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Efficacy and safety of higher doses of levofloxacin for MDR-TB: A randomized placebo-controlled phase 2 trial

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Abstract

Background: Evaluation of optimal dosing has generally been inadequate during TB drug development. Fluoroquinolones are central to TB treatment. We aimed to determine the dose of levofloxacin needed to achieve maximal efficacy and acceptable safety and tolerability as part of a multidrug TB regimen.

Methods: Opti-Q was an international, multi-center, randomized, placebo-controlled, phase II trial. Eligible participants with TB resistant to isoniazid and rifampicin but susceptible to fluoroquinolones (MDR-TB) were randomized to receive one of four weight-adjusted once-daily doses of levofloxacin given for 24 weeks(168 doses): 11mg/kg(750mg), 14mg/kg(750mg/1000mg), 17 mg/kg(1000mg/1250mg) or 20mg/kg(1250mg/1500mg) alongside a multidrug regimen. The primary efficacy outcome was time to sputum culture conversion and the primary safety outcome was grade 3 or higher adverse events.

Findings: 111 participants were randomized from three sites in South Africa and Peru. 83(75%) had cavities on chest x-ray, 55(50%) had a smear grading of 3+, median BMI was 20.4 kg/m². Median levofloxacin AUC/MIC was 573, 633, 918 and 1343 across the four treatment arms. There was no difference in time to culture conversion on solid or liquid media by treatment arm (stratified log-rank p=0.282), by tertile of AUC/MIC (p=0.350), or by dose received (p=0.723); 69.3%, 74.8%, 70.6% and 78.3% achieved culture conversion after 8 weeks on solid media respectively across the treatment arms; 64.6%, 69.5%, 52.6% and 69.6% in liquid culture. More participants experienced a grade 3–5 adverse event by dose (37.0% and 16.0% in the highest and lowest dose groups respectively, p=0.042, Cochran-Armitage test for trend) and by tertile of AUC (p=0.011).

Interpretation: As part of a multidrug regimen, doses of levofloxacin above 1000mg resulted in greater exposures and increased frequency of adverse events but did not result in faster time to sputum culture conversion. A dose of 1000mg daily can achieve the target exposure in nearly all adults and was well tolerated. [ClinicalTrials.gov NCT01918397](https://clinicaltrials.gov/ct2/show/study/NCT01918397)

Introduction

Tuberculosis is the infectious disease associated with most global morbidity and mortality today, a distinction that has returned as we enter a COVID-19 post-pandemic era. The last two years have seen the biggest changes in the treatment of tuberculosis in more than four decades with treatment for drug-sensitive TB (DS-TB) being reduced from 6 to 4 months(1, 2), and treatment for drug-resistant TB (DR-TB) being reduced from 18–24 months to 6 months(3, 4). Despite progress, TB drug dose optimization has generally been inadequate during TB drug development. As part of combination regimens, the initial dosing schedules used for rifampicin(5), rifapentine(6), bedaquiline(7), delamanid(8), and linezolid(9) have subsequently been revised after a period of use (although it is unclear whether the rifampicin dose will change(10)). This is not surprising, as many of the drugs that are part of TB regimens (for example linezolid, moxifloxacin and clofazimine) were used at dosages that had been established for other diseases. Choice of TB dosing for almost all TB drugs has been determined by factors other than efficacy and safety (for example, cost was the main driver of the rifampicin dose (5)). Furthermore, when prospective evaluation of dosing has been done, it is most often done in mono-therapy studies which do not reflect the complex interplay among different drugs in the multi-drug regimens needed to treat TB. Dose-optimization studies are also sometimes done in persons without TB leading to results that differ dramatically from those with the same doses in TB patients (e.g., rifapentine(11, 12)).

Fluoroquinolones have been central to recent shortening of treatment duration for both DS and DR-TB. This class is now part of first line therapy for both, but optimal dosing of levofloxacin for TB treatment is unknown. Moxifloxacin has emerged as the preferred drug from this class, largely due to the absence of data on levofloxacin from clinical trials, and as a consequence of moxifloxacin lower minimum inhibitory concentration (MIC) and marginally better efficacy in the murine model of tuberculosis(13). Nevertheless, levofloxacin offers advantages over moxifloxacin—including less QT prolongation, wider availability, lower cost—and could be a viable alternative for both DS-TB and DR-TB; indeed, South African national guidelines include a levofloxacin-based regimen as first-line therapy for DR-TB for exactly these reasons(14). Levofloxacin has a more favorable PK/PD profile in plasma than moxifloxacin in a rabbit model, although moxifloxacin penetrates better into cavitary lesions(15). In one open-label randomized controlled phase II trial, there was no difference in time to culture conversion or long-term treatment outcomes between levofloxacin 750mg and moxifloxacin 400mg(16), although there were more grade 3–4 adverse events reported over the course of the study in the levofloxacin group (79.2 vs. 63.5%, $P = 0.03$) (17). In a 7-day study, moxifloxacin 400mg, levofloxacin 1000mg and gatifloxacin 400mg all had comparable early bactericidal activity, only slightly less than isoniazid(18, 19).

We designed the Opti-Q trial to determine the optimal dose of levofloxacin as part of a regimen for the treatment of fluoroquinolone susceptible multidrug-resistant TB (MDR-TB). Levofloxacin was given as weight-adjusted doses based on standard practice for levofloxacin dosing at the time with a wide range of doses from 11mg/kg to 20mg/kg. A dose of 5mg/kg would have led to a substantial number of study participants receiving less than the

WHO recommended dose. However, the dose of 11mg/kg was known to be well tolerated in several studies(20, 21) and the 20mg/kg dose had been studied in TB meningitis in study of 15 adults (22) and in a larger study of 2523 children where a small increase in musculoskeletal disorders was seen at this dose(23); this was therefore the rationale for the range of doses evaluated in our trial. Since our goal was to determine if higher doses would be more effective and since weight is an important determinant of levofloxacin exposure, we used weight-based dosing to control for this parameter. We developed our study design to evaluate the contribution of a range of doses of this antimicrobial agent within a multidrug regimen. The goal of the trial was to identify the dose of levofloxacin that would achieve the drug exposure associated with maximal efficacy and acceptable safety and tolerability.

Methods

Study design

Opti-Q was an international, multi-center, randomized, placebo-controlled, superiority phase II trial comparing four different levofloxacin dosing groups for the treatment of TB resistant to isoniazid and rifampicin but susceptible to fluoroquinolones. The trial was conducted as part of the US Centers for Disease Control and Prevention (CDC) Tuberculosis Trials Consortium (TBTC) with additional funding from US NIH/NIAID (DMID) and drug donation from MacLeods Pharmaceuticals, Ltd. The trial was approved by institutional review boards of Boston University, and all study sites.

Participants

Participants with smear-positive pulmonary tuberculosis with evidence of resistance to isoniazid and rifampicin and susceptibility to fluoroquinolones on rapid molecular tests were eligible for the study. Individuals with a QTcF of 450ms or more, use of a fluoroquinolone for 7 days or more within 30 days prior to randomization, poorly controlled diabetes (defined as HgB A1c >9%), aged <18 or weight <40kg were not eligible. Full details of the design have been published previously(24).

Randomization and masking

Eligible participants were randomized in the ratio 1:1:1:1 to receive one of four weight-adjusted once-daily doses of levofloxacin (250mg tablets) given for 28 weeks (168 doses): 11mg/kg (750mg), 14mg/kg (750mg if weight <60kg, 1000mg otherwise), 17 mg/kg (1000mg if <60kg, 1250mg otherwise) or 20mg/kg (1250mg if <60kg, 1500mg otherwise). Levofloxacin dosing was blinded such that all participants received 6 tablets (combination of active and placebo) once-daily for 24 weeks given as part of a background regimen that was consistent with the then current local and WHO guidelines for the treatment of MDR-TB; the background regimen was selected by local investigators(25, 26) and did not include bedaquiline, linezolid, delamanid, or pretomanid (Tables S4.6 and S4.7 in online supplement)

Randomization was achieved using pre-prepared lists with blocks of varying sizes; separate lists were prepared for each site. Randomization was stratified by site and, in South Africa, by HIV status. The randomization lists were prepared by a statistician independent of the

study. Allocation was made by each site pharmacist by opening the next in a series of opaque envelopes.

Participants, clinicians, study staff, laboratory technicians, and study leadership were blinded to treatment allocation. Only the site pharmacist was aware of the allocated dose and only the DSMB reviewed aggregate safety and efficacy data by treatment arm on a 6-monthly basis, supported by the unblinded study statistician. No other individuals in the study were aware of treatment allocation.

Procedures

Participants were followed for 28 weeks from randomization with sputum samples taken for Middlebrook 7H11 Selective agar and BACTEC MGIT 960 liquid culture every two weeks for the first 12 weeks, and then every four weeks to week 28. Blood samples for chemistry and hematology were taken on the same schedule. Targeted symptoms assessment, focused clinical assessment, and recording of all adverse events (irrespective of relatedness to study medications) was done weekly for the first 8 weeks and with the same schedule as sputum samples thereafter. Adverse events were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) published on 28 May 2009.

Pharmacokinetic (PK) sampling for levofloxacin exposures was performed in one 24-hour period between the 14th and 28th day after the start of study regimen (further details have been previously published(27)). All baseline *M. tuberculosis* isolates were shipped to CDC's Division of Tuberculosis Elimination Reference Laboratory for determination of MIC for levofloxacin. MICs were measured both on 7H10 Middlebrook agar and in a broth microdilution assay; the former was considered primary for all analyses.

Outcomes

The primary objectives of the study were to: 1) determine the levofloxacin AUC/MIC that provides the shortest time to sputum culture conversion on solid medium; 2) determine the highest levofloxacin AUC that is both safe and associated with fewer than 25% of patients discontinuing or reducing their dose of levofloxacin; 3) develop a dosing algorithm to achieve the AUC associated with maximal efficacy and acceptable safety and tolerability. For our efficacy objective, based on murine studies, the target AUC/MIC was set as 100(28)

The primary efficacy outcome was time to negative sputum culture conversion on solid medium, which is defined as the time from initiation of treatment to the first of two consecutive negative cultures (without an intervening positive culture) that are not followed by a culture-positive specimen within 28 weeks. Time to negative sputum culture conversion in liquid medium defined similarly was an important secondary efficacy outcome. The primary safety outcome was the proportion of participants with grade 3 or higher adverse events occurring up to and including four weeks after the last dose of study drug. The primary tolerability outcome was the proportion of participants completing 168 daily doses of levofloxacin within 200 days of initiation of the study regimen (excluding patients withdrawn from treatment where the reason was not at least possibly related to study medication).

Sample Size

Planned total enrollment was 120 participants giving 80 evaluable participants (allowing for up to 33% loss to follow-up). This was calculated to give 95% power to detect a correlation of -0.4 or 88% power to detect a correlation of -0.35 between AUC/MIC and time to culture conversion (log transformed) using the Pearson correlation coefficient. This sample size also gives 80% power to detect a relationship between AUC and the proportion of individuals experiencing a grade 3 or above adverse event (AE) assuming 30% AEs at the mean AUC and 54% when the AUC increases by one standard deviation. The sample size gives 80% power to detect a relationship between AUC and the proportion of participants completing treatment, assuming 85% completion at the mean AUC and 70% when the AUC increases by one standard deviation. These sample size assumptions were not based on previously published studies but based on the judgment of the study investigators as to what correlations would likely be enough to inform dosing guidelines.

Statistical Analysis

The primary analysis population for the efficacy analysis included all randomized participants that took at least one dose of trial medication, analyzed in the treatment arm to which they were allocated, excluding those without a positive culture at screening or baseline on either culture media and excluding those without phenotypic evidence of resistance to isoniazid and rifampicin and those without phenotypic susceptibility to levofloxacin. The primary analysis population for safety analyses included all randomized participants who took at least one dose.

Cochrane-Armitage test for trend was used for evaluating trends in proportions across the four treatment arms or across tertiles of PK and MIC parameters.

Time to culture conversion was analyzed using stratified log-rank test and Cox proportional hazards regression. Testing for non-proportional hazards was done using Schoenfeld residuals. When building a multivariable model, covariates were included if univariable likelihood ratio test $p < 0.2$ and retained in the model through backward selection if $p < 0.1$.

Role of funding source

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Results

Enrollment and demographics

Between January 2015 and December 2016, 255 participants were screened for eligibility and 111 randomized to one of four dosing groups from one site in Cape Town, South Africa and two sites in Lima, Peru. Enrollment was stopped at 111, below the target 120, since the total number of evaluable participants was achieved. The main reason for exclusion from randomization was lack of evidence of resistance to rifampicin or isoniazid, or of

susceptibility to fluoroquinolones (Figure 1). Among those randomized, 75 (68%) had no prior diagnosis of TB, 83 (75%) had cavities on chest X-ray, 55 (50%) had a smear grading of 3+, 68 (61%) were of male sex, the median age was 26.0 years old and the median BMI was 20.4 kg/m². Fifty-eight (52%) had disease resistant to pyrazinamide on phenotypic DST. There were 78 (70%) participants who received 5 drugs and 28 (25%) received 6 drugs at baseline, in addition to levofloxacin (Table 1). Baseline characteristics were well balanced between randomized groups.

Three participants never started treatment and were excluded from the ITT analysis population; a further 10 participants had no baseline positive cultures, or had baseline phenotypic DST indicating ofloxacin resistance, rifampicin susceptibility, or indeterminate isoniazid susceptibility (Figure 1).

MIC and PK data

MIC results were available from baseline samples for 77 individuals (75 for primary MIC on agar plate, AP); participants characteristics of these 77 were similar to those with missing MIC (Table S4.3 in online supplement). Median (Interquartile range) levofloxacin MIC was 0.2 µg/ml (0.2, 0.2) on Agar Plate and 0.5 µg/ml (0.5, 0.5) in broth microdilution (BMD), Figure 2. Of 77, 9 participants had no levofloxacin PK data (see Figure 1). Among the remaining 68 participants, median AUC/MIC was 855.0 with the minimum being 332.1, above our pre-specified target AUC/MIC of 100 (Figure 2C.).

Safety

There were 108 participants who started treatment and are included in the safety analysis population. Of these, 25 (23.1%) experienced a grade 3–5 adverse event (AE), 10 (9.3%) experienced a serious AE (SAE) and one participant died as a result of an intracranial IRIS reaction in the setting of unrecognized CNS TB (on the 17mg/kg treatment arm, see supplement table S9.8 for more details). There was evidence of an increasing trend (Cochrane-Armitage test for trend) in the proportion of participants experiencing a grade 3–5 AE ($p=0.042$) and by tertile of AUC ($p=0.022$) and in the proportion of participants experiencing any SAE by tertile of AUC ($p=0.011$, Table 3). The participants with the three highest exposures all experienced grade 3–5 AEs and one of these was the participant that died (see Online Supplement, Figure S9.1). The only grade 3–5 AE that occurred in more than two participants was blood uric acid increase (7 participants). The most common grade 3–5 adverse events (shown in Table 3) are more likely related to companion drugs than to levofloxacin.

A single participant had a QTcF exceeding 500ms (Grade 3); this participant was in the 20mg/kg treatment arm and had the highest recorded AUC, although the QT prolongation was considered likely attributable to concomitant use of azithromycin, a protocol-prohibited drug with known QT prolongation potential. The AE resolved after discontinuation of azithromycin; levofloxacin was not discontinued. One further participant experienced a QTcF of between 470 and 500ms after randomization in the lowest tertile of AUC. Both participants with QT interval of 470 ms or greater subsequently completed study treatment. A further 8 participants experienced a QTcF of greater than between 450 and 470 ms

after randomization. These events occurred more frequently among participants in the highest tertile of AUC, 7 (21.2%), compared to the lowest tertile, 1 (3.0%), $p=0.014$, and $p=0.029$ excluding the participant who received azithromycin. Furthermore, excluding this participant, there was evidence of a linear relationship between maximum QTcF from visits at or after randomization and AUC ($p < 0.001$, Figure 4) with a mean increase of 7.3ms, 95% CI (3.1ms, 11.5ms), per increase in $100 \text{ h} \cdot \mu\text{g/ml}$. The largest difference in QTcF between lower and upper tertile of AUC was seen at 16 weeks (see supplement Figure S12.4) with a mean change from baseline of QTcF of 8.0ms, 95% CI (1.6s, 14.4ms), in the lower tertile and 14.9ms, 95% CI (6.0ms, 23.8ms) in the upper tertile (excluding the participant who received azithromycin), a ΔQTcF of 6.9ms (95% CI -4.0ms , 17.9ms).

Since the actual dose of levofloxacin received depended both on allocated regimen and participant weight, we present safety outcomes by both in the online supplement (Table S9.7). Considering analyses within each weight band which allows us to compare doses directly, 750mg and 1000mg had similar safety outcomes (11–17mg/kg among those $<60\text{kg}$ and 11–14mg/kg among those $\geq 60\text{kg}$) however an increase was observed at the higher doses (1250mg in the lower weight band and 1500mg in the highest weight band).

Tolerability

In addition to the three that never started treatment, six participants were excluded from the tolerability analysis population for withdrawing from study medications for reasons not related to treatment (see Table S11.1 in supplement and Tables S11.2–S11.8 for sensitivity analyses). There were 71 (70%) participants who completed 168 doses within 200 days. There was no change in this tolerability outcome by dose ($p = 0.442$, supplementary table S11.1, Cochran-Armitage test for trend) but tolerability increased slightly by tertile of AUC ($p = 0.025$, supplementary table S11.5, 27 (84%) in highest tertile compared to 25 (81%) in lowest tertile). Of those that did not complete treatment, only 1 participant had a treatment failure outcome (20mg/kg arm, online supplement Table S8.2).

Time to culture conversion

There was no evidence of a difference in time to culture conversion on solid media by treatment arm (stratified log-rank $p = 0.282$), by tertile of AUC/MIC ($p = 0.350$, Table 2, Figure 3), or by actual mg dose received ($p = 0.723$). There was also no difference when considering MGIT liquid culture instead ($p = 0.313$ by treatment arm, $p = 0.121$ by tertile of AUC/MIC, $p = 0.171$ by actual mg dose received), or when considering PK parameters as continuous in a PK-PD analysis rather than as tertiles (supplement S14.23 and S14.30). There were 73.4% participants who achieved culture conversion after week 8 (by week 9) on solid culture (7H11S) and 64.1% in MGIT liquid culture; culture conversion was 93.3% and 87.5% after week 12 (by week 13) on solid culture and in liquid MGIT culture respectively. In multivariable Cox regression models, these findings did not change even after adjusting for important predictors of time to culture conversion. Important predictors were smear grade (likelihood ratio test $p < 0.001$) and study site ($p = 0.07$) for solid culture outcome; and baseline MGIT days to positivity (DTP) on the log scale (likelihood ratio test $p < 0.001$) and age ($p = 0.005$) for MGIT (see online supplement, Tables S15.1–S15.4). Culture results

at 6 months are shown in Tables S16.1 and 16.2, 94% of participants had negative MGIT cultures.

Discussion

We have confirmed previous observations that higher doses of levofloxacin result in higher exposures.(27) However, these higher exposures did not result in faster time to culture conversion. Moreover, the proportion of participants with grade 3 or higher adverse events and serious adverse events was increased in those receiving higher levofloxacin doses above 1000mg. While there was no obvious relationship between levofloxacin and the type of AE, our goal was to determine the type of TB treatment that is associated with the lowest rate of adverse events overall, even if one was not expected based on levofloxacin-related toxicities identified to date. This suggests no benefit in efficacy with increasing doses above 1000 mg daily. There was no observable increase in toxicity when people under 60kg received 1000mg. Although we saw limited variability in AUC in our small study sample, there is wide variability in levofloxacin absorption and a 750mg dose might result in some participants achieving drug levels below the target exposure(18). For this reason, we propose that a dose of 1000mg may be preferred as likely to achieve the target concentration in the largest number of patients. In programs using a fixed dose, 1000mg will make sure everyone is dosed adequately.

Culture conversion was high and treatment failure rare and therefore our study results are therefore not inconsistent with the observation that a levofloxacin AUC_{0-24}/MIC of >100 can be expected to be associated with a successful outcome of MDR-TB treatment with a levofloxacin-containing regimen(29–31). Notably, all patients receiving levofloxacin at any of the doses in our study were able to achieve this target when the MIC was 1.0 $\mu g/ml$ or less (the usual range in *M. tuberculosis* isolates susceptible to levofloxacin). This is in contradiction to the report of Ghimire et al, who concluded that doses of 1000 mg per day did not consistently achieve this target(30). The fact that all of our study participants had AUC_{0-24}/MIC above this threshold indicates that AUC_{0-24}/MIC of >100 was above the inflexion point on the activity/concentration curve; this in turns implies that further increases in AUC may not offer additional clinical benefit in the range of MICs that are encountered with susceptible *M. tuberculosis* isolates. Had we included lower doses of levofloxacin in our study we might have observed this inflexion, but we truncated our dose range so that no participants received less than the recommended adult dose of at least 750 mg of levofloxacin for treatment of TB(32).

We found a minimal increase in QTcF interval prolongation with higher exposures to levofloxacin (a $\Delta QTcF$ of 6.9ms (95% CI $-4.0ms, 17.9ms$) at 16 weeks between lower and upper tertile of AUC). This effect is less pronounced than with moxifloxacin, another member of the fluoroquinolone class.(33, 34) Formal QT prolongation studies have revealed substantial QT prolongation with moxifloxacin at 400 mg daily but none with levofloxacin at doses up to 1500 mg daily.³ This represents one of the advantages of levofloxacin, a safe, tolerable drug that can be safely used in combination with antituberculosis agents that have QT-prolonging effects. Bedaquiline, one such drug, is part of every current WHO-recommended regimen for the treatment of MDR/RR-TB.¹ While a growing body

of literature shows that bedaquiline-linked QT interval prolongations are rarely clinically important—even in combination with delamanid—it will still be beneficial to patients and TB programs to minimize the additive cardiotoxicity risk conferred by companion drugs(34, 35)

Strengths of this clinical trial include the use of randomization to allocate doses to participants, inclusion of sites in both Africa and South America, and the novel dose-finding study design. To our knowledge, this was the first clinical trial to evaluate dosing of an anti-infective agent as part of combination regimen based on efficacy and safety in association with AUC/MIC. The doses of other TB drugs have been chosen based on cost, availability, or dosing decisions from other disease areas; this has often resulted in sub-optimal doses being used in programmatic settings(36). Evaluation of doses has sometimes been deferred until after marketing authorization (e.g. linezolid and bedaquiline in BPaL(9)^{23a}). Our study provides a model of dose-finding in the context of a multi-drug regimen and employs a design that could be used to identify the optimal dose of other drugs included in TB regimens with a relatively modest sample size and intermediate efficacy outcome. Evidence for the optimal dose of moxifloxacin(33) is still lacking and dose-ranging studies are ongoing evaluating doses of several other drugs as part of multidrug regimens. Examples include pyrazinamide, rifampicin (PanACEA STEP2C, [NCT05807399](#)), linezolid (ACTG A5356, [NCT05007821](#)), and new oxazolidinones (ACTG RAD-TB).

Our study had several limitations. Participants were recruited in 2015 and 2016 and the background regimen for the treatment of drug-resistant tuberculosis was therefore not as potent as regimens currently recommended(3). While all participants in our study started on regimens of at least 5 drugs (including levofloxacin), no regimens included bedaquiline, delamanid, pretomanid, or linezolid. Regimens sometimes included drugs to which the TB strain was later shown to be resistant including pyrazinamide, ethambutol, or an injectable agent. Furthermore, only 73.4% had achieved culture conversion by 8 weeks on 7H11S and 64.1% in MGIT compared to around 83% in MGIT in both BPaL trials(9, 37). Nevertheless, we expect the conclusions regarding the optimal dose of levofloxacin also apply to more recent regimens containing bedaquiline and linezolid where the contribution of levofloxacin may be less critical and the safety of the combination regimen is more of a concern. Our study had some missing PK and MIC data due to laboratory factors, although participants with missing data had similar baseline characteristics to those without missing data. A further limitation of our study is that dosing of levofloxacin was weight-banded where such dosing is not usually implemented for adults. Nevertheless, our analysis of safety outcomes within weight bands shows observed comparability between the 750mg and 1000mg doses, despite limited power to compare doses within weight band. We did not reach our intended sample size of 120, but the proportion of participants lost to follow-up was lower than the anticipated 33% therefore we exceeded the target of 80 evaluable participants. A final limitation was that our study only looked at the intermediate outcome of time to culture conversion to examine dose-outcome relationships rather than the definitive outcome of durable cure in the absence of relapse or the emergence of drug resistance; higher doses of levofloxacin might prevent the emergence of fluoroquinolone resistance, but a very large study (or several studies pooled) would be needed to address this.

In conclusion, we have shown that doses of levofloxacin above 1000 mg do not reduce time to culture conversion but do result in an increased risk of grade 3 and above adverse events, with higher exposures also associated with slightly more QTcF prolongation. In our study, a dose of 750mg was adequate to achieve the target AUC/MIC of 100. However, as there was no detectable difference in toxicity between 750 mg and 1000 mg and there is wide variability of AUC achieved with oral levofloxacin (18, 27), we conclude that a dose of 1000 mg daily will most reliably achieve target levels without incurring unnecessary toxicity.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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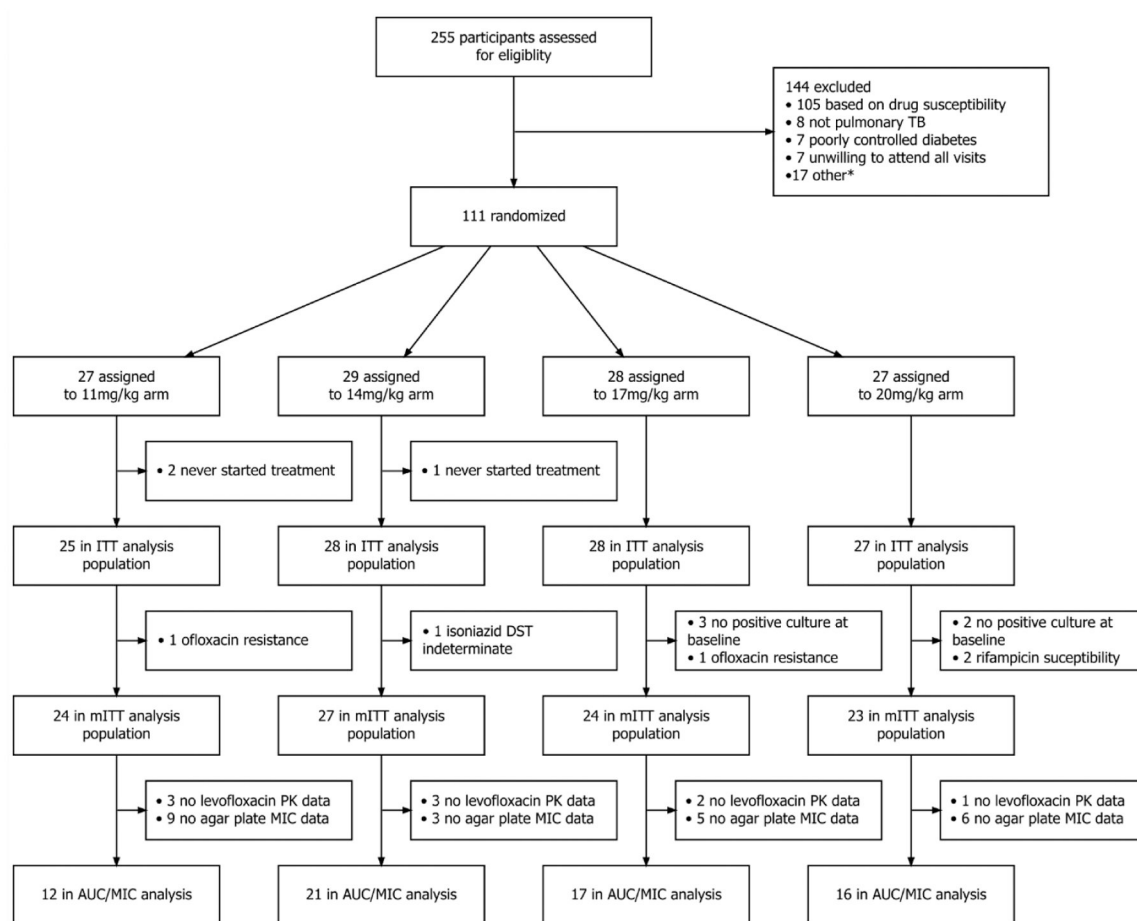


Figure 1.

CONSORT participant flowchart. *Other reasons for exclusion were: reason unavailable (4), concurrent use of known QT-prolonging drugs (3), quinolone use for 7 days within the past 30 days (3), hemoglobin concentration <9.0 g/dL (3), estimated serum creatine clearance <50 mg/dL (2), no negative pregnancy test for woman of childbearing potential (1), not expected to survive for at least 6 months (1).

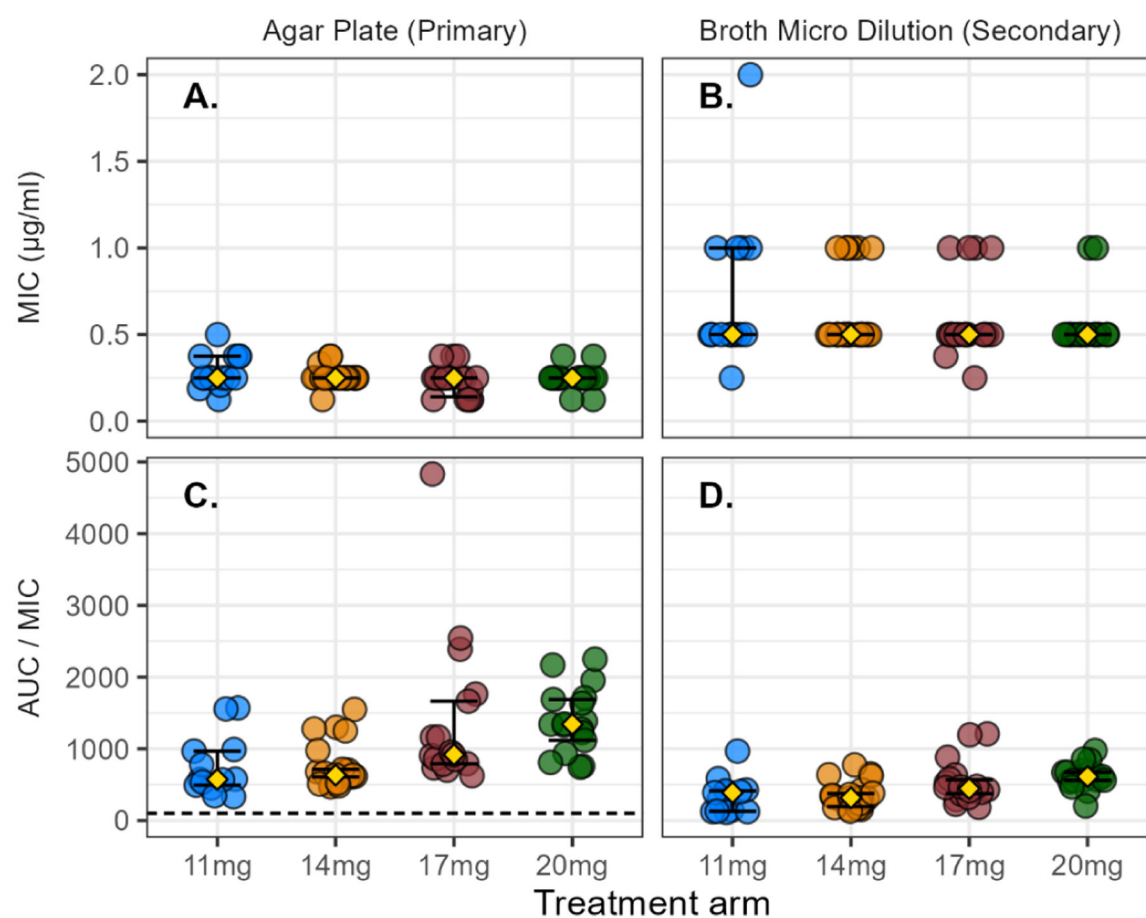


Figure 2. Summary of levofloxacin MIC (A. and B.) and AUC/MIC (C. and D.) done on Agar Plate (A. and C., primary method) and Broth Microdilution (B. and D.). Diamond shows median and error bars show 25th and 75th percentiles.

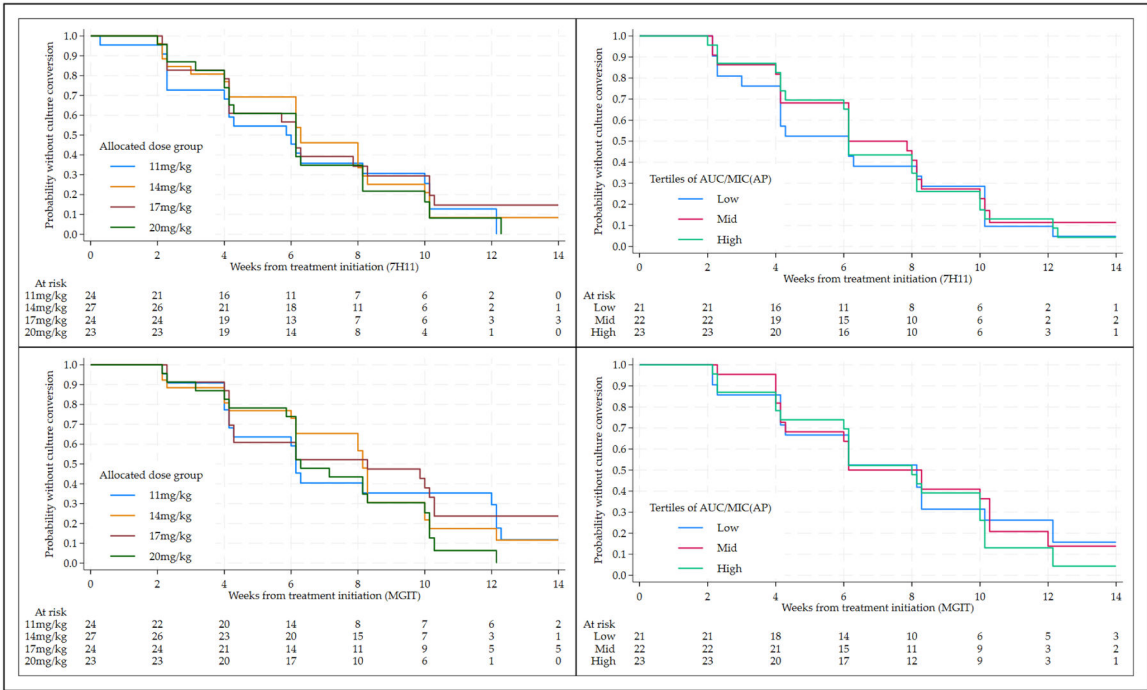


Figure 3: Kaplan-Meier of time to culture conversion in 7H11S (upper panels) and MGIT (lower panels) by allocated dose (left panels) and by tertile of AUC/MIC (right panels).

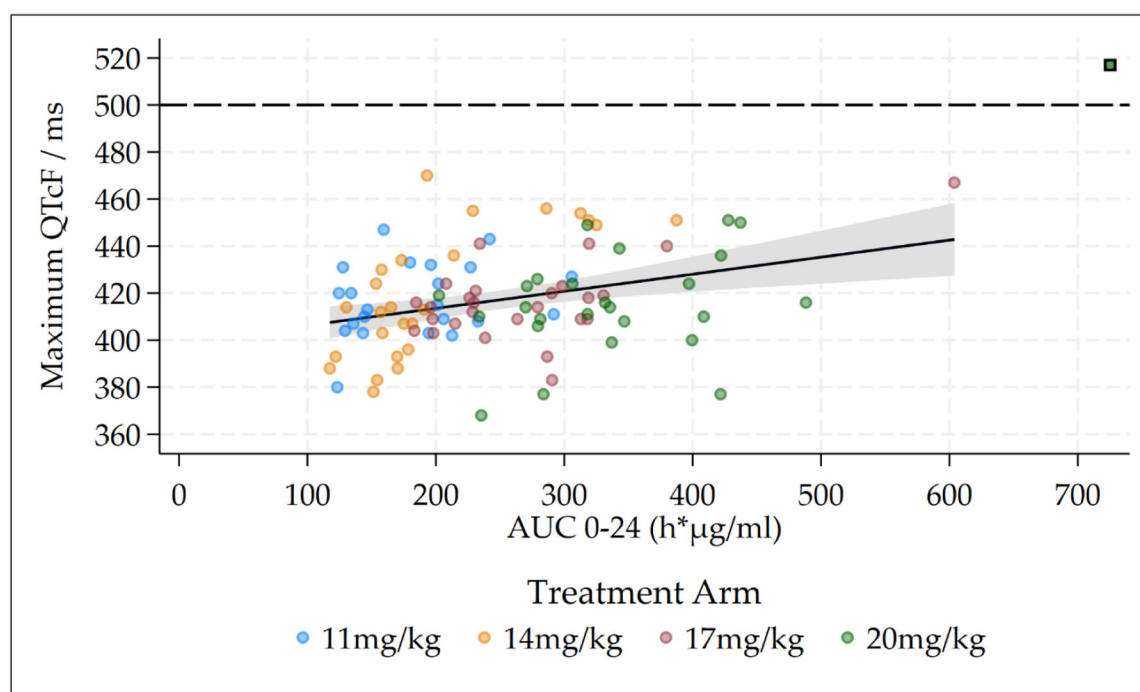


Figure 4.

Plot of AUC against maximum QTcF from visits at or after randomization. Horizontal dashed line shows 500ms threshold. The black square, □, shows a single participant had a QTcF exceeding 500ms (Grade 3); QT prolongation was considered likely attributable to concomitant use of azithromycin, a protocol-prohibited drug with known QT prolongation potential; the AE resolved after discontinuation of azithromycin; levofloxacin was not discontinued. Line of best fit is shown (excluding participant that received azithromycin) as solid black line with 95% confidence region (gray shaded area).

Table 1.

Baseline clinical and demographic characteristics among all participants randomized. Note that levofloxacin dosing was the same, 750mg, for participants less than 60kg in groups 11m/kg and 14mg/kg; summary PK measures by total dose received are shown in the online supplement (Table S7.3).

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total Randomized	27	29	28	27	111
Location					
Cape Town, South Africa	12 (44%)	12 (41%)	12 (43%)	12 (44%)	48 (43%)
Lima, Peru	15 (56%)	17 (59%)	16 (57%)	15 (56%)	63 (57%)
Prior TB diagnoses					
None	16 (59%)	22 (76%)	17 (61%)	20 (74%)	75 (68%)
Treatment for DS-TB only	7 (26%)	7 (24%)	9 (32%)	7 (26%)	30 (27%)
Treatment for MDR-TB	4 (15%)	0	2 (7%)	0	6 (5%)
Persons with HIV	6 (22%)	5 (17%)	5 (18%)	6 (22%)	22 (20%)
CD4 count (cells/mm³), Median (IQR)	293.0 (180.0, 331.0)	366.0 (267.0, 384.0)	383.0 (371.0, 412.0)	266.0 (177.0, 292.0)	312.0 (178.5, 383.5)
Cavitation on chest X-ray					
Absent	5 (19%)	8 (28%)	8 (29%)	7 (26%)	28 (25%)
Present, <4cm	10 (37%)	10 (34%)	8 (29%)	12 (44%)	40 (36%)
Present, ≥4cm	12 (44%)	11 (38%)	12 (43%)	8 (30%)	43 (39%)
Male Sex	17 (63%)	20 (69%)	18 (64%)	13 (48%)	68 (61%)
Ethnicity					
Hispanic or Latino	14 (52%)	17 (59%)	16 (57%)	15 (56%)	62 (56%)
Not Hispanic or Latino	12 (44%)	12 (41%)	12 (43%)	12 (44%)	48 (43%)
Unknown	1 (4%)	0	0	0	1 (1%)
Race					
Black	5 (19%)	7 (24%)	6 (21%)	6 (22%)	24 (22%)
Other	22 (81%)	22 (76%)	22 (79%)	21 (78%)	87 (78%)
Age (years), Median (IQR)	32.0 (25.0, 43.0)	25.0 (23.0, 31.0)	26.0 (22.0, 37.5)	31.0 (21.0, 44.0)	26.0 (22.0, 42.0)
Weight (kg), Median (IQR)	55.5 (48.3, 63.2)	57.0 (49.5, 62.8)	52.4 (49.4, 57.0)	53.8 (50.0, 61.7)	54.1 (49.0, 61.6)
BMI (kg/m²), Median (IQR)	20.9 (17.9, 23.5)	20.5 (19.3, 22.6)	19.5 (18.0, 21.5)	20.1 (18.9, 22.4)	20.4 (18.2, 22.6)

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
TB drugs in regimen at baseline (additional to fluoroquinolones)					
Four	2 (7%)	1 (3%)	0	1 (4%)	4 (4%)
Five	17 (63%)	21 (72%)	20 (71%)	20 (74%)	78 (70%)
Six	7 (26%)	7 (24%)	8 (29%)	6 (22%)	28 (25%)
NA[†]	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Smear grading					
Negative	0	0	2 (7%)	0	2 (2%)
Scanty	1 (4%)	0	3 (11%)	2 (7%)	6 (5%)
1+	8 (30%)	8 (28%)	6 (21%)	7 (26%)	29 (26%)
2+	5 (19%)	4 (14%)	2 (7%)	8 (30%)	19 (17%)
3+	13 (48%)	17 (59%)	15 (54%)	10 (37%)	55 (50%)
Days to positivity in MGIT, Median (IQR)	8.5 (7.5, 11.2)	8.2 (6.7, 11.1)	9.2 (5.5, 10.9)	8.3 (7.1, 10.3)	8.4 (6.7, 11.1)
Pyrazinamide DST					
Sensitive	10 (37%)	10 (34%)	8 (29%)	13 (48%)	41 (37%)
Resistant	14 (52%)	18 (62%)	15 (54%)	11 (41%)	58 (52%)
NA	3 (11%)	1 (3%)	5 (18%)	3 (11%)	12 (11%)
Ethambutol DST					
Sensitive	9 (33%)	17 (59%)	10 (36%)	12 (44%)	48 (43%)
Resistant	15 (56%)	10 (34%)	12 (43%)	12 (44%)	49 (44%)
NA	3 (11%)	2 (7%)	6 (21%)	3 (11%)	14 (13%)
Levofloxacin MIC (µg/ml)					
MIC (Agar plate, primary), median (IQR) / N	0.25 (0.25, 0.38) / 15	0.25 (0.25, 0.25) / 24	0.25 (0.13, 0.25) / 18	0.25 (0.25, 0.25) / 18	0.25 (0.25, 0.25) / 75
MIC (Broth microdilution, secondary), median (IQR) / N	0.5 (0.5, 1.0) / 15	0.5 (0.5, 0.5) / 25	0.5 (0.5, 0.5) / 19	0.5 (0.5, 0.5) / 18	0.5 (0.5, 0.5) / 77
Pharmacokinetics					
Levofloxacin AUC, median (IQR) / N	187.0 (135.8, 212.6) / 22	173.2 (157.1, 214.0) / 25	250.6 (215.0, 313.0) / 26	333.7 (279.5, 408.7) / 26	231.0 (178.4, 318.1) / 99
Levofloxacin C _{Max} , median (IQR) / N	10.8 (8.8, 13.1) / 22	10.8 (8.9, 12.3) / 25	14.8 (12.3, 17.1) / 26	18.6 (15.2, 22.2) / 26	13.5 (10.7, 17.6) / 99
Levofloxacin AUC / MIC agar plate, median (IQR) / N	572.8 (492.7, 967.6) / 13	633.4 (605.4, 713.8) / 21	918.3 (791.7, 1664.0) / 17	1342.5 (1118.0, 1687.2) / 17	855.0 (626.6, 1334.9) / 68

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Levofloxacin pharmacokinetic results from this trial already published(27),
*
† One participant withdrew consent after randomization and treatment logs are not available.

Table 2.

Summary of proportional hazards analysis of time to culture conversion on Middlebrook 7H11S agar medium and MGIT liquid medium by treatment arm and by tertile of AUC/MIC. For each analysis, there was no evidence of non-proportional hazards (test using Schoenfeld residuals). Summary of proportion with culture conversion in online supplement, tables S14.230S14.25.

	By Treatment Arm				By tertile of AUC/MIC		
	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Lower	Middle	Upper
7H11S Solid Medium (primary)							
Hazard ratio (adjusted [*])	Reference	0.79 (0.41, 1.51)	0.68 (0.34, 1.35)	0.92 (0.47, 1.81)	Reference	0.82 (0.42, 1.61)	0.98 (0.43, 2.25)
Log-rank test (stratified [*])				p = 0.282			p = 0.350
Hazard ratio (unadjusted)	Reference	0.87 (0.48, 1.57)	0.74 (0.39, 1.39)	1.00 (0.54, 1.85)	Reference	0.82 (0.44, 1.53)	0.91 (0.50, 1.67)
Log-rank test (unstratified)				p = 0.236			p = 0.505
MGIT Liquid Medium							
Hazard ratio (adjusted [*])	Reference	1.00 (0.52, 1.92)	0.76 (0.38, 1.53)	1.14 (0.58, 2.24)	Reference	0.66 (0.33, 1.29)	1.01 (0.46, 2.25)
Log-rank test (stratified [*])				p = 0.313			p = 0.121
Hazard ratio (unadjusted)	Reference	1.06 (0.57, 1.98)	0.83 (0.44, 1.56)	1.29 (0.68, 2.43)	Reference	0.87 (0.46, 1.65)	1.07 (0.58, 1.97)
Log-rank test (unstratified)				p = 0.151			p = 0.484

^{*} Adjusted/stratified by baseline covariates: pyrazinamide resistance, days to positivity on MGIT, and study site.

^{**} Achieved culture conversion by 8 or 10 weeks, +1 week for late visits.

Table 3a.

Summary of safety outcomes by allocated treatment arm

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total	Cochrane-Armitage Test for trend	Cochrane-Armitage Test for trend excluding participant who received azithromycin [†]
Total participants in safety analysis	25	28	28	27	108		
Any Grade 3–5 AE	4 (16.0%)	4 (14.3%)	7 (25.0%)	10 (37.0%)	25 (23.1%)	p = 0.042	
Any SAE	2 (8.0%)	1 (3.6%)	4 (14.3%)	3 (11.1%)	10 (9.3%)	p = 0.412	
Death	0	0	1 (3.6%)	0	1 (0.9%)	p = 0.667	
QTcF > 450ms	0 (0.0%)	6 (21.4%)	1 (3.6%)	3 (11.1%)	10 (9.3%)	p = 0.604	p = 0.906
QTcF > 500ms	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (0.9%)	p = 0.179	NA
Grade 3–5 AEs *							
Blood uric acid increased	1 (4.0%)	2 (7.1%)	1 (3.6%)	3 (11.1%)	7 (6.5%)		
Bronchospasm	1 (4.0%)	1 (3.6%)	0	0	2 (1.9%)		
Deafness	0	0	0	2 (7.4%)	2 (1.9%)		
Eosinophilia	1 (4.0%)	0	1 (3.6%)	0	2 (1.9%)		
Hepatic function abnormal	1 (4.0%)	0	1 (3.6%)	0	2 (1.9%)		
Total participants in tolerability analysis	23	27	27	25	102		
Completed treatment (168 doses within 200 days)	14 (61%)	21 (78%)	18 (67%)	18 (72%)	71 (70%)	p = 0.442	

[†] One participant in the highest dose group and highest tertile of AUC also received protocol-prohibited azithromycin, so p-values are shown for QTcF analyses with this participant excluded.* MedDRA preferred term (<https://www.meddra.org/>), restricted to those occurring in at least two participants. No participants experienced grade 3 or above AEs in the musculoskeletal/tendonitis category. See online supplement Table S11.5 for reasons for non-completion of treatment.

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Table 3b.

Summary of safety outcomes by tertiles of AUC

	Lower tertile	Middle tertile	Upper tertile	Total	Cochrane-Armitage Test for trend
Total participants in safety analysis	33	33	33	99	
Any Grade 3–5 AE	4 (12.1%)	8 (24.2%)	12 (36.4%)	24 (24.2%)	p = 0.022
Any SAE	0	3 (9.1%)	6 (18.2%)	9 (9.1%)	p = 0.011
Death	0	0	1 (3.0%)	1 (1.0%)	p = 0.221
QTcF > 450ms	1 (3.0%)	2 (6.1%)	7 (21.2%)	10 (10.1%)	p = 0.014
QTcF > 500ms	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.0%)	p = 0.218
Grade 3–5 Aes *					NA
Blood uric acid increased	4 (12.1%)	1 (3.0%)	2 (6.1%)	7 (7.1%)	
Bronchospasm	0	0	2 (6.1%)	2 (2.0%)	
Deafness	0	0	2 (6.1%)	2 (2.0%)	
Eosinophilia	0	1 (3.0%)	1 (3.0%)	2 (2.0%)	
Hepatic function abnormal	0	2 (6.1%)	0	2 (2.0%)	
Total participants in tolerability analysis	31	31	32	94	
Completed treatment (168 doses within 200 days)	25 (81%)	19 (61%)	27 (84%)	71 (76%)	p = 0.025

† One participant in the highest dose group and highest tertile of AUC also received protocol-prohibited azithromycin, so p-values are shown for QTcF analyses with this participant excluded.

* MedDRA preferred term (<https://www.meddra.org/>), restricted to those occurring in at least two participants. No participants experienced grade 3 or above AEs in the musculoskeletal/tendonitis category. See online supplement Table S11.5 for reasons for non-completion of treatment.