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Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

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ABSTRACT

BACKGROUND

Two thirds of children with tuberculosis have nonsevere disease, which may be treatable with a shorter regimen than the current 6-month regimen.

METHODS

We conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 months (16 weeks) or 6 months (24 weeks) of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the World Health Organization. The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified intention-to-treat population). A noninferiority margin of 6 percentage points was used. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment.

RESULTS

From July 2016 through July 2018, a total of 1204 children underwent randomization (602 in each group). The median age of the participants was 3.5 years (range, 2 months to 15 years), 52% were male, 11% had human immunodeficiency virus infection, and 14% had bacteriologically confirmed tuberculosis. Retention by 72 weeks was 95%, and adherence to the assigned treatment was 94%. A total of 16 participants (3%) in the 4-month group had a primary-outcome event, as compared with 18 (3%) in the 6-month group (adjusted difference, –0.4 percentage points; 95% confidence interval, –2.2 to 1.5). The noninferiority of 4 months of treatment was consistent across the intention-to-treat, per-protocol, and key secondary analyses, including when the analysis was restricted to the 958 participants (80%) independently adjudicated to have tuberculosis at baseline. A total of 95 participants (8%) had an adverse event of grade 3 or higher, including 15 adverse drug reactions (11 hepatic events, all but 2 of which occurred within the first 8 weeks, when the treatments were the same in the two groups).

CONCLUSIONS

Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, nonsevere, smear-negative tuberculosis. (Funded by the U.K. Medical Research Council and others; SHINE ISRCTN number, ISRCTN63579542.)

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More than 1 million children become ill with tuberculosis annually, and almost 20% of them die,[1,2] but children have historically been excluded from clinical efficacy trials of antituberculosis treatment. This situation is due in part to low rates of bacteriologic confirmation of disease among children, given high rates of paucibacillary disease and difficulties in obtaining respiratory specimens. Treatment recommendations for children are therefore extrapolated from trials involving adults for which the criteria for treatment entry have often included smear-positive respiratory disease.

In contrast to adults, most children have nonsevere, smear-negative tuberculosis.[3,4] Although spontaneous resolution has been described,[5] it is generally agreed that treatment is appropriate in children with mild forms of tuberculosis because of the risk of disease progression and dissemination, particularly among the youngest children or those with concurrent human immunodeficiency virus (HIV) infection.[6,7] It is likely that nonsevere forms of tuberculosis could be treated with shorter durations of therapy, but data are limited regarding the shortening of treatment for drug-susceptible tuberculosis in children. Current international guidelines recommend 6 months of antituberculosis treatment in children, which is the same duration as in adults.

Early pharmacokinetic studies of first-line antituberculosis treatment showed lower drug exposures in young children than in adults and led to recommendations of increased drug doses from the World Health Organization (WHO) in 2010.[8] New dispersible-formulation tablets with a fixed-dose combination were developed to enable the use of revised doses and became available in 2015.[9,10]

In the SHINE trial, we investigated whether 4 months of antituberculosis treatment would be as good as 6 months of treatment in children with nonsevere, smear-negative, presumably drug-susceptible tuberculosis, using the new fixed-dose combination formulations. In addition, we evaluated the cost-effectiveness of the 4-month treatment approach.

Methods

Trial Design and Oversight

We conducted an international, open-label, parallel-group, randomized, controlled, noninferiority trial comparing 4 months (16 weeks) of antituberculosis treatment with the standard 6 months (24 weeks) of treatment using WHO-recommended pediatric doses.[10] All the relevant national and local ethics committees and the University College London research ethics committee approved the trial protocol, which is available with the full text of this article at NEJM.org. Caregivers provided written informed consent, and children gave assent as appropriate. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Participants

Children younger than 16 years of age who had symptomatic nonsevere tuberculosis that was smear-negative on a respiratory sample and who were due to start first-line antituberculosis treatment were eligible for enrollment. Nonsevere tuberculosis included respiratory tuberculosis confined to one lobe (opacification of <1 lobe) with no cavities, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph-node tuberculosis (see the protocol).[11]

Trial Procedures

Children were seen at screening, at enrollment (randomization), and at weeks 2, 4, 8, 12, 16, 20, 24, 28, 36, 48, 60, and 72. Screening procedures included history taking to identify contacts with persons with tuberculosis and an evaluation of symptoms associated with tuberculosis; performance of a Mantoux tuberculin skin test or interferon γ–release assay, where available; radiography of the chest; and obtaining at least two respiratory samples (gastric aspirate, expectorated sputum, or induced sputum) for smear microscopy, Xpert MTB/RIF assay (Xpert, Cepheid), mycobacterial culture (Löwenstein–Jensen solid-culture medium or a mycobacteria growth indicator tube with liquid culture system), and drug-susceptibility testing. In children with peripheral lymph-node tuberculosis, a fine-needle aspirate was obtained. A baseline radiograph of the chest was assessed by site clinicians for severe respiratory tuberculosis.[3] Blood samples for biochemical and hematologic testing (in all children) and for HIV type 1 viral load and CD4 count (in children with HIV infection) were obtained at screening and at scheduled follow-up visits. Children with confirmed drug resistance or with

known exposure to an adult with any drug-resistant tuberculosis were excluded from the trial.

A symptom checklist was completed and a clinical examination was performed at each visit to detect tuberculosis-associated symptoms and adverse events. Repeat respiratory samples were obtained if previous respiratory specimens were positive on microbiologic testing, if such assessment was clinically indicated to assess recurrence or treatment failure, or if a new contact with drug-resistant tuberculosis was identified.

Radiographs of the chest were retrospectively reviewed centrally by two independent experts. Radiographs with discordant interpretations at the primary reading were reviewed by a third expert, and the majority opinion was used. The radiographic image review was conducted in a blinded manner with the use of a standardized approach (see the protocol). Tuberculosis status at enrollment (confirmed, unconfirmed, or unlikely) was adjudicated by an independent clinical expert committee on the basis of all available clinical, radiologic, and laboratory data.[13,14] An end-point review committee, whose members were unaware of the treatment assignments, reviewed clinical events suggestive of treatment failure or tuberculosis recurrence and all deaths. Clinical and laboratory adverse events of grade 3 or higher were defined with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[15] Additional notable events to be reported included suspected bacterial infection leading to hospitalization, ocular toxic effects, and pregnancy.

Adherence was assessed by means of pill counts at each visit during treatment and by the administration of adherence questionnaires at the end of the intensive phase (first 8 weeks of treatment) and at the end of treatment. Treatment extensions due to excessive missed doses were reconciled against pill-count data.

RANDOMIZATION AND TREATMENT

Eligible children were randomly assigned in a 1:1 ratio to receive 4 months or 6 months of antituberculosis treatment. Randomization was conducted with the use of minimization (with a random element) according to trial center, age (<3 years or ≥3 years), HIV status, and ethambutol use.

All the participants initially received 8 weeks of standard therapy with isoniazid, rifampin, and pyrazinamide (fixed-dose combination formulation), with or without ethambutol according to local guidelines (intensive phase). This treatment was followed by standard therapy with isoniazid and rifampin (continuation phase) in a fixed-dose combination for either 8 weeks in the 4-month group (intervention) or 16 weeks in the 6-month group (control). All antituberculosis treatment was administered 7 days per week, on the basis of WHO weight bands for tuberculosis treatment, with the use of child-friendly formulations[10] that have been found to be acceptable by trial participants and caregivers.[16] Directly observed treatment by health care workers was not used.

PRIMARY AND SECONDARY OUTCOMES

The primary efficacy outcome was unfavorable status by 72 weeks. Unfavorable status was defined as a composite of tuberculosis events (treatment failure, including treatment extension beyond the replacement of missed doses, antituberculosis-treatment drug change or restart due to suspected treatment failure, and tuberculosis recurrence as adjudicated by the end-point review committee), loss to follow-up during treatment, or death from any cause. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment. The key secondary efficacy outcome was unfavorable status at 72 weeks in participants who were adjudicated by the end-point review committee as having tuberculosis at baseline. Other secondary outcomes were death; adverse drug events that were considered by the site investigators to be possibly, probably, or definitely related to a trial drug (adverse drug reactions); bacterial infection leading to hospitalization; adherence to the treatment regimen; and acceptability of treatment as determined by the caregiver (or by the child, when appropriate).

STATISTICAL ANALYSIS

We determined the statistical power of the trial on the basis of a key subgroup analysis involving children who were found on independent adjudication to have tuberculosis at enrollment (80% of the intention-to-treat population). Assuming a 10% loss to follow-up (after treatment), an unfavorable status by 72 weeks (primary efficacy outcome) in 8% of the participants in the control group,[17,18] and a noninferiority margin of 6 per-

centage points, we calculated that the enrollment of 1200 children would provide the trial with 90% power to detect noninferiority at a two-sided significance level of 5% (see the statistical analysis plan, available with the protocol).

The primary modified intention-to-treat population included all the children who had undergone randomization except those who did not complete 4 months of treatment (when the treatment in the two groups was the same) or had a late exclusion (on the basis of data collected before randomization) and those who were clinically well after the completion of treatment but were subsequently lost to follow-up. For the per-protocol population, an additional exclusion criterion was the receipt of trial medications at less than 80% of the daily doses within 120% of the assigned treatment duration (prespecified in the statistical analysis plan).

The primary efficacy analysis was based on the absolute difference between the 4-month and 6-month strategies in the percentages of participants with an unfavorable status in the modified intention-to-treat population, with adjustment for minimization factors with Cochran–Mantel–Haenszel weights. Time-to-event analyses of unfavorable status and death were conducted with the use of log-rank tests and Cox proportional-hazards models. Analyses were performed with the use of Stata software, version 15.1 or later (StataCorp), and SAS software, version 10.1 (SAS Institute). An independent data monitoring committee reviewed data according to treatment group four times during the trial.

We performed economic analyses to estimate costs and health outcomes in terms of life-years and quality-adjusted life-years during the 72-week trial. In these analyses, we used data on resources that had been used in the trial and the unit costs obtained from published sources for each country. Costs were estimated from a health-sector perspective to capture a range of health care resource use, including hospitalization, medication, and testing costs. We estimated quality-adjusted life-years by combining health-related quality-of-life scores, which were estimated with the use of the European Quality of Life–5 Dimensions questionnaire, and survival. Costs and outcomes were discounted at 3% per annum, in line with international recommendations[12] (see Section S7 in the Supplementary Appendix, available at NEJM.org).

RESULTS

PARTICIPANTS

Of the 1461 children who were screened, 1204 underwent randomization between July 2016 and July 2018. A total of 376 participants were in Uganda, 364 in Zambia, 315 in South Africa, and 149 in India. The principal reasons for ineligibility were smear-positive respiratory samples and the presence of severe tuberculosis on chest radiography (Fig. 1).

A total of 59 children (30 in the 4-month group and 29 in the 6-month group) were excluded from the modified intention-to-treat analysis. A total of 36 participants (18 in the 4-month group and 18 in the 6-month group) did not complete 4 months of treatment (i.e., had a protocol-defined unfavorable status before month 4), and 14 participants (8 in the 4-month group and 6 in the 6-month group) were lost to follow-up after successfully completing treatment. The most frequent reason for further exclusion from the per-protocol analysis was nonadherence to the assigned treatment strategy (in 9 participants in the 4-month group and 15 in the 6-month group) (Fig. 1).

The demographic and clinical characteristics of the participating children were similar in the two groups (Table 1). The median age of the participants was 3.5 years (range, 2 months to 15 years). A total of 52% of the participants were male, 88% were African, and 12% were Indian; 11% of the participants had HIV infection. A total of 67% of the participants had respiratory tuberculosis, 3% had peripheral lymph-node tuberculosis, and 29% had mixed tuberculosis (respiratory and peripheral lymph-node disease). A total of 14% of the participants had tuberculosis that was bacteriologically confirmed as positive for *Mycobacterium tuberculosis* on culture or Xpert testing. Xpert semiquantitative results showed that all positive Xpert values were low or very low (Table S1 in the Supplementary Appendix).

RETENTION AND TREATMENT ADHERENCE

Retention, as assessed on the basis of attendance at the final trial visit at week 72, was 95% among those expected (excluding formal withdrawals [8 participants] and deaths [31]). Retention was similar in the two groups (Table S2).

Adherence to the assigned treatment duration was similar in the two groups, with 94% of the

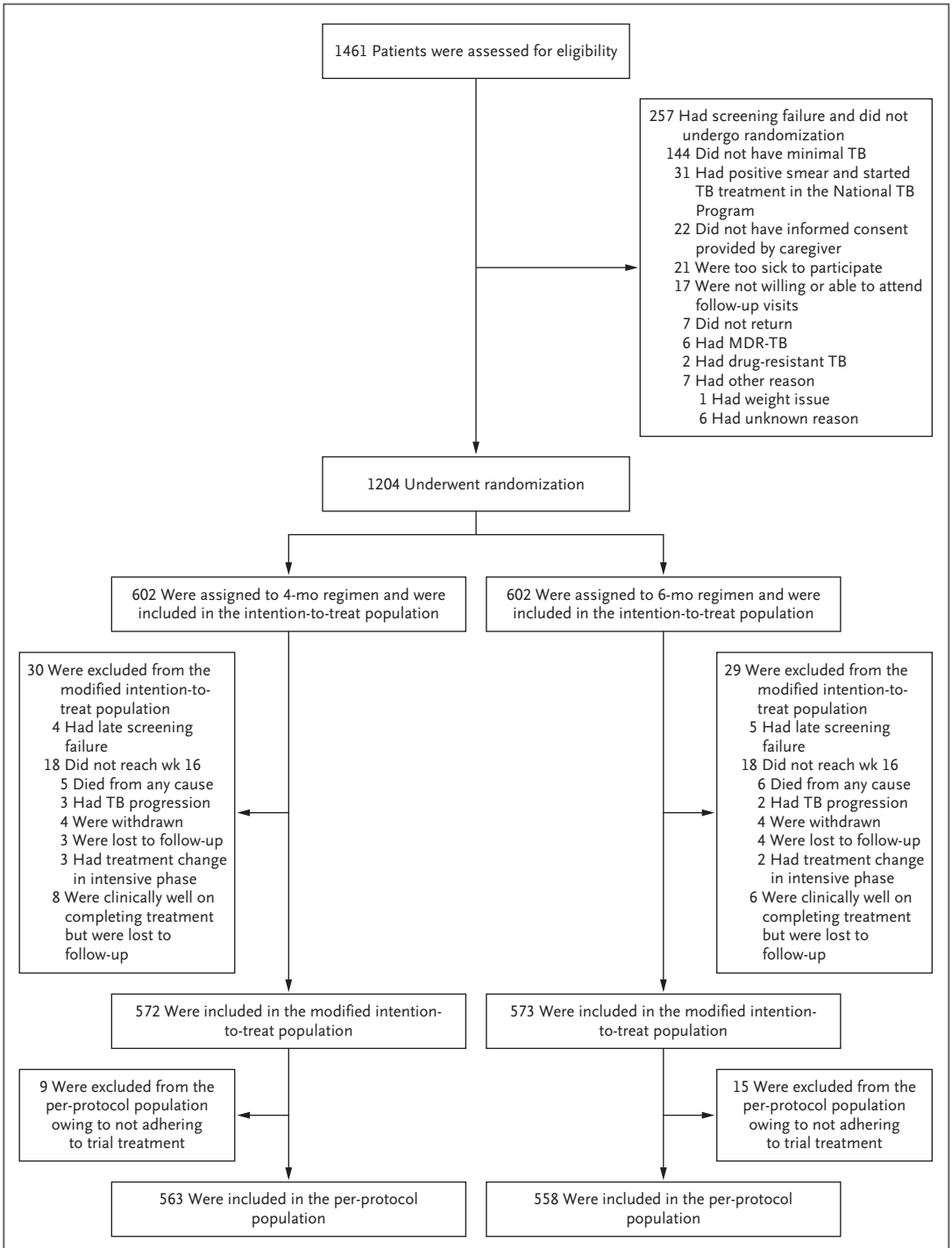

Figure 1. Randomization and Treatment of the Patients.

All the eligible participants with tuberculosis (TB) initially received 8 weeks of standard therapy with isoniazid, rifampin, and pyrazinamide (fixed-dose combination formulation), with or without ethambutol according to local guidelines (intensive phase). This treatment was followed by standard therapy with isoniazid and rifampin (continuation phase) in a fixed-dose combination for either 8 weeks in the 4-month group (intervention) or 16 weeks in the 6-month group (control). MDR-TB denotes multidrug-resistant TB.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	4-Month Treatment (N=602)	6-Month Treatment (N=602)	Total (N=1204)
Age			
Median (interquartile range) — yr	3.4 (1.5 to 6.9)	3.5 (1.5 to 7.1)	3.5 (1.5 to 7.0)
Range	2 mo to 15 yr	2 mo to 15 yr	2 mo to 15 yr
Female sex — no. (%)	297 (49)	286 (48)	583 (48)
Site country — no. (%)			
Uganda	188 (31)	188 (31)	376 (31)
Zambia	183 (30)	181 (30)	364 (30)
South Africa	156 (26)	159 (26)	315 (26)
India	75 (12)	74 (12)	149 (12)
HIV-positive status — no. (%)	65 (11)	62 (10)	127 (11)
WHO weight band — no. (%)			
3–3.9 kg	0	3 (<1)	3 (<1)
4–7.9 kg	86 (14)	92 (15)	178 (15)
8–11.9 kg	162 (27)	152 (25)	314 (26)
12–15.9 kg	126 (21)	116 (19)	242 (20)
16–24.9 kg	142 (24)	153 (25)	295 (25)
≥25 kg	86 (14)	86 (14)	172 (14)
Clinical presentation — no. (%)			
Respiratory tuberculosis	398 (66)	406 (67)	804 (67)
Mixed respiratory and peripheral lymph-node tuberculosis	182 (30)	171 (28)	353 (29)
Peripheral lymph-node tuberculosis	19 (3)	21 (3)	40 (3)
Other†	3 (<1)	4 (1)	7 (1)
M. tuberculosis culture and Xpert MTB/RIF testing results — no. (%)‡			
All positive results	85 (14)	80 (13)	165 (14)
Tuberculosis culture–positive only	40 (7)	40 (7)	80 (7)
Xpert MTB/RIF–positive only	14 (2)	5 (1)	19 (2)
Tuberculosis culture–positive and Xpert MTB/RIF–positive	31 (5)	35 (6)	66 (5)

* HIV denotes human immunodeficiency virus, and WHO World Health Organization.
† These participants did not have a cough for more than 2 weeks or one or more peripheral lymph nodes suggestive of tuberculosis.
‡ Microbiologic confirmation was from respiratory samples (gastric aspirate or washing or induced or expectorated sputum) and fine-needle aspiration of enlarged lymph nodes and was defined as positive for *Mycobacterium tuberculosis* on culture or the Xpert MTB/RIF assay. Cultures were assessed with Löwenstein–Jensen solid-culture medium or a mycobacteria growth indicator tube with liquid culture system.

children taking at least 80% of daily doses within 120% of the assigned days (Fig. S1). Radiographs of the chest with discordant interpretations at the primary (baseline) reading were reviewed by a third expert for 435 of 1174 participants (37%). Chest radiographs that had been obtained at baseline were missing for 30 participants.

PRIMARY OUTCOME

In the modified intention-to-treat analysis, 21 events occurring before month 4 were excluded (11 deaths, 5 events of tuberculosis progression, and 5 treatment extensions or drug changes) (Fig. 1). In the primary modified intention-to-treat analysis, an unfavorable status was observed

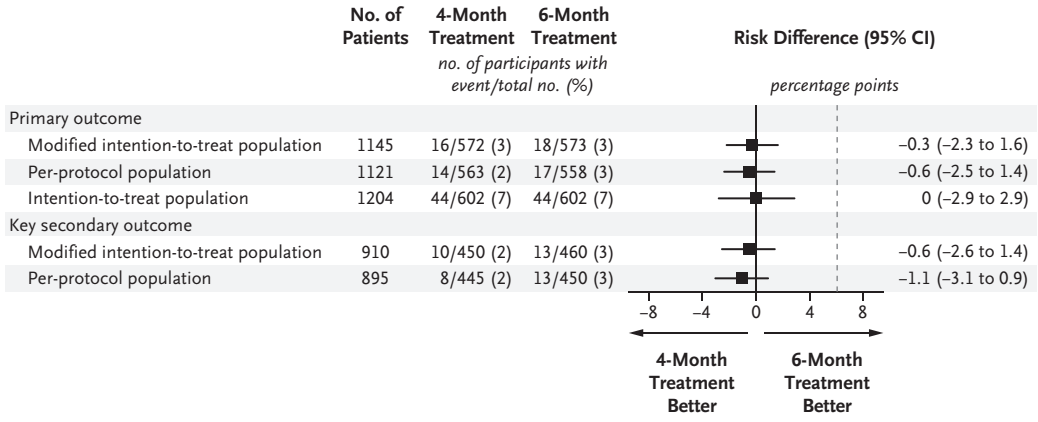

Figure 2. Unadjusted Analysis of the Primary Efficacy and Key Secondary Outcomes in the Trial Populations.

The primary efficacy outcome was unfavorable status by 72 weeks, which was defined as a composite of treatment failure (treatment extension, change, or restart or tuberculosis recurrence), loss to follow-up during treatment, or death, with the exclusion of all the participants who had undergone randomization but did not complete 4 months of treatment (modified intention-to-treat population). The per-protocol population included all the participants in the modified intention-to-treat population except those who had not adhered to the trial regimen. The intention-to-treat population included all the participants who had undergone randomization. Differences have been carried to one decimal place because of the small values. The prespecified margin for noninferiority in the primary efficacy analysis was 6 percentage points (dashed line). The key secondary analysis was unfavorable status at 72 weeks as assessed among the 958 participants who had been independently adjudicated as having tuberculosis at baseline.

in 16 participants (3%) in the 4-month group and in 18 participants (3%) in the 6-month group (unadjusted difference, −0.3 percentage points; 95% confidence interval [CI], –2.3 to 1.6; adjusted difference, −0.4 percentage points; 95% CI, –2.2 to 1.5) (Fig. 2 and Table 2).

Results in the intention-to-treat and per-protocol populations were similar to those of the primary analysis (Fig. 2 and Table S9). In time-to-event analyses, there were no significant between-group differences in the risks of an unfavorable status (hazard ratio, 0.88; 95% CI, 0.45 to 1.74) or death (hazard ratio, 0.63; 95% CI, 0.31 to 1.30) (Figs. S2 and S3).

The most common reasons for an unfavorable status (after month 4) were death from any cause (in 7 participants in the 4-month group and 12 in the 6-month group) and treatment failure (in 9 and 5 participants, respectively). Among participants with treatment failure, 2 (both in the 4-month group) had a treatment extension, 2 (1 in each group) stopped treatment and had their treatment course restarted from the beginning during the first 8 weeks, and 10 (6 in the 4-month group and 4 in the 6-month group) had recurrence of tuberculosis (Table 2).

KEY SECONDARY ANALYSIS

The key secondary analysis included 958 participants who had been independently adjudicated to have tuberculosis at baseline (80% of the enrolled population); 910 of these participants were included in the modified intention-to-treat population. Of these 910 participants, 440 of 450 (98%) in the 4-month group and 447 of 460 (97%) in the 6-month group had a favorable outcome. The adjusted absolute difference in the risk of an unfavorable status in the 4-month group as compared with the 6-month group was −0.6 percentage points (95% CI, –2.6 to 1.4). In the per-protocol analysis, the difference was –1.1 percentage points (95% CI, –3.1 to 0.9) (Fig. 2). Results for the modified intention-to-treat efficacy outcome according to prespecified subgroup analyses (HIV status, region, sex, age, weight band, tuberculosis type, bacteriologic confirmation, and ethambutol given at baseline) were all consistent with the primary result (Fig. S4 and Table S8).

ADVERSE EVENTS

A total of 115 adverse events of grade 3 or higher occurred during treatment or up to 30

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

Outcome	4-Month Treatment (N=572)	6-Month Treatment (N=573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			percentage points	
Unfavorable status — no. (%)	16 (3)	18 (3)	−0.4 (−2.2 to 1.5)	−0.3 (−2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		

* The primary efficacy outcome was unfavorable status by 72 weeks. Unfavorable status was defined as a tuberculosis event (treatment failure, including treatment extension beyond the replacement of missed doses, drug changes or restarts in antituberculosis treatment due to suspected treatment failure, and tuberculosis recurrence as adjudicated by the end-point review committee, whose members were unaware of the treatment assignments), loss to follow-up during treatment, or death from any cause. Favorable status was defined as the completion of treatment and a status of being clinically well, without having had retreatment or another unfavorable outcome. The primary modified intention-to-treat population included all the participants who had undergone randomization except those who did not complete 4 months of treatment or who had a late exclusion (on the basis of data collated before randomization) and those who were clinically well after the completion of treatment but were subsequently lost to follow-up.

† The analysis was adjusted with Cochran–Mantel–Haenszel weighting for trial center, participant age (<3 years or ≥3 years), HIV status, and ethambutol use.

‡ None of the participants extended their treatment beyond 4 months and were subsequently lost to follow-up.

§ Two participants stopped treatment and had their treatment course restarted from the beginning during the first 8 weeks.

days after treatment in 95 participants (8% of all the children enrolled in the trial; 49 events in 47 participants in the 4-month group and 66 events in 48 participants in the 6-month group). Of these 115 adverse events, the most common were pneumonia or other chest infection (29 events [25%]) or liver-related events (11 [10%]); the incidences were similar in the two groups (Tables 3 and S3).

A total of 192 serious adverse events occurred in 150 participants (12%) in the trial, including 31 deaths (12 in the 4-month group and 19 in the 6-month group). Twenty deaths (7 in the 4-month group and 13 in the 6-month group) occurred after month 4, and 13 deaths (5 in the 4-month group and 8 in the 6-month group) were considered by the end-point review committee to be related to tuberculosis. Of the 31 deaths, 25 were in children younger than 2 years of age (Table S5). Hospitalization for a respiratory bacterial infection occurred in 66 participants (5%), with 45 participants (26 in the 4-month group and 19 in the 6-month group) being hospitalized after month 4 (Table 3).

A total of 15 adverse drug reactions of grade 3 or 4 were considered by the investigators to be possibly, probably, or definitely related to trial drugs. These adverse reactions included 11 hepatic events. All the adverse reactions except 2 occurred during the first 8 weeks of therapy (Table S4). Two participants permanently discontinued therapy after treatment interruption for an adverse reaction. None of the adverse reactions led to death.

COST-EFFECTIVENESS ANALYSIS

A cost-effectiveness analysis showed that at 72 weeks, participants who had been treated for 4 months had similar health outcomes as those who had been treated for 6 months but with lower health care costs. A regression analysis controlling for chance differences in demographic

Table 3. Primary Safety Outcome, Serious Adverse Events, Deaths, Adverse Drug Reactions, and Suspected Bacterial Infections Leading to Hospitalization.*

Event	4-Month Treatment (N=602)	6-Month Treatment (N=602)	Total (N=1204)
Primary safety outcome — no. of events	49	66	115
No. of participants with ≥1 event (%)†	47 (8)	48 (8)	95 (8)
At ≤4 mo			
No. of adverse events of grade ≥3	35	52	87
No. of participants with ≥1 event (%)	33 (5)	40 (7)	73 (6)
At >4 mo			
No. of adverse events of grade ≥3	14	14	28
No. of participants with ≥1 event (%)	14 (2)	12 (2)	26 (2)
Serious adverse event — no. of events	88	104	192
No. of participants with ≥1 serious adverse event (%)†	75 (12)	75 (12)	150 (12)
At ≤4 mo			
No. of serious adverse events	35	50	85
No. of participants with ≥1 serious adverse event (%)	33 (5)	40 (7)	73 (6)
At >4 mo			
No. of serious adverse events	53	54	107
No. of participants with ≥1 serious adverse event (%)	47 (8)	44 (7)	91 (8)
Death — no. (%)	12 (2)	19 (3)	31 (3)
At ≤4 mo			
No. of deaths (%)	5 (1)	6 (1)	11 (1)
No. of deaths considered to be related to tuberculosis (%)	3 (<1)	2 (<1)	5 (<1)
At >4 mo			
No. of deaths (%)	7 (1)	13 (2)	20 (2)
No. of deaths considered to be related to tuberculosis (%)	2 (<1)	6 (1)	8 (1)
Adverse drug reaction — no. of participants (%)‡	6 (1)	11 (2)	17 (1)
Bacterial infection leading to hospitalization — no. of events	40	40	80
No. of participants with ≥1 event (%)	36 (6)	30 (5)	66 (5)

* The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was used for grading the severity of adverse events. The primary safety outcome was an adverse event of grade 3 or higher that occurred during treatment and up to 30 days after the last dose of a trial drug. Serious adverse events were defined with the use of International Council for Harmonisation and Good Clinical Practice definitions as an adverse event that resulted in death, was life-threatening, led to hospitalization or prolonged existing hospitalization, resulted in persistent or clinically significant disability or incapacity, consisted of a congenital anomaly or birth defect, or was considered to be another important medical condition.

† Participants may have had events both before and after the 4-month breakdown.

‡ Adverse drug reactions during treatment and within 30 days after completion of treatment were assessed by the site investigator as being possibly, probably, or definitely related to the trial drugs. Further information on the adverse drug reactions, including event types and information on treatment discontinuations, is provided in Table S4.

characteristics and symptom severity estimated that the number of quality-adjusted life-years was similar in the two groups (mean difference, 0.003; 95% CI, −0.009 to 0.014) and that health care costs (assessed in 2019) were $17.34 (95% CI, 3.77 to 30.91) lower per child in the 4-month group (Table S7).

DISCUSSION

The SHINE trial evaluated the duration of antituberculosis treatment in children with nonsevere, drug-susceptible tuberculosis who were living in countries with a high burden of tuberculosis, where nearly 90% of cases of tuberculosis in children occur.[19] The trial showed the noninferiority of 4 months as compared with the standard 6 months of treatment, with the upper boundary of the 95% confidence interval being below the prespecified margin of 6 percentage points. Consistency of results across all the analyses, including a key secondary analysis in a subgroup of children who were adjudicated to have tuberculosis at baseline, was observed. Participants had a good response to treatment with few adverse drug reactions, most of which occurred before 4 months, during the period when the two trial groups had the same treatment regimen.

Shortening treatment for drug-susceptible tuberculosis is a key goal for both adults and children. Early trials showed that it was possible to shorten the treatment duration in adults with culture-negative disease.[20-22] A meta-analysis of treatment-duration trials involving adults showed that 4-month drug regimens were efficacious in adults with paucibacillary tuberculosis who had disease with a sputum-smear grade of less than 2+ (<1 acid-fast bacillus per field) or noncavity disease.[23] Recently, the Tuberculosis Trials Consortium Study 31/AIDS Clinical Trials Group A5349 trial showed the noninferiority of a 4-month rifapentine-based regimen containing moxifloxacin, as compared with the 6-month standard regimen, for all forms of drug-susceptible tuberculosis (including cavity disease) in adults and adolescents.[24] Challenges remain in terms of the availability of child-friendly formulations of rifapentine and moxifloxacin, data on doses in children, and cost. However, our results show that a new regimen with new drugs is not necessary for the shortening of treatment in the majority of children with drug-susceptible tuberculosis, since such treatment shortening can be accomplished with the affordable, child-friendly, fixed-dose combinations that are already available.[25]

This trial showed the feasibility of identifying children with nonsevere disease. We used a pragmatic approach by following routine screening procedures and reviewing chest radiographs to assess the severity of respiratory tuberculosis. Despite perceived difficulties of obtaining respiratory samples in children, such challenges were overcome with appropriate training, and samples were successfully obtained for tuberculosis testing in all 1204 children who underwent randomization. The trial included children with HIV infection as well as those without HIV infection, with consistent results.

Most children with tuberculosis have paucibacillary and nonsevere disease with low rates of microbiologic tuberculosis confirmation in routine care. To ensure the applicability of our results to clinical practice and the spectrum of disease that is most prevalent in children, we did not limit the trial to bacteriologically confirmed tuberculosis. We adapted the pediatric consensus algorithm for diagnosis of intrathoracic tuberculosis[13] to both intrathoracic tuberculosis and peripheral lymph-node tuberculosis and used independent expert review and central reading of chest radiographs, with blinding to the treatment assignments, to ensure objective categorization of tuberculosis status. The end-point review committee, whose members were unaware of the randomized group assignments, reviewed tuberculosis outcomes to minimize the effect of treatment assignment on adjudication.

Our trial had several strengths. It was well-powered, and we observed 94% adherence (to the receipt of ≥80% of the doses) in the assigned groups and 95% retention of trial participants, findings that increase confidence in the results. We assumed in the sample-size calculation that 8% of the participants in the 6-month group would have an unfavorable status, and we observed this result in 7% of the participants overall in the trial. However, events in 3% of the participants occurred after month 4, when the trial groups were receiving different durations of the treatment, which we had not anticipated when we designed the trial.

The trial also has several limitations. One limitation is that this trial was open-label, which had the potential to result in more frequent treatment extensions in the 4-month group, contributing to more unfavorable outcomes in this group. Despite this possible disadvantage in the 4-month group, the results showed consistently

that the 4-month regimen was as good as the 6-month regimen. Another limitation relates to the generalizability of our results to settings where chest radiographs are not available for characterizing nonsevere tuberculosis.

Our inclusion criteria for the trial required smear microscopy to be undertaken to rule out more severe forms of respiratory tuberculosis. With the current rollout of rapid molecular diagnostic tests replacing smear microscopy,[26] this may pose a challenge to implementation on the basis of the trial results. However, smear-grade and Xpert semiquantitative results have been shown to be correlated.[27] In our trial, most Xpert results from respiratory samples were negative and the few positive Xpert samples had low or very low semiquantitative results, which suggest that the trial findings can be extrapolated to settings where Xpert is replacing smear testing and that children with negative, low, or very low positive values on Xpert testing can be categorized as having nonsevere tuberculosis. It will be useful in future implementation studies to explore treatment shortening in all children who are treated for nonsevere, drug-susceptible tuberculosis, regardless of smear or Xpert results.

In this trial, we found that 4 months of antituberculosis treatment was noninferior to 6 months of therapy in children with drug-susceptible, nonsevere, smear-negative tuberculosis. The results suggest that a stratified medicine approach as an alternative to the one-size-fits-all strategy of treatment for presumptive drug-susceptible tuberculosis could be implemented in children with nonsevere tuberculosis.

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APPENDIX

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