A meta-analysis of levofloxacin for contacts of multidrug-resistant TB

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ABSTRACT

Background

Data from randomized trials evaluating the effectiveness of tuberculosis (TB) preventive treatment for contacts of multidrug-resistant (MDR)-TB are lacking. Two recently published randomized trials did not achieve statistical significance, and provide the opportunity for a meta-analysis.

Methods

We conducted combined analyses of two phase 3 trials of levofloxacin MDR-TB preventive treatment, the Vietnam Quinolones for MDR-TB (VQUIN) trial and the Tuberculosis Child Multidrug-resistant Preventive Therapy (TB-CHAMP) trial. Following MDR-TB household exposure, VQUIN enrolled mainly adults in Vietnam; TB-CHAMP enrolled mainly young children in South Africa. Randomization in both trials was 1:1 at the household-level to daily levofloxacin or placebo for 6-months. The primary outcome was incident TB by 54-weeks. We estimated treatment effect overall using individual participant data meta-analysis.

Results

VQUIN (n=2041) randomly assigned 1023 participants to levofloxacin and 1018 to placebo; TB-CHAMP (n=922) assigned 453 participants to levofloxacin and 469 participants to placebo. Median age was 40 years (interquartile range 28-52) in VQUIN and 2.8 years (interquartile range 1.3-4.2) in TB-CHAMP.

Overall, 8 levofloxacin-group participants developed TB by 54-weeks versus 21 placebo-group participants; relative difference in cumulative incidence 0.41 (95% confidence interval 0.18-0.92; P=0.03). No association was observed between levofloxacin and grade ≥3 adverse events; risk ratio (RR) 1.07 (0.70-1.65). Musculoskeletal events of any grade occurred more frequently in the levofloxacin group (RR 6.36, 4.30-9.42), but not among children <10 years. Overall, 4 levofloxacin-group participants and 3 placebo-group participants had grade 3 events.

Conclusions

In this meta-analysis of two randomized trials, levofloxacin was associated with a 60% relative reduction in TB incidence among adult and child household MDR-TB contacts, but an increased risk of musculoskeletal adverse events in adults and adolescents.

BACKGROUND

Nearly 500,000 people each year are estimated to develop rifampin-resistant or multidrug-resistant (MDR) tuberculosis (TB), defined as disease caused by *Mycobacterium tuberculosis* (*Mtb*) resistant to isoniazid and rifampin.[1] TB preventive treatment protects people with latent *Mtb* infection from progression to TB disease, reducing onward transmission.[2,3] While the effectiveness of TB preventive treatment for drug-susceptible TB is well-established,[4,5] there is limited evidence from randomized trials for TB preventive treatment in individuals exposed to people with rifampin-resistant or MDR-TB.

VQUIN (The Vietnam Quinolones for MDR-TB Trial, ACTRN12616000215426) and TB-CHAMP (Tuberculosis Child Multidrug-resistant Preventive Therapy, ISRCTN92634082) were separate randomized placebo-controlled trials evaluating levofloxacin as MDR-TB preventive treatment in adults and children, respectively.[6,7] Both trials observed fewer participants developing TB disease in the levofloxacin group which did not reach statistical significance, potentially due to lower-than-expected underlying TB event rates.[8,9]

Here, we report a prospectively planned individual participant data (IPD) meta-analysis of the two trials evaluating the efficacy and safety of levofloxacin MDR-TB preventive treatment. We used standard methods to estimate overall treatment effects, and a Bayesian method to estimate the efficacy in each trial with more precision.[10] This Bayesian approach accommodates differences in treatment efficacy between study populations, and increases the evidence base to inform guidelines.

METHOD

Study design

VQUIN was conducted in Vietnam between March 2016 and February 2022, and TB-CHAMP was carried out in South Africa between September 2017 and February 2023. The designs for each trial were previously described,[6,7] and the individual trial results reported elsewhere.[8,9]

Both trials enrolled participants with household exposure to an individual with microbiologically-confirmed pulmonary rifampin-resistant/MDR-TB. VQUIN mainly enrolled household contacts aged ≥15 years, and a smaller number of children under 15 years. Participants were required to either have evidence of latent *Mtb* infection (i.e. *Mtb* immune

sensitization), be living with HIV, or have severe malnutrition. TB-CHAMP initially enrolled only children <5 years, with older children and adolescents aged 5-17 who either had evidence of latent *Mtb* infection or be living with HIV later included. Latent *Mtb* infection status was defined as a positive tuberculin skin test (TST) in VQUIN,[6] and positive Interferon-Gamma Release Assay (IGRA, QuantiFERON-TB Gold Plus, Qiagen) in TB-CHAMP.

Participants in both trials were randomly assigned to daily oral levofloxacin or placebo in a 1:1 allocation ratio, stratified by province (n=10) in VQUIN, and by trial site (n=5) in TB-CHAMP. In TB-CHAMP, all participants within a household were allocated to the same treatment group. In VQUIN, where two or more contacts within a household were randomised within a 90-day period, these contacts in that household were allocated to the same treatment group; if additional contacts were enrolled 91 days or more after the first contact was enrolled, they were randomised separately. Treatment was prescribed as 180 doses (26 weeks) in VQUIN and 168 doses (24 weeks) in TB-CHAMP. In both trials, dosing was based on 15-20 mg/kg per day (maximum 750mg), with a weight-banded dosing approach in children. We used the same formulations for levofloxacin and placebo (250 mg tablets, Macleods Pharmaceuticals, India). Follow-up in VQUIN was to 134 weeks post-randomization. In TB-CHAMP, follow-up was originally to 96 weeks, reduced to 72 weeks in May 2019, with final analyses undertaken when all participants were followed for ≥24 weeks. The design and methods for the combined analyses of the trials were prespecified before results for either trial were known.

Endpoints

The primary efficacy endpoint for the combined analysis was microbiologically-confirmed or clinically-defined TB, including TB-related death, by 54-weeks from randomization. This timepoint was chosen based upon previous studies showing most contacts who develop TB disease after exposure to *Mtb* do so within 12 months,[11,12] and concerns that subsequent re-exposure and exogenous re-infection with longer follow-up could dilute the treatment effect. It also allowed alignment in follow-up duration across the two trials.

Secondary efficacy endpoints were 1) microbiologically-confirmed or clinically-defined TB by end of follow-up; 2) microbiologically-confirmed TB by 54-weeks; and 3) all-cause mortality by 134-weeks. In each trial, an independent Endpoint Review Committee, blinded to treatment allocation, adjudicated TB outcomes and cause of death.

Safety endpoints were 1) grade ≥3 adverse events (AEs) from starting treatment to 21 days after last drug dose; 2) grade ≥3 AEs associated with the drug; 3) serious adverse events (SAEs) occurring up to 21 days after last drug dose; 4) discontinuation of treatment due to AE(s) of any grade; and 5) five pre-specified domains of AEs of special interest (Supplement Appendix, S2.7), including musculoskeletal effects (arthritis, arthralgia or tendonitis) occurring any time from starting treatment. In TB-CHAMP, the site clinician treating the participant determined the causal relationship between the trial drug and AEs (including death). In VQUIN, causality was determined by the Endpoint Review Committee for grade 3-5 AEs, and by the treating clinician for grade 1 and 2 AEs.

Statistical methods

IPD meta-analysis

The primary efficacy analysis of time-to-TB by 54-weeks included all randomized participants, apart from any late screening failures with TB at baseline (modified intention-to-treat [mITT] population). Participants without an endpoint observed had follow-up censored at the earliest of 54-weeks from randomization, date of last trial follow-up, or date of non-TB death. Kaplan-Meier cumulative incidence plots were generated.

We estimated an overall treatment effect across the trials using a one-stage common-effect IPD meta-analysis approach. We planned to use Cox regression to estimate the hazard ratio for levofloxacin versus placebo, allowing for separate baseline hazard functions for each trial. Cluster-robust variance accounted for intra-household correlation. We adjusted for province in VQUIN and for site in TB-CHAMP (randomization stratification factors) using Inverse Probability Treatment Weighting, owing to the small number of TB events.[13] Analysis assumed non-informative censoring, but otherwise there were no missing data in the model.

We tested the assumption of proportional hazards using scaled Schoenfeld residuals. If there was evidence of non-proportional hazards, the relative difference in cumulative incidence between treatment groups was estimated using a flexible parametric model with time-dependent treatment effect (Supplemental Appendix, S5.4).[14] Hypothesis testing of the relative difference in cumulative incidence was based on the Wald test. The hazard ratio was also estimated separately for the first 6 months and thereafter.

Per-protocol (PP) analyses were restricted to participants who were adherent to the allocated treatment (defined in Supplemental Appendix, S5.2), excluding any late screening failures.

Pre-specified subgroup analyses assessed heterogeneity of treatment effects. The number-needed-to-treat (NNT) to prevent one TB case was estimated for each trial population, assuming a common relative treatment effect, while allowing for different underlying TB incidence across the two trials (Supplemental Appendix, S5.7).

Safety analyses included all randomized participants who commenced treatment. The risk ratio comparing the proportion of participants experiencing the relevant endpoint between treatment groups was estimated using modified Poisson regression.[15] Analyses of secondary outcomes did not adjust for multiple comparisons; results are reported as point estimates with 95% confidence intervals and should not be used in place of hypothesis testing.

Bayesian analysis

We used a Bayesian method to estimate levofloxacin efficacy (based on the primary endpoint) in the VQUIN population while "borrowing" information from TB-CHAMP, and *vice versa*.[10] This approach increases power compared to standalone analyses of each trial, and addresses a different research question to the IPD primary meta-analysis; here, we assessed separately levofloxacin efficacy within the VQUIN and TB-CHAMP populations. We assumed any difference in treatment efficacy between trials was due to differences in age distribution and prevalence of *Mtb* infection.

To define the weights given to the borrowed information, we elicited opinions from 15 experts with experience in TB prevention on how levofloxacin efficacy may differ by age group and *Mtb* infection status (Supplemental Appendix, S5.5). Experts were selected to provide a breadth of opinions and global perspective. To inform the elicitations, participants were provided with summary data on the estimated effect of TB preventive treatment by age and *Mtb* infection status, based on observational TB contact cohorts.[11] Opinions ascertained were pooled to determine weights for the borrowed information, which was incorporated as prior distributions.[16] For each trial, separate Bayesian analyses were performed within pre-defined subgroups by age group and TB infection status (Supplemental Appendix, S5.5), and combined in an analysis weighted by number of TB events. We present the overall posterior means for the relative difference in cumulative difference, with 95% credible intervals.

Analyses were performed using Stata version 18.0 (StataCorp). The widths of the intervals have not been adjusted for multiplicity and thus should not be used in place of hypothesis testing.

TD, GF, ACH, JAS, and RMT designed the study with input from all authors. JB, FG, CL and TD collated the data. JB and TD analysed the data. TD, GF, ACH, and RMT vouch for the data and the analysis. TD wrote the first draft of the paper. TD, GF, ACH, JAS, RMT, and HSS wrote the paper and decided to publish the paper. There were no agreements concerning confidentiality of the data between the sponsor and the authors or institutions.

RESULTS

In total, 2,963 participants were randomized across both trials: 1,023 from 618 households to levofloxacin, versus 1,018 from 581 households to placebo in VQUIN; and 453 from 248 households to levofloxacin, versus 469 from 249 households to placebo, in TB-CHAMP.

At baseline, the median age was 40 years (IQR 28-52) in VQUIN and 2.8 years (IQR 1.3-4.2) in TB-CHAMP (Table 1). The proportion of participants with evidence of latent *Mtb* infection in VQUIN was 99.8%, and in TB-CHAMP, 20% among children less than 5 years and 95% in those 5-17 years. The proportion of participants living with HIV was 0.4% in VQUIN, and 2.1% in TB-CHAMP.

Follow-up and adherence

In VQUIN, 97% of participants reached end-of-trial follow-up at 134 weeks. In TB-CHAMP, 91% of participants were followed for ≥24 weeks and 73% for ≥54 weeks (Table S7.1).

One-hundred and nineteen (6%) participants in VQUIN and 1 (0.01%) in TB-CHAMP did not start trial treatment. In VQUIN, 70% in the levofloxacin-group and 85% in the placebo-group took ≥80% of allocated doses; in TB-CHAMP, this proportion was 86% in both treatment groups.

Primary efficacy endpoint

IPD meta-analysis

The primary analysis included 2,957 participants, excluding 6 individuals who were considered late screening failures in TB-CHAMP with TB at baseline. Overall, 8 levofloxacin-group participants developed TB by 54-weeks versus 21 placebo-group participants, Figure 1. As there was evidence of non-proportional hazards (P=0.009), we present the relative difference in cumulative incidence by 54-weeks, 0.41 (95% confidence interval [CI] 0.18-0.92; P=0.03).

By trial, the relative difference in 54-weeks cumulative incidence was 0.34 (95%CI 0.09-1.25) for VQUIN and 0.44 (0.16-1.26) for TB-CHAMP. The estimated NNT to prevent 1 TB case by 54 weeks in VQUIN was 193 (95%CI 98-5158), and in TB-CHAMP was 56 (30-466); Table S7.14.

No evidence of heterogeneity in treatment effect was observed in other pre-specified subgroup analyses, including by age group (Table S7.15). Results from the per-protocol analysis were consistent with the primary analysis, with a relative difference in cumulative difference 0.40 (95%CI 0.16-1.02).

Bayesian analyses

Figure 3 illustrates how the data from each trial (within pre-defined subgroups) were combined with information from the other trial in the Bayesian analysis. Borrowing information from TB-CHAMP provided a relative difference in cumulative incidence of TB by 54-weeks of 0.41 (95% Credible Interval (CrI) 0.18-0.95) for VQUIN (Figure 2); the posterior probability that levofloxacin is superior to placebo in the VQUIN population was 98%. The relative difference in cumulative incidence for TB-CHAMP, with information borrowed from VQUIN, was 0.38 (95%CrI 0.16-0.95); the corresponding posterior probability for TB-CHAMP was 98%. For both trials, the Bayesian estimate was numerically similar to the overall IPD meta-analysis estimate.

Secondary efficacy endpoints

During overall trial follow-up up to 134-weeks, 14 participants developed TB in the levofloxacin-group versus 27 in placebo-group. In pre-specified analyses, there was only 1 TB endpoint in the levofloxacin-group versus 14 in placebo-group during the first 6 months post-randomization (hazard ratio [HR] 0.07, 95%CI 0.01-0.56), compared to 13 TB endpoints in each group thereafter (HR 1.00, 95%CI 0.45-2.22); Table S7.12. The overall relative difference in cumulative TB incidence by 134-weeks was 0.62 (95%CI 0.31-1.22); Figure 2.

Overall, 5 deaths occurred in the levofloxacin-group and 4 in placebo-group. None were deemed to be related to TB nor trial drug.

Safety endpoints

Among 2,843 participants who commenced trial treatment, 43 receiving levofloxacin and 42 receiving placebo experienced grade ≥3 AEs; risk ratio (RR) 1.07 (95%CI 0.70-1.65, Table 2).

Grade ≥3 AEs considered to be at least possibly related to trial drug were observed in 14 levofloxacin-group participants and 10 placebo-group participants (RR 1.46, 95%CI 0.65-3.26); Tables 2 and S7.7. In VQUIN, more participants in the levofloxacin group compared to the placebo group had such AEs, with 10 (1.0%) versus 2 (0.2%), respectively (RR 5.26, 95% CI 1.16-23.95); this difference was not observed in TB-CHAMP, with 4 (0.9%) versus 8 (1.7%), respectively (RR 0.53, 95%CI 0.16-1.70).

Participants in the levofloxacin group, compared to placebo group, were more likely to experience musculoskeletal AEs of any grade (RR 6.36, 95%CI 4.30-9.42; P<0.001). However, this association was driven by VQUIN (Table 2). Moreover, the difference between treatment groups was only seen in adolescents and adults (Table S7.8), in a post-hoc analysis. Nearly all musculoskeletal events were either grade 1 (62%) or 2 (35%); Table S7.9. Seven participants (4 levofloxacin-group, 3 placebo-group), all aged above 45 years, had grade 3 musculoskeletal events (Table S7.10). Overall, 3 participants (all in the levofloxacin group) developed tendonitis; two had a grade 2 event and one had a grade 1 event.

Discontinuation of trial treatment early due to any AEs occurred more frequently in the levofloxacin group than placebo group, in both VQUIN (7.4% versus 1.1%, respectively) and TB-CHAMP (1.3% versus 0.2%, respectively); overall RR 6.32 (95%CI 3.43-11.63). In a post-hoc analysis, the likelihood of stopping treatment early for AEs in the levofloxacin group appeared to increase with age (Table S7.5).

DISCUSSION

In this combined analysis of nearly 3,000 children, adolescents and adults from the TB-CHAMP and VQUIN randomized placebo-controlled trials, we demonstrate that 6-month daily levofloxacin was associated with a 60% relative reduction in TB incidence over one year.

While both TB-CHAMP and VQUIN observed fewer participants developing TB in the levofloxacin than placebo group, neither trial individually showed a statistically significant difference.[8,9] This could potentially be due to the underlying TB incidence being substantially

lower than expected, and pooling data led to more precise estimates of the treatment effect. Using a Bayesian method, we also provided evidence of treatment efficacy within each trial population separately, and showed the effect was similar across adults and children.

These findings confirm previous results from observational studies of preventive treatment among contacts of people with rifampin-resistant or MDR-TB. A recent meta-analysis of 11 cohort studies estimated that MDR-TB preventive treatment reduced TB incidence by 66%.[17] Our results are also consistent with previous trials of isoniazid for preventing drug-susceptible. Six to 12 months of isoniazid had 60% efficacy in preventing TB in a meta-analysis of 11 placebo-controlled trials.[4] Similar to isoniazid as TB preventive treatment,[18] the protective effect of levofloxacin appeared to be restricted to the treatment phase in our analysis. During this period, 1 participant in the levofloxacin group developed TB compared to 14 in placebo group, corresponding to approximately 90% efficacy in a pre-specified analysis. Thereafter, TB incidence was similar between treatment groups, which may be due to subsequent *Mtb* re-exposure and re-infection particularly in cases identified late in the follow-up period. It is also possible that levofloxacin did not fully clear the latent *Mtb* infection in some participants, resulting in subsequent progression to TB post-treatment. While data from randomized trials suggest continuous or extended TB preventive treatment for drug-susceptible TB could be more efficacious than the standard 6-month treatment course,[19,20] such an approach may be offset by greater risk of toxicities, increased cost, as well as poorer acceptability and treatment adherence.

Due to the low underlying TB rates, the estimated NNT to prevent one TB case for both trial populations was relatively high, particularly in adults. This is an important consideration for MDR-TB preventive treatment implementation across different settings. Modelling work, however, suggests the long-term population-wide impact of household contact investigation and provision of MDR-TB preventive treatment could have considerably greater effect upon MDR-TB prevalence, including reducing onward transmission.[21]

Reassuringly, our two trials showed little evidence of excess risk of AEs at grade 3 or above, nor of serious AEs with levofloxacin. Participants in the levofloxacin group were, however, more likely to experience AEs that were grade 3 or above at least possibly related to trial drug in VQUIN, although such events were uncommon. We found trial treatment discontinuation for AEs occurred more frequently in the levofloxacin group and, as previously reported,[22]

more so in adults than in children. The AEs leading to treatment discontinuation were mostly low-grade.[8,9]

We observed an association between levofloxacin and musculoskeletal events, with most events being mild. This association was not seen in children under 10 years. Only 3 participants on levofloxacin reported symptoms of tendonitis, none were severe. Musculoskeletal toxicities associated with levofloxacin antibiotic therapy have been reported in adults,[23-26] with symptoms usually self-limiting.[27] Among 2,500 children from open-label randomized trials of levofloxacin for antibiotic treatment of other infections, 12-month incidence of musculoskeletal disorders was higher with levofloxacin compared to non-fluoroquinolone treatment (3.4% vs 1.8%). This difference was largely due to reports of arthralgia, so potentially subjected to reporting bias;[28] moreover, there were no long-term effects observed.[29] Other potential adverse effects of levofloxacin MDR-TB preventive treatment, such as the effect on human microbiome and development of drug-resistance bacteria among other bacterial species, require further evaluation.

Our analysis has several important strengths. During protocol development of the original trials, the VQUIN and TB-CHAMP investigators collaborated to ensure alignment of endpoint definitions and data collection. The same drug formulations and doses were used in both trials. The design and methodology for the combined analyses were developed before the results were available for either trial, reducing potential for bias. Finally, combining data across these complementary trials allowed comparison of the efficacy and safety of levofloxacin MDR-TB preventive treatment between adults and children, and between settings.

These analyses have several limitations. First, our results may not be generalizable to all high-risk groups for TB, including people living with HIV, in whom treatment acceptability, tolerability and/or adherence may differ. Second, further genotypic comparisons between mycobacterial isolates produced by incident cases and their index cases is required to establish whether TB progression was due to the initial exposure or subsequent re-exposure to *Mtb*. Third, the number of TB endpoints was low in subgroup analyses. The Bayesian analyses required data stratification by age and *Mtb* infection status, thus estimates of treatment efficacy may be sensitive to sparse data. Fourth, our analyses did not consider other potential factors that could have influenced treatment efficacy (such as geographical setting and HIV status of the index case), since the Bayesian elicitations and models would otherwise become challenging to implement. In addition, we observed non-proportional hazards in the efficacy

IPD meta-analysis, with this not accounted for *a priori* in the elicitations, which were based on overall hazard ratios (Supplemental Appendix S8). This required utilization and reporting of an alternate treatment effect measure from the one that was prespecified for the Bayesian analyses. We assumed the results from the elicitations could be applied to the estimation of the relative difference in cumulative incidence, because this is expected to be numerically similar to the hazard ratio. Finally, the follow-up data beyond 72 weeks mostly came from the VQUIN trial which had a median duration of follow-up nearly twice that of TB-CHAMP.

These results suggest that that MDR-TB preventive treatment with levofloxacin is effective in adults and children but was associated with increased low grade adverse events (particularly musculoskeletal), which were mainly seen in adults and adolescents. Further evaluation of the risk/benefit balance, tolerability, and cost-effectiveness of MDR-TB preventive treatment in different populations is needed.

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Table 1. Baseline characteristics of multidrug-resistant household contact participants overall and by trial

	VQUIN	TB-CHAMP	Overall
Number of overall participants randomized (levofloxacin group, placebo group)	2041 (1023, 1018)	922 (453, 469)	2963 (1476, 1487)
Age (years)			
Median (interquartile range)	40 (28-52)	2.8 (1.3 – 4.2)	29.0 (4.4-47.0)
Range	(2 - 87)	(0.1 - 17.9)	(0.1-87.0)
<3.0	2 (0.1%)	483 (52.4%)	485 (16.4%)
3.0-4.9	5 (0.2%)	356 (38.6%)	361 (12.2%)
5.0-17.9	149 (7.3%)	83 (9.0%)	232 (7.8%)
18.0-29.9	419 (20.5%)	-	419 (14.1%)
30.0-44.9	614 (30.1%)	-	614 (20.7%)
45.0-59.9	606 (29.7%)	-	606 (20.5%)
≥60.0	246 (12.1%)	-	246 (8.3%)
Sex			
Male	735 (36.0%)	454 (49.2%)	1189 (40.1%)
Female	1306 (64.0%)	468 (50.8%)	1774 (59.9%)
HIV status*			
Positive	8 (0.4%)	19 (2.1%)	27 (0.9%)
Negative	2033 (99.6%)	899 (97.9%)	2932 (99.1%)
Missing	*0*	*4*	*4*
Latent Mtb infection status&			
Positive	2036 (99.8%)	242 (26.9%)$	2278 (77.5%)
Negative	5 (0.2%)	632 (70.4%)	637 (21.7%)
Indeterminate (IGRA)	0 (0%)	24 (2.7%)	24 (0.8%)
Missing	*0*	*24*	*24*
Previously treated for TB disease			
Yes	106 (5.2%)	18 (2.0%)	124 (4.2%)
No	1935 (94.8%)	904 (98.0%)	2839 (95.8%)
BCG vaccination given			
Yes	973 (47.7%)	865 (94.2%)	1838 (62.1%)
No	1068 (52.3%)	53 (5.8%)	1121 (37.9%)
Missing	*0*	*4*	*4*

* This was self-reported in VQUIN.

& latent *Mtb* infection was determined by tuberculin skin test in VQUIN and Interferon-Gamma Release Assay (QuantiFERON-Gold Plus, Qiagen) in TB-CHAMP.

$ In TB-CHAMP, 20% of children <5 years and 95% of those 5-17 years had evidence of latent *Mtb* infection.

Percentages are based on participants without missing information.

Mtb=Mycobacterium tuberculosis; TB=tuberculosis; BCG=bacillus Calmette-Guérin; IGRA=interferon-gamma release assay (QuantiFERON-Gold Plus, Qiagen).

Table 2. Combined safety analyses of the VQUIN and TB-CHAMP trials (based on standard individual patient data meta-analysis methods)

	Trial	Levofloxacin	Placebo	Estimated risk ratio (95% CI^)	P-value for overall treatment effect
Participants who took at least one trial drug dose*	VQUIN	960	962		
	TB-CHAMP	452	469		
	Overall	1412	1431		
Participants with ≥1 safety endpoints					
Grade 3 or above adverse event&	VQUIN	29 (3.0%)	19 (2.0%)	1.55 (0.87 – 2.76)	
	TB-CHAMP	14 (3.1%)	23 (4.9%)	0.67 (0.34 – 1.31)	
	Overall	43	42	1.07 (0.70 – 1.65)	0.75
Grade 3 or above adverse event at least possibly related to drug&	VQUIN	10 (1.0%)	2 (0.2%)	5.26 (1.16 – 23.95)	
	TB-CHAMP	4 (0.9%)	8 (1.7%)	0.53 (0.16 – 1.70)	
	Overall	14	10	1.46 (0.65 – 3.26)	0.36
Any grade 3 or above serious adverse event&	VQUIN	20 (2.1%)	12 (1.3%)	1.72 (0.85 – 3.49)	
	TB-CHAMP	8 (1.8%)	7 (1.5%)	1.23 (0.45 – 3.35)	
	Overall	28	19	1.54 (0.87 – 2.74)	0.14
Discontinuation of treatment due to adverse events of any grade	VQUIN	71 (7.4%)	11 (1.1%)	6.43 (3.42 – 12.09)	
	TB-CHAMP	6 (1.3%)	1 (0.2%)	5.25 (0.64 – 43.13)	
	Overall	77	12	6.32 (3.43 – 11.63)	<0.001
Musculoskeletal adverse event of any grade	VQUIN	220 (22.9%)	32 (3.3%)	7.02 (4.67 – 10.56)	
	TB-CHAMP	6 (1.3%)	4 (0.9%)	1.35 (0.36 – 5.06)	
	Overall	226	36	6.36 (4.30 – 9.42)	<0.001
Severe rash or cutaneous reaction&	VQUIN	1 (0.3%)	1 (0.8%)	1.06 (0.07 – 17.00)	
	TB-CHAMP	1 (0.2%)	0 (0%)	-	
	Overall	2	1	2.06 (0.19 – 22.65)	0.56

Peripheral neuropathy&	VQUIN	1 (0.1%)	0 (0%)	-	
	TB-CHAMP	0 (0%)	0 (0%)	-	
	Overall	1 (0.1%)	0 (0%)	-	
Central nervous system effects&	VQUIN	8 (0.8%)	3 (0.3%)	2.68 (0.71 – 10.05)	
	TB-CHAMP	6 (1.3%)	9 (1.9%)	0.65 (0.23 – 1.88)	
	Overall	14 (1.0%)	12 (0.8%)	1.17 (0.53 – 2.58)	0.70

CI=confidence interval

* Excluded 119 participant in VQUIN and 1 in TB-CHAMP who had not started treatment.
& Up to 21 days after stopping treatment.
^ The estimated confidence intervals were not adjusted for multiplicity.

Note drug-related fever was also a pre-specified adverse event of special interest but there were no events in either arm.