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The importance of Primary endpoints in RCTs

Josep M Llibre, MD, PhD
Infectious Diseases
Univ Hosp Germans Trias i Pujol
Badalona, Barcelona
jmllibre@lluita.org
@DrBike7

Salut/ Germans Trias i Pujol Hospital

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ORIGINAL ARTICLE

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D., Christine Sekaggya-Wiltshire, Ph.D., Anchalee Avihingsanon, M.D., Rohit Sarin, M.D., Padmasayee Papineni, F.R.C.P., Andrew J. Nunn, M.Sc., and Angela M. Crook, Ph.D., for the TRUNCATE-TB Trial Team*

CONCLUSIONS

A strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment for tuberculosis with respect to clinical outcomes. The strategy was associated with a shorter total duration of treatment and with no evident safety concerns. (Funded by the Singapore National Medical Research Council and others; TRUNCATE-TB ClinicalTrials.gov number, NCT03474198.)

The results of this trial suggest that there may be value in considering a shift in tuberculosis management to a strategy involving initial treatment for the minimum duration needed to cure the majority of persons with tuberculosis, extended treatment for persistent clinical disease, and monitoring after treatment to detect relapse in the minority of persons who need retreatment.

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30th CROI 2023
19-22 February 2023

#113

EFFICACY AND SAFETY OF 8-WK TUBERCULOSIS TREATMENT REGIMENS IN THE TRUNCATE-TB TRIAL

Nicholas Paton

National University of Singapore, Republic of Singapore

Disclosure: Grant support from Janssen (NADIA, TRUNCATE-TB, CARES trials

In kind support (drug donations) from Sanofi and Pfizer

Conclusions

Regimen efficacy

- **Unfavourable outcome more frequent with 8wk regimens than 24wk standard regimen, as expected**
- **Difference modest with 5-drug BDQ/LZD regimen (high probability <12%); excess relapses can be managed within the TRUNCATE strategy***
- Biomarkers can identify subgroups with low probability of achieving target relapse rate (< 20%) with 8wk regimen. Refining criteria for treatment extension may improve strategy outcomes further.

Regimen safety

- Regimens were safe overall (severe AEs, serious AEs uncommon)
- Toxicity burden from linezolid appeared manageable
- BDQ resistance in two (1.1%) is a caution; needs monitoring in other studies

* Paton N, Cousins C, Suresh C et al. NEJM published online 20 Feb 2023: DOI: 10.1056/NEJMoa2212537

- Because it was a **strategy-comparison trial**, the **design and the approach to analysis differed** from those used in regimen-comparison trials.
- A seamless **phase 2–3**, prospective, multicenter, international, **adaptive**, multigroup, multistage, randomized, open-label, **noninferiority** trial with a 96-week follow-up

N Paton. NEJM 2023; DOI: 10.1056/NEJMoa2212537

TRIAL POPULATION

Persons were eligible for inclusion in the trial if they were 18 to 65 years of age, had symptoms of tuberculosis or evidence of tuberculosis on a chest radiograph, and had a nucleic acid amplification test (Xpert MTB/RIF test, Cepheid) that was positive for tuberculosis without rifampin resistance. Persons who had a grade 3+ sputum smear, a cavity measuring more than 4 cm on a chest radiograph, or a positive test for human immunodeficiency virus (HIV) antibodies were initially not eligible; these exclusion criteria were later removed. A complete list of eligibility criteria and details regarding the changes are provided in Section S1 in the Supplementary Appendix, available at NEJM.org.

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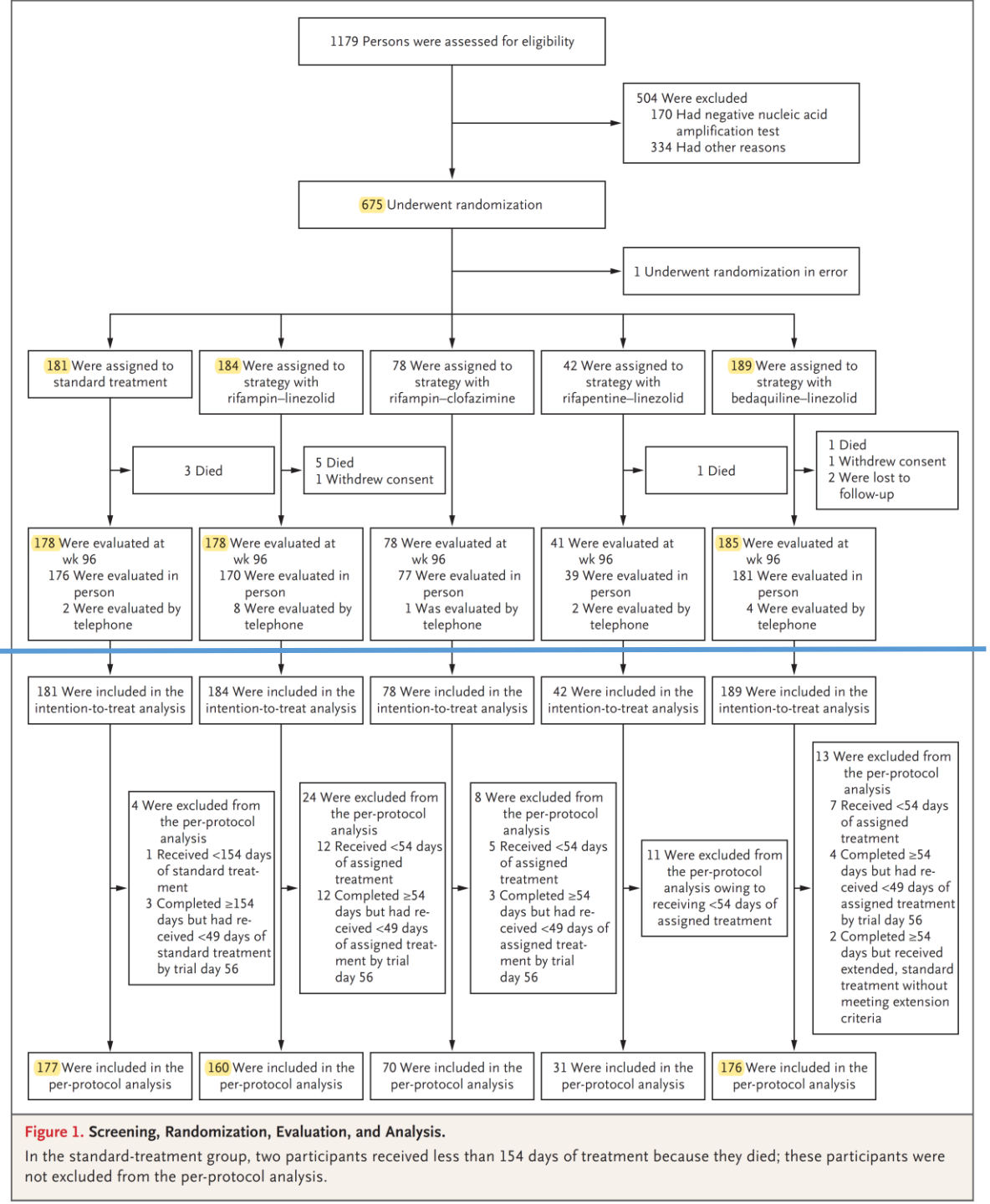

Figure 1. Screening, Randomization, Evaluation, and Analysis.

In the standard-treatment group, two participants received less than 154 days of treatment because they died; these participants were not excluded from the per-protocol analysis.

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TRUNCATE-TB: Trial Regimens (Rif sensitive TB, mild-moderate)

8w: ±Extension (to 12weeks) if persistent clinical disease (symptoms and + smear)

Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin * 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

* The high dose rifampin was 35 mg/kg initially and was reduced to 20 mg/kg on Nov 1, 2019 (one death drug-induced liver injury, G3/4 hepatobiliary events decreased from 6.8% to 2.1%).

The trial steering committee (not the DSMC) discontinued enrollment in two strategy groups to ensure that sample-size requirements could be met for the formal evaluation of noninferiority in the two remaining strategy groups. Pragmatic decision (pill burden, regulatory advice, and import license Restrictions)

N Paton. CROI 2023, #113. NEJM 2023; DOI:10.1056/NEJMoa2212537. ** W Burman. N Engl J Med 2023;388:2296-2298.

Study Primary Outcome: A composite outcome.

The primary outcome was a composite of death before week 96 or ongoing tuberculosis treatment or active tuberculosis at week 96. The primary outcome was assessed with a prespecified algorithm (Section S10). Because detection of and retreatment for relapse are an integral part of the treatment strategy that was assessed in this trial, these outcomes were not considered to be primary-outcome events if retreatment had been completed and the participant did not have active disease at week 96. Secondary outcomes in-

Composite Primary Outcome:

- **Death** before week 96
- **Ongoing TBC treatment** at week 96
- **Active TBC** at week 96

If assessment at week 8 was positive (symptoms and a positive sputum smear) participants continued treatment for another 4 weeks (total 12 weeks).

Those who remained positive at week 12 or relapsed were treated with a standard 24-week regimen (adjusted by susceptibility if needed)

Extension of therapy was therefore not a “failure” but was part of the treatment strategy.

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Why using composite endpoints as the primary study endpoint?

- Useful **when a single primary endpoint is uncommon** (low rate) or does not capture treatment efficacy.
- Most commonly used in "**strategy**" RCTs
- They **reduce sample size requirements**, **follow-up periods**, and **costs**.
- Individual components of the composite outcome **must be equally important to patients** and **with similar frequencies** (otherwise the most common of them will drag the overall endpoint)
- **Caution**: Incorrect interpretation of composite outcomes **can lead to misleading conclusions that impact patient care** (particularly when some of them are more frequent or more important than others).

D Baracaldo-Santamaria. J Clin Med. 2023 Jul; 12(13): 4371. LM Papileo. J Clin Epidemiol 128 (2020) 157e158

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

Characteristic	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Clofazimine (N=78)†	Strategy with Rifapentine–Linezolid (N=42)†	Strategy with Bedaquiline–Linezolid (N=189)	Overall (N=674)
Male sex — no. (%)	119 (66)	113 (61)	48 (62)	25 (60)	116 (61)	421 (62)
Age group — no. (%)						
18–34 yr	104 (57)	109 (59)	51 (65)	26 (62)	95 (50)	385 (57)
35–50 yr	59 (33)	57 (31)	21 (27)	11 (26)	70 (37)	218 (32)
51–65 yr	18 (10)	18 (10)	6 (8)	5 (12)	24 (13)	71 (11)
Country — no. (%)						
Indonesia	78 (43)	73 (40)	38 (49)	23 (55)	82 (43)	294 (44)
Philippines	61 (34)	66 (36)	32 (41)	15 (36)	63 (33)	237 (35)
Thailand	10 (6)	15 (8)	8 (10)	4 (10)	12 (6)	49 (7)
Uganda	28 (15)	25 (14)	0	0	27 (14)	80 (12)
India	4 (2)	5 (3)	0	0	5 (3)	14 (2)
Median body weight (range) — kg	50 (32–81)	50 (30–97)	48 (35–88)	50 (32–71)	50 (32–86)	50 (30–97)
Median body-mass index (range)‡	19 (14–29)	19 (14–33)	19 (14–29)	18 (12–25)	19 (13–30)	19 (12–33)
Body-mass index — no. (%)‡						
<17	39 (22)	42 (23)	21 (27)	13 (31)	47 (25)	162 (24)
17 to <18.5	40 (22)	38 (21)	14 (18)	9 (21)	29 (15)	130 (19)
≥18.5	102 (56)	104 (57)	43 (55)	20 (48)	113 (60)	382 (57)
Employment status — no. (%)						
Working full or part time	94 (52)	99 (54)	35 (45)	16 (38)	100 (53)	344 (51)
Student	10 (6)	15 (8)	10 (13)	10 (24)	15 (8)	60 (9)
Not working	77 (43)	70 (38)	33 (42)	16 (38)	74 (39)	270 (40)
Current smoker — no. (%)	34 (19)	33 (18)	15 (19)	8 (19)	31 (16)	121 (18)
Former smoker — no. (%)	58 (32)	63 (34)	24 (31)	13 (31)	51 (27)	209 (31)
Proportion of lung affected on chest radiograph — no. (%)						
<25%	46 (25)	62 (34)	28 (36)	12 (29)	53 (28)	201 (30)
25–50%	94 (52)	87 (47)	36 (46)	24 (57)	98 (52)	339 (50)
>50%	41 (23)	35 (19)	14 (18)	6 (14)	38 (20)	134 (20)
Cavitation on chest radiograph — no. (%)						
Absent	87 (48)	83 (45)	41 (53)	19 (45)	81 (43)	311 (46)
Largest cavity ≤4 cm	90 (50)	96 (52)	37 (47)	23 (55)	106 (56)	352 (52)
Largest cavity >4 cm	4 (2)	5 (3)	0	0	2 (1)	11 (2)
WHO smear grade — no./total no. (%)§						
Negative	46/180 (26)	57/184 (31)	26/78 (33)	12/41 (29)	50/189 (26)	191/672 (28)
Scanty	27/180 (15)	28/184 (15)	12/78 (15)	7/41 (17)	24/189 (13)	98/672 (15)
1+	38/180 (21)	48/184 (26)	25/78 (32)	13/41 (32)	53/189 (28)	177/672 (26)
2+	44/180 (24)	37/184 (20)	8/78 (10)	7/41 (17)	38/189 (20)	134/672 (20)
3+	25/180 (14)	14/184 (8)	7 /78 (9)	2/41 (5)	24/189 (13)	72/672 (11)
Bacillary burden on nucleic acid amplification test — no./total no. (%)¶						
Very low	25/173 (14)	22/172 (13)	8/74 (11)	3/37 (8)	16/184 (9)	74/642 (12)
Low	40/173 (23)	48/172 (28)	22/74 (30)	11/37 (30)	52/184 (28)	173/642 (27)
Medium	72/173 (42)	80/172 (47)	31/74 (42)	15/37 (41)	73/184 (40)	271/642 (42)
High	36/173 (21)	22/172 (13)	13/74 (18)	8/37 (22)	43/184 (23)	122/642 (19)
Positive sputum culture — no. (%)	166 (92)	168 (91)	68 (87)	39 (93)	171 (90)	612 (91)

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Characteristic	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Clofazimine (N=78)†	Strategy with Rifapentine–Linezolid (N=42)†	Strategy with Bedaquiline–Linezolid (N=189)	Overall (N=674)
Drug resistance — no./total no. (%)‖						
Isoniazid	12/162 (7)	15/166 (9)	5/68 (7)	2/39 (5)	12/169 (7)	46/604 (8)
Pyrazinamide	5/133 (4)	2/135 (1)	5/54 (9)	1/29 (3)	5/136 (4)	18/487 (4)
Ethambutol	1/162 (1)	0	2/68 (3)	0	2/169 (1)	5/604 (1)
Relapse risk — no. (%)**						
Low	47 (26)	57 (31)	26 (33)	13 (31)	50 (26)	193 (29)
Intermediate	105 (58)	111 (60)	45 (58)	27 (64)	113 (60)	401 (59)
High	29 (16)	16 (9)	7 (9)	2 (5)	26 (14)	80 (12)

** Low risk is defined as a negative smear and the absence of a cavity measuring more than 4 cm on a chest radiograph; intermediate risk as a positive smear of grade 2+ or lower and the absence of a cavity measuring more than 4 cm on a chest radiograph; and high risk as a positive smear of grade 3+, the presence of a cavity measuring more than 4 cm on a chest radiograph, or both. Relapse risk categories are based on the highest grade from all smear examinations performed and the largest cavity measurement on any chest radiograph obtained between screening and baseline. Two participants attempted but were unable to produce sputum at these study visits and were regarded as having a negative smear for the classification of relapse risk; neither of these participants had cavitation on a chest radiograph.

N Paton. NEJM 2023; DOI: 10.1056/NEJMoa2212537

Table 2. Primary Efficacy Outcome.*

Outcome	Standard Treatment (N = 181)	Strategy with Rifampin–Linezolid (N = 184)	Strategy with Rifampin–Linezolid vs. Standard Treatment	Strategy with Bedaquiline–Linezolid (N = 189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment
			Adjusted Difference (97.5% CI)†		Adjusted Difference (97.5% CI)†
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (–3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
No evaluation at wk 96 and insufficient evidence of disease clearance when last seen	0	1 (0.5)	—	1 (0.5)	—
Outcomes classified as unassessable — no. (%)	1 (0.6)	1 (0.5)	—	2 (1.1)	—
Single positive culture at wk 96 but no other evidence of active disease‖	0	1 (0.5)	—	0	—
Death from a cause that was definitively unrelated to tuberculosis**	1 (0.6)	0	—	0	—
No evaluation at wk 96 and sufficient evidence of disease clearance when last seen	0	0	—	2 (1.1)	—
No primary outcome or outcome classified as unassessable — no. (%)	173 (95.6)	162 (88.0)	—	176 (93.1)	—
Assessable population††					
Primary outcome — no./total no. (%)	7/180 (3.9)	21/183 (11.5)	7.5 (1.7 to 13.2)	11/187 (5.9)	0.8 (–3.4 to 5.1)
Per-protocol population‡‡					
Primary outcome — no./total no. (%)	6/177 (3.4)	17/160 (10.6)	6.9 (0.9 to 12.8)	9/176 (5.1)	0.9 (–3.3 to 5.1)

Noninferiority margin of 12 percentage points (upper limit of a 97.5% CI, ITT), with the assumption of complete enrollment in two strategy groups, and assuming that a primary-outcome event would occur in 10% of the participants in each trial group (recent trials have used a 6.6 margin for noninf)

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Sensitivity analysis,
Predefined subgroups

B Primary Outcome in Strategy Group with Initial Bedaquiline–Linezolid Regimen vs. Standard-Treatment Group

Subgroup	Strategy with Bedaquiline–Linezolid *no. of participants with event/total no. (%)*	Standard Treatment *no. of participants with event/total no. (%)*	Difference (95% CI) *percentage points*
Sex			
Male	5/116 (4.3)	5/119 (4.2)	0.1 (−4.4 to 4.6)
Female	6/73 (8.2)	2/62 (3.2)	3.6 (−3.9 to 11.2)
Age			
18–34 yr	4/95 (4.2)	5/104 (4.8)	−1.8 (−7.0 to 3.4)
35–65 yr	7/94 (7.4)	2/77 (2.6)	4.8 (−1.1 to 10.7)
Country			
Indonesia or Philippines	6/145 (4.1)	4/139 (2.9)	1.3 (−3.0 to 5.5)
Uganda	4/27 (14.8)	2/28 (7.1)	7.7 (−8.8 to 24.1)
India or Thailand	1/17 (5.9)	1/14 (7.1)	−1.3 (−18.8 to 16.3)
Education			
0–7 yr	3/48 (6.3)	4/49 (8.2)	−2.4 (−12.1 to 7.3)
≥8 yr	8/141 (5.7)	3/132 (2.3)	2.8 (−1.6 to 7.3)
Smoking status			
Never	8/107 (7.5)	2/89 (2.2)	3.7 (−2.2 to 9.5)
Current or former	3/82 (3.7)	5/92 (5.4)	−1.0 (−7.0 to 5.0)
Body-mass index			
<18.5	4/76 (5.3)	5/79 (6.3)	−1.3 (−8.5 to 6.0)
≥18.5	7/113 (6.2)	2/102 (2)	3.3 (−2.0 to 8.6)
Cavitation on chest radiograph			
Absent	5/81 (6.2)	1/87 (1.1)	3.4 (−2.4 to 9.2)
Present	6/108 (5.6)	6/94 (6.4)	−0.6 (−7.0 to 5.9)
Proportion of lung affected on chest radiograph			
≤50%	8/151 (5.3)	3/140 (2.1)	2.8 (−1.0 to 6.6)
>50%	3/38 (7.9)	4/41 (9.8)	−2.2 (−14.4 to 10.1)
WHO smear grade			
Negative	1/50 (2.0)	1/46 (2.2)	0.9 (−16.8 to 18.7)
Scanty or 1+	4/77 (5.2)	0/65	6.4 (−18.7 to 31.6)
2+ or 3+	6/62 (9.7)	5/69 (7.2)	2.0 (−9.8 to 13.8)
Grade on MRC breathlessness scale			
Grade 1	3/112 (2.7)	3/106 (2.8)	1.1 (−3.0 to 5.2)
Grade 2 or higher	8/77 (10.4)	4/75 (5.3)	3.5 (−5.0 to 11.9)
Relapse risk			
Low	1/50 (2.0)	2/47 (4.3)	−0.8 (−7.3 to 5.6)
Intermediate or high	10/139 (7.2)	5/134 (3.7)	2.6 (−2.6 to 7.8)

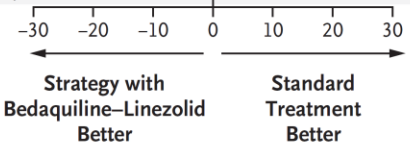

Figure 2. Subgroup Analysis.

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Table 3. Secondary Outcomes.*

Outcome	Standard Treatment (N = 181)	Strategy with Rifampin–Linezolid (N = 184)	Strategy with Rifampin–Linezolid vs. Standard Treatment Difference (95% CI)†	Strategy with Bedaquiline–Linezolid (N = 189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment Difference (95% CI)†
Participant-centered outcomes					
Total treatment time through wk 96 — days‡					
Total duration of treatment	180.2±37.9	105.7±80.1	−74.5 (−87.4 to −61.6)	84.8±65.3	−95.3 (−106.2 to −84.5)
Total qualifying treatment time	177.3±35.6	101.6±74.9	−75.7 (−87.7 to −−63.6)	83.8±64.2	−93.5 (−104.0 to −82.9)

S2 and S3). In the four strategy groups, 91.5% of the participants overall (range, 73.8 to 94.7) completed the initial 8-week treatment course and stopped (mean qualifying time of initial treatment, 58 days), 6.5% overall switched to standard treatment (mainly because of adverse events) and completed a 24-week course, and 17.0% overall (range, 12.7 to 22.8) underwent retreatment.

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The main strengths of this trial are the pragmatic design, the use of outcome measures that are relevant to persons with tuberculosis and to treatment programs, and the inclusion of diverse treatment clinics in high-burden countries, mainly in Asia. The open-label design is a limitation,

centered outcomes. The main secondary outcomes were total treatment time, grade 3 or 4 adverse events, and acquired drug resistance. Details re-

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Background

TRUNCATE-TB Trial

The TRUNCATE strategy:

- 8-week initial treatment (with extension to W12 for persistent clinical disease)
- Post-treatment monitoring, re-treatment of relapse with standard drugs for 6m

- Non-inferior to standard 6m Rx on clinical outcome at W96 (with initial 8-week BDQ-LZD)
- Safe – no excess severe/serious AEs, death, respiratory disability
- Reduced total time on treatment; increased adherence motivation
- **Main trial results published today*** Ongoing work needed to optimize initial treatment and monitoring strategy.

Aims of this analysis

- **To evaluate the efficacy and safety of the main 8-week regimens tested in the TRUNCATE-TB trial (as distinct from the strategy in which they were deployed)**
- **To examine whether can identify subgroups in which the 8-week regimens do less well / better**

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Analysis of regimen efficacy and safety

Efficacy

- Primary outcome: unfavourable outcome
  - **Rx failure, relapse, death by W96**; **not evaluated at W96 & no evidence of cure at last visit**
  - Censored (classified as "unassessable"): inad[illegible] from assigned regimen; missed 7 days by W8[illegible]e)
- Bayesian analysis*
  - Probability of difference in regimen unfavour[illegible]
  - Probability that regimen unfavourable outco[illegible]

Composite Primary Outcome:

- **Death** before week 96
- **Ongoing TBC treatment** at week 96
- **Active TBC** at week 96

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Safety

- Primary outcome: AEs ≥ Grade 3 during initial strict randomised Rx (+30 days)

TRUNCATE-TB: Outcomes: treatment failure, relapse or death w96 (vs death, ongoing treatment, or active disease at week 96, main analysis, non-inf proven BDQ/LZD)

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD	8 weeks BDQ/LZD	
		7.4 (1.7 to 13.2)	0.8 (-3.4 to 5.1)	
Unfavourable outcome – no (%)	7 (3.9%)	46 (25.0%)	26 (13.8%)	
Treatment failure at switch to standard Rx	0 (0.0)	0 (0.0)	1 (0.5)	
Treatment failure at end of treatment	0 (0.0)	0 (0.0)	1 (0.5)	
Confirmed relapse	4 (2.2)	39 (21.2)	20 (10.6)	12.2%
Un-confirmed relapse	0 (0.0)	0 (0.0)	3 (1.6)	
Death by W96, possible TB-related cause	2 (1.1)	5 (2.7)	0 (0.0)	
Did not attend W96, lacks cure at last attended visit	1 (0.6)	2 (1.1)	1 (0.5)	
Unassessable outcome	6 (3.3)	29 (15.8)	16 (8.5)	

SimpliciTB: 4BPaMZ did not meet non-inf vs standard 2RHZE/4RH in drug-sensitive TB: Faster time to culture negative, but high D/C due to toxicity.

M Cevik. CROI 2023; #109

N Paton. CROI 2023, #113

N Paton. CROI 2023, #113. NEJM 2023; DOI:10.1056/NEJMoa2212537

Unfavourable outcome: Bayesian analysis

	24 weeks Standard Rx (N=181)	8 weeks hRIF/LZD (N=184)	8 weeks BDQ/LZD (N=189)
Adjusted proportion (95% BCI)*	3.4% (1.3 to 6.3%)	23.7% (17.2 to 30.9%)	12.5% (7.9 to 18.1%)
Probability that proportion difference <12%*	-	0.01	0.85

Estimate using Bayesian model with flat (uninformative") prior; adjusted for country and baseline relapse risk
Following approach described by Laptook et al, JAMA 2017; DOI: 10.1001/jama.2017.14972

Caution when using composite endpoints as the primary study endpoint. Learnings:

- We must secure that individual components of the composite endpoint **will effectively capture what happens in the trial.**
- Individual components of the composite outcome **must be equally important to patients** and **with similar frequencies** (otherwise the most common will drag the overall endpoint)
- **Caution**: Incorrect interpretation of composite outcomes **can lead to misleading conclusions that impact patient care** (particularly when some are more frequent or more important than others).
- This case exemplifies **that using different composite endpoints in the same RCT lead to different (contradictory) conclusions**.

Composite Primary Outcome:
- Death before week 96
- Ongoing TBC Tx week 96
- Active TBC at week 96

$\neq$

Composite Primary Outcome:
- **Treatment failure**
- **Relapse**
- Death before week 96