Bedaquiline, delamanid, linezolid, and clofazimine for rifampicin-resistant and fluoroquinolone-resistant tuberculosis (endTB-Q): an open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial

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Summary

Background Pre-extensively drug-resistant (pre-XDR) tuberculosis (ie, multidrug-resistant or rifampicin-resistant with additional resistance to any fluoroquinolone) is difficult to treat. endTB-Q aimed to evaluate the efficacy and safety of bedaquiline, delamanid, linezolid, and clofazimine (BDLC) compared with the standard of care for patients with pre-XDR tuberculosis.

Methods This open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial was conducted in ten hospitals in India, Kazakhstan, Lesotho, Pakistan, Peru, and Viet Nam. Participants aged 15 years or older who had pulmonary tuberculosis with resistance to rifampicin and fluoroquinolones were included. Participants were randomly assigned (2:1) to the BDLC group (all-oral bedaquiline 400 mg once per day for 2 weeks followed by 200 mg three times per week, delamanid 100 mg twice per day, linezolid 600 mg once per day for 16 weeks and then either 300 mg once per day or 600 mg three times per week, and clofazimine 100 mg once per day) or the control group (individualised WHO-recommended longer standard of care). Randomisation was stratified by country and baseline disease extent. BDLC was administered for 39 weeks (9-month regimen) for extensive disease and 24 weeks (6-month regimen) for limited disease and extended to 9 months for those with a positive culture at 8 weeks or later or a missing 8-week culture result. Site staff and participants were not masked, whereas investigators and laboratory staff were masked to treatment assignment. The primary endpoint was favourable outcome (two consecutive, negative cultures including one between weeks 65 and 73; or favourable bacteriological, radiological, and clinical evolution) at week 73 after randomisation in the modified intention-to-treat (mITT) and per-protocol populations. We report the risk differences adjusted for stratification variables, with a non-inferiority margin of –12%. This trial is registered with ClinicalTrials.gov, NCT03896685.

Findings Between April 4, 2020, and March 28, 2023, 1030 individuals were screened and 324 (31%) were randomly assigned (219 to the BDLC group and 105 to the control group). 114 (46%) participants were female and 133 (54%) were male. Median age was 30·5 years (IQR 21·6–43·0). 157 (64%) participants had extensive disease at baseline. In the BDLC group, 47 (29%) of 163 were assigned to receive the 6-month regimen and 116 (71%) the 9-month regimen. The core regimen of BDLC plus one or more other drugs was used for 76 (91%) of 84 participants in the control group. At week 73, favourable outcome was reached by 141 (87%) participants in the BDLC group versus 75 (89%) in the control group in the mITT population (adjusted risk difference 0·2% [95% CI –9·1 to 9·5]; $p_{non\text{-}inferiority}$=0·0051) and by 138 (88%) of 157 versus 71 (93%) of 76 in the per-protocol population (adjusted risk difference –3·5% [–12·8 to 5·9]; $p_{non\text{-}inferiority}$=0·037). Overall non-inferiority was not shown. 145 (68%) of 213 participants in the BDLC group and 77 (73%) of 105 in the control group had at least one grade 3 or higher adverse event, with eight (4%) and two (2%) all-cause deaths by week 73, respectively.

Interpretation The shortened BDLC strategy was not non-inferior to the control. Accumulating evidence suggests that this patient population might require longer, reinforced regimens.

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For the Hindi translation of the abstract see Online for appendix 1

For the Marathi translation of the abstract see Online for appendix 2

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Research in context

Evidence before this study

Published phase 3 clinical trials on rifampicin-resistant tuberculosis are rare, particularly for the subgroup of people with pre-extensively drug-resistant (pre-XDR) tuberculosis. Current guidelines on pre-XDR tuberculosis treatment rely on low certainty evidence, partly due to the absence of randomised controlled trials focused exclusively on pre-XDR tuberculosis. We searched PubMed for clinical trials published in English between Jan 1, 2000, and Dec 31, 2024, on standardised and shorter (<12 months) tuberculosis drug regimens using the Medical Subject Headings terms "pre-extensively drug-resistant tuberculosis" OR "pre-XDR-TB" OR "fluoroquinolone-resistant tuberculosis". We excluded results that were not relevant to the latest WHO 2021 definition of pre-XDR tuberculosis (ie, tuberculosis with resistance to rifampicin and any fluoroquinolone). Overall, we found four studies (BEAT-TB India, Nix-TB, TB-PRACTECAL, and ZeNix) that evaluated shorter regimens for drug-resistant tuberculosis, but they did not include an internal control or included a small number of participants with pre-XDR tuberculosis. Another unpublished phase 3 clinical trial from South Africa (BEAT Tuberculosis; NCT04062201) is referenced in WHO 2025 updated guidelines on the treatment of drug-resistant tuberculosis. BEAT Tuberculosis tested a treatment strategy for patients with rifampicin-resistant tuberculosis, regardless of fluoroquinolone resistance, and was not designed to draw conclusions for pre-XDR tuberculosis.

Added value of this study

This phase 3 randomised, controlled, non-inferiority trial assessed the bedaquiline, delamanid, linezolid, and clofazimine (BDLC) regimen against WHO recommended 18-month regimens for pre-XDR tuberculosis. endTB-Q applied a stratified medicine approach, assigning treatment duration according to baseline disease extent and microbiological response. Participants with limited disease and early culture conversion received a 6-month regimen, whereas those with extensive disease or delayed conversion received a 9-month regimen. Our study provides evidence supporting the feasibility of a personalised treatment strategy for pre-XDR tuberculosis. Non-inferiority was not shown; however, the BDLC group reached similar outcomes to the control group in participants with limited disease, whereas those with extensive disease did not respond as well to the 9-month regimen.

Implications of all the available evidence

WHO recommendations increasingly favour shorter, all-oral regimens (including BDLC) for drug-resistant tuberculosis. However, these recommendations are based on low certainty evidence. Our findings support the use of BDLC, alongside other recommended regimens, for people with pre-XDR tuberculosis who have limited disease at baseline. However, for those with pre-XDR tuberculosis and extensive disease, a longer or reinforced regimen might be necessary to prevent unfavourable outcomes. Further research is warranted to optimise regimen composition and duration for this population and to mitigate risks of tuberculosis relapse and acquisition of drug resistance.

Introduction

Patients with pre-extensively drug-resistant (pre-XDR) tuberculosis, defined as multidrug-resistant or rifampicin-resistant tuberculosis with additional resistance to any fluoroquinolone,[1] have historically received long, poorly performing regimens with high toxicity. A 2023 meta-analysis estimated successful treatment in around 60% of patients with pre-XDR tuberculosis who received treatment in 2013 or later, which represents an improvement compared with the previous years.[2] The loss of fluoroquinolone activity against *Mycobacterium tuberculosis* was a well-established risk factor for worse outcomes with longer regimens in the pre-bedaquiline era.[3] The newly WHO-approved 6–9 month all-oral containing regimen of bedaquiline, pretomanid, and linezolid (BPaL) has approximately 90% effectiveness in highly resistant tuberculosis and has improved the outcomes for people with pre-XDR tuberculosis. However, the pivotal NiX-TB study of BPaL had a small sample size of 71 people with pre-XDR tuberculosis and included no internal, concurrent comparator.[4] A second study (ZeNix) was designed to optimise the dose of linezolid in BPaL (evaluated 181 patients) and showed similar rates of treatment success, but still did not include an internal comparator.[5] A third study with a comparator (TB-PRACTECAL) evaluated BPaL in 25 individuals with pre-XDR tuberculosis.[6,7] Another 6-month treatment strategy emerged in 2024, comprising a regimen with bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine; clofazimine is dropped in fluoroquinolone-susceptible tuberculosis and levofloxacin is dropped in pre-XDR tuberculosis. The BEAT Tuberculosis trial testing this strategy included participants regardless of fluoroquinolone resistance and was not designed to draw conclusions for patients with pre-XDR tuberculosis.[8] WHO has conditionally recommended these regimens acknowledging the low certainty of evidence.[9,10]

The extent of tuberculosis disease classification, based on indicators of bacillary load and parenchymal damage on a chest x-ray, is increasingly recognised to modify the effect of shorter regimens compared with longer regimens.[11,12] The stratified-medicine approach suggested by this observation represents the foundation of multiple planned trials of tuberculosis treatment (PRISM-TB [NCT06441006], DATURA [NCT04738812], and NEW-STRAT TB [NCT04951986]).

In this internally controlled endTB-Q (Evaluating Newly Approved Drugs in Combination Regimens for Multidrug-Resistant Tuberculosis with Fluoroquinolone Resistance) trial, we aim to evaluate the efficacy and safety of an all-oral, stratified, shortened regimen of bedaquiline, delamanid, linezolid, and clofazimine (BDLC) compared with the WHO-recommended longer standard of care for patients with pre-XDR tuberculosis.[13]

Methods

Study design

This open-label, multicentre, non-inferiority, stratified, randomised, controlled, phase 3 trial was conducted in ten ambulatory health facilities and hospitals in India, Kazakhstan, Lesotho, Pakistan, Peru, and Viet Nam (appendix 8 pp 23–24). Pre-XDR tuberculosis was defined at trial inception as per the 2020 WHO definition.[1] The trial was conducted by the endTB consortium (Médecins Sans Frontières [MSF], Partners In Health, and Interactive Research and Development). Design and implementation details and the full study protocol are shown in appendix 8 (pp 60–178).[13] The study was approved by the MSF Ethics Review Board (approval number D:1761) and institutional review boards at Harvard Medical School, Interactive Research and Development, Institute of Tropical Medicine (ITM), University of California San Francisco (UCSF), and at each participating site. The Consolidated Standards of Reporting Trials extension for non-inferiority trials guided this trial report.[14] This trial is registered with ClinicalTrials.gov, NCT03896685 (completed).

Participants

Participants (male and female as per sex classification by the investigator) aged 15 years or older who had pulmonary tuberculosis with documented or probable resistance to rifampicin and fluoroquinolones were referred to the trial from health facilities in study catchment areas. Inclusion required resistance to rifampicin and fluoroquinolones by WHO-endorsed rapid molecular tests conducted at a designated trial-site laboratory; inconclusive results of rapid molecular fluoroquinolone resistance testing were sufficient to permit enrolment in India and Pakistan where pretest probability of fluoroquinolone resistance was elevated.[15,16] Inclusion was irrespective of HIV serostatus or $CD4^+$ lymphocyte count. Exclusion criteria were pregnancy; low haemoglobin (grade 3 or higher); elevated liver enzymes (grade 2 or higher) or bilirubin (grade 3 or higher); uncorrectable electrolyte disorders (hypocalcaemia or hypomagnesemia [grade 3 or higher] and hypokalaemia or hyperkalaemia [grade 2 or higher]); serum creatinine (grade 3 or higher); QT interval corrected by the Fridericia formula (QTcF ≥450 ms; grade 1 or higher) or other cardiac risk factors for arrhythmia; resistance or previous exposure (≥30 days) to any drug in the BDLC regimen; and 15 days or longer treatment with any second-line antituberculosis drug during the current tuberculosis episode.[13] All participants provided written informed consent. Full criteria for eligibility for enrolment of all participants and for retention of participants who became pregnant during the study are shown in the appendix 8 (pp 7–9).

Randomisation and masking

Participants were randomly assigned (2:1) with a generated randomisation sequence using a centralised interactive system (VennLife Sciences, Paris, France) to the BDLC group or the standard of care control group (WHO-recommended longer individualised regimen). The unequal allocation ratio was chosen to increase the accumulated evidence in the BDLC group relative to the control. Randomisation was stratified by country and baseline disease extent (limited disease was defined by a negative or scanty smear for *M tuberculosis* irrespective of cavitation or smear 1+ in the absence of cavitation and extensive disease was defined by smear 2+ or 3+ irrespective of cavitation or smear 1+ in the presence of cavitation; appendix 8 p 26) and was performed by site investigators or coordinators. Site staff and participants were not masked to treatment allocation, whereas central investigators and mycobacteriology laboratory study staff were masked to treatment assignment (appendix 8 p 9).

Procedures

The BDLC group included four oral drugs: bedaquiline 400 mg once per day for 2 weeks followed by 200 mg three times per week, delamanid 100 mg twice per day, linezolid 600 mg once per day for 16 weeks and then either 300 mg once per day or 600 mg three times per week (the lower dose was started earlier than 16 weeks in case of linezolid-related toxicity), and clofazimine 100 mg once per day. Reduced linezolid dose was determined using a secondary balanced randomisation; a comparison between the two dose reduction strategies is planned and will be reported in another publication.

The BDLC regimen was administered for 39 weeks (9-month regimen) in participants with extensive disease and 24 weeks (6-month regimen) in those with limited disease and treatment was extended to 9 months for those with a positive culture at 8 weeks or later (for those with results available by week 24) or a missing 8-week culture result. Control group regimens administered for 18 months were individualised and designed in accordance with WHO guidelines for pre-XDR tuberculosis,[10,17] and could include drugs used in the BDLC group and other oral and injected agents for the entire duration of treatment. Treatment was directly observed. Regimen guidance for the control group and the dosing schedule for both study groups is provided in the appendix 8 (pp 26–28). All study drugs were centrally purchased.

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See **Online** for appendix 8

Participants were followed up for a maximum of 104 weeks; follow-up ended when the final participant reached week 73 after random assignment. Clinical, safety, and mycobacteriological assessments occurred once per week until week 12, every 4 weeks until week 47, and every 6–8 weeks thereafter (appendix 8 pp 29–31). Standardised mycobacteriology tests were performed in designated, quality-controlled, trial-site laboratories. Tests included smear microscopy, culture in Mycobacteria Growth Indicator Tube (MGIT) and on solid Löwenstein-Jensen media at in-country laboratories, except for Lesotho for which the culture-based tests were performed only in MGIT in South Africa. Phenotypic drug susceptibility testing was performed in MGIT for at least rifampicin, and fluoroquinolones; drug susceptibility testing for BDLC was gradually introduced at various times in each site. The ITM supported site laboratories and performed central phenotypic and genotypic testing on positive cultures from samples collected at 16 weeks or later and corresponding baseline samples. A strain isolated from a sample collected at 16 weeks or later was classified as the same if there were 12 or fewer single nucleotide polymorphisms different from the strain isolated at baseline (appendix 8 p 12).

Outcomes

For the **Pharmacovigilance Unit Severity Scale** see https://endtb.org/toolkit/endtb-trials-pharmacovigilance

The primary efficacy endpoint was favourable outcome at week 73 after randomisation in the modified intention-to-treat (mITT) and per-protocol populations. Participants were classified as having a favourable outcome at week 73 if, in the absence of an unfavourable outcome: their last two culture results were negative and taken from sputum samples collected on separate visits (the latest between weeks 65 and 73); or the last culture result (between weeks 65 and 73) was negative and there was no other post-baseline culture result or the penultimate culture result was positive due to laboratory cross-contamination and the bacteriological, radiological, and clinical evolution was favourable; or there was no culture result from a sputum sample collected between weeks 65 and 73 or the result of that culture was positive due to laboratory cross contamination and the latest culture result was negative and bacteriological, radiological, and clinical evolution was favourable.

Unfavourable outcomes were all-cause mortality; the replacement or addition of drugs (one or more for the BDLC group and two or more for the control group), including changes on study treatment or upon initiation of a new regimen after treatment discontinuation due to treatment failure, an adverse event, poor treatment adherence or loss to follow up, or withdrawal of consent; the initiation of a new treatment for multidrug-resistant or rifampicin-resistant tuberculosis after treatment completion and before week 73 (classified as recurrence, relapse, or reinfection according to sequencing results; appendix 8 p 12); positive culture after week 16 resulting in treatment discontinuation or between weeks 65 and 73 (both classified as treatment failure); and combination of culture results insufficient to establish a favourable outcome and unfavourable bacteriological, radiological, or clinical evolution (classified as treatment failure).

Favourable and unfavourable outcome definitions were similar for the secondary endpoints at weeks 39 and 104. Other secondary outcomes were initial sputum culture conversion by week 8, time to culture conversion, and change in time to MGIT culture positivity and will be reported separately. Acquired drug resistance was a prespecified exploratory outcome, defined as newly occurring phenotypic or genotypic resistance to any drug in the BDLC regimen in a strain isolated from a sample collected at week 16 or later and classified as the same as the baseline strain (appendix 8 p 11). Treatment outcomes were assigned by site investigators. If assignment required consideration of evolution, outcomes were adjudicated by the central Clinical Advisory Committee (appendix 8 p 12).

Safety outcomes at weeks 73 and 104 were grade 3 or higher adverse events, serious adverse events, death, discontinuation of at least one study drug due to adverse events, and adverse events of special interest defined as grade 3 or higher hepatotoxicity, haematological toxicity, optic neuritis, peripheral neuropathy, or QTcF prolongation. Exploratory post-hoc analysis examined these safety outcomes at 4 weeks after treatment completion. Adverse events were graded by the site investigators according to the MSF Pharmacovigilance Unit Severity Scale. Treatment-emergent adverse events are also reported. The MSF Pharmacovigilance Unit provided support for standardised recording, reporting, grading, and classification of adverse events.

Statistical analysis

Sample size assumptions were based on reaching favourable outcomes at week 73 in 78% of participants in the BDLC group and 75% in the control group, and 6% being excluded from the mITT population and 10% from per-protocol population. A sample size of 324 would give 80% power to establish non-inferiority (margin of –12% and one-sided type I error rate of 2·5%) in the BDLC group in both analysis populations. The non-inferiority margin was set at –12% because the standard therapy received in the control group was expected to perform better than other reference standards[4] and four trials[6,18–20] of tuberculosis treatment have also used a –12% margin for non-inferiority (appendix 8 p 17). Slightly worse efficacy in the BDLC group was considered an acceptable trade-off for the benefits of the shortened treatment duration and reduction of the pill burden.

The efficacy analysis relied on the absolute between-group difference (with 95% CI) in the proportion of participants with a favourable outcome at week 73. Establishment of non-inferiority required the lower

bound of the 95% CI around the difference to be greater than or equal to –12% in both the mITT and per-protocol populations. The safety population included all participants who were randomly assigned and received at least one dose of trial treatment. The mITT population included participants from the safety population who had a culture positive for *Mycobacterium tuberculosis* before random assignment (excluding those with baseline phenotypic resistance to BDLC). The per-protocol population included participants from the mITT population who did not receive more than 7 days of a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration and no more than 120% of the expected doses in participants who were to receive 24 weeks of treatment) or those who did not do so because of treatment failure or death (appendix 8 p 17).

Baseline characteristics were summarised using the number of participants (%) or median (IQR). Risk differences were estimated using a binomial regression model (generalised linear model for a binomial outcome with an identity link function). One-sided p values for non-inferiority were calculated. The primary analysis was adjusted for stratification factors as fixed effects. Kaplan–Meier curves and log-rank tests for differences between groups were used to estimate time to unfavourable outcomes. Schoenfeld residuals were used to test the proportional-hazards assumption. We prespecified exploratory subgroup differences by baseline disease extent (and component parts), country, comorbidities, BMI, age, sex, and previous exposure to tuberculosis treatment. Interaction p values were estimated from an unadjusted binomial regression model. In case of complete separation of the data, a combined approach of Firth's penalised logistic regression and bootstrap methods were used.

Prespecified sensitivity analyses included unadjusted analyses; analyses adjusted for randomisation stratification factors, BMI, and type 1 and 2 diabetes; and primary efficacy analyses performed in differently defined mITT populations (appendix 8 p 17). A post-hoc sensitivity analysis was done by pooling countries with a small sample size (<10 patients in the control group).

All analyses were performed in Stata (version 18.0) and R (version 4.4). Trial oversight was provided by the Data Safety and Monitoring Board, Scientific Advisory Committee, and Global TB Community Advisory Board (appendix 8 pp 24–25). Data were analysed at Epicentre (Paris, France) and validated for the primary efficacy endpoint by UCSF.

Role of the funding source

The funders of the study (except for Unitaid) had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

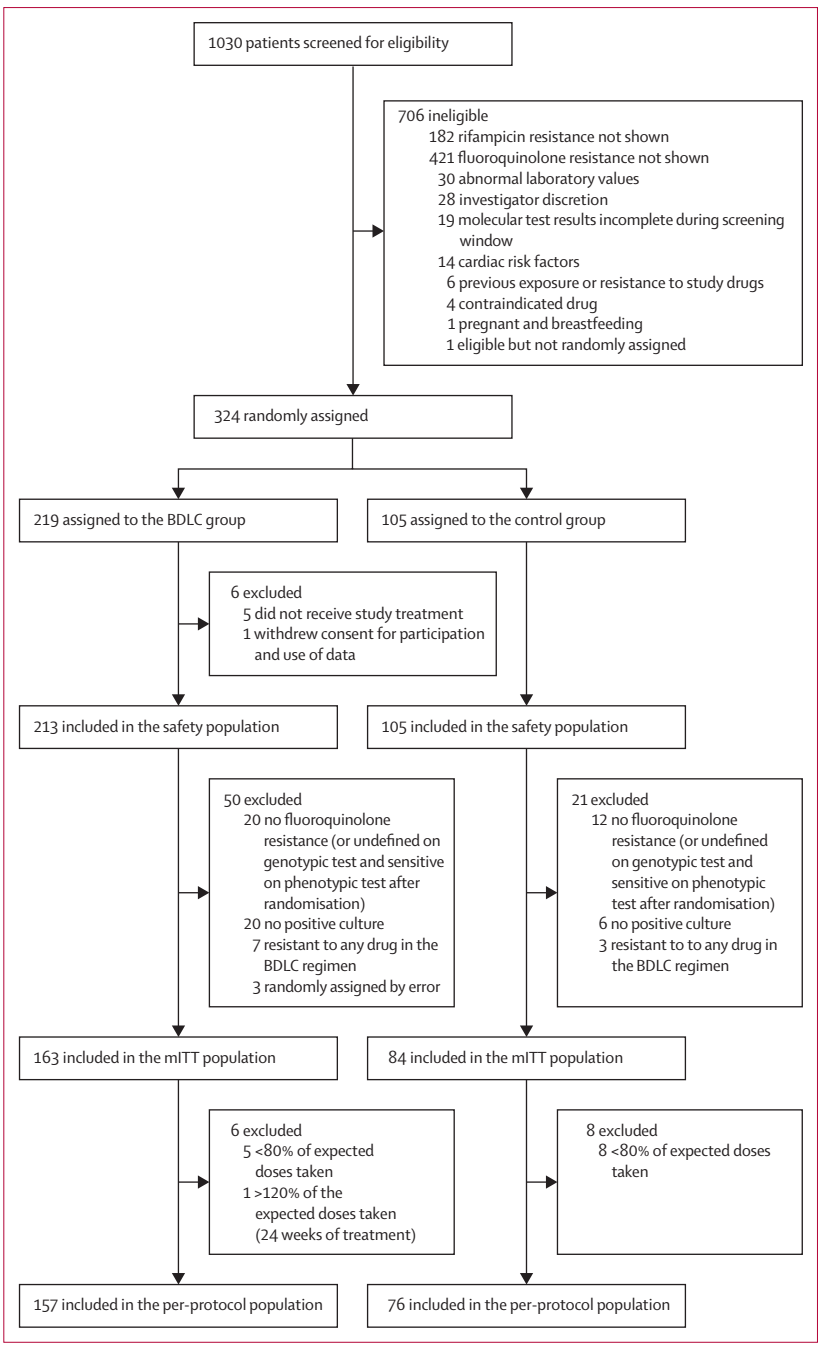

***Figure 1*: Trial profile**
The safety population included all participants who were randomly assigned and received at least one dose of trial treatment. The mITT population included participants from the safety population who had a culture positive for *Mycobacterium tuberculosis* before random assignment (excluding those with baseline phenotypic resistance to BDLC). The per-protocol population included participants from the mITT population who did not receive more than 7 days of a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration and no more than 120% of the expected doses in participants who were to receive 24 weeks of treatment) or those who did not do so because of treatment failure or death. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat.

	BDLC group (n=163)	Control group (n=84)
Sex		
Female	71 (44%)	43 (51%)
Male	92 (56%)	41 (49%)
Median age, years	31·3 (21·7–42·6)	29·1 (20·7–44·6)
Study country		
India	71 (44%)	33 (39%)
Kazakhstan	12 (7%)	6 (7%)
Lesotho	2 (1%)	0
Peru	11 (7%)	7 (8%)
Pakistan	53 (33%)	30 (36%)
Viet Nam	14 (9%)	8 (10%)
Median BMI, kg/m²	17·5 (15·6–20·2)	17·9 (15·3–20·1)
Eastern Cooperative Oncology Group performance status		
0	44 (27%)	24 (29%)
1	95 (58%)	45 (54%)
2	19 (12%)	12 (14%)
3	5 (3%)	3 (4%)
HIV*	1 (1%)	3 (4%)
Hepatitis B, HBsAg positive	2 (1%)	3 (4%)
Hepatitis C, HCVAb positive	7 (4%)	5 (6%)
Type 1 and 2 diabetes	37 (23%)	18 (21%)
Smear result		
Negative or scanty	45 (28%)	23 (27%)
1+	47 (29%)	25 (30%)
2+	33 (20%)	14 (17%)
3+	38 (23%)	22 (26%)
Cavitation	108 (66%)	57 (68%)
Extent of tuberculosis disease†		
Limited	58 (36%)	32 (38%)
Extensive	105 (64%)	52 (62%)
Previous exposure to tuberculosis treatment‡		
None	92 (59%)	39 (49%)
First-line drugs	50 (32%)	34 (43%)
At least second-line drugs	14 (9%)	7 (9%)

Data are n (%) or median (IQR). The mITT population included participants who were randomly assigned, received at least one dose of trial treatment, and had a culture positive for *Mycobacterium tuberculosis* before random assignment (excluding those with baseline phenotypic resistance to BDLC). BDLC=bedaquiline, delamanid, linezolid, and clofazimine. HBsAg=hepatitis B surface antigen. HCV Ab=hepatitis C total antibody. mITT=modified intention-to-treat. *Of four participants living with HIV, two were receiving antiretroviral treatment at baseline (one in the BDLC group and one in the control group) and the other two (in the control group) started antiretroviral treatment within the first 8 weeks after random assignment. †Baseline disease extent (limited disease was defined by a negative or scanty smear for *M tuberculosis* irrespective of cavitation or smear 1+ in the absence of cavitation and extensive disease was defined by smear 2+ or 3+ irrespective of cavitation or smear 1+ in the presence of cavitation). ‡Data on previous exposure to tuberculosis treatment were unknown for 11 participants (seven in the BDLC group and four in the control group).

Table 1: **Baseline characteristics in the mITT population**

Results

Between April 4, 2020, and March 28, 2023, 1030 individuals were screened and 324 (31%) were randomly assigned (219 to the BDLC group and 105 to the control group; figure 1). Overall, 318 (98%) participants were included in the safety population, 247 (76%) in the mITT population, and 233 (72%) in the per-protocol population. Reasons for ineligibility and exclusion from the analysis populations are shown in figure 1. Baseline drug susceptibility testing to all four drugs in the BDLC regimen was performed in 17 participants (appendix 8 p 32).

The mITT population included 247 participants: 104 (42%) randomly assigned in India, 83 (34%) in Pakistan, 22 (9%) in Viet Nam, 18 (7%) in Kazakhstan, 18 (7%) in Peru, and two (1%) in Lesotho (table 1). Overall, 114 (46%) participants were female and 133 (54%) were male, 55 (22%) had diabetes, four (2%) were living with HIV, five (2%) had active hepatitis B virus infection, and 12 (5%) had active hepatitis C virus infection. Median age was 30·5 years (IQR 21·6–43·0), with 18 (7%) participants aged 15–18 years at random assignment. Median BMI was 17·6 kg/m² (15·4–20·1). 157 (64%) participants had extensive disease at baseline and 105 (43%) were previously treated for tuberculosis. Baseline characteristics were well balanced between the two study groups (table 1; appendix 8 p 34).

Among participants in the BDLC group, 47 (29%) of 163 were assigned to receive the 6-month regimen and 116 (71%) were assigned to receive the 9-month regimen using information on baseline disease extent and treatment response. In the control group, all participants received an individualised regimen that initially included four to six drugs, with 71 (85%) of 84 receiving five drugs (appendix 8 p 35). All initial regimens in the control group had bedaquiline, clofazimine, and linezolid; cycloserine (78 [93%]) and delamanid (76 [91%]) were also commonly used. The core regimen of BDLC plus one or more other drugs was used for 76 (91%) participants in the control group. Median treatment duration in the control group was 78·0 weeks (IQR 77·1–78·0; appendix 8 pp 35–36). Median post-treatment follow-up was 63·1 weeks (49·9–68·6) in the BDLC group and 23·9 weeks (16·9–27·0) in the control group (appendix 8 p 36).

In the primary efficacy analysis of the mITT population at week 73, favourable outcome was reached by 141 (87%) of 163 participants in the BDLC group and 75 (89%) of 84 in the control group (adjusted risk difference 0·2% [95% CI –9·1 to 9·5]; $p_{non\text{-}inferiority}$=0·0051). In the per-protocol population, favourable outcome was reached by 138 (88%) of 157 participants in the BDLC group and 71 (93%) of 76 in the control group (adjusted risk difference –3·5% [–12·8 to 5·9]; $p_{non\text{-}inferiority}$=0·037; table 2). The lower bound of the 95% CI around the adjusted risk difference was greater than the non-inferiority margin of –12% in the mITT population and less than the margin in the

per-protocol population; therefore, overall non-inferiority was not shown (figure 2A). In the mITT population, the proportion of participants with treatment failure (seven [4%] in the BDLC group *vs* three [4%] in the control group) and all-cause mortality (four [2%] *vs* two [2%]) were similar between the two groups. Four (5%) participants withdrew consent in the control group and one (1%) in the BDLC group. Recurrent disease occurred in eight (5%) participants in the BDLC group. Central testing at ITM later classified all recurrences as relapses.

Paired testing was available from ITM for 27 participants in the mITT population (appendix 8 pp 37–38). Of those, five (19%) had baseline resistance to bedaquiline and clofazimine (and one also had resistance to delamanid) that had been undetected at trial-site laboratories. Acquired resistance to at least one drug in the BDLC regimen occurred among 14 (9%) of 163 participants—three were among those with undetected baseline resistance. Acquired resistance occurred in two (2%) of 84 participants in the control group and none had baseline resistance to the study drugs. Acquired drug resistance was most common for bedaquiline and clofazimine, followed by delamanid and linezolid (appendix 8 pp 37–39). Overall efficacy results were similar at week 104 in the mITT and per-protocol populations. At week 39 with minimal post-treatment observation, results differed with observed higher efficacy in the BDLC group than in the control group in the mITT population (appendix 8 pp 19, 40–41). Prespecified sensitivity analyses confirmed the primary efficacy findings at week 73 (appendix 8 pp 42–43). One additional relapse had occurred in the BDLC group and none in the control group by week 104. Eight of nine relapses occurred among participants with extensive disease, with a median time to relapse after treatment completion of 30·1 weeks (IQR 14·7–33·3).

In prespecified subgroup analyses at week 73 in the mITT population, treatment efficacy was not statistically significant, except for age ($p_{interaction}$=0·040) and diabetes ($p_{interaction}$=0·0077). Risk of unfavourable outcome with BDLC was higher in people aged 45 years or older and those with diabetes at baseline (appendix 8 pp 20–21). The proportion of favourable outcome was higher in the BDLC group among participants with limited disease (54 [93%] of 58 *vs* 28 [88%] of 32 in the control group; risk difference 5·6% [95% CI –7·6 to 18·8]) and lower in the BDLC group among participants with extensive disease (87 [83%] of 105 *vs* 47 [90%] of 52; risk difference –7·5% [–18·3 to 3·2]; figure 2B and appendix 8 p 22). This observed difference reflects higher relapse rates among participants with extensive than those with limited disease in the BDLC group (figure 3).

At week 73, 317 (100%) of 318 participants included in the safety population had at least one adverse event (table 3). 145 (68%) of 213 participants in the BDLC group versus 77 (73%) of 105 in the control group had at least one grade 3 or higher adverse event and 42 (20%) versus 23 (22%) had at least one serious adverse event. 172 (34%) of 501 grade 3 or higher adverse events and 23 (21%) of 109 serious adverse events were classified by investigators as related to the study drugs. Permanent discontinuation of any study drug due to an adverse event occurred in 30 (14%) participants in the BDLC group and 56 (53%) in the control group. The most frequently discontinued drug was linezolid, followed by cycloserine (appendix 8 p 44).

Eight (4%) participants died in the BDLC group and two (2%) in the control group by week 73, and an additional death occurred in the BDLC group between weeks 73 and 104. The causes of death (each occurring in one participant) were cardiac failure, cardiac failure congestive, cardiogenic shock, coma and renal and hepatic failure, unknown cause, diabetic foot,

	mITT population		Per-protocol population	
	BDLC group (n=163)	Control group (n=84)	BDLC group (n=157)	Control group (n=76)
Favourable outcome				
Number of participants	141 (87%)	75 (89%)	138 (88%)	71 (93%)
Adjusted absolute difference from the control, % (95% CI)*	0·2% (–9·1 to 9·5)	..	–3·5% (–12·8 to 5·9)	..
Participants with negative culture results, weeks 65 and 73	140 (86%)	74 (88%)	137 (87%)	70 (92%)
Participants with favourable bacteriological, clinical, and radiological evolution†	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Unfavourable outcome				
Number of participants	22 (13%)	9 (11%)	19 (12%)	5 (7%)
All-cause mortality‡	4 (2%)	2 (2%)	4 (3%)	2 (3%)
Participants with treatment failure§	7 (4%)	3 (4%)	7 (4%)	3 (4%)
Participants with relapse¶	8 (5%)	0	8 (5%)	0
Participants with permanent treatment discontinuation due to adverse events	1 (1%)	0	0	0
Participants with poor treatment adherence or loss to follow-up	1 (1%)	0	0	0
Participants who withdrew consent	1 (1%)	4 (5%)	0	0

The mITT population included participants who were randomly assigned, received at least one dose of trial treatment, and had a culture positive for *Mycobacterium tuberculosis* before random assignment (excluding those with baseline phenotypic resistance to BDLC). The per-protocol population included participants from the mITT population who did not receive more than 7 days of a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration and no more than 120% of the expected doses in participants who were to receive 24 weeks of treatment) or those who did not do so because of treatment failure or death. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat. *Analyses adjusted for country and baseline extent of tuberculosis disease (mITT n=227, with 20 observations dropped because of perfect separation; per-protocol n=214, with 19 observations dropped because of perfect separation). †Participants without culture results between weeks 65 and 73. ‡Six participants in the mITT died (part of the treatment outcome) and three died in the safety population (excluded from the mITT population). §Participants who permanently discontinued treatment because of a positive sputum culture at week 16 or later or who had a positive sputum culture between weeks 65 and 73 or who had a combination of culture results insufficient to establish favourable outcome and unfavourable bacteriological, radiological, or clinical evolution. ¶Participants who, after treatment completion, started a new treatment regimen and had a confirmed relapse (same strain on baseline and after treatment).

Table 2: **Primary efficacy outcomes at week 73 in the mITT and per-protocol populations**

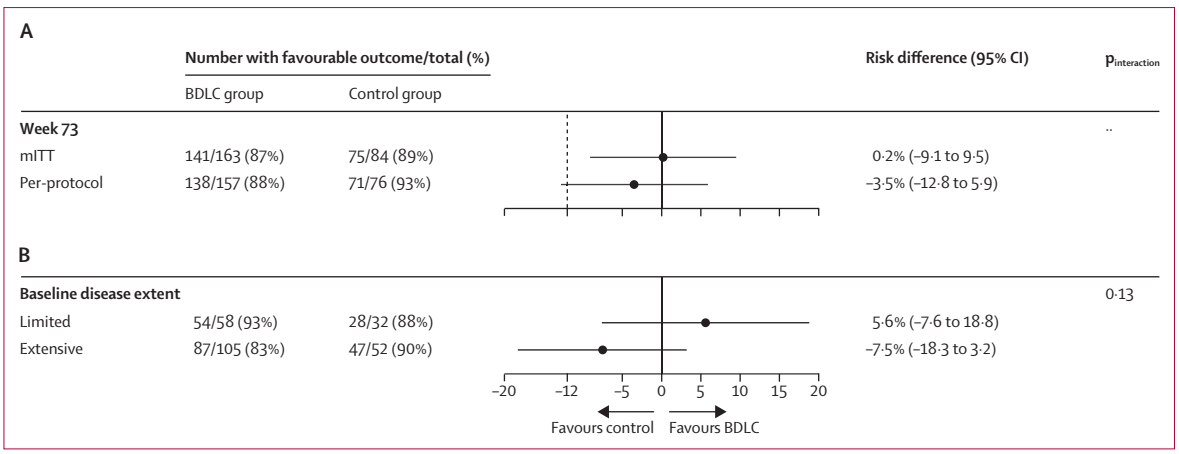

Figure 2: **Primary efficacy analysis at week 73 between the BDLC and control groups**
(A) Forest plot of primary efficacy analysis at week 73 in the mITT and per-protocol populations, adjusted by stratification factors. The non-inferiority margin of –12% is shown by the dashed vertical line. (B) Forest plot at week 73 of the risk difference in the prespecified subgroup analysis, stratified by baseline tuberculosis disease extent. Favourable outcome was defined as two consecutive, negative cultures including one between weeks 65 and 73; or favourable bacteriological, radiological, and clinical evolution) at week 73 after randomisation. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat.

gastrointestinal haemorrhage, lower respiratory tract infection, metabolic acidosis, metastatic colorectal cancer, and death by suicide. Two deaths (one in each group) were assessed by investigators, per pharmacovigilance definitions, as potentially related to the study drugs, although causality was not confirmed (appendix 8 p 45). Of the grade 3–4 adverse events of special interest, peripheral neuropathy occurred in 44 (21%) participants in the BDLC group versus 26 (25%) in the control group and myelosuppression (leukopenia, anaemia, or thrombocytopenia) occurred in 29 (14%) versus 22 (21%; table 3). Grade 3–4 hepatotoxicity (ie, increases in alanine or aspartate aminotransferases) was reported in 13 (6%) participants in the BDLC group and four (4%) in the control group. Three (1%) participants in the BDLC group versus four (4%) in the control group had grade 3–4 prolonged corrected QT interval and two (1%) versus two (2%) had optic neuritis. A prespecified analysis of safety results evaluated at week 104 and post-hoc analysis at 4 weeks after the end of treatment showed similar results to the main safety analysis (appendix 8 pp 46–57). Overall, five participants became pregnant during study participation (appendix 8 p 58).

Discussion

The BDLC strategy showed favourable outcomes at week 73 in 87% (141 of 163) of participants, which is substantially higher than global averages for pre-XDR tuberculosis treatment outcomes[2] and similar to recent trial results in patients with multidrug-resistant or rifampicin-resistant tuberculosis.[7,8,20] However, the BDLC strategy was not non-inferior to the control, which was often similar in terms of regimen composition but supported by one or two additional drugs and given for a longer duration. A possible explanation for this result is the non-significant difference in the efficacy of the BDLC strategy by baseline disease extent. Compared with the control, in those with extensive disease the adjusted risk difference estimate suggests reduced efficacy of BDLC whereas in those with limited disease, the estimate suggests at least a similar efficacy of BDLC. This finding is consistent with the growing body of evidence that extensive disease, defined by measures of bacterial load and lung damage on a chest x-ray, compromises outcomes of several shortened drug-susceptible tuberculosis regimens.[11,12] endTB-Q prospectively applied a stratified medicine approach to overcome this difference between extensive and limited disease, the first such effort in a population comprising exclusively people with pre-XDR tuberculosis. The stratified medicine strategy used in the BDLC group assigned the 9-month regimen—instead of the 6-month regimen—in case of baseline characteristics indicative of extensive disease and absence of a sustained culture conversion by 6 months. This lengthened 9-month treatment does not appear to overcome the increased risk of unfavourable outcome conferred by extensive disease, compared with the control group.

The other main finding of this endTB-Q trial is the apparent increase in relapse in the BDLC strategy 5% (nine of 163) compared with none in the control by week 104. These relapse events occurred mostly among participants with extensive disease. The observed follow-up period after treatment completion was longer in the BDLC group than in the control group (median 63·1 weeks [IQR 49·9–68·6] *vs* 23·9 [16·9–27·0]), possibly leading to an underestimate of relapse in the control group. Scarce data exist on recurrence after longer regimens for multidrug-resistant or rifampicin-resistant tuberculosis. No recurrence occurred in the control group during 132 weeks of post-randomisation follow-up in the STREAM 1 trial for patients with

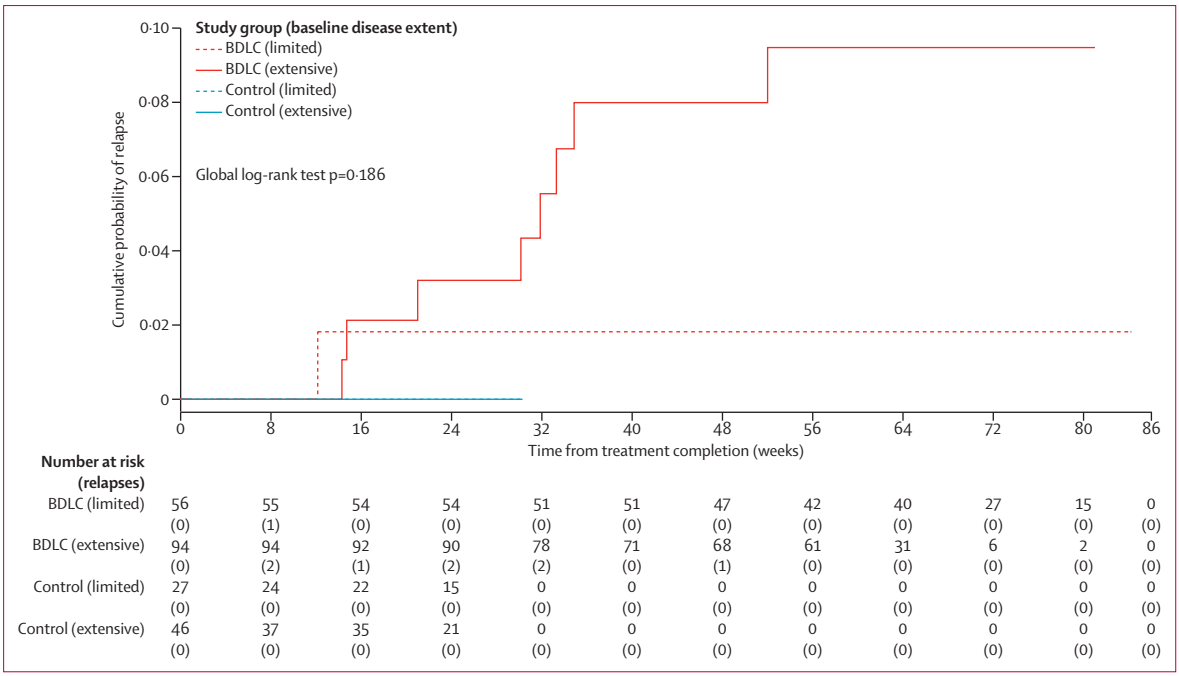

Figure 3: **Kaplan–Meier plot of time to relapse (from treatment completion) by baseline extent of tuberculosis disease in the mITT population**
Observations censored at the time of post-treatment end of follow-up (early study discontinuation, death, or end of follow-up). Baseline disease extent (limited disease was defined by a negative or scanty smear for M tuberculosis irrespective of cavitation or smear 1+ in the absence of cavitation and extensive disease was defined by smear 2+ or 3+ irrespective of cavitation or smear 1+ in the presence of cavitation). BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat.

fluoroquinolone-susceptible tuberculosis.[21] Similarly, in TB-PRACTECAL, no recurrences were observed in the control group (including those receiving shorter 6-month regimens and longer 18-month regimens) during 108 weeks of follow-up for fluoroquinolone-susceptible and fluoroquinolone-resistant tuberculosis.[7] Specific to longer regimens containing new and repurposed drugs, in the endTB observational cohort study which included a high proportion of patients with fluoroquinolone-resistant multidrug-resistant or rifampicin-resistant tuberculosis, ten (<1%) of 1991 had recurrence up to 6 months after treatment completion.[22,23] Although none of these studies offer a direct match to the population and regimens used in our control group, universal reports of minimal or no relapse suggest a low likelihood of substantial unobserved relapse in the control group in endTB-Q. Worryingly, acquired drug resistance was more frequent with the BDLC strategy (14 [9%] of 163 *vs* two [2%] of 84 with the control).

Relapse and acquired drug resistance findings in the endTB-Q BDLC group are consistent with other clinical trials and observational studies evaluating shorter regimens for patients with pre-XDR tuberculosis, which have shown similar rates of these outcomes. The BEAT Tuberculosis trial evaluated, as part of a treatment strategy, an experimental regimen for patients with pre-XDR tuberculosis that was similar to that in endTB-Q. The BEAT Tuberculosis strategy was non-inferior to the standard of care for multidrug-resistant or rifampicin-resistant tuberculosis; however, recurrences occurred in ten (5%) of 202 participants at 76 weeks in the experimental group, with a 6·9% (14 of 202) unfavourable outcome at the end of treatment. Acquired drug resistance to bedaquiline occurred in all five participants in the experimental group who had treatment failure or recurrence and had pretreatment and post-treatment drug susceptibility testing to bedaquiline; all had baseline fluoroquinolone resistance.[8] The BEAT India study tested BDLC given for 6–9 months in a population including 96% of participants with pre-XDR tuberculosis. Follow-up occurred for 48 weeks with recurrence seen in 2% (three of 165). The short follow-up and absence of reported drug-susceptibility testing leave open the possibility of more relapse and acquisition of drug resistance.[24] Other trials evaluating short fluoroquinolone-sparing regimens reported recurrence rates that were similar to endTB-Q: TB-PRACTECAL showed 4% (nine of 226) recurrence at 72 weeks in participants with multidrug-resistant or rifampicin-resistant tuberculosis who received BPaL or BPaLC regimens and ZeNix showed 6% (11 of 181) recurrence at 78 weeks in participants receiving various dosages and durations of BPaL. In TB-PRACTECAL, acquired bedaquiline resistance occurred in three participants with recurrence and who had results available, all three had received BPaL. In ZeNix, acquired drug resistance was detected in 5% (seven of 143) of participants receiving the three-drug BPaL regimen.[25] Compared with these results, four-drug

	BDLC group (n=213)	Control group (n=105)	Absolute difference (%, 95% CI)*
Participants with any adverse event	213 (100%)	104 (99%)	..
Grade 3 or higher adverse events			
Participants with ≥1 event	145 (68%)	77 (73%)	−6·6 (−15·6 to 2·4)
Number of events	319	182	..
Number of events related to study drugs (% of all events)†	93 (29%)	79 (43%)	..
Serious adverse events			
Participants with ≥1 event	42 (20%)	23 (22%)	−0·9 (−10·6 to 8·9)
Number of events	66	43	..
Number of events related to study drugs (% of all events)†	12 (18%)	11 (26%)	..
Death from any cause	8 (4%)	2 (2%)	1·7 (−2·0 to 5·4)‡
Number of events related to study drugs†	1 (13%)	1 (50%)	..
Adverse event of special interest			
Participants with ≥1 event	73 (34%)	47 (45%)	−10·5 (−21·9 to 1·0)‡
Participants with any grade 3–4 increase in alanine or aspartate aminotransferases	13 (6%)	4 (4%)	..
Participants with any grade 3–4 leukopenia, anaemia, or thrombocytopenia	29 (14%)	22 (21%)	..
Participants with any grade 3–4 peripheral neuropathy	44 (21%)	26 (25%)	..
Participants with any grade 3–4 optic neuritis	2 (1%)	2 (2%)	..
Participants with any grade 3–4 prolonged corrected QT interval§	3 (1%)	4 (4%)	..
Participants with permanent discontinuation of any drug due to an adverse event	30 (14%)	56 (53%)	−39·1 (−49·7 to −28·5)

The safety population included all participants who were randomly assigned and received at least one dose of trial treatment. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. *Analyses adjusted for country and baseline extent of tuberculosis disease. †Related was defined as at least a reasonable possibility to be caused by one or more drugs in the regimen. ‡Analyses adjusted for baseline extent of tuberculosis disease, given the absence of convergence when adjusting for all stratification variables. §QT interval corrected according to the Fridericia formula.

Table 3: **Safety analysis at week 73 in the safety population**

and five-drug fluoroquinolone-containing short regimens that are currently recommended for patients with fluoroquinolone-susceptible multidrug-resistant or rifampicin-resistant tuberculosis were shown to effectively prevent relapse and substantially reduce the risk of acquired drug resistance.[7,20,26] Overall, our findings underscore the role of fluoroquinolones as key drugs in shortening multidrug-resistant or rifampicin-resistant tuberculosis treatment; with the antituberculosis drugs currently available, the loss of fluoroquinolone activity in *M tuberculosis* might signal the need for longer or reinforced regimens. Therefore, rapid molecular testing for fluoroquinolone resistance is crucial in all patients with multidrug-resistant or rifampicin-resistant tuberculosis.

Both groups had frequent grade 3 or higher adverse events (145 [68%] of 213 with BDLC *vs* 77 [73%] of 105 with the control). Compared with other reports of similar regimens—eg, 34% (69 of 202) in the BEAT Tuberculosis trial,[8] this frequency is high. Permanent treatment discontinuation of the full regimen due to adverse events was rare in endTB-Q, occurring in one (1%) participant in the BDLC group and none in the control group; this finding is considerably lower than in other trials.[6,20] Adverse events reported in endTB-Q were often considered unrelated to the study drugs. Taken together, this information suggests that the high frequency of reported events might partly reflect the rigorous monitoring and reporting in a clinical trial setting. Although such high rates of events might not be reported in routine care, they could still have implications for treatment completion and other, more person-centred outcomes.[27]

Permanent discontinuation of at least one drug due to an adverse event occurred in 30 (14%) participants in the BDLC group and 56 (53%) in the control group. This difference likely reflects the greater number of drugs in the control regimens—nearly all (98%) contained more than four drugs—and their longer duration, which is relevant because regimens containing more drugs hold greater toxicity potential and investigators unmasked to treatment might be more likely to discontinue a medication in a regimen containing more drugs. Linezolid-related toxic effects, such as peripheral neuropathy (44 [21%] participants in the BDLC group vs 26 [25%] in the control group) and myelosuppression (nine [14%] *vs* 22 [21%]), were frequent in both groups but the proportion was slightly higher in the control group, in which linezolid dose was not routinely reduced at 16 weeks and total linezolid exposure was higher. Linezolid is part of every WHO-recommended regimen for the treatment of pre-XDR tuberculosis. Treatment limiting linezolid toxicity has been observed with other regimens, which is especially worrisome with the three-drug BPaL regimen.[4,5] When linezolid is held or stopped, the resulting two-drug regimen might increase risk of poor outcomes, including acquired drug resistance. The four-drug BDLC regimen used in endTB-Q and BEAT Tuberculosis preserves at least three active drugs even when linezolid is discontinued.

Our study had three main limitations. First, site trial staff and participants were not masked to treatment assignment because of the treatment duration difference between the BDLC and control groups. To mitigate risk of bias, treatment assignment was concealed from laboratory staff and central investigators. Second, the proportion of participants excluded from the mITT population (24%) was higher than expected (6%). Negative pretreatment cultures (26 [8%] with no positive baseline culture excluded from the mITT population) and baseline isolates susceptible to fluoroquinolones (32 [10%] with no fluoroquinolone resistance) in phenotypic drug susceptibility testing were more common than expected (figure 1). This high proportion of participants excluded from the mITT population reduced statistical power (compared with that estimated in the study design) to establish non-inferiority. Third, baseline drug susceptibility testing for new or repurposed drugs was

not available at trial-site laboratories for most participants and at least five with an unfavourable outcome had undetected baseline resistance to these drugs. This limitation might have led to an underestimate of efficacy in BDLC and control groups for the treatment of patients with pre-XDR tuberculosis. This finding also highlights the necessity of improving rapid and reliable resistance testing, especially for newer and repurposed drugs, to ensure that patients receive the most appropriate regimen.

The strengths of our study include the randomised, internally, concurrently controlled design. To our knowledge, this study is the first trial designed to draw conclusions on pre-XDR tuberculosis and the first to apply stratified medicine in this population. The control regimen performed well in terms of the favourable outcome and including a control group as an internal comparator allowed the finding of not showing non-inferiority in the BDLC group. High retention of participants—including in the control group—and completeness of study data indicate high-quality implementation. The study population was heterogeneous, including a range of tuberculosis disease severity and substantial burdens of important comorbidities (such as active hepatitis B or C and diabetes). Although the small number of participants (2%) with HIV coinfection precludes inference from endTB-Q about this population, approximately 50% of participants in the BEAT-Tuberculosis study were living with HIV.[8] Consequently, this complementary study provides important information about the BDLC regimen in this priority population.

In conclusion, the BDLC strategy was not non-inferior to a well performing internal comparator (ie, WHO-recommended longer standard of care). Both treatment strategies produced a high proportion of favourable outcomes, partly due to the support provided (ie, nutritional, economic, and transportation) under trial conditions, highlighting the importance of quality of care in all treatments for patients with pre-XDR tuberculosis. Our findings support the use of the BDLC regimen for people with pre-XDR tuberculosis who have limited disease at baseline. For individuals with extensive pre-XDR tuberculosis, longer individualised regimens including at least five drugs might be better than the available, shorter regimens at reaching relapse-free cure and preventing the acquisition of drug resistance. In all cases, treatment choice should be guided by conversations between patients and providers about the risks and benefits of options and patient preferences, characteristics, and risk factors.

The endTB-Q trial successfully implemented a stratified-medicine approach in tuberculosis treatment, paving the way for future efforts towards personalised medicine.[28,29] Better biomarkers for the prediction of treatment outcomes are sorely needed to improve the efficacy of this approach.[30] Given the key role of the fluoroquinolone, randomised controlled trials performed specifically in populations with tuberculosis resistant to fluoroquinolone—and with sufficient follow-up to detect relapse—are needed to identify the optimum duration and composition of regimens for pre-XDR tuberculosis.

Contributors

BCdJ, CDM, EB, FV, GF, GEV, KS, LG, MB, MLR, PN, and UK designed the trial and study protocol. DVN, DTP, ES-G, LL, LVD, MTA, NS, NVN, PN, SB, SPan, SPat, THP, VC, and ZD were site principal investigators and responsible for participant recruitment. BCdJ, EA, and PR oversaw centrally all microbiology processes. CDM, EB, LG, MB, and MG drafted and approved the statistical analysis plan. MG performed the statistical analysis. PPJP validated the analysis for the primary efficacy endpoint. CDM, FK, FV, GEV, LG, MG, MHA, MLR, PN, SA, and UK initially drafted this manuscript. All authors have access to data, contributed to data interpretation, critical review, and revision of the manuscript and approved the decision to submit for publication. CDM and LG verified the underlying data.

Declaration of interests

SC and NL received support from Unitaid. HM was awarded a Fellowship to the University of Cape Town from the Wellcome Trust. IM received consulting fees from the Médecins Sans Frontières (MSF) Access Campaign as an APH consultant. PPJP received funding from Partners in Health (PIH) for this study. MLR was the coleader on the endTB grant from Unitaid; received cofunding for the endTB-Q clinical trial by MSF; is provided 20% full-time employee equivalent in 2024 and 2025 from PIH for working on Global TB issues, including writing this manuscript and other manuscripts; is a technical project lead for arcTB (possible Unitaid grant at 50% full-time employee equivalent from 2025 to 2027); is a senior global health physician (average 20% full-time employee equivalent in the past 3 years); is the coinvestigator on the STEM-TB grant (average 5% full-time employee equivalent); received a career development grant in nutrition and TB from Brigham and Women's Hospital, a USAID Regional Approaches for Eradicating Tuberculosis in Central Asia grant (10% for 3 years starting Oct 1, 2024), and a grant from USAID Global Resilience Against Drug-Resistant Tuberculosis (expected to average 40% in 5 years starting Oct 1, 2024); provided consulting for WHO EURO (an observational study of modified short MDR-TB regimens in Europe and Central Asia); received travel support from WHO for a 3-day meeting on MDR-TB regimens and treatment in 2023; travel and accommodation support from Unitaid for TB meetings related to the World Union TB conference 2023; travel support for presenting the endTB trial to Unitaid and WHO in August, 2023; travel support for an endTB investigators meeting in September, 2023; and travel and accommodation support to attend the World Union TB conference in 2024. GEV received payments to his institution from Unitaid, MSF, PIH (SPHQ15-LOA-045), National Institutes of Health National Institute of Allergy and Infectious Diseases (NIH NIAID; K08 AI141740); received grants or contracts from NIH NIAID (R01 AI135124, R25 AI147375, R34 AI179568, U01 AI152980, UM1 AI068636, and UM1 AI179699); USAID (7200AA22CA00005); and received consulting fees from the Gates Medical Research Institute. All other authors declare no competing interests. DVN, LVD, and HTTP received funding to their institution from PIH for this study. BCdJ received grants from Janssen Pharmaceuticals for the C211 trial on bedaquiline for pediatric TB and for the BE-PEOPLE trial on leprosy post-exposure prophylaxis; and received grants to their institution from the Research Foundation Flanders (FWO; number FWO G0A7720N and FWO W001822N). CDM received a grant to their institution from Unitaid. CB was an MSF employee from 2015 to 2023. LG received a grant from Unitaid for the endTB project.

Data sharing

De-identified data from the trial database on participants who agreed to future use of data will be made available via the endTB Data Sharing Initiative (https://endtb.org/data-sharing-initiative) no later than 12 months after publication of the trial results. We will also provide access to the study protocol, statistical analysis plan, data dictionary, case report forms, and informed consent forms (https://endtb.org).

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References

1 WHO. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis. 2020. https://www.who.int/publications/i/item/9789240018662 (accessed Jan 5, 2025).

2 Pedersen OS, Holmgaard FB, Mikkelsen MKD, et al. Global treatment outcomes of extensively drug-resistant tuberculosis in adults: a systematic review and meta-analysis. *J Infect* 2023; **87:** 177–89.

3 Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. *Int J Tuberc Lung Dis* 2016; **20:** 177–86.

4 Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* **2020; 382: 893–902.**

5 Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* **2022; 387: 810–23.**

6 Nyang'wa B-T, Berry C, Kazounis E, et al, and the TB-PRACTECAL Study Collaborators. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* **2022; 387: 2331–43.**

7 Nyang'wa B-T, Berry C, Kazounis E, et al. Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med* 2024; **12:** 117–28.

8 Conradie F, Badat T, Poswa A, et al. BEAT Tuberculosis: a randomized controlled trial of a 6-month strategy for rifampicin-resistant tuberculosis. *medRxiv* 2025; published online May 6. https://doi.org/10.1101/2025.05.04.25326549 (preprint).

9 WHO. Key updates to the treatment of drug-resistant tuberculosis: rapid communication, June 2024. 2024. https://www.who.int/publications/i/item/B09123 (accessed Jan 5, 2025).

10 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. 2022. https://www.who.int/publications/i/item/9789240063129 (accessed Jan 5, 2025).

11 Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* **2018; 24: 1708–15.**

12 Chang VK, Imperial MZ, Phillips PPJ, et al. Risk-stratified treatment for drug-susceptible pulmonary tuberculosis. *Nat Commun* 2024; **15:** 9400.

13 Patil SB, Tamirat M, Khazhidinov K, et al. Evaluating newly approved drugs in combination regimens for multidrug-resistant tuberculosis with fluoroquinolone resistance (endTB-Q): study protocol for a multi-country randomized controlled trial. *Trials* 2023; **24:** 773.

14 Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; **308:** 2594–604.

15 Dreyer V, Mandal A, Dev P, et al. High fluoroquinolone resistance proportions among multidrug-resistant tuberculosis driven by dominant L2 *Mycobacterium tuberculosis* clones in the Mumbai Metropolitan Region. *Genome Med* 2022; **14:** 95.

16 Ali S, Khan MT, Khan AS, Abbas Q, Irfan M. Fluoroquinolone resistance among isolates of *Mycobacterium tuberculosis* in Khyber Pakhtunkhwa, Pakistan. *Microb Drug Resist* 2021; **27:** 786–91.

17 WHO. WHO consolidated guidelines on tuberculosis: module 4: treatment and care. 2025. https://www.who.int/publications/i/item/9789240107243 (accessed May 10, 2025).

18 Tweed CD, Wills GH, Crook AM, et al. A partially randomised trial of pretomanid, moxifloxacin and pyrazinamide for pulmonary TB. *Int J Tuberc Lung Dis* 2021; **25:** 305–14.

19 Paton NI, Cousins C, Suresh C, et al. Treatment strategy for rifampin-susceptible tuberculosis. *N Engl J Med* 2023; **388:** 873–87.

20 Guglielmetti L, Khan U, Velásquez GE, et al. Oral regimens for rifampin-resistant, fluoroquinolone-susceptible tuberculosis. *N Engl J Med* 2025; **392:** 468–82.

21 Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; **380:** 1201–13.

22 Sauer SM, Mitnick CD, Khan U, et al. Estimating post-treatment recurrence after multidrug-resistant tuberculosis treatment among patients with and without human immunodeficiency virus: the impact of assumptions about death and missing follow-up. *Clin Infect Dis* 2024; **78:** 164–71.

23 Khan PY, Franke MF, Hewison C, et al. All-oral longer regimens are effective for the management of multidrug-resistant tuberculosis in high-burden settings. *Eur Respir J* 2022; **59:** 2004345.

24 Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. *Clin Infect Dis* 2022; **76:** e938–46.

25 Timm J, Bateson A, Solanki P, et al. Baseline and acquired resistance to bedaquiline, linezolid and pretomanid, and impact on treatment outcomes in four tuberculosis clinical trials containing pretomanid. *PLoS Glob Public Health* 2023; **3:** e0002283.

26 Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet* 2022; **400:** 1858–68.

27 Burman W, Rucsineanu O, Horsburgh CR, Johnston J, Dorman SE, Menzies D. Research on the treatment of rifampin-susceptible tuberculosis-time for a new approach. *PLoS Med* 2024; **21:** e1004438.

28 Makone A, Angami K, Bhattacharya D, et al. One size does not fit all: community views on choices for TB treatment and prevention. *Public Health Action* 2023; **13:** 67–69.

29 Guglielmetti L, Panda S, Abubakirov A, Salahuddin N, Perrin C, Mitnick CD. Equitable, personalised medicine for tuberculosis: treating patients, not diseases. *Lancet Respir Med* 2025; **13:** 382–85.

30 Schildkraut JA, Köhler N, Lange C, Duarte R, Gillespie SH. Advances in tuberculosis biomarkers: unravelling risk factors, active disease and treatment success. *Breathe (Sheff)* **2024;** 20: 240003.