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Limited Sampling Strategies Using Linear Regression and the Bayesian Approach for Therapeutic Drug Monitoring of Moxifloxacin in Tuberculosis Patients

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1 Limited sampling strategies using linear regression and the Bayesian approach for therapeutic drug

- 2 monitoring of moxifloxacin in tuberculosis patients
- 3
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37 Abstract

38	
39	Therapeutic drug monitoring (TDM) of moxifloxacin is recommended to improve response to
40	tuberculosis treatment and reduce acquired drug resistance. Limited sampling strategies (LSSs) are able
41	to reduce the burden of TDM by using a small number of appropriately timed samples to estimate the
42	parameter of interest; the area under the concentration time curve. This study aimed to develop LSSs for
43	moxifloxacin alone (MFX) and together with rifampicin (MFX+RIF) in TB patients.
44	Population pharmacokinetic (popPK) models were developed for MFX (n=77) and MFX+RIF (n=24).
44	Population pharmacokinetic (poper) models were developed for Mirx (n=77) and Mirx+Kir (n=24).
45	Additionally, LSSs using Bayesian approach and multiple linear regression were developed. Jackknife
46	analysis was used for internal validation of the popPK models and multiple linear regression LSSs.
47	Clinically feasible LSSs (1-3 samples; 6 h timespan post-dose; 1 h interval) were tested.
48	Moxifloxacin exposure was slightly underestimated in the one compartment models of MFX (mean -
49	5.1%, standard error [SE] 0.8%) and MFX+RIF (mean -10%, SE 2.5%). The Bayesian LSSs for MFX and
50	MFX+RIF (both 0 and 6 h) slightly underestimated drug exposure (MFX mean -4.8%, SE 1.3%; MFX+RIF
51	mean -5.5%, SE 3.1%). The multiple linear regression LSS for MFX (0 and 4 h) and MFX+RIF (1 and 6 h),
52	showed a mean overestimation of 0.2% (SE 1.3%) and 0.9% (SE 2.1%), respectively.
53	LSSs were successfully developed using the Bayesian approach (MFX and MFX+RIF; 0 and 6 h) and
54	multiple linear regression (MFX 0 and 4 h, MFX+RIF 1 and 6 h). These LSSs can be implemented in clinical
55	practice to facilitate TDM of moxifloxacin in TB patients.

56 Introduction

57	Each year, the global tuberculosis (TB) incidence declines with approximately 2%, while by 2020 an
58	annual 4-5% decline is strived for by the World Health Organization (WHO).(1) Multidrug-resistant TB
59	(MDR-TB) remains a major problem with an estimated number of 458,000 cases in 2017.(1) Currently,
60	the worldwide success rate of MDR-TB treatment is 55% and this is considered low when compared to a
61	success rate of 85% for drug-susceptible TB (DS-TB).(1)
62	Moxifloxacin, a fluoroquinolone, is one of the most important drugs for the treatment of MDR-TB(2), but
63	has also been used as an alternative to first-line anti-TB drugs if not well tolerated or suggested to
64	include in case of isoniazid resistance.(3–5) In general, the toxicity profile of moxifloxacin is rather mild,
65	though it includes concentration dependent QTc interval prolongation and, rarely, tendinopathy.(6–9) A
66	clinically relevant drug-drug interaction is the combination of moxifloxacin with rifampicin, since these
67	two drugs can be used concomitantly in TB treatment. Rifampicin lowers the moxifloxacin area under the
68	concentration-time curve of 0-24 h (AUC $_{0-24}$) with approximately 30% by inducing phase II metabolising
69	enzymes (glucuronosyltransferase and sulphotransferase).(10–12)
70	The efficacy of fluoroquinolones is related to the ratio of $AUC_{0.24}$ to minimal inhibitory concentration
71	(AUC ₀₋₂₄ /MIC).(13, 14) The fluoroquinolone exposure is effective against gram-negative bacteria at an
72	AUC ₀₋₂₄ /MIC >100-125 and against gram-positive species at an AUC ₀₋₂₄ /MIC >25-30.(13, 15, 16) An <i>in vitro</i>
73	moxifloxacin exposure of unbound (f)AUC $_{0.24}$ /MIC of >53 was able to substantially decrease the total
74	population of <i>M. tuberculosis</i> with over $3 \log_{10} CFU/ml$ as well as suppress emergence of drug resistance,
75	while an fAUC ₀₋₂₄ /MIC >102 completely killed the fluoroquinolone sensitive population of <i>M. tuberculosis</i>
76	without observing development of drug resistance.(17) Approximately 50% of moxifloxacin is assumed to
77	be protein bound, although protein binding is highly variable between individuals and might be
78	concentration dependent.(13, 16, 18, 19) Corresponding with <i>f</i> AUC ₀₋₂₄ /MIC>53 and a fraction unbound
79	of 0.5, the target total (bound and unbound) $AUC_{0-24}/MIC > 100-125$ is regularly used in TB, because

81	moxifloxacin while lacking a MIC value of the strain, the target AUC $_{0-24}$ is generally set at >50-65 mg·h/L
82	based on a critical concentration of 0.5 mg/L.(22, 23)
83	Therapeutic drug monitoring (TDM) is recommended by the American Thoracic Society for all second-line
84	drugs, including moxifloxacin. (24, 25) It is important to monitor the moxifloxacin exposure in TB patients
85	to determine an individualized dose, because of substantial inter-individual pharmacokinetic variability
86	and relevant drug-drug interactions with the risk of treatment failure and developing drug resistance.(18,
87	26–28) However, routine TDM to estimate AUC ₀₋₂₄ requiring frequent blood sampling is time-consuming,
88	a burden for patients and health care professionals, and expensive. Optimising the sampling schedule by
89	developing a limited sampling strategy (LSS) could overcome these difficulties with TDM in TB
90	treatment.(29)
91	There are two main methods to develop a LSS; the Bayesian approach and multiple linear regression.(30)
92	The advantages of the Bayesian approach are the flexible timing of samples as the population
93	pharmacokinetic model can correct for deviations and that it takes a number of parameters into account
94	for example sex, age, and kidney function, leading to a more accurate estimation of AUC_{0-24} . The
95	advantage of multiple linear regression-based LSSs is that these do not require modelling software and
96	AUC ₀₋₂₄ can be easily estimated using only an equation and the measurement of drug concentrations.
97	The disadvantage is that samples must be taken exactly according to the predefined schedule and the
98	population of interest should be comparable because patient characteristics are not included in the
99	equations to estimate drug exposure.(30)
100	Pranger et al described a LSS for moxifloxacin for the first time using t=4 and 14 h post-dose samples.(21)
101	This sampling strategy can be considered unpractical to be used in daily practice. Magis-Escurra et al
102	described LSSs to simultaneously estimate AUC ₀₋₂₄ of all first-line drugs together with moxifloxacin (t=1,
103	4, 6 h or t=2, 4, 6 h), but did not differentiate between patients using moxifloxacin alone and

individual data of protein binding is often lacking.(18, 20, 21) In case of a proven susceptibility for

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Therefore, the aim of this study was to develop and validate two population pharmacokinetic models of moxifloxacin (alone and with rifampicin) along with clinically feasible LSSs using the Bayesian approach as well as multiple linear regression for the purpose of TDM of moxifloxacin in TB patients. Results Study population The group with moxifloxacin alone (MFX) included pharmacokinetic profiles of 77 TB patients and the 115 group with moxifloxacin together with rifampicin (MFX+RIF) included profiles of 24 TB patients (Figure 116 1). The baseline characteristics sex, age and height were significantly different (P<0.05) between these 117 two groups (Table 1). Additionally, the AUC₀₋₂₄ calculated with the trapezoidal rule (AUC_{0-24, ref}) was 118 significantly lower and time of peak concentration (T_{max}) was significantly earlier in the MFX+RIF group 119 (P<0.05, Table 2). Several abnormal pharmacokinetic curves (e.g. delayed absorption or single aberrant 120 data point) were observed in both the MFX and MFX+RIF group. 121 122 Population pharmacokinetic model 123 For both MFX and MFX+RIF, an one compartment model with lag time resulted in the lowest Akaike 124 Information Criterion (AIC) values and described the data best (Table 3). Two compartment models were 125 not favourable for either MFX or MFX+RIF. A statistical comparison of the pharmacokinetic parameters 126 of the MFX versus MFX+RIF model was provided in Table 4. Total body clearance (CL) was higher and lag time (T_{lag}) was shorter in the MFX+RIF model (P<0.05). Internal validation of the two models resulted in a 127

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129	underestimation of 10% (SE 2.5%) in the MFX+RIF model (Figure 2A and Figure 3A). In the validation of
130	the MFX model, an r ² of 0.98, y-axis intercept of -0.3 (95% CI -1.1 to 0.5), and slope of 0.96 (95% CI 0.94-
131	0.98) was found in the Passing Bablok regression (Figure 2B). For the MFX+RIF model, an r^2 of 0.94, y-axis
132	intercept of -1.0 (95% CI -4.1 to 0.9), and slope of 0.98 (95% CI 0.92-1.07) was found in the Passing
133	Bablok regression (Figure 3B).
134	
135	LSS using the Bayesian approach
136	The best performing LSSs of MFX and MFX+RIF are shown in Table 5 and Table 6, including mean
137	prediction error (MPE), root mean squared error (RMSE), and r ² to evaluate the performance of the LSSs.
138	The performance of the LSS using t=2 and 6 h samples was evaluated as well, because this strategy is
139	currently used in many health facilities for TDM of anti-TB drugs.(31) Not all strategies met the pre-set
140	acceptance criteria (RMSE<15%, MPE<5%).(21) Low r ² values were observed which were caused by high
141	interindividual variability in performance of the LSSs.
142	For the MFX model, an LSS using t=0 and 6 h samples was chosen for further evaluation (RSME=15.17%,
143	MPE= 2.42%, r ² =0.874), because it required one sample less than the three-sample strategies, while
144	RMSE was only slightly above 15%. The internal validation showed a mean underestimation of 4.8% (SE
145	1.3%). However, low AUC ₀₋₂₄ values were more frequently overestimated in contrast to AUC ₀₋₂₄ >40
146	mg*h/L mainly being underestimated by the LSS (Figure 4A). The Passing Bablok regression showed an r ²
147	of 0.94, y-axis intercept of 3.4 (95% CI 1.6-4.9), and slope of 0.85 (95% CI 0.80-0.91) (Figure 4B).
148	For the MFX+RIF model, an LSS using t=0 h and 6 h samples was chosen for further evaluation
149	(RSME=15.81%, MPE= 2.35%, r ² =0.885), because of the benefit of requiring only 2 samples while

mean underestimation of $AUC_{0\cdot 24}$ of 5.1% (standard error (SE) 0.8%) in the MFX model and a mean

150 performance in terms of RSME and MPE remained acceptable. The internal validation showed a mean

underestimation of 5.5% (SE 3.1%) in the Bland-Altman plot and an r² of 0.90, y-axis intercept of -1.3
(95% Cl -4.4 to 2.8), and slope of 1.0 (95% Cl 0.88-1.10) in the Passing Bablok regression (Figure 5).

154 LSS using multiple linear regression

155 Table 7 and Table 8 show the best performing LSSs for MFX and MFX+RIF. The performance of the

156 frequently used LSS using t=2 and 6 h samples was evaluated as well and included in the tables. None of

157 the MFX LSSs met the acceptance criteria (RMSE<15%, MPE<5%) as bias was above 5% for all

combinations. For MFX+RIF, the two three-sample strategies and LSS using t=1 and 6 h samples met the
 acceptance criteria.

160 The MFX LSS using t=0 and 4 h samples (RSME=9.25%, MPE= 6.85%, r^2 =0.957) had a comparable

161 performance to the three-sample strategies while being more clinically feasible and therefore was

162 chosen for further evaluation. In contrast to the Bayesian LSSs for MFX and MFX+RIF, a t=0 and 6 h

163 strategy was not feasible using a multiple linear regression approach as its performance was

substantially worse (RMSE=12.01, MPE=9.43, r²=0.905) than the LSS using t=0 and 4 h samples. Internal

validation of this t=0 and 4 h LSS for MFX showed a mean overestimation of 0.2% (SE 1.3%) in the Bland-

166 Altman plot and an r² of 0.95, y-axis intercept of 0.1 (95% CI -2.1 to 1.6), and slope of 0.99 (95% CI 0.95-

167 1.06) in the Passing Bablok regression (Figure 6).

168 For MFX+RIF, the LSS using t=1 and 6 h samples (RSME=6.09%, MPE= 4.83%, r²=0.971) was chosen for

169 further evaluation, because of clinical suitability in addition to good performance (RMSE<15%, MPE<5%).

170 Internal validation showed a mean overestimation of 0.9% (SE 2.1%) in the Bland-Altman plot and an r^2

of 0.96, y-axis intercept of -0.2 (95% CI -4.9 to 2.3), and slope of 1.02 (95% CI 0.88-1.15) in the Passing
Bablok regression (Figure 7).

173

174 Discussion

In this study, we successfully developed a population pharmacokinetic model for moxifloxacin alone and
in combination with rifampicin. Furthermore, we developed and validated sampling strategies using the
Bayesian approach (MFX and MFX+RIF t=0 and 6 h) and multiple linear regression (MFX t=0 and 4 h;

178 MFX+RIF t=1 and 6 h) for both groups as well.

179 It was decided to develop two separate population pharmacokinetic models, and therefore also separate 180 LSSs, for moxifloxacin alone and in combination with rifampicin after observing a significant effect of 181 rifampicin on the pharmacokinetics of moxifloxacin. The population pharmacokinetic model of MFX+RIF 182 showed an approximately 35% higher total body clearance of moxifloxacin when compared to the MFX 183 pharmacokinetic model (Table 4). This was to be expected as rifampicin enhances metabolism of 184 moxifloxacin and increases in total body clearance of 45-50% have been reported by others. (10, 32) As a 185 result of this drug-drug interaction, pharmacokinetic profiles of MFX+RIF showed reduced moxifloxacin 186 concentrations and 25% lower median moxifloxacin AUC₀₋₂₄ values after administration of a similar dose 187 (Figure 1, Table 2). The latter is confirmed by a significant -17% difference in dose-corrected AUC_{0-24,ref} 188 between the MFX and MFX+RIF group (Table 2). The decrease in moxifloxacin exposure by rifampicin was 189 estimated at 30% in previous studies (10, 12, 32), although others found non-significant or smaller 190 decreases in moxifloxacin AUC₀₋₂₄.(21, 33) In this study we observed only a slightly smaller effect of 191 rifampicin on the total body clearance and exposure than previously reported. This might be explained 192 by the possibility that maximal enzyme induction was not achieved yet at the moment of sampling in a 193 few cases, since it generally takes around 10-14 days of rifampicin treatment to reach maximal 194 induction.(34) Furthermore, we encountered a significant, but small, difference in lag time between the 195 MFX and MFX+RIF models and in T_{max} of the included pharmacokinetic profiles. The faster absorption of 196 moxifloxacin in combination rifampicin was found in other studies as well, however some reported the 197 opposite effect. This could suggest that lag time and T_{max} was not influenced by rifampicin, but more

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198	likely by other differences between the MFX and MFX+RIF group such as concomitantly taken TB drugs
199	or inter-individual differences in absorption due to disease state.
200	In addition to the population pharmacokinetic models, we developed and validated LSSs using the
201	Bayesian approach as well as multiple linear regression for MFX and MFX+RIF. LSSs of moxifloxacin have
202	been described before. Pranger et al found a Bayesian LSS with a comparable performance (RMSE=15%,
203	MPE=-1.5%, r ² =0.90) when compared to our LSSs for MFX and MFX+RIF.(21) The LSS of Magis-Escurra <i>et</i>
204	al performed better (RMSE=1.45%, MPE=0.58%, r ² =0.9935) than the multiple linear regression LSSs
205	proposed in this study.(20) However, a smaller sample size (n=12) was used to establish the equation
206	and this was not externally validated. Further, we provided suitable sampling strategies for multiple
207	situations; in patients using moxifloxacin alone or together with rifampicin and for centres that either do
208	or do not have pharmacokinetic modelling software available. Health care professionals may select the
209	LSS that is the most applicable to the circumstances.
210	The Bayesian LSS for MFX (t=0 and 6 h) showed a slight downward trend between the bias of the
211	estimated AUC ₀₋₂₄ and the mean of the estimated and actual AUC ₀₋₂₄ (Figure 4). Low AUC ₀₋₂₄ values were
212	more frequently overestimated in comparison to higher AUC_{0-24} values. A possible cause might be that
213	we could not differentiate between metabolic clearance and renal clearance in both population
214	pharmacokinetic models due to a small range of creatinine clearance in the study population. A relatively
215	high exposure of moxifloxacin in patients with renal insufficiency could be underestimated as renal
216	function may be overestimated and the other way around for patients with normal renal function and
217	relatively low exposures. The pharmacokinetic modelling software will fit a curve with the greatest
218	likelihood of being the actual pharmacokinetic curve based on drug concentrations at 0 and 6 h together
219	with patient characteristics and data of the entire population. However, when influence of creatinine
220	clearance is not available the software will pick a fit with average parameters, causing overestimation in
221	low AUC ₀₋₂₄ and underestimation in high AUC ₀₋₂₄ ranges. We decided not to validate one of the better

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performing three-sample strategies from Table 5, since we focussed on developing a clinically feasible LSS with a strong preference for only 2 samples. Furthermore, we aimed to provide a simple and well performing alternative LSS for MFX using multiple linear regression (t=0 and 4 h). We recommend to use this LSS instead of the Bayesian LSS for MFX, particularly when low drug exposure is suspected, because overestimation of AUC₀₋₂₄ can lead to sub therapeutic dosing with treatment failure and acquired drug resistance as possible harmful consequence.(26, 36, 37)

228 In this study we decided to validate one LSS for each situation (Bayesian or multiple linear regression; 229 MFX or MFX+RIF), due to the significant influence of rifampicin on the pharmacokinetics of moxifloxacin 230 and so there would be a suitable LSS for every patient in each health care centre. The LSSs using multiple 231 linear regression performed rather well in our study population, but is less flexible in patients with 232 different characteristics. A Bayesian LSS is therefore preferred for patients who are not comparable to 233 our study populations as the population pharmacokinetic model is able to include some patient 234 characteristics. Clinicians are guided to the best option for TDM of moxifloxacin by following the decision 235 tree in Figure 8. For implementation of moxifloxacin TDM using LSSs in daily practice, it would be 236 convenient to be able to use one sampling strategy for both MFX and MFX+RIF. This study showed that it 237 is possible to use t=0 and 6 h samples in a Bayesian LSS for both MFX as well as MFX+RIF and probably 238 even in a multiple linear regression LSS for MFX+RIF after successful validation. Unfortunately, a multiple 239 linear regression strategy for MFX alone using t=0 and 6 h samples was not feasible because of inferior 240 performance. Considering that TB patients are treated with a combination of multiple anti-TB drugs, one 241 single LSS suitable for all drugs of interest is the ideal situation, but unfortunately also rather challenging 242 due to the various pharmacokinetic properties of the different drugs. Others did succeed in developing a 243 LSS using multiple linear regression for simultaneously estimating exposure of all first-line drugs and 244 moxifloxacin in a small population of TB patients.(20) A 2 and 6 h post-dose sampling strategy is 245 frequently used for TDM of anti-TB drugs as it is believed to be able to estimate C_{max} as well as to detect

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240	delayed absolption.(51) nowever, better performances were round for the L555 proposed in this study,
247	although the 2 and 6 h LSS performed within acceptable limits as well in the Bayesian approach and the
248	multiple linear regression.
249	In general, we noticed large inter-individual pharmacokinetic variation in terms of moxifloxacin
250	concentrations (Figure 1), C_{max} , and AUC ₀₋₂₄ (Table 2) as described earlier,(18) but also in K _a and CL/F
251	(Table 4). Patients received 400, 600, or 800 mg moxifloxacin; this obviously influenced drug
252	concentration, C_{max} , and $AUC_{0.24}$, but not all variation could be explained by different dosage regimes. For
253	MFX, AUC_{0-24} corrected to a 400 mg standard dose was ranged from 10.2 to 79.1 mg*h/L and for
254	MFX+RIF a range of 10.0 to 47.4 mg*h/L. This substantial inter-individual variation is the reason why
255	TDM of moxifloxacin is helpful to assure optimal drug exposure and thus minimize the risk of treatment
256	failure and developing acquired drug resistance. (26, 27) The estimated AUC_{0-24} using one of the LSS
257	proposed together with the MIC of the <i>M. tuberculosis</i> strain will provide valuable information on the
258	optimal moxifloxacin dose to be used in an individual patient.
259	A limitation to the study is the exclusion of the creatinine clearance from the population
260	pharmacokinetic model. As discussed earlier, this could have led to the observed bias in the MFX LSS
261	using 0 and 6 h samples as approximately 20% of moxifloxacin is eliminated unchanged in the urine. On
262	the contrary, a well performing LSS using multiple linear regression (t=0 and 4 h) is a suitable alternative
263	for MFX. The lack of prospective or external validation of the population pharmacokinetic model and
264	LSSs could be considered as another limitation. However, we were able to collect a large dataset to
265	develop the model and clinically feasible LSSs using a sufficient number of pharmacokinetic profiles. A
266	strength of our study was that a large part of our dataset consisted of drug concentrations which were
267	collected as part of daily routine TDM. During visual check of the data we noticed several abnormal
268	curves (both MFX and MFX+RIF) that for instance showed delayed absorption with T_{max} values of 4-6 h.
269	These curves were not excluded from the study. The models and LSSs appeared to be able to adapt to

delayed absorption.(31) However, better performances were found for the LSSs proposed in this study,

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271 similar. For these reasons, we expect the results as reported in this study to represent the clinical 272 practice of TDM using these LSSs very closely. The small sample size of the MFX+RIF group can be 273 considered as a limitation as well, although comparable to previously published LSS studies.(21, 38-41) 274 We consider this sample size as sufficient for exploratory objectives, since this is the first study that 275 developed separate LSSs for moxifloxacin alone and in combination with rifampicin. Future research can 276 build on the results described in this study. 277 In conclusion, we developed and validated two separate pharmacokinetic models for moxifloxacin alone 278 and in combination with rifampicin in TB patients. We provided data to show significant differences in 279 drug clearance and drug exposure between these groups. Furthermore, we developed and validated LSS 280 based on the Bayesian approach (MFX and MFX+RIF 0 and 6 h) and multiple linear regression (MFX 0 and 281 4 h; MFX+RIF 1 and 6 h) that can be used to perform TDM on moxifloxacin in TB patients. 282 283 Materials and methods 284 Study population 285 This study used three databases. Database 1 consisted of retrospective data of routine TDM in 67 286 tuberculosis patients treated at Tuberculosis Center Beatrixoord, University Medical Center Groningen,

this delayed absorption. In most cases, the subsequent decision to either increase the dose or not was

287 The Netherlands and was collected between January 2006 and May 2017, partly published earlier.(18) All

288 patients received moxifloxacin (with or without rifampicin) as part of their daily TB treatment and

289 pharmacokinetic curves were obtained as part of routine TDM care. Each patient was only included once.

- 290 Varying sampling schedules were used, but most profiles included t=0, and 1, 2, 3, 4, and 8 h post-dose
- 291 samples. Pharmacokinetic profiles consisting of less than 3 data points were excluded. The second
- database included data of 25 TB patients participating in a clinical study in Thessaloniki, Greece.(33)
- 293 After at least 12 days of treatment with moxifloxacin with or without rifampicin, blood samples were

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295	pharmacokinetic data of 9 Brazilian TB patients receiving 400 mg moxifloxacin (no rifampicin) daily in an
296	early bactericidal activity study.(14) At the fifth day, blood samples were collected at t=0, and 1, 2, 4, 8,
297	12, 18 and 24 h after drug intake.
298	As steady state is reached within 3-5 days of treatment with moxifloxacin, all data was collected during
299	steady state conditions.(11) In general, no informed consent was required, due to the retrospective
300	nature of the study.
301	The total study population was split in two groups; patients that received moxifloxacin alone (MFX) and
302	patients that received moxifloxacin together with rifampicin (MFX+RIF), because of the pharmacokinetic
303	drug-drug interaction between rifampicin and moxifloxacin.(10) As sample collection in the MFX+RIF
304	group was performed after a median number of days on rifampicin treatment of 35 (IQR 13-87),
305	maximum enzyme induction by rifampicin was expected to be reached in most patients.(35)
306	Patient characteristics of both groups were tested for significant differences, median (interquartile range
307	(IQR)) using the Mann-Whitney U test and n (%) using the Fisher's exact test in IBM SPS Statistics (23,
308	IBM Corp., Armonk, NY). P values <0.05 were considered significant.
309	
310	Population pharmacokinetic model
311	For each group, MFX and MFX+RIF, a population pharmacokinetic model was developed using the
312	iterative two-stage Bayesian procedure of the KinPop module of MWPharm (version 3.82, Mediware,
313	The Netherlands). As the pharmacokinetics of moxifloxacin have been described with one compartment
314	(14, 21) as well as two-compartment models (42, 43), both types were evaluated. The population
315	pharmacokinetic parameters of the models were assumed to be log normally distributed with a residual
316	error and concentration dependent standard deviation (SD=0.1+0.1*C, where C is the moxifloxacin
317	concentration in mg/L). Because the bioavailability (F) of moxifloxacin is almost complete (11) and

collected at t=0, and 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 h after drug intake. The third database consisted of

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510	pharmacokinetic data following intravenous administration was not available, if was fixed at 1 in the
319	analysis and pharmacokinetic parameters are presented relative to F. Moxifloxacin is mainly metabolised
320	in the liver by glucuronosyltransferase and sulfotransferase (approximately 80%).(11) Only total body
321	clearance (CL), the sum of metabolic and renal clearance, was included in the model development,
322	because it was not possible to determine renal clearance due to a small range of creatinine clearance
323	values in our dataset.
324	We started the analysis with a single default one compartment model for both MFX and MFX+RIF
325	developed by Pranger et al using a very similar methodology.(21) This study found comparable
326	pharmacokinetic parameters of MFX and MFX+RIF, although likely due to a small sample size. Two
327	default two compartment models were used, one for MFX and one for MFX+RIF.(42, 44) Modelling was
328	started with all parameters fixed and Akaike Information Criterion (AIC) was used to evaluate the
329	model.(45) Subsequently, one by one parameters were Bayesian estimated and each step was evaluated
330	by calculation of the AIC. A reduction of the AIC with at least 3 points was regarded as a significant
331	improvement of the model. (46) One compartment models included the parameters CL, volume of
332	distribution (V), and absorption rate constant (K_a). Two compartment models included the parameters
333	K _a , CL, inter-compartmental clearance (CL ₁₂), central volume of distribution (V ₁), volume of distribution of
334	the second compartment (V ₂), and lag time for absorption (T_{lag}). Afterwards, T_{lag} was added to the best
335	performing one compartment model and evaluated for goodness of fit as well, because of oral intake of
336	moxifloxacin. The default two compartment models already included T_{lag} . The final models of MFX and
337	MFX+RIF were chosen based on AIC values.
338	The final models were internally validated using 11 different (n-7) sub models for MFX and 12 (n-2) sub
339	models for MFX+RIF, each leaving out randomly chosen pharmacokinetic curves. All pharmacokinetic
340	curves were excluded once (jackknife analysis). The Bayesian fitted AUC_{0-24} of each left out curve (AUC_{0-24} ,

 $_{\rm fit}$) was compared with the AUC_{0-24} calculated with the trapezoidal rule (AUC_{0-24,\,\rm ref}) using a Bland-Altman

pharmacokinetic data following intravenous administration was not available, F was fixed at 1 in the

341

342 plot and Passing Bablok regression (Analyse-it 4.81, Analyse-it Software Ltd, Leeds, United Kingdom). In 343 the calculation of AUC_{0-24, ref}, moxifloxacin concentrations at t=0 and 24 h after drug intake were assumed 344 to be equal due to steady state conditions. C_{max} (mg/L) was defined as the highest observed moxifloxacin 345 concentration and T_{max} (h) as the time at which C_{max} occurred. Non-compartmental parameters (AUC₀₋₂₄, 346 ref, dose-corrected AUC₀₋₂₄, ref to the standard dose of 400 mg, C_{max}, T_{max}) and population pharmacokinetic 347 model parameters of the MFX and MFX+RIF group were compared and tested for significant differences 348 using the Mann-Whitney U test.

349

350 LSS using Bayesian approach

351 Using the Bayesian approach, we performed two separate analyses to develop LSSs; one for MFX and 352 one for MFX+RIF. Using Monte Carlo simulation in MWPharm, 1000 virtual pharmacokinetic profiles 353 were created to represent the pharmacokinetic data used in the development of the LSS. The reference 354 patient for the Monte Carlo simulation was selected based on representative pharmacokinetic data and 355 patient characteristics. For MFX, a 36 year old male with a bodyweight of 57 kg, height of 1.60 m, BMI of 356 22.2 kg/m², serum creatinine of 74 µmol/L, and moxifloxacin dose of 7.0 mg/kg was chosen. For 357 MFX+RIF, a 56 year old male with a bodyweight of 56 kg, height of 1.63 m, BMI of 21.1 kg/m², serum 358 creatinine of 80 μ mol/L, and moxifloxacin dose of 7.1 mg/kg was selected. The LSSs were optimised using 359 the steady state AUC₀₋₂₄. Only clinically feasible LSSs using 1-3 samples between 0 and 6 h post-dose and 360 sample interval of 1 h were tested. The LSSs were evaluated using acceptance criteria for precision and 361 bias (RMSE<15%, MPE<5%).(18) For both MFX and MFX+RIF, one LSS was chosen for internal validation 362 based on performance as well as clinical feasibility. The AUC₀₋₂₄ estimated with the chosen LSS (AUC₀₋₂₄. 363 est) was compared with AUC_{0-24, ref} using a Bland-Altman plot and Passing Bablok regression. Additionally, 364 the performance of a LSS using 2 and 6 h post-dose samples was evaluated, because this is a LSS 365 frequently used for TDM of anti-TB drugs.(31)

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366

- 367 LSS using multiple linear regression
- 368 Two separate analyses (MFX and MFX+RIF) using multiple linear regression were performed.
- 369 Only clinically suitable LSSs (1-3 samples, 0-6 h post-dose, sample interval 1 h) were included in the
- 370 analysis. Each analysis excluded the pharmacokinetic curves without data at the selected time points of
- 371 the LSS, resulting in a variable number of included curves (N). Multiple linear regression in Microsoft
- 372 Office Excel 2010 was used to evaluate the correlation of moxifloxacin concentrations at the chosen time
- points of the LSS and $AUC_{0.24, ref}$. The acceptance criteria (RMSE<15%, MPE<5%) were applied to each
- 374 LSS.(18) Internal validation using 11 different (n-6) sub analyses for MFX and 14 (n-1) sub analyses for
- 375 MFX+RIF was used to evaluate the performance of the LSSs. Each sub analysis excluded randomly chosen
- 376 profiles and all profiles were excluded once (jackknife analysis). Agreement of AUC_{0-24, est} and AUC_{0-24, ref}
- 377 was tested using a Bland-Altman plot and Passing Bablok regression.
- 378

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513 Table 1. Patient characteristics of the study population. Data is presented as median (IQR) unless

J14 Utilei wise stateu.	514	otherwise stated.
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Parameter	MFX	MFX+RIF	P value
	n=77	n=24	
Male sex [n(%)]	47 (61.0)	21 (87.5)	0.023ª
Age (yr)	33 (25-41)	48 (36-62)	<0.001 ^b
Ht (m)	1.65 (1.59-1.74)	1.72 (1.64-1.76)	0.047 ^b
Wt (kg)	58.0 (52.5-68.2)	55.5 (52.3-63.9)	0.500 ^b
Dose (mg/kg bodywt)	7.0 (5.9-8.1)	7.3 (6.4-7.7)	0.629 ^b
BMI (kg/m ²)	21.2 (19.3-23.5)	20.1 (17.6-22.7)	0.053 ^b
Serum creatinine (µmol/L)	71 (59-83)	73 (63-91)	0.752 ^b
Number of samples per	7 (6-8)	10 (7-10)	<0.001 ^b
curve			
Days on rifampicin	NA	35 (13-87)	NA
treatment at time of			
sampling			

^a Fisher exact test

516 ^b Mann-Whitney U test

517

518 Table 2. Non-compartmental parameters (AUC_{0-24, ref}, dose corrected AUC_{0-24, ref} to 400 mg standard dose,

519 C_{max}, and T_{max}) of MFX and MFX+RIF, presented as median (IQR).

Parameter	MFX (n=77)	MFX+RIF (n=24)	P-value
AUC _{0-24, ref} (mg·h/L)	34.0 (25.2-49.2)	25.5 (20.4-31.6)	0.006 ^a
Dose corrected $AUC_{\text{0-24, ref}}$	30.8 (24.7-40.3)	25.5 (19.1-31.3)	0.014 ^a
(mg·h/L, per 400 mg)			
C _{max} (mg/L)	3.00 (2.27-4.64)	2.83 (2.25-3.90)	0.407ª
T _{max} (h)	2 (1-3)	1.5 (1-2)	0.018 ^a

520 ^a Mann-Whitney U test

Table 3. Starting parameters of the default one compartment and two compartment models of MFX and
 MFX+RIF together with the parameters of the final models based on AIC.

Parameter	Default model	Final model	Default model	Final model
	MFX	MFX	MFX+RIF	MFX+RIF
One compartment	I	1		1
CL (L/h)	18.500±8.600	14.655±5.683	18.500±8.600	19.898±8.800
V _d (L/kg bodyweight)	3.000±0.7000	2.7467±1.0077	3.000±0.7000	2.8264±0.6902
K _a (/h)	1.1500±1.1600	6.2904±4.8164	1.1500±1.1600	7.3755±6.8205
T _{lag} (h)	NA	0.8769±0.2357	NA	0.7460±0.1093
AIC	5564	903	1361	236
Two compartments	I	1		
CL (L/h)	11.800±0.740	13.428±5.494	49.100±2.550	18.108±8.570
CL ₁₂ (L/h)	5.620±1.080	5.620±1.080	3.150±0.800	3.150±0.800
V ₁ (L/kg bodyweight)	2.5300±0.0800	2.4898±1.0838	2.8400±0.1500	2.7004±0.7535

	V ₂ (L/kg bodyweight)	0.6900±0.1300	0.6900±0.1300	0.8900±0.1900	0.8900±0.1900
	K _a (/h)	16.7000±2.9200	3.2774±2.9422	2.3200±0.5600	6.2314±9.0508
	T _{lag} (h)	0.4600±0.0800	0.7940±0.3720	0.6000±0.0700	0.7312±0.1995
	AIC	11892	940	2995	249
522		•	•	•	•

523

524 Table 4. Comparison of pharmacokinetic parameters of the population pharmacokinetic model of MFX

525 versus MFX+RIF. Geometric mean±SD.

Parameter	MFX (n=77)	MFX+RIF (n=24)	P value
CL/F (L/h)	14.655±5.683	19.898±8.800	0.004 ^a
V _d /F (L/kg bodyweight)	2.7467±1.0077	2.8264±0.6902	0.534 ^ª
K _a (/h)	6.2904±4.8164	7.3755±6.8205	0.231 ^a
T _{lag} (h)	0.8769±0.2357	0.7460±0.1093	<0.001 ^a

526 ^a Mann-Whitney U test

527

528 Table 5. LSSs of moxifloxacin without RIF using the Bayesian approach, including MPE, RMSE, and r^2 .

Sam	oling ti	me	MPE (%)	RMSE (%)	r ²
poin	t (h)				
5			2.69	24.64	0.659
6			1.74	22.00	0.726
2	6		-2.20	20.83	0.742
0	5		2.84	15.82	0.864
0	6		2.42	15.17	0.874
0	4	6	0.97	13.22	0.883

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530 Table 6. LSSs of moxifloxacin with RIF using the Bayesian approach, including MPE, RMSE, and r².

Sam	pling ti	me	MPE (%)	RMSE (%)	r ²
poin	t (h)				
5			-1.97	22.35	0.768
6			-0.79	19.22	0.826
2	6		-2.89	18.38	0.832
0	5		1.88	16.67	0.877
0	6		2.35	15.81	0.885
0	4	6	1.06	14.10	0.907
0	5	6	0.79	13.73	0.912

531

532 Table 7. LSSs of moxifloxacin without RIF using linear regression, including the equation to calculate

533 AUC_{0-24, est}, number of included curves (N), MPE, RMSE, and r^2 .

Sam	Sampling		Equation ^a	Ν	MPE	RMSE	r ²
time point (h)		t (h)			(%)	(%)	
4			AUC _{0-24, est} = 3.47+12.32*C4	66	12.68	17.02	0.862
6			AUC _{0-24, est} = 2.27+15.01*C6	22	14.85	16.89	0.822
2	6		AUC _{0-24, est} = -1.44+3.55*C2+11.24*C6	22	10.02	12.27	0.901
0	3		AUC _{0-24, est} = 3.61+28.67*C0+5.38*C3	53	10.08	13.36	0.917
0	4		AUC _{0-24, est} = 1.10+20.76*C0+8.68*C4	66	6.85	9.42	0.957

0	2	4	AUC _{0-24, est} = 1.10+20.37*C0+0.92*C2+7.71*C4	65	6.91	9.25	0.958
0	1	4	AUC _{0-24, est} = 1.00+21.06*C0+0.66*C1+8.02*C4	63	7.07	9.23	0.958

^a C0, C1, etc., are moxifloxacin concentrations at t=0 h, t=1 h, etc.

535 Table 8. LSSs of MFX+RIF using multiple linear regression, including the equation to calculate AUC_{0-24, est},

536 number of included curves (N), MPE, RMSE, and r².

Sampling			Equation ^a	Ν	MPE	RMSE	r ²
time	time point (h)				(%)	(%)	
3			AUC _{0-24, est} =-2.76+13.28*C3	18	8.27	11.10	0.907
6			AUC _{0-24, est} = 0.95+16.44*C6	16	6.93	8.87	0.941
2	6		AUC _{0-24, est} = 0.08+1.21*C2+15.02*C6	13	6.23	7.88	0.945
0	6		AUC _{0-24, est} = 1.38+7.40*C0+14.05*C6	16	5.85	6.99	0.960
1	6		AUC _{0-24, est} = 1.43+0.22*C1+16.25*C6	14	4.83	6.09	0.971
0	3	6	AUC _{0-24, est} = 1.20+10.66*C0-0.39*C3+13.52*C6	15	4.85	5.31	0.977
0	2	6	AUC _{0-24, est} = 0.46+9.99*C0+0.13*C2+13.39*C6	13	4.20	4.66	0.978
^a CO	, C1, e	etc., a	re moxifloxacin concentrations at t=0 h, t=1 h, etc.		•	1	

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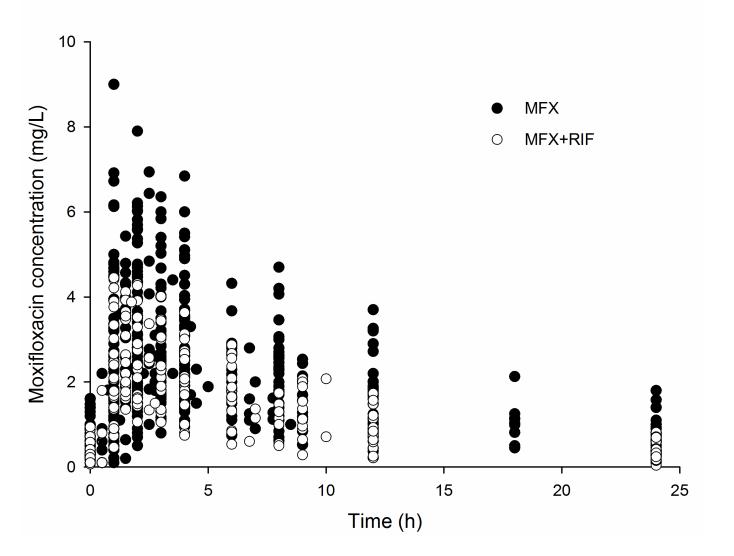
539	Figure 1. Moxifloxacin concentrations of the pharmacokinetic curves of MFX (n=77) and MFX+RIF (n=24)
540	
541	Figure 2. Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation (n-7) of
542	population pharmacokinetic model of MFX (n=77).
543	
544	Figure 3. Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation (n-2) of
545	population pharmacokinetic model of MFX+RIF (n=24).
546	
547	Figure 4. Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation of Bayesian LSS
548	(t=0 and 6 h) of MFX (n=77).
549	
550	Figure 5. Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation of Bayesian LSS
551	(t=0 and 6 h) of MFX+RIF (n=24).
552	
553	Figure 6. Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation (n-6) of LSS using
554	multiple linear regression (t=0 and 4 h) of MFX (n=66).
555	
556	Figure 7. Bland-Altman plot (A) and Passing Bablok regression (B) of internal validation (n-1) of LSS using
557	multiple linear regression (t=1 and 6 h) of MFX+RIF (n=14).
558	

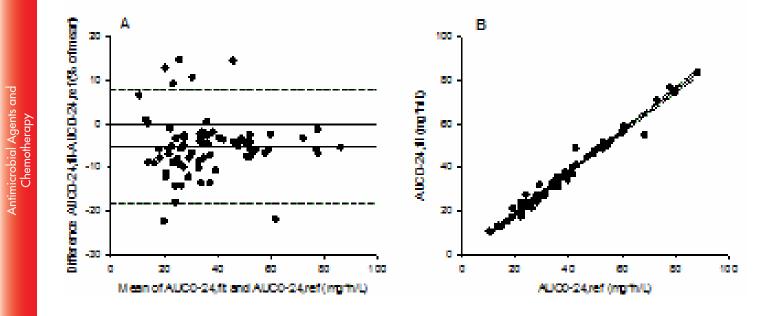
559	Figure 8. Clinical guide for choosing the best LSS for TDM of moxifloxacin alone or in combination with
560	rifampicin.

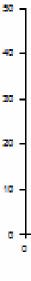
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AAC

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AUC0-24.651000 MUD

В

Difference AU CD/24 gs IAU CD/24 ref (% of mean)

A

20

10

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-10

-20

-30

-40

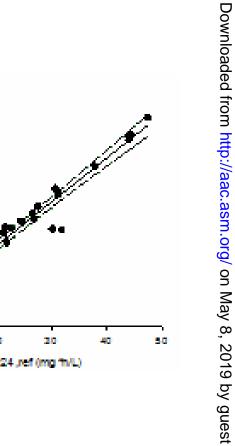
-50

D

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AAC



Mean of AUC0-24,est and AUC0-24,ref (mg*h/L)

50

\$

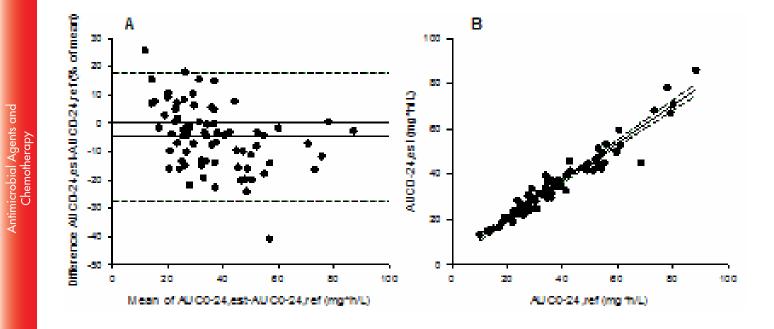
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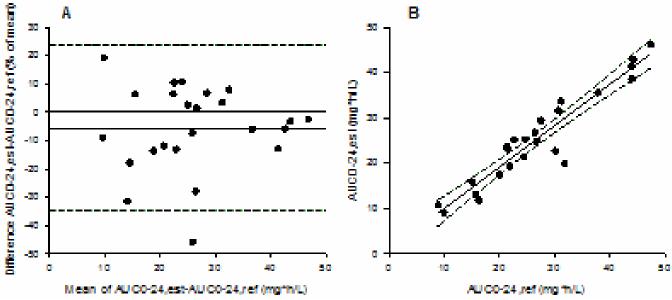
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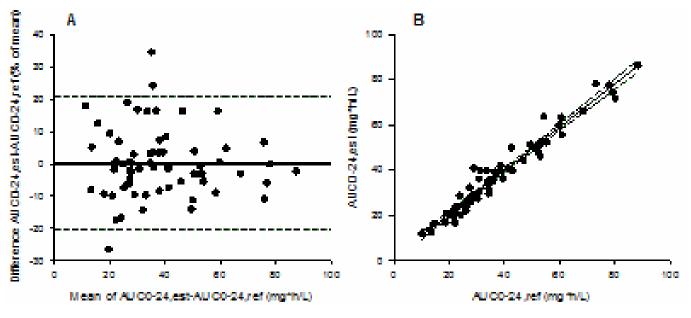
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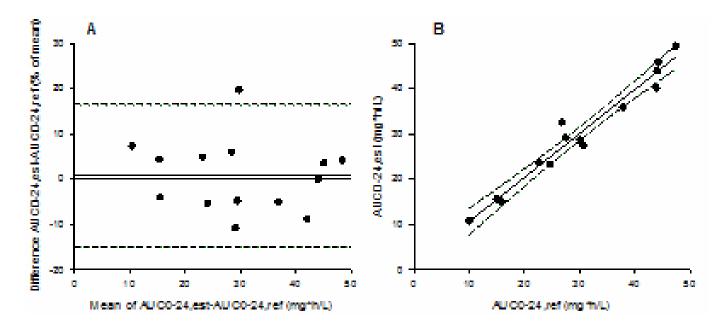
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10 20 AU CO-24 , ref (mg fh/L)









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