ORIGINAL ARTICLE

Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis

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ABSTRACT

BACKGROUND

For decades, poor treatment options and low-quality evidence plagued care for patients with rifampin-resistant tuberculosis. The advent of new drugs to treat tuberculosis and enhanced funding now permit randomized, controlled trials of shortened-duration, all-oral treatments for rifampin-resistant tuberculosis.

METHODS

We conducted a phase 3, multinational, open-label, randomized, controlled noninferiority trial to compare standard therapy for treatment of fluoroquinolone-susceptible, rifampin-resistant tuberculosis with five 9-month oral regimens that included various combinations of bedaquiline (B), delamanid (D), linezolid (L), levofloxacin (Lfx) or moxifloxacin (M), clofazimine (C), and pyrazinamide (Z). Participants were randomly assigned (with the use of Bayesian response-adaptive randomization) to receive one of five combinations or standard therapy. The primary end point was a favorable outcome at week 73, defined by two negative sputum culture results or favorable bacteriologic, clinical, and radiologic evolution. The noninferiority margin was –12 percentage points.

RESULTS

Among the 754 participants who underwent randomization, 699 were included in the modified intention-to-treat analysis, and 562 in the per-protocol analysis. In the modified intention-to-treat analysis, 80.7% of the patients in the standard-therapy group had favorable outcomes. The risk difference between standard therapy and each of the four new regimens that were found to be noninferior in the modified intention-to-treat population was as follows: BCLLfxZ, 9.8 percentage points (95% confidence interval [CI], 0.9 to 18.7); BLMZ, 8.3 percentage points (95% CI, –0.8 to 17.4); BDLLfxZ, 4.6 percentage points (95% CI, –4.9 to 14.1); and DCMZ, 2.5 percentage points (95% CI, –7.5 to 12.5). Differences were similar in the per-protocol population, with the exception of DCMZ, which was not noninferior in that population. The proportion of participants with grade 3 or higher adverse events was similar across the regimens. Grade 3 or higher hepatotoxic events occurred in 11.7% of participants overall and in 7.1% of those receiving standard therapy.

CONCLUSIONS

Consistent results across all the analyses support the noninferior efficacy of three all-oral shortened regimens for the treatment of rifampin-resistant tuberculosis. (Funded by Unitaid and others; endTB ClinicalTrials.gov number, NCT02754765.)

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*A list of the members of the endTB Clinical Trial Team is provided in the Supplementary Appendix, available at NEJM.org.

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Tuberculosis that is resistant to rifampin, a key drug for treatment of tuberculosis, is a major global health threat. According to the World Health Organization (WHO), 410,000 people become sick with rifampin-resistant tuberculosis annually. Only 40% of cases are diagnosed and treated, 65% of them successfully.[1] Historically, poor response was due largely to the suboptimal 18-to-24-month regimens, which included injected aminoglycosides or polypeptides and caused substantial toxic effects.[2] Regimens were devised on the basis of expert opinion and pooled analyses of observational studies because no evidence was available from contemporary randomized, controlled clinical trials.[3,4] In 2016 and 2017, the endTB trial and two other multinational, randomized, controlled trials were launched to examine whether shorter, all-oral regimens of 6 or 9 months' duration could safely and efficaciously treat rifampin-resistant tuberculosis in adults and adolescents. The STREAM 2 study examined a 9-month, 7-drug bedaquiline-containing regimen.[5] The TB-PRACTECAL study assessed three 6-month regimens that included bedaquiline, linezolid, and pretomanid alone or with moxifloxacin or clofazimine.[6] The endTB (Evaluating Newly Approved Drugs for Multidrug-Resistant Tuberculosis) trial, reported here, evaluated the efficacy and safety of five 9-month, all-oral treatment regimens as compared with the evolving standard of care for fluoroquinolone-susceptible, rifampin-resistant tuberculosis. This phase 3 clinical trial aimed to identify shorter, effective, and safe regimens containing newer drugs (bedaquiline and delamanid) and repurposed drugs (clofazimine and linezolid). We used Bayesian response-adaptive randomization[7,8] to concurrently study five regimens containing different combinations of these drugs with the goal of identifying multiple alternatives that would advance patient-centered care.

Methods

Design and Oversight

The endTB trial is a phase 3, multinational, open-label, noninferiority trial that was conducted by the endTB consortium. A full description of the trial design and details regarding the implementation were published previously[9] and are included in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was approved by the institutional or ethics review board that supervised each consortium member and each participating site. All participants provided written informed consent.

The distribution of trial responsibilities across the team and additional oversight, including by an independent data and safety monitoring board, are described in the Supplementary Appendix (Section 2.2 and Tables S1 through S5). All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. The Consolidated Standards of Reporting Trials extension for adaptive-design trials guided this trial report.[10]

A Quick Take is available at NEJM.org

Participants

Persons who were 15 years of age or older with fluoroquinolone-susceptible, pulmonary rifampin-resistant tuberculosis that was confirmed by WHO-endorsed rapid tests were enrolled at 12 sites, which were run by endTB partners (Table S2), in Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa, with the goal of ensuring representativeness (Table S6). Inclusion in the trial was irrespective of human immunodeficiency virus (HIV) serostatus and CD4 lymphocyte count. The trial excluded persons with the following conditions at baseline: pregnancy; elevated liver enzymes; uncorrectable electrolyte disorders; a QT interval corrected according to Fridericia's formula (QTcF) of at least 450 msec; resistance or previous exposure for 30 days or more to bedaquiline, delamanid, clofazimine, or linezolid; and at least 15 days of treatment with any second-line antituberculosis drug during the current episode of tuberculosis.[9] The Supplementary Appendix provides details regarding baseline eligibility criteria and trial retention of participants who became pregnant.

Randomization and Treatment

The treatment group was assigned by Bayesian response-adaptive randomization whereby the probability of randomization to each group was updated monthly according to interim analyses of treatment response (culture at week 8 and efficacy at week 39) in previously enrolled participants as they were progressing through the trial. Details have been published previously.[7,8] Randomization was performed through a centralized interactive randomization system.

The experimental regimens were administered over the course of 39 weeks (9 months) and contained 4 to 5 of the following drugs: bedaquiline (B), delamanid (D), clofazimine (C), linezolid (L), levofloxacin (Lfx), moxifloxacin (M), and pyrazinamide (Z). The regimen combinations were BLMZ, BCLLfxZ, BDLLfxZ, DCLLfxZ, and DCMZ. Standard-therapy regimens reflected the WHO guidelines that were in effect while the trial was being conducted.[4,11,12] These regimens were expected to be mostly individualized regimens of 18-to-24-months' duration composed according to WHO recommendations, which endorsed the use of the new drugs bedaquiline and delamanid as well as the repurposed drugs linezolid and clofazimine, among others. If the WHO-recommended seven-drug, 9-month regimen was offered in routine care, this treatment could be administered in participants with susceptibility to the drugs in that regimen. Treatment was administered 7 days a week, with direct observation occurring on 6 of the days. If the experimental regimen contained linezolid, the dose of linezolid was decreased at week 16 or sooner if necessary to reduce toxic effects (for more details about the regimens, see Fig. S2 and Tables S7 and S8).

PROCEDURES

Clinical, safety, and mycobacteriologic assessments occurred weekly until week 12 and then every 4 weeks until week 47 and every 6 to 8 weeks thereafter (Table S9). Standardized mycobacteriologic tests were performed at designated quality-controlled laboratories at each trial site; the Institute of Tropical Medicine supported site laboratories and performed additional testing. Procedures included smear microscopy and culture performed with the use of the Mycobacteria Growth Indicator Tube (MGIT) system at all laboratories and on solid Löwenstein–Jensen media at all laboratories except the one in South Africa. Phenotypic drug-susceptibility testing was performed with the use of the MGIT system for at least rifampin and fluoroquinolones. Drug-susceptibility testing for bedaquiline, clofazimine, delamanid, and linezolid was gradually introduced.

END POINTS

The primary efficacy end point was a favorable outcome at week 73, which was defined as the absence of an unfavorable outcome and either two consecutive negative cultures (including one between weeks 65 and 73) or favorable bacteriologic, radiologic, and clinical evolution. Unfavorable outcomes included death (from any cause), the replacement or addition of one drug in the experimental regimens or two drugs in the standard-therapy regimen, or the initiation of new treatment for rifampin-resistant tuberculosis (for the full list of unfavorable outcomes, see Section 2.6.2 in the Supplementary Appendix).

The maximum duration of follow-up was 104 weeks. Trial follow-up ended when the final participant reached 73 weeks after randomization. Favorable outcomes at week 39 and at week 104 were secondary end points. Outcomes were adjudicated by the clinical advisory committee.

Safety end points were grade 3 or higher adverse events, serious adverse events, death, discontinuation of at least one trial drug because of adverse events, and adverse events of special interest (hepatotoxic events, hematologic toxic events, optic neuritis, peripheral neuropathy, and QTcF prolongation) that were defined as grade 3 or higher by week 73 (for more details on follow-up and outcomes, see Section 2.6 in the Supplementary Appendix). Adverse events could be established by laboratory values alone and were graded by the site investigators according to the standardized Pharmacovigilance Unit Severity Scale (available at https://endtb.org/toolkit/endtb-trials-pharmacovigilance) from Médecins sans Frontières (Doctors without Borders).

ANALYSIS POPULATIONS

The modified intention-to-treat population and the per-protocol population were the coprimary analysis populations. The modified intention-to-treat population included all the participants who underwent randomization and received at least one dose of trial treatment (safety population) and who had a prerandomization culture positive for *Mycobacterium tuberculosis*. It excluded participants with baseline phenotypic resistance to bedaquiline, clofazimine, delamanid, any fluoroquinolone, or linezolid. The per-protocol population included participants from the modified intention-to-treat population who received for less than 7 days a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol-consistent course of treatment (at least 80% of

expected doses taken within 120% of the regimen duration) or who did not do so because of treatment failure or death. Other analysis populations are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was determined with the assumption that favorable outcomes at week 73 would be seen in 75% of the participants in the experimental regimen groups and in 70% of the participants in the standard-therapy group, that relapse would occur in 10% of the participants, and that 11% of the participants would be ineligible for inclusion in the modified intention-to-treat population and an additional 10% would be ineligible for inclusion in the per-protocol population. We calculated that a sample size of 750 would give the trial 80% power to determine noninferiority (at a one-sided type I error rate of 2.5%) of three experimental regimens in the modified intention-to-treat population and two in the per-protocol population. The noninferiority margin was set at –12 percentage points because the standard therapy received in the trial was expected to perform better than other reference standards.[13,14] Slightly worse efficacy of the experimental regimens was considered an acceptable trade-off for the benefits of the shortened treatment duration and reduction of the pill burden. Finally, three recent trials of tuberculosis treatment used a 12-percentage-point margin for noninferiority.[6,15,16]

The efficacy analysis relied on the absolute between-group difference in the percentages of participants with a favorable outcome at week 73. To sequence regimen comparisons, we used a hierarchical testing approach. Noninferiority in the modified intention-to-treat population was to be established if the lower bound of the 95% confidence interval around the difference exceeded –12 percentage points. In this report, per-protocol analyses provided complementary information but were not used for formal testing of a noninferiority comparison. Risk differences were estimated with the use of a binomial regression model (generalized linear model for a binomial outcome with an identity link function). The primary analysis was unadjusted. Secondary analyses explored confounding according to prespecified covariates. A Cox regression model was used to estimate crude hazard ratios and 95% confidence intervals for the time from randomization to an unfavorable outcome for each experimental group. Schoenfeld residuals were used to test the proportional-hazards assumption. Adjusted, subgroup, sensitivity, and post hoc efficacy analyses are described in Section 2.7 in the Supplementary Appendix. For each group, we estimated the percentages of participants who died, who had serious adverse events, who had adverse events of special interest, and who had grade 3 or higher adverse events. For grade 3 or higher adverse events, we also estimated the percentage of events that were related to a trial drug. All analyses were performed with the use of Stata, version 17.0.

RESULTS

TRIAL POPULATIONS AND BASELINE CHARACTERISTICS

From February 2017 through October 2021, a total of 1542 persons underwent screening and 754 underwent randomization. Nine participants were excluded from the safety population (which now included 745 participants) and 46 from the modified intention-to-treat population (699 participants). The per-protocol population included 562 participants (Fig. 1 and Fig. S4).

Overall, in the modified intention-to-treat population, 264 participants (37.8%) were women. The median age was 32 years, and 25 participants (3.6%) were younger than 18 years of age; 98 participants (14.0%) were living with HIV infection, 568 participants (81.3%) had sputum smear results graded 1+ or higher, and 57.1% of the participants had cavitation on chest radiography. Baseline demographic and clinical characteristics are shown in Table 1 and Tables S10 and S11 and stratified by country in Table S12. Modest variability in severity of tuberculosis and previous treatment of tuberculosis was observed among the groups; expected differences in coexisting conditions (e.g., HIV infection, diabetes, and hepatitis C infection) occurred according to country.

Standard-therapy regimens consisted of at least five drugs at the start of the treatment course in 118 of 119 participants in the standard-therapy group (99.2%). Most participants (114; 95.8%) were assigned to individualized 18-to-24-month regimens, and 97 participants (81.5%) received treatment in accordance with the WHO 2022 recommendations[17] (Tables S13 and S14).

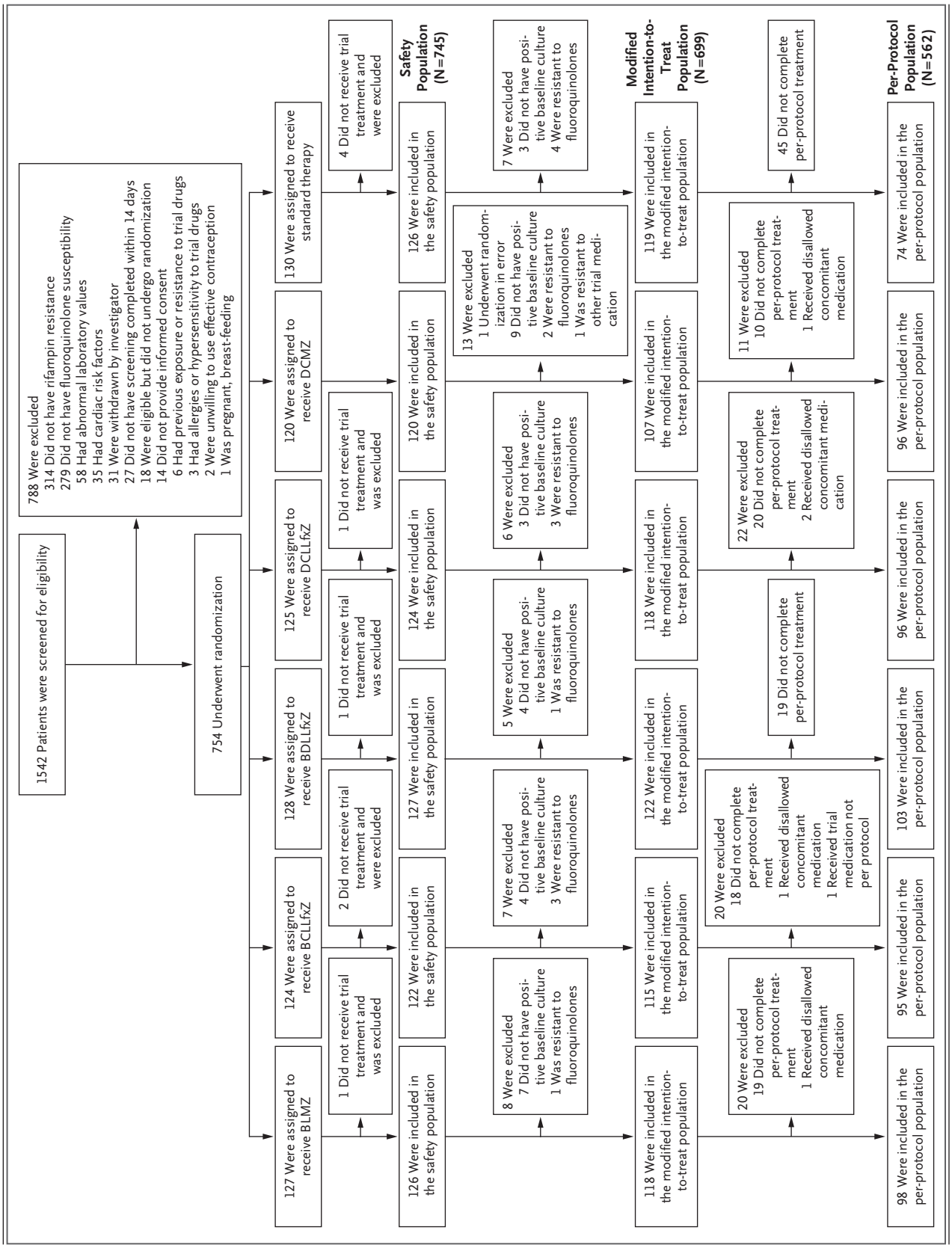

Figure 1 (facing page). Trial Groups and Analysis Populations.

Trial treatments, administered over the course of 9 months, included various combinations of four or five drugs from the following options: bedaquiline (B), delamanid (D), linezolid (L), levofloxacin (Lfx) or moxifloxacin (M), clofazimine (C), and pyrazinamide (Z). The safety population included all participants who underwent randomization and received at least one dose of trial treatment. The modified intention-to-treat population included participants from the safety population who had a prerandomization culture positive for *Mycobacterium tuberculosis* but excluded participants with baseline phenotypic resistance to bedaquiline, clofazimine, delamanid, any fluoroquinolone, or linezolid. The per-protocol population included participants from the modified intention-to-treat population who received for less than 7 days a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol-consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration) or did not complete the course of treatment because of treatment failure or death.

EFFICACY RESULTS

In the primary, unadjusted outcome analysis of the standard-therapy group, favorable outcomes occurred in 80.7% (95% confidence interval [CI], 72.4 to 87.3) of the participants in the modified intention-to-treat population and in 95.9% (95% CI, 88.6 to 99.2) of the participants in the per-protocol population. A hierarchically tested comparison revealed that four of the experimental regimens (BCLLfxZ, BLMZ, BDLLfxZ, and DCMZ) were noninferior to standard therapy in the modified intention-to-treat population. Differences in risk from standard therapy were 9.8 percentage points (95% CI, 0.9 to 18.7) with BCLLfxZ, 8.3 percentage points (95% CI, −0.8 to 17.4) with BLMZ, 4.6 percentage points (95% CI, −4.9 to 14.1) with BDLLfxZ, and 2.5 percentage points (95% CI, −7.5 to 12.5) with DCMZ (Table 2 and Fig. 2). The DCLLfxZ regimen was not noninferior in the modified intention-to-treat population. Per-protocol analyses supported these findings, except for DCMZ (Table S15 and Figs. S5a through S5e), which was not noninferior in this population.

Among the participants in the modified intention-to-treat population, unfavorable outcomes due to positive culture occurred in 4.1% of all the participants, in 7.5% of the DCMZ group, and in 10.2% of the DCLLfxZ group (Table 2). Loss to follow-up and withdrawal of consent occurred in a larger percentage of the participants in the standard-therapy group than in any of the experimental regimen groups. Overall, recurrence occurred in 3 participants (0.4%) — 1 in the DCLLfxZ group and 2 in the DCMZ group. Efficacy outcomes were similar for secondary end points, at week 39 and week 104, in adjusted analyses, and in sensitivity analyses (Tables S16 through S28 and Figs. S5a through S5e).

Overall, treatment effects at week 73 did not differ substantially in subgroup analyses in the modified intention-to-treat population. Possible exceptions were noted for subgroups defined according to country, previous exposure to second-line antituberculosis drugs, cavitation, HIV infection, and low body-mass index. Over the course of the trial period, outcomes generally improved, whereas relative treatment effect did not change meaningfully (Figs. S6a through S6e). The time to an unfavorable outcome was longer in the BCLLfxZ group than in the standard-therapy group (hazard ratio, 0.48 [95% CI, 0.23 to 0.98]) (Figs. S7a through S7e).

SAFETY RESULTS

We report the number of participants in the safety population who had at least one of each safety event by week 73 after randomization. The percentage of participants who had at least one grade 3 or higher adverse event ranged from 54.8% (in the BLMZ group) to 61.4% (in the BDLLfxZ group) and was 62.7% in the standard-therapy group. The incidence of serious adverse events was similar across the groups, ranging from 13.1% in the BCLLfxZ group to 16.7% in the DCMZ and standard-therapy groups. Overall, death from any cause occurred in 15 participants (2.0%) by week 73 (Table 3) and in 18 participants (2.4%) by week 104; the incidence was similar across the groups. No deaths were considered by the investigators to be related to trial drugs (Table S29).

Among all grade 3 or higher adverse events and serious adverse events, 313 of 901 (34.7%) and 54 of 174 (31.0%), respectively, were classified by the investigator as related to trial drugs. At least one adverse event of special interest was reported in 23.9% of all the participants; the most commonly occurring adverse events of special interest, hepatotoxic events, which were defined by any grade 3 or 4 increase in levels of alanine aminotransferase or aspartate aminotransferase,

Table 1. Baseline Characteristics of the Participants (Modified Intention-to-Treat Population).*

Characteristic	BLMZ (N=118)	BCLLfxZ (N=115)	BDLLfxZ (N=122)	DCLLfxZ (N=118)	DCMZ (N=107)	Standard Therapy (N=119)	Total (N=699)
Female sex — no. (%)	41 (34.7)	37 (32.2)	55 (45.1)	38 (32.2)	45 (42.1)	48 (40.3)	264 (37.8)
Age — yr							
Median (IQR)	31 (25–41)	38 (26–50)	32 (22–45)	30 (22–41)	32 (24–46)	31 (22–42)	32 (23–44)
Range	15–69	15–70	15–70	15–69	15–71	15–70	15–71
Country — no. (%)							
Georgia	2 (1.7)	2 (1.7)	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)	12 (1.7)
India	8 (6.8)	4 (3.5)	3 (2.5)	3 (2.5)	1 (0.9)	4 (3.4)	23 (3.3)
Kazakhstan	30 (25.4)	35 (30.4)	33 (27.0)	22 (18.6)	24 (22.4)	23 (19.3)	167 (23.9)
Lesotho	14 (11.9)	11 (9.6)	15 (12.3)	11 (9.3)	14 (13.1)	12 (10.1)	77 (11.0)
Pakistan	18 (15.3)	16 (13.9)	13 (10.7)	11 (9.3)	16 (15.0)	18 (15.1)	92 (13.2)
Peru	38 (32.2)	39 (33.9)	49 (40.2)	54 (45.8)	45 (42.1)	51 (42.9)	276 (39.5)
South Africa	8 (6.8)	8 (7.0)	8 (6.6)	14 (11.9)	6 (5.6)	8 (6.7)	52 (7.4)
Median body-mass index (IQR)†	19.9 (17.5–22.1)	20.0 (18.4–23.6)	20.9 (18.8–22.8)	20.6 (18.1–23.6)	19.9 (17.9–22.2)	20.8 (17.6–23.0)	20.4 (18.0–22.8)
ECOG performance-status score — no. (%)‡							
0	42 (35.6)	35 (30.4)	51 (41.8)	47 (39.8)	35 (32.7)	43 (36.1)	253 (36.2)
1	55 (46.6)	62 (53.9)	53 (43.4)	54 (45.8)	53 (49.5)	63 (52.9)	340 (48.6)
2	17 (14.4)	15 (13.0)	12 (9.8)	16 (13.6)	17 (15.9)	11 (9.2)	88 (12.6)
3	4 (3.4)	3 (2.6)	6 (4.9)	1 (0.8)	2 (1.9)	2 (1.7)	18 (2.6)
HIV infection — no. (%)	15 (12.7)	14 (12.2)	17 (13.9)	18 (15.3)	15 (14.0)	19 (16.0)	98 (14.0)
Median CD4 count among participants with HIV infection (IQR) — cells per mm^3§	170.5 (41.0–505.0)	190 (85.0–377.0)	314.5 (157.0–478.5)	328.5 (170.5–579.5)	404.0 (143.0–643.0)	269.0 (83.0–443.0)	296.0 (118.0–497.0)
Antiretroviral treatment among participants with HIV infection — no./total no. (%)	12/15 (80.0)	9/14 (64.3)	10/17 (58.8)	14/18 (77.8)	11/15 (73.3)	12/19 (63.2)	68/98 (69.4)
Hepatitis B infection, with hepatitis B surface antigen — no. (%)	3 (2.5)	3 (2.6)	0	2 (1.7)	4 (3.7)	4 (3.4)	16 (2.3)
Hepatitis C infection — no. (%)	5 (4.2)	5 (4.3)	3 (2.5)	4 (3.4)	3 (2.8)	6 (5.0)	26 (3.7)
Diabetes — no. (%)¶	19 (16.1)	19 (16.5)	20 (16.4)	16 (13.6)	16 (15.0)	15 (12.6)	105 (15.0)

Peripheral-blood smear result — no. (%)							
Negative or scanty	20 (16.9)	19 (16.5)	31 (25.4)	24 (20.3)	18 (16.8)	19 (16.0)	131 (18.7)
1 to 2+	57 (48.3)	59 (51.3)	58 (47.5)	49 (41.5)	43 (40.2)	52 (43.7)	318 (45.5)
3+	41 (34.7)	37 (32.2)	33 (27.0)	45 (38.1)	46 (43.0)	48 (40.3)	250 (35.8)
Cavitation — no. (%)‖	68 (57.6)	69 (60.0)	73 (59.8)	53 (44.9)	61 (57.0)	75 (63.0)	399 (57.1)
Extent of tuberculosis — no. (%)**							
Limited	21 (17.8)	14 (12.2)	18 (14.8)	23 (19.5)	20 (18.7)	18 (15.1)	114 (16.3)
Moderate	70 (59.3)	77 (67.0)	77 (63.1)	67 (56.8)	64 (59.8)	71 (59.7)	426 (60.9)
Extensive	27 (22.9)	24 (20.9)	26 (21.3)	25 (21.2)	23 (21.5)	29 (24.4)	154 (22.0)
Previous exposure to tuberculosis treatment — no. (%)††							
None	76 (64.4)	67 (58.3)	78 (63.9)	80 (67.8)	72 (67.3)	74 (62.2)	447 (63.9)
First-line drugs only	20 (16.9)	23 (20.0)	27 (22.1)	25 (21.2)	23 (21.5)	31 (26.1)	149 (21.3)
Other drugs	15 (12.7)	19 (16.5)	15 (12.3)	7 (5.9)	11 (10.3)	11 (9.2)	78 (11.2)
Pyrazinamide resistance — no. (%)‡‡	57 (48.3)	63 (54.8)	66 (54.1)	66 (55.9)	66 (61.7)	59 (49.6)	377 (53.9)
Resistance to second-line injectable medication — no. (%)§§	14 (11.9)	18 (15.7)	15 (12.3)	13 (11.0)	14 (13.1)	16 (13.4)	90 (12.9)

* The modified intention-to-treat population included participants who underwent randomization, received at least one dose of trial treatment, and had a prerandomization culture positive for *Mycobacterium tuberculosis*. It excluded participants with baseline phenotypic resistance to bedaquiline, clofazimine, delamanid, any fluoroquinolone, or linezolid. IQR denotes interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The Eastern Cooperative Oncology Group (ECOG) performance-status score ranges from 0 to 5, with higher scores indicating greater disability.

§ Data on CD4 count were unknown for seven participants (one in the BLMZ group, two in the BCLLfxZ group, one in the BDLLfxZ group, two in the DCLLfxZ group, and one in the standard-therapy group).

¶ Data on diabetes were missing for one participant in the BDLLfxZ group.

‖ Data on cavitation were unknown for five participants (one in the BDLLfxZ group, three in the DCLLfxZ group, and one in the standard-therapy group).

** Extent of tuberculosis was classified by the trial investigators as limited (presence of lesions with slight-to-moderate density, but no cavitations, not exceeding the size of the apex of the lung), moderate (lesions present in one or both lungs, not exceeding scattered lesions of slight-to-moderate density that involve the total volume of one lung or partially involve both lungs; dense, confluent lesions that extend up to one third of the volume of one lung; and cavitation with a diameter of <4 cm in any single cavity), or extensive (lesions that are more extensive than those defined as moderate). Data on extent of tuberculosis were unknown for five participants (one in the BDLLfxZ group, three in the BDLLfxZ group, and one in the standard-therapy group).

†† Data on previous exposure to tuberculosis treatment were unknown for 25 participants (7 in the BLMZ group, 6 in the BCLLfxZ group, 2 in the BDLLfxZ group, 6 in the DCLLfxZ group, 1 in the DCMZ group, and 3 in the standard-therapy group).

‡‡ Pyrazinamide resistance was determined by means of phenotypic drug-susceptibility testing. Data on pyrazinamide resistance were unknown for five participants (two in the DCLLfxZ group and three in the standard-therapy group).

§§ Second-line injectable medications are amikacin, capreomycin, and kanamycin. Data on second-line injectable medication were unknown for five participants (two in the DCLLfxZ group and three in the standard-therapy group).

Table 2. Primary Efficacy End Points at Week 73 (Modified Intention-to-Treat Population).*

Outcome	BLMZ (N=118)	BCLLfxZ (N=115)	BDLLfxZ (N=122)	DCLLfxZ (N=118)	DCMZ (N=107)	Standard Therapy (N=119)	Total (N=699)
Favorable†							
Participants with favorable outcome — no. (%)	105 (89.0)	104 (90.4)	104 (85.2)	93 (78.8)	89 (83.2)	96 (80.7)	591 (84.5)
Difference from standard therapy (95% CI) — percentage points	8.3 (–0.8 to 17.4)	9.8 (0.9 to 18.7)	4.6 (–4.9 to 14.1)	–1.9 (–12.1 to 8.4)	2.5 (–7.5 to 12.5)	—	—
Negative culture results, wk 65 and wk 73 — no. (%)	102 (86.4)	100 (87.0)	102 (83.6)	90 (76.3)	87 (81.3)	91 (76.5)	572 (81.8)
Favorable bacteriologic, clinical, and radiologic evolution — no. (%)‡	3 (2.5)	4 (3.5)	2 (1.6)	3 (2.5)	2 (1.9)	5 (4.2)	19 (2.7)
Unfavorable†							
Participants with unfavorable outcome — no. (%)	13 (11.0)	11 (9.6)	18 (14.8)	25 (21.2)	18 (16.8)	23 (19.3)	108 (15.5)
Death from any cause — no. (%)§	2 (1.7)	1 (0.9)	3 (2.5)	3 (2.5)	2 (1.9)	2 (1.7)	13 (1.9)
Positive culture results — no. (%)¶	1 (0.8)	3 (2.6)	4 (3.3)	12 (10.2)	8 (7.5)	1 (0.8)	29 (4.1)
Recurrence — no. (%)‖	0	0	0	1 (0.8)	2 (1.9)	0	3 (0.4)
Permanent treatment discontinuation due to adverse event — no. (%)	3 (2.5)	3 (2.6)	1 (0.8)	1 (0.8)	1 (0.9)	2 (1.7)	11 (1.6)
Poor treatment adherence or loss to follow-up — no. (%)	3 (2.5)	2 (1.7)	3 (2.5)	3 (2.5)	4 (3.7)	8 (6.7)	23 (3.3)
Withdrawal of consent — no. (%)	1 (0.8)	1 (0.9)	4 (3.3)	3 (2.5)	0	7 (5.9)	16 (2.3)
Other unfavorable outcome — no. (%)**	3 (2.5)	1 (0.9)	3 (2.5)	2 (1.7)	1 (0.9)	3 (2.5)	13 (1.9)

* The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

† A favorable outcome at week 73 (the primary efficacy end point) was defined as the absence of an unfavorable outcome and either two consecutive negative cultures (including one between weeks 65 and 73) or favorable bacteriologic, radiologic, and clinical evolution. Unfavorable outcomes included death (from any cause), the replacement or addition of one drug in the experimental regimens or two drugs in the standard-therapy regimen, or the initiation of new treatment for rifampin-resistant tuberculosis (for the full list of unfavorable outcomes, see Section 2.6.2 in the Supplementary Appendix).

‡ This category includes participants without culture results between week 65 and week 73.

§ Thirteen participants in the modified intention-to-treat population died, and one participant in the safety population who was excluded from the modified intention-to-treat population also died. One participant in the modified intention-to-treat population had a positive culture result that was classified as an unfavorable outcome at week 73 and later died.

¶ This category included participants who permanently discontinued treatment because of a positive sputum culture at week 16 or later or who had a positive sputum culture between week 65 and week 73.

‖ Included in this category were participants who had a positive sputum culture or started a new treatment regimen after treatment completion.

** This category comprised participants who were not assessed after treatment completion (6 participants), were deemed by an investigator to have an unfavorable outcome (4 participants), were pregnant or breast-feeding (2 participants), or used a prohibited concomitant medication (1 participant).

occurred in 7.1% of the participants in the standard-therapy group and ranged from 6.3% (in the BDLLfxZ group) to 18.3% (in the BLMZ group) in the experimental groups. Hematologic toxic events, defined as any grade 3 or 4 leukopenia, anemia, or thrombocytopenia, occurred in 10.3% of the participants in the standard-therapy group and ranged from 7.4% (in the BCLLfxZ group) to 10.5% (in the DCLLfxZ group) in the experimental groups. Peripheral neuropathy occurred in 4.8% of the participants in the standard-therapy group and ranged from 2.4% (in the DCLLfxZ group) to 7.1% (in the BDLLfxZ group) in the experimental groups. QTcF interval prolongation occurred exclusively in the DCMZ (4.2%) and BCLLfxZ (3.3%) groups. Other safety details, including drug discontinuations, are reported in Tables S30 through S37. Ten participants (1.3%) became pregnant during trial participation (Table S38).

DISCUSSION

Consistent results across all analyses support the noninferior efficacy of three regimens (BLMZ, BCLLfxZ, and BDLLfxZ) as compared with standard therapy. These three regimens each produced favorable outcomes in more than 85% of participants at week 73; this finding represents an improvement over global averages and is similar to trial results with the regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) (89%).[1,6]

Death was uncommon despite the substantial burden of coexisting conditions and cavitary disease. Grade 3 or higher adverse events were common across all the groups but were often considered by the site investigator to be unrelated to trial drugs. Although the trial was not powered for statistical comparison of safety outcomes, we observed some patterns. Grade 3

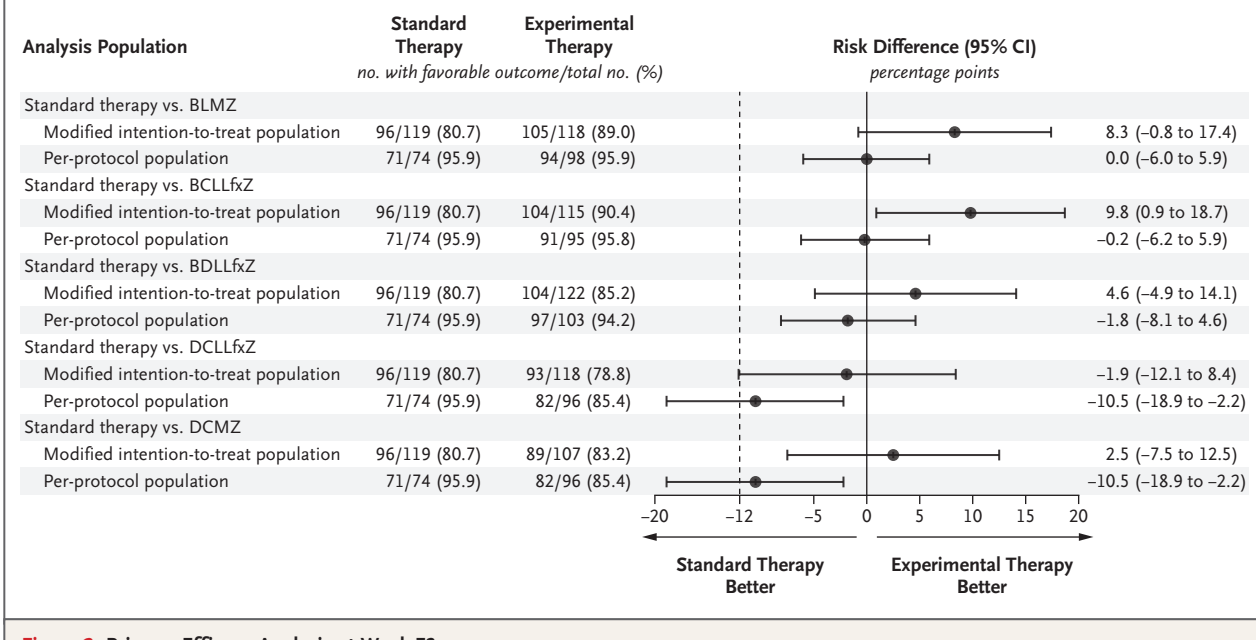

Figure 2. Primary Efficacy Analysis at Week 73.

Shown are the results of the primary efficacy analysis in the modified intention-to-treat population and in the per-protocol population for the BLMZ regimen, the BCLLfxZ regimen, the BDLLfxZ regimen, the DCLLfxZ regimen, and the DCMZ regimen, each as compared with standard therapy. Noninferiority in the modified intention-to-treat population was established if the lower bound of the 95% confidence interval around the difference exceeded –12 percentage points (indicated by the dashed line). In this report, per-protocol analyses provided complementary information but were not used for formal testing of a noninferiority comparison. A favorable outcome at week 73 was defined as the absence of an unfavorable outcome and either two consecutive negative cultures (including one between weeks 65 and 73) or favorable bacteriologic, radiologic, and clinical evolution. Unfavorable outcomes included death (from any cause), the replacement or addition of one drug in the experimental regimens or two drugs in the standard-therapy regimen, or the initiation of new treatment for rifampin-resistant tuberculosis (for the full list of unfavorable outcomes, see Section 2.6.2 in the Supplementary Appendix). The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

Table 3. Safety Analysis at Week 73.*

Adverse Events	BLMZ (N=126)	BCLLfxZ (N=122)	BDLLfxZ (N=127)	DCLLfxZ (N=124)	DCMZ (N=120)	Standard Therapy (N=126)	Total (N=745)
Any adverse event — no. (%)	126 (100)	122 (100)	127 (100)	124 (100)	120 (100)	125 (99.2)	744 (99.9)
Grade 3 or higher adverse events							
≥1 event — no. (%)	69 (54.8)	68 (55.7)	78 (61.4)	75 (60.5)	72 (60.0)	79 (62.7)	441 (59.2)
No. of events related to trial drug or drugs/total no. of events (%)†	49/136 (36.0)	57/166 (34.3)	56/144 (38.9)	58/148 (39.2)	37/148 (25.0)	56/163 (34.4)	313/901 (34.7)
Serious adverse events							
≥1 event — no. (%)	18 (14.3)	16 (13.1)	20 (15.7)	18 (14.5)	20 (16.7)	21 (16.7)	113 (15.2)
No. of events related to trial drug or drugs/total no. of events (%)†	7/26 (26.9)	11/29 (37.9)	11/30 (36.7)	11/26 (42.3)	6/31 (19.4)	8/32 (25.0)	54/174 (31.0)
Death from any cause — no. (%)	3 (2.4)	1 (0.8)	3 (2.4)	4 (3.2)	2 (1.7)	2 (1.6)	15 (2.0)
Adverse events of special interest							
≥1 event — no. (%)	35 (27.8)	33 (27.0)	25 (19.7)	33 (26.6)	26 (21.7)	26 (20.6)	178 (23.9)
Any grade 3 or 4 increase in ALT or AST — no. (%)	23 (18.3)	17 (13.9)	8 (6.3)	18 (14.5)	12 (10.0)	9 (7.1)	87 (11.7)
Any grade 3 or 4 leukopenia, anemia, or thrombocytopenia — no. (%)	11 (8.7)	9 (7.4)	10 (7.9)	13 (10.5)	9 (7.5)	13 (10.3)	65 (8.7)
Any grade 3 or 4 peripheral neuropathy — no. (%)	4 (3.2)	5 (4.1)	9 (7.1)	3 (2.4)	3 (2.5)	6 (4.8)	30 (4.0)
Any grade 3 or 4 optic neuritis — no. (%)	0	1 (0.8)	0	1 (0.8)	0	2 (1.6)	4 (0.5)
Any grade 3 or 4 QT corrected interval prolonged — no. (%)‡	0	4 (3.3)	0	0	5 (4.2)	0	9 (1.2)
Permanent discontinuation of any drug due to adverse event — no. (%)	26 (20.6)	32 (26.2)	35 (27.6)	29 (23.4)	19 (15.8)	51 (40.5)	192 (25.8)

* The safety population included all participants who underwent randomization and received at least one dose of the trial treatment. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† An event was considered to be related if there was at least a reasonable possibility that it was caused by one or more drugs in the regimen.
‡ The QT interval was corrected according to Fridericia's formula.

or higher hepatotoxic events were more common in the experimental groups, except the BDLLfxZ group, than in the standard-therapy group. Pyrazinamide, which was included in all the experimental regimens and in almost half the standard-therapy regimens, can cause elevated liver-enzyme levels, as can bedaquiline, fluoroquinolones, and linezolid; these elevations can be aggravated by alcohol use and active hepatitis B or C infection, which were present in some patients in the cohort.[18-20] Linezolid-related toxic effects were generally less common in the experimental groups than in the standard-therapy group, and this finding may reflect a safety benefit of routinely lowering the weekly dose of linezolid at 16 weeks or earlier.[21-24] QTcF intervals of more than 500 msec were infrequent and occurred only in participants receiving regimens that contained clofazimine and either bedaquiline or moxifloxacin, drugs that are known to cause QT-interval prolongation. These results are consistent with emerging evidence about the safety of bedaquiline in combination with other QT-prolonging antituberculosis drugs.[6,25,26]

Bayesian response-adaptive randomization permitted identification of multiple noninferior tuberculosis regimens in a single trial. Randomization was ultimately relatively balanced because the experimental regimens performed similarly to standard therapy in the interim analyses used to adjust probabilities. Improved surrogate markers for treatment response will enhance the efficiency of adaptive trials in tuberculosis.[27,28]

Our trial had several limitations. Trial staff and participants were aware of the group assignments because of the difference in treatment duration between the experimental and standard-therapy groups. To mitigate risks of bias, we concealed treatment assignment and randomization probabilities from laboratory staff and central investigators. Bayesian adaptation and analysis for reports for the data and safety monitoring board were performed by statisticians who were aware of the group assignments. During the trial enrollment period, the WHO guidelines changed twice. We incorporated these updates into trial guidance on the composition of standard-therapy regimens. The effect on regimen composition was modest because initial trial guidance had already been well aligned with newer WHO recommendations, to which 81.5% of standard-therapy regimens conformed.[17]

A strength of this trial was a design that included an internal, concurrent standard-therapy group (as distinct from trials that are uncontrolled or historically controlled), which is essential to high certainty of evidence for guidance.[29] Other strengths include the consistency of the findings across populations, end points, and analyses. Moreover, the performance of standard therapy, with a favorable outcome in 80.7% of the participants, was better than that reported in other recent studies.[5,6,30-32] That this improved standard could discriminate among well-performing regimens provides confidence in the efficacy of those found to be noninferior. The high retention of participants — including in the standard-therapy group — and completeness of trial data indicate high-quality implementation. The trial included adolescents and retained participants who became pregnant. The population was heterogeneous, representing four continents, a range of severity of tuberculosis, and substantial burdens of important coexisting conditions, all of which contributed to the generalizability of the trial results to the broader population of people affected by rifampin-resistant tuberculosis (Table S6).

These findings support the use of three new, all-oral, shorter-duration regimens for rifampin-resistant tuberculosis in addition to BPaLM. In August 2024, the WHO endorsed the use of these three regimens over the longer all-oral regimen.[33] BPaLM was recommended by the WHO in 2022 for use in nonpregnant persons 14 years of age or older.[17] The BLMZ, BCLLfxZ, and BDLLfxZ regimens can be used in nearly all adults, children, and pregnant persons with fluoroquinolone-susceptible, rifampin-resistant tuberculosis; all the drugs in the endTB regimens have pediatric formulations and are recommended regardless of age.[34,35] Our findings are also relevant to pregnant persons: all the drugs included in the endTB regimens are considered to be acceptable for use during pregnancy.[17,36] Two bedaquiline-sparing regimens (DCMZ and DCLLfxZ) were examined; the overall assessment of these regimens does not support their use as compared with a standard therapy that commonly contains bedaquiline. Percentages of participants with favorable outcomes were higher than those reported in a recent

trial testing a 9-month regimen containing neither bedaquiline nor clofazimine.[31] However, in the endTB trial, unfavorable outcomes due to positive culture during the treatment course or due to recurrence were more common among the participants receiving DCMZ and DCLLfxZ than among the participants receiving other regimens. Development of efficacious, shortened-duration, bedaquiline-sparing regimens warrants further research.

Several implementation considerations arise. First, adoption of endTB regimens by providers and national tuberculosis programs would allow simplification of the standard drug formularies while retaining a range of treatment options. Regimens may be selected according to individual patient characteristics and preferences; they offer alternatives to treatments containing drugs with unacceptable side effects, interactions, contraindications, resistance, and unavailability. Second, further development of — and access to — rapid, reliable resistance testing is essential both to ensure that patients receive the appropriate regimen and to detect the emergence of resistance.[37,38] Finally, this trial underscores the need for diligent monitoring of liver-enzyme levels and of linezolid-associated toxic effects. Hepatotoxic effects are a known risk of many antituberculosis drugs, including pyrazinamide, a component of all the endTB regimens.[17,19,35] Monitoring of QT interval prolongation could be individualized through risk-based strategies — for example, by intensifying monitoring in persons receiving multiple QT-prolonging drugs or persons with arrhythmia risk factors.[39,40]

The results of this trial support the noninferior efficacy of three all-oral shortened regimens for the treatment of rifampin-resistant tuberculosis. The results of the endTB trial improve prospects for effective, simple, all-oral treatment for adults and children with this disease.

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APPENDIX

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