacterials has been shown to substantially affect tissue penetration and the volume of distribution of antimicrobial agents. Independent of the drug concentration, only 40–42% of moxifloxacin is bound to plasma proteins, mainly to serum albumin, leaving most of the drug in an unbound, active form [15]. Many factors other than plasma protein binding play a role in extravascular transfer and tissue distribution of drugs, such as lipid solubility, size of the

molecule and its degree of ionization. A low molecular weight (437), a zwitterionic nature and a low protein binding of moxifloxacin may be a reasons for its high tissue penetration. Host-related factors such as site of infection, presence of biological barriers, local pH and bacterial inoculum size may contribute to the inhibition of antibacterial diffusion and antibacterial activities [20]. In diabetic patients conditions such as acidotic metabolic status, reduced blood flow, altered microenvironment, local inflammatory processes and fibrotic boundaries can impair penetration of antimicrobial agents in the diabetic foot tissue [4, 5].

The mean inflamed DFI tissue to plasma concentration ratio in the present study was about 100% for both PO and IV administration. The measured concentrations were lower than those in other tissues, e.g. gastrointestinal or bronchial tissue [17, 18]. This difference might be explained by a lower perfusion in DFI tissue due to impaired macro- and/or microcirculation. Another reason could be the perinecrotic nature of the resected DFI tissue. Our results confirm previous data of an in vivo microdialysis study, in which an enrichment of moxifloxacin was found in well-perfused inflamed subcutaneous tissue compared to plasma [7]. In the same study diabetes mellitus patients with peripheral arterial occlusive disease were investigated. In this patient population, the tissue to plasma ratio was 0.5 underlining the implication of circulatory disturbances.

The data of the presented study can be analyzed using various pharmacodynamic and pharmacokinetic indices, which are applied to predict clinical outcome. Pharmacokinetic (PK)/pharmacodynamic (PD) considerations are important in optimizing both antibacterial activity and the development of resistance. Optimal PK/PD indices have been described in plasma for the antimicrobial efficacy of moxifloxacin (area under the concentration-time curve over 24 h at steady state divided by the MIC (AUC) >30 [h] as the PK/PD surrogate parameter, which is predictive for a positive clinical outcome) [14]. Assuming that the

PK/PD concept is valid for DFI, the indices calculated from these study data (mean AUC of 108.4-117.4 for *Staphylococcus aureus*) account for a high efficacy.

The present study might be limited by the fact that tissue concentration was measured at one single time point (3 h after administration), what certainly must not correspond to the  $T_{max}$ , so that higher concentrations of moxifloxacin in DFI tissue during a whole dosage interval are possible.

Another limitation might be that moxifloxacin concentration was determined in homogenized tissue samples which do not allow to separate between different compartments. In biopsy samples, the drug is extracted from homogenized tissue comprising cells, extracellular matrix and extracellular space fluid. For drugs that accumulate intracellularly (e.g. fluoroquinolones), the biopsy method can overestimate effective drug concentrations in the interstitial space fluid, which represents the anatomical site for most bacterial infections. Moxifloxacin penetrates phagocytic and nonphagocytic cells (polymorphonuclear leukocytes and epithelial cells), reaching intracellular concentrations several times higher than extracellular ones. The intracellular penetration of moxifloxacin seem to be rapid, reversible, and affected by environmental temperature, pH and metabolic inhibitors. Moxifloxacin seem partially to require an active process, which allow easier penetration of cell membranes. Tissue inactivation of antibacterials can occur at infection sites by binding to interstitial fluid proteins, soluble intracellular proteins or subcellular structures (nucleic acids, leucocytic chromatin, cell membranes and mucopolysaccharides) [21]. The microdialysis technique, as opposed to the biopsy, determines exclusively free concentrations of antibiotics in the interstitial space fluid. This technique is based on the principle of diffusion of solutes through a semipermeable membrane due to a concentration gradient between the interstitial microenvironment and the fluids within a microdialysis probe inserted into a tissue of interest.

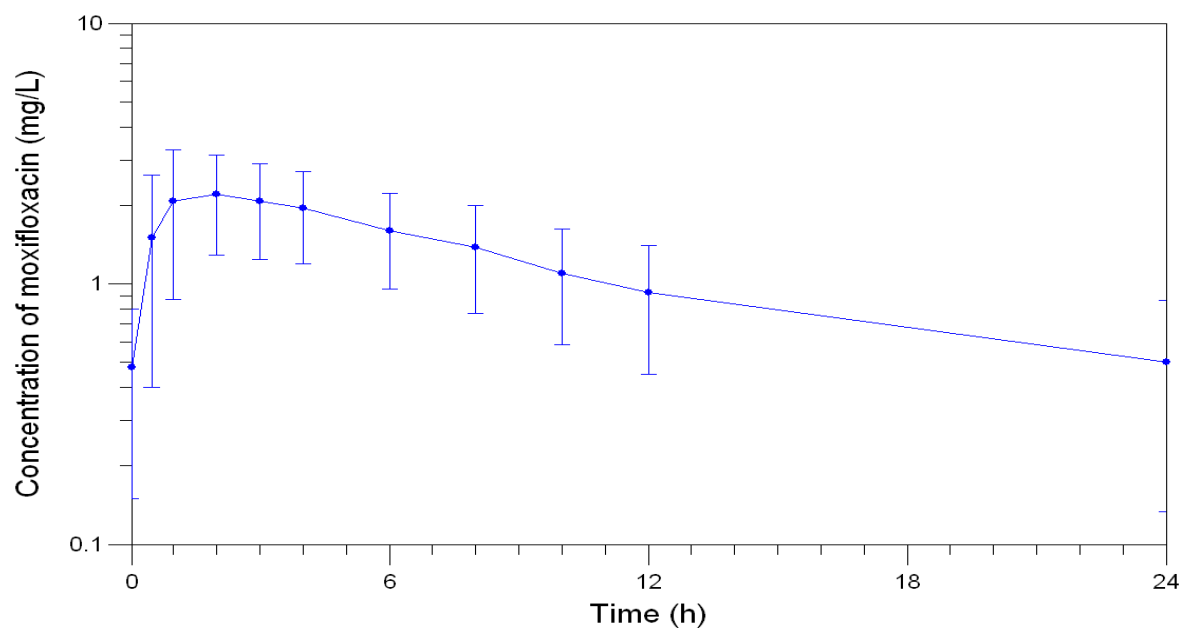
Even if the method of microdialysis has many advantages over a biopsy, the authors consider the biopsy with a lower invasivity and a higher feasibility (equipments, resources) as more suitable to conduct a study at such a large population of patients. The tissue concentrations of moxifloxacin found in the present study support the good clinical results observed with this fluoroquinolone in DFI [2, 11, 16]. In a recent prospective, randomized, multinational clinical study treatment with sequential IV/PO moxifloxacin, 400 mg once daily was clinically comparable to that with IV amoxicillin/clavulanate 1,000 mg/ 200 mg three times daily followed by PO amoxicillin/clavulanate 500 mg/125 mg three times daily for 7-21 days in hospitalized patients with cSSSIs [11]. *Staphylococcus aureus* and *Escherichia coli* were the most frequently isolated pathogens. In a subgroup analysis of 127 patients with DFI from a prospective double-blind study in patients with complicated skin and skin-structure infections, moxifloxacin was shown to be at least as effective as piperacillin-tazobactam (IV) followed by amoxicillin-clavulanate (PO) in the treatment of moderate-to-severe DFI [2]. In the RELIEF study (a prospective, randomised, double-dummy, double-blind, multinational, multicentre study), IV/PO moxifloxacin was clinically non-inferior to IV piperacillin/tazobactam 4.0/0.5 g thrice daily followed by PO amoxicillin-clavulanic acid in the treatment of patients with complicated skin and skin structure infections including those with DFI [16, 19].

## Conclusions

Adequate drug concentrations were achieved in plasma of diabetic patients and in perinecrotic areas of diabetic foot wounds following IV as well as PO administration of moxifloxacin 400 mg once daily in a large cohort of diabetic patients with foot infections.

This finding, taken together with the good clinical data, support a role for moxifloxacin in the initial therapy of patients with DFI.

345

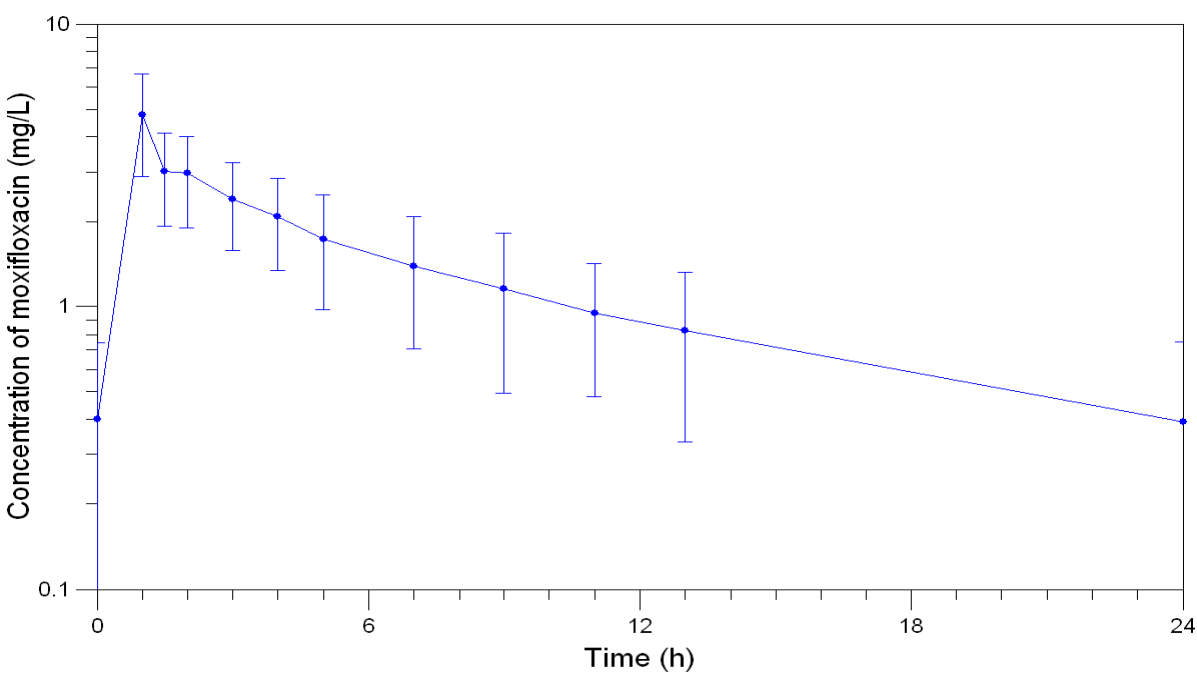


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**Figure 1.** Mean steady-state concentrations of moxifloxacin (400 mg once daily PO) in plasma of diabetic patients (n=28).

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349

350

**Figure 2.** Mean steady-state concentrations of moxifloxacin (400 mg once daily IV) in plasma of diabetic patients (n=25).

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353



354 **Table 1.** Patients' demographic and clinical characteristics at baseline (n=53)

Parameter	PO cohort (n = 28)	IV cohort (n = 25)
Age (years)	68.8 ± 9.8 (47-86)	70.0 ± 11.9 (42-93)
Male/Female ratio	2.1	1.8
Male n (%)	19 (67.9)	16 (64)
Female n (%)	9 (32.1)	9 (36)
Body weight (kg)	87.2 ± 17.4 (52-123)	77.9 ± 17.5 (51-110)
Body mass index (kg/m <sup>2</sup> )	29.5 ± 4.3 (22.9-40.6)	26.7 ± 4.3 (16.0-37.2)
CRP (mg/L)	66.9 ± 76.3 (0.2-329.0)	91.9 ± 89.3 (1.7-345.4)
Leukocyte count (Gpt/L)	10.2 ± 2.1 (7.0-14.5)	11.4 ± 4.4 (4.9-26.4)
Serum creatinine (μmol/L)	118.7 ± 47.7 (52-245)	129.1 ± 139.4 (51.0-755.0)

355 values as mean ± SD (range)

356 **Table 2.**

357 Steady-state pharmacokinetic parameters of moxifloxacin in plasma following PO or IV  
 358 administration of 400 mg once daily to diabetic patients with DFI (n=53)

Route of administration	PK parameter	Mean (SD)	95% CI	Range
PO (n=28)	C <sub>max,ss</sub> (mg/L)	2.69 (0.94)	2.4; 3.0	0.9 – 4.8
	T <sub>max,ss</sub> (h)	2.0 <sup>a</sup>	–	1.0 – 8.0
	AUC <sub>0-24h,ss</sub> (mg·h/L)	27.09 (10.86)	23.1; 31.1	10.4-52.7
	V <sub>ss</sub> (L/kg)	2.34 (0.96)	2.0; 2.7	1.2 – 4.7
	Cl <sub>tot,ss</sub> (L/h)	14.13 (7.5)	11.4; 16.9	4.0 – 35.4
IV (n=25)	C <sub>max,ss</sub> (mg/L)	4.77* (1.87)	4.0; 5.5	2.2 – 8.2
	T <sub>max,ss</sub> (h)	1.0*	–	–
	AUC <sub>0-24h,ss</sub> (mg·h/L)	29.36 (12.47)	24.3; 34.4	16.2-76.1
	V <sub>ss</sub> (L/kg)	1.81 (0.47)	1.6; 2.0	1.0 – 2.8
	Cl <sub>tot,ss</sub> (L/h)	13.38 (4.79)	11.4; 15.3	3.0 – 22.2

CI, confidence interval;  $C_{\max}$ , maximal plasma concentration;  $AUC_{0-24h}$ , area under concentration time curve from time 0 to 24 hours;  $V_{ss}$ , volume of distribution at steady state;  $Cl_{tot}$ , total clearance  
<sup>a</sup> median; \*  $p < 0.01$  vs. PO

**Table 3.**

Steady-state concentration of moxifloxacin in inflamed DFI tissue and tissue/plasma ratio 3 hours following PO (n=28) or IV(n=25) administration of 400 mg moxifloxacin.

	PO (n=28)		IV (n=25)	
	Mean (SD)	Range	Mean (SD)	Range
DFI-tissue concentration ( $\mu\text{g/g}$ )	1.79 (0.82)	0.53 – 3.5	2.2 (1.54)	0.56 – 6.4
DFI tissue/plasma ratio	1.01 (0.57)	0.36 – 2.55	1.09 (0.69)	0.26 – 2.84

**Table 4.**

Predictive PK/PD parameters of moxifloxacin following once daily PO or IV administration of 400 mg for 4 to 8 days in 53 patients with DFI

PK/PD Parameters	$MIC_{90} = 0.25 \text{ mg/L}^{6,9,10}$		$MIC_{90} = 0.06 \text{ mg/L}^6$	
	PO	IV	PO	IV
$C_{\max} / MIC_{90}$	10.8 (3.8)	19.1 (7.5)	44.8 (15.7)	79.5 (31.2)
$AUC_{0-24} / MIC_{90}$	108.4 (43.4)	117.4 (49.9)	451.5 (180.9)	489.3 (207.8)

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