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Phase 2C clinical trial of novel short-course regimens for the treatment of pulmonary tuberculosis: TBTC Study 38/CRUSH-TB design

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Declaration of conflicting interests

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Otsuka commercial interests did not influence the study design; the collection, analysis, or interpretation of data; the preparation of this manuscript; or the decision to submit this manuscript for publication.

Trial status

Recruitment began in November 2023. The last participant in Wave 1 is expected to be enrolled in November 2025. Participant follow-up is expected to be completed by end of 2026.

Disclaimer

The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention (CDC) or the U.S. Department of Health and Human Services.

Ethical Approval

The trial was approved by the CDC Institutional Review Board (IRB). Each participating institution is responsible for reviewing and approving this protocol and its informed consent documents through a local IRB or ethics committee, or formally relying on the CDC IRB approval.

Trial registration

IND Number: 158058.

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Abstract

Introduction: Preclinical and clinical study data show that combining bedaquiline (B or BDQ), moxifloxacin (M), and pyrazinamide (Z), known as BMZ, has potent antimicrobial activity that might shorten treatment duration for drug-susceptible pulmonary tuberculosis.

Methods/Design: We describe the design of Tuberculosis Trials Consortium (TBTC) Study 38/CRUSH-TB (NCT05766267), an open-label multicenter international randomized controlled phase 2C trial that compares two four-month regimens, BMZ plus rifabutin (Rb) (2BMZRb/2BMRb) or BMZ plus delamanid (D or DLM) (2BMZD/2BMD), with standard 6-months isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE). All drugs are administered seven days per week, under direct observation, at least five days per week. A total of 288 participants, aged ≥12 years, newly diagnosed with sputum smear-positive or Xpert MTB/RIF (Ultra)-positive drug-susceptible pulmonary tuberculosis, will be randomized 1:1:1 to receive BMZRb, BMZD, or HRZE. Participants are followed until 78 weeks post-randomization, or until the last enrolled participant completes 52 weeks post-randomization, whichever comes first. The primary endpoint is time to sputum culture negative in liquid media. Secondary endpoints include sustained cure, safety, and additional mycobacteriology and pharmacokinetic and pharmacodynamic outcomes. This trial has an adaptive design, wherein new arms can be added.

Discussion: This trial tests the hypothesis whether four-month BMZ-based regimens with Rb or D can shorten time to culture negativity while being safe and tolerable for participants. The study design is adaptive, allowing for additional study arms as new drugs become available. Findings

from this trial might have important implications for clinically managing drug-susceptible pulmonary tuberculosis at individual and programmatic levels.

Keywords

tuberculosis; TB; randomized clinical trial; bedaquiline; delamanid; rifabutin

Introduction

Tuberculosis (TB), a respiratory disease caused by *Mycobacterium tuberculosis* bacteria, is the leading infectious cause of death worldwide (1). Although effective TB treatments exist, gains made against the epidemic have plateaued. Contemporary TB control and elimination efforts require novel innovative strategies that can shorten the duration and improve the safety of TB treatment. Shorter treatment benefits patients and health care systems because it can decrease missed work or school for patients (2), decrease the logistical burden and expense of extended therapy, and help prevent the emergence of acquired drug resistance through improved adherence.

The Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group A5349 established that regimens of four months are efficacious for treating drug-susceptible TB (3). This finding underscores the need to develop other shortened regimens (3) because learning from different drug combinations can provide insights into the newest advancements in TB treatment regimens. Further, it can help identify the types of drugs and drug combinations that might further reduce treatment duration.

Several new antituberculosis agents demonstrate promising efficacy results to merit testing in a mid-development phase 2 study. Among the novel agents proposed for TB treatment, bedaquiline (B or BDQ) exhibits the most potent sterilizing activity in animal models, with sterilizing potential similar to that of the best currently available sterilizing drug class, the rifamycins. Combining bedaquiline with pyrazinamide significantly enhances this sterilizing activity (4, 5). However, bedaquiline alone, or even in combination with pyrazinamide, does not exhibit significant bactericidal activity during the first week of treatment; therefore, at least one drug with high early bactericidal activity should be included in a proposed bedaquiline-containing regimen to reduce infectiousness and symptoms by quickly reducing the bacterial burden.

Moxifloxacin has bactericidal and sterilizing activity comparable to isoniazid (6). Combining moxifloxacin, bedaquiline, and pyrazinamide is a particularly potent sterilizing combination in animal models (7, 8). In addition, moxifloxacin has potential advantages compared with other fluoroquinolones (9). Moxifloxacin's superiority in these animal studies might, in part, reflect its superior bactericidal potency against drug-tolerant persisters (10, 11). In Study 31/A5349, moxifloxacin was an essential component of the successful four-month regimen (3). Therefore, based on preclinical and clinical safety and efficacy data, TB regimens containing a backbone of bedaquiline, moxifloxacin, and pyrazinamide (BMZ) show the most favorable characteristics, warranting further phase 2 study.

Adding a fourth drug to the BMZ backbone could provide additional benefits, either by increasing the sterilizing activity of the regimen or reducing the potential for acquired drug resistance. We examine the effect of including rifabutin (Rb) and delamanid (D or DLM), each as a fourth drug. Adding Rb to the BMZ backbone shortened the treatment duration necessary to prevent relapse in a BALB/c mouse TB model (12). The four-drug BMZRb regimen was also more effective than the four-month clinical regimen of rifapentine, moxifloxacin, pyrazinamide, and isoniazid (PMZH) in a C3HeB/FeJ mouse model that develops large caseating lung lesions with high bacterial burden (12). The four-drug BMZD regimen was more effective in treating TB than PMZ in BALB/c mouse study (12).

Here, we describe the design of a phase 2C clinical trial assessing the time to culture negativity of two four-month BMZ-containing treatments compared with the conventional six-month treatment regimen (isoniazid, rifampin, pyrazinamide, and ethambutol [HRZE]), including safety and tolerability endpoints.

Methods

Design and Objectives

Study 38/CRUSH-TB is an international, multicenter, randomized, controlled, open-label phase 2C adaptive trial among adolescents and adults with smear- and culture-positive, drug-susceptible pulmonary tuberculosis. The primary objective is to compare the efficacy of each experimental regimen to that of the standard six-month treatment, using the intermediate endpoint of time to sputum culture negativity in liquid media. In the initial “Wave 1,” Study 38/CRUSH-TB has three arms. Due to its adaptive design, in a subsequent study, “Waves,” more arms can be added, with the comparator arm continuing enrollment.

Study setting

The Centers for Disease Control and Prevention (CDC) funds TBTC to conduct Study 38/CRUSH-TB. Recruitment sites are in six countries (Canada, Haiti, South Africa, Uganda, the United States, and Vietnam) across three continents. The sociodemographic characteristics of study participants were expected to represent those populations most affected by TB worldwide.

Study population and eligibility

Inclusion and exclusion criteria are listed in Table 1. Participants must have at screening an expectorated sputum specimen that is either at least 1+ positive for acid-fast bacilli on smear microscopy or positive for *M. tuberculosis* by nucleic acid amplification testing using Xpert® MTB/RIF or Xpert® MTB/RIF Ultra (“Xpert”, Cepheid Inc., Sunnyvale, CA), with semiquantitative result of ‘medium’ or ‘high’ at the sites’ laboratory of record for the trial. This approach maximizes the likelihood that a given participant has cultivable *M. tuberculosis* in their sputum, aligning this study with evidence from other clinical trials regarding severity of pulmonary tuberculosis based on *M. tuberculosis* burden detected in sputum(3, 13–15). Participants must be aged ≥12 years; children and adolescents were included to balance the importance of including children in tuberculosis trials with the specifics of this clinical trial, including flat dosing, which necessitate a population with

similar to adults' drug pharmacokinetics and disease manifestations (e.g., sputum culture positivity). Persons living with HIV with CD4 T-cell counts ≥100 cells/mm^3 were eligible for enrollment.

The schedule of study procedures and assessments are provided in Table 2.

Randomization

Randomization and treatment arm assignments were computer-generated. Eligible patients who satisfied all inclusion and exclusion criteria were randomly assigned in a 1:1:1 ratio to the study arms (Figure 1). Eligible patients were randomized with equal probability to each arm, using Chen's procedure to minimize imbalance (16). Random assignment sequences were generated to limit imbalance between arms within strata while ensuring that the sequence was not predictable based on previous assignments. Randomization was stratified by site, geographical region (Africa versus not Africa), and by the presence of cavitation on chest radiograph at screening.

Dosing strategies in the experimental arms

Doses of study drugs are shown in Table 3.

Bedaquiline is administered at a dose of 200 mg once daily for 56 days, followed by 100 mg daily for the remainder of the treatment. This dosing schedule was used in the ZeNIX TB and SimpliciTB studies, and BDQ at a 200 mg daily dose was used for eight weeks in the NC-005 study (17). Daily dosing throughout TB treatment has significant logistical advantages over the standard licensed regimen, which requires treatment to be administered three times per week after the initial 14 days. This schedule is challenging to coordinate with the other medications in this regimen, which are given daily. Further, pharmacokinetic modeling data support this dosing schedule because it produces similar bedaquiline exposures to the standard licensed dosing regimen (18) and has similar efficacy and safety (18, 19).

Delamanid is used at a dose of 300 mg once daily. This dosing provides overall daily exposures similar to the standard 100-mg dose twice daily for adults, with the convenience and programmatic feasibility advantage of once-daily dosing (20). Additionally, early bactericidal activity (EBA) data demonstrated that of the various daily doses tested (100, 200, 300, and 400 mg), maximal bactericidal activity was seen with 300 mg daily (21).

Rifabutin is used at the standard dose of 300 mg once daily. The rifamycins are considered to have the strongest sterilizing activity among established TB drug classes, but both rifampin and rifapentine reduce bedaquiline plasma concentrations by 70–80% in humans (22); however, rifabutin has a smaller impact (approximately 10% reduction in plasma concentrations) on bedaquiline pharmacokinetics (23).

Pyrazinamide is administered in two weight bands: participants weighing ≤75 kg receive a 1,500-mg dose once daily, and those weighing >75 kg receive a 2,000-mg dose once daily. These doses are selected to produce equivalent therapeutic exposures across patients

of different weights, without systematically underdosing persons who weigh ≤75 kg (24), while maintaining safety (25, 26).

Study regimens

Regimen 1 (investigational regimen) is bedaquiline, moxifloxacin, pyrazinamide, and rifabutin (BMZRb) for eight weeks, followed by bedaquiline, moxifloxacin, and rifabutin for nine weeks (isoniazid (H)-sparing). Regimen 2 (investigational) is bedaquiline, moxifloxacin, pyrazinamide, and delamanid (BMZD) for eight weeks, followed by bedaquiline, moxifloxacin, and delamanid for 9 weeks (isoniazid-and rifamycin-sparing). Regimen 3 (control) is isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE) for eight weeks, then isoniazid and rifampin (HR) for 18 weeks.

Blinding to treatment assignment

In this open-label trial, participants and clinical site staff are not blinded to the treatment assignments of individual participants for two primary reasons. Firstly, implementing blinding with placebos would have significantly increased the already high investigational groups pill burden to about 20 pills daily. We were concerned that this increase could lead to issues with adherence, negatively affect tolerability, and ultimately compromise the validity of the efficacy study results. From a physiological standpoint, the dissolution and absorption of medications in the gastrointestinal tract could be hindered by such a high pill burden, potentially reducing treatment effectiveness and raising the risk of developing drug resistance. Secondly, there is different effect of food on the absorption and bioavailability of rifampin, bedaquiline, and delamanid necessitating different instructions on food versus no food with treatment administration. Therefore, it would not have been practical to implement blinding regarding food intake during treatment administration.

Three key aspects of the study aimed to minimize ascertainment bias given the open-label design. First, the use of frequent, scheduled sputum collections for mycobacterial culture was emphasized, with the point that smear or Xpert results alone should not be used for clinical decision-making. Second, the uniform application of study visits and procedures across arms, including a pre-specified set of triggers and processes for evaluating participants who might not respond well to treatment, or, conversely, do well clinically but experience positive smear or culture at or after 17 weeks post-randomization (“possible poor treatment response” or PPTR procedures) (27). Third, keeping CDC staff members blinded to participant treatment assignment when providing study implementation guidance to the site staff members.

Assessment of study endpoints and duration of follow-up

Participants were followed until 78 weeks post-randomization, or until the last enrolled participant completed 52 weeks post-randomization, whichever came first. The primary efficacy endpoint was time to sputum culture negative in liquid media. Secondary endpoints included long-term lack of sustained cure, safety, and additional mycobacteriology and pharmacokinetic/pharmacodynamic outcomes.

Sputum specimens were collected at each study visit, as outlined in the Schedule of Procedures/Evaluations (Table 2), and sent to the designated site laboratory for smear microscopy and mycobacteriology culture on both liquid and solid media. Phenotypic drug susceptibility testing (pDST) for at least isoniazid, rifampin, ethambutol, and a fluoroquinolone is performed on the first study isolate of *M. tuberculosis* and the first of any *M. tuberculosis* isolates obtained at or after week 17 (time of completion of the four-month regimens). Mycobacteriology laboratory procedures were harmonized across study site laboratories for 23 key elements, and test results were collected on a study-specific case report form. For each participant, the first study *M. tuberculosis* isolate, as well as the first of any *M. tuberculosis* isolates from sputum obtained at or after week 17 post-randomization, were shipped to CDC's Tuberculosis Laboratory, where additional pDST for bedaquiline and delamanid was performed, and pyrazinamide susceptibility was assessed with *pncA* sequencing. Whole-genome sequencing was performed for paired isolates from the first study and at or after week 17 isolates to determine whether recurrent tuberculosis was due to relapse of the same strain or reinfection with a new strain.

The primary safety endpoint was the proportion of participants with a Grade 3 or higher adverse event during 26 weeks from randomization. Adverse events are graded by the site investigator, according to the Common Terminology Criteria for Adverse Events (version 5.0) (28). All adverse events submitted by sites to CDC are reported and reviewed in real-time by pharmacovigilance staff members.

Sample size considerations

Based on Phillips et al. (29) 90 assessable participants per arm were adequate to measure the long-term clinical endpoint with sufficient accuracy to make reliable predictions for future phase 3 trials. This sample size is also adequate to demonstrate a statistically significant reduction in time to culture negativity.

The hazard ratio for time to culture conversion for the moxifloxacin substitution, as compared to HRZE control, was shown to be 1.73 in the OFLOTUB phase 2 trial (30) with 50 participants per arm, but was 1.17 in REMoxTB with 600 participants per arm (13). The hazard ratio for the 35mg/kg rifampin arm in the PanACEA MAMS-TB trial was 1.78, 1.68 for the PaMZ arm in the NC-002 phase 2 trial, and 1.7 and 2.0 for BPaZ in the NC-005 phase 2 trial when bedaquiline was given at the licensed loading dose (400 mg daily for 2 weeks followed by 200 mg three times per week for 24 weeks (18) or daily 200mg dosing, respectively (31). The hazard ratio for the noninferior HZPM arm in Study 31/ACTG 5349 compared to the control arm was 1.38 (3). Based on these results, a hazard ratio of 1.7 could be considered an absolute minimum target for a phase 2 study.

In the REMoxTB trial, approximately 65% of 600 participants in the control arm had achieved culture conversion on MGIT by 12 weeks (13). Similar results were seen in the much smaller PanACEA MAMS-TB trial (32) although this finding was higher (86%) in the larger Study 31/ACTG 5349, with rigorous laboratory testing and reporting standards (3).

Assuming 65% of participants in the control arm achieve culture conversion by 12 weeks, 100 participants per arm would give 81% power to detect a hazard ratio of 1.6 and 90

participants per arm would give 86% power to detect a hazard ratio of 1.7. Therefore 90 participants per arm would be sufficient to give at least 85% power to detect a hazard ratio of 1.7, and greater power for higher hazard ratios, and greater power if more participants achieve culture conversion (as was seen in Study 31/ ACTG 5349).

The only participants excluded from the primary efficacy analysis were those who were late exclusions (Table 1). We expect 6% of these (6% of randomized participants were late exclusions in S31/A5349), and therefore, we will enroll 96 participants on each arm (a total of 288) to account for these late exclusions.

Analysis groups

Intention-to-treat (ITT) analysis group included all enrolled participants who received a treatment assignment. The modified intention-to-treat analysis group (mITT) is the primary analysis population of interest for efficacy analyses, comprising all participants in the ITT population, except for those who were late exclusions. The safety analysis group was the primary analysis population of interest for safety analyses, which included all participants in the ITT population who received at least one dose of study medication.

Analysis plan

The primary analysis of all efficacy endpoints is conducted in the mITT group. The primary analysis of the primary efficacy estimand (Table 4), time to culture negative in liquid media was performed using Cox proportional hazards models stratified by randomization stratification factors (geographical region and presence of cavitation). If there was a larger than expected contaminated or missing culture results data, we conducted multiple imputation using Fully Conditional Specification.

The secondary efficacy outcome of lack of sustained cure was analyzed using a time-to-event analysis, with the difference in proportion of participants meeting the designated endpoint at 52 weeks post-randomization estimated using Kaplan-Meier estimates. These comparisons between arms were a non-inferiority comparison using a 12% non-inferiority margin (NIM). Justification for the 12% NIM is based on a cure rate of untreated TB of 30% (33), and a 95% control arm cure rate, which gives a standard treatment effect of 65% for M1 (34). A NIM of 12% (M2) means that more than 80% of the treatment effect is preserved, exceeding the general recommendation in the Food and Drug Administration guidance of preserving at least 50% of the treatment effect. This secondary analysis was also repeated at 78 weeks post-randomization.

We used the Bayesian methodology proposed in Phillips et al. (29) to estimate the predictive probability of regimens not exceeding certain targets of the proportion of TB-related unsuccessful outcomes (lack of sustained cure) in potential future phase 3 trials. We will conduct a simulation study to estimate the probability of non-inferiority of regimens in potential future phase 3 trials under various scenarios. The calculation of the posterior predictive distribution in Phillips et al. (29) used a fixed value for the estimate of the control arm for the future phase 3 study; an obvious extension is to use the observed data on the control arm from this study, in addition to prior information on control arm performance from other recent trials.

We developed a decision framework in advance of trial opening to rank intervention regimens in terms of safety and efficacy, using results from the analysis of the primary efficacy endpoint (time to culture negativity in liquid media) as well as secondary efficacy endpoints (in particular the long-term efficacy endpoints).

Pharmacokinetic sampling

Sampling for pharmacokinetic (PK) analysis of study tuberculosis drugs is performed for all study participants as a component of the main Study 38/CRUSH-TB protocol (Table 2). Plasma PK samples are shipped to a designated quality-assured laboratory, where concentrations of tuberculosis drugs and their metabolites are measured.

Novel molecular pharmacodynamic marker – RS ratio®

We tested a novel molecular biomarker (the RS ratio®) that quantifies ongoing *M. tuberculosis* rRNA synthesis (35). This marker represents a first-in-class, new category of pharmacodynamic marker that monitors the impact of a drug on a bacterial cellular process, rather than bacterial burden. This marker provides a fundamentally new type of information that is distinct from and complementary to conventional culture-based measures of bacterial burden.

The RS ratio is anticipated to provide value early in treatment and at treatment completion (collection schedule in Table 3). Regimens are compared based on the proportion of participants who continue to have a detectable RS ratio at the end of treatment and in the post-treatment period. RS Ratio analyses are exploratory to supplement the primary analyses and therefore no correction for multiple testing will be applied.

Adaptive design

The adaptive design of this trial allows for possible introduction of novel regimens. Whether or not new drugs in the development pipeline (36) display synergistic activity with components of the BMZ backbone is under evaluation in preclinical animal models. Introduction of additional arms to this trial via adaptive design can be considered in the future, as preclinical and clinical results emerge.

If new arms are added to the trial, the randomization allocation ratio will continue from that time forward, with equal numbers randomized to each arm (i.e., a 1:1:1:1 allocation ratio, etc.). Recruitment to an intervention arm will cease when the required sample size for that arm is reached (and the primary analysis for that arm will then proceed). Recruitment will continue in the control arm and any remaining arms until the required per-arm sample size is reached for all intervention arms. This approach will ensure a 1:1 ratio between each intervention arm and its contemporaneously randomized controls. The primary analyses of existing and any new arms compared to control will always only include control arm participants contemporaneously randomized to the arm in question.

To evaluate the success of the experimental arms, interim efficacy and safety analyses were conducted to have an early assessment of which experimental arm will likely demonstrate an adequate efficacy and safety profile to continue to a phase III trial. Bayesian methodology

was used to assess the predictive probability of the experimental regimens obtaining predefined efficacy and safety thresholds. For efficacy, the successful experimental arm should have at least an 80% probability that the hazard ratio of the time to culture conversion in liquid media is ≥ 1.3 compared to the control arm. For safety, the successful experimental arm should have at least an 80% probability of not having a higher proportion of grade 3 or higher adverse events during 26 weeks from randomization than the control arm. Both efficacy and safety threshold should be met for the successful arm. A Bayesian approach to the Cox proportional hazards regression model was used for the efficacy threshold and a Bayesian analysis with Beta conjugate priors was used for the safety threshold. In both cases, non-informative priors were used.

Discussion

Study 38/CRUSH-TB builds on TBTC's decades of work on treatment shortening and success with the HPMZ regimen from Study 31/A5349. This study is a phase 2C trial, and regimens that demonstrate efficacy in this trial might be considered for a phase 3 trial. Phase 2C is a new design that seeks to reduce the risk of phase 3 trial failure by collecting long-term data (up to 78 weeks post-randomization) on clinically relevant outcomes (failure, relapse) in phase 2, before the start of a phase 3 trial, to inform decision-making (29). The key difference from a phase 2B trial design like that used in TBTC Studies 27, 28, 29, and 29X (37–40) is that the experimental arm is given for the intended duration that will be tested in a subsequent phase 3 trial (e.g., four months). Then, participants are followed for clinically relevant outcomes (e.g., failure or relapse), rather than transitioning to standard therapy after an initial period of experimental therapy. In contrast to standard phase 2 designs, the phase 2C design can provide a quantitative estimate of the likelihood that a regimen will be successful if taken forward to a phase 3 study, while closely following participants to capture any relapse events promptly, allowing retreatment to be initiated immediately. This strategy reduces risk of phase 3 failures, thereby reducing risk of unsuccessful treatment with an inadequate regimen in a larger number of participants. In addition, the current trial is designed to be adaptive, with the possibility of adding new arms as new drugs become available, while amassing data on the safety and efficacy of the BMZ backbone.

Study 38/CRUSH-TB has several strong design and implementation features derived from previously successful TBTC trials. These include rigorous DOT implementation to allow for a detailed understanding of regimen efficacy under pre-specified conditions; frequent, standardized, and comprehensive microbiological testing, which serves as the main component of efficacy outcome assessment; a robust pharmacovigilance system; PK measurements for all participants; including evaluation of the novel biomarker, the RS ratio.

Study eligibility criteria were kept as broad as possible, based on data available before the study start. Inclusion of Xpert MTB/RIF or smear positivity as eligibility criteria added flexibility and anticipated changes in the TB diagnostics algorithms. Children aged <12 years, pregnant women, and patients living with HIV-positive who have low CD4 cell counts are important populations that were excluded from this trial; if one or both investigational

regimens is shown promise to move to phase 3 trials, these populations should be considered for inclusion.

We recognize several important limitations to Study 38/CRUSH-TB design. First, open-label design is a study limitation that could introduce ascertainment and performance bias. Blinding both participants and investigators to treatment assignments is a widely adopted method to minimize bias. In Study 38/CRUSH, however, blinding using placebo would be impractical due to the high pill burden and the varying effects of food on the pharmacokinetics of the study drugs. Nonetheless, several aspects of the trial's design and execution are intended to reduce bias in outcome assessment. The outcomes primarily rely on mycobacteriology data, and laboratory personnel are kept blinded to the treatment assignments and the specific study visits during which sputum samples are collected. Sputum samples are collected at predetermined time points that are consistent across all three treatment arms. The trial also employs an innovative "PPTR" process to ensure that a standardized set of data and specimens is collected whenever a participant met any of the defined trigger criteria, regardless of their treatment arm. Additionally, the CDC staff, who provides guidance for study implementation to site personnel, are blinded to the treatment assignments of participants. Finally, only the unblinded statisticians and DSMB will see any aggregate data by treatment arm. An additional limitation is that we will not have a single central laboratory for blinded microbiological culture results. This would make the trial logistically and financially untenable and so we have instead implemented a rigorous TB lab quality assurance system that over the past ten years of the TBTC which identifies any problems in site laboratories. Furthermore, randomization is stratified by study site to balance between-site differences across treatment arms.

In summary, the Study 38/CRUSH-TB design and standardized implementation in this multicenter trial optimize the likelihood of obtaining valid and generalizable results. The study design is intended to be adaptive, allowing for the addition of new arms as new drugs become available and as more information is gathered about the safety and efficacy of the BMZ backbone. The findings of this trial might have important implications for the direction of future clinical research, as well as for clinically managing tuberculosis at individual and programmatic levels.

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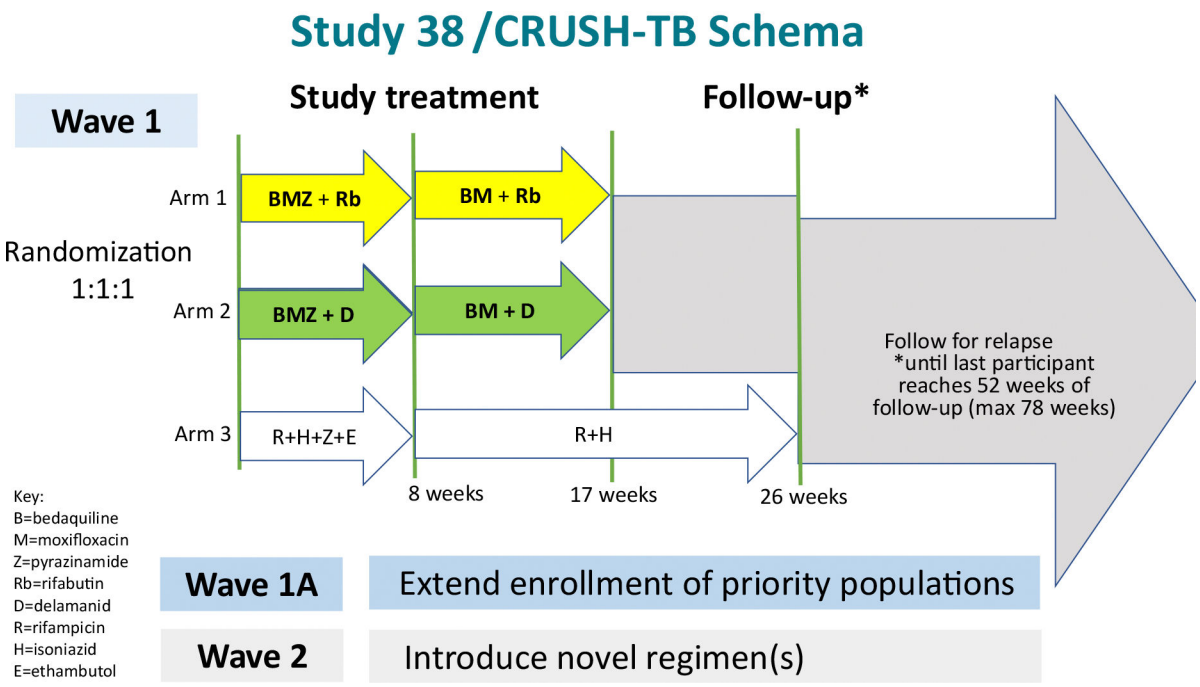

Figure 1.
Study schematic.

Table 1.

Participant inclusion and exclusion criteria for Study 38/CRUSH-TB

Inclusion criteria
Persons must meet all the following inclusion criteria to participate in this study:
(1) Pulmonary tuberculosis with or without suspected or proven concomitant extrapulmonary tuberculosis outside the central nervous system or bones
(2) Acid-fast bacilli in an expectorated sputum specimen of at least 1+ or GeneXpert (or GeneXpert Ultra) positive for *Mycobacterium tuberculosis*, with semiquantitative results of “medium” or “high”.
(3) Aged ≥12 years
(4) Documentation of negative HIV status within the past three months before enrollment or documentation confirming HIV infection.
(5) For participants with HIV: a. current use of dolutegravir-based antiretroviral therapy, or ability and willingness to start or transition to a dolutegravir-based antiretroviral therapy regimen b. CD4 T-cell count greater than or equal to 100 cells/mm^3 based on testing performed at or within 30 days before study enrollment
(6) Written informed consent/assent
(7) Karnofsky score of ≥60 (“requiring some help, can take care of most personal requirements”)
(8) A verifiable address or residence location that is readily accessible for visiting, and willingness to inform the study team of any change of address during the treatment and follow-up period.
(9) For all women of child-bearing potential who have not undergone a surgical sterilization procedure or who do not meet the study definition of postmenopausal, a negative pregnancy test at or within seven days before screening
(10) For all women of child-bearing potential who are not surgically sterilized, agreement to practice a reliable method of contraception (barrier method or nonhormonal intrauterine device) or abstain from sexual activity that could lead to pregnancy while receiving study drug treatment and for 30 days after stopping study treatment
Criteria for exclusion from enrollment
A person meeting any of the following exclusion criteria at the time of enrollment will be excluded from study participation:
(1) Pregnant or breastfeeding
(2) More than five days of tuberculosis treatment in the previous six months
(3) Previous treatment with any drug or combination of drugs known to have activity against *M. tuberculosis* (e.g., isoniazid, rifamycins, pyrazinamide, ethambutol, fluoroquinolones, etc.) for more than five days in the thirty days prior to enrollment
(4) Unable to take oral medications
(5) Hypersensitivity or previous intolerance to any of the study drugs
(6) Current or planned use of medications that have unacceptable drug-drug interactions with any of the study drugs during study treatment
(7) Suspected or proven central nervous system tuberculosis
(8) Suspected or proven bone tuberculosis
(9) Screening electrocardiogram (ECG) with QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 for men or >470 for women
(Note: in case of hypokalemia or hypomagnesemia, ECG can be repeated after electrolyte supplementation)
(10) Clinically significant ECG abnormality in the opinion of the site investigator, including but not limited to second or third degree atrioventricular block, prolongation of the QRS complex more than 120 milliseconds (in both male and female participants), or clinically important arrhythmia
(11) Current clinically relevant cardiovascular disorder in the opinion of the site investigator, including but not limited to heart failure, coronary heart disease, arrhythmia, or tachyarrhythmia
(12) Known family history of Long QT Syndrome in a first-degree relative (i.e., parent, offspring, or sibling)
(13) History of aortic aneurysm or dissection
(14) Hepatic cirrhosis or other serious liver disease
(15) Other medical conditions that, in the investigator’s judgment, make study participation not in the person’s best interest.
(16) Laboratory parameters done at or within 14 days before screening: a. Serum or plasma alanine aminotransferase greater than three times the upper limit of normal

b. Serum or plasma total bilirubin >2.5 times the upper limit of normal
c. Serum creatinine >2 times the upper limit of normal

d. Platelet count <75,000 cells/mm3

e. Absolute neutrophil count <1,000 cells/mm^3

f. Serum or plasma potassium <3.5 meq/L (note: potassium may be repleted and test repeated)

(17) Body weight <40.0 kilogram

(18) Known or suspected resistance to isoniazid or rifamycins (by phenotypic or molecular test)

(19) Previously enrolled in this study or currently enrolled in another therapeutic clinical trial that, in the investigator's judgment, would compromise study integrity or participant safety

(20) Current or planned incarceration or other involuntary detention.

Criteria for exclusion after enrollment ('Late exclusion')

Microbiological confirmation of drug-susceptible tuberculosis is not expected to always be available at the time of enrollment. Enrolled participants, irrespective of allocated treatment arm, who are subsequently determined to meet any of the following criteria, will be classified as 'late exclusions':

A. Screening and baseline study visit sputum cultures all fail to grow *M. tuberculosis*.

B. *M. tuberculosis* cultured or detected through accepted molecular assays (i.e., Cepheid Xpert MTB/RIF, Hain assays) from sputum obtained at screening or baseline is subsequently determined to be resistant to rifampin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, delamanid, or bedaquiline.

Table 2.

Schedule of Procedures/Evaluations

Visit Window		**Up to 7 days after screen**	**+/− three (3) days**											**+/− seven (7) days**					**Possible Poor Treatment Response (PPTR)**	**Early On-Treatment Termination Visit** [k]	**Early Off-Treatment Termination Visit**
Visit	**Screen**	**Baseline**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 14**	**WK 17**	**WK 22**	**WK 26**	**WK 39**	**WK 52**	**WK 65**	**WK 78**			
Informed Consent	X																				
Inclusion/Exclusion	X	X																			
Demographics	X																				
Contact information	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X
Medical history	X																				
Symptoms	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X
Physical exam [a]	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X
Adverse events				X		X		X		X		X	X	X	X	X	X	X	X		
Height	X																				
Weight	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X
Chest radiograph	X											X[m]		X[m]					X		
Electrocardiogram [b]	X	X		X		X		X		X		X		X							
Visual tests [c]		X				X															
HIV test	X																				
CD4 count (if HIV-positive) [d]	X																				
Pregnancy testing [e]	X																				
Randomization		X																			
Sputum for smear and culture [f]	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX[l]	XX	XX	XXX		
Sputum for rapid molecular test [g]	X																				
Sputum for RS ratio assay		X		X		X		X				X		X	X	X	X	X	X		
Storage of Mtb bacterial isolate	X	X										X	X	X	X	X	X	X	X		

Visit Window		Up to 7 days after screen	+/− three (3) days										+/− seven (7) days					Possible Poor Treatment Response (PPTR)	Early On-Treatment Termination Visit [k]	Early Off-Treatment Termination Visit
Visit	**Screen**	**Baseline**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 6**	**WK 8**	**WK 10**	**WK 12**	**WK 14**	**WK 17**	**WK 22**	**WK 26**	**WK 39**	**WK 52**	**WK 65**	**WK 78**			
Diabetes screen [h]	X																			
ALT	X			X		X		X		X		X	X						X	
Bilirubin	X			X		X		X		X		X	X						X	
Creatinine	X			X		X		X		X		X	X						X	
Hemoglobin	X			X		X		X		X		X	X						X	
WBC with differential	X			X		X		X		X		X	X						X	
Platelets	X			X		X		X		X		X	X						X	
Albumin	X																			
Potassium, magnesium, calcium	X																			
PK sampling for TB drugs [i]				Obtain within this interval																
Blood sampling for pharmacogenomics testing (consenting participant only) [j]		Obtain within this interval																		
Blood collection for future research (consenting participant only)		X		X		X		X				X[m]		X[m]					X	

NOTES

[a] At screening, a full physical exam will be done (omitting vaginal and rectal exams). Targeted physical exams will be conducted during study visits, as needed, based on symptoms.

[b] ECG is in triplicate, 5–10 minutes apart at screening, baseline, weeks 2, 4, 8, 12, 17, and 26. Resting ECGs will be conducted on-site using AliveCor KardiaMobile 6L (AliveCor Inc.) or a validated ECG machine.

[c] Control arm only.

[d] Unless results of a test performed at or within 30 days before screening were available.

[e] Pregnancy assessment in women of childbearing potential should be done at study visits at weeks 2, 4, 8, 12, 17, 22, and 26. Repeat pregnancy testing if pregnancy is suspected after enrollment.

[f] All sputa should be sent to the designated study laboratory. At least two sputa should be obtained at each of the following weeks: 1, 2, 3, 4, 6, 8, 10, 12, 14, 17, 22, 26, 39, 52, 65, and 78. At least three sputa should be obtained for PPTR evaluation.

[g] A rapid molecular test at screening to assess for rifampicin resistance, such as Xpert or Xpert Ultra, is strongly encouraged.

[h] Hemoglobin A1C is the preferred test. If such testing is not available, then fasting or random blood glucose can be measured.

[i]'Sparse' plasma PK samples were collected at two time points, around weeks 2–4 (after 14 study doses had been taken) and again at weeks 6–12. 'Intensive' PK sampling is performed among a convenience sample of 40 participants in the experimental arms only, once between 4 and 6 weeks of treatment. All plasma PK samples were collected in reference to an observed dose of intensive phase study drugs -- this reference dose must have been preceded by two directly observed study doses given approximately 24 and 48 hours before. Sparse PK collection includes three blood samples, collected 1 hour before and immediately before the reference dose, and 3 hours after the dose. Intensive PK collection involves the collection of eight blood samples, taken 30 minutes before the reference dose and at 1, 2, 4, 6, 8, 12, and 24 hours post-reference dose.

[j]Blood sampling for pharmacogenomics testing should be done once any time after enrollment.

[k]This visit occurs approximately 14 days after stopping study drugs.

[l]If week 52 sputa is contaminated, then the participant should be asked to provide at least two additional sputa as soon as possible after contamination is recognized.

[m]To be obtained at the end-of-study treatment visit (i.e., either week 17 or week 26).

Abbreviaitons. HIV= human immunodeficiency virus. Mtb=*Mycobacterium tuberculosis*. ALT=alanine transaminase. WBC= white blood cell count. PK= pharmacokinetics. TB=tuberculosis.

Table 3.

Doses of study medications by body weight*

Drug	Dose
Isoniazid (H)	300 mg once daily
Vitamin B6	25–50 mg once daily
Bedaquiline (B)	200 mg once daily for 56 days, followed by 100 mg once daily
Delamanid (D)	300 mg once daily
Pyrazinamide (Z)	1,500 mg once daily for participants weighing ≤75 kg, and 2,000 mg once daily for participants weighing >75 kg for 56 days
Ethambutol (E)	15 mg/kg once daily rounded up to the nearest 400 mg dose
Rifampin (R)	600 mg once daily
Rifabutin (Rb)	300 mg once daily
Moxifloxacin (M)	400 mg once daily

* Drugs and doses used to initiate treatment were automatically assigned by the web-based application during randomization. Initial doses of pyrazinamide and ethambutol were based on the participant's weight at enrollment, and doses are adjusted for the participant's actual weight at each visit during the intensive phase of treatment.

All study drugs were administered orally, seven days per week. Five of seven doses per week are administered under directly observed therapy (DOT) by study personnel or by a health care worker or lay treatment supervisor designated by the site investigator and trained on the study protocol. DOT could be conducted in-person or as a live or recorded video. Doses on weekends and holidays (up to three consecutive days) are either DOT or self-administered.

Table 4.

Definitions for primary outcome status.

Definition of primary efficacy estimand

The primary analysis will be conducted using culture results from liquid media. Each participant will either achieve culture negativity during follow-up or not achieve culture negativity during follow-up, in which case their outcome will be considered censored with time from date of randomization to date of last culture result (positive or negative).

The time to culture negativity will be defined as the time from randomization to the date of the first of at least two consecutive negative sputum cultures, collected on different study visits, irrespective of any subsequent positive cultures that may occur. For purposes of this outcome, a documented failure to obtain sputum from a participant after a witnessed attempt will be counted only as a 'presumed negative' sputum culture and will only be considered as a negative sputum culture in a sensitivity analysis.

Following the ICH E9 (R1) Addendum entitled Estimands and Sensitivity Analyses (https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf), the five attributes of the primary estimand are defined as follows:

A. **Treatment**. The treatment condition of interest is treatment with the allocated combination regimen at specified doses for the allocated duration.

B. **Population**. The population is defined by eligibility criteria for enrollment, excluding those classified as Late Exclusions.

C. **Endpoint**. The primary efficacy endpoint is time to culture negativity on liquid media as defined above.

D. **Accounting for intercurrent events**. Intercurrent events are events that occur after randomization and either preclude observation of the final endpoint or affect its interpretation. Intercurrent events are many and varied in TB trials. Almost all intercurrent events where time-to-culture conversion is subsequently achieved will be considered using the treatment policy strategy, ignoring the intercurrent events. Intercurrent events that result in time to culture conversion not occurring will be considered using the hypothetical strategy, censoring with time from date of randomization to date of last culture result (positive or negative) and estimating a treatment effect, accounting for censoring. Two specific intercurrent events will be handled differently: when a study participant receives off-study medication before achieving culture conversion, the outcome will be censoring at the end of follow-up; and an intercurrent event of death will also result in an outcome of censoring at the end of follow-up. A sensitivity analysis will also be conducted treating these two intercurrent events as above.

E. **Population-level summary**. Hazard ratio comparing each experimental regimen with control will be the primary population-level summary (after testing for the proportional hazard assumption).