PTJA14

Pretomanid

is indicated as part of a combination regimen 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)

Submitted by Mylan

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For agency completion
Date of receipt: 06-05-2020 (initial submission dossier received on 21-04-2020)
V2.0 Amended dossier after formal check of completeness
Identifier: PTJA14

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Abbreviations

aDSM	Active tuberculosis drug-safety monitoring and management
AE:	Adverse Event
AIDS:	Acquired Immune Deficiency Syndrome
AMK:	Amikacin
ATC:	anatomical therapeutic chemical
AUC	Area under curve
B:	Bedaquiline
Bi:	Bilateral
BID	twice daily
BPaL:	treatment regimen consisting of bedaquiline, pretomanid and linezolid
BR:	Baseline Regimen
C:	Clofazimine
CAP:	Capreomycin
CHMP:	Committee for medicinal products for human use
CFU:	Colony forming unit
CI:	confidence interval
CONSORT:	consolidated standards of reporting trials
COPD:	Chronic obstructive pulmonary disease
DM:	Diabetes mellitus
DMD:	Delamanid
DSM:	Diagnostic and Statistical Manual of Mental Disorders
DST:	Drug susceptibility testing
DS-TB:	Drug-susceptible tuberculosis
E:	Ethambutol
EC:	European commission
ECG:	Electrocardiogram
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
ETO:	Ethionamide
FDA	Food and Drug Administration (USA)
FL:	First-line
FLQ:	Fluoroquinolone
GCP	Good Clinical Practice
GDF:	Global drug facility
H:	Isoniazid
HCP:	Healthcare professional
HIV:	Human immunodeficiency virus
HTA:	Health Technology Assessment
HRQoL:	Health-related Quality of Life
ICD:	International Classification of Diseases
ICH:	International Council for Harmonisation
INH:	Isoniazid
ITT:	Intention to Treat
IV:	Intravenous
KAN:	Kanamycin
LPA:	Line probe assay
LTBI:	Latent tuberculosis infection
LVX:	Levofloxacin
LZD:	Linezolid
MDR-TB:	Multidrug-resistant tuberculosis
MedDRA	Medical Dictionary for Regulatory Activities
mITT:	Modified Intention to treat
M/MXF:	Moxifloxacin

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MTB: Mycobacterium tuberculosis
M. tb: Mycobacterium tuberculosis
NICE: National Institute for Health and Care Excellence
NTM: Non-tuberculosis mycobacteria
OFX: Ofloxacin
Pa: Pretomanid
PAS: Para-aminosalicylic acid
PP: Per protocol
PRISMA: preferred reporting items for systematic reviews and meta-analyses
PTB: Pulmonary tuberculosis
PTO: Prothionamide
QD Daily
QoL: Quality of Life
R: Rifampicin
RCT: Randomised controlled trial
RR-TB: Rifampicin-resistant Tuberculosis
S: Streptomycin
SAE: Severe Adverse Events
SCC: Sputum culture conversion
SD: Standard deviation
SL: Second-line
SLID: Second-line injectable drug
SLR: Systematic literature review
SPC: Summary of product characteristics
STROBE: Strengthening the reporting of observational studies in epidemiology
TB: Tuberculosis
TEAEs: Treatment Emergent Adverse Events
TI/NR MDR-TB: Treatment-intolerant/ non-responsive MDR-TB
TST: Tuberculin skin test
TTP: Time to Positive
U: Unilateral
VnR: Nordic Article Number
WHO: World Health Organization
XDR-TB: Extensively drug-resistant tuberculosis
Z: Pyrazinamide

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1 Description and technical characteristics of the technology

Summary of the characteristics of pretomanid:

- Pretomanid is a nitroimidazooxazine antimycobacterial drug with an orphan drug designation. Pretomanid is indicated for extensively drug-resistant tuberculosis (XDR-TB), as well as for Treatment-Intolerant and Non-responsive Multi-drug resistant TB (TI/NR MDR-TB). In doing so, it helps support the global End TB Strategy. Even in the WHO European region, XDR-TB is increasing. [1]
- Pretomanid (Pa) is, in combination with bedaquiline (B) and linezolid (L) (= the BPaL regimen) the first available *in label* treatment option for adult patients with pulmonary XDR-TB. BPaL is also a pure oral treatment regimen, which compares favourably to other regimens recommended for MDR-TB which may include intravenous in addition to oral antibiotics.
- Previous studies with other regimens in XDR-TB patients have not led to label extensions for other drugs (neither those with pre-existing MDR-TB indications, nor those without any prior TB indication). In practice, historical guidelines such as those from the WHO do not make a distinction between treatments for XDR and MDR (multi-drug resistant) TB; they recommend that XDR treatment be chosen from among the longest- and most-intensive MDR regimens.
- The pretomanid-containing BPaL regimen has a treatment duration of only 26 weeks (appx 6 months). By comparison, the so-called “short regimen” for MDR-TB patients – which the World Health Organization (WHO) guidelines do not consider suitable for XDR-TB treatment – has a duration of 9 -11 months. The WHO’s “long regimen”, which is recommended for XDR-TB treatment, has a duration of 18, 20, 24 months or even more. [2] Further advantage is that pretomanid requires only 2 additional antibiotics to form a complete therapeutic regimen. Several other regimens recommended or used for XDR-TB consist of at least 4, and often 8 or more antibiotics, each with an associated side-effect profile.
- Because of the high mortality of XDR-TB treatment, and the lack of a previously approved or widely-used regimen for treatment of XDR-TB, it was considered unethical to have a control arm in the Nix-TB study (the pivotal study for approval of pretomanid). However, this was not seen as a barrier to its approval by EMA given the lack of a viable alternative. It is not unlikely that the BPaL regimen may itself be used as the control in future studies of XDR-TB treatment.

Regulatory status: Pretomanid has FDA approval since 14. August 2019 and a positive CHMP opinion since 26. March 2020. The non-profit 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 marketing authorisation holder of pretomanid in Europe and taking care for the EMA procedure. A marketing authorisation transfer to Mylan in Europe will start immediately after EC approval.

1.1 Characteristics of pretomanid

An overview about features of pretomanid are provided in Table 1.

Table 1 Features of the technology

Non-proprietary name	Pretomanid
Proprietary name	Submitted to EMA, but no final decision yet.
Marketing authorisation holder	Mylan will be final MAH
Class	Antimycobacterials, drugs for treatment of tuberculosis
Active substance(s)	Pretomanid
Pharmaceutical formulation(s)	200 mg tablet
ATC code	Not yet assigned
Mechanism of action	The mechanism of action of pretomanid is thought to involve inhibition of the synthesis of cell wall lipids under aerobic conditions and generation of reactive nitrogen species under anaerobic conditions. Reductive

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	activation of pretomanid by a mycobacterial deazaflavin (F420)-dependent nitro-reductase is required for activity under both aerobic and anaerobic conditions. The activation of pretomanid, which takes place within the bacterial cell, is dependent on enzymes encoded by 5 genes: a co-factor F420-dependent nitroreductase named Ddn; a glucose-6-phosphate dehydrogenase named Fgd1; and the enzymes of the F420 biosynthetic pathway (FbiA, FbiB, and FbiC).

Information about administration and dosing of Pretomanid is summarised in Table 2

Table 2 Administration and dosing of the technology

Method of administration	For 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 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1,200 mg daily orally for up to 26 weeks)
Doses	200 mg (one tablet)
Dosing frequency	Once daily
Average length of a course of treatment	26 weeks. A longer duration of therapy may be considered in patients who have not responded adequately to treatment at 26 weeks on a case by case basis.
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Not applicable

1.1.1 Pretomanid in the context and level of care

Treatment with pretomanid should be initiated and monitored by a physician experienced in the management of multidrug-resistant tuberculosis.

There are only very few hospital centres per country treating drug resistant tuberculosis. Patients often remain inpatient for several weeks until they are no longer contagious, after which they finish the duration of their treatment outpatient. Whether drugs are purchased in hospitals or retail pharmacies during the outpatient phase depends on the country.

1.1.2 ***Benefits of pretomanid***

Pretomanid is a new drug that fills a gap to address an unmet medical need by providing the first specific treatment for adult patients with pulmonary XDR-TB as well as those with TI/NR-MDR-TB. It thus supports the worldwide EndTB strategy and contributes to the fight against antimicrobial resistance (an estimated 25% of all

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deaths associated with antimicrobial resistance over the next 30 years are predicted to come from drug-resistant *M. tb* strains). [3]

XDR-TB is an especially challenging form of TB to treat. According to the WHO, only 39% of worldwide patients in 2016, who started treatment for XDR-TB successfully, completed it, compared to 85% for drug-sensitive TB and 56% for MDR-TB. [4] By contrast, XDR-TB patients on the BPaL regimen in the Nix-TB trial had an 89% treatment success rate. [5]

Furthermore, pretomanid involves a relatively short therapy with only 26 weeks duration and an all-oral regimen. In turn, this both likely increases the chance of treatment completion, which is very important for use of antibiotics to prevent further resistances.

For both, individual patients with tuberculosis and national health systems, a shorter duration of treatment that is effective is beneficial. Visits to health care facilities place a financial and time burden on patients. Income loss often constitutes the largest financial risk for patients. For tuberculosis programs, a shorter duration of treatment translates into fewer patients being in care at any one time, with the potential to reduce loss to follow-up. [5]

1.2 Regulatory status of pretomanid

Pretomanid is already approved in USA (FDA) and has a positive CHMP opinion in Europe (EMA) for the assessed indication. It has no marketing authorisation in other indications than the presented.

Additional comments about the marketing authorisation approval procedure:

- The non-profit 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 marketing authorisation holder of pretomanid in Europe and taking care for the EMA procedure. A marketing authorisation transfer to Mylan in Europe will start immediately after EC approval.
- Pretomanid is available via the Global Drug Facility (GDF) to 150 countries and territories on the basis of US FDA approval alone. Given this, not all countries require the product to be approved locally since they can access Pretomanid via the GDF.

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An overview of the full regulatory status of pretomanid is summarized in Table 3.

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Table 3 Regulatory status of pretomanid

Organisation issuing approval	**Verbatim wording of the (expected) indication(s)**	**(Expected) Date of approval**	**Launched (yes/no). If no include proposed date of launch**
US FDA	Limited Population: Pretomanid Tablet is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients. Limitations of Use: • Pretomanid Tablets are not indicated for patients with: • Drug-sensitive (DS) tuberculosis • Latent infection due to Mycobacterium tuberculosis • Extra-pulmonary infection due to Mycobacterium tuberculosis •MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy • Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen. (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm)	14. Aug. 2019	Mylan Specialty launched Pretomanid on 7. Nov. 2019
EMA	Pretomanid FGK is indicated 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), see sections 4.2, 4.4 and 5.1. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Positive Opinion: 26. Mar. 2020	No January 2021 (possibly sooner in DE)

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1.2.1 Contraindications and special warnings/ precautions for use

- Consideration should be given to official guidance on the appropriate use of antibacterial agents.
- Safety and effectiveness of pretomanid have not been established for its 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.
- Hypersensitivity to the active substance, other nitroimidazoles, or to any of the excipients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, silica, colloidal, sodium lauryl sulphate, povidone
- Elderly population (≥ 65 years of age): There is 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. No data are available.

2 Health problem and current clinical practice

2.1.1 Summary of issues relating to the health problem and current clinical practice

- In the WHO Europe region, XDR-TB cases among pulmonary TB cases increased from 575 in 2013 to 5591 in 2017. And 27.9% of pulmonary TB cases tested for drug susceptibility had MDR-TB. Prevalence of MDR-TB among new and previously treated bacteriologically confirmed pulmonary TB cases was 18.1% and 47.9% respectively [1]
- There is an unmet medical need for treatment options for XDR-TB. Before the availability of pretomanid, the medical guidelines and treatment practice for drug-resistant TB largely focused on MDR-TB; XDR-TB tended to be treated as a subset of these cases. [2] Pretomanid is the first drug to specifically have XDR-TB and TI/NR MDR-TB in the label.
- Treatment outcomes with existing regimens are poor for XDR-TB patients and are characterised by higher mortality. Just 39% of XDR-TB patients in the WHO European Region who started treatment in 2016 are considered to have had treatment success, compared to 57% of MDR-TB cases. [4]
- Current guidance for XDR-TB treatment is to use one of the longer MDR-TB treatment regimens [2]. These options can take 18-20 months, or even longer.
- In some cases, these treatments will include injectable medicines such as amikacin or streptomycin, which may increase the duration, cost, and complexity of treatment.

2.2 Overview of the disease or health condition

Tuberculosis (TB) is an airborne infectious disease caused by organisms of the Mycobacterium tuberculosis (*M. tb*) complex.

2.2.1 ***Pathogenesis***

Mycobacterium tuberculosis (*M. tb*) is characterized by a complex and lipid-rich outer cell wall which is responsible for its slow growth, staining properties and some of its

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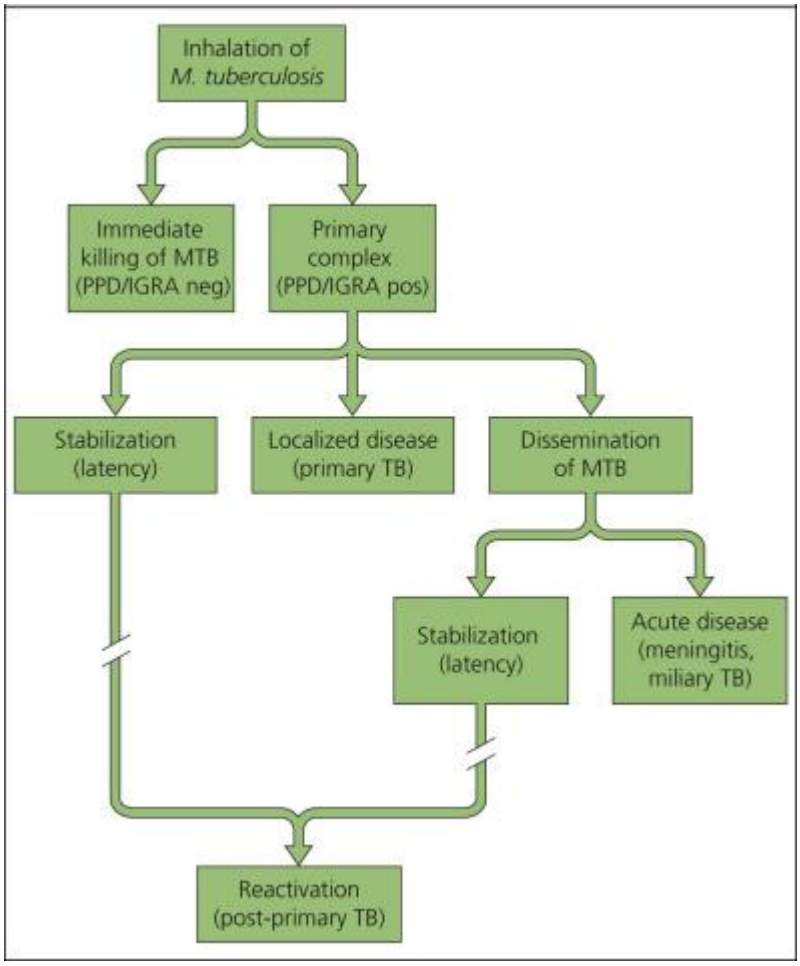
pathogenic features. Mycobacteria are often termed acid-fast bacilli (AFB), as they retain the colour of arylmethane dyes when treated with diluted acid. [6]

After inhalation of M. tuberculosis droplet nuclei, different scenarios may follow (Figure 1), reflecting the balance between the bacillus and host–defense mechanisms. M. tuberculosis may be destroyed by alveolar macrophages or neutrophils. If it is not immediately killed, a primary complex consisting of a small infiltrate and draining lymph nodes develops. Small calcifications may be seen on radiographic examination, and the PPD (purified protein derivative of tuberculin) skin test, a marker of an M. tuberculosis -specific T-cell response, becomes positive several weeks after infection. In a minority of cases active disease develops (progressive primary tuberculosis), either in the lungs or anywhere else after hematogenous dissemination of M. tuberculosis. In the remainder, infection is stabilized, but may reactivate months or years later, if the patient becomes immunocompromised. [6]

Figure 1 Sequence of events after exposure to a patient with active tuberculosis [6]



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Although it mainly affects the lungs, M. tuberculosis can cause disease throughout the body. Furthermore, TB can present as a dynamic spectrum, from asymptomatic infection to a life-threatening disease (Figure 1). From a clinical and public health perspective, patients with TB are classified as having latent TB infection (LTBI), which is an asymptomatic and non-transmissible state, or active TB disease, which is transmissible (in active pulmonary TB) and for which culture-based or molecular diagnostics can be used. Patients with active TB disease clinically present with general symptoms like fever, fatigue, lack of appetite and weight loss, and those with pulmonary disease can have persistent cough and haemoptysis (blood-expectorating cough) in advanced disease. However, some patients with active, culture-positive disease may be asymptomatic and are described as having subclinical TB. [7]

2.2.2 ***Tuberculosis Classifications***

Tuberculosis (TB) is classified based on the pathogenesis of the disease as summarised in Table 4. [8]

Table 4 Classification of tuberculosis [8]

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative reaction to tuberculin skin test
1	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test
2	TB infection No disease	Positive reaction to tuberculin skin test Negative bacteriologic studies (if done) No clinical, bacteriologic, or radiographic evidence of TB
3	TB, clinically active	*M. tuberculosis* cultured (if done) Clinical, bacteriologic, or radiographic evidence of current disease
4	TB Not clinically active	History of episode(s) of TB **or** Abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) **and** No clinical or radiographic evidence of current disease
5	TB suspect	Diagnosis pending TB disease should be ruled in or out within 3 months

The WHO ICD-10-2019 codes which include pulmonary TB are A15 (respiratory tuberculosis, bacteriologically and histologically confirmed) and A16 (respiratory tuberculosis, not confirmed bacteriologically or histologically.

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Further WHO ICD-10-codes reflecting antibiotic resistances are summarised in the next chapter 2.1.3.

2.2.3 Drug Resistance

While drug-susceptible tuberculosis (DS-TB) is curable, poor treatment adherence, incorrect drug prescribing, and toxicity leading to early treatment discontinuation have given rise to drug-resistant strains of *M. tb*, which are progressively more difficult to treat. M. tuberculosis can develop a resistance towards all anti-TB drugs, and resistance is reported in virtually all countries. [7] Multidrug-resistant TB (MDR-TB) is characterized by resistance against rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) by resistance to rifampicin, isoniazid, any fluoroquinolone and any of the three injectable second-line aminoglycosides and (i.e. other first- or second-line TB medicines). [7]

WHO-ICD-10-codes reflecting antibiotic resistance of relevance include:

- U83.2 Resistance to quinolones
- U83.7 Resistance to multiple antibiotics
- U83.8 Resistance to other single specified antibiotic
- U84.3 Resistance to tuberculostatic drug(s)
- U84.8 Resistance to other specified antimicrobial drug

Country-specific ICD-10 modifications may be more precise. For example, the German modification ICD-10-GM-2020 contains a specific code for MDR-TB: U82.1! Multi-Drug Resistant Tuberculosis [MDR-TB]. However, a code for XDR-TB is missing.

2.2.4 Risk factors and co-morbidities worsening the disease course

Several medical conditions are risk factors for TB and for poor TB treatment results, while TB can complicate the disease course of some diseases. When these conditions are highly prevalent in the general population, they can be important contributors to the TB burden. Consequently, reducing the prevalence of these conditions can help prevent TB. [9]

TB and HIV

People living with HIV are 26-31 times more likely to develop TB than persons without HIV. TB is the most common presenting illness among people living with

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HIV, including among those taking antiretroviral treatment and it is the major cause of HIV-related death. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people and an additional 374,000 deaths among HIV-positive people. [9]

TB and diabetes

Diabetes triples the risk of TB. Consequently, rates of TB are higher in people with diabetes than in the general population, and diabetes is a common comorbidity in people with TB. Diabetes can worsen the clinical course of TB, and TB can worsen glycaemic control in people with diabetes. Individuals with both conditions thus require careful clinical management. Strategies are needed to ensure that optimal care is provided to patients with both diseases. [9]

TB and nutrition

Malnutrition increases the risk of TB, and TB can lead to malnutrition. Malnutrition is, therefore, often highly prevalent among people with TB. While appropriate TB treatment often helps normalizing the nutritional status, many TB patients are still malnourished at the end of TB treatment. Therefore, nutritional assessment, counselling and management of malnutrition based on the nutritional status are an important part of the TB treatment package. [9]

TB and tobacco smoking

Tobacco smoking increases the risk of TB 2-3-fold and is associated with poor treatment results. Smoking prevalence is often high among people with TB, and prevalence of other smoking-related conditions can be high as well. People diagnosed with TB should be asked about smoking and should be offered advice about smoking cessation. This is part of the practical approach to lung health. [9]

TB and harmful use of alcohol

Harmful use of alcohol increases the risk of TB threefold and is also a strong risk factor for poor TB treatment adherence. In countries with high prevalence of alcohol misuse, harmful alcohol use can be an important population level risk factor for TB and is often a common co-morbidity among TB patients. As part of a comprehensive

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care package it is important, especially in those countries, to identify problem drinkers, to diagnose alcohol misuse and to implement appropriate interventions. [9]

A few countries have experimented with systematic screening for harmful alcohol use of all TB patients. Screening and diagnosis of other mental health problems may also be warranted. [9]

2.2.5 TB incidence in Europe

TB is the world's leading infectious disease killer. In 2018, the World Health Organization (WHO) estimated that 10 million individuals developed active TB, and 1.6 million died from the disease [10]

Tables 5 and 6 summarize the data about the TB case incidence and incidence rate within the European WHO region as reported for the year 2018 in the most recent WHO Global Tuberculosis Report from 2019 [4]:

Table 5 Incidence: Estimated epidemiological burden of TB in 2018 in the European WHO region (Number in thousands/ population size = 927,000) [4]

	Best estimate	Uncertainty interval
Total TB incidence	259	225 - 296
HIV-positive TB incidence	30	23 - 37
HIV-negative TB mortality	23	22 - 24
HIV-positive TB mortality	4.4	3.3 – 5.6

Table 6 Incidence rate: Estimated epidemiological burden of TB in 2018 in the European WHO region (Rates per 100,000 population) [4]

	Best estimate	Uncertainty interval
Total TB incidence	28	24 - 32
HIV prevalence in incident TB (%)	12	7.5 - 19
HIV-negative TB mortality	2.5	2.4 – 2.6
HIV-positive TB mortality	0.47	0.36 – 0.60

More detailed data about the estimated cases in the target population can be found in section 2.2 and Table 8.

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2.2.6 Symptoms and burden of the disease for the patients

Pulmonary tuberculosis frequently develops slowly, without a definite date of onset. The disease has a wide spectrum of manifestations ranging from tuberculin skin test positivity to far advanced tuberculosis. Symptoms are minimal, until the disease is moderately or far advanced and often attributable to other causes, such as excessive smoking, hard work, pregnancy, or other conditions. [11]

Symptoms may be divided into two categories, constitutional and pulmonary. The frequency of these symptoms differs according to whether the patient has primary tuberculosis or reactivation tuberculosis. Subjects with primary tuberculosis are much more likely to be asymptomatic or minimally symptomatic. See Table 7 for a list of the most common symptoms of patients presenting with active tuberculosis. The constitutional symptom most frequently seen is fever, low grade at the onset but becoming quite marked as the disease progresses. Characteristically, the fever develops in the late afternoon and may not be accompanied by pronounced symptoms. As the fever declines, usually during sleep, sweating occurs—the classic “night sweats”. Other signs of toxaemia, such as malaise, irritability, weakness, unusual fatigue, headache, and weight loss, may also be present. With the development of caseation necrosis and concomitant liquefaction of the caseation, the patient will usually notice cough and sputum, often associated with mild haemoptysis (blood in the sputum). Chest pain may be localized and pleuritic. Shortness of breath usually indicates extensive disease with widespread involvement of the lung and parenchyma or some form of tracheobronchial obstruction and therefore usually occurs late in the course of the disease. [11]

Table 7 Clinical symptoms of patients presenting with active tuberculosis [11]

Symptom	**% of patients affected** [a.]	
	Primary	**Reactivation**
▪ **Cough**	▪ 23–37	▪ 42
▪ **Fever**	▪ 18–42	▪ 37–79
▪ **Weight loss**	▪ NR	▪ 7–24
▪ **Haemoptysis**	▪ 8	▪ 9

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Physical examination of the respiratory system is not useful early in the disease. At this stage, the principal finding is one of fine rales detected on deep inspiration followed by full expiration and a hard, terminal cough (post-tussive rales). This sign is found particularly in the apexes of the lungs, where reactivation disease has its onset in a large majority of patients. As the disease progresses, more extensive findings are present, corresponding to the areas of involvement and type of pathology. Allergic manifestations may occur, usually developing at the time of onset of infection. These include erythema nodosum and phlyctenular conjunctivitis. Erythema nodosum initially occurs in the dependent portion of the body and, if the reaction is severe, may be followed by a more disseminated process. [11]

2.3 Target population

In accordance with the expected label, the target population consists of adult patients with pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).

Pretomanid stands at the end of the patient pathway of care, when first- and second-line antibiotics fail or are not tolerated.

It is intended to receive reimbursement for the whole expected indication. Pretomanid is the only *in label* treatment option for patients who do not tolerate or respond to MDR-TB treatment or those with XDR-TB and addressing an unmet medical need.

In the Nix-TB study, 89% of patients with the most difficult-to-treat form of TB responded favourably to the BPaL treatment regimen, consisting of pretomanid (Pa) in combination with bedaquiline (B) and linezolid (L). This was demonstrated in terms of early culture conversion to negative while on treatment, and more importantly, in terms of disease-free status at 6 months after the end of treatment. Adverse events in the Nix-TB study were as expected with the BPaL regimen and generally manageable through dose adjustments of the linezolid component. Importantly, approximately 85% of patients were able to complete the protocol-specified course of BPaL treatment and a further 9.2% were still receiving study treatment as of the data cut-off date. Overall, the safety concerns with the BPaL regimen are

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manageable and the overall benefit to risk is highly positive given the higher efficacy and lower mortality. [12]

An additional benefit of pretomanid/ the BPaL regimen is the simplified, highly effective, shorter (6 month), and all-oral nature of the regimen, compared with previous alternatives.

We estimate that the total population with an indication for pretomanid in Europe is around 250 patients per year.

Country specific data of WHO databases were analysed to estimate the target population, adult patients with pulmonary XDR-TB or TI/NR MDR-TB, within each European country. [13] The respective results are summarized in Table 8.

Calculation of the XDR-TB population size: Available data on XDR-TB cases from the years 2017 and 2018 were taken. The respectively higher number of XDR-TB patients per country was selected for the further calculations. Only two factors were corrected to align with the expected indication: age and pulmonary TB.

- *Age:* The WHO differentiates between the age groups < and ≥15 years. This can lead to a small overestimation of the eligible treatment population which is the adult population (≥18 years) only by label.
- *Pulmonary TB:* Extrapulmonary cases were subtracted. The ratio was estimated using the pulmonary-to-non-pulmonary ratio reported for all TB cases (i.e. not limited to drug-resistant TB). There may be a difference in the ratio between drug-susceptible and drug-resistant forms. For Latvia no data were available to calculate the relation between pulmonary and extrapulmonary TB. Therefore, an average value was estimated based on the data from Estonia and Lithuania.

Calculation of the TI/NR MDR-TB population size: The WHO data have no differentiation between ordinary and treatment-intolerant/non-responding MDR-TB patients. To estimate this part of the target population, the rate of treatment failures from patients initiating in 2016 was calculated and applied to the MDR-TB cases. (Data from later-initiating patients is not available as patients may not have fully completed their treatment courses). Finally, those data were also corrected for age and pulmonary disease as already described for the XDR-TB patients.

The trend for MDR-TB in Europe is decreasing, whereas XDR-TB demonstrates an increasing trend. [1]

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Table 8 Estimated target population in the Mylan Europe region per country based on WHO data tables [13]

Country	XDR-TB cases 2017 (n=)	XDR-TB cases 2018 (n=)	**Max. number of total XDR-TB population based on data from 2017 and 2018**	MDR-TB cases 2017 (n=)	MDR-TB cases 2018 (n=)	Max. number of total MDR-TB population based on data from 2017 and 2018	% treatment failure (2016 data, *2015 data)	**MDR-TB population representing treatment-intolerant or non-responsive patients** (%failure in 2016; if *, rate from2015; if n.a. =% assumed)	New extrapulmonary TB cases 2018	New laboratory confirmed pulmonary TB cases 2018	Sum of new extrapulmonary and new lab. Conf. Pulmonary TB cases 2018	**% pulmonary TB**	average % of Estonia and Lithuania to be used for an estimate of % patients with pulmonary TB in Latvia	TB patients with age 15plus (best etimate 2018)	TB-patients all age groups (best etimate 2018)	**% in age group 15 plus**	**Eligible XDR-TB patients (n=)**	**Eligible TI/NR MDR-TB patients (n=)**	**Eligible patients total (n=)**
Albania	0		**0**	0	2	2	0	**0**	108	198	306	**65**		500	510	**98**	**0**	**0**	**0**
Austria	2-3	0	**3**	18		18	0	**0**	112	304	416	**73**		610	630	**97**	**2**	**0**	**2**
Belgium	0	3	**3**	5	7	7	0	**0**	265	550	815	**67**		960	1000	**96**	**2**	**0**	**2**
Bosnia and Herzegovina	0		**0**	0		0	n.a.	**0**	65	410	475	**86**		830	830	**100**	**0**	**0**	**0**
Bulgaria	1	0	**1**	29	24	29	14	**4**	263	549	812	**68**		1400	1600	**88**	**1**	**2**	**3**
Croatia	0	0	**0**	0		0	n.a.	**0**	36	287	323	**89**		350	350	**100**	**0**	**0**	**0**
Cyprus	0		**0**	1		1	n.a.	**0**	10	34	44	**77**		61	65	**94**	**0**	**0**	**0**
Czech Republic	2	0	**2**	8	12	12	0	**0**	46	322	368	**88**		570	580	**98**	**2**	**0**	**2**
Denmark	0	0	**0**	2		2	17*	**0**	61	166	227	**73**		300	310	**97**	**0**	**0**	**0**
Estonia	9	8	**9**	36	30	36	5	**2**	7	105	112	**94**		160	170	**94**	**8**	**2**	**10**
Finland	1	1	**1**	5	4	5	0	**0**	73	142	215	**66**		260	260	**100**	**1**	**0**	**1**
France	10	10	**10**	79	82	82	n.a.	**0**	1412	2426	3838	**63**		5500	5800	**95**	**6**	**0**	**6**
Germany	0-4	8	**8**	105		105	0	**0**	1396	3242	4638	**70**		5800	6100	**95**	**5**	**0**	**5**
Greece	2	0	**2**	7		7	n.a.	**0**	58	258	316	**82**		460	470	**98**	**2**	**0**	**2**
Hungary	4	3	**4**		11	11	0	**0**	19	327	346	**95**		620	620	**100**	**4**	**0**	**4**

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Iceland	0		**0**	0		0	n.a.	**0**	2	3	5	**60**		9	9	**100**	**0**	**0**	**0**
Ireland	0-1	0	**1**	5	6	6	0	**0**	79	177	256	**69**		330	340	**97**	**1**	**0**	**1**
Italy	5	4	**5**	66	53	66	n.a.	**0**	1110	2135	3245	**66**		4100	4300	**95**	**3**	**0**	**3**
Latvia	18		**18**	46		46	0*	**0**					**92**	550	560	**98**	**16**	**0**	**16**
Country	XDR-TB cases 2017 (n=)	XDR-TB cases 2018 (n=)	Max. number of total XDR-TB population based on data from 2017 and 2018	MDR-TB cases 2017 (n=)	MDR-TB cases 2018 (n=)	Max. number of total MDR-TB population based on data from 2017 and 2018	% treatment failure (2016 data, *2015 data)	MDR-TB population representing treatment-intolerant or non-responsive patients (%failure in 2016; if *, rate from2015; if n.a. =% assumed)	New extrapulmonary TB cases 2018	New laboratory confirmed pulmonary TB cases 2018	Sum of new extrapulmonary and new lab. Conf. Pulmonary TB cases 2018	% pulmonary TB	average % of Estonia and Lithuania to be used for an estimate of % patients with pulmonary TB in Latvia	TB patients with age 15plus (best etimate 2018)	TB-patients all age groups (best etimate 2018)	% in age group 15 plus	Eligible XDR-TB patients (n=)	Eligible TI/NR MDR-TB patients (n=)	Eligible patients total (n=)
Lithuania	87	58	**87**	249	170	249	4	**10**	75	751	826	**91**		1200	1200	**100**	**79**	**9**	**88**
Luxembourg	0		**0**	1	1	1	n.a.	**0**	10	29	39	**74**		48	48	**100**	**0**	**0**	**0**
Malta	0		**0**	0	0	0	n.a.	**0**	16	29	45	**64**		59	60	**98**	**0**	**0**	**0**
Montenegro	1	0	**1**	1	1	1	0	**0**	10	61	71	**86**		94	97	**97**	**1**	**0**	**1**
Netherlands	0	1	**1**	10	5	10	0	**0**	330	377	707	**53**		890	910	**98**	**1**	**0**	**1**
North Macedonia	0	0	**0**	1	2	2	0	**0**	52	135	187	**72**		260	270	**96**	**0**	**0**	**0**
Norway	0	0	**0**	?	5	5	0	**0**	75	104	179	**58**		210	220	**95**	**0**	**0**	**0**
Poland	5	12	**12**	44	48	48	0	**0**	236	3559	3795	**94**		5900	6000	**98**	**11**	**0**	**11**
Portugal	0	0	**0**	10	7	10	0	**0**	497	1398	1895	**74**		2400	2400	**100**	**0**	**0**	**0**
Romania	43-45	46	**46**	349	350	350	19	**67**	1684	6682	8366	**80**		13000	13000	**100**	**37**	**53**	**90**
Serbia	0	0	**0**	5	3	5	0	**0**	253	704	957	**74**		1500	1500	**100**	**0**	**0**	**0**
Slovakia	1-2	0	**2**	6	3	6	0	**0**	35	148	183	**81**		270	310	**87**	**1**	**0**	**1**

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Slovenia	0		**0**	1		1	n.a.	**0**	15	72	87	**83**		110	110	**100**	**0**	**0**	**0**
Spain	1		**1**	28		28	0	**0**	1246	2762	4008	**69**		4100	4400	**93**	**1**	**0**	**1**
Sweden	0	0	**0**	11	13	13	0	**0**	148	285	433	**66**		510	550	**93**	**0**	**0**	**0**
Switzerland	0	1	**1**		8	8	0	**0**	136	317	453	**70**		510	540	**94**	**1**	**0**	**1**
United Kingdom	3	3	**3**	47	38	47	0	**0**	2025	2150	4175	**51**		5200	5400	**96**	**1**	**0**	**1**
Total			**221**					**83**									**184**	**66**	**251**

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2.4 Clinical management of the disease or health condition

Tuberculosis (TB) is roughly characterized as having three degrees of severity (with some nuance in between): drug-sensitive TB (DS-TB), multi-drug resistant TB (MDR-TB), and extensively drug resistant TB (XDR-TB). The indication for pretomanid is for XDR-TB and treatment-intolerant/ non-responsive MDR-TB. However, because XDR- or NR/TI MDR-TB patients will often first work their way through the algorithm for DS- and MDR- TB, the below covers the diagnostic and treatment algorithms for all forms of TB.

TB treatment aims to cure the disease process, rapidly stop transmission, and prevent relapse. Current treatment of tuberculosis requires multiple antibiotics, guided by predicted or demonstrated antibiotic susceptibility and taken for many months. Context-specific treatment guidelines are usually developed by local health authorities with guidelines and oversight from the WHO. Clinical trials in the twentieth century established current first-line drug regimens. [14, 15]. Treatment success rates of 85 percent or more for new drug-sensitive cases are regularly reported to the WHO from a wide variety of clinical settings. [16, 17].

2.4.1 Diagnosing TB

MDR-TB management requires the diagnosis of TB and resistance to at least rifampicin and isoniazid. Diagnosis of XDR-TB requires additional detection of resistance to fluoroquinolones and second line injectables. Currently, WHO recommends using biomolecular tests like the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) as the initial diagnostic tool in case of presumed TB. Such tools are useful to rapidly identify patients with rifampicin resistance (proxy of MDR-TB). So far, Xpert MTB/RIF remains the most efficient tool and is able to detect TB in several biological fluids and specimens. It is suitable for implementation at the point-of-care level in resource-constrained settings. Further testing is needed to detect resistances beyond rifampicin. Standard/traditional drug susceptibility testing (DST) on solid or liquid culture is essential to confirm MDR-TB diagnosis. [18]

Capacity for microscopy, culture and DST needs to remain, despite molecular diagnostics. Microscopy and culture are particularly important for treatment monitoring. The availability of molecular diagnostic tests does not eliminate the need

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for conventional microscopy, culture and DST capability; microscopy and culture remain necessary for the follow-up of treatment, and culture currently still provides maximum diagnostic sensitivity, while conventional DST is required to support a diagnosis of XDR-TB and provide a tailored patient-regime for M/XDR-TB patients. Demands for conventional techniques might change in the future based on the epidemiological situation.

Drug resistance can be detected by genotypic and phenotypic methods. Automated liquid systems are the current gold standard for FL and SL DST [19]. DST should follow WHO guidelines with stringent quality assurance methods [20, 21]. SL DST should aim to include testing of the aminoglycosides, polypeptides and FLQs used in the country. DST results on these drugs have good reliability and reproducibility and allow a quality-assured diagnosis of XDR-TB. With the introduction of SL-LPA for detecting resistance to FLQs and SLIDs, resistant results to these drugs can be obtained more rapidly.

Currently, the WHO-recommended molecular diagnostic tests for TB and DR-TB include LPAs and the Xpert MTB/RIF assay.

1. Imaging techniques
    a. Chest X-ray
       Chest radiography is an established triage or screening test, and the emergence of digital radiology and computer-aided diagnostic software are important recent advances. Because X-rays lack specificity, abnormal chest X-rays need to be followed up with microbiological tests. [22]
       Advanced imaging modalities are providing new insights into the diversity of lung lesions, although they are too expensive and not recommended for routine use [23]

2. Microscopy
    a. Sputum smear
       Sputum smear microscopy allows a rapid and reliable identification of patients with pulmonary tuberculosis (PTB) where there are more than 5000 bacilli/ml of sputum. If the sputum has less than 5000 bacilli/ml, smear microscopy is highly unlikely to diagnose PTB, thus has an overall low sensitivity for PTB [24, 25].

       Another shortcoming of smear microscopy is its non-specificity, such that M. tuberculosis appears the same as non-tuberculous mycobacteria

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(NTM). However, in areas of high TB prevalence, positive smears have a very high probability of being M. tuberculosis.

The reliability of sputum microscopy depends on the quality of sputum collection. Sputum produced on early morning often shows a higher concentration of M. tuberculosis. Importantly, the reliability of sputum microscopy depends on the proper preparation and interpretation of slides. Thus, laboratory technicians must be properly trained and quality control checks must be regularly carried out in a supervising laboratory.

Light-emitting diode (LED) fluorescence microscopy is the recommended method for microscopy at all levels of laboratory. [20] Both LED microscopy and conventional fluorescence microscopy are at least 10% more sensitive than Ziehl-Neelsen microscopy. Moreover, LED microscopy is less costly compared to conventional fluorescence microscopy [20].

3. Culture-based techniques

Culture allows diagnostic confirmation of TB and is more sensitive than microscopy, 10-100 bacilli/ml are required to obtain a positive result [24]. Only specialized laboratories with regular quality assurance procedures in place can be relied upon for culture. M. tuberculosis is a slow-growing pathogen thus, culture results are obtained after several days.

Culture should play a bigger role in diagnosis and patient follow-up due to the limited value of direct microscopy for:

– Confirmation of failures;
– Diagnosis of EPTB;
– Confirmation of smear negative TB when the diagnosis is in doubt;
– Distinction between M. tuberculosis complex and NTM;
– Monitoring treatment and outcome evaluation for patients on second-line anti-TB drugs.

Once there is growth on either a solid or liquid media, the organism must be identified. There are a number of ways to identify M. tuberculosis. The tests can be phenotypic (the most common being the niacin test) or genotypic (which use DNA analysis). Given the complexities associated with phenotypic identification, genetic tests are preferred. The drawback is their cost. Nonetheless, laboratories performing cultures, at a minimum, should be able to conduct identification tests for M. tuberculosis that follow international guidelines.

4. Antigen detection techniques

- Cutaneous hypersensitivity to tuberculin reflects a delayed hypersensitivity reaction to some M. tuberculosis antigens.

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- A positive reaction signifies that an infection has occurred, but it does not determine if the TB is latent or active. It does not differentiate between infection by M. tuberculosis and hypersensitivity due to mycobacterium other than TB.
- The TST is done by injecting 5 international units of tuberculin intradermally on the ventral surface (side of arm exposed with palm facing up) of the forearm.
- The test is read by a trained health care worker, 48 to 72 hours after the injection. The reaction is the area of induration (swelling that can be felt) around the injection. The diameter of induration is measured with a ruler in millimetres across the forearm. The erythema (redness) around the indurated area is not measured, because the presence of redness does not indicate a reaction.

5. Molecular techniques (nucleic acid amplifications tests)

Molecular (or genotypic) tests can be used to diagnose TB through the amplification of nucleic acids (DNA or RNA). They are also used to detect drug resistance through identifying genetic mutations (drug-resistant alleles) in the bacterium responsible (genotypic DST). Different assays and platforms have been developed.

Line probe Assay (LPA)

LPAs offer the advantage of being able to detect mutations associated with resistance to both INH and RIF, but are accurate only on sputum smear positive specimens or cultured isolates of M. tuberculosis. Phenotypic resistance to RIF and INH highly correlates with resistance conferring mutations detected by LPA (RIF sensitivity 97.7%; specificity 91.8% and INH sensitivity 95.4%; specificity 89.0%). [26] The shorter diagnostic time helps in early detection of drug resistance and early commencement of appropriate treatment. This will have a major impact in reducing the transmission of drug resistant strains.

Line probe assays are rapid molecular diagnostics detecting both MTB and drug resistance. [18] It helps in the detection of resistance to fluoroquinolones and second line injectable drugs (SLID) for patients with confirmed RIF resistant TB or MDR-TB. Results are available in 1-2 days. The shorter diagnostic time helps in early detection of drug resistance and early commencement of appropriate treatment. [27]

Genotype MTBDRplusV1 was WHO-endorsed in 2008 but newer LPAs are now available. LPAs can be used as alternative to conventional DST, but their implementation is still challenged by high costs and complex technical requirements. New LPAs like Genotype MTBDRplus version 2.0 have better sensitivity and

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specificity. LPAs demonstrated high accuracy overall for the detection of rifampicin resistance in pulmonary TB. LPAs demonstrated high specificity for isoniazid-resistance detection with good sensitivity. It has been specifically evaluated in real-life setting showing to be reliable in detecting *M. tb* in sputum smear-negative samples. [18]

Direct sequencing of DNA extracted from sputum samples or cultures are techniques to obtain fast and reliable resistance profiles well before phenotypic DST becomes available. There are presently interlaboratory differences in sensitivity of this assay as different primers are used. A recent article from China reported very high specificity and good sensitivity for rifampicin, but lower sensitivity for isoniazid and fluoroquinolones. The resistance results were available within 3 days. [18]

The following figure 2 summarizes the diagnostic algorithm [28]:

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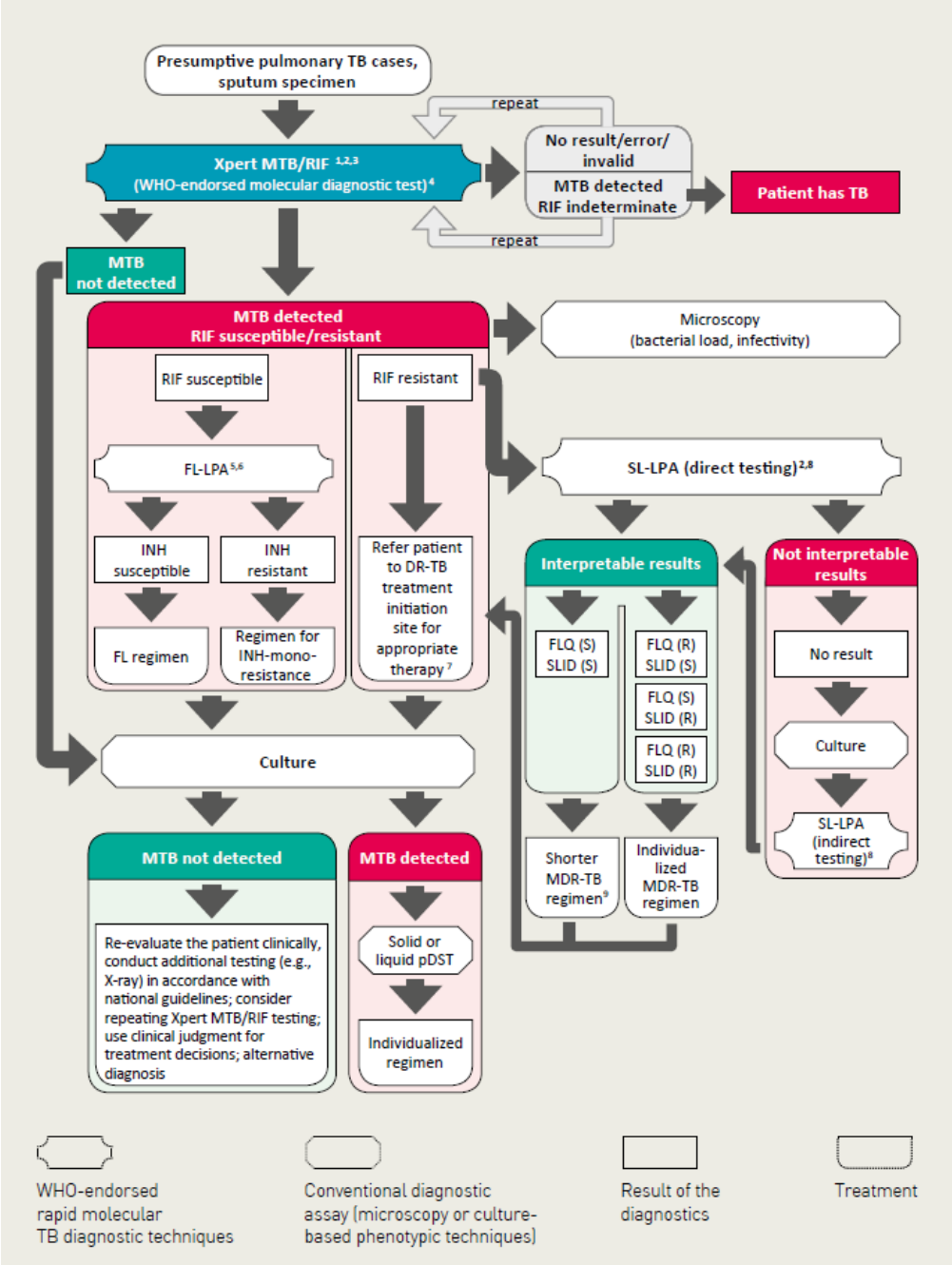
Figure 2 Algorithm for the initial laboratory diagnosis of individuals with symptoms consistent with pulmonary TB [28]



[1]Results of molecular test should be communicated to the clinican without waiting for culture results; [2]Performing a rapid molecular test for drug resistance (e.g. Xpert or LPA) on the primary samples reduces the delay to appropriate phenotypic resistance results; [3]In the absence of Xpert MTB/RIF, sputum smear microscopy can be used as the initial test and the sample should be sent as quickly as possible to a laboratory with the capacity to perform WHO recommended molecular tests in addition to culture; [4]In case Xpert MTB/RIF is absent but FL LPA is available, this test should be used for smear-positive sputum samples, to detect rifampicin and in addition INH resistance. If INH-R is detected this information should guide further diagnostic work and be considered in clinical treatment decisions; [5]To be performed when FL-LPA is available and has not been done already; [6]In the absence of FL-LPA, FL regimen is suggested to be initiated and adjusted once additional DST results are available; [7]In cases SL-LPA results would not become available within one week, empirical MDR-TB treatment may be initiated; [8]SL-LPA are suitable for use at the central or national reference laboratory level; or at regional level with appropriate infrastructure; [9]Following eligibility criteria

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2.4.2 Management schemes

The management schemes depend on the resistance profile.

Drug Resistance

While drug-susceptible tuberculosis (DS-TB) is curable, poor treatment adherence, incorrect drug prescribing, and toxicity leading to early treatment discontinuation have given rise to drug-resistant strains of *M. tb*, which are progressively more difficult to treat. M. tuberculosis can develop a resistance towards all anti-TB drugs, and resistance is reported in virtually all countries. [7] Multidrug-resistant TB (MDR-TB) is characterized by resistance against rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) by resistance to rifampicin, isoniazid, any fluoroquinolone and any of the three injectable second-line aminoglycosides and (i.e. other first- or second-line TB medicines). [4]

Significant progress in the availability of improved diagnostics and more effective medicines in recent years has led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of countries. However, these achievements have not been reproduced globally, and the overall treatment success rate reported in 2018 reached only 56% for MDR/RR-TB patients and 39% for patients with extensively drug-resistant TB (XDR-TB). [4]

DS-TB

Rifampicin and isoniazid are the most potent drugs for susceptible TB and are taken throughout the course of first-line treatment. [29] Pyrazinamide synergistically reinforces the sterilizing activity of rifampicin and, when added to the first two months of treatment, reduces the duration of treatment to six months. [14, 15, 30] Ethambutol is added to the regimen for two months to reduce on-treatment development of drug resistance [29] and is continued for the full duration of therapy in settings with high background prevalence of isoniazid resistance. As effective as standard treatment has been, resistance to isoniazid, rifampicin, and pyrazinamide is increasing in many countries, indicating that new regimens will need to be increasingly incorporated into TB treatment.

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Standard treatment for TB includes administration of four first-line antimicrobials like isoniazid, rifampicin, pyrazinamide and ethambutol.

MDR-TB

The treatment of drug-resistant TB is evolving, and recommendations are changing rapidly. Four factors make it difficult to arrive at clear, generalizable recommendations. First, individual strains vary in their susceptibility, and customized regimens might be more appropriate, when possible. Second, testing susceptibility to pyrazinamide and second- and third-line agents is neither widely available nor consistently reliable. Third, many agents have limited availability due to their cost or limited production. Finally, few comparative studies are available to provide data on which to make optimal treatment decisions.

While drug-resistant disease is curable, the cure rate in several studies is lower than for drug-sensitive disease. In some studies of MDR TB, only 54 to 70 percent of patients achieve treatment completion or cure. [31-35] Treatment requires new drugs, with regimens containing three to seven drugs that have not been previously employed. [36] In general, these second- and third-line agents are less potent and must be administered for a more extended period of time, ranging from 9 to 24 months. They are also more difficult to administer, as most regimens contain agents such as kanamycin and amikacin that must be administered by injection. These drugs are far more toxic than first-line agents, causing a range of drug-specific side effects. Nevertheless, it has been possible to achieve MDR TB cure rates of 60–80 percent irrespective of HIV/AIDS status in settings with severe resource constraints and patients with advanced disease. [37, 38]

Treatment effectiveness has been eroded, however, by the evolution and transmission of multidrug-resistant tuberculosis. Treatment for MDR TB, which is defined as resistance to isoniazid and rifampicin (the two most effective TB drugs) is longer and requires more expensive and more toxic drugs. For most patients with MDR TB, the current regimens recommended by the WHO last 18–24 months, and treatment success rates are much lower, around 60 percent. The WHO now conditionally recommends using seven drugs to reduce the time of treatment to nine months for uncomplicated pulmonary disease. [38]. New drug combinations, for

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example, including bedaquiline or delamanid, which are thought to act on new molecular targets, are being introduced, but an ideal combination is likely several years away. [39, 40]

According the actual WHO treatment guidelines, the recommended treatment regimens should include at least 4 effective medicines, composed of all 3 Group A agents and at least 1 Group B agent. If any agent from Group A or B cannot be used, additional medicines from Groups B and then C are included to complete the recommended 4-medicine regimen. A total treatment duration of 18 to 20 months is recommended for most patients with MDR-TB. [41, 2] Table 9 is taken from this guideline and gives an overview of the group classification. The substances in class C are ranked by the relative balance of benefit to harm usually expected of each.

Table 9 Relative risk for (i) treatment failure or relapse and (ii) death (versus treatment success), 2018 IPD-MA for longer MDR-TB regimens and delamanid Trial213 (ITT population) [2]

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% confidence limits)	Number treated	Adjusted odds ratio (95% confidence limits)
A	Levofloxacin *OR* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *OR* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)*	290	1.2 (0.5–3.0)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

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More details of the actual WHO treatment guideline are summarized in Table 11 at the end of this chapter.

The shorter MDR-TB regimen lasts 9 to 12 months and is only to be considered for patients with MDR-TB or rifampicin-resistant TB 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.

Management of XDR-TB

The design of longer regimens for MDR/RR-TB patients with additional resistance (including XDR-TB) follows a similar logic to that used for other MDR-TB patients. Ideally, all MDR-TB patients should be tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment. If the shorter regimen or amikacin is being considered in the regimen then rapid testing for second-line injectable agents should be performed.

According to the current WHO guidelines, the design of longer regimens for MDR/RR-TB patients with additional resistance (including XDR-TB) follows a similar logic to that used for other MDR-TB patients. However, treatment of XDR-TB, by definition, presents a greater challenge than MDR-TB because of the resistance to fluoroquinolones in addition to at least 1 injectable drug. This resistance limits the choice of drugs from Group A to bedaquiline and linezolid and places more reliance on the added contribution of drugs from Group B and Group C to which the XDR-TB patient is not resistant, but which may be both more toxic and less effective. [41, 2]

The WHO issued an update in December 2019 regarding the use of pretomanid for XDR-TB. [42]. This update states that: “Treatment of extensively drug-resistant forms of TB presents multiple challenges to clinicians and national TB programmes both due to the limited range of medicines available and the life-threatening nature of the disease. The experience in the use of BPaL for treatment of XDR-TB patients is limited and the data from patients treated prospectively using all-oral longer regimens based on a WHO recommended revised priority classification of drugs is not yet available for comparison. Nevertheless, in individual patients for whom design of an effective regimen based on existing recommendations is not possible,

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the BPaL regimen may offer benefits despite potential harms and may be considered under prevailing ethical standards. In such patients the use of BPaL should be accompanied by individual consent, adequate counselling on potential benefits and harms and active monitoring and management of adverse events. Patients should also be advised that reproductive toxicities have been observed in animal studies10 and that the potential effects on human male fertility have not been adequately evaluated at this point in time."

2.4.3 Monitoring of treatment course/success

Monitoring treatment response

Patients should be monitored closely for signs of treatment failure. Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring. Chest radiographs should be taken at least every six months to document progress and to use for comparison if the patient's clinical condition changes. Monthly monitoring of sputum smears and cultures throughout treatment enables to identify conversion or failure to convert in a timely way. Drug susceptibility testing (DST) can be repeated for patients who remain smear and culture positive or who are suspects for treatment failure. [43]

Monitoring for adverse effects

Close monitoring of patients is necessary to ensure that the adverse effects of second-line anti-TB drugs are recognized quickly. Laboratory screening is invaluable for detecting certain adverse effects that are not often detectable by the patient and DOT provider. The schedule of monitoring in Table 10 is the minimal recommended frequency. More frequent screenings may be advisable, particularly for high-risk patients. [43]

Patients on MDR-TB treatment regimens need to be monitored for treatment response or failure and safety, using reasonable schedules of relevant clinical and laboratory testing. [17] Response to treatment and toxicity is monitored through regular history-taking, physical examination, chest radiography, special tests such as audiometry, visual acuity tests, electrocardiography and laboratory monitoring. Using smear microscopy or culture to assess conversion of bacteriological status is an

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important means of assessing response and most patients are usually expected to have converted to a sputum-negative status within the first few months of starting treatment. Persistence of culture positivity beyond that point, or close to the expected end of the intensive phase when injectable agents are in use, is a trigger for a review of the regimen and performance of DST.

Frameworks for the surveillance of bacteriological status, drug resistance and assignment of outcomes have been fairly standardized in past years. [44] In contrast, systematic monitoring of AEs during and after the end of treatment needs to be strengthened in most TB programmes, given the relative novelty of active pharmacovigilance within national TB programmes. In the case of this recommendation, it is important to monitor for hearing loss and kidney function, especially with the use of the aminoglycosides. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and repurposed medications in MDR-TB treatment regimens. The toxicity of certain agents may increase with the duration of use (such as nerve damage with linezolid) and may limit their continued use in a patient, and at times, result in complete cessation of treatment.

Electrocardiography may be indicated as more regimens in future may have two or three agents that are expected to prolong the QT interval if given concurrently. Audiometry and specific biochemical tests should also be made available whenever certain agents are included in the regimens. Treatment in pregnancy with postpartum surveillance for congenital anomalies will help inform future recommendations for MDR-TB treatment during pregnancy.

The prospective collection of accurate data for key variables at the case-based level using an electronic register is strongly advised in the best interests of the individual patient, and to inform local and global policy revisions. [16]

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Table 10 Schedule of clinical and laboratory follow up for uncomplicated MDR-TB patients [43]

Month	Clinical consult	Weight	Smear	Culture	DST	CXR	LFT	CR,K	TSH	Audiometry	HIV testing
0 (baseline)	√	√	√	√	√	√	√	√	√	√	√
1	Every 2 weeks	√	√	√				√		√	Repeat if indicated
2		√	√	√				√		√	
3		√	√	√				√	√	√	
4		√	√	√	If culture +ve			√		√	
5		√	√	√				√		√	
6		√	√	√	If culture +ve	Optional		√	√	√	
7		√	√	√				√		√	
8	Monthly	√	√	√	If culture +ve			√		√	
9		√	√	√				If on inj.	√	If on inj.	
10		√	√	√	If culture +ve			If on inj.		If on inj.	
11		√	√	√				If on inj.		If on inj.	
12		√	√	√	If culture +ve	Optional		If on inj.	√	If on inj.	
Until completion			Monthly	Monthly	If culture +ve	Optional		Every 3 months			

+ ve= positive; DST = Drug susceptibility testing; inj = injectable drug; LFT = liver function testing (liver enzymes); Cr = creatinine; K = potassium. Patient on treatment with bedaquiline, delamanid, or with QT prolonging drugs need special follow up with ECG

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Table 11 Relevant guidelines for diagnosis and management

<table>
<tr><th>Name of society/organisation issuing guidelines</th><th>Date of issue or last update</th><th>Country/ies to which guideline applies</th><th>Summary of recommendations

(Level of evidence/grade of recommendation for the indication under assessment)</th></tr>
<tr><td>WHO consolidated guidelines on drug-resistant tuberculosis treatment [2]
https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/</td><td>March 2019</td><td>Global</td><td>
<table>
<tr><th>Groups & steps</th><th colspan="2">Medicine</th></tr>
<tr><td rowspan="3">Group A:
Include all three medicines</td><td>levofloxacin OR
moxifloxacin</td><td>Lfx
Mfx</td></tr>
<tr><td>bedaquiline[2,3]</td><td>Bdq</td></tr>
<tr><td>linezolid[4]</td><td>Lzd</td></tr>
<tr><td rowspan="2">Group B:
Add one or both medicines</td><td>clofazimine</td><td>Cfz</td></tr>
<tr><td>cycloserine OR
terizidone</td><td>Cs
Trd</td></tr>
<tr><td rowspan="7">Group C:
Add to complete the regimen and when medicines from Groups A and B cannot be used</td><td>ethambutol</td><td>E</td></tr>
<tr><td>delamanid[3,5]</td><td>Dlm</td></tr>
<tr><td>pyrazinamide[6]</td><td>Z</td></tr>
<tr><td>imipenem–cilastatin OR
meropenem[7]</td><td>Ipm–Cln
Mpm</td></tr>
<tr><td>amikacin
(OR streptomycin)[8]</td><td>Am
(S)</td></tr>
<tr><td>ethionamide OR
prothionamide[9]</td><td>Eto
Pto</td></tr>
<tr><td>p-aminosalicylic acid[9]</td><td>PAS</td></tr>
</table>

Duration: 20 months is recommended from WHO. However, common practice and clinical trial data are based on a 24 months treatment.

(The WHO is not giving statements about evidence after each recommendation. However, the evidence is given due to consideration of PICO questions and supportive meta-analyses.)
</td></tr>
</table>

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WHO Rapid Communication 2019: Key changes to the treatment of drug-resistant tuberculosis [42] https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/	December 2019	Global	For the first time own consideration of XDR-TB and mentioning the BPaL regimen: “Treatment of extensively drug-resistant forms of TB presents multiple challenges to clinicians and national TB programmes both due to the limited range of medicines available and the life-threatening nature of the disease. The experience in the use of BPaL for treatment of XDR-TB patients is limited and the data from patients treated prospectively using all-oral longer regimens based on a WHO recommended revised priority classification of drugs is not yet available for comparison. Nevertheless, in individual patients for whom design of an effective regimen based on existing recommendations is not possible, the BPaL regimen may offer benefits despite potential harms and may be considered under prevailing ethical standards. In such patients the use of BPaL should be accompanied by individual consent, adequate counselling on potential benefits and harms and active monitoring and management of adverse events. Patients should also be advised that reproductive toxicities have been observed in animal studies and that the potential effects on human male fertility have not been adequately evaluated at this point in time.” Comment: We expect the final new WHO guideline by end of 2020 and a consideration of further evidence.
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 [28] http://www.euro.who.int/en/publications/abstracts/algorithm-for-laboratory-diagnosis-and-treatment-monitoring-of-pulmonary-tuberculosis-and-drug-resistant-tuberculosis-using-state-of-the-art-rapid-molecular-diagnostic-technologies-2017	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.” (The WHO is not giving statements about evidence after each recommendation. But this document is an expert opinion of the European Tuberculosis Laboratory Initiative core group members for the WHO European Region.)

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2.5 Comparators in the assessment

The primary study which was used for the purpose of marketing authorisation application of pretomanid is the Nix-TB study. [5] Another supporting study, the supporting ZeNix trial (NCT03086486), is still ongoing.

Because of the high mortality and poor treatment outcomes for XDR-TB treatment using pre-existing regimens, the Nix-TB trial did not include a control arm. At the time the trial was designed and initiated, a report of the long-term outcome of patients with XDR-TB treated in South Africa highlighted the very poor prognosis for patients with this disease. After 60 months of follow-up, 73% of 107 patients had died and only 11% had a favourable outcome. [Pietersen et al. 2014]

Moreover, given that the BPaL regimen had already proven to have only little pre-existing resistance among *M. tb* strains, different mode of action and no cross-resistance with other drugs, it would have been unethical to withhold it from patients. Additionally, because mouse models showed that the BPaL regimen led to significantly greater reductions in lung colony forming units than any 2-drug combination of its components, it would not have been ethical to limit treatment to just two out of the three component drugs in the test regimen. [12]

Since the Nix-TB study is an open-label, single-arm study, a direct comparator was originally not available. However, a prospective cohort comparison study has been performed, in which the Nix-TB study is compared with a 102-patient prospectively recruited South African XDR-TB cohort who received an ~18-month bedaquiline-based regimen (median of 8 drugs). A subset of the 102 patients received bedaquiline and linezolid (B-L combination; n=86) and a subgroup of these (n=75) served as individually matched controls in a pairwise comparison to determine differences in regimen efficacy. A subset of this cohort has been previously described. [46] These analyses were conducted by an independent statistician not affiliated with TB Alliance who developed pretomanid or the principal investigator for the XDR-TB cohort. All of the analyses described demonstrated statistically significant differences favouring the Nix-TB cohort. However, because these analyses have been submitted for publication in a peer-reviewed journal, substantive disclosure of the results would jeopardize their acceptance for publication.

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Therefore, the comparator with highest ranking in this dossier is the previous-published subset of the prospectively compared cohort. [46]

Other comparators included below are other antibiotic treatment regimens against XDR- or MDR-TB. These were identified in a search (date: 20. February 2020) for publications that fulfilled the following eligibility criteria:

- Population: MDR- or XDR-TB patients, adult patients (≥18 years)
- Interventions: any pharmacological antituberculosis intervention
- Study design: RCTs and prospective outcome studies
- Time period: 2010-2019
- Language: English

Studies, which were only published as abstract, were excluded from the further assessment.

It is important to note that XDR-TB patients represent a distinct treatment population than MDR-TB patients; by definition, they are resistant to several of the drugs that represent the first option for TB and MDR-TB treatment. Thus, success rates from MDR-TB trials would naturally be expected to be higher than those for XDR-TB trials. However, because TI/NR-MDR TB are *in label* for pretomanid, MDR-TB trials were included in the search.

TI/NR MDR-TB is also distinct from pre-XDR-TB which was studied in one trial below. [47]

The following table 12 gives an overview of the different forms of multidrug and highly resistant TB for better orientation:

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Table 12 Forms of multidrug and highly resistant TB according to WHO definition and clinical trial inclusion criteria

MDR-TB (WHO definition)	Resistant to at least isoniazid and rifampicin
pre-XDR-TB [47]	Additional resistance to at least one of the injectable agents (amikacin, kanamycin, capreomycin) OR to fluoroquinolones
XDR-TB (WHO definition)	Additional resistance to at least one of the injectable agents (amikacin, kanamycin, capreomycin) AND any of the fluoroquinolones (such as levofloxacin or moxifloxacin)
TI/NR MDR-TB (Nix-TB study) [12]	**NR MDR-TB** is documented by culture positive results (for *M.tb*) within 3 months prior to or at screening with documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the Investigator have been adherent to treatment and will be adherent to study regimen; **TI MDR-TB** is documented by culture positive (for *M.tb.*) results within 3 months prior to or at screening who are unable to continue second line drug regimen due to a documented intolerance to: a. PAS, ethionamide, aminoglycosides or fluoroquinolones; b. Current treatment not listed above that renders subject eligible for the study in the Investigator's opinion.

Another limitation for each comparison is that the underlying treatment recommendations change very fast. While the "comparator" clinical trials were conducted, different WHO guidelines for the treatment of drug-resistant TB were in place. WHO recommendations, guidelines, updates and rapid communications were issued in 2008, 2011, 2016 and December 2018/ March 2019. [48, 49, 38, 41, 2]

For instance, since 2018, bedaquiline and linezolid have been upgraded to "group A" (to be used in most MDR-TB regimens); before they were considered only in groups C and D.

The new position of bedaquiline and linezolid in group A support the approach that the ideal comparator to the Bedaquiline (B) + Pretomanid (Pa) + Linezolid (L) regimen is one that combines bedaquiline and linezolid with another baseline regimen (BR). In other words, the best comparator to B+L+Pa is B+L+BR. However, this approach is only used by (a) the previously mentioned unpublished prospective cohort comparison and (b) indirectly with the B+L+BR study arm from Olayanju et al. 2018. [46]

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The WHO rapid communication from December 2019 summarises that in the recent years, more effective drugs contributed to significant process in the treatment of resistant TB, but that these achievements have not been reproduced globally: In 2018, the success rate was only 56% for MDR/RR-TB patients and 39% for XDR-TB patients. To support countries, the WHO Global TB Programme regularly issues evidence-based guidelines. [42] To reflect this potential local delay in implementation of the most recent WHO guideline, other less suitable comparators are presented in this dossier as well.

A final limitation with all described comparator regimens is the number of used antibiotics and the treatment duration. All comparators consist of more than 3 antibiotics, and their treatment duration is much longer than 26 weeks.

The systematic literature reviews were undertaken to identify potential comparators, despite all just mentioned limitations. Details can be found in chapters 5.1 to 5.5.

The following antibiotics were included in at least one of the potential comparator regimens:

- Bedaquiline
- Clofazimine
- Delamanid
- Levofloxacin
- Linezolid
- Metronidazole
- Moxifloxacin
- Pretomanid
- Para-amino salicylic acid
- Pyrazinamide

3 Current use of the technology

3.1.1 Summary of issues relating to current use of the technology

- *The first regulatory approval of pretomanid was granted in the USA. It has FDA-approval since 14. August 2019.*
- *Pretomanid is available and reimbursed in the USA since 7. November 2019*
- *On the basis of the US FDA approval, pretomanid is also available via the Global Drug Facility (GDF) to 150 countries and territories. Given this, not all countries require the product to be approved locally since they can access pretomanid via GDF.*

3.2 Current use of the technology

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Pretomanid is a new orphan molecule awaiting marketing authorisation in Europe and not yet used in Europe. Even in the non-European countries, its use outside clinical trials has just started with launch in November 2019.

3.3 Reimbursement and assessment status of the technology

Pretomanid is not launched in Europe yet. Therefore, no European reimbursement regulations exist currently.

4 Investments and tools required

Summary of issues relating to the investments and tools required to introduce the technology

- With a simplified, highly effective, shorter, and all-oral regimen, BPaL transforms treatment for people diagnosed with XDR-TB and TI/NR MDR-TB and reduces the management burden.
- No additional tools than the already existing ones are needed to monitor special adverse events of interest for Pretomanid.
- Electrocardiograms may be required to detect QT prolongation with the BPaL regimen; however, this is not a new requirement for pretomanid since they are already required for use with bedaquiline-based regimens.
- Close monitoring of complete blood counts to detect myelosuppression is a need due to concomitant linezolid use but also required with other linezolid-containing regimens.
- Because the BPaL regimen lasts for only six months and uses only three antibiotics, it is likely that it reduces the resource burden needed for XDR- and TI/NR MDR- TB treatment versus previously used, more complex, longer regimens.

4.1 Requirements to use the technology

- … indicated in combination with bedaquiline and linezolid…(SmPC 4.1, wording before final linguistic review)
- Consideration should be given to official guidance on the appropriate use of antibacterial agents. (SmPC 4.1, wording before final linguistic review)
- Treatment with pretomanid should be initiated and monitored by a physician experienced in the management of multidrug-resistant tuberculosis. (SmPC 4.2, wording before final linguistic review)
- Pretomanid should be administered by directly observed therapy (DOT) or in accordance with local practice. (SmPC 4.2, wording before final linguistic review)
- No additional requirements in the equipment
- No supplies like syringes etc. needed. *Pretomanid is provided in tablets.*

5 Clinical effectiveness and safety

5.1.1 Summary of the clinical effectiveness

- Clinical data about the technology (pretomanid as part of a combination regimen with bedaquiline and linezolid in adult patients with pulmonary TI/NR MDR-TB or XDR-TB) in this dossier come from the Nix-TB study [5]. The additional ZeNix study (NCT03086486) is still ongoing.

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- Primary endpoint: 92% of the patients in the Nix-TB mITT population had a favourable outcome 6 months after the end of a 6-months BPaL-treatment, with 90% of the XDR-TB patients and 95% of the MDR-TB patients. In the ITT population, 90% of the total patient population, 89% of the XDR-TB patients and 92% of the MDR-TB patients had a favourable outcome (95% CI). [5]
- For comparison: Among other patients with XDR-TB who were treated in one of the Nix-TB study sites, the percentage of patients who were cured was below 20% before the use of bedaquiline or linezolid. This has improved to 66% more recently since bedaquiline and linezolid were added to the regimens. However, these newer regimens still used a median of 8 drugs over 24 months. [5, 45]
- Patients in the Nix-TB trial converted to culture-negative status relatively quickly after initiating treatment, with a median time of less than 6 weeks. [5]
- At 24 months after the end of the end of treatment, the results among the 47 of 109 patients who have already reached this time point were similar to the results at month 6 of follow-up. This is consistent with experience that most relapses will occur within the first 6 months. [5]

5.1.2 Summary of safety

- All patients had at least one adverse event that occurred or worsened during treatment [5], which is similar to a patient population treated with a bedaquiline and linezolid containing regimen, where 90.5% of the patients reported in median 3 adverse events. [46]
- A high percentage of patients had adverse events related to linezolid during the treatment: 81% of the patients reported peripheral neuropathy, and almost half had evidence of hematologic toxic effects. [5]
- A total of 62 patients (57%) had adverse events of grade 3 or higher that occurred or worsened during treatment. Linezolid was discontinued due to a TEAE at a higher rate (27 [24.8%] patients) than bedaquiline or pretomanid (any study drug was discontinued by 33 [30.3%] patients), which is comparable to the interruption rate of linezolid with about 30-60% in other studies [5, 12, 46]
- Serious adverse events (SAEs) occurred in 19 (17.4%) patients. Individual patients experienced more than one SAE. Most SAEs occurred after Day 30 of treatment. SAEs (not pulmonary tuberculosis) occurring in ≥2 patients included pneumonia (n=3, 2.8%), sepsis (n=2, 1.8%), anemia n=(2, 1.8%), hypoglycemia (n=2, 1.8%), pancreatitis (n=2, 1.8%), optic neuritis/optic neuropathy (n=2, 1.8%), seizure (n=2, 1.8%), and upper gastrointestinal hemorrhage/ hematemesis (2, 1.8%). Six of the 19 patients who developed SAEs during the trial also died during treatment. In the other 13 patients, the SAEs resolved or were resolving at the data cut-off date. [12]
- All surviving patients completed 26 weeks of treatment (including two who extended to 39 weeks); only one of these patients had a treatment interruption longer than the allowed 35 consecutive days, and none had the regimen permanently discontinued. [5]
- In total, 37 patients (34%) completed 26 weeks of linezolid treatment without any interruption, although they may have had a dose reduction, and 16 (15%) completed 26 weeks at a total daily dose of 1200 mg of linezolid with no interruptions or dose reductions. [5]

5.2 Identification and selection of relevant studies

The following databases were screened to identify relevant RCTs and prospective studies with patients in or as similar as possible to the target population (adult patients with pulmonary XDR-TB or TI/NR MDR-TB), i.e. comparators to the Nix-TB study [5]:

- Medline via Ovid
- Embase via Ovid
- Cochrane (EBM) Reviews via Ovid.

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In addition, a manual reference check of all included publications at the full-text stage was performed to identify additional relevant publications.

The “hand search” procedure was used to search for conferences of interest in the following conferences websites:

- The 50th Union World Conference on Lung Health 2019
- European Respiratory Society (ERS) International Congress 2019
- CHEST Congress 2019
- Conference on retroviruses and Opportunistic Infections (CROI) 2019
- 10th International Aids Society (IAS) Conference 2019

The search date for the clinical trials and prospective studies was 20. February 2020. The full-text publication of the relevant Nix-TB study became available later (5. March 2020) and was added manually.

Data from clinical trials and prospective studies covering the time period 2010-2019 and limited to documents in English language were included through the search syntax. The quality of the search syntax was assessed based on the PRESS checklist. [50]

Details about search strategy, search terms and the respective hits are presented in Table 29 (Appendix).

The review was conducted under EUnetHTA and NICE guidelines (which are in line with the EUnetHTA guidelines). Two consultants screened the retrieved hits independently considering their title, abstract and finally the information present in the full-text, carried out independently the data extraction and the quality assessment on included studies. A senior researcher settled disagreements between reviewers.

All publications meeting the inclusion and exclusion criteria presented in Table 13 were included. These criteria reflect the pretomanid target population, namely adult patients with pulmonary XDR-TB or TI/NR MDR-TB. However, it was necessary to include studies with every form of MDR-TB since TI/NR MDR is a subgroup within this indication.

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Table 13 Inclusion and exclusion criteria

Inclusion criteria	Population: MDR- or XDR-TB patients, adult patients (≥18 years) Intervention(s): any pharmacological antituberculosis intervention Comparator(s): see intervention(s) Outcomes: Efficacy and safety data in RCTs and prospective outcome studies Settings (if applicable): not applicable Study design: RCTs and prospective outcome studies Language restrictions: English Other search limits or restrictions applied: Year of publication: from 2010 to 2019
Exclusion criteria	Population:Non-MDR-TB & non-XDR-TB patients, children/pediatric population, non-humans Intervention(s): Complementary and alternative medicine Comparator(s): see intervention(s) Outcomes: not applicable Settings (if applicable): not applicable Study design: Case reports, reviews (non-systematic), and editorials/letters Language restrictions: English Other search limits or restrictions applied: Year of full-length publications before 31/12/2009

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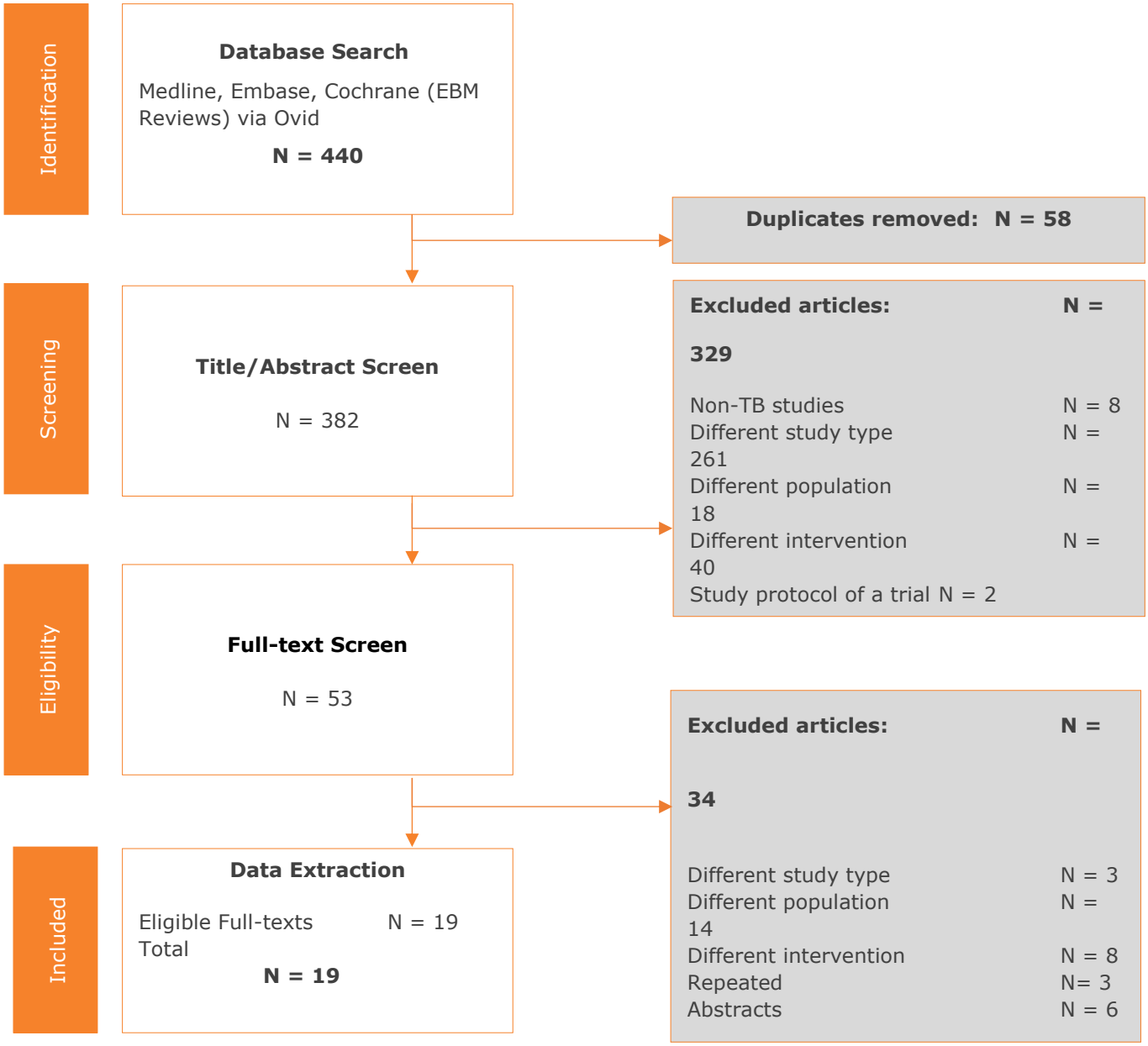
The following PRISMA flow chart provides an overview of the number of identified and excluded studies:



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5.3 Relevant studies

The following tables 14 to16 provide an overview of studies which were in different grades relevant for this dossier. Table 14 informs about the studies with Pretomanid in combination with bedaquiline and linezolid in patients with XDR-TB, (pre-XDR-TB) and TI/NR MDR-TB: NixTB and ZeNix. Since the ZeNix study is still ongoing whereas the NixTB-study provided already outcomes sufficient for marketing authorisation, this dossier is focussing on the Nix-TB study. The ZeNix study is listed for completeness. Table 15 contains potential comparators as outcome of the systematic literature search on clinical trials. They are not ranked according to the status of RCT or non-RCT but by status of suitability as comparator because important clinical trials were single-arm studies. This has following background:

XDR-TB is, with 13,068 notified cases globally, much rarer than RR/MDR-TB with 186,772 cases. For comparison, the total number of all TB-patients was 7,253,116 in 2018. [4]. Among 9,258 patients started on treatment for XDR-TB in 2016, in 57 countries and territories for which outcomes were reported, 39% completed treatment successfully, 26% died, treatment failed for 18%, and 18% were lost to follow-up or their treatment outcome was not evaluated. [4]

Because of the high mortality and poor treatment outcomes for XDR-TB treatment using pre-existing regimens, the Nix-TB trial did not include a control arm. Moreover, given that the BPaL regimen had already proven to have little pre-existing resistance among *M. tb* strains, different mode of action and no cross-resistance with other drugs, it would have been unethical to withhold it from patients. Additionally, because mouse models showed that the BPaL regimen led to significantly greater reductions in lung colony forming units than any 2-drug combination of its components, it would not have been ethical to limit treatment to just two out of the three component drugs in the test regimen. [12]

Table 16 lists finally those studies which were identified by the systemic literature review but do not fit into the scope of this dossier. They are not suitable as comparators because they analyse pretomanid in other treatment regimens for patients in less severe TB indications.

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5.3.1 Pretomanid studies in the target intervention/population

Table 14 List of all relevant phase III studies with pretomanid plus bedaquiline and linezolid in XDR-TB, (pre-XDR-TB) and TI/NR MDR-TB

Study reference/ID	**Available documentation**	**RCT or other**	**Status (ongoing/ complete)**
Nix-TB *Conradie et al. 2020 [5]* *NCT02333799*	•*ClinicalTrials.gov identifier (NCT number): NCT02333799* •*[5]* •*Pretomanid Sponsor briefing document, June 6, 2019, https://www.fda.gov/media/127593/download* •*The prospective comparison with a 102-patient prospectively recruited South African XDR-TB cohort who received an ~18-month bedaquiline-based regimen (median of 8 drugs) is expected in autumn 2020*	*Single-arm study*	*Ongoing, has interim results; estimated Study Completion Date: Oct. 2021*
ZeNix *NCT03086486*	•*ClinicalTrials.gov identifier (NCT number): NCT03086486*	*RCT*	*Ongoing*

5.3.2

5.3.3 Studies of potential comparators identified by the literature search

This table as well as all following tables are ranked by disease in first order. Studies conducted with XDR-TB and pre-XDR patients meet the target population better than studies with MDR-TB patients. In the MDR-TB studies, no TI/NR MDR-TB groups or subgroups were analysed. And DS-TB does not fall into the population definition of this assessment. In the second instance, the studies are ranked by substance with regimens containing bedaquiline and linezolid having the highest ranking, followed by delamanid as new substance. The remaining studies were not raked by special preferences.

Table 15 List of identified studies representing a potential comparator – roughly sorted by level of comparability (TB-type, bedaquiline and/or linezolid in regimen, in the MDR-TB cluster with lower priority also by region (Africa and Europe > Asia) and publication date

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	Available documentation	RCT or other	Status (ongoing/ complete)
Subset of prospective comparator cohort			
Olayanju et al. 2018 [46]	*Olayanju O, Limberis J, Esmail A, Oelofse S, Gina P, Pietersen E, et al. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. Eur Respir J [Internet]. 2018;51(5). Available from: http://www.ncbi.nlm.nih.gov/pubmed/29700106*	*Prospective study*	*Complete*
Another a very similar population			
Pym et al. 2016 [47] NCT00910871	*Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drugresistant tuberculosis. Eur Respir J [Internet]. 2016 Feb 1;47(2):564–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26647431*	*Single-arm study*	*Complete*
*Other trials in patients with **XDR-TB***			
Tang et al. 2015a [51]	*Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: A study in China. Eur Respir J [Internet]. 2015 Jan 1;45(1):161–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25234807*	*RCT*	*Complete*
Lee et al. 2012 [52] NCT00727844	*Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med [Internet]. 2012 Oct 18;367(16):1508–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23075177*	*RCT*	*Complete*
Wang et al. 2018 [53] ChiCTR1800014800	*Wang Q, Pang Y, Jing W, Liu Y, Wang N, Yin H, et al. Clofazimine for treatment of extensively drug-resistant pulmonary tuberculosis in China. Antimicrob Agents Chemother [Internet]. 2018 Apr 1;62(4). Available from: http://www.ncbi.nlm.nih.gov/pubmed/29378718*	*RCT*	*Complete*
*Other trials in patients with **MDR-TB***			
Diacon et al. 2012 [54]	*Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: Long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother [Internet]. 2012 Jun;56(6):3271–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22391540*	*RCT*	*Complete*
Diacon et al. 2014 [55] NCT00449644	*Diacon AH, Pym A, Grobusch MP, De Los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med [Internet]. 2014 Aug 21;371(8):723–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25140958*	*RCT*	*Complete*
Tsuyuguchi et al. 2019 [56] NCT02365623	*Tsuyuguchi K, Sasaki Y, Mitarai S, Kurosawa K, Saito Y, Koh T. Safety, efficacy, and pharmacokinetics of bedaquiline in Japanese patients with pulmonary multidrug-resistant tuberculosis: An interim analysis of an open-label, phase 2 study. Respir Investig [Internet]. 2019 Jul 1;57(4):345–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30745177*	*Single-arm study*	*Complete*
STREAM, Nunn et	*Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A trial of a shorter*	*RCT*	*Ongoing*

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al. 2019 [57] NCT02409290	*regimen for rifampin-resistant tuberculosis. N Engl J Med [Internet]. 2019 Mar 28;380(13):1201–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30865791*		
von Groote-Bidlingmaier et al. 2019 [58] NCT01424670	*von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med [Internet]. 2019 Mar 1;7(3):249–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30630778*	*RCT*	*Complete*
Gler et al. 2012 [59] NCT00685360	*Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012 Jun 7;366(23):2151–60.*	*RCT*	*Complete*
Duan et al. 2019 [60] ChiCTR1800014800	*Duan H, Chen X, Li Z, Pang Y, Jing W, Liu P, et al. Clofazimine improves clinical outcomes in multidrug-resistant tuberculosis: a randomized controlled trial. Clin Microbiol Infect. 2019 Feb 1;25(2):190–5.*	*RCT*	*Complete*
Du et al. 2019 [61] ChiCTR 1800020391	*Du Y, Qiu C, Chen X, Wang J, Jing W, Pan H, et al. Treatment outcome of a shorter regimen containing clofazimine for multidrug-resistant tuberculosis: a randomized control trial in China. Clin Infect Dis [Internet]. 2019 Sep 24; Available from: http://www.ncbi.nlm.nih.gov/pubmed/31549147*	*RCT*	*Complete*
Koh et al. 2013 [62] NCT 01055145 (publication of interim results)	*Koh WJ, Lee SH, Kang YA, Lee CH, Choi JC, Lee JH, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2013 Oct 1;188(7):858–64.*	*RCT*	*Interim results of completed tiral*
Kang et al. 2016 [63] NCT 01055145 (publication of final results)	*Kang YA, Shim TS, Koh WJ, Lee SH, Lee CH, Choi JC, et al. Choice between levofloxacin and moxifloxacin and multidrug-resistant tuberculosis treatment outcomes. Ann Am Thorac Soc [Internet]. 2016 Mar 1;13(3):364–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26871879*	*RCT*	*Complete*
Tang et al. 2015b [64]	*Tang S, Yao L, Hao X, Liu Y, Zeng L, Liu G, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. Clin Infect Dis [Internet]. 2015 May 1;60(9):1361–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25605283*	*RCT*	*Complete*
Carroll et al. 2013 [65]	*Carroll MW, Jeon D, Mountz JM, Lee JD, Jeong YJ, Zia N, et al. Efficacy and safety of metronidazole for pulmonary multidrug-resistant tuberculosis. Antimicrob Agents Chemother [Internet]. 2013 Aug;57(8):3903–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23733467*	*RCT*	*Complete*

5.3.4 Other studies

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The following table 16 lists further clinical trials which met the inclusion criteria of the systematic literature search. However, these trials analysed pretomanid in other treatment regimens which are not in the scope of the assessed intervention and have only very small overlap due to some MDR-TB patients within the analysed population. Therefore, they are not considered in the rest of the dossier.

Table 16 List of further identified studies with patients having MDR-TB but also DS-TB.

Study reference/ID	**Available documentation**	**RCT or other**	**Status (ongoing/ complete)**
NC-005, Tweed et al. 2019 [66] NCT02193776	*Tweed CD, Dawson R, Burger DA, Conradie A, Crook AM, Mendel CM, et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med [Internet]. 2019 Dec 1 [cited 2020 Mar 27];7(12):1048–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31732485*	*RCT*	*Complete*
Dawson et al. 2015 [67] NCT01498419	*Dawson R, Diacon AH, Everitt D, Van Niekerk C, Donald PR, Burger DA, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: A phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet [Internet]. 2015 May 2 [cited 2020 Mar 29];385(9979):1738–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25795076*	*RCT*	*Complete*

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5.4 Main characteristics of studies

This chapter starts with a detailed description of the main characteristics of the Nix-TB trial. The main characteristics of all studies assessed in this dossier are summarized in Table 17. An additional Table 18 provides more details about the treatment regimens. And Table 19 summarises the demographic data of all studies.

Patient flow diagrams of the studies, as far as available, are provided in chapter 7.1 in the appendix.

5.4.1 Main characteristics of the Nix-TB study

5.3.1.1 Objective and design

The objective of the phase 3 single-arm Nix-TB trial is the evaluation of efficacy, safety, tolerability and pharmacokinetics of the BPaL regimen (bedaquiline + pretomanid + linezolid) after 6 months of treatment (with an option to treat for 9 months in patients who were culture positive or reverted to being culture positive between month 4 and month 6) in patients with pulmonary XDR-TB, treatment-intolerant (TI) MDR-TB, or nonresponsive (NR) MDR-TB. The recommended dosing for the BPaL regimen was:

- Bedaquiline: 400 mg daily from day 1 to day 14 and 200 mg three times weekly thereafter
- Pretomanid: 200 mg daily
- Linezolid: 1200 mg daily (600 mg twice daily or 1200 mg once daily after protocol was amended)

A reduction in the dose of linezolid or temporary cessation of linezolid was allowed per investigator's discretion for suspected drug-related toxicity; linezolid could also be discontinued, if necessary, after the first month of treatment. For the entire BPaL regimen, treatment could also be halted for up to 35 consecutive days, and any missed doses would be made up at the end of treatment to complete a full 26 weeks of therapy. Of note, missed doses of linezolid alone were not to be made up at the end of treatment.

Nix-TB consists of a 6-month treatment period, with a 3-month optional extension, and includes 24 months of post-treatment follow-up. The primary endpoint was assessed 6 months after the end of treatment. The study flow is visible in Fig. 3:

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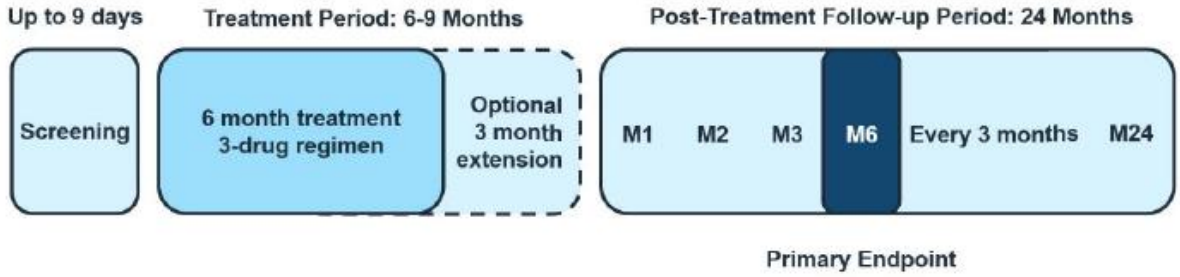
Figure 3 Nix-TB study flow



The patients underwent the treatment phase and a 6 -months-follow-up. The follow-up until month 24 is still ongoing.

5.3.1.2. Inclusion criteria

Patients were eligible for inclusion into the trial if they met each of the following criteria:

1. Provided written, informed consent prior to all trial-related procedures (if under 18 years of age, included consent of legal guardian);
2. Body weight of ≥35 kg (in light clothing and no shoes);
3. Willingness and ability to attend scheduled follow-up visits and undergo trial assessments;
4. Provided consent for HIV testing. If an HIV test was performed within 1 month prior to trial start, it was not to be repeated as long as documentation could be provided (enzyme-linked immunosorbent assay and/or Western Blot). If the HIV status was a confirmed known positive, repeated HIV testing was not needed, provided documentation was available;
5. Male or female, aged ≥14 years;
6. Patients with 1 of the following pulmonary TB conditions:
    a. XDR-TB with:
        i. Documented culture positive (for M. tuberculosis) results within 3 months prior to Screening or M. tuberculosis confirmed in sputum based on molecular test within 3 months prior to or at Screening;
        ii. Documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable historically at any time or at Screening.

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b. MDR-TB documented by culture positive results (for M. tuberculosis) within 3 months prior to or at Screening with documented nonresponse to treatment with the best available regimen for 6 months or more prior to enrolment and the patient, in the opinion of the Investigator would be adherent to treatment;
c. MDR-TB documented by culture positive (for M. tuberculosis) results within 3 months prior to or at Screening and unable to continue second-line drug regimen due to a documented intolerance to:
    i. Para-aminosalicylic acid, ethionamide, aminoglycosides or fluoroquinolones;
    ii. Current treatment not listed above that rendered patient eligible for the trial in the Investigator's opinion.

7. Had a chest X-ray picture (taken within a year prior to Screening) consistent with pulmonary TB in the opinion of the Investigator;
8. Were of nonchildbearing potential or used effective methods of birth control, as defined below:

Nonchildbearing potential:

a. Patient was not heterosexually active or practices sexual abstinence;
b. Female patient/sexual partner – who had undergone a bilateral oophorectomy, bilateral tubal ligation and/or

Male patient/sexual partner – who was vasectomized or had had a bilateral orchidectomy minimally 3 months prior to Screening.

Effective birth control methods:

A double contraceptive method was to be used as follows:

a. Double barrier method which could have included any 2 of the following: a male condom, diaphragm, cervical cap, or female condom (male and female condoms were not to be used together);
b. Barrier method (one of the above) combined with hormone-based contraceptives or an intra-uterine device for the female patient/partner;
c. And patients had to be willing to continue practicing birth control methods throughout treatment and for 6 months (both male and female patients) after the last trial treatment administration or discontinuation from trial treatment in case of premature discontinuation.

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Note: Hormone-based contraception alone may not have been reliable when taking trial treatment; therefore, hormone-based contraceptives alone could not be used by female patients or female partners of male patients to prevent pregnancy.

5.3.1.3 Exclusion criteria

Patients were excluded from the trial if they met any of the following criteria:

Medical history:

1. Any condition in the Investigator's opinion (ie, an unstable disease such as uncontrolled diabetes or cardiomyopathy and extrapulmonary TB requiring extended treatment), where participation in the trial compromised the well-being of patient or could have prevented, limited or confounded protocol-specified assessments;
2. Abuse of alcohol or illegal drugs, that in the opinion of the Investigator compromised the patients' safety or ability to follow through with all protocol-specified visits and evaluations;
3. In the judgment of the Investigator, the patient was not expected to survive for more than 12 weeks;
4. The patient had a Karnofsky score <50 within 30 days prior to Screening;
5. Body Mass index (BMI) <17 kg/m^2;
6. History of allergy or known hypersensitivity to any of the trial treatments or related substances;
7. HIV infected patients with a cluster of differentiation 4 (CD4) + count of ≤50 cells/μL. For HIV infected patients having a CD4+ count >50 cells/μL:
    a. Were being treated with, or needed to initiate, antiretroviral therapy (ART) which was not compatible with the allowed ARTs and was not considered an appropriate candidate for switching to a regimen of antiretroviral drugs (ARVs) which was allowed. If there were any questions, they were to be discussed with the Sponsor Medical Monitor for confirmation of appropriate ARV regimen. Examples of allowed treatment included, but were not limited to the following:
        i. Nevirapine based regimen consisting of nevirapine in combination with any nucleoside reverse transcriptase inhibitors (NRTIs);

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ii. Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia) in combination with any NRTIs;
iii. The combination of tenofovir/lamivudine/abacavir was to be considered for patients with normal renal function to address myelosuppression cross-toxicity of zidovudine and linezolid;
iv. An alternate regimen that may have been considered if the above was not appropriate; a triple NRTI based regimen consisting of zidovudine, lamivudine and abacavir, but had to be used with caution. Regimens including zidovudine were to be used with special caution as zidovudine and linezolid may both cause peripheral nerve toxicity;
v. Raltegravir in combination with NRTIs.

b. Could not ensure a 2-week interval between commencing trial treatment and the start of the ART, if not already on ARTs.

8. Had participated in other clinical trials with administration of investigational agents within 8 weeks prior to the trial start or was currently enrolled in an investigational trial that included treatment with medicinal agents. Patients who were participating in observational trials or who were in a follow-up period of a trial that included drug therapy could have been considered for inclusion;
9. Had significant cardiac arrhythmia requiring medication;
10. Patients who had the following at Screening:
    a. Time required for depolarization and repolarization of ventricles (QT) interval corrected using Fridericia's method (QTcF) interval on ECG >500 msec. Patients with QTcF >450 msec had to be discussed with the Sponsor Medical Monitor before enrolment;
    b. History of additional risk factors for Torsade de Pointes, (eg, heart failure, hypokalemia, and family history of Long QT Syndrome);
    c. Clinically significant ventricular arrhythmias;
    d. Patients with other cardiac abnormalities that may have placed them at risk of arrhythmias were required to be discussed with the Sponsor Medical Monitor before enrolment. Such abnormalities included: evidence of ventricular preexcitation (eg, Wolff Parkinson White syndrome); electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch

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block; evidence of second- or third-degree heart block; and intraventricular conduction delay with a QRS duration more than 120 msec.

11. Female patients who had a positive pregnancy test at Screening or were already known to be pregnant, breastfeeding, or planning to conceive a child during the trial or within 6 months of cessation of trial treatment. Males planning to conceive a child during the trial or within 6 months of cessation of trial treatment;
12. Had peripheral neuropathy of Grade 3 or Grade 4, according to the DMID. Or, patients with neuropathy Grade 1 or Grade 2 which was likely to progress/worsen over the course of the trial, in the opinion of the Investigator.

Specific Treatments:

13. Concomitant use of monoamine oxidase inhibitors or prior use within 2 weeks of the first trial treatment administration;
14. Concomitant use of serotonergic antidepressants or prior use within 3 days of first trial treatment administration if Investigator had foreseen potential risks for serotonin syndrome when combined with linezolid;
15. Concomitant use of any drug known to prolong the corrected QT interval (QTc) (including, but not limited to, amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, fluoroquinolones, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalols, parfloxacin, and thioridazine);
16. Concomitant use of any drug known to induce myelosuppression;
17. Use of any drugs or substances within 30 days prior to trial treatment administration known to be strong inhibitors or inducers of cytochrome P450 (CYP) enzymes (including but not limited to quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafylline, cimetidine, and dextromethorphan). Exceptions may have been made for patients who had received 3 days or less of 1 of these drugs or substances, if there had been a washout period before administration of trial treatment equivalent to at least 5 half-lives of that drug or substance;

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18. Patients may have previously been treated for DS/MDR-TB (with specific exceptions for bedaquiline and/or linezolid as noted below) provided that treatment was discontinued at least 3 days prior to the first trial treatment administration;
19. Patients were not to have received more than 2 weeks of bedaquiline or linezolid prior to enrolment/first administration of trial treatment.

Based on Laboratory Abnormalities

20. Patients with the following toxicities at Screening (laboratory tests may have been repeated) as defined by the enhanced DMID adult toxicity table (November 2007):
    a. Serum potassium less than the lower limit of normal of the laboratory;
    b. Hemoglobin level Grade 2 or greater (<8.0 g/dL);
    c. Platelets Grade 2 or greater (<75 000/mm^3);
    d. Absolute neutrophil count (ANC) <1000/mm^3;
    e. Aspartate aminotransferase (AST):
        - Grade 3 or greater (>3.0 × upper limit of normal [ULN]) were to be excluded;
        - Greater than ULN had to be discussed with and approved by the Sponsor Medical Monitor.
    f. Alanine aminotransferase (ALT)
        - Grade 3 or greater (>3.0 × ULN) were to be excluded;
        - Greater than ULN had to be discussed with and approved by the Sponsor Medical Monitor.
    g. Total bilirubin:
        - Grade 3 or greater (≥2.0 × ULN), or if ≥1.5 up to 2.0 × ULN when accompanied by an increase in other liver function test (ALT, AST, alkaline phosphatase or gamma-glutamyltransferase);
        - 1 to 1.5 × ULN had to be discussed with and approved by the Sponsor Medical Monitor.
    h. Direct bilirubin:
        - Greater than ULN were to be excluded;
    i. Serum creatinine level greater than 2 × ULN.

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j. Albumin <32 g/L.

5.3.1.4 Ethics

The Nix-TB trial was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations. The patients signed a declaration of consent.

5.3.1.5 Primary endpoint

The primary endpoint of the trial was the incidence of bacteriologic failure, relapse or clinical failure through follow-up until 6 months after the End of Treatment. Patients were classified as having a favorable, unfavorable, or unassessable status at 6 months after the End of Treatment.

The following definitions apply:

- Clinical failure (Treatment failure) is defined as being declared an unfavorable status at, or before, the End of Treatment or failing to attain a culture negative status or the patient was withdrawn at, or before, the End of Treatment for clinical (TB) reasons including being retreated (or changing from trial treatment) for TB;
- Bacteriologic relapse (Relapse) is defined as failing to maintain a culture negative status or being declared an unfavorable outcome after the End of Treatment in patients who attained culture negative status by the End of Treatment, and had culture conversion to a positive status with the same M. tuberculosis strain after the End of Treatment in patients who attained culture negative status by the End of Treatment **and** were withdrawn for clinical (TB) reasons including being retreated (or changing from trial treatment) for TB;
- Bacteriologic failure (Reinfection) is defined as failing to maintain culture negative status or being declared an unfavorable outcome (including being withdrawn for clinical [TB] reasons including being retreated or changing from trial treatment for TB) after the End of Treatment in patients who attained 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 to be assumed as having relapsed.

Note:

- Culture conversion required at least 2 consecutive culture negative/positive samples at least 7 days apart;
- Patients who were documented at a visit as unable to produce sputum and who were clinically considered to be responding well to treatment were considered to be culture negative at that visit;
- Positive culture refers to the culture testing positive for M. tuberculosis;
- Culture negative status was achieved when a patient produced at least 2 negative culture results at different visits (at least 7 days apart) without an intervening positive culture result for M. tuberculosis.

5.3.1.6 Secondary endpoints - efficacy

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- Incidence of bacteriologic failure, or relapse, or clinical failure through follow-up until 24 months after the End of Treatment as a confirmatory analysis;
- Time to sputum culture conversion to negative status through the Treatment Period;
- Proportion of patients with sputum culture conversion to negative status at 4, 6, 8, 12, 16, and 26 or 39 weeks;
- Linezolid dosing (actual) and efficacy were explored;
- Change from baseline TB symptoms;
- Change from baseline in the patient-reported health status;
- Change from baseline weight.

5.3.1.7 Secondary endpoints – safety and tolerability

- All-cause mortality;
- Incidence of treatment-emergent adverse events (TEAEs) by severity, (Division of Microbiology and Infectious Diseases [DMID] toxicity grade), drug relatedness, and seriousness, leading to early withdrawal, and leading to death;
- Quantitative and qualitative clinical laboratory measurements, including observed values and change from baseline;
- Quantitative and qualitative electrocardiogram (ECG) measurements, including observed values and change from baseline;
- Descriptive statistics of ophthalmology slit lamp examination data (Age Related Eye Disease Study 2 [AREDS2] lens opacity classification and grading);
- Changes in ophthalmic examination for visual acuity and color vision, including observed values and change from baseline;
- Changes noted in peripheral neuropathy signs and symptoms, including observed and change in the score from baseline.

5.3.1.8 Other secondary endpoints

Other endpoints were: pharmacokinetics, exploratory endpoints, general mycobacteriology.

5.3.1.9 Statistical analysis

The BPaL regimen was determined to be effective if the lower bound of the 95% confidence interval of the percentage of patients with a favorable outcome was greater than 50%.

It was planned to include up to 200 patients into the Nix-TB trial. However, enrollment was stopped after inclusion of 109 patients because the ZeNix study (NCT03086486) for more detailed assessment of the linezolid dosing within the BPaL regimen started meanwhile

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The primary efficacy analysis population as per the statistical analysis plan was the modified intent-to-treat (mITT) population (n=107), which excluded 2 patients from the intent-to-treat (ITT) population (n=109) whose outcome at 6 months following the end of treatment was “unassessable” (one patient had non-TB-related death during follow-up after conversion to culture negative status, and another patient was lost to follow-up after end of treatment and was sputum culture negative when last seen).

All analyses were performed with Stata software, version 15.1 (StataCorp).

No formal statistical tests were performed. The time to an unfavorable outcome and time to culture-negative status were analyzed with standard time-to-event analysis techniques, including Kaplan– Meier plots.

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Table 17 Characteristics of the studies

Study reference/ID	Objective	Study design	Eligibility criteria*	Intervention and Comparator (N enrolled)**	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
NixTB NCT02333799 (Conradie et al. 2020)	Efficacy, safety, tolerability and pharmacokinetics of the BPaL regimen in subjects with XDR-TB and TI/NR MDR-TB	open-label, single-arm phase 3 clinical trial	target population: adult pulmonary XDR-TB and TI/NR MDR-TB	Intervention: BPaL regimen, i.e. bedaquiline, pretomanid and linezolid (n=109)	Incidence of bacteriologic failure, relapse or clinical failure through follow-up until 6 months after the end of the 26 week-treatment	Incidence of bacteriologic failure, or relapse, or clinical failure through follow-up until 24 months after the end of treatment as a confirmatory analysis; time to sputum culture conversion to negative status through the treatment period, and other
ZeNix NCT03086486	Safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in patients with pulmonary TB, XDR-TB, Pre-XDR-TB or TI/NR MDR-TB	phase 3, multi-center, partially-blinded RCT; 4 parallel treatment groups; bedaquiline and pretomanid not blinded. Linezolid dose and duration double-blinded	adult pulmonary XDR-TB, pre-XDR-TB and TI/NR MDR-TB	4 parallel intervention arms: a) 1200mg L x 26 weeks + Pa + B, b) 1200 mg L x 9 weeks + Pa + B, c) 600 mg L x 26 weeks + Pa + B, d) 600 mg L x 9 weeks + Pa + B	Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment [Time Frame: 26 weeks treatment and 26 weeks follow-up]]	Incidence of bacteriologic failure or relapse or clinical failure through follow up until 78 weeks after the end of treatment; time to sputum culture conversion to negative status through the treatment period (26 weeks); proportion of participants with sputum culture conversion to negative status at weeks 4, 6, 8, 12, 16, 26; change from baseline TB symptoms (26 weeks); change from baseline in Patient Reported Health Status (26 weeks), change from baseline weight (26 weeks)

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Olayanju et al. 2018 [46]	To compare long-term outcomes of XDR-TB patients treated with or without bedaquiline in a high TB-incidence setting	prospective observational study	adult pulmonary XDR-TB, pre-XDR-TB, MDR-TB	Intervention: bedaquiline-based treatment regimen; 53 of the 68 (77.9%) patients who received bedaquiline also received linezolid (n=68); Comparator: non-bedaquiline-based anti-TB regimen (n=204) [treatment duration with bedaquiline 24 weeks and BR 24 months]	Outcomes: cure/treatment completion, deceased, treatment failure, treatment default and lost to follow-up [time frame 24 months]	
Study reference/ID	**Objective**	**Study design**	**Eligibility criteria***	**Intervention and Comparator (N enrolled)****	**Primary outcome measure and follow-up time point**	**Secondary outcome measures and follow-up time points**
Pym et al. 2016 [47]	to evaluate the safety, tolerability and effectiveness of bedaquiline [24 weeks] in combination with an individualized background regimen (BR) of antibacterial drugs as 24 month-treatment for MDR-TB	phase 2, multicenter, open-label, single-arm trial	adult pulmonary XDR-TB, pre-XDR-TB, MDR-TB	Intervention: bedaquiline + background regimen for MDR-TB (n=233 for the safety analysis); n=205 for the efficacy analysis, which excluded 3 patients with DS-TB and 25 with negative cultures at screening and/or baseline)	The median time to confirmed sputum culture conversion (two consecutive visits with negative MGIT cultures from spot sputa collected at least 25 days apart and not followed by a confirmed positive culture) during 24 weeks of bedaquiline treatment and 24 months of BR treatment	The percentage of participants with sputum culture conversion up to week 120
Tang et al. 2015a [51]	evaluate the efficacy, safety and tolerability of linezolid in patients with XDR-TB in China.	prospective multicenter RCT	adult pulmonary XDR-TB	Intervention: linezolid (n=33); Comparator: control (n=32)	Time to sputum-culture conversion [tested at least once every 3 months during the 24-month treatment period]; safety	
Lee et al. 2012	to investigate the	phase 2a,	adult pulmonary	Intervention: linezolid	Time to sputum-culture	

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[52]	effectiveness of linezolid in treating patients with XDR TB	randomized, two-group study	XDR-TB	therapy inmediately (n=21/ mITT=19); Comparator: linezolid therapy after 2 months (n=20)	conversion on solid medium, with data censored at 4 months	
Wang et al. 2018 [53]	Efficacy and safety of clofazimine for XDR-TB patients	multicenter, prospective, randomized clinical study	adult pulmonary XDR-TB	Intervention: clofazimine (n=22); Comparator: control (n=27)	Time to sputum culture conversion on solid medium; safety [patients were monitored during 36 months of XDR-TB treatment]	Treatment outcome: cure, complete treatment, treatment failure, death during 36 months of treatment
Diacon et al. 2012 [54]	Describe the long-term outcome, tolerability and, effect on emergence of DR	2-year follow-up of a randomized placebo-controlled study	adult pulmonary MDR-TB who had either not been treated or had received only the first-line	Intervention: bedaquiline + background regimen (n=21; safety: n=47); Comparator: placebo + background regimen (n=23)	Time to sputum conversion, acquired resistance, monitoring of AE [for 24 months]	
Diacon et al. 2014 [55]	Evaluate the efficacy of bedaquiline when added to a background regimen in MDR-TB patients	randomized, double-blind, placebo-controlled phase 2b study	adult pulmonary MDR-TB	Intervention: bedaquiline + background regimen (n=79); Comparator: placebo + background regimen (n=81)	Time to sputum culture conversion in liquid broth, which was defined as two consecutive negative liquid cultures from sputum samples that were collected at least 25 days apart and were not followed by confirmed positive cultures.	rates of culture conversion a2fter 24 weeks and after 120 weeks.
Study reference/ID	**Objective**	**Study design**	**Eligibility criteria***	**Intervention and Comparator (N enrolled)****	**Primary outcome measure and follow-up time point**	**Secondary outcome measures and follow-up time points**
Tsuyuguchi et al. 2019 [56]	identifying the safety and efficacy and pharmacokinetics of bedaquiline in japanese patients	interim analysis ofanopen-label phase 2 study	adult pulmonary MDR-TB	Intervention: bedaquiline + background regimen (n=6)	Safety, efficacy (time to sputum culture conversion), pharmacokinetic [time: up to 126 weeks]	
STREAM, (Nunn et al. 2019) [57]	Comparison of a short regimen with a long regimen for MDR-TB	randomized, phase 3, noninferiority trial	adult pulmonary MDR-TB	Intervention: long regimen (n=142); Comparator: short regimen (n=282)	Negative culture at week 132 and at a previous occasion during the trial	Time to smear and culture conversion during 132 weeks of treatment

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von Groote-Bidlingmaier et al. 2019 [58]	Evaluate the safety and efficacy of delamanid in the first 6 months of treatment	multicenter randomised, double-blind, placebo-controlled, phase 3 trial	adult pulmonary MDR-TB	Intervention: oral delamanid + background regimen (n=341); Comparator: placebo + background regimen (n=170)	Time to sputum culture conversion and difference in distributions of time to sputum culture conversion between the two groups [6 months]	SCC at 2 and 6 months; time to SCC over 6 months, determined by solid culture; sustained SCC between months 18 and 30; treatment outcomes; treatment success or failure at month 30; change from baseline in time to detection M. tuberculosis; and acquired drug resistance
Gler et al. 2012 [59]	The objective of the trial was to evaluate the safety, efficacy, and pharmacokinetics of two doses of delamanid	multicenter, double-blind, stratified, randomized,	adult pulmonary MDR-TB	Intervention: delamanid 100 mg twice daily + background regimen (n=161); Comparator 1: delamanid 200 mg twice daily + background regimen (n=160); Comparator 2: placebo + background regimen (n=160)	Proportion of patients with sputum-culture conversion at 2 months. Pharmacokinetics, safety	
Duan et al. 2019 [60]	Study the efficacy of clofazimine with the standardized regimen in MDR-TB patients	multicenter RCT	adult pulmonary MDR-TB	Clofazimine +standardized regimen (n=66); Comparator: control (n=74)	Proportion of patients with favourable outcomes during 24 months treatment	
Du et al. 2019 [61]	evaluate safety and efficacy of a short-term MDR-TB treatment containing Clofazimine	prospective, randomized, multicenter study	adult pulmonary MDR-TB	Interventions: 12-months clofazimine (n=67); Comparator: 18 months control (n=68)	Proportion of patients with favourable outcomes during 12 vs. 18 months treatment, respectively	Safety and tolerance of the treatment during 12 vs. 18 months treatment, respectively
Koh et al. 2013 [62]	effectiveness (culture conversion) of LFX vs. MXF after 3 months of treatment for MDR-TB	prospective multicenter, stratified, randomized, open-label trial	adult pulmonary MDR-TB	Intervention: levofloxacin LFX (n=90); Comparator: moxifloxacin MXF (n=92)	Proportion of patients who achieved sputum culture conversion at 3 months of treatment	Times to culture conversion and smear conversion,with data censored at 3 months; proportions of any adverse drug reaction
Study reference/ID	**Objective**	**Study design**	**Eligibility criteria***	**Intervention and Comparator (N**	**Primary outcome measure and follow-up time point**	**Secondary outcome measures and follow-up time points**

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				enrolled)**		
Kang et al. 2016 [63]	compare final treatment outcomes between patients with MDR-TB randomized to levofloxacin and Moxifloxacin	follow-up after previous prospective, multicenter, randomized, open-label trial [62]	adult pulmonary MDR-TB	Intervention: levofloxacin LFX (n=77); Comparator: moxifloxacin MXF (n=74)	Treatment success after around 20 months of treatment	Time to culture conversion, safety during around 20 months of treatment
Tang et al. 2015b [64]	evaluate the clinical efficacy and tolerability of Cfz in treating patients with MDR tuberculosis	prospective observational study	adult pulmonary MDR-TB	Intervention: clofazimine (n=53); Comparator: control (n=52)	Sputum culture conversion during 21 months treatment	Cavity closure, incidence of AE during 21 months treatment
Carroll et al. 2013 [65]	Determine the benefit of metronidazole vs placebo added to an individualized background regimen	randomized, double-blind, placebo-controlled phase 2 study	adult pulmonary MDR-TB	Intervention: metronidazole + individualized background regimen (n=17); Comparator: placebo + individualized background regimen (n=18)	Changes in lesions associated with active tuberculosis, 2 and 6 months. Time to conversion to negative sputum and culture. Clinical success. Monitoring of adverse events and pharmacokinetics.	

*Main eligibility criterion is the disease type which should overlap with the assessed pretomanid indication pulmonary XDR-TB and TI/NR in adult patients as much as possible. The studies are ranked with XDR-TB and pre-XDR having highest priority. MDR-TB has lower priority here because no TI/NR subgroups were analysed in the studies. DS-TB does not fall into the population definition of this assessment. Furthermore, the listed studies are ranked by substance with regimens containing bedaquiline and linezolid having the highest ranking.

**More available details about the interventions are summarized in Table 18.

Table 18 Available details about interventions (substance, dose, route, duration, other)

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Study reference/ID	# arms	Arm 1	Arm 2	Arm 3	Arm 4
NixTB NCT02333799 Conradie et al. 2020)	1	bedaquiline 400 mg once daily for 2 weeks then 200mg 3 times per week plus pretomanid 200mg once daily plus linezolid 1200mg once daily			
ZeNix NCT03086486	4	1200mg L x 26 weeks + Pa + B	1200 mg L x 9 weeks + Pa + B	600 mg L x 26 weeks + Pa + B	600 mg L x 9 weeks + Pa + B
Olayanju et al. 2018 [46]	2	Bedaquiline-based treatment regime (dose not reported). Often patients received clofazimine, linezolid and levofloxacin concurrently as major components of their bedaquiline-regimen (53 of the 68 (77.9%) patients who received bedaquiline also received linezolid)	Background treatment regime: backbone of para-aminosalicylic acid (PAS)/clofazimine/capreomycin and second-/fourth-generation fluoroquinolones		
Pym et al. 2016 [47]	1	Bedaquiline, oral, 400mg once daily for 2 weeks, then 200mg three times a week for 22 weeks in combination with a BR of drugs chosen by the investigator in accordance with National TB Programme (NTP) guidelines			
Tang et al. 2015a [51]	2	control group	linezolid therapy group		
Lee et al. 2012 [52]	2	Immediate Start: Linezolid 600 mg/day + after second randomization linezolid 300 mg/day or linezolid 600 mg/day	Delayed Start: existing treatment regimen for 2 additional months after which linezolid 600 mg/day was added		
Wang et al. 2018 [53]	2	6 months: clofazimine, capreomycin, moxifloxacin, (gatifloxacin), pyrazinamide, ethambutol, aminosalicylic acid, (protionamide) + two 4-5 group drugs. 6 months: clofazimine, capreomycin, moxifloxacin, (gatifloxacin), pyrazinamide, ethambutol, aminosalicylic acid, (protionamide) + two 4-5 group drugs. 24 months: moxifloxacin (gatifloxacin), clofazimine, pyrazinamide, ethambutol, aminosalicylic acid (protionamide), + two 4-5 group drugs	6 months: capreomycin, moxifloxacin, (gatifloxacin), pyrazinamide, ethambutol, aminosalicylic acid, (protionamide) + two 4-5 group drugs. 6 months: capreomycin, moxifloxacin, (gatifloxacin), pyrazinamide, ethambutol, aminosalicylic acid, (protionamide) + two 4-5 group drugs. 24 months: moxifloxacin (gatifloxacin), pyrazinamide, ethambutol, aminosalicylic acid (protionamide), + two 4-5 group drugs		
Diacon et al. 2012 [54]	2	Bedaquiline 400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks	Placebo [8 weeks]		
Diacon et al. 2014 [55]	2	Bedaquiline 400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks + 5-drug background regimen	Placebo + 5-drug background regimen		

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Tsuyuguchi et al. 2019 [56]	1	Bedaquiline 400 mg once daily (OD) for 2 weeks followed by 200mg (2 tablets) bedaquiline 3 times a week (TIW) for a further 22 weeks in combination with BR drugs			
Study reference/ID	**# arms**	**Arm 1**	**Arm 2**	**Arm 3**	**Arm 4**
Nunn et al. 2019 [57]	2	SHORT REGIMEN [Less than 33 kg BW: moxifloxacin 400 mg; clofazimine, 50 mg; ethambutol, 800 mg; pyrazinamide, 1000 mg; isoniazid, 300 mg; prothionamide 250 mg. 33-50 kg: moxifloxacin 600 mg; clofazimine, 100 mg; ethambutol, 800 mg; pyrazinamide, 1500 mg; isoniazid, 400 mg; prothionamide, 500 mg. more than 50 kg: moxifloxacine, 800 mg; clofazimine, 100 mg; ethambutol, 1200 mg; pyrazinamide, 2000 mg; isoniazid, 600 mg; prothionamide, 750 mg. Kanamycin 15 mg/kg (max 1 g)] All drugs are given daily except kanamycin that was given three times per week from week 12. Intensive phase 16-20 weeks, can be extended if no culture conversion to 20 or 24, respectively.	LONG REGIMEN: MONGOLIA: Intensive, [Kanamycin 16 mg/kg; pyrazinamide 1600 or 200 mg; levofloxacin 750 mg/100 mg; ethionamide or prothionamide 500/750/1000 mg; cycloserine 500/750/1000 mg. 4-6 months until culture negative] and then continuation phase [at least 12 months:pyrazinamide, ethambutol , levofloxacin and ethionamide]. SOUTH AFRICA: Intensive, [Kanamycin 15 mg/kg; pyrazinamide 1000-1500-1750-2000 mg; moxifloxacin 400 mg; ethionamide 500-750 mg; terizidone 500-750 mg; plus isoniazid 400-600 mg and ethambutol 800-1200 mg in 7 patients. 4 months after the culture conversion, minimum 6 months]. Continuation [at least 12 months to make a total of 18 months: prior august 2015 ofloxacin, pyrazinamide, ehtambutol, and terizidone and ethionamide; after august 2015 moxifloxacin, pyrazinamide, terizidone and ethionamide]. ETHIOPIA: Intensive [Capreomycin 16 mg/kg; pyrazinamide 1000-1500-1750-2000 mg; levofloxacin 750-1000 mg; ethionamide 500-750 mg; cycloserine 500-750 mg. Two patients had ethambutol 1200 mg and 1 isoniazid 300 mg. At least 4 months after culture conversion and a minimum of 8 months] Continuation [for 10-12 months to make a total 18-20 months. Prior april 2013 levofloxacin, pyrazinamide, ethambutol, ethionamide and cycloserine; after april 2013 levofloxacin, pyrazinamide, prothionamide, cycloserine]. VIETNAM: Intensive [Kanamycin 15mg/kg; pyrazinamide 1250-1500-1750-2000 mg; levofloxacin 750 mg; prothionamide 500-750 mg; cycloserine 500-750 mg; ethambutol 800-1000-1200-1400-1600 mg, for minimum 6 months and maximum 10] Continuation [for 13-14 months, pyrazinamide, levofloxacin, prothionamide, ehtambutol and cycloserine].		
von Groote-Bidlingmaier et al. 2019 [58]	2	Oral delamanid [100 mg twice daily 2 months, followed by 200 mg once daily 4 months] + background regimen	Placebo + background regimen		
Gler et al. 2012 [59]	3	OBR plus 100 mg delamanid twice daily	OBR plus 200 mg delamanid twice daily	OBR plus placebo twice daily	
Duan et al. 2019 [60]	2	clofazimine group received 100 mg of clofazimine per day in addition to the baseline regimen throughout the 24-month treatment period.	control group received amikacin (capreomycin), levofloxacin pyrazinamide, ethambutol, para-aminosalicylic acid (protionamide) and amoxicillin/clavulanate for 6 months; and then were subsequently administered a baseline regimen of levofloxacin, pyrazinamide, ethambutol, para-aminosalicylic acid (protionamide) and amoxicillin/clavulanate for 18 months.		

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Du et al. 2019 [61]	2	18-month treatment regimen, with all drugs administrated daily throughout. The intensive phase of treatment consisted of capreomycin, ethambutol, cycloserine (Cs), levofloxacin (Lfx), protionamide (Pto), and pyrazinamide (PZA) for 6 months and the continuation phase consisted of ethambutol, Cs, Lfx, Pto, and PZA for 12 months	received a 6-month intensive phase with capreomycin, CFZ, Cs, Lfx, Pto, and PZA, then were subsequently administered a 6-month continuation treatment with CFZ, Cs, Lfx, Pto, and PZA		
Koh et al. 2013 [62]	2	LFX: Levofloxacin 750 mg	MXF: Moxifloxacin 400mg		
Kang et al. 2016 [63]	2	LFX: Levofloxacin 750 mg	MXF: Moxifloxacin 400mg		
Tang et al. 2015b [64]	2	Clofazimine 100mg for 21 months + WHO treatment regimen	WHO treatment regimen		
Carroll et al. 2013 [65]	2	Metronidazole [500 mg thrice daily, oral, 8 weeks] + Individualized baseline regimen	Placebo [oral, 8 weeks] + Individualized baseline regimen		

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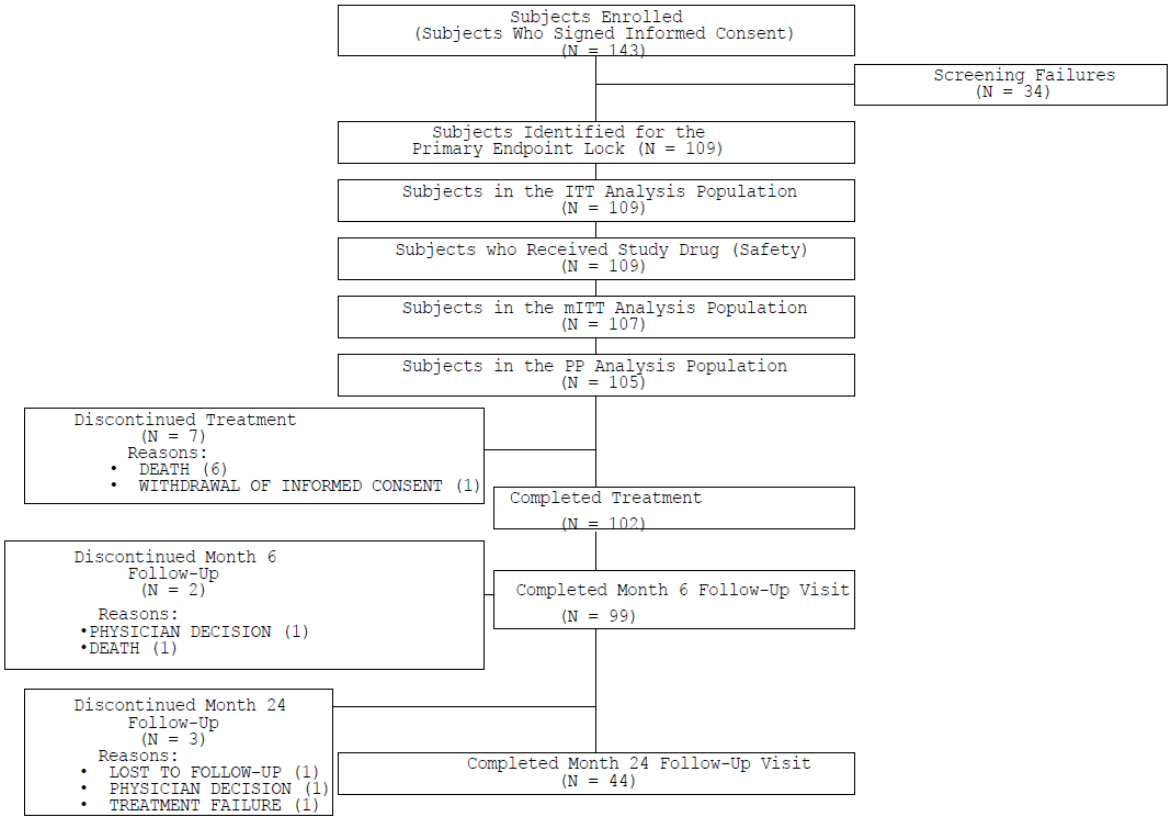
5.4.2 Study patient flow diagram

Patient flow diagram of the Nix-TB study [5]:



All other patient flow diagrams are available in section 7.1 (Appendix).

5.4.3 Demographic data

The patients in the Nix-TB trial had following characteristics:

The median age was 35 years (range: 17 to 60 years), 57 patients (52%) were male, 56 (51%) were HIV-positive, 92 (84%) had cavities on chest radiographs, and the median body-mass index was 19.7. All patients with HIV coinfection were treated with antiretroviral therapy during the trial, and all except 2 had been receiving antiretroviral therapy before enrollment. The median time since the original diagnosis of tuberculosis was 12 months (range: <1 to 141 months). All except 9 patients had received tuberculosis medications in the month before enrollment, with the most common drugs used (by ≥55 patients) being fluoroquinolones, pyrazinamide, terizidone, clofazimine, para-aminosalicylic acid, ethambutol, and ethionamide, with a median of 7 (range, 3 to 13) tuberculosis drugs being taken. A total of 71 cases (65%) were classified as XDR-TB, 19 (17%) were classified as NR MDR-TB, and 19

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(17%) were classified as TI MDR-TB for which treatment was stopped because of side effects.

Baseline characteristics of the NixTB study can also be found in Table 19 below as published from Conradie et al. 2020 [5]:

Table 19 Baseline characteristics of the Nix-TB patients*, taken from Conradie et al. 2020 [5]

Characteristic	Value (N = 109)
Median age (range) — yr	35 (17–60)
Male sex — no. (%)	57 (52)
Race — no. (%)†	
Black	83 (76)
Mixed race	25 (23)
White	1 (1)
Median BMI (range)‡	19.7 (12.4–41.1)
HIV-positive — no. (%)	56 (51)
Median time since HIV diagnosis (range) — yr	4.0 (0.2–14.3)
Median CD4 cell count (range) — cells/mm^3§	343 (55–1023)
Cavities present on chest radiograph — no. (%)	
No	17 (16)
Unilateral	51 (47)
Bilateral	41 (38)
Karnofsky score — no. (%)¶	
100	9 (8)
90	50 (46)
80	29 (27)
70	19 (17)
60	2 (2)
<60	0
Median no. of tuberculosis drugs taken in month before enrollment (range)	7 (3–13)
Median time since original tuberculosis diagnosis (range) — mo	12 (<1–141)

* Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus.

† Race was reported by the patient.

‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Data on CD4 cell count were missing for 5 patients.

¶ The Karnofsky score ranges from 0 to 100, with lower scores indicating greater disability.

An overview of the demographic data of all studies considered in this dossier is given with Table 20.

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Table 20 Demographic data

Identification	Country or region	Arm	Mean age	Median age	% female	%HIV positive	Comorbidities (% of patients)	Radiographic extent of disease- %	Radiographic extent of cavitation- %	TB type	%XDR %MDR	Drug resistance- %	Previous treatment- %
Nix-TB (Conradie et al. 2020)	South Africa			35	43	56			None 16%; Unilateral 47%; Bilateral 38%	XDR-TB, TI/NR MDR-TB	65 XDR-TB; 17 NR MDR-TB; 17 TI MDR-TB		
Olayanju et al. 2018 [46]	South Africa	Bedaquiline (+LZD + BR)		34.5	39.7	51.5				XDR-TB		RR 100; H 100; OFX 100; AMK 100	48.5
		BR		33.5	41.2	48.5						RR 100; H 100; OFX 100; AMK 100	83.8
Pym et al. 2016 [47]	China, South Korea, Philippines, Thailand, Estonia, Latvia, Russia, Turkey, Ukraine, Peru, South Africa	Bedaquiline (+BR)		32	35.6	4			≥2 cm U 51.5; ≥2 cm Bi 12.0%	XDR-TB, pre-XDR-TB, MDR-TB	63.5 MDR; 18.9 Pre-XDR; 16.3 XDR	RR and H 23.6	94.8
Tang et al. 2015a [51]	China	LZD	44		32,3		DM 18.2; COPD 9.1; Bronchiectasis 24.2; Tuberculous pleurisy 18.2; Respiratory failure 21.2		U 48.5; Bi 51.5	XDR-TB		S 90.9; H 100; R 100; E 87.9; OFX 100; AMK 78.8; CAP 75.8;	⩾1 year <5 years before randomisation 66.7; ⩾5 years before randomisation 33.3;

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		Control	43		34,4		DM 18.8; COPD 12.5; Bronchiectasis 28.1; Tuberculous pleurisy 15.6; Respiratory failure 18.8		U 46.9; Bi 53.1			S 93.8; H 100; R 100; E 93.8; OFX 100; AMK 78.1; CAP 78.1;	⩾1 year <5 years before randomisation 68.7; ⩾5 years before randomization 31.3;
Identification	**Country or region**	**Arm**	**Mean age**	**Median age**	**% female**	**%HIV positive**	**Comorbidities (% of patients)**	**Radiographic extent of disease- %**	**Radiographic extent of cavitation- %**	**TB type**	**%XDR %MDR**	**Drug resistance- %**	**Previous treatment- %**
Lee et al. 2012 [52]	South Korea	Immediate start LZD	42.1		37	0	Diabetis mellitus, 37	Far advance tuberculosis 79; Cavitary tuberculosis 47; bilateral lesions 95		XDR-TB		N of R anti-TB drugs, mean: 11.6	
		Delayed start LZD	40.4		20	0	Diabetis mellitus, 35	Far advance tuberculosis 75%; Cavitary tuberculosis 40%; bilateral lesions 100%				N of R anti-TB drugs, mean: 10.4	
Wang et al. 2018 [53]	China	Clofazimine	42,4		22,7		DM 4.5; COPD 4.5; Cardiopathy 0;			XDR-TB		H 100; R 100; E 59.1; OFX 100; AMK 100; CAP 90.9;	100

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		Control	42,46		29,6		DM 3.7; COPD 7.4; Cardiopathy 3.7;					H 100; R 100; E 59.3; OFX 100; AMK 100; CAP 88.9;	88,9
Diacon et al. 2012 [54]	South Africa	Bedaquiline (+BR)		33	22	13			≥2 cm Bi 26; ≥2 cm U 61	MDR-TB		Z 59, E 65, KAN 6, OFX 6, ETO 12	
		Placebo (+BR)		33	29	12			≥2 cm Bi 29; ≥2 cm U 54			Z 70, E 55, KAN 10, OFX 10, ETO 5	

Identification	Country or region	Arm	Mean age	Median age	% female	%HIV positive	Comorbidities (% of patients)	Radiographic extent of disease- %	Radiographic extent of cavitation- %	TB type	%XDR %MDR	Drug resistance- %	Previous treatment- %
Diacon et al. 2014 [55]	Brazil, India, Latvia, Peru, Philippines, Russia, South Africa, Thailand	Bedaquiline + BR		32	32	8			Cavity ≥2 cm Bi, 18,2; cavity ≥2 cm U, 63,6; no cavity, 18,2	MDR-TB		H and R, 72; pre-XDR, 28; fluoroquinolone resistance, 11; AMK, KAN, or CAP, 17; ≥3 drugs in background regimen, 75; Z, 68	
		Placebo + BR		34	39	21			Cavity ≥2 cm Bi, 22,7; cavity ≥2 cm U, 62,1; no cavity, 15,2			H and R, 79; pre-XDR, 21; fluoroquinolone resistance, 7; AMK, KAN, or CAP, 14; ≥3 drugs in background	

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													regimen, 80; Z, 56	
Tsuyuguchi et al. 2019 [56]	Japan	Bedaquiline + BR		45,5	50				Cavitation >=2cm in one lung 33.3;	MDR-TB		R 100; H 100; E 33.3; ETO 33.3; S 16.7; Z 33.3; KAN 0; OFX 0; Other 16.7;		
STREAM, Nunn et al. 2019 [57]	Asia, Africa	Long regimen	<25, 31; 25-34, 45; 35-44, 33; ≥45, 21		36,2	31		None/minimal, 22,4; moderate, 57,6; advanced, 31,2	None, 22,4; single, 10,4; multiple, 67,2	MDR-TB		H, 93; OFX, 3; KAN or CAP, 1; Z, 59	None, 12; drug susceptible-TB treatment, 81; second-line treatment, 7	
		Short regimen	<25, 56; 25-34, 88; 35-44, 58; ≥45, 51		40,3	34		None/minimal, 11,7; moderate, 52,7; advanced, 35,6	None, 23; single, 14,2; multiple, 62,8			H, 94; OFX, 1; KAN or CAP, 1; Z, 63	None, 7; drug susceptible-TB treatment, 87; second-line treatment, 6	
Identification	**Country or region**	**Arm**	**Mean age**	**Median age**	**% female**	**%HIV positive**	**Comorbidities (% of patients)**	**Radiographic extent of disease- %**	**Radiographic extent of cavitation- %**	**TB type**	**%XDR %MDR**	**Drug resistance- %**	**Previous treatment- %**	
von Groote-Bidlingmaier et al. 2019 [58]	Estonia, Latvia, Lithuania, Moldova, Peru, Philippines, South Africa	Oral delamanid (+BR)		32	28,3	5,3			Bi 22,6	MDR-TB (mainly)	XDR 4,4	Quinolone resistance 7,1; injectable resistance 10,2	90	
		Placebo (+BR)		31	24,8	5,9			Bi 20,8		XDR 2	Quinolone resistance 4; injectable resistance 15,8	90	

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Gler et al. 2012 [59]	Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, USA	DMD 100 mg twice daily + BR		36	35,5				Absent, 31,2; U, 42,6; Bi, 26,2	MDR-TB			First line only, 51,1; second line with or without first-line, 28,4; third line with or without first-line or second-line, 12,8
		DMD 200 mg twice daily + BR		33	30,1				Absent, 31,6; U, 41,2; Bi, 27,2				First line only, 53,7; second line with or without first-line, 19,9; third line with or without first-line or second-line, 16,2
		Placebo + BR		35	28,8				Absent, 30,4; U, 41,2; Bi, 27,2				First line only, 54,4; second line with or without first-line, 18,4; third line with or without first-line or second-line, 17,6
Identification	Country or region	Arm	Mean age	Median age	% female	%HIV positive	Comorbidities (% of patients)	Radiographic extent of disease- %	Radiographic extent of cavitation- %	TB type	%XDR %MDR	Drug resistance- %	Previous treatment- %
Duan et al. 2019 [60]	China	Clofazimine (+BR)	36,8		33,3	0	DM 3; COPD 3; cardiopathy 1,5			MDR-TB			95,5
		Control	36,4		40,5	0	DM 2,8; COPD 2,7; cardiopathy 1,4						93,2

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Du et al. 2019 [61]	China	12-months Clofazimine	39		33,8		DM 4.4; Ankylosing spondylitis 1.5; Pulmonary infection 5.9	U 36.8; Bi 63.2	85,3	MDR-TB				77,9
		Control	37,9		34,3		DM 1.5; Ankylosing spondylitis 1.5; Pulmonary infection 4.5	U 32.8; Bi 67.2;	71,6					8,06
Koh et al. 2013 [62]	South Korea	LFX		44	30,8		6,4		57,7	DS- and MDR-TB	0 XDR	N of R anti-TB drugs, median: 4		
		MXF		42	35,1		11,7		55,8		3.9 XDR	N of R anti-TB drugs, median: 4		
Kang et al. 2016 [63]	South Korea	LFX		44	29,9		5,2	2,5 cm	57,1	MDR-TB	0 XDR	N of R anti-TB drugs, median: 4		49,4
		MXF		42	35,1		9,5	2,8 cm	56,8		1.4 XDR	N of R anti-TB drugs, median: 4		48,6
Identification	**Country or region**	**Arm**	**Mean age**	**Median age**	**% female**	**%HIV positive**	**Comorbidities (% of patients)**	**Radiographic extent of disease- %**	**Radiographic extent of cavitation- %**	**TB type**	**%XDR %MDR**	**Drug resistance- %**	**Previous treatment- %**	
Tang et al. 2015b [64]	China	Clofazimine	42		70,2		DM 18.9; COPD 9.4; bronchiectasis 24.5; Tuberculosis pleurisy 17; respiratory failure 18.9;		U 41.5; Bi 45.3	MDR-TB		S 66; H 100; R 100; E 60.4; OFX 62.3; AMK 24.5; CAP 22.6	6 m to <1 y before randomization 32.1; 1 y to <5 y before randomization 49; ≥5 y before randomization 18.9;	

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		Control	43	26,9	DM 21.2; COPD 11.5; bronchiectasis 23.1; Tuberculosis pleurisy 15.4; respiratory failure 17.3;		U 42.3; Bi 44.28		S 63.5; H 100; R 100; E 67.3; OFX 59.6; AMK 23.1; CAP 26.9;	6 m to <1 y before randomization 34.6; 1 y to <5 y before randomization 44.2; ≥5 y before randomization 21.2;
Carroll et al. 2013 [65]	South Korea	Metronidazole (+BR)	36	13	DM 7	Bi 60	Cavitary 40	MDR-TB	Fluoroquinolone 33; Resistant drugs 4 median	
		Placebo (+BR)	38	25	DM 13	Bi 75	63		Fluoroquinolone 38; resistant drugs 5 median	

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5.5 Individual study results (clinical outcomes)

This chapter starts with a detailed description of the available clinical outcomes in the Nix-TB study. A narrative comparison with potential comparator scenarios as identified with the systematic literature search follows in the second part.

5.5.1 Clinical outcomes of the Nix-TB trial

The primary endpoint, a favourable outcome 6 months after treatment end, was achieved from 92% (95% CI) of the patients in the Nix-TB mITT population. Results by disease type were 90% efficacy in the XDR-TB subpopulation and 95% of the subpopulation of TI/NR MDR-TB patients. In the ITT population, 90% of the total patient population, 89% of the XDR-TB patients and 92% of the MDR-TB patients had a favourable outcome.[5]

An unfavourable outcome at 6 months after the end of treatment had 11 patients (10%) within the ITT population (9 patients in the mITT population). The unfavorable outcomes were 7 deaths (6 during treatment and 1 from an unknown cause during follow-up), 1 withdrawal of consent during treatment, 2 relapses during follow-up, and 1 loss to follow-up.

All primary efficacy data are summarized in Table 21.

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Table 21 Primary efficacy analysis of the Nix-TB trial, taken from Conradie et al. 2020 [5]

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡
Per-protocol population			
No. of patients	68	37	105
Favorable outcome			
No. of patients	62	35	97
Percent of patients (95% CI)	91 (82–97)	95 (82–99)	92 (86–97)
Unfavorable outcome — no. (%)	6 (9)	2 (5)	8 (8)
Deaths — no.	5	1	6
Relapse — no.	1	1	2‡

* An unfavorable outcome was defined as treatment failure (bacteriologic or clinical) or disease relapse, with clinical treatment failure defined as a change from the protocol-specified tuberculosis treatment as a result of treatment failure, retreatment for tuberculosis, or tuberculosis-related death through follow-up until 6 months after the end of treatment. Patients were considered to have had a favorable outcome if their clinical tuberculosis disease had resolved, they had a negative culture status at 6 months after the end of therapy, and they had not already been classified as having had an unfavorable outcome. All patients in this study had either a favorable or an unfavorable outcome at 6 months after the end of treatment.
† The intention-to-treat and modified intention-to-treat analyses were prespecified in the protocol. Two patients were excluded from the modified intention-to-treat population: one who died from non–tuberculosis-related causes during follow-up, and one who was lost to follow-up after the end of treatment. Two additional patients were excluded from the per-protocol population: one who received an inadequate amount of drug, and one who was withdrawn (not for treatment failure) during treatment.
‡ A baseline isolate was not available for one patient who had a relapse.

Primary Efficacy Endpoint – Sensitivity and Subgroup Analyses

The prespecified sensitivity analysis demonstrated that the results of the primary outcome were similar when evaluating only those patients who had positive cultures for *M. tb* at baseline. Of the 93 patients who were culture-positive at baseline, 82 patients (90%) had favorable outcomes at Month 6 of follow-up (lower bound of 95% CI, 82%). Subgroup analyses by HIV status (positive vs negative) and linezolid dosing (600 mg BID vs 1200 mg QD) revealed no difference in clinical outcomes

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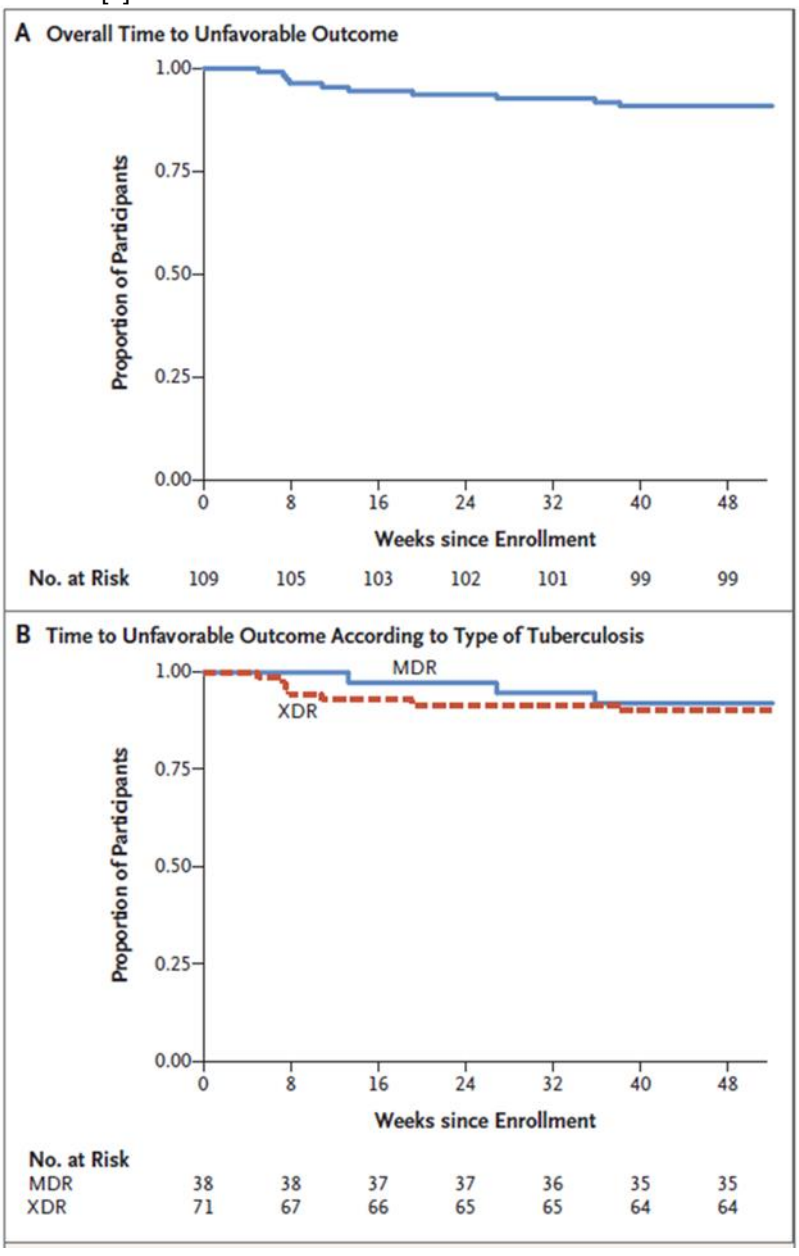
based on these factors, as the rate of favorable outcomes was 90% or greater across all subgroups (lower bound of 95% CI, 75% or greater).

Secondary Endpoint

The time to an unfavourable outcome is shown in Figure 4.

Figure 4 Time to an unfavourable outcome (Intention-to-Treat Population), taken from Conradie et al. 2020 [5]



An unfavorable outcome was defined as treatment failure (bacteriologic or clinical) or disease relapse, with clinical treatment failure defined as a change from the protocol-specified tuberculosis treatment as a result of treatment failure, retreatment for tuberculosis, or tuberculosis-related death through follow-up until 6 months after the end of treatment. MDR denotes multidrug-resistant, and XDR extensively drug-resistant.

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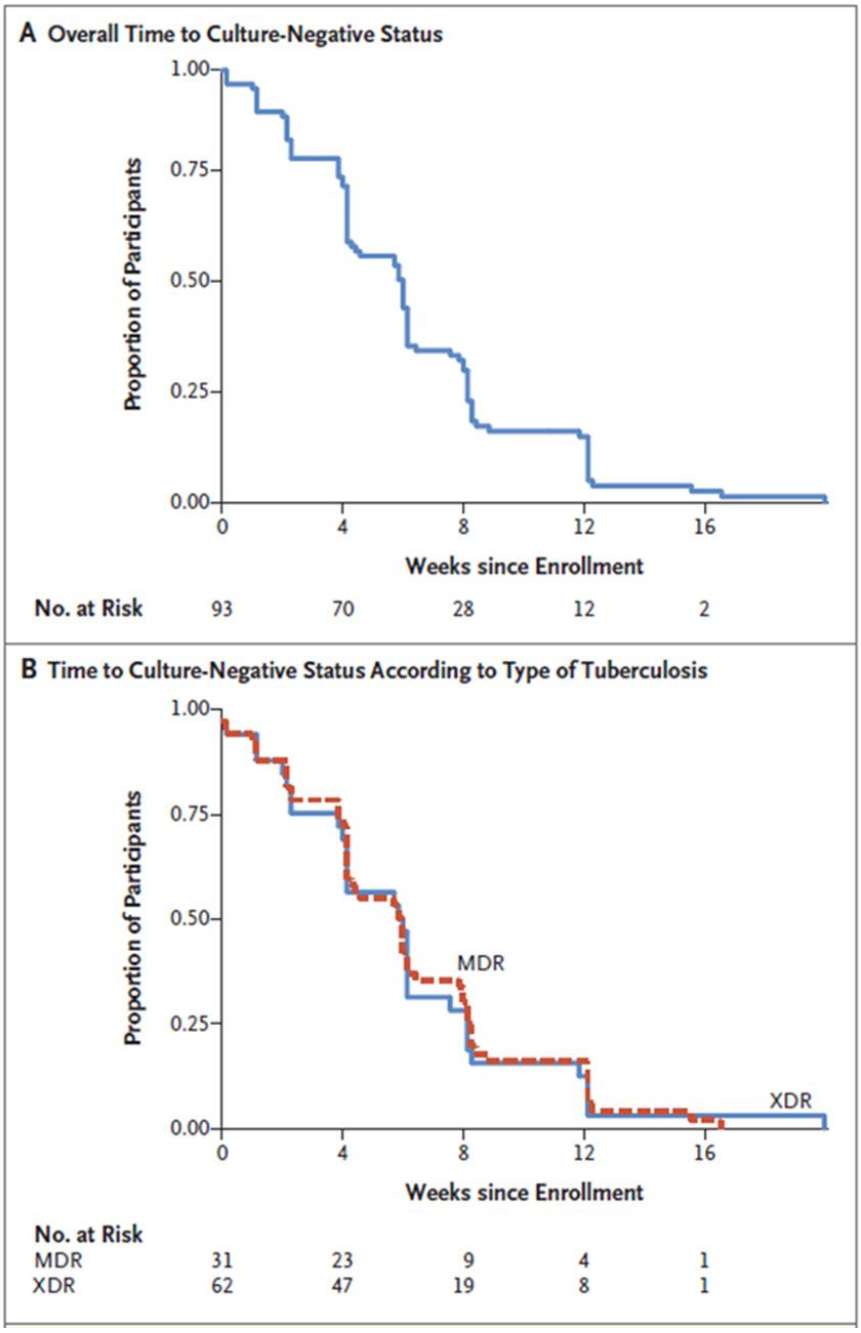
Patients in the Nix-TB trial achieved culture conversion quickly; among patients with positive baseline cultures, the median time to conversion was 6 weeks (Figure 5).

Figure 5 Time to culture-negative status among patients who were positive at baseline (Intention-to-Treat Population), taken from Conradie et al. 2020 [5]



Secondary Endpoint – Incidence of Bacteriologic Failure or Relapse at 24 Months

Outcomes at 24 months following the end of treatment were similar to the results at Month 6 of follow-up, consistent with experience that most relapses will occur within 6 months.

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5.5.2 Clinical outcomes in comparison to other studies

Relevant outcomes to assess the efficacy of antibiotics in the treatment of TB are the following:

- Cure (according to WHO definition [44] or other clinically relevant definition)
- Treatment completed (according to WHO definition [44] or other clinically relevant definition)
- Treatment success (includes cure and treatment completed)
- Favourable outcome
- Treatment failure including bacteriological/clinical failure and relapse (according to WHO definition* or other clinically relevant definition)
- Unfavourable outcome
- Proportion of subjects with sputum culture (± smear microscopy) conversion to negative status and time to culture conversion (± smear microscopy) to negative status
- Mortality

Quality of Life (QoL) or Health-related Quality of Life (HRQoL) plays a minor role in the evaluation of antibiotics for the treatment of multiple drug-resistant TB forms. It was not identified as outcome parameter in the literature search for RCTs and prospective clinical trials. Therefore, it is not possible to assess the QoL/ HRQoL benefits of the short, all-oral, 3-drug regimen compared to other regimens in more detail.

Studies with XDR-TB patients tend to prioritise the proportion of patients having a favourable or unfavourable outcome (i.e. cured or failed). In contrast, studies with MDR-TB patients tend to focus on time to event, mainly time to culture conversion. (This may be another indicator of the pressure to find a viable treatment option to specifically help those patients with highest levels of antibiotic resistance.) Mortality is also of interest in the treatment of the potentially life-threatening disease.

The focus on proportion outcomes supports the approach to compare the Nix-TB study rather with studies having an XDR-TB population. Another argument for the careful handling of comparators is the disease severity. It is easier to achieve a cure/ favourable outcome in patients with fewer resistances. Since no other study included TI/NR MDR-TB patients explicitly, comparisons with MDR-TB patients should be handled with care.

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The timepoint of the study has also an influence on the general comparability. Different guideline recommendations may play a role for a selected baseline regimen. Furthermore, the outcome parameters are defined differently.

For the definition of cure, success, favourable outcome, treatment completion, failure, death, default in context with treatment completion, different guideline versions were used. [44, 48, 49, 68, 69, 70]. The information about the selected definition is available in the methods of data collection, Table 28 (Appendix).

With a favourable outcome in 89% of patients in the Nix-TB study (ITT population, 90% in the mITT population) 6 months after end of treatment, this study result surpasses all previous outcome results in XDR-TB studies. The study from Olayanju et al. 2018 [46] is the study with the highest comparability, which examined outcomes for XDR-TB patients. The study arm consisted of those who took bedaquiline, 80% of whom also received linezolid. Altrogether, they were treated with an average total of 8 antibiotics. The control arm consisted of those patients who did not receive a bedaquiline-containing regimen. In the bedaquiline arm, 66.8% achieved cure. Those who received the baseline regimen without bedaquiline and linezolid experienced a cure rate of only 13.2%.

In another study [47] that used a bedaquiline + baseline study regimen, the population consisting of patients with XDR-TB, pre-XDR-TB and MDR-TB, the cure rate was still a little lower at 61%. And in a Chinese study with a linezolid-containing regimen [51], the treatment success rate for XDR-TB patients was 69.7% vs. 34.4% in the control group not receiving linezolid. It is worth also noting that in this study, linezolid was given for an average of 12 months (from 6 to 24 months) which is a long duration for this component which is known for its unfavourable tolerability profile.

Mortality was with about 6% comparable in the different XDR-TB studies with the exception of the study published from Olayanju et al. 2018 [46]. Here, 15% of patients in the bedaquiline + linezolid + baseline regimen died within 24 months; death rates were 34% in the comparator arm.

Those and more data can be seen in the summarizing Tables 22 and 23.

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To get a deeper insight into the treatment regimen of the most suitable comparator [46], the respective information was added in Table 24.

The methods of data collection are summarized in Table 28 (Appendix)

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Table 22 Clinical outcomes summary 1 of 2 for all identified studies

Identification	TB type	Arm	Treatment completed %, (n/N)	significance	Cure/ Treatment success (includes cure and treatment completed) %, (n/N)	Significance	Favourable outcome %, (n/N)	significance	Treatment failure %, (n/N)	significance	Unfavourable outcome %, (n/N)	significance
Nix-TB (Conradie et al. 2020)	XDR-TB	BPaL	90 (64/71) here interim analysis, but 6 months after end of treatment				**89** [79–95, 95% CI, ITT population] (63/71) 6 months after end of treatment		**11** (8/71)			
	MDR-TB		95 (36/38) here interim analysis, but 6 months after end of treatment				**92** [79–98, 95% CI, ITT population] (35/38) 6 months after end of treatment		**8** (3/38)			
	overall		92 (100/109) here interim analysis, but 6 months after end of treatment				**90** [83–95] (n=98/109) 6 months after end of treatment		**10** (11/109)			
Olayanju et al. 2018 [46]	XDR-TB	Bedaquiline (+LZD + BR)			**66.2** (45/68)	<0.005			**33.8** (23/68) [deceased: 14.7 (10/68), default:1.5 (1/68) , treatment failed: 5.9 (4/68), LTFU: 11.8 (8/68)]	<0.005		
		BR			**13.2** (27/204)				**85.8** (175/204) [[deceased: 33.8 (69/204), default:15.2 (31/204) , treatment failed: 26.0 (53/204), LTFU: 10.8 (22/204)]			
Pym et al. 2016 [47]	XDR-TB, pre-XDR-TB, MDR-TB	Bedaquiline (+BR)			**61.0** [mIIT population size n= 205, week 120, WHO definition]				**15.6** mIIT population size n= 205, [week 120, WHO definition]			

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Tang et al. 2015a [51]	XDR-TB	LZD	18.2% (6/33)	0.526	success: **69.7** (23/33), cure: 51.5 (17/33)	success: p=0.004, cure: p=0.013			12.1 (4/33)	0.002		
		Control	12.5% (4/32)		success: **34.4** (11/32), cure: 21.9 (7/32)				46.9 (15/32)			
Lee et al. 2012 [52]	XDR-TB	Immediate start LZD										
		Delayed start LZD										

Identification	TB type	Arm	Treatment completed %, (n/N)	significance	Cure/ Treatment success (includes cure and treatment completed) %, (n/N)	significance	Favourable outcome %, (n/N)	significance	Treatment failure %, (n/N)	significance	Unfavourable outcome %, (n/N)	significance
Wang et al. 2018 [53]	XDR-TB	Clofazimine	Treatment completion: 4.5 (n=1) after 36 months treatment	0.178	Cure: 31.8 (n=7) after 36 months treatment	0.449		0.493				
		Control	Treatment completion: 22.2 (n=6) after 36 months treatment		Cure: 22.2 (n=6) after 36 months treatment							
Diacon et al. 2012 [54]	MDR-TB	Bedaquiline (+BR)										
		Placebo (+BR)										
Diacon et al. 2014 [55]	MDR-TB	Bedaquiline + BR	58 (of N=66]						8 (of N=66]			
		Placebo + BR	32 (of N=66]						30 (of N=66]			

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Tsuyuguchi et al. 2019 [56]	MDR-TB	Bedaquiline + BR												
STREAM Nunn et al. 2019 [57]	MDR-TB	Long regimen					79.8 (99/130, mITT)	p = 0.02 for noninferiority			20.2 (25/130)			
		Short regimen					78.8 (193/253, mITT)				21.2 (52/253)			
Identification	**TB type**	**Arm**	**Treatment completed %, (n/N)**	**significance**	**Cure/ Treatment success (includes cure and treatment completed) %, (n/N)**	**significance**	**Favourable outcome %, (n/N)**	**significance**	**Treatment failure %, (n/N)**	**significance**	**Unfavourable outcome %, (n/N)**	**significance**		
von Groote Bidlingmaier et al. 2019 [58]	MDR-TB (mainly)	Oral delamanid (+BR)					Investigator-assessed favourable end-of-treatment (OBR) outcome (MITT-MGIT): 81.3 (182/224)	0,53						
		Placebo (+BR)					Investigator-assessed favourable end-of-treatment (OBR): 84.2 (85/101)							
Gler et al. 2012	MDR-TB	DMD 100 mg twice daily + BR												

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[59]		DMD 200 mg twice daily + BR										
		Placebo + BR										
Duan et al. 2019 [60]	MDR-TB	Clofazimine (+BR)	10.6 (7/66)		54.5 (36/66)			0.034	13.6 (9/66)			
		Control	12.2 (9/74)		35.1 (26/74)				32.4 (24/74)			
Du et al. 2019 [61]	MDR-TB	12-months Clofazimine	6.0 (4/67)		62.7 (42/67)			0.701	10.4 (7/67)			
		Control	2.9 (2/68)		61.8 (42/68)				14.7 (19/68)			
Koh et al. 2013 [62]	MDR-TB	LFX										
		MXF										

Identification	TB type	Arm	Treatment completed %, (n/N)	significance	Cure/ Treatment success (includes cure and treatment completed) %, (n/N)	significance	Favourable outcome %, (n/N)	significance	Treatment failure %, (n/N)	significance	Unfavourable outcome %, (n/N)	significance
Kang et al. 2016 [63]	MDR-TB	LFX (+BR)	WHO 2008: 16.9 (13/77); WHO 2013: 1.3 (1/77)		WHO 2008: 70.1 (54/77) / 87.0 (67/77); WHO 2013: 83.1 (64/77) / 84.4 (65/77)				WHO 2008: 3.9 (3/77); WHO 2013: 5.2 (4/77)			
		MXF (+BR)	WHO 2008: 8.1 (6/74); WHO 2013: 1.4 (1/74)		WHO 2008: 73.0 (54/74) / 81.1 (60/74); WHO 2013: 78.4 (58/74) / 79.7 (59/74)				WHO 2008: 5.4 (4/74); WHO 2013: 6.8 (5/74)			

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Tang et al. 2015b [64]	MDR-TB	Clofazimine	22.6 (12/53)	0.34	50.9 (27/53)	0.20	73.6 (39/53	0.04	11.3 (6/53)	0.03	26.4 (14/53)	0.04
		Control	15.4 (8/52)		38.5 (20/52)		53.8 (28/52)		28.8 (15/52)		46.2 (24/52)	
Carroll et al. 2013 [65]	MDR-TB	Metronidazole (+BR)					80 (12/15)		20 (3/15)			
		Placebo (+BR)					81 (13/16)		6 (1/16)			

Table 23 Clinical outcomes summary 2 of 2 for all identified studies

Identification	TB type	Arm	Mortality % (n/N)	significance	Time to sputum culture conversion	Proportion of patients with sputum culture conversion	Other
Nix-TB (Conradie et al. 2020)	XDR-TB	BPaL	8.5 (6/71) 6 months after end of treatment		5.9 weeks (mITT population)		
	MDR-TB		2.6 (1/38) 6 months after end of treatment		4.1 weeks (mITT poulation)		
	overall		6.4 (7/109) 6 months after end of treatment		5.7 weeks (mITT population)		
Olayanju et al. 2018 [46]	XDR-TB	Bedaquiline (+LZD + BR)	14.7 (10/68)	0.004	67.6 [24 months]		

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		BR	33.8 (69/204)		32.8 [24 months]		
Pym et al. 2016 [47]	XDR-, pre-XDR-, MDR-TB	Bedaquiline (+BR)	6.8 [mIIT population size n= 205 week 120, WHO definition]		57 days (median time based on 24-week data); 84 days (median time based on 120-week data)	79.5 [week 24]; 72.2 [week 120]	72.2% of patients converted; 11.7% discontinued after converted; 3.9% reverted to positive; 12.2% failed to convert [week 120]
Tang et al. 2015a [51]	XDR-TB	LZD	6.1% (2/33)	0.619	60.6 days	78.8 (24 months)	default: 12.1 (4/33)
		Control	9.4(3/32)			37.6 (24 months)	default: 9.1 (3/32)
Lee et al. 2012 [52]	XDR-TB	Immediate start LZD				79, solid medium (4 months); 63, liquid medium (4 months)	
		Delayed start LZD				35, solid medium (4 months); 55, liquid medium (4 months)	
Wang et al. 2018 [53]	XDR-TB	Clofazimine	9.1 (n=2)		19.7 months	31.80 (cured); 4.5% (treatment completion) (at 36 months)	
		Control	11.1 (n=3)		20.3 months		
Identification	**TB type**	**Arm**	**Mortality % (n/N)**	**significance**	**Time to sputum culture conversion**	**Proportion of patients with sputum culture conversion**	**Other**
Diacon et al. 2012 [54]	MDR-TB	Bedaquiline (+BR)				100 (24 weeks); 91.67 (104 weeks)	
		Placebo (+BR)				88.23 (24 weeks); 100 (100 weeks)	
Diacon et al. 2014 [55]	MDR-TB	Bedaquiline + BR	12 (of N=66]		83 days (mITT)	79 (week 24); 62 (week 120)	Withdrawal:23 (of N=66]

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		Placebo + BR	3 (of N=66]		125 days (mITT)	58 (week 24); 44 (week 120)	Withdrawal: 35 (of N=66]
Tsuyuguchi et al. 2019 [56]	MDR-TB	Bedaquiline + BR			15 days		
STREAM Nunn et al. 2019 [57]	MDR-TB	Long regimen			Median: mIIT, 4 weeks; PP, 4 weeks		Acquired resistance: fluoroquinolone, 1.6%; second-line injectable resistance, 0.8%
		Short regimen			Median: mIIT, 4 weeks; PP, 4 weeks		Acquired resistance: fluoroquinolone, 2.0%; second-line injectable resistance, 1.6%
von Groote-Bidlingmaier et al. 2019 [58]	MDR-TB (mainly)	Oral delamanid (+BR)			51 days; Sensitivity analysis last observational carried forward analysis, 44 days; Sensitivity analysis bookending method, 51 days	58.4 (week 8); 87.6 (week 24); 79.6 (month 18); 76.5 (month 30)	Acquired resistance: pyrazinamide 1.2%; ethambutol, 3.7%, injectable agents, 5.2%, ofloxacin, 3%; moxifloxacin, levofloxacin or both, 1.1%
		Placebo (+BR)			57 days; Sensitivity analysis last observational carried forward analysis, 57 days; Sensitivity analysis bookending method, 64 days	53.5 (week 8); 86.1 (week 24); 82.2 (month 18); 77.2 (month 30)	Acquired resistance: pyrazinamide 5.1%; streptomycin, 2.8%; ethambutol, 9.4%, injectable agents, 6%, ofloxacin, 3.7%; moxifloxacin, Levofloxacin or both, 3.5%
Identification	**TB type**	**Arm**	**Mortality % (n/N)**	**significance**	**Time to sputum culture conversion**	**Proportion of patients with sputum culture conversion**	**Other**
Gler et al. 2012 [59]	MDR-TB	DMD 100 mg twice daily + BR				45.40 (2 months)	Cmax1 (ng/mL), 414; Cmax2 (ng/mL), 400; Cmin (ng/mL), 304; AUC0-24h (h*ng/mL), 7.925
		DMD 200 mg twice daily + BR				41.90 (2 months)	Cmax1 (ng/mL), 611; Cmax2 (ng/mL), 588; Cmin (ng/mL), 460; AUC0-24h (h*ng/mL), 11,837

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		Placebo + BR				29.60 (2 months)	
Duan et al. 2019 [60]	MDR-TB	Clofazimine (+BR)	6.1 (4/66)			54.5 (cured); 10.6 (treatment completion) (at 24 months)	default: 15.2 (10/66)
		Control	2.7 (2/74)			47 (cured); 12,2 (treatment completion) (at 24 months)	default: 17.6 (13/74)
Du et al. 2019 [61]	MDR-TB	12-months Clofazimine	3.0 (2/67)		3 months	55.90 (3 months)	
		Control	1.5 (1/68)		3 months	68.70 (3 months)	
Koh et al. 2013 [62]	MDR-TB	LFX				88.3% (86/77)	
		MXF				90.5% (67/74)	
Kang et al. 2016 [63]	MDR-TB	LFX (+BR)	2.6 (2/77)				
		MXF (+BR)	0				
Tang et al. 2015b [64]	MDR-TB	Clofazimine	7.5 (4/53)	1		88.30	default: 7.5 (4/53)
		Control	7.7 (4/52)			90.50	default: 9.6 (5/52)
Carroll et al. 2013 [65]	MDR-TB	Metronidazole (+BR)			smear conversion: 19 days; Liquid culture 28 days, Solid culture 21 days		Lost to follow-up: 0
		Placebo (+BR)			smear conversion: 43.5 days; Liquid culture 66.5 days; Solid culture 42.5 days		Lost to folow-up: 13 (2/16)

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For deeper understanding of the results achieved with the most suitable comparator [46], the underlying treatment regimen is provided in Table 24 in detail.

Table 24 Treatment regimen of most suitable comparator, taken from Olayanju et al. 2018 [46]

	Bdq (n=68)		Non-Bdq (n=204)		
Drugs	**Patients who received drug**	**Patients in whom drug was withdrawn due to adverse events (grade≥3)**	**Patients who received drug**	**Patients in whom drug was withdrawn due to adverse events (grade≥3)**	**p-values (comparing proportions of patients who received drug)**
Capreomycin	7 (10.3)	6 (85.7)	196 (95.6)	43 (21.9) **	<0.001
Kanamycin	1 (1.5)	1 (100)	110 (53.9)	12 (10.9)	<0.001
Amikacin	0	0	2 (1.0)	0	N/A
#Any aminoglycoside	8 (11.8)	0	202 (99.0)	0	<0.001
Para-amino salicylic acid	64 (94.1)	10 (15.6)	194 (95.1)	13 (6.7)	0.75
Pyrazinamide	66 (97.1)	3 (4.5)	201 (98.5)	10 (5.0)	0.60
Terizidone	61 (89.7)	8 (13.1)	201 (98.5)	10 (5.0)	0.003
Moxifloxacin	13 (19.1)	1 (7.7)	101 (49.5)	3 (3.0)	<0.001
Ofloxacin	0	0	127 (62.3)	3 (2.4)	N/A
Levofloxacin	67 (98.5)	0	0	0	N/A
Ciprofloxacin	0	0	1 (0.5)	0	N/A
##3rd or 4th generation fluoroquinolone	68 (98.5)	0	101 (49.5)	0	<0.001
Clofazimine	67 (98.5)	1 (1.5)	65 (31.9)	2 (3.1)	<0.001
Linezolid	55 (80.9)	18 (32.7)	0	0	N/A
Ethambutol	26 (38.2)	5 (19.2)	189 (92.7)	15 (7.9)	<0.001
Ethionamide	15 (22.1)	6 (40)	198 (97.1)	12 (6.1)	<0.001
High dose isoniazid	22 (32.4)	3 (13.6)	133 (65.2)	13 (9.8)	<0.001
Dapsone	0	0	34 (16.7)	0	N/A
Co-amoxiclavulanate	2 (2.9)	0	79 (38.7)	0	<0.001
Clarithromycin	0	0	43 (21.1)	0	N/A
Amoxycillin	0	0	13 (6.4)	0	N/A
Azithromycin	0	0	1 (0.5)	0	N/A
Meropenem	1 (1.5)	0	0 (0.0)	0	N/A
Bedaquiline	68 (100)	0	0 (0.0)	0	N/A

#combination of amikacin, kanamycin and capreomycin; kanamycin was replaced by capreomycin in the course of the treatment ##treatment with either moxifloxacin or levofloxacin; **significant difference between number of patients from whom drugs were withdrawn.

5.6 Individual study results (safety outcomes)

The Nix-TB safety database includes data available through the 29 March 2019 cut-off date. As of 29 March 2019, 102 (93.6%) of the 109 patients enrolled in Nix-TB had completed the protocol-specified 26 weeks of investigational drug therapy, 6 patients died and 1 patient withdrew before completing study treatment.

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All 109 patients reported at least 1 AE, with an average of 11.5 AEs reported per patient. Fifty-eight patients (53.2%) experienced an average of 2.1 AEs with a maximum AE severity of either Grade 3 (37.6%) or Grade 4 (15.6%). Twenty-seven patients (24.8%) permanently discontinued linezolid because of an AE. The only patients who discontinued BPaL early were 6 patients who died before completing study treatment. Nineteen patients (17.4%) reported at least 1 SAE, including 6 patients (5.5%) who experienced AEs that were fatal.

The safety outcomes reflect the known limitations in tolerability of antibiotics in the use for multi-resistant forms of TB. In the BPaL regimen, linezolid contributes the expected neurological and haematological adverse events.

Discontinuation, interruption, and dose reduction of linezolid alone were allowed as a way to manage toxicity (Note: per the study protocol, patients could continue to take bedaquiline plus pretomanid and complete the 26-week study regimen without making up missed doses of linezolid). In the Nix-TB trial, 32.1% of patients discontinued linezolid, 63.4% had linezolid dose reductions, and 48.6% had linezolid interrupted for a total mean duration of 40.7 days. AEs reported by more than 1 patient leading to dosing changes were: peripheral sensory neuropathy, neuropathy peripheral, and anemia (discontinuation); peripheral sensory neuropathy, anemia, and neuropathy peripheral (dose reduction); and peripheral sensory neuropathy, anemia, neuropathy peripheral, neutropenia, thrombocytopenia, and visual acuity reduced (interruption).

The entire BPaL regimen was discontinued in 7 patients (6.4%) and interrupted in 25 patients (22.9%). 6 patients who discontinued the regimen were those who died prior to completing treatment and 1 patient withdrew consent; all remaining patients were able to complete their study regimen or were still receiving treatment at the time of the data cut-off (29 March 2019). Among the 25 patients who had interruptions in BPaL dosing, the mean total duration of all interruptions was 12.1 days (±7.34). The most common AEs leading to interruption of the entire treatment regimen were transaminases increased (5.5%) and abdominal pain (2.8%), with other events each occurring in 2 or fewer patients.

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The combination with bedaquiline can enhance QT-prolongation effects. However, the maximum mean increase in the QT interval was 10 msec at week 16; no patient had an increase of more than 480 msec. [5]

A detailed adverse event reporting of the Nix-TB study is added in Table 25. Published adverse events from the most suitable comparator [46] are added in Table 26. It was not possible to match the tables because the comparator publication did not use MedDRA terms. This may be an explanation for differences in the linezolid-specific adverse events. Whereas the BPaL regimen is reported having a high proportion (81%) of patients with peripheral neuropathy symptoms, this is not as high in the comparator bedaquiline/linezolid-arm. [46] Instead of this, hearing impairment (43%) appeared more often in the bedaquiline/linezolid-arm but was not reported in the BPaL regimen.

Table 27 gives an overview of adverse events in all assessed studies. The corresponding reported assessment methods are summarised in Table 29 (Appendix)

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Table 25 Detailed adverse event documentation Nix-TB study with AEs of special interest in blue, n (%) [5]

	Grade 1		Grade 2		Grade 3		Grade 4		Any		
MedDRA System Organ Class Preferred Term	related	**not related**	**related**	**not related**	**related**	**not related**	**related**	**not related**	**related**	**not related**	**N (%)**
NERVOUS SYSTEM DISORDERS	55(50.5)	13(11.9)	45(41.3)	5(4.6)	24(22.0)	4(3.7)	1(0.9)	0	91(83.5)	20(18.3)	92(84.4)
#PERIPHERAL SENSORY NEUROPATHY	29(26.6)	0	38(34.9)	1(0.9)	20(18.3)	0	0	0	76(69.7)	1(0.9)	76(69.7)
HEADACHE	20(18.3)	7(6.4)	2(1.8)	1(0.9)	0	1(0.9)	0	0	22(20.2)	9(8.3)	30(27.5)
#NEUROPATHY PERIPHERAL	4(3.7)	0	7(6.4)	0	3(2.8)	0	0	0	10(9.2)	0	10(9.2)
DIZZINESS	3(2.8)	2(1.8)	0	0	0	0	0	0	3(2.8)	2(1.8)	5(4.6)
DYSGEUSIA	5(4.6)	0	0	0	0	0	0	0	5(4.6)	0	5(4.6)
#PARAESTHESIA	5(4.6)	0	0	0	0	0	0	0	5(4.6)	0	5(4.6)
#HYPOAESTHESIA	3(2.8)	0	0	0	0	0	0	0	3(2.8)	0	3(2.8)
#PERIPHERAL SENSORIMOTOR NEUROPATHY	2(1.8)	0	0	0	1(0.9)	0	0	0	3(2.8)	0	3(2.8)
#BURNING SENSATION	2(1.8)	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)
#PERIPHERAL MOTOR NEUROPATHY	2(1.8)	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY	0	0	0	0	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
DIZZINESS POSTURAL	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
DYSTONIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
#GENERALISED TONIC- CLONIC SEIZURE	0	0	0	0	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
#HYPOREFLEXIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
MIGRAINE	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
#OPTIC NEURITIS	0	0	0	0	0	0	1(0.9)	0	1(0.9)	0	1(0.9)
#SEIZURE	0	0	0	0	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
SINUS HEADACHE	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
#SYNCOPE	0	0	0	1(0.9)	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
TENSION HEADACHE	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TREMOR	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
GASTROINTESTINAL DISORDERS	54(49.5)	37(33.9)	17(15.6)	8(7.3)	3(2.8)	1(0.9)	2(1.8)	0	60(55.0)	40(36.7)	73(67.0)
NAUSEA	35(32.1)	2(1.8)	8(7.3)	1(0.9)	0	0	0	0	39(35.8)	3(2.8)	40(36.7)
VOMITING	22(20.2)	9(8.3)	10(9.2)	3(2.8)	0	0	0	0	31(28.4)	10(9.2)	37(33.9)
DYSPEPSIA	18(16.5)	8(7.3)	1(0.9)	1(0.9)	0	0	0	0	19(17.4)	9(8.3)	26(23.9)

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ABDOMINAL PAIN	4(3.7)	3(2.8)	3(2.8)	1(0.9)	0	0	0	0	7(6.4)	4(3.7)	11(10.1)
DIARRHOEA	6(5.5)	6(5.5)	0	0	0	0	0	0	6(5.5)	6(5.5)	11(10.1)
CONSTIPATION	4(3.7)	4(3.7)	0	1(0.9)	0	0	0	0	4(3.7)	5(4.6)	9(8.3)
GASTRITIS	5(4.6)	2(1.8)	4(3.7)	0	0	0	0	0	8(7.3)	2(1.8)	9(8.3)
ABDOMINAL PAIN UPPER	5(4.6)	0	2(1.8)	0	2(1.8)	0	0	0	7(6.4)	0	7(6.4)
ABDOMINAL PAIN LOWER	1(0.9)	2(1.8)	0	0	0	0	0	0	1(0.9)	2(1.8)	3(2.8)
ABDOMINAL TENDERNESS	3(2.8)	0	0	0	0	0	0	0	3(2.8)	0	3(2.8)
GASTROOESOPHAGEAL REFLUX DISEASE	2(1.8)	1(0.9)	0	1(0.9)	0	0	0	0	2(1.8)	1(0.9)	3(2.8)
HAEMATEMESIS	0	1(0.9)	1(0.9)	0	0	1(0.9)	0	0	1(0.9)	2(1.8)	3(2.8)
HAEMORRHOIDS	0	3(2.8)	0	0	0	0	0	0	0	3(2.8)	3(2.8)
GLOSSODYNIA	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
HAEMORRHOIDAL HAEMORRHAGE	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
#PANCREATITIS	0	0	1(0.9)	0	1(0.9)	0	0	0	2(1.8)	0	2(1.8)
TOOTHACHE	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
UPPER GASTROINTESTINAL HAEMORRHAGE	0	0	0	0	0	0	2(1.8)	0	2(1.8)	0	2(1.8)
ABDOMINAL DISCOMFORT	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
ABDOMINAL DISTENSION	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
ATROPHIC GLOSSITIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
CHRONIC GASTRITIS	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
DENTAL CARIES	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
DYSPHAGIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
FAECALOMA	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
GASTRIC POLYPS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HAEMATOCHEZIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HIATUS HERNIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HYPERTROPHY OF TONGUE PAPILLAE	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
MELAENA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HAEMORRHOIDS	0	3(2.8)	0	0	0	0	0	0	0	3(2.8)	3(2.8)
GLOSSODYNIA	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
HAEMORRHOIDAL HAEMORRHAGE	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
MOUTH ULCERATION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
ORAL DISORDER	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
#PANCREATITIS HAEMORRHAGIC	0	0	0	0	0	0	1(0.9)	0	1(0.9)	0	1(0.9)
PROCTALGIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)

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STOMATITIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TONGUE ULCERATION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TOOTH DISCOLOURATION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TOOTH LOSS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	45(41.3)	31(28.4)	3(2.8)	4(3.7)	0	0	0	0	47(43.1)	34(31.2)	69(63.3)
DERMATITIS ACNEIFORM	16(14.7)	8(7.3)	1(0.9)	1(0.9)	0	0	0	0	17(15.6)	9(8.3)	26(23.9)
RASH	11(10.1)	8(7.3)	0	2(1.8)	0	0	0	0	11(10.1)	9(8.3)	18(16.5)
ACNE	16(14.7)	1(0.9)	0	0	0	0	0	0	16(14.7)	1(0.9)	17(15.6)
PRURITUS	11(10.1)	7(6.4)	0	0	0	0	0	0	11(10.1)	7(6.4)	16(14.7)
DRY SKIN	5(4.6)	4(3.7)	0	0	0	0	0	0	5(4.6)	4(3.7)	8(7.3)
RASH PRURITIC	0	3(2.8)	1(0.9)	0	0	0	0	0	1(0.9)	3(2.8)	4(3.7)
RASH PAPULAR	1(0.9)	2(1.8)	0	0	0	0	0	0	1(0.9)	2(1.8)	3(2.8)
SKIN HYPERPIGMENTATION	1(0.9)	1(0.9)	0	1(0.9)	0	0	0	0	1(0.9)	2(1.8)	3(2.8)
ALOPECIA	2(1.8)	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)
PRURITUS GENERALISED	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
RASH MACULO-PAPULAR	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	0	2(1.8)
DERMATITIS ALLERGIC	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
DERMATITIS ATOPIC	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
DERMATITIS CONTACT	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
NAIL DYSTROPHY	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
PENILE ULCERATION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
RASH ERYTHEMATOUS	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
RASH MACULAR	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
RASH VESICULAR	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SKIN DISCOLOURATION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SKIN MASS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SKIN ULCER	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
URTICARIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
INFECTIONS AND INFESTATIONS	5(4.6)	57(52.3)	0	18(16.5)	0	4(3.7)	0	6(5.5)	5(4.6)	63(57.8)	64(58.7)
UPPER RESPIRATORY TRACT INFECTION	0	19(17.4)	0	2(1.8)	0	1(0.9)	0	0	0	21(19.3)	21(19.3)
LOWER RESPIRATORY TRACT INFECTION	0	7(6.4)	0	1(0.9)	0	0	0	0	0	7(6.4)	7(6.4)
URINARY TRACT INFECTION	0	5(4.6)	0	2(1.8)	0	0	0	0	0	7(6.4)	7(6.4)
INFLUENZA	0	6(5.5)	0	0	0	0	0	0	0	6(5.5)	6(5.5)

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ANGULAR CHEILITIS	1(0.9)	4(3.7)	0	0	0	0	0	0	1(0.9)	4(3.7)	5(4.6)
ORAL CANDIDIASIS	2(1.8)	2(1.8)	0	0	0	1(0.9)	0	0	2(1.8)	3(2.8)	5(4.6)
TINEA INFECTION	1(0.9)	3(2.8)	0	1(0.9)	0	0	0	0	1(0.9)	4(3.7)	5(4.6)
CONJUNCTIVITIS	1(0.9)	3(2.8)	0	0	0	0	0	0	1(0.9)	3(2.8)	4(3.7)
PNEUMONIA	0	1(0.9)	0	1(0.9)	0	2(1.8)	0	2(1.8)	0	4(3.7)	4(3.7)
FUNGAL SKIN INFECTION	0	3(2.8)	0	0	0	0	0	0	0	3(2.8)	3(2.8)
PULMONARY TUBERCULOSIS	0	0	0	1(0.9)	0	0	0	2(1.8)	0	3(2.8)	3(2.8)
TINEA CRURIS	0	2(1.8)	0	1(0.9)	0	0	0	0	0	3(2.8)	3(2.8)
TINEA PEDIS	0	2(1.8)	0	1(0.9)	0	0	0	0	0	3(2.8)	3(2.8)
TINEA VERSICOLOUR	0	2(1.8)	0	1(0.9)	0	0	0	0	0	3(2.8)	3(2.8)
VIRAL UPPER RESPIRATORY TRACT INFECTION	0	3(2.8)	0	0	0	0	0	0	0	3(2.8)	3(2.8)
ABSCESS LIMB	0	0	0	2(1.8)	0	0	0	0	0	2(1.8)	2(1.8)
ACARODERMATITIS	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
GASTROENTERITIS	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
GASTROENTERITIS VIRAL	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
SEPSIS	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)	2(1.8)
TINEA CAPITIS	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
INFLUENZA	0	6(5.5)	0	0	0	0	0	0	0	6(5.5)	6(5.5)
TONSILLITIS	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
ABSCESS	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
BACTERIAL VAGINOSIS	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
BALANITIS CANDIDA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
BRONCHITIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
CELLULITIS	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
CONJUNCTIVITIS BACTERIAL	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
DEVICE RELATED SEPSIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
DISSEMINATED TUBERCULOSIS	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)	1(0.9)
DYSENTERY	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
EYE INFECTION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
FUNGAL INFECTION	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
GENITAL CANDIDIASIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
GENITAL ULCER SYNDROME	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HERPES SIMPLEX	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
LYMPH NODE TUBERCULOSIS	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
ORAL FUNGAL INFECTION	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)

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ORAL HERPES	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TONSILLITIS	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
OTITIS EXTERNA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
OTITIS MEDIA	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
OTITIS MEDIA ACUTE	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
OTITIS MEDIA CHRONIC	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
PHARYNGITIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SEPTIC SHOCK	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)	1(0.9)
SKIN BACTERIAL INFECTION	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
SKIN CANDIDA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TUBERCULOMA OF CENTRAL NERVOUS SYSTEM	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)	1(0.9)
TUBERCULOSIS	0	0	0	0	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
VIRAL INFECTION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
VULVOVAGINAL CANDIDIASIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	20(18.3)	0	26(23.9)	3(2.8)	9(8.3)	2(1.8)	3(2.8)	0	49(45.0)	5(4.6)	53(48.6)
#ANAEMIA	15(13.8)	0	19(17.4)	1(0.9)	4(3.7)	1(0.9)	2(1.8)	0	38(34.9)	2(1.8)	40(36.7)
#NEUTROPENIA	1(0.9)	0	4(3.7)	1(0.9)	3(2.8)	0	1(0.9)	0	8(7.3)	1(0.9)	9(8.3)
#THROMBOCYTOPENIA	4(3.7)	0	1(0.9)	0	1(0.9)	0	0	0	6(5.5)	0	6(5.5)
#BONE MARROW FAILURE	0	0	1(0.9)	0	2(1.8)	0	0	0	3(2.8)	0	3(2.8)
#LEUKOPENIA	1(0.9)	0	0	0	1(0.9)	0	0	0	2(1.8)	0	2(1.8)
#BICYTOPENIA	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
DISSEMINATED INTRAVASCULAR COAGULATION	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
LEUKOCYTOSIS	0	0	0	0	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
#LYMPHOPENIA	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
#PANCYTOPENIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5(4.6)	50(45.9)	1(0.9)	8(7.3)	1(0.9)	1(0.9)	0	2(1.8)	7(6.4)	51(46.8)	53(48.6)
PLEURITIC PAIN	2(1.8)	18(16.5)	0	1(0.9)	1(0.9)	0	0	0	3(2.8)	19(17.4)	21(19.3)
HAEMOPTYSIS	1(0.9)	12(11.0)	1(0.9)	1(0.9)	0	0	0	1(0.9)	2(1.8)	12(11.0)	14(12.8)
COUGH	0	9(8.3)	0	0	0	0	0	0	0	9(8.3)	9(8.3)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	5(4.6)	0	3(2.8)	0	0	0	0	0	8(7.3)	8(7.3)
BRONCHOSPASM	0	5(4.6)	0	0	0	0	0	0	0	5(4.6)	5(4.6)

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DYSPNOEA	0	1(0.9)	0	2(1.8)	0	1(0.9)	0	1(0.9)	0	5(4.6)	5(4.6)
PRODUCTIVE COUGH	1(0.9)	4(3.7)	0	0	0	0	0	0	1(0.9)	4(3.7)	5(4.6)
NASAL CONGESTION	0	4(3.7)	0	0	0	0	0	0	0	4(3.7)	4(3.7)
RHINORRHOEA	0	4(3.7)	0	0	0	0	0	0	0	4(3.7)	4(3.7)
EPISTAXIS	1(0.9)	2(1.8)	0	0	0	0	0	0	1(0.9)	2(1.8)	3(2.8)
PULMONARY PAIN	0	3(2.8)	0	0	0	0	0	0	0	3(2.8)	3(2.8)
ASTHMA	0	0	0	1(0.9)	0	1(0.9)	0	0	0	2(1.8)	2(1.8)
OROPHARYNGEAL PAIN	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
RHINITIS ALLERGIC	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
PNEUMOTHORAX SPONTANEOUS	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)	1(0.9)
RESPIRATORY DISTRESS	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
INVESTIGATIONS	20(18.3)	8(7.3)	18(16.5)	6(5.5)	16(14.7)	7(6.4)	2(1.8)	2(1.8)	41(37.6)	20(18.3)	51(46.8)
#GAMMA- GLUTAMYLTRANSFERASE INCREASED	2(1.8)	0	9(8.3)	0	3(2.8)	3(2.8)	2(1.8)	1(0.9)	16(14.7)	4(3.7)	20(18.3)
#TRANSAMINASES INCREASED	2(1.8)	0	2(1.8)	0	5(4.6)	2(1.8)	0	1(0.9)	9(8.3)	3(2.8)	12(11.0)
#ALANINE AMINOTRANSFERASE INCREASED	2(1.8)	1(0.9)	5(4.6)	0	2(1.8)	0	0	0	9(8.3)	1(0.9)	10(9.2)
AMYLASE INCREASED	2(1.8)	0	1(0.9)	0	4(3.7)	2(1.8)	0	0	7(6.4)	2(1.8)	9(8.3)
#ASPARTATE AMINOTRANSFERASE INCREASED	2(1.8)	1(0.9)	3(2.8)	1(0.9)	2(1.8)	0	0	0	7(6.4)	2(1.8)	9(8.3)
#ELECTROCARDIOGRAM QT PROLONGED	6(5.5)	0	0	0	0	0	0	0	6(5.5)	0	6(5.5)
#BLOOD CREATINE PHOSPHOKINASE INCREASED	1(0.9)	0	1(0.9)	2(1.8)	1(0.9)	0	0	0	3(2.8)	2(1.8)	5(4.6)
BLOOD UREA INCREASED	2(1.8)	2(1.8)	0	1(0.9)	0	0	0	0	2(1.8)	3(2.8)	5(4.6)
LIPASE INCREASED	1(0.9)	0	1(0.9)	0	4(3.7)	0	0	0	5(4.6)	0	5(4.6)
#BLOOD ALKALINE PHOSPHATASE INCREASED	3(2.8)	0	0	0	0	0	0	0	3(2.8)	0	3(2.8)
BLOOD CREATININE INCREASED	1(0.9)	1(0.9)	0	1(0.9)	0	0	0	0	1(0.9)	2(1.8)	3(2.8)
BLOOD PRESSURE INCREASED	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
#HEPATIC ENZYME INCREASED	2(1.8)	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)
WHITE BLOOD CELL COUNT INCREASED	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
ALBUMIN URINE PRESENT	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
BLOOD CREATINE PHOSPHOKINASE MB INCREASED	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)

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#BLOOD LACTIC ACID INCREASED	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
BLOOD URIC ACID INCREASED	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
CREATININE RENAL CLEARANCE DECREASED	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
WHITE BLOOD CELL COUNT INCREASED	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
ALBUMIN URINE PRESENT	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
BLOOD CREATINE PHOSPHOKINASE MB INCREASED	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
#BLOOD LACTIC ACID INCREASED	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
BLOOD URIC ACID INCREASED	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
CREATININE RENAL CLEARANCE DECREASED	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
METABOLISM AND NUTRITION DISORDERS	23(21.1)	19(17.4)	15(13.8)	9(8.3)	4(3.7)	3(2.8)	2(1.8)	2(1.8)	33(30.3)	28(25.7)	51(46.8)
DECREASED APPETITE	17(15.6)	3(2.8)	6(5.5)	0	0	0	0	0	21(19.3)	3(2.8)	24(22.0)
HYPOGLYCAEMIA	2(1.8)	3(2.8)	1(0.9)	3(2.8)	1(0.9)	0	1(0.9)	2(1.8)	5(4.6)	7(6.4)	12(11.0)
ABNORMAL LOSS OF WEIGHT	3(2.8)	4(3.7)	3(2.8)	2(1.8)	0	1(0.9)	0	0	6(5.5)	7(6.4)	11(10.1)
HYPERAMYLASAEMIA	0	1(0.9)	3(2.8)	0	2(1.8)	0	0	0	5(4.6)	1(0.9)	6(5.5)
HYPOMAGNESAEMIA	0	4(3.7)	1(0.9)	0	0	0	0	0	1(0.9)	4(3.7)	5(4.6)
DEHYDRATION	1(0.9)	0	0	3(2.8)	0	0	0	0	1(0.9)	3(2.8)	4(3.7)
HYPERGLYCAEMIA	3(2.8)	2(1.8)	0	0	0	0	0	0	3(2.8)	2(1.8)	4(3.7)
HYPERKALAEMIA	0	1(0.9)	0	2(1.8)	0	1(0.9)	0	0	0	3(2.8)	3(2.8)
#HYPERLACTACIDAEMIA	1(0.9)	0	1(0.9)	1(0.9)	0	0	0	0	2(1.8)	1(0.9)	3(2.8)
#LACTIC ACIDOSIS	0	0	1(0.9)	0	1(0.9)	0	1(0.9)	0	3(2.8)	0	3(2.8)
HYPOCALCAEMIA	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
HYPOKALAEMIA	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
HYPONATRAEMIA	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
#ACIDOSIS	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
DIABETES MELLITUS INADEQUATE CONTROL	0	0	0	0	0	1(0.9)	0	0	0	1(0.9)	1(0.9)
HYPERLIPASAEMIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
HYPERURICAEMIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HYPOPHOSPHATAEMIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HYPOVOLAEMIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
MUSCULOSKELETAL AND CONNECTIVE	19(17.4)	19(17.4)	2(1.8)	3(2.8)	0	0	0	0	20(18.3)	22(20.2)	37(33.9)

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TISSUE DISORDERS											
BACK PAIN	3(2.8)	7(6.4)	1(0.9)	2(1.8)	0	0	0	0	4(3.7)	9(8.3)	13(11.9)
PAIN IN EXTREMITY	4(3.7)	3(2.8)	1(0.9)	0	0	0	0	0	5(4.6)	3(2.8)	8(7.3)
ARTHRALGIA	5(4.6)	2(1.8)	0	0	0	0	0	0	5(4.6)	2(1.8)	6(5.5)
COSTOCHONDRITIS	1(0.9)	5(4.6)	0	0	0	0	0	0	1(0.9)	5(4.6)	6(5.5)
#MYALGIA	3(2.8)	4(3.7)	0	0	0	0	0	0	3(2.8)	4(3.7)	6(5.5)
MUSCLE SPASMS	2(1.8)	2(1.8)	0	0	0	0	0	0	2(1.8)	2(1.8)	4(3.7)
FLANK PAIN	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
MUSCULOSKELETAL CHEST PAIN	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
CHEST WALL MASS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
#MUSCULOSKELETAL PAIN	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
MUSCULOSKELETAL STIFFNESS	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
#MYALGIA INTERCOSTAL	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
TEMPOROMANDIBULAR JOINT SYNDROME	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
EYE DISORDERS	17(15.6)	13(11.9)	6(5.5)	1(0.9)	0	0	0	0	22(20.2)	14(12.8)	34(31.2)
#VISUAL ACUITY REDUCED	3(2.8)	1(0.9)	2(1.8)	0	0	0	0	0	5(4.6)	1(0.9)	6(5.5)
CONJUNCTIVITIS ALLERGIC	0	5(4.6)	0	0	0	0	0	0	0	5(4.6)	5(4.6)
EYE PAIN	3(2.8)	1(0.9)	1(0.9)	0	0	0	0	0	4(3.7)	1(0.9)	5(4.6)
EYE PRURITUS	1(0.9)	3(2.8)	0	0	0	0	0	0	1(0.9)	3(2.8)	4(3.7)
#VISUAL IMPAIRMENT	3(2.8)	0	1(0.9)	0	0	0	0	0	4(3.7)	0	4(3.7)
VISION BLURRED	3(2.8)	0	0	0	0	0	0	0	3(2.8)	0	3(2.8)
CONJUNCTIVAL HAEMORRHAGE	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
DRY EYE	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
EYE IRRITATION	2(1.8)	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)
PTERYGIUM	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
#AMBLYOPIA	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
EYE SWELLING	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
HYPERMETROPIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
IRIDOCYCLITIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
LENS DISORDER	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
MYOPIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
#OPTIC DISC HYPERAEMIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
#OPTIC NEUROPATHY	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
#PAPILLOEDEMA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
PRESBYOPIA	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)

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RETINAL HAEMORRHAGE	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6(5.5)	10(9.2)	1(0.9)	2(1.8)	0	1(0.9)	1(0.9)	0	7(6.4)	13(11.9)	20(18.3)
OEDEMA PERIPHERAL	0	3(2.8)	0	1(0.9)	0	0	0	0	0	4(3.7)	4(3.7)
FATIGUE	3(2.8)	0	0	0	0	0	0	0	3(2.8)	0	3(2.8)
ASTHENIA	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	0	2(1.8)
CHEST DISCOMFORT	0	1(0.9)	0	0	0	1(0.9)	0	0	0	2(1.8)	2(1.8)
NON-CARDIAC CHEST PAIN	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
PYREXIA	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
CHEST PAIN	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
MALAISE	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
MULTIPLE ORGAN DYSFUNCTION SYNDROME	0	0	0	0	0	0	1(0.9)	0	1(0.9)	0	1(0.9)
THIRST	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
VESSEL PUNCTURE SITE PAIN	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
XEROSIS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3(2.8)	13(11.9)	1(0.9)	0	0	0	0	0	4(3.7)	13(11.9)	15(13.8)
VAGINAL DISCHARGE	0	4(3.7)	1(0.9)	0	0	0	0	0	1(0.9)	4(3.7)	4(3.7)
METRORRHAGIA	1(0.9)	2(1.8)	0	0	0	0	0	0	1(0.9)	2(1.8)	3(2.8)
ERECTILE DYSFUNCTION	2(1.8)	0	0	0	0	0	0	0	2(1.8)	0	2(1.8)
MENORRHAGIA	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
VAGINAL HAEMORRHAGE	0	2(1.8)	0	0	0	0	0	0	0	2(1.8)	2(1.8)
GALACTORRHOEA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
GENITAL RASH	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
GENITAL ULCERATION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
PERINEAL PAIN	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
VASCULAR DISORDERS	0	6(5.5)	0	7(6.4)	1(0.9)	0	0	0	1(0.9)	11(10.1)	12(11.0)
HYPERTENSION	0	3(2.8)	0	5(4.6)	0	0	0	0	0	8(7.3)	8(7.3)
HYPOTENSION	0	1(0.9)	0	1(0.9)	1(0.9)	0	0	0	1(0.9)	1(0.9)	2(1.8)
DEEP VEIN THROMBOSIS	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
FLUSHING	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HAEMATOMA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
PERIPHERAL COLDNESS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
CARDIAC DISORDERS	4(3.7)	3(2.8)	1(0.9)	2(1.8)	0	0	0	0	5(4.6)	5(4.6)	10(9.2)
#PALPITATIONS	1(0.9)	1(0.9)	1(0.9)	0	0	0	0	0	2(1.8)	1(0.9)	3(2.8)

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ANGINA PECTORIS	1(0.9)	0	0	1(0.9)	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
#BRADYCARDIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
CARDIAC FAILURE	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
COR PULMONALE	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
#SINUS BRADYCARDIA	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
#SINUS TACHYCARDIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
#TACHYCARDIA	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
EAR AND LABYRINTH DISORDERS	1(0.9)	6(5.5)	0	4(3.7)	0	0	0	0	1(0.9)	9(8.3)	10(9.2)
EAR PAIN	0	2(1.8)	0	1(0.9)	0	0	0	0	0	3(2.8)	3(2.8)
TYMPANIC MEMBRANE PERFORATION	0	2(1.8)	0	1(0.9)	0	0	0	0	0	3(2.8)	3(2.8)
EXCESSIVE CERUMEN PRODUCTION	0	1(0.9)	0	1(0.9)	0	0	0	0	0	2(1.8)	2(1.8)
AURICULAR SWELLING	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
CERUMEN IMPACTION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
DEAFNESS	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
EAR PRURITUS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
MASTOID EFFUSION	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	7(6.4)	0	3(2.8)	0	0	0	0	0	10(9.2)	10(9.2)
ARTHROPOD BITE	0	3(2.8)	0	1(0.9)	0	0	0	0	0	4(3.7)	4(3.7)
GINGIVAL INJURY	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
INCISION SITE PAIN	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
LACERATION	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
LIGAMENT SPRAIN	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
POST-TRAUMATIC PAIN	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SKIN ABRASION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SOFT TISSUE INJURY	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
PSYCHIATRIC DISORDERS	3(2.8)	5(4.6)	2(1.8)	3(2.8)	0	0	0	1(0.9)	4(3.7)	7(6.4)	10(9.2)
INSOMNIA	2(1.8)	3(2.8)	1(0.9)	1(0.9)	0	0	0	0	3(2.8)	4(3.7)	6(5.5)
ANXIETY	1(0.9)	1(0.9)	0	0	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
DEPRESSION	0	0	1(0.9)	1(0.9)	0	0	0	0	1(0.9)	1(0.9)	2(1.8)
DEPRESSION SUICIDAL	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)	1(0.9)
GENERALISED ANXIETY DISORDER	0	1(0.9)	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
MAJOR DEPRESSION	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
HEPATOBILIARY DISORDERS	2(1.8)	0	3(2.8)	1(0.9)	1(0.9)	0	1(0.9)	0	7(6.4)	1(0.9)	8(7.3)
#DRUG-INDUCED LIVER INJURY	0	0	1(0.9)	0	1(0.9)	0	0	0	2(1.8)	0	2(1.8)
#HYPERBILIRUBINAEMIA	0	0	1(0.9)	0	0	0	1(0.9)	0	2(1.8)	0	2(1.8)

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BILE DUCT STONE	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
#HEPATIC FUNCTION ABNORMAL	0	0	1(0.9)	0	0	0	0	0	1(0.9)	0	1(0.9)
#HEPATOMEGALY	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
#JAUNDICE	1(0.9)	0	0	0	0	0	0	0	1(0.9)	0	1(0.9)
RENAL AND URINARY DISORDERS	0	3(2.8)	0	1(0.9)	0	0	0	0	0	4(3.7)	4(3.7)
AZOTAEMIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
POLLAKIURIA	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
PROTEINURIA	0	0	0	1(0.9)	0	0	0	0	0	1(0.9)	1(0.9)
RENAL FAILURE	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
IMMUNE SYSTEM DISORDERS	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)
SEASONAL ALLERGY	0	1(0.9)	0	0	0	0	0	0	0	1(0.9)	1(0.9)

MedDRA: Medical Dictionary for Regulatory Activities. NR: Not related. R: Related. n = Number of subjects with at least one TEAE in each category (subjects with multiple AEs in each category are counted only once in each category). N = Total number of subjects in the relevant analysis population. % = Percentage of subjects with at least one TEAE in each category relative to the total number of subjects in the relevant analysis population. Treatment-emergent adverse events (TEAEs): Defined as AEs which started or worsened on or after the first study drug administration up to and including 14 days after the last study drug administration. Grade I,II,III, IV TEAEs: Defined as TEAEs for which the severity (DMID grade) is indicated as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (potentially life-threatening) respectively. #: Indicates TEAEs of special interest. TEAEs of special interest: Identified by pre-specified SMQ codes as confirmed by TB Alliance . Adverse events: Coded using MedDRA Version 20.0.

Table 26 For comparison: Published AE table of the already available subset comparator n (%) [46]

Adverse Event	**Bdq group (N=68)**	**Non-Bdq group (N=204)**	**p-value**
Peripheral neuropathy	15 (22.1)	13 (6.4)	<0.001
Dizziness/disorientation	11 (16.2)	35 (17.2)	0.85
Depression	2 (2.9)	27 (13.2)	0.02
Headache	2 (2.9)	12 (5.9)	0.53
Psychosis	3 (4.4)	17 (8.3)	0.42
Blurred vision	5 (7.4)	5 (2.5)	0.14
Hearing impairment	29 (42.7)	31 (15.2)	<0.001
Tinnitus	1 (1.5)	4 (2.0)	1
Abdominal pain	15 (22.1)	34 (16.7)	0.41
Vomiting	16 (23.5)	58 (28.4)	0.71
Nausea	16 (23.5)	59 (28.9)	0.65
Diarrhoea	6 (8.8)	21 (10.3)	0.91
Acute liver failure	1 (1.5)	6 (2.9)	0.68

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Dyspepsia	3 (4.4)	5 (2.5)	0.42
Skin reaction	20 (29.4)	40 (19.6)	0.13
Arthralgia	13 (19.1)	15 (7.4)	0.011
Body pains	19 (27.9)	32 (15.7)	0.04
Anaemia	14 (20.6)	2 (1.0)	<0.001
Deranged renal function	14 (20.6)	41 (20.1)	0.93
Pruritus	3 (4.4)	12 (5.9)	0.77
Hypothyroidism	6 (8.8)	10 (4.9)	0.37
Haematogical disorders	2 (2.9)	2 (1.0)	0.26
Oedema	1 (1.4)	1 (0.5)	0.44
Anxiety	1 (1.5)	N/A	N/A
Sore throat	1 (1.5)	N/A	N/A
Insomnia	0 (0)	4 (2.0)	N/A
Prolonged QT interval	7 (10.3)	N/A	N/A

Table 27 Overview of adverse events in the broader comparative assessment

Identification	Arm	Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness, leading to TB related or non-TB related death	Adverse Events- % of patients with AE/SAE	Drug related adverse events-% (report AE that have a higher percentage than placebo)	Death %	Discontinuation %
NixTB Conradie et al. 2020	BPaL	6	100% (at least 1 AE); 17% (SAE); 57% (grade 3 or higher)		6.42 (6 months after treatment)	0.9 (not TB or drug-related)
Olayanju et al. 2018 [46]	Bedaquiline (+LZD + BR)		95,6	Peripheral neuropathy, 22.1; Hearing impairment, 42.7; Arthralgia, 19.1; Body pains, 27.9; Anaemia 20.6	14,7 (24 months)	58,8 (at least one drug of the BR withdrawn due to SAE)
	BR		70,1	Peripheral neuropathy 6.4; Hearing impairment 15.2; Arthralgia 7.4; Body pains 15.7; Anaemia 1.0	33,8 (24 months)	32.8 (at least one drug of the BR withdrawn due to SAE)

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Pym et al. 2016 [47]	Bedaquiline (+BR)		91 (any AE up to week 24); 94 (any AE up to week 120); 6.4 (SAE up to week 24); 20.2 (SAE up to week 120); 2.1 (grade 4 AE up to week 24); 10.3 (grade 4 AE up to week 120)		5% (all patients while on the 120-week study); 3.8% (patients who completed 24 weeks of bedaquiline treatment at week 120)	15.1 (for any reason)
Tang et al. 2015a [51]	LZD		81.8	Anaemia, 51.5; nausea/vomiting, 4.5; optic neuropathy, 24.2; peripheral neuropathy, 18.2	6.1	12.1 (for any reason)
	Control		3.1		9.4	9.4 (for any reason)
Lee et al. 2012 [52]	Immediate start LZD		87.5 (in overall population)			20% (in overall population), 7.9% (due to drug toxicity)
	Delayed start LZD					
Identification	**Arm**	**Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness, leading to TB related or non-TB related death**	**Adverse Events- % of patients with AE/SAE**	**Drug related adverse events-% (report AE that have a higher percentage than placebo)**	**Death %**	**Discontinuation %**
Wang et al. 2018 [53]	Clofazimine		54.5	Skin discoloration 22.7	9.1	22.7 (for any reason)
	Control			Skin discoloration 0	11.1	14.8 (for any reason)
Diacon et al. 2012 [54]	Bedaquiline (+BR)			Nausea 26.1	4.35	42.86 (for any reason)
	Placebo				0	52.17 (for any reason)

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	(+BR)					
Diacon et al. 2014 [55]	Bedaquiline + BR	13	99% (any); 70% (related to treatment); 43% (grade 3 or 4); 23% (SAE)			5 (due to AE)
	Placebo + BR	2	98% (any); 69% (related to treatment); 36% (grade 3 or 4); 19% (SAE)			6 (due to AE)
Tsuyuguchi et al. 2019 [56]	Bedaquiline + BR	0	83.30			0
STREAM Nunn et al. 2019 [57]	Long regimen	6.4	Grade 3-5, 45.4; serious, 37.6		6.4	5.4 (for any reason)
	Short regimen	8.5	Grade 3-5, 48.2; serious, 32.3		8.5	2.3 (for any reason)
von Groote-Bidlingmaier et al. 2019 [58]	Oral delamanid (+BR)	4.4	26.10 (SAE)	Worsening of tuberculosis, 3.2; hypokalaemia, 2.6; ECG-QT prolongation, 1.8	4.40	2.30 (due to AE)
	Placebo (+BR)	3.5	27.60 (SAE)		3.50	1.80 (due to AE)
Identification	**Arm**	**Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness, leading to TB related or non-TB related death**	**Adverse Events- % of patients with AE/SAE**	**Drug related adverse events-% (report AE that have a higher percentage than placebo)**	**Death %**	**Discontinuation %**
Gler et al. 2012 [59]	DMD 100 mg twice daily + BR		91.30	Anaemia, 11.2: reticulocytosis, 11.8; nausea, 36; vomiting, 29.8; upper abdominal pain, 25.5; palpitations, 8.1; prolonged QT interval on ECG, 9.9; Haemoptysis, 11.8; headache, 22.4; paraesthesia, 10.6; tremor, 11.8; insomnia, 26.1; tinnitus, 9.9; asthenia,		2.50 (due to AE)

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				12.4; malaise, 7.5; anorexia, 14.3; hyperhidrosis, 5.6; hyperuricemia, 19.3; hypokalaemia, 12.4		
	DMD 200 mg twice daily + BR		94.40	Anaemia, 6.2: reticulocytosis, 12.5; nausea, 40.6; vomiting, 36.2; upper abdominal pain, 22.5; palpitations, 12.5; prolonged QT interval on ECG, 13.1; Haemoptysis, 9.4; headache, 25.6; paraesthesia, 12.5; tremor, 10.0; insomnia, 31.9; tinnitus, 13.8; asthenia, 16.9; malaise, 1000; anorexia, 21.2; hyperhidrosis, 10.6; hyperuricemia, 23.8; hypokalaemia, 19.4		3.80 (due to AE)
	Placebo + BR		94.40	Anaemia, 8.8: reticulocytosis, 10.6; nausea, 33.1; vomiting, 27.5; upper abdominal pain, 23.8; palpitations, 6.2; prolonged QT interval on ECG, 3.8%; Haemoptysis, 10.6; headache, 18.8; paraesthesia, 7.5; tremor, 8.1; insomnia, 26.2; tinnitus, 7.5; asthenia, 12.5; malaise, 7.5; anorexia, 15; hyperhidrosis, 5.0; hyperuricemia, 21.9; hypokalaemia, 15		2.50 (due to AE)
Duan et al. 2019 [60]	Clofazimine (+BR)		45.45 (any AE during 24 months); 9.09 (SAE during 24 months)	Skin discoloration, 12.1; Hepatic damage, 12.1	6.1	15.2 (for any reason)
	Control		18.92 (any AE during 24 months); 4.05 (SAE during 24 months)	Skin discoloration 0; Hepatic damage 2.7	2.7	17.6 (for any reason)
Identification	**Arm**	**Incidence of Treatment Emergent Adverse Events (TEAEs) presented by incidence, and seriousness,**	**Adverse Events- % of patients with AE/SAE**	**Drug related adverse events-% (report AE that have a higher percentage than placebo)**	**Death %**	**Discontinuation %**

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		leading to TB related or non-TB related death			
Du et al. 2019 [61]	12-months Clofazimine	47	Skin discoloration 10.4	1.50	
	Control	52.2	Skin discoloration 0	3	
Koh et al. 2013 [62]	LFX	79.2		2.6	3.9 (due to AE)
	MXF	63.5		0	9.5 (due to AE)
Kang et al. 2016 [63]	Clofazimine			7.5	7.5 (for any reason)
	Control			7.7	9.6 (for any reason)
Tang et al. 2015b [64]	LFX	69.2 (any AE); 7.7 (grade 3 or 4)			5.1 (due to AE)
	MXF	59.7 (any AE); 5.2 (grade 3 or 4)			2.6 (due to AE)
Carroll et al. 2013 [65]	Metronidazole (+BR)	Aspergilloma 6.3; Diarrhea 6.3; gastritis 6.3; Hemoptysis 6.3; hepatitis/elevated transaminases 6.3; hyperglycemia 6.3; Hyperuricemia 18.8; hypokalemia 6.3; nausea 6.3; peripheral neuropathy 50; seizure 12.5	Peripheral neuropathies 50	3	
	Placebo (+BR)	Diarrhea 5.9; fracture 5.9; hypercholesterolemia 5.9; hyperglycemia 5.9; hyperuricemia 17.6; myalgia 5.9; peripheral neuropathy 11.8; pneumothorax 5.9; rash 5.9; seizure 5.9		1	

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5.7 Conclusions

Prior to the development of pretomanid, no treatment regimen had ever demonstrated sufficient efficacy against XDR-TB to be approved for *in label* treatment of the disease.

Moreover, pre-existing (quasi ad hoc) treatments for XDR-TB required the use of many different antibiotics (including injectables), with varying side effects, and treatment durations lasting up to and over two years. By contrast, the pretomanid-based BPaL regimen takes only 6 months and uses only 3 orally taken drugs.

TB and antimicrobial resistance are global concerns. Although strategies to end TB have made progress, it is still not given that the End TB milestones can be achieved in Europe, and XDR-TB shows even an increasing trend in Europe. [1] This underlines the emergence in providing patients access to this new treatment option. But this is not only a patient-individual issue. As an infectious disease accompanied by resistance issues, TB concerns the whole society.

The regulatory authorities accepted this emerging need and admitted pretomanid to the approval process based on the totality of the so far existing evidence, although the phase 3 studies Nix-TB and ZeNix are still ongoing with their post-treatment phase and Nix-TB is a single arm study. Meanwhile, pretomanid has FDA-approval and a positive CHMP opinion.

<u>Clinical outcomes:</u>
Pretomanid provides a new, highly effective treatment option for patients affected from highly resistant TB (XDR-TB and TI/NR MDR-TB). Trials of previous treatment regimens demonstrated, at best, favourable outcomes in 2/3 of patients. Today, the Nix-TB trial results indicate that approximately 90% of affected patients could benefit from a favourable outcome.

<u>Safety outcomes:</u>
Linezolid as combination partner to pretomanid within the BPaL regimen is dominating the adverse events and causing a known profile of limited tolerability, especially causing peripheral neuropathy and haematological disorders. However, in

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the majority of cases, the symptoms were mild to moderate and reversible after linezolid interruption or discontinuation. Only one of the surviving patients had a treatment interruption longer than the allowed 35 consecutive days, and none had the regimen permanently discontinued.

The theoretical potential to enhance the QT-prolonging effect of bedaquiline was no special concern.

Finally, there are no unknown adverse event monitoring requirements.

Taken together, pretomanid provides a favourable risk-benefit-relation considering the efficacy in highly resistant forms of TB never seen before and a manageable adverse event profile.

5.8 Strengths and limitations

Because of the lack of a pre-existing regimen with demonstrated effectiveness at the time of the design of the Nix-TB trial, it would have been unethical to include a control arm for the study. However, a prospective cohort comparison study has been conducted, which compares the performance of the BPaL regimen in the Nix-TB trial against other regimens used at the same time for a matched set of other (non-trial) patients in the same treatment sites. However, this data has just been submitted for publication. Unfortunately, because the EUNetHTA procedure cannot guarantee confidentiality of data, there is a risk that the publication of the prospective cohort study results in a public report could compromise the journal approval of the paper. This would have grave consequences for the goal of making data available for public health, and as a consequence the data has not been submitted in this document.

For the same reason, of keeping data unpublished, we decided also not to use patient-level data of the available mentioned subset population [46] for a direct comparison. Alternatively, we have analysed published evidence about different treatment strategies and provide a narrative comparison. We ranked the different comparators by disease and drug regimens, giving treatment regimens containing bedaquiline and/or linezolid, the obligatory combination products to pretomanid (BPaL regimen), priority. No other regimen with published data was excluded. The evidence level of the identified publications is not always high, i.e. not every study is randomised and controlled. However, the orphan nature of the disease, especially

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the highly resistant forms, and the ethical commandment to provide patients with high mortality risk at the end of all therapy options must not be forgotten.

The lack of a pre-existing effective treatment for highly resistant TB has also meant that trials have focused on clinical outcomes, without attempting to measure QoL and patient satisfaction. Therefore, an additional benefit of the BPaL regimen may not be immediately visible in the data: significantly reduced treatment burden due to a much shorter time to both culture-conversion and completion of treatment overall, strongly reduced pill-count, and the elimination of injections.

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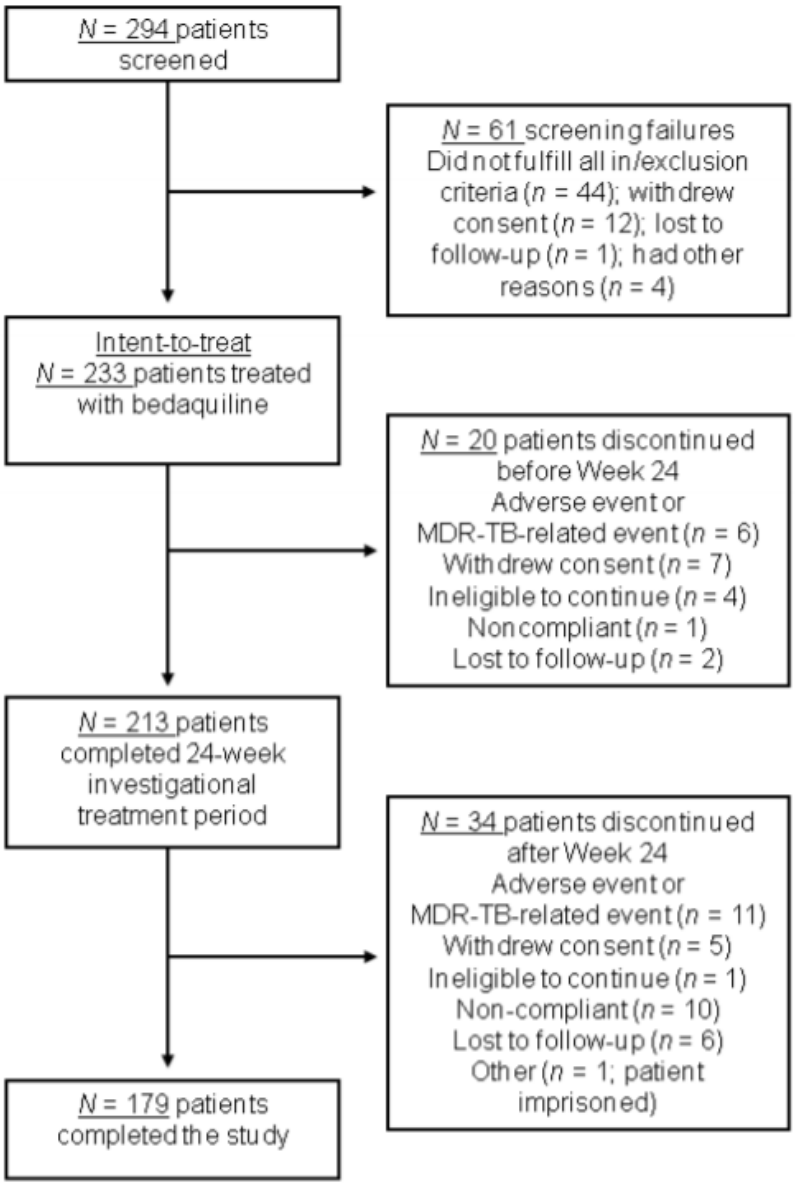
7 Appendix
7.1 Comparator patient flow diagrams

Patient flow diagram Olayanju et al. 2018 [46]: not available

Patient flow diagram Pym et al. 2016 [47]:



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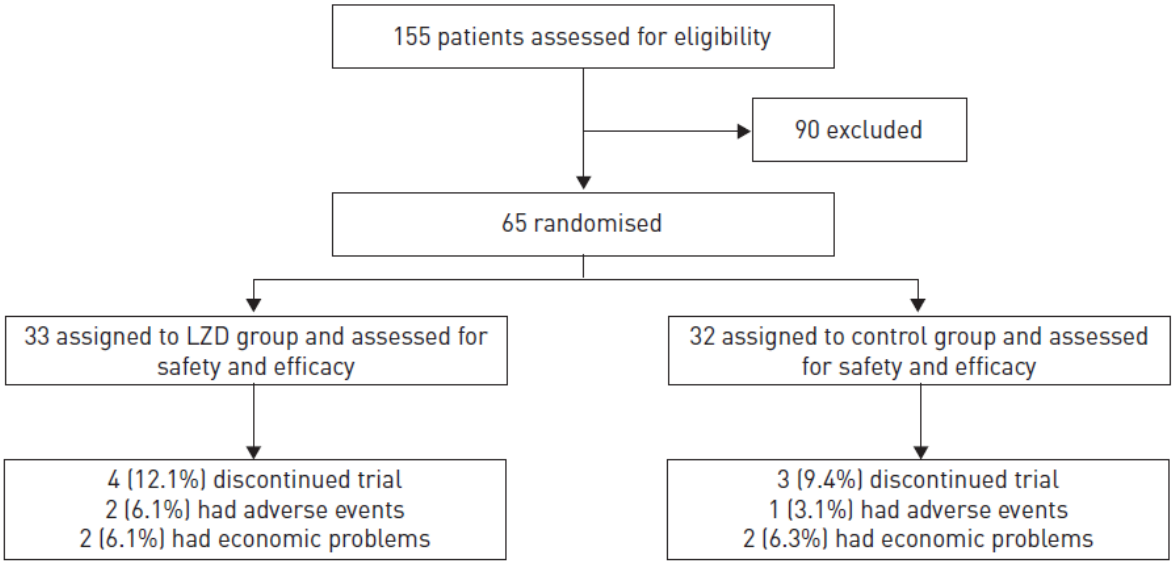
Patient flow diagram Tang et al. 2015a [51]:



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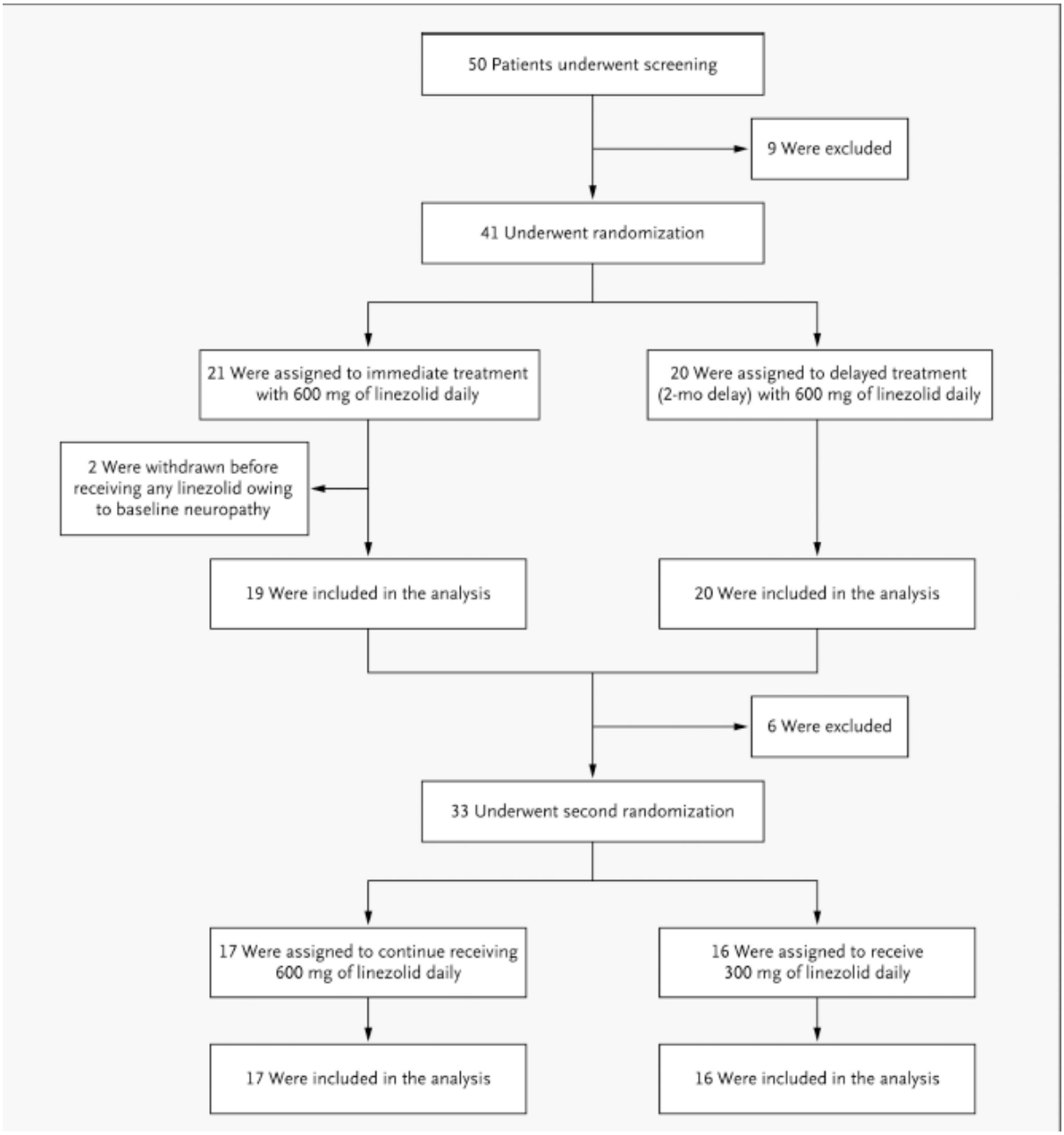
Patient flow diagram Lee et al. 2012 [52]



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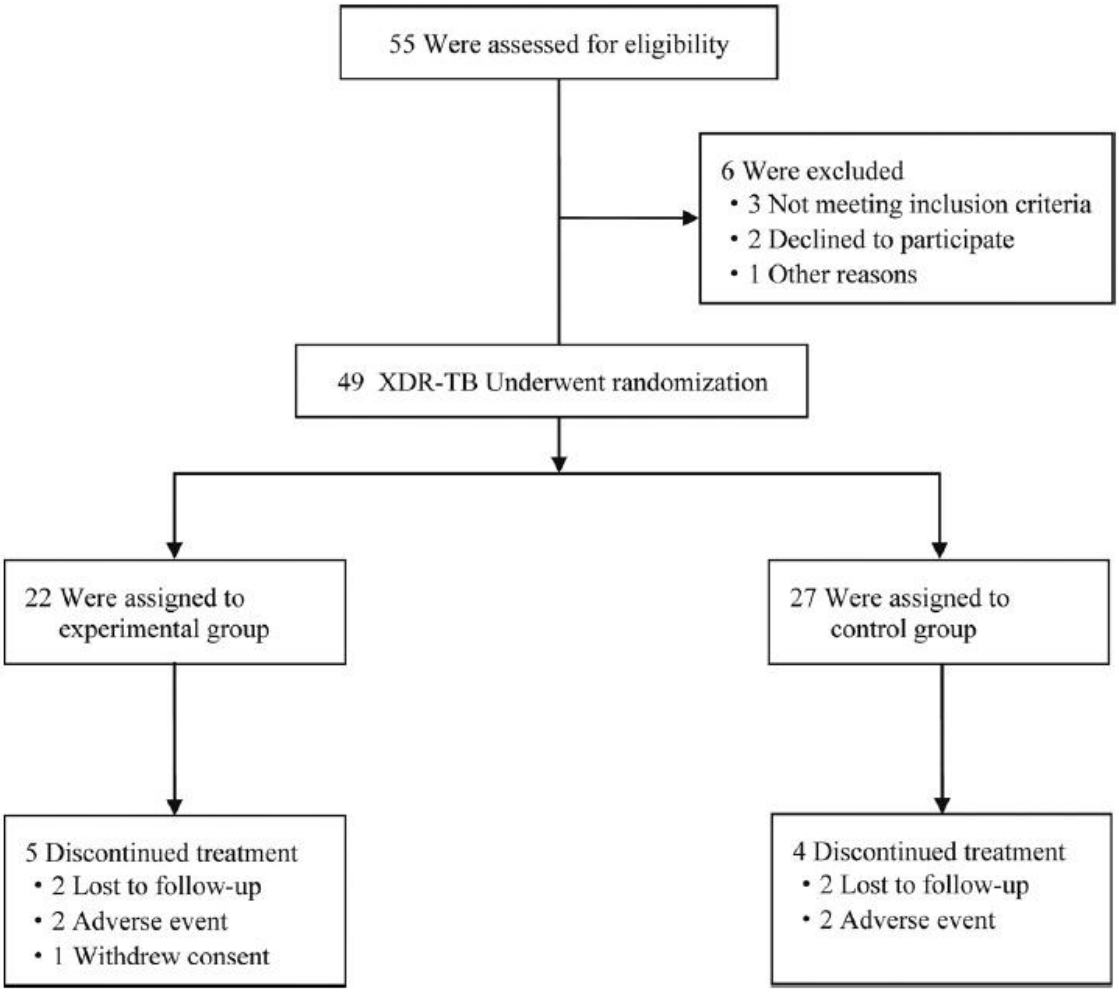
Patient flow diagram Wang et al. 2018 [53]:



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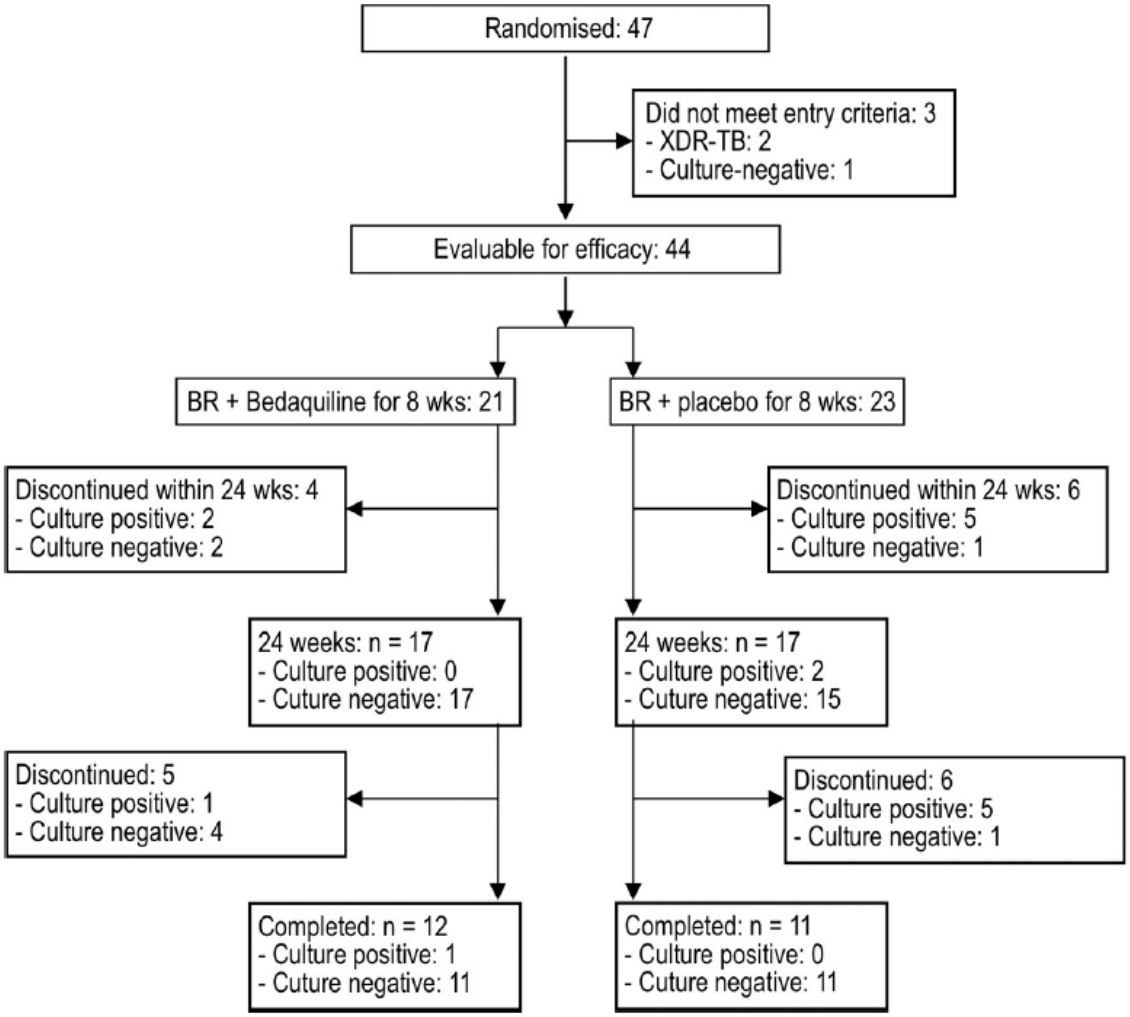
Patient flow diagram Diacon et al. 2012 [54]:



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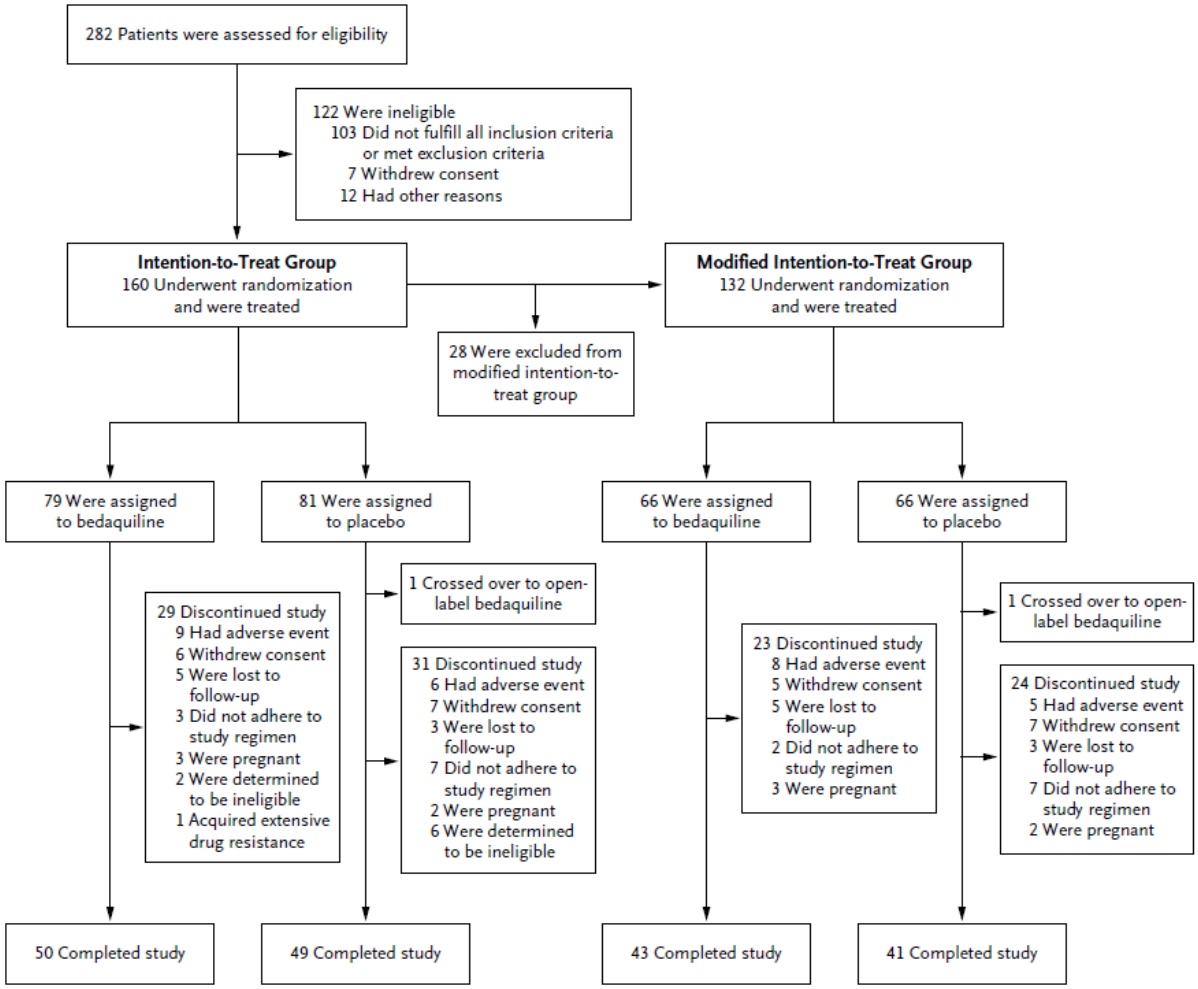
Patient flow diagram Diacon et al. 2014 [55]



Patient flow diagram Tsuyuguchi et al. 2019 [56]: not available

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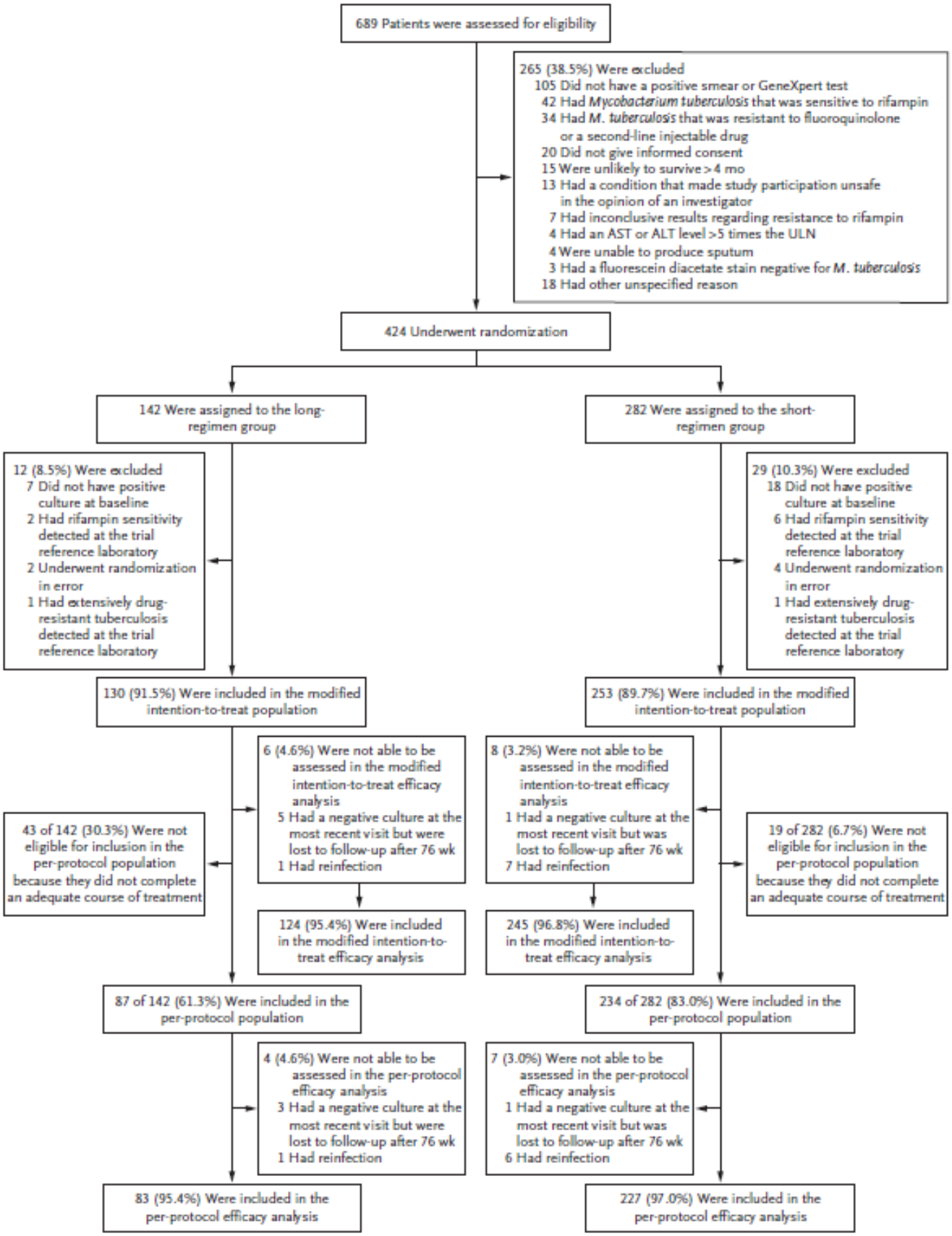
Patient flow diagram Nunn et al. 2019 [57]:



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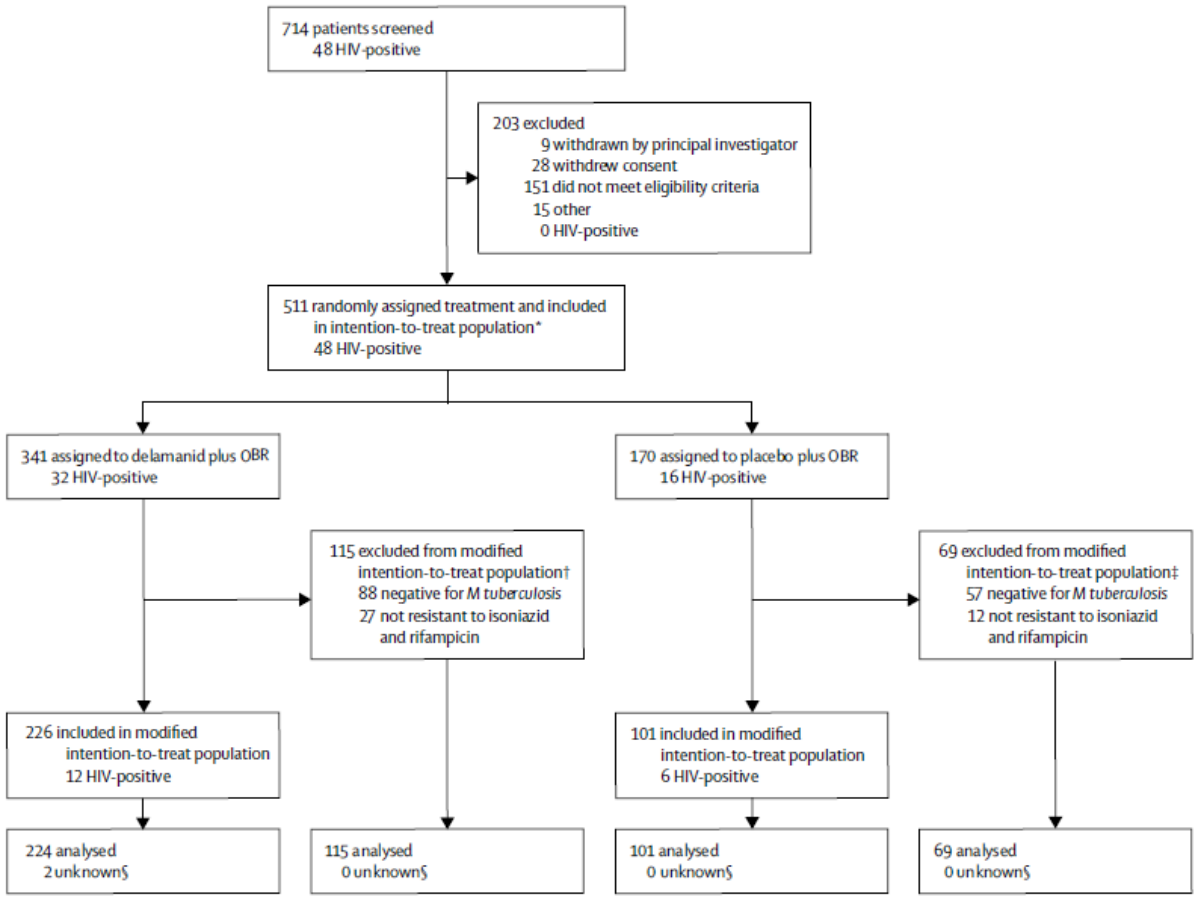
Patient flow diagram von Groote-Bidlingmaier et al. 2019 [58]:



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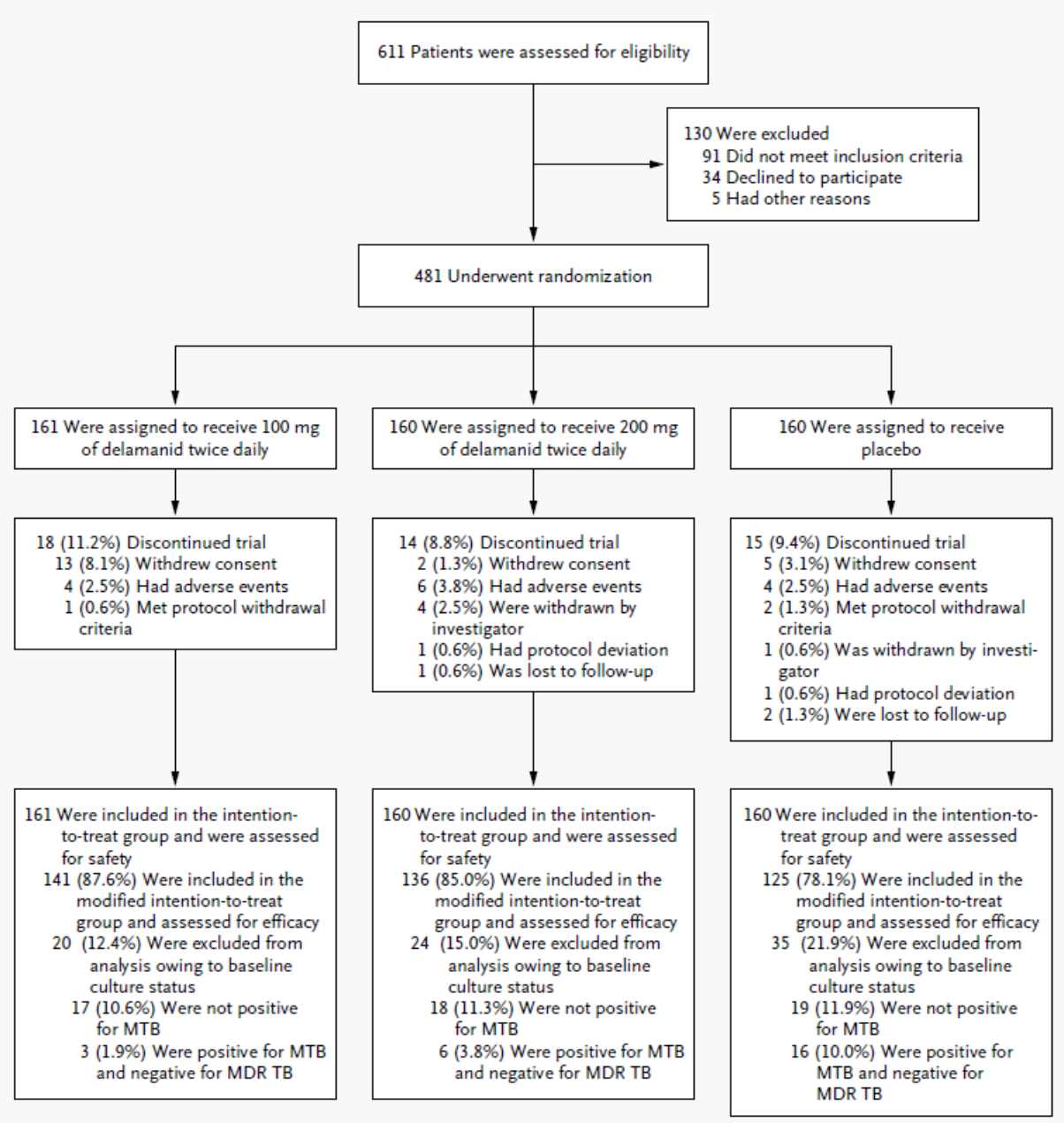
Patient flow diagram Gler et al. 2012 [59]:



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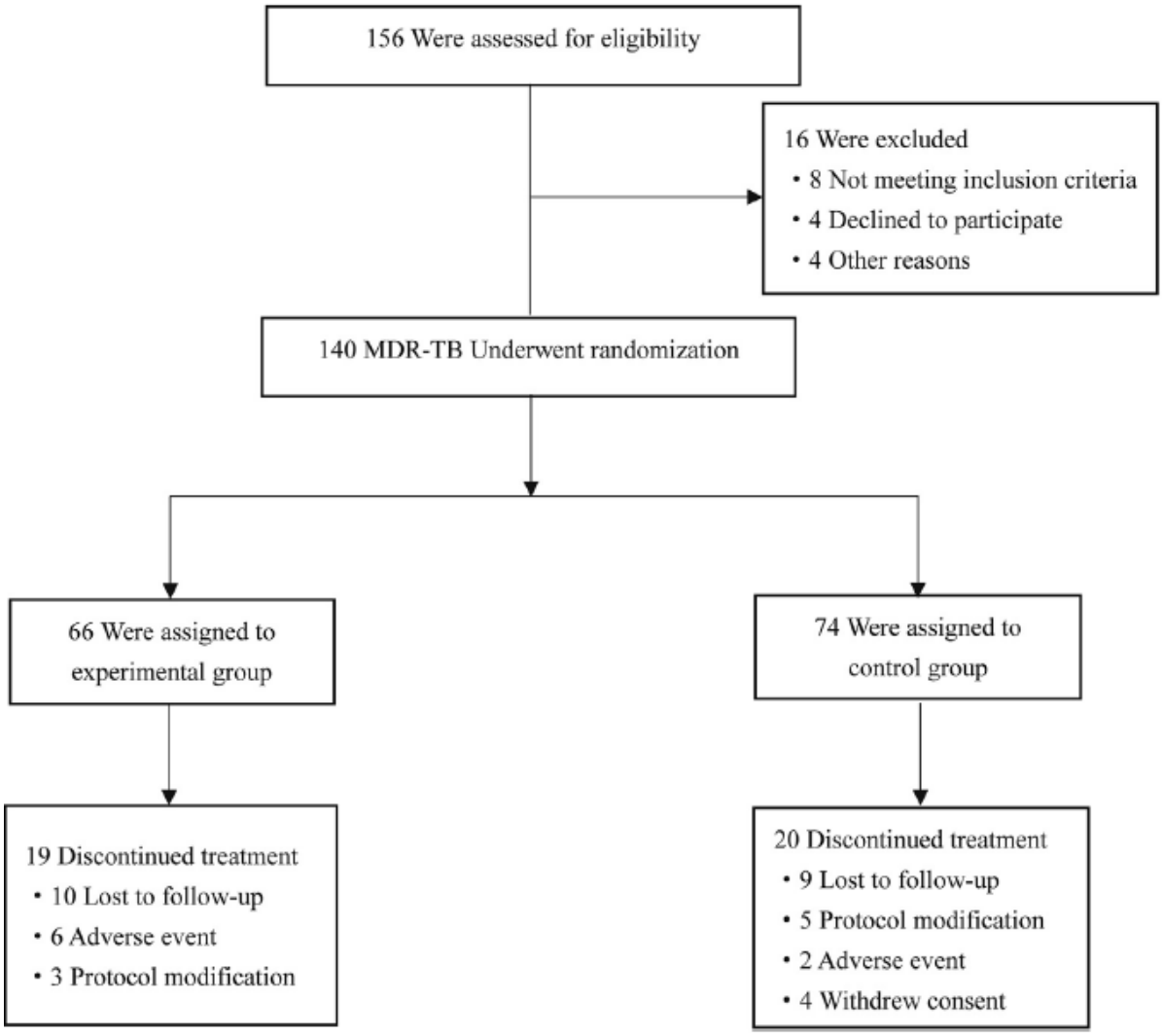
Patient flow diagram Duan et al. 2019 [60]:



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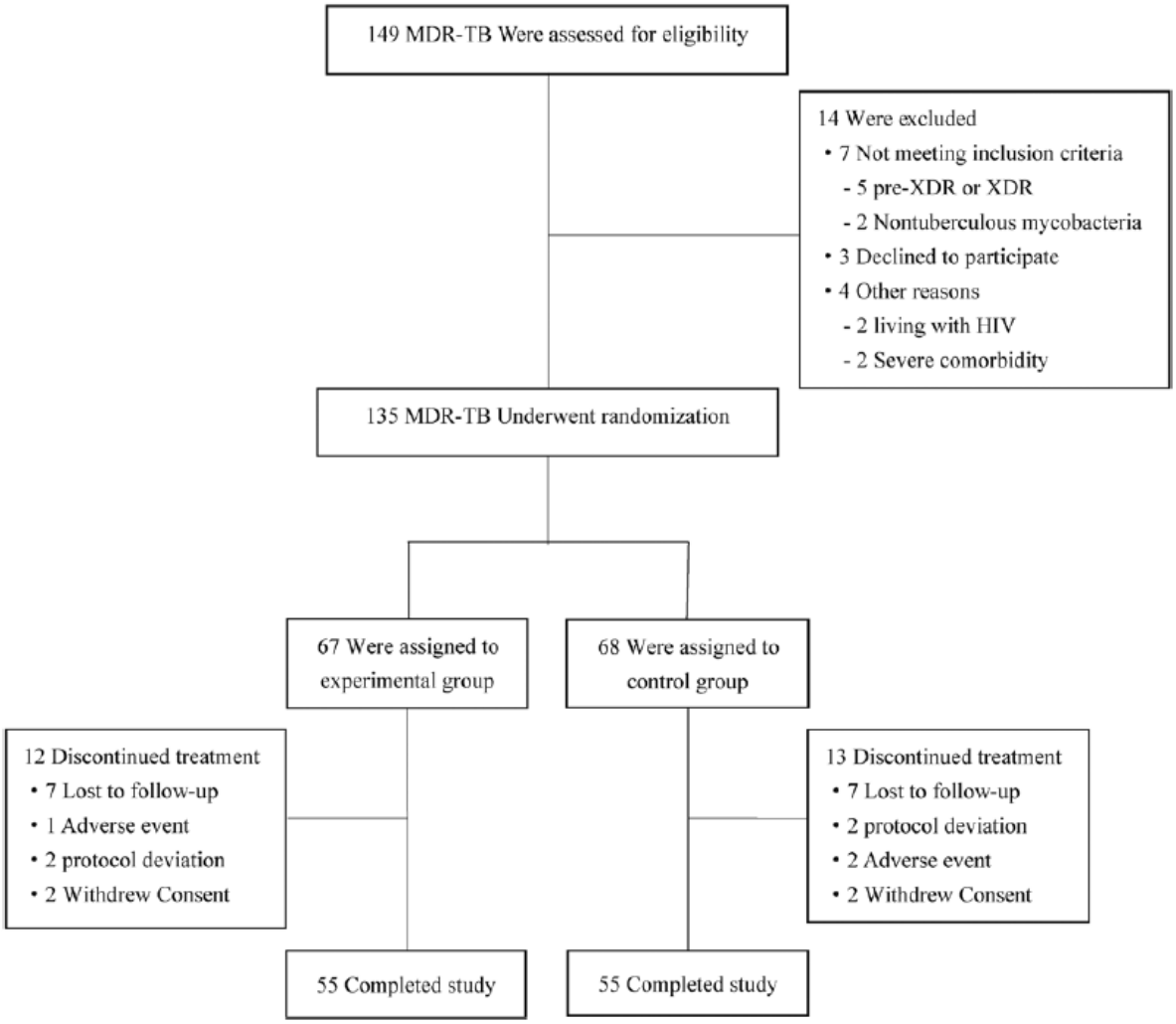
Patient flow diagram Du et al. 2019 [61]:



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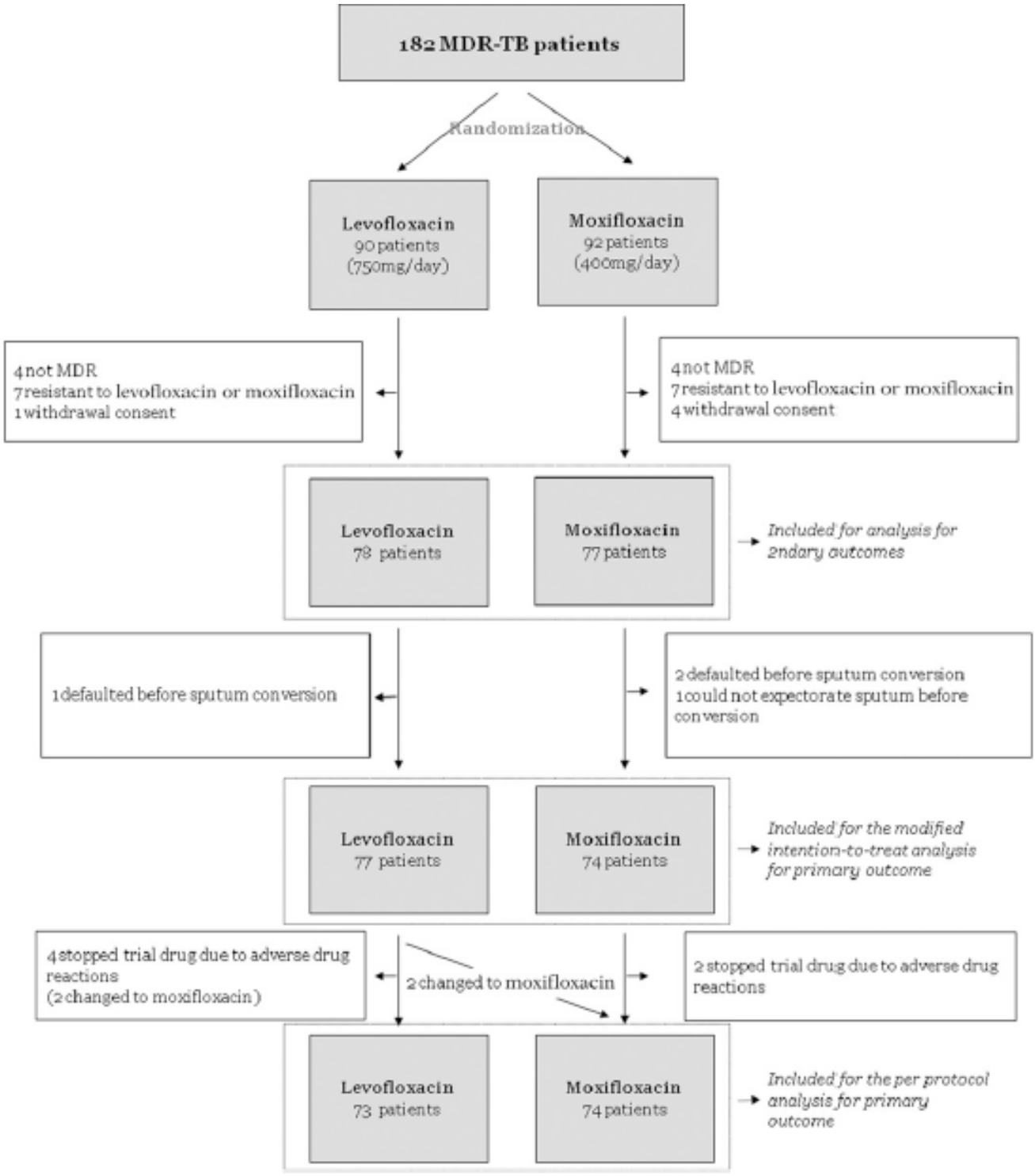
Patient flow diagram Koh et al. 2013 [62]:



Patient flow diagram Kang et al. 2016 [63]: not available (see flow diagram from previous publication [62]

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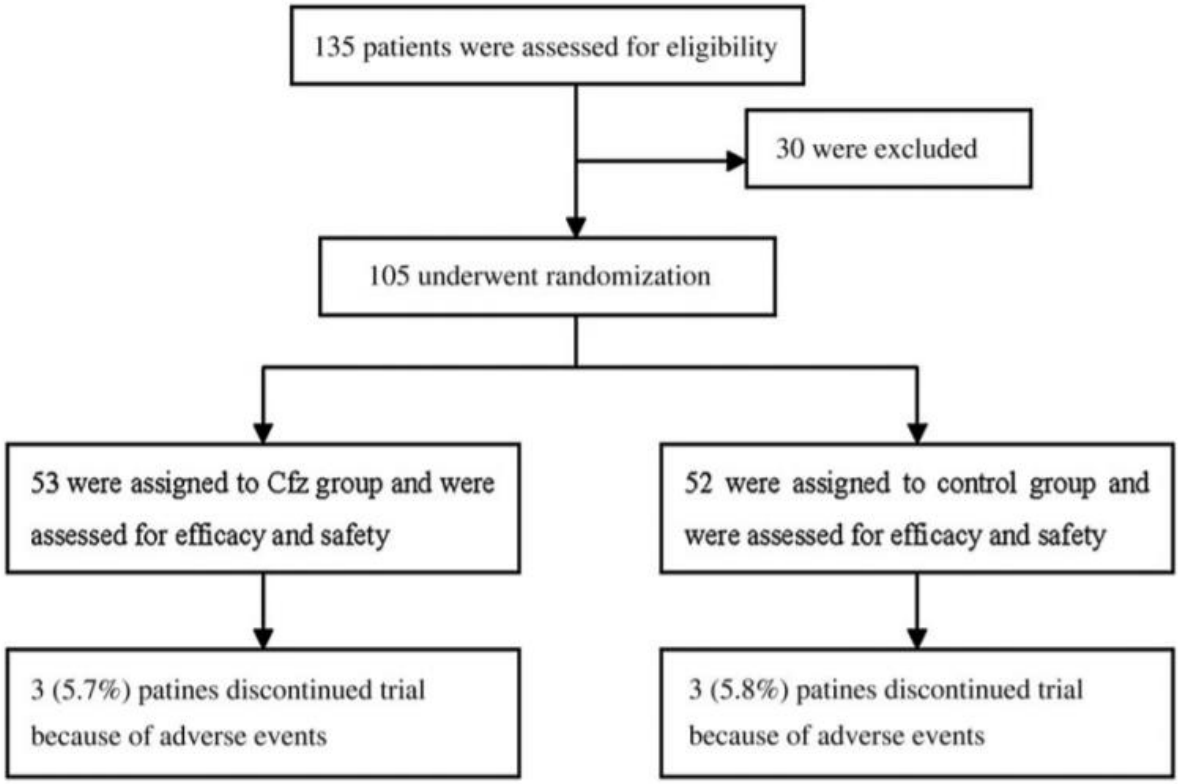
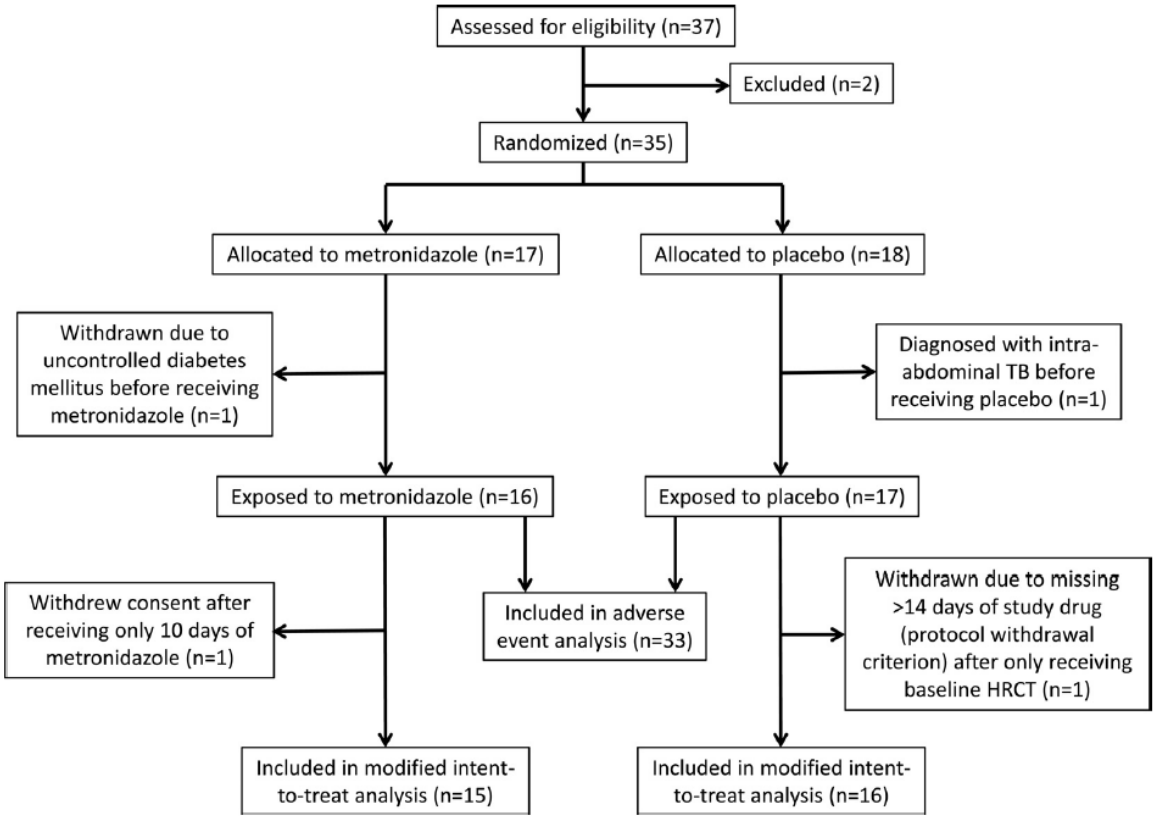
Patient flow diagram Tang et al. 2015b [64]:



Patient flow diagram Carroll et al. 2013 [65]:



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7.2 Methods of data collection (clinical outcome)

Table 28 Methods of data collection and analysis (clinical outcome)

Study reference/ID	Endpoint definition	Further definitions	Method of analysis
NixTB (Conradie et al. 2020) NCT02333799	Primary endpoint: incidence of unfavourable outcome, defined as treatment failure (bacteriologic or clinical) or disease relapse, 6 months after end of treatment Secondary endpoints included time to an unfavourable outcome and time to sputum culture conversion through the treatment period.	**Clinical treatment failure:** change from the protocol-specified tuberculosis treatment as a result of a lack of clinical efficacy, retreatment for tuberculosis, or tuberculosis related death through follow-up until 6 months after the end of treatment. **Favorable outcome:** clinical tuberculosis disease resolved, negative culture status at 6 months after the end of therapy, and not already been classified as having had an unfavorable outcome. **Culture conversion:** at least 2 consecutive culture-negative samples collected at least 7 days apart.	Measure Type: Number, Percent of Measure: participants
ZeNix NCT03086486	Primary endpoint: Incidence of bacteriologic failure or relapse or clinical failure through follow up until 26 weeks after the end of treatment (Time Frame: 26 weeks)		Measure Type: Number, Percent of Measure: participants
Olayanju et al. 2018 [46]	Favourable outcome according to WHO definitions 2013 [44] and the proposed core definitions for drug-resistant TB clinical trials recommended by Furin et al. 2016 [68] up to 24 months. Time-to-event outcomes.	**Culture conversion:** 2 consecutive negative sputum culture results, taken at least ~30 days apart (1 missing or contaminated culture was allowed between negative cultures), inability to produce sputum was considered to be a negative	Univariate Cox proportional hazards models were used to estimate the relation between explanatory variables and time-to-event outcomes. Multivariate Cox proportional hazards models included variables that were significantly associated with outcome ($p<0.1$) with clinical relevance and the preselected variable, gender

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Pym et al. 2016 NCT00910871 [47]	**Primary endpoint**: Median time to sputum culture conversion (Time Frame: Up to Week 24). **Further relevant endpoint**: Cure rate assessment based on WHO outcomes for MDR-TB 2009 [70] with the modification that definition of completion of treatment and cure were determined based on completing the study rather than completing treatment	**Culture conversion:** 2 consecutive visits with negative MGIT cultures from spot sputa collected at least 25 days apart and not followed by a confirmed positive culture) during 24 weeks of bedaquiline treatment	The efficacy analyses were performed on the modified ITT (mITT) population that excluded patients with drug-susceptible TB or patients with negative cultures at screening and/or baseline. Median (95% Confidence Interval), Unit of Measure: Days
Tang et al. 2015a [51]	Cure, treatment completion, death, failure, default according to the WHO and IUATLD (International Union Against Tuberculosis and Lung Disease) guidelines [48, 49, 69]. (time frame: 24 months)	“Cured” was defined as a patient who had completed treatment according to programme protocol and had provided consistently negative cultures (with at least five results) for the final 12 months of treatment for TB. “Completed treatment” was defined as a patient who had completed the treatment according to the programme protocol but did not meet the definition for cured, because of lack of bacteriological results. The “died” category included any patient who had died, for any reason, during the course of the TB treatment. “Treatment failure” included any patient for whom two or more of the five cultures recorded in the final 12 m of therapy were positive, or if any one of the final three cultures was positive. “Defaulted” was defined as a patient whose TB treatment was interrupted for $\geqslant$2 consecutive months for any reason. Additionally, cured and completed treatment categories were combined as “treatment success”, whereas others were combined as “poor treatment outcome”.	Qualitative and quantitative variables were summarised using percentages and medians (interquartile range (IQR)). Chi-squared or Fisher exact tests were used to compare qualitative variables, and the Mann–Whitney test was used to statistically compare quantitative variables.
Lee et al. 2012 [52] NCT00727844	Primary outcome: Number of Patients Converted to Sputum Culture Negative in Each Arm, With Data Censored at 4 Months. (Time Frame: Sputum smear conversion or max 4 months after the start of Linezolid therapy.)	Conversion was defined as negative sputum samples on solid (Löwenstein–Jensen) medium for 3 consecutive weeks.	Measure Type: Number, Unit of Measure: participants. For primary analysis (time to culture conversion): generalized Wilcoxon test and modified ITT analysis

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Wang et al. 2018 [53] ChiCTR1800014800	Primary endpoint: rate of conversion at the end of the course of treatment. Relevant clinical outcomes according to definitions from Laserson et al. [69]		
Diacon et al. 2012 [54]	culture conversion; time to resistance against concomittant drugs (not considered in this dossier)		
Diacon et al. 2014 [55] NCT00449644	Primary: time to sputum culture conversion (week 24); relevant: cure according to definition in 2008 WHO guideline [48]		Median (95% Confidence Interval), Unit of Measure: Days
Tsuyuguchi et al. 2019 [56] NCT02365623	Percentage of Participants With Sputum Culture Conversion (Time Frame: Week 24)		Measure Type: Number, Percent of Measure: participants
STREAM, (Nunn et al. 2019) [57] NCT02409290	Primary efficacy outcome was a favourable status (culture negative) at 132 weeks	Definition of unfavorable outcome: initiation of 2 or more drugs not included in assigned regimen, treatment extension, death from any cause, a positive culture from one of the two most recent specimens, or no visit at 76 weeks or later.	Measure Type: Number, Percent of Measure: participants
von Groote-Bidlingmaier et al. 2019 [58] NCT01424670	Time To Sputum Culture Conversion (SCC) During 6-Month Intensive Period Using The Mycobacteria Growth Indicator Tube (MGIT) System (Time Frame: Month 6); success or failure at month 30	success defined as achieving SCC by the end of 6 months and maintaining SCC to the end of the 30-month trial	Median (95% Confidence Interval), Unit of Measure: Days
Gler et al. 2012 [59] NCT00685360	a) The primary efficacy endpoint is the proportion of patients who achieve sputum mycobacterial culture conversion within 56 full days or less of treatment. [Time Frame: 84 days]; b) Reported adverse events, physical examination, vital signs (blood pressure, heart rate, body temperature and weight), standard 12-lead ECG, clinical laboratory assessment results (hematology, chemistry, urinalysis). [Time Frame: 84 days]		Measure Type: Number, Percent of Measure: participants

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Duan et al. 2019 [60] ChiCTR1800014800	Proportion of patients with successful outcome according to definitions from Laserson et al. [69]		
Du et al. 2019 [61] ChiCTR 1800020391	The rate of conversion at the end of the course of treatment. The treatment outcomes were defined according to Laserson et al. 2005 [69] and the 2011 WHO guidelines [49]		
Koh et al. 2013 [62] NCT 01055145	proportion of patients who achieved sputum culture conversion at 3 months of treatment. Secondary outcomes were time to culture conversion and time to smear conversion, with data censored at 3 months		
Kang et al. 2016 [63] NCT 01055145	outcome according to 2008 World Health Organization [48] definitions as well as 2013 definitions [44]		
Tang et al. 2015b [64]	Treatment outcomes according to the WHO and International Union Against Tuberculosis and Lung Disease guidelines [48, 49, 69]		
Carroll et al. 2013 [65]	time to conversion to negative sputum smear and culture; clinical success: repeatedly culture negative on therapy and without evidence of disease 6 months after EOT by either microbiologic confirmation or a clinical report.	Deaths were considered failures. Those lost to follow-up included subjects who did not complete therapy and those who successfully completed therapy but could not be contacted 6 months after EOT.	

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7.3 Methods of data collection (safety)

Table 29 Methods of data collection and analysis of the adverse event profiles

Study reference/ID	Endpoint definition	Method of analysis
NixTB (Conradie et al. 2020) NCT02333799	All-cause mortality and incidence of adverse events that occurred or worsened during the treatment period (from the start of treatment through 14 days after the end of treatment)	Severity of adverse events was categorized according to the National Institute of Allergy and Infectious Diseases [71] and judged by the investigators to be related to the study medication.
ZeNix NCT03086486		
Olayanju et al. 2018 [46]	all reported adverse events	Active adverse event reporting + grading according to the modified American National Institute of Health common terminology of criteria for adverse events. Hearing impairment was measured by trained audiologists.
Pym et al. 2016 [47] NCT00910871	baseline and serial safety evaluations	Incidence of treatment-emergent adverse events (safety [ITT] population)
Tang et al. 2015a [51]		
Lee et al. 2012 [52] NCT00727844	serial safety evaluations, including complete blood counts, blood chemical measurements, and liver-function tests, neurological and vision examinations	
Wang et al. 2018 [53] ChiCTR1800014800	safety was assessed	not described
Diacon et al. 2012 [54]	Assessment of vital signs, physical examination, laboratory profiling, electrocardiography, and chest radiography were performed at regular intervals.	Adverse events were graded according to the Division of Microbiology and Infectious Diseases adult toxicity tables.
Diacon et al. 2014 [55] NCT00449644	Adverse Events during 120 weeks in the ITT population	
Tsuyuguchi et al. 2019 [56] NCT02365623	reported TEAEs ,clinical laboratory tests, monitoring of vital signs, ECG ,physical examination, chest X-rays + severity grading according to the Division of Microbiology and Infectious Diseases (DMID) adult toxicity tables 2007	

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STREAM, (Nunn et al. 2019) [57] NCT02409290	Reported adverse events, physical examination, vital signs (blood pressure, heart rate, body temperature and weight), standard 12-lead ECG, clinical laboratory assessment results (hematology, chemistry, urinalysis). [Time Frame: 84 days]	
von Groote-Bidlingmaier et al. 2019 [58] NCT01424670	Safety assessments included physical examinations, vital signs, standard 12-lead ECGs, audiometric testing, and clinical laboratory tests (including haematological testing, urinalysis, chemistries, liver function tests, and thyroid and adrenal function tests). Post-treatment follow-up included safety and microbiological assessments for 6–12 months after the 18–24 month treatment period.	
Gler et al. 2012 [59] NCT00685360	Safety tests included the following: monthly physical examinations, weekly assessment of vital signs, standard 12-lead ECG, clinical laboratory tests (including a hematologic profile, coagulation measurements, a urinalysis, and measurements of hepatic aminotransferase and thyroid and adrenal hormone levels), and baseline audiometry.	
Duan et al. 2019 [60] ChiCTR1800014800	routine blood counts, biochemical tests and urinalysis were assessed monthly to monitor the occurrence of adverse events.	
Du et al. 2019 [61] ChiCTR 1800020391	reported adverse events	
Koh et al. 2013 NCT [62] 01055145	proportion of adverse drug reactions	
Kang et al. 2016 [63] NCT 01055145	proportion of adverse drug reactions	
Tang et al. 2015b [64]	monthly baseline and serial safety evaluations	
Carroll et al. 2013 [65]	baseline and serial safety evaluations (complete blood count, chemistries, and liver function tests)	

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7.4 Search Syntax

Table 30 Search syntax for clinical trials and prospective studies

Database name	Medline, Embase, Cochrane (EBM) Reviews
Search interface	Ovid
Search date	20 February 2020
Period covered	2010 to 2020 (week 8)
Search filter	

#	Search terms	Results
1	Multi drug resistant tuberculosis.ti,ab.	1368
2	Multi- drug resistant tuberculosis.ti,ab.	1368
3	Treatment-intolerant multi-drug resistant tuberculosis.ti,ab.	0
4	Non-responsive multi-drug resistant tuberculosis.ti,ab.	1
5	Multi-drug resistant pulmonary tuberculosis.ti,ab.	120
6	Multidrug resistant pulmonary tuberculosis.ti,ab.	229
7	Multi-drug resistant tuberculosis.ti,ab.	1368
8	Multidrug resistant tuberculosis.ti,ab.	7215
9	Multi-drug resistant TB.ti,ab.	490
10	Multidrug resistant TB.ti,ab.	1968
11	MDR-TB.ti,ab.	8961
12	MDR TB.ti,ab.	8961
13	Extensively Drug-Resistant Tuberculosis.ti,ab.	1764
14	Extensively Drug Resistant Tuberculosis.ti,ab.	1764
15	XDR-TB.ti,ab.	2682
16	XDR TB.ti,ab.	2682
17	Pre-XDR.ti,ab.	347
18	TI MDR-TB.ti,ab.	0
19	NR TB-MDR.ti,ab.	2
20	Treatment intolerant multi-drug resistant tuberculosis.ti,ab.	0
21	Nonresponsive multi-drug resistant tuberculosis.ti,ab.	0
22	Bedaquiline.ti,ab.	1260
23	Sirturo.ti,ab.	35
24	Delamanid.ti,ab.	543
25	Deltyba.ti,ab.	25
26	Pretomanid.ti,ab.	175
27	Para-aminosalicylic acid.ti,ab.	1005
28	242-07-204	0
29	242-07-208	0
30	242-10-116	0

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31	242-08-210	0
32	242-09-213	0
33	NCT01424670	3
34	NCT02409290	3
35	ISRCTN78372190	9
36	NCT02333799	0
37	PACTR201409000848428	0
38	NCT02583048	0
39	NCT01856634	0
40	NCT01859923	0
41	NCT01936831	2
42	NCT01918397	9
43	ISRCTN92634082	4
44	NCT02365623	0
45	NCT03086486	0
46	NCT02409290	3
47	ACTRN12616000215426	2
48	NCT02619994	3
49	NCT03141060	0
50	NCT02589782	2
51	NCT02754765	0
52	NCT03338621	0
53	NCT02906007	0
54	NCT04062201	0
55	NCT02354014	0
56	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	17383
57	Clinical trial*.ti,ab.	1033689
58	Controlled clinical trial*.ti,ab.	85698
59	Controlled stud*.ti,ab.	217564
60	Randomized trial*.ti,ab.	242371
61	Double-Blind Stud*.ti,ab.	68143
62	Single-Blind Stud*.ti,ab.	5349
63	Control group*.ti,ab.	1265943
64	Placebo.ti,ab.	807702
65	Randomized clinical trial.ti,ab.	100461
66	Phase 1.ti,ab.	54210

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67	Phase 2.ti,ab.	68868
68	Phase 3.ti,ab.	70706
69	Single-arm.ti,ab.	25196
70	Historical control.ti,ab.	10420
71	Long-term prospective outcome.ti,ab.	20
72	57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71	3289243
73	56 and 72	1107
74	limit 73 to human	950
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