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

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1 Title:

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

4

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41 Running title: Pharmacokinetics and penetration of moxifloxacin into infected diabetic foot
42 tissue

43

44 Keywords: pharmacokinetics in diabetes, tissue penetration, moxifloxacin, diabetic foot, skin
45 and skin structure infection

46

47 **Abstract**

48 Objectives:

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

53

54 Patients and methods:

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

60

61 Results:

62 A total of 53 patients with diabetes mellitus type 2 (mean age of 69.4 ± 10.8 years) were
63 included in the study, of whom 28 received PO and 25 IV moxifloxacin therapy for a median
64 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
65 a median of 2.0 h (T_{max} range of 1.0-8.0 h) and 1h after administration, respectively. An
66 AUC_{0-24h} with a mean of 29.36 mg/L (PO) and 27.09 mg·h/L (IV) was achieved. Mean
67 moxifloxacin concentrations in perinecrotic tissue of infected diabetic foot wounds following
68 PO or IV administration were $1.79 \pm 0.82 \mu\text{g/g}$ and $2.20 \pm 1.54 \mu\text{g/g}$, thus exceeding the
69 MIC_{90} for *Staphylococcus aureus* (0.25 mg/L) 7-fold and 8.5-fold and the MIC_{90} for *E. coli*
70 (0.06 mg/L) 29-fold and 36-fold, respectively. The mean tissue-to-plasma ratios of
71 moxifloxacin concentration 3 h after administration were 1.01 ± 0.57 (PO) and 1.09 ± 0.69
72 (IV), respectively. Significant differences between the routes of administration were observed

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

75

76 Conclusions:

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

82

83

84

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

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

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

117
118 The present study was set up to investigate the penetration of moxifloxacin into perinecrotic
119 tissue of infected diabetic foot lesions in a large patient cohort and to evaluate its
120 pharmacokinetic profile in a pharmacological risk population of diabetic patients.

121

122

123 **Patients and methods**

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

128

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

134

135 Written informed consent was obtained from all patients, and the study protocol was approved
136 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 NH₄OAc, and 20 µl of the mixture subjected to HPLC/fluorescence analysis. The
155 chromatographic system consisted of a guarded YMC Pro C₁₈ 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 NH₄OAc/H₂O 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

163 50 µg/L allowing for a deviation of CV and RE < ±20%. Recoveries ranged between 85 and
164 90% based on spiking solution.

165

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

173

174 **Pharmacokinetic calculations and statistics**

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

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

187 Relationships were evaluated using nonparametric Spearman-Rho correlation coefficient.

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

189

190 **Results**

191 Fifty three patients with DFI were enrolled into the study at nine centres in Germany. At
192 study entry, the patients had a mean age of 69.4 ± 10.8 years, a mean body weight of $82.9 \pm$
193 17.9 kg and a mean body mass index (BMI) of 28.2 ± 4.5 kg/m². Mean C-reactive protein
194 (CRP) was 76.9 ± 80.4 mg/L, mean leukocyte count was 11.0 ± 3.5 Gpt/L and average serum
195 creatinine was 121.6 ± 97.5 μ mol/L.

196

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

201

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

204

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

207 The most frequent treatment-emergent adverse event was diarrhea, occurring in 6 patients
208 (10.5%).

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

211 Steady-state concentrations of moxifloxacin in plasma (median for both cohorts: day 6) are
212 shown in Figures 1 and 2 and summed-up in Table 2. Significant differences between the
213 routes of administration (IV vs PO) were only observed for C_{max} and T_{max} in plasma ($p < 0.01$),
214 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].

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

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

246

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

256

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

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

274

275 The mean inflamed DFI tissue to plasma concentration ratio in the present study was about
276 100% for both PO and IV administration. The measured concentrations were lower than
277 those in other tissues, e.g. gastrointestinal or bronchial tissue [17, 18]. This difference might
278 be explained by a lower perfusion in DFI tissue due to impaired macro- and/or
279 microcirculation. Another reason could be the perinecrotic nature of the resected DFI tissue.
280 Our results confirm previous data of an in vivo microdialysis study, in which an enrichment
281 of moxifloxacin was found in well-perfused inflamed subcutaneous tissue compared to
282 plasma [7]. In the same study diabetes mellitus patients with peripheral arterial occlusive
283 disease were investigated. In this patient population, the tissue to plasma ratio was 0.5
284 underlining the implication of circulatory disturbances.

285

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

293 PK/PD concept is valid for DFI, the indices calculated from these study data (mean AUIC of
294 108.4-117.4 for *Staphylococcus aureus*) account for a high efficacy.

295

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

300

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

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

337

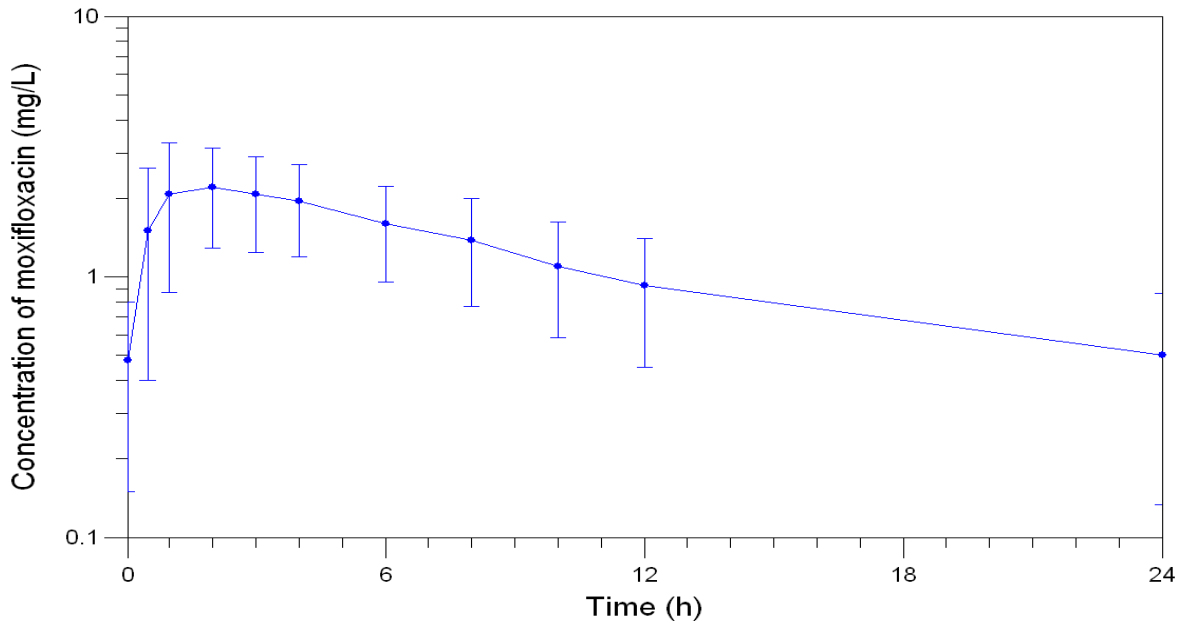
338 **Conclusions**

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

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

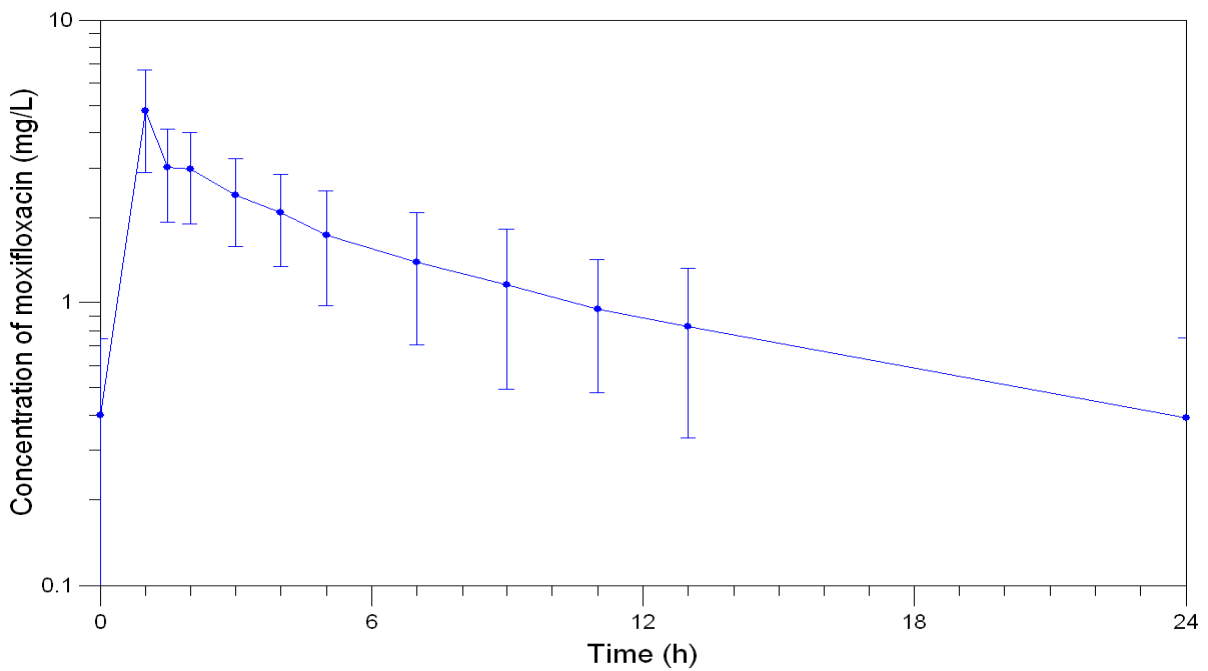
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346

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



349

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

352

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 ²)	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 _{max,ss} (mg/L)	2.69 (0.94)	2.4; 3.0	0.9 – 4.8
	T _{max,ss} (h)	2.0 ^a	–	1.0 – 8.0
	AUC _{0-24h,ss} (mg·h/L)	27.09 (10.86)	23.1; 31.1	10.4-52.7
	V _{ss} (L/kg)	2.34 (0.96)	2.0; 2.7	1.2 – 4.7
IV (n=25)	Cl _{tot,ss} (L/h)	14.13 (7.5)	11.4; 16.9	4.0 – 35.4
	C _{max,ss} (mg/L)	4.77* (1.87)	4.0; 5.5	2.2 – 8.2
	T _{max,ss} (h)	1.0*	–	–
	AUC _{0-24h,ss} (mg·h/L)	29.36 (12.47)	24.3; 34.4	16.2-76.1
	V _{ss} (L/kg)	1.81 (0.47)	1.6; 2.0	1.0 – 2.8
	Cl _{tot,ss} (L/h)	13.38 (4.79)	11.4; 15.3	3.0 – 22.2

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

362

363 **Table 3.**

364 Steady-state concentration of moxifloxacin in inflamed DFI tissue and tissue/plasma ratio 3
 365 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

366

367 **Table 4.**

368 Predictive PK/PD parameters of moxifloxacin following once daily PO or IV administration
 369 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)

370

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