THINK
TB & HIV INVESTIGATIVE NETWORK

Stop TB Partnership
TB REACH

Programmatic introduction of the BPaL regimen:

A practical implementation guide

November 2021

INDEX

ABBREVIATIONS[i]

aDSM	Active TB drug safety monitoring and management
AE	Adverse event
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
aIPD	Adult individual patient data
aOR	Adjusted odds ratio
aRD	Adjusted risk difference
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BDQ	Bedaquiline
BPaL regimen	Bedaquiline + Pretomanid + Linezolid
CDC	Centers for Disease Control and Prevention
CL	(95%) confidence limits
CNS	Central nervous system
DALY	Disability-adjusted life year
DCGI	Drug Controller General of India
DOI	WHO Declaration of Interest
DOT	Directly observed therapy
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug susceptibility tuberculosis
DST	Drug susceptibility testing
EC	European Commission
EML	Essential Medicines List
ERG	External Review Group
FDC	Fixed-dose combination (medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEPro	Online tool to create guideline materials (see https://gradepro.org/)
GRC	WHO Guideline Review Committee
GTB	WHO Global TB Programme
H	Isoniazid
HALT	Hepatitis and Latent TB infection study
HIV	Human immunodeficiency virus
Hr-TB	Confirmed rifampicin-susceptible, isoniazid-resistant TB
(H)REZ	(Isoniazid)–rifampicin–ethambutol–pyrazinamide
IQR	Interquartile range
ITR	Individualized Treatment Regimens
ITRC	International Tuberculosis Research Center
ITT	Intention to treat
KNCV	KNCV Tuberculosis Foundation

LIFT-TB	Leveraging Innovation for Faster Treatment of Tuberculosis
LPA	Line probe assay
LTBI	Latent tuberculosis infection
LZD	Linezolid
M.tuberculosis / M.tb	*Mycobacterium tuberculosis*
MDR/RR-TB	Multidrug/rifampicin-resistant tuberculosis
MDR-TB	Multidrug-resistant tuberculosis
mITT	Modified intention to treat
MTBDRsl	GenoType Mycobacterium tuberculosis drug-resistant second-line assay
NCAC	National Clinical Advisory Committee
OR	Odds Ratio
Pa	Pretomanid
PICO	Population, Intervention, Comparator and Outcomes
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics
PLHIV	People living with HIV
Pre-XDR-TB	Pre-extensively drug-resistant tuberculosis
RCT	Randomized controlled trial
RR-TB	Rifampicin-resistant tuberculosis
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SAT	Self-administered treatment or unsupervised treatment
SMS	Short message service (mobile phone text message)
TB	Tuberculosis
US NIH (NIAID)	United States National Institutes of Health (National Institute of Allergy and Infectious Diseases)
USFDA	United States Food and Drug Administration
VOT	Video-observed treatment
WHO	World Health Organization
WHO/GTB	Global TB Programme of the World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

KEY DEFINITIONS

Drug resistance categories as per 2021 World Health Organization (WHO) guidance:

- Monoresistance: resistance to one first-line anti-TB drug only.
- Polydrug resistance: resistance to more than one first-line anti-TB drug (other than both rifampicin and isoniazid).
- Multidrug resistance (MDR): resistance of *M. tuberculosis* to at least both rifampicin and isoniazid.
- Pre-extensively drug-resistant tuberculosis (Pre-XDR): TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin are currently WHO recommended for inclusion in longer regimens).
- Extensively drug-resistant tuberculosis (XDR-TB): TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (Group A drugs are the most potent group of drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise levofloxacin, moxifloxacin, bedaquiline and linezolid).
- Rifampicin resistance: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance. The highest level of resistance will be used to categorize the isolate.

Treatment outcome definitions as per WHO guidelines: [ii]

- Cured: a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriologic response and no evidence of failure.

  "Bacteriological response" refers to bacteriological conversion with no reversion.

  "Bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for drug-resistant tuberculosis (DR-TB) and drug-sensitive tuberculosis (DS-TB)) or smears (for DS-TB only), taken on different occasions at least 7 days apart are negative.

  "Bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

- Treatment completed: A patient who completed treatment as recommended by national policy whose outcome does not meet the definition for cure or treatment failure.

- Treatment failed: A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy. Reasons for change include Reasons for the change include:
    - no clinical response and/or no bacteriological response
    - adverse drug reactions; or
    - evidence of additional drug resistance to medicines in the regimen
- Died: a patient who died for any reason before starting treatment or during the course of treatment.
- Lost to follow-up: a patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- Not evaluated: a patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit and those whose treatment outcome is unknown; however, it excludes those lost to follow-up.
- Treatment success: the sum of cured and treatment completed.
- “Sustained treatment success”: Used for operational research only for the post-TB treatment period. This suggests that successfully treated TB patients be assessed at 6 months (DS-TB and DR-TB) and 12 months (DR-TB) after the end of treatment, to determine whether they are alive and TB free.

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EXECUTIVE SUMMARY

Research shows the BPaL regimen (Bedaquiline + Pretomanid + Linezolid) is a promising and highly effective new drug regimen that offers a high impact, shortened treatment option to patients diagnosed with drug-resistant tuberculosis (DR-TB). The popularity and need for the BPaL regimen are evident in its roll-out operationally or through implementation research in various countries. Through this guide, the authors aim to give pragmatic guidance on the use of this regimen in a programmatic or research setting. The content has been gathered from and reviewed by various subject experts to offer relevant information for safe and effective roll-out.

The various sections include among others, the background and research development of the regimen, drug information, clinical guidance on the regimen, related safety monitoring, adverse event management and use in special populations. Key points are highlighted at the end of each section as the most important take-home concepts. Lessons learnt in the field and Frequently Asked Questions (FAQs) were also collected from physicians and other BPaL implementors. In addition to the clinical guidance provided, consideration for country-level implementation has been documented to assist TB Programme implementors with the roll-out of the BPaL regimen in their countries.

In summation of the key points, clinical notes for the implementation of BPaL clinical access programmes are:

- The BPaL regimen is simpler to use than any other DR-TB regimen currently in use.
- The BPaL regimen is very efficacious, is short and tolerable, has a low pill burden, but will not work effectively if patients have pre-existing resistance.
- Health care providers should have a high index of suspicion for pre-existing resistance and investigate for resistance as far as possible with the available sensitivity assays (for the individual BPaL drugs).
- Bedaquiline and linezolid are already being widely used and there are few absolute contraindications.
- In a patient already receiving bedaquiline, ensure the patient receives the full 14 days of 400mg loading dose of bedaquiline orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks. It is not necessary to restart the 400mg ‘loading’ dose when initiating BPaL, unless one suspects the initial administration (of BDQ) was not completed or was given incorrectly (I.e., concomitant use of EFV).
- Both linezolid 1200mg daily and 600mg daily are effective at treating DR-TB but can cause moderate to severe (although predictable and manageable) adverse events. When lowering the dose to manage adverse events caution should be taken when lowering to 300mg.
- Linezolid side-effects are common, but manageable.

    - Monitor haemoglobin closely as it can drop quickly. Note that patients respond well and quickly to linezolid interruptions. Monitor the Hb closely when rechallenging patients with LZD if temporarily interrupted.
    - Hyperlactataemia is seen in patients, especially if they are also HIV co-infected on ART. Suspect this diagnosis if they present with nausea/vomiting and tiredness. Interrupt LZD until lactate returns to normal and symptoms resolve. Rechallenge at LZD 600mg.
    - Absolute neutrophil count and platelets rarely require linezolid interruptions. Repeat both these parameters before making changes to linezolid administration since they fluctuate.
    - Optic neuritis is an uncommon side-effect of LZD. All patients need to be counselled on the signs and symptoms of optic neuritis and instructed to contact the treating healthcare provider and/ or site promptly.
    - Peripheral neuropathy (PN) management can vary from patient to patient depending on how well they tolerate the associated symptoms and how severe their TB disease is. PN management requires consultation with the patient with continuous emphasis of the balance between effective TB treatment and reduction of adverse events.
- Hepatotoxicity from BPaL is not common but can be severe and needs to be managed closely. Many patients will present with elevated transaminases before presenting with symptoms. Be sure to check the results of the liver panel when they become available.

As the BPaL regimen is still being researched in various studies globally, these guidelines may need to be updated as new evidence comes to light. At the time of writing, the most up to date data available have been used to develop this implementation guide.

With mounting evidence on BPaL use, global policy will recommend programmatic use in the not-too-distant future. This guide is aimed to equip countries in preparation for this.

Enjoy using BPaL in your patients – they will generally culture convert quickly and be grateful for the lower pill burden. It is a wonderful privilege to help patients regain their health and autonomy and not present a risk to their loved ones – more easily than ever before!

BACKGROUND

In August of 2019, the United States Food and Drug Administration (USFDA) approved the new anti-tuberculous drug pretomanid within the context of a six to nine-month, three-drug regimen that also includes bedaquiline and high dose linezolid. This regimen—known as the BPaL regimen—was approved under a new USFDA pathway known as the "Limited Population Pathway for Antibacterial and Antifungal Drugs[iii]." Pretomanid is only the third new anti-tuberculosis (TB) drug approved for use by the USFDA in more than 40 years and the first non-conditional approval. The BPaL regimen, studied in the Nix-TB clinical trial[iv], received approval for people with extensively drug-resistant tuberculosis (XDR-TB), intolerance to multidrug-resistant tuberculosis (MDR-TB) treatment, or non-response to MDR-TB treatment. Nix-TB data have demonstrated a successful outcome in 90 percent of patients after six months of treatment with BPaL and six months of post-treatment follow-up. After the primary endpoint, one patient relapsed 15 months after treatment, and one was lost to follow up. Favourable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% MITT) independent of sex or HIV status.[v]

In a December 2019 Rapid Communication[vi], the World Health Organization (WHO) made the following recommendation on the BPaL regimen: "Limitations in study design and the small number of participants (108), observed adverse events preclude programmatic implementation of the regimen worldwide until additional evidence has been generated. However, BPaL regimen may be used under operational research conditions conforming to WHO standards." The WHO recommended that BPaL be used in persons with XDR-TB without prior exposure to bedaquiline or linezolid for more than two weeks which was aligned to the definition of XDR-TB at the time (to note: the 2020 updated definition is referenced in this guide). Most recently, the WHO confirmed this recommendation in their June 2020 Consolidated Guidelines[i] on Tuberculosis, stating that the BPaL regimen may be used under operational research conditions in MDR-TB patients with additional fluoroquinolone resistance who either had no previous exposure to bedaquiline and linezolid or had been exposed for no more than two weeks. Interestingly the South African BPaL CAP is only excluding more than 28 days of BDQ/LZD.

The use of BPaL should be accompanied by individual informed consent, adequate counselling on benefits and potential harms, and active monitoring and management of adverse events. Reproductive toxicities have been observed in animal studies; thus, BPaL should not be used in pregnant women and children. Examples of consent forms, developed by the WHO and KNCV, can be found in Annex A and be adapted to the local context in which the regimen is being used.

Following the initial USFDA approval, there have been additional approvals for the BPaL regimen. In June 2020, the Drug Controller General of India (DCGI) approved the anti-tuberculosis drug pretomanid for conditional access under the National Tuberculosis Elimination Program program, making India the second country in the world to provide regulatory approval for this product. European Commission (EC) conditional marketing authorization for pretomanid, as part of the BPaL regimen, was granted in August 2020; pretomanid was listed as a prequalified medicinal product by the WHO in November 2020. Pretomanid has been made available for 150 low and middle-income countries through Stop TB Partnership's Global Drug Facility, a mechanism for the procurement of TB therapies, at a

price of $364 for a six-month treatment course. A costing study conducted by KNCV in Indonesia, Kyrgyzstan and Nigeria showed that BPaL would save US$ 4000-9500/patient in drug costs and US$ 6500-11000/patient in overall costs (drugs + treatment + treatment monitoring) in these countries. This study was conducted from a programmatic perspective and did not include patient costs or savings.

Given these approvals and WHO guidance, there are efforts to expand global access to the BPaL regimen. TB Alliance, the non-profit organization that developed pretomanid, announced an initiative in October 2020 to broaden the adoption and scale-up of new TB treatment regimens, beginning with the BPaL regimen. This initiative, known as LIFT-TB (Leveraging Innovation for Faster Treatment of Tuberculosis), will also seek to increase treatment completion rates for drug-resistant forms of TB in some of the countries most affected by this form of TB across the Southeast and Central Asian regions, namely Indonesia, Myanmar, The Philippines, Vietnam, Kyrgyzstan, Ukraine, and Uzbekistan. The five-year project is a commitment by the TB Alliance and the Republic of Korea and will be implemented in partnership with the International Tuberculosis Research Center (ITRC) in Korea; the project will rely on technical assistance from other international and national technical partners, including KNCV Tuberculosis Foundation.

In March 2021, the South African National Department of Health began a prospective cohort study under a clinical access programme of the BPaL regimen for approximately 400 patients at several sites across the country. The study's protocol was approved by the South African Health Products Regulatory Authority (SAHPRA) and had oversight from the National Clinical Advisory Committee (NCAC). Persons 14 years and over, with pre-XDR-TB, XDR-TB, and both the inhA and katG mutations, will be included. Additionally, persons with RR-TB/MDR-TB not qualifying for the national MDR-TB short regimen, with a compelling indication for BPaL, may be enrolled at individual clinician discretion and with individual approval of the NCAC. Bedaquiline and linezolid resistance testing will be done at baseline for all persons to rule out resistance.

Research and Development Studies

Completed research:

Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines. During early development, pretomanid was referred to as PA-824. Pretomanid is an oral tablet formulation for the treatment of tuberculosis in combination with other anti-tuberculosis agents.

The approval of pretomanid for use in the BPaL regimen was based on a single-arm study, namely the Nix-TB trial,[v] that included 109 participants. In the FDA's review, the 89% favourable outcomes of the BPaL regimen were compared to a non-concurrent historical control group that excluded anyone who had received bedaquiline and/or linezolid as part of another regimen. As a result, the non-concurrent historical control group consisted mostly of persons treated with regimens comprised of drugs that have been deprioritised or are no longer recommended by the WHO.

A follow-up study to Nix-TB was another TB Alliance study called ZeNix[vii], a four-arm, randomized, double-blinded study that enrolled 181 patients with highly drug-resistant forms

of TB in South Africa, Russia, Georgia and Moldova. Blinding was in relation to the dosage and duration of linezolid. Per the intent to treat analysis, the success rate for participants receiving the highest dosage of linezolid (1200mg for six months) was 93%. The efficacy level was similarly high in the remaining arms, reported as 89% among participants receiving 1200mg of linezolid for 2 months, 91% for those receiving 600mg of linezolid for six months, and 84% among those receiving 600mg of linezolid for 2 months. Dosing of bedaquiline and pretomanid was consistent across the four arms.

Current research:

- Enrollment was completed in TB Alliance's phase 3 SimpliciTB clinical trial evaluating the safety and efficacy of Pretomanid-containing regimens. BPaMZ is one of the regimens used in the trial. Results are expected later in 2021.
- The TB PRACTECAL study, also closed to enrollment, utilises BPaL in a modified regimen. It is a multi-centre, multi-arm, open-label, randomised, controlled, phase II-III trial aimed at identifying a shortened, safe, effective and tolerable new treatment regimen for adults with pulmonary MDR-TB. Treatment options include various BPaL-containing experimental regimens with or without an additional drug. The BPaL only arm prescribes bedaquiline at 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks, pretomanid at 200mg once daily for 24 weeks and linezolid at 600mg daily for 16 weeks, then 300mg daily (or 600mg x3/wk) for the remaining 8 weeks or earlier when moderately tolerated.)
- Disease population & burden/epidemiological data (e.g., WHO, local data)
- Currently, there are various implementation research projects conducted globally utilising this regimen.

Country-wise Overview of BPaL Implementation Research (as of Aug 2021)

COUNTRY	LIFT-TB	TB REACH	Local/other donors	Planning
Indonesia	Schedule: TBD/TBC			
Vietnam	Imminent			
Philippines	Commenced			
Myanmar	Schedule: TBD/TBC			
Kyrgyzstan	Imminent			
Uzbekistan	Imminent			
Ukraine	Commenced	Commenced		
Tajikistan		Commenced		
Nigeria			Commenced	
India			Schedule: TBD/TBC	
South Africa			Commenced	
Kazakhstan				Schedule: TBD/TBC
Ghana			Commenced	
Lao PDR			Commenced	

Source: TB Alliance *https://www.tballiance.org/access/countries* Accessed: 2 September 2021

KEY POINTS:

- In August 2019 BPaL received FDA approval for use in approval for people with extensively drug-resistant tuberculosis (XDR-TB), intolerance to multidrug-resistant tuberculosis (MDR-TB) treatment, or non-response to MDR-TB treatment.
- Initial approval followed the results of the TB Alliance Nix-TB trial, showing a successful outcome in 90 percent of patients after six months of treatment with BPaL and six months of post-treatment follow-up.
- Various other studies are/have also been conducted globally using the BPaL regimen, including clinical trials and implementation research.
- The most recent clinical trial to present results is ZeNix which included dose finding for the optimization of linezolid. Results showed that treatment success for participants receiving the highest dosage of linezolid (1200mg for six months) was 93%. The efficacy level was similarly high in the remaining arms, reported as 89% among participants receiving 1200mg of linezolid for 2 months; 91% for those receiving 600mg of linezolid for six months, and 84% among those receiving 600mg of linezolid for 2 months.
- The recent ZeNix results could alter the FDA approved dosing in future

DRUG INFORMATION

The information provided below (in Table 1) on bedaquiline and Linezolid encompasses their role in MDR-TB management overall whereas the information for pretomanid is **only** in relation to its role in the BPaL regimen. (Further information captured in Annex B)

Table 1: Bedaquiline (B), Pretomanid (Pa) and Linezolid (L) Drug Information

	Bedaquiline (B)	Pretomanid (Pa)	Linezolid (L)
Indication and usage	• Indicated as part of combination therapy in the treatment of adult and paediatric patients (6 years and older and weighing at least 15 kg) with pulmonary MDR-TB.	• Indicated for use in a limited and specific population of patients. • Registered for used in combination with bedaquiline and linezolid for the treatment of adults with pulmonary XDR or treatment-intolerant or nonresponsive MDR- TB.	• Indicated for gram-positive infections and approved for, amongst other indications, the treatment of bacterial pneumonia • Also used off-label for treatment of DRTB.
Dosage and administration (see footnote for method of administration)	• Adults: Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week;	• Adults: 200mg once daily orally	• **Use of LZD outside of the BPaL regimen:** Adults: 600 mg, once daily. (Reduce to 400–300 mg/day, with caution, if serious adverse effects develop). • **Within the BPaL regimen, LZD is dosed at 1200mg.** • Children: 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg), twice daily in older children. 5 10 mg/kg/dose every 12 hours.

	Bedaquiline (B)	Pretomanid (Pa)	Linezolid (L)
			• Vitamin B6: All patients should receive vitamin B6 while receiving linezolid.
Contraindications (C/I)	• Should not be administered: ○ with EFV ○ in patients with known Torsades de Point or existing QtcF prolongation	• If used in the BPaL regimen, should not be administered if bedaquiline and/or linezolid is contraindicated.	• Should not be administered if: ○ Hypersensitivity to oxazolidinones. ○ Severe peripheral neuropathy (pain, numbness, tingling or weakness in the extremities). Grade 1 PN is not a C/I nor is grade 2 if balance favours LZD use • Certain concomitant medications are contraindicated, see Table 3
Warnings and precautions	**Increased Mortality** No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat tuberculosis, HIV status, or severity of disease was observed. **QT Prolongation**	**Hepatotoxicity / Hepatic adverse reactions**	• **Problems with vision** such as blurred vision, changes in colour vision, difficulty in seeing detail, field of vision becomes restricted. • **Severe diarrhoea** containing blood and/or mucus which in rare circumstances may develop into complications that are life-threatening. • **Peripheral neuropathy** • **Anaemia**

Method of Administration for Bedaquiline

Each administration method requires BDQ to be taken with food.

There is one method of administration of BDQ 100 mg tablet and four different methods of administration of BDQ 20 mg tablet as follows:

- For BDQ 100 mg tablet, administer the tablet whole with water.
- For BDQ 20 mg tablet, the four different methods of administration are outlined below.

*Administration of 20 mg Tablets to Patients who **Can** Swallow Intact Tablets:*

- Administer BDQ 20 mg tablet whole or divided in half along the functional score line into two equal halves of 10 mg each. Administer BDQ 20 mg tablet with water. Take with food.

*Administration of 20 mg Tablets to Patients who **Cannot** Swallow Intact Tablets:*

- Dispersed in Water and Administered with Beverage or Soft Food

For patients who have difficulty swallowing intact tablets, BDQ 20 mg tablet can be dispersed in water and administered. To aid with administration, the dispersed mixture in water can be further mixed with a beverage (e.g., water, milk products, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g., yogurt, apple sauce, mashed banana or porridge) as follows:

- Disperse tablets in water (maximum of 5 tablets in 5 mL of water) in a drinking cup.
- Mix the contents of the cup well until the tablets are completely dispersed and then orally administer the contents of the cup immediately with food. To aid with administration, the dispersed mixture in water can be further mixed with at least 5 mL of beverage or 1 teaspoonful of soft food and then orally administer the contents of the cup immediately.
- If the total dose requires more than 5 tablets, repeat the above preparation steps with the appropriate number of additional tablets until the desired dose is reached.

Method of administration for LZD

This medicine may be taken with or without food. Take it with food if it irritates the stomach. Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers and red wines.

Method of administration for Pa

For oral use. Pretomanid should be taken with food (preferably with a high-fat, high-calorie meal) and tablets should be swallowed with water.

KEY POINTS:

Warnings/ side effects with the individual drugs:

- BDQ: QT prolongation
- Pretomanid: Liver toxicity/ adverse events
- Linezolid: PN, anaemia, severe diarrhoea and visual disturbances

Precautions:

- BDQ should not be administered to patients with pre-existing QT prolongation or on EFV.
- Linezolid should not be administered to patients with pre-existing PN.
- *Warnings and precautions related to bedaquiline and linezolid also apply to their use in the combination regimen with pretomanid tablets.

Administration:

- BDQ is administered with food; for patients experiencing difficulty in swallowing disperse maximum of 5 tablets in 5 ml water. An additional 5ml can be followed by immediate administration. These preparation steps can be repeated for doses requiring more than 5 tablets.
- Linezolid can be taken with or without food, preferably with food if causing GI upset.

TREATMENT REGIMENS

This section describes the patient population to benefit from this regimen while limiting risk profile using set inclusion and exclusion criteria and limitations of use.

Patient Selection

The BPaL[viii] regimen was approved in August 2019 by the U.S. Food and Drug Administration (FDA) for the treatment of adults with pulmonary XDR-TB or MDR-TB that is treatment-intolerant or non-responsive.

Limitations of Use:

Pretomanid Tablets are not indicated for patients with:

- Drug-sensitive (DS) tuberculosis
- Latent infection due to Mycobacterium tuberculosis
- Extra-pulmonary infection (EPTB) due to *Mycobacterium tuberculosis**

  **Although EPTB is listed as a contra-indication, some patients have been enrolled into clinical trials provided that their EPTB does not involve bone or brain, and there is also evidence of pulmonary TB.*
- MDR-TB that is not treatment-intolerant or non-responsive to standard therapy
- The safety and effectiveness of pretomanid has not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen.
- Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1,200 mg daily orally for up to 26 weeks). This is the current recommendation.

BPaL is registered for use in certain patients; inclusion and exclusion criteria still apply to select patients for this regimen. A more pragmatic approach can, however, be applied as compared to that of the clinical trial setting. The following criteria is taken directly from the South African Clinical Access Program protocol and is unaltered for research terminology. It does however offer valuable guidance on patient selection in a programme setting as well.[ix]

Inclusion criteria:

1. Provide written, informed consent prior to all study-related procedures (if under 18, include legal guardian consent).
2. Body weight of ≥35 kg (in light clothing and no shoes).
3. Willingness and ability to attend scheduled follow-up visits and undergo study assessments.

4. Provide consent to HIV testing (if an HIV test was performed within 1 month prior to study start, it should not be repeated as long as documentation can be provided [ELISA and/or Western Blot]. If HIV status is a confirmed known positive, repeated HIV test is not needed provided documentation is available.)
5. Male or female, aged 14 years or above.
6. Participants with one of the following TB conditions:
    a) Pulmonary Pre XDR-TB with documented resistance to rifamycins and a fluoroquinolone at any time or at screening by any approved method- genotypic or phenotypic;
    b) Pulmonary RR-TB with documented resistance to rifamycins in selected patients whom the investigator thinks will benefit from the BPaL regimen. (e.g, non-response or intolerance)
    c) Some patients with extra-pulmonary DR-TB (resistance as per a and b) could qualify if there is evidence pulmonary involvement and no brain or bone involvement.
7. Chest X-Ray picture (taken within three months prior to screening) consistent with pulmonary TB in the opinion of the Investigator.
8. Be of non-childbearing potential or using effective methods of birth control, as defined below:
    a) Non-childbearing potential:
        - Participant - not heterosexually active or practices sexual abstinence; or
        - Female Participant/sexual partner - bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy or has been postmenopausal with a history of no menses for at least 12 consecutive months; or
        - Male Participant/sexual partner - vasectomised or has had a bilateral orchiectomy minimally three months prior to screening.
    b) Effective birth control methods:

        A double contraceptive method should be used as follows:

        - Double barrier method which can include any 2 of the following: a male condom, diaphragm, cervical cap, or female condom (male and female condoms should not be used together); or
        - Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female Participant/partner;
        - And are willing to continue practicing birth control methods throughout treatment and for six months (both male and female Participants) after the last dose of study medication or discontinuation from study medication in case of premature discontinuation.

Exclusion Criteria:

Based on Medical History

1. History of allergy or known hypersensitivity to any of the Investigational Medicinal Products or related substances.
2. Having participated in other clinical studies with dosing of investigational agents within 8 weeks prior to study start or currently enrolled in an investigational study that includes treatment with medicinal agents. Participants who are participating in observational studies or who are in a follow up period of a study that included drug therapy may be considered for inclusion.
3. Significant cardiac arrhythmia requiring medication.
4. Participants with the following at Screening:
    a) QTcF interval on ECG >500 msec
    b) History of additional risk factors for Torsade de Pointes, (e.g., heart failure, hypokalaemia, family history of Long QT Syndrome);
    c) Clinically significant ventricular arrhythmias.
5. Females who have a positive pregnancy test at screening or already known to be pregnant, breast-feeding, or planning to conceive a child during the study or within six months of cessation of treatment. Males planning to conceive a child during the study or within six months of cessation of treatment.
6. A peripheral neuropathy of Grade 3 or 4, according to DMID (Appendix 2). Or, participants with a Grade 1 or 2 neuropathy which is likely to progress/worsen over the course of the study, in the opinion of the Investigator.

Based on Specific Treatments

7. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of treatment assignment.
8. Concomitant use of serotonergic antidepressants or prior use within 3 days of treatment assignment if Investigator foresees potential risks for serotonin syndrome when combined with linezolid.
9. Concomitant use of any drug known to prolong QTc interval (including, but not limited to, amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, fluoroquinolones, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
10. Concomitant use of any drug known to induce myelosuppression.
11. Use of any drugs or substances within 30 days prior to dosing known to be strong inhibitors or inducers of cytochrome P450 enzymes (including but not limited to quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin,

cocaine, furafylline, cimetidine, dextromethorphan). Exceptions may be made for participants that have received 3 days or less of one of these drugs or

12. Participants may have previously been treated for DS/MDR-TB (with specific exceptions for bedaquiline and/or linezolid as noted below)
13. Participants should not receive more than 4 weeks of bedaquiline or linezolid prior to enrolment/first dose of BPaL.

Based on Laboratory Abnormalities

14. Participants with the following toxicities at screening (labs may be repeated) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007):
    a) Haemoglobin level < 8.0 g/dl
    b) Platelets grade 2 or greater(<75,000/mm3);
    c) Absolute neutrophil count (ANC) < 1000/ mm3;
    d) Alanine aminotransferase Grade 3 or greater (> 3.0 x ULN) to be excluded
    e) Serum creatinine level greater than 2 times upper limit of the normal laboratory reference range.

Dosage:

BPaL regimen should be administered orally for six months with a possible extension up to nine months.

The dosing intervals are as follows, with all 3 drugs to be given simultaneously:

- Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week;
- Pretomanid 200mg once daily;
- Linezolid 1200mg once daily.

Alternate regimen:

Considerations in altering the above approved dosages are underway following the recently published ZeNix study results showing the efficacy of a reduced linezolid dose. This is however still pending FDA approval.

If approved, the new dosing schedule will be as follows:

- Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week;
- Pretomanid 200mg once daily;
- Linezolid 600mg once daily.

The route and duration of treatment will be as for the current dosing regimen, with the extension until 9 months if indicated.

Special populations

According to the WHO Operational Handbook on Tuberculosis[x] the following considerations should be taken when managing special populations.

Children. Adolescents above 14yrs of age can start the BPaL regimen if they weigh above 35kg. The regimen is not yet registered for children younger than 14. Countries should defer to their regulatory frameworks.[x]

As children aged 0–13 years were excluded from the Nix-TB study; no analysis specific to this subgroup of patients could be performed. It is recommended that children with pulmonary MDR/RR-TB with additional resistance to fluoroquinolones be given the same consideration for longer treatment regimens as adults so as to include components with a better-established safety profile. Bedaquiline is currently only recommended for children aged 6 years and above. Additional data on the use of BPaL in eligible children would be useful, and this may be a feature of carefully planned and monitored future research.

People living with HIV. PLHIV represented half of those enrolled in the Nix-TB study; however, it was impossible to perform any adjusted stratified analyses for PLHIV, owing to the small sample size. It is important to note drug–drug interactions when co-administering TB and HIV medications, including the documented interactions between bedaquiline and efavirenz. Efavirenz also reduces pretomanid exposures significantly – therefore, an alternative antiretroviral agent should be considered if the BPaL regimen is used. Regimens including zidovudine should be used with special caution because zidovudine and linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross toxicity.

Pregnant and lactating women were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. For pregnant and lactating women, a longer regimen should be individualized to include components with a better-established safety profile. Where this is the case, documentation of the treatment and pregnancy outcomes (including infant characteristics), and postpartum surveillance for congenital anomalies would help inform future recommendations for MDR-TB treatment during pregnancy. The use of bedaquiline in pregnancy is associated with infants born with a lower mean birth weight when compared with infants whose mothers did not take Bedaquiline; however, this did not appear to be a clinically significant finding when infants were followed up over time. Breastfeeding is not recommended for women taking BPaL.

Extrapulmonary TB. Patients with lone extrapulmonary TB were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. The WHO recommendations on MDR-TB regimens apply to patients with extrapulmonary disease, including for those with TB meningitis. There is limited data on the CNS penetration of bedaquiline or pretomanid.

Patients with very limited treatment options. In some instances, patients will have extensive drug-resistance profiles that may make it difficult (or impossible) to construct a regimen based on existing WHO recommendations. In such situations, the patient's life may be endangered. Therefore, for individual patients for whom it is not possible to design an effective regimen based on existing recommendations, the BPaL regimen may be considered as a last resort under prevailing ethical standards. In such patients, the use of BPaL should

be accompanied by individual patient informed consent, adequate counselling on the potential benefits and harms, and active monitoring and management of adverse events. Patients should also be advised that reproductive toxicities have been observed in animal studies, and that the potential effects on human male fertility have not been adequately evaluated at this time.

Key Points:

- The BPaL regimen is currently approved by the FDA only for the treatment of adults (>14years) with pulmonary XDR-TB or MDR-TB that is treatment-intolerant or non-responsive.
- There are inclusion and exclusion criteria to consider when deciding to start a patient on BPaL to ensure its safety and efficacy.
- The current approved dosing schedule and interval is as follows, with the drugs prescribed for that day to be taken simultaneously:
    - Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week;
    - Pretomanid 200mg once daily;
    - Linezolid 1200mg once daily.
- The above dosing of linezolid could be reduced to 600mg daily in the near future pending FDA approval (based on the ZeNix study results).
- Since bedaquiline and linezolid are being used widely already, there are few absolute contraindications. It is however not currently recommended in pregnant and lactating women as well as in patients with EPTB involving the brain and bone.
- BPaL can be given to HIV positive patients and adolescents (with certain considerations).

PATIENT MONITORING

Monitoring Table

Table 2: Suggested Schedule of examinations (as proposed in the SA BPaL CAP Protocol)

Period	Screening[a]		Treatment								9 Month Treatment ONLY[p]			Early With-drawal (Treatment)	Post Treatment Follow-up Period[b]					
Time of Visit	**Up to 30 days prior to Treatment**	**Day 1[c]**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**Week 30**	**Week 34**	**Week 39**		**4 weeks**	**8 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**52 weeks**
Visit Window[n]	N/A																			
Informed Consent	X																			
Demography	X																			
Medical/Treatment History	X																			
Inclusion/Exclusion	X	X																		
HIV Status[d]	X																			
CD4 Count[e]	X																			
Chest X-Ray[f]	X																			
Urine Pregnancy Test[g]	X	X		X	X					x[h]			x[h]	X						

Period	Screening[a]		Treatment								9 Month Treatment ONLY[p]			Early With-drawal (Treatment)	Post Treatment Follow-up Period[b]					
Time of Visit	Up to 30 days prior to Treatment	Day 1[c]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 26	Week 30	Week 34	Week 39		4 weeks	8 weeks	12 weeks	24 weeks	36 weeks	52 weeks
Ophthalmic Exam[i]	X			X	X	X	X	X	X	X	X	X	X	X				X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X
Single 12-LeadECG	X	X		X	X		X			x[h]	X		x[h]	X						
Physical Exam[j]	X	X	X	X	X	X	X	X	X	x[h]			x[h]	X			X	X	X	X
Laboratory Safety Tests[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication / Compliance[l]		X	X	X	X	X	X	X	X	X	X	X	X	X						
Sputum[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy	X			X	X	X	X	X	X	X	X	X	X	X			X	X	X	X

Notes:

- Unscheduled visits should be planned to assess, confirm, and follow up on clinically relevant AEs or laboratory abnormalities.
- On days where the following assessments are done the order should be: ECG before vital signs, blood draws (for Safety).
    a. Screening: Screening assessments can occur on different days within 30 days prior to treatment.
    b. Post Treatment Follow-up Period: Participants will be followed for 52 weeks following the end of treatment.
    c. Day 1 (baseline): All procedures are to be completed prior to dosing.
    d. HIV testing: If HIV status is a confirmed known positive, repeated HIV test is not needed provided documentation is available. If HIV status is unknown or suspected negative, HIV test should be requested.
    e. CD4 count: For all HIV-positive Participants.
    f. Chest X-Ray: Chest X-Ray at Screening or within 3 months prior to Screening. The Investigator is responsible for its review and analysis for participant inclusion.
    g. Serum or Urine Pregnancy: Women of child-bearing potential only, whether they are sexually active or not.
    h. Final Treatment Visit: Urine Pregnancy Test, Full Physical Examination, 12-lead ECG.
    i. Ophthalmic Exam: To include Ophthalmologic Medical history at Screening; All exams to include Visual Acuity. Can be done by any trained study staff throughout the study.
    j. Physical Exam: Full Physical Exam to include gross neurological exam. All other PEs should be limited to weight and a pulmonary, cardiovascular and abdominal exam.
    Safety Laboratory Assessments: Refer to section 6.2 for details of laboratory safety assessments.
    k. Study Medication/Compliance: Study medication administration will be supervised per local site practice to assure compliance to regimen.
    l. Sputum Sampling: One sputum sample will be taken at each visit, when possible, an early morning specimen.
    m. Visit Windows
- Week 1 through Week 16: ± 3 days
- Weeks 20 through End of Treatment (Week 26 or 39): ± 7 days
- Post-Treatment Follow-Up Visits (4 – 52 weeks): ± 2 weeks

The visit windows noted on the flowchart for timing of visit also apply to timing within a visit. For example, procedures that are difficult to schedule such as ophthalmology exams, should be scheduled within +/- 3 days of scheduled visit.

BPaL Treatment Discontinuation

Treatment can be discontinued for the following reasons:

- Withdrawal of consent;
- Lost to Follow-Up;
- In the interest of the patient based on safety reasons;
- Pregnancy;
- Patient non-compliance (to BPaL and associated treatment requirements).

Upon discontinuation of BPaL, patients should be referred to and managed by a unit specializing in the treatment of complex DR-TB cases.

Temporary Dose Interruptions and Modifications

- For patients experiencing suspected drug related toxicities due to linezolid, the daily dose of linezolid may be reduced or may be temporarily halted. Generally, if temporarily halted, it should be re-instituted at a lower dose. Generally, a step down in dose could proceed from 1200 mg QD to 600 mg QD. In some instances, the dose of linezolid may be re-started at the same dose at discretion of the attending physician.
- If patients experience toxicity issues with linezolid that would prohibit further treatment with that drug, they can remain on the bedaquiline and pretomanid if they received the initial 1200 mg QD dose of linezolid for at least the first four weeks of treatment and they are smear negative or with trace results and judged to be clinically improving by the attending physician.
- For patients experiencing suspected drug related toxicities due to other drugs in the BPaL regimen, the full regimen may be halted for up to 35 consecutive days.
- Patients on six months of treatment should complete a full course of treatment (i.e., 26 weeks of prescribed doses) within an eight-month treatment period (a total halt of up to 60 days if on six months) while patients on nine months of treatment should complete a full course of (i.e., 39 weeks of prescribed doses) treatment within a 12-month treatment period (a total halt of 90 days if on nine months of treatment).
- For patients who complete the first four consecutive weeks of treatment on the 1200 mg linezolid total dose and later in treatment period only halted linezolid, treatment can be considered complete at six months, even if there were multiple interruptions and rechallenges of linezolid alone while the patient remained on pretomanid and bedaquiline.
- When the total of missed dosing days and/or pauses is greater than seven days, the same number of missed dosing days should be dispensed/treatment extended to make up for the total missed doses.

At no time should the patient be treated with a single agent.

Stopping Rules

There are no specific stopping rules advised for clinical access programmes and country specific regulations should be followed.

Restrictions

Prior and Concomitant Medications and Other Treatments

Concomitant medications should be kept to a minimum. However, if concomitant medications are considered to be necessary for the patient's welfare and are unlikely to interfere with the TB regimen, they may be given at the discretion of the treating clinician.

The prescribing information for all concomitant medication should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected in order to prevent any potentially serious and/or life-threatening drug interactions.

The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the TB regimen:

- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
- Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g., phenelzine, isocarboxazid).
- Concomitant use of any drug known to prolong the QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
    - Treatment with fluoroquinolones is strongly discouraged as they are known to prolong the QTc interval. They should only be used to treat intercurrent non-TB infections and only if the benefit of treatment outweighs the risk of a prolonged QTc interval.
- Concomitant use of any drug known to induce myelosuppression.
- The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days.
- The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, rifamycins and systemic dexamethasone.

Concomitant use of serotonergic antidepressants should be avoided if possible as patients on these agents and linezolid are at risk for serotonin syndrome.

Caution should be used in treating diabetic patients receiving insulin or oral hypoglycaemic agents as cases have been reported of hypoglycaemic reactions when patients on these agents have been treated with linezolid.

Any drug known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period

Antiretroviral Therapy

Patients taking bedaquiline should avoid efavirenz due to drug-drug interactions with bedaquiline, and thus examples of allowed treatment include but are not limited to the following:

- Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia™) in combination with either TDF or ABC with 3TC/FTC;
- Raltegravir or dolutegravir in combination with appropriate nucleoside reverse transcriptase inhibitors TDF or ABC with 3TC/FTC

Other Restrictions

Alcohol should be avoided while on the TB regimen, especially in patients with impaired hepatic function.

Investigational Medicinal Product

Treatment regimen

Patients will receive oral dosing as described below.

- Bedaquiline Days 1-14: 400mg once daily (4 x bedaquiline 100 mg tablets),
- Bedaquiline Weeks 3-26/39*: 200mg three times per week (2 x bedaquiline 100 mg tablets); **plus**
- Linezolid 1200mg once daily day 1 through week 26 or 39* (2 x scored linezolid 600 mg tablets); **plus**
- Pretomanid 200mg once daily Day 1 through week 26 or 39* (1 x pretomanid 200 mg tablet)**.**

Patients will receive a minimum of six months of treatment. If a patient is culture positive or reverts to being culture positive between their week 16 and 26 visits and their clinical condition suggests they may have ongoing TB infection, they may have treatment extended to 36 weeks (with 52 weeks of follow up).

If culture results between week 16 and 26 are contaminated, missing, or considered an isolated positive without clinical significance, use available culture results to make this decision and consult with local clinical advisory committee. All decisions regarding treatment extension should be discussed with local clinical advisory committee before implementation.

BPaL Administration

The patient should be instructed to:

- Take BPaL orally once daily with food for 26 weeks, preferably at the same time every day, with a glass of water;
- Take BPaL either 30 minutes before to 30 minutes after a meal;
- If the patient vomits up to half an hour after taking treatment, the dose may be repeated only once.

Overdose

Overdose of anti-tuberculosis medicines will be assessed by the clinician to determine whether the overdose was as a result of an adverse event e.g., suicidal ideation, or led to an adverse event.

Key Points:

- It is important to follow a set monitoring schedule that includes screening tests prior to initiation as well as monitoring of microbiology, safety test and clinical assessments such as peripheral neuropathy checks over the course of treatment.
- Patients experiencing LZD toxicity can have their LZD dose lowered or temporarily halted. The entire regimen can be halted for up to 35 days if toxicity to one of the other drugs are experienced. Lowering of the dose is recommended as a step down in dose approach. dose lowered or temporarily halted. The entire regimen can be halted for up to 35 days if toxicity to one of the other drugs are experienced. Lowering of the dose is recommended as a step down in dose approach.
- At no time should the patient be treated with a single agent.
- Concomitant medication should be kept to a minimum if feasible as certain medication is considered prohibited concomitant meds.
- HIV positive patients taking BDQ should avoid efavirenz due to drug-drug interactions and an alternative ARV regimen should be given. Similarly, interactions between zidovudine and linezolid are noted and concomitant administration should be avoided.

SIDE-EFFECT MANAGEMENT

Clinical Management of Adverse Events

The BPaL regimen has various adverse events associated with its use. These events are common, but manageable. Management of key adverse events are described below with further guidance available in the appendices. The adverse events should be reported according to the country's active drug-safety monitoring and management.

The most notable adverse events are associated with the use of high dose LZD. The following section is intended to guide clinicians in managing specific toxicities related to LZD. Decisions must be made in the context of the overall health status of the participant.

Note on linezolid toxicity management:

The expected LZD toxicities of peripheral neuropathy and myelosuppression are common, but generally manageable. While adverse events tend to occur more commonly with higher doses, they usually improve or resolve after interruption of treatment, with re-challenge at half the dose after improvement of the symptoms. Immediate dose reduction without interruption is also an option for mild to moderate adverse events.

Efforts should be made for patients to complete at least 8 weeks of LZD at 1200mg or 600mg/day before discontinuing LZD altogether. In patients with cavitary or otherwise severe disease the clinician should err on the side of giving as much LZD as possible before discontinuation for toxicity reasons. Further detailed guidance can be found below under each system.

The below algorithm guides the management of linezolid adverse events.

Figure 1: Algorithm for the management of linezolid toxicity

BPaL Adverse Events Management per physiological system:

The below clinical management guidance was adapted from the MSF TB-PRACTECAL Clinical trial AE guide. As the trial AE guide is aimed towards the management of clinical trial patients, additional guidance was obtained from clinicians implementing BPaL to make it more pragmatic for the TB programme setting.

Neurological

Peripheral neuropathy

Symptoms: Tingling or burning sensation of the toes/feet and/or fingers in glove and stocking distribution and/or impairment of sensation. May only be detected on clinical examination.

Peripheral neuropathy may be more common when patients have other conditions or treatment that may also cause PN, notably diabetes mellitus, HIV, medicines including the thymidine analogues in HIV treatment, and terizidone and INH in TB treatment. Peripheral neuropathy is more commonly seen after several months of treatment.

The more commonly seen progression of symptoms is as follows: patient complains of coldness or numbness of the distal feet, which tends to progress to pins and needles, and sometimes a burning sensation. Some patients complain of a cramping sensation. These symptoms tend to move proximally with time. Objectively the clinician may note an antalgic gait and toe-walking, hyperesthesia, and reduced vibration sense at the first metatarsal joint.

The decision to interrupt LZD dose is usually made in consultation with the patient, as patients have differing levels of tolerance for this adverse event.

Generally, once PN is judged to interfere significantly with walking or sleeping, and there is pain, either pins and needles or burning, the LZD dose should be interrupted and re-challenged at half dose after the patient experiences improvement in symptoms. If there is no vibration sense at the toe, or symptoms are said to spread to the level of the knee or higher, also interrupt LZD.

Since this adverse event is believed to be related to mitochondrial toxicity, it is possible that symptoms will continue to worsen before they subjectively improve. Interruptions often span several weeks. If significant enough, LZD may be permanently discontinued.

Analgesia is usually ineffective, with opioids leading to dependence after extended periods. Some patients find gabapentin/pregabalin helpful.

Peripheral neuropathy improves over time, usually with resolution of burning and pins and needles, leaving the patient with residual numbness or coldness. This may be permanent. Early and active management of PN can mitigate this.

See Annex C for brief PN screening tool (developed and validated by the US ACTG network) to assist in diagnosis and screening

Differential diagnosis (causes). Hypokalaemia, hypothyroidism, alcohol, diabetes, B12 deficiency

Contraindicated medications: Carbamazepine Amitriptyline	**Use with caution:** SSRI/NSRI

Possible Responsible Drugs	
Lzd (Trd, Eto, H)	**Adverse event management** 1. Perform a neurological examination. 2. Consider differential diagnoses. Check electrolytes, TSH, blood sugar, HbA1c and review concomitant medications and alcohol history. 3. If grade 1, incremental increase in pyridoxine dose to a maximum of 150 mg/day 4. If grade 2, counsel patient and monitor closely. Start gabapentin if painful. Reduce linezolid dose to 600mg daily. 5. If grade 3 or 4 and diagnosis is confirmed, for a grade 3 it is advised to discuss treatment options with patient and in a grade 4, discontinue linezolid. Linezolid should NOT be reintroduced. Peripheral neuropathies caused by LZD are extremely painful and often irreversible. 6. Paracetamol may be helpful in refractory cases. 7. Counselling may be organized with the patient to better understand the symptoms and screen for other symptoms linked to LZD use (e.g., optic nerve neuropathy).

Gabapentin 300mg capsule	Peripheral neuropathy	*Neuropathic pain*, initially Day 1 – 300 mg once a day Day 2 – 300 mg two times a day Day 3 - 300 mg three times a day Some patients settle at this dose and can continue on 300mg tds for rest of the duration. Based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days Usual range 1.8g up to a maximum dose of 3600 mg/day (in 3 divided doses).	Adverse events: drowsiness Caution: Dose adj. in renal failure. Avoid stopping abruptly as this may cause anxiety, insomnia, nausea, pain and sweating; rather gradually reduce dose over at least a week

		The value and use of a dose above 1800g (for PN) is still debated. Pregabalin may be available in some centres. Dose according to Package Insert	

Optic neuropathy (optic nerve disorder)

Symptoms: Decreased visual acuity

Usually painless, acute presentation over days to weeks, usually later in course of linezolid use.

Clinicians should have a high index of suspicion for this adverse event, and patients should be counselled to inform the site if any visual changes are noted. Fortunately, optic neuritis from LZD seems to be reversible if detected early. A drop in distance visual acuity of two or more lines or new visual symptoms requires further investigation and interruption of LZD. Exclude other causes, i.e., patient not wearing glasses/contact lenses, migraine, etc. If optic neuritis is likely or confirmed LZD should not be re-challenged.

Differential diagnosis. Retinopathy, cataract, syphilis, other ophthalmic conditions.

NB: Optic neuropathy is idiosyncratic and may be irreversible. Early identification is essential to minimise permanent visual loss.

Possible Responsible Drugs	
Lzd	**Adverse event management** 1. Interrupt LZD while investigated. 2. Perform visual acuity. 3. Consult ophthalmologist for fundoscopic examination and to exclude other causes of visual changes. 4. Confirmed cases will lead to permanent discontinuation of linezolid.

QTc prolongation

Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval. This should be calculated as the mean QTcF of the machine recorded triplicate Electrocardiograms (ECGs).

Symptoms: Usually asymptomatic.

Contraindications: QT prolonging drugs. Use of concomitant fluconazole is sometimes not to be avoided. ECG frequency should be increased.

Possible Responsible Drugs	
B, Pa, Lzd	**Adverse event management** **QTcF 451-480 ms (Grade 1)*** 1. Check with patient any history of symptoms – syncope, chest pain, palpitations or dizziness. 2. Review medication history for any possible contributing non-TB drugs and cease if possible. 3. Check Mg2+ and K+. Replace as per schedule below. 4. If no concerning symptoms, repeat ECG at next visit. * This is not a concerning level, especially if patient was receiving MFX before starting BPaL. **QTcF 481-500 ms (Grade 2)** 1. Check with patient any history of symptoms – syncope, chest pain, palpitations or dizziness. 2. Review medication history for any possible contributing non-TB drugs and cease if possible. 3. Check for family history of torsades de pointes (TdP). 4. Check Mg2+ and K+. Replace as per schedule below. 5. Repeat ECG in 1 week (unless investigational schedule states prior – whichever is sooner). **QTcF >500 ms (Grade 3)** 1. Patients with a QTcF >500 ms are at 2-3 times an increased risk of TdP. This risk increases with increasing QTcF so patients with extremely long QTcF and/or marked deformation of the T and U waves should be treated cautiously. 2. The event of concern is TdP or other associated serious ventricular dysrhythmia. 3. Withhold all TB medications. **If patient is hospitalized:** 1. Take a full history to rule out palpitations, presyncope or syncope and any systemic factors. 2. Perform a full clinical examination. 3. Withhold QT prolonging medication or medication causing electrolyte disturbance. This includes quinolones, Pretomanid, Bedaquiline, and clofazimine as well as any diuretics. 4. Check electrolytes (especially K+, Mg2+, Ca2+) and replace as per electrolyte section – Renal and metabolic, maintaining values within the high-normal range (K+ between 4 and 5 mmol/L and Mg2+ between 0.75 and 0.90 mmol/L).

5. If no documented arrhythmia and QTcF>500ms (grade 3), consider continuous cardiac monitoring.
6. If documented arrhythmia (even if asymptomatic), always monitor.
7. Ensure access to an external cardiac defibrillator.
8. Minimum of a daily ECG to monitor the QT interval and to look for other adverse signs which may include bradycardia, frequent ventricular ectopy or T- wave macroalternans (alternating amplitude of T waves).
9. If QTcF is between 501 ms and 510 ms, contact cardiologist to discuss further steps.

If patient is in ambulatory care:

1. If electrolytes results will not be available within 24 hours, commence empirical magnesium therapy.
2. Take a full history to rule out palpitations, presyncope or syncope and any systemic factors. If the history suggests arrhythmia, then plan for hospitalisation (see “High-Risk” below).
3. Perform a full clinical examination.
4. Withdraw QT prolonging medication or medication causing electrolyte disturbance.
5. Assess the resting ECG for the severity of QT prolongation and for any adverse features as described above.
6. Check electrolytes (especially K+, Mg2+, Ca2+) and replace to achieve and maintain high-normal values.
7. The severity of the increase in QTc and the presence of any adverse features will inform the intensity of further monitoring. Clinical judgement will be required to classify risk:
    - Low risk– QTcF just over 500 ms, no other adverse clinical or ECG features. Patient has friends or family or is able to call for medical assistance themselves in case of clinical change. Consider repeat clinical assessment, ECG and serum electrolytes in 1 week.
    - Medium risk– QTcF > 550 ms but <600 ms, no other adverse clinical or ECG features. Patient has friends or family or is able to call for medical assistance themselves in case of clinical change. Admission may be indicated.
    - High risk– QTcF > 600 ms or any QTcF interval with adverse clinical or ECG features. Consider hospitalisation to allow daily assessment and access to cardiac monitoring and an external defibrillator.
8. QTc >= 501 and TdP or signs and symptoms of serious arrhythmia (Grade 4)
9. Follow local cardiac arrest protocol.
10. Once grade 3 (but QTcF above 510 msec) or 4 QT prolongation is confirmed by cardiologist, discontinue the regimen.

Haematologic

Platelets and absolute neutrophil counts are variable, and results should be repeated (within 3 days) * before interrupting LZD. Exclude other causes as far as possible, i.e., concomitant medications, known infective processes.

Interrupt LZD if any of the following criteria are noted:

- Confirmed* Absolute Neutrophil Count (ANC) – grade 3 or higher
- Confirmed* platelets – grade 3 or higher
- Haemoglobin below 8.0g/dL or symptomatic anaemia

* ANC and platelets can be variable. Repeat test before changing LZD dosing. Interruption for thrombocytopaenia secondary to LZD is uncommon. If thrombocytopaenia persists, investigate further for possible causes.

Haemoglobin levels do not have the same variability as platelets and ANC. If the haemoglobin is below 8.0g/dL, LZD should be interrupted and haemoglobin repeated at least weekly. If Hb is very low or patient symptomatic and unstable, blood transfusion is indicated. LZD may be restarted when the Hb is more than 8.0g/dL.

Re-challenge LZD once counts have improved (refer to Figure 1). Consider rechallenging at half dose. If no or little evidence of improvement within 1-2 weeks, continue investigating for other causes.

For patients on LZD requiring dose reduction or interruption, attempts should be made to reintroduce LZD potentially at a lower dose. Linezolid can also be reduced in a step wise manner from 1200mg to 600mg depending on the toxicity level. Once haematologically stable, FBC should be checked regularly during the subsequent 4 weeks following reintroductions.

Anaemia

Symptoms – pallor, shortness of breath, dizziness, angina,
Differential diagnosis: Haemolysis, anaemia of chronic disease, iron deficiency anaemia such as GI loss, B12 deficiency, renal failure, malabsorption

NB. In general, transfusion is only indicated if the patient is symptomatic (postural dizziness, short of breath on minimal exertion). Transfusion should be undertaken according to local guidelines. Many younger patients with reasonable cardio-respiratory reserve will tolerate levels lower than 7.0g/dL. Linezolid induced anaemia is reversible and patients will recover over days to weeks. Patients usually respond well to rechallenge at 600mg without further drops in Hb.

Possible Responsible Drugs	
Lzd	**Adverse event management** 1. **Hb 10.5 - 9.5 g/dL** - Monitor closely 2. **Hb 9.4 - 8.0 g/dL -** Consider reduction of dose of linezolid to 600mg daily 3. **Hb. 8.0 - 6.5 g/dL / < 6.5 g/dL** linezolid should be interrupted, consider transfusion. 4. Correct other causes incl. iron replacement if relevant. Give iron supplementation at least 2 hours before or after TB drugs. Iron supplementation may exacerbate GI adverse events and will not correct anaemia of chronic disease. 5. After cessation, when Hb > 8.0g/dL, the reintroduction of LZD should be considered. 6. FBC should be checked regularly for the subsequent 4 weeks during such reintroduction.

Ferrous sulphate	Treatment of iron deficiency anaemia	1-2 tablets per day for 3 months, then repeat haemoglobin. Preferably taken in evening with dinner to reduce stomach upset	Adverse events: abdominal pain, constipation, changes in stool to dark colour Cautions: reduces absorption of levofloxacin and moxifloxacin. Must be taken more than **2 hours before or after anti-TB drugs**.

Neutropenia

Symptoms: Fever with rapid progression to septic shock. Otherwise, patients may be asymptomatic.

Differential diagnosis: Occasionally associated with beta-lactam antibiotics and other medications.

Possible Responsible Drugs	
LZD,	**Adverse event management** 1. **1500 - 1000/mm3 and 999 - 750/mm3 -** Repeat to confirm. Monitor regularly. 2. **749 - 500/mm3** - At risk of neutropenic sepsis - linezolid should be interrupted. 3. **<500/mm3** should be placed in isolation until recovery above 0.5 x 10^3/µL. In case of fever, patients should commence an antipseudomonal

agent other than an aminoglycoside or fluoroquinolone. Meropenem, ceftazidime or piperacillin-tazobactam would be good choices.

Once the neutrophil rate returns above 1.0 x 10^3/µL the reintroduction of LZD should be considered. For patients requiring dose reduction or interruption, attempts should be made to reintroduce linezolid at 600mg once neutrophils are stable. FBC should be checked regularly for the subsequent 4 weeks during such reintroduction.

Hepatitis / elevated liver enzymes

Many anti-TB drugs can cause alterations in liver function tests. Patients using BPaL will have active TB and therefore elevation in liver function tests are not unexpected. Concomitant illnesses, including HIV infection, and other medication, such as ART, may also alter these laboratory parameters. Patients must be counselled on alcohol use, traditional medicine use and detection of symptoms. Therefore, changes in liver function enzymes or ALT should be evaluated within the history and clinical context of the abnormalities. All patients who have new Grade ≥3 elevation of ALT should be evaluated for hepatitis viruses relevant to their context (i.e., Hepatitis A, B, C and E virus infection) and have a full LFT and an INR checked.

For patients with normal or Grade 1 LFTs at entry who develop asymptomatic or symptomatic Grade 3 elevations during treatment, TB drugs and ART, where applicable should be interrupted until levels and symptoms are Grade ≤2.

For patients with a baseline Grade 2 elevation and present with grade 3 elevation, they will be allowed to continue the drugs unless they are symptomatic or the attending physicians feel it is unsafe for the patient to continue the medication.

If Grade 3 toxicity develops after re-introduction of the medications and the Grade 3 toxicity does not resolve within 14 days, then the patient may be discontinued from medication and expert advice will be sought. The patient should continue to be followed up, on appropriate therapy. All medication may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. TB drugs (but not DTG) can be restarted if there has been documented acute viral hepatitis and the ALT or bilirubin take longer than 14 days to reach Grade ≤2 toxicity.

TB drugs and study ART will be interrupted if any of the following liver chemistry criteria are met (according to DAIDS grading tables): refer Annex D

- Aminotransferase elevations are accompanied by total bilirubin elevation greater than 2 times the upper limit of normal.
- Aminotransferase elevations are greater than 8 times the upper limit of normal.
- Aminotransferase elevations are greater than 5 times the upper limit of normal and persist beyond 2 weeks.

Careful assessments should be done to rule out the use of alcohol, non-TB medication-related toxicity, or viral hepatitis (including viral hepatitis complicated by immune reconstitution inflammatory syndrome) as the cause for any liver toxicity that warrants permanent drug discontinuation is based on the liver stopping criteria specified above.

Evaluations to be considered include:

- Viral hepatitis serology including: Hepatitis A IgM antibody; Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (IgM)
- Syphilis screening
- Drugs of abuse screen including alcohol
- Liver imaging to evaluate liver disease
- Other: yellow fever, leptospirosis, etc. per context

Symptoms: Anorexia, yellowing of skin/eyes, darkening of urine, nausea, pruritus, vomiting and epigastric pain. Some patients may not have any signs or symptoms with elevated liver enzymes being the only sign.

Differential diagnosis. Gastritis, viral hepatitis, alcoholic hepatitis, steatohepatitis, Gilbert's syndrome, haemolysis, cholecystitis or choledocholithiasis

NB: Patients with a grade 3 or 4 hepatitis should have their TB treatment temporarily or permanently discontinued.

Re-challenge of TB treatment should NOT be considered if Grade 4 ALT/ AST/ BR, if INR is elevated > 2.0, if encephalopathy due to hepatic failure is present or the liver function abnormalities fulfil the criteria for "Hy's Law" *

"Hy's Law":

- The drug causes hepatocellular injury, generally defined as an elevated ALT or AST by 3-fold or greater above the upper limit of normal. Often with aminotransferases much greater (5-10x) the upper limit of normal.
- Among patients showing such aminotransferase elevations, they also have an elevation of their serum total bilirubin of greater than 2× the upper limit of normal, without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2× the upper limit of normal).
- No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, pre-existing liver disease, or another drug capable of causing the observed injury.

Possible Responsible Drugs	
B, Pa	**Adverse event management** 1. Treatment is supportive and dependant on early identification and timely withdrawal of the offending agent. 2. **Grade 1 >ULN - 3.0 x ULN:** (liver enzymes or hyperbilirubinaemia) **and** otherwise asymptomatic: Repeat liver function in 2 weeks or next scheduled visit (whichever is sooner). 3. **Grade 2 >3.0 - 5.0 x ULN:** Review history and do work up for other possible causes of hepatitis (e.g., alcohol, cotrimoxazole, paracetamol overdose, hepatitis B & C, biliary disease, pancreatitis). Consider performing abdomen ultrasound if timely available (to check for hard evidence of cirrhosis. HCC, ascites). Recheck liver enzymes in 3 days or consider hospitalisation for monitoring. 4. Grade 3 (>5.0 - 20.0 x ULN) or 4 (>20.0 x ULN) toxicity or clinically jaundiced patients (regardless of grade of liver enzymes elevation): • Stop all drugs and hospitalise patient. • Perform a full clinical evaluation. Check skin, renal function and full blood count to assess for DRESS syndrome (Drug Reaction, Eosinophilia and Systemic Symptoms). • Once hospitalised, monitor the trends of ALT, AST and synthetic function (bilirubin, glucose, albumin and coagulation if available). This should be daily until there is clinical and laboratory evidence of improvement. • Anti-TB drugs should not be considered for re-introduction unless the ALT/AST returns to less than 2x ULN within 2 weeks and jaundice resolved. In such a case, the patient should be discussed for a re-introduction plan after exploring all therapeutic options with the advisory committee. If regimen change is considered medications can be restarted beginning with the drugs least likely to be hepatotoxic (suggested order LZD - Cm/Km – Cs/TRD – Lfx – Pto – PAS – Mfx – Cfz – Pa – B – Z.), following ALT every 3 days for at least 2 weeks). If symptoms return or ALT/AST increases, the last drug added should be withdrawn and a decision on the regimen made. In this case, the patient would have failed the re-introduction and permanent discontinuation is advised.

Renal toxicity

Symptoms: Renal toxicity is detected by measuring creatinine levels and calculating creatinine clearance using patient's age and weight. In its early forms it is asymptomatic. Severe renal toxicity may present with decreased urine production, oedema and shortness of breath.

Differential diagnosis. Aminoglycoside nephrotoxicity, interstitial nephritis (any agent), dehydration, tuberculoma, diabetic nephropathy, obstructive uropathy

Calculate (for units using µmol/mL):

- **CrCl (male) = 1*(140 - Age) x wt (kg) / (Plasma Creatinine * 0.8136)**
- **CrCl (female) = 0.85 * (140 - Age) x wt (kg) / (Plasma Creatinine * 0.8136)**

Possible Responsible Drugs	
Pa (isolated Cr elevations) *	**Adverse event management** 1. Assess fluid balance and check electrolytes. Check protein dipstick and blood pressure. 2. Consider pre-renal, intra-renal and post-renal (obstructive) causes. 3. Stop any nephrotoxic agents – ibuprofen, enalapril, bactrim, second line injectable drugs. 4. **Grade 1 (1.1 - 1.5 x ULN)** creatinine elevations (or with a creatinine clearance <60 ml/min) should have their renal function checked weekly. 5. **Grade 2 (1.6 - 3.0 x ULN) or above** creatinine elevations (or with a creatinine clearance <30ml/min) should be admitted for evaluation and treatment. Consider abdominal ultrasound.

*Pa induced raised Cr levels are rare and often of limited clinical significance, note that there is a short period of increased Cr due to DTG which is much more common.

Lactic Acidosis / Hyperlactataemia

Lactic acidosis or hyperlactataemia should be suspected if patients report nausea and/or vomiting, tiredness, or other symptoms of lactic acidosis. Exclude other causes of the symptoms (especially hepatotoxicity). If suspected, investigate further and manage appropriately. If confirmed, interrupt LZD and other possible causative medicines, e.g., antiretroviral treatment, until improved. Consider rechallenging LZD at half dose.

Symptoms often non-specific but may include fatigue, repeated episodes of nausea and vomiting, abdominal pain, Kussmaul breathing.

Differential diagnosis. Hepatitis, pancreatitis, severe sepsis, renal failure

N.B Patients who develop recurrent nausea or vomiting while receiving LZD should receive immediate medical evaluation.

N.B. Lactic acidosis is more commonly seen in HIV co-infected patients.

Possible Responsible Drugs	
LZD, NRTIs (e.g., TDF)	**Adverse event management** 1. Measure blood lactate and bicarbonate levels. 2. Check it is a true result. A raised lactate in the absence of symptoms or a low bicarb/PCO2 may be a pre-analytical error. Suggest repeat. 3. Exclude other causes of severe vomiting and abdominal pain such as hepatitis, renal failure, or pancreatitis (blood tests + consider ultrasound). 4. Admit to hospital and withhold all medications. 5. Provide adequate fluid management (intravenous or oral as tolerated). 6. Monitor electrolytes daily until symptomatic and biochemical resolution. 7. Reconsider reintroduction of the regimen once stable.

Cataract formation

Symptoms: Decreased visual acuity. Seen in animal studies only (no evidence in Human studies). A theoretic risk with pretomanid.

Differential diagnosis: Optic neuritis, glaucoma.

Possible Responsible Drugs	
Pa	**Adverse event management** 1. Take history, visual acuity and Ishihara exam. 2. Refer for formal ophthalmological opinion.

Overdose Management

There is no documented experience with the treatment of acute overdose with the BPaL regimen. Take general measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) in case of deliberate or accidental overdose.

It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma.

* Pretomanid was studied at significantly higher doses than currently given and overdose is generally not associated with adverse events.

Prohibited and precautionary concomitant medication

Table 3: Contraindications and Relative contra-indications list (Mostly due to QtCf prolongation)

Contraindication	Relative contraindication (use with caution/check side- effect guide)	Ok to use drugs
Amiodarone	Azole Antifungals less than 2 weeks BUT Fluconazole more than 2 weeks	Abacavir
Amitriptyline (QT Prolong)	Biperiden	Acyclovir
Azathioprine	Bisoprolol	Albendazole (for Helminth)
Carbamazepine	Chlorphenamine	Amoxicillin
Chlorpromazine	Dexamethasone	Aspirin (low dose)
Cimetidine	Doxepin	Azithromycin
Clarithromycin (Qt Prolong)	Duloxetine	Beclometasone Inh.
Cyclizine	Ferrous Sulphate	Bisacodyl
Disopyramide	Fluoxetine	Calamine Lotion
Efavirenz	Furosemide	Clotrimazole Vaginal Tablets
Encainide	Hydrochlorothiazide	Cloxacillin
Erythromycin	Hydroxyzine Dihydrochloride	Dextrose (Glucose) 5%
Flecainide	Lopinovir	Dolutegravir
Fluoroquinolones	Magnesium Chloride (away from drugs)	Enalapril
Fluphenazine	Metoclopramide	Gabapentin
Fluphenazine	Mirtazapine	Glibenclamide
Haloperidol	Nevirapine (check HIV guideline)	Hydrocortisone Ointment
Immunosuppressants	Ondansetron	Hyoscine Butylbromide
Isocarboxazid	Other Ssri/Nsris	Ibuprofen
Methotrexate	Prednisone (short course only)	Ipratropium Bromide
Metronidazole	Risperidone	Insulin
Other Maois	Ritonavir	Lamivudine

Contraindication	Relative contraindication (use with caution/check side- effect guide)	Ok to use drugs
Pericycline	Roxithromycin <2 weeks	Lansoprazole
Phenytoin	Venlafaxine	Loperamide
Pimozide	Zidovudine (in Anaemia)	Metformin
Procainamide		Miconazole Gum Patches/Cream Nystatine
Prochlorperazine		Paracetamol
Promethazine		Plasma Substitute, Gelatin
Quinidine		Raltegravir
Quinoline Antimalarials And Hydroxychloroquine		Ranitidine
Sertindole		Ringer Lactate
Sotalol		Salbutamol
St John's Wart (Serotonin Sx)		Sodium Chloride 0.9%
Statins (Hmg Co-Reductase Inhibitors)		Tenofovir (except in Renal Imp)
Thioridazine		Tetracycline
Tranylcypromine		Valproate
Trifluoperazine		

KEY POINTS:

- Bedaquiline and linezolid are being used widely already, and there are few absolute contraindications.
- Linezolid side-effects are common, but manageable.
- With linezolid toxicity:
    - Monitor haemoglobin closely – it can drop quickly. However, patients respond well and quickly to linezolid interruptions. Monitor closely when rechallenging them.
    - Hyperlactataemia is seen in patients, especially if they are also HIV co-infected on ART. Suspect this diagnosis if they present with nausea/vomiting and tiredness. Interrupt LZD until lactate returns to normal and symptoms resolve. Rechallenge at LZD 600mg.
    - Absolute neutrophil count and platelets rarely lead to linezolid interruptions. Repeat these before making changes to linezolid since they fluctuate quite a lot.
    - Optic neuritis is uncommon, but all patients need to be counselled that this could happen, and they should contact the site promptly.
    - Peripheral neuropathy management can vary from patient to patient depending on how well they tolerate it, and how severe their TB disease is. PN management is done in consultation with the patient, continually emphasizing the balance between effective TB treatment, and reductions of adverse events.
- Hepatotoxicity from BPaL is not common but can be quite severe and needs to be managed closely. Many patients will present with elevated transaminases before symptoms. Be sure to check the results of blood tests promptly when they become available.
- Drug contraindications are most often due to the impact on the QtcF interval, interactions with BDQ or LZD, or cross-toxicity (i.e. AZT and LZD).

Any nausea and vomiting on BPaL should be investigated, with high level of suspicion for hyperlactataemia and should always exclude transaminitis.

GENERAL CARE AND SUPPORT OF PATIENTS

Informed Consent [i]

The WHO recommends, in their 2020 guidelines, that patients undergo informed consent when started on the BPaL regimen. The consent should cover the necessary information in a format that is easily understood without being overly burdensome for patients and should be offered in the patient's language of choice. It should include information on the novel nature of the regimen and Pretomanid, including the risks and benefits of the regimen.

Additional topics to be covered in the consent process:

- sufficient information on potential adverse events including low blood cell counts (e.g. anaemia, thrombocytopenia and neutropenia), liver toxicities, and peripheral and optic neuropathy;
- advised that reproductive toxicities have been observed in animal studies, and that the potential effects on human male fertility have not been adequately evaluated at this time; and
- informed that pretomanid is excreted in breast milk, and its safety in infants and children has not been adequately evaluated

These guidelines could change as more information becomes available.

Adherence Monitoring

BPaL offers a shorter, all oral treatment with a significantly reduced pill burden. Bedaquiline dosing involves a more complicated dosing schedule than other daily dosed drugs. Adherence was excellent within the clinical trials and is expected to be better in programmatic settings than in conventional treatment.

Offering patient support and preventing treatment interruptions throughout the duration of treatment is key to achieving successful outcomes. Support should be tailored to patient needs to maximize adherence and early detection of patients experiencing difficulties with treatment.

Video Observed Treatment is a remote digital adherence technology that employs both live (synchronous) or recorded (asynchronous) video monitoring of medication dosing via a smartphone, tablet, or computer. Synchronous VOT involves real-time adherence monitoring whereby a health worker observes a patient ingest their tablets through an application such as Skype. Asynchronous DOT involves the use of a dedicated VOT application on a smart device that allows the user to record a video which is automatically uploaded onto a secure database for review by the healthcare team once the patient has access to internet service. VOT has the potential to provide an alternative method of adherence support that is simpler, more convenient, and cost-effective for the management of TB in South Africa. South Africa currently follows the model of classic face-to-face DOT but implementation of this is limited and facility specific.

Evidence from studies on asynchronous VOT showed high level of acceptability, decreased costs as compared to (traditional) DOT, and programmatic evidence of effectiveness.

Successful adherence to any form of TB treatment requires that a complete social support package is co-administered with DOT/VOT. National TB programmes need to look at other support measures including psychological support, counselling, home visits, food and financial support as well as staff training on topics such as stigma and gender sensitivity.

The following recommendations for a social support package from the 2017 WHO Guidelines update[i] continue to apply to patients with drug-susceptible and drug-resistant TB:

Recommendation 8.1 Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (Strong recommendation, moderate certainty in the evidence)

Recommendation 8.2 A package of treatment adherence intervention may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option (Conditional recommendation, low certainty in the evidence)

Recommendation 8.3 One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers:

a) tracers or digital medication monitor (conditional recommendation, very low certainty in the evidence);

b) material support to patient (conditional recommendation, moderate certainty in the evidence);

c) psychological support to patient (conditional recommendation, low certainty in the evidence)

d) staff education (conditional recommendation, low certainty in the evidence).

Recommendation 8.4 The following treatment administration options may be offered to patients on TB treatment:

a) Community- or home-based DOT is recommended over health facility-based DOT or unsupervised treatment (conditional recommendation, moderate certainty in the evidence)

b) DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment (conditional recommendation, very low certainty in the evidence)

c) Video observed treatment (VOT) can replace DOT when the video communication technology is available and can be appropriately organized and operated by health care providers and patients (conditional recommendation, very low certainty in the evidence)

Recommendation 8.5 Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (Conditional recommendation, very low certainty in the estimates of effect)

Recommendation 8.6 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment (Conditional recommendation, very low certainty in the estimates of effect)

Post treatment follow up:

It is important that patients are followed up after completion of treatment. The recommended follow up period is six months at minimum. Country level guidance on the follow up of DR-TB patients should be followed. The section under patient monitoring provides a detailed description of proposed tests and monitoring frequency.

KEY POINTS:

- It is important to conduct informed consent with patients before starting the regimen.
- Specific attention should be given to explaining the side-effects.
- Although adherence is expected to be improved given the shorter nature of the regimen, it is still crucial to offer support.
- Clinicians need to implement comprehensive adherence support measures coupling DOT/VOT with psychological support, counselling, home visits, food and financial support and staff training.

LESSONS LEARNT IN THE FIELD

Case Studies from BPaL Clinical Trial Experience

CASE 1:

Participant B is a 43 year old man known with well-controlled HIV infection and newly diagnosed cavitary XDR-TB (previous WHO definition).

His occupation is a long-haul trucker.

He had two previous episodes of DS-TB for which he received treatment 10 and 6 years ago and had cure of both.

He had baseline grade 1 peripheral neuropathy when starting on a trial using BPaL, involving numbness of bilateral toes, reduced vibration sense of 8 seconds at metatarsal joints and hypoactive Achilles reflex.

At 8 weeks of trial, it was noted that his peripheral neuropathy was progressing, with vibration sense of 7 seconds on the right and 6 seconds on the left metatarsal joints respectively. The participant did not complain of this affecting his sleep or walking. There was mild new onset pins and needles of his toes.

At 12 weeks of trial, he complained that his feet had pins and needles of both feet, extending to the ankles, and that it was painful to have the blankets on his feet at night (hyperaesthesia). Vibration sense and Achilles reflex were unchanged from week 8. By this time, the participant had been discharged from hospital and was back at work. The participant expressed his frustration that he could no longer feel the pedals of the truck when driving and was concerned for his safety and future employment prospects.

Although still considered grade 2 peripheral neuropathy, it was decided to interrupt linezolid treatment due to the impact on his sleeping and direct impact on his ability to safely drive the truck. Treatment with BPa continued.

The peripheral neuropathy subjectively continued to worsen for the next week before slowly improving. The sensation of pins and needles improved. Vibration sense was 8 seconds at bilateral metatarsal joints and Achilles reflex was unchanged. Gabapentin did not help the pins and needles sensation at all according to the patient after one month of treatment, and this was stopped.

The clinician discussed the balance of adequately treating his cavitary XDR-TB and maintaining function in his feet. The clinician and participant agreed to rechallenge LZD at 600mg after 3 weeks, which the participant managed to take for a further 2 months until the end of the treatment period without further worsening of his PN.

He culture converted after 6 weeks of treatment and remained culture negative until end of trial.

The participant had residual coldness and some numbness of only the distal toes at 2 years after completion of treatment and was able to continue driving.

Learning points:

- Peripheral neuropathy is a common but manageable side effect of Linezolid use.
- Consultation with the participant is important in managing peripheral neuropathy.
- Clinical examination is important but is not the only consideration in making decisions regarding drug interruption and/ or re-challenge.
- If peripheral neuropathy affects a person's ability to walk or sleep consider interrupting LZD and rechallenging later at half dose if necessary.
- Different patients will be able to tolerate peripheral neuropathy in differing degrees.
- Gabapentin/pregabalin may be useful in some patients.

CASE 2:

Patient M is a 38-year-old woman with TB that is resistant to rifampicin and subsequent detection of resistance to fluoroquinolones. This is her first episode of TB. She does not have HIV, diabetes or any other co-morbidities. She had started TB treatment 10 days previously with Kanamycin/MFX/PZA/ETO/TZD and INH when she was diagnosed with RR-TB which was standard of care at the time.

She is enrolled onto a BPaL trial with a grade 1 LFT at baseline and mild hepatomegaly of 3cm. Her other TB treatment is stopped, and BPaL is started at enrolment.

At week 4, her routine blood results show an ALT and AST of more than 4x ULN with normal bilirubin and normal INR. She is completely asymptomatic, denies any alcohol use and denies any other medicine use, including traditional/herbal treatments. Her BPaL is stopped. Her only concomitant medicine, pyridoxine, is stopped too.

She undergoes regular LFTs which show that her ALT continues to climb and is more than 5x ULN after 1 week. Her bilirubin increases to 1xULN. She reports no symptoms and examination is unremarkable, with hepatomegaly of 3-4cm ongoing. ALT improves to 1x ULN after 2 weeks of interruption and BPaL is rechallenged at original doses. ALT increases again to 5x ULN and participant's treatment is interrupted again, this time more than the trial allowable time, and participant is withdrawn from trial. The participant is recommenced on injectable-based DR-TB treatment and attains cure.

Learning points:

- Drug induced liver injury (DILI) is a recognized side effect of the BPaL regimen.
- **Hy's law** provides the rule of thumb that a patient is at high risk of a fatal DILI if given a medication that causes hepatocellular injury (not hepatobiliary injury) with jaundice.
- Patients on BPaL may be completely asymptomatic for the duration of their DILI and for this reason ALT results should be carefully checked for every patient.
- DILI can be managed with interruption and rechallenge but can occasionally be a reason for discontinuation of BPaL, especially if Hy's Law is fulfilled.

Quotes from implementors in the field

An online survey was conducted with clinicians and programme implementors currently the using the BPaL regimen in South Africa. Below are some **direct quotations** taken from their responses:

What advice would you give clinicians using the regimen for the first time?

- Know the Protocol and management of side effects.
- Watch out for LZD toxicities. Watch TB response closely, especially if multiple cavitations. Ensure BDQ and LZD sensitivity.
- I would advise to make sure that clinicians stress that peripheral neuropathy and bone marrow suppression S/E are extremely common and to warn patients that we would need to push as far as they can tolerate the linezolid to ensure that their TB is cured.
- Really take the eye exams seriously as some patients do develop optic neuritis.
- Monitor adherence, closely monitor any adverse effects and treat them promptly.
- Determine what adverse events are present prior to starting a patient- optimise patient especially haemoglobin(>10g/dl) prior to commencing treatment. Monitor patients closely. Note event slight abnormalities in blood results- weekly monitoring initially is required.
- To be familiar with the common side effects and their management.
- Close monitoring in the first 2 months.

What lessons have you learnt in the field that would be useful for others?

- Importance of accurate data collection.
- close monitoring of adherence in participants.
- Know the previous TB regimens and changes made (qualifier: treatment regimens for the patient currently being managed).
- Good communication and gaining the trust of patients help improve their treatment course- continuously asking patients about their side effects at each visit helps manage them. Explaining their treatment course to them and what they may expect in terms of side effects may improve their own knowledge and improve adherence. Seeing the same clinician/team throughout their treatment course helps the patient feel comfortable to communicate and side effects are managed more effectively.
- Management of common side effects like peripheral neuropathy etc.
- Patients need a lot of support irrespective of which regimen they receive. It is especially important for patients to receive the support they need to be fully compliant with a 6-month regimen as the consequences of not doing so results in an even longer regimen and a shortage of drugs.

FREQUENTLY ASKED QUESTIONS

Can a shorter all-oral bedaquiline containing MDR-TB regimen be used in HIV-co-infected patients? [xi]

Yes. The data from South Africa used for the analysis included a high proportion of HIV co-infected patients (71%).

Are three drugs sufficient?

Yes. Nix-TB data demonstrated successful treatment outcome in 95 of the first 107 patients after six months of treatment with BPaL at six months of post-treatment follow-up.

Can bedaquiline be used in pregnant women? [xii]

Yes. The use of bedaquiline as a part of an all-oral longer MDR-TB regimen was shown to be generally safe in pregnant women in a study in South Africa. In this study, exposure to bedaquiline (most frequently used together with clofazimine and levofloxacin), was associated with an increased risk of low birth weight (<2500g), although normal growth was achieved in these babies.

Can all MDR-TB patients be treated with the BPaL regimen? [xii]

No. The WHO states that the BPaL regimen is relevant in patients with confirmed XDR-TB who have not had previous exposure to bedaquiline and linezolid for more than two weeks. This might be different under programmatic conditions, for example with the South African BPaL programme, this is restricted to 28 days of BDQ and/or LZD. It has also been tested in patients with MDR-TB with treatment intolerance or treatment failure. This regimen is not appropriate for programmatic use worldwide until additional evidence on efficacy and safety has been generated. Nevertheless, in individual XDR-TB patients for whom the design of an effective regimen based on existing WHO recommendations is not possible, the BPaL regimen may be considered as a last resort under prevailing ethical standards.

Can pretomanid be added to other TB treatment regimens? [xii]

No. In August 2019, pretomanid (Pa) was approved by the US Food and Drug Administration as part of the BPaL regimen, i.e. in combination with bedaquiline and linezolid. The data from Nix-TB study provided for the review by the GDG in November 2019 also included the data on BPaL regimen and use of pretomanid in combination with two other medicines. There is no currently available evidence on the use of Pa outside the BPaL regimen and it is therefore not included in the priority grouping of TB medicines recommended by WHO. Although it is a nitroimidazole (i.e., in a similar class as delamanid) it is a new chemical compound and cannot be used as a replacement for delamanid or added on its own to first- and second-line treatment regimens.

Should DST be done before bedaquiline and linezolid are used? [xii]

The availability of DST for these medicines is currently limited in many settings and the resistance levels are likely to be very low at this point. Performing DST to bedaquiline and linezolid is therefore, at this stage, not essential before using these medicines. However, national TB programmes are strongly advised to start building capacity for drug resistance surveillance of bedaquiline and linezolid. If resistance is suspected during treatment and DST is not available, the strains should be conserved and referred to SRLs for further testing.

What should patients be aware of regarding the new MDR-TB treatments? [xii]

The new treatment guidelines will emphasize the need for improved communication with persons who are starting MDR-TB treatment about the potential benefits of the new regimen and the potential risks. Cautions about key adverse reactions, such as QT-interval prolongation with drugs like moxifloxacin and Bedaquiline, neuropathy for linezolid, and skin discoloration for clofazimine (see more complete list in Chapter 11 of the Companion handbook). Patients should also be informed that with the use of pretomanid containing regimen (BPaL), reproductive toxicities have been observed in animal studies and that the potential effects on human male fertility have not been adequately evaluated at this point in time although male fertility studies are due to start Q2 2021.

The patient and treatment provider need to find the most acceptable form of communication to ensure continued treatment follow-up.

Patients also need to be aware that the benefits of the medication depend upon completing them as prescribed. Adherence support is important. The basic principle that applies to any TB regimen - to take all the medicines prescribed for the recommended duration – remains critical. If treatment interruptions occur, the clinical team needs to address them rapidly to ensure resumption of care.

Is informed consent mandatory? [xii]

Informed consent and participatory decision-making are key elements of patient-centered care. All patients receiving TB care should be informed of the procedures and treatments they are being offered or are receiving in a manner by which they appreciate the uncertainties, potential risks and benefits, alternative treatment options, as well as the commitments needed. Ahead of enrolment on any MDR/RR-TB and XDR-TB treatment, with or without new TB drugs, all patients should be counselled to understand the main issues involved with their treatment. This process needs to comply with the local requirements, including written or verbal consent as necessary. Any patient information material previously developed for this purpose needs to be updated to reflect the new changes, so that patients are appropriately informed about their treatment options. Sample information material to use when explaining the options to patients are available in the WHO Companion handbook.

What doses of each drug are optimal and what is the most adequate dosing interval and duration?

BPaL regimen should be administered orally for 26 weeks (six months) with a possible extension up to 39 weeks (9 months).

The dosing intervals are as follow (all 3 drugs to be given simultaneously:

- Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week;
- Pretomanid 200mg once daily;
- Linezolid 1200mg once daily.

What are the reported drug- drug interactions observed when using the BPAL combination?

The following concomitant medications are prohibited during the treatment period to avoid possible drug interactions with the TB regimen:

- Medicinal products used to treat pulmonary TB: including but not limited to gatifloxacin, amikacin, cycloserine, rifabutin, kanamycin, para-aminosalicylic acid, rifapentine, thioacetazone, capreomycin, quinolones, thioamides, and metronidazole.
- Concomitant use of Monoamine Oxidase Inhibitors (MAOIs). (e.g. phenelzine, isocarboxazid)
- Concomitant use of any drug known to prolong QTc interval (including but not limited to amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
    - Treatment with fluoroquinolones (as they are known prolong QTc), are strongly discouraged. They should only be used to treat intercurrent non-TB infections and if the benefit of treatment outweighs the risk of prolonged QTc.
- Concomitant use of any drug known to induce myelosuppression.
- The systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolids such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days;
- The systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John’s wort, rifamycins and systemic dexamethasone.

Concomitant use of serotonergic antidepressants should be avoided if possible as participants on these agents and linezolid are at risk for serotonin syndrome.

Caution should be used in treating diabetic participants receiving insulin or oral hypoglycaemic agents as cases have been reported of hypoglycaemic reactions when participants on these agents have been treated with linezolid.

Any drug known to be hepatotoxic should be avoided as much as possible during screening and throughout the treatment period

How does one manage treatment interruption and missed doses?

Patients on six months of treatment should complete a full course of treatment (i.e., 26 weeks of prescribed doses) within eight months of treatment assignment (a total halt of up to 60 days if on six months) while participants on nine months of treatment should complete a full course of (i.e., 39 weeks of prescribed doses) treatment within twelvemonths of treatment assignment (a total halt of 90 days if on nine months of treatment).

For participants who completed the first four consecutive weeks of treatment on the 1200 mg linezolid total dose and later in treatment only halted linezolid, treatment can be considered complete at six months, even if there were multiple interruptions and rechallenges of linezolid while the participant remained on pretomanid and bedaquiline.

When the total of missed dosing days and/or pauses is greater than seven days for BPa, the same number of missed dosing days should be dispensed to make up for the total missed doses which will result in extension of the treatment duration. Linezolid doses do not need to be made up if doses are missed.

At no time should the participant be treated with a single agent.

When should the BPaL regimen be discontinued pre-maturely?

Patients should discontinue treatment under the following conditions:

- Withdrawal of consent.
- Lost to Follow-Up.
- In the interest of the patient based on safety reasons.
- Pregnancy.
- Non-compliance to BPaL and associated treatment requirements.

COUNTRY-LEVEL IMPLEMENTATION CONSIDERATIONS

Regimens vary in terms of efficacy, safety, cost, and complexity of administration, which has implications for overall patient outcomes and the feasibility of implementation and scale-up in programmatic settings. It is important to carefully compare the BPaL regimen with the current standard of care, and to understand benefits and shortcomings of the former when making decisions.

The main considerations recommended when implementing a new regimen such as BPaL are:

- Benefits of the new regimen compared with currently used regimens mainly with respect to clinical outcomes, complexity of treatment, and financial and economic advantages.
- Implementation considerations with respect to implementation pathway, regulatory aspects, diagnostics infrastructure, and funding requirements.

Benefits of the new regimen

Clinical Outcomes

BPaL, which thus far has been approved by regulatory authorities in 11 countries (and increasing), is currently the only regimen that has been proven in clinical trials or approved by a regulatory authority for curing pre-XDR-TB. Prior to the availability of BPaL, healthcare providers have tended to individualize treatment, often using antibiotics not normally used for TB, as well as highly toxic medicines not intended to be used for the duration of time that TB treatment requires.

Treatment of pre-XDR-TB with individualized treatment regimens (ITR) routinely lasts 18 months or longer and consists of seven to nine drugs and thousands of pills that cause serious side effects. Despite the length and complexity of ITR, outcomes are extremely poor. Only one in three people with DR-TB is currently being detected globally, of which, just over one-half are treated successfully. The global average success rate of pre-XDR-TB treatment is only 43 percent[xii].

In comparison, the BPaL regimen has been studied under the Nix-TB and ZeNix trials, and has a reported 90 percent favourable outcome. One of the key challenges for patients using the BPaL regimen initially, in the Nix-TB trial, was the high dose of linezolid (1,200 mg/day) that resulted in a high but manageable incidence of side effects, specifically peripheral neuropathy and anemia. However, the recent ZeNix trial has demonstrated that lower doses of linezolid may reduce side effects while maintaining the regimen's efficacy, delivering close to a 90 percent success rate in treatment of pre-XDR-TB. Side effects of the regimen observed in Nix-TB and more so in ZeNix, were at manageable levels compared with ITR[xiii].

The dataset accompanying the World Health Organisations (WHO's) Global TB Report, published annually, includes success rates for pre-XDR-TB (defined as XDR-TB until the 2020

report). It is recommended that countries looking to implement BPaL consider the success rate of pre-XDR-TB treatment observed in their country.

Complexity of Treatment

Further, countries should compare length and complexity of current pre-XDR-TB treatments in use with BPaL, which comprises less than 750 pills, over the course of treatment, while ITRs may require as many as 14,000 pills. Research has shown that patients find it easier to complete a shorter, all oral DR-TB regimen of up to 12 months compared to the longer regimens[xiv]It is expected that shorter regimens of six months such as with BPaL may be better accepted. A study conducted by The KNCV Tuberculosis Foundation (KNCV) in Indonesia, Kyrgyzstan and Nigeria showed BPaL acceptability to be up to 1.9 times higher compared with ITR among health care professionals, programmatic stakeholders, and laboratory stakeholders. The study also showed the overall likeliness of implementation of BPaL at 88 percent. This study is under publication.

Cost of Treatment

A country looking to implement BPaL, or a shorter regimen should also compare the cost of treatment with the new regimen to the average cost of treatment with ITRs. A costing study conducted by KNCV in Indonesia, Kyrgyzstan and Nigeria showed that BPaL would save US$ 4,000-9,500/patient in drug costs and US$ 6,500-11,000/patient in overall costs (drugs + treatment + treatment monitoring) in these countries. Note that this study was conducted from a programme perspective and did not include patient costs or savings. For example, a shorter treatment regimen may require fewer trips to healthcare facilities and quicken return to work. Also, note that costs vary across countries and a country should make its own assessment of the costs and benefits of a new regimen. This is discussed further under the “Funding” section.

Implementation considerations

Apart from direct benefits, while implementing a new regimen such as BPaL, countries are encouraged to keep in mind the following considerations:

- Inclusion in national guidelines and the essential medicines list
- Whether currently available evidence is sufficient, or further or local evidence must be generated prior to programmatic use
    - Process, time and cost for local study/implementation
- Requirements and time taken for regulatory approval of new drugs
- Diagnostic infrastructure
- Funding requirements; source of funding
- Procurement of drugs in country

These are discussed in further detail below.

Introduction Pathway

National Guidelines

A country's national policy or guidelines reflect the decision to use a new regimen either in limited operational research (OR) settings or nation-wide. The process for updating national policy is usually driven by the national TB programme, with decisions, depending on the country, taken in consultation with a relevant group of experts.

A country may consider obtaining technical assistance (TA) from experts and technical partners, who are usually able to support the process of national guideline development by collating and presenting all available evidence and managing efficient discussions that result in the speedy development of a locally owned decision. Inclusion of a drug or regimen in national guidelines and national essential medicines list may facilitate inclusion of the drug(s) in local procurement or tender list or formulary, which may be important for inclusion of the drug in health budgets in several countries. This important step must be kept in mind to ensure a smooth roll-out and scale-up of a new drug or regimen. TA providers are also able to develop models to support the budgeting and understanding of savings due to, or financing requirements for, a novel regimen such as BPaL.

Additionally, a country can appoint a focal point such as a National TB Programme resource, a technical partner, or an independent consultant to bring together key stakeholders to rapidly develop an implementation plan and, later, a scale-up plan for the innovation. TB Alliance has sponsored this work in a growing list of six countries so far. This has proven effective for countries to be able to determine their direction of either conducting OR, or clinical trials, or wait for WHO guidelines.

Evidence Generation

While deciding on nationwide implementation or generating additional local evidence through OR clinical trials, a country should carefully review evidence already available from clinical studies that may soon become available from ongoing trials and operations research (or other implementation research). Key considerations are the time and cost required to prepare for and conduct local studies, and whether such research will add to existing evidence.

There is a growing body of evidence about the BPaL regimen, outlined below, that a country is encouraged to consider when deciding whether to conduct local studies involving BPaL.

The first study for BPaL was the Nix-TB clinical trial that was done in South Africa[xv]. Based on this, the use of pretomanid in the regimen was approved by the United States Food and Drug Administration (USFDA) followed by another 10 regulatory agencies so far. On the basis of Nix-TB, WHO recommended in June 2020 that BPaL may be used under OR conditions for patients with XDR-TB and in patients who are either unable to tolerate or failed MDR-TB treatment until further evidence was generated[xvi]. Since then, six countries have commenced BPaL use under OR (South Africa, Ukraine, the Philippines, Nigeria, Tajikistan and Kyrgyzstan), while several others are expected to do so shortly. Availability of results from these ORs is expected to start from early 2022. Additionally, results from the ZeNix trial on BPaL conducted in South Africa, Russia, and Moldova have added to the evidence base for BPaL. Further, results from an MSF (Medicins Sans Frontieres) sponsored TB-Practecal study

that compared BPaL-based regimens (BPaL, BPaL+Moxifloxacin, BPaL+Clofazimine) for all people with DR-TB (at least rifampicin-resistant), with the standard of care in Belarus, South Africa, and Uzbekistan are expected to be read out in late 2021. Earlier in 2021, the TB-Practecal study stopped enrolling patients earlier than planned after its independent data safety and monitoring board indicated that the regimen being studied is superior to current care, and more patient data were extremely unlikely to change the trial's outcome. Physicians in the United States have been using BPaL since November 2019, and some experts are expected to publish their experience with the regimen shortly.

The decision to conduct ORs may also be driven by donor considerations: if the regimen is recommended by WHO for use under OR conditions, Global Fund funding may not be used to procure the relevant drug for programmatic use. If budgeted and approved, Global Fund funding may be used to implement a new regimen such as BPaL under OR conditions. In light of this, some countries decided to rapidly conduct ORs so as to provide access of BPaL to patients, while also generating local evidence and gaining experience with the regimen. Some countries with a proportionately smaller burden of pre-XDR-TB in relation to their national health budget, have found it more practical to simply pay for drugs with their own funds and not conduct OR. Note that while OR for BPaL is currently ongoing in six countries with another five to six on the anvil, pretomanid has been procured by more than thirty countries as of August 2021.

Process, time and cost for a local study

The starting point for a local study, whether an OR or a clinical trial should be the key research question(s) to be answered. It is important to design the study and related protocol keeping the research question in mind. It is important to identify and onboard a principal investigator who would usually lead in writing the protocol, designing the study, identifying study sites and engaging site coordinators, apart from leading the process of seeking required approvals and eventually the analysis and publication of results. Multiple approvals, including from an institutional review board (IRB), also known as an independent ethics committee, an ethical review board or a research ethics board, and approval by a central or national regulatory or licensing authority, are required prior to study commencement. There may be other approvals required depending on the country. If drug(s) to be used in the study are not approved by the national regulatory agency, the process of importing the drug(s) may be complex and time consuming and must be well understood and included in the planning in advance. It may also be easier in some countries to procure such drug(s) through donations since usage of state funds for unapproved drug(s) may be complex. Once approvals are obtained and study sites identified and ready, laboratory and clinical staff at sites will need to be trained on relevant aspects of the study, the use of regimens, screening, testing, and monitoring requirements, case report forms, and so forth.

TDR (a global programme of scientific collaboration) and the Global TB Programme at the WHO launched ShORRT (Short, all-Oral Regimens For Rifampicin-resistant Tuberculosis), an operational research package to assess the effectiveness, safety, feasibility, acceptability, cost and impact of the use of all-oral shorter treatment regimens for people with MDR/RR-TB. This OR package may be used with local modifications as necessary[xvii]. A country may also consider obtaining technical assistance (TA) from experts and technical partners who have

been supporting ORs for BPaL such as KNCV International, The Hague, and the International Tuberculosis Research Institute, Seoul. TB Alliance has been supporting KNCV, International Tuberculosis Research Center in South Korea (ITRC), and others to carry out OR and can also help countries get started rapidly with knowledge and insights from other countries.

It must be kept in mind that clinical trials and OR take significant time and effort to establish. A good quality clinical trial could take anywhere between 10-18 months to get started and ORs could take 6-8 months to start. Study duration will depend on how fast patients are enrolled which can take several months, followed by a follow-up phase of several months as prescribed in the protocol, and concluded by the analysis of data and reporting.

It is recommended that timelines and budgets for local studies and evidence generation are considered carefully, along with the availability of similar evidence from other ORs or clinical trials happening elsewhere in the world, and upcoming WHO guidelines. A country may be able to avoid the heavy effort of an OR or clinical trial if results from other studies aiming to answer the same questions will be available before the end of the contemplated study, or WHO guidelines may render the study irrelevant. However, if the objective is that a country must have its own experience of using a regimen before scaling it up, then OR or similar implementation research should be considered as soon as possible so as not to delay access to a new, potentially life-saving new drug or regimen for patients.

WHO is expected to review recently published results of the ZeNix trial, as well as results from the TB-Practecal study. This may result in revised guidance on the use of BPaL in the coming months.

Regulatory Approval

New MDR-TB drugs have the potential to save lives that could otherwise not be saved - as is evident from the low success rate of current MDR-TB treatments. In most countries, barring a few exceptions, especially in those with high TB burden, it is usually possible to obtain a regulatory waiver for a new MDR-TB drug due to urgent unmet need. Waivers are routine and relatively easy to obtain in most countries by drug manufacturers or procurement agencies like the Global Drug Facility (GDF). However, this cannot remain a long-term solution, and manufacturers need to obtain regulatory approvals for smooth and continued use and scale-up, including after ORs. It is important for a drug to be approved by the national drug regulatory agency, especially for countries with a sizeable burden of the disease. Regulatory approval also eases the ability of the national program to procure the drug using the national health budget on a consistent basis. As the process of regulatory approval may be long and complex, at times taking up to three years, the earlier the process is started the better. Depending on the country, it may be possible to fast-track approval of a new drug if the TB programme makes a case citing urgent unmet need to the regulatory agency. TA providers are usually able to provide assistance in developing such cases, if required.

TB Alliance's global commercialization partner, Viatris, has filed for pretomanid approval in a growing list of 30 high burden countries, with approvals received from the following 11 countries so far: United States Food and Drug Administration, European Medical Agency, India, the Democratic Republic of Congo, Georgia, Mozambique, South Africa, Tajikistan,

Turkmenistan, Uzbekistan, and Zimbabwe. Additionally, pretomanid has been prequalified by the World Health Organization.

In countries where regulatory approval or other access mechanisms for BPaL are not yet available, patients can access pretomanid through the Named Patient Access Program (NPAP) instituted by Viatris. The pretomanid NPAP allows the treating physician to submit a request for pretomanid to Viatris prior to regulatory approval in their respective country on a named-patient basis, provided it is permitted by applicable local laws.

The following criteria* must be met by a patient to participate in Viatris' NPAP:

- The patient seeking treatment has highly drug resistant TB (adults with pulmonary XDR or TI / NR MDR TB#) and there is no satisfactory alternative therapy available to treat the disease
- The patient is not eligible to enroll in a clinical trial
- The potential benefit of treatment use outweighs the potential risk in the context of the disease to be treated as confirmed by the treating physician at the time of request
- The product is not yet approved by the local regulatory body in the treating physician's respective country
- Pretomanid should be used as part of a combination regimen with bedaquiline and linezolid.

** All above criteria are subject to local laws and regulations*

#Based on written request from country regulatory authority, MDR TB patients outside of TI/NR category can be considered for access to pretomanid

An NPAP request can be submitted by a physician at: https://www.accesspretomanid.com/# and a response to the request is received with 10 business days.

TB Alliance has developed a repository of information on accessibility in countries, either in terms of regulatory approval, in access through NPAP, or through ongoing operational research or similar projects in specific countries. This information can be accessed at https://www.tballiance.org/access/countries.

Diagnostic Infrastructure

As per the WHO Global TB report 2020, there is an increasing level of drug susceptibility testing (DST) over the last few years – from 9 percent to 26 percent between 2015-2018 for first-line DST and 22 percent to 56 percent between 2015-2018 for second line DST. However, this is an area in which all countries need urgent additional focus and investments. With new drugs for TB coming to market for the first time in decades, there is an increased need for such testing, as well as for developing tests for products like bedaquiline and pretomanid.

To be able to use BPaL, countries require access to DST or the ability to quickly build capacity for this testing, as well as access to GeneXpert testing. The national algorithm may need to

be updated to test for drug susceptibility to isoniazid, rifamycins, and fluoroquinolone to determine eligibility for BPaL. Additional drug susceptibility for bedaquiline may be considered where available to rule out resistance to bedaquiline, especially in settings where bedaquiline has been in use or where there is a high level of known resistance.

It is critical to plan procurement and distribution of laboratory commodities necessary in advance to perform DST using methods currently available in the respective settings so as not to delay the roll-out of the BPaL regimen. Additionally, the national sample transport network may need to be reconfigured to optimize the transport routes connecting facilities offering the regimen and the laboratories conducting drug susceptibility testing for regimen eligibility.

Funding

TB Programs can treat more patients with their current resources if the cost of treatment is lower than current treatment. As seen from Figure 2, funding gaps remain, despite growth in overall funding since 2010.

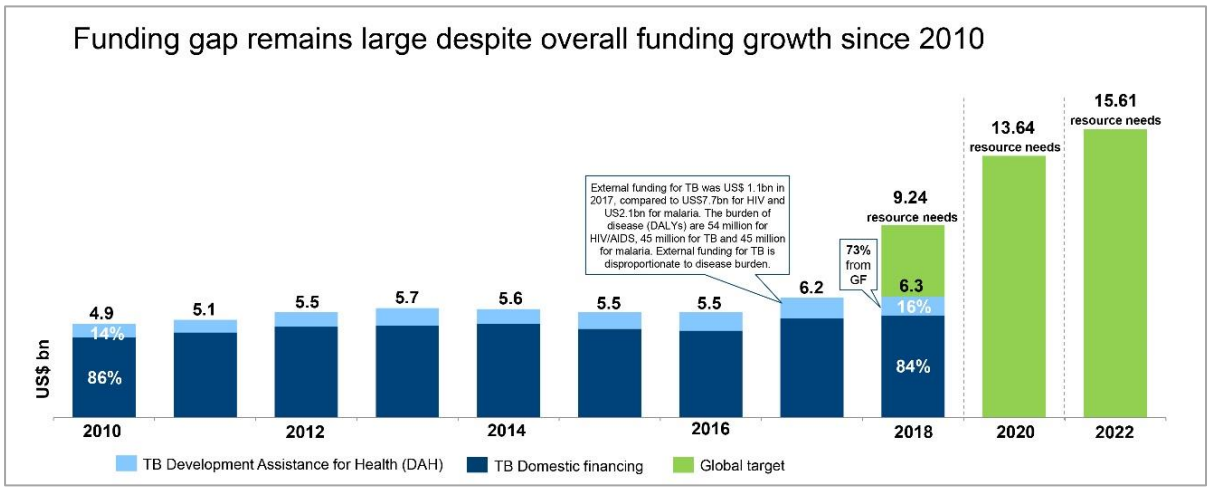

Figure 2: Funding Gap Remains Large Despite Overall Funding Growth since 2010. Source: https://www.theglobalfund.org/media/9685/strategydevelopment_2020tuberculosis_landscapeanalysis_en.pdf

When considering implementing a new regimen or intervention such as BPaL, a country or TB programme should include all of the following to estimate its total funding needs:

- Cost of implementation, including the cost of local or international TA, cost of operations research or conditional access programs, cost of training and capacity building, cost of any incremental investment in laboratory infrastructure, and cost of active drug safety monitoring (DSM)
- Add to it the cost of new treatment implemented over the proposal period
- Deduct from these the cost of already budgeted ITR that will not be used anymore
- Factor in higher success rate and compare difference in cost/lives saved

The improvement in the success rate and/or reduction in cost/lives saved may serve as a strong justification when making a request for further funding or reprogramming.

As discussed earlier in this section, a TB Alliance supported costing study conducted by KNCV in Indonesia, Kyrgyzstan and Nigeria showed that BPaL would save US$ 4,000-9,500/patient in drug costs and US$ 6,500-11,000/patient in overall costs (drugs + treatment + treatment monitoring). This work can be made available to countries to adapt to their own settings for an estimation of their cost savings with BPaL.

Additionally, there are other studies to help countries evaluate the cost-effectiveness or cost savings by the use of the BPaL regimen for XDR-TB patients.

1. The London School of Hygiene and Tropical Medicine, along with TB Alliance, have studied the economic evaluation of BPaL for treatment of XDR-TB in South Africa, Georgia, and the Philippines. The study shows that the BPaL regimen has the potential to be cost saving at a price of US$ 364 per treatment course for pretomanid, and GDF list prices for bedaquiline and linezolid. The magnitude of these savings increased if the inclusion criteria is expanded to MDR-TB treatment intolerant or failures.

   This study also showed that the use of BPaL compared to the current standard of care averted 15,500 disability-adjusted life years (DALYs) in South Africa.

2. A second study done by KNCV and Johns Hopkins Bloomberg School of Public Health, along with ministries of health in Indonesia, Kyrgyzstan and Nigeria shows that adoption of the BPaL regimen would result in an average reduction of between 15 percent to 32 percent in XDR-TB related expenditure at country levels.

Note that funding for the BPaL regimen may be requested from the Global Fund, currently for use under OR conditions[xviii]. Other donors that have funded ORs for BPaL are United States Agency for International Developmentthe Philippines, Vietnam, Ukraine, Kyrgyzstan and Uzbekistan.

Drug Procurement

Global Drug Facility

Pretomanid has been added to the Stop TB Partnership's GDF product catalog just two months after receiving approval by the USFDA. GDF's global access price of US $364 per pretomanid treatment course is available to 150 countries and territories and puts the cost of the FDA approved BPaL regimen (which also includes bedaquiline and linezolid) at US $785 per treatment course (when bought from GDF at access prices)[xix,xx].

To place an order with GDF, the following steps are to be taken:

1. Request an online client account at GDF Order Management System (http://www.stoptb.org/gdf/oms/). Post submission, the client is assigned an account and a GDF Country Supply Officer (CSO) responsible for their country.
2. Log in and complete your client profile on the GDF Order Management System.
3. Generate an online Procurement Request Form (PRF) for medicines accompanied by a document showing quantification of products, which is to be uploaded.

4. The CSO will provide you with a price quotation.
5. Sign the price quotation and send a scanned copy back to the CSO.
6. Transfer the necessary funds to the account indicated on the price quotation. Your order will then be placed with the supplier/s. You will be able to track the status of your orders on the GDF Order Management System.
7. Once your products are ready for shipment and quality control has been carried out, you will receive an Authorization Request for shipment.
8. Review and verify the shipping documents provided with the Authorization Request and confirm your readiness to receive the shipment.
9. Delivery is arranged according to the agreed-upon INCOTERM.

Standard lead times from final order placement (i.e., step 6 above) to delivery vary from four to six months. This lead time comprises production, quality control, pre-shipment inspection, internal processing, and transport to the destination.

Direct procurement

Another option is to procure each product directly through manufacturers. This can be done through a tender process in countries or by directly approaching manufacturers for each product in the regimen.

Named patient access program

A third option for countries where pretomanid is not yet approved is to buy through the Named Patient Access Program which was explained above.

ANNEXES

Additional information and figures referenced, but not captured, in the main guide.

Annex A: Informed Consent

ShORRT Informed Consent

The following example consent forms part of the ShORTT (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis), research package developed by TDR and the WHO. It provides standardised methodology to facilitate the conduct of operational research on all-oral shorter MDR/RR-TB treatment regimens by countries, and to generate data that are harmonized across different implementation settings. These tools can be adapted to be country specific.

Consent form [xxi]

Part I: Information sheet

Title of study: All-oral shorter treatment regimens for multi-drug and rifampicin-resistant tuberculosis: Evaluating their effectiveness, safety, feasibility, cost and impact on the quality of life of patients in (name of country)

Co-Principal Investigators (PI): [complete as relevant]

Site Address: [complete as relevant]

Contact number: [complete as relevant]

Sir/Madam,

You have been invited to take part in a research study because you have been diagnosed with Drug-resistant tuberculosis (DR-TB), a serious disease with difficult treatment options. Please take some time to read the information presented here, which will explain details of this study. Please ask us any questions about any part of the study that you do not fully understand. It is very important that you are fully satisfied, that you clearly understand what this research entails and how you could be involved. Your participation is entirely voluntary, and you are free to decline to participate. If you say no, this will not negatively affect you and the quality of care provided to you in any way, including health care now and in the future. If you say yes, you will also be free to withdraw from the study at any point without having to give reasons for your withdrawal.

Ethics approval for this study was obtained from [complete as relevant], and from [complete as relevant]. This study will be conducted according to ethical guidelines and principles of the International Declaration of Helsinki, as well as local ethical guidelines.

What is this study all about?

Drug-resistance tuberculosis (DR-TB) is a difficult disease to treat. The treatment usually lasts 20-24 months and includes a daily injection for 8 months which has high rates of adverse effects and not good rate of favourable outcomes. A shorter regimen (9 to 11

months), injectable-free and using new and repurposed drugs like bedaquiline may provide improved treatment outcomes and a lower rate of adverse events.

Why have I been invited to participate?

You have been selected to participate in this study because you are an adult who has been diagnosed with drug or multi-drug resistant tuberculosis eligible to be treated with the injectable-free short course regimen.

What will happen to me if I take part?

If you accept to be part of the study, you will sign a consent form and an identification number will be assigned to you. Different information collected by the clinical team as part of the routine care will be recorded on a database, which will be analysed throughout and at the end of the study period. This information includes demographic data such as your age and gender, and clinical information on the disease, the clinical examination, the treatm-nt and its effects, as well as laboratory results and other related exam results. All the information included in the database will not be identified with your name, but only with the code that will be assigned to you if you agree to participate in order to preserve confidentiality. If you feel uncomfortable providing some sensitive information about you, please feel free to discuss it with the medical staff.

If you accept to take part in this study, you will be assigned to a short course regimen with only oral drugs. The regimen will take 9-12 months to complete. The treatment will be provided to you by direct observation and you will be accompanied throughout your treatment by a treatment supporter who will help you with your medication. Your tuberculosis regimen will consist of 7 drugs provided for four to six months followed by another 5 months with 5 drugs provided [complete/adapt as relevant].

Since there is a possibility for your disease to reappear after treatment, you will also be asked to complete visits at 6 and 12 months after completing treatment [complete/adapt as relevant]. This will allow checking for any recurrence of the disease and appropriate clinical measures will be taken by the clinical team based on the results.

What do I have to do?

There is no difference for you regarding the clinical care you will receive. You must come to the clinic to have medical consultations and to receive the medicines according to the protocol of the treatment. Your visits to the clinic and the tests that you will do as part of this study will consist of tests that you would anyway do as part of the regular follow-up that is usually required for the follow-up of the patients affected with multi-drug resistant tuberculosis. Additional tests might be run as part of this study during your visits that will require additional sputum samples from you.

How will the data that we collect be treated?

No name will be written on the study collection forms. Also information entered into the computer in an electronic database of the study will not use your name. A number (code) will be used instead. When information is needed from your medical file, it will only be accessed by the clinical and the research team, as they will be locked and kept safely. All reports and communication related to the study (including the publication of the findings)

will also not use your name. The blood and sputum collected for the routine follow-up of your disease and treatment will not be used for any other purpose. Your consent form will be kept separately and safely.

How will I benefit from taking part in this research?

This research will help us in preparing better treatment regimens and algorithms for Drug-resistant tuberculosis patients in the future and also might help you in the course of your treatment, however this is not guaranteed. It might help the wider community in [name of country] to have access to improved treatment regimen, but again this is not guaranteed.

What are the possible side effects of the study regimen?

All drugs can have side effects, and every patient is different. You will be checked by your doctor at every visit for possible side effects and treated accordingly. One of the reasons why you will be requested to give blood samples and perform some other tests such as an electrocardiogram (test for the heart) during your visits is to allow your treating physician to check for any possible side effect related of the treatment. You might experience gastrointestinal effects such as nausea, vomiting and gastric reflux. You might also feel muscle weakness and other neurological side effects, and might experience, among others, a skin rash, dry eyes, and sputum and urine discolouration. It is possible that the short multi-drug resistant tuberculosis regimen may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Always tell your health-care provider of any side effects or problems you are experiencing.

What monitoring tests do I need while taking the short DR-TB regimen?

You will need the same monitoring test that all patients on multi-drug resistant tuberculosis treatment need; these are a first visit and a visit in 2 weeks' time followed by monthly visits. Some additional tests will be requested from you such as blood tests, vision tests, tests to check your heart (electrocardiogram) in order to follow-up on the possible unfavourable effects that the regimen might cause. You will be informed about the signs that should trigger you to see your doctor if you experience them.

Are there any risks involved in this research?

All the different procedures will be performed in the frame of the recommended medical protocol. There might be some risks related to your participation but necessary measures and close follow-up will be done by the clinical and research team accordingly. If you are currently pregnant or are planning to become pregnant during your treatment or in the six months following the end of your treatment, you should be aware that information on the safety during pregnancy of the drugs that you will be given is limited. There is no evidence that they are harmful either. Information on safety during pregnancy of the drugs used as standard of care in your country is also limited. There is a risk that you do not benefit from this regimen as much as you would benefit from the standard regimen in use in your country, and that your treatment may fail. In that case, your regimen will be accordingly adjusted. Risk of failing treatment also exists with the standard treatment. You might also experience, as mentioned earlier, side effects some of which might be severe. A close monitoring of your side effects will be done regularly and at each visit to make sure signs are detected early and treated accordingly. We will make sure that your data will be kept confidential with

no identification with your name. All paper data related to the study will be kept locked and all data entered on a computer will be protected by a password. In all cases, al study related information will be only accessible to the study team.

Can I have the right to refuse or withdraw?

You do not have to agree to take the short course regimen if you do not wish to do so. Instead, you can take the regular regimen for drug-resistant tuberculosis. Your participation is entirely voluntarily and you are free to decline to participate. If you say no, this will not affect you negatively in any way, including your treatment now or in the future. You are also free to withdraw from the study at any point, even if you do agree to take part now. The treating physician might also withdraw you from the study if they deemed it clinically necessary or better for you, after consulting the Clinical Committee members and will provide you with an explanation for the decision. In case you decide to withdraw from the study, the data that was collected related to you up to your withdrawal will still be used for analysis without the identification of your name and only for the purpose of the study, if you agree. After your withdrawal, no further analysis on any of the specimens obtained from you under the study will be carried out.

Are there any costs involved and will I be paid to take part in this study? Investigators should decide whether any reimbursement is given to patients You will be reimbursed the costs related to transportation you will pay for every visit to the tuberculosis medical unit in [insert name of the clinic] where you will present at the start of the treatment and for the further examination visits for check-up and drug collection.

If I have any other questions about the research in the future?
If you have any question, you may contact any of the following persons: [complete as relevant]

You will receive a copy of this information sheet and the signed consent form for your own records.

Part II: Certificate of consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it, and the questions I have asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant _____

Signature/Thumb print of Participant _____

Date _____
day/month/year

Witness

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

Print name of witness _____

Signature _____

Date _____
day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose, procedures, potential risks and benefits of the study. I confirm that the participant was given an opportunity to ask questions about the study, 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 ICF has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____
day/month/year

The information provided below on bedaquiline and Llnezolid encompasses their role in MDRTB management overall whereas the information for Pretomanid is only in relation to its role in the BPaL regimen.

KNVC: Patient Information Sheet BPaL regimen

The following example consent forms part of the generic protocol developed by the KNCV TB Foundation, with support under the KOICA-funded LIFT-TB project, for the scale-up and introduction of BPaL under operational research conditions[xxii].

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.
- **Effects on male fertility.** In animal studies, the drug pretomanid caused impaired fertility in male rats, the potential effects on human male fertility have not yet been adequately evaluated. Talk to your health care provider if this is a concern to you.
- **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: 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 B: DRUG Information

Table 4: Bedaquiline (B), Pretomanid (Pa) and Linezolid (L) Drug Information

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
Description	• Each SIRTURO 100 mg tablet contains 100 mg of bedaquiline (equivalent to 120.89 mg of bedaquiline fumarate). • Bedaquiline fumarate is a white to almost white powder and is practically insoluble in aqueous media.	Pretomanid is a white to off-white to yellow-colored powder.	Linezolid is an antibiotic of the oxazolidinones group that works by stopping the growth of certain bacteria (germs) that cause infections. It is used to treat pneumonia and some infections in the skin or under the skin. Your doctor will have decided if Linezolid is suitable to treat your infection.
Mechanism of action	Bedaquiline is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *M. tuberculosis*.	Pretomanid is a nitroimidazooxazine antimycobacterial drug	Has in vitro bactericidal activity – increasing clinical experience; inhibits protein synthesis
Pharmacokinetics	400 mg for 2 weeks followed by 200 mg three times per week for 22 weeks.	Pretomanid AUC and Cmax were approximately dose proportional over a range of single oral doses from 50 mg (0.25 times the approved recommended dosage) to 200 mg (approved recommended dosage); at single doses greater than 200 mg and up to 1,000 mg (5 times the approved recommended dosage),	

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
		AUC and Cmax increased in a less than dose proportional manner. Steady-state Pretomanid plasma concentrations were achieved approximately 4 to 6 days following multiple dose administration of 200 mg, and the accumulation ratio was approximately 2.	
Pharmacodynamics	Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (4-fold to 6-fold lower) compared to the parent compound. However, M2 plasma concentrations appeared to correlate with QT prolongation.	Cardiac Electrophysiology A randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg), crossover, thorough QT study of Pretomanid was performed in 74 healthy adult subjects. At 400 mg (2 times the approved recommended dosage) and 1,000 mg (5 times the approved recommended dosage) single doses of Pretomanid, no significant QT prolongation effect was detected. In Study 1, patients received the combination regimen of Pretomanid Tablets, Bedaquiline, and Linezolid for six months. No patient had QTcF intervals greater than 480 msec, and 1 subject had a post-baseline increase of QTcF of greater than 60 msec.	
Microbiology	Resistance	Resistance	

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	A potential for development of resistance to bedaquiline in *M. tuberculosis* exists Isolates that are phenotypically resistant to bedaquiline should be tested for cross-resistance to clofazimine, if clofazimine is being considered as part of the treatment regimen.	Mutations in five M. tuberculosis genes (ddn, fgd1, fbiA, fbiB, and fbiC) have been associated with Pretomanid resistance.Cross resistance of Pretomanid with other compounds in the same class has been observed.	
Indication & usage	Indicated as part of combination therapy in the treatment of adult and paediatric patients (6 years and older and weighing at least 15 kg) with pulmonary MDR-TB.	• Indicated for use in a limited and specific population of patients. • Registered for used in combination with bedaquiline and Linezolid for the treatment of adults with pulmonary XDR or treatment-intolerant or nonresponsive MDR- TB.	• Indicated for gram-positive infections and approved for, amongst other indications, the treatment of bacterial pneumonia • Also used off-label for treatment of DRTB.
Dosage and administration	Adults: Bedaquiline 400 mg once daily for 2 weeks then 200 mg 3 times per week;	Adults: 200mg once daily orally	• Adults: 600 mg, once daily. (Reduce to 400–300 mg/day if serious adverse effects develop). • **Within the BPaL regimen, LZD is dosed at 1200mg.** • Children: 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg), twice daily in older children. 5 10 mg/kg/dose every 12 hours.

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
			• Vitamin B6: All patients should receive vitamin B6 while receiving Linezolid
Contraindications	Should not be administered: • with EFV • in patients with known Torsades de Point or existing QtcF prolongation	If used in the BPaL regimen, should not be administered if bedaquiline and/or Linezolid is contraindicated.	• Should not be administered if: ○ Hypersensitivity to oxazolidinones. ○ Severe peripehral neuropathy (pain, numbness, tingling or weakness in the extremities). Grade 1 PN is not a C/I nor is grade 2 if balance favours LZD use • Certain concomitant medications are contraindicated, see Table 2
Warnings and precautions	**Increased Mortality** No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat tuberculosis, HIV status, or severity of disease was observed. **QT Prolongation**	**Hepatotoxicity/ Hepatic adverse reactions**	• **Problems with vision** such as blurred vision, changes in colour vision, difficulty in seeing detail, field of vision becomes restricted. • **Severe diarrhoea** containing blood and/or mucus which in rare circumstances may develop into complications that are life-threatening. • **Peripheral neuropathy** • **Anaemia**
Drug Interactions	CYP3A4 inducers/inhibitors bedaquiline is metabolized by CYP3A4 and its systemic exposure and therapeutic effect	**CYP3A4 Inducers** Pretomanid may be in part metabolized by CYP3A4. Avoid co-administration of strong or moderate CYP3A4	Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	may therefore be reduced during co-administration with inducers of CYP3A4. Avoid co-administration of strong CYP3A4 inducers, such as rifamycins (i.e., rifampin, rifapentine and rifabutin), or moderate CYP3A4 inducers, such as efavirenz, during treatment with Bedaquiline.	inducers, such as rifampin or efavirenz, during treatment with Pretomanid.	reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants, etc. as it may cause serious CNS reactions such as serotonin syndrome.
Use in specific populations	**Hepatic Impairment:** • After single-dose administration of 400 mg SIRTURO to 8 adult patients with moderate hepatic impairment (Child-Pugh B), mean exposure to bedaquiline and M2 (AUC672h) was approximately 20% lower compared to healthy subjects. SIRTURO has not been studied in patients with severe hepatic impairment. **Renal Impairment:** • SIRTURO has mainly been studied in adult patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial (less than or equal to 0.001%). • In a population pharmacokinetic analysis of MDR-TB adult patients treated with SIRTURO 200 mg three	• Pregnancy Risk Summary There are no studies or available data on Pretomanid use in pregnant women to inform any drug-associated risks. There are risks associated with active tuberculosis during pregnancy. When Pretomanid Tablets are administered in combination with bedaquiline and Linezolid, the pregnancy information for bedaquiline and Linezolid also applies to this combination regimen. Refer to the bedaquiline and Linezolid prescribing information for more information on bedaquiline and Linezolid associated risks of use during pregnancy. In animal reproduction studies, there was increased post-implantation loss in the	• Pregnancy Risk Summary There are no studies or available data on Pretomanid use in pregnant women to inform any drug-associated risks. There are risks associated with active tuberculosis during pregnancy. When Pretomanid Tablets are administered in combination with bedaquiline and Linezolid, the pregnancy information for bedaquiline and Linezolid also applies to this combination regimen. Refer to the bedaquiline and Linezolid prescribing information for more information on bedaquiline and Linezolid associated risks of use during pregnancy. In animal reproduction studies, there was increased post-implantation loss in the

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	times per week, creatinine clearance was not found to influence the pharmacokinetic parameters of Bedaquiline. It is therefore not expected that mild or moderate renal impairment will have a clinically relevant effect on the exposure to Bedaquiline. However, in patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis bedaquiline concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As bedaquiline is highly bound to plasma proteins, it is unlikely that it will be significantly removed from plasma by hemodialysis or peritoneal dialysis **Sex:** • In a population pharmacokinetic analysis of MDR-TB adult patients treated with SIRTURO no clinically relevant difference in exposure between men and women were observed. **Race/Ethnicity:**	presence of maternal toxicity (reduced bodyweight and feed consumption) with oral administration of Pretomanid during 10 organogenesis in rats at doses about 4 times the exposure at the recommended dose in humans. There were no adverse embryo fetal effects in rats or rabbits dosed with oral Pretomanid during organogenesis at doses up to approximately 2 times the exposure in humans. • The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. • Clinical Considerations Disease-Associated Maternal and/or Embryo/Fetal Risk Active tuberculosis in	presence of maternal toxicity (reduced bodyweight and feed consumption) with oral administration of Pretomanid during 10 organogenesis in rats at doses about 4 times the exposure at the recommended dose in humans. There were no adverse embryo fetal effects in rats or rabbits dosed with oral Pretomanid during organogenesis at doses up to approximately 2 times the exposure in humans. • The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. • Clinical Considerations Disease-Associated Maternal and/or Embryo/Fetal Risk Active tuberculosis in

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	• In a population pharmacokinetic analysis of MDR-TB adult patients treated with SIRTURO, systemic exposure (AUC) to bedaquiline was found to be 34% lower in Black patients than in patients from other race categories. This lower exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials of MDR-TB. Furthermore, response rates were comparable in patients of different race categories that completed 24 weeks of bedaquiline treatment. **HIV Co-infection:** • There are limited data on the use of SIRTURO in HIV co-infected patients. **Geriatric Population:** • There are limited data on the use of SIRTURO in tuberculosis patients 65 years of age and older. • In a population pharmacokinetic analysis of MDR-TB adult patients treated with SIRTURO, age	pregnancy is associated with adverse maternal and neonatal outcomes including maternal anemia, caesarean delivery, preterm birth, low birth weight, birth asphyxia, and perinatal infant death.	pregnancy is associated with adverse maternal and neonatal outcomes including maternal anemia, caesarean delivery, preterm birth, low birth weight, birth asphyxia, and perinatal infant death.

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	was not found to influence the pharmacokinetics of Bedaquiline. **Pediatric Population:** • Pediatric patients 12 years to less than 18 years of age with MDR-TB • The pharmacokinetic parameters of bedaquiline in 15 pediatric patients (body weight at baseline: • 38 to 75 kg) who received the same adult dosage regimen of SIRTURO (400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks) in combination with a background regimen were comparable to those in adults. There was no impact of body weight on • Bedaquiline pharmacokinetics in this cohort. • Pediatric patients 5 years to less than 12 years of age with MDR-TB • Fifteen MDR-TB pediatric patients (body weight at baseline: 14 to 36 kg) received SIRTURO (200 mg once daily for the first 2 weeks and 100 mg 3		

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	times/week for the following 22 weeks) in combination with a background regimen. Of these 15 pediatric patients, complete pharmacokinetic data were obtained for 10 patients at the aforementioned dosage regimen of SIRTURO. In 9 of these 10 pediatric patients who weighed at least 15 kg at baseline, the mean • Bedaquiline Cmax and AUC24h were similar to that of adult MDR-TB patients receiving the recommended adult dosage regimen. In 1 of these 10 pediatric patients who weighed 14 kg at baseline, the bedaquiline mean Cmax and AUC24h were 3.8-fold and 2.6-fold, respectively, higher than the mean Cmax and AUC24h in adult MDR-TB patients administered the recommended adult dosage regimen. The clinical significance of this higher pharmacokinetic plasma exposure in this one pediatric patient is not known.		
Overdose	There is no experience with the treatment of acute overdose with	There is no experience with the treatment of acute overdose with	

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	SIRTURO. Take general measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) in case of deliberate or accidental overdose. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma.	Pretomanid. Take general measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) in case of deliberate or accidental overdose.	
Storage and handling	**SIRTURO 20 mg Tablet** Store in original container. Bottle contains desiccant. Do not discard desiccant. Protect from light and moisture. Keep the container tightly closed. Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP] **SIRTURO 100 mg Tablet** Dispense in original container. Store tablets dispensed outside the original container in a tight light-resistant container with an expiration date not to exceed 3 months. Protect from light. Keep the container tightly closed. Store at 25°C (77°F); excursions	Pretomanid Tablet 200 mg is packaged in either white, round, high-density polyethylene bottles with polypropylene child-resistant closure or child-resistant blister packages comprised of a polyvinylchloride film with foil and paper backing. Store below 30 °C (86 °F). Dispense only in original container and keep container tightly closed.	Store tablet at room temperature (15–25 °C). Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze). Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml: 100, 200 or 300 mg bags. Intravenous doses are administered over 30–120 minutes. Oral powder for suspension: 100 mg/5 ml, 240 ml bottle.

	Bedaquiline (B)	Pretomanmid (Pa)	Linezolid (L)
	permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Approved for use by:	FDA	FDA; EMA within BPaL	FDA

Annex C: BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL

BRIEF PERIPHERAL NEUROPATHY SCREEN

Patient Initials				Patient ID										
1. Visit (Circle One)	All Subjects	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 26						
		3 Month		6 Month		12 Month		24 Month						
	9 Month Treatment **ONLY**	Week 30		Week 34		Week 39								
	Other	Early Withdrawal				Unscheduled For new onset or worsening peripheral neuropathy during treatment								
2. Date of Assessment		D	D	M	M	M	Y	Y	Y	Y				

INTERFERENCE WITH WALKING OR SLEEPING

3. In the last two weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one)	Y	N

*If **YES**, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one).*

3a.	Minimal			Modest				Severe		
	01	02	03	04	05	06	07	08	09	10

SUBJECT ELICITED SYMPTOMS

- *Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.*
- *Enter a score for each symptom.*
- *If a symptom has been present in the past, but not since the last visit, enter '00 – Currently Absent'*
- *If a symptom has never been present, enter '11 – Always Been Normal'*

00	02	04	06	08	10
Very Happy, No Symptoms	Just a little bit	A little more	Even more	A whole lot	Worst

During the last 14 days, have you experienced:		Severity	
	4. Pain, aching or burning in feet or legs?		
	5. "Pins and needles" in feet or legs?		
	6. Numbness (lack of feeling) in feet or legs?		

BRIEF PERIPHERAL NEUROPATHY SCREEN

Patient Initials				Patient ID									

PERCEPTION OF VIBRATION

- *Press the ends of a 128 Hz tuning fork together so the sides touch and let go. Place the vibrating tuning fork on the bony prominence on the patient's wrist to be sure that they can recognize the vibration or "buzzing" quality of the tuning fork.*
- *Again, press the ends of the tuning fork hard enough so that the sides touch and let go. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of the great toe and begin counting the seconds. Instruct the Subject to tell you when they stop feeling the vibration or "buzzing".*
- *Repeat for the great toe on the other foot*

Vibration Perception Grade Scale:
0 – Vibration felt for >10 seconds (normal)
1 – Vibration felt for 6-10 seconds (mild loss)
*2 – Vibration felt for 5 seconds or less (moderate loss)**
*3 – No feeling of vibration (severe loss)**
*9 – Unable to evaluate or did not assess**

	Right	Left
7. Measured vibration grade of great toe DIP joint		

DEEP TENDON REFLEXES

- *The examiner uses one hand to press upward on the ball of the foot, dorsiflexing the Subject's ankle to 90 degrees. Using the reflex hammer (preferably long handled), the examiner strikes the Achilles tendon.*
- *The tendon reflex is felt by the examiner's hand as plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck.*
- *Repeat for ankle on other leg*

Ankle reflex grade scale:
0 – Absent
1 – Hypoactive
2 – Normal deep tendon reflexes
3 – hyperactive deep tendon reflexes ***(e.g. with prominent spread of toes)***
4 – clonus
9 – unable to evaluate or did not assess

	Right	Left
8. Measured ankle reflex grade		

COMMENTS

Name of Person Completing Form										Name of Clinician (if required)									
Signature of Person Completing Form										Signature of Clinician (if required)									
Date	D	D	M	M	M	Y	Y	Y	Y	Date	D	D	M	M	M	Y	Y	Y	Y

Annex D: DAIDS GRADING TABLE[xxiii]

Below are select excerpts from the DAIDS grading table applicable to the toxicity management mentioned in the guide.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

Table 5: Grading of parameters not identified

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Table 6: Excerpts from the DAIDS grading table

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Neurological:				
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Cardiac:				
Prolonged QTc Interval	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Haematology:				
Absolute Neutrophil Count (ANC), Low (cells/mm3; cells/L)	800 to 1,000 0.800 x 10^9 to 1.000 x 10^9	600 to 799 0.600 x 10^9 to 0.799 x 10^9	400 to 599 0.400 x 10^9 to 0.599 x 10^9	< 400 < 0.400 x 10^9
Haemoglobin, Low (g/dL; mmol/L)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
Platelets, Decreased (cells/mm3; cells/L)	100,000 to < 125,000 100.000 x 10^9 to < 125.000 x 10^9	50,000 to < 100,000 50.000 x 10^9 to < 100.000 x 10^9	25,000 to < 50,000 25.000 x 10^9 to < 50.000 x 10^9	< 25,000 < 25.000 x 10^9
WBC, Decreased (cells/mm3; cells/L) > 7 days of age	2,000 to 2,499 2.000 x 10^9 to 2.499 x 10^9	1,500 to 1,999 1.500 x 10^9 to 1.999 x 10^9	1,000 to 1,499 1.000 x 10^9 to 1.499 x 10^9	< 1,000 < 1.000 x 10^9
Hepatic Chemistry:				
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT or SGPT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bilirubin Direct Bilirubin13, High > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
				symptoms of liver failure)
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Renal:				
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance 14 or eGFR, Low *Report only one	NA	< 90 to 60ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline

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