Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL):

an open-label, randomized controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial

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Introduction

Each year, around 500 000 people worldwide develop rifampicin-resistant tuberculosis, defined as tuberculosis disease that is resistant to at least rifampicin.

Until 2020, treatment was 9–20 months in duration, had considerable toxicity, and was of inadequate effectiveness.

In 2022, successful outcomes were reported for only 60% of patients who started treatment for rifampicin-resistant tuberculosis.

Introduction

The TB-PRACTECAL trial was designed to examine if combinations of new and repurposed antitubercular drugs could provide effective 24-week treatment regimens for rifampicin-resistant tuberculosis that were at least non-inferior to standard care.

Previous TB-PRACTECAL trial: stage 1

Patient with rifampicin-resistant, randomly assigned in a 1:1:1:1 ratio, stratified by site

Standard care group	BPaL group	BPaLM group	BPaLC group
	• Bedaquiline • Linezolid • Pretomanid	• Bedaquiline • Linezolid • Pretomanid • Moxifloxacin	• Bedaquiline • Linezolid • Pretomanid • Clofazimine

36-80 week

24-week

Previous TB-PRACTECAL trial: stage 1

The BPaLM group was chosen on the basis of

- Higher culture-conversion rates at 8 weeks (BPaLM 77%, BPaLC 67%, and BPaL 46%)
- Lower regimen cost (the prices of clofazimine are higher than those of moxifloxacin)

TB-PRACTECAL trial: stage 2 (24-108 week)

Standard care group

BPaLM group

- Bedaquiline
- Linezolid
- Pretomanid
- Moxifloxacin

24 - 108 week

- Efficacy and safety monitoring was conducted at least every 8 weeks for the subsequent 84 weeks.

Primary outcome

- Unfavourable status at 72 weeks.

composite of
- ❑ death
- ❑ treatment failure
- ❑ treatment discontinuation
- ❑ recurrence of tuberculosis
- ❑ loss to follow-up

Secondary efficacy outcomes

- Unfavourable outcomes at 24 weeks

composite of
- ❑ death
- ❑ treatment failure
- ❑ treatment discontinuation

- Unfavourable outcomes at 108 weeks

composite of
- ❑ death
- ❑ treatment failure
- ❑ treatment discontinuation
- ❑ recurrence of tuberculosis
- ❑ loss to follow-up
- ❑ still receiving treatment at 108 weeks

Safety outcomes

composite of
- ❑ adverse events of grade 3 or higher
- ❑ serious adverse events

- at week 72 and 108.

Prolongation of the QTcF interval

- At week 24.

Post-hoc analyses

BPaL group
- Bedaquiline
- Linezolid
- Pretomanid

BPaLC group
- Bedaquiline
- Linezolid
- Pretomanid
- Clofazimine

Standard care group

- at week 24, 48, 72 and 108.

Statistical analysis

Sample size calculation based on

- A non-inferiority comparison for a composite unfavourable outcome at 108 weeks
  - assumed to be 50% in the standard care group
  - 45% in the investigational groups)
- A non-inferiority margin of 12%
- A power of 85%
- a one-sided type I error of 1.7% was assumed

➢181 participants per group would be required.

Statistical analysis

Non-inferiority margin

- Noninferiority margin of 12 percentage points

- This noninferiority margin was congruent with that in recent trials involving patients with drug-resistant tuberculosis in which the noninferiority margin was 10 to 12 percentage points

Statistical analysis

- Intention-to-treat population
  - all randomly assigned participants who were dispensed study medication on at least one occasion.

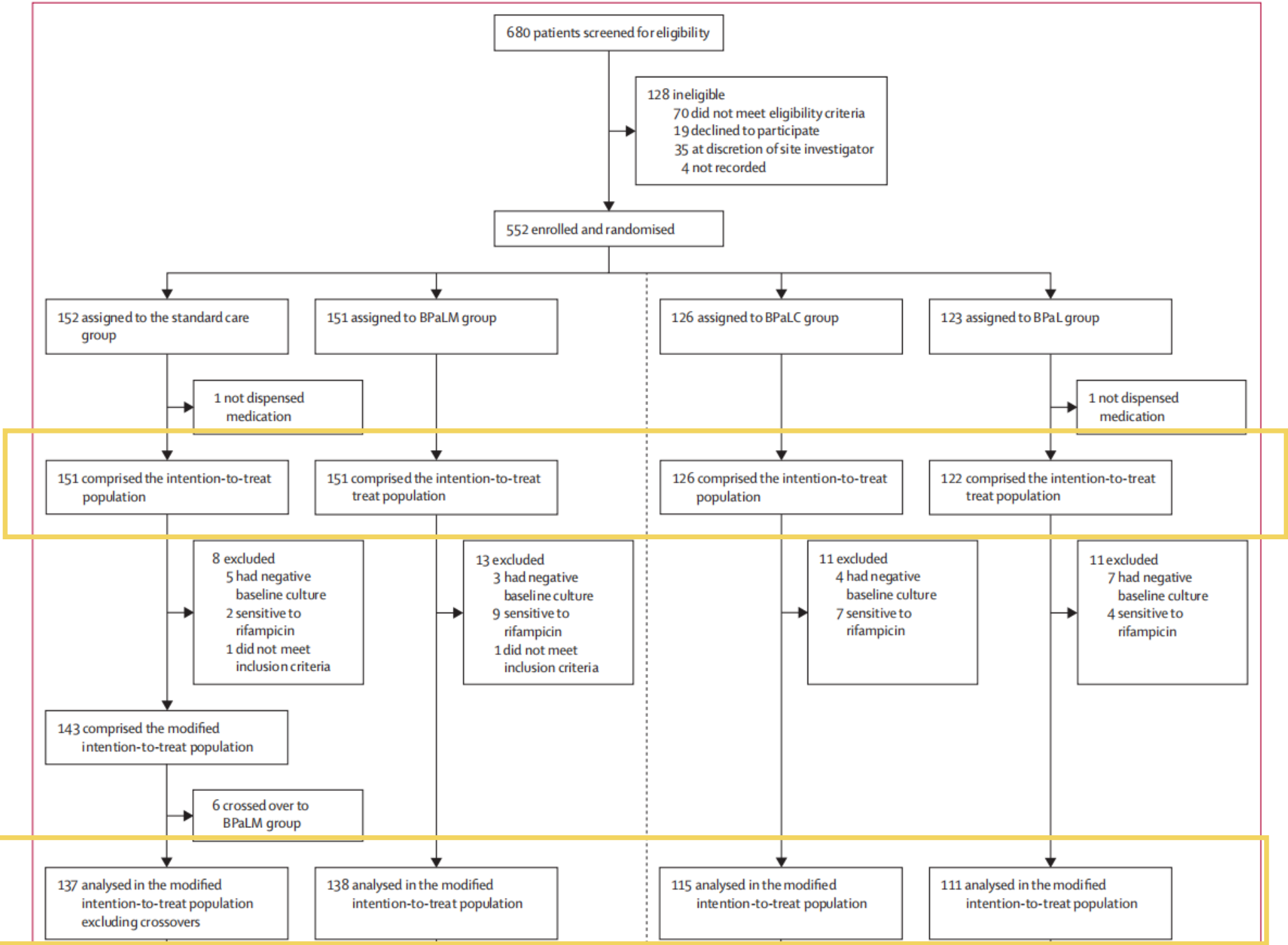
- Modified intention-to-treat population
  - all randomly assigned participants who were dispensed study medication on at least one occasion.
  - had evidence of resistance to at least rifampicin by culture.

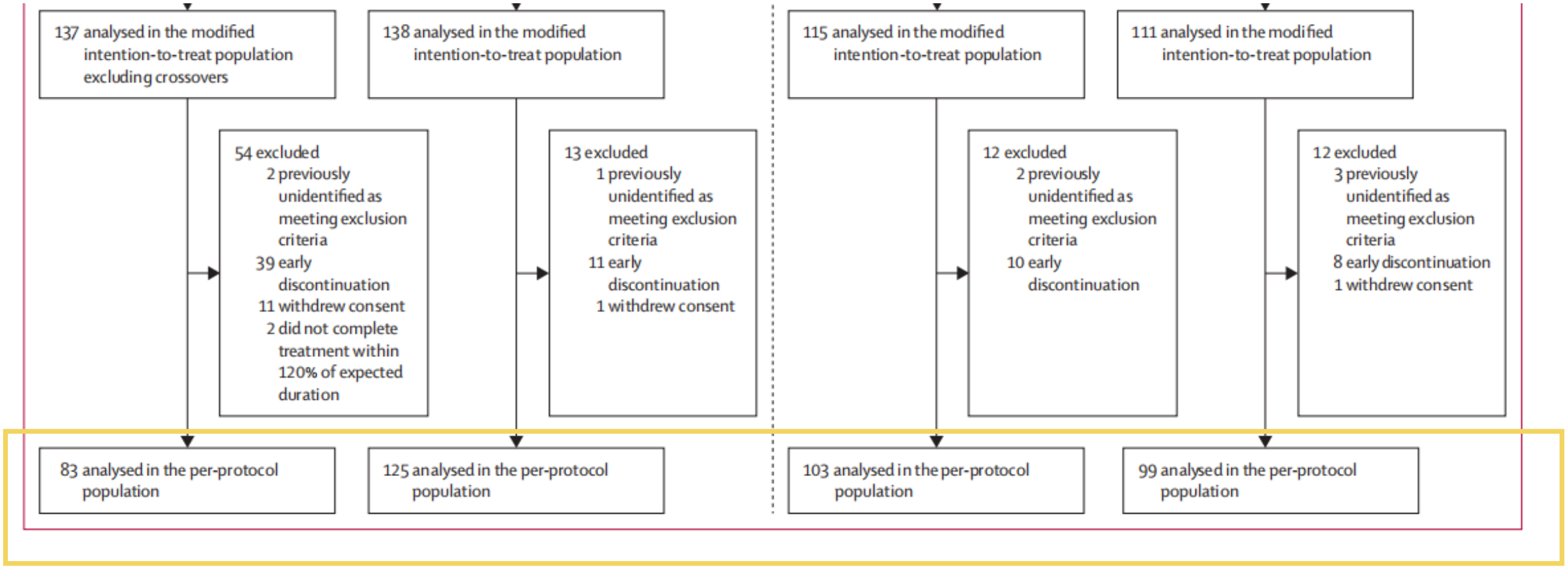
Statistical analysis

- Per-protocol population

(subset of the modified intention-to-treat population)

  - excluded participants who did not complete a protocol-adherent course of treatment (other than because of treatment failure or death).
  - participants who discontinued treatment early because they violated at least one of the inclusion or exclusion criteria.


680 patients screened for eligibility
128 ineligible
70 did not meet eligibility criteria
19 declined to participate
35 at discretion of site investigator
4 not recorded
552 enrolled and randomised
152 assigned to the standard care group
151 assigned to BPaLM group
126 assigned to BPaLC group
123 assigned to BPaL group
1 not dispensed medication
1 not dispensed medication
151 comprised the intention-to-treat population
151 comprised the intention-to-treat treat population
126 comprised the intention-to-treat population
122 comprised the intention-to-treat treat population
8 excluded
5 had negative baseline culture
2 sensitive to rifampicin
1 did not meet inclusion criteria
13 excluded
3 had negative baseline culture
9 sensitive to rifampicin
1 did not meet inclusion criteria
11 excluded
4 had negative baseline culture
7 sensitive to rifampicin
11 excluded
7 had negative baseline culture
4 sensitive to rifampicin
143 comprised the modified intention-to-treat population
6 crossed over to BPaLM group
137 analysed in the modified intention-to-treat population excluding crossovers
138 analysed in the modified intention-to-treat population
115 analysed in the modified intention-to-treat population
111 analysed in the modified intention-to-treat population


137 analysed in the modified intention-to-treat population excluding crossovers
138 analysed in the modified intention-to-treat population
115 analysed in the modified intention-to-treat population
111 analysed in the modified intention-to-treat population
54 excluded
2 previously unidentified as meeting exclusion criteria
39 early discontinuation
11 withdrew consent
2 did not complete treatment within 120% of expected duration
13 excluded
1 previously unidentified as meeting exclusion criteria
11 early discontinuation
1 withdrew consent
12 excluded
2 previously unidentified as meeting exclusion criteria
10 early discontinuation
12 excluded
3 previously unidentified as meeting exclusion criteria
8 early discontinuation
1 withdrew consent
83 analysed in the per-protocol population
125 analysed in the per-protocol population
103 analysed in the per-protocol population
99 analysed in the per-protocol population

- 302 participants in intention-to-treat population (and the safety population)
  - 151 in the standard care group
  - 151 in the BPaLM group
- 275 participants in the modified intention-to-treat population
  - 137 in the standard care group
  - 138 in the BPaLM group
- 208 were included in the per-protocol population
  - 83 in the standard care group
  - 125 in the BPaLM group

- 6 participants in the standard care group switched to the BPaLM group after enrolment was terminated, and these participants were not included in the primary analysis.

Statistical analysis

- The primary efficacy and safety comparisons assumed a two-sided 96·6% CI for investigational groups assessed in stage two.

- For binary outcomes report the absolute difference in the percentages of participants experiencing the outcome using a generalised linear model for a binomial outcome with an identity link function.

- All secondary efficacy outcomes were reported with corresponding two-sided 95% CIs.

Results

	Standard care (n=143)	BPaLM (n=138)	BPaLC (n=115)	BPaL (n=111)
Country of enrolment				
Belarus	29 (21%)	26 (19%)	19 (17%)	20 (18%)
South Africa	49 (34%)	49 (36%)	43 (37%)	41 (37%)
Uzbekistan	65 (46%)	63 (46%)	53 (46%)	50 (45%)
Age, years	37 (30–46)	35 (27–45)	32 (25–40)	34 (27–44)
Sex				
Female	54 (38%)	61 (44%)	39 (34%)	54 (49%)
Male	89 (62%)	77 (56%)	76 (66%)	57 (51%)
BMI, kg/m²	19·9 (17·5–22·8)	19·7 (17·7–22·7)	19·4 (17·6–22·1)	20·0 (18·1–22·5)

Results

HIV status				
HIV negative	104 (73%)	104 (75%)	84 (73%)	75 (68%)
HIV-positive	39 (27%)	34 (25%)	31 (27%)	36 (32%)
CD4 count, cells per µL	250 (143–445)	330 (223–547)	297 (115–511)	383 (161–550)
CD4 count missing	2 (5%)	2 (6%)	1 (3%)	1 (3%)
Sputum smear				
Smear-positive	94 (66%)	86 (62%)	79 (69%)	73 (66%)
Smear-negative	49 (34%)	52 (38%)	36 (31%)	38 (34%)
Pulmonary cavities				
Present	90 (63%)	76 (55%)	74 (64%)	68 (61%)
Absent	53 (37%)	62 (45%)	41 (36%)	43 (39%)
Fluoroquinolone sensitivity status				
Resistant	32 (22%)	32 (23%)	22 (19%)	25 (23%)
Sensitive	95 (66%)	92 (67%)	87 (76%)	73 (66%)
Resistance status missing	16 (12%)	14 (10%)	6 (5%)	13 (12%)
Bedaquiline sensitivity status				
Resistant	1 (1%)	1 (1%)	2 (2%)	1 (1%)
Sensitive	124 (87%)	116 (84%)	104 (90%)	93 (84%)
Resistance status missing	18 (13%)	21 (15%)	9 (8%)	17 (15%)
QTcF interval, ms	400 (19)	399 (19)	395 (18)	399 (19)
Alanine aminotransferase concentration (IU/L)	20 (15–28)	19 (14–28)	17 (14–26)	19 (14–29)
Data missing	2 (1%)	1 (1%)	1 (1%)	0
Liquid culture at baseline				
Positive	127 (89%)	120 (87%)	107 (93%)	96 (86%)
Negative	17 (12%)	18 (13%)	8 (7%)	15 (14%)
Previous treatment for multidrug-resistant tuberculosis	13 (9%)	18 (13%)	12 (10%)	16 (14%)

Data are n (%), median (IQR), or mean (SD) unless otherwise stated. Percentages may not total 100% owing to rounding. BPaL=bedaquiline, linezolid, and pretomanid. BPaLC=BPaL plus clofazimine. BPaLM=BPaL plus moxifloxacin. IU=international units. QTcF=Fridericia-corrected QT.

Table 1: **Baseline characteristics of the modified intention-to-treat population, including crossover participants**

Results

At 72 weeks

Modified ITT

Non-inferiority margin = 12%

Unadjusted risk difference= BPaLM – Standard care

	Modified intention-to-treat population				Per-protocol population (primary analysis)	
	Primary analysis		Post-hoc analysis			
	Standard care	BPaLM	BPaLC	BPaL	Standard care	BPaLM
Number of participants	137	138	115	111	83	125
Number with no unfavourable outcome	81 (59%)	121 (88%)	88 (77%)	96 (86%)	77 (93%)	120 (96%)
Number with an unfavourable outcome	56 (41%)	16 (12%)	27 (23%)	15 (14%)	6 (7%)	5 (4%)
Number non-assessable	0	1 (1%)	0	0	0	0
Unadjusted risk difference*	..	−29·2% (−39·8% to −18·6%)	−17·4% (−28·7% to −6·1%)	−27·4% (−37·8% to −17·0%)	..	−3·2% (−10·3% to 3·9%)
Non-inferiority p value (margin 12%)	..	<0·0001	<0·0001	<0·0001	..	<0·0001
Superiority p value	..	<0·0001	0·0026	<0·0001	..	0·24
Unadjusted risk ratio*	..	0·29 (0·17 to 0·49)	0·57 (0·39 to 0·85)	0·33 (0·20 to 0·55)	..	0·55 (0·16 to 1·93)
Deaths	5 (4%)	0	1 (1%)	1 (1%)	5 (6%)	0
Early discontinuation	50 (37%)	11 (8%)	11 (10%)	11 (10%)	0	0
Adherence issues	11 (8%)	1 (1%)	4 (3%)	3 (3%)	..	..
Adverse event	23 (17%)	7 (5%)	6 (5%)	5 (5%)	..	..
Not meeting inclusion or meeting exclusion criteria†	2 (1%)	1 (1%)	1 (1%)	2 (2%)	..	..
Withdrew consent during treatment	11 (8%)	1 (1%)	0	1 (1%)	..	..
Other	3 (2%)	1 (1%)	0	0	..	..
Treatment failure	0	0	1 (1%)	0	0	0
Lost to follow-up at 72 weeks	1 (1%)	4 (3%)	9 (8%)	0	1 (1%)	4 (3%)
Lost to follow-up	1 (1%)	1 (1%)	6 (5%)	0	1 (1%)	1 (1%)
Withdrew consent	0	3 (2%)	3 (3%)	0	0	3 (2%)
Disease recurrence	0	1 (1%)	5 (4%)	3 (3%)	0	1 (1%)

Results

- The main reason for meeting the unfavourable outcome definition was early discontinuation
  - 50 [89%] of 56 participants with unfavourable outcomes in the standard care group
  - 11 [69%] of 16 in the BPaLM group
- which was mainly attributed to adverse events
  - 23 [46%] in the standard-care group
  - 7 [64%] in the BPaLM group

Results

At 72 weeks

Per-protocol

Non-inferiority margin = 12%

Unadjusted risk difference= BPaLM – Standard care

	Modified intention-to-treat population				Per-protocol population (primary analysis)	
	Primary analysis		Post-hoc analysis			
	Standard care	BPaLM	BPaLC	BPaL	Standard care	BPaLM
Number of participants	137	138	115	111	83	125
Number with no unfavourable outcome	81 (59%)	121 (88%)	88 (77%)	96 (86%)	77 (93%)	120 (96%)
Number with an unfavourable outcome	56 (41%)	16 (12%)	27 (23%)	15 (14%)	6 (7%)	5 (4%)
Number non-assessable	0	1 (1%)	0	0	0	0
Unadjusted risk difference*	..	−29·2% (−39·8% to −18·6%)	−17·4% (−28·7% to −6·1%)	−27·4% (−37·8% to −17·0%)	..	−3·2% (−10·3% to 3·9%)
Non-inferiority p value (margin 12%)	..	<0·0001	<0·0001	<0·0001	..	<0·0001
Superiority p value	..	<0·0001	0·0026	<0·0001	..	0·24
Unadjusted risk ratio*	..	0·29 (0·17 to 0·49)	0·57 (0·39 to 0·85)	0·33 (0·20 to 0·55)	..	0·55 (0·16 to 1·93)
Deaths	5 (4%)	0	1 (1%)	1 (1%)	5 (6%)	0
Early discontinuation	50 (37%)	11 (8%)	11 (10%)	11 (10%)	0	0
Adherence issues	11 (8%)	1 (1%)	4 (3%)	3 (3%)	..	..
Adverse event	23 (17%)	7 (5%)	6 (5%)	5 (5%)	..	..
Not meeting inclusion or meeting exclusion criteria†	2 (1%)	1 (1%)	1 (1%)	2 (2%)	..	..
Withdrew consent during treatment	11 (8%)	1 (1%)	0	1 (1%)	..	..
Other	3 (2%)	1 (1%)	0	0	..	..
Treatment failure	0	0	1 (1%)	0	0	0
Lost to follow-up at 72 weeks	1 (1%)	4 (3%)	9 (8%)	0	1 (1%)	4 (3%)
Lost to follow-up	1 (1%)	1 (1%)	6 (5%)	0	1 (1%)	1 (1%)
Withdrew consent	0	3 (2%)	3 (3%)	0	0	3 (2%)
Disease recurrence	0	1 (1%)	5 (4%)	3 (3%)	0	1 (1%)

Results

- The difference in the risk of an unfavourable outcome between BPaLM and standard care may varied depending on country of enrolment or HIV status.

Results

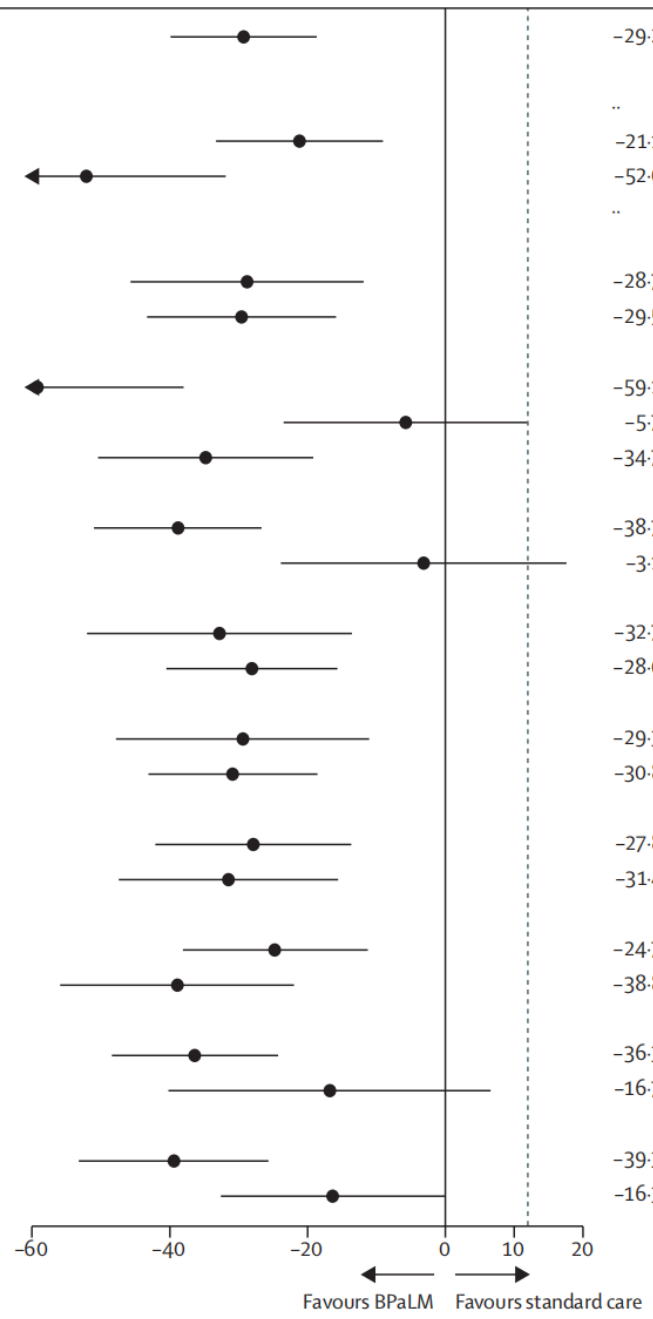
Risk difference in the **prespecified subgroup analyses**

- standard care - BPaLM
- at week 72
- modified intention-to-treat population

Almost all participants who were HIV-positive were enrolled in South Africa (127 [91%] of 139)

C

	Standard care n/N (%)	BPaLM n/N (%)	Risk difference (two-sided 96·6% CI)	$p_{interaction}$
Primary outcome	56/137 (41%)	16/137 (12%)	−29·2% (−39·8 to −18·6)	
Age (years)				
<18	0/0	0/1	..	
18 to <45	33/100 (33%)	12/101 (12%)	−21·1% (−33·2 to −9·0)	
45 to <65	22/36 (61%)	3/33 (9%)	−52·0% (−72·3 to −31·8)	
≥65	1/1 (100%)	1/2 (50%)	..	NA
Sex				
Female	21/52 (40%)	7/60 (12%)	−28·7% (−45·6 to −11·8)	
Male	35/85 (41%)	9/77 (12%)	−29·5% (−43·2 to −15·8)	0·94
Country				
Belarus	17/27 (63%)	1/26 (4%)	−59·1% (−80·4 to −37·9)	
South Africa	12/49 (24%)	9/48 (19%)	−5·7% (−23·4 to 11·9)	
Uzbekistan	27/61 (44%)	6/63 (10%)	−34·7% (−50·3 to −19·1)	0·0002
HIV status				
Negative	47/99 (47%)	9/103 (9%)	−38·7% (−50·9 to −26·6)	
Positive	9/38 (24%)	7/34 (21%)	−3·1% (−23·8 to 17·6)	0·0017
Sputum smear				
Negative	23/46 (50%)	9/52 (17%)	−32·7% (−51·9 to −13·5)	
Positive	33/91 (36%)	7/85 (8%)	−28·0% (−40·4 to −15·6)	0·67
Tuberculosis cavities				
Absent	25/51 (49%)	12/61 (20%)	−29·3% (−47·7 to −11·0)	
Present	31/86 (36%)	4/76 (5%)	−30·8% (−43·0 to −18·5)	0·89
Previous tuberculosis treatment				
No	32/78 (41%)	11/83 (13%)	−27·8% (−42·0 to −13·6)	
Yes	24/59 (41%)	5/54 (9%)	−31·4% (−47·3 to −15·5)	0·72
Smoking status				
Not currently smoking	36/91 (40%)	14/94 (15%)	−24·7% (−38·0 to −11·2)	
Currently smoking	20/46 (43%)	2/43 (5%)	−38·8% (−55·8 to −21·9)	0·16
Fluoroquinolone resistance status				
Sensitive	38/91 (42%)	5/91 (5%)	−36·3% (−48·3 to −24·2)	
Resistant	11/31 (35%)	6/32 (19%)	−16·7% (−40·1 to 6·6)	0·12
Enrolment relative to COVID-19 pandemic				
Pre-COVID-19 pandemic	37/78 (47%)	6/74 (8%)	−39·3% (−53·1 to −25·6)	
Post-COVID-19 pandemic	19/59 (32%)	10/63 (16%)	−16·3% (−32·5 to 0·0)	0·022



Results

Modified ITT

Safety outcome

	Standard care (n=151)	BPaLM (n=151)	BPaLC (n=126)	BPaL (n=122)
QTcF interval at 24 weeks				
Number with QTcF interval measured	96	128	101	99
Mean QTcF interval, ms	440·9	425·1	436·3	421·8
Mean difference *vs* standard care, ms*	..	−17·5 (−22·0 to −12·9)	−4·4 (−8·8 to −0·1)	−21·1 (−25·6 to −16·6)
Grade ≥3 adverse effects or serious adverse effects during or within 30 days after treatment				
Participants with at least one event	71 (47%)	26 (17%)	31 (25%)	26 (21%)
Number of events	118	40	42	33
Serious†	46	10	16	12
Grade ≥3†	107	39	41	29
Risk difference *vs* standard care, percentage points‡	..	−29·8 (−40·6 to −19·0)	−22·4 (−33·4 to −11·5)	−25·7 (−36·5 to −14·9)
Grade ≥3 adverse effects or serious adverse effects within 108 weeks				
Participants with at least one event	75 (50%)	35 (23%)	40 (32%)	30 (25%)
Number of events	127	58	54	51
Serious†	53	13	26	22
Grade ≥3†	116	56	52	47
Risk difference *vs* standard care, percentage points‡	..	−26·5 (−37·8 to −15·2)	−17·9 (−29·3 to −6·5)	−25·1 (−36·1 to −14·0)
Grade ≥3 adverse effects or serious adverse effects within 72 weeks				
Participants with at least one event	72 (48%)	34 (23%)	38 (30%)	29 (24%)
Number of events	121	53	52	45
Serious†	48	13	24	20
Grade ≥3†	110	51	50	41
Risk difference *vs* standard care, percentage points‡	..	−25·2 (−36·4 to −13·9)	−17·5 (−28·8 to −6·2)	−23·9 (−34·9 to −12·9)

Data are n, n (%), mean, mean difference (CI), or risk difference (CI). CIs are 96·6% for BPaLM *vs* standard care comparisons and 95% for BPaLC *vs* standard care and BPaL *vs* standard care comparisons. BPaL=bedaquiline, linezolid, and pretomanid. BPaLC=BPaL plus clofazimine. BPaLM=BPaL plus moxifloxacin. QTcF=Fridericia-corrected QT.
*Adjusted for site and baseline QTcF interval. †Not mutually exclusive. ‡Unadjusted for site.

***Table 3*: Safety outcomes in the safety population**

Results

- 9 participants died by week 108
  - 6 (4%) in the standard care group
  - 0 in the BPaLM group
  - 1 (1%) in the BPaLC group
    - chronic obstructive pulmonary disease; unrelated to treatment
  - 2 (2%) in the BPaL group
    - seizure (unrelated to treatment)
    - lower respiratory tract infection (unrelated to treatment)

Limitations

- Many participants receiving an outdated standard of care that is no longer recommended.

- The WHO consolidated guidelines on drug-resistant tuberculosis treatment were revised in March, 2019, and subsequent participants received standard of care in line with these guidelines.

Limitations

- This change to the standard of care is reflected in the updated analysis, in which
  - the majority (95 [69%] of 137) of participants received the then-current standard of care.
  - A sensitivity analysis showed the effect estimate remained at −19·1% (−31·9% to −6·3%) when participants recruited before the 2019 WHO drug-resistant tuberculosis guidelines were implemented were excluded.

- The heterogeneity in standard of care could have influenced the interaction analysis by country and HIV status.

Limitations

- The sponsor, participants, and investigators were made aware that the trial was stopped for efficacy, which could have introduced bias.
- Six participants who crossed over from the standard care group to the BPaLM group were excluded from the modified intention-to-treat population.
- Three grade 3 adverse events occurred in this group of six participants after switching to BPaLM.
- Outcome adjudication was conducted by unmasked investigators, which could also have introduced bias.

Thank you for your attention