

ORIGINAL ARTICLE

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

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ABSTRACT

BACKGROUND

Cohort studies in Bangladesh showed promising cure rates among patients with multidrug-resistant tuberculosis who received existing drugs in regimens shorter than that recommended by the World Health Organization (WHO) in 2011.

METHODS

We conducted a phase 3 noninferiority trial in participants with rifampin-resistant tuberculosis that was susceptible to fluoroquinolones and aminoglycosides. Participants were randomly assigned, in a 2:1 ratio, to receive a short regimen (9 to 11 months) that included high-dose moxifloxacin or a long regimen (20 months) that followed the 2011 WHO guidelines. The primary efficacy outcome was a favorable status at 132 weeks, defined by cultures negative for *Mycobacterium tuberculosis* at 132 weeks and at a previous occasion, with no intervening positive culture or previous unfavorable outcome. An upper 95% confidence limit for the between-group difference in favorable status that was 10 percentage points or less was used to determine noninferiority.

RESULTS

Of 424 participants who underwent randomization, 383 were included in the modified intention-to-treat population. Favorable status was reported in 79.8% of participants in the long-regimen group and in 78.8% of those in the short-regimen group — a difference, with adjustment for human immunodeficiency virus status, of 1.0 percentage point (95% confidence interval [CI], -7.5 to 9.5) ($P=0.02$ for noninferiority). The results with respect to noninferiority were consistent among the 321 participants in the per-protocol population (adjusted difference, -0.7 percentage points; 95% CI, -10.5 to 9.1). An adverse event of grade 3 or higher occurred in 45.4% of participants in the long-regimen group and in 48.2% in the short-regimen group. Prolongation of either the QT interval or the corrected QT interval (calculated with Fridericia's formula) to 500 msec occurred in 11.0% of participants in the short-regimen group, as compared with 6.4% in the long-regimen group ($P=0.14$); because of the greater incidence in the short-regimen group, participants were closely monitored and some received medication adjustments. Death occurred in 8.5% of participants in the short-regimen group and in 6.4% in the long-regimen group, and acquired resistance to fluoroquinolones or aminoglycosides occurred in 3.3% and 2.3%, respectively.

CONCLUSIONS

In persons with rifampin-resistant tuberculosis that was susceptible to fluoroquinolones and aminoglycosides, a short regimen was noninferior to a long regimen with respect to the primary efficacy outcome and was similar to the long regimen in terms of safety. (Funded by the U.S. Agency for International Development and others; Current Controlled Trials number, ISRCTN78372190; ClinicalTrials.gov number, NCT02409290.)

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*A complete list of the STREAM study collaborators is provided in the Supplementary Appendix, available at nejm.org.

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MULTIDRUG-RESISTANT TUBERCULOSIS is resistant to isoniazid and rifampin (also called rifampicin), key drugs used in the treatment of tuberculosis.¹ The condition affects almost 500,000 new persons worldwide each year and is considerably more difficult to treat than drug-susceptible tuberculosis. Less than a quarter of patients start treatment, and the reported success rates were 48% in 2012² and 54% in 2017.¹ Despite the magnitude of the problem, data from phase 3 randomized trials of combination drug regimens for multidrug-resistant tuberculosis are lacking. Recommendations from the World Health Organization (WHO) for the treatment of multidrug-resistant tuberculosis (published in 2011) are based on evidence that was classified as very low quality and were described as conditional (i.e., “the desirable effects of adherence to a recommendation probably outweigh the undesirable effects”).³ The 2011 WHO guidelines recommended an intensive treatment phase of 8 months and a total treatment duration of 20 months.³

In view of the lack of an effective standardized regimen that is appropriate for resource-poor settings, Van Deun and colleagues conducted observational cohort studies in Bangladesh to evaluate several regimens for multidrug-resistant tuberculosis in patients who had not received previous treatment with second-line drugs. The sixth regimen, administered to 206 participants for 9 to 11 months, yielded encouraging results, with relapse-free cure occurring in 87.9% (95% confidence interval [CI], 82.7 to 91.6).⁴ Although such a regimen could have considerable advantages over the much longer WHO-recommended regimen, we considered that a randomized trial would be necessary for reproducibility and generalizability of results, particularly because human immunodeficiency virus (HIV) coinfection and second-line drug resistance were rare among the participants in the Bangladesh study.

METHODS

DESIGN AND OVERSIGHT

We conducted a randomized, phase 3, noninferiority trial (Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB [STREAM]⁵) to compare a short regimen (9 to 11 months) for multidrug-resistant tuberculosis that

was similar to the one used in a Bangladesh study⁴ with a long regimen (20 months), used locally at each trial site, that followed the 2011 WHO guidelines.³ The trial methods have been published previously,⁵ and additional details are provided in the Supplementary Appendix and in the protocol and statistical analysis plan, all available with the full text of this article at NEJM.org. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Participants were eligible for inclusion in the trial if they were 18 years of age or older and had pulmonary tuberculosis (as confirmed by a positive sputum smear or, if coinfecting with HIV, a nucleic acid amplification test [GeneXpert, Cepheid]) with evidence of resistance to rifampin. In practice, the management of rifampin-mono-resistant tuberculosis and the management of multidrug-resistant tuberculosis are similar. Participants were ineligible if they were infected with a strain of *Mycobacterium tuberculosis* that was resistant to a second-line injectable drug or a fluoroquinolone (as determined by line-probe assay).⁶ Written informed consent was obtained from all participants.

TREATMENT

The short regimen consisted of moxifloxacin (high-dose), clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin, isoniazid, and prothionamide in the first 16 weeks (dose information is provided in the Supplementary Appendix). The intensive phase could be extended to 20 or 24 weeks for participants who did not have conversion to a negative smear by 16 or 20 weeks, respectively. The regimen was identical to that used by Van Deun and colleagues in Bangladesh,⁴ except that moxifloxacin was substituted for gatifloxacin because quality-assured gatifloxacin was not available. Moxifloxacin was administered in doses determined according to body-weight category (400-mg dose for <33 kg, 600-mg dose for 33 to 50 kg; and 800-mg dose for >50 kg). The medications in the long regimen were provided by the National Tuberculosis Programs in the respective countries. The medications in the short regimen were purchased by the International Union against Tuberculosis and Lung Disease from quality-assured sources.

PROCEDURES

Participants and clinicians were aware of treatment-group assignments, but the laboratory staff was not. Only the members of the independent data monitoring committee and the statisticians reviewed the aggregate data according to the treatment-group assignment during the trial. The participants had scheduled weekly visits during the first 4 weeks and thereafter were clinically evaluated at 4-week intervals through week 132; sputum samples for smear and culture were obtained at every visit starting at the week 4 visit. *M. tuberculosis* isolates were sent to the trial reference laboratory for drug susceptibility testing and strain genotyping to distinguish relapses from reinfections. Regular electrocardiographic (ECG) monitoring was performed because of the risk of prolongation of the QT interval with high-dose moxifloxacin and clofazimine.^{7,8} Prolongations of the corrected QT interval, calculated with the use of Fridericia's formula (QTcF), to 500 msec or greater were investigated, and treatment was modified if the prolongation was considered to be drug related by the site investigators. A full list of the assessments performed in the trial is provided in the Supplementary Appendix.⁵

PRIMARY OUTCOMES

The primary efficacy outcome was a favorable status at 132 weeks, which was defined by cultures that were negative for *M. tuberculosis* at 132 weeks after randomization and at a previous occasion during the trial period, with no intervening positive culture or previous unfavorable outcome. An unfavorable outcome was defined by the initiation of two or more drug therapies that were not included in the assigned regimen, treatment extension beyond the permitted duration, death from any cause, a positive culture from one of the two most recent specimens, or no visit at 76 weeks or later. Participants who had reinfections with a different strain and those whose last two cultures were negative (including one at 76 weeks) but were lost to follow-up thereafter were considered to be unable to be assessed and were excluded from the primary analysis.

The primary safety outcome was the occurrence of a (severe) adverse event of grade 3 or higher (as classified according to the Division of AIDS, National Institute of Allergy and Infectious Diseases⁹) at any time during the treatment

or follow-up period. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0. An independent death review committee, the members of which were unaware of the treatment-group assignments, classified the probable cause of death as being related to tuberculosis, tuberculosis treatment, HIV or HIV treatment, or other or uncertain.

SECONDARY OUTCOMES

Secondary efficacy outcomes were times to smear and culture conversions; acquired resistance to fluoroquinolones, aminoglycosides, and pyrazinamide; and a Bayesian interpretation of the results. Secondary safety outcomes were death during the treatment and follow-up periods, an analysis of severe adverse events by MedDRA class, an analysis of QT interval prolongation, and changes in liver function test results.

RANDOMIZATION AND TRIAL POPULATIONS

Participants were assigned in a 2:1 ratio to the short regimen or the long regimen; randomization was stratified according to trial site and HIV status. The modified intention-to-treat population comprised all participants who underwent randomization and had a culture that was positive for *M. tuberculosis* at screening or randomization, with the exception of those in whom isolates obtained before randomization were subsequently found to be susceptible to rifampin or resistant to both fluoroquinolones and second-line injectable drugs on phenotypic drug-susceptibility testing. The per-protocol population comprised the participants in the modified intention-to-treat population, with the exception of those who did not complete a protocol-adherent course of treatment for reasons other than treatment failure or death. All participants who received at least one dose of a trial medication were included in the safety analyses.

STATISTICAL ANALYSIS

Assuming that 75% of the participants in the short-regimen group and 70% in the long-regimen group would attain favorable status and assuming that in a per-protocol analysis efficacy would not be able to be assessed in up to 20% of the participants, we estimated that 398 participants would need to be enrolled for the trial to have 80% power to show the noninferiority of the short

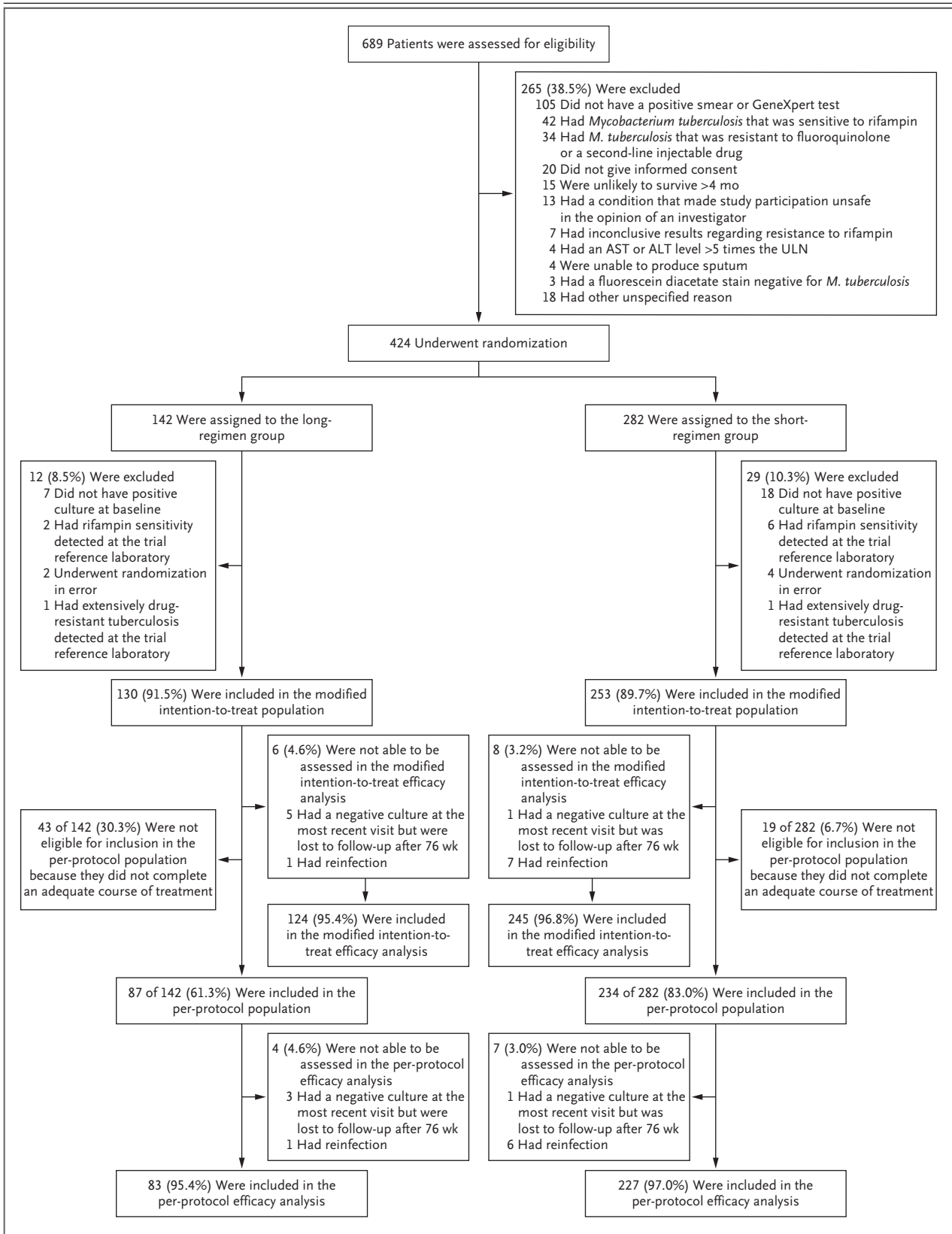


Figure 1 (facing page). Screening, Randomization, and Analysis of the Trial Populations.

The modified intention-to-treat population comprised all participants who underwent randomization and had a positive culture for *Mycobacterium tuberculosis* at screening or randomization, with the exception of those in whom isolates obtained before randomization were subsequently found to be susceptible to rifampin or resistant to both fluoroquinolones and second-line injectable drugs on phenotypic drug susceptibility testing. The per-protocol population comprised the participants in the modified intention-to-treat population, with the exception of those who did not complete a protocol-adherent course of treatment for reasons other than treatment failure or death. The short regimen (9 to 11 months) consisted of moxifloxacin (high-dose), clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin, isoniazid, and prothionamide in the first 16 weeks; the intensive phase could be extended to 20 or 24 weeks for participants who did not have a conversion to a negative smear by 16 or 20 weeks, respectively. The long regimen (20 months) followed the 2011 World Health Organization guidelines. Four participants assigned to the short-regimen group underwent randomization in error and were immediately withdrawn from the trial — one had a rapid test positive for fluoroquinolone-resistant tuberculosis, one was underage, one had a positive pregnancy test, and one had a GeneXpert (Cepheid) result that was misinterpreted. Two participants assigned to the long-regimen group underwent randomization in error and were immediately withdrawn from the study — one had a rapid test positive for aminoglycoside-resistant tuberculosis, and one had rifampin sensitivity detected on a GeneXpert test. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

regimen to the long regimen, at one-sided level of significance of 0.025. Additional details are provided in the Supplementary Appendix. In the primary efficacy analysis, we calculated the absolute between-group difference (with the 95% confidence interval) in the percentage of participants who attained favorable status, with adjustment for HIV status using Cochran–Mantel–Haenszel weights.¹⁰ Noninferiority would be shown if the upper boundary of the 95% confidence interval was 10 percentage points or less in both the modified intention-to-treat and per-protocol populations. A 10 percentage-point noninferiority margin was considered to be an acceptable difference in efficacy, given the shorter treatment duration.

One-sided tests for noninferiority and calculations of the 95% confidence intervals were per-

formed with the use of the Wald standard error. We also conducted a post hoc secondary Bayesian analysis of noninferiority.¹¹

RESULTS

PARTICIPANTS

From July 2012 through June 2015, a total of 689 participants were screened, of whom 424 underwent randomization; 282 participants were assigned to the short-regimen group and 142 to the long-regimen group. A total of 126 participants resided in Ethiopia, 33 in Mongolia, 165 in South Africa, and 100 in Vietnam. The modified intention-to-treat population comprised 383 participants, of whom 369 were included in the modified intention-to-treat efficacy analysis, and the per-protocol population comprised 321 participants, of whom 310 were included in the per-protocol efficacy analysis. Reasons for exclusion are shown in Figure 1.

The demographic characteristics of participants at baseline did not differ significantly between the treatment groups (Table 1, and Table S2 in the Supplementary Appendix). In the modified intention-to-treat population, 32.6% of the participants were infected with HIV and 77.2% had cavitation. The median duration of treatment among those who completed the assigned regimen was 40.1 weeks (5th and 95th percentiles, 37.0 and 46.3) in the short-regimen group and 82.7 weeks (5th and 95th percentiles, 72.1 and 102.3) in the long-regimen group. In the short-regimen group, the intensive phase of treatment was extended by 4 weeks in 10 participants (4.0%) and by 8 weeks in 3 participants (1.2%) because of a delayed conversion to a negative smear.

At 132 weeks, 94.1% of the participants in the short-regimen group and 90.0% in the long-regimen group in the modified intention-to-treat population were either assessed or were known to have died, and 1.2% and 5.4%, respectively, were lost to follow-up (Table S3 in the Supplementary Appendix). In the modified intention-to-treat population, 75.1% of the participants in the short-regimen group and 43.1% in the long-regimen group were fully adherent to the assigned regimen (Fig. S1 in the Supplementary Appendix).

PRIMARY EFFICACY OUTCOME

In the modified intention-to-treat efficacy analysis, favorable status was reported in 99 of 124 par-

Table 1. Baseline Characteristics of the Participants in the Modified Intention-to-treat Population.*

Characteristic	Long Regimen (N = 130)	Short Regimen (N = 253)	Total (N = 383)
Male sex — no./total no. (%)	83/130 (63.8)	151/253 (59.7)	234/383 (61.1)
Age — no./total no. (%)			
<25 yr	31/130 (23.8)	56/253 (22.1)	87/383 (22.7)
25–34 yr	45/130 (34.6)	88/253 (34.8)	133/383 (34.7)
35–44 yr	33/130 (25.4)	58/253 (22.9)	91/383 (23.8)
≥45 yr	21/130 (16.2)	51/253 (20.2)	72/383 (18.8)
Weight — no./total no. (%)			
<33 kg	0	1/253 (0.4)	1/383 (0.3)
33–50 kg	59/130 (45.4)	116/253 (45.8)	175/383 (45.7)
>50 kg	71/130 (54.6)	136/253 (53.8)	207/383 (54.0)
Positive HIV status — no./total no. (%)	40/130 (30.8)	85/253 (33.6)	125/383 (32.6)
Median CD4 cell count in HIV-infected participants (IQR)†	298 (166–532)	239 (139–394)	248 (143–429)
Radiographic extent of disease — no./total no. (%)‡			
None or minimal	14/125 (11.2)	28/239 (11.7)	42/364 (11.5)
Moderate	72/125 (57.6)	126/239 (52.7)	198/364 (54.4)
Advanced	39/125 (31.2)	85/239 (35.6)	124/364 (34.1)
Radiographic extent of cavitation — no./total no. (%)‡			
None	28/125 (22.4)	55/239 (23.0)	83/364 (22.8)
Single	13/125 (10.4)	34/239 (14.2)	47/364 (12.9)
Multiple	84/125 (67.2)	150/239 (62.8)	234/364 (64.3)
QTcF interval — no./total no. (%)			
<400 msec	58/130 (44.6)	112/253 (44.3)	170/383 (44.4)
400–449 msec	71/130 (54.6)	136/253 (53.8)	207/383 (54.0)
450–499 msec	1/130 (0.8)	5/253 (2.0)	6/383 (1.6)

* The modified intention-to-treat population comprised all participants who underwent randomization and had a culture positive for *Mycobacterium tuberculosis* at screening or randomization, with the exception of those in whom isolates obtained before randomization were subsequently found to be susceptible to rifampin or resistant to both fluoroquinolones and second-line injectable drugs on phenotypic drug susceptibility testing. The short regimen (9 to 11 months) consisted of moxifloxacin (high-dose), clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin, isoniazid, and prothionamide in the first 16 weeks; the intensive phase could be extended to 20 or 24 weeks for participants who did not have a conversion to a negative smear by 16 or 20 weeks, respectively. The long regimen (20 months) followed the 2011 World Health Organization guidelines. There were no significant between-group differences in the characteristics at baseline. A complete list of the baseline characteristics is provided in Table S2 in the Supplementary Appendix. HIV denotes human immunodeficiency virus, IQR interquartile range, and QTcF corrected QT interval, calculated with Fridericia's formula.

† CD4 cell counts were missing for 52 HIV-infected participants (13 in the long-regimen group and 39 in the short-regimen group).

‡ The results of chest radiography could not be assessed in 19 participants (5 in the long-regimen group and 14 in the short-regimen group).

participants (79.8%) in the long-regimen group and in 193 of 245 participants (78.8%) in the short-regimen group — a difference, with adjustment for HIV status, of 1.0 percentage point (95% CI, –7.5 to 9.5) (P=0.02 for noninferiority). The time to an unfavorable outcome did not differ significantly between the treatment groups (Fig. 2A). In the per-protocol efficacy analysis, favorable status

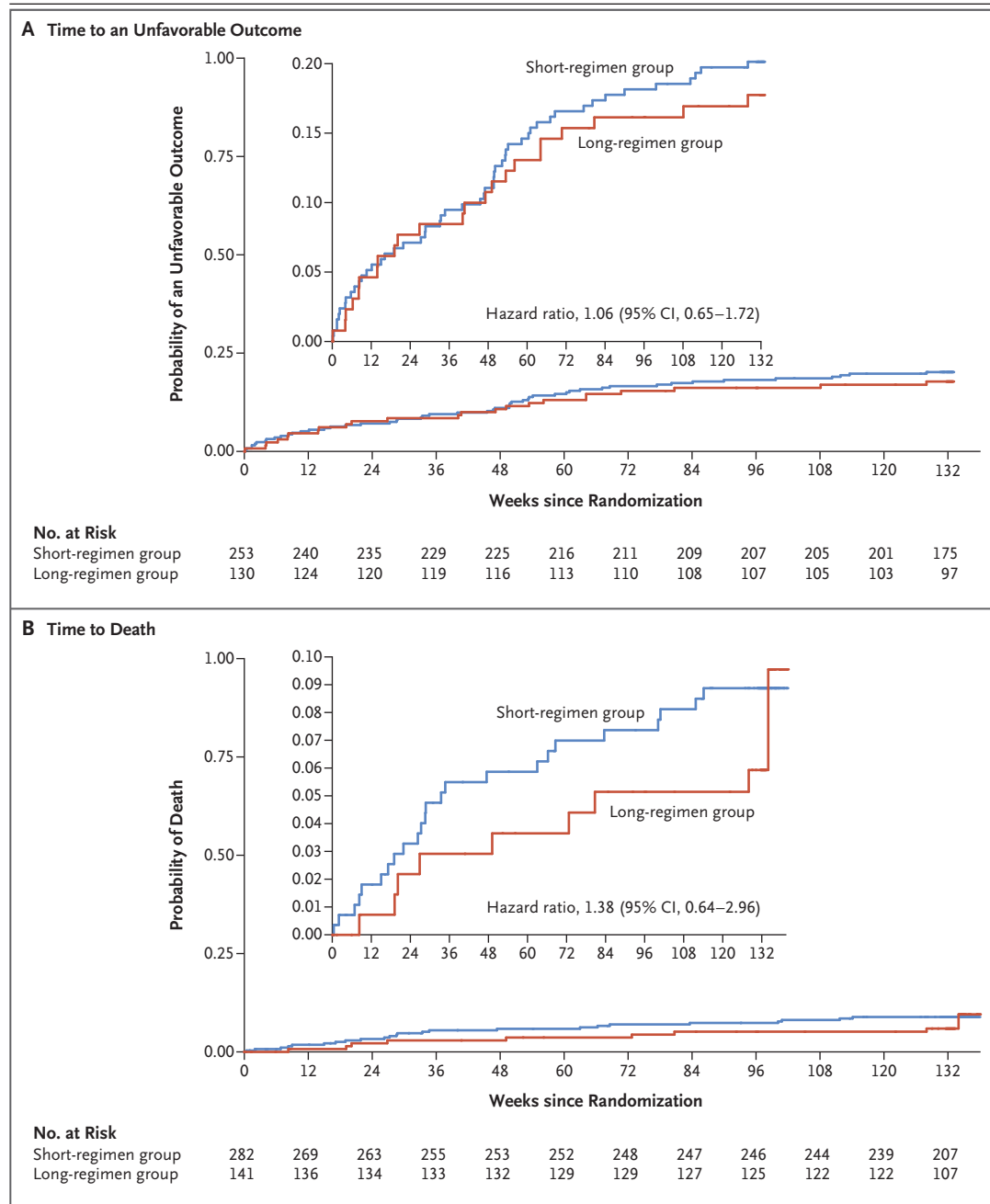


Figure 2. Kaplan–Meier Estimates of the Time to an Unfavorable Outcome and the Time to Death.

Panel A shows the Kaplan–Meier estimates of the time to an unfavorable outcome, which was defined by the initiation of two or more drug therapies that were not included in the assigned regimen, treatment extension beyond the permitted duration, death from any cause, a positive culture for *Mycobacterium tuberculosis* from one of the two most recent specimens, or no visit at 76 weeks or later. In contrast, favorable status at 132 weeks (the primary outcome) was defined by cultures that were negative for *M. tuberculosis* at 132 weeks after randomization and at a previous occasion during the trial period, with no intervening positive culture or previous unfavorable outcome. Panel B shows the Kaplan–Meier estimates of the time to death. In both panels, insets show the same data on an enlarged y axis.

Table 2. Primary Efficacy Analysis in the Modified Intention-to-Treat and Per-Protocol Populations.*

Variable	Modified Intention-to-Treat Population			Per-Protocol Population		
	Long Regimen	Short Regimen	Total	Long Regimen	Short Regimen	Total
Disposition of the participants						
Underwent randomization — no.	142	282	424	142	282	424
Were included in the population — no.	130	253	383	87	234	321
Were considered not able to be assessed — no.						
Had reinfection with a different strain	1	7	8	1	6	7
Had a negative culture at 76 weeks but lost to follow-up thereafter	5	1	6	3	1	4
Were included in primary outcome analysis — no.	124	245	369	83	227	310
Outcome						
Attained favorable status — no. (%)†	99 (79.8)	193 (78.8)	292 (79.1)	67 (80.7)	186 (81.9)	253 (81.6)
Had an unfavorable outcome — no. (%)	25 (20.2)	52 (21.2)	77 (20.9)	16 (19.3)	41 (18.1)	57 (18.4)
Determined on the basis of bacteriologic findings‡						
Had no negative cultures§	1	5	6	1	5	6
Had bacteriologic reversion during treatment period¶	4	13	17	4	11	15
Had bacteriologic relapse after treatment period and started ≥2 additional drug therapies	0	7	7	0	7	7
Had positive culture at last assessment**	2	1	3	2	1	3
Determined on the basis of criteria other than bacteriologic findings						
Had negative culture at last assessment but died during the treatment or follow-up period	5	9	14	5	9	14
Had treatment extended or changed after adverse event	3	4	7	2	3	5
Started ≥2 additional drug therapies owing to decision by the investigator††	3	2	5	2	0	2
Withdrew consent for treatment, was given a different regimen, or was lost to follow-up before 76 weeks	4	8	12	0	3	3
Had treatment extended or changed after poor adherence or loss to follow-up	0	2	2	0	1	1
Had negative culture at last assessment but was lost to follow-up before 76 weeks	3	1	4	0	1	1

* The per-protocol population comprised the participants in the modified intention-to-treat population, with the exception of those who did not complete a protocol-adherent course of treatment for reasons other than treatment failure or death. When a participant had more than one event leading to an unfavorable outcome (e.g., relapse and then death), the outcome classification was based on the first event. Additional information is provided in Table S4 in the Supplementary Appendix.

† The primary efficacy outcome was favorable status, defined by negative results on a culture for *M. tuberculosis* at 132 weeks after randomization and at a previous occasion during the trial period, with no intervening positive culture or previous unfavorable outcome. The unadjusted between-group difference in the percentage of participants who attained favorable status (long-regimen group minus short-regimen group) was 1.1 percentage points (95% confidence interval [CI], -7.7 to 9.8) in the modified intention-to-treat analysis ($P=0.02$ for noninferiority) and -1.2 percentage points (95% CI, -11.1 to 8.6) in the per-protocol analysis ($P=0.01$ for noninferiority). After adjustment for human immunodeficiency virus status, the corresponding between-group differences were 1.0 percentage point (95% CI, -7.5 to 9.5) and -0.7 percentage points (95% CI, -10.5 to 9.1) ($P=0.02$ for noninferiority in both analyses).

‡ Participants were considered to have bacteriologic reversion or relapse if they started at least two new additional drug therapies after the recurrence of positive cultures either during the treatment period (reversion) or after the treatment period (relapse).

§ All the participants who had no negative cultures throughout the trial died, except for one participant in the short-regimen group who had started at least two additional drug therapies.

¶ All the participants who had bacteriologic reversion during treatment period started at least two additional drug therapies, except for one participant in the short-regimen group for whom treatment was extended beyond what was permitted, one participant in each regimen group who died, and one participant in the short-regimen group who was lost to follow-up before 76 weeks. One reversion that occurred in the long-regimen group was determined on the basis of limited bacteriologic findings (i.e., only an isolated positive culture that was associated with clinical signs and symptoms).

|| One relapse that occurred in the short-regimen group was determined on the basis of limited bacteriologic findings (i.e., an isolated positive culture that was associated with clinical signs and symptoms).

** One participant in the short-regimen group had a positive culture when last assessed before death, and two participants in the long-regimen group had a positive culture when last assessed at the end of follow-up (week 132).

†† The investigator's decision to start two or more additional drug therapies was based on the following reasons: results of baseline drug susceptibility testing (three participants in the long-regimen group), pregnancy (one participant in the short-regimen group), and switch to the same regimen as received by a participant's child (one participant in the short-regimen group).

was reported in 67 of 83 participants (80.7%) in the long-regimen group and in 186 of 227 participants (81.9%) in the short-regimen group — an adjusted difference of -0.7 percentage points (95% CI, -10.5 to 9.1) ($P=0.02$ for noninferiority). Among the participants included in the modified intention-to-treat efficacy analysis, unfavorable bacteriologic outcomes were more common in the short-regimen group than in the long-regimen group (26 participants [10.6%] vs. 7 participants [5.6%]); an unfavorable outcome due to loss to follow-up was more common in the long-regimen group than in the short-regimen group (3 participants [2.4%] vs. 1 participant [0.4%]) (Table 2). The treatment effect did not differ significantly between the treatment groups in any subgroup evaluated in the modified intention-to-treat analysis population, including the subgroup defined according to HIV status (Fig. S2 in the Supplementary Appendix).

SECONDARY OUTCOMES

The median times to conversion to a negative smear and culture did not differ significantly between the treatment groups. Resistance to fluoroquinolones or aminoglycosides developed in 8 participants (3.3%) in the short-regimen group and in 3 (2.3%) in the long-regimen group ($P=0.62$). Resistance to pyrazinamide developed in no participants. Using a flat uninformative prior distribution, we calculated that the Bayesian probability that the between-group difference in the percentage of participants who would attain favorable status would be less than 10 percentage points was 0.98 and the probability that it would be less than 5 percentage points was 0.83. The Bayesian mean estimate of the risk difference was 0.8 percentage points (95% credible interval, -8.1 to 9.3). (Additional details on the secondary outcome analyses are provided in Figs. S4 through S7 and Fig. S11 and Table S6 in the Supplementary Appendix.)

SAFETY

In the safety population, a severe adverse event occurred in 136 of 282 participants (48.2%) in the short-regimen group, as compared with 64 of 141 participants (45.4%) in the long-regimen group. A total of 33 participants died during the treatment or follow-up period — 24 (8.5%) in the short-regimen group and 9 (6.4%) in the long-regimen group (hazard ratio, 1.38; 95% CI, 0.64 to 2.96) (Table 3 and Fig. 2B); most of the

difference between the treatment groups occurred during the first year, after which the rates became similar. Four cases of sudden death at home occurred during the treatment period — two deaths (one in the short-regimen group and one in the long-regimen group) were attributed by the death review committee to tuberculosis treatment, and the remaining two deaths (both in the short-regimen group) were attributed to other causes (Table S7 in the Supplementary Appendix). In the two of the three sudden deaths that occurred in the short-regimen group, a QT or QTcF interval of 500 msec or more had been recorded; one of these deaths was attributed to treatment and the other to other causes. Among the participants who had HIV coinfection at baseline, 18 of 103 (17.5%) in the short-regimen group died, as compared with 4 of 50 (8.0%) in the long-regimen group (hazard ratio in a post hoc analysis, 2.23; 95% CI, 0.76 to 6.60).

Five of the MedDRA system organ classes accounted for the majority of severe adverse events (Table S8 in the Supplementary Appendix). More participants in the short-regimen group than in the long-regimen group had cardiac disorders, particularly those classified as conduction disorders (9.9% vs. 5.0%), whereas more participants in the long-regimen group than in the short-regimen group had metabolic disorders, particularly those classified as hypokalemia (7.1% vs. 1.1%). Hepatobiliary disorders were slightly more common in the short-regimen group than in the long-regimen group (8.9% vs. 5.7%), but the percentage of patients with either ear and labyrinth or respiratory disorders did not differ notably.

The ECG monitoring showed that prolongation of the QT or QTcF interval to 500 msec or more developed in more participants in the short-regimen group than in the long-regimen group (11.0% vs. 6.4%, $P=0.14$); such prolongations occurred throughout the treatment period (Fig. S8 in the Supplementary Appendix). There was little difference with respect to prolongation of the QT or QTcF interval between the two high doses of moxifloxacin that were used in the trial (Table S10 in the Supplementary Appendix). The treatment was modified in response to prolongation of the QT or QTcF interval in 33 participants (32 [11.3%] in the short-regimen group); the moxifloxacin dose was reduced in 21 participants, and moxifloxacin was switched to levofloxacin in 12 participants, of whom 3 also discontinued clofazimine and 1 continued clofazimine at half the dose.

Table 3. Summary of Safety Outcomes.*

Outcome	Long Regimen (N=141)	Short Regimen (N=282)	Total (N=423)
Grade 3 to 5 adverse event — no. (%)	64 (45.4)	136 (48.2)	200 (47.3)
Serious adverse event — no. (%)	53 (37.6)	91 (32.3)	144 (34.0)
Death — no. (%)	9 (6.4)	24 (8.5)	33 (7.8)
Related to tuberculosis	2	7	9
Related to tuberculosis treatment	1	1	2
Related to HIV or HIV treatment	3	6	9
Other or uncertain	3	10	13
Grade 3 to 5 adverse events according to the five most common MedDRA system organ classes — no. (%)			
Metabolism and nutrition disorders	28 (19.9)	41 (14.5)	69 (16.3)
Hypokalemia†	10 (7.1)	3 (1.1)	13 (3.1)
Cardiac disorders	10 (7.1)	30 (10.6)	40 (9.5)
Conduction disorder†	7 (5.0)	28 (9.9)	35 (8.3)
Hepatobiliary disorders	8 (5.7)	25 (8.9)	33 (7.8)
Ear and labyrinth disorders	8 (5.7)	21 (7.4)	29 (6.9)
Respiratory, thoracic, and mediastinal disorders	6 (4.3)	15 (5.3)	21 (5.0)

* All participants who received at least one dose of a trial medication were included in the safety analysis population. The primary safety outcome in the trial was a grade 3 to 5 adverse event at any point during the treatment and follow-up periods. Adverse events were coded with the use of *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0. An independent death review committee, the members of which were unaware of the treatment-group assignments, classified the probable cause of death as being related to tuberculosis, tuberculosis treatment, HIV or HIV treatment, or other or uncertain.

† Hypokalemia and conduction disorder are preferred terms in MedDRA, version 20.0.

An alanine aminotransferase level exceeding five times the upper limit of the normal range was reported in 18 of 272 participants (6.6%) in the short-regimen group, as compared with 2 of 139 participants (1.4%) in the long-regimen group ($P=0.03$); in a time-to-event analysis, the hazard ratio for a measurement exceeding five times the upper limit of the normal range after randomization in the short-regimen group as compared with the long-regimen group was 5.64 (95% CI, 1.30 to 24.38) (Table S11 and Fig. S9 in the Supplementary Appendix). Aspartate aminotransferase levels did not differ significantly between the treatment

dose gatifloxacin) was noninferior to the long regimen (20 months) that followed the 2011 WHO recommendations. Both regimens resulted in a long-term successful outcome in more than 78% of the participants, with more participants in the short-regimen group having an unfavorable outcome (HIV-adjusted difference, 1.0 percentage point), although this difference could have been 7.5 percentage points in favor of the short regimen or 9.5 percentage points in favor of the long regimen. The Bayesian analysis yielded a probability of 0.83 that this difference would be no more than 5 percentage points. Our final estimate of the difference in efficacy between the two regimens, based on data from 369 participants in the modified intention-to-treat analysis, did not differ notably from the preliminary findings that were based on data from 318 participants (adjusted difference, 2.1 percentage points; 95% CI, -6.9 to 11.2) that we reported at the Union World Conference on Lung Health in October 2017.¹²

DISCUSSION

We found that the efficacy of the short regimen (9 to 11 months) that had been studied previously in Bangladesh (modified in the current trial to include high-dose moxifloxacin in place of high-

The percentage of participants who had severe adverse events did not differ notably between the treatment groups. ECG monitoring was performed in all the participants in the trial; this was shown to be necessary to identify and manage QT or QTcF interval prolongation that occurred in some participants in the short-regimen group throughout the treatment period. Unfavorable bacteriologic outcomes were more common among the participants in the short-regimen group and consisted mainly of bacteriologic reversion (during the treatment period) and relapses (after the treatment period). This finding may be due in part to the fact that few participants in the short-regimen group had an extension of the intensive phase because of slow conversion to a negative smear; in contrast, in the Bangladesh study, half the patients received treatment for more than 9 months.¹³ Although the follow-up time from randomization was the same in the two treatment groups, the difference in treatment duration allowed less time for post-treatment relapses to be identified among the participants in the long-regimen group. In the modified intention-to-treat analysis, the short regimen was not shown to be inferior or superior to the long regimen in any subgroup evaluated.

Some acquired fluoroquinolone resistance was observed, but the percentage of participants in whom this developed did not differ significantly between the treatment groups. This finding is in contrast to the Bangladesh study, in which no such acquired resistance was observed in more than 500 patients¹³ and may be a consequence of the use of moxifloxacin in place of gatifloxacin, poorer adherence, or differences in clinical management.

The trial showed no evidence that the short regimen was associated with fewer severe adverse events over the 132 weeks of treatment and follow-up. The type of event differed between the groups, particularly in relation to cardiac conduction disorders and hepatobiliary disorders, both of which were more common in the short regimen group, and metabolic disorders, which were more common in the long regimen group. Hearing loss with second-line injectable drugs is an important cause of disability. No evidence of a between-group difference in ear and labyrinth disorders was found, although these events may have been underestimated because trial sites outside South Africa did not have access to formal

audiometry. There was limited evidence of a difference in mortality, with more deaths reported in the short-regimen group than in the long-regimen group in the first year after starting treatment. This difference was more pronounced among participants coinfecting with HIV.

Regular ECG monitoring in all participants led to the recognition that the percentage of participants with severe conduction disorders (defined by a prolongation of the QT or QTcF interval to 500 msec or more) was twice as high in the short-regimen group as in the long-regimen group. Similarly, regular liver function testing during the intensive phase showed that the percentage of participants with grade 3 alanine aminotransferase elevations was higher in the short-regimen group than in the long-regimen group, which may have contributed to the excess of hepatobiliary disorders in the short-regimen group.

It was not possible to conduct the trial in a double-blind manner, and thus clinical decisions about when to change treatment may have been influenced by knowledge of the treatment-group assignment rather than have been based solely on the clinical condition of the participants. The open-label design may have influenced reporting of adverse events; however, trial sites were asked to report all grade 3 to 5 adverse events irrespective of whether they might be considered to be drug reactions. The current trial provides no evidence regarding which of the seven drugs in the short regimen are essential. Other studies may assist in answering this question.¹⁴⁻¹⁷ The between-country variation in the constitution of the long regimen might be considered a limitation, but there is no evidence of differential treatment effects between countries. Although the results of the per-protocol analysis were consistent with those of the modified intention-to-treat analysis with respect to the noninferiority of the short regimen to the long regimen, the larger percentage of participants in the long-regimen group than in the short-regimen group who were excluded from the per-protocol analysis (30.3% vs. 6.7%) limits the clinical usefulness of the findings.

These results are applicable only to patients infected with bacilli for which there was no genotypic evidence of resistance to fluoroquinolones or injectable drugs. A second stage of the STREAM study (Current Controlled Trials number, ISRCTN18148631; and ClinicalTrials.gov number, NCT02409290) is currently evaluating wheth-

er a fully oral short regimen would be effective and thereby avoid the toxic effects associated with aminoglycosides.¹⁴

Regular ECG monitoring to identify QT interval prolongation and allow treatment modification if required was shown to be useful throughout the treatment period in the short-regimen group¹⁸; QT-related treatment modifications, most commonly a reduction in moxifloxacin dose, were made in 11.3% of participants assigned to the short-regimen group. There was little difference between the two moxifloxacin doses with respect to QT interval prolongation. Our findings suggest that implementation of the short regimen with high-dose moxifloxacin would require regular ECG monitoring throughout the treatment period. This would present a considerable challenge for clinical services, and in view of these findings, the fluoroquinolone used in the modified Bangladesh regimen in the second-stage STREAM study has been changed to levofloxacin to evaluate whether this change would allow ECG monitoring to be reduced.

Our results were consistent with those of the Bangladesh study that involved more than 500 participants,¹³ as well as those from smaller studies in Cameroon, Niger, Uzbekistan, and Swaziland.¹⁹⁻²¹ Key strengths of the trial were its randomized design, the inclusion of participants coinfecting with HIV, the diverse population (sites in four countries with different ethnic compositions and health care systems), and a greater than 90% rate of retention.

After reviewing the results of the STREAM study and of observational studies, the WHO re-

leased updated guidelines for multidrug-resistant and rifampin-resistant tuberculosis in December 2018 that continued to include the short regimen as an option for patients “who have not been previously treated for more than one month with second-line medicines used in the shorter MDR [multidrug-resistant] regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded.”²² Although the results of this trial are encouraging, further research remains essential to find a short, simple regimen for multidrug-resistant tuberculosis that results in efficacy and safety outcomes that are similar to those for drug-susceptible tuberculosis.

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APPENDIX

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REFERENCES

1. Global tuberculosis report 2017. Geneva: World Health Organization, 2017.
2. Global tuberculosis report 2012. Geneva: World Health Organization, 2012.
3. STOP TB Department. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization, 2011.
4. Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010;182:684-92.
5. Nunn AJ, Rusen ID, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials* 2014;15:353.
6. Brossier F, Veziris N, Aubry A, Jarlier V, Sougakoff W. Detection by GenoType MTBDRsl test of complex mechanisms of resistance to second-line drugs and ethambutol in multidrug-resistant Mycobacterium tuberculosis complex isolates. *J Clin Microbiol* 2010;48:1683-9.
7. Florian JA, Tornøe CW, Brundage R, Parekh A, Garnett CE. Population pharmacokinetic and concentration-QTc models for moxifloxacin: pooled analysis of 20 thorough QT studies. *J Clin Pharmacol* 2011;51:1152-62.
8. Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. *Am J Respir Crit Care Med* 2015;191:943-53.
9. National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS table for grading the severity of adult adverse events. Bethesda, MD: Department of Health and Human Services, 1992.
10. Mohamed K, Embleton A, Cuffe RL. Adjusting for covariates in non-inferiority studies with margins defined as risk differences. *Pharm Stat* 2011;10:461-6.
11. Laptook AR, Shankaran S, Tyson JE, et al. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial. *JAMA* 2017;318:1550-60.
12. Nunn AJ, Meredith SM. STREAM Stage 1 preliminary efficacy results. Presented at the 48th Union World Conference on Lung Health, Guadalajara, Mexico; October 11–14, 2017.
13. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014;18:1180-7.
14. Moodley R, Godec TR. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. *Eur Respir Rev* 2016;25:29-35.
15. RESIST-TB. DR-TB clinical trial progress report. 2018 (http://www.resisttb.org/?page_id=1602).
16. Cellamare M, Venz S, Baudin E, Mitnick CD, Trippa L. A Bayesian response-adaptive trial in tuberculosis: the endTB trial. *Clin Trials* 2017;14:17-28.
17. Burki TK. The uphill battle to find new TB treatments. *Lancet Respir Med* 2017;5:250.
18. Joy JP, Coulter CV, Duffull SB, Isbister GK. Prediction of torsade de pointes from the QT interval: analysis of a case series of amisulpride overdoses. *Clin Pharmacol Ther* 2011;90:243-5.
19. Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trébuq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis* 2015;19:517-24.
20. Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014;18:1188-94.
21. Ahmad Khan F, Salim MAH, du Cros P, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017;50:1700061.
22. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis: 2018 update. Geneva: World Health Organization, 2018 (WHO/CDS/TB/2018.15) (<https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf>).

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