Pilot study to estimate the effectiveness and safety of the BPaL treatment regimen in (Country Name)

Version 5, July 2022

BPaL introduction and scale-up under operational research conditions

Generic Protocol developed by KNCV Tuberculosis Foundation

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Contents

Acknowledgements

This document is based on the operational research protocol template published by the Global Drug-resistant TB Initiative (GDI) at the Stop TB Partnership in May 2018[1] and ShORRT protocol published by TDR/World Health Organization (WHO) in April 2020.[2] It is also based on the following WHO documents: 1. WHO consolidated guidelines on tuberculosis. Module 4: Treatment. Drug-resistant tuberculosis treatment, 2020; 2. WHO Operational Handbook on tuberculosis. Module 4: Treatment. Drug-resistant tuberculosis treatment, 2020; 3. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020; and 4. WHO Rapid communication: Key changes to the treatment of drug-resistant tuberculosis, May 2022.

[1] Global Drug-resistant TB Initiative, Stop TB Partnership (May 2018). The Evaluation of Effectiveness and Safety of Novel Shorter Treatment Regimens for Multidrug-Resistant Tuberculosis. http://www.stoptb.org/wg/mdrtb/assets/documents/GDI%20OR%20generic%20protocol%20final.pdf.

[2] TDR / WHO. (April 2020). All-oral shorter treatment regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB): Evaluating their effectiveness, safety, feasibility, cost-effectiveness and impact on the quality of life of patients. Unpublished protocol version 3.

Abbreviations

aDSM	Active Tuberculosis Drug-safety Monitoring and Management
AE	Adverse Event
ALT	Alanine Aminotransferase
ARV	Anti-retroviral Treatment
AST	Aspartate Aminotransferase
Bdq	Bedaquiline
BMI	Body Mass Index
BPaL	Bedaquiline, Pretomanid and Linezolid
BSL	Blood Sugar Level
Cfz	Clofazimine
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
Dlm	Delamanid
DMP	Data Management Plan
DOT	Directly Observed Therapy
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	U. S. Food and Drug Administration
FQ	Fluoroquinolones
GDF	Global Drug Facility
GF	Global Fund
HbA1c	Haemoglobin A1c (glycated hemoglobin)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ITR	Individualized Treatment Regimen
LPA	Line Probe Assay
Lzd	Linezolid
MDR-TB	Multidrug-resistant Tuberculosis
OR	Operational Research
Pa	Pretomanid
pDST	Phenotypic Drug Susceptibility Testing
Pre-XDR-TB	Pre-Extensively Drug-resistant TB
RR-TB	Rifampicin-resistant Tuberculosis
SAE	Serious Adverse Event

STR	Shorter Treatment Regimen
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant Tuberculosis

Summary

This operational research protocol concerns a prospective cohort study using the BPaL treatment regimen. In August 2019, the US Food and Drug Administration (FDA), and in March 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) have recommended approval of the new drug pretomanid (Pa) for the treatment of pulmonary extensively drug-resistant forms of tuberculosis (XDR-TB) or treatment-intolerant or non-responsive multidrug-resistant tuberculosis (MDR-TB), in a combination with bedaquiline (Bdq) and linezolid (Lzd). This BPaL regimen, sponsored by the TB Alliance, was trialed for use in patients with XDR-TB,[3] or intolerance or failure of an MDR-TB treatment regimen, in the Nix-TB study.[4] The regimen was given for 6 months with the possibility to extend the duration to 9 months. Final results of the study were published in the New England Journal of Medicine in March 2020. At 6 months after the end of treatment in the intention-to-treat analysis, 11 patients (10%) had an unfavorable outcome and 98 patients (90%; 95% confidence interval (CI), 83-95) had a favorable outcome.[5]

The primary objective of the study is to estimate the effectiveness and safety of the BPaL regimen in MDR/RR-TB patients with additional fluoroquinolone (FQ) resistance and MDR-TB patients with documented treatment intolerance or failure. The secondary objectives were: time to culture conversion; and assessment of the TB recurrence rates at 6 and 12 months post-treatment completion.

The operational research will enroll # patients over a period of (number of years) years in (number of sites) sites and will inform scale-up decision.

Patients will be enrolled based on the inclusion and exclusion criteria after informed consent.

Through the OR study the capacity of the respective NTP will be strengthened to implement the BPaL regimen, and the results of the OR will be used to support national scale-up of the regimen.

[3] Using a previous WHO definition of XDR-TB, which was MDR/RR-TB plus resistance to FQ and any of the SLI.

[4] A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis. https://clinicaltrials.gov/ct2/show/NCT02333799

[5] Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020; 382(10): 893–902.

1 Background

For many years MDR-TB patients have been treated with a World Health Organization (WHO) recommended conventional MDR-TB regimen which generally has an intensive phase of treatment of 8 months and a total duration of treatment of 20 months. Since the WHO "Rapid Communication" of August 2018, patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and for whom resistance to FQs was excluded or considered to be highly unlikely, a shorter treatment regimen (STR), including a second-line injectable agent, could be used instead of a longer (preferably all-oral) regimen.[6] The recommended STR was composed of a later generation FQ (high dose), clofazimine (Cfz), pyrazinamide and ethambutol throughout, supplemented by amikacin, protionamide, and high-dose isoniazid in the intensive phase. The treatment duration of the intensive phase is four months (extended to a maximum of six months until sputum smear conversion), and the duration of the continuation phase is five months. This regimen was evaluated in Stage 1 of the STREAM trial. The most recent WHO Guidelines on the treatment of drug-resistant tuberculosis, released in June 2020, recommends countries to replace the injectable in this regimen with Bdq, with the use of an all-oral Bdq-containing STR as the preferred treatment option. The guidelines also include updates for the recommended all oral longer treatment regimen related to the safety of Bdq use for longer than 6 months, concurrent use of Bdq with delamanid (Dlm), and the use of Bdq during pregnancy. There is another new section in the guidelines with recommendations on the use of the "bedaquiline, pretomanid and linezolid" (BPaL) regimen under OR conditions. The guidelines stress the increased requirements for drug susceptibility testing (DST) and active TB drug safety monitoring and management (aDSM).[7]

Patients with extensively drug-resistant tuberculosis (XDR-TB – MDR-TB patients with additional resistance to any FQ and any second-line injectable agent)[3] traditionally had even fewer treatment options and no standard treatment regimen. Published success rates for treatment of XDR-TB were low and consistent across South Africa, averaging 14% and ranging from 2 to 22%.[8,9]

In addition to the shorter all-oral Bdq-containing MDR/RR-TB regimen recommended by the WHO, there are other shorter regimens currently being evaluated in clinical trials for the same and/or different patient groups. Many of these regimens employ new or repurposed medicines and appear to have common desirable features: good tolerability, all-oral and with shorter treatment duration.

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[6] WHO. *Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. August 2018*

[7] WHO. WHO consolidated guidelines on tuberculosis. Module 4: Treatment. Drug-resistant tuberculosis treatment, 2020. Available from: https://www.who.int/publications/i?healthtopics=6ddcec69-ad73-435e-af81-4a10bc4e921a

[8] Gandhi NR, Moll A, Sturm, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368: 1575-80.

[9] O'Donnell MR, Padayatchi N, Kvasnovsky C, et al. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis* 2013; 19: 416-24.

This operational research protocol concerns a prospective cohort study using the BPaL treatment regimen. This regimen, sponsored by the TB Alliance, was trialed for use in patients with XDR-TB, or intolerance or failure of an MDR-TB treatment regimen, in the Nix-TB study.[3] The regimen consists of Bdq, Pa and Lzd given for 6 months with the possibility to extend the duration to 9 months. Final results of the study were published in the New England Journal of Medicine in March 2020. At 6 months after the end of treatment in the intention-to-treat analysis, 11 patients (10%) had an unfavorable outcome and 98 patients (90%; 95% confidence interval (CI), 83-95) had a favorable outcome.[4] Based on the outcomes of this study, in August 2019 the US FDA and in March 2020 the CHMP of the EMA, have recommended approval of the new drug pretomanid for the treatment of pulmonary XDR-TB or treatment-intolerant or non-responsive MDR-TB, in a combination with Bdq and Lzd.

In May 2022, WHO issued a "Rapid communication: Key changes to the treatment of drug-resistant tuberculosis" which mainly dealt with the analysis of data from the Nix, Zenix and TB PRACTECAL trials and upcoming changes in WHO's recommendations in relation to the programmatic use of BPaL-based regimens in DR-TB patients. The "Rapid Communication" deals also with the issues of the optimal linezolid dose to be used and the further evidence that now shows any earlier concerns of the potential risk of using pretomanid to male reproductive health are unfounded. These 2 topics and other areas have necessitated an updating of the Version 4 (October 2021) of the generic BPaL OR protocol.

2 DR-TB in (Country Name)

2.1 DR-TB epidemiology (Country specifics)

Hr-TB, RR-TB, MDR-TB, MDR-TB plus FQ resistance, and XDR-TB

2.2 DR-TB treatment (Country specifics) …

Table 1. Currently used DR-TB treatment regimens.

Regimen	Composition	Duration
Shorter Regimen		
Longer Regimen		
Individualized Regimen		

2.3 Health financing, social protection and drug procurement (Country specifics)

3 Evidence on the drugs proposed in this study [10]

The characteristics of new and repurposed drugs proposed in this study are described in this section in alphabetical order.

3.1 Bedaquiline

Chemical composition and dosing

Bdq fumarate (bedaquiline or SIRTURO™) is a diarylquinoline anti-mycobacterial drug. It inhibits adenosine triphosphate synthesis, a novel mechanism of action. The drug has a 5.5-month half-life. It is indicated for use against MDR-TB (US FDA, EMA). Bdq requires a loading dose of 400 mg daily for 14 days followed by a maintenance dosing of 200 mg thrice weekly. However, rigorous evaluation of the safest and most effective dose, the dose response relative to TB outcomes, the singular contribution of Bdq when added to other active drugs in a regimen, and the use of Bdq together with other new anti-TB drugs is as yet quite limited.

Efficacy

Strong bactericidal and sterilizing activity against *Mycobacterium tuberculosis (M.tb)* organisms have been shown in both pre-clinical laboratory setting as well as in animal experiments. Data gathered from a clinical trial and operational studies provided enough evidence to classify this agent in the group A during the 2019 revision of the WHO guidelines. There is reported cross-resistance of Bdq with Cfz due to mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump. Bdq shows linear pharmacokinetics and better absorption when the drug is taken with food versus when taken fasting (resulting in approximately a two-fold increase in serum drug levels).

Safety and tolerability

The phase IIB trial of Bdq found higher all-cause mortality among persons who received Bdq compared with placebo - although recent research has shown that Bdq-containing regimens were associated with lower risk of death compared to those regimens not containing Bdq when used in a programmatic setting.[11] Bdq is associated with QTc prolongation in 5-20% of persons who have received the drug. Such QTc prolongation has not yet been associated with an increase in fatal arrhythmias but it does warrant careful monitoring. Bdq may also be associated with elevated transaminase levels but that has been reported with multiple drugs used for the treatment of MDR-TB. For patients on Bdq, it is essential that a baseline QTc interval be assessed with regular follow-up while on the drug and the continued monitoring of liver function.

In people living with HIV, anti-retroviral treatment (ARV) with efavirenz, should be considered with caution. Based on a single dose study, it appears to reduce the amount of Bdq by inducing CYP3A4. Knowledge about the safety of Bdq in pregnancy and while

[10] ShORRT Generic protocol v1 December 2019

[11] Schnippel K, Njdeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018; 6: 699-706.

breastfeeding is sparse. The FDA has therefore classified it as Category B as animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. However, recent programmatic data from 58 mothers in South Africa who received Bdq as part of a longer treatment regimen during pregnancy, showed that fetal exposure in utero was associated with lower mean birth weight (<2500 gm) compared to infants whose mothers did not take Bdq. However, this did not appear to be clinically significant, and was not associated with other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in the infants until 1 year of age.[6]

3.2 Linezolid

Chemical composition and dosing

Linezolid (Lzd) is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by binding 23S ribosomal RNA, and is active in vitro against M. tuberculosis, including MDR and XDR-TB strains, at concentrations of 1 µg/mL or less in most studies. Lzd has been used in combination with other second-line anti-TB drugs and re-purposed drugs for the treatment of MDR-TB and XDR-TB with variable success. However, rigorous evaluation of the safest and most effective dose, the dose response relative to TB outcomes, the singular contribution of Lzd when added to other active drugs in a regimen, and the use of Lzd together with other new anti-TB drugs are as yet all quite limited.

Linezolid was originally developed to treat serious non-*M.tb* bacterial infections, at a dose up to 600 mg twice daily. Currently it is recommended that the drug be started at a dose of 600 mg daily and given for the entire course of therapy: linezolid can either be decreased to 300 mg daily or stopped if limiting toxicity develops. During the Nix-TB study, a dose of 1200 mg daily was used for Lzd with the option to reduce or stop after one month of treatment in case of toxicity (more details on dosing in this pilot study are included in paragraph 7.1 and 8.1).

Efficacy

Linezolid is an antibiotic that has been demonstrated in two randomized controlled trials and in observational studies to increase culture conversion and treatment success in DR-TB patients. It is viewed to be an effective agent, but its use is limited by safety concerns (see below). This drug is classified in the group A of agents for the treatment of MDR-TB in the consolidated 2019 WHO MDR-TB guidelines.

Safety and tolerability

The toxicity profile of linezolid – which includes myelosuppression, optic neuritis, neuropathy, and lactic acidosis – limits its use. Studies have shown that treatment limiting toxicity i.e. discontinuation of linezolid use can occur in as many as 18% of persons who receive treatment with linezolid.[12] Adverse events appear to be more frequent when

[12] Singh B, Cocker D, Ryan H, Sloan DJ. Linezolid for drug-resistant pulmonary tuberculosis. *Cochrane Database of Systematic Reviews* 2019, Issue 3.

linezolid is given at doses of more than 600 mg a day, but they can usually be identified early with routine monitoring and are often reversible upon discontinuation of the drug or lowering of the dose.[13] Knowledge about the safety of linezolid during pregnancy and breastfeeding is limited so caution is advised.

3.3 Pretomanid

Chemical composition and dosing

Pretomanid is a nitroimidazole and it is a prodrug that is metabolically activated by a nitroreductase, producing various metabolites that are responsible for its therapeutic action. Pretomanid inhibits cell wall biosynthesis and under anaerobic conditions, it causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species. Pretomanid was approved in August 2019 by the US FDA and in March 2020, the CHMP of the EMA, in combination with bedaquiline and linezolid as part of the BPaL regimen (also referred to as Nix-TB), an all-oral 6-9 months regimen for the treatment of XDR-TB or treatment-intolerant/non-responsive MDR-TB patients. The dose of pretomanid in the Nix-TB study was 200 mg daily.

Safety and effectiveness [14]

Phase 2 Early Bactericidal Activity studies established that pretomanid has *M.tb* bactericidal activity as a single drug in addition to the efficacy demonstrated in the Nix trial.[4, 15] As yet the safety and effectiveness of pretomanid have not been established for its use in combination with drugs *other* than bedaquiline and linezolid as part of the recommended dosing regimen.

Pretomanid as part of the BPaL regimen has been tested in drug-resistant TB patients co-infected with HIV, including those receiving antiretrovirals. In animal studies, pretomanid caused testicular atrophy and impaired fertility in male rats but not in monkeys. Further evidence obtained now clearly shows that the concern about the potential risk to male fertility by use of pretomanid is unfounded.[16, 17] There are no data available on the use of pretomanid in pregnant women.

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[13] Lifan Z, Sainan B, Feng S, Siyan Z, Xiaoqing L. Linezolid for the treatment of extensively drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2019; 23(12):1293–1307.

[14] www.tballiance.org/access/pretomanid-and-bpal-regimen

[15] Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14-Day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; 380: 986-93.

[16] Burke A, Alffenaar J, Denholm J. Evidence of safety for pretomanid and male reproductive health. Editorial. Int J Tuberc Lung Dis 2022; 26(6):473–474.

[17] Boekelheide K, Olugbosi M, Nedelman J, et al. Male reproductive hormones in patients treated with pretomanid. Int J Tuberc Lung Dis 2022; 26(6): 558-565.

4 Type of study

This is a prospective observational cohort study.

5 Study objectives

Primary objectives:

- To estimate the effectiveness of the BPaL regimen by assessing the end of treatment outcome among patients treated with the regimen
- To estimate the safety of the BPaL regimen by determining the rates of serious adverse events (SAE)

Secondary objectives:

- To determine the time to sputum culture conversion among patients treated with the BPaL regimen
- To determine the proportion of patients with recurrence-free 6 and 12 months after the successful treatment with the BPaL regimen.
- To determine the proportion of patients treated with the BPaL regimen who experience adverse events of special interest (AESI): QT-prolongation, hepatotoxicity, myelosuppression, optic neuritis, and peripheral neuropathy

6 Patient selection

All TB patients will be assessed using a triage approach, see Figure 1. It is preferable that all detected TB patients are tested for both FL and SL resistance, using rapid molecular methods (including Xpert/XDR cartridge once available). If this is not feasible, SL DST could be limited to only those TB patients who have detected H and/or R resistance. A culture isolate obtained from a sample collected prior to the start of the BPaL treatment will be frozen for each enrolled patient for further analysis once pDST methods for Bdq, Pa and Lzd are available, and for comparison of genotype and resistance conferring mutations in case of possible relapse wherever possible.

6.1 Inclusion criteria

A patient, who:

1. is diagnosed with TB in any of the following circumstances:
    a. has a laboratory-confirmed (rapid and/or phenotypic DST) resistance to at least rifampicin and fluoroquinolones (i.e Pre-XDR-TB)* within the last three months# of the screening date; or
    b. has strong clinical and radiological evidence of active TB AND has been a close household contact of an index patient with a laboratory-confirmed resistant TB to at least rifampicin and fluoroquinolones and no documented resistance to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid) within the last three months# of the screening date; or
    c. Has been treated for MDR/RR-TB, has documented non-response$ to treatment, has bacteriologically confirmed active TB (irrespective of resistance to FQ) within the last three months# of the screening date, and a decision has been made by the Expert Committee to shift the patient to the BPaL regimen; or
    d. Has been treated for MDR/RR-TB, has documented intolerance to treatment,+ has bacteriologically confirmed active TB (irrespective of resistance to FQ) within the last three months# of the screening date and a decision has been made by the Expert Committee to shift the patient to the BPaL regimen; and
2. is at least 18 years old at the time of enrolment; and
3. is willing and able to give informed consent to be enrolled in the operational research (OR) and adhere to the OR procedures and the follow-up schedule (signed or witnessed consent if illiterate).

Notes

* In early 2021, WHO issued a "Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020". Pre-extensively drug-resistant tuberculosis (Pre-XDR-TB is defined as TB caused by M.tb strains that fulfil the definition of MDR/RR-TB and that are also resistant to any FQ (Lfx or Mfx). Extensively drug-resistant tuberculosis (XDR-TB) is now defined as TB caused by M.tb strains that fulfil the definition of MDR/RR-TB and that are also resistant to any FQ and at least one additional Group A drug. The Group A drugs are currently Lfx or Mfx, Bdq and Lzd; therefore, XDR-TB is MDR/RR-TB that is resistant to a FQ and either Bdq or Lzd (or both). The Group A drugs may change in the future; therefore, the terminology "Group A" is appropriate here and will apply to any Group A drugs in the future.

Otherwise Xpert and 2nd line LPA testing or Xpert must be done for the patient before enrollment in the study. Documented proof of active TB (LPA or culture) is required within the last 3 months before deciding that a patient is eligible for the BPaL regimen, regardless of history or timing of previous TB treatment. If the patient has not been on treatment during the previous 3 months, a repeat LPA, culture, and pDST are needed.

$ Non-response is defined as: a) two consecutive positive cultures of sputum samples collected after the end of the 2nd month (separated by 30 days) of treatment with lack of clinical improvement or deterioration; or b) treatment outcome of "failure" according to the

WHO definition. A DST should be performed immediately and an individualized treatment regimen or BPaL is to be used. If Bdq or Lzd or Dlm have been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs is required for the patient to be eligible for BPaL regardless of the timing of the previous exposure, with the respective Expert TB Committee subsequently deciding whether the patient is to be enrolled on BPaL.

[+] Intolerance is defined as: Inability to continue the second line MDR-/RR-TB regimen due to a documented adverse event to any of the component drugs. If Bdq or Lzd or Dlm have been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs is required for the patient to be eligible for BPaL regardless of the previous exposure, with the respective Expert TB Committee subsequently to decide whether the patient is to be enrolled on BPaL. However, if either bedaquiline or linezolid is the suspected drug causing the intolerance, the patient is immediately deemed to be ineligible for the BPaL regimen.

6.2 Exclusion criteria

A patient, who:

1. has been previously exposed to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid) or delamanid (Dlm) for more than four weeks unless DST confirms susceptibility to these drugs;[&] or
2. has DST showing infection with a strain resistant to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid); or
3. has a known allergy to any of the BPaL component drugs; or
4. has a known severe adverse event associated to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid); or
5. has a form of extrapulmonary TB that would require treatment longer than would be usual for pulmonary TB (e.g TB meningitis, other central nervous system (CNS) TB, or TB osteomyelitis); or
6. is unable to take oral medications; or
7. has body weight of <35 kgs; or
8. is pregnant; or
9. has childbearing ability and is reluctant to use effective contraception whilst on the BPaL treatment regimen; or
10. is breastfeeding; and
11. The expert committee decides that it is not in the best interest of the patient to be enrolled on the BPaL OR due to the necessity of an individualized TB treatment regimen.

Notes

[&] A DST should be performed immediately and an individualized treatment regimen or BPaL can be used. If Bdq or Lzd or Dlm have been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs is required for the patient to be eligible for BPaL regardless of the timing of the previous exposure, with the respective Expert TB Committee subsequently to decide whether the patient is to be enrolled on BPaL.

Figure 1. Patient Triage Algorithm

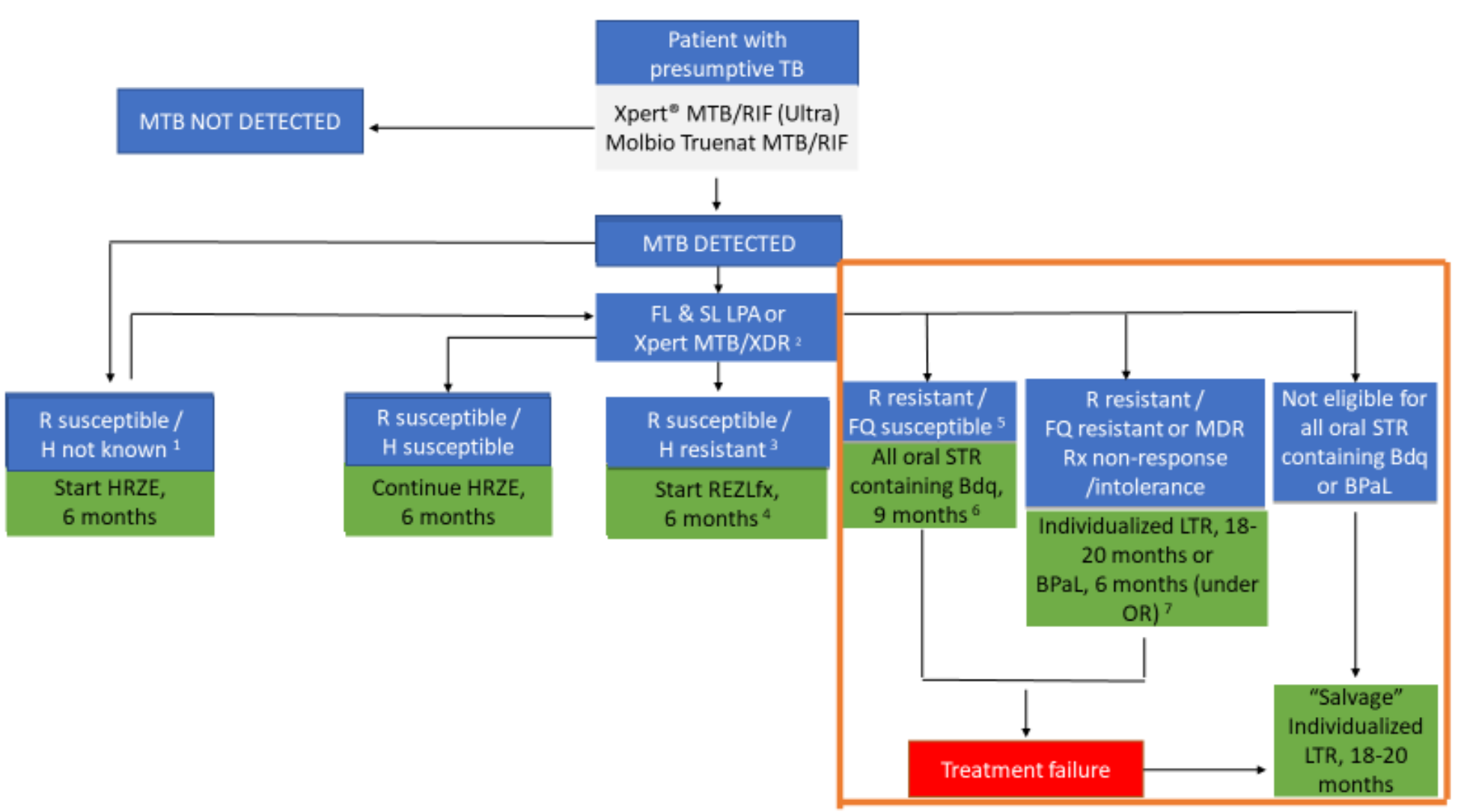

Figure 1 footnotes

[1] Preferable to have DST result for H before treatment, but treatment should not be delayed if the result is unavailable.

[2] Preferably all detected TB patients are tested for both FL and SL resistance. If not feasible, SL DST could be limited to only those TB patients who have detected H and/or R resistance. Treatment initiation for DR-TB patients should not be delayed while waiting for results with a 2-weeks cut-off timeframe for result → safety of treatment "delay" to be judged by expert group / Concilium.

[3] Preferable to have ruled out FQ resistance prior to starting the 6REZLfx regimen. If H resistance demonstrated after one month of HRZE treatment, need to repeat DST for R and treat according to the DST result.

[4] Or according to National guidelines.

[5] If the patient is detected to be H resistance with both *inhA* and *katG* mutations present, then they should not receive the all-oral STR.

[6] Eligibility criteria as per WHO's June 2020 Guidelines on treatment of DR-TB. Standardized all-oral STR may be used under programmatic conditions, other all-oral STRs under OR conditions.

[7] Eligibility criteria as per WHO's June 2020 Guidelines on treatment of DR-TB or as per National policy and capacity.

6.3 Contraindications

There are relative contraindications for the BPaL regimen. Some of the most relevant of these are listed in Table 2. If the clinician judges that the potential benefits outweigh the potential risk (considering alternative treatment options also) treatment may proceed with caution as part of the OR study. In these situations, advice needs to be sought from the assigned expert TB committee.

Table 2. Selected relative contraindications to the use of the BPaL treatment regimen for patients with DR-TB

Relative contraindication	**Notes**
Concurrent use of medications that have known interactions or overlapping toxicities with BPaL component drugs	Inducers of CYP450 enzymes: • Efavirenz • Rifamycin • Antiepileptics Inhibitors of CYP450 enzymes: • Ritonavir-boosted PIs • Fluconazole/itraconazole • Clarithromycin/erythromycin First line TB drugs (HRZE) Drugs that prolong the QT interval (refer to

Relative contraindication	Notes
	https://crediblemeds.org/new-drug-list/). Drugs that increase serotonin levels (refer to https://www.msdmanuals.com/professional/multimedia/table/v1114640)
High risk of cardiac arrhythmia	Baseline QTcF > 500ms History of syncopal episodes, ventricular arrhythmias, heart failure or severe coronary artery disease Family history of long-QT syndrome
Severe anaemia Moderate thrombocytopaenia Moderate neutropaenia	Haemoglobin level < 8.0 g/dL Platelet count <75,000/mm3 Absolute neutrophil count < 1000/ mm3
Severe peripheral neuropathy	Grade 3 or Grade 4, according to the Division of Microbiology and Infectious Diseases (DMID) [18]
Evidence of hepatic impairment	AST/ALT > 3.0 x ULN Total bilirubin > 2.0 x ULN Albumin < 32 g/L
Significant renal insufficiency	Serum creatinine > 3.0 x ULN No dose adjustment, other than an interruption for an adverse event, should be made for Bdq or Pa. Lzd dose reductions, interruptions or discontinuations are allowed (see section 8.1). Primary metabolites of Lzd accumulate in patients with renal impairment and the clinical significance of this is unknown. Due to limited experience, caution should be exercised in patients with significant renal impairment.

6.4 Special circumstances

Use of the BPaL regimen in adolescents, patients with extrapulmonary TB and those living with HIV, may be considered under this protocol by balancing the benefits with the risks, and with the advice of an assigned expert TB committee. Considerations in these circumstances are described in Table 3.

[18] Paresthesia grade 3: severe discomfort; narcotic analgesia required with symptomatic improvement; and /or BPNS subjective sensory neuropathy scare 7-10 on any side. Grade 4: incapacitating; or not responsive to narcotic analgesia.

Table 3. Notes on the use of the BPaL regimen in special circumstances.

Circumstance	Notes
Adolescents	Bdq is recommended for use in patients aged 6 and over by the WHO,[19] and Lzd for all ages. There is no recommendation for Pa. Adolescents from 15 years of age could be included in treatment with the BPaL regimen on the decision of the respective Expert TB Committee.
Extrapulmonary TB	Meningitis / CNS TB • There is limited experience of use of the BPaL regimen. • CNS infections usually require a longer course of treatment than pulmonary TB • BPaL regimen should not be used for treatment of CNS TB Osteomyelitis • There is limited experience of use of the BPaL regimen. • These infections often warrant extended treatment durations, in which case BPaL should not be used. Patients with other "minor" forms of extrapulmonary TB can be included for treatment with BPaL on the decision of the respective Expert TB Committee. Consideration should be given to the planned duration of treatment, and any planned strategies for monitoring treatment response in the absence of sputum testing.
HIV infection	People living with HIV may be included for treatment with the BPaL treatment regimen. In the Nix-TB study, 50% of participants were HIV-positive and treatment outcomes were similar between groups. There are two important drug-drug interactions between antiretroviral drugs and bedaquiline, also mentioned above: • Efavirenz: induces metabolism of Bdq, reducing drug levels • Ritonavir: inhibits metabolism of Bdq, increasing drug levels Antiretroviral therapy regimens including these drugs should be modified at least one week before commencing an HIV-positive patient on treatment with BPaL. Antiretroviral therapy including zidovudine should be used with special caution as zidovudine and linezolid may both cause peripheral nerve toxicity and are known to have myelosuppression cross toxicity.

[19] In August 2021, WHO released a "Rapid Communication on updated guidance on the management of tuberculosis in children and adolescents" informing NTPs and other stakeholders that Bdq may be used in children of all ages as part of the shorter all-oral Bdq-containing regimen or as part of longer treatment regimens. Updated Guidelines and Operational Handbooks are expected to be released by the end of 2021.

6.5 Informed consent

Patients who are eligible for inclusion in the study will be given information about MDR-/Pre-XDR-TB and the BPaL treatment regimen. Patients will be provided with information in a language that is understandable to them. Consent for enrolment should be based on a Patient Information Sheet. Patients should have the opportunity to discuss the Patient Information Sheet with the medical officer/treatment supporter. The patients will be assured that their decision to participate in the study or not will not affect the quality of care they will receive. Once the patient agrees to participate in the pilot project, the patient will be asked to sign the consent form.

All patients who are not eligible for the study, or refuse to be enrolled, or withdraw after enrolment, will be managed with a DR-TB treatment regimen according to the national guidelines.

6.6 Treatment sites and number of patients (Country Specifics)

7 Treatment of patients

7.1 Dosing

Suggested dosing of BPaL component drugs for adults *[and adolescents]* is described in Table 4.

Table 4. Dosing of component drugs for adults (aged 18 and over) [and adolescents] based on a minimum of 26 weeks treatment.

Drug	Dose	Total number of tablets
Bedaquiline (100 mg tablets) [@]	400 mg once daily for 2 weeks, then 200 mg 3 times per week for 24 weeks afterwards	200
Pretomanid (200 mg tablets)	200 mg once daily	182
Linezolid (600 mg tablets)	600 mg once daily	182

Notes

[@] If a patient who is eligible for the BPaL regimen but has recently taken the WHO-recommended Bdq-containing all-oral STR, a concern would be whether the patient may have developed resistance to Bdq. If Bdq has been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs (Bdq, plus Lzd if used in previous regimen) is required for the patient to be eligible for BPaL regardless of the timing of the previous exposure. The respective Expert TB Committee needs to review the individual patient and decide whether the patient can be enrolled on BPaL.

However, as Bdq DST may not always be available, there will need to be an individual patient judgement on their risk of exposure having led to resistance developing based on drug history and response:

Dosing recommendations after interruption of Bdq

Interruption at week	Duration of interruption	Required loading dose
1 -2 (during loading)	≤ 2 weeks	Finish remaining loading days, then continue with Bdq 200 mg/day thrice weekly until end of treatment
1 -2 (during loading)	> 2 weeks	1 week of 400 mg/day
≥ 3	≤ 2 weeks	No need for reloading, proceed with Bdq 200 mg/day thrice weekly until end of treatment
≥ 3	> 2 weeks – < 6 months	1 week of 400 mg/day, then continue with Bdq 200 mg/day thrice weekly until end of treatment
≥ 3	> 6 months	2 weeks of 400 mg/day, then continue with Bdq 200 mg/day thrice weekly until end of treatment

If the patient has been treated for MDR/RR-TB with a Bdq-containing regimen for more than 4 weeks, susceptibility to Bdq (plus Lzd if used in previous regimen for more than 4 weeks) is required for the patient to be eligible for BPaL. If DST shows susceptibility to Bdq (and Lzd) and there is no documented intolerance to Bdq (or Lzd), the patient is eligible for BPaL. Bdq should be given throughout the full course of the BPaL regimen i.e **6 to 9 months**. Previous Bdq exposure should not alter the duration of Bdq use in the BPaL regimen. Previous Bdq exposure should only be considered in relation to the adjustment of loading dose of Bdq as described above. Remember: Use of Pa is only recommended as part of the BPaL regimen.

If a patient has had 4 weeks or more of Bdq and/or Lzd, whilst awaiting their DST results to be available, their treatment depends on their clinical condition. Hence:

- If the patient's clinical condition is good and hence the patient can wait for the DST results, stop treatment in the interim and hope for eligibility to a shorter regimen (BPaL/M), as per country policy if allowed; and
- If the patient cannot wait, the best individual longer regimen should be designed and initiated based on WHO guidelines.

More evidence is needed to better understand the resistance patterns in such patients.

The dose of 600mg linezolid (Lzd) daily optimally should be continued throughout the whole duration of the BPaL treatment course. If a patient develops Lzd-induced peripheral neuropathy or myelosuppression, the Lzd should be stopped (see paragraph 8.1. for more details) Dose modifications for Bdq and Pa are not allowed. For more information on managing AEs, a clinical guide has been made available to the study sites.

7.2 Duration

The BPaL regimen is given for a duration of 6-9 months (26 – 39 weeks):

- The standard treatment duration is 6 months.
- If the sputum culture taken after the patient has taken 4 months of treatment is still positive, the patient can receive an additional 3 months of treatment (total 9 months) as long as the patient is clinically well and /or improving. During the Nix-TB trial treatment was extended to 9 months in only 2 out of 109 enrolled patients. Positive cultures after extension of treatment should be dealt with on a 'case by case" basis, considering the clinical response of the patient as well.

7.3 Inpatient and ambulatory treatment

(Describe here organization of treatment management, DOT and treatment support in practice in the country)

Regardless of the treatment modality, all patients will have a case manager and a treatment supporter. Inpatient treatment is not mandatory, but patients may be hospitalized at the initiation of DR-TB treatment for a short period of time to ensure the patient is well informed, baseline tests are done and that patients can tolerate the regimen. The need for admission should also be considered when AEs occur during treatment.

Ambulatory treatment from the onset without initial hospitalization may be feasible in settings where management of DR-TB in the community is strong. Regardless of whether treatment is started ambulatory or during an initial period of hospitalization, all patients will have a trained treatment supporter. DOT will be administered seven days a week throughout the whole treatment course. Ambulatory DOT services will be either “facility-based” in which patients visit a health care facility daily for treatment, or “community-based” in which a trained treatment supporter visits the patients daily for drug administration (or *vice versa*) and accompanies the patient to follow-up visits and liaises with the clinical staff (depending on the country policy). Enablers to cover travel expenditures (and food supplements if relevant) will be provided during the whole treatment course.

In the case of community-based DOT, a trained treatment supporter who is not directly related to the patient will be identified. The treatment supporter has the following responsibilities:

- Strictly administer DOT daily.
- Ensure that the patient attends all scheduled follow-up visits and examinations.
- Monitor AEs closely and address AEs in a timely manner by informing clinical staff.
- Update the patient treatment card daily.
- Initiate contacting the patient if the patient fails to return for treatment as per the schedule.

7.4 Procedure following missed treatment

Interruption of the full BPaL regimen may occur at any time during the treatment period. In cases were the full BPaL regimen is interrupted for more than 35 consecutive days,[20] the patient will be referred to the expert TB clinical committee to decide on further management including need for change to a new individual regimen, based on clinical assessment and reason for interruption. Any missed doses of the full BPaL regimen (including both consecutive and non-consecutive) should be made up to complete 26 or 39 weeks of therapy within a maximum period of 60 days after the intended end of treatment duration. Missed doses of Lzd alone due to AEs, are not to be made up at the end of treatment. See details on the modification and discontinuation of the BPaL regimen and drugs in paragraphs “7.6” and “8.1”.

Interruption of treatment for two months or more in a row will be classified as "lost to follow-up" and in this case the patient will no longer be eligible for further BPaL treatment.

Reasons for missing treatment must be identified and addressed early and noted in the patient’s file for analysis for factors associated with (lack of) treatment success.

[20] Dr. F. Conradie: NiX-TB trial experience: safety reporting and recommendations for programmatic implementation of the regimen. The 50th Union World Conference on Lung Health; 2019 Nov 1; Hyderabad India.

7.5 Examinations at baseline and during treatment

Patients should undergo appropriate evaluation at baseline, during and after treatment. This should include clinical evaluation, bacteriological and laboratory testing, as described in the following Table 5. The baseline visit refers to the beginning of the treatment with the BPaL treatment regimen. The monitoring schedule should be applied to all patients receiving treatment with the BPaL regimen.

Additional remarks:

- Laboratory and ECG monitoring should be continued at monthly intervals (where indicated) for the duration of treatment (i.e up to 9 months in case of treatment prolongation).
- More frequent monitoring may be advisable in specific situations, including elderly people, patients infected with HIV, affected by HBV- or HCV, diabetes mellitus, or with moderate to severe hepatic or renal impairment.
- In case of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed (refer to clinical guidelines).

TABLE 5. SCHEDULE OF BASELINE, TREATMENT AND AFTER TREATMENT EVALUATION					
	Baseline	**2 weeks**	**Monthly**	**End of treatment**	**6- and 12-months after treatment completion**
Clinical evaluation					
Clinical assessment*[1]	X	X	X	X	X
Psychosocial assessment*[2]	X	X	X	X	X
Performance status[3]	X				
Weight / BMI	X	X	X	X	X
Peripheral neuropathy screen[4]	X	X	X	X	X
Chest X-Ray	X		X-If no response to treatment	X	X
ECG	X	X	X	X	X-If indicated
Visual acuity and colour vision screen	X	X	X	X	X
Assessment and follow-up of AEs	X	X	X	X	X
Treatment outcome assessment				X	X
Bacteriological evaluation					
Gene Xpert	X				
Sputum smear	X		X	X	X
Sputum culture[5]	X		X	X	X
Sputum drug susceptibility testing [6]	X		X-If culture positive[7]		
Other sample smear	X		X-If no response to treatment		
Other sample culture	X		X-If no response to treatment		
Other sample drug susceptibility testing	X		X-If culture positive[7]		
Laboratory evaluation					
Full blood count	X	X	X	X	X-if indicated
Liver function tests (AST, ALT, bilirubin)	X	X	X	X	X-if indicated
Thyroid stimulating hormone (TSH)	X		X - if indicated		
Serum electrolytes (Na, K, Ca, Mg)	X		X	X	X-if indicated
Serum amylase			X - if indicated		

TABLE 5. SCHEDULE OF BASELINE, TREATMENT AND AFTER TREATMENT EVALUATION					
	Baseline	**2 weeks**	**Monthly**	**End of treatment**	**6- and 12-months after treatment completion**
Kidney function tests (Urea, Creatinine)	X		X - if indicated		
BSL (fasting or random)[8]	X				
HIV / HBV / HCV tests	X				
CD4/Viral load (if HIV +)[9]	X - if indicated				
Pregnancy test[10]	X		X - if indicated		

* Guidance for physicians, no standardized data collection is required.

[1] Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea, candidiasis, mental status assessment. Clinical assessment should focus on a) monitoring response to treatment and b) addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.
[2] Food security, housing, mental state, substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible per country-specific questionnaires.
[3] Assessed by Karnofsky Performance Status Scale.
[4] Assessed by Brief Peripheral Neuropathy Screen developed and validated by the National Institutes of Health-funded AIDS Clinical Trials Group.
[5] Isolates from all positive cultures collected during every visit, including baseline and after treatment completion, will be stored to allow additional investigations if necessary.
[6] Xpert MTB/RIF, second line LPA, second line pDST, if available, Xpert/XDR, pDST for the BPaL component drugs, and next generation sequencing. A culture collected before the start of BPaL treatment should be stored for each enrolled patient for further analysis once pDST methods for Bdq, Pa, and Lzd are available and for comparison of genotype and resistance-conferring mutations in case of a possible relapse.
[7] Repeat pDST, if the culture still positive at month 4, end of treatment or post-treatment follow up.
[8] If abnormal at baseline, diabetes mellitus should first be ruled out. If a patient is found to have diabetes mellitus, they should be treated and followed up accordingly.
[9] Perform a viral load test if it has not been done within the last 6 months of the study enrollment date. And perform a CD4 count if it has not been done within the last 3 months of the study enrollment date.
[10] Only for women of reproductive age.

7.6 Discontinuation of treatment due to toxicity or treatment failure

The study regimen will be discontinued in some patients. In such cases, patients will be evaluated by the expert TB committee and switched to an individualized regimen, based on the WHO guidelines for regimen design. The most common situations in which the regimen may be discontinued include:

Intolerable Toxicity[21]. In case Bdq and/or Pa need to be suspended permanently owing to intolerable toxicity, the patient will need to be shifted to another regimen as advised by the Expert Committee. In case of intolerable toxicity to Lzd, the drug may be suspended permanently only after completing a total of at least 9 weeks of Lzd treatment with a daily dose of 600mg. A permanent discontinuation of Lzd with a total exposure of less than 9 weeks with 600mg Lzd daily, should be avoided if at all possible, and any proposal to permanently discontinue the Lzd prior to 9 weeks of use needs to be discussed with the Expert Committee. The patient can remain in the BPaL cohort at the discretion of the Expert Committee, considering the clinical response to treatment and the adequacy/duration of Lzd dosing in the patient's regimen. See further details on modification and discontinuation of the BPaL regimen and/or drugs in paragraph "8.1 Safety reporting".

- **Treatment failure**. If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. DST should be repeated if culture is still positive at month 4, whether or not the regimen is changed, in order to inform future management decisions. See details on treatment failed criteria in paragraph 9. Outcome measurement.
- **Resistance to drugs in the BPaL regimen**. For patients who submit a sputum sample for culture-based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to any of the BPaL component drugs is discovered after treatment is initiated, the BPaL regimen must be discontinued and the patient switched to another regimen.
- **Pregnancy during treatment**. For patients who become pregnant during BPaL treatment, it may be advisable to discontinue the BPaL regimen. The patient needs referral to the Expert Committee for review and discussion on future treatment. The patient needs to be involved in any discussions and decision making in relation to future treatment.

7.7 Post treatment follow-up

After completion of treatment, patients will be informed of the risk of recurrent TB and advised to return for clinical assessment, including follow-up of AEs. Patients will also be advised to return for sputum examinations at 6 and 12 months after completion of treatment. A single sputum specimen for smear and culture will be collected at each follow-up visit. If culture positive without clinical signs and symptoms or radiographic deterioration the second sputum specimen will be collected 30 days a part for smear and culture as an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB. These visits at

[21]WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. ISBN 978-92-4-000699-7

months 6 and 12 should also be incorporated into the routine monitoring for DR-TB patients.

8 Detection and management of adverse events

Patients should be screened monthly by a clinician trained in the diagnosis and management of AEs. An AE is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment. AEs may be mild, moderate, severe, or life-threatening.[22]

Most patients taking the BPaL regimen will experience an AE of some kind (in the Nix-TB study, all patients experienced at least one AE). Management of AEs should take patient safety and treatment requirements into consideration. Mild or moderate AEs can usually be managed by using adjunct medications, reducing the dose of Lzd, or temporarily stopping the regimen. For refractory and more severe AEs, one of the BPaL component drugs may need to be permanently discontinued. Each AE should be graded according to the EndTB Pharmacovigilance Severity Grading Scale for AEs.[23] All AEs leading to the study therapy being temporarily or permanently discontinued should be carefully managed and recorded.

8.1 Safety reporting

(Countries should describe the aDSM framework and the (site) specific roles and responsibilities regarding the monitoring, grading, administration, and reporting of AEs will be noted here —by whom, to whom and when)

All serious adverse events (SAEs) should be reported to the relevant national pharmacovigilance authority according to national guidelines (e.g within 72 hours). An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Causes a congenital anomaly or a birth defect
- Is otherwise medically important

When an AE occurs, the investigator responsible for the care of the patient must first assess whether the event is serious. If it is serious, then an SAE form must be completed and sent to the principal investigator and the relevant pharmacovigilance authority.

Modification and discontinuation of the BPaL regimen

Safe management of AEs may warrant modification of the regimen as noted below. However, the BPaL regimen has been studied as a standardized course of treatment.

[22] World Health Organization. Active TB drug safety monitoring and management: framework for implementation. WHO Geneva. WHO/HTM/TB/2015.28

[23] EndTB Severity Grading Scale for Adverse Events, version 5.0. Available from: http://endtb.org/resources/pharmacovigilance

Modification of the regimen through replacement of any of the component drugs or early discontinuation may result in poor treatment outcomes. Favorable results (with 24 months' relapse-free follow up) were achieved in a group of patients who received 4-6 months of Lzd as part of the BPaL regimen. In the Nix trial, patients who had 1200mg total daily dose of Lzd for 4 weeks, were included in the final trial analyses as deemed to have followed the protocol. Although no patient discontinued Lzd permanently during the first month of treatment, 11 did have interruptions or reductions in their Lzd dose during the first month. Of these patients, 2 ultimately died as an outcome (but the death was not in the first month), 1 was un-assessable in the MITT analysis, and 8 had favorable outcomes. The recently completed Zenix trial observed that lower doses and/or shorter durations of linezolid than 1200mg for 6 months appear to have high efficacy and improved safety.

Acceptable modifications in the management of AEs for BPaL regimen:

- Linezolid can be temporarily or permanently interrupted or the dosage can be reduced. However, a permanent discontinuation of Lzd with a total exposure of less than 9 weeks with 600mg Lzd daily, should be avoided and any proposal to permanently discontinue the Lzd prior to 9 weeks of use needs to be discussed with the Expert Committee.
  - Temporary interruption of Lzd or dose reduction from 600mg once daily (while Bdq and Pa are continued) is only allowed after every effort has been made for participants to receive a total of at least nine weeks of treatment with a daily Lzd dose of 600mg. Any interruption or dose reduction should be discussed with the Expert Committee and followed by a careful clinical assessment to observe the effect and managed accordingly, as specified in the clinical guide.
  - If an AE which requires an interruption for more than **14 days** within **the first 9 weeks of treatment with 600mg Lzd daily,** the patient needs to be withdrawn from the BPaL regimen and transferred to an alternative regimen.
  - Permanent discontinuation of Lzd while Bdq and Pa are continued, is only allowed for patients with toxicity issues that prohibit further treatment with Lzd, after every effort has been made for them to receive a total of at least nine weeks of treatment of Lzd with 600mg daily, and evidence of bacteriological and clinical improvement. If not, the patient needs to be withdrawn from the BPaL regimen and transferred to an alternative regimen.
  - If there are toxicities due to Lzd requiring interruption/dose reduction, then the Expert Committee (including external expert) should balance the risk of inadequate treatment and relapse with the burden of additional/prolonged treatment. The regimen may need to be strengthened (and the patient withdrawn from the study).
- If there are any concerns about the clinical progress and response to treatment, then interruptions to Lzd ought to be minimized, or the regimen should be strengthened (and the patient withdrawn from the study).
- Response to treatment must always be closely monitored. Interruptions/reductions to Lzd without clinical improvement should be regarded with additional caution.
- Neither Bdq nor Pa may be interrupted or discontinued alone any time during the treatment. If Bdq or Pa need to be interrupted, then the full BpaL regimen must be interrupted at once. If Bdq or Pa need to be discontinued, then the full BpaL regimen must be discontinued, and the patient transferred to an alternative regimen.
- The doses of Bdq and Pa are fixed (except for the routine reduction of Bdq 400mg daily

to 200mg 3-times a week after the first 14 days of treatment with Bdq), and dose modification of neither medicine is allowed at any time during treatment with the BpaL regimen (only dose modification of Lzd is allowed, according to the restrictions above).

- If an AE occurs during the first four weeks of treatment that does not require a dose modification, interruption, or discontinuation of Lzd, then an interruption of the **FULL BPaL REGIMEN** is allowed for a maximum of 14 days (all three component medicines must be withheld together during this time), after which the **FULL BPaL REGIMEN** should be recommenced, including Lzd 600mg daily. If the interruption exceeds 14 days, the patient must be withdrawn from the BPaL treatment cohort and provided with an alternative regimen.

Any treatment interruptions should be discussed within preferably 1-2 days with the Expert Committee (including external experts whenever necessary), and optimally prior to interruption of treatment.

Based on evidence from the Nix and Zenix trials, mandatory discontinuation of the BPaL regimen as detailed in 7.6 and above may occur and will require the patient to be switched to another regimen. Reasons for this include:

- Permanent discontinuation of Lzd only or dose reduction of Lzd before completion of at least nine weeks of Lzd 600mg daily. However, a permanent discontinuation of Lzd with a total exposure of less than 9 weeks of 600mg Lzd daily, should be avoided and any proposal to permanently discontinue the Lzd prior to 9 weeks of use needs to be discussed with the Expert Committee.
- Permanent discontinuation of either Bdq or Pa.

If a patient is failing treatment, he/she should be referred to the Expert Committee for review and design of a new individualized regimen.

9. Outcome measurement

Patients may be retrospectively removed from the outcome analysis in specific circumstances. Culture conversion and final treatment outcome of cure will not be possible for patients who are truly culture-negative at baseline. However, these patients should continue BPaL and remain part of analysis, but at best they can only be given an outcome of “treatment completed” in the end. They cannot be included in the analysis on culture conversion. The number of such patients and rationale for removal from analysis should be reported.

In general, a culture of any sputum sample obtained up to 90 days before the treatment start date may be used for the baseline culture if the patient has not received treatment during this period.

Outcomes are modified from those included in the *Definitions and reporting framework for tuberculosis (December 2013, updated December 2014)* document released by WHO in

2014.[24] The outcome is assigned on the principle of "first outcome met" and is not revised during the follow up period.

- **Cured**: BPaL treatment completed without evidence of failure AND two or more consecutive cultures taken at least 30 days apart within the last three months of treatment, are negative.
- **Treatment completed**: BPaL treatment completed without evidence of failure BUT no record that two or more consecutive cultures taken at least 30 days within the last three months of treatment, are negative.
- **Treatment stopped due to baseline drug resistance**: Patients who receive culture-based DST results several months after starting the BPaL regimen are to be switched to an individualized regimen if resistance to any of the BPaL component drugs is discovered. For such patients, this outcome should be reported.
- **Treatment failed**:
  - Lack of culture conversion* at the 6th month of treatment, or
  - Culture reversion** at 5th month or later in a patient with previous culture conversion to negative
  - Decision to terminate treatment early because of:
    - poor clinical or radiological response as decided by the expert committee; or
    - permanent discontinuation of either Bdq or Pa, or both at any time due to adverse event; or
    - Permanent discontinuation of Lzd if having less than nine weeks of 600mg daily, due to adverse event.
- **Died**: A patient who dies for any reason during the course of treatment.
- **Lost to follow-up**: A patient whose treatment was interrupted for 2 consecutive months or more.
- **Not evaluated**: A patient for whom no treatment outcome is assigned, including but not limited to patients withdrawn from the BPaL treatment due to the protocol violation.
- **Treatment success**: The sum of cured and treatment completed.

The terms "conversion" and "reversion" of culture results are defined as follows:

*** Conversion** (to negative): culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion.

**** Reversion** (to positive): culture is considered to have reverted to positive when after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive.

"Recurrent TB" is defined as being either of the following circumstances any time after cure or completion of treatment is declared:

- Two consecutive positive cultures at least 30 days apart, or
- One positive culture with clinical signs and symptoms or radiographic deterioration

[24] World Health Organization. Definitions and reporting framework for tuberculosis (updated December 2014). WHO-Geneva. HO/HTM/TB/2013.2

(an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB).

If genotyping is available, recurrent TB may be further classified as relapse, reinfection, or undetermined as defined below:

- **Relapse**: isolates of the recurrent episode share the same genotype pattern with isolates taken at baseline of the most recent episode of MDR-TB.
- **Reinfection**: isolates of the recurrent episode and isolates taken at baseline of the most recent episode of MDR-TB have different genotype patterns.
- **Undetermined:** there is insufficient information to determine whether the recurrent episode is due to relapse or reinfection.

10. Protocol Deviations and violations [25]

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol whether by the subject or investigator.

A protocol violation is any change, divergence, or departure from the study design or procedures defined in the protocol, whether by the subject or investigator, that may significantly impact the completeness, accuracy, and reliability of the study data or affect a subject's rights, safety, or well-being substantially.

Examples of the protocol deviation:

- Patient missed 14 days on treatment with good clinical progress;
- Patient enrolled on treatment without baseline Hep C testing;
- Patient missed 14 days of treatment in every month of the first 3 months; or
- The patient fails to complete a maximum of 14 doses out of all required BPaL treatment doses within 60 days after the intended end of the BPaL treatment.

A patient who has a protocol deviation, is to be referred to and discussed at the Expert Committee in regard to their further BPaL treatment.

Examples of the protocol violation:

- Patient started on treatment without baseline ECG and following ECG monitoring not conducted;
- Patient misses total of >14 doses within the first four weeks of the BPaL treatment;
- Patient misses >35 consecutive doses of the BPaL treatment; or
- Patient fails to complete required number of the BPaL treatment doses within maximum period 60 days after intended end of the treatment.

A patient who has a protocol violation, is to be removed from the BPaL OR cohort, and referred to and discussed at the Expert Committee in regard to the starting of an alternative treatment regimen.

11. Data management and project monitoring

The principle is that the existing recording and reporting system of the country will be used. Hence patient data will be recorded on the programmatic treatment cards and documents However additional elements will be needed for example additional data collection forms are created for the purpose of this study for the elements not included in the national recording system.

The objectives of project monitoring are:

- To ensure that people's rights are protected and that the conduct of the operational research is following the approved protocol.

[25] https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-5.pdf

- To identify constraints in the identification of presumptive MDR-TB patients, sputum examinations, diagnosis by drug susceptibility pattern, identification of eligible patients for the BPaL regimen, timely enrolment, pre-treatment assessment, initiation of treatment, management of AEs, monitoring examinations during treatment, storage status of cultured isolates, DOT services in the community, contacting of patients late for their planned appointments, and assessment of outcome of treatment. Information can be collected via routine field supervision and monitoring activities and use of the quality improvement checklist (developed by KNCV under the Challenge TB Project).
- To verify that the reported data are complete, timely and accurate.

Newly enrolled patients are reviewed weekly by a clinical team at the site with supervision from the programme manager or technical advisor; progress of patient on treatment is reviewed on a quarterly basis by the expert committee, NTP and study partners. (To be adapted for the country setting).

Data will be aggregated across countries and analysed on a quarterly basis and will be shared with national health authorities, stakeholders, and the larger scientific community with the aim to influence and improve MDR-TB treatment within the country and globally.

12. Human subjects' protection

The study will follow the principles of the Declaration of Helsinki.[26] The study protocol will be submitted to the relevant ethics review committee for it's approval prior to initiation of the study. No patient will be enrolled into this study until the investigator has obtained the patient's informed consent.

[26] WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

13. Indicators

The study will use the following indicators to monitor BPaL treatment coverage and treatment success every quarter. The study will mainstream gender-disaggregated data to analyze the BPaL treatment coverage, effectiveness, and safety.

Treatment Coverage Indicators	
1	Number of patients screened for eligibility for enrollment on the BPaL regimen
2	Number and proportion of patients eligible for enrolment on the BPaL regimen from all the screened
3	Number and proportion of patients enrolled on the BPaL regimen from all the eligible
Treatment Safety Indicators[27]	
1	Number and proportion of enrolled patients with SAE(s)
2	Number and proportion of enrolled patients with AESI(s)
3	Number and proportion of enrolled patients with permanent dose reduction of Lzd due to AE(s)
4	Number and proportion of enrolled patients with temporary interruption of Lzd due to AE(s)
5	Number and proportion of enrolled patients with permanent interruption of Lzd due to AE(s)
6	Number and proportion of enrolled patients with temporary interruption of the BPaL regimen due to AE(s)
7	Number and proportion of enrolled patients with permanent interruption of the BPaL regimen due to AE(s)
8	Number and proportion of enrolled patient who died during the BPaL treatment
Treatment effectiveness Indicators	
1	Number and proportion of enrolled patients with sputum smear conversion after 2 months of treatment with BPaL regimen
2	Number and proportion of enrolled patients with sputum smear conversion after 6 months of treatment with BPaL regimen
3	Number and proportion of enrolled patients with sputum culture conversion after 2 months of treatment with BPaL regimen
4	Number and proportion of enrolled patients with sputum culture conversion after 6 months of treatment with BPaL regimen
5	Number and proportion of enrolled patients required the BPaL treatment duration extension from 26 to 39 weeks
6	Number and proportion of enrolled patients with successful treatment outcome ("cure" and "treatment completion") after full course of treatment with the BPaL regimen
7	Number and proportion of enrolled patients with TB recurrence at 6 months after the end of a full course of treatment with the BPaL regimen
8	Number and proportion of enrolled patients with TB recurrence at 12 months after the end of a full course of treatment with the BPaL regimen

[27] Indicators in this category are not mutually exclusive.

Annex 1. Informed consent or assent form

Part I. Patient Information Sheet BPaL regimen

Introduction

You are being invited to take part in a research study, the details of which are described in this information sheet. This study is being conducted at _____. Before you decide to take part in this study, it is important for you to understand why the research is being done and what it will involve. A member of our study team will talk to you about the study and answer any questions that you may have.

Please take time to read the following information carefully and discuss it with relatives, friends, and your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to participate. After you are properly satisfied that you understand this study, and all your queries/questions have been satisfactorily answered, and that you wish to participate, you must sign an informed consent form attached with this information sheet. Your participation in this study is voluntary. This means you will take part in the study if you want to or decide to do so out of your own choice. You do not have to be in this study if you do not want to. Even if you decide to participate in this study, you may withdraw (take back your decision to participate) from this study at any time during the course of the study. Your refusal to participate or withdrawal will not affect any medical or health benefits.

What is the purpose of this study?

As you may know, TB is a disease caused by bacteria usually affecting the lungs and spreads from person to person through air, when he or she coughs or sneezes. TB is treatable; however, some TB bacteria stop responding to the two most important and commonly used anti-TB medicines (isoniazid and rifampicin), and this is called multi-drug resistant tuberculosis (MDR-TB). Furthermore bacteria may develop resistance to more drugs e.g. fluoroquinolones, which is called pre-extensively drug-resistant (Pre-XDR-TB).

Current treatment of Pre-XDR-TB involves the use of less common anti-TB drugs (also known as second-line drugs) for long treatment durations which may extend up to two years and with more side effects and less chance of cure. Therefore, new TB drugs and novel regimens are urgently required to enable faster, safer and more effective treatment for persons with drug-resistant TB. A new regimen that is now available in (Country Name) is called BPaL. Its anti-TB effects have been tested previously in human beings in a study in South Africa, including patients suffering from XDR-TB or patients with intolerance or failure of MDR-TB treatment and was approved for use in these patient groups. It has been found effective and side effects were manageable. Treatment duration is only 6 months and the pill burden is lower than the currently used regimens. The purpose of this study is to evaluate the ability of this short BPaL regimen to kill TB bacteria (antibacterial activity) and the safety of this regimen in pre-XDR-TB patients and patients with intolerance or failure of MDR-TB treatment in

(Country Name). This study will be conducted at X sites in the country and only include patients ≥ 18 years.

Why have I been chosen?
You are being invited to participate in this study since you have been diagnosed with pre-XDR-TB or you have a documented intolerance or failure to the currently used MDR-TB treatment regimen. It is up to you to decide whether or not to take part in this study. Before starting the treatment with the BPaL regimen we will perform a set of baseline tests, similar to patients treated with other DR-TB regimens. The results of these tests will determine whether it is safe for you to participate in this study. The tests include a sputum sample for additional TB tests, blood tests for full blood count, glucose, liver and kidney function, test for HIV and hepatitis, ECG, Chest X-ray, vision test and a pregnancy test for women. In addition to the tests, we will also ask you some general questions about your personal life and health. In case you are found not eligible or do not wish to participate in the study you will be treated according to the national guidelines for drug-resistant tuberculosis. If you do decide to take part in the study, you will be given this information sheet to keep and will be asked to sign a consent form.

What is the most important information I should know about the BPaL regimen?

- The BPaL regimen consists of a combination of three drugs: bedaquiline, pretomanid and linezolid. The safety and effectiveness of pretomanid have only been established in this combination and not in combination with other TB drugs.
- Your total participation in this study will be for 6 months, with a possibility to extend the duration of treatment to 9 months (depending on your response to the drugs).
- DR-TB is a serious disease that can result in death, and for which treatment options are limited. It is therefore important to complete the full course of treatment with the BPaL regimen and not skip doses.
- Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will become more resistant and very difficult to treat with other less effective TB medicines.
- Most drugs in the regimen should be taken once a day with food. You will be instructed accordingly.

It is not yet known if the BPaL regimen is safe in:

- Children under 18 years.
- In pregnancy or when breastfeeding.
- In forms of TB that are not drug-resistant.
- In patients with heart, kidney, liver or other health problems.

Before you start treatment with the BPaL regimen, tell your healthcare provider if:

- You have had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem called congenital long QT syndrome.
- You have liver or kidney problems or any other medical conditions such as decreased thyroid gland function or seizures.
- You are HIV-infected. The BPaL regimen can also be used when HIV-infected but your doctor might need to change your ARV regimen to prevent interaction with the TB drugs.
- You are pregnant or plan to become pregnant. If you are pregnant when assessed initially, you will not be treated with the BPaL regimen. If you become pregnant whilst on BPaL treatment, your health care provider may decide to continue or discontinue the BPaL regimen following discussions with yourself and a team of clinical experts.
- You are breastfeeding or plan to breastfeed. It is not known if the BPaL regimen passes into breast milk.
- You are taking any prescription and nonprescription medicines, vitamins and herbal supplements.

What will happen after the treatment has started?

- You will have to take the treatment daily under supervision at the health care facility or in the community supervised by a treatment supporter.
- If for some reason you miss a dose, inform your treatment supporter right away, and he or she will tell you what to do.
- You will also have to visit the health care center at the study site after 2 weeks and then monthly for 6 – 9 months.
- During these visits, besides physical examination, monitoring tests similar to the baseline tests will be done to see how you respond to treatment and to check for any side effects to the drugs.
- You will also have to come for follow-up visits, 6 and 12 months after finishing the treatment, for a physical examination, sputum test and chest X-ray.

What should I avoid while taking the BPaL regimen?

- You are advised to not drink alcohol while taking this regimen.
- It may not be safe to take some medicines or herbal products while you are on this regimen. Inform your health care provider if you are taking medicines given to you by other health care practitioners.

What are the possible side effects of the BPaL regimen?

The following are serious side effects (unwanted effects on patient's health) which have been known to occur with the three drugs included in this study:

- **Heart rhythm changes.** Tell your health-care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), feel dizzy or if you faint. Your heart will be monitored monthly with an ECG machine that checks that the heart rhythm is normal.

- **Liver problems.** Tell your health care provider of symptoms such as nausea or vomiting, abdominal pain, fever, weakness, itching, unusual tiredness, loss of appetite, light colored bowels, dark colored urine, yellowing of your skin or yellowing of the whites of your eyes. Your blood will be monitored monthly to check on this.
- **Low blood cell counts.** Tell your doctor of symptoms such as tiredness, weakness and looking pale. This can cause anaemia (low red blood cells), leukopenia (low white blood cells) or thrombocytopaenia (low platelet count). Your blood will be monitored monthly to check on this.
- **Nerve problems.** Tell your health care provider if you feel any numbness, "pins and needles" or a burning pain in your extremities. Your doctor will monitor this monthly with a physical examination.
- **Eye problems.** Tell your health care provider if you experience any change in your vision. Your vision will be monitored monthly with a test.
- **Build-up of acid in your blood (lactic acidosis).** Tell your health care provider if you experience recurrent nausea, vomiting or abdominal pains.
- **Other more common side effects** include headache, nausea, vomiting, diarrhea, muscle/joint pain, coughing up blood, abdominal pain, chest pain, acne or rash.

It is possible that the BPaL regimen may also cause some problems that we are not yet aware of, hence it is important to always tell your health care provider of any side effects or problems you experience. Sometimes because of side effects the drugs may need to be adapted or (temporarily) stopped or you can be given other medicines to decrease or prevent the symptoms of the side effect. Most of these side effects were found to be reversible. Missed doses due to safety reasons can be made up at the end of treatment. Your health care provider will advise you on this.

What are the possible risks or benefits of taking part in this study?

Risks:

- It is possible that you will be at greater risk than you would otherwise be of certain side effects due to the drugs.
- It is possible that a side effect could be serious and even result in death.
- There is risk of increased drug resistance if you do not respond to the given treatment.
- There may also be a possibility of failure of the BPaL regimen to provide intended therapeutic effect. In such cases you will be given treatment as per the sputum drug susceptibility results.

Benefits:

- There is a greater chance that you will be cured of drug-resistant tuberculosis with this regimen.
- You will possibly be cured sooner with a shorter duration of only 6 months treatment and a lower pill burden compared to the standard used regimens of 18- 20 months for highly drug resistant TB, however this cannot be guaranteed.

Confidentiality and sharing information

Because BPaL is a new regimen for which we have limited experience, we are collecting information on patients taking them.

- The information we get from this study may help us to treat future patients with drug-resistant TB better.
- The results of clinical tests performed as part of this study will be included in your medical record.
- Isolates from positive cultures will be stored for further analysis and future research to understand the characteristics of drug resistant tuberculosis.
- The information that we collect from you will be kept confidential. Apart from the clinical staff, your records may be checked by the sponsor and/or its representatives or people from the regulatory authorities and ethics committees to ensure that the study is being carried out correctly.
- The information and results from this study, if published in scientific journals or presented at scientific meetings, will be unlinked to your name (made anonymous).

Right to refuse or withdraw

- You do not have to agree to take the BPaL regimen if you do not wish to do so, and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this health care facility in any way. You will still have all the benefits that you would otherwise have.
- If you agree to take the BPaL regimen, you may also at any point after you start wish to stop without losing any of your rights as a patient here. Your treatment at this health care facility will not be affected in any way.
- Also, you may be taken out of the study without your consent based on your doctor's decision. This may happen for the reasons such as, your doctor feels that your continuing participation in the study may be detrimental to your health, or you do not follow doctor's instructions. Even if your participation is terminated, there would be no effect on the regular care being offered to you.

Contact person

If you have any further questions about the study or study related concerns, please contact the responsible health care provider at the study site:

Name: _____

Phone: _____

Part II: Certificate of Consent or assent

Statement from the patient:

I have read the provided Patient Information Sheet, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive the BPaL regimen for treating the drug-resistant tuberculosis disease that I am suffering from.

Print name of patient: _____

Signature or thumbprint of patient: _____

Date: _____ (Day/month/year)

If illiterate, a literate witness must sign. (If possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

Statement from the witness:

I have witnessed the accurate reading of the consent form to the potential recipient of the BPaL regimen, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____

Signature of witness: _____

Date: _____ (Day/month/year)

Statement from the person taking consent:

I confirm that the participant was given an opportunity to ask questions about the treatment, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.
A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____(Day/month/year)
(Footnote [28])

[28] If the expert committee decides to enroll an adolescent (15-17 years of age), then an additional consent from the parents or legal guardian will need to be obtained.

Annex 2. Data collection and entry overview

The OR data will be collected using the specially designed standardized data collection forms (Annex 3). The OR Data collection will occur at the OR sites from multiple sources: patient interview, data abstraction from patient medical cards, routine TB recording (registers and forms), and aDSM systems in (Country Name). Patient interviews will be conducted by the medical doctor specially trained in the OR protocol.

Data from the paper forms will be entered in the specially designed standardized electronic collection system (REDCap, Epi Info, or OpenMRS) with core set of variables for the OR.

If a country decides to use REDCap following information can be included in the protocol and country data management plan (DMP).

REDCap is a user-friendly, cost-effective, and secure platform to capture and manage research study data. It is not open source or freeware, and individuals cannot download it. KNCV Tuberculosis Foundation has acquired a REDCap license from the Vanderbilt University and can use this license for all KNCV projects.

All survey owners require two-factor authentication to gain access to their surveys. Survey owners cannot see other surveys for which they have no permission, and they have no access to anyone else's data. A limited number of system administrators have complete access, but their activities are highly regulated and documented.

KNCV's REDCap database's physical infrastructure is completely maintained within KNCV's highly secure, limited-access Data Centre. All collected data is saved on the server while it exists within the REDCap database. Each survey owner is responsible for their own specific data management plan. They wish to extract the data for analysis or storage purposes if they use other systems for the analysis and/or long-term storage.

The KNCV REDCap administrators are members of the REDCap Consortium community, providing additional support for specific topics and system troubleshooting. The REDCap platform includes the following features:

- Research-centric design;
- Secure capture and storage of sensitive or confidential information;
- Centralized online access;
- Online data entry (mobile and web);
- While logged into REDCap (databases);
- While not logged into REDCap (surveys);
- Built-in tools for managing data collection; and
- Data is downloadable in spreadsheet format for analysis in R, SPSS, STATA, SAS, Microsoft Excel.)

Annex 3. Data Collection Forms

Form 1. Screening

SCREENING DATE: _____-_____-_____
DD-MM-YYYY

PATIENT INFORMATION

COUNTRY: _____

STUDY SITE: _____ / _____
Code / Name of DR-TB treatment center

PATIENT STUDY SCREENING NUMBER: _____

PATIENT DR-TB REGISTRATION NUMBER: _____
Unique identifier of the patient on DR-TB treatment in the country

PATIENT IN INITIALS: _____
First letters of the patient names

GENDER: ☐ **Male** ☐ **Female**

DATE OF BIRTH: _____-_____-_____
DD-MM-YYYY

AGE[29]: _____ years

PATIENT STUDY ID: _____-_____-_____
STUDY SITE CODE - STUDY SCREENING NUMBER - DR-TB REGISTRATION NUMBER

[29] If less <15 years of age patient does not meet the eligibility criteria; if ≥15 and <18 years old, patient should be evaluated by the Expert Committee

PATIENT STUDY ID: _____-_____-_____

SECTION 1. INCLUSION CRITERIA

Check all that apply

1. Has the patient had laboratory-confirmed (rapid and/or conventional DST) resistant TB to at least rifampicin and fluoroquinolones within the last three months of the screening date?
   ☐ YES ☐ No ☐ Unknown[30]
2. Has the patient had strong clinical and radiological evidence of active TB
   AND
   has the patient been a close household contact of an **index patient with**
   - active laboratory-confirmed resistant TB to at least rifampicin and fluoroquinolones within the last three months of the screening date, AND
   - no documented resistance to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid) within the last three months of the screening date?

   ☐ YES ☐ No ☐ Unknown[31]
3. Has the patient documented MDR/RR-TB treatment non-response and bacteriologically confirmed active TB (irrespective of resistance to FQ) within the last three months of the screening date? [32]
   ☐ YES ☐ No
4. Has the patient documented intolerance to MDR/RR-TB treatment and bacteriologically confirmed active TB (irrespective of resistance to FQ) within the last three months of the screening date?[30]
   ☐ Yes ☐ No

If none of the questions above is answered "yes", the patient does not meet the inclusion criteria. Go to Section 5

PATIENT STUDY ID: _____-_____-_____

[30] Answer "Unknown" is acceptable only if the patient is a close household contact of an index patient with active laboratory-confirmed resistant TB to at least rifampicin and fluoroquinolones and no documented resistance to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid) within the last three months of the screening date.

[31] Answer "Unknown" is acceptable only if the patient had laboratory-confirmed (rapid and/or conventional DST) resistant TB to at least R and FQ within the last three months of the screening date.

[32] Only ask if previously treated patient.

SECTION 2. EXCLUSION CRITERIA

Check all that apply

1. Does the patient have a known previous exposure to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid) or delamanid for >4 weeks?
   ☐ Yes ☐ No

2. Does the patient's DST show infection with a strain resistant to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid)?
   ☐ Yes ☐ No ☐ Unknown

3. Does the patient have a known allergy to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid)?
   ☐ Yes ☐ No

4. Does the patient have a known serious adverse event associated to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid)?
   ☐ Yes ☐ No

5. Does the patient have a known form of extrapulmonary TB that would require treatment longer than would be usual for pulmonary TB (e.g TB meningitis, other central nervous system TB, or TB osteomyelitis)?
   ☐ Yes ☐ No

6. Is the patient unable to take oral medication?
   ☐ Yes ☐ No

7. Does the patient weight <35 kg?
   ☐ Yes ☐ No

PATIENT STUDY ID: _____-_____-_____

SECTION 2. EXCLUSION CRITERIA (continued)
Check all that apply

8. Is the patient pregnant? [33]
☐ Yes ☐ No ☐ Unknown, offer pregnancy test [32]

9. Pregnancy test result:[34]
☐ Positive ☐ Negative ☐ Not done

10. Is the patient reluctant to use effective contraception while on the BPaL treatment? [32]
☐ Yes ☐ No

11. Is the patient breastfeeding? [32]
☐ Yes ☐ No

If none of the questions above is answered "yes" and patient has a negative pregnancy test, go to Section 3

If any question is answered "Yes" or patient has a positive pregnancy test, the patient does not meet the eligibility criteria. Go to Section 5.

[33] Only ask if woman is less than 55 years of age.

[34] Women aged less than 55 years of age must do the pregnancy test before starting the BPaL treatment regimen.

PATIENT STUDY ID: _____-_____-_____

SECTION 3. RELATIVE CONTRA-INDICATIONS[35,36]
Check all that apply

1. Does patient have baseline QTcF [37] > 500ms? ☐ Yes ☐ No
2. Does patient have hemoglobin level < 8.0 g/dL? ☐ Yes ☐ No
3. Does patient have severe peripheral neuropathy? [38] ☐ Yes ☐ No
4. Does patient have AST/ALT > 3.0 x ULN? ☐ Yes ☐ No
5. Does patient have serum creatinine > 3.0 x ULN? ☐ Yes ☐ No

If none of the questions above is answered "yes" in Sections 3, go to Section 4

If any question is answered "Yes", patient should be evaluated by the Expert Committee. The Expert Committee should make decision about the patient's enrollment in the study.

6. Has the Expert Committee decided to enroll the patient in the study?
   ☐ Yes, go to question 7
   ☐ No, go to section 5

7. What is (are) the status of the relative contra-indication(s) at the time of the patient enrollment on the BPaL regimen?
   Check all that apply
   QTcF [35] > 500ms ☐ Yes ☐ No
   Hemoglobin level < 8.0 g/dL? ☐ Yes ☐ No
   Severe peripheral neuropathy[36] ☐ Yes ☐ No
   AST/ALT > 3.0 x ULN ☐ Yes ☐ No
   Serum creatinine > 3.0 x ULN? ☐ Yes ☐ No

If none of the questions above is answered "yes" in Sections 3, go to Section 4

If any question is answered "Yes", patient should be evaluated by the Expert Committee. The Expert Committee should make decision about the patient's enrollment in the study.

[35] Patient must be evaluated for the relative contraindications within the last 14 days of the screening date.

[36] If relative contraindication is resolved at the time of the patient enrollment, then check "No."

[37] Fredericia corrected QT Interval

[38] Brief Peripheral Neuropathy Screen developed and validated by the National Institutes of Health, funded the AIDS Clinical Trials Group

PATIENT STUDY ID: _____-_____-_____

SECTION 4. WRITTEN INFORMED CONSENT

Discuss the study with the patient and explain informed consent and obtain written informed consent from the patients as per the procedure described in the protocol.

Has the consent form for the BPaL study been signed?

☐ **Yes, patient consented to participate**
☐ **No, patient declined to participate**

SECTION 5. ENROLLMENT STATUS

☐ **PATIENT WILL BE ENROLLED IN THE STUDY, GO TO FORM COMPLETION SECTION**

☐ **PATIENT WILL NOT BE ENROLLED IN THE STUDY, GO TO SECTION 6**

PATIENT STUDY ID: _____-_____-_____

SECTION 6. REASONS FOR NON-ENROLLMENT

1. ☐ Patient does not meet eligibility criteria
2. ☐ Patient declined to participate

Check all that apply

2.1. ☐ Patient does not understand the study informed consent form
2.2. ☐ Patient is scared of anticipated adverse events during the treatment
2.3. ☐ Patient does not believe in effectiveness of treatment with the regimen offered
2.4. ☐ Patient thinks that it is difficult to adhere to the study protocol
2.5. ☐ Other, *elaborate under comments*
Comments:_____
_____

3. ☐ Site has decided to not enroll patient

Check all that apply

3.1. ☐ Patient has relative contra-indication(s) as listed in **Section 3** and enrollment was not approved by the Expert Committee
3.2. ☐ Patient does not understand the study informed consent form
3.3. ☐ Patient has a situation that may cause problems with adherence to the treatment protocol, *elaborate under comments*
Comments:_____
_____
3.4. ☐ Patient has a medical condition, which in the investigator's opinion, would make study participation unsafe, *elaborate under comments*
Comments:_____
_____
3.5. ☐ Patient has symptoms of a comorbidity that requires medical evaluation, *elaborate under comments*
Comments:_____
_____
3.6. ☐ Other, *elaborate under comments*
Comments:_____
_____

FORM COMPLETION

FULL NAME OF PERSON COMPLETING THE FORM:_____

FORM COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

Form 2. Enrolment

ENROLMENT DATE: _____-_____-_____
DD-MM-YYYY

PATIENT STUDY ID: _____-_____-_____

SECTION 1. PATIENT'S SOCIOECONOMIC STATUS

1. Highest education completed

☐ No formal education
☐ Primary ☐ Secondary ☐ Tertiary
☐ Vocational training
☐ Other, specify:_____
☐ Unknown

2. Current employment status:

☐ Unemployed
☐ Employed
☐ Retired
☐ Other, specify: _____
☐ Unknown

3. Current marital status:

☐ Not married
☐ Lives with partner
☐ Married
☐ Divorced
☐ Separated
☐ Widowed

4. Unemployed within the past year:

☐ Yes
☐ No
☐ Unknown

PATIENT STUDY ID: _____-_____-_____

SECTION 1. PATIENT'S SOCIOECONOMIC STATUS (CONTINUED)

5. Homeless within the past year:
☐ Yes
☐ No
☐ Unknown

6. Illicit drug(s) use within the past year:
☐ Yes
☐ No
☐ Unknown

7. History of being resident of correctional facility:
☐ Yes
☐ No
☐ Unknown

8. Alcohol use led to problems in relationships, health, employment, work performance, or finances within the past year:
☐ Yes
☐ No
☐ Unknown

9. History of tobacco smoking within the past five years:
☐ Yes
☐ No
☐ Unknown

10. **If "Yes",** how many years has the patient smoked? ☐☐ years

11. Current tobacco smoking:
☐ Yes
☐ No
☐ Unknown

12. **If "Yes",** how many packs per day? ☐☐ packs

PATIENT STUDY ID: _____-_____-_____

SECTION 2. TB TREATMENT HISTORY

1. Was patient ever treated for TB disease prior to current episode?

☐ Yes
☐ No, *go to Section 3*
☐ Unknown, *go to Section 3*

2. If "yes", enter month and year of treatment initiation for TB disease prior to current episode _____-_____
   MM-YYYY

3. Has patient ever received treatment with second-line anti-TB drugs for ≥1 month prior to this episode of TB disease?

☐ Yes
☐ No
☐ Unknown

4. Enter month and year of treatment outcome for TB disease prior to current episode?
   _____-_____
   MM-YYYY

5. What was outcome of the TB treatment prior to current episode as per the medical records?

☐ Cured
☐ Treatment completed
☐ Treatment failed
☐ Lost to follow-up
☐ Not evaluated
☐ Unknown, explain_____

PATIENT STUDY ID: _____-_____-_____

SECTION 3. CURRENT EPISODE OF TB DISEASE

1. Site of current episode of TB disease
   Check all that apply

☐ Pulmonary ☐ Extrapulmonary, Specify _____

2. ☐ Xpert MTB/RIF ☐ Not done, *go to the next section*

Date of sample collection: _____-_____-_____
DD-MM-YYYY

Date of testing: _____-_____-_____
DD-MM-YYYY

Method: ☐ Xpert MTB/RIF ☐ Xpert MTB/RIF Ultra ☐ Other, Specify_____

Result: ☐ MTB Detected, ☐ Trace (Ultra only)
☐ Rifampicin Resistance Detected ☐ Rifampicin Resistance Detected
☐ Rifampicin Resistance Indeterminate
☐ MTB Not Detected

If the result is "Invalid," "No result," or "Error," repeat the test and report a valid result.
If the result is "Rifampicin Resistance Indeterminate," repeat the test and report the result.

SECTION 4. PERFORMANCE STATUS [39]

1. Karnofsky Performance Status Score: _____

SECTION 5. BMI

Weight: _____kg Height: _____cm BMI: [40] _____

[39] Assessed by Karnofsky Performance Status Scale. i. Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144. Ii. de Haan R, Aaronson A, et al. Measuring quality of life in stroke. Stroke. 1993; 24:320- 327. Iii. Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-2098. iv. O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387. Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109. V. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.v

[40] BMI is weight in kilograms divided by height in meters squared. Height is measured in centimeters, divide by 100 to convert this to meters

PATIENT STUDY ID: _____-_____-_____

SECTION 6. HIV STATUS

1. Is patient HIV positive?

   ☐ Yes, *go to Question 2*
   ☐ No,[41] *go to Section 7*
   ☐ Unknown, *offer HIV counseling and testing and go to Question 7*

2. Is patient on ART?

   ☐ Yes, ART regimen (write regimen out here):_____
   _____, *go to the next question*
   ☐ No, *go to question 4*

3. How long has patient been on Antiretroviral Therapy (ART)?

   ☐ <6 months
   ☐ 6-12 months
   ☐ 1-3 years
   ☐ >3 years
   ☐ Unknown

4. Is patient on Cotrimoxazole Preventive Therapy (CPT)?

   ☐ Yes
   ☐ No

5. Was viral load assessed in **the last 6 months**?

   ☐ No, test and record the result below
   ☐ Yes, Date of sample collection**:** _____-_____-_____
   DD-MM-YYYY
   Viral load: _____RNA copies/ml

6. Was CD4 count assessed in the **last 3 months**?

   ☐ No, test and record the result below
   ☐ Yes, Date of sample collection: _____-_____-_____
   DD-MM-YYYY
   CD4 count: _____cells/mm^3

[41] If test was done >1 month ago, select "Unknown"

PATIENT STUDY ID: _____-_____-_____

SECTION 6. HIV STATUS (Continued)

7. Did patient agree on HIV counseling and testing?

☐ Yes, *go to Question 8*
☐ No, *go to Section 7*

8. Was HIV testing done?

☐ No, *go to Section 7*
☐ Yes, Date of sample collection: _____-_____-_____
DD-MM-YYYY

HIV test result: ☐ **Positive** ☐ **Negative**

If invalid result, repeat the test and report a valid result
If "Positive", complete Questions 2, 4, 5, 6 of this section (**SECTION 6. HIV STATUS)**

SECTION 7. VIRAL HEPATITIS

1. Does the patient have laboratory confirmed viral hepatitis?

Check all that apply

Hep A	**Hep B**	**Hep C**
☐ Yes	☐ Yes	☐ Yes
☐ No	☐ No	☐ No
☐ Unknown	☐ Unknown	☐ Unknown

SECTION 8. BPAL REGIMEN INITIATION

1. Date the patient takes the first dose of the BPaL regimen:
_____-_____-_____
DD-MM-YYYY
2. The patient started the BPaL treatment ☐ Inpatient ☐ Outpatient

FORM COMPLETION

FULL NAME OF PERSON COMPLETING THE FORM:_____

FORM COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

Form 3. Evaluation

EVALUATION DATE: _____-_____-_____
DD-MM-YYYY

PATIENT STUDY ID: _____-_____-_____

SECTION 1. REASON FOR EVALUATION (check one):

- ☐ **Baseline**
- ☐ **Treatment, Week_____**
- ☐ **End of treatment, Week _____**
- ☐ **After treatment Follow-up, Month _____**

PATIENT STUDY ID: _____-_____-_____

SECTION 2. CLINICAL EVALUATION

1. WEIGHT ☐ Not done, *go to next question*

Date of measurement: _____-_____-_____
DD-MM-YYYY

Weight: _____ kg

2. PERIPHERAL NEUROPATHY SCREEN[42] ☐ Not done, *go to next question*

Date of examination: _____-_____-_____
DD-MM-YYYY

Result: ☐ Normal ☐ Abnormal, indicate grade (1-4) _____

3. CHEST X-RAY ☐ Not done, *go to next question*

Date of examination: _____-_____-_____
DD-MM-YYYY

Method: ☐ Analog ☐ Digital ☐ Other, specify[43] _____

Result: ☐ Normal ☐ Abnormal Unilateral ☐ Abnormal Bilateral

Cavities: ☐ No ☐ Yes Unilateral ☐ Yes Bilateral ☐ Unknown

4. ECG ☐ Not done, *go to next section*

Date of examination: _____-_____-_____
DD-MM-YYYY

Method: ☐ 12-LEAD ☐ Other, specify:_____

Result: QT interval (uncorrected): _____ msec

Heart rate: _____bpm

QTc interval (Fredericia): _____msec

[42] Assessed by Brief Peripheral Neuropathy Screen developed and validated by the National Institutes of Health–funded AIDS Clinical Trials Group

[43] E.g. computer tomography (CT)

PATIENT STUDY ID: _____-_____-_____

SECTION 3. VISUAL ACUITY AND COLOUR VISION SCREEN [44]

1. VISUAL ACUITY ☐ Not done, *go to next question*

Date of examination: _____-_____-_____
DD-MM-YYYY

Method: ☐ Snellen chart ☐ Other, specify:_____

Result:

Right Eye (OD) ____-_____	Left Eye (OS) ____-_____
or ☐ Counting fingers	or ☐ Counting fingers
or ☐ See hand movement	or ☐ See hand movement
or ☐ No light perception	or ☐ No light perception

2. COLOUR VISION ☐ Not done, *go to next section*

Date of examination _____-_____-_____
DD-MM-YYYY

Method: ☐ Ishihara ☐ Other, specify:_____

Result: Color vision:

Right Eye (OD)	Left Eye (OS)
☐ Normal	☐ Normal
☐ Abnormal,	☐ Abnormal,
specify number of plates ☐☐ missed out of in ☐☐ plate book:	specify number of plates ☐☐ missed out of in ☐☐ plate book:

[44] Visual acuity, colour discrimination, or both tests must only be used as a screening test(s) to alert about the possibility of optic neuritis. Suppose any of the test results are abnormal or worsened compared to the previous examination results. In that case, the patient must be referred to an ophthalmologist for a diagnosis of optic neuritis. Refer to the clinical guide for detailed actions in patients with abnormal vision.

PATIENT STUDY ID: _____-_____-_____

SECTION 4. COVID-19 ☐ Not done, *go to next section*

1. Has the patient laboratory confirmed COVID-19 now?

☐ Yes
☐ No
☐ Unknown

SECTION 5. PREGNANCY

1. Is the patient pregnant? [31]
   ☐ Yes ☐ No ☐ Unknown, *offer pregnancy test* [32]

2. Pregnancy test result:
   ☐ Positive ☐ Negative ☐ Not done, *go to next section*

PATIENT STUDY ID: _____-_____-_____

SECTION 6. BACTERIOLOGICAL EVALUATIONS

1. XPERT MTB-XDR ☐ Not done, *go to the next section*

Date of sample collection: _____-_____-_____

DD-MM-YYYY

Date of testing: _____-_____-_____

DD-MM-YYYY

Xpert MTB-XDR Result:

☐ MTB Detected, ☐ H Resistance Detected ☐ H Low Resistance Detected

☐ H Resistance Indeterminate

☐ FQ Resistance Detected ☐ FQ Low Resistance Detected

☐ FQ Resistance Indeterminate

☐ Am Resistance Detected ☐ Am Resistance Indeterminate

☐ Eto Resistance Detected ☐ Eto Resistance Indeterminate

☐ MTB Not Detected

If the results are "Invalid," "No result," or "Error," repeat the test and report a valid result.

If the results are "FQ Resistance Indeterminate," repeat the test and report the result.

2. Genome sequencing ☐ Not done, go to the next section

Reason for test:

For resistance prediction ☐

For relapse/reinfection investigation ☐

Date of sample collection: _____-_____-_____

DD-MM-YYYY

Date of testing: _____-_____-_____

DD-MM-YYYY

Type of sequencing performed: whole genome sequencing (WGS) ☐

targeted genome sequencing ☐

Sequencing results:

☐ MTBC Detected:

Other Mycobacterium species detected: ☐ _____

Detected spolygotype:_____

Detected lineage:_____

☐ H resistance predicted, the following mutations associated with resistance were detected:_____

☐ FQ resistance predicted, the following mutations associated with resistance were detected:_____

☐ Am resistance predicted, the following mutations associated with resistance were detected:_____

☐ Eto resistance predicted, the following mutations were detected:_____

☐ Lzd resistance predicted, the following mutations were detected:_____

☐ Bdq/Cfz resistance predicted, the following mutations were detected:_____

☐ Pa resistance predicted, the following mutations were detected:_____

If the results are unsuccessful repeat the T/WGS test or another test and report a valid result.

3. SECOND-LINE LPA ☐ Not done, *go to the next question*

Date of sample collection: _____-_____-_____
DD-MM-YYYY

Date of testing: _____-_____-_____
DD-MM-YYYY

Hain MTBDR*sl* result:

☐ MTB Detected ☐ FQ Resistance Detected

☐ FQ Resistance Indeterminate

☐ MTB Not Detected

If the result is “FQ Resistance Indeterminate,” repeat the test and report the result.

PATIENT STUDY ID: _____-_____-_____

3. SMEAR MICROSCOPY ☐ Not done, *go to the next question*

Date of sample collection: _____-_____-_____
DD-MM-YYYY

Date testing: _____-_____-_____
DD-MM-YYYY

Result:

☐ Negative

☐ Positive, specify: ☐ Scanty ☐ +1 ☐ +2 ☐ +3 ☐ +4

4. SPUTUM CULTURE ☐ Not done, *go to the next question*

Date of sample collection: _____-_____-_____
DD-MM-YYYY

Date of Culture inoculation: _____-_____-_____
DD-MM-YYYY

Date of Culture growth: _____-_____-_____
DD-MM-YYYY

Method: ☐ LJ ☐ MGIT ☐ Other, specify_____

Culture result: ☐ No growth ☐ MTB growth ☐ NTM ☐ Contaminated

Store in/on: ☐ Solid media ☐ Liquid media ☐ in _____ % Glycerol ☐ Not stored

Store at: ☐ Deep freezer ☐ Freezer ☐ Refrigerator ☐ Room Temperature

If culture is stored in/on media, transfer into final 20% glycerol and keep in the deep freezer

☐ Done ☐ Not done

PATIENT STUDY ID: _____-_____-_____

5. PHENOTYPIC SUSCEPTIBILITY TESTING (DST) ☐ Not done, *go to the next section*

Date of sample collection: _____-_____-_____
DD-MM-YYYY

Date of testing: _____-_____-_____
DD-MM-YYYY

	Susceptible	Resistant	Not done
H	☐	☐	☐
R	☐	☐	☐
Mfx	☐	☐	☐
Lfx	☐	☐	☐
Km	☐	☐	☐
Am	☐	☐	☐
Cm	☐	☐	☐
Bdq	☐	☐	☐
Pa	☐	☐	☐
Lzd	☐	☐	☐

PATIENT STUDY ID: _____-_____-_____

SECTION 7. LABORATORY EVALUATION

Test	Date DD-MM-YYYY	Value	Unit	Check if Not done
1. BLOOD COUNT				
Hemoglobin			☐ **g/dL** ☐ **g/L**	☐
Platelets			☐ **x10³/mm³** ☐ **(10⁹/L)**	☐
White Blood Cells (WBC)			☐ **x10³/mm³** ☐ **(10⁹/L)**	☐
Absolute Neutrophil Count (ANC)			☐ **x10³/mm³** ☐ **(10⁹/L)**	☐
2. LIVER FUNCTION TESTS				
ALT/SGPT			☐ **U/L**	☐
AST/SGOT			☐ **U/L**	☐
Total bilirubin			☐ **mg/dL** ☐ **µmol/L**	☐
3. KIDNEY FUNCTION TESTS				
Creatinine			☐ **mg/dL** ☐ **µmol/L**	☐
Urea			☐ **mmol/L**	☐
4. SERUM ELECTROLYTES				
Sodium			☐ **mEq/L** ☐ **mmol/L**	☐

Test	Date DD-MM-YYYY	Value	Unit	Check if Not done
Potassium			☐ mEq/L ☐ mmol/L	☐
Magnesium			☐ mEq/L ☐ mmol/L	☐
Calcium			☐ mEq/L ☐ mmol/L	☐
5. OTHER TESTS				
Glucose				☐
☐ **Fasting**			☐ mg/dL ☐ µmol/L	
☐ **Random**			☐ mg/dL ☐ µmol/L	
TSH			☐ mIU/L	☐
Serum Amylase			☐ U/L	☐
Other test *(specify):*			☐	☐
Other test *(specify):*				
Other test *(specify):*				

PATIENT STUDY ID: _____-_____-_____

SECTION 8. TREATMENT ADHERENCE [45]

1. Did the patient miss any days of treatment since the last evaluation visit?
   ☐ Yes ☐ No ☐ Unknown

2. If "Yes", how many day(s)?
   ☐☐☐day(s) out of ☐☐☐day(s) since the last visit

SECTION 9. TREATMENT REGIMEN

1. Was the treatment discontinued, interrupted, or modified by the clinician since the last visit?
   ☐ Yes ☐ No

2. If "Yes" indicate change:
   ☐ Permanent discontinuation of the full regimen
   ☐ Interruption of the full regimen, number of days _____
   ☐ Daily dose reduction of linezolid from 1200 to 600 mg
   ☐ Daily dose reduction of linezolid from 600 mg to 300 mg
   ☐ Interruption of linezolid, number of days _____
   ☐ Restarted of linezolid with _____mg daily dose
   ☐ Permanent discontinuation of linezolid

   Describe reason for permanent discontinuation, interruption, or dose modification

   _____

   _____

3. Since the last evaluation visit, the patient
   ☐ was transferred from inpatient to outpatient treatment

Date: _____-_____-_____
DD-MM-YYYY
Describe reason_____
_____

☐ was transferred from outpatient to inpatient treatment

Date: _____-_____-_____
DD-MM-YYYY
Describe reason_____
_____

☐ remains on inpatient treatment

[45] Skip this section at baseline.

☐ remains on outpatient treatment

PATIENT STUDY ID: _____-_____-_____

SECTION 10. COMORBIDITIES AND CONCOMITANT MEDICATION

1. Does the patient have any comorbidities?
   ☐ Yes
   ☐ No
   ☐ Unknown

2. If "Yes", list below:

   _____
   _____
   _____
   _____
   _____

3. Does the patient take any concomitant medication? [46]
   ☐ Yes
   ☐ No
   ☐ Unknown

4. If "Yes", list below:

   _____
   _____
   _____
   _____
   _____
   _____

[46] If the patient is already on ART at baseline, the ART regimen should be filled in Form 2 Enrolment, Section 6. If the patient starts ART during BPaL treatment, the ART regimen should be filled in here.

FORM COMPLETION

FULL NAME OF PERSON COMPLETING THE FORM:_____

FORM COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

Form 4. Treatment Completion

TREATMENT COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

PATIENT STUDY ID: _____-_____-_____

SECTION 1. TREATMENT COMPLETION

1. Total number of the BPaL treatment doses taken: _____

Date of the first dose of the BPaL regimen: _____-_____-_____
DD-MM-YYYY

Date of the last dose of the BPaL regimen: _____-_____-_____
DD-MM-YYYY

2. Did participant complete treatment according to protocol?

☐ Yes, *go to section 3*
☐ No, *go to the next section*

PATIENT STUDY ID: _____-_____-_____

SECTION 2. REASON FOR NOT COMPLETING THE STUDY TREATMENT AS PER PROTOCOL

1. Select the primary reason why participant did not complete study treatment as per protocol. (select one reason only):

☐ The BPaL regimen not started, *go to Form Completion Section*

Specify reason:_____
_____

☐ Participant was withdrawn after enrollment due to protocol violation(s), *complete Section 3 if relevant, skip Section 4, and go to Form Completion Section*

Specify reason:_____
_____

☐ Physician judged it no longer advisable for patient to continue the BPaL regimen, *complete Section 3 if relevant, skip Section 4, and go to Form Completion Section*

Specify reason:_____
_____

☐ Participant refused further treatment and withdrew consent*, complete Section 3 if relevant, skip Section 4, and go to Form Completion Section*

Specify reason:_____
_____

☐ Participant became pregnant during the study treatment, *complete Section(s) 3 and/or 4 if relevant and go to Form Completion Section. Also, complete Form 6. Adverse Event*

☐ Failure to complete required number of study treatment doses within maximum period of 60 days after the intended end of the treatment, *complete Section(s) 3 and/or 4 if relevant and go to Form Completion Section.*
Specify reason:_____
_____

☐ Other, *complete Section(s) 3 and/or 4 if relevant and go to Form Completion Section.*

Specify reason:_____
_____

PATIENT STUDY ID: _____-_____-_____

SECTION 3. INTERIM TREATMENT OUTCOME (SPUTUM CULTURE CONVERSION)

Date of initial sputum culture conversion:[47] _____-_____-_____
DD-MM-YYYY

SECTION 4. END OF TREATMENT OUTCOME

1. End-of-treatment outcome:

☐ Cured

☐ Treatment completed

☐ Treatment failed

- ☐ Lack of culture conversion at 6th month of treatment
- ☐ Culture reversion[48] at 5th month or later in a patient with previous culture conversion to negative
- ☐ Treatment termination due to poor clinical or radiologic response
- ☐ Permanent discontinuation of Bdq, Pa, or both at any time due to Adverse Event, *complete Form 6. Adverse Event*
- ☐ Permanent discontinuation of Lzd if having less than nine weeks of 600mg daily, due to adverse event, *complete Form 6. Adverse Event*

☐ Died*, complete Form 6. Adverse Event*

☐ Lost to follow up

☐ Treatment termination due to baseline resistance to any of the BPaL component drugs (bedaquiline, pretomanid, linezolid)

☐ Not evaluated

FORM COMPLETION

FULL NAME OF PERSON COMPLETING THE FORM:_____

FORM COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

[47] Two consecutive cultures taken at least 30 days apart are found to be negative. Record the specimen collection date of the first negative culture.
[48] Two consecutive cultures taken at least 30 days apart are found to be positive

Form 5. After treatment Follow-up

After treatment Follow-up visit date: _____-_____-_____
DD-MM-YYYY

PATIENT STUDY ID: _____-_____-_____

SECTION 1. AFTER TREATMENT FOLLOW-UP VISIT

1. After treatment Follow-up, Month _____

2. Did participant complete study follow-up visit as per protocol?

   ☐ Yes, *go to Section 3*
   ☐ No, *go to the next section*

SECTION 2. REASON FOR NOT COMPLETING STUDY FOLLOW-UP

1. Select the primary reason why participant did not complete study follow-up visit (select one reason only):
   ☐ Participant died, *complete Section 4.*
   ☐ Participant withdrew consent, *go to Form Completion Section*
   Specify reason:_____
   _____

   ☐ Participant is lost to follow-up, *go to Form Completion Section*
   Specify reason:_____
   _____

   ☐ Other, *go to the next section, skip Section 4, and go to Form Completion Section*
   Specify reason:_____
   _____

SECTION 3. PATIENT STATUS AT THE FOLLOW-UP VISIT

1. Status at the follow-up visit:
   ☐ No TB
   ☐ TB recurrence
   ☐ Not evaluated

PATIENT STUDY ID: _____-_____-_____

SECTION 4. INFORMATION CONCERNING DEATH

1. Did the participant die during the follow-up period after the BPaL treatment completion?
   ☐ Yes Date of death: _____-_____-_____
   DD-MM-YYYY
   ☐ No, *go Form Completion Section*

2. Was (were) the cause(s) of death known?
   ☐ Yes
   ☐ No, *go to Form Completion Section*

3. If "yes," list the primary cause(s) of death stated on the death certificate if the certificate is available.
   May indicate up to four diagnoses, one per line:
   1. _____
   2. _____
   3. _____
   4. _____

FORM COMPLETION

FULL NAME OF PERSON COMPLETING THE FORM:_____

FORM COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

Form 6. Adverse Event (AE)[49]

EVALUATION DATE: _____-_____-_____
DD-MM-YYYY

PATIENT STUDY ID: _____-_____-_____

SECTION 1. REASON FOR EVALUATION

Check only one

- ☐ Treatment, Week _____
- ☐ End of treatment, Week _____
- ☐ Follow-up after treatment completion, Month _____

SECTION 2. AE TYPE

Check all that apply

1. ☐ AE leading to treatment discontinuation or change in drug dosage
2. AE of Special Interest (AESI)
   - ☐ QT-prolongation
   - ☐ Hepatotoxicity
   - ☐ Myelosuppression
   - ☐ Optic neuritis
   - ☐ Peripheral neuropathy
3. **SAE**
   - ☐ Death
   - ☐ Life-threatening
   - ☐ Hospitalization required/prolonged
   - ☐ Persistent or significant disability / incapacity
   - ☐ Congenital anomaly / birth defect
   - ☐ Otherwise medically important

[49] If multiple AE, complete separate form for each AE.

PATIENT STUDY ID: _____-_____-_____

SECTION 3. DETAILS OF AE

1. Description of AE: _____
_____
_____

Date Started: _____-_____-_____
DD-MM-YYYY

Date Stopped: _____-_____-_____
DD-MM-YYYY

2. Suspected drug(s):
Check all that apply

- ☐ Bedaquiline
- ☐ Pretomanid
- ☐ Linezolid

3. Concomitant medication(s), list [50] _____
_____
_____

4. AE Severity Grade
Check only one

- ☐ Grade I
- ☐ Grade II
- ☐ Grade III
- ☐ Grade IV
- ☐ Unknown

[50] All medications should be listed here, including ART medication.

PATIENT STUDY ID: _____-_____-_____

SECTION 4. ACTION TAKEN IN RESPONSE TO AE

1. Was the treatment discontinued, interrupted, or modified by the clinician since the last visit?

   ☐ Yes, go to Question 2
   ☐ No, go to Section 5

   If "Yes" indicate change:

2. ☐ Permanent discontinuation of the full regimen
   Date: _____-_____-_____
   DD-MM-YYYY
3. ☐ Interruption of the full regimen, number of days _____
   Date: _____-_____-_____
   DD-MM-YYYY
4. ☐ Linezolid dose modification, interruption, or permanent discontinuation, if done, specify:
   4.1 ☐ Dose reduction from 1200 to 600 mg daily
   Date: _____-_____-_____
   DD-MM-YYYY
   4.2 ☐ Dose reduction from 600 mg to 300 mg daily
   Date: _____-_____-_____
   DD-MM-YYYY
   4.3☐ Interruption of linezolid, if done, specify:
   Initial dose_____ mg daily, number of days ____
   Date of interruption: _____-_____-_____
   DD-MM-YYYY
   ☐ Restarted with dose _____mg daily
   Date of restart: _____-_____-_____
   DD-MM-YYYY
   4.4☐ Permanent discontinuation of linezolid
   Date: _____-_____-_____
   DD-MM-YYYY
5. AE faded after drug(s) stopped/dose reduced?
   ☐ Yes
   ☐ No

6. AE reappeared after drug(s)/dose reintroduction?
   ☐ Yes
   ☐ No
   ☐ Not Applicable

PATIENT STUDY ID: _____-_____-_____

SECTION 5. OUTCOME OF AE

☐ Resolved, *go to Form Completion Section*

☐ Resolving, *go to Form Completion Section*

☐ Resolved with sequelae, *go to Form Completion Section*

☐ Not resolved, *go to Form Completion Section*

☐ Died, *go to Section 6*

☐ Unknown, *go to Form Completion Section*

Date of AE status assessment: _____-_____-_____
DD-MM-YYYY

SECTION 6. INFORMATION CONCERNING DEATH ☐ Not Applicable

4. Did participant die during the BPaL treatment?

   ☐ Yes Date of death: Date: _____-_____-_____
   DD-MM-YYYY

   ☐ No, go Form Completion Section

5. Was (were) the cause(s) of death known?
   ☐ Yes
   ☐ No, go to Form Completion Section

6. If "yes," list the primary cause(s) of death stated on the death certificate if the certificate is available.
   May indicate up to four diagnoses, one per line:
   5. _____
   6. _____
   7. _____
   8. _____

PATIENT STUDY ID: _____-_____-_____

SECTION 7. INFORMATION CONCERNING PREGNANCY ☐ Not Applicable

1. Date of 1st day of last menstrual period	_____-_____-_____ *DD-MM-YYYY*	2. Estimated date of delivery	_____-_____-_____ *DD-MM-YYYY*
3. Pregnancy test	_____-_____-_____ *DD-MM-YYYY*		
4. Pregnancy outcome			
4.1. Did the patient experience any complication during pregnancy?	☐ Yes. Specify:		
	☐ No		
4.2. Did the patient give birth to (a) live infant(s)?	☐ Yes. Date of delivery _____-_____-_____ *DD-MM-YYYY*		
	☐ No. Specify reason:		
4.3. Was the infant normal at birth?	☐ Yes		
	☐ No. Specify abnormality and reason:		
4.4. Additional comment on pregnancy/delivery			

PATIENT STUDY ID: _____-_____-_____

SECTION 8. INFORMATION CONCERNING INFANT(S)

☐ Not Applicable

Infant number	Infant sex	Infant length *(cm)*	Infant weight *(g)*	APGAR score	Exposure during breastfeeding	Comment
1	**F** ☐ **M** ☐				**Yes** ☐ **No** ☐	
2	**F** ☐ **M** ☐				**Yes** ☐ **No** ☐	
3	**F** ☐ **M** ☐				**Yes** ☐ **No** ☐	

PATIENT STUDY ID: _____-_____-_____

FORM COMPLETION

FULL NAME OF PERSON COMPLETING THE FORM:_____

FORM COMPLETION DATE: _____-_____-_____
DD-MM-YYYY

Annex 4. BRIEF PERIPHERAL NEUROPATHY SCREEN [51]

Grading of subjective symptoms

Ask the patient to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for right and left feet/legs. Enter the score for each symptom in the columns marked Right and Left

Normal	Mild ---------- Severe									
00	01	02	03	04	05	06	07	07	09	10

Symptoms	Right	Left
a. Pain, aching, or burning in feet, legs		
b. "Pins and needles" in feet, legs present for at least 2 weeks		
c. Numbness (lack of feeling) in feet, legs present for at least 2 weeks		

Use the single highest severity score above to obtain a subjective sensory neuropathy score

Subjective Sensory Neuropathy Score	Severity grade [52]
00	0
01 – 03	1
04 – 06	2
07 – 10	3
Life-threatening	4

[51] Developed and validated by the National Institutes of Health–funded AIDS Clinical Trials Group

[52] For more details, please refer to the clinical guide

Annex 5. KARNOFSKY PERFORMANCE STATUS SCALE [53]

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Definitions	Rating (%)	Criteria
Able to carry on normal activity and to work; no special care needed.	**100**	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

[53] References: i. Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144. Ii. de Haan R, Aaronson A, et al. Measuring quality of life in stroke. Stroke. 1993; 24:320- 327. Iii. Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-2098. iv. O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387. Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109. V. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.