EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

PRETOMANID IN COMBINATION WITH BEDAQUILINE AND LINEZOLID IN ADULTS FOR THE TREATMENT OF PULMONARY EXTENSIVELY DRUG-RESISTANT (XDR), OR TREATMENT-INTOLERANT OR NONRESPONSIVE MULTIDRUG-RESISTANT (MDR) TUBERCULOSIS (TB)

Project ID: PTJA14

Assessment Report

Version 1.0, 19 August 2020

Template version 2.2, April 2020

This Joint Assessment is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V0.1	**01/06/2020**	First draft
V0.2	**29/06/2020**	Input from dedicated reviewers has been processed
V0.3	**13/07/2020**	Input from medical editor and manufacturer has been processed.
V0.4	**15/07/2020**	Final editorial version. Publication was postponed with 5 weeks, due to the EPAR not being available.
V1.0	**19/08/2020**	Final assessment report, reflecting updates to the EPAR.

Disclaimer

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Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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How to cite this assessment

Please cite this assessment as follows:

EUnetHTA PTJA14. Haute Autorité de Santé (HAS), Ministry of Health of the Republic of Croatia (MIZ). Relative effectiveness assessment of pharmaceutical technologies. Pretomanid in combination with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug-resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Joint Assessment. Diemen (The Netherlands): EUnetHTA; [2020]. [date of citation]. 49 pages. Report No.: PTJA14. Available from: https //www.eunethta.eu

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LIST OF ABBREVIATIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical [Classification System]
BID	Twice daily
BPal	Bedaquiline plus pretomanid plus linezolid
CI	Confidence interval
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
DOI	Declaration of interest
DS	Drug-susceptible
EMA	European Medicines Agency
EOT	End of treatment
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life-5 dimensions-5 levels
EU	European Union
EUnetHTA	European Network Health Technology Assessment
HIV	Human immunodeficiency virus
IQR	Interquartile range
ITT	Intention to treat
MAH	Marketing authorisation holder
MAIC	Matching-adjusted indirect comparison
MDR-TB	Multidrug-resistant TB
MeSH	Medical Subject Headings
mITT	Modified intention to treat
NMA	Network meta-analysis
NR	Nonresponsive
PAS	para-Aminosalicylic acid
PICO	Population; Intervention; Comparator(s); Outcome(s)
PLEG	Post-launch evidence generation
PTJA	Pharmaceutical Joint Assessment
OD	Once daily
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ class
STC	Simulated treatment comparison
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TI	Treatment-intolerant
VAS	Visual Analogue Scale
WHO	World Health Organization
WP4	Work Package 4
XDR	Extensively drug-resistant

EXECUTIVE SUMMARY OF THE ASSESSMENT OF PRETOMANID

Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis.* It typically affects the lungs but can also affect organs (extrapulmonary TB). Worldwide, it is estimated that around 10 million individuals were infected with active TB in 2019 [1, 2].

While drug-susceptible TB (DS-TB) is curable, multidrug-resistant TB (MDR-TB), defined as resistance to rifampicin and isoniazid or rifampicin alone (standard-of-care treatment in the first line), and extensively drug-resistant TB (XDR-TB), defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of three second-line injectable drugs, are more difficult to treat [1, 3].

For patients with MDR-TB or XDR-TB, long treatment regimens are recommended with at least four effective medicinal products, depending on strain susceptibility [4].

Pretomanid is an oral antimycobacterial drug that is a member of the nitroimidazooxazine class. (whereas delamanid is a member of the nitroimidazooxazole class). Its mechanism of action involves inhibition of the synthesis of cell-wall lipids under aerobic conditions and the generation of reactive nitrogen species under anaerobic conditions.

On 26th March 2020, a positive opinion was given on a conditional marketing authorisation for the treatment of adults with pulmonary XDR-TB or treatment-intolerant (TI) or nonresponsive (NR) MDR-TB with pretomanid in combination with bedaquiline and linezolid. This is the first approved utilisation of pretomanid in the treatment of TB.

Objective and scope

The aim of this EUnetHTA joint relative effectiveness assessment (REA) is to compare the clinical effectiveness and safety of pretomanid in the target patient population with relevant comparators. The target patient population and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

Table 0.1. Scope of the assessment

<table>
<tr><th>Description</th><th>Assessment scope [a]</th></tr>
<tr><td>Population</td><td>Adult patients with pulmonary XDR-TB or treatment-intolerant or nonresponsive MDR-TB</td></tr>
<tr><td>Intervention</td><td>Pretomanid is indicated as part of a combination regimen with bedaquiline and linezolid.
Posology
The recommended dosage for pretomanid is 200 mg orally (one tablet of 200 mg) daily for 26 weeks.
Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg three times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1200 mg daily orally for up to 26 weeks).</td></tr>
<tr><td>Comparison</td><td>Treatments authorised in MDR-TB in association with other tuberculosis medicines:
Bedaquiline;
Delamanid;
p-Aminosalicylic acid.
Other treatments not authorised in MDR-TB but recommended for use by WHO (it should be noted that the certainty for the effect of these products is moderate or very low according to WHO) [4]: List of medicines recommended for use in longer MDR-TB regimens (cf. 2019 WHO consolidated guidelines on DR tuberculosis treatment for further details on the composition of the recommended regimens)
<table>
<tr><td>Group A</td><td>Levofloxacin OR moxifloxacin
Bedaquiline
Linezolid</td></tr>
<tr><td>Group B</td><td>Clofazimine
Cycloserine OR terizidone</td></tr>
<tr><td>Group C</td><td>Ethambutol
Delamanid
Pyrazinamide</td></tr>
</table>
</td></tr>
</table>

		Imipenem–cilastatin OR meropenem Amikacin (OR streptomycin) Ethionamide OR prothionamide *p*-Aminosalicylic acid	
Outcomes	• Proportion of subjects with sputum culture (± smear microscopy) conversion to negative status and time to culture conversion (± smear microscopy) to negative status; • Cure (according to the WHO definition [5] or other clinically relevant definition); • Treatment failure including bacteriological/clinical failure and relapse (according to the WHO definition [5] or other clinically relevant definition); • Treatment completed (according to the WHO definition [5] or other clinically relevant definition); • Treatment success (including cure and treatment completed); • Mortality; • Health-related quality of life; • Safety, including serious adverse events and treatment-related adverse events.		

[a] Additional outcomes not captured in the PICO may be described in the assessment report as submitted by the marketing authorisation holder.
Abbreviations: MDR-TB=multidrug-resistant tuberculosis; WHO=World Health Organization; XDR-TB=extensively drug-resistant tuberculosis.

Methods

The assessment was based on a dossier submitted by the marketing authorisation holder (MAH; Mylan) that included a systematic literature review (SLR) to identify relevant data for this rapid relative effectiveness assessment (REA) regarding the intervention and its comparators identified in the scoping phase.

The authoring team critically assessed the method for information retrieval submitted. Data were also checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. The completeness of the data on pretomanid in combination with other drugs and/or for a different indication was not assessed, as these situations are beyond the scope of this assessment.

The authoring team concluded that this SLR was generally too specific in the choice of terms. Moreover, appropriate descriptors and search tools were not used and there was a lack of sensitivity. Overall, the authoring team considers that there is a risk of not detecting relevant studies. Details of the search can be found in the submission dossier (Section 5 Clinical effectiveness and safety and Appendix 7.4).

The SLR performed by the MAH identified 19 relevant publications on randomised controlled trials (RCTs) or prospective studies. Among these 19 studies:

- Two evaluated the efficacy and safety of pretomanid in combination with bedaquiline and linezolid (BPal regimen) in patients with XDR-TB and TI/NR MDR-TB:
  - Nix-TB, a noncomparative phase III study. Data from this pivotal study were extracted from the submission dossier and verified against the Clinical Study Report;
  - ZeNix, an RCT to further validate the optimal linezolid dosage (no control group without pretomanid). The results of this ongoing study (included in the post-authorisation measures for conditional marketing approval) are not yet available.
- The remaining 17 studies were RCT or prospective studies conducted in a similar population (adult patients with XDR-TB and TI/NR MDR-TB) with other treatment alternatives. This study pool with comparators was not used by the MAH to perform indirect comparisons.

The authoring team considered the study pool used to assess the intervention to be complete and exhaustive. However, given the limitations identified in the SLR method, the information retrieval for comparators cannot be considered exhaustive. This is not expected to impact the assessment as no comparative data were submitted by the MAH, but information retrieval on comparators might not be appropriate for future indirect comparisons that could be performed by national agencies.

Overall, this rapid REA mainly relies on the Nix-TB trial data. Conclusions on the relative effectiveness of pretomanid for this rapid REA are therefore limited and the aim of comparing the clinical effectiveness and safety of pretomanid in the target patient population with relevant comparators could not be achieved in this joint assessment. Given the noncomparative nature of the Nix-TB study, use of the quality rating tool developed by the Cochrane Collaboration was not considered applicable by the authoring team without substantial adaptations (see the Results section of the Submission Dossier for the risk of bias).

The president of the French patient organisation ACTUME was interviewed by HAS to collect the patient perspective on quality of life (QoL) and the current standard of care. The minutes of this interview are available in Appendix APPENDIX 4: PATIENT INVOLVEMENT.

Results

The evidence submitted by the MAH for this assessment mostly relies on a single noncomparative phase III study conducted in South Africa and originally conceived as an exploratory trial by the investigators: the Nix-TB study [6]. Data from this trial were mainly extracted from an interim analysis performed at a cutoff date of 29th March 2019. At this date, 99/109 patients (90.8%) had completed the 6-month follow-up period. The remaining patients had discontinued the trial before evaluation of the primary endpoint. At the latest cutoff, 44/109 patients (40.4%) had completed the 24-month follow-up visit.

Several studies conducted in similar populations treated with alternative therapies were identified via the SLR performed by the MAH. However, the MAH did not use this study pool with comparators to conduct indirect comparisons. Conclusions on the relative effectiveness of pretomanid are therefore limited.

Given the noncomparative design of the Nix-TB study, use of the Risk of Bias tool or ROBINS-I tool was not considered applicable by the authoring team without substantial adaptations. However, the authoring team considers that the Nix-TB study may not be reliable for determining the true therapeutic effect of pretomanid on the outcomes listed in the project plan. In particular, two limitations that might overestimate the effect size were identified:

- A major limitation of noncomparative studies is that it is impossible to know the contribution of the treatment effect and the patient characteristics, including prior TB treatments received, to the endpoint value. A particular favourable endpoint value could be confounded by initial good patient condition, with no possibility of detecting this confounding without a control group. As a result, it is always difficult to estimate whether the results observed are related to the intervention itself or to the patient characteristics;
- Consecutive enrolment of all eligible patients in the trial was not explicitly mentioned in the study protocol. Consequently, selection of participants by the investigators cannot be excluded.

Main efficacy data

A total of 109 adult patients were included in Nix-TB to receive the BPal regimen for 6 months (could be extended to 9 months if needed). The modified intention to treat (mITT) population was 107 after exclusion of two patients. The study originally planned to enrol a total of up to 200 patients. However, to facilitate enrolment in the ZeNix study, inclusion in Nix-TB was stopped after 109 patients had been enrolled.

The treatment duration was 26 weeks according to the study protocol. A total of 2/109 patients had the treatment duration extended for an additional 3 months (up to 9 months), while 16/109 patients (14,7%) received the 1200-mg total daily dose of linezolid without interruption over the full 26 weeks of therapy. For subjects experiencing suspected drug-related toxicities due to linezolid, the protocol allowed a reduction in the daily dose of linezolid (with a stepdown approach from 1200 mg once daily [QD] to 600 mg and then to 300 mg QD). A total of 37/109 patients (33.9%) received a full uninterrupted 26 weeks of linezolid at any dose.

Most patients had XDR-TB (65%). Approximately 96% of the patients had received at least one prior TB therapy and the median number of prior TB treatments was seven. Prior use of fluoroquinolones was

reported for 103 patients (94.5%), prior use of thiocarbamide derivatives (the group that includes ethionamide and prothionamide) for 83 patients (76.1%) and prior use of drugs for treatment of leprosy (covering drugs such as clofazimine also used for TB treatment) for 82 patients (75.2%). In accordance with the inclusion criteria, all patients were resistant to isoniazid and rifampicin and many patients were also resistant to fluoroquinolone, in particular to ofloxacin (84 of the 106 patients evaluable). Half of the patients were co-infected with human immunodeficiency virus (HIV).

The primary endpoint was the incidence of treatment failure, a composite outcome of clinical failure, bacteriologic relapse or bacteriologic failure (reinfection) through to 6 months after the end of treatment. Favourable status was defined as patients with a negative culture status at 6 months after the end of therapy who had not already been classified as having an unfavourable outcome and whose last positive culture result was followed by at least two negative culture results. At 6 months after the end of treatment, a high rate of favourable status (primary endpoint) was observed: 98/107 patients (92%, 95% confidence interval [CI] 85%–96%) in the mITT analysis and 98/109 (90%, 95% CI 83%–95%) in the ITT analysis. Subgroup analyses by TB status (XDR-TB vs. TI/NR MDR-TB) were consistent with results for the whole population. Among the cases considered as unfavourable outcomes in the mITT analysis, two relapses, six deaths and one withdrawal of consent were reported.

The incidence of relapse or reinfection at 24 months after the end of treatment was assessed as a secondary endpoint. However, in this interim analysis, only 44/109 patients (40.4%) have completed the 24-month follow-up visit and were evaluable for this outcome. Among these 44 patients, one experienced a relapse 15 months after the end of treatment. Final results of Nix-TB trial are expected in Q2 2021.

The number of patient with culture conversion status to negative increased at each time point from baseline to the end of treatment. All patients but one who were assessable for culture conversion (93/109) were negative by week 16. For this patient, BPal treatment was extended by 3 months in accordance with the study protocol. At the end of treatment, all living patients showed a culture conversion status to negative. The median time to negative culture was 6.0 weeks (interquartile range [IQR] 4.0–8.1).

Data on health-related QoL were collected using the European Quality of Life-5 dimensions-5 levels (EQ-5D-5L) questionnaire at baseline, 8 weeks after the start of treatment and at the end of treatment, and were summarised by category (no problems vs. problems) for each item in the clinical study report (CSR). Owing to the bias and limitations identified in the Nix-TB study and additional limits specific to QoL (Section 4.5.2), these data were not considered suitable for this REA. No disease-specific QoL data were collected in the study.

Main safety data

Every patient included in the Nix-TB study experienced at least one treatment-emergent adverse event (TEAE), mainly sensory neuropathy or peripheral neuropathy (67/109, 78%) and anaemia (40/109, 37%). Serious adverse events (AEs) were reported for 19/109 patients (17%). A total of eight deaths were reported in the study, of which six occurred during the treatment period and two during the follow-up period. Of note, one patient who died during the follow-up period had previously relapsed and had an unfavourable outcome due to the relapse. In one case, causality with respect to treatment cannot be ruled out (acute haemorrhagic pancreatitis). The other five deaths that occurred during the treatment period are not indicative of regimen causality according to the European Public Assessment Report (EPAR). Peripheral neuropathy, optic neuropathy and myelosuppression are known adverse reactions associated with linezolid. Over the course of the trial, 35/109 patients (32%) discontinued linezolid treatment, mainly because of AEs (27.5% of the patients), primarily peripheral sensory neuropathy (22.0% of the patients). Dose interruption of linezolid because of AEs was reported for 46% of the patients and a dose reduction in linezolid because of AEs was reported for 40%, mostly for peripheral sensory neuropathy or anaemia.

Discussion and conclusion

Results from the single noncomparative Nix-TB trial suggest a high rate of favourable outcomes (92%, 95% CI 85%–96%) at 6 months after the end of 6-month treatment with the BPal oral regimen in a population known to be very difficult to treat (MDR-TB and XDR-TB).

However, results from this study have several limitations:

- Direct comparative evidence versus the current standard of care are lacking and no indirect comparative data were generated by the MAH to try to address this issue. As the care pathway recently evolved with an update of the World Health Organization (WHO) guidelines [4], it is difficult to put the results observed in the Nix-TB trial into perspective. The paucity of efficacy data with other comparators is acknowledged by the authoring team. On an indicative basis, recent publications revealed that favourable outcomes (cured/treatment completed) for XDR-TB patients ranged from an average of 40% to 70%, depending on the treatment regimen and patient characteristics [7, 8] . A cohort of similar patients treated with bedaquiline and linezolid in South Africa is mentioned in the submission dossier (Section 2.4, page 41). According to the MAH, data for this cohort, including indirect comparison with data from the Nix-TB trial, should be published soon. To favour the publication of data for this cohort, the MAH did not submit these data for this joint assessment, which is highly regrettable considering that it might be a very appropriate external control from a health technology assessment (HTA) perspective;
- From a methodological perspective, the authoring team considers that the Nix-TB study may not be reliable for determining the true therapeutic effect of pretomanid on the outcomes listed in the project plan (see Section 4.3 for details);
- This study was performed in only three centres, all located in South Africa. Although the authoring team acknowledges that the feasibility of a study in XDR-TB or TI/NR MDR TB in Europe might be more complex because of the lower disease prevalence, results from the Nix-TB trial may not be fully generalisable to the European population. The low sample size (*n*=109) due to early cessation of enrolment further limits the evaluation of data generalisability. It is noted that coinfection with HIV was reported for half of the patients in Nix-TB, whereas HIV prevalence among incident TB cases in Europe was 12% in 2016 [1];
- Pretomanid has been evaluated in patients who were not pretreated with bedaquiline and linezolid, in accordance with the Nix-TB inclusion/exclusion criteria. No data are available for the BPal regimen in patients pretreated with bedaquiline and linezolid, which are now recommended for the treatment of MDR-TB (group A agents according to the WHO guidelines on drug-resistant TB treatment) [4];
- Patients could be enrolled on the basis of a positive culture within 3 months before screening or, for XDR-TB patients only, molecular testing within 3 months before or at screening. In the study, a total of 16/109 patients (14.6%) did not have a positive culture at baseline. According to the clinical expert, these patients could possibly have already responded to the preceding therapy and the effect observed in the study might not be attributable to the BPal regimen alone in these 16 cases;
- Exact assessment of the resistance profile of patients is limited by the inclusion criteria. Resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable could have been verified by the investigators at screening instead of documented at any time before screening according to the protocol. Therefore, the extent of the data differed for each TB treatment (available for <50% of the patients for most TB treatments except rifampicin, isoniazid, kanamycin and ofloxacin). In addition, TI/NR status for MDR-TB treatment was based on a declaration by the investigators and is therefore subject to assessment bias;
- Long-term evidence of efficacy is missing, as only an interim analysis was provided. Only 40% of the patients completed the 24-month follow-up visit and final results from Nix-TB are not expected until Q2 2021. It should also be underlined that cure, which is strictly defined by WHO guidelines [5], was not an endpoint specified in Nix-TB, so it was not possible to assess this aspect of the efficacy of the BPal regimen;
- The safety is considered acceptable according to the EPAR. However, the optimal dosage of linezolid (which is associated with an unfavourable safety profile, with risks of peripheral neuropathy and myelosuppression notably) in this combination is still unknown. In the Nix-Tb trial this drug was given at a high dose (1200 mg per day) throughout the 26 weeks of therapy, but a lower dosage could be used depending on the results of the ongoing ZeNix study exploring four different linezolid dosages;
- Finally, the president of the French patient organisation ACTUME underlined that patients expect new therapies to facilitate treatment adherence and completion. This includes having treatments

that are well tolerated, ideally for shorter durations, and easier to take (e.g., with as small a number of tablets to be taken as possible). Although this fully oral regimen given over a relatively short duration (6 months for 108/109 patients and extended to 9 months for 2/109 patients in Nix-TB) is expected to have a positive impact on QoL and compliance, no robust data are available to confirm this hypothesis. Indeed, health-related QoL was not assessed using a disease-specific questionnaire and data from the EQ-5D-5L questionnaire were not suitable for this assessment (Section 4.5.2);

1 BACKGROUND

1.1 Overview of the disease or health condition

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis.* It typically affects the lung parenchyma, tracheobronchial tree or larynx (pulmonary TB) but can also affect organs or anatomic sites other than the lungs, such as the pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones and meninges (extrapulmonary TB) [[1, 2].

A few outcomes are possible after inhalation of *M. tuberculosis* droplet nuclei, depending on the immune response [9]:

- Immediate elimination of the pathogen by alveolar macrophages or neutrophils;
- Primary TB (immediate onset of active disease);
- Latent TB infection; and
- Reactivation of TB (onset of active disease after a period of latent infection).

TB can present as a dynamic spectrum that ranges from asymptomatic infection to active TB, including life-threatening disease. Symptoms of pulmonary TB are usually minimal until the disease is moderately or very advanced. The most common clinical symptoms among patients with active lung TB include cough, fever, weight loss, fatigue and haemoptysis. Other signs, such as chest pain and shortness of breath, may also be present in advanced stages [10, 11].

Disease prognosis usually depends on drug sensitivity, which is classified in three main categories:

- DS-TB: curable with a rifampicin-based regimen (including isoniazid);
- MDR-TB: defined as resistance to rifampicin and isoniazid or rifampicin alone; and
- XDR-TB: defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin). MDR-TB and XDR-TB are more difficult to treat than DS-TB is.

In addition, prognosis can vary with comorbidities; the risk of developing TB disease is higher for immunocompromised individuals. Individuals infected with HIV are 26–31 times more likely to develop TB than those without HIV. TB is the most common presenting illness among people living with HIV, including those taking antiretroviral treatment, and is the major cause of HIV-related death [1, 3]. HIV prevalence among incident TB cases in Europe was 12% in 2016 [1].

In 2019, WHO estimated that 10 million individuals developed active TB and 1.6 million died from the disease [12]. In the WHO European region, an estimated 275,000 new and relapsing TB cases (range 238,000–314,000) occurred in 2017, equivalent to an average incidence of 30 cases (range 26–34) per 100,000 population. Among pulmonary cases notified in the WHO European region in 2017, there were an estimated 77,000 cases of MDR-TB. In EU/EEA countries alone, MDR-TB was reported for 1041 of 27,339 cases (3.8%) after the relevant drug susceptibility test results, and MDR-TB continues to be highest (>10%) in the three Baltic states. XDR-TB showed an increasing trend: 18.6% of pulmonary MDR-TB cases had XDR-TB in 2017. In absolute numbers, XDR-TB cases among pulmonary TB cases increased from 575 in 2013 to 5591 in 2017. XDR-TB was reported for 24.3% of 770 MDR-TB cases tested for second-line drug susceptibility [1]

1.2 Current clinical practice

Management schemes for TB treatment depend on the resistance profile of the *M. tuberculosis* strain. Decisions on particular appropriate regimens should be made according to patient preference and clinical judgement, as well as considering susceptibility testing results, patient treatment history, and the severity and site of the disease [4].

For active DS-TB, a 6-month rifampicin-based regimen is recommended (2 months of isoniazid-rifampicin-pyrazinamide-ethambutol/4 months of isoniazid-rifampicin to be taken orally) [13].

For MDR-TB and for patients with strains resistant to rifampicin only, longer treatment regimens are recommended (usually for a total duration of 18–20 months). A shorter regimen of 9–12 months may be used for patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded. Groups of WHO-recommended medicinal products are listed in Table 1.1. Treatment regimens should include at least four effective medicines comprising all three group A agents and at least one group B agent. If any agent from group A or group B cannot be used, additional medicines from group B and then group C are included to complete the recommended four-agent regimen [4].

Patients with XDR-TB globally follow the same treatment pathway as MDR-TB patients, taking into consideration additional resistance and previous treatment exposure. Because of resistance to fluoroquinolones in addition to at least one injectable drug, the choice of medicines from group A is limited to bedaquiline and linezolid. Consequently, drugs from groups B and C are more frequently used in these patients [4, 8].

Table 1.1. Grouping of medicines recommended for use in longer MDR-TB regimens

Group and steps	Medicine
Group A[a]: Include all three medicines	Levofloxacin OR moxifloxacin
	Bedaquiline
	Linezolid
Group B[b]: Add one or both medicines	Clofazimine
	Cycloserine OR terizidone
Group C[c]: Add to complete the regimen and when medicines from groups A and B cannot be used	Ethambutol
	Delamanid
	Pyrazinamide
	Imipenem–cilastatin OR meropenem
	Amikacin (OR streptomycin)
	Ethionamide OR prothionamide
	p-Aminosalicylic acid

Source: Adapted from the 2019 World Health Organization consolidated guidelines on drug-resistant tuberculosis treatment [4]
[a]Group A: considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.
[b]Group B: conditionally recommended as agents of second choice.
[c]Group C: all other medicines that can be used when a regimen cannot be composed of group A and B agents.

1.3 Features of the intervention

Pretomanid is an antimycobacterial drug and a member of the nitroimidazooxazine class (whereas delamanid is a member of the nitroimidazooxazole class).

Pretomanid is indicated in combination with two agents from group A (bedaquiline and linezolid; BPal regimen) in adults for the treatment of XDR-TB or TI/NR MDR-TB. This is the first approved utilisation of pretomanid in the treatment of TB (information taken from the pretomanid EPAR and summary of product characteristics [SmPC]).

The mechanism of action of pretomanid is complex and has not been fully elucidated. It appears that under aerobic conditions, pretomanid inhibits the biosynthesis of cell-wall lipids in *M. tuberculosis* by inhibiting the synthesis of mycolic acid, while under anaerobic conditions it generates reactive nitrogen species and a concomitant drop in intracellular ATP levels. Reductive activation of pretomanid by a mycobacterial deazaflavin-dependent nitroreductase is required for activity under both aerobic and anaerobic conditions. Pretomanid is active against both actively replicating *M. tuberculosis* and dormant bacilli (i.e., it exhibits both bactericidal and sterilising activity). Pretomanid displays activity against drug-susceptible as well as drug-resistant (including multi-drug resistant and extensively drug resistant)

strains of Mycobacterium tuberculosis with a minimal inhibitory concentration generally in the range of ≤ 0.015 to 2 µg/mL. (Information taken from the pretomanid EPAR and SmPC).

Pretomanid features and administration are described in Table 1.2 and Table 1.3. Information on linezolid and bedaquiline is in the relevant SmPCs. The posology of bedaquiline in the BPal regimen is in line with the posology already approved for bedaquiline (400 mg QD for 2 weeks followed by 200 mg three times per week orally, for a total of 24 weeks, compared to 26 weeks in the BPal regimen). Linezolid is an antibiotic not approved for the treatment of TB, but experience with linezolid in the treatment of TB indicates that it is mostly used at a dose of 600 mg/day (lower than the dose recommended in the BPal regimen) for a treatment duration that can go beyond 6 months, depending on tolerability [4].

Use of the antiretroviral efavirenz with the BPal regimen is contraindicated to avoid drug–drug interactions with bedaquiline. However, this contraindication might have a limited impact on use of the BPal regimen in HIV-positive patients, as efavirenz tends to be used less and less in Europe (can be replaced by integrase inhibitors).

Table 1.2. Features of pretomanid

Nonproprietary name	Pretomanid
Proprietary name	Pretomanid FGK
Registered EMA indication	Pretomanid FGK is indicated in combination with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug-resistant or treatment-intolerant or nonresponsive multidrug-resistant tuberculosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Prospective MAH	Mylan
Contraindications	Hypersensitivity to the active substance, other nitroimidazoles or any of the excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, silica [colloidal], sodium lauryl sulfate, povidone). The safety and effectiveness of pretomanid have not been established for use in combination with medicinal products other than bedaquiline and linezolid as part of the recommended dosing regimen, and thus pretomanid should not be used as part of any other regimen.
Drug class	Antimycobacterial drug for the treatment of tuberculosis
Active substance(s)	Pretomanid
Pharmaceutical formulation(s)	200 mg tablet
ATC code	Not yet assigned
In vitro diagnostics required	No
Monitoring required	This medicinal product is subject to additional monitoring
Orphan designation	This product was designated as and orphan medicine during its development. The European Medicines Agency will review the information available to date to determine if the orphan designation can be maintained.
Advanced therapy medicinal product	No

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019).
Abbreviations: ATC=Anatomical Therapeutic Chemical; MA=marketing authorisation.

Table 1.3. Administration and dosing of pretomanid in combination with bedaquiline and linezolid (BPal regimen)

Parameter	Details
Method of administration	Oral use. Pretomanid should be taken with food. Tablets should be swallowed with water. Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg three times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1200 mg daily orally for up to 26 weeks).
Doses	200 mg (one tablet)
Dosing frequency	Once daily
Standard length of a course of treatment	26 weeks A longer duration may be considered in patients who have not responded adequately to treatment at 26 weeks on a case-by-case basis.
Standard interval between courses of treatments	Not applicable
Standard number of repeat courses of treatment	Not applicable
Dose adjustments	Not applicable

Source: Pretomanid SmPC.

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA joint REA is to compare the clinical effectiveness and safety of pretomanid in the target patient population with relevant comparators. The target patient population and relevant comparators (based on the requirements of EUnetHTA partners) are defined in the project scope in Table 2.1.

The assessment was based on the submission dossier submitted by the pMAH (Mylan).

Table 2.1. Scope of the assessment

<table>
<tr><th>Description</th><th>Assessment scope [a]</th></tr>
<tr><td>Population</td><td>Adult patients with pulmonary XDR-TB or treatment-intolerant or nonresponsive MDR-TB.</td></tr>
<tr><td>Intervention</td><td>Pretomanid is indicated as part of a combination regimen with bedaquiline and linezolid.
Posology
The recommended dosage for pretomanid is 200 mg orally (one tablet of 200 mg) daily for 26 weeks. 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 (1200 mg daily orally for up to 26 weeks).</td></tr>
<tr><td>Comparison</td><td>Treatments authorised in MDR-TB in association with other tuberculosis medicines:
Bedaquiline;
Delamanid;
p-Aminosalicylic acid.
Other treatments not authorised in MDR-TB but recommended for use by WHO (it should be noted that the certainty for the effect of these products is moderate or very low according to WHO) [4]: List of medicines recommended for use in longer MDR-TB regimens (cf. 2019 WHO consolidated guidelines on DR tuberculosis treatment for further details on the composition of the recommended regimens)
<table>
<tr><td>Group A</td><td>Levofloxacin OR moxifloxacin
Bedaquiline
Linezolid</td></tr>
<tr><td>Group B</td><td>Clofazimine
Cycloserine OR terizidone</td></tr>
<tr><td>Group C</td><td>Ethambutol
Delamanid
Pyrazinamide
Imipenem–cilastatin OR meropenem
Amikacin (OR streptomycin)
Ethionamide OR prothionamide
p-Aminosalicylic acid</td></tr>
</table></td></tr>
<tr><td>Outcomes</td><td>Proportion of subjects with sputum culture (± smear microscopy) conversion to negative status and time to culture conversion (± smear microscopy) to negative status
Cure (according to the WHO definition [5] or other clinically relevant definition)
Treatment failure including bacteriological/clinical failure and relapse (according to the WHO definition [5] or other clinically relevant definition)
Treatment completed (according to the WHO definition [5] or other clinically relevant definition)
Treatment success (includes cure and treatment completed)
Mortality
Health-related quality of life
Safety, including serious adverse events and treatment-related adverse events</td></tr>
</table>

Source: Project plan (v1.0).
[a] Additional outcomes not captured in the PICO may be described in the assessment report as submitted by the marketing authorisation holder.
Abbreviations: MDR-TB=multidrug-resistant tuberculosis; WHO=World Health Organization; XDR-TB=extensively drug-resistant tuberculosis.

3 METHODS

3.1 Information retrieval and data extraction

The assessment was based on a dossier submitted by the MAH (Mylan). This dossier includes a review of the literature to identify relevant data for this rapid REA regarding the intervention and its comparators identified in the scoping phase.

The authoring team critically assessed the method for information retrieval that the MAH submitted. Data were also checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. The completeness of the data on pretomanid in combination with other drugs and/or for a different indication was not assessed, as these situations are beyond the scope of this REA.

3.1.1 Method

The MAH searched the MEDLINE, Embase and CENTRAL bibliographic databases. These databases are relevant, complementary and sufficient for the subject under discussion. The search strategy is reproduced. Other databases could have been searched, as TB is a disease with high incidence outside Europe and the USA. The 2010–2020 date limits are not justified. A 10-year search is common practice, but without justification it is arbitrary. This is likely to have little impact on the outcome of the evaluation because if a major study was published before the research period, it can be assumed that it would have been cited in subsequent studies and thus identified, provided that analysis of the articles and their reference lists was rigorous. The search was limited to publications in English without justification, but English is generally considered to be the main language for scientific publications.

No search of study registries was described by the MAH, but this must have been carried out because the strategy for searching the bibliographic databases uses identification numbers for the studies in trial registries (clinicaltrials.gov). However, it is not possible to evaluate the completeness of this search. There is no mention in the dossier of additional research (reports, literature not referenced in bibliographic databases), although several WHO reports are referenced in the bibliography, which implies a search for the work of this body. There is no mention either of a search for the work of other evaluation bodies or recommendations and guidelines.

Critical assessment of the method

The essential PICO elements are reflected in the search strategy. However, all the terms describing pathology, treatments and clinical study numbers are combined into a single term group with the Boolean operator OR, which is not relevant. Terms related to the pathology were searched for as a strict expression and were searched for only in titles and abstracts. The search can therefore be considered too restrictive and lacking in sensitivity. Searches for certain expressions gave no results and this should have alerted the person in charge of the search and led to a search for other expressions. The use of proximity operators in title and abstract searches would have made these searches more fruitful. No MeSH or Emtree terms were used, which is a restrictive factor, although there are appropriate terms in these thesauri, such as “Tuberculosis, multidrug resistant” and “Extensively drug-resistant tuberculosis” in MeSH and “Tuberculosis drug resistant” in Emtree.

Concerning the filters used to target the study type searched for (RCTs), the descriptors in the databases were not used, nor was the Document Type field used, which allows effective targeting of publication types. The flow chart reproduced in the draft shows that out of 382 abstracts, 261 were discarded because they did not correspond to the type of study sought, which represents a considerable waste due to poor knowledge of the search tools.

It can therefore be concluded that the search was generally too specific in the choice of terms. Moreover, appropriate descriptors and search tools were not used and there was a lack of sensitivity. Overall, the authoring team considers that there is a risk of not detecting relevant studies. Details of the search are included in the submission dossier (Section 5 Clinical effectiveness and safety and Appendix 7.4).

Main results for the SLR and data extraction

The SLR performed by the MAH identified 25 relevant publications on RCTs or prospective studies. Among these 25 studies, six were excluded because there was only an abstract available. Of the 19 remaining studies, two evaluated the efficacy and safety of pretomanid in combination with bedaquiline and linezolid in patients with XDR-TB and TI/NR MDR-TB:

- Nix-TB, a noncomparative phase III study; and
- ZeNix, an RCT to further validate the optimal linezolid dosage (no control group without pretomanid).

Data from the pivotal Nix-TB study were extracted from the submission dossier and verified against the CSRs also submitted by the MAH. However, as the ZeNix study is still ongoing, no results from this clinical trial were submitted by the MAH for this assessment. The results of this study are expected by the EMA as a specific obligation to complete post-authorisation measures for the conditional marketing approval. According to the EPAR, results from the ZeNix study are expected in Q4 2022. No study included in the submission dossier and that evaluated pretomanid for the indication granted in the marketing authorisation was excluded. The authoring team also verified that no meta-analysis that included results from the Nix-TB study had been published.

The remaining 17 studies were RCTs or prospective studies conducted in a similar population (adult patients with XDR-TB and TI/NR MDR-TB) with other treatment alternatives. Given the paucity of recent data for XDR-TB, identification of retrospective studies might have been interesting to further assess the clinical context. This study pool with comparators was not used by the MAH to perform indirect comparisons. Details on this information retrieval (which could potentially be used as a historical control) can be found in the submission dossier (Section 5.2.2).

Table 3.1. Study pool: list of relevant studies used for assessment

Study reference/ID	Study category		
	Study for MA for the technology under assessment [a]	**Sponsored or third-party study [b]**	**Available documentation [c]**
Nix-TB study NCT02333799	Yes	Third-party study [d]	Conradie et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020;382:893–902 [6] CSR dated 19th October 2018 CSR dated 29th October 2019

Source: European Public Assessment Report for pretomanid.
[a] If "yes", also indicate the respective reference of the data reference(s).
[b] Study sponsored by the MAH or in which the MAH participated financially in some other way.
[c] Include references of the study registry entries and, if available, the reports on study design and/or results listed in the study registries.
[d] Pretomanid was developed by TB Alliance, a nonprofit drug developer. TB Alliance and Mylan have a global collaboration on the new chemical entity pretomanid. Currently, a service provider for regulatory approval procedures (FGK) is the MA holder for pretomanid in Europe and is responsible for the European Medicines Agency procedure. MA transfer to Mylan in Europe will start immediately after approval.
Abbreviations: CSR=clinical study report; MA=marketing authorisation.

Conclusions

Overall, the authoring team considered the study pool used to assess the intervention to be complete and exhaustive. However, given the limitations identified in the SLR method, the information retrieval for comparators cannot be considered exhaustive. This is not expected to impact the assessment, as no comparative data were submitted by the MAH, but information retrieval on comparators might not be appropriate for future indirect comparisons that could be performed by national agencies.

3.2 Risk of bias assessment

EUnetHTA guidelines recommend the use of a quality rating tool developed by the Cochrane Collaboration in rapid REAs: the Risk of Bias tool for randomised trials and the ROBINS-I tool for nonrandomised trials.

As this assessment is mostly based on a noncomparative trial without external or indirect comparisons, these tools were not considered applicable by the authoring team without substantial adaptations. However, methodological limitations identified in the Nix-TB study are discussed in Section 4.3 of this report.

3.3 Results and analyses from the studies included

The information in the submission dossier on the study design, study methods, populations, endpoints (patient relevance, validity and operationalisation) and study results were evaluated by the authoring team. The results of this evaluation are presented and were used for identification of relevant analyses and considered for the conclusions of the assessment report.

3.3.1 Meta-analysis

Not applicable.

3.3.2 Sensitivity analysis

To evaluate the robustness of the results, sensitivity analyses with regard to methodological factors presented in the submission dossier and the corresponding methods applied were evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, specification of the cutoffs for the time points for data collection and the choice of effect measures.

3.3.3 Subgroup analysis and other effect modifiers

The assessment evaluated the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied. The evaluation also includes the justification for the choice of cutoffs if quantitative characteristics were categorised.

3.3.4 Indirect comparisons

Not applicable.

3.4 Patient involvement

From 20th January 2020 to 23rd March 2020 an open call for patient input was published on the EUnetHTA website. This open call asked patient organisations to provide answers to the questions from a patient and/or caregiver perspective and to detail experiences by engaging with a wide range of patients and their carers.

The open call used by EUnetHTA asks general questions to collect the patient perspective on living with the disease, important outcomes to be considered in this assessment and expectations regarding the drug under assessment. The questions were based on the Health Technology Assessment International questionnaire template; more information on the development of this template is available on the https://htai.org/ website.

Relevant European and national patient and consumer organisations were asked to provide an organisational perspective on the questions in English. In the survey, the term “patient” refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated. For this specific open call and considering the potentially low number of patients for whom the BPal regimen could be indicated in Europe, questions did not specifically target patients with XDR-TB or TI/NR MDR-TB, but rather every patient with TB.

Unfortunately, no patient organisations completed the survey.

In addition, an interview with the president of the French patient organisation ACTUME was conducted by HAS. The objective of this consultation was to collect data from the perspective of the patient community on the impact of TB on patient QoL and the current standard of care. This interview did not aim to collect data representative of the entire TB community.

The main results and conclusion from the patient interview are summarised in Section 5 of this assessment report and the minutes of the interview with ACTUME can be found in Appendix APPENDIX 4: PATIENT INVOLVEMENT

4 RESULTS

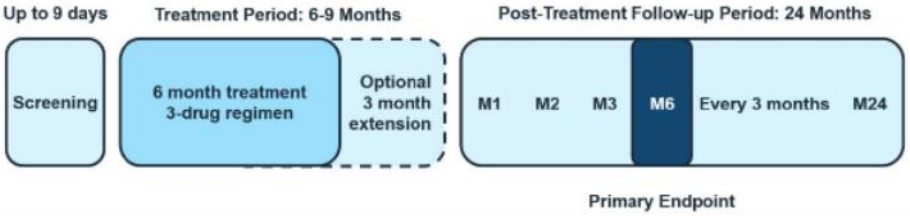
The assessment of pretomanid in combination with bedaquiline and linezolid is based on a single noncomparative phase III clinical study: the Nix-TB study. The study methods and results are described below.

4.1 Nix-TB study: methods

Table 4.1 describes the study used for the assessment (Nix-TB study).

Table 4.1. Description of the Nix-TB study

Reference	Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020;382:893–902 [6]
Clinicaltrials. gov	NCT02333799
Primary objective of the study	To evaluate the efficacy and safety of pretomanid in association with bedaquiline and linezolid (BPal regimen) in adult patients with pulmonary XDR-TB or pulmonary TI/NR MDR-TB
Main characteristics of the study design	Phase III, multicentre, single-arm study
Conduct of the study	First patient included: 16th April 2015 Last patient included: 15th November 2017 Enrolment was stopped after 109 patients were included. The study is ongoing. The end of the study is scheduled after all patients will achieve follow-up to 24 months after the end of treatment. The efficacy and safety analyses were based on the following data cutoffs (for which CSRs have been submitted): 29th June 2018 and 29th March 2019. Patients were included in three investigator centres, all located in South Africa.
Key inclusion criteria	• Body weight ≥35 kg; • Provided consent for HIV testing or had documented positive HIV result; • Age ≥14 years; • Subjects with one of the following pulmonary TB conditions: a. XDR-TB with: (i) Documented culture-positive results (for *M. tuberculosis*) within 3 months before screening or *M. tuberculosis* confirmed in sputum based on molecular testing within 3 months before or at screening; (ii) Documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable historically at any time before or at screening; b. NR MDR-TB with MDR-TB documented by culture-positive results (for *M. tuberculosis*) within 3 months before or at screening with documented nonresponse to treatment with the best available regimen for 6 months or more before enrolment who, in the investigator's opinion, have adhered to treatment and will be adherent to the study regimen c. TI MDR-TB with MDR-TB documented by culture-positive results (for *M. tuberculosis*) within 3 months before or at screening who are unable to continue a second-line drug regimen due to a documented intolerance to: (i) PAS, ethionamide, aminoglycosides or fluoroquinolones ; (ii) Current treatment not listed above that renders subject eligible for the study in the investigator's opinion; • Had a chest X-ray image (taken within 1 year before screening) consistent with pulmonary TB in the investigator's opinion; • Were of non-childbearing potential or used effective methods of birth control.
Key exclusion criteria	• Karnofsky performance score <50 within 30 days before screening; • HIV-infected patients with a CD4 count of ≤50 cells/μL; • HIV-infected patients being treated with or needing to initiate antiretroviral therapy that was not allowed; • Significant cardiac arrhythmia requiring medication; • Peripheral neuropathy of grade 3 or grade 4, according to the DMID, or neuropathy grade 1 or grade 2 that was likely to progress/worsen over the course of the trial, in the opinion of the investigator;

	• Concomitant use of monoamine oxidase inhibitors, serotonergic antidepressants, any drug known to prolong the QT interval, any drug known to induce myelosuppression or any drugs known to be strong inhibitors or inducers of cytochrome P450 3A4 enzymes; • Received more than 2 weeks of bedaquiline or linezolid before enrolment or first administration of trial treatment; • Toxicities at screening as defined by the enhanced DMID adult toxicity table (DMID 2007).
Overview of study design	
Treatments	The BPal regimen being studied is an oral combination of three products administered for 6 months (26 weeks): • Bedaquiline: 400 mg QD for 2 weeks then 200 mg three times per week thereafter; • Pretomanid: 200 mg QD; • Linezolid: 1200 mg daily (600 mg BID, changed to 1200 mg QD based on protocol amendment on 22nd January 2016). If subjects were still culture-positive or reverted to being culture-positive between month 4 and month 6, it was possible to continue treatment for an additional 3 months. **Dose adjustments** • For subjects experiencing suspected drug-related toxicities due to linezolid, the daily dose of linezolid may be reduced or temporarily halted for up to 35 consecutive days. Generally, a step down in dose was to proceed from 1200 mg QD to 600 mg and then to 300 mg QD. If subjects have toxicity issues with linezolid that would prohibit further treatment with that drug, they can remain on the bedaquiline and pretomanid regimen if they receive the initial 1200 mg QD dose of linezolid for at least the first 4 weeks of treatment and are smear-negative. It should be noted that the optimal posology for linezolid is still under discussion and that the efficacy and safety of alternative linezolid dosing schedules in association with pretomanid and bedaquiline are currently being explored in the ZeNix study; • For subjects experiencing suspected drug-related toxicities due to bedaquiline and/or pretomanid, the full regimen may be halted for up to 35 consecutive days; • For subjects who completed the first 4 consecutive weeks of treatment on the 1200 mg linezolid total dose and only halt linezolid later in treatment, treatment can be considered complete at 6 months.
Concomitant treatments	The following concomitant medications were prohibited during the treatment period: medicinal products used to treat pulmonary TB, monoamine oxidase inhibitors, any drug known to prolong the QT interval, any drug known to induce myelosuppression, strong inhibitors or inducers of cytochrome P450 3A4 enzymes for more than 3 consecutive days. Regarding antiretroviral therapy, patients had to avoid efavirenz because of drug–drug interactions with bedaquiline.
Primary endpoint	The primary endpoint was the incidence of treatment failure, a composite outcome of clinical failure [a], bacteriologic relapse [b] or bacteriologic failure [c] (reinfection) through to 6 months after the end of treatment. The mITT analysis was considered primary (see the statistical analysis methodology below for the definition of the mITT population). According to the statistical analysis plan, patients were classified as having favourable, unfavourable or unassessable status at 6 months after the end of therapy. **Favourable status was defined as:** Patients with a negative culture status at 6 months after the end of therapy who had not already been classified as having an unfavourable outcome and whose last positive culture result was followed by at least two negative culture results. **Unfavourable status in the mITT population included any of the following:** • Patients not classified as having achieved or maintained culture-negative status when last seen; • Patients previously classified as having culture-negative status who, following the end of treatment, have two positive cultures without an intervening negative culture; • Patients who had a positive culture not followed by at least two negative cultures when last seen; • Patients dying from any cause during treatment, except violent or accidental cause (e.g., road traffic accident), not including suicide;

	• Patients definitely or possibly dying from TB-related cause during the follow-up phase; • Patients requiring extension of their treatment beyond that permitted by the protocol or a restart or change of treatment for any reason except reinfection or pregnancy; • Patients lost to follow-up or who withdraw from the study before the end of treatment.
Secondary endpoints	• Incidence of bacteriologic failure (reinfection) or relapse at 24 months after the end of treatment; • Time to sputum culture conversion to negative status; • Culture conversion status at 4, 6, 8, 12 and 16 weeks; • Change from baseline in the TB Symptom Profile score; • Change from baseline in patient-reported health status, collected using the EQ-5D-5L questionnaire; • Change from baseline in weight (not described in this report as the clinical relevance of this endpoint in this situation is doubtful).
Sample size	No sample size calculation was performed for this noncomparative study. The study originally planned to enrol a total of up to 200 patients. However, to facilitate enrolment in the ZeNix study, enrolment in Nix-TB was stopped after the inclusion of 109 patients.
Statistical analyses	**Analysis of the primary endpoint** The CSR presents the proportions of assessable patients with favourable and unfavourable outcomes. No statistical analysis was performed and there was no adjustment for multiplicity. The trial was considered successful if the lower bound of the 95% confidence interval for the proportion of assessable patients with a favourable outcome was >50%. No justification was provided in the submission dossier for this threshold of 50%. The probability of treatment failure (unfavourable outcome) through follow-up until 6 months after the end of treatment, as a function of time after assignment of treatment, was analysed via Kaplan–Meier analysis. The binomial proportion of patients with bacteriologic failure was presented. **Analysis of secondary endpoints** All secondary endpoints were exploratory. The time to culture-negative status was analysed using Kaplan–Meier plots and Cox proportional-hazards regression analysis. Changes in TB symptoms were collected via the TB Symptom Profile questionnaire. Ten symptoms are evaluated by patients over the previous 7 days and graded as none, mild, moderate or severe: cough, chest pain, coughing up blood, coughing up mucus, excessive sweating, feeling chills, feeling feverish, feeling unwell, shortness of breath and tiredness/weakness. The TB Symptom Profile total score was defined by the number of TB symptoms (between 0 and 10). These were summarised at baseline, week 8 and end of treatment. Patient-reported health status was measured using the five domains of the EQ-5D. These were summarised at baseline, week 8, end of treatment, and 6 and 24 months after the end of treatment, and the change from baseline was recorded at each follow-up assessment. **Sputum sampling for evaluation of bacteriological failure/relapse and culture conversion** At screening (day −9 to −1): A single spot sputum will be collected for smear microscopy for acid-fast bacilli, culture and molecular or antigen-based testing to confirm *M. tuberculosis* At all visits from day 1 (baseline) up to and including month 24: two sputum samples will be collected for culture (and speciation at baseline and the first positive at the end of treatment or during follow-up or any positive at or after the week 16 visit). Culture conversion was defined as at least two consecutive culture-negative samples collected at least 7 days apart. **Analysis populations** The primary analysis was performed for the mITT population. mITT analysis excludes the following patients: • Patients who, having completed treatment, were lost to follow-up or withdrew from the study, their last status being culture-negative and their last positive culture result followed by at least two negative culture results at different visits; • Women who became pregnant during treatment and stopped their allocated treatment. • Patients who died from violent or accidental cause during treatment (e.g., road traffic accident); death from suicide will be considered an unfavourable outcome; • Patients who died during follow-up with no evidence of failure or relapse of their TB, their last status being culture-negative and their last positive culture result followed by at least two negative culture results at different visits;

	• Patients who, after being classified as having culture negative status, are reinfected with a new strain different from that with which they were originally infected; • Patients who are able to produce sputum at their primary endpoint visit whose sputum samples are all contaminated or missing. As a reminder, patients already classified as having an unfavourable outcome were not excluded. **Sensitivity analyses** Sensitivity analyses of the primary endpoint data by ITT (defined as all patients, excluding late screening failures) and per protocol were planned, as well as other sensitivity analyses, such as excluding patients with negative baseline culture. Sensitivity analysis by ITT and excluding patients with negative culture baseline culture will be presented in this assessment report. In the ITT analysis, patients without a favourable outcome at 6 months after the end of therapy were considered to have an unfavourable response. Interim analyses were prespecified to be performed once the first 15, 30, 45, and 75 patients either completed the treatment period and the 6-month post-treatment follow-up, withdrew from the trial, were lost to follow-up, or died. No results were available in the submission dossier for these interim analyses and they are not presented in the assessment report. **Subgroup analyses** Subgroup analyses were planned for the primary endpoint according to age, gender, race, smoking status, TB type (XDR or MDR), cavitation, HIV status, initial bacterial load in sputum and antiretroviral drugs taken during the treatment period. Finally, the following sub-group analysis were performed by HIV status, by type of TB (XDR or MDR) and by linezolid dosing. An ad hoc analysis by linezolid dosing at enrolment was performed due to a change in the dosing administration schedule. In the absence of formal statistical tests and multiplicity adjustment for type I errors, these analyses are exploratory. **Main protocol amendments** Amendment 1 dated 18th March 2015: allowance for patients to continue on bedaquiline and pretomanid alone after linezolid toxicity issues if they have completed at least 1 full month of linezolid treatment and were smear-negative. Amendment 2 dated 22nd January 2016: linezolid dosing changed from 600 mg BID to 1200 mg QD based on preliminary data from a linezolid clinical trial that noted a similar bactericidal effect on TB when either dosing scheme was given for 14 days. A single daily dose of the total amount may have less toxicity, as the time over expected toxicity concentrations was lower when administered QD. This amendment also added exclusion of patients who had received more than 2 weeks of bedaquiline or linezolid and added strong cytochrome P450 inhibitors and inducers to specific treatment exclusions.

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019); study protocol dated 16th February 2018 and statistical analysis plan dated 11th July 2017.
[a] Clinical failure is defined as declaration of unfavourable status at or before the end of treatment or failure to attain a culture-negative status or patient withdrawal at or before the end of treatment for clinical (TB) reasons including retreatment (or changing from trial treatment) for TB.
[b] Bacteriologic relapse is defined as failure to maintain a culture-negative status or declaration of an unfavourable outcome after the end of treatment for patients who attained a culture-negative status by the end of treatment and had culture conversion to positive status with the same *M. tuberculosis* strain after the end of treatment or patient withdrawal for clinical (TB) reasons including retreatment (or changing from trial treatment) for TB.
[c] Bacteriologic failure is defined as failure to maintain culture-negative status or declaration of an unfavourable outcome (including withdrawal for clinical [TB] reasons including retreatment or changing from trial treatment for TB) after the end of treatment for patients who attained a culture-negative status by the end of treatment and had culture conversion to positive status with a *M. tuberculosis* strain that was different from the infecting strain at baseline. If reinfection could not be distinguished from relapse, the patient was assumed to have relapsed.
Abbreviations: BID=twice daily; CSR=clinical study report; DMID=Division of Microbiology and Infectious Diseases; EQ-5D-5L=European Quality of Life-5 dimensions-5 levels; HIV=human immunodeficiency virus; ITT=intention to treat; MA=marketing authorisation; MDR=multidrug-resistant; mITT=modified intention to treat; NR=nonresponsive; PAS=*p*-aminosalicylic acid; QD=once daily; TB=tuberculosis; TI=treatment-intolerant; XDR=extensively drug-resistant.

4.2 Results from the Nix-TB study

4.2.1 Data cutoffs

Two CSRs are available in the submission dossier:

- One dated 19th October 2018 presents data from an interim analysis using the data available at a cutoff date of 29th June 2018. At this data cutoff, analysis of the primary endpoint was not feasible for all patients, as only 80/109 patients (73.4%) had completed the 6-month follow-up period;
- One dated 29th October 2019 presents data from an interim analysis using the data available at a cutoff date of 29the March 2019. At this date, 99/109 patients (90.8%) had completed the 6-month follow-up period. The remaining patients had discontinued the trial before evaluation of the primary endpoint (see Section 4.2.2 Participant flow). At this latest cutoff, 44/109 patients (40.4%) had completed 24-month follow-up visit. Follow-up to 24 months after the end of treatment is ongoing (final results expected Q2 2021).

In this rapid REA, data presentation is focused on the second cutoff date with longer follow-up. However, to evaluate the consistency of the effect across time, results from the first cutoff date are detailed for the primary endpoint only.

4.2.2 *Participant flow*

Figure 4.1 summarises the participant flow in the Nix-TB study.

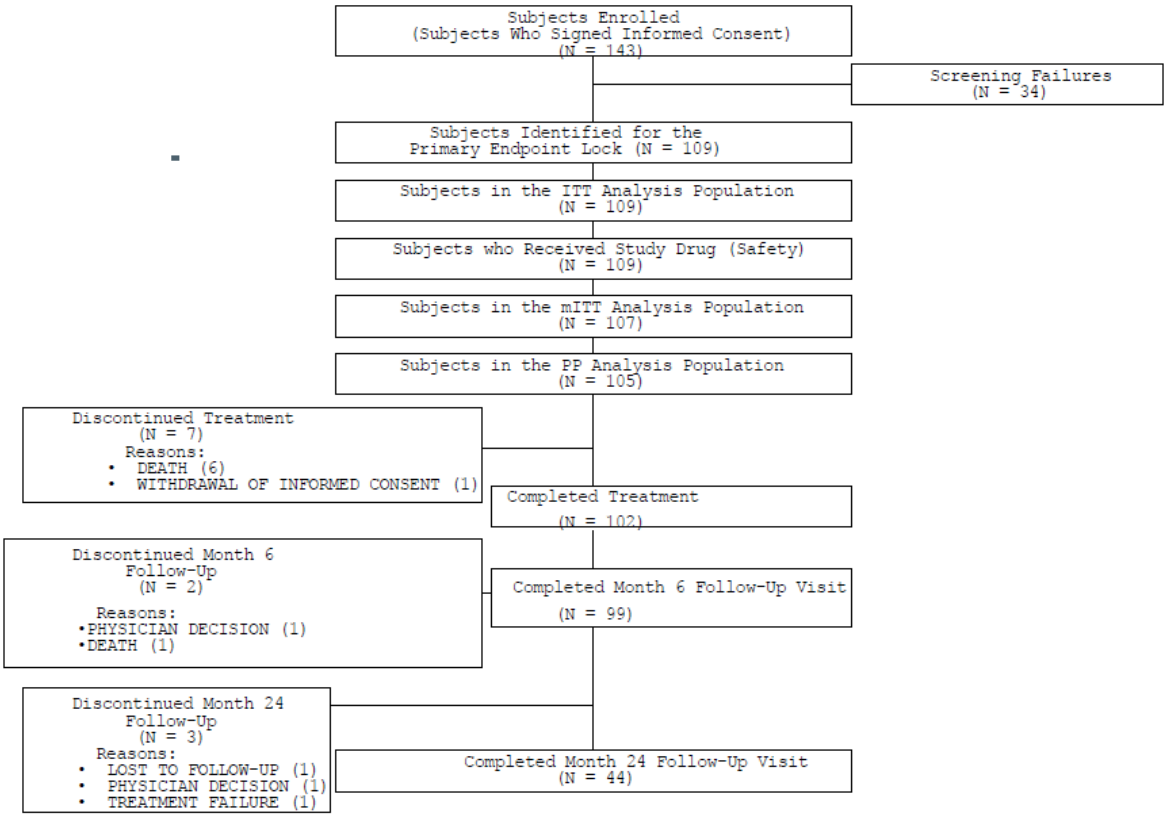


Figure 4.1. Nix-TB study: participant flow

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019).
Abbreviations: mITT=modified intention to treat.

A total of 109 patients were enrolled in the study. The first 44 patients were started on linezolid at 600 mg twice daily (BID) and the remaining 65 were started on 1200 mg QD after the second protocol amendment, dated 22nd January 2016.

The treatment duration was 26 weeks according to the study protocol. One patient out of 109 had an extension of the treatment duration for an additional 3 months (up to 9 months) because of a positive culture at week 16.

Of the 109 patients, 16 (14.7%) received the 1200-mg total daily dose of linezolid without interruption over the full 26 weeks of therapy. For subjects experiencing suspected drug-related toxicities due to linezolid, the daily dose of linezolid could be reduced (with a stepdown approach from 1200 mg QD to 600 mg and then 300 mg QD). A dose reduction of linezolid was applied for 69/109 patients (63.3%). A total of 37/109 patients (33,9%) received a full uninterrupted 26 weeks of linezolid at any dose. Premature discontinuation of linezolid administration occurred for 35/109 patients (32,1%).

Concomitant use of any medication to treat TB (which was not allowed according to the protocol) was limited, as it was reported for only 3/109 patients (2.8%). For one patient, the protocol-specified washout period did not happen (at most there was 1 day of overlap with the prior TB treatment). The other two patients received non-trial TB medications starting before treatment with the trial drug until an unknown stop date in the year of starting the trial drug. There was a note added to the screening source stipulating that the medications were stopped before starting the trial drug, although the specific month of stopping was unknown.

4.2.3 Major protocol deviations

A total of 24 deviations were reported. These mainly pertain to prior TB treatment not stopped at least 3 days before the first dose of the experimental treatment (*n*=6), chest X-ray image not available (*n*=5) and use of a double-barrier contraceptive method not specified (*n*=8).

4.2.4 Baseline characteristics of the study population

Table 4.2 shows the baseline characteristics of the study population in the Nix-TB study. Patients included had a median age of 35 years (range 17–60 years) and 52.3% were male. Approximately half of the patients were HIV-positive (51.4%). At baseline, the majority of these patients were being treated with lopinavir/ritonavir-based (25/56) or nevirapine-based therapy (17/56). However, after the second protocol amendment, use of strong cytochrome P450 3A4 inhibitors and inducers was no longer allowed. Most patients had cavities present on chest X-ray (unilateral for 46.8% and bilateral for 37.6%). The median time since the current TB diagnosis was 3.1 months. The current diagnosis was XDR-TB for 65.1% of the patients and TI/NR MDR-TB for 34.9%.

Patients could be enrolled on the basis of a positive culture within 3 months before screening or, for XDR-TB patients only, molecular testing within 3 months before or at screening. A total of 16/109 patients (14.6%) did not have a positive culture at baseline.

Table 4.2. Baseline characteristics of the ITT Nix-TB study population

Parameter	Result (N=109)
Median age, years (range)	35 (17–60)
Male, *n* (%)	57 (52.3)
Race, *n* (%) Black Mixed race White	 83 (76.1) 25 (22.9) 1 (0.9)
Median body mass index, kg/m^2 (range)	19.6 (12.4–41.1)
Positive HIV status, *n* (%)	56 (51.4)
Mean CD4 count, cells/µl (range) [a]	394.0 (55–1023)
Cavities present on chest X-ray, *n* (%) No Unilateral Bilateral	 17 (15.6) 51 (46.8) 41 (37.6)
Karnofsky performance score, *n* (%) 100 90 80 70 60	 9 (8.3) 50 (45.9) 29 (26.6) 19 (17.4) 2 (1.8)
Median time since current TB diagnosis, months (range)	3.1 (0.4–90.3)
Current TB diagnosis, n (%) XDR-TB MDR-TB Nonresponsive MDR-TB Treatment-intolerant MDR-TB	 71 (65,1) 19 (17.4) 19 (17.4)

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019).
[a] CD4 count available for 51/56 HIV-positive patients.
Abbreviations: HIV=human immunodeficiency virus; ITT=intention to treat; MDR=multidrug-resistant; TB=tuberculosis; XDR=extensively drug-resistant.

Prior use of TB medications

A total of 105/109 patients (96.3%) received at least one prior TB medication. Prior use of fluoroquinolones was reported for 103/109 patients (94.5%), prior use of thiocarbamide derivatives (the group that includes ethionamide and prothionamide) for 83/109 patients (76.1%) and prior use of drugs for the treatment of leprosy (covering drugs such as clofazimine also used for TB treatment) for 82/109 patients (75.2%). The median number of prior TB treatments used was seven (range 3–13) according to Conradie et al. [6] (this information could not be retrieved from the CSR as it required a request directed to the journal according to the MAH).

According to the Nix-TB exclusion criteria, patients should not have been pretreated with bedaquiline and/or linezolid. Detailed results for prior TB medications received can be found in Table 4.3.

Table 4.3. Prior TB medications in the ITT Nix-TB study population [a]

Medication by ATC class (level 4)	Patients, n (%) (N=109)
Any prior TB medication	105 (96.3)
Other drugs for the treatment of TB	105 (96.3)
Fluoroquinolones	103 (94.5)
Thiocarbamide derivatives	83 (76.1)
Drugs for the treatment of leprosy	82 (75.2)
Aminosalicylic acid and derivatives	80 (73.4)
Other aminoglycosides	60 (55.0)
Hydrazides	59 (54.1)
Antibiotics	40 (36.7)
Combinations of penicillins, including beta-lactamase inhibitors	24 (22.0)
Other antibacterials	23 (21.1)
Macrolides	14 (12.8)
Combinations of drugs for the treatment of TB	11 (10.1)
Carbapenems	2 (1.8)
Other plain vitamin preparations	1 (0.9)
Penicillins with extended spectrum	1 (0.9)
Streptomycins	1 (0.9)

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019).
[a] Prior medications: Medications starting and ending before first administration of the trial drug. TB medications: Where the indication for a medication was indicated as extensively drug-resistant or multidrug-resistant on the concomitant medications electronic case report form and confirmed by the TB Alliance.
Abbreviations: ATC=Anatomical Therapeutic Chemical; TB=tuberculosis.

Data on drug resistance history, as extracted from the electronic case report form according to the CSR, indicate that data were available with differing extent for the following TB treatments: amikacin, capreomycin, clarithromycin, ethambutol, ethionamide, isoniazid, kanamycin, levofloxacin, moxifloxacin, ofloxacin, pyrazinamide, rifampicin and streptomycin. As expected according to the inclusion criteria, all patients (109/109) were found to be resistant to isoniazid and rifampicin. Resistance to fluoroquinolones was also found, in particular for ofloxacin (information available for 106 patients, of whom 84 were resistant). Missing data were more important for levofloxacin and moxifloxacin (information available for <50% of the patients, so details are not given here). Regarding resistance to kanamycin, information is available for 76/109 patients, of whom 52 were found to be resistant. For other TB treatments, missing data are too substantial so the details are not given here.

4.3 Risk of bias

Given the noncomparative design of Nix-TB, use of the Risk of Bias tool or ROBINS-I tool was not considered applicable by the authoring team without substantial adaptations. However, the following methodological limitations were identified:

- Although analyses were conducted for the mITT cohort rather than the strict ITT population, no major changes in results for efficacy and safety measures because of selected missing values are foreseen by the authoring team. Deviations from the intended intervention are considered in line with what is expected in usual practice (only two patients were excluded from the mITT analysis). However, given the number of missing values for the EQ-5D analysis (101 patients evaluable at the end of treatment), the risk of underestimation or overestimation of the real value is considered critical for this patient-reported outcome;
- Given the open-label design, safety analyses and patients-reported outcomes are associated with a critical bias in the measurement of outcomes. As most of the efficacy analyses are laboratory findings, the authoring team considered that the efficacy measures have not been substantially influenced by knowledge of the intervention received;
- The statistical analysis plan in this trial, which was initially designed as exploratory, is not very detailed. The timing of the analyses was also significantly impacted by the early cessation of inclusion. As only interim data are available, final analyses at 24 months after the end of treatment

are partly (efficacy/safety outcomes) or completely (EQ-5D) missing. Consequently, the bias in selection of the reported results is considered critical for all outcomes in the trial;

- In addition, two limitations that might overestimate the effect size were identified:
  - A major limitation of noncomparative studies is that it is impossible to know the contribution of the treatment effect and the patient characteristics, including prior TB treatments received, to the endpoint value. A particular favourable endpoint value could be confounded by initial good patient condition, with no possibility of detecting this confounding without a control group. As a result, it is always difficult to estimate whether the results observed are related to the intervention itself or to the patient characteristics;
  - Consecutive enrolment in the trial was not explicitly mentioned in the study protocol. Consequently, selection of participants cannot be excluded.

For all these reasons, the authoring team considers that the Nix-TB study may not be reliable for determining the true therapeutic effect of pretomanid on the outcomes listed in the project plan.

4.4 External validity

The population included in the Nix-TB study and the intervention are in line with the population and intervention defined in the PICO (Section 2).

As Nix-TB is a noncomparative trial, direct comparative data versus the comparators listed in the PICO are not available. In addition, the MAH did not submit indirect comparisons based on the SLR performed (Section 3.1).

Most of the outcomes listed in the project plan are available in the study report, except for cure and treatment success (Table 4.4).

Table 4.4. Outcomes listed in the project plan

Outcomes listed in the project plan	Available in the Nix-TB study report
Proportion of subjects with sputum culture (± smear microscopy) conversion to negative status and time to culture conversion (± smear microscopy) to negative status	Yes: the proportion of patients with negative culture status at 6 months after the end of therapy who had not already been classified as having an unfavourable outcome and whose last positive culture result was followed by at least two negative culture results (primary endpoint). Time to culture conversion to negative status is also available.
Cure (according to the WHO definition [5] [a] or other clinically relevant definition)	No
Treatment failure including bacteriological/clinical failure and relapse (according to the WHO definition [5] or other clinically relevant definition)	Yes
Treatment completed (according to the WHO [5] definition or other clinically relevant definition)	Yes
Treatment success (includes cure and treatment completed)	No
Mortality	Yes
Health-related QoL	Yes (measured using the EQ-5D questionnaire)
Safety, including serious and treatment-related AEs	Yes

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019)..
[a] According to WHO, cure is defined as treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Abbreviations: AE=adverse event; EQ-5D=European Quality of Life-5 dimensions; QoL=quality of life; TB=tuberculosis; WHO=World Health Organization.

4.5 Results for clinical effectiveness and safety

4.5.1 Primary endpoint: patient status at 6 months after the end of treatment (mITT analysis)

Two patients were excluded from the primary mITT analysis: one was lost to follow-up or withdrew during follow-up and the other died from a non-TB cause. Both patients had culture-negative status when last seen and had not been already classified as having an unfavourable outcome. The mITT population comprises 107 patients.

At the last available cutoff (29th March 2019), a favourable outcome was observed for 98/107 patients (92%, 95% CI 85%–96%) and an unfavourable outcome for the other nine (8%). The main reason for unfavourable status at 6 months after the end of treatment was death. In one case, causality with respect to treatment cannot be ruled out (acute haemorrhagic pancreatitis). The other five deaths that occurred during the treatment period are not indicative of regimen causality according to the EPAR (Section 4.5.3).

Two relapses were reported after the end of treatment. For one relapse case, the isolate at failure was fully susceptible to all three drugs. For the other relapse case, the minimum inhibitory concentration for the trial drugs was 0.12 µg/mL for pretomanid and 0.5 µg/mL for linezolid at both baseline and 3-month follow-up, and 0.5 µg/mL for bedaquiline at baseline, which increased to 4.0 µg/mL at 3-month follow-up.

The remaining unfavourable outcomes were related to withdrawal from the study: one case related to withdrawal of consent and two related to relapses. Of note, one of the patients who experienced a relapse eventually died from gangrene and sepsis. Table 4.5 presents detailed results.

Table 4.5. Primary endpoint: patient status at 6 months after the end of treatment (mITT analysis) in the Nix-TB study

Patient status at 6 months after the end of treatment	mITT analysis	
	Cutoff 29th June 2018 (*N*=80)	**Cutoff 29th March 2019 (*N*=107)**
Favourable, *n* (%) [95% confidence interval]	72 (90) [81–96]	98 (92) [85–96]
Unfavourable, *n* (%) [a]	8 (10)	9 (8)
During treatment		
Death (not violent or accidental)	6	6
Lost to follow-up	0	0
Withdrew (not for failure)	0	1 [b]
Retreatment for TB	0	0
Treatment failure (culture confirmed)	0	0
After treatment		
Withdrew; never had culture-negative status	0	0
Never had culture-negative status by 6 months after treatment	0	0
Withdrew; relapse	1	1
Withdrew; relapse (not confirmed by gene sequencing)	1	1
Relapse at 6 months after treatment	0	0
Death (tuberculosis-related)	0	0

Source: Clinical study reports dated 19th October 2018 (cutoff 29th June 2018) and 29th October 2019 (cutoff 29th March 2019).
[a] No confidence interval is available for the proportion of patients with unfavourable status
[b] Withdrawal of informed consent.
Abbreviations: CI=confidence interval; mITT=modified intention to treat.

Subgroup analysis (mITT)

Results by TB status (XDR-TB or TI/NR MDR-TB)
Results by TB status were consistent with results observed in the mITT population: 63/70 patients (90%, 95% CI 80%–96%) with XDR-TB and 35/37 patients (95%, 95% CI 82%–99%) with TI/NR MDR-TB had a favourable outcome at 6 months after the end of treatment (mITT analysis). Regarding the reasons for unfavourable status, most deaths (not violent or accidental) were reported for patients with XDR-TB (5/6 deaths). One relapse was reported in a patient with TI/NR MDR-TB and one in a patient with XDR-TB (both patients withdrew from the study).

Results by HIV status at enrolment
Results by HIV status were consistent with results observed in the mITT population: 50/55 patients (91%, 95% CI 80%–97%) with HIV-positive status and 48/52 patients (92%, 95% CI 81%–98%) had a favourable outcome at 6 months after the end of treatment.

Results by linezolid dosing schedule
Results by linezolid dosing schedule at enrolment were consistent with results observed in the mITT population: 59/63 patients (94%, 95% CI 85%–98%) taking 1200 mg QD and 39/44 patients (89%, 95% CI 75%–96%) taking 600 mg BID had a favourable outcome at 6 months after the end of treatment.

Sensitivity analyses

The sensitivity analyses for the ITT population and patients with a positive baseline culture were consistent with the primary analysis for the mITT cohort.

- ITT population: At 6 months after the end of treatment, 98/109 patients (90%, 95% CI 83%–95%) had a favourable outcome and 11 (10%) had an unfavourable outcome, including seven deaths, one patient with withdrawal of consent, two relapses during follow-up (after treatment) and one patient lost to follow-up. The additional death versus the mITT analysis was from an unknown cause during follow-up and was not considered by the investigators to be TB- or drug-related;
- Excluding patients with a negative baseline culture: Among the 93 patients with a positive baseline culture, 82 (90%, 95% CI 82%–95%) had a favourable outcome at 6 months after the end of treatment.

Table 4.6. Primary endpoint: patient status at 6 months after the end of treatment (sensitivity analysis) in the Nix-TB study

Patient status at 6 months after the end of treatment	ITT population (*N*=109)	Patients with positive culture at baseline (*N*=93)
Favourable, ***n*** **(%) [95% confidence interval]**	98 (90) [83–95]	82 (90) [82–95]
Unfavourable, *n* (%) [a]	11 (10)	11 (10)

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019).
[a] No confidence interval is available for the proportion of patients with unfavourable status.
Abbreviations: ITT=intention to treat.

4.5.2 *Secondary endpoints*

Results for secondary endpoints are presented for the mITT population unless explicitly stated otherwise.

Incidence of bacteriological failure or relapse at 24 months after the end of treatment

Three cases of relapse were observed at this cutoff date. The relapses were reported during the 6-month follow-up (see above) and 15 months after the end of treatment. Information on the TB treatments received after relapse is available in the appendices of the CSR. The two patients who relapsed during the 6-month follow-up received the following agents for treatment of their relapse:

- Bedaquiline, linezolid, isoniazid, clofazimine, terizidone, PAS, pyrazinamide, ethambutol, pyridoxine and levofloxacin;
- Bedaquiline, linezolid, ethambutol, terizidone, PAS, clofazimine, ertapenem and amoxicillin/clavulanate;
- The patient who relapsed at 15 months after the end of treatment received the following agents: bedaquiline, delamanid, linezolid, clofazimine, PAS, pyrazinamide, moxifloxacin and rifabutin.

It is underlined that only 44/109 patients (40.4%) have completed the 24-month follow-up visit and that final results are not expected until Q2 2021.

Time to sputum culture conversion to negative status

A total of 91 patients in the mITT population had a positive culture at baseline (requested for this analysis) and 87/91 patients had a conversion to negative status at 6 months after the end of treatment. The median time to a negative culture was of 6.0 weeks (IQR 4.0–8.1).

Culture conversion status at 4, 6, 8, 12 and 16 weeks (results only available for ITT cohort)

The number of patients with culture conversion to negative status increased at each time point. At week 16, 93/109 patients were assessable for culture conversion. All patients but one were negative by week 16. This patient with a positive culture at week 16 had the trial drug treatment extended by 3 months as allowed in the protocol. At the end of treatment, all living patients showed culture conversion to negative status.

Change from baseline in the TB Symptom Profile score

Patients evaluated their own TB symptoms using the TB Symptom Profile questionnaire (Section 4.1). No information on the validity and reliability of this questionnaire is available in the submission dossier, so it was not possible to assess the validity of this scale. Furthermore, the total score was defined by the number of TB symptoms, so the interpretation in terms of clinical relevance is not straightforward. For all of these reasons and because of the bias and limitations identified in the Nix-TB study (Section 4.3), this outcome is not detailed in this report.

Health-related QoL

Results for each item of the EQ-5D questionnaire, as summarised in two categories (no problems vs. problems), are reported in the CSR. The EQ-5D is not a disease-specific questionnaire and is only useful for utility measurement. Furthermore, the timing of data collection (at baseline, 8 weeks and the end of treatment) was not justified in the study protocol or in the submission dossier. For all these reasons, and because of the bias and limitations identified in the Nix-TB study (Section 4.3), data from the EQ-5D-5L questionnaire were not suitable for this assessment. However, as QoL was included as an outcome in the PICO, detailed results are reported in Appendix APPENDIX 2: Quality of life data.

4.5.3 Adverse events

Every patient experienced at least one TEAE in the Nix-TB study, as detailed in Table 4.7**Fout! Verwijzingsbron niet gevonden.**.

Table 4.7. Overview of TEAEs in the Nix-TB study

Adverse events	Patients, *n* (%)
Any AE	109 (100.0)
Serious AEs	19 (17.4)
Study drug-related AEs	108 (99.1)
Subjects with at least one serious drug-related TEAE	10 (9.2)
Grade 3 and/or 4 TEAEs	62 (56.9)
TEAEs of special interest	107 (98.2)
TEAEs leading to discontinuation of one or all drugs in the trial regimen [a]	30 (27.5)
TEAEs leading to discontinuation of linezolid	30 (27.5)
TEAEs leading to discontinuation of BPal	2 (1.8)
TEAEs leading to death	6 (5.5)

Source: Clinical study report dated 29th October 2019 (cutoff 29th March 2019).
[a] According to investigator judgment.
Abbreviations: AE=adverse event; BPal=bedaquiline plus pretomanid plus linezolid; TEAE=treatment-emergent adverse event.

The most frequently reported TEAEs (≥20%) were peripheral sensory neuropathy/peripheral neuropathy (67/109, 78%), anaemia (40/109, 37%), nausea (40/109, 37%), vomiting (37/109, 34%), headache (30/109, 27%), dermatitis acneiform (26/109, 24%), dyspepsia (26/109, 24%) and decreased appetite (24/109, 22%).

It should be noted that with the 600 mg BID linezolid regimen, the term peripheral sensory neuropathy was less frequently reported, in contrast to the term anaemia. Increased transaminase levels were less frequently reported with the 1200 mg QD linezolid dosing. However, according to the EPAR, overall the safety profile did not differ markedly by QD or BID dosing.

The incidence of TEAEs by severity and relationship by system organ class and preferred term is detailed in the submission dossier (Table 25).

Serious adverse events

The most frequently reported SAEs were pneumonia (3/109, 2.8%), pulmonary TB (2/109, 1.8%), sepsis (2/109, 1.8%) and anaemia (2/109, 1.8%).

With regard to HIV status, the proportion of patients who had a serious TEAE was similar in the HIV-positive and HIV-negative groups (16.1% vs. 18.9%). With regard to linezolid administration, the proportion of patients who had a serious TEAE was greater in the 600 mg BID group than in the 1200 mg QD group (29.5% vs. 9.2%).

Appendix APPENDIX 3: additional safety data has further details on the SAEs.

Deaths

A total of eight deaths were reported in the study, of which six occurred during the treatment period (considered as a TEAE) and two during the follow-up period. Of note, one patient who died during the follow-up period had previously relapsed and experienced an unfavourable outcome due to the relapse. In one case, causality with respect to treatment cannot be ruled out (acute haemorrhagic pancreatitis). The other five deaths that occurred during the treatment period are not indicative of regimen causality according to the EPAR and the deaths were definitely or possibly related to TB. Appendix APPENDIX 3: additional safety data lists further details on causes of death.

AEs leading to discontinuation/interruption/dose reduction

Discontinuation/interruption of BPal regimen
Over the course of the trial, 7/109 patients (6.4%) discontinued the BPal regimen, of whom six patients (5.5%) died during the treatment period and one patient (0.9%) withdrew consent. At least one interruption of the BPal regimen was reported for 25/109 patients (23%), primarily because of AEs (18.3% of the patients).

Discontinuation/interruption/dose reduction of linezolid:
Over the course of the trial, 35/109 patients (32%) discontinued linezolid treatment, mainly because of AEs (27.5% of the patients), primarily peripheral sensory neuropathy (22.0%). A larger proportion of patients prematurely discontinued linezolid treatment in the 600 mg BID group than in the 1200 mg QD group (38.6% vs. 27.7%).

At least one linezolid dose interruption was reported for 53/109 patients (48.6%), primarily because of AEs (46%). The most frequent AEs leading to interruption of linezolid were peripheral sensory neuropathy (24.8% of the patients) and anaemia (14.7%). Overall, 37/109 patients (34%) received an uninterrupted 26 weeks of linezolid treatment at any dose.

For subjects experiencing suspected drug-related toxicities due to linezolid, the daily dose of linezolid could be reduced (with a stepdown approach from 1200 mg QD to 600 mg and then 300 mg QD). At least one linezolid dose reduction was reported for 69/109 patients (63.3%) primarily because of AEs (39.4% of the patients), most frequently peripheral sensory neuropathy (24.8%) or anaemia (11.9%). According to the EPAR, the incidence of the onset of peripheral neuropathy events increased steadily over time (5% ≤2 weeks, 21% >2 weeks to 8 weeks and 65% >8 weeks to 26 weeks after the start of treatment). The rate of dose interruption/reduction due to myelosuppression (in practice, anaemia) was greatest from week 4 to week 12. As a consequence of (mainly) these two major toxicities (neuropathy and anaemia), the rate of linezolid dose reductions/interruptions increased steadily from week 4 to week 20.

AEs of special interest (according to the pretomanid SmPC)

Increased transaminases
In the Nix-TB trial in which 109 patients were treated with BPal, 21% experienced increased transaminases (very common). Except for one patient who died from pneumonia and sepsis, all patients who experienced increased transaminases were able to continue or resume therapy after interruption and complete the full course of treatment.

Peripheral neuropathy
Peripheral neuropathy is a known AE related to linezolid. In Nix-TB, 81% of patients experienced peripheral neuropathy (very common). Most of these AEs occurred after 8 weeks of treatment and resulted in dosing interruption, dose reduction or discontinuation of linezolid. No AEs related to peripheral neuropathy led to discontinuation of the entire study regimen.

Optic neuropathy
Optic neuropathy is a known AE related to linezolid. Two patients (2%, common) in Nix-TB developed optic neuropathy, both after 16 weeks of treatment. Both were serious, confirmed via retinal examination as optic neuropathy/neuritis, and resulted in discontinuation of linezolid; both AEs subsequently resolved.

Myelosuppression
Myelosuppression is a known AE related to linezolid. In Nix-TB, 37% of patients experienced anaemia (very common) as the most common AE of haematopoietic cytopenia attributed to linezolid. The majority of cytopenias began after 2 weeks of treatment. Overall, three patients experienced cytopenias that were considered serious: neutropenia in one patient and anaemia in two patients. All three SAEs resulted in interruption of either linezolid or BPal, and all subsequently resolved.

QT interval prolongation
QT prolongation is a known AE related to bedaquiline. Bedaquiline in combination with pretomanid appears to result in higher QT prolongation than expected with bedaquiline alone. However, the impact of pretomanid has not been fully characterised. In the Nix-TB trial, six patients (5.5%, common)

experienced QT prolongation. In the entire Nix-TB trial, no patient was reported to have a treatment-emergent QT interval corrected for heart rate using Fridericia's formula (QTcF) exceeding 480 ms. One subject was reported to have a change from baseline in QTcF exceeding 60 ms.

Special populations (according to the pretomanid SmPC)

Elderly population (≥65 years of age)
There are limited clinical data on the use of pretomanid in elderly patients. Hence, the safety and efficacy of pretomanid in elderly patients have not been established.

Hepatic impairment
The safety and efficacy of pretomanid in populations with hepatic impairment have not been established.

Renal impairment
The safety and efficacy of pretomanid in populations with renal impairment have not been established. No data are available. Use in patients with renal impairment is not recommended.

Paediatric population
The safety and efficacy of pretomanid in children and adolescents have not yet been established.

5 PATIENT INVOLVEMENT

Unfortunately, no patient organisations contributed to the open call for patient input published on the EUnetHTA website from 20th January 2020 to 23rd March 2020.

However, HAS contacted and interviewed the president of the French patient association ACTUME. The objective was to collect feedback on QoL and the current standard of care from a patient perspective, without being representative of all TB patient associations. The president of ACTUME was himself diagnosed with TB in 2001. He founded the association in 2002 with the initial objective of providing information and raising awareness among students and migrants about TB, in partnership with a preventive medicine strategy in particular.

During the interview, the president of ACTUME underlined that information and prevention campaigns are important so that people know more about the disease and that it can be treated. Many TB deaths can be attributed to late diagnosis and treatment, particularly in countries where TB is a shameful disease and where the entire family is stigmatised. As TB in its most common form (pulmonary TB, localised to the lungs) is transmitted via airborne droplets of saliva, information on how it is transmitted is part of any prevention measures.

It was also underlined that in its pulmonary form, the most common symptoms of TB are night sweats, coughing and fatigue. People with TB can live relatively well with the disease, which can further delay treatment. Concerning the disease and symptoms, there are no specific features related to having XDR-TB (as compared to drug-sensitive or MDR-TB).

Effective treatment of TB requires strict adherence to prescribed treatments, with an obligation to take the tablets in front of the doctor. Sometimes this means taking many tablets at the same time every day for several weeks. According to the president of ACTUME, patients expect new therapies to facilitate treatment adherence and completion. This includes having treatments that are well tolerated, ideally for shorter durations, and easier to take (e.g., reducing the number of tablets for oral treatment). It is also important that health care professionals closely monitor patients for the first 3 months of treatment, especially for the management of adverse events.

The minutes of the interview can be found in Appendix APPENDIX 4: PATIENT INVOLVEMENT.

6 DISCUSSION AND CONCLUSION

This aim of this assessment was to compare the clinical effectiveness and safety of pretomanid in combination with bedaquiline and linezolid (BPal regimen) in adult patients with pulmonary XDR-TB or TI/NR MDR-TB with relevant comparators according to the scope defined in the project plan.

Pretomanid is an antimycobacterial drug and a member of the nitroimidazooxazine class (whereas delamanid is a member of the nitroimidazooxazole class).

Pretomanid is indicated in combination with two agents from group A (bedaquiline and linezolid; BPal regimen) in adults, for the treatment of XDR-TB or TI/NR MDR-TB. This is the first approved utilisation of pretomanid in the treatment of TB.

Pretomanid should be taken with food, in combination with bedaquiline (400 mg QD for 2 weeks followed by 200 mg three times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1200 mg QD orally for up to 26 weeks). Use of the antiretroviral efavirenz is contraindicated with the BPal regimen to avoid drug–drug interactions with bedaquiline. However, this contraindication might have a limited impact on use of the BPal regimen in HIV-positive patients, as efavirenz tends to be used less and less in Europe (can be replaced by integrase inhibitors).

The evidence for this assessment submitted by the MAH mostly relies on a single noncomparative phase III study conducted in South Africa and originally conceived as an exploratory trial by the investigators: the Nix-TB study [6]. Data from this trial were mainly extracted from an interim analysis performed at a cutoff date of 29th March 2019. At this date, 99/109 patients (90.8%) had completed the 6-month follow-up period. The remaining patients had discontinued the trial before evaluation of the primary endpoint. At the latest cutoff date, 44/109 patients (40.4%) had completed the 24-month follow-up visit.

Several studies conducted in similar populations treated with alternatives therapies were identified through a systematic literature review (SLR) performed by the MAH. However, this study pool with comparators was not used by the MAH to conduct indirect comparisons. It is also underlined that the SLR was generally too specific in the choice of terms and due to the non-use of appropriate descriptors and search tools, and that it lacked sensitivity with a real risk that relevant studies were not found. This is not expected to impact the assessment as no comparative data were submitted by the MAH, but information retrieval for comparators might not be appropriate for future indirect comparisons that could be performed by national agencies.

For all these reasons, conclusions on the relative assessment of pretomanid for this rapid REA are limited.

6.1 Main efficacy data

A total of 109 adult patients were included in the Nix-trial to receive the BPal regimen for 6 months (could be extended to 9 months if needed). The mITT population was 107 after the exclusion of two patients. The study originally planned to enrol a total of up to 200 patients. However, to facilitate enrolment in the ZeNix study, enrolment in Nix-TB was stopped after the inclusion of 109 patients.

The treatment duration was 26 weeks according to the study protocol. A total of 2/109 patient had extension of treatment duration for an additional 3 months (up to 9 months), while 16/109 patients (14.7%) received the 1200-mg total daily dose of linezolid without interruption over the full 26 weeks of therapy. For subjects experiencing suspected drug-related toxicities due to linezolid, the daily dose of linezolid could be reduced (with a stepdown approach from 1200 mg QD to 600 mg and then 300 mg QD). A total of 37/109 patients (33.9%) received a full uninterrupted 26 weeks of linezolid at any dose.

Most patients had XDR-TB (65%). Approximately 96% of the patients had received at least one prior TB therapy and the median number of prior TB treatments was seven. Prior use of fluoroquinolones was reported for 103 patients (94.5%), prior use of thiocarbamide derivatives (the group that includes ethionamide and prothionamide) for 83 patients (76.1%) and prior use of drugs for treatment of leprosy (covering drugs such as clofazimine also used for TB treatment) for 82 patients (75.2%). In accordance with the inclusion criteria, all patients were resistant to isoniazid and rifampicin and many patients were

also resistant to fluoroquinolone, in particular to ofloxacin (84 of the 106 patients evaluable). Half of the patients were co-infected with HIV.

The primary endpoint was the incidence of treatment failure, a composite outcome of clinical failure, bacteriologic relapse or bacteriologic failure (reinfection) through to 6 months after the end of treatment. Favourable status was defined as patients with a negative culture status at 6 months after the end of therapy who had not already been classified as having an unfavourable outcome and whose last positive culture result was followed by at least two negative culture results. At 6 months after the end of the treatment, a high rate of favourable status (primary endpoint) was observed: 98/107 patients (92%, 95% CI 85%–96%) in the mITT analysis and 98/109 patients (90%, 95% CI 83%–95%) in the ITT analysis. Subgroup analyses by TB status (XDR-TB vs. TI/NR MDR-TB) were consistent with results for the entire population. Among the cases considered as unfavourable outcomes in the mITT analysis, two relapses, six deaths and one withdrawal of consent were reported.

The incidence of relapse or reinfection at 24 months after the end of the treatment was assessed as a secondary endpoint. However, for the interim analysis only 44/109 patients (40.4%) had completed the 24-month follow-up visit and were evaluable for this outcome. Among these 44 patients, one experienced a relapse 15 months after the end of treatment. Final results from the Nix-TB trial are expected in Q2 2021.

The number of patients with culture conversion to negative status increased at each time point from baseline to the end of treatment. All but one patient assessable for culture conversion (93/109) were negative by week 16. For this patient, BPal treatment was extended by 3 months in accordance with the study protocol. At the end of treatment, all living patients had culture conversion to negative status. The median time to negative culture was 6.0 weeks (IQR 4.0–8.1).

Data on health-related QoL were collected using the EQ-5D-5L questionnaire at baseline, 8 weeks after the start of treatment and at the end of treatment, and are summarised by category (no problems vs. problems) for each item in the CSR. Owing to the bias and limitations identified in the Nix-TB study and additional limits specific to QoL (Section 4.5.2), these data were not considered suitable for this REA. No disease-specific QoL data were collected in the study.

6.2 Main safety data

Every patient included in the Nix-TB study experienced at least one TEAE, mainly sensory neuropathy or peripheral neuropathy (67/109, 78%) and anaemia (40/109, 37%). SAEs were reported for 19/109 patients (17%). A total of eight deaths were reported in the study, six of which occurred during the treatment period and two during the follow-up period. Of note, one patient who died during the follow-up period had previously relapsed and had an unfavourable outcome due to the relapse. In one case, causality with respect to treatment cannot be ruled out (acute haemorrhagic pancreatitis). The other five deaths that occurred during the treatment period are not indicative of regimen causality according to the EPAR. Peripheral neuropathy, optic neuropathy and myelosuppression are known adverse reactions associated with linezolid. Over the course of the trial, 35/109 patients (32%) discontinued linezolid treatment, mainly because of AEs (27.5% of the patients), primarily peripheral sensory neuropathy (22.0% of the patients). A dose interruption of linezolid because of AEs was reported for 46% of the patients and a dose reduction of linezolid because of AEs was reported for 40%, mostly because of peripheral sensory neuropathy or anaemia.

6.3 Strength and limitations of the evidence

Results from the single noncomparative trial suggest a high rate of favourable outcomes (92%, 95% CI 85%–96%) at 6 months after the end of 6-month treatment with the BPal oral regimen in a population known to be very difficult to treat (MDR-TB and XDR-TB).

However, the results from this study have several limitations:

- Direct comparative evidence versus the current standard of care is lacking and no indirect comparative data were generated by the MAH to try to address this issue. As the care pathway recently evolved after an update of the WHO guidelines [4], it is difficult to put the results observed in the Nix-TB trial into perspective. The paucity of efficacy data with other comparators is acknowledged by the authoring team. On an indicative basis, recent publications reported that favourable outcomes for XDR-TB patients (cured/treatment completed) ranged from an average of 40% to 70%, depending on the treatment regimen and patient characteristics [6, 7]. A cohort of similar patients treated with bedaquiline and linezolid in South Africa is mentioned in the submission dossier (Section 2.4, page 41). According to the MAH, data from this cohort, including an indirect comparison with data from the Nix-TB trial, should be published soon. To favour the publication of data for this cohort, the MAH did not submit these data for this joint assessment, which is highly regrettable considering that it might be a very appropriate external control from a HTA perspective;
- From a methodological perspective, the authoring team considers that the Nix-TB study may not be reliable in determining the true therapeutic effect of pretomanid for the outcomes listed in the project plan (see Section 4.3 for details);
- This study was performed in only three centres, all located in South Africa. Although the authoring team acknowledges that the feasibility of a study in XDR-TB or TI/NR MDR-TB in Europe might be more complex because of lower disease prevalence, results from the Nix-TB trial may not be fully generalisable to the European population. The low sample size (n=109) due to early cessation of enrolment further limits the evaluation of data generalisability. It is noted that coinfection with HIV was reported for half of the patients in Nix-TB, whereas HIV prevalence among incident TB cases in Europe was 12% in 2016 [1];
- Pretomanid was evaluated in patients who were not pretreated with bedaquiline and linezolid, in accordance with the Nix-TB inclusion/exclusion criteria. No data are available for the BPal regimen in patients pretreated with bedaquiline and linezolid, which are now recommended for the treatment of MDR-TB (group A agents according to WHO guidelines on drug-resistant TB treatment) [4];
- Patients could be enrolled on the basis of a positive culture within 3 months before screening or, for XDR-TB patients only, molecular testing within 3 months before or at screening. In the study, a total of 16/109 patients (14.6%) did not have a positive culture at baseline. According to the clinical expert, these patients could possibly have already responded to the preceding therapy and the effect observed in the study might not be attributable to the BPal regimen alone in these 16 cases;
- Exact assessment of the resistance profile of patients is limited by the inclusion criteria. Resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable could have been verified by the investigators at screening instead of documented at any time before screening according to the protocol. Therefore, the extent of the data available for each TB treatment differed (available for <50% of the patients for most TB treatments except rifampicin, isoniazid, kanamycin and ofloxacin). In addition, TI/NR status for MDR-TB treatment was based on a declaration by the investigators and is therefore subject to assessment bias;
- Long-term evidence of the efficacy is missing as only an interim analysis was provided. Only 40% of the patients completed the 24-month follow-up visit and final results from Nix-TB are not expected until Q2 2021. It should also be underlined that cure, which is strictly defined by WHO guidelines [5], was not an endpoint specified in Nix-TB, so it was not possible to assess this aspect of the efficacy of the BPal regimen;
- The safety is considered acceptable according to the EPAR. However, the optimal dosage of linezolid (which is associated with an unfavourable safety profile, with risks of peripheral neuropathy and myelosuppression notably) in this combination is still unknown. In Nix-TB this drug was given at a high dose (1200 mg per day) throughout the 26 weeks of therapy, but a lower dosage could be used, depending on results from the ongoing ZeNix study exploring four different linezolid dosages;

- Finally, the president of the French patient organisation ACTUME underlined that patients expect new therapies to facilitate treatment adherence and completion. This includes having treatments that are well tolerated, ideally for shorter durations, and easier to take (e.g., with as small a number of tablets to be taken as possible). Although this fully oral regimen given over a relatively short duration (6 months for 108/109 patients and extended to 9 months for 2 patients in Nix-TB) is expected to have a positive impact on QoL and compliance, no robust data are available to confirm this hypothesis. Indeed, health-related QoL was not assessed via a disease-specific questionnaire and data from the EQ-5D-5L utility questionnaire were not suitable for this assessment (Section 4.5.2).

7 REFERENCES

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APPENDIX 1: GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

Table A1. Overview of guidelines used for this assessment

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
World Health Organization [WHO] consolidated guidelines on drug-resistant tuberculosis treatment	2019	Applicable worldwide	Treatments recommended for use in longer MDR-TB regimens are currently classified into three groups (A, B and C). MDR-TB longer regimens should be composed in accordance with WHO guidelines.	Not applicable. The WHO doesn't give statements about evidence after each recommendation.
World Health Organization [WHO] consolidated guidelines on drug-susceptible tuberculosis and patient care	2017	Applicable worldwide	For DS-TB, a 6-month rifampicin-based regimen is recommended.	Not applicable. The WHO doesn't give statements about evidence after each recommendation.
WHO EU algorithm for laboratory diagnosis and treatment-monitoring of pulmonary tuberculosis and drug-resistant tuberculosis using state-of-the-art rapid molecular diagnostic technologies	2017	Europe	"Most techniques have already been introduced to the majority of countries of the Region, particularly in the high MDR-TB burden countries. However, to yield the maximum benefit of each technique, the appropriate and accurately timed sequence of different laboratory tests and correct interpretation and communication of results between laboratories and clinicians need to be ensured."	Not applicable. The WHO doesn't give statements about evidence after each recommendation.

Source: Submission dossier.
Abbreviations: DS=Drug-susceptible; EU=European Union; MDR-TB= Multidrug-resistant TB; TB=Tuberculosis; WHO=World Health Organization.

APPENDIX 2: QUALITY OF LIFE DATA

Table A2. Patient Self-reported Health Status (collected via EQ-5D-5L questionnaire)

Level		BPal regimen N = 109		
		Baseline	Week 8	End of treatment
		N with data[a] = 109	N with data = 100	N with data = 101
Anxiety/Depression	No problems	72 (66%)	84 (84%)	95 (94%)
	Problems	37 (34%)	16 (16%)	6 (6%)
Mobility	No problems	98 (90%)	97 (97%)	86 (85%)
	Problems	11 (10%)	3 (3%)	15 (15%)
Pain/Discomfort	No problems	64 (59%)	88 (88%)	81 (80%)
	Problems	45 (41%)	12 (12%)	20 (20%)
Self-care	No problems	106 (97%)	100 (100%)	101 (100%)
	Problems	3 (3%)	0	0
Usual activities	No problems	99 (91%)	98 (98%)	99 (98%)
	Problems	10 (9%)	2 (2%)	2 (2%)
VAS score	Mean	82	88	92
	Median	88	90	95
	IQR	75 to 95	80 to 100	90 to 100
	Range	0 to 100	40 to 100	50 to 100

Source: CSR dated 29th October 2019 (cut-off 29 March 2019).
[a]One patient had a missing VAS score at every time point but filled in all other questions. Therefore, the N with data is one less for the VAS than all other categories.
Abbreviations: BPaL=Bedaquiline plus pretomanid plus linezolid; EQ-5D-5L=European Quality of Life-5 dimensions-5 levels.

APPENDIX 3: ADDITIONAL SAFETY DATA

Table A3.Serious TEAEs by SOC/Fatality/Relationship

Subjects with at least one serious TEAE	19 (17.4)	Fatal	Severity/R
Infections and infestations	7 (6.4)		
Pneumonia	3 (2.8)	(2, both also sepsis)	Severe/NR Life threatening/NR Life threatening /Unlikely R
Tuberculosis (pulmonary/disseminated)	4 (3.7)	2	Life threatening /NR
Sepsis/ septic shock	3 (2.8)	2	Life threatening /NR Life threatening /NR Life threatening / Unlikely R
Disseminated tuberculosis	1 (0.9)		Life threatening /NR
Tuberculoma of central nervous system	1 (0.9)		Severe/NR
Gastrointestinal disorders			
Abdominal pain upper	5 (4.6)		Severe/Possibly R
Haematemesis	1 (0.9)		Severe/Unlikely R
Pancreatitis	1 (0.9)		Severe/Possibly R
Pancreatitis haemorrhagic	1 (0.9)	(1, also multiorgan failure)	Life threatening/Possibly R
Upper gastrointestinal haemorrhage	1 (0.9)]	1	Life threatening/Possibly R
Metabolism and nutrition disorders	4 (3.7)		
Hypoglycaemia	2 (1.8)		Life threatening/NR Life threatening/Possibly R
Abnormal loss of weight	1 (0.9)		Severe/NR
Lactic acidosis	1 (0.9)		Life threatening/Probably R
Nervous system disorders	4 (3.7)		
Generalised tonic-clonic seizure	1 (0.9)		Severe/Unlikely R
Optic neuritis	1 (0.9)		Life threatening/Probably R
Seizure	1 (0.9)		Severe/NR
Syncope	1 (0.9)		Severe/NR
Blood and lymphatic system disorders	3 (2.8)		
Anaemia	2 (1.8)		Life threatening/Probably R Life threatening/R
Neutropenia	1 (0.9)		Life threatening/Probably R
Respiratory, thoracic, mediastinal disorders	3 (2.8)		
Asthma	1 (0.9)]		Severe/Unlikely R
Dyspnoea	1 (0.9)		Severe/Unlikely R
Haemoptysis	1 (0.9)		Life threatening/NR
Pneumothorax spontaneous	1 (0.9)		Life threatening/NR
Psychiatric disorders	2 (1.8)		
Depression suicidal	1 (0.9)		Life threatening/NR
Generalised anxiety disorder	1 (0.9)		Moderate/Unlikely R
Eye disorders	1 (0.9)		
Optic neuropathy	1 (0.9)		Mild/Probably R
General disorders	1 (0.9)		
Multiple organ failure	1 (0.9)	1	Life threatening/Possibly R
Investigations	1 (0.9)		
Transaminases increased	1 (0.9)		

Source: CSR dated 29th October 2019 (cut-off 29 March 2019); EPAR.
Abbreviations: NR=Not related; R=Related; SOC=System organ class; TEAE=Treatment-emergent adverse event.

Table A4. Death in Nix-TB trial

Subject	Cause of death	Relation to study drugs
During treatment period		
1	Severe (disseminated) tuberculosis	Not related
2	Upper gastrointestinal bleeding	Not related
3	Acute severe worsening of pulmonary tuberculosis	Not related
4	Acute haemorrhagic pancreatitis and multiorgan failure	Possibly related
5	Worsening pneumonia	Not related
6	Septic shock secondary to pneumonia	Not related
During Follow-up		
7	Sepsis secondary to gangrene (peripheral vascular disease)	Occurred more than 1 year after EOT
8	Natural causes	

Source: CSR dated 29th October 2019 (cut-off 29 March 2019); EPAR.
Abbreviations: EOT=End of Treatment

APPENDIX 4: PATIENT INVOLVEMENT

Minutes of the phone interview with president of patients' association ACTUME (conducted on 20th March 2020 by HAS)

1. Information on the patients' association

Name of the association: ACTUME
Contact person: Oumar KANE
Role: President of the association, developed bone tuberculosis in 2001 which was treated by surgery.
Type of association: association created in 2002 in Bordeaux (France) with the initial objective of informing and raising awareness among students and migrants about tuberculosis, in partnership with preventive medicine in particular.

Aims pursued by the association: to inform, educate and advise populations on all aspects of the fight against tuberculosis and endemic diseases (AIDS, malaria...), several projects have been carried out since the creation of the association (loyalty program for tuberculosis patients lost to follow-up, health caravans in Mauritania, training of community health workers on site to improve compliance of tuberculosis patients to take their treatment, awareness campaigns on tuberculosis...).

Ongoing project for 2018-2020: creation of a community pharmacy in the commune of Tekane in Mauritania, with the aim of facilitating access to health care for all by making the community pharmacy a place for guidance, information and exchanges dedicated to the health of the most disadvantaged. A project for the promotion of medicinal plants is associated with it.

2. Impact of disease / health status

- How does the disease (or condition) for which the drug is being developed affect the quality of life of patients and their families?

Patients' quality of life depends on the social structure in which they live. In Africa, tuberculosis is a shameful disease, people tend to hide it. If one person is affected in a family, the whole family is stigmatized. Information and prevention are important actions so that people know more about the disease and know that it can be treated. Many deaths are due to delays in starting treatment. Tuberculosis in its most common form, pulmonary tuberculosis (localized to the lungs), is transmitted through airborne droplets of saliva, information on how it is transmitted is part of prevention measures.

In its pulmonary form, the most common symptoms are night sweats, coughing and fatigue. People with the disease can live relatively well with it, which has consequences for delay in management.

There are other, less common, extra-pulmonary forms that can be very serious, such as tuberculosis of the bones or tuberculosis of the brain.

Concerning the disease and symptoms, there is no specificity related to having XDR-TB.

3. Experience with current therapeutics

- To what extent do patients manage their health with current therapies?

Effective treatment of tuberculosis requires strict adherence to the prescribed treatment, with the obligation to take the tablets in front of the doctor. Sometimes this means taking many tablets at the same time every day for several weeks.

Hospitalization with isolation is necessary until the culture is negative, with subsequent transfer to a rest home.

It is pointed out that explanations are not always given to patients on the reasons for following the treatment scrupulously to the end and on the consequences of not taking the treatment on recovery.

Adherence could be improved through such explanations, especially as treatments are usually long (6 to 9 months) and may involve many tablets to be taken daily (for oral treatments).

Health care professionals should closely monitor the patients for the first three months of treatment, especially for the management of adverse events. The President of the association mentions digestive side effects with some treatments (such as nausea).

In the case of extra-pulmonary tuberculosis, surgical management may be necessary, sequelae may remain after treatment.

- What are patients' expectations for new treatments, especially for patients with XDR-TB?

Patients' expectations are about anything that can improve adherence and completion of treatment. This includes having treatments that are well tolerated, ideally for shorter durations and easier to take (e.g. reducing the number of tablets for oral treatment).

4. Further information

BCG vaccine is no longer mandatory in France. Vulnerable populations, such as migrants living in shelters, can benefit from vaccination and are well identified in France thanks to the departmental committees for respiratory diseases.

APPENDIX 5: EVIDENCE GAPS

Table A5. Recommendations for research

Additional evidence generation needs	
Research question: To compare the clinical effectiveness and safety of pretomanid in the target patient population with relevant comparators. The target patient population and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope (see Project Plan, published on EUnetHTA website).	
Evidence	Evidence gaps identified are mainly related to the absence of comparative data in the scope defined in the Project Plan: • Direct comparative trial of the BPal regimen versus comparators listed in the PICO was not performed by the MAH. • Indirect comparative data were not provided by the MAH but could be generated in national submission dossiers, taking into account the different possible combination regimens and the data available for each one. As stated in EUnetHTA guideline on Comparators & Comparisons: Direct and indirect comparisons, the preferred option for indirect comparison is network meta-analysis (NMA). Because the pivotal trial is a single arm study, a NMA will not be feasible. In this case the authoring team does not advocate for a specific method (other types of indirect comparison should be explored, notably population-adjusted indirect comparison such as MAIC or STC). Acceptability of these evidence gaps will be part of the appraisals that will be perform by each European country, notably taking into consideration medical need and national context. It might involve PLEG request at national level.
Population	Adult patients with pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).
Intervention	Pretomanid is indicated in combination with bedaquiline and linezolid. Posology: The recommended dosage for pretomanid is 200 mg orally (1 tablet of 200 mg), daily, for 26 weeks. 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 (1200 mg daily orally for up to 26 weeks).

Comparator	• Treatments authorised in MDR-TB in association with other tuberculosis medicines:
	  ○ Bedaquiline;
	  ○ Delamanid;
	  ○ Para-amino salicylic acid.
	• Other treatments not authorized in MDR-TB but recommended for use by WHO. It should be considered that the certainty on the effect of these products is moderate or very low according to WHO.
	See Project Plan for further details on the list of medicines recommended for use in longer MDR-TB regimens.

Outcome(s)	• Proportion of subjects with sputum culture (± smear microscopy) conversion to negative status and time to culture conversion (± smear microscopy) to negative status; • Cure (according to WHO definition or other clinically relevant definition) [**Fout! Verwijzingsbron niet gevonden.**]; • Treatment failure including bacteriological/clinical failure and relapse (according to WHO definition* or other clinically relevant definition); • Treatment completed (according to WHO definition* or other clinically relevant definition); • Treatment success (includes cure and treatment completed); • Mortality; • Health-related QoL; • Safety, including serious adverse events (AEs) and treatment-related AEs.
Study design	See Evidence section above.
Ongoing studies	No ongoing studies have been identified.

Source: WHO [**Fout! Verwijzingsbron niet gevonden.**].

[a] Additional outcomes not captured in the PICO may be described in the assessment report as submitted by MAH.

Abbreviations: AE=Adverse event; BPaL= Bedaquiline plus pretomanid plus linezolid; DS=Drug-susceptible; EQ-5D-5L=European Quality of Life-5 dimensions-5 levels; MAIC=Matching-adjusted indirect comparison; MAH=Marketing authorisation holder; MDR-TB=Multidrug-resistant TB; mITT=Modified intention to treat; NMA=Network meta-analysis; PLEG=Post-launch evidence generation; QoL=Quality of life; REA=Relative effectiveness assessment; STC=Simulated treatment comparison; TB=Tuberculosis; TEAE=Treatment-emergent adverse event; WHO=World Health Organization; XDR=Extensively drug-resistant.