BMJ Open

Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058606
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2021
Complete List of Authors:	Padmapriyadarsini, C; ICMR-National Institute for Research in Tuberculosis Devaleenal, Bella; ICMR-National Institute for Research in Tuberculosis Ponnuraja, C.; ICMR-National Institute for Research in Tuberculosis Ramraj, Balaji; ICMR-National Institute for Research in Tuberculosis Parmar, Malik; 3World Health Organization, Country Office for India, New Delhi Mattoo, Sanjay; Ministry of Health & Family Welfare Mandal, Sudarsan; Ministry of Health & Family Welfare Singla, R; National Institute of Tuberculosis and Respiratory Diseases
Keywords:	Thoracic medicine < INTERNAL MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE

Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Chandrasekaran Padmapriyadarsini[1], Bella Devaleenal[1], C.Ponnuraja[1], Balaji Ramraj[1],

Rupak Singla[2], Malik Parmar[3], Sanjay Mattoo[4], Sudarsan Mandal[4]

[1]*ICMR-National Institute for Research in Tuberculosis, Chennai*

[2]*National Institute of Tuberculosis and Respiratory Diseases, New Delhi*

[3]*World Health Organization, Country Office for India, New Delhi*

[4]*Central TB Division, Ministry of Health & Family Welfare, New Delhi*

Word Count: Abstract: 302 / Main manuscript: 4,048

Corresponding author

Dr.C. Padmapriyadarsini, DNB, MS, PhD

ICMR-National Institute for Research in Tuberculosis

No.1, Mayor Sathyamoorthy Road

Chetput, Chennai 600031

Phone: +91 9498022949

Fax No: 04428362525

e-mail: padmapriyadarsinic@nirt.res.in

Abstract

Introduction: Drug-resistant tuberculosis (DR-TB) is a global public health problem, where patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation and completion play a major role in treatment success. However, longer regimens with injectable result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety, and tolerability of various doses and duration of Linezolid (Lzd) in combination with Bedaquiline (Bdq) and Pretomanid (Pa) after 26 weeks of treatment in adults with Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant ($MDR_{TI/NR}$) Pulmonary Tuberculosis.

Methods and analysis: A multicentric, randomized pragmatic clinical trial in India will enroll participants to one of the three arms - Control arm (Arm 1): Bdq, Pa, and Lzd 600mg daily for 26 weeks OR Intervention arms (Arm 2): Bdq, Pa and Lzd 600mg for 9 weeks followed by 300mg for 17 weeks OR Arm 3: Bdq, Pa and Lzd 600mg for 13 weeks followed by 300mg for 13 weeks. The primary endpoint is the proportion of patients with favourable outcomes in terms of sustained cure and treatment completion while the secondary endpoint is unfavourable outcomes including deaths, treatment failure, and loss to follow-up. Safety and tolerability of the various Lzd combinations and TB recurrence will be recorded till 48-weeks post-treatment.

Ethics and dissemination: The study has been approved by the Ethics committees of participating institutes. The trial results will help in establishing evidence towards a safe and effective dose of Lzd that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared with the National TB Elimination Programme of

the country, and World Health Organization guidelines development group through publications, and dissemination meetings.

Trial Registration: The protocol (version 3.1 dated 20 July 2021) has been registered on the Clinical Trial Registry of India as CTRI/2021/03/032189 on 22nd March 2021 and ClinicalTrials.gov with the identifier: NCT05040126 on 10th September 2021.

Article Summary

Strength and Limitations

- Pragmatic Randomized trial design will add considerable value to the study as it will consider real-life patients under field conditions in a clinical trial thus decreasing bias and minimizing unequal distribution.
- The study results and outcomes will be more generalizable and can be easily scaled up under the Country's TB elimination program.
- The trial lacks stratification based on disease severity. This may result in the possibility of more severe cases in one group of treatment. We hope randomization should be able to cover this.
- As there is no blinding in this trial, the treating physician may be biased to assign causality of all adverse events to the drug concerned.
- The heterogeneity of data may be present as it's a planned multicentric study.

Keywords: Linezolid Dose, Pretomanid, Randomized trial, Treatment Intolerant, Drug-resistant TB

Introduction:

World Health Organization estimates that globally in 2020, 132 222 cases of multi-drug resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25 681 cases of pre-extensively – drug-resistant (pre-XDR-TB) or extensively drug-resistant (XDR-TB), totaling 157,903 cases were detected, though testing for resistance to fluoroquinolones remains much lower, at just over 50% worldwide in 2020.[1] Of these, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, lesser than the previous years. The treatment success rate of the 2018 MDR/RR-TB cohort was 59%; though improved from earlier cohorts the treatment failure, loss to follow-up and death remain high.[1] Also, this was not uniform across the globe – for instance, the treatment success rate was below 50% in countries like India and Indonesia due to high death and loss to follow-up. Globally the treatment success rate of highly drug-resistant TB remains unacceptably low.

With the availability of newer drugs and using patient-friendly approaches, it is now possible to design newer regimens that are less toxic, safer, and of shorter duration. The WHO consolidated treatment guidelines for drug-resistant TB recommends longer and shorter treatment regimens for MDR/RR-TB treatment.[2] A South African study using a combination of Bedaquiline (Bdq), Pretomaid (Pa), and Linezolid (Lzd) to treat highly drug-resistant forms of TB showed a favorable outcome of 90% at the end of 6-months of treatment. [3] However, the high dose of linezolid used in this study led to more than 70% of patients having adverse events to Lzd often leading to either treatment interruption or dose reduction of linezolid between two to

three months of the treatment period. Though Lzd is efficacious for drug-resistant TB, adverse events and treatment discontinuation also are found to be common.[4]

The multicountry ZeNIX study with consistent dosing of Bdq and Pa reported a 93% success rate with linezolid 1200 mg for 6 months and 91% with linezolid 600mg for 6 months. Adverse reactions were reported in 38% of those receiving 1200mg linezolid for 6 months and 24% of those receiving 600mg of linezolid for 6 months.[5] Though there seemed to be a modestly greater early bactericidal effect over 14 days at the highest 1200 mg daily (NC-003 study), this dose appeared to be associated with a greater incidence of neuropathic and myelosuppressive effects than the 600 mg daily dose in the ZeNIX and NixTB trials. While a full 6 months of linezolid therapy in the regimen may give greater culture conversion and avoid relapse, the mouse model found that more than 2 months of linezolid, when combined with Bdq and Pa, does not increase relapse-free cure.[6] The study also found that Lzd increases the sterilizing activity of the Bdq-Pa combination; no MTB could be cultured from the lungs of mice 3 months after cessation of 3 months of treatment with this combination.

Given the above evidence, both in terms of safety and toxicity of higher dose and longer duration of Lzd and the ability of Lzd to act synergistically with the combination of Bdq and Pa, the current study is planned with a primary objective to determine the effectiveness of various doses and duration of Lzd in combination with Bdq and Pa given for 26-weeks in adults with either Pre-Extensively Drug-Resistant (Pre-XDR) OR Non-responsive / Treatment Intolerant multidrug-resistant ($MDR_{NR/TI}$) pulmonary TB. Secondary objectives include

a) to determine the safety and tolerability of various doses and duration of Linezolid with Pretomanid and Bedaquiline following 26 weeks of therapy among adults with either Pre-XDR or $MDR_{TI/NR}$ pulmonary TB

b) to determine the baseline resistance to the newer and repurposed drugs

c) to determine the M.tb strain mutation by whole genome sequencing in participants with treatment failure while on treatment or recurrence of TB during the follow-up period

Methods and Analysis

Study design and oversight: Modified BPaL (mBPaL) study is a multi-center, pragmatic randomized clinical trial under field conditions. A total of 400 adult Pre-XDR or MDRTI/NR pulmonary TB patients meeting all study eligibility criteria will be enrolled in the study after the screening procedure. The enrolled patients will be randomized to receive any one of the 3 regimens using block randomization. The study is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the Union and implemented by the ICMR-National Institute of Research in Tuberculosis in collaboration with the National TB Elimination Programme through its tertiary care DR-TB centers and WHO Country Office for India. This study has been approved by the institutional ethics committee of NIRT (NIRT-IEC ID: 2021004, 12 July 2021) and the participating sites and will begin enrollment tentatively by 20th October 2021.

Study setting: mBPaL trial will be implemented in eight sites in India. The study sites were selected based on the 2019 census of XDR and MDR_{FQ} TB patients attending the DR-TB centers in the country. The study sites include DR-TB centers at Sarvodaya Charitable Trust Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavanagar, Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu

Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

Study patients and eligibility: Adults between 18 to 65 years of age diagnosed with Pre-XDR-TB or as $MDR_{TI/NR}$ accessing TB care services in selected DR TB centers of the country.

(i) Pre-XDR-TB is defined as TB that is documented by culture positive or a molecular test positive for *M. tb* in sputum specimen collected within 3 months before screening AND documented resistance to rifamycins with or without isoniazid resistance AND, additionally resistant to at least a fluoroquinolone (FQ).[7]

(ii) $MDR\text{-}TB_{TI/NR}$ is documented by culture positive or a molecular test positive for *M.tb* in sputum specimen collected within 3 months before screening AND documented resistance to rifamycins with or without isoniazid resistance AND with documented intolerance or non-response to the current treatment regimen for 6-months or more when the participant was adherent to the treatment regimen.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study

Table 1: Study Eligibility criteria

Inclusion Criteria	Exclusion criteria
Adults aged between 18 years – 65 years	A patient who has received more than 2 weeks of Bdq or Lzd before the first dose of the mBPaL regimen OR If the result of DST for FQ or Lzd is not available and h/o more than 2 weeks consumption of drugs used in the study regimen
Pulmonary Pre-XDR-TB patients or MDR-TBTI/NR patients	
Bodyweight of ≥30 kg (in light clothing)	Intolerance or risk of toxicity from medicine in the

	treatment regimens
Provide informed written consent before all study-related procedures, including HIV testing	All forms of Extrapulmonary TB (except Lymph node TB or pleural effusion associated with Pulmonary DR-TB)
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) < 2.5 x ULN; Total bilirubin lesser than ULN	Platelet count <1,00,000 /mm^3 or Haemoglobin level of < 9.0 g/dl
QTc(f) less than or equal to 450 ms at baseline	QTc(f) > 450 at baseline & normal electrolytes, ECG to be repeated after 6 hours and if both ECGs show QTc(f) >450 msec, then the patient should not be challenged with cardiotoxic drugs. Having risk factors for Torsade de Pointes, e.g. hypokalaemia, heart failure, history of long QT syndrome among family members Currently having an uncontrolled cardiac arrhythmia that requires medication
Female patients should not be pregnant or should be using a birth control method	Pregnant or Lactating
	HIV infected patient with a CD4+ count of ≤ 50 cells
	Grade III or IV peripheral neuropathy Major Psychiatric illness
	Very seriously ill patients (Karnofsky scores < 50 within last 30 days)

Recruitment process: Potential trial participants who visit the DR-TB centers in the selected trial sites will be approached by the study staff and explained in detail about the study in their native language. Patients willing to participate in the trial will be given a patient information sheet and also the consent form that explains all study-related procedures. After getting their consent on a written consent form, patients will be screened for study participation and the eligible participants will be enrolled within the next 14 days.

Study regimen and drug dosing: The study participants will be randomized in the ratio of 1:1:1 to receive one of the mentioned treatment regimens -

Arm 1: 26 wks. Bdq +Pa + Lzd (600mg)

Arm 2: 9 wks. Bdq +Pa + Lzd (600mg) followed by 17 wks. Bdq +Pa+ Lzd (300mg)

Arm 3: 13 wks. Bdq +Pa + Lzd (600mg) followed by 13 wks. Bdq +Pa+ Lzd (300mg)

Four 100 mg tablets (400 mg) of Bedaquiline will be administered by mouth once a day for 2 weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks. Pretomanid will be administered as (200mg) one tablet once a day for 26 weeks In Arm 2, the Lzd dose will be reduced from 600mg to 300 mg after 9 weeks and after 13 weeks in Arm 3 irrespective of the smear and culture results. All dosing of Lzd is given with the ability to interrupt or reduce the dose if needed based on Grade 3 toxicity. The continuation of the regimen beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.

Randomization procedures: Computer-generated list of random numbers using REDCAP software will be used for Randomization centrally. The site physician using these computer-generated randomizations will be able to randomize the study participants to any one of the three arms in the ratio of 1:1:1. Block randomization will be used to randomize participants in the trial. NIRT statistician will assign the unique study identification number after confirming all the study-related eligibility criteria. There is no blinding in the trial.

Treatment Allocation: The study participants will be randomized to receive one of the 3 treatment regimens in a 1:1:1 ratio using block randomization. NIRT center will be generating the Allocation codes at the time of the inclusion of patients to the study at the recruiting sites,

using a computer-generated list of random numbers. Separate randomization lists for each site will be prepared in advance by an independent statistician and at the time of patient's admission to the study, the site Physician will be able to randomize them at the site on RedCAP software based on pre-defined factors.

Treatment delivery, compliance, and retention: The study participants will be hospitalized for two weeks wherever feasible and study drugs will be administered under supervision. Ambulatory care can also be offered if hospitalization is not feasible. After discharge, drugs will be supplied – weekly for the first month, then fortnightly till 3rd month, and then monthly till the end of treatment. A health care provider or a family member will be assigned and trained to supervise the drug intake and monitor adherence to treatment. During the treatment phase, the patient will be reviewed every week till 16 weeks of treatment, then monthly thereafter until the end of the treatment phase (26/39 weeks). During these visits treatment adherence will be assessed by review of treatment card, empty pill covers, on-time drug refill, and hospital attendance. Treatment compliance will be enhanced by offering enhancers like nutrition supplements, reimbursing nominal costs for loss of wage, or transportation costs. Follow-up visits will be conducted for 48 weeks after treatment.

Concomitant medication while in the trial: Any medications that are consumed while in the trial will be entered on the concomitant medications page of the case record form. Medication entries shall be specific to the generic name, the dose, unit, frequency, and route of administration, the start, and the stop date, and the reason for use. Drugs prohibited to be used during the study include aspirin or ibuprofen or drugs that can cause gastrointestinal bleeding, any antibiotics until clinically warranted, and efavirenz-based antiretroviral therapy.

Criteria for discontinuation/withdrawal of study participants: The trial regimen may be discontinued in some patients in situations such as resistance to study drugs, intolerable or severe toxicity, and treatment failure. A patient may be withdrawn from the study for non-willingness of the patient to continue for any reason, pregnancy, drug-drug interaction, non-compliance & non-availability, drug resistance, or recommendation by the Data Safety & Monitoring Board.

Study Outcome: The primary outcome of the trial is the proportion of patients with favorable treatment outcomes, defined as sustained treatment success at 12 months post successful TB treatment, being alive & free of TB. Successful TB treatment includes Cure and Treatment Completed as defined by WHO.[8] The secondary outcome includes the proportion of patients with unfavorable outcomes comprising of death, bacteriological or clinical failure, and loss to follow-up. We will also record the proportion of serious adverse events occurring among patients in the study during the treatment and follow-up period.

Participant timeline: Each participant involved in the trial will have a screening period of 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture result at week 16 and a post-treatment follow-up for 12 months. Figure 1 shows the entire schedule of enrolment of a patient, the interventions to be given, and assessments to be done for a participant in the trial.

Patient and public involvement: Since the scientific problem is still not proven, patients were not involved in the research question development or the design of this study. However, learning from the difficulties faced by patients on the higher dose of Lzd there is an urgent need to find the right dose of Lzd with lower toxicity, better tolerability and at the same time not compromise on the efficacy of the regimen to prevent recurrence of TB. The study proposal is

discussed among the members of the Institutional Scientific advisory committee, Institutional Ethics committee, Drug Controller General of India, and Community Advisory Board. Study results will be widely disseminated through meetings, conference presentations, and publication.

Sample size assumption: mBPaL trial will evaluate the effectiveness of various doses and duration of Lzd with Bdq and Pa after 26 weeks of treatment in adults with Pre-XDR, or MDR (TI/NR) pulmonary TB patients. The efficacy of Bdq with Pa and Lzd (600 mg) for 26 weeks is reported to be about 91%.[5] Assuming that the effectiveness of treatment arms of Bdq + Pa with either Lzd 600mg for 9 weeks followed by 300mg for 17 weeks or Lzd 600mg for 13 weeks followed by 300mg for 13 weeks would be about the same based on the recently released interim outcomes of ZeNIX trial results, we hypothesize that these treatment arms with planned reduction of Lzd would be non-inferior to Lzd 600 mg for 26 weeks arm with a non-inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and alpha error of 5% we require about 111 patients in each arm. Factoring in a loss of 20% (due to default or migration), we require 133 patients in each arm or a total of 399 patients (approx. 400) to achieve our study objective.

Data collection, management, and interim analysis: Clinical and demographic information and laboratory reports will be collected from the individual participants in the paper case report forms and entered in Redcap software at all the participating sites. Data will be verified for accuracy and completeness. Data access would be restricted to the study statisticians at NIRT and Central TB Division. Third party access to data is restricted and will be made available only on request to NIRT. Data analysis will be done using SPSS software by statisticians at NIRT. An interim analysis is planned when at least 33% (approximately 120) of

the study participants complete 26 weeks of treatment and sputum smear and MGIT culture results are available.

Study outcome analysis: The primary effectiveness analysis will be conducted using culture results from MGIT culture. Modified Intent-to-treat (mITT) analysis will be carried out to evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis, that the investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-XDR-TB, $MDR_{/TI/NR}$ in terms of favorable outcome (including sustained cure and treatment completed) and unfavorable outcome (including death, treatment failure and lost to follow-up) in the field settings. Time to culture conversion and adverse events at the end of 9 weeks and 26/39 weeks will be estimated using survival analysis methods. Deaths and study withdrawals within the first 7-days of treatment and those excluded at baseline due to study drug resistance will be considered as initial exclusions and will not be included in the final mITT analysis. Per protocol analysis will be done for those patients who comply with the treatment regimen to which they were assigned as the mITT method is biased towards null hypothesis in non-inferiority trials. All participants who have consumed >80% of the drugs will be included in this analysis. Safety analysis will include data from all who received at least one dose of the study regimen.

Data and Safety Monitoring Board (DSMB): The DSMB comprises a statistician, clinical trial experts, pharmacologist, and pulmonologist. They will review data from this trial on pre-specified time points as defined in the study protocol. They will review the progress of the trial, safety issues for the trial participants in the early stages focusing majorly on grade 3 or 4 adverse events, serious adverse events, and discontinuation of treatment due to adverse events. DSMB can recommend continuing or terminating/making modifications to the trial based on the findings.

Study site monitoring and quality assurance: Study monitoring committee formed by the sponsor and other stakeholders will monitor the study data quality as per trial standard operating procedures. The monitoring plan will be followed to perform field visits and audits at various stages. The CRFs, patient records, and all source documents of the study participants in this study will be made available to be reviewed by the study monitors. To discuss the study progress and the problems incurred by the sites during the conduct of the trial, regular virtual meetings with the investigators of each study site will be conducted. Any critical protocol modifications during the conduct of the research will be informed to the Institutional Ethics Committee, CTRI, and the participants involved in the trial. At any time during or after completion of the study, the Sponsor through independent non-study staff may conduct a quality assurance assessment of the site records, and the regulatory agencies may conduct a regulatory inspection.

Confidentially of trial data: All study-related CRFs, documents related to the trial will remain in the custody of the site Principal Investigator under lock and key until transferred to archives. The records identifying the patient will be kept confidential and will not be made publicly available. All electronic data will be saved securely in password-protected systems. The final data of the study will be accessible only to the statisticians in NIRT and the Central TB division. When the results of the trial are published, the patient's identity will remain confidential. The confidentiality of the patients included in this trial will be maintained during the conduct of the study period following the Indian-GCP and the relevant regulations by the laws of India.

Ethics and dissemination

The current ICH Good Clinical Practice and the ICMR ethical guidelines for biomedical research in human participants will be followed in the current trial. This will ensure public

assurance that the well-being, safety, and rights of the participants are considered, which is consistent with the principles originating from the Helsinki Declaration and will maintain the credibility of the clinical trial data. The personal data that are necessary to analyze the safety, tolerability and antibacterial activity of the investigational product will be used. Manuscripts preparation, result dissemination and publication materials are the responsibility of the Principal investigator. After the completion of the trial, the investigators anticipate publishing the study results in peer-reviewed scientific journals, presenting the findings in meetings and sharing the results widely with the program managers and policymakers.

Discussion

WHO has released the Global list of High Burden Countries for MDR/RR-TB for the year 2021–2025. The list contains the top 20 countries with an estimated absolute number of incident cases and the top 10 countries with a severe burden of incident rate totaling thirty countries. As compared to 2016-2020, few countries like Ethiopia have transitioned out while countries like Nepal have been added to the list.[1] Average success rate of conventional XDR-TB patients put on treatment (without Bdq) from 2016 to 2018 is 29%. This has increased to 48% in 2018.[9] Managing MDR-TB and XDR-TB remains a major challenge in the elimination of TB. It is expected that DR-TB patients treated with short regimens with newer oral drugs would have a better quality of life compared to patients on standard (either short or long) DR-TB regimens due to multiple reasons. Adherence of patients improves with injectable-free treatment and facilitates the implementation of community programs. This would reduce the costs incurred for the patients on travel to health facilities for injections, loss of wages or hospitalization expenses during the intensive phase of treatment of standard regimens. Hence, it is reasonable to assume that injectable-free treatment regimens that potentially reduce the occurrence of adverse

reactions would likely improve the overall health-related quality of life of patients. Second, BDQ-containing regimens reduce the costs per treatment success by 18–20% in short course regimens and 49–50% in long course regimens. It was estimated that approximately 61,000 more patients could be treated successfully over 5 years with Bdq containing regimens.[10] The success rate of DR TB patients treated under the Bdq conditional access program (Bdq-Cap) is 71%.[9]

Studies in the past have compared the outcomes of a longer oral regimen containing Bdq with the shorter oral regimen. More beneficial effects were observed in the shorter all-oral Bdq-containing regimen compared to injectable-free longer regimen containing Bdq. The favorable odds ratio of 3.9 (1.7-9.1) was observed for success versus failure/recurrence, 1.6 (1.2–2.2) for success versus all unfavorable outcomes and 0.5 (0.4-0.8) for loss to follow-up, thereby supporting the use of all-oral shorter regimen.[11] Also studies have evaluated the safety of the newer drugs in shorter oral regimens. In the NIXTB study, Lzd toxicity such as peripheral neuropathy and myelosuppression was reported among 81% and 48% of the study population respectively. Adverse events leading to death and serious adverse events were 9% and 30% respectively in the 600 mg twice daily Lzd group and 3% and 9% in the 1200 mg once daily Lzd group.[3] In ZeNIX trial peripheral neuropathy was reported in 38% of those receiving 1200mg of Lzd for six months; 24% of those receiving 1200mg of Lzd for two months; 24% of those receiving 600mg of Lzd for six months and 13% of those receiving 600mg of Lzd for two months. Similarly, anemia, secondary to linezolid exposure was noticed in 22% of those receiving 1200mg of Lzd for six months; 17% of those receiving 1200mg of Lzd for two months; 2% of those receiving 600mg of Lzd for six months and 7% in those receiving 600mg of Lzd for two months.[5] Modified BPaL study will determine the effectiveness in the management of DR-

TB patients by comparing the varying dose of Lzd with Bdq and Pa regimens. Safety assessment in the mBPaL study is one of the major components in measuring the outcome of the regimens.

We are proposing to conduct a pragmatic clinical trial (mBPaL study) which has varying doses of Lzd along with Bdq and Pa as planned reduction of Lzd for the treatment of Pre-XDR and $MDR_{TI/NR}$ pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased frequency of dose interruption in regimens containing Lzd, this trial will help us in deciding the effective dosing of Lzd to be given with Bdq and Pa for a fully oral short-course regimen to treat highly drug-resistant TB in the field setting. The main drivers of the acceptability of BPaL regimen were the short duration of treatment, fully oral regimen without injectables, reduced pill burden, anticipated higher treatment success, lower financial burden for patients and the program, reduced burden on the health system, using existing diagnostic processes and lesser burden to TB laboratories for monitoring of bacteriological treatment. This study will create a new standard of care for Pre-XDR and $MDR_{TI/NR}$-pulmonary TB patients that will not only have better and earlier culture conversion but also reduce the proportion of patients who do not adhere to the full course of therapy.

- ***Authors' contributions***: CPP, CPR & RS – conceived & designed the study / CPP, BD, CPR & BR – development and writing of the study protocol / CPP, BD, CPR, BR, MP, SM & SuM – writing and editing this manuscript

- ***Funding***: This Study/ Pragmatic Clinical Trial is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the UNION; Cooperative Agreement No. 72038620CA00007. It is made possible by the support of the American People through the United States Agency for International Development (USAID). The contents of this study document are the sole responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government. Trial Sponsors: ICMR-National Institute for Research in Tuberculosis

- ***Competing interests***: None

References

1. Global tuberculosis report 2021. Geneva: World Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO. Accessed on 21st October 2021. https://www.who.int/publications/digital/global-tuberculosis-report-2021/tb-disease-burden/incidence

2. World Health Organization. WHO consolidated guidelines on **drug-resistant** tuberculosis treatment. Geneva: World Health Organization; 2019.

3. Conradie F, Diacon AH, Ngubane N et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med. 2020; 382(10): 893-902.

4. Singh B, Cocker D, Ryan H, et al. Linezolid for drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev. 2019; 3(3): CD012836

5. Conradie F, Everitt D, Olugbosi M, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquilline, and alternative doses and durations of linezolid [Conference presentation]. IAS 2021, Berlin, Germany. Accessed on 25/09/2021 https://theprogramme.ias2021.org/Abstract/Abstract/2405

6. Tasneen R, Tyagi S, Williams K, et al. Enhanced bactericidal activity of rifampin and/or pyrazinamide when combined with PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother. 2008; 52(10): 3664-3668.

7. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis. 27-29 October 2020. Accessed on 27.9.2021. https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis

8. Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions. 17-19 November 2020. Accessed on 27.9.2021. https://www.who.int/publications/i/item/9789240022195

9. Central TB Division (CTD), Ministry of Health and Family Welfare, Government of, India. India TB report 2021. National Tuberculosis Elimination program Annual Report. https://tbcindia.gov.in/showfile.php?lid=3587 (accessed September 28, 2020)

10. Mpobela Agnarson A, Williams A, Kambili C, et al. The cost-effectiveness of a bedaquiline-containing short-course regimen for the treatment of multidrug-resistant tuberculosis in South Africa. Expert Rev Anti Infect Ther 2020; 18: 475–483.

11. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment:drug-resistant tuberculosis treatment. 2020. https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf.

Figure 1. Schedule of enrolment, interventions, and assessments of a participant in the trial

COMPLETED WEEKS	-2	0	1	2	3	4	5	6	7	8	9Ɜ	10	11	12	13£	14	16	20	26#	30	38	50	62	74
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/color vision	X										X				X				X					
12 lead ECG [B]	X			X		X		X			X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X																X		X					
Sputum smear (1EM/1 spot)*	X					X					X				X		X	X	X		X	X	X	X
Sputum culture (LJ/MGIT) and DST for 1st and 2nd line drugs incl. LZD	X					X					X				X		X	X	X		X	X	X	X

WGS (NIRT site)	X																						
LPA and Ist and 2nd line DST (at sites) ¥	X																						
MGIT DST (Bdq/Pretomanid) at NIRT∞	X																						
CBC	X			X		X		X			X		X						X		X	X		X
LFT	X			X		X		X			X		X						X		X	X		X
RFT	X					X					X								X		X			X
Blood glucose	X					X					X								X		X			X
HbA1C	X												X						X					
Serum amylase and lipase	X					X							X						X		X			X
S. Electrolytes (Na, K, Cl) & Ca, Mg	X					X							X						X		X			X
Urine Gravindex test	X					X					X				X		X	X	X	X	X			
HBsAg, HCV, and HIV	X																							
HRQoL	X																		X					X
Adverse events$^{\$}$		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Patients will give 2EM and 1Spot sputum sample at baseline

¥ LPA performed only if sputum results are positive

± DST performed at baseline (with storage of the strain at -20c), 16th week in case of positive culture and if any culture is found positive during the 48 weeks after the end of the treatment (with storage of the strain of the recurrent episode for genotyping analysis)

∞ Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and Pretomanid and for Whole Genome Sequencing. Isolates will also be saved at the regional labs until sub-culture results are available for any further DST required for patient management

[B] Baseline ECG should be obtained and additional ECGs conducted daily for the first two weeks after starting treatment (if hospitalized)

ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

ɔ Week 9 – Linezolid dose will be modified at week 9 in arm 2

£ Week 13 - Linezolid dose will be modified at week 13 in arm 3

end of treatment for patients whose 12th week cultures are negative and if 16th week cultures are not available then no clinical or radiological evidence of TB

$ Adverse event monitoring over phone weekly from 17th week onwards till the end of treatment (except during the days of the scheduled visit)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13, 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11,12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12,20,21,22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12,14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,13

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13,14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14,15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14,15

	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	20,21,22

BMJ Open

Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058606.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Jul-2022
Complete List of Authors:	Padmapriyadarsini, Chandrasekaran; National Institute for Research in Tuberculosis Devaleenal, Bella; ICMR-National Institute for Research in Tuberculosis Ponnuraja, C.; ICMR-National Institute for Research in Tuberculosis Ramraj, Balaji; ICMR-National Institute for Research in Tuberculosis Singla, R; National Institute of Tuberculosis and Respiratory Diseases, Parmar, Malik; 3World Health Organization, Country Office for India, New Delhi Mattoo, Sanjay; Ministry of Health & Family Welfare Mandal, Sudarsan; Ministry of Health & Family Welfare
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	Thoracic medicine < INTERNAL MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE

Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Chandrasekaran Padmapriyadarsini[1], Bella Devaleenal[1], C.Ponnuraja[1], Balaji Ramraj[1], Rupak Singla[2], Malik Parmar[3], Sanjay Mattoo[4], Sudarsan Mandal[4]

[1]*ICMR-National Institute for Research in Tuberculosis, Chennai*

[2]*National Institute of Tuberculosis and Respiratory Diseases, New Delhi*

[3]*World Health Organization, Country Office for India, New Delhi*

[4]*Central TB Division, Ministry of Health & Family Welfare, New Delhi*

Word Count: Abstract: 290 / Main manuscript: 4,318

Corresponding author

Dr.C. Padmapriyadarsini, DNB, MS, PhD

ICMR-National Institute for Research in Tuberculosis

No.1, Mayor Sathyamoorthy Road

Chetput, Chennai 600031

Phone: +91 9498022949

Fax No: 04428362525

e-mail: pcorchids@gmail.com

Abstract

Introduction: Drug-resistant tuberculosis (DR-TB) is a global public health problem. Patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation, and completion play a significant role in treatment success. However, extended regimens with injectables result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety, and tolerability of various doses and duration of Linezolid (LZD) in combination with Bedaquiline (BDQ) and Pretomanid (Pa) after 26 weeks of treatment in adults with Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant ($MDR_{TI/NR}$) Pulmonary Tuberculosis.

Methods and analysis: A multicentric, randomized pragmatic clinical trial in India will enroll participants in one of the three arms - Control arm (Arm 1): BDQ, Pa, and LZD 600mg daily for 26 weeks OR Intervention arms (Arm 2): BDQ, Pa and LZD 600mg for nine weeks followed by 300mg for 17 weeks OR Arm 3: BDQ, Pa and LZD 600mg for 13 weeks followed by 300mg for 13 weeks. The primary endpoint is the proportion of patients with favorable outcomes as sustained cure and treatment completion. The secondary endpoint is unfavorable outcomes, including deaths, treatment failure, toxicity/adverse events, and loss of follow-up till 48 weeks post-treatment.

Ethics and dissemination: The study has been approved by the Ethics committees of participating institutes and the National Institute for Research in Tuberculosis. The trial results will help establish evidence towards a safe and effective dose of LZD that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared

with the National TB Elimination Programme of the country and the World Health Organization guidelines development group through publications and dissemination meetings.

Trial Registration: The protocol (version 3.1 dated 20th July 2021) has been registered on the Clinical Trial Registry of India as CTRI/2021/03/032189 on 22nd March 2021 and ClinicalTrials.gov with the identifier: NCT05040126 on 10th September 2021.

Article Summary

Strength and Limitations

- Pragmatic Randomized trial design will add considerable value to the study as it will consider real-life patients under field conditions in a clinical trial, thus decreasing bias and minimizing unequal distribution.
- The Country's TB elimination program can use the results of the study to scale up the regimen as it will be more generalizable
- The trial lacks stratification based on disease severity. This may result in the possibility of more severe cases in one group of treatment. We hope randomization should be able to cover this.
- As there is no blinding in this trial, the treating physician may be biased to assign causality of all adverse events to the drug concerned.
- Data heterogeneity may be present as it's a planned multicentric study.

Keywords: Linezolid Dose, Pretomanid, Randomized trial, Treatment Intolerant, Drug-resistant TB

Introduction:

World Health Organization (WHO) estimates that globally in 2020, 132222 cases of multi-drug resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25681 cases of pre-extensively –drug-resistant (pre-XDR-TB) or extensively drug-resistant (XDR-TB), totaling 157903 cases were detected. However, testing for fluoroquinolone resistance remains much lower, at just over 50% worldwide in 2020.[1] Of these, 150359 people with MDR/RR-TB were enrolled in treatment in 2020, less than the previous years. The treatment success rate of the 2018 MDR/RR-TB cohort was 59%; though improved from earlier cohorts, the treatment failure, loss to follow-up, and death remain high.[1] Also, this was not uniform across the globe – the treatment success rate was below 50% in countries like India and Indonesia due to increased death and loss-to-follow-up. Globally the treatment success rate of highly drug-resistant TB (DR-TB) remains unacceptably low.

With the availability of newer drugs and patient-friendly approaches, it is now possible to design newer regimens that are less toxic, safer, and of shorter duration. The WHO consolidated treatment guidelines for DR-TB recommend longer and shorter treatment regimens for MDR/RR-TB treatment.[2] A South African study using a combination of Bedaquiline (BDQ), Pretomaid (Pa), and Linezolid (LZD) to treat highly DR-TB showed a favorable outcome of 90% at the end of 6-months of treatment. [3] However, the high dose of LZD used in this study led to more than 70% of patients having adverse events to LZD, often leading to either treatment interruption or dose reduction of LZD between two to three months of treatment. Though LZD is efficacious for DR-TB, adverse events and treatment discontinuation also are found to be expected.[4]

The multicountry ZeNIX study with consistent dosing of BDQ and Pa reported a 93% success rate with linezolid 1200 mg for six months and 91% with linezolid 600mg for six

months. Among those receiving 1200mg linezolid for six months, adverse events reported was 38%, while in those receiving 600mg of linezolid for six months, it was 24%.[5] Though there seemed to be a modestly greater early bactericidal effect over 14 days at the highest 1200 mg daily (NC-003 study), this dose appeared to be associated with a greater incidence of neuropathic and myelosuppressive effects than the 600 mg daily dose in the ZeNIX and NixTB trials. While a full six months of linezolid therapy in the regimen may give higher culture conversion and avoid relapse, the mouse model found that more than two months of linezolid, combined with BDQ and Pa, does not increase relapse-free cure.[6] The study also found that LZD increases the sterilizing activity of the BDQ-Pa combination; no MTB could be cultured from the lungs of mice three months after cessation of 3 months of treatment with this combination.

Given the above evidence, both in terms of safety and toxicity of higher dose and longer duration of LZD and the ability of LZD to act synergistically with the combination of BDQ and Pa, the current study is planned with a primary objective to determine the effectiveness of various doses and duration of LZD in combination with BDQ and Pa given for 26-weeks in adults with either Pre-Extensively Drug-Resistant (Pre-XDR) OR Non-responsive / Treatment Intolerant multidrug-resistant ($MDR_{NR/TI}$) pulmonary TB. Secondary objectives include

a) to determine the safety and tolerability of various doses and duration of Linezolid with Pretomanid and Bedaquiline following 26 weeks of therapy among adults with either Pre-XDR or $MDR_{TI/NR}$ pulmonary TB

b) to determine the baseline resistance to the newer and repurposed drugs

c) to determine the M.tb strain mutation by whole genome sequencing in participants with treatment failure while on treatment or recurrence of TB during the follow-up period

Methods and Analysis

Study design and oversight: Modified BPaL (mBPaL) study is a multi-center, pragmatic randomized clinical trial under field conditions. The study will enroll 400 adults, Pre-XDR or $MDR_{TI/NR}$ pulmonary TB patients meeting all study eligibility criteria after the screening procedure. The enrolled patients will be randomized to receive any of the three regimens using block randomization. The study is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the Union, Cooperative Agreement No. 72038620CA00007, and implemented by the ICMR-National Institute of Research in Tuberculosis (NIRT) in collaboration with the National TB Elimination Programme through its tertiary care DR-TB centers and WHO Country Office for India. The institutional ethics committee of NIRT (ID:2021004, 12 July 2021), and the participating sites approved the study and began enrollment by 20th October 2021.

Study setting: Eight sites in India will implement the mBPaL trial. The study sites were selected based on the 2019 census of XDR and MDR_{FQ} TB patients attending the DR-TB centers in the country and their capacity in conducting clinical trials, including trained personnel, reporting to regulators, expertise in managing DR-TB patients and severe adverse events, and previous record of conducting drug trials. The study sites include DR-TB centers at Sarvodaya Charitable Trust Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavanagar, Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

Study patients and eligibility: Adults between 18 to 65 years of age diagnosed with Pre-XDR-TB or $MDR_{TI/NR}$ accessing TB care services in selected DR TB centers of the country.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study

Table 1: Study Eligibility criteria

Inclusion Criteria	Exclusion criteria
Adults aged between 18 years – 65 years	A patient who has received more than two weeks of BDQ or LZD before the first dose of the mBPaL regimen OR If the result of DST for FQ or LZD is not available and h/o more than two weeks of consumption of drugs used in the study regimen
Pulmonary Pre-XDR-TB patients or MDR-TBTI/NR patients	
Bodyweight of ≥30 kg (in light clothing)	Intolerance or risk of toxicity or allergic any of the drugs in the treatment regimens should not be enrolled in the study
Provide informed written consent before all study-related procedures, including HIV testing	All forms of Extrapulmonary TB (except Lymph node TB or pleural effusion associated with Pulmonary DR-TB)
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) < 2.5 x ULN; Total bilirubin lesser than ULN	Platelet count <1,00,000 /mm^3 or Haemoglobin level of < 9.0 g/dl
QTc(f) less than or equal to 450 ms at baseline	QTc(f) > 450 at baseline & normal electrolytes, ECG to be repeated after 6 hours, and if both ECGs show QTc(f) >450 msec, then the patient should not be challenged with cardiotoxic drugs. Having risk factors for Torsade de Pointes, e.g., hypokalaemia, heart failure, history of long QT syndrome among family members Currently having an uncontrolled cardiac arrhythmia that requires medication

Female patients should not be pregnant or should be using a birth control method	Pregnant or Lactating
	HIV-infected patient with a CD4+ count of ≤ 50 cells
	Grade III or IV peripheral neuropathy Major Psychiatric illness
	Very seriously ill patients (Karnofsky scores < 50 within last 30 days)

Recruitment process: Potential trial participants who visit the DR-TB centers in the selected trial sites will be approached by the study staff and explained in detail about the study in their native language. Patients willing to participate in the trial will be given a patient information sheet and a consent form explaining all study-related procedures. After obtaining written informed consent, a detailed medical, surgical, medication, and alcohol history will be collected to assess the eligibility for trial participation along with investigations as outlined in Table 2. Diagnosis of Pre-XDR TB will be made by *Mycobacterium tuberculosis* positivity in the culture of sputum specimen collected within three months AND with documented resistance to rifamycins with or without isoniazid resistance AND, additionally resistant to at least a fluoroquinolone (FQ)[7] while MDR-$TB_{TI/NR}$ was all of the above AND with documented intolerance or non-response to the current treatment regimen for 6-months or more when the participant was adherent to the treatment regimen. Eligible participants will be enrolled within the next 14 days.

Study regimen and drug dosing: The study participant will be randomized in the ratio of 1:1:1 to receive one of the mentioned treatment regimens -

Arm 1: 26 wks. BDQ +Pa + LZD (600mg)

Arm 2: 9 wks. BDQ +Pa + LZD (600mg) followed by 17 wks. BDQ +Pa+ LZD (300mg)

Arm 3: 13 wks. BDQ +Pa + LZD (600mg) followed by 13 wks. BDQ +Pa+ LZD (300mg)

Table 2. Schedule of enrolment, interventions, and assessments of a participant in the mBPaL trial

COMPLETED WEEKS	-2	0	1	2	3	4	5	6	7	8	9Ɔ	10	11	12	13£	14	16	20	26#	30	38	50	62	74
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/ colour vision	X										X				X				X					
12 lead ECG [B]	X			X		X		X			X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X																X		X					
Sputum smear (1 early monring/1 spot)*	X					X					X				X		X	X	X		X	X	X	X

Sputum culture (LJ/MGIT) and DST for 1st and 2nd line drugs incl. Linezolid	X					X				X				X		X	X	X		X	X	X	X
Whole-genome sequencing (NIRT site)	X																						
Line Probe assay and Ist and II-line DST (at sites) ¥	X																						
MGIT DST (Bedaquiline/ Pretomanid) at NIRT∞	X																						
Complete blood count	X			X		X		X			X			X	X	X	X	X	X	X	X		X
Liver function test	X			X		X		X			X			X	X	X	X	X	X	X	X		X
Renal function test	X					X				X								X		X			X
Blood glucose	X					X				X								X		X			X
HbA1C	X													X				X					
Sr.amylase and lipase	X					X								X				X		X			X
S. Electrolytes (Na, K, Cl) & Calcium, Magnesium	X					X								X				X		X			X
Urine Gravindex test	X					X				X				X		X	X	X	X	X			
HBsAg, HCV, and HIV	X																						

HRQoL	X																		X					X
Adverse events$		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Patients will give 2EM and 1Spot sputum sample at baseline

¥ LPA performed only if sputum results are positive

± DST performed at baseline (with storage of the strain at -20c), 16th week in case of positive culture and if any culture is found positive during the 48 weeks after the end of the treatment (with storage of the strain of the recurrent episode for genotyping analysis)

∞ Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and Pretomanid for Whole Genome Sequencing. Isolates will also be saved at the regional labs until sub-culture results are available for any further DST required for patient management

[B] Baseline ECG should be obtained and additional ECGs conducted daily for the first two weeks after starting treatment (if hospitalized)

ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

ɜ Week 9 – Linezolid dose will be modified at week 9 in arm 2

£ Week 13 - Linezolid dose will be modified at week 13 in arm 3

end of treatment for patients whose 12th-week cultures are negative and if 16th week cultures are not available then no clinical or radiological evidence of TB

$ Adverse event monitoring over the phone weekly from the 17th week onwards till the end of treatment (except during the days of the scheduled visit)

HRQoL – health-related Quality of Life
LJ-Lowenstein-Jensen; MGIT-Mycobacterial Growth Inhibitor Tube; DST – Drug susceptibility test;
HCV-Hepatitis C virus; HIV-Human immunodeficiency virus

Four 100 mg tablets (400 mg) of Bedaquiline will be administered by mouth once a day for two weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks. Pretomanid will be administered as (200mg) one tablet daily for 26 weeks. In Arm 2, the LZD dose will be reduced from 600mg to 300 mg after nine weeks and 13 weeks in Arm 3, irrespective of the smear and culture results. At the time of randomization, dosing of LZD and other drugs is not weight-based and is pre-fixed in the protocol. LZD is given the ability to interrupt or reduce the dose if needed based on Grade 3 toxicity. The continuation of the regimen beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.

Randomization procedures: Computer-generated list of random numbers using REDCAP software will be used for randomization centrally. The site physician using these computer-generated randomizations will be able to randomize the study participants to any one of the three arms in a ratio of 1:1:1. Block randomization will be used to randomize participants in the trial. NIRT statistician will assign the unique study identification number after confirming all the study-related eligibility criteria. There is no blinding in the trial.

Treatment Allocation: The study participants will be randomized to receive one of the three treatment regimens in a 1:1:1 ratio using block randomization. A computer-generated list of random numbers using REDCAP software will be used for randomization centrally. NIRT center will generate the allocation codes at the time of the study At the time of patients' admission to the study, the site Physician will be able to randomize them at the site on RedCAP software based on pre-defined factors.

Treatment delivery, compliance, and retention: The study participants will be hospitalized for two weeks wherever feasible, and study drugs administered under supervision.

Ambulatory care can also be offered if hospitalization is not needed. After discharge, medications will be supplied – weekly for the first month, then fortnightly till 3rd month, and then monthly till the end of treatment. A health care provider or a family member will be assigned and trained to supervise the drug intake and monitor adherence to treatment. During the treatment phase, the patient will be reviewed every week for 16 weeks, then monthly until the end of the treatment phase (26/39 weeks). During these visits, detailed medical history will be collected; adverse drug reactions and tolerability to study drugs will be monitored. The site medical officer does the management of adverse events (AE) and the causality assessment with the grading of AEs as per DAIDS criteria.[8]. Treatment adherence will be assessed by reviewing treatment cards, empty pill covers, on-time drug refills, and hospital attendance. Offering enhancers like nutrition supplements, reimbursing nominal costs for loss of wage, or transportation will strengthen the treatment compliance. Post-treatment follow-up visits will be done for 48 weeks.

Concomitant medication while in the trial: A detailed medical history will be collected during every study visit Any medications consumed while in the trial will be entered on the concomitant medications page of the case record form. Medication entries shall be specific to the generic name, dose, unit, frequency, route of administration, start, stop date, and reason for use. Drugs prohibited to be used during the study include aspirin or ibuprofen or medicines that can cause gastrointestinal bleeding, any antibiotics until clinically warranted, and efavirenz-based antiretroviral therapy.

Criteria for discontinuation/withdrawal of study participants: The trial regimen may be discontinued in some patients in situations such as resistance to study drugs, intolerable or severe toxicity, and treatment failure. A patient may be withdrawn from the study for non-willingness of

the patient to continue for any reason, pregnancy, drug-drug interaction, non-compliance & non-availability, drug resistance, or recommendation by the Data Safety & Monitoring Board.

Study Outcome: The primary outcome of the trial is the proportion of patients with favorable treatment outcomes, defined as sustained treatment success at 12 months post successful TB treatment, being alive & free of TB. Indicators of Successful TB treatment include Cure (patient who has completed 26 or 39 weeks of treatment without evidence of failure and with at least two consecutive negative sputum cultures taken at least 7-days apart) and Treatment Completed (patient who has completed 26 or 39 weeks of treatment whose outcome does not meet the definition for cure or treatment failure) as defined by WHO.[9] The secondary outcome includes the proportion of patients with(i) serious adverse events or adverse drug reactions, including tolerability of the study drugs during the treatment and follow-up period, and (ii) unfavorable outcomes comprising death, bacteriological or clinical failure, and loss to follow-up.

Participant timeline: Each participant involved in the trial will have a screening period of 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture result at week 16 and a post-treatment follow-up for 12 months. Table 2 shows the entire schedule of enrolment of a patient, the interventions to be given, and assessments to be done for a participant in the trial.

Patient and public involvement: Since the scientific problem is still not proven, patients were not involved in the research question development or the design of this study. However, learning from the difficulties faced by patients on the higher dose of LZD, there is an urgent need to find the correct dose of LZD with lower toxicity, better tolerability, and, at the same time, not compromise the efficacy of the regimen to prevent recurrence of TB. The study proposal is

discussed among the members of the Institutional Scientific advisory committee, Institutional Ethics committee, Drug Controller General of India, and Community Advisory Board. Study results will be widely disseminated through meetings, conference presentations, and publications.

Sample size assumption: mBPaL trial will evaluate the effectiveness of various doses and duration of LZD with BDQ and Pa after 26 weeks of treatment in adults with Pre-XDR or MDR (TI/NR) pulmonary TB patients. The efficacy of BDQ with Pa and LZD (600 mg) for 26 weeks is reported to be about 91%.[5] Assuming that the effectiveness of treatment arms of BDQ + Pa with either LZD 600mg for nine weeks followed by 300mg for 17 weeks or LZD 600mg for 13 weeks followed by 300mg for 13 weeks would be about the same based on the recently released interim outcomes of ZeNIX trial results, we hypothesize that these treatment arms with planned reduction of LZD would be non-inferior to LZD 600 mg for 26 weeks arm with a non-inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and an alpha error of 5%, we require about 111 patients in each arm. Factoring in a loss of 20% (due to default or migration), we need 133 patients in each arm or a total of 399 patients (approx. 400) to achieve our study objective.

Data collection, management, and interim analysis: Clinical and demographic information and laboratory reports will be collected from the individual participants in the paper case report forms and entered in Redcap software at all the participating sites. During the weekly and monthly visits, adverse events will be monitored by physical examination, history taking, and laboratory investigations as given in the study schedule. Solicited and unsolicited adverse events will be recorded and managed per DAIDS criteria. Data will be verified for accuracy and completeness. Data access would be restricted to the study statisticians at NIRT and Central TB

Division. Third-party access to data is restricted and will be made available only on request to NIRT. Data analysis will be done using SPSS software by statisticians at NIRT. An interim analysis is planned when at least 33% (approximately 120) of the study participants complete 26 weeks of treatment and the results of sputum smear and MGIT culture are available.

Study outcome analysis: The primary effectiveness analysis will be conducted using culture results from MGIT culture. Modified Intent-to-treat (mITT) analysis will be carried out to evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis that the investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-XDR-TB, $MDR_{/TI/NR}$ in terms of favorable outcomes (including sustained cure and treatment completed) and unfavorable outcomes (including death, treatment failure and lost to follow-up) in the field settings. Time to culture conversion and adverse events at the end of 9 weeks and 26/39 weeks will be estimated using survival analysis methods. Deaths and study withdrawals within the first 7-days of treatment and baseline study drug resistance will be considered initial exclusions. They will not be included in the final mITT analysis. Kaplan Meier survival curves will be constructed and time to culture conversion and adverse events will be calculated at the end of 9 and 26/39 weeks and compared among regimens using the Log-rank test. To identify the important covariates with culture conversion Cox regression model will be used. Count regression models will be employed to compare the number of adverse events experienced across treatment regimens adjusting for other covariates. The HRQOL between the regimens will be compared using ANOVA or the nonparametric alternative. Ordinarily least square regression will be used to compare the quality of life across regimens after adjusting for other variables. Per protocol analysis will be done for those patients who comply with the treatment regimen they were assigned. All participants who have consumed >80% of the drugs will be included in this

analysis. Safety analysis will include data from all who received at least one dose of the study regimen.

Data and Safety Monitoring Board (DSMB): The DSMB comprises a statistician, clinical trial experts, pharmacologist, and pulmonologist. They will be notified about the safety data after every ten patients get enrolled in the trial and complete nine weeks of treatment in each of the three arms. This review will mainly be by circulation to members. An in-person review will be conducted when at least 33% (approximately 120) of the enrolled patients have completed 26 weeks of treatment and sputum smear, and MGIT culture results are available. They will review the progress of the trial and safety issues for the trial participants in the early stages focusing majorly on grade 3 or 4 adverse events and serious adverse events. DSMB may ask for ad-hoc analysis and can recommend continuing or discontinuing or making modifications in the protocol based on any of these criteria - Grade 3 or Grade 4 AE >10%; Deaths due to any cause > 15%; Non-cardiac Notifiable events >15% and QTc(F)> 500ms in more than 10% of enrolled patients.

Study site monitoring and quality assurance: Study monitoring committee formed by the sponsor and other stakeholders will monitor the study data quality per trial standard operating procedures. The monitoring plan will be followed to perform field visits and audits at various stages. The CRFs, patient records, and all source documents of the study participants in this study will be made available to be reviewed by the study monitors. Regular virtual meetings with the investigators of each study site will be conducted to discuss the study's progress. Any critical protocol modifications during the research will be informed to the Institutional Ethics Committee, CTRI, and the participants involved in the trial. At any time during or after completion of the study, the Sponsor, through independent non-study staff, may conduct a

quality assurance assessment of the site records, and the regulatory agencies may conduct a regulatory inspection.

Confidentially of trial data: All study-related CRFs and documents related to the trial will remain in the custody of the site Principal Investigator under lock and key until transferred to archives. The records identifying the patient will be kept confidential and will not be made publicly available. All electronic data will be saved securely in password-protected systems. The final data of the study will be accessible only to the statisticians in NIRT and the Central TB division. When trial results are published, the patient's identity will remain confidential. The confidentiality of the patients included in this trial will be maintained during the conduct of the study period following the Indian-GCP and the relevant regulations by the laws of India.

Ethics and dissemination

The study has been approved by the Ethics committees of participating institutes and the ICMR-National Institute for Research in Tuberculosis. The current ICH Good Clinical Practice and the ICMR ethical guidelines for biomedical research in human participants will be followed in the current trial. This will ensure public assurance that the well-being, safety, and rights of the participants are considered, which is consistent with the principles originating from the Helsinki Declaration and will maintain the credibility of the clinical trial data. The personal data necessary to analyze the safety, tolerability, and antibacterial activity of the investigational product will be used. Manuscript preparation, result dissemination, and publication materials are the principal investigator's responsibility. After the completion of the trial, the investigators anticipate publishing the study results in peer-reviewed scientific journals, presenting the findings in meetings, and sharing the results widely with the program managers and policymakers.

Discussion

WHO has released the Global list of High Burden Countries for MDR/RR-TB for 2021–2025. The list contains the top 20 countries with an estimated absolute number of incident cases and the top 10 countries with a severe burden of incident rate totaling thirty countries. Compared to 2016-2020, few countries like Ethiopia have transitioned out, while countries like Nepal have been added to the list.[1] Average success rate of conventional XDR-TB patients put on treatment (without BDQ) from 2016 to 2018 is 29%. This has increased to 48% in 2018.[10.] Managing MDR-TB and XDR-TB remain a significant challenge in eliminating TB. DR-TB patients treated with short regimens with newer oral drugs are expected to have a better quality of life than patients on standard (either short or long) DR-TB regimens for multiple reasons. Patients' adherence improves with injectable-free treatment and facilitates the implementation of community programs. This would reduce the costs incurred for the patients on travel to health facilities for injections, loss of wages, or hospitalization expenses during the intensive phase of treatment of standard regimens. Hence, it is reasonable to assume that injectable-free treatment regimens that potentially reduce adverse reactions would likely improve patients' overall health-related quality of life. Second, BDQ-containing regimens reduce the costs per treatment success by 18–20% in short course regimens and 49–50% in long course regimens. Approximately 61,000 more patients are estimated to be treated successfully over five years with BDQ-containing regimens.[11] The success rate of DR TB patients treated under the BDQ conditional access program (BDQ-CAP) is 71%.[10]

Studies have compared the outcomes of an extended oral regimen containing BDQ with the shorter oral regimen. A shorter all-oral BDQ-containing regimen showed more beneficial effects than an injectable-free longer regimen containing BDQ. The favorable odds ratio of 3.9

(1.7-9.1) was observed for success versus failure/recurrence, 1.6 (1.2–2.2) for success versus all unfavorable outcomes, and 0.5 (0.4-0.8) for loss to follow-up, thereby supporting the use of all-oral shorter regimen.[12] Also, studies have evaluated the safety of the newer drugs in shorter oral regimens. The NIXTB study reported LZD toxicity such as peripheral neuropathy and myelosuppression among 81% and 48% of the study population. Adverse events leading to death and serious adverse events were 9% and 30%, respectively, in the 600 mg twice daily LZD group and 3% and 9% in the 1200 mg once daily LZD group.[3] In the ZeNIX trial, peripheral neuropathy was reported in 38% of those receiving 1200mg of LZD for six months; 24% of those receiving 1200mg of LZD for two months; 24% of those receiving 600mg of LZD for six months and 13% of those receiving 600mg of LZD for two months. Similarly, anemia, secondary to linezolid exposure, was noticed in 22% of those receiving 1200mg of LZD for six months; 17% of those receiving 1200mg of LZD for two months; 2% of those receiving 600mg of LZD for six months and 7% in those receiving 600mg of LZD for two months.[5] Modified BPaL study will determine the effectiveness in managing DR-TB patients by comparing the varying dose of LZD with BDQ and Pa regimens. Safety assessment in the mBPaL study is one of the significant components in measuring the outcome of the regimens.

We are proposing to conduct a pragmatic clinical trial (mBPaL study) with varying doses of LZD along with BDQ and Pa as a planned reduction of LZD for the treatment of Pre-XDR and $MDR_{TI/NR}$ pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased frequency of dose interruption in regimens containing LZD, this trial will help us decide on the effective dosing of LZD to be given with BDQ and Pa for an entirely oral short-course regimen to treat highly drug-resistant TB in the field setting. The main drivers of the acceptability of the BPaL regimen were the short duration of treatment, fully oral regimen without injectables,

reduced pill burden, anticipated higher treatment success, the lower financial burden for patients and the program, reduced load on the health system, using existing diagnostic processes and lesser burden to TB laboratories for monitoring of bacteriological treatment. This study will create a new standard of care for Pre-XDR and $MDR_{TI/NR}$-pulmonary TB patients that will not only have better and earlier culture conversion but also reduce the proportion of patients who do not adhere to the entire course of therapy.

- ***Authors' contributions***: CPP, CPR & RS – conceived & designed the study / CPP, BD, CPR & BR – development and writing of the study protocol / CPP, BD, CPR, BR, MP, SM & SuM – writing and editing this manuscript
- ***Funding***: This Study/ Pragmatic Clinical Trial is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the UNION; Cooperative Agreement No. 72038620CA00007. It is made possible by the support of the American People through the United States Agency for International Development (USAID). The contents of this study document are the authors' sole responsibility and do not necessarily reflect the views of USAID or the United States Government. Trial Sponsors: ICMR-National Institute for Research in Tuberculosis
- ***Competing interests***: None

References

1. Global tuberculosis report 2021. Geneva: World Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO. Accessed on 21st October 2021. https://www.who.int/publications/digital/global-tuberculosis-report-2021/tb-disease-burden/incidence

2. World Health Organization. WHO consolidated guidelines on **drug-resistant** tuberculosis treatment. Geneva: World Health Organization; 2019.

3. Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med. 2020; 382(10): 893-902.

4. Singh B, Cocker D, Ryan H, et al. Linezolid for drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev. 2019; 3(3): CD012836

5. Conradie F, Everitt D, Olugbosi M, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline, and alternative doses and durations of linezolid [Conference presentation]. IAS 2021, Berlin, Germany. Accessed on 25/09/2021 https://theprogramme.ias2021.org/Abstract/Abstract/2405

6. Tasneen R, Tyagi S, Williams K, et al. Enhanced bactericidal activity of rifampin and/or pyrazinamide when combined with PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother. 2008; 52(10): 3664-3668.

7. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis. 27-29 October 2020. Accessed on 27.9.2021. https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis

8. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. Accessed on 21st September 2021 from https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

9. Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions. 17-19 November 2020. Accessed on 27.9.2021. https://www.who.int/publications/i/item/9789240022195

10. Central TB Division (CTD), Ministry of Health and Family Welfare, Government of India. India TB report 2021. National Tuberculosis Elimination program Annual Report. https://tbcindia.gov.in/showfile.php?lid=3587 (accessed September 28, 2020)

11. Mpobela Agnarson A, Williams A, Kambili C, et al. The cost-effectiveness of a bedaquiline-containing short-course regimen for the treatment of multidrug-resistant tuberculosis in South Africa. Expert Rev Anti Infect Ther 2020; 18: 475–483.

12. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment:drug-resistant tuberculosis treatment. 2020. https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13, 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11,12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12,20,21,22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12,14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,13

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13,14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14,15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14,15

	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	20,21,22

BMJ Open

Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058606.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Aug-2022
Complete List of Authors:	Padmapriyadarsini, Chandrasekaran; National Institute for Research in Tuberculosis Devaleenal, Bella; ICMR-National Institute for Research in Tuberculosis Ponnuraja, C.; ICMR-National Institute for Research in Tuberculosis Ramraj, Balaji; ICMR-National Institute for Research in Tuberculosis Singla, R; National Institute of Tuberculosis and Respiratory Diseases, Parmar, Malik; 3World Health Organization, Country Office for India, New Delhi Mattoo, Sanjay; Ministry of Health & Family Welfare Mandal, Sudarsan; Ministry of Health & Family Welfare
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	Thoracic medicine < INTERNAL MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Respiratory infections < THORACIC MEDICINE

Randomized trial to Evaluate the Effectiveness and Safety of Varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant or Treatment Intolerant/Non-responsive Multidrug-Resistant Pulmonary Tuberculosis: Study protocol

Chandrasekaran Padmapriyadarsini[1], Bella Devaleenal[1], C.Ponnuraja[1], Balaji Ramraj[1], Rupak Singla[2], Malik Parmar[3], Sanjay Mattoo[4], Sudarsan Mandal[4]

[1]*ICMR-National Institute for Research in Tuberculosis, Chennai*

[2]*National Institute of Tuberculosis and Respiratory Diseases, New Delhi*

[3]*World Health Organization, Country Office for India, New Delhi*

[4]*Central TB Division, Ministry of Health & Family Welfare, New Delhi*

Word Count: Abstract: 290 / Main manuscript: 4,318

Corresponding author

Dr.C. Padmapriyadarsini, DNB, MS, PhD

ICMR-National Institute for Research in Tuberculosis

No.1, Mayor Sathyamoorthy Road

Chetput, Chennai 600031

Phone: +91 9498022949

Fax No: 04428362525

e-mail: pcorchids@gmail.com

Abstract

Introduction: Drug-resistant tuberculosis (DR-TB) is a global public health problem. Patients suffer for months if undiagnosed or treated inadequately, transmitting DR-TB in the community before succumbing to the disease. Early diagnosis, prompt treatment initiation, and completion play a significant role in treatment success. However, extended regimens with injectable result in poor treatment adherence and outcomes. Our objective is to evaluate the effectiveness, safety, and tolerability of various doses and duration of Linezolid (LZD) in combination with Bedaquiline (BDQ) and Pretomanid (Pa) after 26 weeks of treatment in adults with Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant ($MDR_{TI/NR}$) Pulmonary Tuberculosis.

Methods and analysis: A multicentric, randomized pragmatic clinical trial in India will enroll participants in one of the three arms - Control arm (Arm 1): BDQ, Pa, and LZD 600mg daily for 26 weeks OR Intervention arms (Arm 2): BDQ, Pa and LZD 600mg for nine weeks followed by 300mg for 17 weeks OR Arm 3: BDQ, Pa and LZD 600mg for 13 weeks followed by 300mg for 13 weeks. The primary endpoint is the proportion of patients with favourable outcomes as sustained cure and treatment completion. The secondary endpoint is unfavourable outcomes, including deaths, treatment failure, toxicity/adverse events, and loss of follow-up till 48 weeks post-treatment.

Ethics and dissemination: The study has been approved by the Ethics committees of participating institutes and the National Institute for Research in Tuberculosis. The trial results will help establish evidence towards a safe and effective dose of LZD that can be used in a fully, all-oral short course regimen for highly DR-TB patients. The results of this study will be shared

with the National TB Elimination Programme of the country and the World Health Organization guidelines development group through publications and dissemination meetings.

Trial Registration: The protocol (version 3.1 dated 20th July 2021) has been registered on the Clinical Trial Registry of India as CTRI/2021/03/032189 on 22nd March 2021 and ClinicalTrials.gov with the identifier: NCT05040126 on 10th September 2021.

Article Summary

Strength and Limitations

- Pragmatic Randomized trial design will add considerable value to the study as it will consider a real-world population under field conditions in a clinical trial, thus decreasing bias and minimizing unequal distribution.
- The trial includes an active control arm (appropriate comparison arm) instead of a placebo arm and has relevant outcomes for optimal healthcare decisions at the end of the study.
- The trial lacks stratification based on disease severity. This may result in the possibility of more severe cases in one group of treatment. We hope randomization will be able to cover this.
- As there is no blinding in this trial, the treating physician may be biased to assign the causality of all adverse events to the drug concerned.
- Data heterogeneity may be present as it's a planned multicentric study.

Keywords: Linezolid Dose, Pretomanid, Randomized trial, Treatment Intolerant, Drug-resistant TB

Introduction:

The World Health Organization (WHO) estimates that globally in 2020, 132222 cases of multi-drug resistant (MDR)/rifampicin-resistant tuberculosis (RR-TB) and 25681 cases of pre-extensively drug-resistant (pre-XDR-TB) or extensively drug-resistant (XDR-TB), totaling 157903 cases, were detected. However, testing for fluoroquinolone resistance remains much lower; at just over 50% worldwide in 2020.[1] Of these, 150359 people with MDR/RR-TB were enrolled in treatment in 2020, fewer than in the previous years. The treatment success rate of the 2018 MDR/RR-TB cohort was 59%; though improved from earlier cohorts, the treatment failure, loss to follow-up and death remain high.[1] Also, this was not uniform across the globe–the treatment success rate was below 50% in countries like India and Indonesia due to increased death and loss-to-follow-up. Globally, the treatment success rate of highly drug-resistant TB (DR-TB) remains unacceptably low.

With the availability of newer drugs and patient-friendly approaches, it is now possible to design newer regimens that are less toxic, safer, and of shorter duration. The WHO consolidated treatment guidelines for DR-TB recommend longer and shorter treatment regimens for MDR/RR-TB treatment.[2] A South African study using a combination of Bedaquiline (BDQ), Pretomanid (Pa), and Linezolid (LZD) to treat highly DR-TB showed a favorable outcome of 90% at the end of six-months of treatment. [3] However, the high dose of LZD used in this study led to more than 70% of patients having adverse events to LZD, often leading to either treatment interruption or dose reduction of LZD between two to three months of treatment. Though LZD is efficacious for DR-TB, adverse events and treatment discontinuation are also to be expected.[4]

The multicountry ZeNIX study with consistent dosing of BDQ and Pa reported a 93% success rate with linezolid 1200 mg for six months and 91% with linezolid 600mg for six months. Among those receiving 1200 mg linezolid for six months, adverse events reported were

38%, while in those receiving 600 mg of linezolid for six months, it was 24%.[5] Though there seemed to be a modestly greater early bactericidal effect over 14 days at the highest dose of 1200 mg/day (NC-003 study), this dose appeared to be associated with a greater incidence of neuropathic and myelosuppressive effects than the 600 mg/day dose in the ZeNIX and NixTB trials. While a full six months of linezolid therapy in the regimen may give higher culture conversion and avoid relapse, the mouse model found that more than two months of linezolid, combined with BDQ and Pa, does not increase relapse-free cure.[6] The study also found that LZD increases the sterilizing activity of the BDQ-Pa combination; no MTB could be cultured from the lungs of mice three months after cessation of three months of treatment with this combination.

Given the above evidence, both in terms of safety and toxicity of higher doses and longer duration of LZD and the ability of LZD to act synergistically with the combination of BDQ and Pa, the current study is planned with the primary objective of determining the effectiveness of various doses and duration of LZD in combination with BDQ and Pa given for 26-weeks in adults with either Pre-Extensively Drug-Resistant (Pre-XDR) OR Non-responsive / Treatment Intolerant multidrug-resistant ($MDR_{NR/TI}$) pulmonary TB. Secondary objectives include

a) to determine the safety and tolerability of various doses and duration of Linezolid with Pretomanid and Bedaquiline following 26 weeks of therapy among adults with either Pre-XDR or $MDR_{TI/NR}$ pulmonary TB.

b) to determine the baseline resistance to the newer and repurposed drugs.

c) to determine the M.tb strain mutation by whole genome sequencing in participants with treatment failure while on treatment or recurrence of TB during the follow-up period.

Methods and Analysis

Study design and oversight: Modified BPaL (mBPaL) Study is a multi-center, pragmatic randomized clinical trial under field conditions. The study will enrol 400 adults, Pre-XDR or $MDR_{TI/NR}$ pulmonary TB patients meeting all study eligibility criteria after the screening procedure. The enrolled patients will be randomized to receive any of the three regimens using block randomization. The study is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the Union, Cooperative Agreement No. 72038620CA00007, and implemented by the ICMR-National Institute of Research in Tuberculosis (NIRT) in collaboration with the National TB Elimination Programme through its tertiary care DR-TB centers and WHO Country Office for India. The institutional ethics committee of NIRT (ID: 2021004, 12th July 2021), and the participating sites approved the study and began enrollment on 20th October 2021.

Study setting: Eight sites in India will implement the mBPaL trial. The study sites were selected based on the 2019 census of XDR and MDR_{FQ} TB patients attending the DR-TB centres in the country and their capacity for conducting clinical trials, including trained personnel, reporting to regulators, expertise in managing DR-TB patients and severe adverse events, and a previous record of conducting drug trials. The study sites include DR-TB centers at Sarvodaya Charitable Trust Hospital and Shatabdi Centenary Hospital, Mumbai; King George's Medical College and University, Lucknow; SN Medical College, Agra; Govt. Medical College, Surat and Bhavnagar, Gujarat, National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi and Govt. Rajaji Medical College and Hospital, Madurai, Tamilnadu.

Study patients and eligibility: Adults between the ages of 18 to 65 years diagnosed with Pre-XDR-TB or $MDR_{TI/NR}$ accessing TB care services in selected DR TB centers across the country are eligible for the study.

Table 1 provides the detailed eligibility criteria based on which patients visiting the study sites will be screened for participation in the study.

Table 1: Study Eligibility criteria

Inclusion Criteria	Exclusion criteria
Adults aged between 18 years – 65 years	A patient who has received more than two weeks of BDQ or LZD before the first dose of the mBPaL regimen OR If the result of DST for FQ or LZD is not available and h/o more than two weeks of consumption of drugs used in the study regimen
Pulmonary Pre-XDR-TB patients or MDR-TBTI/NR patients	
Bodyweight of ≥30 kg (in light clothing)	Intolerance or risk of toxicity or allergic any of the drugs in the treatment regimens should not be enrolled in the study
Provide informed written consent before all study-related procedures, including HIV testing	All forms of Extra pulmonary TB (except Lymph node TB or pleural effusion associated with Pulmonary DR-TB)
Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) < 2.5 x ULN; Total bilirubin lesser than ULN	Platelet count <1,00,000 /mm^3 or Haemoglobin level of < 9.0 g/dl
QTc(f) less than or equal to 450 ms at baseline	QTc (f) >450 msec at baseline & normal electrolytes, ECG to be repeated after 6 hours, and if both ECGs show QTc (f) >450 msec, then the patient should not be challenged with cardiotoxic drugs. Having risk factors for Torsade de Pointes, e.g., hypokalaemia, heart failure, history of long QT syndrome among family members

	Currently having an uncontrolled cardiac arrhythmia that requires medication
Female patients should not be pregnant or should be using a birth control method	Pregnant or Lactating
	HIV-infected patient with a CD4+ count of ≤ 50 cells
	Grade III or IV peripheral neuropathy Major Psychiatric illness
	Very seriously ill patients (Karnofsky scores < 50 within last 30 days)

Recruitment process: Potential trial participants who visit the DR-TB centres in the selected trial sites will be approached by the study staff and explained in detail about the study in their native language. Patients willing to participate in the trial will be given a patient information sheet and a consent form explaining all study-related procedures. After obtaining written informed consent, a detailed medical, surgical, medication, and alcohol history will be collected to assess the eligibility for trial participation along with investigations as outlined in Table 2. The diagnosis of Pre-XDR TB will be made by *Mycobacterium tuberculosis* positivity in the culture of sputum specimen collected within three months AND with documented resistance to rifamycins with or without isoniazid resistance AND, additionally resistant to at least one fluoroquinolone (FQ)[7] while MDR-$TB_{TI/NR}$ was all of the above AND with documented intolerance or non-response to the current treatment regimen for six-months or more when the participant was adherent to the treatment regimen. Eligible participants will be enrolled within the next 14 days.

Study regimen and drug dosing: The study participant will be randomized in the ratio of 1:1:1 to receive one of the mentioned treatment regimens -

Arm 1: 26 wks. BDQ +Pa + LZD (600mg)

Arm 2: 9 wks. BDQ +Pa + LZD (600mg) followed by 17 wks. BDQ +Pa+ LZD (300mg)

Arm 3: 13 wks. BDQ +Pa + LZD (600mg) followed by 13 wks. BDQ +Pa+ LZD (300mg)

Table 2. Schedule of enrolment, interventions, and assessments of a participant in the mBPaL trial

COMPLETED WEEKS	-2	0	1	2	3	4	5	6	7	8	9Ɜ	10	11	12	13£	14	16	20	26#	30	38	50	62	74
Informed Consent	X																							
Inclusion/Exclusion Criteria	X																							
Demography	X																							
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination & vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus examination/ colour vision	X										X				X				X					
12 lead ECG [B]	X			X		X		X			X		X		X	X	X	X	X	Monthly once for 6 months				
Chest X-ray	X																X		X					
Sputum smear (1 early monring/1 spot)*	X					X					X				X		X	X	X		X	X	X	X
Sputum culture (LJ/MGIT) and DST for 1st and 2nd line drugs incl. Linezolid	X					X					X				X		X	X	X		X	X	X	X

Whole-genome sequencing (NIRT site)	X																							
Line Probe assay and Ist and II-line DST (at sites) ¥	X																							
MGIT DST (Bedaquiline/ Pretomanid) at NIRT∞	X																							
Complete blood count	X			X		X		X			X		X		X	X	X	X	X	X	X	X		X
Liver function test	X			X		X		X			X		X		X	X	X	X	X	X	X	X		X
Renal function test	X					X					X								X		X			X
Blood glucose	X					X					X								X		X			X
HbA1C	X														X				X					
Sr.amylase and lipase	X					X									X				X		X			X
S. Electrolytes (Na, K, Cl) & Calcium, Magnesium	X					X									X				X		X			X
Urine Gravindex test	X					X					X				X		X	X	X	X	X			
HBsAg, HCV, and HIV	X																							
HRQoL	X																		X					X
Adverse events$^{\$}$		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Patients will give 2EM and 1Spot sputum sample at baseline

¥ LPA is performed only if sputum results are positive.

± DST performed at baseline (with strain stored at -20c), 16th week in case of positive culture and if any culture is found positive during the 48 weeks following the end of the treatment (with strain of the recurrent episode stored for genotyping analysis)

∞ Sputum isolates at baseline, at time of treatment failure and relapse will be sent to NIRT for MGIT DST to Bdq, and Pretomanid for Whole Genome Sequencing. Isolates will also be saved at the regional labs until sub-culture results are available for any further DST required for patient management

[B] Baseline ECG should be obtained and additional ECGs conducted daily for the first two weeks after starting treatment (if hospitalized)

ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

ɔ Week 9 – Linezolid dose will be modified at week 9 in arm 2

£ Week 13 - Linezolid dose will be modified at week 13 in arm 3

end of treatment for patients whose 12th-week cultures are negative and if 16th week cultures are not available then no clinical or radiological evidence of TB

$ Adverse event monitoring over the phone weekly from the 17th week onwards till the end of treatment (except during the days of the scheduled visit)

HRQoL – health-related Quality of Life
LJ-Lowenstein-Jensen; MGIT-Mycobacterial Growth Inhibitor Tube; DST – Drug susceptibility test;
HCV-Hepatitis C virus; HIV-Human immunodeficiency virus

Four 100 mg tablets (400 mg) of Bedaquiline will be administered by mouth once a day for two weeks, followed by 200 mg (two 100 mg tablets) orally thrice a week for 24 weeks. Pretomanid will be administered as one 200mg tablet daily for 26 weeks. In Arm 2, the LZD dose will be reduced from 600mg to 300 mg after nine weeks and 13 weeks in Arm 3, irrespective of the smear and culture results. At the time of randomization, dosing of LZD and other drugs is not weight-based and is pre-fixed in the protocol. LZD is given the ability to interrupt or reduce the dose if needed based on Grade 3 toxicity. The continuation of the regimen beyond 26 weeks and up to 39 weeks will be based on the culture results of week 16.

Randomization procedures: A Computer-generated list of random numbers using REDCAP software will be used for randomization centrally. The site physician using these computer-generated randomizations will be able to randomize the study participants to any one of the three arms in a ratio of 1:1:1. Block randomization will be used to randomize participants in the trial. The NIRT statistician will assign the unique study identification number after confirming all the study-related eligibility criteria. There is no blinding in the trial.

Treatment Allocation: The study participants will be randomized to receive one of the three treatment regimens in a 1:1:1 ratio using block randomization. A computer-generated list of random numbers using REDCAP software will be used for randomization centrally. NIRT center will generate the allocation codes at the time of the study. At the time of patient's admission to the study, the site Physician will be able to randomize them at the site on RedCAP software based on pre-defined factors.

Treatment delivery, compliance, and retention: The study participants will be hospitalized for two weeks wherever feasible, and study drugs will be administered under

supervision. Ambulatory care can also be offered if hospitalization is not needed. After discharge, medications will be supplied – weekly for the first month, then fortnightly till the 3rd month, and then monthly till the end of treatment. A healthcare provider or a family member will be assigned and trained to supervise the drug intake and monitor adherence to treatment. During the treatment phase, the patient will be reviewed every week for 16 weeks, then monthly until the end of the treatment phase (26/39 weeks). During these visits, a detailed medical history will be collected; adverse drug reactions and tolerability to study drugs will be monitored. The site medical officer does the management of adverse events (AE) and the causality assessment with the grading of AEs as per DAIDS criteria.[8] Treatment adherence will be assessed by reviewing treatment cards, empty pill covers, on-time drug refills, and hospital attendance. Offering enhancers such as nutrition supplements, reimbursing nominal costs for loss of wage, or transportation will improve the treatment compliance. Post-treatment follow-up visits will be done for 48 weeks.

Concomitant medication while in the trial: A detailed medical history will be collected during every study visit. Any medications consumed while in the trial will be entered on the concomitant medications page of the case record form. Medication entries shall be specific to the generic name, dose, unit, frequency, route of administration, start, stop date, and reason for use. Drugs prohibited from being used during the study include aspirin or ibuprofen or medicines that can cause gastrointestinal bleeding; any antibiotics until clinically warranted, and efavirenz-based antiretroviral therapy.

Criteria for study participants discontinuation/withdrawal: The trial regimen may be discontinued in some patients in situations such as resistance to study drugs, intolerable or severe toxicity, or treatment failure. A patient may be withdrawn from the study if he or she is unwilling

to participate due to any reason, including pregnancy, drug-drug interaction, non-compliance & non-availability, drug resistance, or recommendation by the Data Safety & Monitoring Board.

Study Outcome: The primary outcome of the trial is the proportion of patients with favorable treatment outcomes, defined as sustained treatment success at twelve months post successful TB treatment, being alive and free of TB. Indicators of successful TB treatment include Cure (patient who has completed 26 or 39 weeks of treatment without evidence of failure and with at least two consecutive negative sputum cultures taken at least seven days apart) and Treatment Completed (patient who has completed 26 or 39 weeks of treatment whose outcome does not meet the definition of cure or treatment failure) as defined by WHO.[9] The secondary outcome includes the proportion of patients with(i) serious adverse events or adverse drug reactions, including tolerability of the study drugs during the treatment and follow-up period, and (ii) unfavorable outcomes, comprising death, bacteriological or clinical failure, and loss to follow-up.

Participant timeline: Each participant involved in the trial will have a screening period of 2 weeks, followed by a treatment period of 26 weeks to 39 weeks based on sputum culture results at week 16, and a post-treatment follow-up of 12 months. Table 2 shows the entire schedule of enrolment of a patient, the interventions to be given, and the assessments to be done for a participant in the trial.

Patient and public involvement: Since the scientific problem is still not proven, patients were not involved in the research question development or the design of this study. However, learning from the difficulties faced by patients on the higher dose of LZD, there is an urgent need to find the correct dose of LZD with lower toxicity, better tolerability, and, at the same time, not

compromise the efficacy of the regimen to prevent recurrence of TB. The study proposal is discussed among the members of the Institutional Scientific Advisory Committee, the Institutional Ethics Committee, the Drug Controller General of India, and the Community Advisory Board. Meetings, conference presentations, and publications will be used to disseminate study findings.

Sample size assumption: mBPaL trial will evaluate the effectiveness of various doses and duration of LZD with BDQ and Pa after 26 weeks of treatment in adults with pre-XDR or MDR (TI/NR) pulmonary TB patients. The efficacy of BDQ with Pa and LZD (600 mg) for 26 weeks is reported to be about 91%.[5] Assuming that the effectiveness of treatment arms of BDQ + Pa with either LZD 600mg for nine weeks followed by 300mg for 17 weeks or LZD 600mg for 13 weeks followed by 300mg for 13 weeks would be about the same based on the recently released interim outcomes of ZeNIX trial results, we hypothesize that these treatment arms with planned reduction of LZD would be non-inferior to the LZD 600 mg for 26 weeks arm with a non-inferiority margin of about 10% ineffectiveness. To demonstrate this, with a power of 80% and an alpha error of 5%, we require about 111 patients in each arm. Factoring in a loss of 20% (due to default or migration), we need 133 patients in each arm, or a total of 399 patients (approx. 400) to achieve our study objective.

Data collection, management, and interim analysis: Clinical and demographic information and laboratory reports will be collected from the individual participants in the paper case report forms and entered in Redcap software at all the participating sites. Adverse events will be monitored during weekly and monthly visits through physical examination, history-taking, and laboratory investigations as specified in the study schedule.

Solicited and unsolicited adverse events will be recorded and managed per DAIDS criteria. The data will be verified for accuracy and completeness. Data access would be restricted to the study statisticians at NIRT and Central TB Division. Third-party access to data is restricted and will be made available only on request to NIRT. Data analysis will be done using SPSS software by statisticians at NIRT. An interim analysis is planned when at least 33% (approximately 120) of the study participants complete 26 weeks of treatment and the results of sputum smear and MGIT culture are available.

Study outcome analysis: The primary effectiveness analysis will be conducted using the culture results from MGIT culture. A modified Intent-to-treat (mITT) analysis will be carried out to evaluate the effectiveness of the newer regimens. We will evaluate the hypothesis that the investigational regimens are non-inferior to the standard of care regimen for the treatment of Pre-XDR-TB, $MDR_{/TI/NR}$ in terms of favorable outcomes (including sustained cure and treatment completed) and unfavorable outcomes (including death, treatment failure, and lost to follow-up) in the field settings. Time to culture conversion and adverse events at the end of 9 weeks and 26/39 weeks will be estimated using survival analysis methods. Deaths and study withdrawals within the first 7-days of treatment and baseline study drug resistance will be considered initial exclusions. They will not be included in the final mITT analysis. Kaplan-Meier survival curves will be constructed, and time to culture conversion and adverse events will be calculated at the end of 9 and 26/39 weeks and compared among regimens using the Log-rank test. To identify the important covariates with culture conversion, a Cox regression model will be used. Count regression models will be employed to compare the number of adverse events experienced across treatment regimens adjusting for other covariates. The HRQOL between the regimens will be compared using ANOVA or the nonparametric alternative. Ordinarily least square regression

will be used to compare the quality of life across regimens after adjusting for other variables. Per protocol analysis will be done for those patients who comply with the treatment regimen they were assigned. All participants who have consumed >80% of the drugs will be included in this analysis. Safety analysis will include data from all who received at least one dose of the study regimen.

Data and Safety Monitoring Board (DSMB): The DSMB comprises a statistician, clinical trial experts, a pharmacologist, and a pulmonologist. They will be notified about the safety data after every ten patients are enrolled in the trial and complete nine weeks of treatment in each of the three arms. This review will mainly be by circulation to members. An in-person review will be conducted when at least 33% (approximately 120) of the enrolled patients have completed 26 weeks of treatment and sputum smear, and MGIT culture results are available. They will review the progress of the trial and safety issues for the trial participants in the early stages focusing majorly on grade 3 or 4 adverse events and serious adverse events. DSMB may ask for ad-hoc analysis and can recommend continuing or discontinuing or making modifications in the protocol based on any of these criteria: Grade 3 or Grade 4 AE >10%; Deaths due to any cause > 15%; Non-cardiac Notifiable events >15% and QTc(F)> 500 ms in more than 10% of enrolled patients.

Study site monitoring and quality assurance: A study monitoring committee formed by the sponsor and other stakeholders will monitor the study data quality per trial standard operating procedures. The monitoring plan will be followed to perform field visits and audits at various stages. The CRFs, patient records, and all source documents of the study participants in this study will be made available to be reviewed by the study monitors. Regular virtual meetings with the investigators of each study site will be conducted to discuss the study's progress. Any critical protocol changes made during the research will be communicated to the Institutional Ethics

Committee, CTRI, and the trial participants. At any time during or after completion of the study, the sponsor, through independent non-study staff, may conduct a quality assurance assessment of the site records, and the regulatory agencies may conduct a regulatory inspection.

Confidentially of trial data: All study-related CRFs and documents related to the trial will remain in the custody of the site Principal Investigator under lock and key until transferred to archives. The records identifying the patient will be kept confidential and will not be made publicly available. All electronic data will be saved securely in password-protected systems. The final data from the study will be accessible only to the statisticians in NIRT and the Central TB division. When trial results are published, the patient's identity will remain confidential. The confidentiality of the patients included in this trial will be maintained during the conduct of the study period following the Indian-GCP and the relevant regulations by the laws of India.

Ethics and dissemination

The study has been approved by the ethics committees of participating institutes and the ICMR-National Institute for Research in Tuberculosis. The current ICH Good Clinical Practice and the ICMR ethical guidelines for biomedical research in human participants will be followed in the current trial. This will ensure public assurance that the well-being, safety, and rights of the participants are considered, which is consistent with the principles originating from the Helsinki Declaration and will maintain the credibility of the clinical trial data. The personal data necessary to analyze the safety, tolerability, and antibacterial activity of the investigational product will be used. Manuscript preparation, result dissemination, and publication materials are the principal investigator's responsibility. After the completion of the trial, the investigators anticipate publishing the study results in peer-reviewed scientific journals, presenting the

findings in meetings, and sharing the results widely with the program managers and policymakers.

Discussion

WHO has released the Global list of High Burden Countries for MDR/RR-TB for 2021–2025. The list contains the top 20 countries with an estimated absolute number of incident cases and the top 10 countries with a severe burden of incident rate totaling thirty countries. Compared to 2016-2020, few countries like Ethiopia have transitioned out, while countries like Nepal have been added to the list.[1] Average success rate of conventional XDR-TB patients put on treatment (without BDQ) from 2016 to 2018 is 29%. This has increased to 48% in 2018.[10.] Managing MDR-TB and XDR-TB remain a significant challenge in eliminating TB. DR-TB patients treated with short regimens with newer oral drugs are expected to have a better quality of life than patients on standard (either short or long) DR-TB regimens for multiple reasons. Patients' adherence improves with injectable-free treatment and facilitates the implementation of community programs. This would reduce the costs incurred for the patients on travel to health facilities for injections, loss of wages, or hospitalization expenses during the intensive phase of treatment of standard regimens. Hence, it is reasonable to assume that injectable-free treatment regimens that potentially reduce adverse reactions would likely improve patients' overall health-related quality of life. Second, BDQ-containing regimens reduce the costs per treatment success by 18–20% in short course regimens and 49–50% in long course regimens. Approximately 61,000 more patients are estimated to be treated successfully over five years with BDQ-containing regimens.[11] The success rate of DR TB patients treated under the BDQ conditional access program (BDQ-CAP) is 71%.[10]

Studies have compared the outcomes of an extended oral regimen containing BDQ with the shorter oral regimen. A shorter all-oral BDQ-containing regimen showed more beneficial effects than an injectable-free longer regimen containing BDQ. The favorable odds ratio of 3.9 (1.7-9.1) was observed for success versus failure/recurrence, 1.6 (1.2–2.2) for success versus all unfavorable outcomes, and 0.5 (0.4-0.8) for loss to follow-up, thereby supporting the use of all-oral shorter regimen.[12] Also, studies have evaluated the safety of the newer drugs in shorter oral regimens. The NIXTB study reported LZD toxicity such as peripheral neuropathy and myelosuppression among 81% and 48% of the study population. Adverse events leading to death and serious adverse events were 9% and 30%, respectively, in the 600 mg twice daily LZD group and 3% and 9% in the 1200 mg once daily LZD group.[3] In the ZeNIX trial, peripheral neuropathy was reported in 38% of those receiving 1200mg of LZD for six months; 24% of those receiving 1200mg of LZD for two months; 24% of those receiving 600mg of LZD for six months and 13% of those receiving 600mg of LZD for two months. Similarly, anemia, secondary to linezolid exposure, was noticed in 22% of those receiving 1200mg of LZD for six months; 17% of those receiving 1200mg of LZD for two months; 2% of those receiving 600mg of LZD for six months and 7% in those receiving 600mg of LZD for two months.[5] The mBPaL study will determine the effectiveness in managing DR-TB patients by comparing the varying dose of LZD with BDQ and Pa regimens. Safety assessment in the mBPaL study is one of the significant components in measuring the outcome of the regimens.

We are proposing to conduct a pragmatic clinical trial (mBPaL study) with varying doses of LZD along with BDQ and Pa as a planned reduction of LZD for the treatment of Pre-XDR and $MDR_{TI/NR}$ pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased frequency of dose interruption in regimens containing LZD, this trial will help us decide on the

effective dosing of LZD to be given with BDQ and Pa for an entirely oral short-course regimen to treat highly drug-resistant TB in the field setting. The main drivers of the acceptability of the BPaL regimen were the short duration of treatment, fully oral regimen without injectable, reduced pill burden, anticipated higher treatment success, the lower financial burden for patients and the program, reduced load on the health system, using existing diagnostic processes and lesser burden to TB laboratories for monitoring of bacteriological treatment. This study will create a new standard of care for Pre-XDR and $MDR_{TI/NR}$-pulmonary TB patients that will not only have better and earlier culture conversion but also reduce the proportion of patients who do not adhere to the entire course of therapy.

- ***Authors' contributions***: CPP, CPR & RS – conceived & designed the study / CPP, BD, CPR & BR – development and writing of the study protocol / CPP, BD, CPR, BR, MP, SM & SuM – writing and editing this manuscript
- ***Funding***: This Study/ Pragmatic Clinical Trial is supported by the United States Agency for International Development (USAID), under the iDEFEAT TB Project with the UNION; Cooperative Agreement No. 72038620CA00007. It is made possible by the support of the American People through the United States Agency for International Development (USAID). The contents of this study document are the authors' sole responsibility and do not necessarily reflect the views of USAID or the United States Government. Trial Sponsors: ICMR-National Institute for Research in Tuberculosis
- ***Competing interests***: None

References

1. Global tuberculosis report 2021. Geneva: World Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO. Accessed on 21st October 2021. https://www.who.int/publications/digital/global-tuberculosis-report-2021/tb-disease-burden/incidence

2. World Health Organization. WHO consolidated guidelines on **drug-resistant** tuberculosis treatment. Geneva: World Health Organization; 2019. PMID: 30946559.

3. Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med. 2020; 382(10): 893-902.

4. Singh B, Cocker D, Ryan H, et al. Linezolid for drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev. 2019; 3(3): CD012836

5. Conradie F, Everitt D, Olugbosi M, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of Pretomanid, bedaquiline, and alternative doses and durations of linezolid [Conference presentation]. IAS 2021, Berlin, Germany. Accessed on 25/09/2021 https://theprogramme.ias2021.org/Abstract/Abstract/2405

6. Tasneen R, Tyagi S, Williams K, et al. Enhanced bactericidal activity of rifampin and/or pyrazinamide when combined with PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother. 2008; 52(10): 3664-3668.

7. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis. 27-29 October 2020. Accessed on 27.9.2021. https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis

8. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. Accessed on 21st September 2021 from https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

9. Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions. 17-19 November 2020. Accessed on 27.9.2021. https://www.who.int/publications/i/item/9789240022195

10. Central TB Division (CTD), Ministry of Health and Family Welfare, Government of India. India TB report 2021. National Tuberculosis Elimination program Annual Report. https://tbcindia.gov.in/showfile.php?lid=3587 (accessed September 28, 2020)

11. Mpobela Agnarson A, Williams A, Kambili C, et al. The cost-effectiveness of a bedaquiline-containing short-course regimen for the treatment of multidrug-resistant tuberculosis in South Africa. Expert Rev Anti Infect Ther 2020; 18: 475–483.

12. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment:drug-resistant tuberculosis treatment. 2020. https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13, 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5,6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11,12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12,20,21,22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12,14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13,14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12,13

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13,14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14,15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14,15

	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	20,21,22