1   **Analysis of the effects on the QT interval of a gatifloxacin-containing regimen**

2   **versus standard treatment of pulmonary tuberculosis**

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

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1

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

Introduction

56

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

Materials and methods

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).

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.

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.

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.

7

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 $>37.7^{o}$ 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 $>37.7^{o}$ 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

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

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 befit subjects of box 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.

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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 μM (48.8 μg/ml) for the hERG channel I_{Kr} with blocking

245   activities for other quinolones ranging from 18 μM (sparfloxacin) as the most active to 1420 μM

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 μM (sparfloxacin), 26.5 μM

248   (gatifloxacin) and 27.2 μM (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 μM (37.5 μg/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

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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

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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[1]	(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[2]	Positive	147	(17.5)	156	(18.8)	141	(17.6)	150	(18.9)
Cavitation[3]	Yes	438	(52.0)	417	(50.0)	413	(51.5)	394	(49.8)
Heart rate[4]	Mean (sd)	95.6	(17.4)	95.1	(17.8)	95.6	(17.5)	95.2	(17.5)
Temperature[5]	>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 [1]Age not known for n=1 in the test arm; [2] 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); [3] Cavitary 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); [4] Heart rate unknown in analysis (ii) for n=4 (n=2 in the test arm, n=2 in the

367 control arm); [5] 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

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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

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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 stat 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^2	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^2	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^2	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^2	0.000	0.044	0.053	0.092

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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)

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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[1], % (n)	4.3% (35)	4.4% (35)	0.2% (-1.6%, 2.0%)	0.83
Peak value in follow-up	>480ms[2], % (n)	0.9% (7)	1.8% (14)	-0.9% (-2.0%, 2.3%)[4]	0.12
Peak value in follow-up	>500ms[3], % (n)	0.6% (5)	0.5% (4)	0.1% (-0.6%, 0.9%)[4]	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 [1]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; [2]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; [3]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; [4] not adjusted for country; CI confidence interval; sd standard deviation

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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[1]
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   [1]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
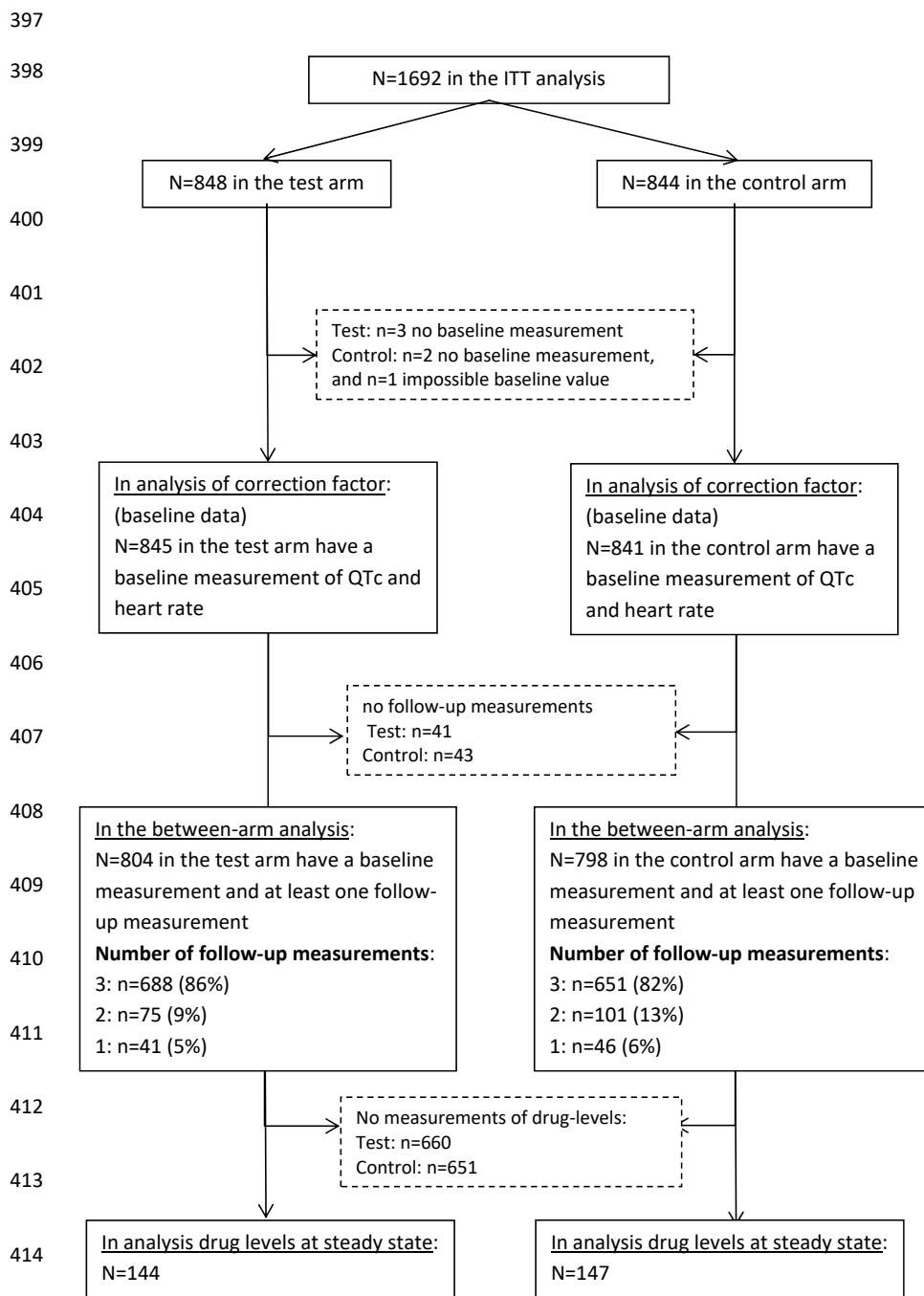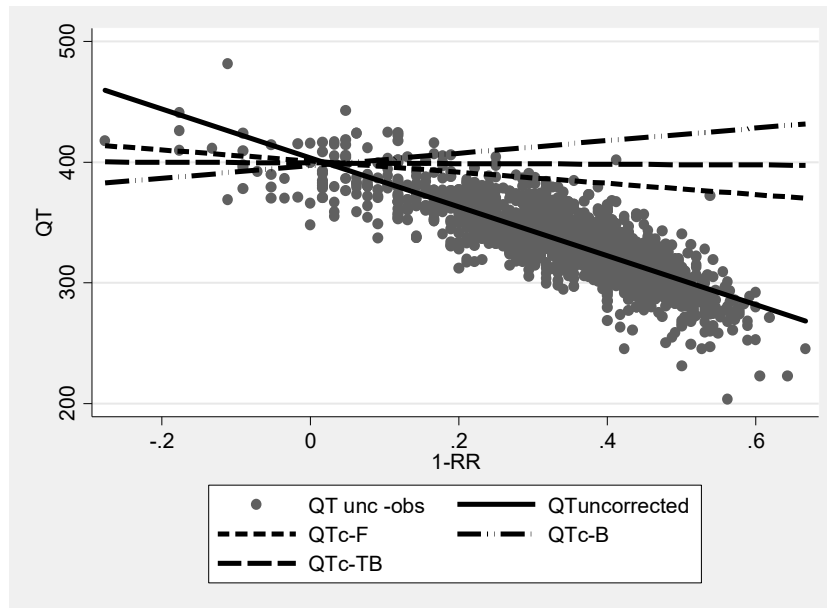
395   confidence interval.

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N=1692 in the ITT analysis

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N=848 in the test arm

N=844 in the control arm

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401

Test: n=3 no baseline measurement
Control: n=2 no baseline measurement,
and n=1 impossible baseline value

402

403

In analysis of correction factor:
(baseline data)
N=845 in the test arm have a
baseline measurement of QTc and
heart rate

In analysis of correction factor:
(baseline data)
N=841 in the control arm have a
baseline measurement of QTc
and heart rate

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no follow-up measurements
Test: n=41
Control: n=43

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In the between-arm analysis:
N=804 in the test arm have a baseline
measurement and at least one follow-
up measurement
Number of follow-up measurements:
3: n=688 (86%)
2: n=75 (9%)
1: n=41 (5%)

In the between-arm analysis:
N=798 in the control arm have a baseline
measurement and at least one follow-up
measurement
Number of follow-up measurements:
3: n=651 (82%)
2: n=101 (13%)
1: n=46 (6%)

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No measurements of drug-levels:
Test: n=660
Control: n=651

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In analysis drug levels at steady state:
N=144

In analysis drug levels at steady state:
N=147

414

415   **FIG 1 Study f**low diagram

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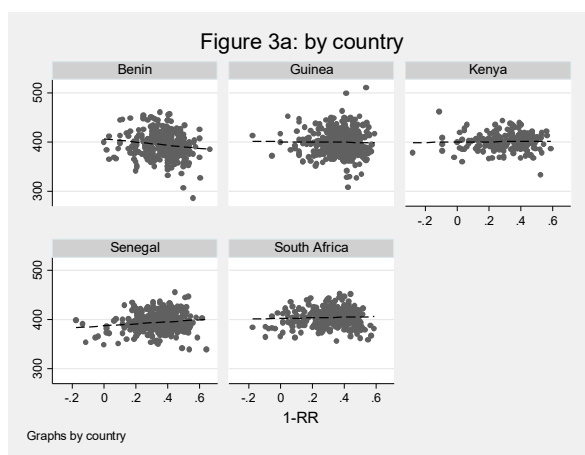
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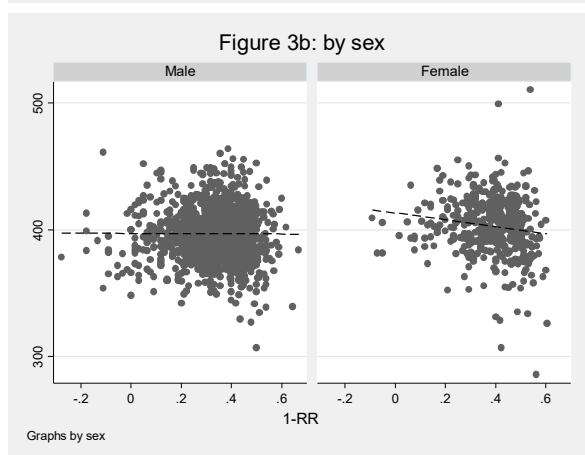420   Footnote: QT unc-obs QT uncorrected observed data; QTuncorrected regression line; QTc-F

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

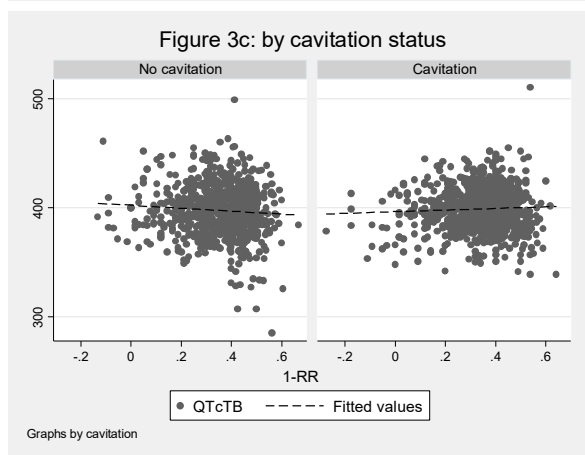422   regression line using correction factor of 0.4081.
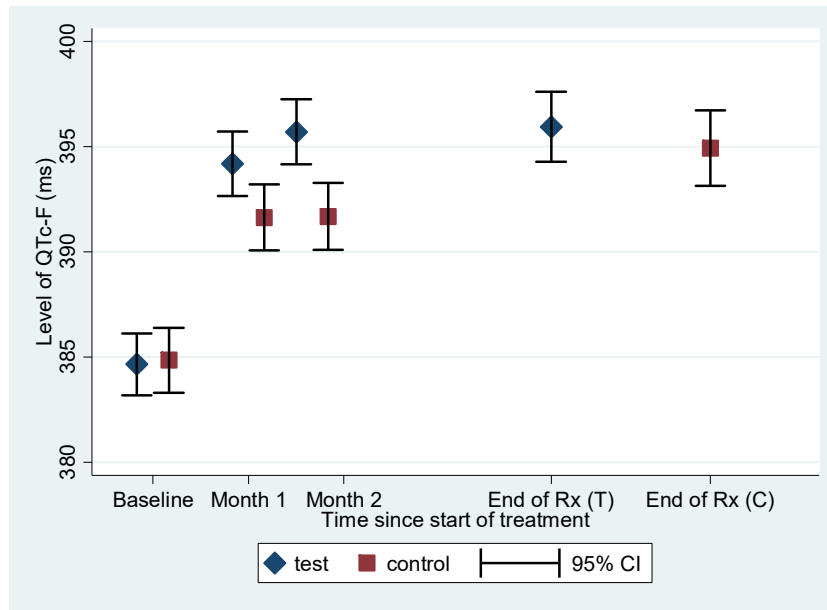
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427   **FIG 3** Plot of QTcTB (0.4081) against 1-RR (where RR=60/heart rate), using data at baseline

FIG 4. Boxplots of QTcF values at baseline, months 1 and 2, and end of treatment (month 4 and 6, respectively) for the gatifloxacin and standard treatment arm.