Bedaquiline-pretomanid-moxifloxacin-pyrazinamide for drug-sensitive and drug-resistant pulmonary tuberculosis treatment: a phase 2c, open-label, multicentre, partially randomised controlled trial

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Summary

Background The current tuberculosis (TB) drug development pipeline is being re-populated with candidates, including nitroimidazoles such as pretomanid, that exhibit a potential to shorten TB therapy by exerting a bactericidal effect on non-replicating bacilli. Based on results from preclinical and early clinical studies, a four-drug combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) regimen was identified with treatment-shortening potential for both drug-susceptible (DS) and drug-resistant (DR) TB. This trial aimed to determine the safety and efficacy of BPaMZ. We compared 4 months of BPaMZ to the standard 6 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) in DS-TB. 6 months of BPaMZ was assessed in DR-TB.

Methods SimpliciTB was a partially randomised, phase 2c, open-label, clinical trial, recruiting participants at 26 sites in eight countries. Participants aged 18 years or older with pulmonary TB who were sputum smear positive for acid-fast bacilli were eligible for enrolment. Participants with DS-TB had *Mycobacterium tuberculosis* with sensitivity to rifampicin and isoniazid. Participants with DR-TB had *M tuberculosis* with resistance to rifampicin, isoniazid, or both. Participants with DS-TB were randomly allocated in a 1:1 ratio, stratified by HIV status and cavitation on chest radiograph, using balanced block randomisation with a fixed block size of four. The primary efficacy endpoint was time to sputum culture-negative status by 8 weeks; the key secondary endpoint was unfavourable outcome at week 52. A non-inferiority margin of 12% was chosen for the key secondary outcome. Safety and tolerability outcomes are presented as descriptive analyses. The efficacy analysis population contained patients who received at least one dose of medication and who had efficacy data available and had no major protocol violations. The safety population contained patients who received at least one dose of medication. This study is registered with ClinicalTrials.gov (NCT03338621) and is completed.

Findings Between July 30, 2018, and March 2, 2020, 455 participants were enrolled and received at least one dose of study treatment. 324 (71%) participants were male and 131 (29%) participants were female. 303 participants with DS-TB were randomly assigned to 4 months of BPaMZ (n=150) or HRZE (n=153). In a modified intention-to-treat (mITT) analysis, by week 8, 122 (84%) of 145 and 70 (47%) of 148 participants were culture-negative on 4 months of BPaMZ and HRZE, respectively, with a hazard ratio for earlier negative status of 2·93 (95% CI 2·17–3·96; p<0·0001). Median time to negative culture (TTN) was 6 weeks (IQR 4–8) on 4 months of BPaMZ and 11 weeks (6–12) on HRZE. 86% of participants with DR-TB receiving 6 months of BPaMZ (n=152) reached culture-negative status by week 8, with a median TTN of 5 weeks (IQR 3–7). At week 52, 120 (83%) of 144, 134 (93%) of 144, and 111 (83%) of 133 on 4 months of BPaMZ, HRZE, and 6 months of BPaMZ had favourable outcomes, respectively. Despite bacteriological efficacy, 4 months of BPaMZ did not meet the non-inferiority margin for the key secondary endpoint in the pre-defined mITT population due to higher withdrawal rates for adverse hepatic events. Non-inferiority was demonstrated in the per-protocol population confirming the effect of withdrawals with 4 months of BPaMZ. At least one liver-related treatment-emergent adverse effect (TEAE) occurred among 45 (30%) participants on 4 months of BPaMZ, 38 (25%) on HRZE, and 33 (22%) on 6 months of BPaMZ. Serious liver-related TEAEs were reported by 20 participants overall; 11 (7%) among those on 4 months of BPaMZ, one (1%) on HRZE, and eight (5%) on 6 months of BPaMZ. The most common reasons for discontinuation of trial treatment were hepatotoxicity (ten participants [2%]), increased hepatic enzymes (nine participants [2%]), QTcF prolongation (three participants [1%]), and hypersensitivity (two participants [<1%]).

Interpretation For DS-TB, BPaMZ successfully met the primary efficacy endpoint of sputum culture conversion. The regimen did not meet the key secondary efficacy endpoint due to adverse events resulting in treatment withdrawal. Our study demonstrated the potential for treatment-shortening efficacy of the BPaMZ regimen for DS-TB and DR-TB,

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providing clinical validation of a murine model widely used to identify such regimens. It also highlights that novel, treatment-shortening TB treatment regimens require an acceptable toxicity and tolerability profile with minimal monitoring in low-resource and high-burden settings. The increased risk of unpredictable severe hepatic adverse events with 4 months of BPaMZ would be a considerable obstacle to implementation of this regimen in settings with high burdens of TB with limited infrastructure for close surveillance of liver biochemistry. Future research should focus on improving the preclinical and early clinical detection and mitigation of safety issues together and further efforts to optimise shorter treatments.

Funding TB Alliance.

Introduction

After a gap of 50 years in developing new drugs for treatment of tuberculosis (TB), novel classes of anti-tuberculosis antibiotics have become available over the past decade.[1] In drug-susceptible tuberculosis (DS-TB), the treatment-shortening potential of moxifloxacin alongside optimised-dose rifapentine has been established,[2,3] with a 4-month drug combination showing non-inferiority to the standard 6-month regimen.[3] For drug-resistant tuberculosis (DR-TB), new agents such as bedaquiline (a diarylquinoline) and pretomanid (a nitroimidazole) have been successfully incorporated alongside linezolid into regimens which are approved for use by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and are incorporated into current WHO guidelines.[4–9]

A regimen of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) performed best in murine models, producing stable cure after 2 months of

Research in context

Evidence before this study

We searched PubMed for clinical trials published between Jan 1, 1970, and Dec 31, 2023, studying tuberculosis drug regimens using MeSH terms "bedaquiline" AND "pretomanid" AND "moxifloxacin" AND "pyrazinamide". The regimen of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) has been studied singularly and in different combinations. Data from preclinical studies suggested this regimen to have high bactericidal and bacteriostatic potency and it was the best performing regimen producing stable cure after 2 months of treatment, making it appropriate for treating both drug-sensitive (DS-TB) and drug-resistant tuberculosis (DR-TB) with treatment-shortening potential. Results from an 8-week phase 2b trial (NC005) showed that this combination regimen was effective as measured by time-dependent decline of viable bacteria demonstrating promising 8 week safety and efficacy of BPaZ and BPaMZ in DS-TB and DR-TB, respectively. The combination was also shown to be safe and well tolerated, supporting late-phase clinical trial evaluation. The results of a phase 3 clinical trial (NC006) which were available after the start of this study, comparing three experimental PaMZ regimens were inconclusive as the trial was stopped early after phase 2 trial data (NC005) suggested that the addition of bedaquiline to the PaMZ combination was associated with greater efficacy. However, a higher proportion of serious adverse events most commonly hepatic in nature was reported in the experimental arms of NC006.

Added value of this study

Following phase 2 and 2b studies sponsored by the TB Alliance, this phase 2c trial was the first clinical study to evaluate the efficacy and safety of the combination of BPaMZ given for longer than 8 weeks. The regimen was administered for 4 months to patients with DS-TB and for 6 months to patients with DR-TB.

Implications of all the available evidence

Patients with DS-TB receiving 4 months of BPaMZ had faster sputum culture conversion by 8 weeks compared with standard-of-care control treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol (conversion to sputum culture negative of 84% *vs* 47%, respectively). 86% of participants with DR-TB receiving 6 months of BPaMZ reached culture negative status by week 8. However, by week 52, 4 months of BPaMZ did not meet the non-inferiority margin in pre-defined microbiologically eligible and assessable analysis DS-TB populations due to higher withdrawal rates for adverse hepatic events. A similarly high hepatotoxicity event rate was observed with 6 months of BPaMZ for DR-TB. Importantly, our BPaMZ data showed bactericidal activity similar to previous preclinical studies, providing clinical validation of a murine model widely used to identify regimens with treatment-shortening potential. However, our results also highlight the need for better preclinical models to predict clinical safety as novel, treatment-shortening TB treatment regimens also require an acceptable toxicity and tolerability profile for programmatic use in low-resource and high-burden settings. The study shows significant potential in the treatment of DS-TB and DR-TB, but also highlights challenges in terms of safety and tolerability. Future research should focus on improving resistance detection, developing new drug regimens, and assessing the overall feasibility of these treatments.

treatment.[10–14] This generated interest in BPaMZ as a regimen with the potential to shorten DS-TB treatment, and as an option for DR-TB. In phase 2 clinical trials, BPaMZ was safe, well tolerated, and accelerated sputum culture conversion by 8 weeks,[15–17] supporting progression to late-phase clinical trials.

In 2015, the phase 3 STAND trial[18] was initiated to assess three experimental pretomanid, moxifloxacin, and pyrazinamide (PaMZ) regimens without bedaquiline.[18] The trial was suspended after three fatal hepatic adverse events in the experimental groups. Detailed review of the data reported no conclusive evidence of increased risk for severe drug-induced liver injury on PaMZ and the independent Data Safety Monitoring Committee (DSMC) recommended resuming enrolment with additional safety monitoring. However, by that time data showing BPaMZ having more promising bactericidal activity were available.[17] Therefore, the SimpliciTB study was developed to evaluate BPaMZ in participants with pulmonary DS-TB and DR-TB.

In SimpliciTB, we aimed to determine the safety and efficacy of a combination regimen of 4 months of BPaMZ compared with standard 6-month tuberculosis therapy in patients with newly diagnosed DS-TB. We also assessed the response in patients with DR-TB to a 26-week course of the same BPaMZ dosing regimen.

Methods

Study design and participants

SimpliciTB was a partially randomised, open-label, phase 2c multicentre study comparing 4 months of BPaMZ with a standard 6-month regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) as a control in participants with DS-TB, and evaluating a 6-month BPaMZ regimen in participants with DR-TB. The trial recruited participants from 26 sites across South Africa, Tanzania, Uganda, Georgia, Russia, the Philippines, Malaysia, and Brazil between July 30, 2018, and March 2, 2020. Full details of the design and implementation of the trial are provided in the protocol.

All local and national ethics committees approved the protocol (appendix pp 5–6). A DSMC of clinicians and statisticians reviewed the unblinded data and oversaw the conduct of the trial.

Participants aged 18 years or older with pulmonary TB who were sputum smear positive for acid-fast bacilli (score of ≥1 using the IUATLD/WHO criteria)[19] were eligible for enrolment after written informed consent. Participants with DS-TB were either newly diagnosed or untreated for at least 3 years after they were cured from a previous TB episode, and had growth from sputum of *Mycobacterium tuberculosis* sensitive to rifampicin and isoniazid. Participants with DR-TB were defined as those whose sputum cultures showed resistance to rifampicin, isoniazid, or both.

Detection of baseline fluoroquinolone resistance by rapid sputum-based molecular screening or phenotypic drug susceptibility testing resulted in study exclusion. Participants who were HIV positive with a $CD4^+$ cell count greater than 100 cells per mm^{-3} could be enrolled. Participants with a baseline QT/QTc prolongation over 500 ms, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase three times the upper limit of normal (×ULN) or greater, and total bilirubin more than 1·5×ULN were excluded. Participants with QTcF over 450 were recruited only after discussion with a medical monitor. Full inclusion and exclusion criteria are described in the protocol and the appendix (pp 7–11).

Randomisation and masking

Participants with DS-TB were randomly assigned in a 1:1 ratio, stratified by cavitation on chest radiograph and HIV status (with a target of up to 50% of participants being HIV positive) using balanced block randomisation with a fixed block size of four to either 4 months of BPaMZ or 6 months of standard WHO weight-based HRZE treatment. Those on 4 months of BPaMZ received bedaquiline 200 mg once daily for 8 weeks, followed by bedaquiline 100 mg daily for 9 weeks, together with daily pretomanid 200 mg, moxifloxacin 400 mg, and pyrazinamide 1500 mg for all 17 weeks. Those on HRZE received standard WHO weight-based dosing of isoniazid, rifampicin, pyrazinamide, and ethambutol for 8 weeks, followed by isoniazid and rifampicin for 17 weeks. A third group of patients with DR-TB was concurrently enrolled, using bedaquiline 200 mg daily for 8 weeks, then 100 mg daily for 18 weeks, together with pretomanid 200 mg plus moxifloxacin 400 mg plus pyrazinamide 1500 mg daily for 26 weeks, primarily to examine the consistency of response between the drug-sensitive and drug-resistant populations treated with the same regimen to which both populations were sensitive, thus providing insights into a potential pan-TB regimen that would be agnostic to rifampicin susceptibility.

All participants received their first dose of treatment within 9 days of screening (day 1) and were reviewed weekly to week 8, at weeks 12, 17, and 26, then every 3 months until week 104 (24 months). Allocation concealment was not performed. Participants, trial investigators, and staff (including laboratory staff) were not masked to treatment randomisation and allocation. However, outside of the interim analysis, aggregate data by study group were only seen by the DSMC during the trial.

See Online for appendix

Procedures

TB diagnosis was established from one spot sputum sample for smear microscopy and molecular testing for resistance to isoniazid, rifampicin, and fluroquinolones by line-probe (Hain; Nehren, Germany). Two sputum samples were collected for liquid culture (Mycobacterial Growth Indicator Tube system, MGIT; Wokingham, UK) at all visits thereafter. Minimum inhibitory concentration

determination and whole-genome sequencing was performed on *M tuberculosis* isolates from baseline cultures, and on isolates from the first positive culture at or after week 17 at a central laboratory (University College London, Central Laboratory, London, UK) to identify resistance, and to distinguish relapse from reinfection in recurrent disease.[20] Participants randomly assigned to DS-TB therapy with subsequently detected phenotypic isoniazid or rifampicin resistance were withdrawn from the study if allocated to HRZE standard treatment to continue appropriate treatment in local national TB programme clinics. If randomly assigned to BPaMZ, participants were allowed to complete therapy following medical monitoring review but were classified as late exclusions (as participants with DS-TB did not fulfil the inclusion criteria once isoniazid or rifampicin resistance was detected). Participants with DR-TB with subsequently detected sensitivity to both rifampicin and isoniazid were allowed to complete therapy, but were classed as late exclusions. The laboratory manual can be found in the appendix (p 94).

Outcomes

The primary efficacy endpoint was time to culture-negative (TTN) status by 8 weeks, defined by two consecutive culture-negative sputum samples at least 7 days apart. Participants with clinical improvement who were unable to produce sputum were considered culture-negative.

The key secondary endpoint was the proportion of participants experiencing unfavourable outcomes at 52 weeks (12 months). Outcomes were considered favourable in participants who reached and maintained culture-negative status without any additional treatment. Unfavourable outcomes were defined as treatment failure (persistently positive sputum culture, or ongoing clinical TB in the view of the investigator) or relapse. Relapse was defined microbiologically as recurrent isolation of an *M tuberculosis* isolate with fewer than 12 single nucleotide polymorphisms difference from the baseline strain by whole-genome sequencing. Adequate adherence was defined as taking 80% or more of the allocated regimen. Participants interrupting treatment for more than 35 cumulative days were considered to have unfavourable outcomes.[2]

Other secondary analyses were unfavourable status at 104 weeks (24 months); a Bayesian analysis of the key secondary endpoint with the posterior distribution of the effect size graphed under different prior distributions (for example, sceptical, uninformative, and optimistic); sensitivity analyses on the key secondary endpoint (analysis of participants in the microbiologically eligible and assessable analysis population [TB-mITT] and per-protocol populations where reinfections were re-classified as unfavourable outcomes and analysis of the TB-mITT and per-protocol populations treating all deaths as unfavourable); time to unfavourable status (in days from the date of enrolment up to the first date associated with the reason for unfavourable status); time to sputum culture conversion to negative status; culture conversion status at weeks 4, 6, 12, and 17; adherence; change in weight and BMI from baseline weight at week 8 and end of treatment and at months 12 and 24 after the end of therapy; change in TB symptoms; and participant-reported health status (domains included anxiety and depression, mobility, pain or discomfort, self-care, usual activities, and the visual analogue scale score). All secondary endpoints are outlined in the appendix (pp 13–15).

Laboratory safety assessments included regular monitoring of haematological and biochemical parameters. Based on previous experience in the STAND trial, with three fatal hepatic adverse events occurring on days 28, 34, and 39,[18] a higher frequency of safety laboratory testing was conducted, including weekly blood samples, and liver function tests, for the first 8 weeks for safety monitoring. Slit lamp examination for visual acuity and colour vision was performed by an ophthalmologist. Regular electrocardiography was performed, with centralised analysis. Adverse events were graded according to the Division of Microbiology and Infectious Diseases criteria, and local investigators assessed whether they were probable to be related to treatment. Key safety endpoints were the proportion of participants with treatment-emergent adverse events (TEAEs).

Statistical analysis

In the efficacy analyses, four analysis populations were used: intention-to-treat (ITT), modified intention-to-treat (mITT), TB-mITT, and a per-protocol population. Analysis populations are defined in the panel, and more details can be found in the appendix, (pp 11–12).

For the primary efficacy endpoint, only the mITT population was examined, per the statistical analysis plan. For the key secondary endpoint all populations were analysed, with the TB-mITT being the primary analysis population. All other secondary endpoints were analysed according to the mITT, TB-mITT, and per-protocol populations, with mITT being the primary analysis population.

For the primary endpoint among participants with DS-TB, the sample size assumed that 50% of control participants would be culture-negative by 8 weeks after randomisation. A total of 150 participants per group would provide over 99% power to detect a hazard ratio of at least 2 (for 4 months of BMPaZ *vs* HRZE). For the key secondary endpoint, 150 participants per group was considered to provide 74% power to detect non-inferiority (non-inferiority margin of 12%) of 4 months of BPaMZ based on assumptions made in previous phase 3 TB trials.[2,18] We assumed that the control group would have 16% unfavourable outcomes and 13% unassessable outcomes at 52 weeks post-randomisation. The sample size was increased by 13% to account for loss to follow-up.

Panel: **Analysis populations**

ITT population: all participants who were enrolled, whether or not they started treatment

mITT population: all participants who were enrolled and started treatment, excluding any late screening failures

TB-mITT* population: the mITT population with additional exclusions

- Late exclusions due to resistance pattern, lack of culture confirmation, or protocol violation at enrolment
- Patients who, having completed treatment, were lost to follow-up or withdrew from the study with their last status being culture-negative
- Women who became pregnant during treatment and stopped their allocated treatment
- Participants with suspected or confirmed COVID-19 during treatment and who stopped their allocated treatment
- Participants who died during treatment from violent or accidental causes
- Participants who died during follow-up (after the end of treatment) with no evidence of failure or relapse of their TB†
- Participants who, after being classified as having culture-negative status, were deemed culture-positive and were infected with a new strain that is different from that with which they were originally infected (reinfection defined specifically as a participant infected with a strain that is genetically different from their initial infection strain)
- Participants who were able to produce sputum at the endpoint visit, but whose endpoint visit sputum samples were all contaminated or missing, and who could not be brought back for repeat cultures‡

Per-protocol population: the TB-mITT population with additional exclusions

- Late exclusions due to resistance pattern, lack of culture confirmation, or protocol violation at enrolment
- Patients who, having completed treatment, were lost to follow-up or withdrew from the study with their last status being culture-negative
- Women who became pregnant during treatment and stopped their allocated treatment
- Patients who died during treatment from violent or accidental causes
- Patients who died during follow-up (after the end of treatment) with no evidence of treatment failure or relapse of their TB†
- Patients who, after being classified as having culture-negative status, are reinfected with a strain other than that with which they had been originally infected
- Patients who were able to produce sputum at 12 months, but whose 12-month visit sputum samples were all contaminated or missing, who could not be brought back for repeat cultures‡
- Patients lost to follow-up or withdrawn before the end of treatment‡
- Patients whose treatment was modified or extended for reasons other than an unfavourable therapeutic response to treatment‡
- Patients who did not meet the definition of having received an adequate amount of their allocated study regimen (80% of treatment by self-reporting)‡
- Patients who were classified as having major protocol deviations‡

Safety population: all enrolled participants who received at least one dose of trial treatment. Participants were analysed based on the treatment they received, regardless of allocation.

ITT=intention-to-treat. mITT=modified intention-to-treat. TB=tuberculosis. TB-mITT=TB-specific mITT. WGS=whole-genome sequencing. SNP=single-nucleotide polymorphism. *The TB-mITT population is unique to the TB field and is a key analysis that has been used in the literature of long-term outcome trials of durable cure in TB, although it has generally been referred to simply as the mITT analysis. This analysis excludes participants based on data collected post-randomisation. A true mITT analysis, as recognised by regulatory authorities, does not exclude any participants due to missing data post-enrolment. †Relapse was declared if positive cultures after the end of treatment were considered identical to the baseline sample using WGS (difference of <12 SNPs), or if WGS was not available. Recurrence was considered to be reinfection if the *Mycobacterium tuberculosis* strain was different by more than 100 SNPs from the baseline strain. ‡Unless already declared as unfavourable.

A non-inferiority margin of 12% was chosen based on the similarly designed STAND study, and was discussed with the FDA.[18] All statistical tests were two-sided α level of 5%. A Cox regression model to estimate the hazard ratio was used to analyse primary efficacy determination of TTN up to 8 weeks, censoring for death and loss to follow-up or withdrawal from the study. Data are described using Kaplan–Meier plots.

The difference in proportions with unfavourable status at 52 weeks was analysed using the Cochran–Mantel–Haenszel test adjusting for stratification factors. Sensitivity analyses were carried out in the TB-mITT and per-protocol populations, and included an analysis with all deaths classed as unfavourable. Stepwise logistic regression with backwards elimination was used to assess baseline predictors of favourable status at week 52 (with $p<0·05$ for selection). No formal statistical comparisons were made for the participants enrolled with DR-TB.

Subgroup analyses (with tests for interaction) of the key secondary week 52 endpoint using the mITT population were conducted. Secondary safety and tolerability outcomes are presented as descriptive analyses. Post hoc analyses of baseline predictors of hepatotoxicity events (>5×ULN and >8×ULN) were conducted for participants on the BPaMZ regimens in the safety population. Multivariable logistic regression was used to assess baseline predictors of hepatotoxicity, and is presented as odds ratios. Details of exploratory and secondary analysis are found in the appendix (pp 13–16).

There was one planned interim analysis after 60 participants randomly allocated to the control group had reached the 8 week primary endpoint, to determine

whether the sample size should be increased to adequately power the trial on the key secondary 12-month endpoint, which would then have become the primary endpoint. This was based on the intermediate outcome of TTN status in liquid media by 8 weeks. The interim analysis included a test of the risk difference between the DS-TB treatment groups using a one-sided 10% significance level. STATA 17.0 and SAS 9.4 were used for analyses.

This study is registered with ClinicalTrials.gov, NCT03338621 and is complete.

Role of the funding source

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

Results

1059 participants were screened. Of these, 604 (57%) were excluded, most commonly due to a negative or scanty sputum smear (appendix pp 16–17).

Between July 30, 2018, and March 2, 2020, 455 participants were enrolled and received at least one dose of study treatment. 303 participants with DS-TB were randomly assigned to the 4-month schedule of BPaMZ (n=150) or HRZE (n=153). 152 participants with DR-TB were allocated to the 6-month schedule of BPaMZ. The trial profile is shown in figure 1 and the appendix (pp 18–19). Demographic and clinical characteristics of the participants are provided in table 1. The median age was 35 years (IQR 26·0–46·0); 324 (71%) of 455 participants were male and 131 (29%) of 455 participants were female; 87 (19%) were HIV positive; 220 (48%) had a WHO smear grade of 3 or more; and 355 (78%) had cavitation on chest radiographs at diagnosis. The most frequently reported comorbidities, occurring in 2% or more of participants, were hypertension (28 [6%] of 455), anaemia (14 [3%] of 455), and diabetes (13 [3%] of 455). Concomitant medications received by all participants are shown in the appendix (p 20). Overall adherence to allocated drug

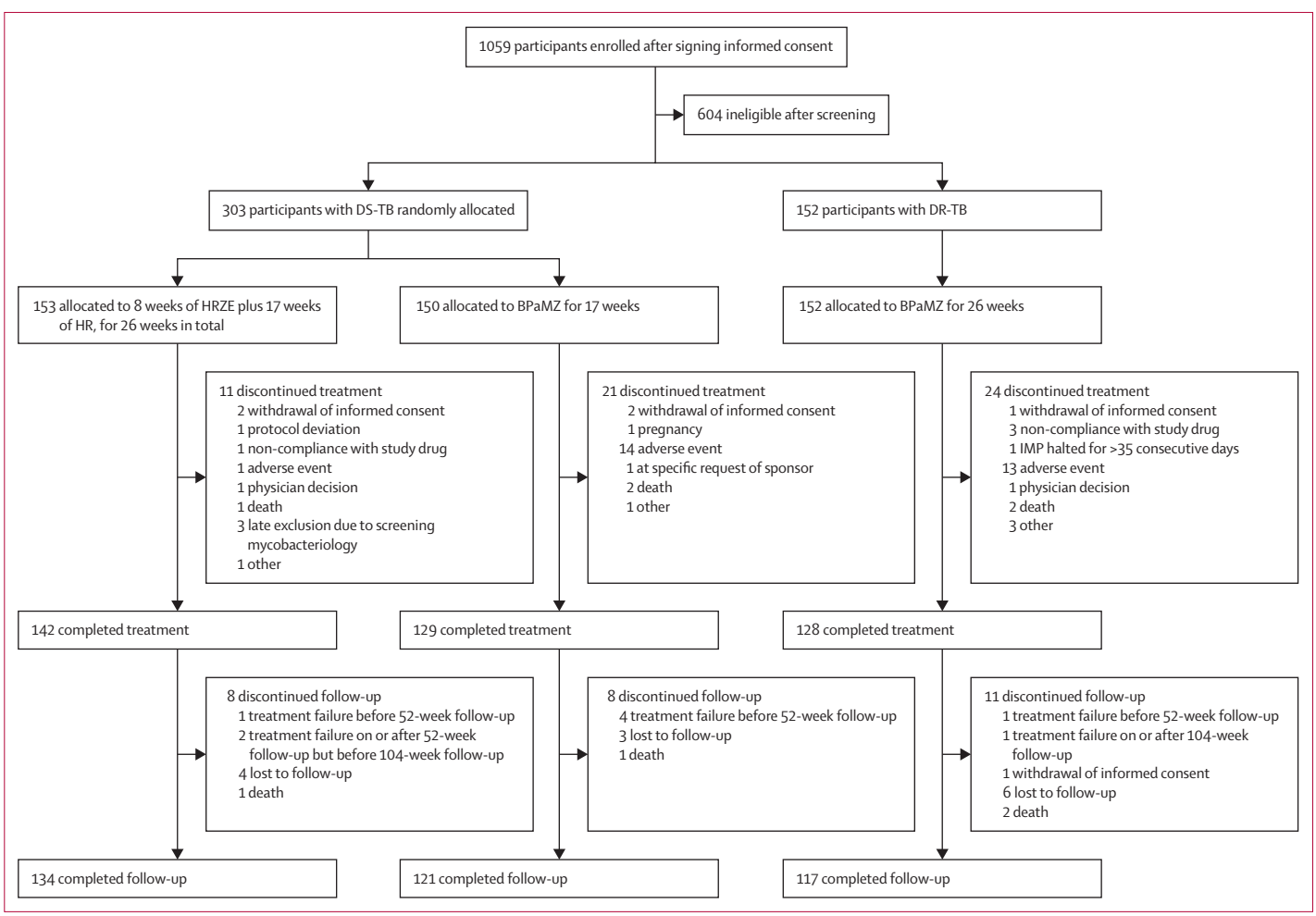

Figure 1: **Consort diagram**

BPaMZ=bedaquiline, pretomanid, moxifloxacin, and pyrazinamide. DR-TB=drug-resistant tuberculosis. DS-TB=drug-sensitive tuberculosis. HR=isoniazid and rifampicin. HRZE=isoniazid, rifampicin, pyrazinamide, and ethambutol. IMP=investigational medicinal product.

regimens was 370 (88%) of 421 (134 [93%] of 144 for HRZE, 124 [86%] of 144 for 4 months of BPaMZ, and 112 [84%] of 133 for 6 months of BPaMZ). Total median follow-up was 104·0 weeks (IQR 103·6–104·7).

Baseline *M tuberculosis* isolates were available for MGIT drug susceptibility testing from 448 participants. Baseline resistance for all participants is detailed in the appendix (pp 20–22). Pyrazinamide resistance was found in one participant (<1%) of the 153 receiving HRZE, seven (5%) of 150 participants on the 4-month schedule of BPaMZ, and 55 (36%) of 152 participants on the 6-month schedule of BPaMZ. One participant on HRZE had pre-existing resistance to bedaquiline. Two participants had pre-existing pretomanid resistance at baseline; one was assigned to HRZE and was unassessable (lost to follow-up) and the other was assigned to BPaMZ and had a favourable outcome.

293 (97%) of 303 participants with DS-TB were included in the mITT population (appendix pp 22–23). By week 8, 122 (84%) of 145 participants on 4 months of BPaMZ and 70 (47%) of 148 participants on HRZE culture converted to negative status. The hazard ratio derived from the primary time-to-event endpoint comparison was 2·93 (95% CI 2·17–3·96, p<0·0001; figure 2). Of the 133 assessable participants in the DR-TB group, 114 (86%) receiving 6 months of BPaMZ were culture-negative by week 8 (appendix p23).

At week 52, 120 (83%) of 144 participants with DS-TB in the TB-mITT population had favourable outcomes on 4 months of BPaMZ compared with 134 (93%) of 144 patients on HRZE. The absolute difference in unfavourable outcomes was 9·7% (95% CI 2·4 to 17·1). As the upper bound exceeded 12%, the 4-month schedule of BPaMZ did not meet the criterion for non-inferiority. In the per-protocol population, 120 (95%) of 126 participants on 4 months of BPaMZ had favourable outcomes compared to 131 (97%) of 135 favourable outcomes on HRZE, with an absolute difference of 1·8% (–2·9 to 6·5), meeting the non-inferiority threshold (figure 3A). Sensitivity analyses of the week 52 secondary endpoint were similar to the primary TB-mITT and per-protocol analyses. No association between baseline resistance to any of the trial drugs and treatment outcomes could be inferred (appendix pp 23–24). For the secondary analysis of the week 52 endpoint, using either flat, sceptical, or expected prior distributions, the results were similar to that of the main results with the proportion unfavourable being around 9–10% for all Bayesian distributions (appendix pp 26–27).

At week 104, favourable outcomes were reported for 116 (79%) of 146 participants on the 4-month schedule of BPaMZ (95% CI 72·0–85·7) compared with 132 (89%) of 148 participants on on HRZE (83·0–93·7) in the mITT population (figure 3B). The unadjusted difference in the time to unfavourable status was 10·1% (95% CI 2·6–17·6), with participants in the 4-month BPaMZ group having a shorter time to unfavorable status (figure 3C). Favourable status was reached by 111 (83·5%) of 133 participants (95% CI 76·0–89·8) and 102 (81·0%) of 126 participants (73·0–87·4) on the 6-month BPaMZ schedule, at week 52 and week 104, respectively, in the TB-mITT population. Of all factors considered for the subgroup analysis of the week 52 endpoint, only age and region showed a significant interaction with treatment (p=0·0001 and p=0·0029, respectively; appendix p 26), indicating a difference in the treatment effect (ie, risk difference for 4 months of BPaMZ *vs* HRZE) between the age groups (<35 years and ≥35 years) and regions (South Africa and rest of the world).

The median TTN was 6 weeks (IQR 4 to 8) on 4 months of BPaMZ compared with 11 weeks (6 to 12) on HRZE for participants with DS-TB (figure 3D) and 5 weeks (IQR 3 to 7) for participants with DR-TB. 41 (29%) of 139 assessable participants in the 4 months of BPaMZ group had negative culture from week 4, rising to 122 (95%) of 128 at week 12. At week 17, similar percentages of participants had reached negative culture

	DS-TB		DR-TB 6 months of BPaMZ (n=152)
	2 months of HRZE plus 4 months of HR (n=153)	4 months of BPaMZ (n=150)	
Median age, years (IQR)	34·0 (26·0–46·0)	35·0 (25·0–45·0)	35·0 (26·0–47·0)
Sex			
Male	118 (77%)	112 (75%)	94 (62%)
Female	35 (23%)	38 (25%)	58 (38%)
Race			
White	25 (16%)	29 (19%)	31 (20%)
Black	119 (78%)	108 (72%)	82 (54%)
Mixed race	6 (4%)	5 (3%)	26 (17%)
Asian	3 (2%)	8 (5%)	13 (9%)
Other	0	0	0
HIV positivity	27 (18%)	25 (17%)	35 (23%)
Median bodyweight, kg (IQR)	54·0 (49·0–59·0)	53·7 (48·8–62·0)	54·1 (48·3–63·6)
Median BMI, kg/m² (IQR)	18·7 (17·2–20·4)	19·3 (17·6–21·4)	19·3 (17·1–22·2)
Current smoker	64 (42%)	59 (39%)	39 (26%)
WHO smear grade			
1+	28 (18%)	20 (13%)	37 (24%)
2+	53 (35%)	49 (33%)	47 (31%)
3+	72 (47%)	81 (54%)	67 (44%)
Median time to positive at baseline, days (IQR)	5·0 (4·2–6·5)	4·6 (3·9–6·2)	6·2 (4·7–8·9)
Cavities in chest radiograph			
Absent	37 (24%)	31 (21%)	31 (20%)
Unilateral	76 (50%)	75 (50%)	70 (46%)
Bilateral	40 (26%)	44 (29%)	50 (33%)
Missing	0	0	1 (<1%)

Data are n (%) unless otherwise stated. BPaMZ=bedaquiline, pretomanid, moxifloxacin, and pyrazinamide. DR-TB=drug-resistant tuberculosis. DS-TB=drug-sensitive tuberculosis. HR=isoniazid and rifampicin. HRZE=isoniazid, rifampicin, pyrazinamide, and ethambutol. ITT=intention-to-treat.

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

in both groups. For participants in the 6 months of BPaMZ group, culture conversion at weeks 4, 6, 12, and 17 were 38%, 63%, 95%, and 97%, respectively. There was an increase in median bodyweight and BMI over time, with a median weight gain of 5·7 to 7·3 kg and a median BMI increase of 2·0 to 2·4 kg/m² from baseline to week 104. The median change in the number of TB symptoms ranged from –4·0 at week 8 to –6·0 at week 104 for the 4 months of BPaMZ group, –5·0 to –6·0 for the HRZE group, and –4·0 to –5·0 for the 6 months of BPaMZ group. The percentage of participants reporting no problems with the health status domains increased during participation in the trial. Overall, 96·9% of participants had a 90% or greater adherence to trial medications, with 99·3%, 97·4%, and 94·0% with 90% or greater adherence in the 4 months of BPaMZ group, HRZE group, and 6 months of BPaMZ group, respectively. All secondary endpoint data are displayed in the appendix (pp 26–46).

Two participants on 6 months of BPaMZ acquired resistance to at least one of the study drugs; one participant who acquired resistance to both bedaquiline and pretomanid and was withdrawn due to investigator decision and another, with uncontrolled diabetes, had a relapse with pretomanid resistance.

Table 2 lists the incidence of TEAEs by regimen. A total of 176 participants (39%) had 271 grade 3 (severe) or

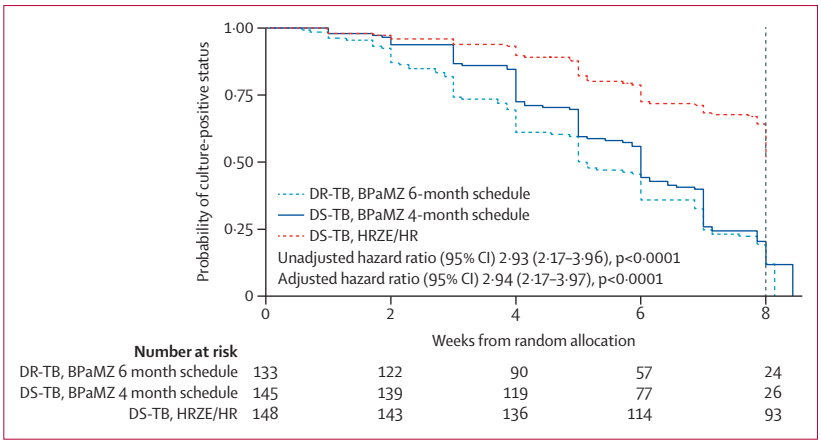

Figure 2: **Primary efficacy analysis in the mITT population—time to culture-negative status by 8 weeks**
BPaMZ=bedaquiline, pretomanid, moxifloxacin, and pyrazinamide. DR-TB=drug-resistant tuberculosis. DS-TB=drug-sensitive tuberculosis. HR=isoniazid and rifampicin. HRZE=isoniazid, rifampicin, pyrazinamide, and ethambutol.

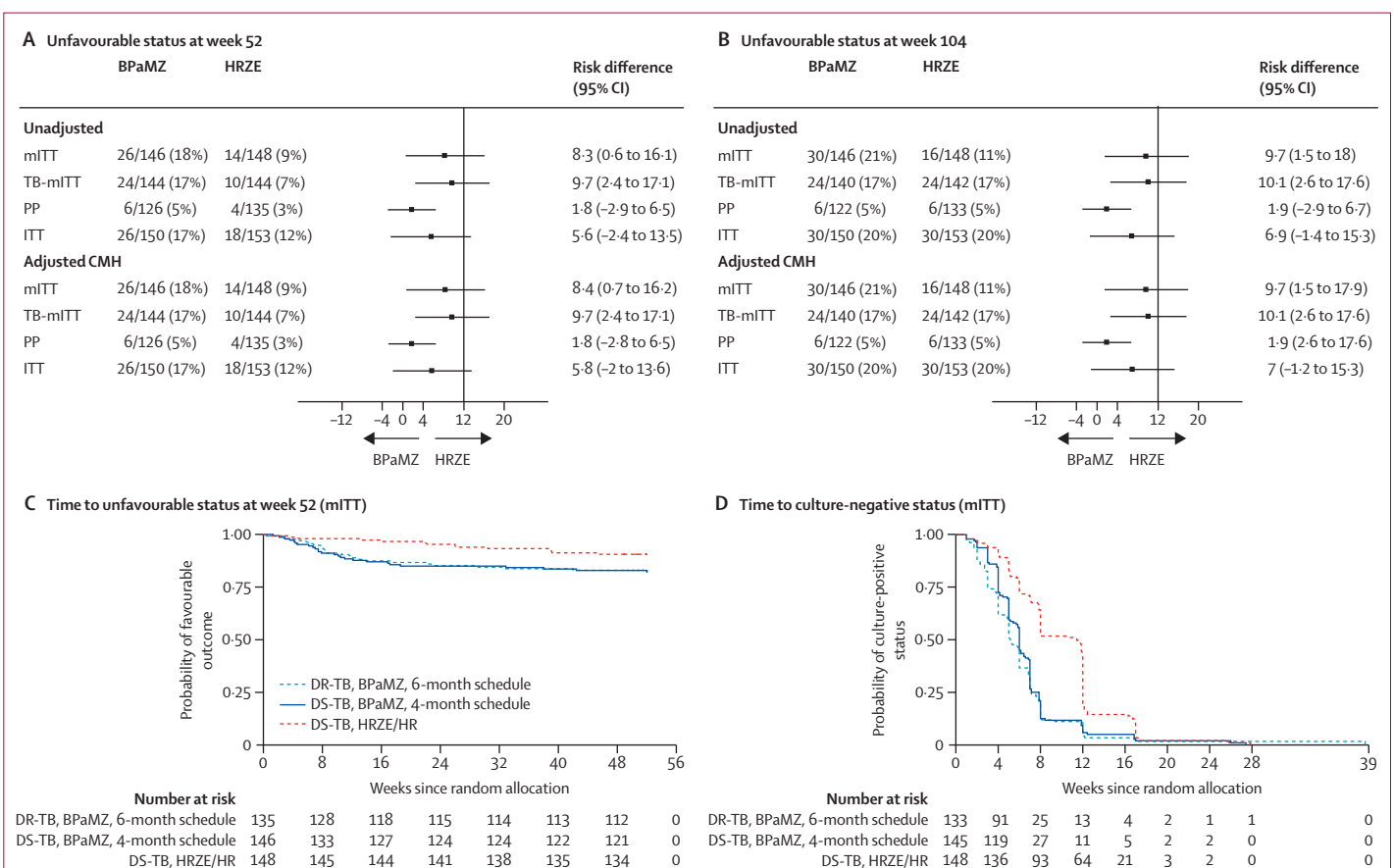

Figure 3: **Secondary efficacy analyses including time to an unfavourable outcome and time to culture-negative status**
BPaMZ=bedaquiline, pretomanid, moxifloxacin, and pyrazinamide. CMH=Cochran–Mantel–Haenszel. DR-TB=drug-resistant tuberculosis. DS-TB=drug-sensitive tuberculosis. HR=isoniazid and rifampicin. HRZE=isoniazid, rifampicin, pyrazinamide, and ethambutol. ITT=itention-to-treat. mITT=modified ITT. TB-mITT=microbiologically eligible and assessable mITT. PP=per-protocol.

grade 4 (life-threatening) TEAEs. 68 (45%) of 150 participants with DS-TB on 4 months of BPaMZ experienced one or more grade 3 or 4 TEAEs compared with 61 (40%) of 153 paricipants on HRZE and 47 (32%) of 149 patients with DR-TB on 6 months of BPaMZ. 46 serious TEAEs were reported by 40 participants (9%): 17 (11%) on 4 months of BPaMZ, seven (5%) on HRZE, and 16 (11%) on 6 months of BPaMZ. The number of participants who interrupted trial treatment due to a TEAE was 15 (10%) for 4 months on BPaMZ, 14 (9%) for HRZE, and 22 (15%) for 6 months of BPaMZ. 36 (8%) participants discontinued trial treatment due to TEAE: 17 participants (11%) on 4 months of BPaMZ, three (2%) on HRZE, and 16 (11%) on 6 months of BPaMZ. The most common reasons for discontinuation of trial treatment were hepatotoxicity (ten of 452 participants, 2%), increased hepatic enzymes (nine participants, 2%), QTcF prolongation (three participants, 1%), and hypersensitivity (two participants, <1%).

Overall, 116 (26%) of 452 participants had a total of 197 liver-related TEAEs. At least one liver-related TEAE occurred among 45 (30%) of 150 participants on 4 months of BPaMZ, 38 (25%) of 153 on HRZE, and 33 (22%) of 149 on 6 months of BPaMZ. The median time to first liver event from randomisation was 27 days (IQR 14–49) for 4 months of BPaMZ, 14 days (6–35) for HRZE, and 35 days (14–84) for 6 months of BPaMZ (appendix p 47). Of those with a known outcome after presentation of first liver event, 74 (94%) of 79 on 4 months of BPaMZ, 51 (91%) of 56 on HRZE, and 38 (79%) of 50 on 6 month BPaMZ recovered, and three (6%) on 6 months of BPaMZ recovered with sequelae (appendix p 48). Serious liver-related TEAEs were reported by 20 participants overall: 11 (7%) among those on 4 months of BPaMZ, one (1%) on HRZE, and eight (5%) on 6 months of BPaMZ.

64 participants (14%) experienced abnormal hepatic biochemistry events grade 3 and above. The overall rate of more than 3×ULN ALT or AST elevation was similar across groups. 12 (8%) participants with DS-TB on 4 months of BPaMZ demonstrated a peak ALT or AST or both over 8×ULN, compared with three (2%) receiving HRZE and nine (6%) participants with DR-TB on 6 months of BPaMZ. For the 19 events of ALT over 8×ULN, predictors of hepatotoxicity included age over 35 years (odds ratio 3·26 [95% CI 1·11–9·64], p=0·032) and baseline hepatitis C seropositivity (9·37 [1·42–61·25], p=0·019; appendix pp 51–53).

A maximum change from baseline QTcF interval of more than 60 ms occurred in 67 participants (15%): 28 (19%) of 150 on 4 months of BPaMZ, 11 (7%) of 153 on HZRE, and 28 (18%) of 149 on 6 months of BPaMZ. Four participants with normal baseline QTcF subsequently developed QTcF values of more than 500 ms during treatment, and three were withdrawn due to investigator decision (two on 4 months of BPaMZ and one on 6 months of BPaMZ).

	DS-TB		DR-TB 6 months of BPaMZ (N=149)
	2 months of HRZE plus 4 months of HR (N=153)	4 months of BPaMZ (N=150)	
TEAE of grade 3 or above	61 (40%)	68 (45%)	47 (32%)
Any study drug related TEAE	99 (65%)	119 (79%)	123 (83%)
Any serious TEAE	7 (5%)	17 (11%)	16 (11%)
Any TEAE leading to death	1 (1%)	3 (2%)	2 (1%)
Any liver-related TEAE	38 (25%)	45 (30%)	33 (22%)
Any serious liver-related TEAE	1 (1%)	11 (7%)	8 (5%)
ALT, AST, or both at 3×ULN or over	17 (11%)	24 (16%)	21 (14%)
ALT, AST, or both 3–8×ULN	14 (9%)	12 (8%)	12 (8%)
ALT, AST, or both over 8×ULN	3 (2%)	12 (8%)	9 (6%)
Any TEAE leading to study drug discontinuation	3 (2%)	17 (11%)	16 (11%)
Any TEAE leading to study discontinuation	0	6 (4%)	2 (1%)

Data are n (%). Participants with multiple adverse events in each category are counted only once in each category. ALT=alanine aminotransferase. AST=aspartate aminotransferase. BPaMZ=bedaquiline, pretomanid, moxifloxacin, and pyrazinamide. DR-TB=drug-resistant tuberculosis. DS-TB=drug-sensitive tuberculosis. HR=isoniazid and rifampicin. HRZE=isoniazid, rifampicin, pyrazinamide, and ethambutol. TEAE=treatment-emergent adverse event. ULN=upper limit of normal.

Table 2: **Safety and premature discontinuation of assigned regimen (safety population)**

Nine deaths occurred during the study; six were attributed to a TEAE: three receiving 4 months of BPaMZ (one each for hepatotoxicity meeting the criteria for Hy's law, hypokalaemia, and pulmonary embolism), one on HZRE (TB disease progression), and two on 6 months of BPaMZ (COVID-19 and acute kidney injury; appendix p 53).

A single prospectively planned interim analysis was conducted on 8-week data from 130 participants with DS-TB. This showed a hazard ratio for TTN of 2·55 (95% CI 1·62–4·00, p<0·0001; appendix p 55) for 4 months of BPaMZ versus HRZE. The independent DSMC were not involved in the interim analysis but conducted periodic, pre-specified reviews of unblinded safety data and recommended completion of enrolment. The TB Alliance, as sponsor, decided not to expand the sample size to power a 12-month endpoint because it appeared that excess premature withdrawals, primarily due to hepatic adverse events, in the BPaMZ group would preclude demonstration of non-inferiority in an mITT analysis.

Discussion

In this clinical trial, participants with DS-TB on 4 months of BPaMZ reached culture-negative status faster than those on HRZE, and were more likely to be culture-negative by week 8, meeting the primary trial endpoint and confirming the potent anti-mycobacterial activity of BPaMZ reported in preclinical studies.[10,11,13] However, 4 months of BPaMZ did not meet the non-inferiority threshold for unfavourable outcome at week 52 compared

with HRZE in the TB-mITT population due to adverse events leading to participant withdrawal.

Adverse events on BPaMZ were mainly related to elevated hepatic enzymes. While the rate of elevation over 3×ULN ALT, AST, or both was similar across regimens, a higher proportion of serious liver-related adverse events and discontinuations were reported on BPaMZ than HZRE. Previous reports from the phase 3 STAND trial,[18] and the phase 2 Assessing Pretomanid for Tuberculosis (APT) trial[21] also described hepatic treatment-emergent severe adverse events on regimens which combined pretomanid and pyrazinamide. In comparison, trials of other bedaquiline-pretomanid based regimens (eg, BPaL [bedaquiline, pretomanid, linezolid] and BPaL and moxifloxacin [BPaLM] for DR-TB) have not shown such hepatotoxicity signal; in these studies only modest liver enzyme elevations were observed, rarely requiring discontinuation.[5,6,22,23] This suggests that severe hepatic events are likely driven by co-administration of pretomanid and pyrazinamide.

SimpliciTB was not designed or powered to assess risk factors for hepatotoxicity on BPaMZ. While an ad hoc retrospective analysis suggested higher risk with age older than 35 years or baseline hepatitis C seropositivity, caution must be exercised when interpreting these findings due to the small number of participants in this group. Overall, population groups at a higher risk of liver injury are not well defined, and there are no established biomarkers to prospectively evaluate the risk of hepatotoxicity. The increased risk of unpredictable severe hepatic adverse events with 4 months of BPaMZ would be a considerable obstacle to implementation of this regimen in settings with a high burden of TB with limited infrastructure for close surveillance of liver biochemistry.

The recent TRUNCATE-TB trial demonstrated successful 8-week treatments for DS-TB with careful monitoring for relapse.[24] Additional rapidly effective drug combinations could be evaluated in a similar short format. With sputum culture conversion by 8 weeks over 80% on BPaMZ, this type of regimen may be suitable for such assessment if the hepatic safety signal were addressed. It is notable that 36% of participants in the DR-TB group of SimpliciTB had pyrazinamide-resistant TB but this had minimal effect on time to sputum culture-negative status, or outcomes at week 52 or 104. Tentatively, this suggests that bedaquiline and pretomanid regimens without pyrazinamide, or with a lower dose, could be explored to establish whether bactericidal efficacy could be retained with better liver safety. However, this would require additional clinical trials with careful drug susceptibility testing evaluation of each patient on recruitment.

As the DR-TB cohort in this study did not have a direct control group, firm conclusions cannot be drawn on the use of 6 months of BPaMZ in that population. At the time of trial initiation sufficient resources for a randomised DR-TB comparison were not available. Nevertheless, to provide insight into the potential for a pan-TB regimen without rifampicin, it was useful to examine the consistency of treatment response between patient populations traditionally defined as drug-sensitive and drug-resistant. In that regard, reaching 8 week culture-negative status and favourable week 104 clinical outcome status in 86% of participants on 6 months of BPaMZ is valuable. A 26-week course of BPaL is approved for the treatment of extensively drug-resistant, treatment-intolerant or non-responsive multidrug-resistant pulmonary TB.[7,8] Recent data show 24 weeks of BPaLM to be superior to conventional 18 months therapy for rifampicin-resistant TB.[22] Our results further underline the potency of bedaquiline and pretomanid based regimens for DR-TB.

This rigorous study with comprehensive safety and mycobacteriology analysis included participants from diverse populations. Limitations, including insufficient data to comprehensively investigate all risk factors for hepatic adverse events and the absence of a comparator standard-care group for DR-TB, are acknowledged. Additionally, participants with fluoroquinolone-resistant TB were excluded from all parts of this study, reducing the scenarios in which BPaMZ could be applied, and reminding us that improved laboratory capacity for drug susceptibility testing is required alongside new regimen development. We cannot exclude the possibility of selection bias due to missing outcome data, but our main conclusions were robust to sensitivity analysis across a range of pre-defined populations. Like many TB trials, our key secondary endpoint is a composite measurement. Novel analytical approaches including the estimand framework[25] provide alternative strategies for defining populations and endpoints as well as handling intercurrent events, but in this primary trial report it is important to present results according to the prospectively written statistical analysis plan. Future work will include re-assessment of study data using the estimand framework.

In conclusion, participants with DS-TB receiving the 4 months of BPaMZ regimen had almost three-fold higher likelihood of reaching earlier culture-negative status than those receiving HRZE. The effect of withdrawals from adverse events, predominantly due to elevated hepatic enzymes, prevented 4 months of BPaMZ from meeting the non-inferiority threshold for favourable outcomes. Participants with DR-TB on 6 months of BPaMZ had high favourable outcomes comparable to the other new DR-TB regimens with BPaL and BPaLM.[5,6,22] These results provide clinical validation of a murine model widely used to identify regimens with treatment-shortening potential, and illustrate that BPa-based regimens for DR-TB make this form of the disease as amenable to successful treatment as DS-TB. However, our results also highlight the need for better preclinical models to predict clinical safety and remind us that

shorter TB treatment regimens also require an acceptable toxicity and tolerability profile before consideration for programmatic use. The challenge is to develop regimens with the bactericidal efficacy of BPaMZ but with lower risk of severe adverse events.

Contributors

The TB Alliance designed the trial and study protocol. All authors enrolled participants and oversaw clinical follow-up and data collection at their site. TM, RH, and PS oversaw all microbiology processes. LCT and SF carried out the primary statistical analysis, including figures and tables, overseen by AMC. This manuscript was drafted by MC, DJS, and SHG. All authors contributed to data interpretation, critical review, and revision of the manuscript, and approved the decision to submit for publication. LCT and AMC have accessed and verified the study data. MC was responsible for the decision to submit the manuscript. All authors provided written comments and feedback during manuscript development and were directly involved in the execution of the study.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymised individual level data have been transferred to the Critical Path Institute (C-Path) TB Platform for Aggregation of Clinical TB Studies (TB-PACTS) where it will be available to the TB research community following publication. Qualified researchers may register to the TB-PACTS platform to obtain specific de-identified clinical trial data. Researchers must agree to the terms and conditions for use of the TB-PACTS data platform and submit an online application form to request access to the data platform.

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