South African National Essential Medicines List
Adult Hospital Level Medication Review Process
Component: Respiratory conditions

MEDICINE SCOPING REVIEW

EXECUTIVE SUMMARY

Date: 31 October 2019

Medicine (INN): Pretomanid

Medicine (ATC): n/a

Indication (ICD10 code): Pretomanid is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with pulmonary extensively drug resistant tuberculosis (XDR-TB), or treatment-intolerant or nonresponsive multidrug-resistant tuberculosis. This medicine is not yet registered in South Africa but has been used in clinical trials nationally. [A15.0-3, A15.7-8, A16.0-2, A16.7-9, B20.0 + (U50.00-01, U50.10-11)]

Patient population: Adults with pulmonary XDR-TB, or treatment-intolerant or nonresponsive MDR-TB

Prevalence of the condition: WHO estimated that there were approximately 558,000 cases of MDR-TB worldwide in 2017, and of these 8.5% were estimated to have extensively drug resistant TB (XDR-TB) [https://www.who.int/tb/publications/global_report/en/].

Level of Care: Tertiary / TB centres

Prescriber level: Specialist

Current Standard of Care: Patients with pre-XDR-TB and XDR-TB currently receive long, individualized regimens containing new and repurposed medicines. Treatment regimens include a combination of second- and third-line oral drugs with an injectable antimycobacterial for a duration of 18-20 months.

Findings: We searched for published (electronic databases and relevant websites e.g. FDA) and ongoing trials (clinicaltrials.gov) of pretomanid for drug-resistant TB. There are no published trials and 9 phase II and III trials in the pipeline according to clinicaltrials.gov registry (3 completed, 6 in-progress/planned). We did not limit our search for dates or publication status.

The unpublished results of one ongoing controlled clinical trial, NIX-TB, was available through the TB Alliance and FDA website, and informed the FDA decision to register pretomanid with a limited indication. The Nix-TB trial, conducted in three sites in South Africa, is a phase III controlled-clinical trial with historical controls including 109 participants. The trialists reported that 95/107 (89%) of participants who were evaluated six months after the end of treatment with the bedaquiline, pretomanid and linezolid regimen had a successful outcome, while 12/107 (11%) were classified as treatment failures (95% CI [81%-94%]). This was significantly higher than the 50% rate pre-specified as the historical control rate threshold. [https://www.fda.gov/media/127592/download].

Summary: [can be finalized after committee meets]

Reviewers: Maryke Wilkinson, Tamara Kredo

PTC affiliation: n/a

Funding support: South African Medical Research Council, Evidence Response Initiative

2. NAME OF REVIEWERS

Maryke Wilkinson, Tamara Kredo,

3. AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS

- Maryke Wilkinson: Affiliated with South African Medical Research Council; no relevant financial or academic interests to declare.

- Tamara Kredo: Affiliated with South African Medical Research Council; no relevant financial or academic interests to declare.

4. INTRODUCTION/BACKGROUND

The World Health Organization (WHO) estimated that there were approximately 558,000 cases of MDR-TB worldwide in 2017, and of these it is estimated that there were 230,000 deaths due to MDR-TB. Among the cases of MDR-TB in 2017, 8.5% were estimated to have extensively drug resistant TB (XDR-TB) (1).

Patients with XDR-TB or treatment intolerant/non-responsive MDR-TB have a high mortality rate and limited treatment options (2). Treatment outcomes are poor, with only 48% of XDR-TB patients who started in treatment in 2015 reported as successfully treated (1).

Patients with pre-XDR-TB and XDR-TB currently receive long, individualized regimens containing new and repurposed medicines. Treatment regimens include a combination of second- and third-line oral drugs with an injectable antimycobacterial for a duration of 18-20 months. The intensive phase of treatment is usually 6 months, but this may be extended to 8 months. The continuation phase duration is 12 months (3).

Major treatment challenges include poor efficacy, adverse reactions, non-compliance, intolerance, and drug-drug interactions with antiretroviral drugs and other concomitant medications (2).

Pretomanid: scoping the evidence for a new medicine

The product prescribing information for pretomanid can be viewed on the following link: https://www.tballiance.org/sites/default/files/assets/Pretomanid_Full-Prescribing-Information.pdf

Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazooxazines. Pretomanid inhibits cell wall biosynthesis via blockage of the oxidation of hydroxymycolate to ketomycolate. Under anaerobic conditions, pretomanid causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species (4).

Pretomanid is part of a three-drug, six-month, all-oral regimen for the treatment of people with XDR-TB or treatment-intolerant or nonresponsive MDR-TB (collectively termed “highly drug-resistant TB”) (5)

Table 1. Product overview (2,6)

Type	New molecular entity
Name of company	TB Alliance (non-profit organisation)
Regulatory status in US	Approved 19 August 2019[1]
Regulatory status in EU	Pre-registration (filed)
Orphan drug US	Yes
Orphan drug EU	Yes
Pharmacology	Inhibition of cell-wall synthesis; inhibition of protein synthesis
Indication	Treatment of XDR-TB or treatment-intolerant or nonresponsive MDR-TB in combination with bedaquiline and linezolid (BPaL regimen)
Method of administration	Oral (immediate-release tablets)
Dosing regimen	Pretomanid 200mg tablet once daily, as part of a regimen with bedaquiline and linezolid
Duration of treatment	26 weeks

Limitations of Use (7)

Pretomanid Tablets are not indicated for patients with:

- Drug-sensitive (DS) tuberculosis

[1] Approved by the FDA under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway) which provides approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in a limited population of patients with unmet need.

- Latent infection due to *Mycobacterium tuberculosis*
- Extra-pulmonary infection due to *Mycobacterium tuberculosis*
- MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy

The safety and effectiveness of pretomanid tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen.

Pretomanid used in combination with bedaquiline and linezolid are contraindicated in patients for whom bedaquiline and/or linezolid is contraindicated.

Safety

The FDA drug application contained data on 1168 people who have received pretomanid either alone (411 [35.2%] subjects) or in combination with other antimycobacterial drugs (757 [64.8%] subjects) (2) in 19 clinical trials conducted across 14 countries. A list of the clinical trials that were referenced in the FDA registration application for pretomanid is presented in Appendix 1.

The safety population for the BPaL regimen is limited and only includes 124 patients. Adverse reactions reported during the Nix-TB trial of the BPaL regimen include hepatotoxicity, myelosuppression, as well as peripheral and optic neuropathy (2).

Safety data from the Nix-TB study (n = 109 subjects) (7):

- Hepatotoxicity: 28% of patients experienced increased transaminases. Of these, one patient died due to pneumonia and sepsis, but the rest were able to continue therapy and complete the full course of treatment.
- Myelosuppression: A know adverse reaction of linezolid. The most common hematopoietic cytopenia was anemia (37%). The majority of cytopenias began after 2 weeks of treatment, and in three serious cases resulted in interruption of linezolid or all components of the combination regimen of pretomanid, bedaquiline, and linezolid, after which the adverse reactions resolved.
- Peripheral neuropathy: A know adverse reaction of linezolid. Reported in 81% of patients. Most reactions occurred after 8 weeks of treatment and resulted in dosing interruption, dose reduction, or discontinuation of linezolid, but none led to a discontinuation of the entire study regimen.
- Optic neuropathy: A know adverse reaction of linezolid. Two patients (2%) developed optic neuropathy after 16 weeks of treatment. Both were serious and resulted in discontinuation of linezolid. Both adverse reactions resolved.

Most common adverse reactions (≥10%) are peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea (7).

Pretomanid caused testicular toxicity and infertility in male rats. Male hormone levels were within the normal range in the Nix-TB trial and in a Phase III trial of another pretomanid-containing antimycobacterial regimen. The effects of pretomanid on human male fertility is not known (2).

5. SCOPING REVIEW OBJECTIVE

To evaluate the effectiveness, safety and cost of the use of the bedaquiline, pretomanid and linezolid (BPaL) regimen compared to non-pretomanid-containing regimens for patients with XDR-TB at TB centres or in South African public sector

Population: Adults with pulmonary XDR-TB, or treatment-intolerant or nonresponsive MDR-TB.

Intervention: Six-month treatment with three-drug regimen consisting of bedaquiline, pretomanid and linezolid (BPaL regimen). Option for 9 months for subjects who remain culture positive at month 4.

Comparison: Long-term treatment (18-20 months) with individualized regimens containing new and repurposed medicines (oral and injectables).

Outcomes:

- Mortality

- Incidence of bacteriologic failure or relapse or clinical failure through follow up until 6 months after the end of treatment
- Time to sputum culture conversion to negative status through the treatment period.
- Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness, leading to TB related or non-TB related death.
- Loss to follow up.

6. METHODS AND FINDINGS

Part 1: Guidelines

Summary of methods used to find and appraise the guidelines

Electronic searches for guidelines was completed on 17 October 2019. Pretomanid and PA-824 was used as search terms in the following databases:

Table 2. Clinical guideline database search description

Name	Website	Searched (x)
WHO – World Health Organization	www.who.int/publications/guidelines/en/	x
GIN – Guidelines International Network	www.g-i-n.net	x
NICE – National Institute for Health Care Excellence (England and Wales)	www.nice.org.uk/guidance	x
SIGN – Scottish Intercollegiate Guidelines Network (Scotland)	www.sign.ac.uk	x
National Guideline Clearinghouse (USA)	www.guideline.gov	x
Clinical Practice Guidelines Portal (Australia)	www.clinicalguidelines.gov.au/portal	x
Electronic search (e.g. google)	https://www.fda.gov/ https://www.tballiance.org/	x

No guidelines were identified.

WHO issued a public notice in 2018 of their intent to update the WHO guidelines on drug-resistant TB (8). At the start of 2019, WHO issuing a public call to industry, researchers, national TB programmes and other agencies to provide the most recent evidence and scientific analysis on the treatment of MDR/RR-TB that can contribute to the process of the WHO guideline update (9). In addition, WHO's public call for comments/objections relating to the selected Guideline Development Group closed on 10 October 2019. The guideline development process should therefore commence shortly.

The upcoming update will focus on:

- the use of a modified all-oral shorter MDR/RR-TB regimen (i.e. less than 12-month duration);
- the use of a novel regimen combining pretomanid, bedaquiline and linezolid; and
- the use of bedaquiline for more than 6 months and its concurrent use with delamanid.

Part 2: Systematic reviews

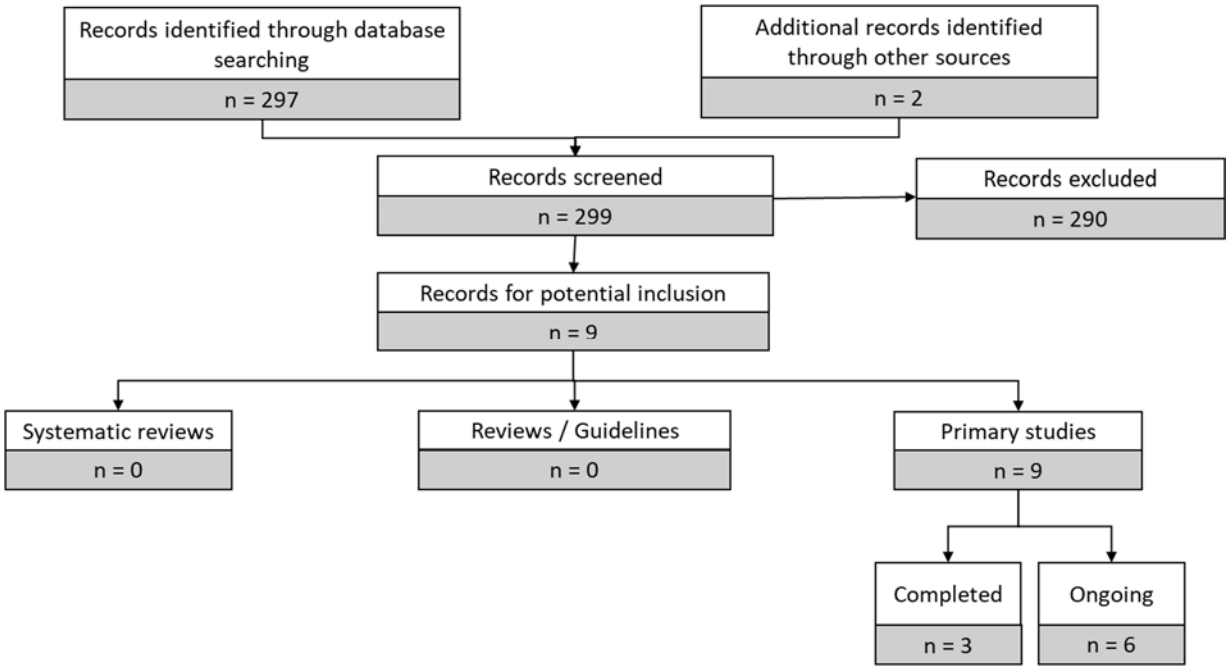
Summary of methods used to find and appraise the systematic reviews

Electronic searches for systematic reviews and primary studies were done on 16 October 2019 in PubMed, Scopus and clinicaltrials.gov. The search strategies are shown in Table 3. We did a single screening of all records to review the title and abstract. Only full texts of systematic reviews were sought for further appraisal and reporting below. The Prisma flow diagram for the search output is shown below (Figure 1).

Table 3. Search strategies for PubMed, Scopus and clinicaltrials.gov

Search	Query	Items found
PubMed		
#4	Search ((#1 AND #2) NOT (animals[mh] NOT humans[mh]))	160
#3	Search (#1 AND #2)	192
#2	Search (tuberculosis[mh] OR tuberculosis[tiab])	246699
#1	Search (pretomanid[tiab] OR "PA-824"[tiab])	215
Scopus		
	(TITLE-ABS-KEY (pretomanid) OR TITLE-ABS-KEY (pa-824)) AND (TITLE-ABS-KEY (tuberculosis)) AND NOT INDEX (medline) AND (LIMIT-TO (EXACTKEYWORD , "Human"))	123
Clinicaltrials.gov		
	pretomanid OR "PA-824" | tuberculosis	23

Figure 1. Prisma flow diagram of search results



No systematic reviews were found.

The most recent and applicable assessment of the available evidence was conducted by the US Food and Drug Administration (FDA). The FDA reviewed and approved pretomanid under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway) which provides approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in a limited population of patients with unmet need.

Summary of findings from primary studies (some as presented in FDA regulatory review)

The FDA approval of pretomanid as part of the BPaL regimen was based on clinical data from one phase III RCT: Nix-TB (10). In addition, a dose-optimisation study (ZeNIX) is currently underway for the BPAL regimen.

List of all studies that have/are investigating pretomanid as part of a treatment regimen is presented in Appendix 2 (drug-resistant TB), Appendix 3 (drug-susceptible TB) and Appendix 4 (healthy volunteers).

a) Nix-TB

An overview of the Nix-TB study is provided in Table 4 and Figure 2. The study started in March 2015, final primary outcome measure data was collected by January 2019, and the projected study completion date[2] is October 2021 (10).

Table 4. Nix-TB study overview (2,4,10)

Study title	**A Phase III, Open-Label Trial Assessing the Safety and Efficacy of Bedaquiline plus Pretomanid plus Linezolid in Subjects with Pulmonary Infection of Either XDR-TB or treatment-intolerant or nonresponsive MDR-TB.**
Study design	Phase III, multicentre, single group, open-label trial evaluating the efficacy, safety, tolerability and pharmacokinetics of the three-drug regimen consisting of bedaquiline, pretomanid and linezolid (BPaL regimen) after 6 months of treatment (option for 9 months for subjects who remain culture positive at month 4) in people with either pulmonary XDR-TB~, treatment-intolerant or nonresponsive MDR-TB†. Follow-up visits were performed at 1 and 2 months after treatment completion and then every 3 months for 24 months.
Population	Patients ≥14 years of age with either pulmonary XDR-TB, treatment-intolerant or nonresponsive MDR-TB. The study population included patients who are co-infected with HIV with a CD4 count of 50 or higher.
Intervention(s)	Bedaquiline + Pretomanid + Linezolid • Bedaquiline 400 mg once daily for 2 weeks then 200mg 3 times per week • Pretomanid 200mg once daily • Linezolid 1200mg once daily
Comparator(s)	XDR-TB historical controls (no active comparator)
Reported outcomes*	Primary outcome • Incidence of bacteriologic failure or relapse or clinical failure through follow up until 6 months after the end of treatment. Secondary outcomes • Time to sputum culture conversion to negative status through the treatment period. • Proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks. • Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness, leading to TB related or non-TB related death. • All Subjects- Pre-dose sampling at weeks 2, 8 and 16 to measure C_{trough} levels of bedaquiline, bedaquiline metabolite M2, Linezolid and pretamanid. • Time to sputum culture positivity
Trial sites	South Africa • Brooklyn Chest Hospital (Ysterplaat, Cape Town) • King DinuZulu Hospital Complex (Sydenham, Durban) • Sizwe Tropical Disease Hospital (Sandringham, Johannesburg)
Trial setting	Hospital

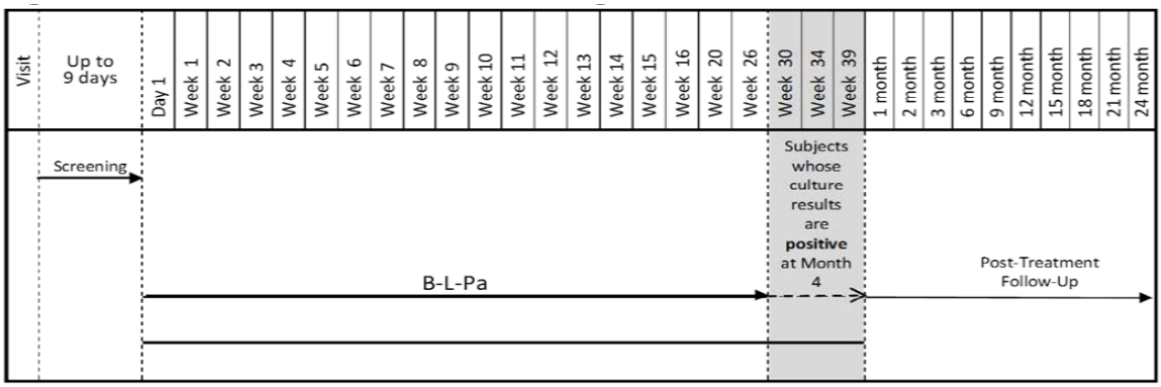
*More detail on the reported outcomes are presented in Appendix 5

~ XDR-TB was defined by documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable drug.

†TI/NR MDR-TB was defined by resistance to isoniazid and rifampin and documented non-response to treatment with the best available regimen for 6 months or more prior to enrollment, or inability to continue a second-line drug regimen due to documented intolerance to para-aminosalicylic acid, ethionamide, aminoglycosides, or fluoroquinolones.

[2] Date on which the last participant is examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events

Figure 2. Schematic of Nix-TB study design (4)



Results

The trial enrolled 109 people (aged 17 to 60) across three sites in South Africa (Cape Town, Durban, Johannesburg) (11). All 109 participants were evaluated for adverse events and included in the safety population.

Table 5. Nix-TB Baseline Demographics (4)

Variable	BPaL population (n = 109)
Mean age (years)	36 (ranged from 17 to 60)
Gender	Male: 57/109 (52.3%) Female: 52/109 (47.7%)
Race	Black or African: 83/109 (76.1%) Mixed race: 25/109 (22.9%) White 1/109 (0.9%)
Trial Centre	Johannesburg: 40/109 (36.7%) Cape Town: 57/109 (52.3%) Durban: 12/109 (11.0%)

Fifty-six (51%) of the patients were HIV-positive.

Eight patients died in the course of the study - six of those patients were still receiving treatment at the time of their death. All surviving patients (excluding one patient who withdrew consent) completed treatment (n = 101 [92.7%]) (4,7).

The starting dose of linezolid was amended after the start of the study from 600 mg twice daily (received by 44/109 [40.4%] subjects) to 1200 mg once daily (received by 65/109 [59.6%]) subjects. Premature discontinuation of the entire BPaL regimen was uncommon, but 30/109 (27.5%) patients discontinued linezolid treatment due to an adverse event, 53/109 (48.6%) interrupted linezolid due to an adverse event at least once, and 69/109 (63.3%) had at least one linezolid dose reduction. These discontinuations, interruptions, and dose reductions were most commonly due to peripheral neuropathy (4).

Nix-TB data have demonstrated that of the 107 patients who were evaluated six months after the end of treatment with the BPaL regimen, 95 (89%) had a successful outcome, while 12 (11%) were classified as treatment failure[3] [95% CI: 81%-94%]. This was significantly higher than the 50% rate pre-specified as the historical control rate threshold (threshold based on findings from a literature review). For two patients, treatment was extended to nine months (11). Two patients' primary outcome assessments were outstanding at time of analysis.

[3] An unsuccessful outcome/treatment failure was defined as the incidence of bacteriologic failure (reinfection – culture conversion to positive status with different M. tuberculosis strain), bacteriological relapse (culture conversion to positive status with same M. tuberculosis strain), or clinical failure through follow-up until 6 months after the end of treatment (7).

The clinical outcomes were similar in both HIV negative and HIV positive patients.

An overview of the results is presented in Table 6.

Table 6. Outcomes Six Months After the End of Treatment (analysis of accessible data) (7)

Outcome		**All patients (n = 107)**	**XDR-TB (n = 71)**	**TI/NR MDR-TB (n = 36)**
Success	Success (culture negative status at 6 months post treatment)	95 (89%)	63 (89%)	32 (89%)
Failure	Death	7	6	1
	Relapse post treatment	2	1	1
	Withdrawal, loss to follow-up, or contaminated cultures	3	1	2
	Total Failure	12 (11%)	8 (11%)	4 (11%)

TI/NR MDR-TB = treatment-intolerant or nonresponsive multidrug-resistant tuberculosis; XDR-TB = extensively drug resistant tuberculosis

b) ZeNix (NC-007)

The purpose of the ZeNix study is to evaluate the efficacy and safety of various doses and treatment durations of the three-drug BPaL regimen. An overview of the ZeNix study is provided in Table 7.

The study started in November 2017, final primary outcome measure data will be collected by December 2020, and the projected study completion date[4] is December 2021 (12).

The ZeNix study is currently recruiting patients, with an estimated trial enrolment of 180 people (12).

[4] Date on which the last participant is examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events

Table 7. Overview of ZeNix study (12)

<table>
<tr><td>Study title</td><td colspan="4">A Phase 3, Open Label, Randomized Trial Assessing the Safety and Efficacy of Bedaquiline plus Pretomanid plus Various Doses and Treatment Durations of Linezolid in Participants with Either Pulmonary XDR-TB, pre-XDR-TB or treatment-intolerant /nonresponsive MDR-TB.</td></tr>
<tr><td>Study design</td><td colspan="4">Phase III, multicentre, parallel group, open-label trial assessing the safety and efficacy of bedaquiline plus pretomanid plus various doses and treatment durations of linezolid in participants with either pulmonary XDR-TB, pre-XDR-TB or treatment-intolerant or nonresponsive MDR-TB for 26 weeks~.</td></tr>
<tr><td>Population</td><td colspan="4">Patients ≥14 years of age with either pulmonary XDR-TB, pre-XDR-TB, or treatment-intolerant or nonresponsive MDR-TB.</td></tr>
<tr><td>Intervention(s)</td><td colspan="4"><table>
<tr><td>Experimental Arm 1</td><td>Bedaquiline 200 mg once daily for 8 weeks, then once daily for 18 weeks</td><td>Pretomanid 200 mg once daily for 26 weeks</td><td>Linezolid 1200mg once daily for 26 weeks</td></tr>
<tr><td>Experimental Arm 2</td><td>Bedaquiline 200 mg once daily for 8 weeks, then once daily for 18 weeks</td><td>Pretomanid 200 mg once daily for 26 weeks</td><td>Linezolid 1200mg once daily for 9 weeks (thereafter placebo up to 26 weeks)</td></tr>
<tr><td>Experimental Arm 3</td><td>Bedaquiline 200 mg once daily for 8 weeks, then once daily for 18 weeks</td><td>Pretomanid 200 mg once daily for 26 weeks</td><td>Linezolid 600mg once daily for 26 weeks</td></tr>
<tr><td>Experimental Arm 4</td><td>Bedaquiline 200 mg once daily for 8 weeks, then once daily for 18 weeks</td><td>Pretomanid 200 mg once daily for 26 weeks</td><td>Linezolid 600mg once daily for 9 weeks (thereafter placebo to 26 weeks)</td></tr>
</table></td></tr>
<tr><td>Comparator(s)</td><td colspan="4">Active control arms</td></tr>
<tr><td>Reported outcomes*</td><td colspan="4">Primary outcome
• Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment
Secondary outcomes
• Incidence of bacteriologic failure or relapse or clinical failure through follow up until 78 weeks after the end of treatment.
• Time to sputum culture conversion to negative status through the treatment period
• Proportion of participants with sputum culture conversion to negative status
• Change from baseline TB symptoms
• Change from baseline in Patient Reported Health Status
• Change from baseline weight.</td></tr>
<tr><td>Trial sites</td><td colspan="4">• Georgia (1 site)
• Republic of Moldova (1 site)
• Russian Federation (5 sites)
• South Africa (4 sites)</td></tr>
<tr><td>Trial setting</td><td colspan="4">Hospital / research centers</td></tr>
</table>

~ Each participant will receive 26 weeks of treatment, but investigators may consider extending current treatment to 39 weeks if a participant's week 16 sputum sample is culture positive between the week 16 and week 26 treatment visits and their clinical condition suggests they may have an ongoing TB infection (12).

*The study definitions and secondary outcome measures are presented in Appendix 6.

Part 3: Costing

Pretomanid (as part of BPaL regimen) was approved in August 2019 by the FDA. Pretomanid was developed by TB Alliance. TB Alliance has granted the first license to manufacture, register and supply pretomanid to Mylan. The license is non-exclusive in low- and middle-income countries and exclusive in high-income markets (13).

TB Alliance announced on 28 October 2019 that the three drug BPaL treatment will be available in South Africa priced at $1,040 (ZAR 15,320) for the complete regimen, with the cost of pretomanid at $364 (ZAR 5,362) per treatment course (14).

Part 4: Summary of Findings

Pretomanid has been approved by the FDA as part of the three-drug BPaL regimen for the treatment of XDR-TB, or treatment-intolerant/nonresponsive MDR. Treatment duration is 6 months, with the option for 9 months for patients who remain culture positive at month 4. The suggested dose for Pretomanid is 200 mg (tablet) taken orally once a day. The Nix-TB study demonstrated that 89% (95/107) of patients treated with the BPaL regimen had a successful outcome [95% CI: 81%-94%].

WHO is in the process of updating its guideline on MDR-TB.

Recommendation: The Adult Hospital Level Committee acknowledges that there is currently insufficient evidence to inform a recommendation for pretomanid in MDR- or XDR-TB . However, a number of trials are underway (see Appendix 2 and 3), and the WHO is in the process of updating Guidelines for MDR-TB.

Review indicators: SAHPRA Registration, Evidence of efficacy and safety, Price reduction

Level of Evidence: III Phase 3 RCT

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APPENDIX 1: FDA REVIEWED PHASE II/III STUDIES (PRETOMANID-CONTAINING ANTIMYCOBACTERIAL REGIMENS)

Study ID	Title	Status
NC-002	A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin Plus PA-824 Plus Pyrazinamide After 8 Weeks of Treatment in Adult Patients with Newly Diagnosed Smear-Positive Pulmonary DS or MDR-TB	Completed
NC-005 (not conducted under IND)	A Phase 2, Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of Combinations of Bedaquiline, Moxifloxacin, Pa-824 And Pyrazinamide During 8 Weeks of Treatment in Adult Subjects With Newly Diagnosed Smear-Positive Pulmonary DS or MDR-TB	Completed
NC-006 (STAND)	A Phase 3, Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin Plus PA-824 Plus Pyrazinamide After 4 and 6 Months of Treatment in Adult Subjects with Smear-Positive Pulmonary DS-TB and After 6 Months of Treatment in Adult Subjects with Smear-Positive Pulmonary MDR-TB.	Completed
Nix-TB	A Phase 3, Open-Label Trial Assessing the Safety and Efficacy of Bedaquiline plus Pretomanid plus Linezolid in Subjects with Pulmonary Infection of Either XDR-TB or TI/NR MDR-TB.	Ongoing
ZeNix (NC-007)	A Phase 3, Open Label, Randomized Trial Assessing the Safety and Efficacy of Bedaquiline plus Pretomanid plus Various Doses and Treatment Durations of Linezolid in Participants with Either Pulmonary XDR-TB, pre-XDR-TB or (TI/NR MDR-TB).	Ongoing
Simplici TB NC-008	An Open-Label, Phase 2c, Multicenter, Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of a 4-month Treatment of Bedaquiline plus Pretomanid plus Moxifloxacin plus Pyrazinamide (BPaMZ) Compared to a 6-month control Treatment with HRZE/HR [isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol)] in Adult Participants Smear-Positive Pulmonary DS-TB and a 6-month Treatment of BPaMZ in Adult Participants with Drug Resistant, Smear-Positive Pulmonary Tuberculosis (DR-TB).	Ongoing

APPENDIX 2: PHASE 2 AND 3 STUDIES - PRETOMANID-CONTAINING ANTIMYCOBACTERIAL REGIMENS IN MDR-TB PATIENTS

Clinicaltrials.gov identifier	Name of study	URL	Description	Recruitment status	Start date Completion date
NCT01498419	Evaluation of 8 Weeks of Treatment With the Combination of Moxifloxacin, PA-824 and Pyrazinamide in Patients With Drug Sensitive and Multi Drug-Resistant Pulmonary Tuberculosis (TB) (NC-002).	https://clinicaltrials.gov/ct2/show/NCT01498419	Phase 2 open-label partially randomized trial that assessed the mycobactericidal activity of the moxifloxacin plus PA-824 plus pyrazinamide regimen after 8 weeks of treatment.	Completed	Mar 2012 July 2013
NCT02193776	A Phase 2 to Evaluate the Efficacy, Safety and Tolerability of Combinations of Bedaquiline, Moxifloxacin, PA-824 and Pyrazinamide in Adult Subjects With Drug-Sensitive or Multi Drug-Resistant Pulmonary Tuberculosis.	https://clinicaltrials.gov/ct2/show/NCT02193776	Phase 2, multi-center, open-label, partially randomized clinical trial in four parallel treatment groups. Subjects with drug-sensitive tuberculosis (DS-TB) will be randomized to receive either J(loading dose/three times a week)PaZ; or J(200mg)PaZ; or HRZE. Subjects with multi drug-resistant tuberculosis will receive J(200mg)MPaZ. The HRZE treatment arm is included as a control for the drug-sensitive treatments and as a control for the quantitative laboratory mycobacteriology testing.	Completed	23 Oct 2014 7 Feb 2018
NCT02342886	Shortening Treatment by Advancing Novel Drugs	https://clinicaltrials.gov/ct2/show/NCT02342886	Phase 3, open-label, partially randomized trial that assessed the efficacy, safety and tolerability of a combination of moxifloxacin, PA-824, and pyrazinamide treatments with varying doses and treatment lengths from 4 to 6 months in subjects with DS pulmonary TB compared to standard HRZE treatment.	Completed	Feb 2015 May 2018
NCT02333799	A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis	https://clinicaltrials.gov/ct2/show/NCT02333799	Phase 3 study evaluating the efficacy, safety, tolerability and pharmacokinetics of bedaquiline plus PA-824 plus linezolid after 6 months of treatment (option for 9 months for subjects who remain culture positive at month 4) in Subjects with either pulmonary XDR-TB, treatment intolerant or non-responsive MDR-TB.	Active, not recruiting	Mar 2015 Oct 2021

Clinicaltrials.gov identifier	Name of study	URL	Description	Recruitment status	Start date Completion date
NCT02589782	Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB PRACTECAL)	https://clinicaltrials.gov/ct2/show/NCT02589782	Phase 2-3, multi-centre, open label, multi-arm, randomised, controlled trial evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and re-purposed anti-TB drugs for the treatment of biologically confirmed pulmonary MDR-TB.	Recruiting	Jan 2017 Mar 2021
NCT03086486	Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix).	https://clinicaltrials.gov/ct2/show/NCT03086486	Phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either XDR-TB, Pre-XDR-TB or treatment-intolerant or nonresponsive MDR-TB	Recruiting	21 Nov 2017 31 Dec 2021
NCT03338621	Trial to Evaluate the Efficacy, Safety and Tolerability of BPaMZ in Drug-Sensitive (DS-TB) Adult Patients and Drug-Resistant (DR-TB) Adult Patients.	https://clinicaltrials.gov/ct2/show/NCT03338621	Phase 2c multi-center, open-label, partially randomized trial to evaluate the efficacy, safety and tolerability of a 4-month treatment of bedaquiline plus pretomanid plus moxifloxacin plus pyrazinamide (BPaMZ) compared to a 6-month treatment of HRZE/HR (control) in adult participants with drug-sensitive smear-positive pulmonary tuberculosis and a 6-month treatment of BPaMZ in adult participants with drug resistant, smear-positive pulmonary tuberculosis	Recruiting	30 Jul 2018 31 Jan 2022
NCT03942354	Patient-reported Experiences and Quality of Life Outcomes in the TB-PRACTECAL Clinical Trial	https://clinicaltrials.gov/ct2/show/NCT03942354	Sub-study of a TB-PRACTECAL clinical trial for multidrug resistant Tuberculosis. It evaluates the effectiveness of TB-PRACTECAL interventions from the patient perspective in terms of their quality of life, shared decision making and satisfaction with services.	Not yet recruiting	1 Sept 2019 31 Mar 2021
NCT04081077	PRACTECAL-PKPD Sub Study	https://clinicaltrials.gov/ct2/show/NCT04081077	PRACTECAL-PKPD is an exploratory pharmacokinetic and pharmacodynamic sub-study investigating the relationship between the patients' exposure to anti- tuberculosis (TB) drugs in the TB-PRACTECAL trial investigational regimens and their respective treatment outcomes.	Not yet recruiting	1 Oct 2019 31 Mar 2021

APPENDIX 3: PHASE 2 STUDIES - PRETOMANID-CONTAINING ANTIMYCOBACTERIAL REGIMENS IN DRUG-SUSCEPTABLE TB PATIENTS

Clinicaltrials.gov identifier	Name of study	URL	Description	Recruitment status	Start date Completion date
NCT00567840	PA-824-CL-007: Phase IIa Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis	https://clinicaltrials.gov/ct2/show/NCT00567840	Phase 2a trial to evaluate the safety, tolerability, extended early bactericidal activity and pharmacokinetics of 14 days' treatment with four oral doses of PA-824 in adult participants with newly diagnosed, uncomplicated, smear-positive, pulmonary tuberculosis	Completed	Aug 2007 Dec 2007
NCT00944021	Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis (CL-010).	https://clinicaltrials.gov/ct2/show/NCT00944021	Phase 2, dose ranging trial to evaluate the extended early bactericidal activity, safety, tolerability, and pharmacokinetics of PA-824 in adult participants with newly diagnosed, uncomplicated, smear-positive, pulmonary tuberculosis	Completed	Aug 2009 May 2010
NCT01215851	Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis With(J-M-Pa-Z) (NC-001).	https://clinicaltrials.gov/ct2/show/NCT01215851	Phase 2 trial to evaluate the early bactericidal activity, safety and tolerability of the following: TMC207 alone, TMC207 plus Pyrazinamide,TMC207 plus PA-824,PA-824 plus Pyrazinamide and PA-824 plus Pyrazinamide and Moxifloxacin, in adult patients with newly diagnosed, smear-positive pulmonary tuberculosis.	Completed	Oct 2010 Aug 2011
NCT01691534	Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis With Clofazimine (C)-TMC207 (J)-PA-824 (Pa)-Pyrazinamide (Z).	https://clinicaltrials.gov/ct2/show/NCT01691534	Phase 2 trial that evaluated the extended bactericidal activity of 14 consecutive days of oral administration of TMC207 plus PA-824 plus Pyrazinamide plus Clofazimine, TMC207 plus PA-824 plus Pyrazinamide, TMC207 plus PA-824 plus Clofazimine alone, TMC207 plus Pyrazinamide plus Clofazimine, Pyrazinamide alone, Clofazimine alone, and standard first line TB treatment as per South African TB Guidelines (Rifafour e-275) as determined by the rate of change of log CFU per ml sputum over the time period Day 0-14 in participants with smear positive pulmonary tuberculosis (TB). A control group will receive standard treatment.	Completed	Oct 2012 May 2013
NCT02256696	Assessing PA-824 for Tuberculosis (the APT Trial).	https://clinicaltrials.gov/ct2/show/NCT02256696	A Phase 2, randomized, open-label trial of PA-824-containing regimens versus standard treatment for drug-sensitive sputum smear-positive pulmonary tuberculosis	Recruiting	Apr 2015 Sept 2021

APPENDIX 4: PHASE 1 STUDIES - PRETOMANID-CONTAINING ANTIMYCOBACTERIAL REGIMENS IN HEALTH VOLUNTEERS

Clinicaltrials.gov identifier	Name of study	URL	Description	Recruitment status	Start date Completion date
NCT01828827	Food Effect Study on the Bioavailability and PK of PA-824 Tablets in Healthy Adult Subjects	https://clinicaltrials.gov/ct2/show/NCT01828827	Phase 1, single-center, randomized, balanced, single-dose, two-treatment, two-period, two-sequence, crossover, open-label study to evaluate the effect of food on the pharmacokinetics of PA-824.	Completed	Mar 2007 Mar 2007
NCT03202693	A Study of the Safety, Tolerability, and Absorption, Metabolism, and Excretion of PA-824 in Healthy Adult Male Subjects	https://clinicaltrials.gov/ct2/show/NCT03202693	Phase 1, single-center, open-label, single-dose study to evaluate (1) the absorption, metabolism, and excretion patterns of a single dose of [14C] PA-824, and (2) the pharmacokinetics, safety, and tolerability of a single oral-suspension dose of unlabeled PA-824 in healthy adult male subjects.	Completed	Mar 2006 May 2006
NCT01830439	Food Effect Study on the Bioavailability and PK of PA-824 Tablets in Healthy Adult Subjects (CL-009).	https://clinicaltrials.gov/ct2/show/NCT01830439	Phase 1, single-center, randomized, balanced, single-dose, two-period, two-sequence, crossover, open-label study to evaluate the effect of food on the pharmacokinetics of PA-824.	Completed	Sept 2009 Jan 2010
NCT01571414	Evaluating the Safety and Drug Interaction of PA-824, an Investigational Tuberculosis Medication, Together With Efavirenz, Ritonavir-Boosted Lopinavir, or Rifampin.	https://clinicaltrials.gov/ct2/show/NCT01571414	Phase 1, three-arm study that evaluated the safety and tolerability of PA-824 when combined with efavirenz (EFV) or ritonavir-boosted lopinavir (LPV/r), which are medications used to treat HIV infection, or rifampin (RIF), which is a medication used to treat TB	Completed	May 2012 May 2013
NCT01674218	Effect of PA-824 and of PA-824 Plus Moxifloxacin on the QTc Interval in Healthy Volunteers.	https://clinicaltrials.gov/ct2/show/NCT01674218	Phase 1, single-center, double-blinded, randomized, placebo-controlled, five-period cross-over clinical study of PA-824 to evaluate the effect of PA-824 and of PA-824 plus moxifloxacin on cardiac repolarization (QT/QTc interval duration) in a total of 75 healthy male and female participants, aged 18 to 45 years.	Completed	Sept 2012 Dec 2012

Clinicaltrials.gov identifier	Name of study	URL	Description	Recruitment status	Start date Completion date
NCT01768273	Evaluation of the Pharmacokinetic Interaction Between PA-824 and Midazolam.	https://clinicaltrials.gov/ct2/show/NCT01768273	Phase 1, open label, fixed sequence design. To determine the safety and tolerability of PA-824 when given with a single dose of midazolam, and to determine whether PA-824 inhibits CYP3A to a clinically important degree as measured by the effect of PA-824 on the pharmacokinetics of midazolam, a known CYP3A substrate.	Completed	Dec 2009 Apr 2010
NCT02422524	Pharmacokinetics and Safety of PA-824 in Subjects With Mild, Moderate, and Severe Hepatic Impairment to Matched, Non-Hepatically Impaired Subjects	https://clinicaltrials.gov/ct2/show/NCT02422524	Phase 1, single dose (200 mg), open-label, sequential group study comparing the pharmacokinetics and safety of PA-824 in subjects with mild, moderate, and severe hepatic impairment to matched, non-hepatically impaired subjects.	Recruiting	11 Dec 2017 11 Dec 2019
NCT03896750	Single-Dose Study to Evaluate the PKs of Pretomanid in Subjects With Renal Impairment Compared to Subjects With Normal Renal Function	https://clinicaltrials.gov/ct2/show/NCT03896750	Phase I, open-label, single dose, sequential group study to compare the safety and pharmacokinetics of pretomanid in the following two groups of subjects: 1) those with mild, moderate, and severe renal impairment including those with End Stage Renal Disease (ESRD) not needing dialysis; and 2) matched subjects with normal renal function.	Recruiting	1 Aug 2019 1 Oct 2020

APPENDIX 5: NIX-TB TRIAL - PRIMARY AND SECONDARY OUTCOME MEASURES (10)

Outcome Measure	Time Frame	Terms definitions and notes
Primary Outcome Measure		
Incidence of bacteriologic failure or relapse or clinical failure through follow up until 6 months after the end of treatment.	*Treatment Period:* Day 1, Week 1, 2, 4, 6, 8, 12, 16, 20, 26, 30, 34, 39 *Follow Up:* Month 1, 2, 3, 6, 9, 12, 15, 18, 21, 24	Bacteriologic failure: During the treatment period, failure to attain culture conversion to negative. Bacteriologic relapse: During the follow-up period, failure to maintain culture conversion to negative status in culture, with culture conversion to positive status with a Mycobacterium tuberculosis strain that is genetically identical to the infecting strain at baseline. Clinical failure: A change from protocol-specified TB treatment due to treatment failure, retreatment for TB during follow up, or TB-related death. Note: Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart. Subjects who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered to be culture negative at that visit.
Secondary Outcome Measure		
Time to sputum culture conversion to negative status through the treatment period.	Day 1, Week 1, 2, 4, 6, 8, 12, 16, 20, 26, Month 1, 2, 3, 6, 9, 12, 15, 18, 21, 24	
Proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks.	Week 4, 6, 8, 12, 16, 26, 39	
Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness, leading to TB related or non-TB related death.	Day 1, Week 1, 2, 4, 6, 8, 12, 16, 20, 26, 30, 34, 39, *Follow-up:* Month 3, 6, 9, 12, 15, 18, 21, 24	
All Subjects- Pre-dose sampling at weeks 2, 8 and 16 to measure Ctrough levels of bedaquiline, bedaquiline metabolite M2, Linezolid and PA-824.	Weeks 2, 8 and 16	
Time to sputum culture positivity	*Treatment Period:* Day 1, Week 1, 2, 4, 6, 8, 12, 16, 20, 26, 30, 34, 39 *Follow Up:* Month 1, 2, 3, 6, 9, 12, 15, 18, 21, 24	If liquid culture in the MGIT platform is used, the rate of change in time to sputum culture positivity (TTP) over time in the Mycobacterial Growth Indicator Tube (MGIT) system in sputum, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time.

APPENDIX 6: ZENIX TRIAL - PRIMARY AND SECONDARY OUTCOME MEASURES (12)

Outcome Measure	Time Frame	Terms definitions and notes
Primary Outcome Measure		
Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment	26 weeks	Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
Secondary Outcome Measure		
Incidence of bacteriologic failure or relapse or clinical failure through follow up until 78 weeks after the end of treatment.	78 weeks	Culture conversion requires at least 2 consecutive culture negative/positive samples at least 7 days apart.
Time to sputum culture conversion to negative status through the treatment period	26 weeks	Culture conversion is a diagnostic criterion indicating the point at which samples taken from a patient infected with a tuberculosis can no longer produce tuberculosis cell cultures
Proportion of participants with sputum culture conversion to negative status	Week 4, 6, 8, 12, 16, 26,	Culture conversion is a diagnostic criterion indicating the point at which samples taken from a patient infected with a tuberculosis can no longer produce tuberculosis cell cultures
Change from baseline TB symptoms	26 weeks	Severity of symptoms compared to start of treatment
Change from baseline in Patient Reported Health Status	26 weeks	Comparison of Patient Reported Health Status to start of treatment
Change from baseline weight.	26 weeks	Comparison of weight from start of treatment until end of treatment