# TB-PRACTECAL: Frequently Asked Questions

*For more information, please contact us: tb-practecal@london.msf.org*

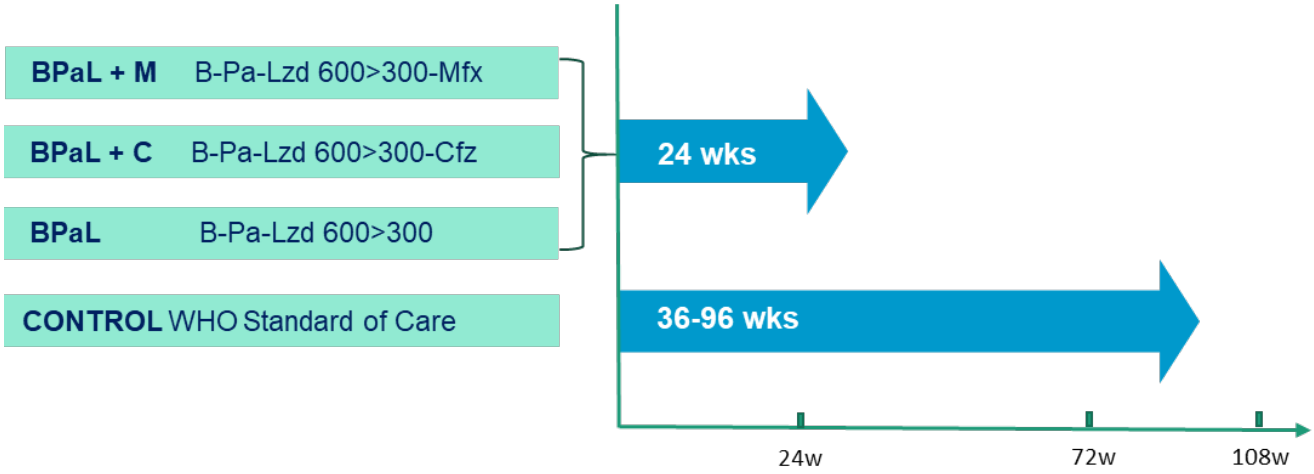
## Contents

# 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 for treatment of rifampicin-resistant tuberculosis. The study has two stages, with a seamless transition between them.

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 Practecal arm-1 and Practecal arm-2 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 - Practecal arm-1 – should be taken forward to Stage 2. Stage 2 commenced in November 2020.




## 1.2 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 BDQ, LZD, Delamanid or pretomanid for more than 1 month. Also excluded were patients with TB meningo-encephalitis, brain abscesses, osteomyelitis, and arthritis.

- The trial enrolled 552 patients overall. In this primary analysis, 301 patients were included in these results

## 1.3 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 XDR by the FDA in 2019, in combination with bedaquiline and linezolid. Pretomanid was prescribed as a daily dose of 200mg. Expected adverse reactions included hepatotoxicity, 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.

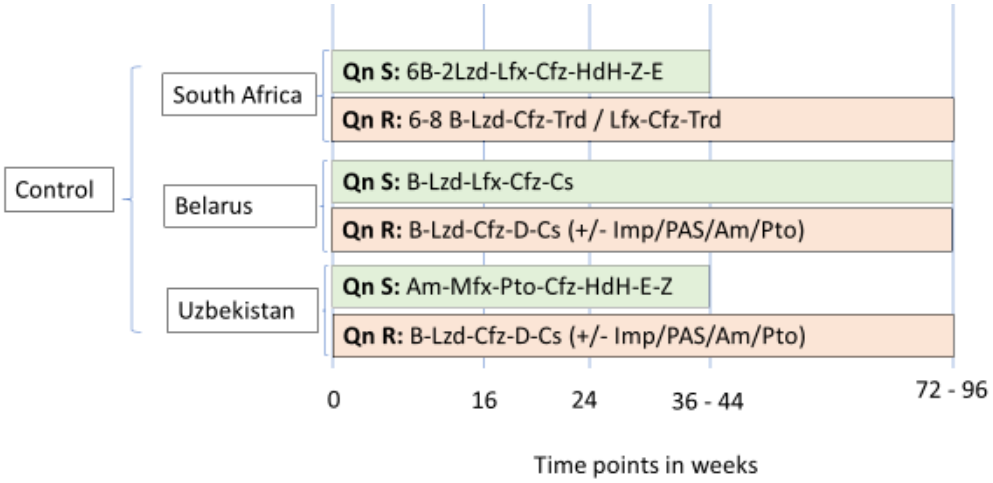
- **Bedaquiline:** Bedaquiline is a diarylquinoline antimycobacterial, currently a WHO group A drug for rifampicin resistant tuberculosis. Bedaquiline was given as a loading dose of 400mg daily for 2 weeks and then 200mg three times weekly for the remainder of the 24 weeks. The main adverse events of 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 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.

## 1.4 What Standard of Care regimens did the patients receive in the control arms:




The protocol allowed for the Standard of Care regimen to be updated according to WHO updated guidelines throughout the trial. This meant that the duration of regimens varied from 36 to 96 weeks. Short injectable regimens were available at all sites from the beginning. Bedaquiline and Linezolid were both available to all sites from the begging. Non-inferiority design means that if the newer treatment is as good as the best available treatment, it should still meet non-inferiority. Sensitivity analyses are planned.

## 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 outcomes (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 Arm 1 (BPaLM) and Arm 2 (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, Arm 1 was selected to enter stage 2 which commenced in November 2020.

### 1.8 Why did it take so long to endorse the transition from Stage 1 to Stage 2?

Recruitment 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.

### 1.9 How is TB-PRACTECAL different from NIX and Ze-NIX?

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

d. Results:
   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. Ze-NIX trial:
   a. Ze-Nix 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 are not yet published

## 1.10 When a participant discontinued the SOC arm, what therapy were they offered?

As defined in the protocol, trial patients were offered a salvage regimen, following the local TB guidelines and with the support of the medical monitor. The trial ensured there was access to any drugs required to construct the best possible individualised regimen. Patients were also given the option to either follow up through the trial or through the regular TB program. If they continued to consent, they were followed for safety up to 108 weeks from randomisation.

## 1.11 How has 'cured' been defined in this trial?

During the trial, sputum samples are taken at regular intervals. After two consecutive negative sputum cultures, patients are classified as having 'converted' provided they no longer show signs of TB. After 72 weeks, if patients' sputum culture had remained negative and they no longer had signs of TB and are considered 'cured' at that point. In the TB-PRACTECAL results, 89% of patients who completed treatment and follow up showed no signs of TB and were considered cured at the 72-week mark. 72 weeks is a standard period to benchmark against in trials for TB treatment.

## 1.12 How was discontinuation defined in the trial?

As per protocol patients were to be discontinued on any of the following grounds:

- Grade 3 or higher QT prolongation and other cardiac rhythm disturbances
- Grade 3 or higher hearing loss
- Patients who were felt to be non-adherent by the Investigator as evidenced by missing more than 2 consecutive weeks of treatment or using other site-specified criteria.
- Patient withdrew consent
- Permanently stopping or adding at least one drug in an investigational arm or two drugs in the SOC. Dose reduction or short holidays of less than 2 weeks will not be considered as significant modifications.
- At the discretion of the Investigator, a patient may discontinue treatment in case of any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued study regimens use.

### 1.13 What are TB PRACTECAL's sub-studies?

- PRACTECAL PKPD sub-study - 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
- PRACTECAL PRO sub-study - Patient reported outcome analysing the evolution of symptoms including adverse events, functioning and other quality of life measures.
- PRACETCAL EE sub-study – A study to evaluate 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 will be collected at baseline and on a defined interval.

## 2. Early termination

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

The 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 7.2). The DSMB requested an interim analysis in November 2020 including Arm 1 and Control 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 Investigational Arm 1 (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 SAC 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.

At the time of writing, follow up is ongoing. Last patient, last visit is expected in August 2022 when the last patient randomised reaches 72 weeks post-randomization. At that point, all remaining patients will be censored, the database will be locked, and the Sponsor will produce the end of study report.

# 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 What was the total number of patient's enrolled broken down per arm?

| | **control** | | | **Practecal arm-1** | | | **Practecal arm-2** | | | **Practecal arm-3** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ITT | mITT | PP | ITT | mITT | PP | ITT | mITT | PP | ITT | mITT | PP |
| All randomizations | 150 | 141 | 42 | 151 | 138 | 98 | 126 | 116 | 93 | 122 | 111 | 92 |

## 3.3 What were the baseline characteristics?

Baseline characteristics of patients in the Intention-to-treat population

| | **control** | **Practecal arm-1** | **Practecal arm-2** | **Practecal arm-3** |
|---|---|---|---|---|
| Total number | 150 | 151 | 126 | 122 |
| Age (years), median (range) | 37 (18 to 71) | 35 (17 to 71) | 32 (15 to 67) | 36 (15 to 72) |
| Female, n (%) | 55 (36.7) | 66 (43.7) | 42 (33.3) | 58 (47.5) |
| Body mass index (MBI) (kg/m$^2$), median (interquartile range, IQR) | 19.9 (17.5 to 22.8)<br>Missing = 1 | 19.8 (17.7 to 22.7)<br>Missing = 0 | 19.5 (17.7 to 22.2)<br>Missing = 0 | 20.2 (18.1 to 22.4)<br>Missing = 0 |
| HIV positive, n (%) | 40 (26.7) | 38 (25.2) | 33 (26.2) | 41 (33.6) |
| CD4 count (cells/µL), median (IQR) | 260 (132 to 460) | 330 (209 to 547) | 297 (114 to 481) | 326 (153 to 550) |

| | | | | |
|---|---|---|---|---|
| | Missing = 2 | Missing = 2 | Missing = 1 | Missing = 2 |
| Smear positive, n (%) | 97 (64.7) | 91 (60.3) | 84 (66.7) | 77 (63.1) |
| Cavity present, n (%) | 94 (62.7) | 80 (53.0) | 79 (62.7) | 73 (59.8) |
| Fluoroquinolone resistant, n (%) | 32 (24.8)<br>Missing = 21 | 32 (23.9)<br>Missing = 17 | 22 (18.6)<br>Missing = 8 | 25 (24.3)<br>Missing = 19 |
| QTcF (ms), mean (SD) | 401 (19) | 398 (19) | 395 (19)<br>Missing = 0 | 398 (19)<br>Missing = 0 |
| ALT (IU/l), median (IQR) | 20 (15 to 28)<br>Missing = 1 | 19 (14 to 28)<br>Missing = 1 | 17 (14 to 26)<br>Missing = 1 | 20 (14 to 29)<br>Missing = 0 |

### 3.4 The global population affected by TB is often more diverse than the population typically included in TB clinical trials. Is there any available data for these vulnerable groups?

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:

- PLHIV: 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 possible operational research.

- Participants who fell pregnant, or participants who impregnated partners were able to continue on the trial and the investigators' discretion and 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. These findings will be published on the MSF Science Portal soon

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

- Extra-pulmonary Tuberculosis was not an exclusion criterion except at the sites where there was no known penetration - see above question for participants who were included and excluded.

## 4. Efficacy

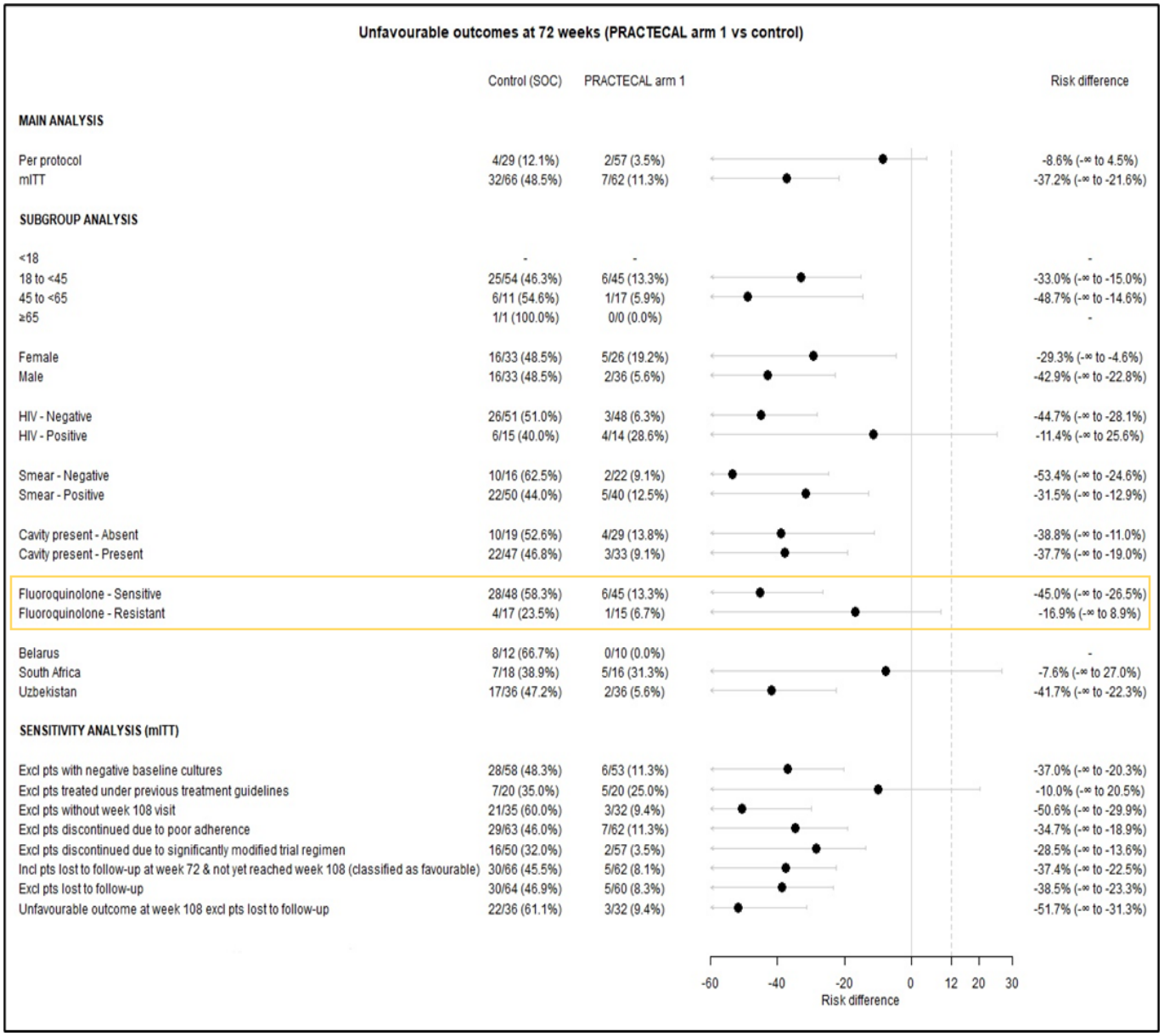
### 4.1 How many people on Arm 1 (BPaLM regimen) had reached the primary endpoint for stage 2 of the trial at 72 weeks post-randomization?

At the date enrolment was stopped, 145 (73 control, 72 Practecal arm-1), 128 (66 control, 62 Practecal arm-1) and 90 (33 control, 57 Practecal arm-1) were in the intention-to-treat, modified intention-to-treat and per-protocol populations, respectively, and had the opportunity for 72 weeks follow-up. By 72 weeks of follow up, in the modified intention-to-treat population, 48.5% (32/66) and 11.3% (7/62) of patients satisfied the unfavourable composite outcome in the control and Practecal arm-1, respectively.

### 4.2 What was the main finding of the study?

In this phase II/III trial, for the primary composite outcome, Practecal arm-1 was both non-inferior and superior to the control arm in the modified-intention-to-treat population, with 88.7% of patients with a favourable outcome compared with 51.5% in the control.

### 4.3 Is there anything you can share regarding the efficacy in the subgroup of patients with fluoroquinolone resistance?




## 4.5 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 discontinuations 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 SoC regimen to manage adverse events. In the per protocol analysis, which excluded early discontinuations, the difference between the control arm and the investigational arms was less pronounced. This suggests the control arm was comparatively efficacious when well tolerated by the participants.

Primary efficacy analysis in the modified intention-to-treat and per-protocol 72-week populations

| | Modified intention-to-treat population | | Per-protocol population | |
|---|---|---|---|---|
| | **control (n = 66)** | **Practecal arm-1 (n = 62)** | **control (n = 33)** | **Practecal arm-1 (n = 57)** |
| No unfavourable outcome | 34 (51.5) | 55 (88.7) | 29 (87.9) | 55 (96.5) |
| Unfavourable outcome | 32 (48.5) | 7 (11.3) | 4 (12.1) | 2 (3.5) |
| Deaths | 2 (3.0) | 0 (0.0) | 2 (6.1) | 0 (0.0) |
| Early discontinuations | 28 (42.4) | 5 (8.1) | - | - |
| Adherence issues | 3 | 0 | - | - |
| Adverse event | 17 | 5 | - | - |
| Not meeting inclusion/exclusion criteria (detected after 1st dose) | 0 | 0 | - | - |
| Withdrew consent whilst still on treatment | 6 | 0 | - | - |
| Other* | 2 | 0 | - | - |
| Treatment failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Lost to follow-up at 72 weeks | 2 (3.0) | 2 (3.2) | 2 (6.1) | 2 (3.5) |
| Recurrence | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | | | |
| Risk difference (one-sided 98.3% CI) | - | -37.2% (- to -21.6%) | - | -8.6% (- to 4.5%) |
| Non-inferiority p-value** | - | p<0.001 | - | p<0.001 |
| Superiority p-value | - | p<0.001 | - | p=0.13 |

## 4.6 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 hepatotoxicity. We now have multiple trials available providing good data on the safety of Pretomanid, including previously mentioned Ze-NIX (https://www.tballiance.org/portfolio/trial/11883), and NIX (https://www.nejm.org/doi/full/10.1056/NEJMoa1901814)

- Efficacy: TB-PACTECAL doesn't portray 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)

## 4.8 Given early end of randomisation, will TB PRACTECAL have enough trial data to comment on recurrence between the arms?

Around 390 patients, 97 per arm, had the opportunity to reach week 48 i.e. 6 months post completion of treatment of the investigational regimen. This is the time when most relapses

occur reflecting as a useful and comparable outcome that has been measured in recent TB trials. This exposure time should bias toward the null hypothesis.

## 5. Safety

### 5.1 Were there any differences in QTcF prolongation between SOC and Arm 1

Serious or Grade ≥3 Events occurring in the week 72, intention-to-treat population, by preferred term

| | Control (n=73) | | Practecal arm-1 (n=72) | | Practecal arm-2 (n=72) | | Practecal arm-3 (n=69) | |
|---|---|---|---|---|---|---|---|---|
| | events | patients | events | patients | events | patients | events | patients |
| QT prolongation** | 12 | 10 | 1 | 1 | 3 | 3 | 0 | 0 |
| Number related and % | 11 | 91.7% | 0 | 0% | 2 | 66.67% | - | - |

** Electrocardiogram QT prolonged (9 control and 2 Practecal arm-2); Syncope (3 control, 1 Practecal arm-1 and 1 Practecal arm-2).

### 5.2 What was the cause of the reported deaths?

| Study site | Cause of death | Timing | Treatment related? | TB related? | TB-PRACTECAL Arm |
|---|---|---|---|---|---|
| UZ-01 | Enterocolitis | Post early discontinuation | No | No | control |
| UZ-01 | Seizure | During follow-up | No | No | PRACTECAL arm 3 |
| UZ-01** | Completed suicide | On treatment | Yes | No | control |
| SA-03 | Pancreatitis acute | Post early discontinuation | Yes | No | control |
| BY-02 | Sudden death | On treatment | Yes | No | control |
| UZ-04** | Covid-19 pneumonia | On treatment | No | No | control |
| UZ-01 | Pneumonia | Post early discontinuation | No | No | PRACTECAL arm 2 |
| BY-02 | Sudden cardiac death | On treatment | Yes | No | control |
| SA-03** | COPD | During follow-up | No | No | PRACTECAL arm 2 |
| SA-03 | Stab wound | During follow-up | No | No | control |

*All recruited up to 18th March 2021 who had been dispensed medication.

**Deaths which were included in the composite primary outcome at week 72, including additional analyses

### 5.3 Monitoring cataracts will be tough under programmatic conditions? Do the TB PRACTECAL findings suggest that this is not a required safety measure?

The concern around cataracts was derived from pre-clinical data. As a result, PRACTECAL and other pretomanid studies monitored for cataract in participants. The cumulative evidence to date has not identified unexpected cataract formation and we do not recommend routine monitoring.

### 5.4 Is there any data on Pretomanid causing reproductive toxicity?

There is currently a trial looking at Pretomanid's effect on male sperm. Recruitment is ongoing (May 2022) https://clinicaltrials.gov/ct2/show/NCT04179500

### 5.5 How common was Peripheral Neuropathy in the investigational arms?

| | **Control (n=150)** | | **Practecal arm-1 (n=151)** | | **Practecal arm-2 (n=126)** | | **Practecal arm-3 (n=122)** | |
|---|---|---|---|---|---|---|---|---|
| | **events** | **pts** | **events** | **pts** | **events** | **pts** | **events** | **pts** |
| Neuropathy peripheral | 14 | 14 | 3 | 3 | 4 | 4 | 4 | 4 |

## 6. Community engagement

### 6.1 Describe the levels of community engagement throughout the trial from design to execution?

TB-Practecal was designed with patients on the forefront and came from listening carefully to patients all over the world where MSF has worked, for examples: https://blogs.msf.org/blogs/topics/tb-me

Within the trial community engagement could be broken down as below:

- Patient engagement included:
    a. Community consultation on the initial aims of the project
        i. 'Principles of designing future MDR-TB treatment'
            1. Fed into protocol development
            2. initial development on patient materials & ICFs
    b. Direct TB Patients groups at sites in UZB
        i. Screening process
        ii. Informed consent process
        iii. Hospital visits
        iv. Counselling support

    c. Indirect engagement via Community Advisory Board in South Africa – patient representative group
- Covid related patient engagement
    - VOT testing / feedback
    - Drug delivery, home sample collection / privacy issues

## 7. Statistical issues

### 7.1 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 plan will be available with the manuscript. 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.

### 7.2 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. 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.

## 8. Access

### 8.1 Pretomanid is a new drug and now recommended for a broader range of patients. Can you describe how access barriers are being addressed?

TB Alliance is now contracted with 4 manufacturers for the supply of pretomanid (Viatris, Macleods, Lupin and Hongqi). We have been reassured by the 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.

### 8.2 How much do you predict Pretomanid is going to cost?

Latest STOP TB GDF drug Catalog:
https://www.stoptb.org/sites/default/files/gdfmedicinescatalog_1.pdf and website:
https://www.stoptb.org/global-drug-facility-gdf/gdf-product-catalog

May 2022: Pretomanid was priced at $52 USD per pack of 26 tablets = $ 2 USD per tablet. This would equate to $336 USD per patient per 6-month regimen for pretomanid alone.

## 9. Clinical context

### 9.1 WHO's rapid communication as of 3rd May 2022, continues to recommend a 9-month all oral regimen. Where might BPaLM be more useful to implement?

- BPaLM was used for patients irrespective of fluroquinolone resistance in TB PRACTECAL and is a safer, efficacious option for patients with rifampicin-resistance – i.e. identified using the GeneXpert or similar rapid diagnostic tests. This means that patients don't need to wait for a test of fluoroquinolone resistance or worry that their treatment might not be effective if FQ tests come back as resistant.

- The efficacy of BPaLM is unknown where fluoroquinolone resistance has been established as this was only a quarter of patients in PRACTECAL. BPaL is recommended for this group. The good news is that in TB-PRACTECAL, BPaLM had similar rates of serious and severe side effects as BPaL so the risk to an individual patient if BPaLM is started and subsequently, FQ-resistance is demonstrated.

- The 9 month regimen is inappropriate for patients with extensive lung disease, however BPaLM was shown to be efficacious irrespective of smear or cavity status.

- The current all oral 9 month regimen has a high pill burden when compared to BPaLM.

### 9.2 Are there any concerns from TB PRACTECAL that the presence of Moxifloxacin in the regimen conflicts with the expected approval of 4HPMZ in terms of resistance?

We expect at least in the short term, this regimen will be for a limited number of contexts where either there is confidence there is minimal population fluoroquinolone resistance or the regions are able to do rapid fluoroquinolone DSTs.

### 9.3 What are the knowledge gaps about this regimen?

More data is needed in certain groups I.e: Pregnancy, adolescents and children, osteomyelitis, meningo-encephalitis. For fluoroquinolone resistance, it is recommended to use the BPaL regimen. 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.

### 9.4 What are the take home messages from this trial, amongst others?

These clinical trials have clearly demonstrated that the characteristics of the best treatment regimens for RR, MDR and pre-XDR TB today are:

- Bedaquiline, Pretomanid and Linezolid-based
- All oral
- Maximum of 6 months duration
- Maximum of 5 pills a day
- Once daily dosing
- Success rate is comparable to DS-TB treatment at 8-9 in every 10 patients

The trials have also provided the following conclusion around the use of B-Pa-Lzd based regimens:

- Pretomanid is generally safe with no new signals

## 9.5 What are the key differences between WHO rapid communication and the regimen in TB PRACTECAL?

- The WHO rapid recommendation highlights the use Ze-NIX's dosing of 600mg LZD for 26 weeks. TB PRACTECAL used a Linezolid dosing regimen that tapered to 300mg daily after 16 weeks. It might be that dose reduction will be advised in cases of toxicity.

## 9.6 What were the most challenging/ common side effects that clinicians using this regimen should be comfortable managing?

- **Peripheral neuropathy** – Linezolid related PN was one of the more challenging adverse events to deal with due to the chronicity, severity and access to adequate analgesics for some sites.
- **Deranged liver enzymes** – Given the diverse population in the trial, investigators needed to be aware of the differential causes of liver enzyme abnormalities. Concomitant medications, including antiretrovirals, and alcohol use disorder was common among participants.
- **Myelosuppression** - Commonly seen in patients taking Linezolid. Whilst many patients had baseline anaemia, which may have been attributable to TB diagnosis, it's important to know when to consider Linezolid toxicity and what to do about it. In TB- Practecal we used a tapering dose of Linezolid to manage such toxicities.
- **Prolonged QTcF** – Given that the regimen contains multiple drugs with the potential to prolong QTcF intervals, it is advisable clinicians know how to diagnose, monitor and look for other causes of prolonged QTcF. This was common in the trial in both SoC and investigational arms.