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1 **Analysis of the effects on the QT interval of a gatifloxacin-containing regimen**  
2 **versus standard treatment of pulmonary tuberculosis**

3

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20 **Running Head:** QT interval prolongation and Gatifloxacin TB regimen

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## 22 Abstract

### 23 Background

24 The effects on ventricular repolarisation – recorded on the ECG as lengthening of the QT interval – of  
25 acute tuberculosis and those of standard and alternative anti-tuberculosis regimens are under-  
26 documented. A correction factor (QTc) is introduced to make the QT independent of the heart rate,  
27 translating into the slope of the regression line between QT and heart rate being close to zero.

### 28 Methods

29 ECGs were performed pre- and 1-5 hours post-dosing (month 1, 2, end of treatment) around drugs’  
30 peak concentration time in tuberculosis patients treated with either the standard 6-month treatment  
31 (rifampicin and isoniazid for 6 months, pyrazinamide and ethambutol for 2 months; “control”) or a test  
32 regimen with gatifloxacin, rifampicin and isoniazid given for 4 months (pyrazinamide for the first 2  
33 months) as part of the OFLOTUB study, a randomized controlled trial conducted in five African countries.  
34 Drug levels were measured at steady-state (month 1) in a subset of patients. We compared treatment  
35 effects on the QTc and modelled the effect of individual drugs’  $C_{\max}$  on the Fredericia-corrected QT  
36 interval.

### 37 Results

38 1686 patients were eligible for the correction-factor analysis of QT at baseline (mean age 30.7 years,  
39 27% female). Median heart rate decreased from 96/min at baseline to 71/min at end of treatment, and  
40 body temperature from 37.2 to 36.5 C. Pre-treatment, the non-linear model estimated the best  
41 correction factor at 0.4081 in-between Bazett’s (0.5) and Fridericia’s (0.33) corrections. On treatment,  
42 Fridericia (QTcF) was the best correction factor.

43 1602 patients contributed to the analysis of QTcF by treatment arm. The peak QTcF value during follow-  
44 up was >480ms for 21 patients (7 and 14 in the test and control arm) and >500ms for 9 (5 and 4,  
45 respectively), corresponding to a risk difference of -0.9% (95% CI: -2.0% to 2.3%, p=0.12) and 0.1% (95%  
46 CI: -0.6% to 0.9%, p=0.75), respectively between the test and control arms. 106 (6.6%) patients had a  
47 peak measurement change from baseline >60ms (adjusted between-arm difference 0.8%, 95% CI -1.4%  
48 to 3.1%, p=0.47). No evidence was found of an association between  $C_{max}$  of the anti-tuberculosis drugs  
49 1 month into treatment and the length QTcF.

#### 50 **Conclusions**

51 Neither a standard 6-month nor a 4-month gatifloxacin-based regimen appear to carry a sizeable risk of  
52 QT prolongation in patients with newly-diagnosed pulmonary tuberculosis. This is to-date the largest  
53 dataset studying the effects of anti-tuberculosis regimens on the QT, both for the standard regimen and  
54 for a fluoroquinolone-containing regimen.

55

## 56 Introduction

57 The time for ventricular depolarisation and repolarisation is measured on the surface electrocardiogram  
58 (ECG) as the time from the start of the Q wave to the end of the T wave. Prolonged repolarisation is  
59 recorded on ECG as lengthening of the QT interval (1). This condition is considered to increase the risk  
60 for ventricular arrhythmias and the potentially fatal 'Torsade de Pointe' (TdP). Ventricular repolarisation  
61 is mediated mostly by the outflow of potassium ( $K^+$ ) from the myocytes. Attenuation of the voltage-  
62 dependent  $K^+$  channels' ability to repolarize can prolong the QT interval and create the conditions for  
63 TdP.

64 There is very little knowledge about how acute tuberculosis affects the QT interval, or about the  
65 potential for anti-tuberculosis treatments to affect ventricular repolarisation. With prospects of having  
66 them added to the anti-tuberculosis armoury of drugs, drugs belonging to the fluoroquinolone (FQ)  
67 family have attracted attention, as they can variably affect ventricular repolarisation(2). These drugs  
68 have different affinities for binding to the rapid component of the delayed-rectifier current  $I_{Kr}$ , which is  
69 expressed by the human ether-a-go-go-related gene hERG(3). In particular, it has been suggested that  
70 compounds such as gatifloxacin and moxifloxacin, both considered in anti-tuberculosis regimens, which  
71 have a methoxy substitution at position C8, might inhibit hERG at therapeutically-achievable  
72 concentrations(4).

73 Establishing the risk for QT prolongation associated with the use of a drug is not straightforward.  
74 The length of the QT interval varies during the day and from day to day and with gender and age, and is  
75 influenced by potassium levels, body temperature, heart rate (HR), and factors such as disease and  
76 drugs. It is customary to introduce a correction factor to account for the effect of the heart rate (heart  
77 rate-corrected QT, or QTc). The correction factor is introduced to make the QT independent of the heart  
78 rate, hence the need for the slope of the regression line to be as close to zero when the QT is plotted  
79 against the heart rate. The QTc is calculated by dividing the QT by RR (calculated as 60 / heart rate). The

80 International Conference for Harmonisation (ICH) recommends analysing the QT using the Bazett and  
81 the Fridericia corrections (QTcB and QTcF), which use fixed exponents of 0.5 and 0.33, respectively, for  
82 the RR, and exploring other corrections whenever appropriate. The Bazett correction QTcB ( $QT/RR^{0.5}$ ) is  
83 considered most suited for HR 60 – 100 bpm (it under-corrects if HR < 60 and over-corrects if HR > 100  
84 bpm); the Fridericia formula QTcF ( $QT/RR^{0.33}$ ) is generally regarded as more appropriate outside this  
85 range. Various other corrections exist. Population-based corrections are also recommended for specific  
86 conditions (5, 6). There is no information on the appropriateness of these corrections in patients with  
87 pulmonary tuberculosis (PTB) – i.e. how good they are in making the QT interval independent of the  
88 heart rate.

89 We analysed the QT of patients with PTB enrolled in a randomised trial with a non-inferiority  
90 design comparing the standard 6-month treatment to a gatifloxacin-containing 4-month regimen (the  
91 OFLOTUB trial) (7). We also evaluated the effect of exposure, expressed as  $C_{max}$  of the individual drugs of  
92 both treatment arms, in the patients who participated in a pharmacokinetic sub-study (nested  
93 pharmacokinetic/pharmacodynamic (PK/PD) study).

94

## 95 **Materials and methods**

### 96 **Study design**

97 The study was a non-inferiority randomized, open-label, controlled trial, conducted in five African  
98 countries: Benin, Guinea, Kenya, Senegal and South-Africa with a nested PK/PD study for subset of  
99 patients. Its objective was to assess the efficacy and safety of a gatifloxacin containing 4-month regimen  
100 for the treatment of drug-susceptible pulmonary tuberculosis compared to standard World Health  
101 Organisation recommended 6-month treatment (8). The protocol was approved by relevant ethics  
102 committee and regulatory authorities of all partner's institutions. This study was registered at Clinical-

103 Trials.gov under registration number NCT00216385. More details on study design have been published  
104 elsewhere (7).

#### 105 **Subjects**

106 Male and female patients, aged 18 to 65 years, newly diagnosed with microscopically-proven pulmonary  
107 tuberculosis and providing informed consent for inclusion in the trial were considered for enrolment.  
108 Patients with congenital QTc interval prolongation >480 ms, clinically significant bradycardia (40  
109 beats/minute), hypokalaemia grade 1 and above (i.e. < 3.0 mEq/l), and patients using drugs known to  
110 prolong QT interval, were excluded at enrolment.

#### 111 **Treatment arms**

112 Patients were randomised, stratified by country, to one of two treatment arms. The control treatment  
113 regimen included isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given daily for 2  
114 months followed for 4 months with isoniazid and rifampicin (i.e. 2RHEZ/4RH). In the intervention arm  
115 (referred to as test), gatifloxacin (G) was substituted for ethambutol in the 2-month intensive phase and  
116 was maintained for the 2-month continuation phase (i.e. 2RHGZ/2GRH). Gatifloxacin was given at a dose  
117 of 400 mg per day, irrespective of body weight. The doses of HRZE followed World Health Organization  
118 (WHO) recommendations (8) and were provided as fixed dose combination tablets.

#### 119 **Measurements**

120 Along with clinical and laboratory evaluations, twelve-lead electrocardiograms (ECGs) were performed  
121 at baseline (pre-treatment), at months 1 and 2 of TB treatment and at the end of the treatment. ECGs  
122 were obtained with a Shiller CP300 machine which was configured to report automatically QT intervals  
123 automatically and to calculate the corrected QT interval (QTc) by Bazett's formula. Exact heart rate at  
124 the time of ECG measurement was also automatically measured and recorded. This allowed us to  
125 calculate *a posteriori* QTc interval using other formulas such as Fredericia's. The following information

126 was also recorded for each patient: gender, age, medical history, vital signs (including body  
127 temperature), clinical examination and concomitant medication.

128 Plasma samples were taken for drug concentration measurements at baseline and month 1 as part of a  
129 population PK study. Patients were randomised to one of three sampling schedules (A, B and C), each  
130 with three sampling times: (A) Sample 1: within the hour before the treatment dose (-1 to 0 hours),  
131 Sample 2: between 1 and 2 hours after the treatment dose, Sample 3: between 2.5 and 3.5 hours after  
132 the treatment dose; (B) Sample 1: between 1 and 2 hours after the treatment dose, Sample 2: between  
133 2.5 and 3.5 hours after the treatment dose, Sample 3: between 4 and 6 hours after the treatment dose; (  
134 C) Sample 1: between 1 and 2 hours after the treatment dose, Sample 2: between 2.5 and 3.5 hours  
135 after the treatment dose, Sample 3: between 8 and 10 hours after the treatment dose.

136 Population pharmacokinetic models were used to generate individual estimates of peak drug  
137 concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ) at steady state. (9,10)

138 Drug safety was closely monitored during the course of the study in compliance with ICH/GCP  
139 guidelines.

#### 140 **Statistical methods**

##### 141 *Review of the correction factor*

142 The QT measurement at enrolment, combined across treatment arm, was used to assess the correction  
143 factor in this sample of TB patients. We calculated the linear regression coefficients of gradient and  
144 intercept for the Bazett corrected (correction factor  $RR^{0.5}$ ) and Fridericia-corrected (correction factor  
145  $RR^{0.33}$ ) QT against  $1-RR$ . These analyses were repeated for each measurement post randomisation:  
146 month 1, month 2 and at the end of treatment (either month 4 or 6 for the test and control arms,  
147 respectively) combined across treatment arm for the purpose of assessing the adequacy and robustness  
148 of the correction factors.



149 In addition, a non-linear model was fitted to the uncorrected QT at baseline to estimate the population-  
150 specific correction factor for the pre-treatment patients with active pulmonary tuberculosis.

151 *Definition of outcomes*

152 According to ICH guidelines (6), QTc data are presented as both continuous and binary variables using  
153 the Fridericia correction (QTcF). Continuous measurements were summarised using the arithmetic  
154 mean, standard deviation (sd). Peak QTc was defined as the maximum QTc interval from up to a possible  
155 3 follow-up recordings (week 4, 8 or end of treatment).

156 *Between-treatment arm comparisons*

157 Peak QTcF during follow-up and change of this measurement from baseline were compared between  
158 treatment arms using linear regression, adjusting for country where possible. Peak values were also  
159 classed as binary variables using cutpoints at >450ms >480ms, and >500ms, and change from baseline as  
160 >60ms; between-treatment comparisons were expressed as risk difference, adjusted for country.  
161 Patients with a baseline measurement and at least one follow-up measurement contribute to these  
162 analyses.

163 **PKPD analysis**

164 In the subset of patients who have drug concentrations measurements, the effect of  $C_{max}$  for each drug  
165 separately, on QTcF at month 1 was assessed using linear regression, adjusting for country, sex, age and  
166 QTcF at enrolment, and study arm (only adjusting for study arm for the effect of  $C_{max}$  for isoniazid,  
167 rifampicin and pyrazinamide).

168

169 **Results**

170 **Patients' characteristics**

171 Of the 1692 patients in the ITT population, 1686 (99.6%) were eligible for the correction-factor analysis  
172 of QT at baseline (see flow diagram Figure 1). Mean age was 30.7 years, 27% were female, 18% HIV-  
173 positive, 51% had cavitation and 25% had a temperature  $>37.7^{\circ}$  C (Table 1).

174 **Heart rate and Temperature**

175 Median heart rate decreased progressively from 96/min at baseline throughout treatment to reach 71 at  
176 end of treatment. Median baseline body temperature was 37.2 and decreased to approximately 36.5 on  
177 treatment. The percentage of participants with temperature  $>37.7^{\circ}$  C fell over follow-up to 2.7%  
178 (43/1582) and 2.4 % (37/1539) at months 1 and 2 after the start of TB treatment, respectively, and to  
179 0.7% (10/1445) at the end of treatment. (Table 2)

180 **Correction factors**

181 In these patients with active PTB about to initiate treatment, the uncorrected QT increased with the  
182 heart rate overall (coefficient -202.7 95% confidence interval [CI] -209.6 to -195.9, adjusted  $R^2 = 0.67$ )  
183 (Table 3).

184 At baseline, neither the Bazett and Fridericia corrections were optimal; QTcB tended to under-  
185 correct (gradient 51.8, 95% CI 43.5, 60.1) and QTcF over-correct (gradient -46.3, 95% CI -54.1, -38.5) the  
186 QT (Fig 2, Table 3). The non-linear model estimated the correction factor to be 0.4081 (95% CI 0.3949,

187 0.4213) (QTcTB), in between the Bazett and Fridericia correction factors. This correction factor was  
188 independent of the country, sex and presence or absence of cavitation (Fig 3)

189 Applying the Bazett, Fridericia and the new correction factor to QT data measured 1 and 2  
190 months after the start of TB treatment and at the end of treatment (month 4 in the test arm and month  
191 6 in the control arm) showed the QTcF to be a better correction, with the gradient coefficient close to  
192 zero (Table 3).

### 193 **Between-treatment comparison**

194 The QTcF was therefore applied for between-treatment comparisons. A total of 1602 patients  
195 contribute to these analyses (Fig 1). Baseline characteristics were similar between the two treatment  
196 arms (Table 1).

197 The peak QTcF value during follow-up was >480ms in 21 patients overall: 0.9% (7/804) and 1.8%  
198 (14/798) in the test and control arms, respectively (Table 3). There were nine occasions of QTcF >500ms  
199 (see Table 3 and Table 4). Five occurred in the test arm (0.6%) at month 1 (506 and 514ms), month 2  
200 (518ms) and month 4 (502 and 511ms), and four in the standard treatment arm (0.5%) at month 2 (510  
201 and 517ms) and month 6 (507 and 569ms). The risk difference for QTcF >480ms and >500 were -0.9%  
202 (95% CI: -2.0% to 2.3%, p=0.12) and 0.1% (95% CI: -0.6% to 0.9%, p=0.75), respectively, between the test  
203 and control arms. Overall 107 (6.7%) patients had a peak measurement change from baseline >60ms,  
204 with no difference between the two treatment arms (adjusted difference 0.7%, 95% CI -1.5% to 3.0%,  
205 p=0.53).

206 The overall mean peak QTc value was moderately higher in the test versus control arm; adjusted  
207 mean difference 2.6ms (95%CI 0.2, 4.9)ms, p=0.030). The mean and 95%CI QTcF values at baseline,  
208 month 1, month 2 and end of treatment were: 384.7ms (383.2-386.1), 394.2ms (392.6-395.7), 395.7ms  
209 (394.1-397.3), and 395.9ms (394.2-397.5) for the test arm; and 385.1ms (383.6-386.6), 391.6ms (390.1-  
210 393.2), 391.7ms (390.1-393.3), and 394.9ms (393.1-396.7) for the control arm, respectively. (Fig 4)

211

212 **Drug levels**

213 Pharmacokinetic measures were available for 291 patients at month 1 (144 and 147 respectively in the  
214 test and control arms). The  $C_{max}$ ,  $T_{max}$  and AUC achieved by the individual drugs in the two treatment  
215 arms are summarised in Table 5. There was no evidence that  $C_{max}$  of any of the drugs individually were  
216 associated with QTc-F at month 1 (see Table 5).

217

218 **Discussion**

219 This study shows that the risk of QT prolongation with either a 4-month regimen including gatifloxacin or  
220 a standard 6-month treatment is low: only five (0.6%) and four (0.5%) subjects respectively had a value  
221  $>500$  ms, and 7% and 6.3% had a prolongation relative to their baseline value of  $>60$  ms.

222 We also found that in this African population with active PTB, the Bazett formula QTcB  
223 ( $QT/RR^{0.5}$ ) under-corrects, and the Fridericia formula QTcF ( $QT/RR^{0.33}$ ) over-corrects QT as RR increases;  
224 the QTcTB ( $QT/RR^{0.4081}$ ) fits best this population. For instance, screening patients for values  $>480$  ms with  
225 the QTcF would have missed 1 of the 2 cases, and the QTcB would have excluded 3 more cases. While  
226 the TB correction factor appears to benefit subjects of both sexes in all the countries of this study, it will be  
227 important to verify the appropriateness of this correction on larger and more diverse TB patient  
228 populations. This may have implications for entry criteria when recruiting into a TB treatment trial, as  
229 well as measuring relative changes in the QT after treatment. As patients on treatment recover, the  
230 Fridericia formula becomes more appropriate, and QTcB and QTcTB over-estimate the prolongation  
231 (with 11, 13 and 8 cases having QTcB, and 2, 3 and 3 cases having QTcTB,  $>480$  msec at week 4, 8 and  
232 end of treatment, respectively). The correction factor is introduced to make the QT independent of the  
233 heart rate, which translates to the regression lines displayed in Figures 2 and 3 for corrected QTc; the  
234 slope is closest to zero (a horizontal line) when using the population-specific QTcTB.

235 ECGs were done before starting and during anti-tuberculosis treatment. During treatment the  
236 ECGs were done 1 – 5 hours post-dosing (corresponding to the interval when drug concentrations are  
237 expected to be highest in plasma) at month 1, 2 and at the end of treatment (month 4 for the  
238 gatifloxacin-containing regimen or month 6 for standard treatment). These measurements occurred  
239 when drug concentrations were at steady-state, and patients were improving or convalescent.

240 It is becoming increasingly clear that, while FQs are generally known to block the inward delayed  
241 rectifier current  $I_{Kr}$  through the potassium channel, QT prolongation and TdP risk cannot be considered  
242 as a class effect, as the individual FQ affinities for the hERG-  $I_{Kr}$  receptor (both in absolute terms and  
243 relative to plasma levels) vary widely.

244 *In vitro*, gatifloxacin had an  $IC_{50}$  of 130  $\mu$ M (48.8  $\mu$ g/ml) for the hERG channel  $I_{Kr}$  with blocking  
245 activities for other quinolones ranging from 18  $\mu$ M (sparfloxacin) as the most active to 1420  $\mu$ M  
246 (ofloxacin) as the least active quinolone(4). A similar range of blocking activities for  $I_{Kr}$  has been  
247 determined in the mouse tumour cell line AT-1, with  $IC_{50}$  values of 0.23  $\mu$ M (sparfloxacin), 26.5  $\mu$ M  
248 (gatifloxacin) and 27.2  $\mu$ M (grepafloxacin)(11). The influence of a series of fluoroquinolones on action  
249 potential duration (APD) was also studied in isolated Guinea pig right ventricular myocardia: while some  
250 of the drugs tested did not influence APD, gatifloxacin increased the APD by 13% at a concentration of  
251 100  $\mu$ M (37.5  $\mu$ g/ml); at the same concentration, sparfloxacin increased the APD by 41%, while  
252 grepafloxacin and moxifloxacin showed intermediate values of 24% and 25%, respectively(12).

253 All the FQ tested showed propensities for a prolongation of the QT and/or the QTc interval  
254 (Carlsson correction:  $QT - 0.175(RR - 300)$ ) in an *in vivo* anaesthetized rabbit model. The compounds  
255 were infused intravenously at a dose of 2 mg/kg/min for 30 minutes, with sparfloxacin producing the  
256 highest absolute QT prolongation (+129 ms from baseline); gatifloxacin showed a minimal prolongation  
257 of the QT interval (increase from baseline = 14 ms). Ventricular tachycardia and TdP were only elicited  
258 by sparfloxacin, and only when the infusion was extended to a duration of 60 minutes(11). A similar

259 model in rabbits using intravenous infusion doses of 4 mg/kg/min yielded QT and QTc interval  
260 prolongation values for gatifloxacin similar to those of sparfloxacin, with increases in interval times from  
261 about 160 ms at baseline to about 320 ms at 30 minutes after the start of the infusion(13).

262 In order to put the non-clinical data into perspective, these concentrations that evoke cardiac  
263 effects in experimental in-vitro and in-vivo models must be compared to plasma levels achieved in  
264 patients. According to the Tequin® (gatifloxacin) label, a 400 mg intravenous bolus given to healthy  
265 volunteers leads to a  $C_{max}$  of ~5.5 µg/ml, a concentration which is ~23-times lower than the  $IC_{50}$  for hERG  
266 inhibition and ~5-times lower than the  $IC_{50}$  for  $I_{Kr}$  blockade in AT-1 cells; in this phase 3 trial (oral  
267 treatment with 400 mg/d) the  $C_{max}$  was 3.9 µg/ml after the first dose and 3.8 µg/ml at steady state  
268 [ $IC_{50}/C_{max}$  ratio ~34 (95%CI 21 – 54)]. Both indicate a substantially lower risk than that inferred by Kang  
269 et al(4). In addition, when applying a scaling factor of 0.324 for the dose administered to extrapolate the  
270 *in vivo* rabbit data to humans, the intravenous infusion of 2 mg/kg/min, resulting in only a minimal  
271 prolongation of the QT interval, will then correspond to a human equivalent bolus dose of ~20 mg/kg, or  
272 1000 mg for a 50 kg human. Similarly, the FDA data for Tequin® in mongrel dogs, where no influence on  
273 the ECG was seen at an intravenous infusion of 10 mg/kg/min, can be translated into a human  
274 equivalent bolus dose of ~162 mg/kg, or a dose of >8000 mg. All these data suggest a low risk for  
275 gatifloxacin to induce serious cardiovascular adverse events.

276 Furthermore, there is no clear correlation between hERG-  $I_{Kr}$  receptor affinity and risk of QT  
277 prolongation or risk of TdP. The risk of TdP with FQs is in actual facts very low, and is estimated to be at  
278 ~27 for 10 million prescriptions for gatifloxacin, including subjects with concomitant risk factors(14). The  
279 Uppsala Monitoring Centre database reports(15), as of 01/03/2014 a total of 13,556 cardiac adverse  
280 events with fluoroquinolones, of which 767 are QT prolongation and 451 TdP, 100 and 53 respectively  
281 with gatifloxacin, 207 and 166 with levofloxacin and 269 and 113 with moxifloxacin. Direct comparisons

282 are obviously not possible due to the absence of the denominator (number of people exposed to the  
283 different FQs).

284 The main methodological limitation of this study is that there was no external review of QTc  
285 measurement, but all were measured automatically with the same machine in all study sites, and all QTc  
286 values reported in the CRF were reviewed by an external monitor; furthermore, there was only one QTc  
287 measurement done at each time point. Another potential limitation is that, assuming that  $C_{max}$  is the  
288 main determinant of the risk for QT prolongation, ECGs were done during treatment when all drugs  
289 were at steady-state, but peak plasma concentrations might have been higher in the earlier phases of  
290 treatment.

291 In summary, this study indicates that neither a standard 6-month TB treatment, nor a 4-month,  
292 six-day-a-week regimen including gatifloxacin at 400 mg/d in combination with three (rifampicin,  
293 isoniazid and pyrazinamide) other anti-tuberculosis drugs for the first two months, and two (rifampicin,  
294 isoniazid) for the following two months, appear to carry a sizeable risk of QT prolongation.

295 These results are significant and novel for a number of reasons. To our knowledge, this is to-  
296 date the largest dataset studying the QT interval during acute active tuberculosis itself, documenting  
297 the effects on the QT interval of the standard regimen as well as a fluoroquinolone-containing regimen,  
298 and investigating the relationship between drug levels and the QT. As such, they fill a knowledge gap,  
299 and are useful for future studies. It will be important to verify in other sets of patients, including those  
300 with other forms of tuberculosis, whether and how active disease affects the QT interval, and which  
301 formula is best suited to correct it so as to make it independent of the heart rate. This knowledge will  
302 improve also our understanding of treatment effects, as it will refine the classification of QT values as  
303 being normal or prolonged – both for eligibility to treatment and for assessing risks. This study also  
304 provides a reference point for other studies which will aim to evaluate the effects on ventricular

305 repolarisation of standard and alternative treatments on both newly-diagnosed and drug-resistant

306 tuberculosis, as the latter in particular may include drugs with potential for QT prolongation.

307

308

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313

### 314 **Disclaimer**

315 PO, CM and CL are staff members of the World Health Organization; the authors alone

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361 **Table 1:** Baseline demographics and clinical variables for patients in the (i) correction factor analysis  
362 (n=1686) and (ii) the comparison of QTC by treatment arm (n=1602)

		Correction factor analysis (i)				Between-arm comparison (ii)			
		Test (n=845)		Control (n=841)		Test (n=804)		Control (n=798)	
		n	%	n	%	n	%	n	%
Country	Benin	158	(18.7)	158	(18.8)	150	(18.7)	151	(18.9)
	Guinea	219	(25.9)	225	(26.7)	216	(26.9)	213	(26.7)
	Kenya	100	(11.8)	97	(11.5)	100	(12.4)	95	(11.9)
	Senegal	178	(21.1)	180	(21.4)	154	(19.1)	163	(20.4)
	South Africa	190	(22.5)	181	(21.5)	184	(22.9)	176	(22.1)
Age, years	Mean(sd)	30.8 <sup>1</sup>	(9.1)	30.6	(9.0)	30.8	(9.1)	30.6	(8.9)
Sex	Female	229	(27.1)	232	(27.6)	215	(26.7)	224	(28.1)
HIV <sup>2</sup>	Positive	147	(17.5)	156	(18.8)	141	(17.6)	150	(18.9)
Cavitation <sup>3</sup>	Yes	438	(52.0)	417	(50.0)	413	(51.5)	394	(49.8)
Heart rate <sup>4</sup>	Mean (sd)	95.6	(17.4)	95.1	(17.8)	95.6	(17.5)	95.2	(17.5)
Temperature <sup>5</sup>	>37.7	216	(25.6)	198	(23.6)	201	(25.0)	187	(23.5)
BMI	Mean (sd)	17.4	(4.9)	17.5	(5.0)	17.3	(4.9)	17.5	(5.0)

363 <sup>1</sup>Age not known for n=1 in the test arm; <sup>2</sup> HIV status unknown in analysis (i) for n=11 (n=5 in the test arm, n=6 in  
364 the control arm) and in analysis (ii) for n=10 (n=5 in the test arm, n=5 in the control arm); <sup>3</sup> Cavitory status  
365 unknown in analysis (i) for n=10 (n=3 in the test arm, n=7 in the control arm) and in analysis (ii) for n=9 (n=2 in the  
366 test arm, n=7 in the control arm); <sup>4</sup> Heart rate unknown in analysis (ii) for n=4 (n=2 in the test arm, n=2 in the  
367 control arm); <sup>5</sup> Temperature unknown in analysis (i) for n=3 (n=1 in the test arm, n=3 in the control arm) and in  
368 analysis (ii) n=3 (n=1 in the test arm, n=2 in the control arm)  
369 sd standard deviation; BMI body mass index

370 **Table 2:** Heart rate and Temperature during the treatment phase, restricted to samples with data

371 available for the correction analysis

		Baseline	Month 1	Month 2	End of treatment*
Heart rate	Median	96	81	78	71
	IQR	83-106	71-95	68-90	62-81
	n	1686	1562	1512	1402
Temperature	Median	37.2	36.6	36.5	36.4
	IQR	36.6-37.7	36-37	36-36.9	36-36.9
	n	1682	1582	1512	1445
	>37. 7° C	24.6%	2.7%	2.4%	0.7%
	% (n/N)	(414/1682)	(43/1582)	(37/1539)	(10/1445)

372 \* month 4 (gatifloxacin) or month 6 (control / IQR interquartile range

373

**Table 3:** Linear regression coefficients (gradient and intercept) for uncorrected QT, Bazett (QTcB), Fridericia (QTcF) and new correction (QTcTB) vs 1-RR at baseline (randomisation), 1 and 2 months from start of treatment and at the end of treatment

		Baseline (n=1686)	Month 1 (n=1560)	Month 2(n=1512)	End of treatment* (n=1402)
Uncorrected QT	Gradient (95% CI)	-202.7 (-209.6, -195.9)	-162.3 (-168.8, -155.8)	-154.5 (-161.1, -148.0)	-134.4 (-141.3, -126.7)
	Intercept (95% CI)	403.8 (401.2, 406.3)	396.3 (394.4, 398.3)	395.1 (393.4, 396.9)	395.1 (391.9, 395.0)
	R <sup>2</sup>	0.67	0.61	0.59	0.48
QTcB	Gradient (95% CI)	51.8 (43.5, 60.1)	80.8 (73.5, 88.1)	80.8 (73.6, 88.0)	90.0 (82.3, 97.7)
	Intercept (95% CI)	397.1 (394.1, 400.2)	394.1 (392.0, 396.3)	394.5 (392.5, 396.4)	394.7 (393.0, 396.3)
	R <sup>2</sup>	0.08	0.23	0.24	0.27
QTcF	Gradient (95% CI)	-46.3 (-54.1, -38.5)	-9.8 (-16.8, -2.8)	-5.5 (-12.5, 1.4)	9.7 (2.2, 17.2)
	Intercept (95% CI)	401.0 (398.1, 403.9)	395.4 (393.3, 397.4)	394.9 (392.0, 396.7)	394.1 (392.5, 395.7)
	R <sup>2</sup>	0.075	0.005	0.002	0.005
QTcTB**	Gradient (95% CI)	-2.9 (-10.9, 5.1)	30.7 (23.6, 37.8)	33.3 (26.2, 40.3)	46.0 (38.4, 53.6)
	Intercept (95% CI)	399.5 (396.5, 402.4)	394.9 (392.8, 397.0)	394.7 (392.8, 396.6)	394.3 (392.7, 395.9)
	R <sup>2</sup>	0.000	0.044	0.053	0.092

QTcB	>450	5.5% (93)	7.0% (109)	6.7% (101)	6.3% (88)	374
	>480	0.3% (5)	1.22% (19)	1.2% (18)	1.1% (16)	375
	>500	0.1% (2)	0.7% (11)	0.5% (8)	0.2% (3)	376
QTcF	>450	0.24% (4)	1.7% (27)	1.3% (20)	2.2% (31)	377
	>480	0.06% (1)	0.5% (8)	0.3% (5)	0.6% (8)	378
	>500	0% (0)	0.1% (2)	0.2% (3)	0.3% (4)	379
QTcTB**	>450	0.89% (15)	2.4% (38)	2.7% (41)	3.3% (46)	380
	>480	0.12% (2)	0.6% (10)	0.5% (8)	0.78% (11)	381
	>500	0.06% (1)	0.51% (8)	0.20% (3)	0.29% (4)	382
						383

384 \* month 4 (gatifloxacin) or month 6 (control) \*\* correction factor 0.4081 (95% CI 0.3949, 0.4213)

385

**Table 4:** Comparison of on-treatment Fredericia correction QT values by study arm

		Test (n=804)	Control (n=798)	difference (95% CI)	P-value
Peak value in follow-up	Mean (sd), ms	407.2 (23.3)	404.5 (25.3)	2.6 (0.2, 4.9)	0.030
Peak value in follow-up – change from baseline	Mean (sd), ms	22.9 (26.2)	19.1 (28.1)	3.8 (1.1, 6.4)	0.005
Risk difference (95% CI)					
Peak value in follow-up	>450ms <sup>1</sup> , % (n)	4.3% (35)	4.4% (35)	0.2% (-1.6%, 2.0%)	0.83
Peak value in follow-up	>480ms <sup>2</sup> , % (n)	0.9% (7)	1.8% (14)	-0.9% (-2.0%, 2.3%) <sup>4</sup>	0.12
Peak value in follow-up	>500ms <sup>3</sup> , % (n)	0.6% (5)	0.5% (4)	0.1% (-0.6%, 0.9%) <sup>4</sup>	0.75
Peak value in follow-up – change from baseline	>60ms, % (n)	7.0% (56)	6.4% (51)	0.7% (-1.5%, 3.0%)	0.53

386 <sup>1</sup>timing of peak value >450ms - test arm n=12, 10 and 13 at month 1,2 and end of treatment, control arm n=15, 9 and 24 at month 1,2 and end of  
 387 treatment; <sup>2</sup>timing of peak value >480ms - test arm n=3, 1 and 3 at month 1,2 and end of treatment, control arm n=5, 4 and 5 at month 1,2 and end of  
 388 treatment; <sup>3</sup>timing of peak value >500ms - test arm n=2, 1 and 2 at month 1,2 and end of treatment, control arm n=0, 2 and 2 at month 1,2 and end of  
 389 treatment; <sup>4</sup> not adjusted for country; CI confidence interval; sd standard deviation

390

391

392 **Table 5:**  $C_{max}$ ,  $T_{max}$  and AUC at steady state for each drug, by study arm (n=291)

Drug	At steady state	Test (n=144) Median (minimum, maximum)	Control (n=147) Median (minimum, maximum)	Estimated gradient (95% CI), P-value <sup>1</sup>
Gatifloxacin	$C_{max}$	3.8 (2.5-5.8)	NA	-3.82 (-11.78, 4.14), 0.34
	$T_{max}$	1.7 (0.8-3.6)	NA	NA
Ethambutol	$C_{max}$	NA	3.2 (1.5-5.5)	-1.99 (-5.96, 1.98), 0.32
	$T_{max}$	NA	2.5 (1.5-4.5)	NA
Isoniazid	$C_{max}$	3.1 (0.7-8.0)	3.1 (0.5-6.0)	0.86 (-1.11, 2.83), 0.39
	$T_{max}$	0.9 (0.6-3.2)	0.8 (0.3-3.6)	NA
Rifampicin	$C_{max}$	6.3 (1.4-13.2)	6.9 (2.0-15.6)	0.16 (-1.08, 1.39), 0.81
	$T_{max}$	2.2 (1.3-5.6)	1.9 (1.1-5.3)	NA
Pyrazinamide	$C_{max}$	35.9 (23.8-60.4)	35.0 (21.9-62.1)	-0.28 (-0.66, 0.10), 0.15
	$T_{max}$	1.7 (0.9-4.5)	1.5 (0.8-5.0)	NA

393 <sup>1</sup>for the association of each drug  $C_{max}$  individually on QTcF at month 1, adjusted for country, sex, age

394 and QTcF at enrolment, and study arm (only for Isoniazid, Rifampicin and Pyrazinamide). CI

395 confidence interval.

396



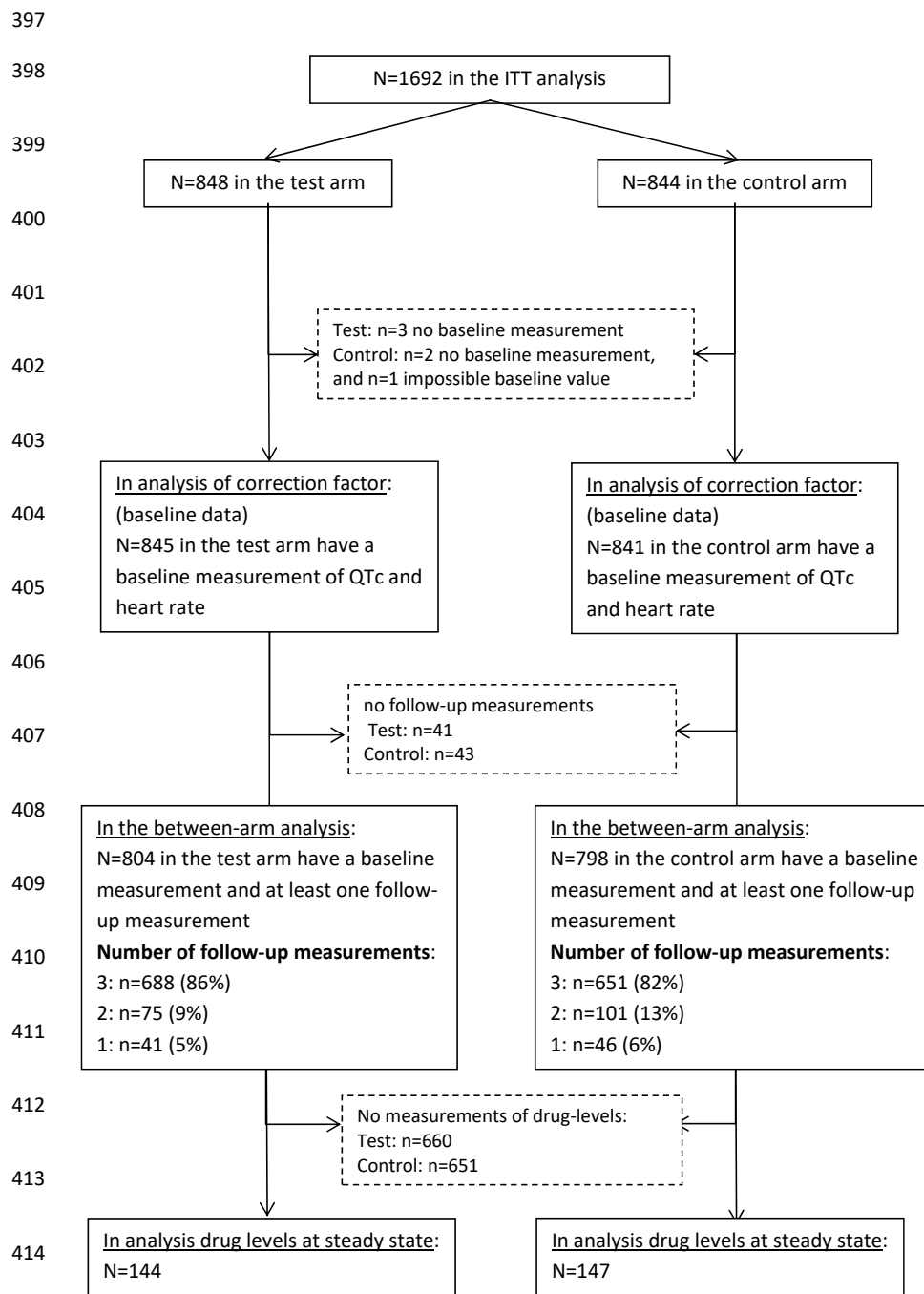
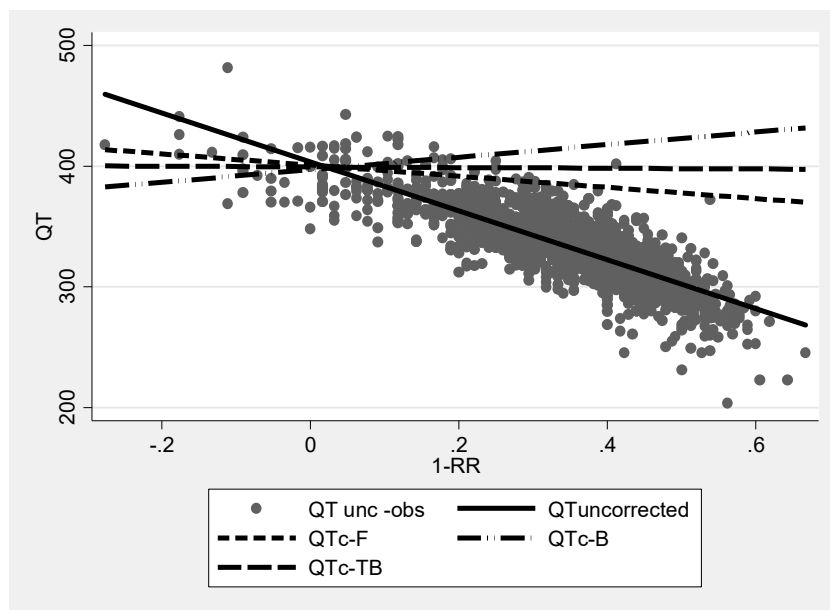


FIG 1 Study flow diagram



416

417 **FIG 2** Plot of uncorrected data and regression line; and regression lines for Bazett-corrected,  
418 Fridericia-corrected and new-corrected QT (QTcTB), using data at baseline (n=1686)

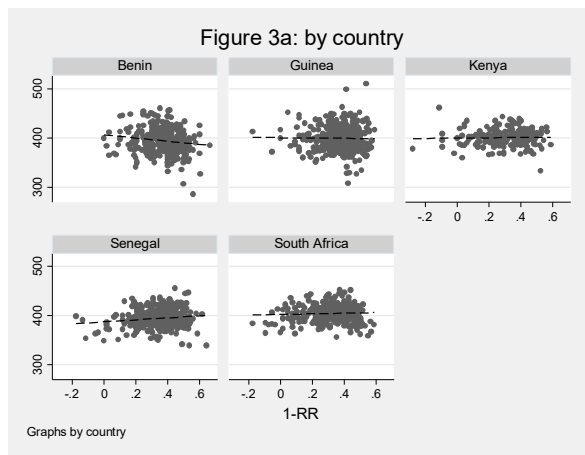
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420 Footnote: QT unc-obs QT uncorrected observed data; QTUncorrected regression line; QTc-F

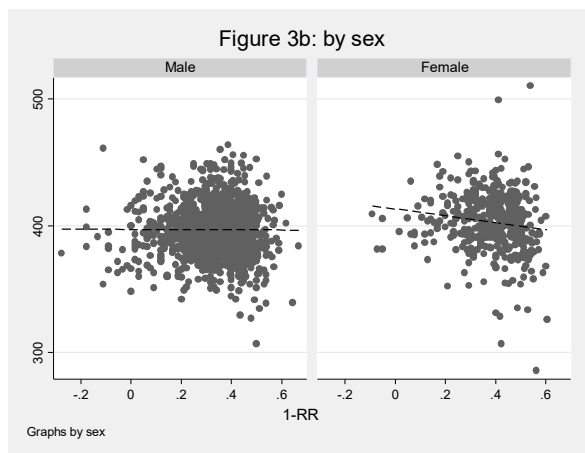
421 Fridericia corrected regression line; QTc-Bazett corrected regression line; QTc-TB corrected

422 regression line using correction factor of 0.4081.

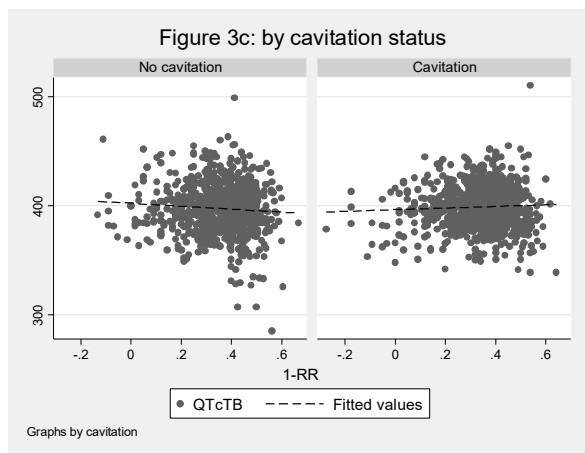
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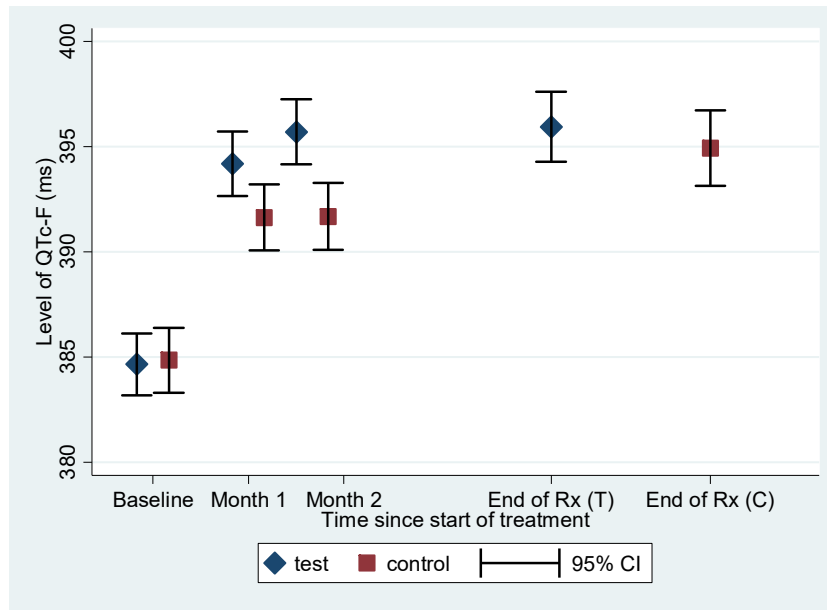


425



426

427 **FIG 3** Plot of QTcTB (0.4081) against 1-RR (where RR=60/heart rate), using data at baseline



428

429 **FIG 4.** Boxplots of QTc-F values at baseline, months 1 and 2, and end of treatment (month 4 and 6,

430 respectively) for the gatifloxacin and standard treatment arm.

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