TB-PRACTECAL: Frequently Asked Questions

The results discussed in this FAQ are from the analysis done on a snapshot of data on 18 March 2021 and are published in the New England Journal of medicine here: A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis | NEJM*, for more info or requests on the latest analysis please contact*: *tb-practecal@london.msf.org*

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1. Trial Design and Conduct

1.1 What is TB-PRACTECAL?

TB-PRACTECAL is an open-label phase II/III multicentre randomised, controlled, non-inferiority trial evaluating the safety and efficacy of 3 all-oral 24-week regimens containing bedaquiline, pretomanid and linezolid (BPaL), with the addition of either moxifloxacin (BPaLM) or clofazimine (BPaLC) or none, for treatment of rifampicin-resistant tuberculosis. The study has two stages, with a seamless transition between them.

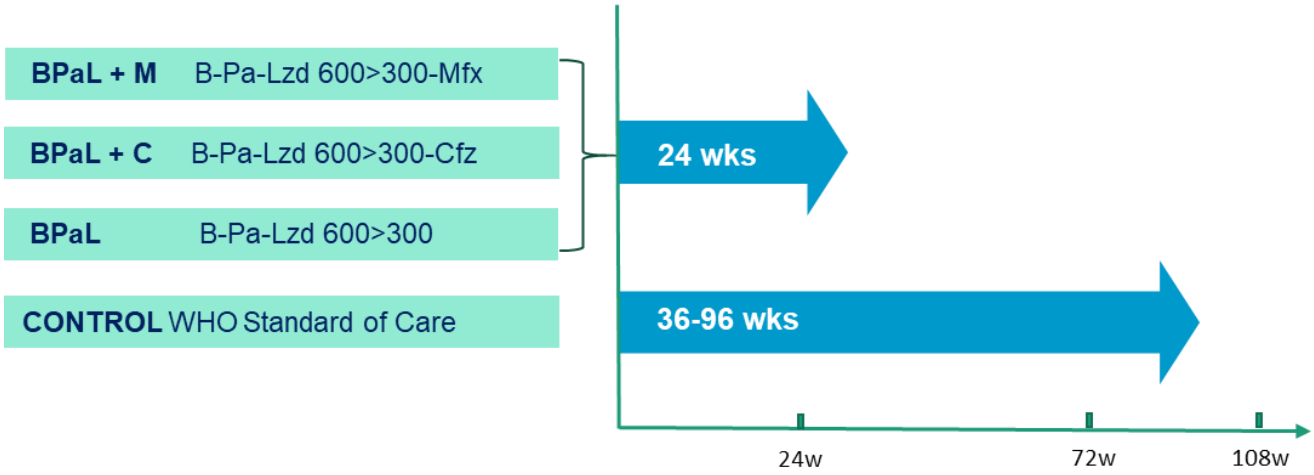
The trial protocol can be found here: https://scienceportal.msf.org/assets/7812

And the trial results can be found here: A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis | NEJM

ClinicalTrials.gov Identifier: NCT02589782

Patients were randomised into 3 investigational arms and a control arm in stage 1, corresponding to a phase IIB study. The investigational arm regimens are assessed for eligibility for Stage 2 (Phase III). Stage 1 patients enrolled into any arm(s) that continue to stage 2 are included in the sample size for stage 2. At the end of Stage 1 (240 patients recruited, August 2019) all 3 investigational arms were assessed against predefined safety and efficacy criteria. All 3 investigational regimens were eligible to be evaluated in Stage 2. After considering Stage 1 data (blinded to arm), the Scientific Advisory Committee (SAC) recommended that BPaLM and BPaLC be taken forward to Stage 2. The Trial Steering Committee after consideration of recruitment delays and consultation with the SAC and Data Safety

and Monitoring Board (DSMB) concluded that one arm – BPaLM – should be taken forward to Stage 2. Stage 2 commenced in November 2020. The last patient last visit was 5th August 2022.



1.2 What results were published in the NEJM?

The results published in the NEJM article are from the analysis done on the data snapshot taken on 18 March 2021. This was the same dataset which was provided to WHO and assessed by the guideline development group.

1.3 Which groups of people were included and excluded in the trial?

- Patients who were 15 years and older, regardless of HIV status or CD4 count, from Belarus, Uzbekistan, and South Africa with confirmed rifampicin-resistant tuberculosis (**irrespective** of fluoroquinolone resistance) and who gave informed consent were included.

- Patients that were excluded from the trial were the following: pregnant and breastfeeding patients, patients with baseline QTcF >450 or with one or more risk factors for QTcF prolongation, structural heart disease, ALT/AST > grade 3, and patients with prior use of bedaquiline, linezolid, delamanid or pretomanid for more than 1 month. Also excluded were patients with TB meningo-encephalitis, brain abscesses, osteomyelitis, and arthritis.

1.4 What were the drugs used in PRACTECAL?

- **Pretomanid:** An oral nitroimidazole developed by the Global Alliance for TB Drug Development. It was approved for use against pre-XDR and retreatment MDR/RR-TB by the FDA in 2019, in combination with bedaquiline and linezolid. Pretomanid was prescribed as a daily dose of 200mg. Expected adverse reactions included liver dysfunction, acneiform rash, and benign elevations of creatinine. Pretomanid has several potential drug – drug

interactions, specifically with CYP 3A4 inducers. It is not recommended to be co-administered with Efavirenz or Rifampicin.

- **Bedaquiline:** Bedaquiline is a diarylquinoline antimycobacterial, currently a WHO group A drug for MDR/RR-TB. Bedaquiline was given as a loading dose of 400mg daily for 2 weeks and then 200mg three times weekly for the remainder of the 24 weeks. The main adverse events of concern are liver dysfunction, QT prolongation and an association with raised amylase in one trial. Bedaquiline exposure is affected by strong inducers of CYP3A4. Coadministration with Efavirenz was contraindicated within the trial, during the trial integrase inhibitors became recommended first line treatment for HIV making this less problematic for co-infected patients. Protease inhibitors do increase the AUC of bedaquiline and need to be used with caution.

- **Linezolid** is an oxazolidinone antibiotic repurposed for use in mycobacterial infections. In 2019, it was recognised as a WHO group A drug following increasing clinical trial, cohort and programmatic information supporting its efficacy. Linezolid was given at 600mg daily for 16 weeks and then tapered to 300mg daily for 8 weeks. Linezolid carries well recognised adverse reactions of myelotoxicity and neurotoxicity as well as rare but serious events of lactic acidosis and pancreatitis.

- **Moxifloxacin** is an 8-methoxyquinolone that is highly active against Gram-positive and Gram-negative bacteria and anaerobes. The drug is rapidly bactericidal and achieves high levels in tissues including the lung. Moxifloxacin was given as a daily dose of 400mg orally. The most common adverse drug reactions expected were nausea, diarrhoea, headache and dizziness. Tendinopathy and tendon rupture, and QT prolongation are some of the serious adverse drug reactions that may occur with moxifloxacin.

- **Clofazimine**, an iminophenazine bright-red dye, remains a WHO group B drug and is administered orally. It was given as a weight dependent daily dose; patients weighing >33kg received 100mg daily dose and <33kg received 50mg daily dose. Several clinical trials have suggested the added benefit to an optimised background regimen and in shortening a regimen to 9-12 months. Expected adverse reactions were QT prolongation, especially when co-administered with BDQ and Pretomanid. It also causes a reversible red-black discolouration of the skin.

1.5 What were the primary and secondary outcomes?

Primary outcomes included:

- Stage 1:
  - Efficacy: The percentage of patients in each investigational arm with culture conversion in MGIT liquid media at 8 weeks post-randomization
  - Safety: The primary safety outcome was the proportion of patients who died or discontinued treatment for any reason by week 8.

- Stage 2:
  - Percentage of patients with an unfavourable outcome (treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) at 72 weeks post-randomisation.

Secondary Outcomes:

- Stage 1
  - Percentage of patients with grade 3 or higher QT prolongation, grade 3 or higher Adverse Event, and experiencing at least one Serious Adverse Event within 8 weeks post randomisation
- Stage 2
  - Efficacy: outcomes were culture conversion at 12 weeks, time to culture conversion, composite unfavourable outcomes at 24 weeks and 108 weeks post-randomization, and recurrence by week 48 post-randomization (investigational arms only).
  - Safety: outcomes for stage 2 were the percentage of patients with at least one serious adverse event or grade 3 or higher adverse event at 72- and 108-weeks post-randomization, at the end of treatment, and QT interval prolongation at week 24. Deaths and adverse events of special interest were also reported.

1.6 What were the predefined safety and efficacy criteria for transitioning to stage 2?

The predefined efficacy criteria for Stage 1 was >40% culture conversion by week 8. The predefined safety criteria for Stage 1 was <45% with a composite unfavourable outcome.

1.7 How was it determined that only the BPaLM arm would advance from stage 1 to 2 (phase II to III)?

At the end of stage 1 in August of 2019, the data collection on the 8-week safety and efficacy outcomes was complete. This was provided to the DSMB for review, and it was confirmed that all three investigational arms met the prespecified criteria and were eligible to be used stage 2. The blinded data was presented to the Scientific Advisory Committee who then recommended BPaLM and BPaLC. The Trial Steering Committee considering this recommendation and challenges with recruitment and the COVID-19 pandemic elected to move to Stage 2 with **one arm only**. Given previous studies showing the superior bactericidal performance of moxifloxacin, as well as growing concerns around the shared resistance mechanisms of clofazimine and bedaquiline, BPaLM was selected to enter stage 2 which commenced in November 2020.

1.8 Why is there so much data for the dropped arms despite the trial meeting stopping criteria early?

Recruitment for stage 1 ended in July 2019, however participants still had to complete 8 weeks of treatment, and their MGIT cultures required processing (taking up to 6 weeks). The data was then cleaned for analysis. After this process the decision did not take that long but it did coincide with recruitment issues, and the start of the COVID-19 pandemic which brought delays in Stage 2 approvals, data collection was ongoing during this process.

1.9 How is TB-PRACTECAL different from NIX and ZeNIX?

In general: These three clinical trials have studied eight BPaL-based regimens with minor differences in duration, drug dosages, or addition of Moxifloxacin or Clofazimine. None of these trials were designed to compare these regimens against each other. A comparison of ZeNix and PRACTECAL is

limited by not only different study populations but also differences in the protocols, especially, thresholds of early discontinuation.

1. Nix trial:
    a. is an open-label, single-group study involving patients with MDR/RR-TB and pre-XDR that is not responsive to treatment or for which a second-line regimen had been discontinued because of side effects.
    b. All patients received 26 weeks of daily oral treatment, with an option to extend treatment to 39 weeks if they were culture-positive at week 16.
    c. Treatment design was as follows:
        i. Bedaquiline at a dose of 400 mg once daily for 2 weeks followed by 200 mg three times a week for 24 weeks
        ii. Pretomanid at a dose of 200 mg daily for 26 weeks
        iii. Linezolid at a dose of 1200 mg daily for up to 26 weeks, and could be stopped completely
    d. Results: https://www.nejm.org/doi/full/10.1056/NEJMoa1901814
        i. At 6 months after the end of treatment 11 patients (10%) had an unfavourable outcome and 98 patients (90%; 95% confidence interval, 83 to 95) had a favourable outcome. The expected linezolid toxic effects of peripheral neuropathy occurred in 81% of patients and myelosuppression occurred in 48%.
2. ZeNix trial:
    a. ZeNix is a phase 3, multi-centre, partially blinded clinical trial successor to Nix evaluating whether the efficacy of the BPaL drug regimen can be maintained, while reducing toxicity, through a lower dose and shorter duration of linezolid.
    b. Patients received 26 weeks of treatment with the option of extending to 39 weeks if patients remained culture positive with clinical evidence of active TB between week 16 and 26.
    c. Treatment design was as follows: All patients received pretomanid 200mg daily + bedaquiline 200mg daily for 8 weeks then 100mg daily for 18 weeks and were randomized to the following linezolid arms:
        i. 1200mg daily for 26 weeks OR
        ii. 1200mg daily for 9 weeks OR
        iii. 600mg daily for 26 weeks
        iv. 600mg daily for 9 weeks
    d. Results: https://www.nejm.org/doi/full/10.1056/NEJMoa2119430
        i. Patients who received BPaL with linezolid dose at 1200mg for 26 weeks or 9 weeks or 600mg for 26 weeks or 9 weeks, 93%, 89%, 91% and 84% respectively had favourable outcomes; peripheral neuropathy occurred in 38%, 24%, 24%, and 13%, respectively; myelosuppression occurred in 22%, 15%, 2%, and 7% respectively; of note, the linezolid dose was modified (ie interrupted, reduced or discontinued) in 51%, 30%, 13%, and 13% respectively. In summary the lower doses and shorter duration of Linezolid were comparatively effective, but the higher dose and longer duration was associated with more frequent modifications due to toxicity. Three participants with unfavourable outcomes received the shorter duration of LZD at 1200mg.

1.10 What was the observed difference in culture conversion between TB-PRACTECAL, Nix, and ZeNix?

The trials had different frequencies of sputum collection and different definitions for culture conversion making a direct comparison difficult:

- Nix defined culture conversion as two negative cultures 7 days apart and reported majority had culture converted by **week 12** of treatment.
- ZeNix defined culture conversion as two negative cultures 7 days apart and reported a **median time to culture conversion of 6 weeks** (interquartile range from 3 to 8 weeks) in the group receiving linezolid given at 600mg daily for 26 weeks.
- TB-PRACTECAL defined culture conversion as two negative cultures taken 4 weeks apart (+/- 2 weeks) and reported 88.5% of BPaLM arm had culture converted **by 12 weeks of treatment**

1.11 How has 'cured' been defined in TB-PRACTECAL?

Patients were carefully monitored with regular sputum sample collection, a chest Xray at week 24, and clinical evaluation at every visit. After 72 weeks of follow up if a patient completed their treatment, remained culture negative and there was sufficient evidence of life with no symptoms of TB they were considered cured. In the BPaLM arm this was **89%** of patients.

2. Early termination

2.1 What was the premise of the trial's early termination?

The Data and Safety Monitoring Board (DSMB) was provided with safety data quarterly and efficacy data biannually as per the DSMB charter. The DSMB charter stipulated the DSMB should consider recommending termination of the trial if the analysis met the predefined stopping rules (see 8.2). The DSMB requested an interim analysis in November 2020 including BPaLM and standard care arm from the start of the trial. A pre-defined statistically significant difference in the primary outcome between the randomised arms in Stage 2 had been met, favouring BPaLM compared to the control arm. In February 2021, the DSMB recommended that further randomization into the study be terminated. The Sponsor, in accordance with the Trial Steering Committee's decision and on the advice of the Trial Scientific Advisory Committee accepted this recommendation and the last patient was randomised on the 18th of March 2021 with 552 patients recruited. 75% of the planned sample size for stage 2 of 201 patients per arm had been included at that time point. All patients on the trial were followed up for a minimum of 72 weeks post randomization.

3. Population and generalisability

3.1 What does ITT/ mITT and PP mean?

- **Intention to Treat**: this included all participants who were dispensed study medication at least once
- **Modified Intention to Treat**: comprised of the Intention to Treat population excluding those who did not have microbiologically proven Rifampicin resistance.
- **Per Protocol**: The per-protocol population comprised of the modified intention-to-treat population with the exclusion of 1) patients not completing a protocol-adherent course of treatment (>80% of doses within 120% of the prescribed duration), other than for treatment failure or death, and 2) patients who discontinued treatment early due to not meeting inclusion/exclusion criteria

3.2 The global population affected by TB is often more diverse than the population typically included in TB clinical trials. Is there available data from this trial to support the use of these regimens in special populations, for example, PLHIV, children, pregnant women, people who use substances, people with diabetes, people with viral hepatitis, and people with extra-pulmonary TB?

TB Practecal was designed to include as many different populations as safely as possible as allowable by regulatory bodies and ethics committees. Patients who were too ill to participate in trial investigations (such as slit lamp and audiograms) had to be considered, along with those who may have been directly harmed by the investigational regimen I.e.: cardiac abnormalities or hepatic dysfunction. Speaking on specific special populations we have the following to add:

- **People living with HIV**: All persons in this group, regardless of CD4 count were included in the trial resulting in just under a quarter of the trial population being HIV positive. Trial sites were selected with this in mind.

- **Adolescents** from the age of 15 were included but there is a gap in this research that would benefit from further trials and operational research. Currently the WHO recommends use of the regimen from the **age of 14** and upwards.

- Participants who fell **pregnant** were able to continue on the trial at the investigators' discretion providing it met the local ethical approvals. All pregnancies were reported to the pharmacovigilance unit and were followed up where possible to ascertain pregnancy outcomes as well as neonatal and infancy outcomes. The early results were reported at MSF Scidays: https://scienceportal.msf.org/assets/7713 . Final results will be published soon and can be found at: MSF Science Portal: https://scienceportal.msf.org/

- Patients were screened for **Hepatitis B and C** and were retained in the trial.

- **Extra-pulmonary tuberculosis** was not an exclusion criterion except in tissues where there was no data on tissue penetration e.g. CNS and bone - see also Inclusion and exclusion criteria.

- **Paediatric** dosing studies are currently underway but are still in early stages.

4. Efficacy

4.1 How was efficacy defined in the study?

Stage 2 statistical analysis was designed as a non-inferiority design with a delta of 12% and a conservative alpha of 1.7%. This is in line with other drug resistant tuberculosis trials.

In layman's terms the trial was designed to evaluate if an investigational arm was no worse than the standard of care by more than 12%. For further explanation on why this design was chosen for PRACTECAL please see above protocol publication. For further explanation on non-inferiority design, you can read here.

4.2 Treatment discontinuations was the biggest driver for the difference in unfavourable outcomes between the two groups, do you have details on this?

The criteria for early discontinuation in the trial was the same across all arms. There was flexibility within the protocol for investigators to stop or replace one drug in the standard care regimen to manage adverse events. In the per protocol analysis, which excluded early discontinuations, the difference between the standard care arm and BPaLM was less pronounced. This suggests the control arm was comparatively efficacious when well tolerated by the participants.

4.3 Is there anything you can share regarding the efficacy in the subgroup of patients with fluoroquinolone resistance, HIV status, and cavity presence?

Yes, a subgroup analysis was performed and can be found in the supplementary appendix of the published article: TB-PRACTECAL NEJM Supplementary appendix_proof

4.4 What does TB-PRACTECAL add to what we know about Pretomanid?

- **Safety:** TB PRACTECAL found Pretomanid to be well tolerated, easy to administer, generally safe, with manageable liver dysfunction. We now have multiple trials available providing good data on the safety of Pretomanid, including previously mentioned ZeNix and Nix

- **Efficacy**: TB-PRACTECAL doesn't portray the efficacy of Pretomanid alone, and there are no placebo-controlled trials but it has shown to have bactericidal effects in previous phase II trials (https://aac.asm.org/content/56/6/3027.short)

4.5 Can you tell us about any recurrences on the trial?

A breakdown of recurrences by Week 72 is in the article. For the latest update on recurrences, email us at the email address above.

4.6 Did any patients have baseline resistance to the investigational regimen?

None of the recurrences had detectable resistance to their allocated regimen at baseline.

5. Safety

5.1 Which population in the trial was used to analyse the safety of the regimen?

The safety analyses were done on the **Intention to Treat Population** I.e., the population of participants that were randomized and received at least one dose of the study medication.

5.2 How was QTcF measured and what were the findings?

At every visit a minimum of 3 ECGs were done pre-dose. The QTcF was calculated as a mean of the 3 ECGs done. Grade 3 was defined as a mean of these 3 ECGs of more than/ equal to 501ms, grade 3 was also criteria to discontinue treatment. The differences found between arms can be seen in the publication. Ongoing analysis to help determine recommended monitoring is planned along with a post-hoc study on determinants of QTcF interval prolongation across different investigational regimens

5.3 What was the most common side effect of linezolid within the first 8 weeks?

The most common early side effect is myelotoxicity especially in HIV population and those with pre-existing anaemia not due to TB infection. In this trial, patients with baseline HB <8g/dL were not included. Those with reversible causes of anaemia could be re-screened once the anaemia was improving.

5.4 Was there a difference in early discontinuations due to adverse events between the arms?

The standard of care arm had a total of 17 patients discontinued due to an adverse event, the most common cause being QTcF prolongation (6) and liver dysfunction (4). The BPaLM arm had a total of 5 discontinued patients, 3 of which was due to myelosuppression (specifically, neutropenia).

5.5 What were the outcomes of those that fell pregnant on the trial?

They were offered follow up and data was collected on maternal and neonatal outcomes, which had the following findings:

- 16 participants in the trial fell pregnant – 12 of these fell pregnant post treatment completion. All had favourable TB outcomes, 0 maternal deaths occurred. Further data can be provided on request at: tb-practecal@london.msf.org

5.6 Is there any data on Pretomanid causing reproductive toxicity?

The WHO's 2022 consolidated guidelines on DR-TB report promising findings on hormonal studies from four clinical and a paternity survey, suggesting adverse effects on male fertility is unlikely. In summary evidence of testicular toxicity was found in rodent studies but not found in monkey studies. Hormonal studies found no changes consistent with testicular toxicity. The paternity survey reported 44 children were fathered by 38 men (12%) of those who participated in pretomanid studies. Semen study is currently ongoing.

5.7 Was adherence similar across all the arms and administered by directly observed therapy?

An analysis on adherence has not yet been performed, however, if a participant missed two weeks of treatment, then this was grounds for an early discontinuation. In the standard care arm, **13** participants were discontinued early due to adherence issues and **1** was discontinued early due to adherence issues in the BPaLM arm. All patients in the mITT population took 80% of the treatment prescribed.

6.1 Sub-studies

6.1 What are TB PRACTECAL's sub-studies?

- PRACTECAL PKPD sub-study – The main aim of the study is to examine the relationship between the patients' exposure to anti-TB drugs in the TB-PRACTECAL trial investigational regimens and their respective treatment outcomes. The pharmacokinetics and pharmacodynamics study's primary objective is to measure the plasma concentrations of bedaquiline, linezolid, pretomanid, moxifloxacin or clofazimine in a subset of patients in the TB-PRACTECAL trial and using pharmacokinetic population models estimate the population exposure to the individual drugs. The PKPD study protocol can be found at: https://bmjopen.bmj.com/content/11/9/e047185.info ClinicalTrials.gov Identifier: NCT04081077
- PRACTECAL PRO sub-study -A Patient reported outcome study examining the evolution of symptoms including adverse events, functioning and other quality of life measures. Capturing

patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods substudy protocol, TB PRACTECAL-PRO | BMJ Open
ClinicalTrials.gov Identifier: NCT03942354

- PRACTECAL EE sub-study – A study to evaluating the economic burden of MDR-TB. Data on costs incurred in adhering to the treatment and management of side effects as well as details to ascertain socioeconomic status of the patients was collected at baseline and on a defined interval thereafter. Cost-effectiveness of new MDR-TB regimens: study protocol for the TB-PRACTECAL economic evaluation substudy | BMJ Open
ClinicalTrials.gov Identifier: NCT04207112

6.2 Population pharmacokinetics and pharmacodynamics of investigational regimens in the TB-PRACTECAL study

6.2.1 Why was a PKPD sub-study done?

There is limited published data on the pharmacokinetics of second line anti-TB drugs. Less is known about the drug-drug interactions, optimal dosing and relationship between pharmacokinetics and pharmacodynamics of the TB-PRACTECAL trial drugs. This study seeks to add to the individual drugs dosing, pharmacokinetics knowledge. Also, through non-linear mixed effects population modelling to explore the more complex relationships between various drugs, individual characteristics, bacilli characteristics, and the treatment outcomes.

6.2.2 What were the findings of the PKPD sub-study?

The aim of the study is to estimate exposure for all 5 of the investigational drugs, currently we have the results of Linezolid discussed below. The results were presented at TB Science as an e-poster during the 53rd World Conference on Lung Health, The Union in November 2022, an abstract can be found here: TheUnionAbstractBook

- 59 participants (62.7% males) with median BMI 20.6 kg/m contributed 553 drug measurements for analyses.
- Median of the linezolid trough concentrations was 331.38 (range 80–9991.4) ng/mL.
- A one-compartment model with transit absorption (N=6) and bodyweight allometry best described the data in the above graph.
- Median MIC of 0.5mg/L (range 0.25–1), using Uzbekistan study data as reference.
- Probability of Target Attainment (PTA) was below 80% for all investigated doses.

In conclusion:
Despite TB-PRACTECAL regimens showing high efficacy, linezolid PTA was low, aligned with previous reports.
Further exploration of linezolid PK/PD targets used in combination with bedaquiline and pretomanid is merited.

6.3 TB-PRACTECAL economic evaluation sub-study

6.3.1 How was costing data collected for the Health Economic Study?

The study for the health economics component took a 'real world' cost data collection approach. Data were collected retrospectively for the most recent fiscal year (2021), took a bottom-up approach and included both MSF and MoH perspective where possible. The time period studied was per one patient episode of care. Price data was sourced from the Global Drug Facility catalogue, local purchase prices, and MSF Green List and Value TB cost data. The study took into account all services provided to patients, including outpatient visits, inpatient bed days, community-level services, lab & monitoring tests, and drugs.

6.3.2 What were the main findings of the economic evaluation study?

The health economics study shows that it is far more cost effective to implement BPaL and BPaLM than current standard of care. Patients on both BPaL and BPaLM are likely to incur reduced costs and have less poor health (measured in disability adjusted life years or DALYs) as compared with those on the standard of care.

6.3.3 Where can we find the published data of the economic evaluation study?

https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0001337

6.4 Patient Reported Outcomes in TB-PRACETCAL

6.4.1 How was the PRO study conducted?

We used two questionnaires measuring health-related quality of life and conducted individual interviews to collect our data. 137 trial participants taking part in the TB-PRACTECAL clinical trial also took part in PRO. They completed 2 questionnaires up to four times: when they joined the trial; then 3, 6, and 12 months later. These participants were either taking investigational treatment or the standard of care treatment. For each participant, the investigators found a local 'healthy control', a person of the same age and sex but without TB. Each healthy control completed the two questionnaires just once.
In addition, we conducted individual in-depth interviews with 55 PRO participants who were taking investigational treatment. Interviews were carried out at various stages of the treatment journey.

6.4.2 What were the key findings of PRO?

- Overall, those being treated for DR-TB reported improvement to their health-related quality of life; that is, both the group taking investigational treatments and the group taking the standard ocare treatment for DR-TB. The shorter length of investigational treatment did not

adversely affect how participants reported their health-related quality of life. At the beginning of treatment, both these groups reported a worse level of health-related quality of life than the healthy control group.

- Individual interviews indicated that patients taking investigational treatment started feeling significantly better after just one month of treatment. It was clear that ongoing support from clinicians, counsellors and family members was an essential component of the treatment received. Support from family and friends was reported to improve as treatment progressed. This may be because previously held ideas of drug-resistant tuberculosis not being curable were being challenged.

6.4.3 What do the findings of PRO mean for countries wanting to implement BPaL/M?

PRO has demonstrated that patients' health-related quality of life will improve despite taking a shorter length of treatment. Treatment acceptability and a shorter length of treatment does not however remove the need for support from the healthcare team, family, friends, and peers. Supportive care should be seen as an ongoing service from the day of diagnosis, through treatment, and during follow-up. Countries must strive to deliver supportive and effective care within their means.

6.4.4 Where will PRO be published if we want to read more about it?

We are currently writing our findings for academic journals. The details of publications will be added here.

7. Community engagement

7.1 How were communities involved in the trial process?

A TB-PRACTECAL specific Community Engagement (CE) Strategy was developed to describe over-arching strategies for building relationships and engaging with community stakeholders, in line with Good Participatory Practice, Guidelines for TB Drug Trials 2012. Site-specific plans for each trial site were developed and updated as needed throughout the trial. More information was published in a BMJ Opinion blog: Engaging communities in tuberculosis research: The experience of the TB-PRACTECAL trial and further reporting is anticipated in 2023.

In this context, community stakeholders includes, but is not limited to, trial patients and their families, individuals living where the research is being conducted, including those with TB, local health care providers, local NGOs, community groups, and community-based organisations. Engagement and communication strategies of other national and global stakeholders such as trial partners and Ministry of Health colleagues have not been included here.

Patient and community stakeholder engagement included, but was not limited to:

- Community consultation on the initial aims of the project
  - Fed into protocol development and initial development of patient materials & ICFs
- Collaboration with Community Advisory Boards at all sites in South Africa

  - Board members represent the key stakeholders in the site's catchment area, including former TB/HIV survivors, community activists, non-governmental organisations, the religious sector and LGBTI representatives.
  - They collaborated on the CE site-specific plans, consulted on patient material development, and participated in communicating the trial results.
- Patient engagement throughout the trial process:
  - The recruitment, screening, treatment and follow up processes were designed to engage with and inform patients via various communication methods throughout the trial. Patient materials, such as a videos, leaflets, booklets, and flipbooks (in addition to ICFs) were key tools used to inform patients and support counselling sessions. Sites adapted the recruitment process where needed, adding more counselling sessions in contexts where it was beneficial for the patients.
- Explored trial patient and practitioner perspectives through a qualitative study to address recruitment challenges in Uzbekistan, as published in Trial Journal, 2021 (Optimising recruitment to a late-phase tuberculosis clinical trial: a qualitative study exploring patient and practitioner experiences in Uzbekistan).
- Community sensitization and education including research literacy.
  - Conducted in person events/activities throughout the trial where feasible, usually in collaboration with the standardised activities already occurring in the TB clinics/projects.
- COVID-19 specific patient engagement
  - VOT testing and feedback
  - Drug delivery, home sample collection / privacy issues
- Peer support and former trial participants directly supporting DR-TB patients during their treatment
  - Informally, peer support was naturally initiated by patients communicating in the in-patient department, building trust, and providing encouragement.
  - In Karakalpakistan, Uzbekistan, the Peer Support Worker program (MSF-led Pilot Project), was set up August 2022 – Jan 2023, for patients taking treatment as part of the regular MSF/MoH project. The aim of the program was to help improve adherence and consisted of current patients with TB connecting directly with previous patients (including former trial participants) to act as peer support workers. The peer support workers were on paid MSF contracts and provided formal feedback in the evaluation of the project. The project anticipates the peer support to be included as part of the routine counseling activities.

Results dissemination for trial participants and community stakeholders was conducted in quarter 3 and 4 of 2022 at in person events and activities.

- Trial participants also helped conduct the activities, voluntarily sharing their experiences within the groups as well as publicly.
- Leaflets were used as an additional communication tool.
- Trial participants also participated alongside TB-PRACTECAL team members, sharing their perspectives in scientific conferences such as at The Union World Conference on Lung Health in 2021 and 2022.
- Posters explaining the results were disseminated widely at sites, placed in TB clinics and DOTs centres.
- Social media campaigns with the opportunity for users to anomalously ask questions and feedback.

Future communications, advocating for seeking treatment and treatment adherence

- Some trial participants have voluntarily provided their testimonies and perspectives to form part of future communication and education activities.

8. Statistical issues

8.1 TB PRACTECAL was designed as a non-inferiority trial, but there have been public claims regarding the Arm 1 regimen's superiority to the control arm. Was a test for superiority conducted given that non-inferiority was met?

The statistical analysis is available in the protocol paper in section 1. If an endpoint met non-inferiority, a test for superiority was also performed.

The discussion around superiority is largely linked to the early termination where really this should be achieved before a non-inferiority trial is terminated for efficacy.

8.2 What was the predefined statistical criteria required for early termination, and when was the analysis done?

There was only one interim analysis, per protocol, for the stage 1 to stage 2 transition and only examining stage 1 outcomes. A second analysis was planned after 90 patients were included in stage 2, but we never reached that point. The DSMB charter stipulated the DSMB should consider recommending termination of the trial if a difference of at least three standard deviations was reached in the interim analysis of a major endpoint, similar to the Haybittle-Peto rule. The DSMB requested an interim analysis in November 2020 including Arm 1 and Control arm from the start of the trial. As we understand, the DSMB did do additional analyses once they became aware that the stopping rules were satisfied.

9. Access

9.1 Given WHO's updated consolidated guidelines on DR-TB and the trial's use of new and repurposed TB medicines which are expensive and difficult to access, can you describe how access barriers are being addressed?

- Countries who have adopted the regimen have had little barrier to accessing Pretomanid, although, access campaigners are vouching for the price of anti-tuberculosis drugs to drop.

- TB Alliance is now contracted with 4 manufacturers for the supply of pretomanid (Viatris, Macleods, Lupin and Hongqi). We have been reassured by the TB Alliance that supply of pretomanid will not be a limiting factor in meeting demand. This will be a point MSF will be continuously monitoring over coming months.

- Following the release of WHO's consolidated guidelines on DR-TB, Viatris, MedAccess, and TB Alliance announced a volume guarantee agreement to reduce the price of pretomanid by 34% to $240, bringing the lowest global price of BPaLM to $600 per person for a six-month treatment course (Here) . Moreover, MSF's Access Campaign are calling Johnson & Johnson to bring down the price of bedaquilineso that a complete DR-TB treatment course is no more than $500 per person.

- The 1/4/6 × 24 Campaign launched at the 2022 International AIDS Society Conference in Montreal, Canada, campaigns to rally energy, political will & funding to end TB. The Campaign's name comes from its central demand: that countries and other duty bearers take action to implement the shortest available regimens – one month or once-weekly for TB prevention, four months for drug-sensitive TB, and six months for drug-resistant TB — by the end of 2024. The 1/4/6×24 Campaign draws inspiration from the legacy of the late Partners in Health (PIH) co-founder Dr. Paul Farmer, who stressed the so-called "five S's" that countries must have in place to deliver equitable care to the poorest people: stuff, staff, space, systems and support.

- In October 2022, MSF approved and published its first Clinical Trial Transparency Policy which includes a commitment to publishing a minimum set of cost items for clinical trial costs; a critically important step towards increasing access to medical products for all who need them.

- The WHO's 2022 updated guidelines stated that due to the reduced complexity and shorter duration of BPaLM/BPaL it could increase equity via decentralized care to more rural, underserved, and disadvantaged populations.

9.2 How much do you predict Pretomanid is going to cost?

Given the rapidly changing environment we recommend checking the latest updates available in the medicine's catalogue of the Stop TB Partnership's Global Drug Facility found here.

Whilst the costs of the regimen drugs are still unacceptably high, it is still cost saving to implement BPaLM/BPaL due to the reduced time in care

Non-drug costs will vary depending on each country's current program constituents and implementation plan. General costs to plan for include overhead costs, staff, utilities, maintenance, consumable costs (medical supplies, transport), and capital costs. Specific costs required for the rollout of this regimen will include:

- Inpatient days (vary on health policy and illness severity)
- Outpatient visits: initiation visit, monthly visits (at minimum during treatment) and two follow-up visits, DOT services if provided.
- Community-level services: home visits, telephonic visits, tracing those that are lost-to-follow up
- Initiation visits: recommendations include history and examination, sputum for smear, culture, GeneXpert, and country available DST. Patients should also be screened where possible and relevant for HIV, hepatitis, and pregnancy.
- Lab and monitoring required for this regimen at a minimum of monthly intervals (in brackets are the minimum requirements): visual acuity testing, Ishihara colour plates, ECGs, sputum collection for smear and culture depending on country availability. Blood monitoring (requirements include monthly haematology (Haemoglobin, white cell count, platelets), liver function (ALT, AST), creatinine clearance (creatinine), and glucose (fingerpick). Audiometry is also required.
- Follow up: Two follow up visits are recommended, one at 6 months and 1 at 12 months post treatment. These will require history, clinical exam and at minimum sputum for smear and culture.

- Drug procurement: GDF fee, transport costs of drugs, drug insurance, taxes, VAT, security clearances, etc
- Mental Health support: (variable per country availability) vital at initiation visit, follow up visits and post treatment and should be supplied by doctors, nurses, counsellors, or health educators. (Patient materials to assist health education can be found here: https://msf.org.uk/tb-practecal)
- Social Support: Depending on availability per country considerations should include: food packages, peer support, ongoing health education, transport costs for patients to clinics.
- Active Drug Safety Management and Monitoring systems

For more information on TB drug costing please see: https://msfaccess.org/dr-tb-drugs-under-microscope-8th-edition

9.3 Is a Fixed Dose Combination of these drugs available?

TB alliance and Viatris are of the opinion that this is an issue with LZD due to dose adaptations. There may be possibility with BDQ and Pretomanid in future as the WHO's updated guidelines suggest that a daily dose of BDQ may be used when implementing BPaLM/BPaL.

10. Clinical context

10.1 What do we need to consider before prescribing this regimen?

The WHO's guidelines have been updated as of December 2022, here. The 2022 updated guidelines now recommend BPaLM regimen for MDR/RR-TB and pre-XDR. Before prescribing, take the following into consideration:

- Drug-resistance profile
- Previous TB treatment exposure
- Drug resistance profile of close contacts
- Patient's age
- Localization of extrapulmonary lesions
- If applicable, pregnancy and breast-feeding status

10.2 Who is now eligible for BPaLM?

- Age **14** and above WITH
  - **MDR/RR-TB or pre-XDR** OR
  - Clinically diagnosed with TB with strong contact history of exposure to MDR/RR-TB
- **Regardless** of HIV status

10.3 What are absolute contraindications to using BPaLM?

- Known **hypersensitivity** to any of the drugs
- Known **resistance** to the drugs (XDR-TB)
- Previous exposure of more than 1 month to bedaquiline, linezolid, pretomanid, or delamanid **unless** DST has ruled out resistance
- **QTcF** more than 500ms at baseline / significant **cardiac** history
- **Extrapulmonary TB** of the following sites: CNS, miliary, and osteoarticular
- **Pregnant, breastfeeding women** (more data need)
- Patient is **on contraindicated medication** that cannot be altered prior to starting the regimen, see the WHO guidelines for an extensive list and recommendations

10.4 What about Fluoroquinolone resistance?

DST should always be done to ascertain resistance to FLQs, however, BPaLM can be initiated without delay. If FLQ resistance is **confirmed**, then Moxifloxacin may be dropped from the regimen and the regimen continued. In this scenario there is room to extend treatment for 9 months if clinically required.

If FLQ resistance remains **indetermined or suspected** then continue with BPaLM, the benefits outweigh the risks.

If FLQ resistance is highly likely from patient history and exposure, then it is reasonable to omit FLQ from the onset of treatment

10.5 In which scenarios would I still opt for the current all oral 9-month regimen?

In patients who:

- **Age:** 14 years and below
- Are **pregnant and breastfeeding:** And who wish to continue breastfeeding
- **Fluoroquinolone susceptibility is confirmed**
- Do not have **extensive pulmonary disease**
- Do not have **severe extrapulmonary disease**
- Have had less than **1 month exposure** to: bedaquiline, fluoroquinolone, ethionamide or linezolid, and clofazimine.
- Have an anaemia with a **haemoglobin of <8g/dl** or platelets of **<75 000/mm^3** that is not easily reversible or cannot be easily monitored should be considered for a LZD sparing regimen

10.6 If we are using the BPaL/BPaLM and we must omit a drug due to an AE what would be the consequence to the patient

The WHO has supplied guidance on this:

- If bedaquiline/pretomanid needs to be discontinued, then the entire regimen will need to be discontinued and the patient is likely to require an individualised longer regimen
- If linezolid is discontinued in the first 9 weeks, then the entire regimen will need to be discontinued
- If linezolid is withheld and there is less than 8 weeks left of the regimen duration left, then the regimen can be considered to be complete
- If moxifloxacin is discontinued, then the regimen may continue without it

10.7 What are the key differences between WHO's latest guidelines and the regimen in TB PRACTECAL?

- The WHO's Operational Handbook on the Treatment of DR-TB recommends the of **600mg LZD** for 26 weeks. TB PRACTECAL used a Linezolid dosing regimen that tapered to 300mg daily after 16 weeks. The WHO states that dose reduction of LZD to 300mg daily is allowable but clinicians should strive towards a minimum of 9 weeks of LZD dosed at 600mg.
- Total duration of treatment recommended by the **WHO is 26 weeks**, whereas 24 weeks of treatment was given in TB-PRACTCEAL
- The WHO recommends either BDQ dosing regimen be used
- The WHO recommends that if a woman falls pregnant whilst on the regimen that the regimen be stopped, whilst TB-PRACTECAL allowed continuation on the trial.

10.8 Can you take BPaLM while being pregnant or planning a pregnancy:

- Discuss the possibility of pregnancy with patients of childbearing potential and check local regulations. Currently the WHO is recommending against the use of BPaLM/BPaL during pregnancy due to lack of data
- All women of child-bearing potential who are diagnosed with TB should be offered appropriate family planning
- There is seemingly no added risk from our data as compared to a pregnancy on other second line regimens, but data is scarce
- It is never recommended to plan a pregnancy on treatment so contraception should be recommended, and pregnancy test should be taken at baseline (and offered as needed during follow-up)
- If a patient becomes pregnant whilst on treatment, we recommend carefully counselling the patient on risks and lack of current evidence. Shared decision making is recommended weighing up the risks and benefits of changing to an alternate regimen.

10.9 How should we manage patients who are a contact of someone with known resistance to BDQ/LZD/Pa?

Every effort should be made to expedite DST for the patient and contact to make as informed a decision as possible.

10.10 What are the gaps knowledge about this regimen?

The gaps are the areas where we need more data to recommend to certain groups I.e: Pregnancy, adolescents and children, osteomyelitis, meningo-encephalitis. Fluoroquinolone resistance is recommended to use the BPaL. The role of BPaLC is uncertain and not been recommended by WHO at this stage but will continue to be subject to operational research through MSF. Dose finding trials in children are expected to start towards the end of 2022. Close observation of patients with severe liver dysfunction or cardiac anomalies will be needed.

10.11 What countries are currently implementing BPaL/BPaLM? And if so, how is it going?

Currently MSF is involved in the implementation of the regimen as programmatic or operational research in 6 countries, with more expected to roll out the regimen in 2023.

It is going well in the countries listed with over 300 patients currently enrolled on the regimen.

10.12 What are the concerns of emerging BDQ resistance when using this regimen?

Emerging bedaquiline resistance is concerning and countries implementing this regimen should be aware of this as a possibility. It is imperative to increase access to DST testing for BDQ and associated surveillance activities however the challenges with this are acknowledged. The WHO recommends BPaLM/BPaL be implement in parallel to the upscaling of DST in all NTPs.

The emergence of bedaquiline resistance further emphasises the need for excellent patient support through treatment through psychosocial care and adherence support activities.