Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial

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Summary

Background Around 500 000 people worldwide develop rifampicin-resistant tuberculosis each year. The proportion of successful treatment outcomes remains low and new treatments are needed. Following an interim analysis, we report the final safety and efficacy outcomes of the TB-PRACTECAL trial, evaluating the safety and efficacy of oral regimens for the treatment of rifampicin-resistant tuberculosis.

Methods This open-label, randomised, controlled, multi-arm, multicentre, non-inferiority trial was conducted at seven hospital and community sites in Uzbekistan, Belarus, and South Africa, and enrolled participants aged 15 years and older with pulmonary rifampicin-resistant tuberculosis. Participants were randomly assigned, in a 1:1:1:1 ratio using variable block randomisation and stratified by trial site, to receive 36–80 week standard care; 24-week oral bedaquiline, pretomanid, and linezolid (BPaL); BPaL plus clofazimine (BPaLC); or BPaL plus moxifloxacin (BPaLM) in stage one of the trial, and in a 1:1 ratio to receive standard care or BPaLM in stage two of the trial, the results of which are described here. Laboratory staff and trial sponsors were masked to group assignment and outcomes were assessed by unmasked investigators. The primary outcome was the percentage of participants with a composite unfavourable outcome (treatment failure, death, treatment discontinuation, disease recurrence, or loss to follow-up) at 72 weeks after randomisation in the modified intention-to-treat population (all participants with rifampicin-resistant disease who received at least one dose of study medication) and the per-protocol population (a subset of the modified intention-to-treat population excluding participants who did not complete a protocol-adherent course of treatment (other than because of treatment failure or death) and those who discontinued treatment early because they violated at least one of the inclusion or exclusion criteria). Safety was measured in the safety population. The non-inferiority margin was 12%. This trial is registered with ClinicalTrials.gov, NCT02589782, and is complete.

Findings Between Jan 16, 2017, and March 18, 2021, 680 patients were screened for eligibility, of whom 552 were enrolled and randomly assigned (152 to the standard care group, 151 to the BPaLM group, 126 to the BPaLC group, and 123 to the BPaL group). The standard care and BPaLM groups proceeded to stage two and are reported here, post-hoc analyses of the BPaLC and BPaL groups are also reported. 151 participants in the BPaLM group and 151 in the standard care group were included in the safety population, with 138 in the BPaLM group and 137 in the standard care group in the modified intention-to-treat population. In the modified intention-to-treat population, unfavourable outcomes were reported in 16 (12%) of 137 participants for whom outcome was assessable in the BPaLM group and 56 (41%) of 137 participants in the standard care group (risk difference –29·2 percentage points [96·6% CI –39·8 to –18·6]; non-inferiority and superiority p<0·0001). 34 (23%) of 151 participants receiving BPaLM had adverse events of grade 3 or higher or serious adverse events, compared with 72 (48%) of 151 participants receiving standard care (risk difference –25·2 percentage points [96·6% CI –36·4 to –13·9]). Five deaths were reported in the standard care group by week 72, of which one (COVID-19 pneumonia) was unrelated to treatment and four (acute pancreatitis, suicide, sudden death, and sudden cardiac death) were judged to be treatment-related.

Interpretation The 24-week, all-oral BPaLM regimen is safe and efficacious for the treatment of pulmonary rifampicin-resistant tuberculosis, and was added to the WHO guidance for treatment of this condition in 2022. These findings will be key to BPaLM becoming the preferred regimen for adolescents and adults with pulmonary rifampicin-resistant tuberculosis.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 2006, and Jan 16, 2017, using the search terms "bedaquiline" AND "pretomanid" AND "linezolid". We found nine articles, none of which reported treatment outcomes of regimens comprising bedaquiline, pretomanid, and linezolid. One was excluded as no abstract was available; three reported on preclinical studies, none of which reported on the bedaquiline, pretomanid, and linezolid (BPaL) regimen. Five were reviews of new anti-tuberculosis drugs and the design of planned and ongoing tuberculosis studies, only one of which referred to the design of a BPaL regimen study (NiX-TB); the others described studies of the pretomanid, moxifloxacin, and pyrazinamide regimen. To our knowledge, TB-PRACTECAL is the first randomised controlled trial of 24-week regimens containing bedaquiline, pretomanid, and linezolid (BPaL), BPaL plus clofazimine (BPaLC), and BPaL plus moxifloxacin (BPaLM) for the treatment of rifampicin-resistant tuberculosis. At the time of protocol finalisation in June, 2016, only varying results regarding the clinical safety and efficacy of the component drugs had been published. Personal correspondence (Spigelman M, Global Alliance for TB Drug Development, New York, NY, USA) was available on the preliminary outcomes of the NiX-TB study, which was later published in 2020, showing that treatment with BPaL for 6–9 months led to favourable outcomes in 90% of participants with highly drug-resistant forms of tuberculosis. In 2022, the interim analysis of the TB-PRACTECAL study was published, showing fewer unfavourable outcomes in the BPaLM group than in the standard care group (risk difference −37·2 percentage points [96·6% CI −52·8 to −21·6]). The analysable modified intention-to-treat populations in the interim analysis comprised 66 patients in the standard of care group and 62 patients in the BPaLM group.

Added value of this study

This final analysis of the TB-PRACTECAL trial substantiates, with improved precision, the non-inferiority of the BPaLM regimen when compared with the standard of care. The majority of participants (95 [69%] of 137) included in the control group of this final analysis received an improved standard treatment, in line with 2019 WHO recommendations, and the modified intention-to-treat populations were larger than those in the interim analysis, comprising 137 participants in the standard care group and 138 participants in the BPaLM group.

Implications of all the available evidence

These data add strength to the WHO recommendation to include BPaLM as a preferred regimen for treatment of adolescents and adults with pulmonary rifampicin-resistant tuberculosis. The duration of treatment is now in line with that of most regimens for the treatment of drug-sensitive tuberculosis.

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.[1]

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.

In a multi-arm, multistage trial, three candidate regimens were considered, containing bedaquiline, linezolid, and pretomanid (BPaL) with and without the addition of either moxifloxacin (BPaLM) or clofazimine (BPaLC).[2] After a planned first-stage analysis, the BPaLM group was the most promising based on phase 2B efficacy and safety findings.[3]

In 2022, after early termination of the trial for efficacy, WHO convened a guideline development group to consider the interim data. The interim analysis of data collected up to early termination showed that BPaLM was superior to standard care.[3,4] On this basis, the guidance development group concluded that a BPaLM regimen for 6 months should be the preferred regimen for the treatment of rifampicin-resistant tuberculosis without additional resistance to fluoroquinolones, and the BPaL regimen[5] was recommended for rifampicin-resistant tuberculosis with additional resistance to fluoroquinolones.

After the termination of recruitment on March 18, 2021, participants were followed up for at least 72 weeks from randomisation. Here we present the final analysis of the TB-PRACTECAL trial, evaluating the safety and efficacy of the 24-week BPaLM regimen compared with standard care.

Methods

Study design

We conducted an open-label, randomised, controlled, multi-arm, multicentre, non-inferiority trial at seven hospital and community sites in Uzbekistan, Belarus, and South Africa. The trial was designed to transition from a phase 2B (stage one) to a phase 3 (stage two) trial with up to two investigational groups. Recruitment to all four groups continued throughout the transition period provided that the data safety monitoring board had no concerns. The scientific advisory committee was provided masked efficacy and safety data at the end of stage one and, on this basis, recommended which investigational groups should progress to stage two for phase 3

evaluation (appendix p 5). Details of the protocol and trial conduct have been previously published.[2]

Ethics approval was obtained from two central institutional ethics boards (London School of Hygiene & Tropical Medicine Research Ethics Committee and Médecins Sans Frontières Ethics Review Board) as well as local ethics committees and national regulatory authorities in Belarus, South Africa, and Uzbekistan.

Participants

Investigators were notified by laboratory staff of new patients with microbiologically diagnosed rifampicin-resistant tuberculosis from within the catchment areas of the trial sites. Patients aged 15 years or older who had pulmonary *Mycobacterium tuberculosis* disease, with rifampicin resistance confirmed by molecular or culture-based drug susceptibility testing, were offered enrolment. Participants were included irrespective of fluoroquinolone resistance status, HIV status, or CD4 count.

Patients were excluded if they were pregnant or if they had an alanine aminotransferase concentration or an aspartate aminotransferase concentration higher than three times the upper limit of the normal range; a Fridericia-corrected QT (QTcF) interval longer than 450 ms; structural heart disease; or a known or high risk of resistance to bedaquiline, pretomanid, or linezolid. Sex was self-reported with binary options. Full inclusion and exclusion criteria have previously been described.[2] All participants provided written informed consent.

Randomisation and masking

Randomisation lists were computer-generated and prepared by the trial statisticians. Using variable block randomisation, participants were randomly assigned in a 1:1:1:1 ratio to receive standard care, BPaL, BPaLC, or BPaLC in stage one of the trial, and in a 1:1 ratio to receive standard care or BPaLM in stage two of the trial. Participants were stratified by trial site. For allocation concealment, sites used sequentially numbered opaque envelopes at the start of the trial, but subsequently transitioned to computer assignment. After enrolment by investigators, randomisation was conducted by trial site pharmacists who notified investigators of the treatment allocation. Site pharmacists had no other direct role in participant care.

The trial was open-label. Trial site laboratory staff and central sponsor staff were masked to group assignment.

After the early termination of recruitment on March 18, 2021, all participants were notified that the trial had been terminated for benefit. Participants in the standard care group with at least 6 months remaining before completion of their intended regimen were given the option to cross over to the BPaLM group. Investigators and participants were given the discretion to individualise this decision in accordance with the wishes and best interests of the participant. Participants in the BPaLC and BPaL groups continued their allocated treatments.

Procedures

All participants allocated to the investigational groups were prescribed BPaL as the backbone of the regimens, comprising linezolid 600 mg daily for 16 weeks and 300 mg daily for 8 weeks (the lower dose was started earlier if the higher dose was not sufficiently well tolerated), pretomanid 200 mg daily for 24 weeks, and bedaquiline 400 mg daily for 2 weeks followed by 200 mg three times per week for 22 weeks. Participants in the BPaLM group were given BPaL plus moxifloxacin 400 mg daily and those in the BPaLC group were given BPaL plus clofazimine 100 mg daily (or 50 mg if weight <33 kg). Treatment duration was 24 weeks and all drugs were administered orally. Participants allocated to the standard care group were treated according to the locally accepted standard of care, which was continuously updated in line with WHO guidance. At the start of the trial, standard care regimens included both shorter, standardised 9–11-month (36–44-week) regimens as well as longer, individualised 18–20-month (72–80 week) regimens. From 2017 to 2019, these regimens generally included a second-line injectable agent and criteria for including bedaquiline were stringent. From 2019, participants received all-oral versions of these regimens and most regimens included bedaquiline. In South Africa, a 9–11-month regimen was used from 2018 and was subsequently approved by WHO in 2022.[3] Treatment was prescribed by investigators in line with trial guidelines. All medication was administered with food and either directly observed or observed through video by treatment supporters.

Efficacy and safety monitoring was conducted at least every 4 weeks for the first 24 weeks and then at least every 8 weeks for the subsequent 84 weeks. Efficacy was monitored through clinical evaluation and sputum smear and culture.[2] Chest radiography was conducted at baseline and at week 24. Safety was monitored through electrocardiograms, audiometry, blood chemistry analysis, and regular eye and physical examinations. The full investigational schedule has previously been described.[2]

Participants were followed up to week 108 (or to at least week 72 if censored). Those who reached an endpoint continued to be followed up to week 108 for safety. Serious adverse events, adverse events of special interest, pregnancy, and overdoses were reported as part of pharmacovigilance in line with Good Clinical Practice.

Outcomes

Outcomes from stage one of the trial were assessed at 8 weeks after randomisation and have been described and reported previously.[3] In stage two of the trial, the primary outcome was an unfavourable status (a composite of death, treatment failure, treatment discontinuation, recurrence of tuberculosis, or loss to follow-up) at 72 weeks after randomisation. The criterion for an outcome of recurrence was a participant who completed treatment without treatment failure and who had subsequently been diagnosed with and required

treatment for multidrug-resistant tuberculosis. Genetic sequencing was planned to differentiate between disease relapse and re-infection but, owing to technical challenges, has not been completed at the time of publication. Outcomes were assigned by investigators and verified centrally. Uncertain outcomes were referred to an independent outcome adjudication committee.

The prespecified secondary efficacy outcomes were composite unfavourable outcomes at 24 weeks (death, treatment failure, or treatment discontinuation) and 108 weeks (death, treatment failure, treatment discontinuation, recurrence of tuberculosis, loss to follow-up, or still receiving treatment at 108 weeks) after randomisation. Other secondary outcomes were culture conversion at 12 weeks, time to culture conversion, and recurrence of tuberculosis by week 48 post-randomisation (in the investigational groups only). Planned subgroup analyses included age, sex, country of enrolment, fluoroquinolone resistance status, bedaquiline resistance status, HIV status, smoking status, and disease severity. Recruitment before and after the declaration of COVID-19 as a public health emergency was added as an additional subgroup analysis. Other planned analyses, including sensitivity analyses and listing of deaths, were conducted according to the statistical analysis plan (appendix pp 19–49).

The safety outcomes in stage two of the trial were a composite of one or more adverse events of grade 3 or higher or serious adverse events at the end of treatment (plus a 30-day window), at 72 weeks, and at 108 weeks following randomisation, and prolongation of the QTcF interval at 24 weeks post-randomisation. Adverse events of special interest were also reported.

As post-hoc analyses, the efficacy and safety outcomes were also analysed in the BPaLC and BPaL groups at weeks 24, 48, 72 and 108. The outcomes of crossed-over participants were also reported.

Statistical analysis

The sample size for stage one was based on the number of participants required to detect culture conversion of less than 40% and a percentage of treatment discontinuation for any cause and death of greater than 45% in an investigational group. 60 participants in each group were required to achieve 80% power to reject both null hypotheses. The detailed assumptions have been previously reported.[2]

The sample size calculation for stage two was based on a non-inferiority comparison for a composite unfavourable outcome at 108 weeks (assumed to be 50% in the standard care group and 45% in the investigational groups), a non-inferiority margin of 12%, and a power of 85%. Allowing for both the adaptive nature of the design and the multiple comparisons due to the possible three investigational groups being assessed at the end of stage two, a one-sided type I error of 1·7% was assumed, and 181 participants per group would be required.

The intention-to-treat population was defined as all randomly assigned participants who were dispensed study medication on at least one occasion, with participants analysed in the study group to which they were allocated. The modified intention-to-treat population, in which the primary outcome was analysed, included all randomly assigned participants who were dispensed study medication on at least one occasion and had evidence of resistance to at least rifampicin; the tests conducted were dependent on the protocol version under which the participant was enrolled. Participants who switched from standard care to BPaLM after enrolment was stopped on March 18, 2021, were excluded from the modified intention-to-treat population for the main analysis. Participants were analysed on the basis of the group to which they were allocated at enrolment. The per-protocol population was a subset of the modified intention-to-treat population and excluded participants who did not complete a protocol-adherent course of treatment (other than because of treatment failure or death) and participants who discontinued treatment early because they violated at least one of the inclusion or exclusion criteria. A planned sensitivity analysis of the modified intention-to-treat population including participants who switched from standard care to BPaLM after enrolment was also conducted. The safety population was defined as the intention-to-treat population but with participants analysed according to the regimen received. All safety analyses were conducted on the safety population. For crossed-over participants, the safety analyses also excluded any events that occurred after the time at which participants switched groups.

The primary efficacy and safety comparisons assumed a two-sided 96·6% CI for investigational groups assessed in stage two. For binary outcomes we 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. Adjusting for site was planned as a fixed effect in the regression model, although was changed post-hoc to use the Cochran-Mantel-Haenszel approach owing to non-convergence issues. All secondary efficacy outcomes were reported with corresponding two-sided 95% CIs. Time to unfavourable outcome by 72 weeks was summarised using Kaplan-Meier curves. Post-hoc analyses of all stage 2 primary and secondary outcomes between standard care and investigational groups that did not continue after stage one are also presented, with two-sided 95% CIs. Statistical analyses were conducted using Stata (version 16 or later). The margin used to establish non-inferiority was 12%. A between-group difference of at least 3 SD in the interim analysis of a major endpoint was needed to justify stopping or modifying the study prematurely. The trial was overseen by an independent data safety monitoring board, and is registered at ClinicalTrials.gov, NCT02589782.

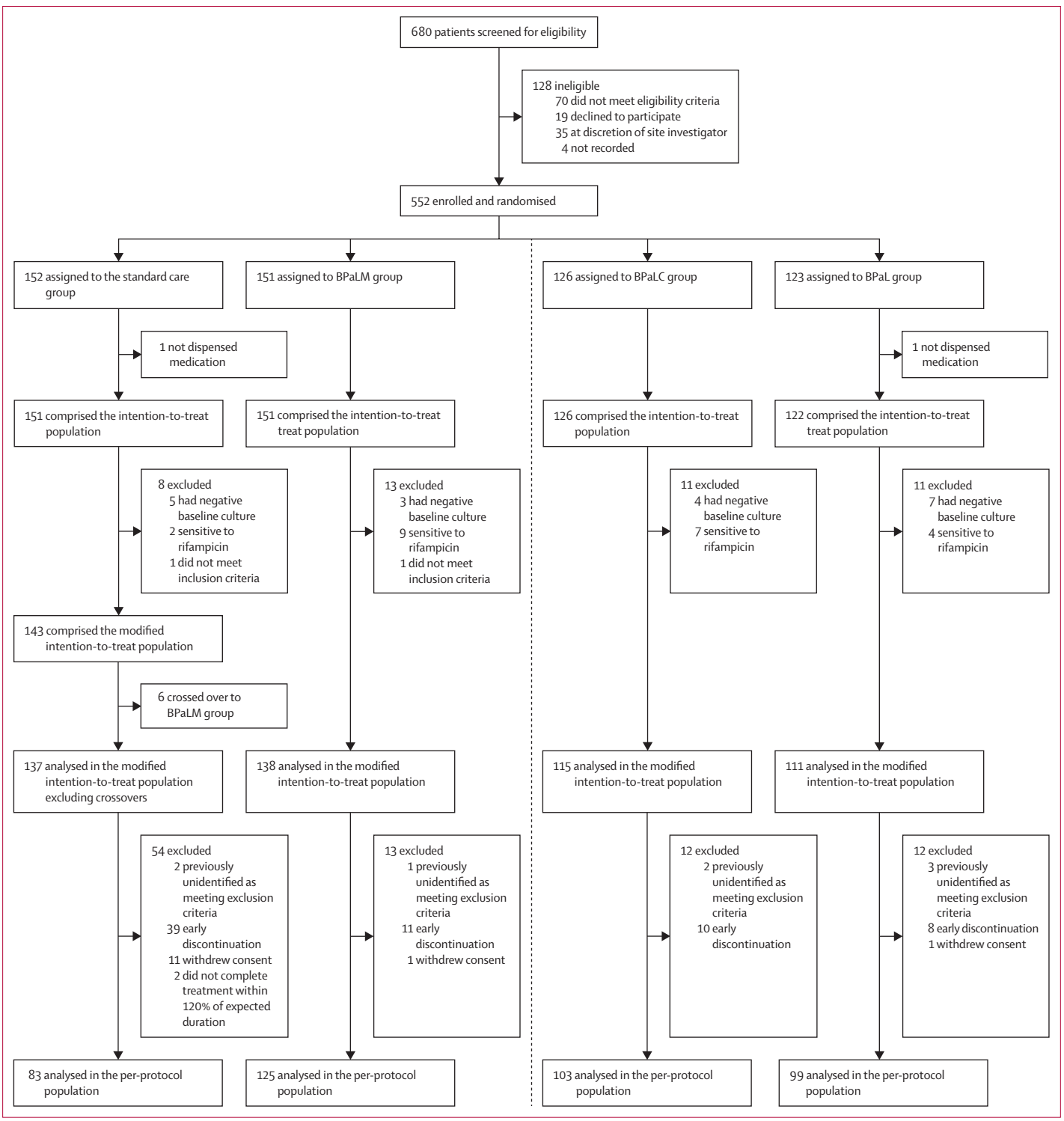


Figure 1: **Trial profile**
The groups to the left-hand side of the dashed line are the standard care and BPaLM groups, which were included in stage two of the study. To the right of the dashed line are the BPaLC and BPaL groups, which discontinued recruitment after transition to stage two. BPaL=bedaquiline, pretomanid, and linezolid. BPaLC=BPaL plus clofamizine. BPaLM=BPaL plus moxifloxacin.

	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)
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**

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

From Jan 16, 2017, to March 18, 2021, 680 patients were assessed for eligibility, of whom 552 were randomly assigned to receive standard care (n=152), BPaLM (n=151), BPaLC (n=126), or BPaL (n=123; figure 1). Of the 507 participants comprising the modified intention-to-treat population, 208 (41%) were female and 299 (59%) were male, the median age was 35 years (IQR 27–43), 140 (28%) were living with HIV (median CD4 count 319 cells per µL [IQR 156–512]), 332 (65%) had smear-positive tuberculosis, 308 (61%) had tuberculosis cavities, and 450 (89%) had culture-positive tuberculosis. A higher proportion of participants had cavitary disease in the BPaLC and standard care groups than in the BpaLM and BpaL groups; markers of disease severity were otherwise similar across groups (table 1). The characteristics of the whole trial population were generally similar (appendix p 6).

179 participants met the criteria for inclusion in the stage one intention-to-treat population (60 in the BPaLM group, 60 in the BPaLC group, and 59 in the BPaL group) and the results have been previously reported.[4] All groups met the eligibility criteria to proceed to stage two. The two groups with higher culture conversion rates, BPaLC and BPaLM, were recommended by the scientific advisory committee to progress. However, owing to recruitment delays and on March 4, 2020, 1 week before COVID-19 was declared as a pandemic, the trial steering committee—in consultation with the scientific advisory committee and the data safety monitoring board—decided to progress only one group to ensure a faster completion of the trial. The BPaLM group was chosen on the basis of higher culture-conversion rates at 8 weeks (BPaLM 77%, BPaLC 67%, and BPaL 46%),[3] lower regimen cost (the prices of clofazimine are higher than those of moxifloxacin), and the classification by WHO of moxifloxacin as a group A drug for tuberculosis; other considerations included the high efficacy of the NiX-TB regimen in quinolone-resistant tuberculosis and, to a lesser extent, concerns surrounding the adverse event profile of clofazimine (such as skin discolouration) as well as its potential cross-resistance with bedaquiline.

On the recommendation of the data safety monitoring board, the trial was stopped for benefit on March 18, 2021, after an unplanned analysis, conducted by request of the board, was found to meet the pre-specified stopping rules. 302 participants met the criteria for inclusion in the stage two intention-to-treat population (and the safety population): 151 in the standard care group and 151 in the BPaLM group. 275 participants were included in the modified intention-to-treat population (137 in the standard care group and 138 in the BPaLM group) and 208 were included in the per-protocol population (83 in the standard care group and 125 in the BPaLM group). Six 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 (figure 1).

Regarding the primary outcome at 72 weeks among the modified intention-to-treat population, 56 (41%) of 137 participants in the standard care group and 16 (12%)

	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%)

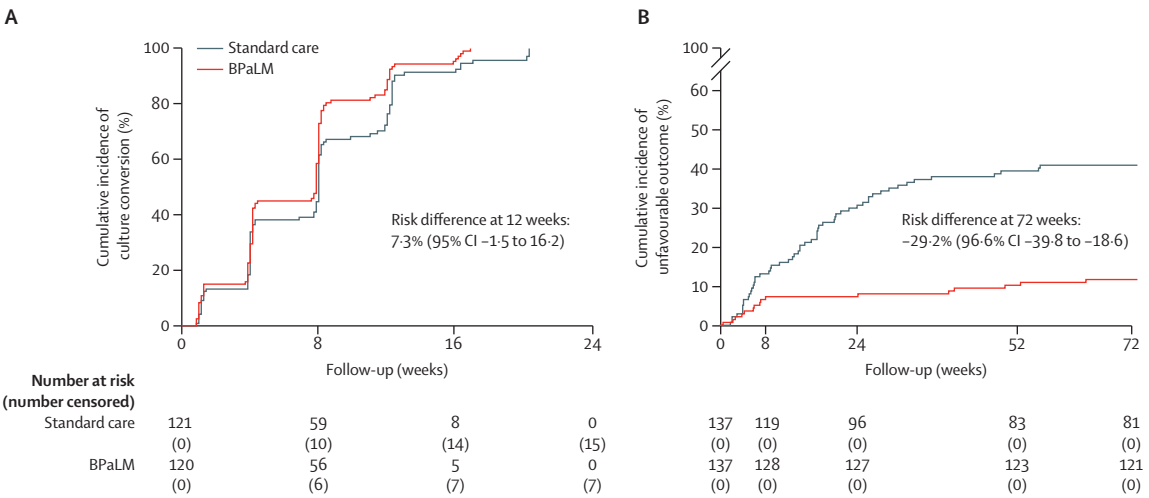
Data are n or n (%) unless otherwise stated. BPaL=bedaquiline, linezolid, and pretomanid. BPaLC=BPaL plus clofazimine. BPaLM=BPaL plus moxifloxacin. *Two-sided 96·6% CI for primary analyses and two-sided 95% CI for post-hoc analysis. Owing to convergence issues, adjusted analyses were conducted using the Cochran-Mantel-Haenszel approach and are reported in the appendix (p 13). †Established after the first dose had been administered.

Table 2: **Primary and post-hoc analyses in the modified intention-to-treat population and primary analyses in the per-protocol population 72 weeks after randomisation**

of 137 participants in the BPaLM group met criteria for the unfavourable outcome (unadjusted risk difference −29·2 percentage points [96·6% CI −39·8 to −18·6]; non-inferiority and superiority p<0·0001; one participant in the BPaLM group had a drug-susceptible disease recurrence and was therefore considered non-assessable). 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 and 11 [69%] of 16 in the BPaLM group), which was mainly attributed to adverse events (23 [46%] in the standard-care group and seven [64%] in the BPaLM group; table 2). The difference in the risk of an unfavourable outcome between BPaLM and standard care varied depending on country of enrolment or HIV status, and was less pronounced in South Africa (risk difference −59·1 percentage points [96·6% CI −80·4 to −37·9] in Belarus, −5·7 percentage points [−23·4 to 11·9] in South Africa, and −34·7 percentage points [−50·3 to −19·1] in Uzbekistan; $p_{interaction}$=0·0002) and for people living with HIV (risk difference −38·7 percentage points [96·6% CI −50·9 to −26·6] for HIV-negative status and −3·1 percentage points [−23·8 to 17·6] for HIV-positive status; $p_{interaction}$=0·0017; figure 2C).

In the per-protocol population, six (7%) of 83 participants in the standard care group and five (4%) of 125 participants in the BPaLM group met the criteria for the unfavourable outcome, giving an unadjusted risk difference of −3·2 percentage points with the upper CI bound of less than 12% (96·6% CI −10·3 to 3·9; $p_{non\text{-}inferiority}$<0·0001).

Adjustment using the Cochran-Mantel-Haenszel approach and sensitivity analyses were also conducted on



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

***Figure 2*: Primary composite outcome, culture conversion, and subgroup analysis of the modified intention-to-treat population at week 72**

(A) Kaplan-Meier plot for culture conversion in the modified intention-to-treat populations of the BPaLM and standard care groups. (B) Kaplan-Meier estimates of the time to an unfavourable outcome by week 72 in the modified intention-to-treat populations of the BPaLM and standard care groups. No patients are censored because deaths, withdrawals, and losses to follow-up are all part of the composite outcome. (C) Forest plot of the risk difference in the prespecified subgroup analyses between the standard care and BPaLM regimens, analysed at week 72 in the modified intention-to-treat population. Dashed vertical line shows the non-inferiority margin at 12%. BPaLM=bedaquiline, pretomanid, and linezolid plus moxifloxacin. NA=not applicable. Pre-COVID-19 pandemic is defined as the period before Jan 30, 2020, when COVID-19 was declared as a Public Health Emergency of International Concern by WHO; post-COVID-19 pandemic is defined as Jan 30, 2020 onwards.

the primary outcome. For all comparisons between study groups, the adjusted risk differences were consistent with the unadjusted effects (appendix p 13), as was the sensitivity analysis based on the modified intention-to-treat population that included the six participants in the standard care group who switched treatment (appendix pp 14–15). A sensitivity analysis excluding participants who were recruited before the implementation of the 2019 WHO guidelines[3] for standard care showed that non-inferiority was maintained (risk difference –19·1 percentage points [95% CI –30·9 to –7·3]; appendix p 14).

Results for the unfavourable outcome at 108 weeks in the modified intention-to-treat population were consistent with those for the primary outcome (appendix p 10). Two disease recurrences had occurred by 108 weeks: one in the standard care group and one in the BPaLM group. In the per-protocol population, the unadjusted risk difference for BPaLM versus standard care was larger at 108 weeks (–10·1 percentage points [95% CI –18·9 to –1·3]) than at 72 weeks (–3·2 percentage points [–10·3 to 3·9]), mostly driven by the number of deaths in the standard-care group (zero in the BPaLM group *vs* six in the standard care group; appendix p 16). Of the deaths, four were considered related to treatment (sudden cardiac death, sudden death, acute pancreatitis, and suicide) and two were not (stab wound and COVID-19 pneumonia). Study group effects on unfavourable outcomes (death, treatment failure, and treatment discontinuation) at 24 weeks in the modified intention-to-treat population were consistent with the 72-week and 108-week outcomes (appendix p 11).

Culture conversion at 12 weeks was observed for 99 (82%) of 121 patients for whom conversion could be defined in the standard care group and 107 (89%) of 120 patients in the BPaLM group (risk difference 7·3 percentage points [95% CI –1·5 to 16·2]; figure 2A). Median time to culture conversion was 56 days (IQR 28 to 83) in the standard care group and 55 days (28 to 57) in the BPaLM group (unadjusted hazard ratio 1·38 [95% CI 1·05 to 1·81]; appendix p 12).

A post-hoc evaluation of long-term outcomes was conducted in the BPaLC and BPaL groups. By week 72, in the modified intention-to-treat population and compared with standard care, unadjusted risk differences were –17·4 percentage points (95% CI –28·7 to –6·1) for BPaLC and –27·4 percentage points (–37·8 to –17·0) for BPaL, indicating non-inferiority (table 2). Non-inferiority was also shown in the per-protocol population for BPaL (–3·2% [–10·0 to 3·6]) but not for BPaLC (8·3% [–0·1 to 17·2]; appendix p 7).

By week 108 after randomisation, the effect estimates remained similar to those measured at week 72: in the

	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**

modified intention-to-treat population, BPaLC remained non-inferior to standard care at week 108 (appendix p 9). Of note, disease recurrence occurred in five (4%) of 115 participants in the BPaLC group, four (4%) of 111 in the BPaL group (appendix p 9). New resistance to bedaquiline was observed in three of four isolates from participants with disease recurrence, all in the BPaL group; of these, an isolate from one participant also showed resistance to clofazimine (appendix p 13).

Among the safety population, 72 (48%) of 151 participants in the standard care group had at least one adverse event of grade 3 or higher or serious adverse events within 72 weeks (121 events in total), compared with 34 (23%) of 151 participants in the BPaLM group (53 events; risk difference −25·2 percentage points [96·6% CI −36·4 to −13·9]; table 3). Common adverse events included hepatic disorders (22 events in 15 (10%) participants receiving standard care *vs* 17 events in 12 (8%) participants receiving BPaLM); cardiac disorders (19 *vs* two), most of which were due to QT-prolongation; and anaemia (13 *vs* six; appendix pp 16–18). Compared with the BPaLM group, the proportions of participants with adverse events of grade 3 or higher or serious adverse events was similar in the BPaL group (29 [24%] of 122 participants; 45 events) and higher in the BPaLC group (38 [30%] of 126 participants; 52 events). Similar results were found when assessing adverse events over 108 weeks (table 3). Mean Fridericia-corrected QT (QTcF) intervals at 24 weeks were 440·9 ms in the standard care group and 425·1 ms in the BPaLM group (mean difference −17·5 ms [96·6% CI −22·0 to −12·9]). Mean QTcF intervals were 436·3 ms in the BPaLC group and 421·8 ms in the BPaL group (table 3). Nine participants died by week 108: six (4%) in the standard care group, zero in the BPaLM group, one (1%) in the BPaLC group (chronic obstructive pulmonary disease; unrelated to treatment), and two (2%) in the BPaL group (seizure and lower respiratory tract infection; unrelated to treatment).

Discussion

This study corroborates, with increased precision, the findings from the interim analysis of the TB-PRACTECAL trial that a 24-week oral regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin is non-inferior to standard care for the treatment of patients with pulmonary rifampicin-resistant tuberculosis.[4] In post-hoc analyses, BPaLC and BPaL were also shown to be non-inferior to standard care. The BPaLM, BPaLC, and BPaL groups had fewer serious adverse events and adverse events of at least grade 3 than the standard care group. To our knowledge, this study is the first randomised controlled trial to examine BPaL-based regimens for rifampicin-resistant tuberculosis. The study provides robust, generalisable data showing efficacy among similar numbers of male and female participants from three countries, and is inclusive of people with HIV coinfection and severe rifampicin-resistant disease with and without fluoroquinolone resistance; as such, the participants are broadly representative of adult and adolescent patients with rifampicin-resistant tuberculosis worldwide.

The effect estimate for the primary outcome comparing BPaLM versus standard care at 72 weeks was smaller in this final analysis (risk difference −29·2 percentage points) than in the interim findings (−37·2 percentage points).[3] This difference can be mostly explained by the better performance of the standard care group in the final analysis,[3] which is possibly due to improvements in standard care throughout the trial. In 2019, the update to the WHO consolidated guidelines on drug-resistant tuberculosis treatment prioritised the addition of bedaquiline and linezolid to most regimens, withdrew the use of second-line injectable agents, and allowed shorter regimens of 9–12 months duration.

In secondary and post-hoc analyses, culture conversion was faster in the BPaLM group than in the standard care group, and fastest in BPaLM among all three investigational groups (appendix p 12). Deaths were uncommon in the investigational groups; three deaths occurred among all three investigational groups compared with six in the standard care group by week 108 (appendix p 10). Despite disruptions due to the COVID-19 pandemic, BPaLM maintained high efficacy in participants recruited after WHO's declaration of the disease as a Public Health Emergency of International Concern on Jan 30, 2020.

The subgroup analyses showed that all risk difference point estimates favoured BPaLM over standard care at 72 weeks post-randomisation in the modified intention-to-treat population, including by sex, age, disease severity, re-treatment status, and smoking status. The upper bounds of the CIs were greater than zero but within the 12% non-inferiority margin in participants with baseline fluoroquinolone resistance and in those who were enrolled in South Africa; having HIV at baseline, however, resulted in a upper bound higher than the 12% non-inferiority margin. We note a significant interaction ($p<0·05$) between the BPaLM and standard care groups for country of enrolment, HIV status, and for those enrolled after the declaration of COVID-19 as a public health emergency on Jan 30, 2020. Almost all participants who were HIV-positive were enrolled in South Africa (127 [91%] of 139); however, whether the interaction was driven by the location of participants or their HIV status is difficult to establish. The standard of care performed better in HIV-positive patients than in HIV-negative patients, which was unexpected. Further elucidation of these potential interactions in real-world settings is warranted.

Our data are consistent with those from other studies showing that BPaL-based regimens are associated with around 7–16% unsuccessful outcomes.[5,6] A network meta-analysis was conducted to inform WHO guideline development. This analysis included the interim TB-PRACTECAL data (participants with outcomes up to March 18, 2021). The BPaL regimen was shown to have

higher efficacy than standard care regimens (relative risk of treatment success 1·32 (95% CI 1·19–1·39) for the 18–20-month, all-oral regimen, 1·45 (1·38–1·52) for the WHO 9–11-month short regimen, and 1·52 (1·38–1·55) for the South African 9–11-month short regimen). A 600 mg dose of linezolid for 26 weeks was found to have similar efficacy to a 1200 mg dose but with fewer grade 3–5 adverse events (six [14%] of 43 patients with 600 mg *vs* eight [19%] of 44 patients with 1200 mg) at 12 months after randomisation. Finally, the network meta-analysis found successful outcomes in 55 (89%) of 62 patients treated with BPaLM compared with 46 (77%) of 60 of those treated with BPaL (absolute risk reduction 1·15 [95% CI 0·95–1.38]).[4] This difference is more pronounced than the absolute outcomes found in this final analysis. However, other considerations—such as time to culture conversion, recurrence, and resistance development—would need to be included when deciding on the appropriate regimen to use.

The performance of the standard of care was lower than in trials of rifampicin-resistant or multidrug-resistant tuberculosis reported in the past 4 years (STREAM[7] and MDR-END[8]). A very tight limit was set in which participants missing treatment for 2 continuous weeks would be discontinued from the trial. This limit was intended to protect participants in investigational groups in case the barrier to acquired drug resistance was very low. Ultimately, we found that meeting these criteria for continuation was most difficult for participants in the standard care group who were struggling with adverse events or adherence to treatment, and these difficulties led to early discontinuation in a high proportion of participants.

Disease recurrence occurred in one participant in the BPaLM group, five of those in the BPaLC group, and four of those in the BPaL group. New resistance to bedaquiline was observed only in the BPaL group in isolates from three of four recurrences. No other new resistance to bedaquiline, linezolid, or pretomanid was detected among the other nine participants who developed recurrence or treatment failure across the four groups. Analysis of paired genome sequencing results to confirm relapse is ongoing, so some of these recurrences could be due to reinfection. The ZeNix trial, which studied BPaL regimens with different doses of linezolid, reported recurrence in four (2%) of 181 participants.[4,5]

This study has several limitations, including those described previously.[3] We previously acknowledged the indirectness of the analysis, with 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 (appendix p 7). 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.

Additionally, 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 because the regimen that induced efficacy could not be established (appendix p 15). Sensitivity analyses suggest that the inclusion of these participants would not have changed the effect estimate in a clinically important way (appendix pp 14–15). Three grade 3 adverse events occurred in this group of six participants after switching to BPaLM (appendix p 18). Outcome adjudication was conducted by unmasked investigators, which could also have introduced bias. Difficult cases were assessed by an independent committee masked to the treatment group, when possible.

As a conservative measure, we included loss to follow-up in the composite unfavourable outcome. The smaller effect estimate seen with BPaLC versus standard care was principally driven by participants lost to follow-up and we do not have a hypothesis linked to the treatment allocation that explains this difference. The differences in loss to follow-up across groups had largely resolved by week 108 and could have occurred by chance (appendix p 10). However, the trial was not powered to compare the investigational groups with each other. The inclusion of loss to follow-up as part of composite unfavourable outcomes, as is the case in programmatic classifications, has drawbacks as it is more likely to be an issue of missing data rather than unaccounted-for adverse outcomes. We agree, as others have suggested, that future late-phase tuberculosis trials should reconsider including loss to follow-up as an assessable outcome.[9]

Several outstanding research questions remain. The optimal dose of linezolid remains unknown. A starting dose of 600 mg seems to be the most tolerable; however, the optimal duration of treatment is less clear, as is the role of dose reduction. Ongoing pharmacokinetic studies could assist in answering this question.[10] Some argue that therapeutic drug monitoring could have a role in personalising dosing,[11] but this is unlikely to be accessible in all settings. Whether similar results can be achieved with alternative fluoroquinolones (such as levofloxacin) or with nitroimidazoles (such as delamanid) is unknown, although early results are promising.[12] Newer oxazolidinones could also offer a better safety and tolerability profile than linezolid.[13] Phenotypic drug susceptibility testing breakpoints for pretomanid need to be confirmed and further information is also needed on the performance of the regimen in settings with a high

prevalence of *Mycobacterium tuberculosis* lineage 1.[14] Data are also needed in children, pregnant people, and those with extrapulmonary tuberculosis. The country and HIV-status subgroup findings in our study warrant further investigation, as almost all the participants with HIV were from South Africa. Additionally, South African participants in the standard care group were treated with the 9–11 month shorter oral regimen including linezolid for 8 weeks; this regimen was not in use at other sites during recruitment.

Despite the limitations and outstanding questions, these BPaL-based regimens perform better than the 9–20-month standard of care; they are shorter, have a lower pill burden, improve quality of life, and have been shown to be cost-effective.[15] BPaLM, BPaLC, and BPaL have the potential to improve the outcomes of thousands of people with rifampicin-resistant tuberculosis, and we call on national tuberculosis programmes and partners to accelerate the implementation of these regimens.[16]

Contributors

B-TN, PdC, and DAM conceived the study. B-TN, CB, EK, and IM led the sponsor project management team. MD compiled reports for the data safety monitoring board. NP, ZT, RM, VS, IL, SR, and MR were site principal investigators and were responsible for participant recruitment and data collection. TM oversaw the laboratory set-up and monitoring. MS, DAM, KR, and PdC provided study oversight via the trial steering committee. Statistical analysis was done by MD and KF. The first draft of the manuscript was written by CB, IM, EK, B-TN, KF, and MD. The manuscript was revised, edited, and read by all authors. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. KF, MD, CB, IM, EK, and B-TN accessed and verified all data in the study.

Declaration of interests

B-TN, CB, EK, and IM are employees of Médecins Sans Frontières. MR participates on the data safety monitoring board for the BEAT-TB trial (NCT04062201). PdC is a former employee of Médecins Sans Frontières and received consultancy fees and conference attendance support from the organisation between 2020 and 2022. He has also received grants from the Department of Foreign Affairs and Trade and the Medical Research Future Fund of the Australian Government; FIND; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and STOP TB; and honoraria for training sessions from the regional Green Light Committee (Western Pacific Regional Office), of which he is an unpaid committee member. TM has received grants from the Global Alliance Against Tuberculosis, the European & Developing Countries Clinical Trials Partnership, and the EU Innovative Medicines Initiative; is co-editor in chief of *Annals of Clinical Microbiology and Antimicrobials* (Springer Nature); and is the chair of the Acid Fast Club (unpaid). MD and KF received salary funding paid to the London School of Hygiene & Tropical Medicine (London, UK) by Médecins Sans Frontières. All other authors declare no competing interests.

Data sharing

De-identified individual patient data and a data dictionary will be made available on one or more scientific data repositories following publication. The study protocol, informed consent form, and statistical plan have previously been made available.[2,3] The sponsor of this trial (Médecins Sans Frontières) intends to make all data publicly available by the end of March, 2024, via TB-PACTS (Critical Path Institute; https://c-path.org/programs/tb-pacts/accessing-tb-pacts/).

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