

## ORIGINAL ARTICLE

# A Pragmatic Trial of a 6-Month Strategy for Rifampicin-Resistant Tuberculosis

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## ABSTRACT

**BACKGROUND**

Safer, more effective treatment regimens for rifampicin-resistant tuberculosis are needed.

**METHODS**

We conducted a phase 3, open-label, pragmatic, randomized, controlled noninferiority trial in South Africa to assess a 6-month treatment strategy for pulmonary rifampicin-resistant tuberculosis. Participants with pulmonary rifampicin-resistant tuberculosis who were 6 years of age or older were randomly assigned to a regimen consisting of bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months (trial-strategy group) or the 9-month standard-of-care treatment regimen that was current in South Africa (control group). Persons who were pregnant or breastfeeding and those who had fluoroquinolone-resistant tuberculosis were included in the trial population. Treatment in both groups was adjusted on the basis of results of second-line drug susceptibility testing. The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomization. The noninferiority margin was 10 percentage points. The primary safety end point was an adverse event of grade 3 or higher.

**RESULTS**

Among the 432 persons who were screened, 403 underwent randomization; 203 were assigned to the trial-strategy group, and 200 to the control group. A successful outcome was observed in 174 of 202 participants (86.1%) in the trial-strategy group and in 172 of 200 (86.0%) in the control group. The adjusted risk difference was  $-0.2$  percentage points (95% confidence interval [CI],  $-6.9$  to  $6.5$ ;  $P=0.001$  for noninferiority). Adverse events of grade 3 or higher occurred during treatment in 63 of 202 participants (31.2%) in the trial-strategy group and in 74 of 200 (37.0%) in the control group; 10 participants in each group died.

**CONCLUSIONS**

Among participants in South Africa with rifampicin-resistant tuberculosis, the 6-month trial strategy was noninferior to the standard-of-care strategy with respect to a successful outcome. The safety profiles of the two strategies were similar. (Funded by the U.S. Agency for International Development and others; BEAT Tuberculosis ClinicalTrials.gov number, NCT04062201.)

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THE WORLD HEALTH ORGANIZATION (WHO) estimated that tuberculosis that is resistant to rifampin (also known as rifampicin) developed in 400,000 persons in 2023.<sup>1</sup> Until recently, treatment regimens for rifampicin-resistant tuberculosis included up to seven medications and were administered for 9 to 18 months. The pill burden and complexity of these regimens, coupled with associated adverse events, resulted in poor treatment outcomes.<sup>2</sup>

Since 2012, three new drugs for rifampicin-resistant tuberculosis — bedaquiline, pretomanid, and delamanid — have been approved by at least one stringent regulatory authority as well as the South African Health Products Regulatory Authority. In addition, treatment with repurposed medications such as linezolid, levofloxacin, moxifloxacin, and clofazimine has shown improved outcomes in patients with rifampicin-resistant tuberculosis.

In several studies, including Nix-TB,<sup>3</sup> ZeNix,<sup>4</sup> and TB-PRACTECAL,<sup>5</sup> 6-month regimens containing bedaquiline, linezolid, and pretomanid resulted in cure in approximately of 80 to 90% of patients. As a result, the WHO revised its guidelines for treating rifampicin-resistant tuberculosis in 2022 to include a 6-month regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin as the recommended standard of care.<sup>6</sup> There are, however, notable gaps: pretomanid is currently not recommended for children younger than 14 years of age or for persons who are pregnant or breastfeeding. The BEAT (Building Evidence for Advancing New Treatment) Tuberculosis trial assessed a regimen of bedaquiline, delamanid, linezolid, and levofloxacin or clofazimine or both as compared with the standard of care in South Africa. The objective was to evaluate the efficacy and safety of a 6-month treatment strategy for rifampicin-resistant tuberculosis that would be appropriate for children 6 years of age or older, pregnant or breastfeeding women, and persons with fluoroquinolone-resistant tuberculosis.

## METHODS

### TRIAL DESIGN AND PARTICIPANTS

In this phase 3, open-label, pragmatic, randomized, controlled noninferiority trial, we enrolled a broad group of participants with pulmonary rifampicin-resistant tuberculosis from two urban

sites in South Africa. Eligible participants had pulmonary tuberculosis with resistance to rifampicin with or without resistance to isoniazid or fluoroquinolones (or both). Children who were 6 years of age or older and pregnant or breastfeeding women were eligible. Full inclusion and exclusion criteria are provided in the protocol and the Supplementary Appendix, both available with the full text of this article at NEJM.org.

### ENROLLMENT AND INTERVENTIONS

Participants were randomly assigned to receive bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months (trial-strategy group) or the 9-month standard-of-care treatment for rifampicin-resistant tuberculosis (control group). Randomization was performed with the use of a Web-based system, in blocks of varying sizes, with concealed assignment and with stratification according to trial site and human immunodeficiency virus (HIV) status.

When the results of fluoroquinolone susceptibility testing were available for the participants in the trial-strategy group, either levofloxacin (if the results showed fluoroquinolone resistance) or clofazimine (if the results showed fluoroquinolone susceptibility) was discontinued. If the results were available at the time of randomization, either levofloxacin or clofazimine was not initiated. The control strategy adhered to the standard treatment in South Africa for rifampicin-resistant tuberculosis at the time of enrollment. The medications were taken orally for 9 months; if resistance to fluoroquinolones was identified, a longer individualized regimen was used. Complete information regarding both regimens is provided in Section 2.5 in the Supplementary Appendix.

Scheduled visits occurred every 2 weeks for the first 8 weeks, then every 4 weeks until treatment was completed. Post-treatment appointments occurred monthly for the first 3 months, then every 3 months thereafter. All the participants were monitored for 76 weeks. Microbiologic specimens were routinely processed at the National Health Laboratory Service. Xpert MTB/RIF Ultra was typically used as the first diagnostic test. Line-probe assays (GenoType MTB-DRplus and MTBDRsl, Hain Lifescience) were used to determine susceptibility to isoniazid, second-line injectables, and fluoroquinolones. If the acid-fast bacilli smear was positive, the

clinical specimen was used for the assays; if the smear was negative, cultured specimens were used. In addition, phenotypic bedaquiline susceptibility was evaluated among fluoroquinolone-resistant specimens. Sputum specimens for mycobacterial cultures were obtained monthly for 3 months after the completion of treatment, and then every 3 months until 76 weeks after randomization.

Among pregnant women, live intrauterine pregnancy was confirmed with ultrasonography, followed by a formal scan for anomalies at 16 weeks. After delivery, the infant was examined for anomalies and signs of tuberculosis.

#### **SUPPORT FOR TREATMENT ADHERENCE**

Most participants were treated as outpatients unless inpatient care was warranted for clinical or social reasons. The participants selected a family or community member supporter to facilitate directly observed therapy. This community-based supporter received standardized training and completed an adherence log. Medication was packed into daily labeled bags, which the participants returned at the scheduled visits. If missed doses were noted, the supporter was contacted to intervene.

#### **DOSE MODIFICATIONS AND SAFETY**

Adverse events were recorded at every trial visit, and laboratory testing for safety monitoring was performed at every scheduled visit during treatment. Adverse events were graded with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.<sup>7</sup> Electrocardiographic monitoring, visual acuity examinations, and assessments for peripheral neuropathy with the use of a Brief Peripheral Neuropathy rating scale were performed at scheduled intervals.

No changes to the medication doses in the trial-strategy group were allowed unless the body-weight category changed in children. If a participant had an adverse reaction to linezolid, treatment with the drug could be stopped either temporarily or permanently. After the severity lessened to grade 1 or returned to the baseline level, treatment with linezolid was resumed at the standard dose of 600 mg. There was no provision for dose reduction in the case of an adverse reaction related to linezolid. Treatment could be extended if culture conversion had not occurred by 16 weeks.

#### **END POINTS**

The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomization. The definition was derived from WHO definitions.<sup>8</sup> Cure was defined as adequate treatment adherence ( $\geq 80\%$  of doses taken) and two negative sputum specimens obtained before the end of treatment, at least 14 days apart. Completion of treatment was defined as adequate adherence without evidence of treatment failure (defined as lack of sputum culture conversion, bacteriologic reversion, or substitution of two or more drugs because of adverse effects) but no record of two or more consecutive negative sputum specimens obtained at least 14 days apart. An unsuccessful outcome was defined as treatment failure, death, loss to follow-up, or no evaluation. The primary safety end point was an adverse event of grade 3 or higher. The composite efficacy–safety end point was a successful outcome at the end of follow-up and no adverse events of grade 3 or higher during treatment. Additional details regarding definitions are provided in Section 2.9 in the Supplementary Appendix.

#### **TRIAL OVERSIGHT**

All the participants provided written informed consent. Assent was obtained from participants who were younger than 18 years of age, and consent was obtained from their parents or guardians. An independent data monitoring committee reviewed safety and efficacy data every 6 months. The trial was approved by the human research ethics committee at the University of the Witwatersrand. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

#### **STATISTICAL ANALYSIS**

The primary efficacy analysis was performed in the intention-to-treat population, which included all the participants who had undergone randomization. For the primary analysis, we used Mantel–Haenszel weights to assess the between-group difference (reported as the risk difference) in the percentage of participants who met the criteria for the primary end point (a successful outcome) at the end of treatment and at 76 weeks after randomization.<sup>9</sup> Noninferiority was indicated if the upper boundary of the 95% confidence interval for the risk difference was less

than 10 percentage points. Safety was assessed in all the participants who had undergone randomization and had received at least one dose of the assigned treatment. The percentage of participants who had an adverse event of grade 3 or higher that occurred up to 14 days after the last dose of any tuberculosis medication was estimated, and the between-group difference with 95% confidence interval was calculated.

## RESULTS

## PARTICIPANTS

From August 2019 through October 2022, a total of 432 participants were screened, and 403 (93.3%) underwent randomization (Table 1 and Fig. 1). The median age was 35.0 years, and 30 participants (7.4%) were 8 to 17 years of age. A total of 205 participants (50.9%) had HIV infection. The

**Table 1. Characteristics of the Participants at Baseline.\***

| Characteristic                               | Trial Strategy<br>(N = 203) | Control Strategy<br>(N = 200) | Total<br>(N = 403) |
|----------------------------------------------|-----------------------------|-------------------------------|--------------------|
| Site of enrollment — no. (%)                 |                             |                               |                    |
| Gqeberha                                     | 184 (90.6)                  | 182 (91.0)                    | 366 (90.8)         |
| Durban                                       | 19 (9.4)                    | 18 (9.0)                      | 37 (9.2)           |
| Age                                          |                             |                               |                    |
| Median (IQR) — yr                            | 35.0 (28.0–43.0)            | 34.5 (27.0–44.0)              | 35.0 (28.0–43.0)   |
| <18 yr — no. (%)                             | 13 (6.4)                    | 17 (8.5)                      | 30 (7.4)           |
| Female sex — no. (%)                         | 85 (41.9)                   | 85 (42.5)                     | 170 (42.2)         |
| Race — no. (%)†                              |                             |                               |                    |
| Black                                        | 150 (73.9)                  | 160 (80.0)                    | 310 (76.9)         |
| Mixed                                        | 50 (24.6)                   | 40 (20.0)                     | 90 (22.3)          |
| White                                        | 3 (1.5)                     | 0                             | 3 (0.7)            |
| Body-mass index                              |                             |                               |                    |
| Median (IQR)                                 | 19.1 (17.0–22.0)            | 19.3 (17.2–22.4)              | 19.2 (17.1–22.2)   |
| <18.5 — no. (%)                              | 85 (41.9)                   | 82 (41.0)                     | 167 (41.4)         |
| HIV status — no. (%)                         |                             |                               |                    |
| Positive                                     | 105 (51.7)                  | 100 (50.0)                    | 205 (50.9)         |
| Negative                                     | 98 (48.3)                   | 100 (50.0)                    | 198 (49.1)         |
| CD4 count                                    |                             |                               |                    |
| Median (IQR) — cells/mm <sup>3</sup>         | 168.0 (85.0–298.5)          | 229.0 (87.0–395.0)            | 194.0 (87.0–362.0) |
| <200 cells/mm <sup>3</sup> — no. (%)         | 50 (24.6)                   | 38 (19.0)                     | 88 (21.8)          |
| Missing data — no. (%)                       | 17 (8.4)                    | 19 (9.5)                      | 36 (8.9)           |
| Highest level of education — no. (%)         |                             |                               |                    |
| No schooling                                 | 1 (0.5)                     | 0                             | 1 (0.2)            |
| Primary school not completed                 | 20 (9.9)                    | 16 (8.0)                      | 36 (8.9)           |
| Primary school completed                     | 12 (5.9)                    | 11 (5.5)                      | 23 (5.7)           |
| High school not completed                    | 125 (61.6)                  | 126 (63.0)                    | 251 (62.3)         |
| High school completed                        | 32 (15.8)                   | 45 (22.5)                     | 77 (19.1)          |
| Tertiary education not completed             | 6 (3.0)                     | 2 (1.0)                       | 8 (2.0)            |
| Tertiary education completed                 | 7 (3.4)                     | 0                             | 7 (1.7)            |
| Previous diagnosis of tuberculosis — no. (%) |                             |                               |                    |
| None                                         | 92 (45.3)                   | 98 (49.0)                     | 190 (47.1)         |
| Drug-susceptible tuberculosis                | 105 (51.7)                  | 99 (49.5)                     | 204 (50.6)         |
| Rifampicin-resistant tuberculosis            | 6 (3.0)                     | 3 (1.5)                       | 9 (2.2)            |

**Table 1. (Continued.)**

| Characteristic                                                                       | Trial Strategy<br>(N=203) | Control Strategy<br>(N=200) | Total<br>(N=403) |
|--------------------------------------------------------------------------------------|---------------------------|-----------------------------|------------------|
| Cavities on chest radiography — no. (%)                                              |                           |                             |                  |
| No                                                                                   | 55 (27.1)                 | 58 (29.0)                   | 113 (28.0)       |
| Yes                                                                                  | 37 (18.2)                 | 40 (20.0)                   | 77 (19.1)        |
| Missing data                                                                         | 111 (54.7)                | 102 (51.0)                  | 213 (52.9)       |
| Drug resistance profile — no. (%)                                                    |                           |                             |                  |
| Susceptible to fluoroquinolones, no susceptibility testing for bedaquiline performed | 123 (60.6)                | 123 (61.5)                  | 246 (61.0)       |
| Resistant to fluoroquinolones, no susceptibility testing for bedaquiline performed   | 7 (3.4)                   | 15 (7.5)                    | 22 (5.5)         |
| Resistant to fluoroquinolones and susceptible to bedaquiline                         | 35 (17.2)                 | 24 (12.0)                   | 59 (14.6)        |
| Resistant to fluoroquinolones and bedaquiline                                        | 0                         | 4 (2.0)                     | 4 (1.0)          |
| No susceptibility testing for fluoroquinolones or bedaquiline performed              | 38 (18.7)                 | 34 (17.0)                   | 72 (17.9)        |
| Susceptible to linezolid                                                             | 35 (17.2)                 | 28 (14.0)                   | 63 (15.6)        |

\* Participants in the trial-strategy group received bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months; participants in the control group received the standard treatment for rifampicin-resistant tuberculosis that was current in South Africa at the time of enrollment, taken orally for 9 months or longer. Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, and IQR interquartile range.

† Race was reported by the participants.

body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was less than 18.5 in 167 participants (41.4%). The characteristics at baseline were well balanced between the groups (Table 1). Of the 170 female participants (42.2%), 9 (5.3%) were pregnant at baseline.

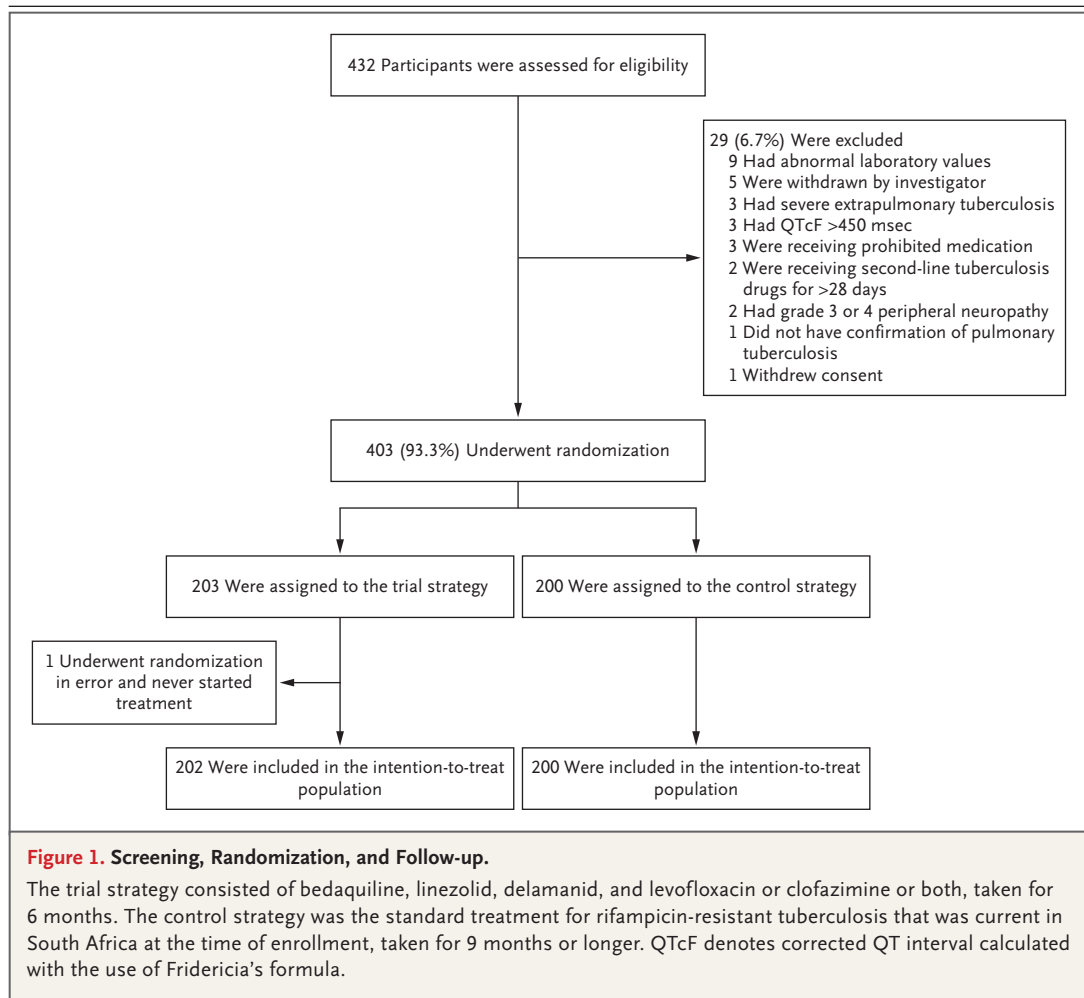
A total of 72 participants (17.9%), whose specimens were assessed with Xpert MTB/RIF Ultra, had no subsequent fluoroquinolone resistance results available because the cultures were contaminated or did not grow. Fluoroquinolone resistance was found in the specimens of 85 participants (21.1%). Phenotypic bedaquiline susceptibility testing was successfully performed in 63 isolates (74.1%); bedaquiline resistance was found in 4 isolates (6.3%) obtained before the participants started treatment. These participants, who were all in the control group, had their treatment modified to an individualized rescue regimen.

#### EFFICACY

One participant in the trial-strategy group underwent randomization in error and did not start

treatment. Therefore, the intention-to-treat population included 202 participants in the trial-strategy group and 200 participants in the control group. A total of 174 participants (86.1%) in the trial-strategy group and 172 (86.0%) in the control group had a successful outcome at the end of treatment and at 76 weeks (adjusted risk difference, −0.2 percentage points; 95% confidence interval [CI], −6.9 to 6.5;  $P=0.001$  for non-inferiority) (Table 2 and Fig. 2). A prespecified sensitivity analysis that reclassified all losses to follow-up as unsuccessful outcomes yielded results that were similar to those of the primary analysis (Tables S3.28 and S3.29 in the Supplementary Appendix).

There was no apparent between-group difference in the time to stable negative culture conversion according to strategy or fluoroquinolone susceptibility (Figs. S3.24 and S3.25). There appeared to be no convincing evidence that treatment effects varied according to age, sex, HIV status, status of sputum smear at baseline (positive vs. negative), presence of cavities on chest radiography, or fluoroquinolone resistance (Section 3.12 in the Supplementary Appendix),



although the trial was not powered to rule out differences across subgroups. Findings suggested that participants in the trial-strategy group who had cavities on chest radiography at baseline may have had poorer outcomes than those without cavities, but this observation must be interpreted with caution owing to the large number of subgroup analyses that were performed.

#### RESISTANCE ACQUISITION

Treatment failure occurred in 7 participants (3.5%) in the trial-strategy group and in 10 (5.0%) in the control group. Bedaquiline resistance at the time of treatment failure was noted in 3 participants in the trial-strategy group and in 5 in the control group (Tables S3.23 and S3.24). A total of 14 participants had recurrence: 10 (5.0%) in the trial-strategy group and 4 (2.0%) in the control group.

Specimens from 2 participants in the trial-strategy group showed resistance to bedaquiline at the time of relapse. However, because this was a pragmatic trial that used standard laboratory testing, data on resistance were missing for some of the participants.

#### SAFETY

A total of 20 participants (10 [5.0%] in each group) died during treatment or follow-up. An adverse event of grade 3 or higher that occurred during treatment (the primary safety end point) was observed in 63 participants (31.2%) in the trial-strategy group and in 74 (37.0%) in the control group. There appeared to be no meaningful difference between the groups in any of the safety end points — all the 95% confidence intervals for the risk differences included 0 (Table 3).

**Table 2. Primary Efficacy Analysis (Intention-to-Treat Population).\***

| Variable                                                                          | Trial Strategy<br>(N = 202) | Control Strategy<br>(N = 200) | Total<br>(N = 402) |
|-----------------------------------------------------------------------------------|-----------------------------|-------------------------------|--------------------|
|                                                                                   | <i>number (percent)</i>     |                               |                    |
| Primary end point: successful outcome at end of treatment and at end of follow-up | 174 (86.1)                  | 172 (86.0)                    | 346 (86.1)         |
| Cure at end of treatment and at end of follow-up                                  | 160 (79.2)                  | 162 (81.0)                    | 322 (80.1)         |
| Cure at end of treatment and negative culture at last visit                       | 14 (6.9)                    | 10 (5.0)                      | 24 (6.0)           |
| Unsuccessful outcome at end of treatment                                          | 14 (6.9)                    | 22 (11.0)                     | 36 (9.0)           |
| Treatment failure                                                                 | 7 (3.5)                     | 10 (5.0)                      | 17 (4.2)           |
| Lost to follow-up during treatment                                                | 2 (1.0)                     | 4 (2.0)                       | 6 (1.5)            |
| Died during treatment                                                             | 4 (2.0)                     | 7 (3.5)                       | 11 (2.7)           |
| Not evaluated because of withdrawn consent                                        | 1 (0.5)                     | 1 (0.5)                       | 2 (0.5)            |
| Unsuccessful outcome at end of follow-up                                          | 14 (6.9)                    | 6 (3.0)                       | 20 (5.0)           |
| Recurrence after cure at end of treatment                                         | 10 (5.0)                    | 4 (2.0)                       | 14 (3.5)           |
| Died after cure at end of treatment                                               | 4 (2.0)                     | 2 (1.0)                       | 6 (1.5)            |

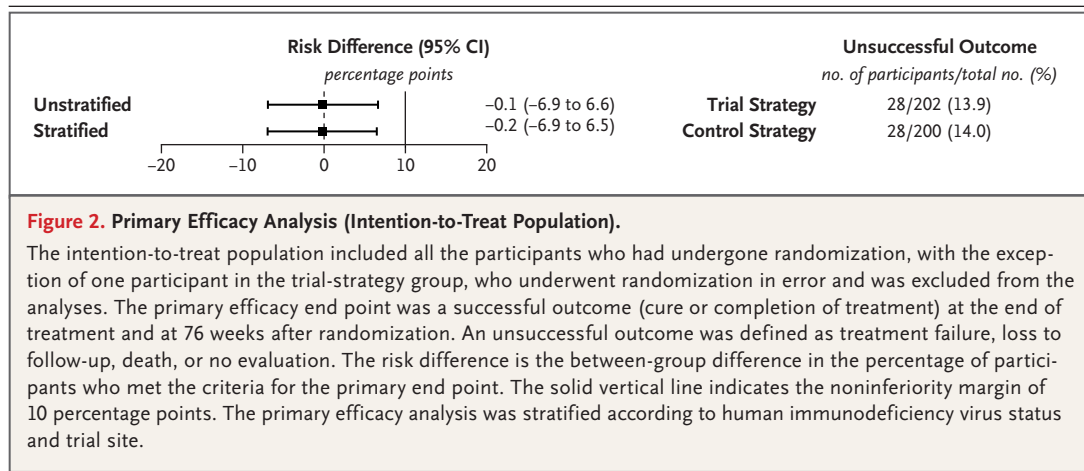
\* The intention-to-treat population included all the participants who had undergone randomization, with the exception of one participant in the trial-strategy group, who underwent randomization in error and was excluded from the analyses. Participants were followed for 76 weeks after randomization. A successful outcome was defined as cure or completion of treatment. An unsuccessful outcome was defined as treatment failure (lack of sputum culture conversion, bacteriologic reversion, or substitution of two or more drugs because of adverse effects), loss to follow-up, death, or no evaluation.

A serious adverse event occurred in 38 participants (18.8%) in the trial-strategy group and in 44 (22.0%) in the control group during treatment. The most common serious adverse event that occurred during or after treatment was anemia, which was attributed by the investigators to linezolid and occurred in 33 participants (16.3%) in the trial-strategy group and in 29 (14.5%) in the control group (Table S3.17). Most cases of anemia occurred within the first 8 weeks of treatment (Fig. S3.17). Anemia was managed by interrupting linezolid treatment for a few days and transfusing packed red cells. Twenty of 202 participants (9.9%) in the trial-strategy group and 11 of 200 (5.5%) in the control group received a transfusion. Other manifestations of myelosuppression, such as thrombocytopenia and neutropenia, were rare. Peripheral neuropathy resulting in the permanent discontinuation of linezolid occurred in 10 participants (5.0%) in the trial-strategy group and in 7 (3.5%) in the control group. Optic neuritis was observed in 9 participants (2.2%); in 7 (3.5%) in the trial-strategy group and in 2 (1.0%) in the control group. Severe liver-related adverse events occurred in 4 participants (2.0%) in the trial-strategy group and in 9 (4.5%) in the control group.

Asymptomatic prolongation of the corrected QT interval (calculated with the use of Fridericia's formula) of more than 500 msec, possibly related to bedaquiline or clofazimine, occurred in 5 participants (2.5%) in the trial-strategy group and in 7 (3.5%) in the control group. One child with fluroquinolone resistance in the control group had neuropsychiatric adverse reactions, which were attributed by the investigator to delamanid. A total of 123 participants (60.9%) in the trial-strategy group and 115 (57.5%) in the control group completed the trial with a successful outcome and without any adverse events of grade 3 or higher (the composite efficacy-safety end point) (Table S3.27).

#### TREATMENT INTERRUPTIONS AND EXTENSIONS IN THE TRIAL-STRATEGY GROUP

Of the 202 participants in the trial-strategy group who began treatment, 8 (4.0%) did not complete 24 weeks of treatment because of death or loss to follow-up. Among the 194 participants who completed treatment, 154 (79.4%) completed 24 weeks without interruptions of any drug, including linezolid. A total of 20 participants (10.3%) discontinued linezolid before 24



weeks, with a median time to discontinuation of 16 weeks (interquartile range, 8 to 20). In addition, 23 participants (11.9%) had at least one physician-directed treatment interruption of linezolid for at least 3 days; 3 of these participants discontinued linezolid early. Three participants (1.5%) in the trial-strategy group had their treatment extended beyond 24 weeks because of late culture conversion.

#### SPECIAL POPULATIONS

Of the nine participants who were pregnant at the time of enrollment, one was in the first trimester, six were in the second trimester, and two were in the third trimester (Table S3.18). One participant became pregnant during the trial. All pregnancies resulted in singleton live births, with one premature delivery. One pregnant participant in the trial-strategy group had a recurrence of tuberculosis disease (Table S3.19). Among the pregnant participants, two serious adverse events occurred that were not related to treatment.

A total of 30 participants with confirmed rifampicin-resistant tuberculosis who were enrolled were 8 to 17 years of age (13 in the trial-strategy group and 17 in the control group); 7 (23.3%) had fluoroquinolone-resistant tuberculosis (Table S3.31). One 17-year-old participant was identified as having bedaquiline-resistant and clofazimine-resistant tuberculosis at baseline and was subsequently switched to an individualized rescue regimen. One serious adverse event related to linezolid occurred in a child in the trial-strategy group. Delamanid was discontinued in one child because of neuropsychiatric adverse

reactions. All the participants younger than 18 years of age had a successful outcome at the end of treatment and at the end of follow-up.

#### DISCUSSION

The treatment regimen used in this trial (bedaquiline, delamanid, and linezolid with levofloxacin or clofazimine or both for 6 months) was noninferior to the standard-of-care strategy in South Africa for rifampicin-resistant tuberculosis. Our findings are consistent with those of other studies of shorter regimens containing bedaquiline, delamanid or pretomanid, and linezolid,<sup>3,4,10</sup> including a single-group study in which bedaquiline, delamanid, linezolid, and clofazimine were given for fluoroquinolone-resistant tuberculosis.<sup>11</sup>

The results of the current trial have already informed WHO guidelines for the treatment of drug-resistant tuberculosis, with this four- or five-drug regimen included as one of the recommended regimens in the June 2024 update.<sup>12</sup> The population enrolled in the trial was broadly representative of the population of persons in South Africa who have rifampicin-resistant tuberculosis (Table S4.1).

The safety and efficacy results in this trial with the 6-month regimen that contained delamanid were similar to those that have been observed with 6-month pretomanid-based regimens containing bedaquiline and linezolid. Although delamanid and pretomanid belong to the same class, evidence from clinical research studies comparing the drugs directly are lacking; however, preclinical studies suggest that each one

**Table 3. Safety (Safety Population).\***

| Adverse Event                                              | Trial Strategy<br>(N=202) | Control Strategy<br>(N=200) | Total<br>(N=402) | Risk Difference<br>(95% CI)† |
|------------------------------------------------------------|---------------------------|-----------------------------|------------------|------------------------------|
| Grade ≥3 event                                             | 69 (34.2)                 | 76 (38.0)                   | 145 (36.1)       | 3.8 (−5.5 to 13.2)           |
| Grade ≥3 event during treatment                            | 63 (31.2)                 | 74 (37.0)                   | 137 (34.1)       | 5.8 (−3.4 to 15.1)           |
| Treatment-related grade ≥3 event‡                          | 52 (25.7)                 | 56 (28.0)                   | 108 (26.9)       | 2.3 (−6.4 to 10.9)           |
| Serious adverse event at any time                          | 45 (22.3)                 | 44 (22.0)                   | 89 (22.1)        | −0.3 (−8.4 to 7.8)           |
| Serious adverse event during treatment                     | 38 (18.8)                 | 42 (21.0)                   | 80 (19.9)        | 2.2 (−5.6 to 10.0)           |
| Notable event§                                             | 36 (17.8)                 | 31 (15.5)                   | 67 (16.7)        | −2.3 (−9.6 to 5.0)           |
| Death at any time                                          | 10 (5.0)                  | 10 (5.0)                    | 20 (5.0)         | 0.0 (−4.2 to 4.3)            |
| Death during treatment                                     | 6 (3.0)                   | 8 (4.0)                     | 14 (3.5)         | 1.0 (−2.6 to 4.6)            |
| Death after treatment                                      | 4 (2.0)                   | 2 (1.0)                     | 6 (1.5)          | −1.0 (−3.3 to 1.4)           |
| Anemia leading to treatment discontinuation                | 10 (5.0)                  | 8 (4.0)                     | 18 (4.5)         | −1.0 (−5.0 to 3.1)           |
| Anemia leading to blood transfusion                        | 20 (9.9)                  | 11 (5.5)                    | 31 (7.7)         | −4.4 (−9.6 to 0.8)           |
| Grade ≥3 liver abnormality                                 | 4 (2.0)                   | 9 (4.5)                     | 13 (3.2)         | 2.5 (−0.9 to 6.0)            |
| Peripheral neuropathy leading to treatment discontinuation | 10 (5.0)                  | 7 (3.5)                     | 17 (4.2)         | −1.5 (−5.4 to 2.5)           |
| Optic neuropathy leading to treatment discontinuation      | 7 (3.5)                   | 2 (1.0)                     | 9 (2.2)          | −2.5 (−5.3 to 0.4)           |
| QTcF ≥480 msec                                             | 12 (5.9)                  | 19 (9.5)                    | 31 (7.7)         | 3.6 (−1.7 to 8.8)            |
| QTcF ≥500 msec                                             | 5 (2.5)                   | 7 (3.5)                     | 12 (3.0)         | 1.0 (−2.3 to 4.4)            |
| Treatment-related serious adverse events‡                  |                           |                             |                  |                              |
| Related to linezolid                                       | 20 (9.9)                  | 16 (8.0)                    | 36 (9.0)         | −1.9 (−7.5 to 3.7)           |
| Related to bedaquiline                                     | 4 (2.0)                   | 7 (3.5)                     | 11 (2.7)         | 1.5 (−1.7 to 4.7)            |
| Related to levofloxacin                                    | 3 (1.5)                   | 4 (2.0)                     | 7 (1.7)          | 0.5 (−2.0 to 3.1)            |
| Related to clofazimine                                     | 6 (3.0)                   | 7 (3.5)                     | 13 (3.2)         | 0.5 (−2.9 to 4.0)            |
| Related to delamanid                                       | 2 (1.0)                   | 2 (1.0)                     | 4 (1.0)          | 0.0 (−1.9 to 2.0)            |

\* The safety population included all the participants who had undergone randomization and received at least one dose of the assigned treatment. QTcF denotes corrected QT interval calculated with the use of Fridericia's formula.

† The risk difference is the difference in percentage points.

‡ Included are events that were at least possibly related to treatment.

§ Notable events included grade 3 or 4 cardiotoxic effects, increase in aspartate aminotransferase or alanine aminotransferase level, pregnancy, and peripheral neuropathy.

could replace the other in a regimen.<sup>13</sup> Our findings provide evidence for an effective treatment strategy for priority populations (such as children and pregnant or lactating women) in whom pretomanid is currently contraindicated, offering more therapeutic options for all persons with rifampicin-resistant tuberculosis.

The main strength of this trial is that it included a comparison with a well-established and standardized control regimen.<sup>14</sup> The two studies supporting the evidence for the bedaquiline–pretomanid–linezolid regimen (Nix-TB<sup>3</sup> and ZeNix<sup>4</sup>) did not have an internal comparison group. In contrast, other recent trials in rifampicin-resistant tuberculosis have included randomized internal

control groups that used different control strategies between sites (such as in TB-PRACTECAL<sup>5</sup>) and during the conduct of the trial (as in STREAM stage 2).<sup>15</sup> In addition, this trial was designed around a single pragmatic strategy that involved participants who were representative of persons who receive care in the South Africa National TB Programme. Another strength was the high percentage of participants who were enrolled after screening, which allowed for more accurate representation of the population needing treatment for rifampicin-resistant tuberculosis.

The drug that caused the most adverse events in the trial regimen was linezolid, but most participants were able to take the standard 600-mg

dose for 6 months. Short interruptions, usually because of anemia, could be managed at the site level. Regarding hepatic safety, it should be noted that only the alanine aminotransferase (ALT) level was assessed routinely (every month), and a full liver-function assessment was performed only when the ALT level exceeded 3 times the upper limit of the normal value. This approach may underestimate hepatic events as compared with studies in which the entire panel is assessed during each hepatotoxicity evaluation.

Bedaquiline resistance is becoming increasingly challenging in the treatment of rifampicin-resistant tuberculosis. In this trial, only fluoroquinolone-resistant specimens underwent phenotypic testing for bedaquiline resistance, the standard practice at the time. The acquisition of bedaquiline resistance was more common among participants with fluoroquinolone-resistant specimens than among those without resistance. Because of the long half-life of bedaquiline, any treatment interruptions owing to adherence challenges would result in effective monotherapy.

The trial followed a pragmatic approach that was similar to that used by the South Africa National TB Programme with respect to adherence support; clinic-based directly observed therapy is not considered to be part of the standard of care. Persons with risk factors for poor adherence were eligible for enrollment in this trial, unlike many other clinical trials in tuberculosis. However, the adherence measures implemented in this trial, which included pill counts and return verifications, were more stringent than those of the standard of care.

The trial had several limitations. It was conducted in only one country, which limits the generalizability of the strategy to other regions with different resistance patterns and HIV prevalence. This strategy may require examination in other settings and against other control regimens to assess its broader generalizability and importance. In addition, concealment of the trial-group assignments was not feasible because of the number of medications in each regimen and the different durations. Furthermore, although a bedaquiline–pretomanid–linezolid regimen or a bedaquiline–pretomanid–linezolid–moxifloxacin regimen may have been more suitable than the

9-to-18-month standard-of-care regimen as a control, trial enrollment began in August 2019, before the 2022 revision of the WHO guidelines. The South Africa National TB Programme adopted the bedaquiline–pretomanid–linezolid–levofloxacin regimen in September 2022.

An additional limitation was missing data. This was a pragmatic trial conducted within the National TB Programme, and we adhered to the diagnostic pathways outlined by the program. The diagnosis of rifampicin-resistant tuberculosis was established primarily with the use of the Xpert system and was followed by drug susceptibility testing, which was conducted with line-probe assays and did not yield a result in approximately 20% of cases. When the cultures obtained during follow-up returned negative results, it was impossible to determine drug susceptibility. In the case of unknown fluoroquinolone resistance, participants assigned to the trial strategy continued to receive all five drugs, whereas those in the control group received the standard regimen, which typically consists of seven drugs. In addition, bedaquiline susceptibility testing was performed only when fluoroquinolone resistance was confirmed. The trial was also conducted during the coronavirus disease 2019 pandemic and the subsequent lockdowns. Owing to disruptions in the health care system and the relocation of the research site, chest radiography was not always performed. Having chest radiography results that aligned with a diagnosis of tuberculosis before the start of treatment was not a criterion for participation. Nevertheless, among the participants who had cure at the end of treatment, few were lost to follow-up during treatment or after treatment.

Among participants with rifampicin-resistant tuberculosis, the efficacy and safety profile of the trial strategy were similar to that of the standard-of-care treatment that was current in South Africa at the time. This trial provides evidence to support a 6-month strategy that offers a treatment option for both fluoroquinolone-susceptible and fluoroquinolone-resistant, rifampicin-resistant tuberculosis and that is applicable to children and pregnant or breastfeeding women.

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