PRETOMANID

SPONSOR BRIEFING DOCUMENT

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE

MEETING DATE: JUNE 6, 2019

ADVISORY COMMITTEE BRIEFING MATERIALS:
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AREDS2	Age-Related Eye Disease Study 2
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUC_{0-24}	Area under the concentration curve from time 0 to 24 hours
AUC_{0-inf}	Area under the concentration curve from time 0 to infinity
BID	Twice daily
BMI	Body mass index
BPaL	Bedaquiline-pretomanid-linezolid
BPaMZ	Bedaquiline-pretomanid-moxifloxacin-pyrazinamide
BPaZ	Bedaquiline-pretomanid-pyrazinamide
C_{avg}	Average concentration at steady-state
CL/F	Oral clearance
C_{max}	Maximum concentration
C_{min}	Minimum (trough) concentration
CNS	Central nervous system
CD4	Cluster of differentiation 4
CFU	Colony forming units
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
DMID	Division of Microbiology and Infectious Diseases
DS	Drug-susceptible
EBA	Early bactericidal activity
ECG	Electrocardiogram
EOT	End of treatment
ERPF	Effective renal plasma flow
FDA	Food and Drug Administration
FF	Filtration fraction
GFR	Glomerular filtration rate

Abbreviation	Definition
GGT	Gamma-glutamyltransferase
hERG	Human Ether-à-go-go-Related Gene
HRZE	Isoniazid, rifampicin, pyrazinamide, and ethambutol
HIV	Human immunodeficiency virus
IQR	Interquartile range
ITT	Intent-to-treat
LPV/r	Ritonavir-boosted loprinavir
LS	Least-squares
MOX	Moxifloxacin
MDR	Multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacterial growth indicator tube
MIC	Minimum inhibitory concentration
mITT	Modified intent-to-treat
M. tb	*Mycobacterium tuberculosis*
NDA	New Drug Application
NICD	National Institute for Communicable Diseases Laboratory
PaMZ	Pretomanid-moxifloxacin-pyrazinamide
PD	Pharmacodynamic
PE	Physical examination
PK	Pharmacokinetic
PopPK	Population pharmacokinetic
PZA	Pyrazinamide
OAT	Organic anion transporter
QD	Once daily
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QTcI	QT interval with individual corrections
QTcN	QT interval corrected using data-specific correction
RIF	Rifampicin
REMA	Resazurin microtiter assay
SAE	Serious adverse event
SD	Standard deviation
SMQ	Standardized MedDRA query
TB	Tuberculosis
TI/NI	Treatment-intolerant or nonresponsive
TIW	Three times a week

Abbreviation	Definition
$T_{1/2}$	Half life
T_{max}	Time to maximum concentration
TSCC	Time to sputum culture conversion to negative
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization
XDR	Extensively drug-resistant

1 EXECUTIVE SUMMARY

TB Alliance is a not-for-profit, product development partnership working on the discovery and development of new drugs and regimen-based paradigms to treat tuberculosis (TB). TB Alliance is seeking approval for pretomanid, a new chemical entity nitroimidazooxazine that is active against *Mycobacterium tuberculosis* (*M. tb*). The proposed indication is:

> Pretomanid is a nitroimidazooxazine antimycobacterial drug indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug-resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) TB.

Note that for the remainder of this document, "XDR-TB and TI/NR MDR-TB" will be used interchangeably with "highly resistant TB."

The new bedaquiline-pretomanid-linezolid (BPaL) regimen is the first all-oral, 6-month treatment to be evaluated in patients with highly resistant TB, for which no approved treatment regimen exists. The short, fixed BPaL regimen is a breakthrough treatment found to cure 90% of patients with highly resistant TB.

Adverse events (AEs) were as expected with this regimen. AEs were generally manageable through dose modifications, and the majority of patients were able to complete therapy.

1.1 Background and Unmet Need

TB is the world's leading infectious disease killer. In 2017, the World Health Organization (WHO) estimated that 10 million individuals developed active TB, and 1.6 million died from the disease (WHO 2018a). 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.

An estimated 457,000 people developed MDR-TB globally in 2017. *M. tb* strains responsible for MDR-TB are resistant to rifampicin and isoniazid, 2 of the most effective first-line drugs (WHO 2018b). Among these cases, an estimated 8.5% were further classified as XDR-TB, which are caused by *M. tb* strains resistant to not only rifampicin and isoniazid, but also to at least 1 fluoroquinolone and 1 second-line injectable agent. While TB, including highly resistant TB, is most common in South-East Asia and Western Pacific regions, all regions of the world including the US are affected by the disease. In the US, 123 cases of MDR-TB and 2 cases of XDR-TB were reported in 2017 (CDC 2017).

Prior to 2018, the WHO-recommended treatment for MDR-TB and XDR-TB included a regimen of at least 5 drugs administered for 18 months or more and usually required daily injections for at least the first 6 months (WHO 2016). The prognosis for patients with XDR-TB was extremely poor, with rates of favorable outcomes noted in the literature ranging from 2% to 22% in South Africa and 15% to 60% outside of South Africa, with only 2 out of 18 articles having rates above 50% (Banerjee et al. 2008; Dheda et al. 2017; Gandhi et al. 2012; Gandhi et al. 2006; Keshavjee

et al. 2008; Kim et al. 2008; Kvasnovsky et al. 2016; Leimane et al. 2010; Liu et al. 2011; Migliori et al. 2008; Mitnick et al. 2008; Mor et al. 2014; O'Donnell et al. 2013; Olayanju et al. 2018; Padayatchi et al. 2014; Pietersen et al. 2014; Tabarsi et al. 2010; Tang et al. 2011).

In 2018, the WHO reprioritized the list of recommended drugs for MDR-TB regimens to include bedaquiline and linezolid in the first tier of prioritized drugs. This was based on increasing evidence of the effectiveness of these agents (WHO 2018b). Inclusion of bedaquiline and linezolid into treatment regimens has led to higher rates of favorable outcomes (ie, 51% to 66% in XDR-TB) (Collaborative Group for the Meta-Analysis of Individual Patient Data et al. 2018; Olayanju et al. 2018) However, these drugs were used as "add-ons" to regimens that were still highly variable and lengthy, with a median of 8 oral and injectable drugs and a total treatment duration of 24 months (Olayanju et al. 2018).

There is an urgent need for an effective, well-defined regimen for highly resistant TB that will shorten treatment duration, simplify administration, and have a more manageable safety profile, allowing for successful completion of the regimen and improved rates of favorable outcomes.

1.2 Product Description

Pretomanid, as a single agent, possesses significant activity against infections caused by both drug-susceptible and drug-resistant strains of *M. tb*. Combining pretomanid with bedaquiline and linezolid presented an opportunity to evaluate an all oral, 3-drug regimen, where each drug has a different mechanism of action with minimal pre-existing resistance among *M. tb* strains.

Pretomanid was developed as a 200 mg oral tablet. It was granted Orphan Drug Designation (2007), qualified infectious disease product designation (2017), and priority review (2019) based on the potential to benefit patients with a significant unmet medical need.

Bedaquiline received conditional approval from the US Food and Drug Administration (FDA) in 2012 to be used in combination with other agents for the treatment of pulmonary MDR-TB at a dose of 400 mg once daily (QD) for 2 weeks then 200 mg thrice weekly (TIW) for 22 weeks. Linezolid was approved by the FDA in 2002 for the treatment of Gram-positive bacterial infections; the recommended dose is up to 600 mg every 12 hours for up to 28 days. While not approved by the FDA to treat TB, the WHO recommends the use of linezolid in all regimens for the treatment of drug-resistant TB unless contraindicated (WHO 2019).

The BPaL regimen is to be orally administered as follows:

- Pretomanid 200 mg QD for 26 weeks; plus
- Bedaquiline 400 mg QD for 2 weeks followed by 200 mg TIW for a total of 26 weeks; plus
- Linezolid 1200 mg daily for up to 26 weeks

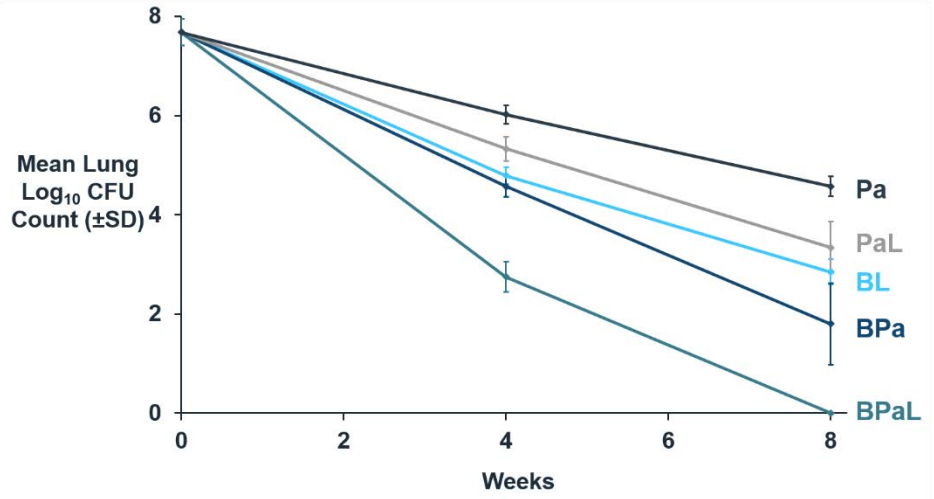
1.3 Clinical Pharmacology and Nonclinical Overview

Key pharmacokinetic (PK) findings from the clinical pharmacology studies were:

- Under fasted conditions, pretomanid exposure increases with dose but less than dose-proportionally.
- Under fed conditions, exposure increases dose-proportionally up to the recommended clinical dose of 200 mg, where the exposure is 88% higher than under fasted conditions.
- PK variability based on weight, body mass index (BMI), sex, age, race, HIV status, TB type, and pretomanid regimen had no clinically meaningful impact on exposure to pretomanid.
- Because pretomanid may be in part metabolized by cytochrome P450 (CYP) 3A4 and inhibits organic anion transporter (OAT) 3, co-administration of pretomanid with strong CYP3A4 inducers or drugs that are mainly eliminated through OAT3 is not recommended.
- Interactions among bedaquiline, pretomanid, and linezolid were not expected based on their known metabolism. PK data for each drug showed no evidence of clinically relevant interactions.
- Together the results from early bactericidal activity (EBA) and time to sputum culture conversion (TSCC) studies showed evidence of a dose response across doses of 50 to 200 mg, with no additional efficacy at doses up to 1200 mg. Based on these results, 200 mg was selected as the dose for the BPaL regimen.
- Exposure-response models evaluating different assessments of safety demonstrated that a lower dose than the proposed 200 mg dose of pretomanid is not predicted to have a notable impact on safety, confirming that 200 mg is an appropriate dose.

Based on a strategy determined in agreement with the FDA, nonclinical data was used to demonstrate the contribution of each of the individual components of the regimen, and thus to support the use of pretomanid as a component of the BPaL regimen. In a series of nonclinical studies in a mouse model of TB, pretomanid demonstrated bactericidal activity when dosed alone, and the BPaL regimen consistently exhibited greater bactericidal activity than any 2-drug combination of its components (Figure 1). The sterilizing activity of the BPaL regimen was also improved compared to that of bedaquiline-linezolid, with significantly fewer relapses observed 3 months after the end of treatment, supporting the added contribution of pretomanid to bedaquiline and linezolid. These results indicate that each component in the BPaL regimen contributes independently to the regimen's overall efficacy against TB.

Figure 1: Lung Colony Forming Unit Counts in Murine Tuberculosis with Different Combinations of Pretomanid, Bedaquiline, and Linezolid



Female BALB/c mice were infected with MTB H37Rv via aerosol with a mean lung $\log_{10}$ CFU count of 4.19 at 13 days prior to the beginning of treatment. They were treated for up to 8 weeks with oral, once-daily dosing (5 days/week) and lung CFU evaluated at 4 or 8 weeks after the start of treatment (n=5 per treatment arm per time point). Dosages: bedaquiline 25 mg/kg, pretomanid 100 mg/kg, linezolid 100 mg/kg
B=bedaquiline; CFU=colony forming units; L=linezolid; Pa=pretomanid; SD=standard deviation

1.4 Efficacy Findings

Study Design

The primary study supporting the efficacy of pretomanid in the New Drug Application (NDA) is Nix-TB, an ongoing Phase 3 pivotal, single-arm study in patients with XDR-TB and TI/NR MDR-TB. A total of 109 patients aged 17 years and older with pulmonary XDR-TB or TI/NR MDR-TB were enrolled at 3 centers in South Africa.

The conduct of a single-arm study outside of the US was considered acceptable for a pivotal study based on the following considerations:

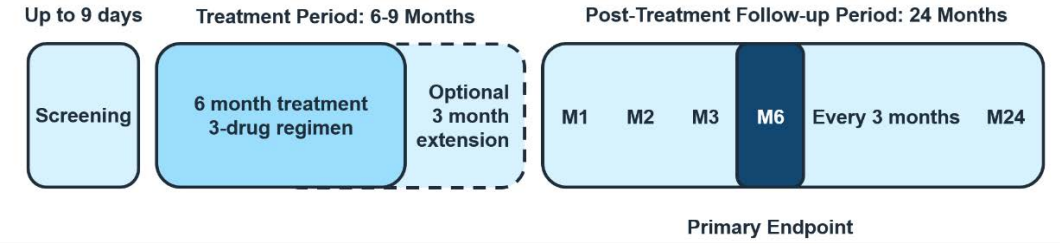
- Patients with XDR-TB have limited treatment options due to their resistance profile. At the time of study initiation in 2015, the recommended treatments had many side effects, including hearing loss and renal damage, and very poor treatment outcomes, with response rates of 2% to 60%, including only 2 articles reporting rates above 50%. Additionally, there was no established standard of care. The commonly used courses of therapy involved treatment for 20 months or more, including 8 months with an injectable agent (WHO 2014a), and various combinations of anti-TB drugs. Thus, there was no appropriate control to use for comparison.
- Highly resistant TB is rare in the US, and it was not feasible to conduct the Nix-TB trial domestically. South Africa was chosen based on prior literature and clinical experience which indicated a high prevalence and generally poor outcomes for patients with XDR-

TB in that region. South Africa also has excellent clinical investigators and a good trial infrastructure and regulatory environment for conducting TB studies.

Additionally, PK data from studies conducted at sites across the world demonstrated that pretomanid exposure was comparable by race and across disease states. Thus, a positive result in the South African population is expected to be generalizable to highly resistant TB in other regions, including the US.

Nix-TB consists of a 6-month treatment period, with a 3-month optional extension, and includes 24 months of post-treatment follow-up (Figure 2). The primary endpoint was assessed 6 months after the end of treatment.

Figure 2: Nix-TB Study Flow



Patients were to be treated with the following regimen for 6 months, with the option to extend treatment to a total of 9 months for patients who were culture positive between Month 4 and Month 6:

- Pretomanid 200 mg QD; plus
- Bedaquiline 400 mg QD (Day 1-14) and 200 mg TIW (after Day 14); plus
- Linezolid 1200 mg daily (600 mg twice daily [BID] or 1200 mg QD 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.

In Nix-TB, the efficacy of the BPaL regimen is evaluated using a clinical endpoint rather than a biomarker or surrogate endpoint. The primary endpoint is the patient status at 6 months after the end of treatment, where patients are categorized as having a favorable or unfavorable outcome. A favorable outcome is defined as a negative culture status at 6 months from the end of therapy (where the last positive culture result is followed by at least 2 negative culture results) and not previously classified as having an unfavorable outcome. An unfavorable outcome includes any of the following:

- During treatment:
    - Death from any cause, except from violent or accidental cause
    - Not having achieved culture-negative status
    - Lost to follow-up
    - Withdrawn from study
- During follow-up after the end of treatment:
    - Death from causes definitely or possibly related to TB
    - Withdrawal from study for TB-related reasons, including retreatment for TB
    - Bacteriologic relapse, ie, culture conversion to positive status with the *M. tb* strain present at baseline
    - Bacteriologic reinfection, ie, culture conversion to positive status with a *M. tb* strain different from the infecting strain at baseline.

The primary endpoint analysis was the proportion of patients in the modified intent-to-treat (mITT) population with a favorable outcome. For success of the trial, the lower bound of the 95% confidence interval (CI) for a favorable outcome must be greater than 50%. The 50% threshold was selected as a favorable rate as it was much higher than those previously reported for patients with highly resistant TB before either bedaquiline or linezolid were in use.

Study Population

An interim efficacy analysis based on data available as of 29 June 2018 was submitted in the pretomanid NDA and is presented in this document. As of 29 June 2018, 101 of the 109 patients who enrolled and initiated study therapy completed treatment with the BPaL regimen, 81 patients completed the 6-month primary efficacy assessment, and 23 patients completed the study with 24 months of follow-up.

Of the 109 patients, 52.3% were male, 76.1% were black or African. Patients had a mean age of 36 years and mean BMI of 20.6 (range, 12.4 to 41.1) kg/m^2.

The majority (65.1%) of patients had a TB diagnosis of XDR-TB at Screening. On average, patients were first diagnosed with their TB infection 23.6 months prior to Screening (median, 12.1 months; maximum, more than 11 years). Prior TB medication use was reported in 96.3% of patients; the average number of prior TB medications used was 8.9.

At Screening, 51.4% of patients were HIV positive with a mean duration since diagnosis of 4.7 years. All HIV positive patients were on antiretroviral therapy (ART).

The primary efficacy analysis population as per the statistical analysis plan was the mITT population (n=80), which excluded 1 patient from the intent-to-treat (ITT) (n=81) whose outcome at 6 months following the end of treatment was “unassessable” (this patient completed

study treatment, was culture negative as of his last follow-up visit, and died of causes unrelated to TB thereafter).

Primary Efficacy Endpoint – Patient Status at 6 Months After End of Treatment

As of the 29 June 2018 efficacy analysis data cut-off date, the criterion for trial success was met. The proportion of patients who achieved a favorable outcome at 6 months following the end of treatment was 90% in the mITT population (Table 1). The lower bound of the 95% CI of the proportion with a favorable outcome was 81%, which exceeded the 50% prespecified threshold for success. Similar rates of favorable outcome were observed for patients with XDR-TB and patients with TI/NR MDR-TB.

Table 1: Primary Efficacy Analysis (mITT Analysis Population)

	XDR N=55 n (%)	TI/NR MDR N=25 n (%)	Total N=80 n (%)
Favorable	**49 (89%)**	**23 (92%)**	**72 (90%)**
95% CI	**78%, 96%**	**74%, 99%**	**81%, 96%**

CI=confidence interval; MDR=multidrug-resistant; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

Eight out of 80 patients had an unfavorable outcome: 6 patients died within 14 weeks of starting study drug treatment, and 2 patients had bacteriologic relapse at Month 2 and Month 3 after end of treatment, following culture conversion to negative and completion of study treatment. Of the 6 patients who died during treatment, 4 had highly advanced TB on autopsy and 3 of these had multi-organ involvement. Three of the patients who died had HIV co-infection, and 5 of them had had low BMIs on Screening of <17.2 kg/m^2.

Similar results were obtained for the ITT population, which differed from the mITT population by only 1 patient.

Primary Efficacy Endpoint – Sensitivity and Subgroup Analyses

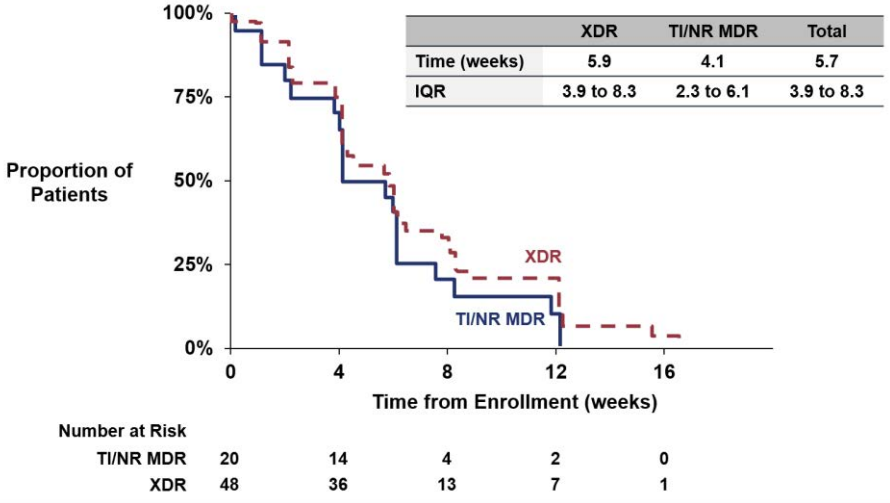
The prespecified sensitivity analysis demonstrated that the results of the primary outcome were similar when evaluating only those patients who had positive cultures for *M. tb* at baseline. Of the 68 patients who were culture-positive at baseline, 60 patients (88%) had favorable outcomes at Month 6 of follow-up (lower bound of 95% CI, 78%).

Subgroup analyses by HIV status (positive vs negative) and linezolid dosing (600 mg BID vs 1200 mg QD) revealed no difference in clinical outcomes based on these factors, as the rate of favorable outcomes was 89% or greater across all subgroups (lower bound of 95% CI, 75% or greater).

Secondary Endpoint – Time to Sputum Culture Conversion to Negative

Patients in Nix-TB achieved culture conversion quickly; among patients with positive baseline cultures, the median time to conversion was 5.7 weeks (Figure 3).

Figure 3: Time to Culture Negative Status (mITT Analysis Population)



IQR=interquartile range; MDR=multidrug-resistant; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

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 (Johnson and Thiel 2012; Nunn et al. 2010). As of the data cut-off date, 19 of the 23 patients with available 24-month results remained culture negative and 1 patient relapsed 15 months after completion of study treatment. The remaining 3 patients were among those who died during treatment and counted as having unfavorable outcomes for the 6-month primary endpoint.

Secondary Endpoint – Patient-Reported TB Symptom Profile

Patients reported improvement in a number of individual TB symptoms (eg, cough, chest pain, coughing up mucus, feeling unwell, etc.) by Week 8 and showed further improvement through the end of treatment, consistent with the change in disease status. Overall, 41% of patients had 5 to 9 symptoms at baseline compared to 10% at Week 8 and 2% at the end of treatment. Conversely, 13% of patients had 0 to 1 symptom at baseline which increased to 70% at the end of treatment.

Comparison to Historical Control Cohort

Because Nix-TB is an uncontrolled, single-arm study, a case-matched analysis was conducted using historical control data as the control for the first 45 patients enrolled in Nix-TB. This strategy was agreed upon with the FDA.

The historical control cohort was composed of patients with XDR-TB who were treated at Brooklyn Chest Hospital in Cape Town, South Africa, one of the 3 sites at which Nix-TB was conducted. The historical cohort had demographics and baseline characteristics similar to the Nix-TB cohort. Patients in the matched control cohort received treatment with various drug

combinations (which did not include bedaquiline, linezolid, pretomanid, or delamanid) between January 2008 and September 2014 (Olayanju et al. 2018).

Treatment outcomes in the control cohort were assessed based on patient status at 24 months after the start of treatment (treatment was planned to last 18 months or longer); treatment outcomes for the Nix-TB cohort were based on the Nix-TB primary endpoint analysis. Overall, 13.4% of the control cohort achieved a favorable outcome, defined as achieving a cure[1] or completing treatment. In comparison, 88.9% of the Nix-TB cohort achieved a favorable outcome, a 6.6-fold increase over the control cohort. Similar results were obtained in the sensitivity analysis after adjustment for sex, age, body weight, and HIV status at baseline.

While there are several limitations to the comparison of Nix-TB study data with that of a non-contemporaneous cohort being followed outside of a clinical study, the comparative analyses are robust. These analyses support the findings that the BPaL regimen leads to favorable outcomes in a large percentage of patients with highly resistant TB compared to the rates of favorable outcomes that were achievable without the use of bedaquiline, pretomanid, and linezolid, and further support the prespecified threshold for success of the trial.

1.5 Safety Findings

As of the safety data cut-off date of 26 March 2018, a total of 1,168 individuals, including 223 patients with either XDR-TB or MDR-TB, 656 patients with DS-TB, and 289 healthy volunteers, were exposed to pretomanid, either alone or as part of combination therapy. The safety results presented in this document focus primarily on the 109 patients enrolled in Nix-TB; additional safety findings from the pretomanid clinical program are provided in Section 7.1.

The Nix-TB safety database includes data available through the 26 March 2018 cut-off date.[2] As of 26 March 2018, 93 (85.3%) of the 109 patients enrolled in Nix-TB had completed the protocol-specified 26 weeks of investigational drug therapy, and 10 (9.2%) were still receiving study treatment; 6 patients died before completing study treatment.

Adverse Events

All 109 patients experienced at least 1 AE during the treatment period and up to 14 days after the last dose of study drug (Table 2). Patients experienced an average of 11.5 AEs, and 53.2% experienced an average of 2.1 AEs with a maximum AE severity of either Grade 3 (severe; 37.6%) or Grade 4 (potentially life threatening; 15.6%; Table 33).

Many of the most frequently (≥10% of patients) reported AEs in Nix-TB (peripheral sensory neuropathy and anemia) are known adverse effects of linezolid (Pfizer 2018); other common

[1] The definition of cure was treatment completed as recommended by the national policy without evidence of failure AND 3 or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
[2] Comprehensive safety analyses based on the 26 March 2018 cut-off date were submitted in the pretomanid NDA. Updated safety analyses as of 15 October 2018 have been recently provided to the FDA for this ongoing study. The additional safety data showed no change in the overall safety profile of the BPaL regimen and no change to the overall safety conclusions of the study.

AEs are consistent with the expected safety profile of bedaquiline, pretomanid, and linezolid (Table 4) as well as the underlying conditions found in the study population.

Table 2: Treatment-Emergent Adverse Events Occurring in ≥10% of Patients (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any AE	**109 (100%)**
Preferred term	
Peripheral sensory neuropathy	**75 (68.8%)**
Anaemia	**40 (36.7%)**
Nausea	**40 (36.7%)**
Vomiting	**37 (33.9%)**
Headache	**28 (25.7%)**
Dermatitis acneiform	**26 (23.9%)**
Dyspepsia	**26 (23.9%)**
Decreased appetite	**24 (22.0%)**
Pleuritic pain	**20 (18.3%)**
Upper respiratory tract infection	**20 (18.3%)**
Gamma-glutamyltransferase increased	**18 (16.5%)**
Rash	**17 (15.6%)**
Acne	**16 (14.7%)**
Pruritus	**15 (13.8%)**
Haemoptysis	**14 (12.8%)**
Back pain	**13 (11.9%)**
Hypoglycaemia	**12 (11.0%)**
Transaminases increased	**12 (11.0%)**
Abdominal pain	**11 (10.1%)**
Abnormal loss of weight	**11 (10.1%)**
Diarrhoea	**11 (10.1%)**

AE=adverse event

Adverse Events Leading to Dose Modifications

The entire BPaL regimen was discontinued in 6 patients (5.5%) and interrupted in 20 patients (18.3%). All 6 patients who discontinued the regimen were those who died prior to completing treatment; all remaining patients were able to complete their study regimen or were still receiving treatment at the time of the data cut-off (26 March 2018). Among the 20 patients who had interruptions in BPaL dosing, the mean total duration of all interruptions was 19.6 days (range, 2 to 48 days). The most common AEs leading to interruption of the entire treatment regimen were transaminases increased (4.6%) and abdominal pain (2.8%), with other events each occurring in 2 or fewer patients (Table 30).

Discontinuation, interruption, and dose reduction of linezolid alone were also 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, 25.7% of patients discontinued linezolid due to AEs, 39.4% had linezolid dose reductions, and 44.0% had linezolid interrupted for a total mean duration of 44.5 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).

In general, the rate of dose reduction and interruption increased steadily over the treatment period, with a median time to first dose reduction of approximately 110 days, and a median time to first dose interruption of approximately 140 days.

Serious Adverse Events

Nineteen patients (17.4%) in Nix-TB reported at least 1 serious adverse event (SAE; Table 32). The most frequently reported SAEs were pneumonia (2.8%) and pulmonary TB (2.8%), reflective of patients' underlying disease, followed by sepsis (1.8%), hypoglycemia (1.8%), and anemia (1.8%). All other SAEs were reported by 1 patient each.

Deaths

To date, 8 deaths were reported in Nix-TB; 6 were due to SAEs that occurred during study treatment (Patient 1–6) and 2 were due to SAEs occurring during follow-up after completion of study treatment (Patient 7 and Patient 8; Table 3). Two patients died of fatal SAEs considered possibly related to study treatment; the remaining fatal SAEs were deemed unrelated to study treatment. An overview of each death is provided in Section 7.5.

Table 3: Deaths (Nix-TB)

Patient	Day of Death	Fatal SAEs (Preferred Term)	Relationship to Study Drug According to Investigator	HIV Status
1	Day 35	Pulmonary tuberculosis Disseminated tuberculosis	Not related	Positive
2	Day 51	Upper gastrointestinal haemorrhage	Possibly related	Negative
3	Day 55	Pulmonary tuberculosis	Not related	Positive
4	Day 53	Pancreatitis haemorrhagic Multiple organ dysfunction syndrome	Possibly related	Positive
5	Day 93	Sepsis Pneumonia	Not related	Negative
6	Day 76	Septic shock Pneumonia	Unlikely related	Negative
7	Day 369 (185 days after EOT)	Natural causes	Not related	Positive
8	Day 486 (303 days after EOT)	Thrombotic thrombocytopenic purpura Sepsis Dry gangrene Peripheral vascular disorder Infected skin ulcer	Not related	Positive

EOT=end of treatment; HIV=human immunodeficiency virus; SAE=serious adverse event

Adverse Events of Special Interest

Adverse events of special interest (AESIs) for any of the 3 drugs in the BPaL regimen were specified in the Nix-TB protocol and evaluated using standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs). As shown in Table 4, these AESIs were identified based on the nonclinical and clinical studies for pretomanid, the product label and investigator brochure for bedaquiline, the product label for linezolid, and literature reports of linezolid long-term toxicity.

Table 4: Adverse Events of Special Interest Prospectively Identified for Each Component of the Regimen

AESIs	Pretomanid	Bedaquiline	Linezolid	Patients with Any AESIs from SMQs n (%)
Lens disorders	X[a]			14 (12.8%)
Testicular toxicity	X[a]			0
Convulsions	X[a]		X	2 (1.8%)
ECG QT prolongation	X[a]	X		7 (6.4%)
Hepatic toxicity	X	X		40 (36.7%)
Myopathy/rhabdomyolysis		X[a]		11 (10.1%)
Pancreas-related events		X[a]		22 (20.2%)
Peripheral neuropathy			X	87 (79.8%)
Optic nerve disorders			X	13 (11.9%)
Myelosuppression			X	51 (46.8%)
Lactic acidosis			X	8 (7.3%)

a. Potential adverse effects identified from animal toxicology studies.
AESI=adverse event of special interest; ECG=electrocardiogram; SMQ=standardized MedDRA query

AESIs related to lens disorders, convulsions, QT prolongation, hepatic toxicity, pancreas-related events, peripheral neuropathy, optic nerve disorders, and myelosuppression are summarized below. Section 7.6 provides additional information on these events and the remaining categories of AESIs (testicular toxicity, myopathy/rhabdomyolysis, and lactic acidosis).

- **Lens disorders:** In pretomanid toxicology studies, cataracts were observed in rats. Based on the findings in rats, cataracts and lens disorders were assessed in Nix-TB using slit-lamp examinations with Age-Related Eye Disease Study 2 (AREDS2) scoring of lens opacities. Overall, there were a similar number of increases and decreases of scores, suggesting variation within and between raters over time and not any clinically meaningful effect of pretomanid. The lens disorder AESIs reported in 12.8% of patients in Nix-TB were visual acuity decreased, vision blurred, vision impairment, and lens disorder, all of which were Grade 1 (mild) or 2 (moderate) in severity; no AESI of cataract was reported.
- **Convulsions:** Central nervous system (CNS) related effects including convulsions were observed in rodents and monkeys treated with high doses of pretomanid. In addition, convulsion is a known risk of linezolid (Pfizer 2018). In Nix-TB, 2 patients (1.8%) experienced AESIs of convulsion: one with generalized tonic-clonic seizure and the other with seizure. Both events were SAEs, and neither was considered related to study drug. One patient had a prior history of seizures and completed study therapy after the event. The other patient had a tuberculoma of the right temporal lobe diagnosed and excised after completion of the drug regimen. This patient had neurosurgical removal of the tissue, which was positive for molecular and microscopic evidence of *M. tb*, although the tissue was culture negative. The patient remained seizure free following the surgery.

- **QT prolongation:** Bedaquiline labeling contains a black box warning for QT prolongation (Janssen 2018). Additionally, there was a potential QT prolongation concern for pretomanid based in vitro human Ether-à-go-go-Related Gene (hERG) channel effects and findings of QT prolongation in monkeys. In Nix-TB, 7 patients had AESIs from the QT prolongation SMQ; 6 of these were solely electrocardiogram (ECG) findings, and 1 was an AE of syncope. The patient who experienced syncope had no evidence of QT prolongation on ECG. No QT prolongation AESI resulted in a change in study drug dosing.

  In addition, a thorough QT safety study of pretomanid in healthy volunteers revealed no effect on the QT interval of clinical significance at either the 400 or 1000 mg dose.

- **Hepatic toxicity:** Bedaquiline labeling contains a warning for hepatotoxicity and recommends monitoring with liver-related laboratory tests (Janssen 2018). Hepatotoxicity was also a potential adverse effect for pretomanid based on nonclinical and clinical safety findings. In Nix-TB, the majority of hepatic AESIs were Grade 1 or 2, and the most common events (occurring in ≥5% of patients) included gamma-glutamyltransferase increased (16.5%), transaminases increased (11.0%), alanine aminotransferase increased (9.2%), and aspartate aminotransferase increased (7.3%). Eight patients had BPaL dosing interruptions due to hepatic AESIs; all were able to resume and complete therapy after transaminases decreased, including 2 patients who met the laboratory criteria as potential Hy's Law cases. One event of transaminases increased was considered an SAE in a patient who had sepsis and pneumonia and died. Importantly, all other patients with hepatic events completed the full 26 weeks of dosing or were still receiving treatment at the time of the data cut-off.

- **Pancreas-related events:** Pancreas-related events were AESIs based on animal toxicology findings for bedaquiline (Janssen 2018). In Nix-TB, the majority of potential pancreas-related events were asymptomatic increases in amylase or lipase and were Grade 3 or 4. Two patients had SAEs. In 1 patient with an SAE of pancreatitis, BPaL treatment was interrupted; the patient resumed study drug shortly thereafter and completed the course of treatment without further interruptions or any symptoms suggestive of pancreatitis. One patient died and was found to have hemorrhagic pancreatitis on autopsy. All remaining patients completed the full 26 weeks of dosing or were still receiving treatment at the time of the data cut-off.

- **Peripheral neuropathy:** Peripheral neuropathy is a known clinical side effect associated with linezolid (Pfizer 2018). AESIs related to peripheral neuropathy were common in Nix-TB. The majority of these events were Grade 1 or 2 in severity and none were considered serious. The most frequently reported events (occurring in ≥5% of patients) were peripheral sensory neuropathy (68.8%) and neuropathy peripheral (9.2%). Approximately 55% of peripheral neuropathy AESIs led to linezolid dose changes, which were generally observed in the last 3 months of treatment. In general, peripheral neuropathy AESIs gradually diminished after study treatment was completed.

- **Optic nerve disorder:** Optic neuropathy is also a known clinical side effect associated with linezolid (Pfizer 2018). Two patients in Nix-TB experienced SAEs – Grade 4 optic neuritis for one and Grade 1 optic neuropathy for the other; both started after 16 weeks of study treatment and were confirmed on retinal examination. In both cases, linezolid was discontinued, and the symptoms resolved, with visual acuity returning to baseline levels.
- **Myelosuppression:** Myelosuppression is another known clinical side effect associated with linezolid (Pfizer 2018). In Nix-TB, anemia was the most prevalent AESI in the hematopoietic cytopenia SMQ, followed by neutropenia and thrombocytopenia. The majority of myelosuppression-related AESIs were Grade 1 or 2 in severity. Approximately 54% of myelosuppression AESIs led to linezolid dose changes, which generally occurred in the first 3 months and were primarily for cases of anemia. Three patients experienced events that were considered serious; the SAEs were neutropenia (1 patient) and anemia (2 patients), and all were considered related to study drug. For all 3 patients, study drug was interrupted (linezolid only in 1 patient and BPaL in 2 patients), and all 3 SAEs resolved.

Risk Mitigation

The proposed prescribing information for pretomanid includes warnings and precautions to limit the extent of myelosuppression, peripheral and optic neuropathy, and hepatic toxicity, which are risks associated with the treatment regimen. The warnings for myelosuppression and peripheral and optic neuropathy are consistent with the prescribing information for linezolid.

To reduce the risk of significant hepatic toxicity, the proposed labeling for pretomanid recommends that patients receiving BPaL are monitored regularly for symptoms of liver toxicity and with liver function tests at baseline, monthly while on therapy, and as needed. The labeling also proposes guidelines for interrupting treatment based on liver function test results. Finally, patients are advised to avoid other hepatoxic drugs and alcohol while on treatment. Bedaquiline, per its label, also requires regular monitoring of liver function.

1.6 Benefit-Risk Summary

A new defined regimen to which there is little to no resistance is urgently needed for patients with highly resistant TB. It should shorten treatment duration, simplify administration, have manageable side-effects, and improve cure rates. The BPaL regimen was developed specifically to 1) shorten treatment duration and simplify drug administration, in order to facilitate treatment adherence; and 2) provide more effective and tolerable treatment to curtail the spread of highly drug-resistant strains of *M. tb*.

The Nix-TB results show that approximately 90% of patients with the most difficult-to-treat forms of TB responded favorably to the treatment. 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. Efficacy outcomes were very similar in patients either with HIV or without HIV and in patients with either XDR-TB or TI/NR MDR-TB. When compared with a historical control population, Nix-TB had a 6.6-fold greater probability of

attaining a favorable clinical response. Together these results show the substantial potential for treatment improvement with the BPaL regimen.

Overall, the results from Nix-TB demonstrated that AEs were as expected with the BPaL regimen. The safety concerns are manageable and the overall benefit to risk is highly positive given the higher efficacy and lower mortality. Importantly, approximately 85% of patients were able to complete the protocol-specified course of BPaL treatment and a further 9.2% were still completing study treatment as of the data cut-off date. This type of completion rate is similar to completion rates for patients being treated for DS-TB and is greater than those seen with highly resistant TB.

The promising results of the Nix-TB study bring hope to people around the world with highly resistant TB. With a simplified, shorter, and all-oral regimen, BPaL transforms treatment for people diagnosed with XDR-TB and TI/NR MDR-TB. Access to the BPaL regimen would be an important step in closing the treatment gap for patients with highly resistant TB who are most in the need of new therapies.

2 BACKGROUND ON XDR-TB AND TI/NR MDR-TB

Summary

- TB is the world's leading cause of death from a single infectious disease.
  - In 2017, an estimated 10 million people developed TB and an estimated 1.6 million deaths were attributed to the disease (WHO 2018a).
- An estimated 457,000 people worldwide develop MDR-TB annually, with an estimated 8.5% being XDR-TB (WHO 2018b).
- *M. tb* strains causing XDR-TB and MDR-TB are the most difficult to treat, as they are resistant to many available anti-TB drugs.
  - Patients with TI/NR MDR-TB are resistant to at least isoniazid and rifampicin and do not tolerate and/or respond to therapy for their MDR-TB.
  - XDR-TB is resistant to isoniazid, rifampicin, at least 1 fluoroquinolone, and at least 1 second-line injectable agent (capreomycin, kanamycin, or amikacin).
- Highly resistant TB is a worldwide concern, reported in over 100 countries, including, uncommonly, cases in the US.
- Treatment of highly resistant TB (XDR-TB and TI/NR MDR-TB) requires treatment with 5 or more medications for a total duration of 18 months or longer, often including an injectable agent for at least 6 months.
  - Not only are regimens complex and not well-defined, some have severe toxicities, such as hearing loss and kidney damage.
- Prior to introduction of bedaquiline and linezolid, patients with XDR-TB had an extremely poor prognosis, with rates of treatment success in South Africa ranging from 2% to 22% and outside South Africa, 14% to 60%.
  - Treatment more recently with bedaquiline and linezolid has led to rates of favorable outcomes of 51% to 66% (Collaborative Group for the Meta-Analysis of Individual Patient Data et al. 2018; Olayanju et al. 2018). Treatment typically required 24 months to complete, where both drugs were used as "add-ons" to regimens consisting of a median total of 8 oral and injectable drugs (Olayanju et al. 2018).
- Well characterized and defined treatment regimens are needed to:
  - Shorten treatment duration and simplify drug administration, improving adoption and adherence by patients.
  - Provide more effective, safer, and tolerable treatment than currently available.

2.1 Overview of Highly Resistant TB

Tuberculosis is the world's leading cause of death from a single infectious disease. In 2017, an estimated 10 million people developed TB and an estimated 1.6 million deaths were attributed to

the disease (WHO 2018a). *M. tb* is spread through airborne droplets from a person infected with TB (CDC 2016). General symptoms of TB include a severe cough that produces sputum, frequently bloody in nature, and typically lasting 3 weeks or longer. Additionally, patients may experience chills, fever, night sweats, fatigue, unintentional weight loss, and chest pain or difficulty breathing.

While DS-TB is curable, treatment outcomes for patients with drug-resistant TB are substantially worse. Among the most difficult-to-treat strains of *M. tb* are those causing XDR-TB and MDR-TB, both relatively uncommon types of TB. Patients with XDR-TB are infected with strains of *M. tb* that are resistant to rifampicin, isoniazid, at least 1 fluoroquinolone, and at least 1 second-line injectable agent (amikacin, capreomycin, or kanamycin). MDR-TB is caused by strains of *M. tb* resistant to at least isoniazid and rifampicin, and patients with TI/NR MDR-TB are intolerant of, or do not respond to, the treatment prescribed for already difficult-to-treat MDR-TB. According to the WHO dataset, the global rate of treatment success was 34% for XDR-TB and 55% for MDR-TB, compared to 82% for TB overall (WHO 2018a).

Drug-resistant TB continues to be a public health crisis (WHO 2018a). Drug-resistant TB is spread by primary transmission, similar to DS-TB. Coupled with poor treatment adherence, incorrect drug prescribing, and treatment toxicity, drug resistance has become more common, and the likelihood of an epidemic with difficult-to-treat strains is growing.

In 2017, an estimated 457,000 people developed MDR-TB, with an estimated 8.5% of cases identified as XDR-TB (WHO 2018a). Drug-resistant TB is a worldwide concern, reported in over 100 countries, including the US, where 123 cases of MDR-TB and 2 cases of XDR-TB were reported in 2017 (CDC 2017). Although the prevalence in the US is low, urgent action is needed to improve the treatment and care for people with drug-resistant TB across the world (WHO 2018a). As global health authorities often consider the FDA's decisions regarding the efficacy and safety of drugs as a prerequisite for national or regional licensure, access to new medications for highly resistant TB would not only benefit Americans, but potentially thousands of patients abroad.

2.2 Current Treatment Options

2.2.1 World Health Organization Recommendations

Treatment regimens for drug-resistant TB have historically relied on a combination of second-line drugs tailored to the patient depending on drug susceptibility testing. In the 2016 WHO treatment guidelines (WHO 2016), the recommended treatment regimen for MDR-TB consisted of at least 5 effective TB medicines, including pyrazinamide and 4 second-line TB medicines – 1 chosen from Group A, 1 from Group B, and at least 2 from Group C (Table 5). If the minimum number of 5 effective TB medicines could not be reached using agents from Groups A–C, an agent from Group D2 and other agents from Group D3 were added to bring the total to 5. The recommended total treatment duration was 20 months, depending on the patient's response to therapy.

Table 5: Medicines for MDR-TB Treatment Regimens from 2016 World Health Organization Treatment Guidelines

Group A Fluoroquinolones	Group B Second-Line Injectable Agents	Group C Other Core Second-Line Agents	Group D Add-On Agents
Levofloxacin Moxifloxacin Gatifloxacin	Amikacin Capreomycin Kanamycin	Ethionamide/ prothionamide Cycloserine/ terizidone Linezolid Clofazimine	D1: Pyrazinamide Ethambutol High-dose isoniazid D2: Bedaquiline Delamanid D3: p-aminosalicylic acid Imipenem–cilastatin Meropenem Amoxicillin-clavulanate

In August 2018, the WHO released a "Rapid Communication" that included reclassification of priority drugs for the treatment of MDR-TB (WHO 2018b) (Table 6). Of note, bedaquiline and linezolid had been listed in Group D and C in the 2016 guidelines, respectively, yet both were prioritized as Group A medicines with the 2018 reclassification. Under the latest guidelines, the recommended regimens should include at least 4 effective medicines, composed of all 3 Group A agents and at least 1 Group B agent, with at least 3 agents being continued for the rest of the treatment once bedaquiline is stopped (WHO 2019). 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.[3]

[3] 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.

Table 6: Medicines for MDR-TB Treatment Regimens from 2019 World Health Organization Treatment Guidelines[a]

Group A	Group B	Group C
Levofloxacin or moxifloxacin	Clofazimine	Ethambutol
Bedaquiline	Cycloserine or terizidone	Delamanid
Linezolid		Pyrazinamide
		Imipenem-cilastatin or meropenem
		Amikacin or streptomycin
		Ethionamide or prothionamide
		p-aminosalicylic acid

a. Grouping was first introduced in 2018 (WHO 2018b).

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.

2.2.2 New or Repurposed Drugs

The success rate of treatment for highly resistant TB was very poor before the introduction of new (ie, bedaquiline) or repurposed (linezolid) drugs for which there is little pre-existing resistance. Without bedaquiline and linezolid, the average rates of treatment success in XDR-TB across South African studies ranged from 2% to 22% (Dheda et al. 2017; Gandhi et al. 2012; Gandhi et al. 2006; Kvasnovsky et al. 2016; O'Donnell et al. 2013; Olayanju et al. 2018; Padayatchi et al. 2014; Pietersen et al. 2014). Outside of South Africa, rates of treatment success were more variable, ranging from 15% to 60%, with only 2 studies reporting rates above 50% (Banerjee et al. 2008; Keshavjee et al. 2008; Kim et al. 2008; Leimane et al. 2010; Liu et al. 2011; Migliori et al. 2008; Mitnick et al. 2008; Mor et al. 2014; Tabarsi et al. 2010; Tang et al. 2011).

Linezolid (Pfizer) and bedaquiline (Janssen) are 2 of the newer antimycobacterial drugs investigated for treatment of highly resistant TB. Linezolid, although not approved for treatment of TB, was identified in a small study as a potentially efficacious drug in patients with XDR-TB when added to a failing regimen (Lee et al. 2012). Bedaquiline received conditional approval from the FDA in 2012 and the European Medicines Agency in 2013 as an add-on to standard regimens for treatment of adults with MDR-TB who could not otherwise be successfully treated.

Inclusion of bedaquiline and linezolid into treatment regimens has led to higher rates of favorable outcomes (ie, 51% to 66% in XDR-TB) (Collaborative Group for the Meta-Analysis of Individual Patient Data et al. 2018; Olayanju et al. 2018). However, these drugs were used as "add-ons" to regimens with a median total of 8 oral and injectable drugs and a total treatment duration of 24 months (Olayanju et al. 2018). The latest WHO treatment guidelines confirm the

importance of linezolid and bedaquiline in the treatment of patients with highly resistant TB (WHO 2019).

2.3 Unmet Medical Need

People with highly resistant TB face complex and extremely onerous treatment options. The rates of favorable outcomes are low and mortality rates are high. According to the WHO, among 8,399 patients who started on treatment for XDR-TB in 2015, only 34% completed treatment successfully, and 26% died (WHO 2018a).

Patients with highly resistant TB have a difficult treatment path forward, requiring at least 5 different drugs, often including a daily injectable, with a minimum of 18 months of treatment. Some of the medicines, particularly the injectables, have severe toxicities, such as permanent hearing loss and kidney damage. Even after attempting multiple different treatment regimens over the course of many months, more than 50% of patients will have unfavorable outcomes. Additionally, due to resistance to most first- and second-line drugs, patients with highly resistant TB are left with treatment options which are less effective and more toxic (WHO 2018b).

The recent availability of bedaquiline and linezolid is promising, yet there is a need for novel drug combinations that are shorter, simplified, and easy-to-administer in addition to having improved treatment outcomes.

Well-characterized and defined regimens are needed to shorten treatment duration, simplify drug administration route and schedule, and improve adoption and adherence by patients. Additionally, defined regimens are needed to provide more effective and more tolerable treatment regimens compared to those currently being used.

3 PRODUCT DESCRIPTION

Summary

- TB Alliance has sponsored the development of pretomanid to be used in a new orally administered, 3-drug regimen to cure highly resistant TB infections with 6 months of treatment.
- Proposed indication: Pretomanid is a nitroimidazooxazine antimycobacterial drug indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary XDR, treatment-intolerant or nonresponsive MDR TB.
- The BPaL regimen includes 3 antibiotics that have never been combined before to treat highly resistant pulmonary TB: pretomanid, bedaquiline, and linezolid.
  - Pretomanid is a new chemical entity designed to treat TB.
  - Bedaquiline is indicated for MDR-TB and has been increasingly used in recent years in the treatment of TB.
  - Linezolid is currently indicated for the treatment of skin infections and pneumonia caused by Gram-positive bacteria. However, studies have demonstrated its benefit in the treatment of drug-resistant TB.
  - Since 2018, both bedaquiline and linezolid have been drugs recommended by the WHO for the treatment of MDR-TB and XDR-TB.
- These 3 drugs have little pre-existing resistance among *M. tb* strains, offering a potentially promising treatment option for patients with highly resistant TB.
- The 6-month treatment period of the BPaL regimen is the same amount of time needed to treat "standard" or DS-TB.

3.1 Pretomanid Overview and Rationale for Development

Pretomanid, a new chemical entity, is a nitroimidazooxazine antimycobacterial drug with a narrow spectrum of antibacterial activity. Besides *M. tb*, pretomanid exhibits antimycobacterial activity against *M. tb* complex subspecies *M. bovis*, *M. africanum*, *M. pinnipedii*, and *M. ulcerans*. In vitro antimicrobial activity against several Gram-positive and Gram-negative anaerobic bacteria has also been demonstrated. Pretomanid did not exhibit antibacterial activity against other mycobacterial species tested nor against non-mycobacterial aerobic bacteria and yeast.

Pretomanid is provided as an immediate-release 200 mg tablet to be administered in combination with bedaquiline and linezolid tablets. Combining pretomanid, bedaquiline, and linezolid (designated the BPaL regimen), 3 drugs for which there is very little pre-existing resistance among *M. tb* strains, offered the opportunity to provide a novel, all-oral regimen that could be administered on a daily basis for 6 months to treat patients with XDR-TB and TI/NR MDR-TB.

3.2 Proposed Indication and Limitations of Use

Indication

Pretomanid is a nitroimidazooxazine antimycobacterial drug indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).

Limitations of Use

Do not use pretomanid for the treatment of:

- Latent infection due to *M. tb*
- Extra-pulmonary infection due to *M. tb*
- DS-TB
- MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy

3.3 Bedaquiline and Linezolid Overview

Bedaquiline is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (18 years and older) with pulmonary MDR-TB. Bedaquiline is presently labeled to be administered in combination with at least 3 other drugs. The recommended dosage of bedaquiline is 400 mg orally QD for the first 2 weeks, followed by 200 mg orally TIW for 22 weeks (total duration of 24 weeks).

Linezolid is an oxazolidinone-class antibacterial indicated in adults and children for the treatment of infections caused by susceptible Gram-positive bacteria, including vancomycin-resistant *Enterococcus faecium* infections among others. For these indications, the recommended dose is 400 or 600 mg orally every 12 hours for durations up to 28 days.

3.4 Recommended Dosage

The recommended dosage for the oral regimen is:

- Pretomanid 200 mg (1 tablet of 200 mg) QD for 26 weeks; plus
- Bedaquiline 400 mg QD for 2 weeks followed by 200 mg TIW for a total of 26 weeks; plus
- Linezolid 1200 mg daily for up to 26 weeks

Based on the requirement for bedaquiline to be taken with food, pretomanid should also be taken with food as part of the BPaL regimen.

Modification or interruption of linezolid dosing may be needed during the course of therapy to manage the known linezolid toxicities of myelosuppression, peripheral neuropathy, and optic

neuropathy. Any missed doses of the entire regimen can be made up at the end of treatment; missed doses of linezolid alone due to linezolid adverse reactions should not be made up.

3.5 Mechanism of Action

Pretomanid has a complex mode of action. Pretomanid kills actively replicating *M. tb* under aerobic conditions by inhibiting mycolic acid biosynthesis and blocking cell wall production. Under anaerobic conditions against nonreplicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release. All of these activities require nitro-reduction of pretomanid within the mycobacterial cell by a deazaflavin-dependent nitroreductase, which is dependent on the reduced form of the cofactor F420. Reduction of F420 is accomplished by F420-dependent glucose-6-phosphate dehydrogenase.

3.6 Mechanism of Resistance

Mutations in 5 *M. tb* genes (*ddn, fgd1, fbiA, fbiB, fbiC*) have been associated with pretomanid resistance in the laboratory. The products of these genes are involved in bioreductive activation of pretomanid within the bacterial cell. Not all isolates with increased minimum inhibitory concentrations (MICs) have mutations in these genes, suggesting the existence of at least one other mechanism of resistance.

3.7 Susceptibility

In vitro susceptibility tests can be performed using either the resazurin microtiter assay (REMA) (Palomino et al. 2002) or the mycobacterial growth indicator tube (MGIT) (Rusch-Gerdes et al. 2006).

Based on the limited information available, a critical concentration for pretomanid is provisionally set at 1 μg/mL for both REMA and MGIT methods, with MIC values ≤1 μg/mL indicating susceptibility to pretomanid and values >1 μg/mL indicating resistance. Over 95% of clinical isolates surveyed showed MIC values at or below 1 μg/mL. Conversely, all *M. tb* isolates with known mechanisms of resistance to pretomanid had MIC values above this concentration.

4 DEVELOPMENT AND REGULATORY HISTORY

Summary

- The clinical development program for pretomanid comprises the following studies:
  - 1 ongoing pivotal Phase 3 single-arm study (Nix-TB) of the BPaL regimen in patients with XDR-TB and TI/NR MDR-TB
  - 10 Phase 1 studies of pretomanid alone or in combination with other agents in healthy volunteers
  - 6 Phase 2 studies of pretomanid alone or in combination with other agents in patients with DS-TB and MDR-TB
  - 1 Phase 3 study of pretomanid in a different regimen for the treatment of MDR-TB and DS-TB
  - 1 recently initiated Phase 3 study (ZeNix) of the BPaL regimen with different linezolid and bedaquiline dosing in patients with XDR-TB, pre-XDR-TB, and TI/NR MDR-TB
- Interim analyses from Nix-TB provide the primary efficacy and safety data supporting approval of pretomanid for the proposed indication.

4.1 Clinical Development Program

The clinical development program supporting the approval of pretomanid for the proposed indication includes 19 clinical studies (3 Phase 3, 6 Phase 2, and 10 Phase 1).

The primary study supporting the efficacy of pretomanid is Nix-TB, an ongoing Phase 3 pivotal, single-arm study in patients with XDR-TB and TI/NR MDR-TB. As of the efficacy database cut-off date of 29 June 2018, 81 patients had completed the 6-month primary efficacy assessment and 23 patients had completed the study with 24 months of post-treatment follow-up. Supporting the Nix-TB results, pretomanid has demonstrated antimycobacterial activity in patients with pulmonary TB as a stand-alone agent across 2 Phase 2 studies and in various combinations in 4 Phase 2 and 1 Phase 3 studies.

The safety of pretomanid is supported by Nix-TB, with a safety data cut-off date of 26 March 2018, as well as the safety database comprising all Phase 1–3 studies of pretomanid. A total of 109 patients are being treated in Nix-TB and 1,168 healthy volunteers or patients with TB have been or are being treated with pretomanid across the development program.

The 19 Phase 1–3 studies are outlined below. The majority of this briefing document focuses on the efficacy and safety results of Nix-TB. However, a summary of efficacy findings from the completed Phase 2 and 3 studies is provided in Appendix 10.1.1. Appendix Table 45 (completed studies), and Appendix Table 46 (ongoing studies) provide additional details on the individual study designs and key findings of completed studies.

Phase 3 Studies

- Nix-TB (ongoing): a pivotal single-arm safety and efficacy study of BPaL in patients with XDR-TB and TI/NR MDR-TB
- NC-006 (completed): a randomized, active-controlled safety and efficacy study of pretomanid in combination with moxifloxacin and pyrazinamide (PaMZ) in patients with MDR-TB and DS-TB. Enrollment into this study was suspended by the Data and Safety Monitoring Committee, but upon review of safety data, enrollment was allowed to proceed. TB Alliance chose not to resume enrollment but to focus resources to a new Phase 2c study of pretomanid in combination with bedaquiline, moxifloxacin, and pyrazinamide (BPaMZ) which had promising results in the Phase 2 NC-005 study.
- ZeNix (recruiting): a randomized safety and efficacy study of BPaL in patients with XDR-TB, pre-XDR-TB, and treatment-resistant or nonresponsive MDR-TB[4]

Phase 2 Studies

- 2 dose-ranging studies of pretomanid as a stand-alone agent in patients with DS-TB (CL-007 and CL-010)
- 4 studies of pretomanid in various combinations in patients with DS-TB or MDR-TB (NC-001, NC-002, NC-003, and NC-005)

10 Phase 1 Studies in Healthy Volunteers

- 1 single-ascending dose study evaluating PK
- 1 multiple-ascending dose study evaluating PK
- 2 food-effect studies evaluating PK
- 2 studies evaluating absorption, metabolism, and excretion
- 3 studies evaluating effects of co-administration with midazolam or ART drugs and effects on renal function parameters
- 1 QT interval study

4.2 Regulatory History

The NDA for the approval of pretomanid for use in the BPaL regimen is currently under priority review with the FDA. Pretomanid was granted Orphan Drug Designation and was designated a qualified infectious disease product by the FDA on 05 July 2007 and 15 August 2017, respectively. Priority review was granted on 12 February 2019. Bedaquiline was granted

[4] ZeNix, is currently being conducted to assess BPaL regimens with different doses and/or treatment durations of linezolid and bedaquiline. This recently initiated study was designed to optimize linezolid dosing with the aim of potentially limiting toxicity while preserving efficacy. Efficacy data are not yet available for this study.

conditional approval for MDR-TB in 2012, and linezolid has been approved for Gram-positive bacterial infections since 2000.

Agreement with the FDA was reached regarding the following elements to support the pretomanid NDA:

- Based on the favorable and consistent findings at each prespecified interim data analysis (every 15 patients accrued) from the ongoing pivotal Phase 3 study (Nix-TB), the FDA concurred with submission of interim study results. The pretomanid NDA submitted on 14 December 2018 included interim efficacy results on the first 81 patients available through 29 June 2018, and interim safety results based on data available through 26 March 2018. Updated efficacy analyses based on data through 18 January 2019 and safety analyses based on data through 15 October 2018 were recently provided to the FDA in a 120-Day Update to the NDA on 5 April 2019.
- To support the efficacy outcomes in Nix-TB, a literature review and case-matched analysis of historical control data were conducted for XDR-TB patients.
- The contribution of pretomanid to the efficacy of the 3-drug regimen could be supported primarily with preclinical data demonstrating the contribution of each of the individual components of the regimen.

5 NONCLINICAL AND CLINICAL PHARMACOLOGY

Summary

- Two key determinants of pretomanid exposure are dose level and food conditions.
  - Under fasted conditions, exposure increases with dose but less than dose-proportionally.
  - Under fed conditions, exposure increases dose-proportionally up to the recommended clinical dose of 200 mg, where the exposure is 88% higher than under fasted conditions.
- According to a population pharmacokinetic (PopPK) model, pretomanid exposure varies with weight allometrically, with exposures at 35 and 75 kg being around 40% higher and 20% lower, respectively, than at the reference weight of 55 kg.
- At a given weight, females have around 20% higher exposure than males.
- No change in dose is recommended based on sex, age, race, BMI, weight, HIV status, TB type, and pretomanid regimen.
- Pretomanid reaches a maximum concentration 4 to 5 hours after dosing, and then elimination proceeds with a half-life of 18 hours
- Pretomanid may be in part metabolized by CYP3A4, and co-administration of strong CYP3A4 inducers with pretomanid is not recommended.
- Pretomanid inhibits OAT3, and co-administration of pretomanid with drugs that are mainly eliminated through OAT3 is not recommended.
- Interactions among bedaquiline, pretomanid, and linezolid were not expected based on their known metabolism. PK data for each drug showed no evidence of clinically relevant interactions.
- Together, the results regarding EBA and TSCC from Phase 1 and 2 studies showed evidence of a dose response across doses of 50 to 200 mg, with no additional efficacy at doses up to 1200 mg. Based on these results and on the safety profile, 200 mg was selected as the dose for the BPaL regimen.
- In a mouse model of TB, the BPaL regimen consistently exhibited greater bactericidal activity than any 2-drug combination of its components, indicating that each component contributes to the anti-TB effect of the 3-drug regimen.
- Murine studies demonstrated the superior sterilizing effect of adding pretomanid to bedaquiline and linezolid.

5.1 Pharmacokinetics

5.1.1 General Properties

The clinical pharmacology of pretomanid was evaluated in 10 clinical pharmacology studies and 8 clinical studies; 10 studies evaluated patients or healthy subjects in the US.

Pretomanid PK was studied at doses ranging from 50 to 1500 mg. Under fasting conditions, exposure increased less than dose-proportionally, and saturated at 1000 mg. However, under fed conditions, the increase was dose-proportional up to the recommended clinical dose of 200 mg.

Dosing with food increased the relative bioavailability of pretomanid in 2 food-effect studies, one at 1000 mg and one at 50 and 200 mg. At the 200 mg dose, exposure (area under the concentration-time curve [AUC]) in the fed state was 88% higher than in the fasted state. Bedaquiline is labeled for administration with food, and therefore the proposed pretomanid labeling recommends pretomanid to be administered with food as part of the BPaL regimen.

Pretomanid exhibited a moderately prolonged absorption, with a typical time to maximum concentration (T_{max}) of 4 to 5 hours, independent of dose, and with no consistent effects from food. ("Typical," used here and in the remainder of Section 5, refers to the median value for an individual with the reference covariates, as defined in Section 5.1.2, below.)

Pretomanid's elimination is monophasic, with a typical half-life of 18 hours. Typical oral clearance was estimated in a PopPK model as 3.5 L/h under fed conditions at steady-state. Pretomanid is cleared via metabolism through multiple reductive and oxidative pathways, with no single pathway considered major. In mass balance studies, only about 1% of the dose was eliminated as parent and the remainder as metabolites in urine and feces.

The PopPK model estimated the typical apparent volume of distribution as 93 L, which is much larger than plasma volume, suggesting distribution of pretomanid to spaces outside of plasma but, given the monophasic elimination, in rapid equilibrium with plasma.

5.1.2 Dependence on Intrinsic Factors

PopPK modeling identified differences in exposure for subgroups of individuals relative to a reference subgroup defined as male, HIV-negative, having DS-TB, weighing 55 kg, and taking pretomanid alone in the fed state. The alternative subgroups were defined by varying these parameters one at a time. The following effects were identified:

- Females had around 20% higher exposures than males.
- HIV-positive patients had around 10% lower exposures than HIV-negative.
- Healthy individuals and patients with MDR-TB not in the Nix-TB study had around 10% lower exposures than patients with DS-TB. Exposures among patients with TI/NR MDR-TB and XDR-TB in Nix-TB were around 10 to 20% higher than patients with DS-TB.

- Pretomanid exposure varied with weight because of allometric scaling of clearance and volume. Exposures at 35 and 75 kg were around 40% higher and 20% lower, respectively, than the exposure at the reference weight of 55 kg.
- For effects of concomitant drugs, see Section 5.1.3.
- For the effect of food, see Section 5.1.1.

No additional effects were found for age, race, or BMI. No effects of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were found, but there were small associations with bilirubin and albumin. A separate study in hepatically impaired subjects is ongoing. No effects of estimated creatinine clearance and glomerular filtration rate were found. A separate study in renal-impaired subjects is planned.

The above quantifications represent average behaviors. Inter-individual variability in PK response could generate differences of around ±50% across individuals within the same subgroup. Therefore, no changes in dose are recommended based on based on weight, sex, HIV status, TB type, and pretomanid regimen.

5.1.3 Drug-Drug Interactions

Several in vitro and 2 clinical studies were conducted to evaluate the drug interaction potential of pretomanid as possibly mediated by CYP450 enzymes and transporters.

In vitro analyses with isolated hepatocytes and CYP profiling showed insignificant CYP metabolism of pretomanid, with the possible exception of CYP3A4. A clinical pharmacology study was conducted to explore the potential for pretomanid exposure to be affected by drugs that affect CYP3A4: rifampicin and 2 ARTs, efavirenz and lopinavir/ritonavir. These 3 drugs reduced pretomanid exposure by 66%, 35%, and 16%, respectively. Therefore, strong inducers such as rifampicin should not be used with pretomanid. Because efavirenz is contraindicated with bedaquiline, labeling will advise that concomitant administration of efavirenz and the BPaL regimen should be avoided.

In vitro studies demonstrated that pretomanid does not significantly induce nor inhibit CYP activity, with the exception of CYP3A4/5. Pretomanid was found to be a weak, time-dependent inhibitor at CYP3A4/5, albeit with a high IC_{50} (>5 µg/mL) relative to concentrations likely to be seen at 200 mg (typical maximum concentration [C_{max}] around 3 µg/mL). Study CL-006 explored the potential for pretomanid to act as a perpetrator on drugs metabolized by CYP3A4, using midazolam as a probe. The C_{max} and AUC values for midazolam on the 14th day of pretomanid administration at 400 mg/day were approximately 85% of those observed with midazolam prior to pretomanid exposure. At the recommended daily dose of 200 mg, pretomanid is unlikely to affect concomitant drugs metabolized via CYP3A4 in a clinically meaningful way.

In vitro studies found that pretomanid was not an inhibitor or substrate of the transporters examined, with the exception of inhibition of OAT3. Because a potential interaction between

pretomanid and OAT3 substrates could not be excluded, co-administration of pretomanid with drugs mainly eliminated through OAT3 is not recommended.

Based on the above information about pretomanid and based on what is known about bedaquiline and linezolid, interactions among the 3 components of BPaL would not be expected. As seen in Section 5.1.2, PopPK modeling found that pretomanid exposures in the Nix-TB study, ie, as part of a regimen with bedaquiline and linezolid, were generally 10% to 20% higher than for pretomanid alone (in other populations). Exposures of bedaquiline and linezolid did not vary markedly across studies with and without pretomanid. Thus, there is no evidence for clinically relevant interactions among bedaquiline, pretomanid, and linezolid.

5.2 Pharmacodynamics

5.2.1 Early Bactericidal Activity of Pretomanid Monotherapy

As a single agent, pretomanid showed mycobactericidal activity over 14 days spanning a wide range of doses from 50 to 1200 mg/day. In a Phase 2 EBA study (CL-010), patients with pulmonary TB who were administered pretomanid at doses of 200 mg had a mean 1.5-log reduction in colony forming units (CFU) cultured from sputum from baseline to the end of 14 days of treatment.

5.2.2 Rationale for the Dose of Pretomanid

Efficacy

Two Phase 2 studies of pretomanid examined the dose response of EBA as measured by two markers of the decline of *M. tb* in sputum over 14 days of dosing: 1) the rate of reduction in CFU; and 2) the rate of increase in time to positivity in the MGIT. The first study (CL-007) examined doses of 200 to 1200 mg QD, and found significant bactericidal activity at all doses, but no differentiation among doses with regard to response. The second study (CL-010) examined doses of 50, 100, 150, and 200 mg QD, and again found significant bactericidal activity at all doses. Both EBA measures exhibited trends of response increasing with dose. Although the study was not powered to distinguish statistical differences between doses, some comparisons did yield statistical significance, or nearly so, leading to separation of 50 mg from the other three doses.

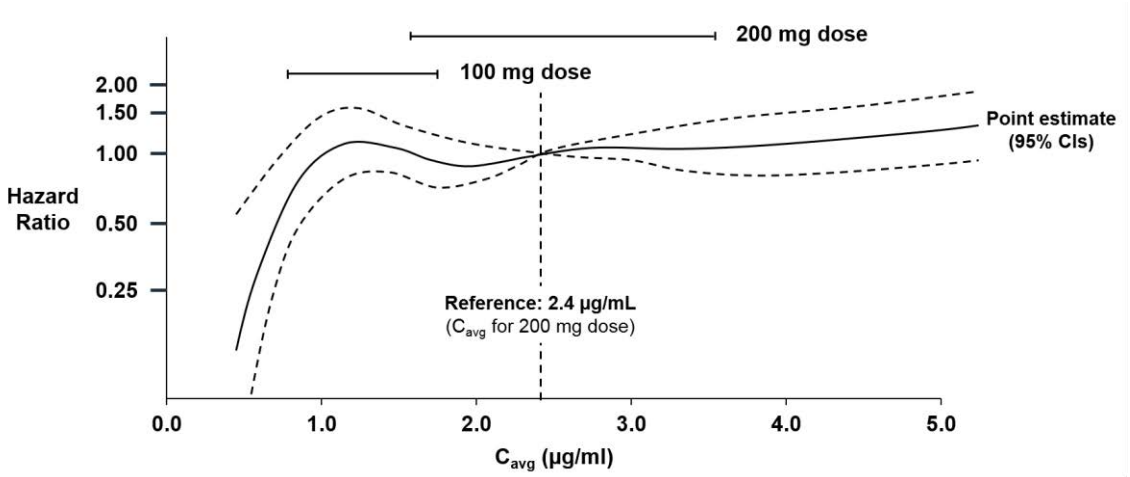
Another Phase 2 trial (NC-005) evaluated pretomanid at doses of 100 and 200 mg QD in combination with moxifloxacin and pyrazinamide relative to a regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) as a control. In this 8-week trial, the primary endpoint was the rate of reduction in CFU over the treatment period. Although results were similar for the 100 and 200 mg pretomanid arms, the 200 mg arm was statistically significantly better than the HRZE control group, but the 100 mg arm was not. Safety was also similar between the groups, although the 200 mg group had more Grade 2 AEs than either the 100 mg arm or the HRZE control arm.

Given this background of results regarding dose response, it was decided to use the 200 mg dose of pretomanid as part of the BPaL regimen in Nix-TB.

Results from Nix-TB were combined with those of 3 other studies that monitored TSCC in patients with TB over at least 8 weeks, and where doses of 100 and 200 mg were used, to examine the relationship between TSCC and pretomanid exposure. Cox proportional hazards modeling was employed. Pretomanid exposure was found to be a significant predictor of response.

In the model, pretomanid exposure was quantified as the average concentration at steady-state (C_{avg}). PopPK modeling found that a typical value of C_{avg} for 200 mg pretomanid taken under fed conditions was 2.4 µg/mL. Figure 4 displays the hazard ratios for TSCC at different values of C_{avg} relative to a C_{avg} of 2.4 µg/mL. The solid curve shows the estimated hazard ratio, and the dashed curves delimit pointwise 95% CIs. The horizontal line segments demarcate ranges of exposure, from the 10th to 90th percentile for the 100 and 200 mg dose under fed conditions, as predicted by the PopPK modeling.

Figure 4: Hazard Ratios for Time to Sputum Culture Conversion to Negative as a Function of Pretomanid C_{avg}



Solid curve and dashed lines show the estimated hazard ratio and pointwise 95% CIs, respectively, for pretomanid C_{avg} relative to a C_{avg} of 2.4 µg/mL, the median C_{avg} for the 200-mg dose under fed conditions, using a Cox proportional hazards analysis of TSCC. The segments indicate the 10th to 90th percentile C_{avg} for pretomanid 100 and 200 mg administered in a fed state.
C_{avg}=average concentration; CI=confidence interval; TSCC=time to sputum culture conversion to negative

The following observations were made:

- The hazard ratio for sputum conversion rises to a plateau at a C_{avg} of between 1 and 1.5 µg/mL.
- The range of exposures for pretomanid 200 mg is robustly on the plateau of response, with enough room to the left to allow for the lower exposures that some individuals will experience due to PK variability.
- On the other hand, the range of exposures for the 100 mg dose extends to the left over the edge of the plateau, indicating a risk of potentially significant loss of bactericidal activity for individuals with lower exposures.

Thus, the sputum-conversion outcome is consistent with the outcomes from the EBA studies in that there is no advantage to increasing the dose above 200 mg and that there is a greater probability of achieving faster sputum conversion at exposures associated with the 200 mg dose.

Safety

In order to evaluate the effects of pretomanid, as well as the influence of the regimen on safety, PK/pharmacodymics (PD) modeling was performed on selected safety events. Safety events analyzed included prolongation of corrected QT interval (QTc), elevation of liver enzymes, and the risk of several AEs. The 200 mg dose was further supported by the fact that the quantitative improvements to be gained by halving the pretomanid dose to 100 mg were not large.

In assessing QT prolongation, a linear mixed-effects model was developed relating change from baseline of QTc to plasma concentrations of pretomanid and potential combination partners, with a focus on the BPaL regimen. A data-specific correction called QTcN was found to better eliminate dependence on heart rate among pre-treatment observations than Bazett's (QTcB) or Fridericia's (QTcF) corrections. In the BPaL regimen, at a typical C_{max} corresponding to pretomanid 100 and 200 mg, the predicted concentration dependent prolongation of QTcN ($\Delta\Delta$QTcN) had a median value of 7.1 and 9.5 msec, respectively, and upper 95% confidence level of 8.1 and 10.8 msec, respectively. In both measures the difference based on pretomanid dose was small.

Total bilirubin, ALT, AST, and alkaline phosphatase (ALP) from studies of different pretomanid regimens were examined for exposure-response relationships with pretomanid. Based on the results of the analyses, there was a tendency for all 4 parameters to increase with increasing pretomanid concentration, although none of the relationships were statistically significant in the BPaL regimen. PK/PD modeling of liver parameters for the BPaL regimen for Weeks 12 through 26 showed that reducing the C_{avg} of pretomanid by half from that typical of a 200 mg dose to that typical of a 100 mg dose would result in only about a 5% expected reduction in maximum-fold parameter increase.

Logistic regression was used to examine the relationship between pretomanid exposure in the BPaL regimen in the Nix-TB study and a variety of AEs: any Grade 3 or 4 AEs, the 5 most common AEs in Phase 2b and 3 studies, and AEs of special interest for pretomanid. The models were used to estimate the probabilities of individuals experiencing the AEs as a function of their steady-state pretomanid exposure. Table 7 displays those probabilities for pretomanid exposures typical of 100 and 200 mg in the BPaL regimen. Halving the exposure from the proposed dose of 200 mg has a generally small effect on AE probabilities.

Table 7: Probabilities of Adverse Events in BPaL Regimen by Pretomanid C_{avg}

	Estimated Probability of Occurrence	
	Pretomanid C_{avg} Typical of 100 mg	Pretomanid C_{avg} Typical of 200 mg
Grade 3 or 4 Adverse Events	**0.40**	**0.52**
Alanine aminotransferase increase[a]	**0.10**	**0.11**
Arthralgia[a]	**0.04**	**0.05**
Headache[a]	**0.30**	**0.27**
Nausea[a]	**0.26**	**0.33**
Vomiting[a]	**0.20**	**0.29**
Hepatic disorders (SMQ)	**0.28**	**0.34**
Lens disorders (SMQ)	**0.13**	**0.13**
Convulsions (SMQ)	**0.06**	**0.02**
Fertility disorders (SMQ)	**0**	**0**
Severe cutaneous adverse reaction (SMQ)	**0.06**	**0.06**
Skin and subcutaneous tissue disorders (SMQ)	**0.54**	**0.54**
Headache[b]	**0.31**	**0.29**
Gastrointestinal symptoms[c]	**0.32**	**0.43**

a. Single event preferred term
b. Predefined grouping of 2 high level terms
c. Predefined grouping of 2 high level terms: 1) Nausea and vomiting symptoms; and 2) Diarrhoea (excluding infective)
BPaL=Bedaquiline, pretomanid, and linezolid; C_{avg}=Steady-state average plasma concentration over a dosing interval; MedDRA=Medical Dictionary for Regulatory Activities; SMQ=Standardized MedDRA query

All models looking at exposure-response relationships for safety demonstrated that a 100 mg dose of pretomanid is not predicted to have a notable impact on safety relative to the proposed 200 mg dose.

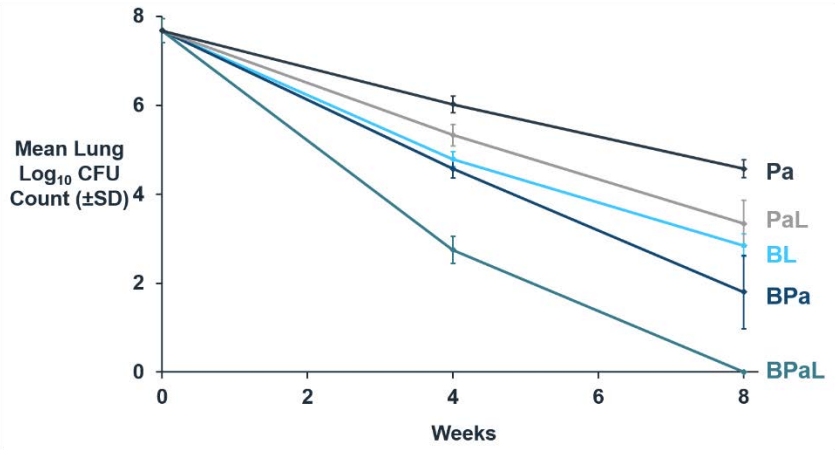
5.2.3 Rationale for Each Component of Regimen

Combining pretomanid, bedaquiline, and linezolid in a standardized regimen for patients with highly resistant TB was appropriate for the following considerations: 1) each agent has little pre-existing resistance among *M. tb* strains; and 2) each agent attacks *M. tb* via a different mechanism of action and has no cross-resistance with the others.

In order to assess the contribution of pretomanid to the BPaL regimen and evaluate the activity of the 3 agents when combined, several independent studies were conducted in a mouse model of TB. The studies demonstrated that pretomanid exhibited activity against *M. tb* in vivo, as shown by a reduction in lung CFU (Figure 5). Moreover, results showed that the BPaL regimen led to significantly greater reductions in lung CFU than any 2-drug combination of its components (bedaquiline-pretomanid, bedaquiline-linezolid, and pretomanid-linezolid) (Figure 5). This

indicates that each of the components of the BPaL regimen contributes significantly to the bactericidal efficacy of the BPaL regimen.

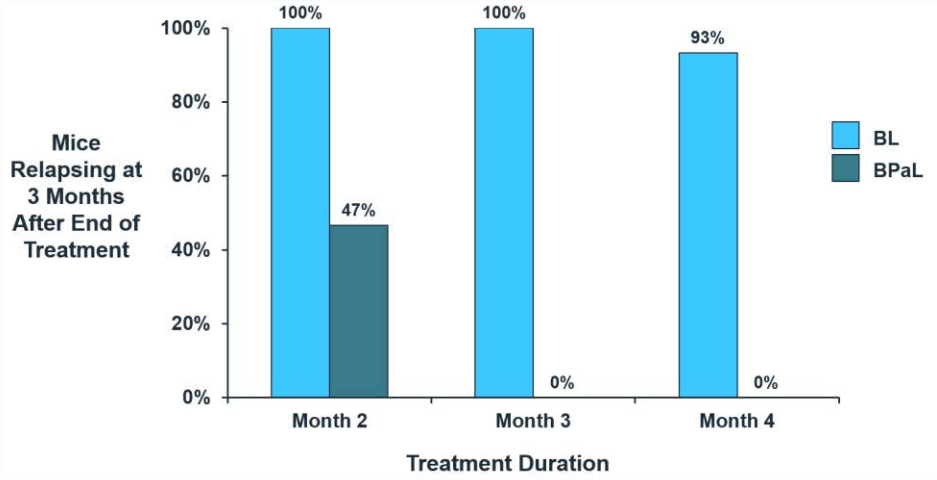
Figure 5: Lung Colony Forming Unit Counts in Murine Tuberculosis After Treatment with Pretomanid Alone and Different Combinations of Pretomanid, Bedaquiline, and Linezolid



Female BALB/c mice were infected with MTB H37Rv via aerosol with a mean lung $\log_{10}$ CFU count of 4.19 at 13 days prior to the beginning of treatment. They were treated for up to 8 weeks with oral, once-daily dosing (5 days/week) and lung CFU evaluated at 4 or 8 weeks after the start of treatment (n=5 per treatment arm per time point). Dosages: bedaquiline 25 mg/kg, pretomanid 100 mg/kg, linezolid 100 mg/kg
B=bedaquiline; CFU=colony forming units; L=linezolid; Pa=pretomanid; SD=standard deviation

The murine studies also demonstrated the superior sterilizing effect of adding pretomanid to bedaquiline and linezolid. Sterilizing activity was assessed by holding cohorts of animals for an additional 3 months following the completion of therapy, then evaluating lung CFU. The cohorts that received the BPaL regimen had significantly fewer relapses following 2, 3, or 4 months of treatment, compared to the bedaquiline-linezolid arms (Figure 6), providing further support for the contribution of pretomanid to the 3-drug regimen.

Figure 6: Relapse in Murine Tuberculosis After Treatment with Bedaquiline and Linezolid with and without Pretomanid



Female BALB/c mice were infected with approximately 4 log10 CFU MTB H37Rv via aerosol 2 weeks prior to the beginning of treatment. They were treated for up to 4 months with oral, once-daily dosing (5 days/week) and held for an additional 3 months after the end of treatment (n=15 per treatment arm per time point). Dosages: bedaquiline 25 mg/kg, pretomanid 100 mg/kg, linezolid 100 mg/kg
B=bedaquiline; CFU=colony forming units; L=linezolid; Pa=pretomanid; SD=standard deviation

6 CLINICAL EFFICACY

Summary

- Nix-TB is a multicenter single-arm study evaluating the efficacy of the BPaL regimen for the treatment of highly resistant TB using a rigorous clinical endpoint that does not rely on a biomarker or surrogate endpoint.
- As of 29 June 2018, the data cut-off date for the efficacy interim analyses, 81 of the 109 patients were followed to the 6-month post-treatment primary endpoint.
- The criterion for trial success was met, with 90% of patients achieving relapse-free cure at 6 months following completion of therapy (lower bound of 95% CI, 81%). This is similar to the rates of treatment success for DS-TB.
- Results did not differ by HIV status or by linezolid dosing schedule.
- Patients converted to culture-negative status very quickly after initiating treatment, with a median time of less than 6 weeks.
- In an analysis comparing the first 45 patients enrolled in Nix-TB to a cohort of historically matched controls, 89% of the Nix-TB cohort versus 13% of the control cohort had a favorable outcome.

6.1 Nix-TB Study Design

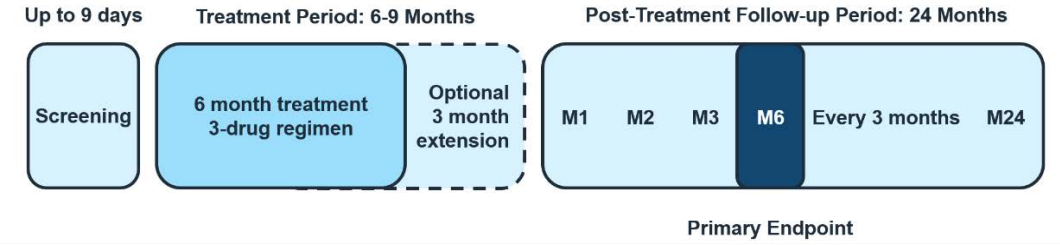
6.1.1 Overview of Study

Nix-TB is a Phase 3 single-arm trial assessing the efficacy, safety, and tolerability of BPaL in patients aged 17 years or older with either pulmonary XDR-TB or pulmonary TI/NR MDR-TB at 3 centers in South Africa. The primary endpoint is patient status through 6 months following the end of treatment. The study includes long-term follow-up through 24 months following the end of treatment.

Study treatment includes 6 months of treatment (extendable to 9 months if necessary) with the BPaL regimen (Figure 7) consistent with recommended dosing described in Section 3.4 and includes the following:

- Bedaquiline: 400 mg QD on Days 1 to 14 and 200 mg TIW thereafter; plus
- Pretomanid: 200 mg QD; plus
- Linezolid: 1200 mg daily (600 mg BID, changed to 1200 mg QD based on protocol amendment on 22 January 2016)

Figure 7: Nix-TB Study Flow



Study medication is orally administered with food due to the requirement for bedaquiline to be taken with food. There is an option for patients who are culture positive or revert to being culture positive between Month 4 and Month 6 to continue treatment for an additional 3 months. Study visits occur weekly through Week 16, monthly through 3 months after the end of treatment, and every 3 months thereafter.

Nix-TB is ongoing, and interim efficacy results are presented in this briefing document based on available data through 29 June 2018. To supplement the outcomes from Nix-TB, the efficacy of BPaL is compared against historical treatment outcomes reported in the literature as well as case-matched historical controls for XDR-TB. The results from these reviews can be found in Section 6.5.

6.1.2 Rationale for Study Design

A single-arm study was chosen because at the time of study initiation in 2015, patients with XDR-TB had limited treatment options due to their resistance profile. The available treatments (Section 2.2) had many side effects, including hearing loss and renal damage, and very poor treatment outcomes, with response rates of ≤2% to 60%, with only 2 studies reporting rates above 50%. Additionally, there was no standard of care. The therapies used were highly variable, usually including multiple drugs administered for at least 20 months, including 8 months with an injectable agent (WHO 2014a). Thus, there was no appropriate control to use for comparison.

Because of the low incidence of highly resistant TB in the US, conducting a study at a US center was not feasible. Therefore, a geography that would support a clinical trial in highly resistant TB was chosen. South Africa has excellent investigators and a good clinical trial infrastructure and regulatory environment, and it has one of the world's highest national levels of TB (WHO 2018a). Additionally, PK data from studies conducted at sites across the world, with variable racial backgrounds and comorbidities, demonstrated that pretomanid exposure was comparable by race and across disease states. Furthermore, prior literature and clinical experience in South Africa indicate generally poor outcomes for patients with XDR-TB. A positive result in the South African population is expected to be generalizable to highly resistant TB in other regions, including the US.

6.1.3 Enrollment Criteria

The study enrolled male or female patients with pulmonary XDR-TB or TI/NR MDR-TB who met the following key eligibility criteria:

Inclusion Criteria

- Body weight of ≥30 kg
- Provided consent for HIV testing or had documented positive HIV result
- Aged ≥14 years
- For XDR-TB:
    - Documented culture or molecular probe positive results for *M. tb* or *M. tb* confirmed in sputum based on molecular test within 3 months prior to or at Screening
    - Documented resistance to isoniazid, rifamycins, a fluoroquinolone, and an injectable at any time or prior to or at Screening
- For NR MDR-TB:
    - Documented culture or molecular probe positive results for *M. tb* within 3 months prior to or at Screening
    - Documented non-response to MDR-TB treatment for 6 months or more prior to enrollment
- For TI MDR-TB:
    - Documented culture or molecular probe positive results for *M. tb* within 3 months prior to or at Screening
    - Unable to continue second-line drug regimen due to a documented intolerance to para-aminosalicylic acid, ethionamide, aminoglycosides, fluoroquinolones, or other treatment that rendered the patient eligible for the trial in the Investigator's opinion
- Had a chest x-ray picture (taken within a year prior to Screening) consistent with pulmonary TB in the opinion of the Investigator
- Were of non-childbearing potential or used effective methods of birth control

Exclusion Criteria

- Karnofsky score <50 within 30 days prior to Screening
- HIV-infected patients with a cluster of differentiation 4 (CD4) count of ≤50 cells/μL
- HIV-infected patients being treated with, or needed to initiate ART that was not allowed
- Significant cardiac arrhythmia requiring medication
- Peripheral neuropathy of Grade 3 or Grade 4, according to the Division of Microbiology and Infectious Diseases (DMID), or neuropathy Grade 1 or Grade 2 which was likely to progress/worsen over the course of the trial, in the opinion of the Investigator

- Concomitant use of monoamine oxidase inhibitors, serotonergic antidepressants, any drug known to prolong QTc, any drug known to induce myelosuppression, any drugs known to be strong inhibitors or inducers of CYP enzymes
- Received more than 2 weeks of bedaquiline or linezolid prior to enrollment/first administration of trial treatment
- Toxicities at Screening as defined by the enhanced DMID adult toxicity table (DMID 2007)

6.1.4 Dosing Adjustments

6.1.4.1 Dose Adjustments: Linezolid

For patients who experience suspected toxicities due to linezolid, a reduction in the daily dose of linezolid or temporary cessation of linezolid (for up to 35 consecutive days) at the Investigator's discretion is allowed. If patients have toxicity issues that prohibit further treatment with linezolid, patients can remain on the bedaquiline and pretomanid trial treatment if they received the 1200 mg/day dose for at least the first 4 consecutive weeks of trial treatment, were smear-negative or had trace/scanty results, and were judged to be clinically improving by the Investigator. Missed doses of linezolid alone are not made up.

6.1.4.2 Dose Adjustments: BPaL Regimen

For patients who experience suspected drug-related toxicities due to bedaquiline and/or pretomanid, the entire 3-drug regimen can be halted for up to 35 consecutive days. Missed doses of the regimen are to be made up at the end of treatment.

6.1.5 Efficacy Endpoints

6.1.5.1 Primary Endpoint

The primary endpoint is the patient status at 6 months after the end of treatment. Patients are classified as having either a favorable or unfavorable outcome. A favorable outcome is defined as a negative culture status at 6 months from the end of therapy (where the last positive culture result was followed by at least 2 negative culture results) and not previously classified as having an unfavorable outcome. An unfavorable outcome includes any of the following:

- During treatment:
    - Death from any cause, except from violent or accidental cause
    - Not having achieved culture-negative status
    - Lost to follow-up
    - Withdrawn from study
- During follow-up after the end of treatment:
    - Death from causes definitely or possibly related to TB
    - Withdrawal from study for TB-related reasons, including being retreated for TB

- Bacteriologic relapse, ie, culture conversion to positive status with the *M. tb* strain present at baseline
- Bacteriologic reinfection, ie, culture conversion to positive status with a *M. tb* strain different from the infecting strain at baseline.

6.1.5.2 Key Secondary Endpoints

Key secondary endpoints are the following measures:

- TSCC to negative status during the treatment period
- Change from baseline on the TB Symptom Profile, a patient-reported outcome that records the severity of common TB symptoms
- Change from baseline on the EQ5D5L questionnaire, a patient-reported outcome that evaluates status of key dimensions of well-being and daily function
- Change from baseline in body weight

6.1.6 Statistical Methods

Interim analyses were prespecified to be performed once the first 15, 30, 45, and 75 patients either completed the treatment period and the 6-month post-treatment follow-up, withdrew from the trial, were lost to follow-up, or died. The efficacy results presented in this document are based on an interim analysis performed for all patients with data available through 29 June 2018 (which includes the first 81 patients to have completed the 6-month follow-up period after the end of treatment) in order to provide the most comprehensive efficacy data possible. Note: The Nix-TB safety analyses were based on a data cut-off date of 26 March 2018.

The prespecified primary endpoint analysis is the proportion of patients in the mITT population with a favorable outcome. For success, the lower bound of the 95% CI for the proportion of assessable patients with a favorable outcome is set at >50%. A threshold of 50% was selected because it was considered a favorable rate as it was substantially higher than historic rates of treatment success when neither bedaquiline nor linezolid were used.

The mITT analysis population excludes the following (patients already classified as having an unfavorable outcome are not excluded):

1. Women who become pregnant during treatment and stop their trial treatment;
2. Patients who die during treatment from a violent or accidental cause (eg, road traffic accident), not including suicide;
3. Patients who complete treatment and are lost to follow-up or withdraw from the trial, with no evidence of failure or relapse of their TB;
4. Patients who complete treatment and die during follow-up, with no evidence of bacteriologic relapse or reinfection;

5. Patients who, after being classified as having culture-negative status, are re-infected with a new strain different from the infecting strain at baseline;
6. Patients who are able to produce sputum at their primary endpoint visit, but whose sputum samples are all contaminated or missing, provided they had no evidence of bacteriologic relapse or reinfection and provided their last positive culture was followed by at least 2 negative cultures.

6.2 Study Population

6.2.1 Patient Disposition

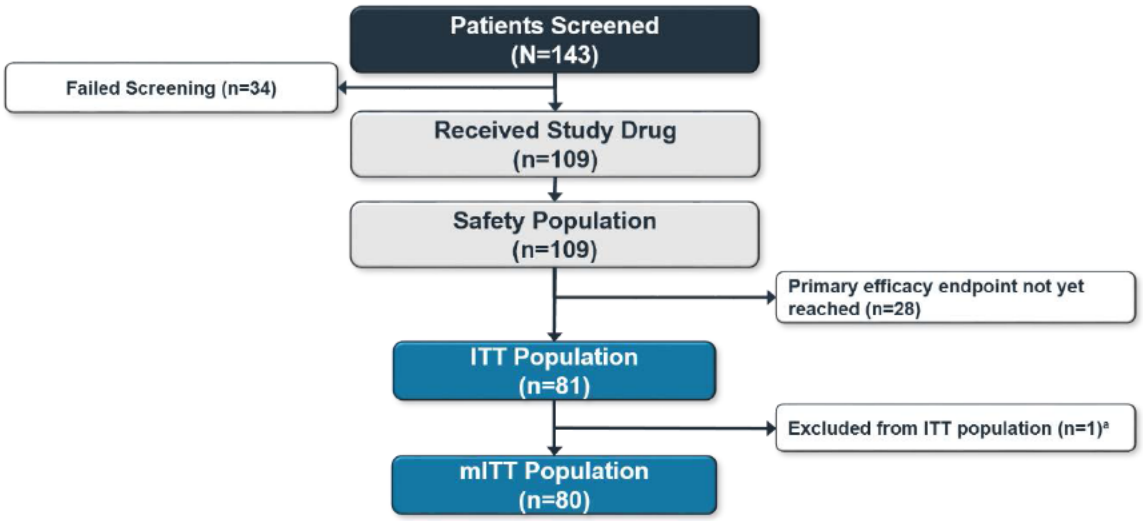
In total, 143 patients were screened in Nix-TB and 109 patients enrolled and received at least 1 dose of study medication. The majority, 101 (92.7%) patients, completed treatment (Figure 8). Of the 8 patients who did not complete treatment, 6 (5.5%) died during treatment, 1 withdrew consent before the end of treatment, and 1 was still continuing treatment as of the efficacy data cut-off date of 29 June 2018. Only 2 patients had delayed culture conversion and therefore had their treatment extended by 3 months in accordance with the protocol.

At the time of the data cut-off, 81 patients had traversed their anticipated 6-month follow-up period. Of these 81 patients, 1 patient died of causes unrelated to TB after completing treatment; he was culture negative at last follow-up, and was deemed "unassessable," as specified in the statistical analysis plan. Thus, this patient was excluded from the mITT population, resulting in a total of 80 patients available for the prespecified primary endpoint.

At the time the data were extracted, 23 patients had completed the 24-month follow-up period.

Forty-four (44) patients in the trial received linezolid 600 mg BID, while 65 received linezolid 1200 mg QD; as of 29 June 2018, 44 and 37 patients in the linezolid 600 mg BID and 1200 mg QD dosing groups completed the 6-month follow-up period.

Figure 8: Disposition of Patients in Nix-TB



a. One patient who died after completing treatment but was culture negative when last seen, was excluded from the mITT analysis as specified in the statistical analysis plan.
ITT=intent-to-treat; mITT=modified intent-to-treat; TB=tuberculosis

6.2.2 Demographics and Baseline Medical History

The demographics and baseline characteristics of patients enrolled in Nix-TB were generally reflective of patients with highly resistant TB in South Africa. The age of the patients ranged from 17 to 60 years; 52.3% were male, and 76.1% were Black or African (Table 8).

Table 8: Patient Demographics

		Nix-TB N=109
Age, years	**Mean (SD)**	35.6 (10.1)
	Min, max	17, 60
Sex	**Male**	57 (52.3%)
Race, n (%)	**Black or African**	83 (76.1%)
	White	1 (0.9%)
	Mixed race	25 (22.9%)

SD=Standard deviation

Enrolled patients weighed between 29 and 112 kg (Table 9). The reported Karnofsky scores ranged from 60% to 100% (median, 90%), with the largest proportion of patients having a score of 90% (45.9% patients).

At Screening, 51.4% patients were HIV positive with a mean duration since diagnosis of 4.7 years. All HIV-positive patients were on ART. The mean CD4 count for the HIV-positive patients with a CD4 count available was 394 cells/μL.

The majority of the patients had a TB diagnosis of XDR-TB at Screening (65.1%). The overall mean duration since the initial TB diagnosis was 23.6 months (median, 12.1 months), with the

longest duration being 141 months (more than 11 years). The mean time since the current TB diagnosis (MDR- or XDR-TB) was 11.3 months. Abnormal chest x-ray results compatible with TB were reported for all patients, the majority of whom had unilateral (46.8%) or bilateral cavities (37.6%).

Prior TB medication use was reported in 96.3% of patients. Those that were used in at least 50% of patients were fluoroquinolones (94.5%), thiocarbamide derivatives (76.1%), clofazimine (75.2%), aminosalicylic acid and derivatives (73.4%), other aminoglycosides (55.0%), and hydrazides (54.1%). The average number of TB medications used prior to study enrollment was 8.9 per patient.

Table 9: Baseline Characteristics and Medical History

		Nix-TB N=109
Weight, kg	**Mean (SD)**	57 (15)
	Min, max	29, 112
BMI, kg/m^2	**Mean (SD)**	20.6 (5.0)
	Min, max	12.4, 41.1
Karnofsky score, n (%)	**100%**	9 (8.3%)
	90%	50 (45.9%)
	80%	29 (26.6%)
	70%	19 (17.4%)
	60%	2 (1.8%)
HIV status, n (%)	**Positive**	56 (51.4%)
Duration since HIV diagnosis, years	**Mean (SD)**	4.7 (3.9)
	Min, max	0.2, 14.3
CD4 count, cells/µL	**Mean (SD)**	394 (212)
Duration since initial TB diagnosis, months	**Mean (SD)**	23.6 (27.9)
	Median	12.1
	Min, max	0.5, 141.0
Current TB diagnosis, n (%)	**XDR**	71 (65.1%)
	NR MDR	19 (17.4%)
	TI MDR	19 (17.4%)
Duration since current TB diagnosis, months	**Mean (SD)**	11.3 (16.3)
	Min, max	0.4, 90.3
Chest x-rays, n (%)	**Abnormal**	109 (100%)
	No cavities	17 (15.6%)
	Unilateral cavities	51 (46.8%)
	Bilateral cavities	41 (37.6%)

BMI=body mass index; CD4=cluster of differentiation 4; HIV=human immunodeficiency virus; MDR=multidrug-resistant; NR=nonresponsive; SD=standard deviation; TB=tuberculosis; TI=treatment-intolerant; XDR=extensively drug-resistant

6.2.3 Minimum Inhibitory Concentration

The baseline MICs for linezolid, bedaquiline, and pretomanid were determined using the MGIT system. The protocol defined the baseline period for the microbiological assessment as based on sputum collected at Screening through Week 4 of treatment.

All 58 baseline isolates tested for linezolid showed MIC values below or equal to the critical concentration recommended by the WHO (1 µg/mL) (WHO 2018c). Two out of 56 baseline isolates tested for bedaquiline had MIC values above the critical concentration recommended by the WHO (1 µg/mL). One of the corresponding patients had a favorable outcome 6 months after the end of treatment; the other died at Day 76. The range of MIC values observed for pretomanid for the 57 baseline isolates analyzed was ≤0.06 (the lowest limit of detection) to 1 µg/mL (median, 0.25 µg/mL; Table 10). These values are below or equal to the proposed critical concentration to be used to determine susceptibility to pretomanid (1 µg/mL; Section 3.7).

Table 10: Pretomanid Minimum Inhibitory Concentration at Baseline

Minimum Inhibitory Concentration, µg/mL	Nix-TB Patients (N=57)	
	Actual n (%)	Cumulative n (%)
≤0.06	7 (12%)	7 (12%)
0.12	19 (33%)	26 (46%)
0.25	25 (44%)	51 (89%)
0.5	5 (9%)	56 (98%)
1	1 (2%)	57 (100%)

6.3 Primary Endpoint – Patient Status at 6 Months After End of Treatment

The criterion for trial success was met; of the 80 patients in the mITT population, 8 (10%) had an unfavorable outcome while 72 (90%) had a favorable outcome (Table 11). The lower bound of the 95% CI for the proportion with a favorable outcome was 81%, exceeding the 50% prespecified threshold for success. These results were consistent for patients with either XDR-TB or TI/NR MDR-TB.

Table 11: Primary Efficacy Analysis (mITT Analysis Population)

	XDR N=55 n (%)	TI/NR MDR N=25 n (%)	Total N=80 n (%)
Favorable	49 (89%)	23 (92%)	72 (90%)
95% CI	78%, 96%	74%, 99%	81%, 96%

CI=confidence interval; MDR=multidrug-resistant; mITT=modified intent-to-treat; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

Outcomes are broken down further in Table 12 for the overall analysis set and for individual cases of treatment failure in Table 13. All patients who had a favorable outcome had a negative sputum culture at Month 6. Of the 8 patients with unfavorable outcomes, 6 died during treatment

(Patients 1–6, Table 13), all within the first 14 weeks of therapy, and 2 relapsed within 6 months following the end of treatment (Patients 8 and 9). Of the 6 patients who died during treatment, 4 had highly advanced TB on autopsy and 3 of these had multi-organ involvement. Three of the patients who died had HIV co-infection, and 5 of them had had low BMIs on Screening of <17.2 kg/m^2. Additional information on patient deaths is provided in Section 7.5 and patient narratives of the deaths are provided in Appendix 10.2.1.

The 2 cases of relapse are discussed below and patient narratives for these patients are provided in Appendix 10.2.2:

- Patient 8, a 55-year-old male, had XDR-TB and HIV co-infection, with a low CD4 count (67 cells/μL) despite a suppressed viral load. PK samples were available for him only at Week 8, and at that time, trough concentrations for all 3 drugs were not unusual. He relapsed with pulmonary TB in Month 3 of follow-up after completing the protocol-specified treatment. His Month 3 isolate contained the same *M. tb* strain as his baseline isolate. The MIC values for the trial drugs were 0.12 μg/mL for pretomanid and 0.5 μg/mL for linezolid, both at baseline and at the Month 3 follow-up; the MIC value for bedaquiline increased from 0.5 μg/mL at baseline to 4.0 μg/mL at the Month 3 follow-up. The patient was withdrawn from the trial and transferred to the National TB Treatment program for further therapy while being followed up for safety assessments according to the protocol. This patient later died of sepsis related to gangrene and severe peripheral vascular disease after he withdrew from the study.
- Patient 9 was a 21-year-old female who was HIV negative. She had MDR-TB that was nonresponsive to therapy. After completing the protocol-specified treatment, she relapsed at the Month 2 follow-up. PK samples were available for her at Weeks 2, 8, and 16; at all 3 time points, her linezolid trough concentrations were below the limit of quantification, her pretomanid concentrations were very low but quantifiable, and her bedaquiline and M2 concentrations were somewhat low relative to other patients in the study, suggesting that her adherence to the drug regimen may have been less than adequate. Although the patient had no baseline isolate to test for comparison, her Month 2 follow-up isolate had not acquired resistance to any of the trial drugs based on MICs of 0.5, 0.25, and 1 μg/mL for bedaquiline, pretomanid, and linezolid (MICs of ≤1 μg/mL considered sensitive). While the lack of a baseline isolate precluded comparison with the positive Month 2 sample by whole genome sequencing, the patient was considered to have relapsed. She was withdrawn from the trial and transferred to the National TB Treatment program for further therapy while being followed up for safety assessments according to the protocol.

An additional patient completed study treatment, had a negative sputum culture following treatment, and died approximately 6 months after the end of treatment of causes unrelated to TB (Appendix 10.2.1, Patient 7). This patient was excluded in the mITT analysis population (outcome considered unassessable) but was included in the ITT analysis population as having an unfavorable outcome (Section 6.3.2).

An additional patient who had a favorable outcome at Month 6 relapsed at Month 15 of follow-up (Appendix 10.2.3, Patient 10).

Table 12: Details of Primary Efficacy Endpoint (mITT Analysis Population)

Status	XDR N=55 n (%)	TI/NR MDR N=25 n (%)	Total N=80 n (%)
Favorable	**49 (89%)**	**23 (92%)**	**72 (90%)**
Culture negative status at Month 6 after EOT	49	23	72
Unfavorable	**6 (11%)**	**2 (8%)**	**8 (10%)**
During treatment			
Death	5	1	6
Post-treatment			
Withdrawn; Relapse	1	0	1
Withdrawn; Relapse (not confirmed by gene sequencing)	0	1	1

EOT=end of treatment; MDR=multidrug-resistant; mITT=modified intent-to-treat; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

Table 13: Reasons for Unfavorable/Unassessable Outcome (mITT Analysis Population)

		Reason for Treatment Failure	Study Time Point	Comments
Primary endpoint in mITT analysis population	**Patient 1**	Death[a]	Day 35	-
	Patient 2	Death[a]	Day 51	-
	Patient 3	Death[a]	Day 55	-
	Patient 4	Death[a]	Day 53	-
	Patient 5	Death[a]	Day 93	-
	Patient 6	Death[a]	Day 76	-
	Patient 8	Relapse	Month 3 of follow-up	Died on Day 486 of causes unrelated to TB or study drug[a]
	Patient 9	Relapse	Month 2 of follow-up	-
Additional patient in primary endpoint of ITT analysis population	**Patient 7**	Death[a]	Day 367	Completed study treatment and culture negative from Week 4 to Month 3 post-treatment (last study visit) Not TB-related
Relapsed after Month 6 of follow-up	**Patient 10**	Relapse	Month 15 of follow-up	After relapse, treated with individualized regimen and converted to culture negative

a. Additional information is provided in Section 7.5.
ITT=intent-to-treat; mITT=modified intent-to-treat; TB=tuberculosis

6.3.1 Sensitivity Analysis

Sensitivity analysis showed consistent results with the primary efficacy analyses. A sensitivity analysis examined treatment outcomes for patients who were culture positive during the baseline period. This analysis excluded patients who were never culture positive during the baseline period (Screening through Week 4) but were eligible based on documented *M. tb* by culture or molecular test within 3 months prior to Screening (Table 14). Of the 68 patients who were culture positive during the baseline period, 60 patients (88%) had favorable outcomes, with the lower bound of the 95% CI being 78%, which is greater than the prespecified lower bound of 50%.

Table 14: Primary Efficacy Analysis Including Only Patients with Positive Cultures at Baseline (mITT Analysis Population)

	XDR N=71 n (%)	TI/NR MDR N=38 n (%)	Total N=109 n (%)
Patients with positive culture during baseline period, n	**48**	**20**	**68**
Favorable	**42 (88%)**	**18 (90%)**	**60 (88%)**
95% CI	**75%, 95%**	**68%, 99%**	**78%, 95%**

CI=confidence interval; MDR=multidrug-resistant; mITT=modified intent-to-treat; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

6.3.2 Analysis Based on ITT Population

The primary endpoint results were also similar when analyzed for the ITT population (Table 15).

Table 15: Primary Efficacy Analysis (ITT Analysis Population)

	XDR N=56 n (%)	TI/NR MDR N=25 n (%)	Total N=81 n (%)
Favorable	**49 (88%)**	**23 (92%)**	**72 (89%)**
95% CI	**76%, 95%**	**74%, 99%**	**80%, 95%**

CI=confidence interval; ITT=intent-to-treat; MDR=multidrug-resistant; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

6.3.3 Subgroup Analyses

No difference in clinical outcome was seen based on HIV status or linezolid dosing at enrollment (600 mg BID vs 1200 mg QD dosing) based on subgroup analyses of the primary endpoint (Table 16 and Table 17, respectively).

Table 16: Primary Endpoint Analysis by HIV Status (mITT Analysis Population)

	HIV Positive N=39 n (%)	HIV Negative N=41 n (%)	Total N=80 n (%)
Favorable	35 (90%)	37 (90%)	72 (90%)
95% CI	76%, 97%	77%, 97%	81%, 96%

CI=confidence interval; HIV=human immunodeficiency virus; mITT=modified intent-to-treat

Table 17: Post Hoc Primary Endpoint Analysis by Linezolid Dosing at Enrollment (mITT Analysis Population)

	1200 mg QD N=36 n (%)	600 mg BID N=44 n (%)	Total N=80 n (%)
Favorable	33 (92%)	39 (89%)	72 (90%)
95% CI	78%, 98%	75%, 96%	81%, 96%

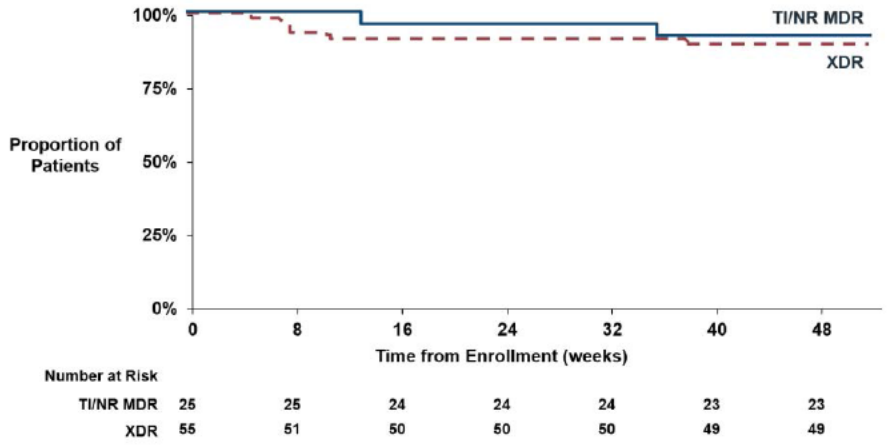
BID=twice daily; CI=confidence interval; mITT=modified intent-to-treat; QD=once daily

6.4 Secondary Endpoint

6.4.1 Time to Event

Few patients had an unfavorable outcome and, those who did generally had treatment failure within the first 14 weeks of initiating treatment. Figure 9 shows the time to unfavorable outcome analysis. The time to event is the number of days from the date of enrollment up to the first date associated with the reason for unfavorable status or, if favorable, the date of the Month 6 follow-up after the end of treatment visit.

Figure 9: Time to Unfavorable Outcome by Tuberculosis Type (mITT Analysis Population)



MDR=multidrug-resistant; mITT=modified intent-to-treat; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

6.4.2 Incidence of Bacteriologic Failure or Relapse at 24 Months

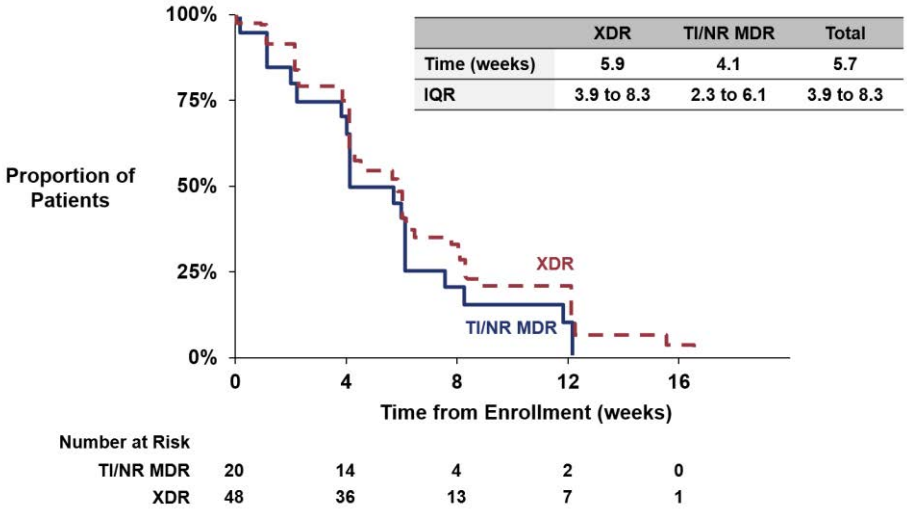
The long-term 24-month data show the favorable outcomes observed at 6 months following the end of treatment were durable, consistent with experience that most relapses will occur within 6 months (Johnson and Thiel 2012; Nunn et al. 2010).

At the time the data were extracted, 23 patients were "expected" to have data for the 24-month endpoint. Of the 23 expected patients, 3 died during treatment (captured in primary 6-month endpoint classification), 1 relapsed 15 months after completion of trial drug treatment and was treated with individualized therapy, and 19 remained negative. Of the 19 patients with negative status, 10 had their culture results based on samples collected between Months 21 and 24 following the end of treatment.

6.4.3 Time to Sputum Culture Conversion to Negative Status

Patients in Nix-TB achieved culture conversion quickly, with a median time to conversion of 5.7 weeks. In the mITT analysis population, 68 patients had positive culture at baseline. Of these 68 patients, 64 changed to negative status, and the remaining 4 were patients who died during treatment. Patients with TI/NR MDR-TB generally converted to culture-negative status faster than those with XDR-TB (Figure 10).

Figure 10: Time to Culture Negative Status (mITT Analysis Population)



	XDR	TI/NR MDR	Total
Time (weeks)	5.9	4.1	5.7
IQR	3.9 to 8.3	2.3 to 6.1	3.9 to 8.3

IQR=interquartile range; MDR=multidrug-resistant; mITT=modified intent-to-treat; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

6.4.4 Patient-Reported TB Symptom Profile

The TB Symptom Profile is a checklist of 10 common TB symptoms where patients are asked how much of a problem the symptom was over the prior 7 days. In Nix-TB, patients reported improvement in a number of TB symptoms by Week 8; that improvement increased through the end of treatment, consistent with the change in disease status. Overall, 41% of patients had 5 to 9 symptoms at baseline compared to 10% at Week 8 and 2% at the end of treatment (Table 18).

Conversely, 13% of patients had 0 to 1 symptom at baseline which increased to 70% at the end of treatment.

Table 18: Change in Patient-Reported TB Symptoms

Number of TB Symptoms	Baseline N=109 n (%)	Week 8 N=101 n (%)	End of Treatment N=99 n (%)
0	5 (5%)	39 (36%)	54 (55%)
1	9 (8%)	27 (25%)	15 (15%)
2	17 (16%)	14 (13%)	14 (14%)
3	14 (13%)	15 (14%)	9 (9%)
4	19 (17%)	4 (4%)	5 (5%)
5	11 (10%)	6 (6%)	1 (1%)
6	10 (9%)	2 (2%)	0
7	13 (12%)	1 (1%)	0
8	4 (4%)	1 (1%)	1 (1.1%)
9	7 (6%)	0	0

TB=tuberculosis

6.4.5 EQ5D5L

The EQ5D5L evaluates the status of key dimensions of well-being and daily function. At baseline, 34% and 41% of patients reported problems in the Anxiety/Depression and Pain/Discomfort domains of the EQ5D5L; improvement was seen by the end of treatment, with only 6% and 20% of patients affected in these areas (Table 19). Not many patients reported problems with Mobility, Self-care, and Usual activities on the EQ5D5L during the study. Overall, mean visual analogue scale scores improved from 82 before treatment to 92 at the end of treatment.

Table 19: Patient-Reported Health Status on EQ5D5L

	Baseline N=109[a] n (%)	Week 8 N=100[a] n (%)	End of Treatment N=100[a] n (%)
Patients with no problems in domain, n (%)			
Anxiety/depression	72 (66%)	84 (84%)	94 (94%)
Mobility	98 (90%)	97 (97%)	85 (85%)
Pain/discomfort	64 (59%)	88 (88%)	80 (80%)
Self-care	106 (97%)	100 (100%)	100 (100%)
Usual activities	99 (91%)	98 (98%)	99 (99%)
VAS score			
Mean	82	88	92
Min, max	0, 100	40, 100	55, 100

a. Number of patients providing data for 5 domains; 1 patient had a missing VAS score at every time point but filled in all other questions.
VAS=visual analogue scale

6.4.6 Body Weight

Changes in body weight were assessed from baseline to Week 8, Week 26, and 6 months after the end of treatment. Median weight increases were noted at each assessment time point (0.5 kg at Week 8, 2.8 kg at Week 26, and 3 kg at 6 months after the end of treatment.

6.4.7 Post-Baseline Minimum Inhibitory Concentration

Because few patients had positive cultures at or after Week 16 – the time stipulated in the protocol for characterization of post-baseline isolates – data for only 4 post-baseline isolates were available as of 29 June 2018. These were for the 3 patients with relapse (Patients 8-10) and 1 patient with treatment extension from 6 to 9 months. Of these 4 post-baseline isolates, the only patient that showed any development of resistance was Patient 8, who relapsed at 3 months following the end of treatment and had a post-baseline bedaquiline MIC equal to 4 µg/mL. All other post-baseline MIC values for bedaquiline, pretomanid, and linezolid were below or equal to 1 µg /mL.

6.5 Comparative Assessment of Nix-TB Outcomes

In order to provide a background of reference data for comparative assessment of the outcomes observed in the Nix-TB trial, TB Alliance conducted two assessments of historical XDR-TB treatment. First, TB Alliance performed a comprehensive review of published outcome data in XDR-TB patients treated with drugs not included in the Nix-TB study regimen. Second, outcomes were evaluated against a historical comparator group using patient-level data from a cohort of patients that closely matched the Nix-TB study population.

6.5.1 Literature Review Examining Outcomes in XDR-TB

A comprehensive literature review was conducted to identify all peer-reviewed articles that reported treatment outcomes in patients with XDR-TB. The search results were then selected to exclude articles in which treatment included any of the Nix-TB regimen components (pretomanid, bedaquiline, and linezolid) or delamanid (similar drug class as pretomanid).

Eighteen articles that met search criteria and that described outcomes that could be mapped to the standardized WHO outcome of treatment success were identified. These articles reported outcomes in 1,731 patients from 18 articles, of which 1,300 patients from 8 articles were from South Africa. Rates of treatment success across South African studies averaged 14%, with a range of 2% to 22%. Outside of South Africa, reported rates of treatment success were more varied, ranging from 15% to 60%; 2 articles reported rates above 50%.

6.5.2 Matched Historical Control Cohort

The historical control cohort comprised 204 patients with XDR-TB who were treated at Brooklyn Chest Hospital in Cape Town, South Africa, one of the 3 sites at which Nix-TB was conducted. Patients in the matched control cohort received treatment with various drug combinations (which did not include bedaquiline, linezolid, pretomanid, or delamanid) between January 2008 and September 2014 (Olayanju et al. 2018) (Note: enrollment in Study Nix-TB started April 2015). Patients in both the historical control cohort and Nix-TB were from the same geographic area, and were very similar in age, sex, body weight, and HIV status distribution at baseline.

Outcomes based on patient-level data for the control cohort were analyzed and compared to Nix-TB:

- Favorable/unfavorable status: This treatment outcome was defined for the control population according to the adapted 2013 WHO criteria as modified by Furin et al. (Furin et al. 2016; WHO 2014b); that is, favorable outcomes were achieving a cure[5] or completing treatment, and unfavorable outcomes were death, failed treatment, defaulting on treatment, or lost to follow-up (Olayanju et al. 2018). The assessment time point was 24 months after the start of treatment (treatment was planned for 18 months or longer). The primary efficacy endpoint in Nix-TB was used, where patient status was assessed 6 months after the end of treatment.
- All-cause mortality at 12 and 24 months after the start of treatment.

As shown in Table 20, 88.9% of the Nix-TB population had favorable outcomes compared with 13.4% of the control population, which is consistent with the response rates from South African studies reported in the literature. The probability of a favorable outcome was 6.6-fold greater in Nix-TB than in the historical control population ($p<0.0001$). Similar results were obtained in the sensitivity analysis after adjustment for sex, age, body weight, and HIV status at baseline.

[5] The definition of cure was treatment completed as recommended by the national policy without evidence of failure AND 3 or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Table 20: Patient Outcome in Nix-TB and Matched Historical Controls

	Unfavorable n (%)	Favorable n (%)	Risk Ratio (Nix-TB/Control)
Control (N=202)[a]	175 (86.6%)	27 (13.4%)	6.6 95% CI (4.6-9.6) p<0.0001
Nix-TB (N=45)	5 (11.1%)	40 (88.9%)	

a. Only those with outcome data from the 204 patients were included in the analysis.
CI=confidence interval

The proportion of deaths in the two populations at 12 and 24 months was statistically significantly different, with an approximately 3.3-fold higher likelihood of dying in the control cohort compared to the Nix-TB population at both time points (Table 21).

Table 21: All-Cause Mortality in Nix-TB and Matched Historical Controls

		Alive n (%)	Died n (%)	Risk Ratio (Nix-TB/Control)
12 months	Control (N=190)[a]	135 (71.1%)	55 (28.9%)	3.3 95% CI (1.3-8.5) p=0.0024
	Nix-TB (N=45)[a]	41 (91.1%)	4 (8.9%)	
24 months	Control (N=182)[a]	113 (62.1%)	69 (37.9%)	3.4 95% CI (1.5-8.0) p=0.0002
	Nix-TB (N=45)[a]	40 (88.9%)	5 (11.1%)	

a. Only those with outcome data from the 204 patients were included in the analysis.
CI=confidence interval

6.5.3 Limitations of Comparative Assessments

There are several limitations in the comparative assessments of literature and historical patient-level data to Nix-TB. These include:

- Accuracy differences between real-world datasets and clinical study datasets
- Wide heterogeneity in the populations studied, clinical care, and quality of follow-up (literature review)
- Differences in quality of follow-up as a result of different study protocols (historical control cohort)
- Differences in clinical care arising from changes over the time (historical control cohort; treated during 2008–2014 vs 2015–2016 for Nix-TB)
- Variable criteria for reporting population characteristics, treatments administered, and treatment success

Notwithstanding the limitations noted above, the literature-reported and matched historical control outcomes together with the robust findings of efficacy with BPaL in Nix-TB provide assurance that the results in Nix-TB reflect a meaningful benefit.

6.6 Nix-TB Efficacy Update (18 January 2019 Data Cut-Off)

Recent efficacy results with a data cut-off date of 18 January 2019 were provided to the FDA in the 120-Day Update to the pretomanid NDA in order to provide additional follow-up on the patients in Nix-TB.

As of 18 January 2019, primary endpoint data were available for 107 patients who had completed at least 6 months of follow-up after completion of study therapy. The results of both the mITT and the ITT analyses are consistent with the data from the previous data cut-off date. Approximately 90% of patients achieved a favorable outcome at Month 6 of follow-up (Table 22).

Table 22: Updated Primary Efficacy Analysis (mITT and ITT Analysis Populations)

	XDR n (%)	TI/NR MDR n (%)	Total n (%)
mITT Population, N	**70**	**34**	**104**
Favorable	**63 (90%)**	**32 (94%)**	**95 (91%)**
95% CI	**80%, 96%**	**80%, 99%**	**84%, 96%**
ITT Population, N	**71**	**36**	**107**
Favorable	**63 (89%)**	**32 (89%)**	**95 (89%)**
95% CI	**79%, 95%**	**74%, 97%**	**81%, 94%**

CI=confidence interval; ITT=intent-to-treat; MDR=multidrug-resistant; mITT=modified intent-to-treat; TI/NR=treatment-intolerant/nonresponsive; XDR=extensively drug-resistant

As of 18 January 2019, 38 patients had completed the post-treatment 24-month follow-up period. Outcomes at 24 months were similar to those at 6 months following end of treatment. Of the 38 patients, 6 had an unfavorable outcome and 32 remained culture negative. The 6 patients with unfavorable outcomes were all previously described; 4 patients died during treatment (Table 13, Patients 1–4), 1 relapsed before the 6-month follow-up time point (Table 13, Patient 8), and 1 relapsed at the Month 15 follow-up (Table 13, Patient 10).

6.7 Efficacy Conclusions

In Nix-TB, the first clinical trial ever to evaluate the BPaL regimen, approximately 90% of patients with highly resistant TB achieved relapse-free cure status 6 months after the end of treatment. The Nix-TB rate of favorable outcomes is similar to the rates of treatment success for DS-TB (WHO 2018a). The study met the prespecified threshold for success with the lower bound of patients with favorable outcome exceeding 50%. Furthermore, the percentage of patients who had a favorable status following this 6-month regimen was substantially higher than the rate of favorable outcomes in the reported literature with existing regimens lasting 18 months or longer.

Patients on the BPaL regimen converted to culture-negative status quickly, with a median time of less than 6 weeks. The vast majority of patients remained relapse-free at 6 months after the end of treatment with preliminary 24-month data indicating that virtually all patients with culture conversion remained relapse free. Efficacy outcomes were similar for patients who were HIV

positive or HIV negative and for patients with XDR-TB or TI/NR MDR-TB. A reduction of symptoms and improvement in patient-report health status accompanied the change in TB status. With these results, the BPaL regimen can potentially transform the treatment of highly resistant TB, with patients being cured by taking a short, simplified, and effective regimen.

7 CLINICAL SAFETY

Summary

- Throughout the clinical development program, 1,168 individuals have received at least 1 dose of pretomanid alone or in combination with other medications.
- The Nix-TB safety database includes safety information on 109 patients with XDR-TB and TI/NR MDR-TB treated with BPaL and followed for a maximum of 24 months post-therapy.
- The spectrum of AEs in Nix-TB reflects the general status of patients with highly resistant TB, many of whom had HIV co-infections, and the known or expected safety profiles of bedaquiline, pretomanid, and linezolid.
  - Patients experienced an average of 11.5 AEs, and 53% of patients experienced an average of 2.1 AEs that were Grade 3 or 4 in severity.
  - Some of the most frequently reported AEs in Nix-TB (ie, peripheral sensory neuropathy, anemia) are known side effects of linezolid and were uncommon in other Phase 1 and 2 studies with pretomanid regimens that did not contain linezolid.
  - Nineteen (17.4%) patients experienced 36 SAEs during treatment. The most common SAEs were pneumonia and pulmonary TB, which were reflective of the underlying disease, followed by sepsis, hypoglycemia, and anemia.
- Approximately 85% of patients were able to complete the protocol-specified course of BPaL. An additional 10 (9.2%) were still receiving study treatment but had not yet completed the full course of study therapy.
  - Per protocol, linezolid dosing was interrupted (44.0% of patients), reduced (39.4% of patients), or permanently discontinued (25.7% of patients) to manage drug-related toxicity.
- Six patients, mostly with severe TB infections, died within the first 14 weeks of therapy. Two patients died of non-TB related causes after completing treatment.
- AESIs included the following (incidence):
  - Hepatotoxicity (36.7%): All 8 patients who had BPaL dosing interruptions due to hepatic AESIs were able to resume and complete therapy after transaminases decreased, including 2 patients who met the laboratory criteria as potential Hy's Law cases. One patient with an SAE of transaminases increased died of sepsis and pneumonia.
  - Peripheral neuropathy (79.8%): 55% of peripheral neuropathy AESIs led to linezolid dose changes, which were generally observed in the last 3 months of treatment. No event was considered serious, and the events generally diminished after study treatment was completed.

  - Optic neuropathy (11.9%): SAEs of optic neuritis/neuropathy occurred in 2 patients. Both started after 16 weeks of study treatment and resolved after discontinuation of linezolid.
  - Myelosuppression (46.8%): 54% of myelosuppression AESIs led to linezolid dose changes, which generally occurred in the first 3 months and were primarily for cases of anemia. Three patients experienced events that were considered serious; all 3 SAEs resolved after an interruption in study drug administration.
- AEs in the BPaL regimen were generally manageable through dose adjustments, and the majority of patients were able to complete therapy.

7.1 Safety Datasets

As of the safety data cut-off date of 26 March 2018, a total of 1,168 individuals, including 223 patients with either XDR-TB or MDR-TB, 656 patients with DS-TB, and 289 healthy volunteers, were exposed to pretomanid, either alone or as part of combination therapy.

The safety data presented in this document focus primarily on results from Nix-TB, which characterizes the safety profile of pretomanid in patients with XDR-TB and TI/NR MDR-TB treated with the BPaL regimen; these patients and this regimen represent the population and product combination, respectively, wherein pretomanid approval is sought. The Nix-TB safety database includes data available through the 26 March 2018 cut-off date[6].

Data from other studies in the clinical program are presented to support the safety of the BPaL regimen as needed. A diagram showing the different safety datasets in the clinical program is provided in Figure 11. Specifically, the following 2 datasets from Phase 1 and 2 studies provide supplemental information specific to pretomanid, and an overview of AEs in these datasets is provided in Section 7.2:

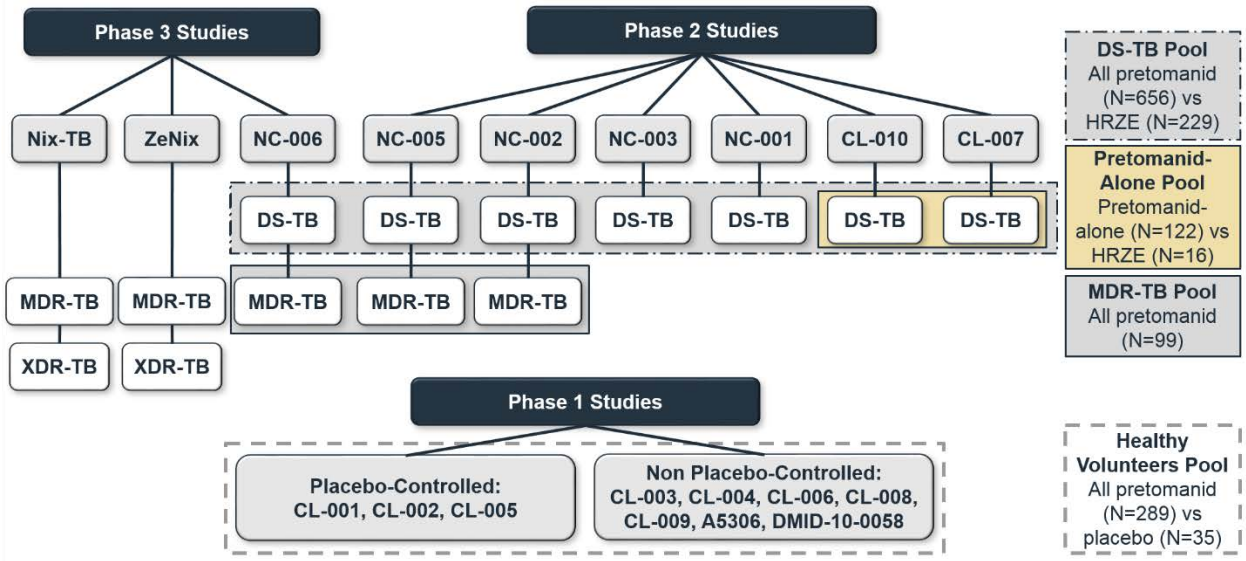
- The Phase 1 pretomanid safety dataset comprises 324 healthy volunteers from all Phase 1 studies in the clinical program, some of which included a placebo control arm. In these studies, 289 subjects received single or repeated daily doses of pretomanid (up to 14 days) ranging from 50 to 1500 mg (alone or in combination with other agents) and 35 received placebo. This dataset allows for comparisons of pretomanid at a variety of dose levels and regimens to a placebo control.
- The Phase 2 pretomanid-alone safety dataset includes 138 patients with DS-TB from 2 Phase 2 studies of pretomanid monotherapy compared with HRZE control (CL-007 and CL-010). This dataset comprises 122 patients who received pretomanid 50 to 1200 mg and 16 patients who received treatment with HRZE for 14 days. While not a placebo-

[6] Comprehensive safety analyses based on the 26 March 2018 cut-off date were submitted in the pretomanid NDA. Updated safety analyses as of 15 October 2018 have been recently provided to the FDA for this ongoing study. The additional safety data showed no change in the overall safety profile of the BPaL regimen and no change to the overall safety conclusions of study.

controlled dataset, this population allows for an understanding of the comparative safety of pretomanid alone versus a well-known regimen (HRZE) in patients with DS-TB.

Additional safety datasets are referenced in the discussion of AESIs. These include the DS-TB pooled dataset, and the MDR-TB pooled dataset (Figure 11). Key aspects of each study are outlined in Appendix Table 45 and Appendix Table 46.

Figure 11: Safety Datasets in Pretomanid Clinical Program



DS=drug-susceptible; HRZE=isoniazid-rifampicin-pyrazinamide-ethambutol; MDR=multidrug-resistant; TB=tuberculosis; XDR=extensively drug-resistant

7.2 Summary of Adverse Events from Phase 1 and Phase 2 Studies

7.2.1 Phase 1 Pretomanid Versus Placebo Dataset (Healthy Subjects)

As summarized in Table 23, AEs were reported in 64.4% and 40.0% of all pretomanid and placebo subjects, respectively. Of note, the mean time on treatment for the all pretomanid group was 17.2 (range, 1 to 43) days, while the mean time on treatment for placebo was shorter at 5.0 (range, 1 to 8) days. The most frequently (≥5% of patients) reported AEs in the all pretomanid group and observed at a higher frequency than placebo are listed in Table 24.

Four pretomanid subjects (1.4%) and no placebo subjects experienced a Grade 3 AE, and no Grade 4 AEs were reported. The Grade 3 events consisted of blood creatine phosphokinase increased, aspartate aminotransferase abnormal, neutrophil count decreased, and rash generalized.

No subject died due to an AE. One SAE (road traffic accident; as a passenger) was reported for a pretomanid-treated subject.

Ten pretomanid subjects (3.5%; 9 patients taking single or multiple pretomanid doses >200 mg and 1 patient taking multiple-dose pretomanid 200 mg) and no placebo subjects experienced AEs that led to permanent discontinuation of study drug. The most frequently reported event leading

to study drug discontinuation was blood creatinine increased. All 5 subjects were in the pretomanid 1000 mg group of Study CL-002, and the study was stopped because of the creatinine elevations (which did not exceed 1.60 mg/dL). Elevation of serum creatinine is a known effect of pretomanid, and the findings of Study CL-005 suggest that the effect is due to inhibition of tubular secretion of creatinine, rather than due to a toxic effect of pretomanid on glomerular filtration. All remaining AEs leading to discontinuation of study drug in the Phase 1 studies were reported in 1 subject each. These included electrocardiogram QT prolonged (single-dose pretomanid >200 mg), sinus tachycardia (single-dose pretomanid >200 mg), ventricular extrasystoles (single-dose pretomanid >200 mg), mental status changes (multiple-dose pretomanid 200 mg), and rash papular (single-dose pretomanid >200 mg).

Table 23: Overview of Adverse Events (Phase 1 Pretomanid Studies)

	Phase 1 Pretomanid Studies	
	All Pretomanid N=289 n (%)	Placebo N=35 n (%)
Subjects with any AE	186 (64.4%)	14 (40.0%)
Grade 1	145 (50.2%)	10 (28.6%)
Grade 2	37 (12.8%)	4 (11.4%)
Grade 3	4 (1.4%)	0
Grade 4	0	0
AEs leading to discontinuation of study drug	10 (3.5%)	0
SAE[a]	1 (0.3%)	0
Fatal AEs	0	0

a. Road traffic accident
AE=adverse event; SAE=serious adverse event

Table 24: Adverse Events Occurring in ≥5% in Pretomanid-Treated Subjects and More Frequently than Placebo (Phase 1 Pretomanid Studies)

	Phase 1 Pretomanid Studies	
	All Pretomanid N=289 n (%)	Placebo N=35 n (%)
Subjects with any AE	186 (64.4%)	14 (40.0%)
Preferred term		
Headache	91 (31.5%)	8 (22.9%)
Nausea	34 (11.8%)	0
Dermatitis contact	33 (11.4%)	0
Haemoglobin decreased	31 (10.7%)	0
Diarrhoea	25 (8.7%)	0
Dizziness	24 (8.3%)	1 (2.9%)

AE=adverse event

7.2.2 Phase 2 Pretomanid-Alone Versus HRZE Control Safety Dataset

In the Phase 2 studies of pretomanid alone in patients with DS-TB, similar percentages of pretomanid and HRZE control patients reported at least 1 AE (38.5% and 43.8%, respectively; Table 25). In the pretomanid group, the most frequently (≥2% of subjects) reported preferred terms of AEs were nausea, pruritus generalized, rash, vomiting, rash papular, pruritus, headache, and hemoptysis, with each occurring in less than 5% of patients (Table 26).

In both treatment groups, AEs were predominantly Grade 1 and Grade 2 in severity. One pretomanid patient (0.8%) and 1 HRZE control patient (6.3%) experienced a Grade 3 AE of confusional state and hemoptysis, respectively. No Grade 4 AEs or AEs leading to death were reported.

Two pretomanid patients (1.6%) and 1 HRZE patient (6.3%) reported 3 SAEs. These events were hemoptysis and pneumothorax for the 2 pretomanid patients and hemoptysis in the HRZE patient; none of the SAEs was considered related to study drug.

Three pretomanid patients (2.5%) and no control patients experienced AEs that led to discontinuation of study drug. The AEs leading to treatment discontinuation were pneumothorax (1 patient); Wolff-Parkinson-White syndrome (1 patient); and nausea, vomiting, urinary tract infection, and confusional state in 1 patient.

Table 25: Overview of Adverse Events (Phase 2 Pretomanid-Alone Studies)

	Phase 2 Pretomanid-Alone Studies	
	Pretomanid N=122 n (%)	HRZE N=16 n (%)
Patients with any AE	47 (38.5%)	7 (43.8%)
Grade 1	40 (32.8%)	5 (31.3%)
Grade 2	6 (4.9%)	1 (6.3%)
Grade 3	1 (0.8%)	1 (6.3%)
Grade 4	0	0
AEs leading to discontinuation of study drug	3 (2.5%)	0
SAE	2 (1.6%)	1 (6.3%)
Fatal AEs	0	0

AE=adverse event; HRZE=isoniazid-rifampicin-pyrazinamide-ethambutol; SAE=serious adverse event

Table 26: Adverse Events Occurring in ≥2% of Pretomanid-Treated Patients (Phase 2 Pretomanid-Alone Studies)

	Phase 2 Pretomanid-Alone Studies	
	Pretomanid N=122 n (%)	HRZE N=16 n (%)
Patients with any AE	**47 (38.5%)**	**7 (43.8%)**
Preferred term		
Nausea	**5 (4.1%)**	**1 (6.3%)**
Vomiting	**4 (3.3%)**	**1 (6.3%)**
Pruritus generalised	**4 (3.3%)**	**0**
Rash	**4 (3.3%)**	**0**
Rash papular	**4 (3.3%)**	**0**
Pruritus	**3 (2.5%)**	**2 (12.5%)**
Haemoptysis	**3 (2.5%)**	**1 (6.3%)**
Headache	**3 (2.5%)**	**0**

AE=adverse event; HRZE=isoniazid-rifampicin-pyrazinamide-ethambutol

Overall, the comparisons between pretomanid versus placebo and HRZE demonstrate that pretomanid was generally safe and well tolerated in healthy subjects and patients with DS-TB, with no signals to indicate toxicities of clinical concern.

7.3 Nix-TB Treatment Exposure

As of 26 March 2018, 93 (85.3%) of the 109 patients enrolled in Nix-TB had completed the protocol-specified 26 weeks of investigational drug therapy, and 10 (9.2%) were still receiving study treatment; 6 patients died before completing study treatment (Table 27). Thus, the mean duration of study treatment, with or without linezolid, was 23.2 weeks.

As described in Section 6.1.4, linezolid could be reduced, interrupted and resumed, or discontinued to manage linezolid-related adverse effects while treatment with bedaquiline and pretomanid continued. Of the 93 patients who completed study treatment, 34 patients completed the BPaL regimen without any interruption or missed doses of linezolid; this was achieved in a higher proportion of patients taking linezolid 1200 mg QD versus 600 mg BID. Overall, the mean duration of linezolid dosing was 22.5 weeks and the average daily dose was 864 mg (Table 27).

Table 27: Exposure to Treatment (Nix-TB)

		Nix-TB N=109
BPaL regimen		
Completed 26-week study treatment	**n (%)**	**93 (85.3%)**
Study treatment ongoing	**n (%)**	**10 (9.2%)**
Terminated study treatment early	**n (%)**	**6 (5.5%)**
Duration of dosing[ab], weeks	**Mean (SD)**	**23.2 (6.6)**
Linezolid (with bedaquiline and pretomanid)		
Completed 26-weeks of linezolid uninterrupted	**n (%)**	**34 (31.2%)**
Duration of linezolid dosing[b], weeks	**Mean (Range)**	**22.5 (7.9, 29.0)**
Dose of linezolid, mg	**Mean (SD)**	**864 (341)**
Time in follow-up after end of treatment, months	**Mean (SD)**	**10.1 (8.2)**

a. Dosing of BPaL regimen, with or without linezolid.
b. Interruption time was not included.

7.4 Nix-TB Safety Dataset

In this document, the focus for safety is on treatment-emergent AEs, that is, AEs that started or worsened on or after the first trial drug administration up to 14 days after the last trial drug administration. The exception is deaths (Section 7.5), which include any that occurred during treatment or in post-treatment follow-up.

All 109 patients reported at least 1 AE, with an average of 11.5 AEs reported per patient (Table 28). 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. (Two additional deaths that occurred in post-treatment follow-up are covered in Section 7.5).

Table 28: Overview of Adverse Events (Nix-TB)

	Nix-TB (N=109)	
	Patients n (%)	Events n
Any AE	**109 (100%)**	**1254**
Grade 1	**8 (7.3%)**	**872**
Grade 2	**43 (39.4%)**	**261**
Grade 3	**41 (37.6%)**	**90**
Grade 4	**17 (15.6%)**	**31**
AEs leading to discontinuation of any study drug	**33 (30.3%)**	**44**
AEs leading to discontinuation of linezolid	**27 (24.8%)**	**29**
AEs leading to discontinuation of BPaL	**6 (5.5%)**	**12**
SAE	**19 (17.4%)**	**36**
Fatal AEs	**6 (5.5%)**	**10**

AE=adverse event; SAE=serious adverse event

7.4.1 Common Adverse Events

Common AEs are listed in Table 29. Some of the most frequently (≥10% of patients) reported AEs in Nix-TB (peripheral sensory neuropathy and anemia) are known key adverse effects of concern for linezolid (Zyvox label 2018); other common AEs are consistent with the expected safety profile of bedaquiline and pretomanid, as well as with linezolid, and the underlying conditions found in the study population.

Table 29: Adverse Events Occurring in ≥5% of Patients (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any AE	**109 (100%)**
Preferred term	
Peripheral sensory neuropathy	**75 (68.8%)**
Anaemia	**40 (36.7%)**
Nausea	**40 (36.7%)**
Vomiting	**37 (33.9%)**
Headache	**28 (25.7%)**
Dermatitis acneiform	**26 (23.9%)**
Dyspepsia	**26 (23.9%)**
Decreased appetite	**24 (22.0%)**
Pleuritic pain	**20 (18.3%)**
Upper respiratory tract infection	**20 (18.3%)**
Gamma-glutamyltransferase increased	**18 (16.5%)**
Rash	**17 (15.6%)**
Acne	**16 (14.7%)**
Pruritus	**15 (13.8%)**
Haemoptysis	**14 (12.8%)**
Back pain	**13 (11.9%)**
Hypoglycaemia	**12 (11.0%)**
Transaminases increased	**12 (11.0%)**
Abdominal pain	**11 (10.1%)**
Abnormal loss of weight	**11 (10.1%)**
Diarrhoea	**11 (10.1%)**
Alanine aminotransferase increased	**10 (9.2%)**
Neuropathy peripheral	**10 (9.2%)**
Amylase increased	**9 (8.3%)**
Constipation	**9 (8.3%)**
Gastritis	**9 (8.3%)**
Neutropenia	**9 (8.3%)**
Aspartate aminotransferase increased	**8 (7.3%)**
Cough	**8 (7.3%)**
Dry skin	**8 (7.3%)**
Hyperamylasaemia	**8 (7.3%)**
Abdominal pain upper	**7 (6.4%)**
Chronic obstructive pulmonary disease	**7 (6.4%)**
Lower respiratory tract infection	**7 (6.4%)**
Pain in extremity	**7 (6.4%)**
Urinary tract infection	**7 (6.4%)**

	Nix-TB N=109 n (%)
Arthralgia	**6 (5.5%)**
Costochondritis	**6 (5.5%)**
Electrocardiogram QT prolonged	**6 (5.5%)**
Hypertension	**6 (5.5%)**
Influenza	**6 (5.5%)**
Insomnia	**6 (5.5%)**
Myalgia	**6 (5.5%)**
Visual acuity reduced	**6 (5.5%)**

AE=adverse event; SAE=serious adverse event

7.4.2 Adverse Events Leading to Change in Study Drug

7.4.2.1 Discontinuation or Interruption of BPaL Regimen

The BPaL regimen was discontinued in 6 patients (5.5%) who died due to SAEs (Section 7.5). All remaining patients were able to complete or were completing their study regimen at the time of the data cut-off date (26 March 2018).

Interruptions of the 3-drug regimen occurred in 20 patients (18.3%; Table 30) with the interruptions lasting a total of 19.6 days on average (ie, less than 3 weeks throughout the 26-week course of the study regimen; range, 2 to 48 days). The most common AEs leading to interruption of the entire treatment regimen were transaminases increased (5 patients [4.6%]) and abdominal pain (3 patients [2.8%]), with other events each occurring in only 1 to 2 patients.

Table 30: Adverse Events Leading to Interruption of BPaL (Nix-TB)

	Nix-TB (N=109) n (%)
Patients with interruption due to AE	**20 (18.3%)**
Preferred term	
Transaminases increased	**5 (4.6%)**
Abdominal pain	**3 (2.8%)**
Anaemia	**2 (1.8%)**
Lactic acidosis	**2 (1.8%)**
Vomiting	**2 (1.8%)**
Drug-induced liver injury	**2 (1.8%)**
Haematemesis	**2 (1.8%)**
Pancreatitis	**2 (1.8%)**
Abdominal pain upper	**2 (1.8%)**
Peripheral sensory neuropathy	**1 (0.9%)**
Thrombocytopenia	**1 (0.9%)**
Nausea	**1 (0.9%)**
Acidosis	**1 (0.9%)**
Amylase increased	**1 (0.9%)**
Bicytopenia	**1 (0.9%)**
Bone marrow failure	**1 (0.9%)**
Diarrhoea	**1 (0.9%)**
Gastritis	**1 (0.9%)**
Generalised tonic-clonic seizure	**1 (0.9%)**
Hepatic enzyme increased	**1 (0.9%)**
Hyperamylasaemia	**1 (0.9%)**
Sepsis	**1 (0.9%)**
Visual impairment	**1 (0.9%)**

AE=adverse event; SAE=serious adverse event

7.4.2.2 Discontinuation, Interruption, Dose Reduction of Linezolid

Discontinuation, interruption, and dose reduction of linezolid were also allowed as a way to manage known linezolid toxicities.

Of the Nix-TB population, 25.7% discontinued linezolid due to AEs. The most frequently reported AEs leading to discontinuation were peripheral sensory neuropathy and neuropathy

peripheral (Table 31), which are known adverse effects of linezolid. Peripheral sensory neuropathy led to linezolid discontinuation in 22 patients, peripheral neuropathy in 3, and anemia in 2; all other AEs leading to discontinuation of linezolid were reported in 1 patient each.

AEs resulting in linezolid dose reduction occurred in 39.4% of patients (Table 31). The most frequent of these were peripheral sensory neuropathy (27 patients), anemia (13 patients), and neuropathy peripheral (3 patients). All other AEs were reported in 1 patient each. In general, the rate of dose reduction increased steadily over time from approximately Day 20 to approximately Day 150, with a median time to first dose reduction of approximately 110 days.

Linezolid dosing interruptions due to AEs were common, occurring in 48 patients (44.0%); among these 48 patients, the total duration of dose interruption was 44.5 days on average. The most frequently reported AEs leading to interruption of linezolid were peripheral sensory neuropathy, anemia, neuropathy peripheral, and neutropenia. All other events were reported in 1 or 2 patients each. The rate of interruption increased steadily over time from approximately Day 10 to Day 180, with a median time to first dose interruption of approximately 140 days.

Table 31: Adverse Events Leading to Discontinuation, Dose Reduction, or Interruption of Linezolid (Nix-TB)

	Nix-TB (N=109)		
	Discontinuation of Linezolid n (%)	Linezolid Dose Reduction n (%)	Linezolid Dose Interruption n (%)
Patients with change in study treatment due to AE	28 (25.7%)[a]	43 (39.4%)	48 (44.0%)
Preferred term			
Peripheral sensory neuropathy	22 (20.2%)	27 (24.8%)	25 (22.9%)
Neuropathy peripheral	3 (2.8%)	3 (2.8%)	6 (5.5%)
Anaemia	2 (1.8%)	13 (11.9%)	16 (14.7%)
Hypoglycaemia	1 (0.9%)	1 (0.9%)	0
Multiple organ dysfunction syndrome	1 (0.9%)	1 (0.9%)	0
Pancreatitis haemorrhagic	1 (0.9%)	1 (0.9%)	0
Upper gastrointestinal haemorrhage	1 (0.9%)	1 (0.9%)	0
Optic Neuropathy	1 (0.9%)	1 (0.9%)	1 (0.9%)
Rash	1 (0.9%)	1 (0.9%)	1 (0.9%)
Neutropenia	0	1 (0.9%)	3 (2.8%)
Thrombocytopenia	0	1 (0.9%)	2 (1.8%)
Visual acuity reduced	0	0	2 (1.8%)
Abdominal discomfort	0	0	1 (0.9%)
Blood lactic acid increased	0	0	1 (0.9%)
Gamma-glutamyltransferase increased	0	0	1 (0.9%)
Gastroenteritis viral	0	0	1 (0.9%)
Haemoptysis	0	0	1 (0.9%)
Hyperlactacidaemia	0	0	1 (0.9%)
Hyperlipasaemia	0	0	1 (0.9%)
Hypomagnesaemia	0	0	1 (0.9%)
Lactic acidosis	0	0	1 (0.9%)
Nausea	0	0	1 (0.9%)
Vomiting	0	0	1 (0.9%)

a. Primary reason for change in study treatment
AE=adverse event; SAE=serious adverse event

7.4.3 Serious Adverse Events

Nineteen patients (17.4%) in Nix-TB reported at least 1 SAE (Table 32). The most frequently reported SAEs were pneumonia (2.8%) and pulmonary TB (2.8%), related to the patients' underlying disease. Other more commonly reported terms were sepsis (1.8%), hypoglycemia (1.8%), and anemia (1.8%). All other SAEs were reported by 1 patient each.

Table 32: Serious Adverse Events (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any SAE	**19 (17.4%)**
Preferred term	
Pneumonia	**3 (2.8%)**
Pulmonary tuberculosis	**3 (2.8%)**
Anaemia	**2 (1.8%)**
Hypoglycaemia	**2 (1.8%)**
Sepsis	**2 (1.8%)**
Abdominal pain upper	**1 (0.9%)**
Abnormal loss of weight	**1 (0.9%)**
Asthma	**1 (0.9%)**
Depression suicidal	**1 (0.9%)**
Disseminated tuberculosis	**1 (0.9%)**
Dyspnoea	**1 (0.9%)**
Generalised anxiety disorder	**1 (0.9%)**
Generalised tonic-clonic seizure	**1 (0.9%)**
Haematemesis	**1 (0.9%)**
Haemoptysis	**1 (0.9%)**
Lactic acidosis	**1 (0.9%)**
Multiple organ dysfunction syndrome	**1 (0.9%)**
Neutropenia	**1 (0.9%)**
Optic neuritis	**1 (0.9%)**
Optic neuropathy	**1 (0.9%)**
Pancreatitis	**1 (0.9%)**
Pancreatitis haemorrhagic	**1 (0.9%)**
Pneumothorax spontaneous	**1 (0.9%)**
Seizure	**1 (0.9%)**
Septic shock	**1 (0.9%)**
Syncope	**1 (0.9%)**
Transaminases increased	**1 (0.9%)**
Tuberculoma of central nervous system	**1 (0.9%)**
Upper gastrointestinal haemorrhage	**1 (0.9%)**

SAE=serious adverse event

7.4.4 Grade 3 or 4 Adverse Events

Maximum AE Grades of 3 and 4 were reported in 37.6% and 15.6% of patients, respectively (Table 33). Many of the most frequently reported Grade 3 or 4 events are those evaluated as AESIs (Section 7.6).

Table 33: Grade 3 or 4 Adverse Events Occurring in ≥2 Patients (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Grade 3 AE	**41 (37.6%)**
Preferred term	
Peripheral sensory neuropathy	**19 (17.4%)**
Transaminases increased	**6 (5.5%)**
Amylase increased	**6 (5.5%)**
Gamma-glutamyltransferase increased	**5 (4.6%)**
Lipase increased	**4 (3.7%)**
Anaemia	**4 (3.7%)**
Neuropathy peripheral	**3 (2.8%)**
Neutropenia	**3 (2.8%)**
Hyperamylasemia	**3 (2.8%)**
Bone marrow failure	**2 (1.8%)**
Alanine aminotransferase increased	**2 (1.8%)**
Abdominal pain upper	**2 (1.8%)**
Patients with any Grade 4 AE	**17 (15.6%)**
Preferred term	
Hypoglycemia	**3 (2.8%)**
Upper gastrointestinal hemorrhage	**2 (1.8%)**
Pneumonia	**2 (1.8%)**
Pulmonary tuberculosis	**2 (1.8%)**
Sepsis	**2 (1.8%)**
Anemia	**2 (1.8%)**
Gamma-glutamyltransferase increased	**2 (1.8%)**

AE=adverse event

7.5 Deaths

To date, 15 out of 1,507 individuals receiving pretomanid or other therapies (1.0%) in the clinical development program have died due to treatment-emergent AEs. This includes 6 out of 109 patients (7.3%) in Nix-TB, 1 out of 99 patients (1.0%) in the MDR-TB pooled dataset, 7 out of 656 pretomanid-treated patients (1.1%) in the DS-TB pooled dataset, and 1 out of 229 HRZE-treated patients (0.4%) in the DS-TB pooled dataset.

In Nix-TB, in addition to the 6 deaths that occurred during study treatment (Patients 1–6), there were 2 deaths that occurred during follow-up after the end of study treatment (Patient 7 and Patient 8; Table 34). An overview of each death is provided below; detailed patient narratives are provided in Appendix 10.2.1 (Patient 1–7) and Appendix 10.2.2 (Patient 8).

Table 34: Deaths (Nix-TB)

Patient	Day of Death	Fatal SAEs (Preferred Term)	Relationship to Study Drug According to Investigator	HIV Status
1	Day 35	Pulmonary tuberculosis Disseminated tuberculosis	Not related	Positive
2	Day 51	Upper gastrointestinal haemorrhage	Possibly related	Negative
3	Day 55	Pulmonary tuberculosis	Not related	Positive
4	Day 53	Pancreatitis haemorrhagic Multiple organ dysfunction syndrome	Possibly related	Positive
5	Day 93	Sepsis Pneumonia	Not related	Negative
6	Day 76	Septic shock Pneumonia	Unlikely related	Negative
7	Day 369 (185 days after EOT)	Natural causes	Not related	Positive
8	Day 486 (303 days after EOT)	Thrombotic thrombocytopenic purpura Sepsis Dry gangrene Peripheral vascular disorder Infected skin ulcer	Not related	Positive

EOT=end of treatment; HIV=human immunodeficiency virus; SAE=serious adverse event

Patient 1 was a 34-year-old male with XDR-TB and HIV co-infection who had a BMI of 14.6 kg/m^2, an albumin of 27 g/L (<lower limit of reference range = 35 g/L), a CD4 count of 259 cells/µL and a suppressed HIV viral load of <20 copies/mL on Screening. The patient developed acute worsening epigastric pain and died 35 days after beginning investigational treatment. The autopsy report noted the cause of death was severe pulmonary and disseminated TB and emaciation. The Investigator and the Sponsor considered the events of pulmonary TB and disseminated TB not related to trial therapy, but caused by the disease under study.

Patient 2 was a 20-year-old female with XDR-TB who was HIV negative and had a BMI of 15.4 kg/m^2 and an albumin of 30 g/L (<lower limit of reference range = 35 g/L) on Screening. On Trial Day 47, the patient complained of dyspepsia, weakness, and vomiting. She died on Day 51 of the trial. Autopsy found severe emaciation with markedly destroyed and contracted upper lung lobes, and the esophagus was filled with "coffee grounds," with loss of surface epithelium distally, and invasive candida with an acute inflammatory infiltrate into the wall and ulcerative esophagitis. The Investigator reported that the event of upper gastrointestinal bleeding, as a cause of death, was possibly related to trial treatment, and that the upper gastrointestinal bleeding was probably linked to the ulcerated esophagitis with invasive candida. The Sponsor considered the event unlikely related to the trial treatment since the autopsy result did not support marrow suppression.

Patient 3 was a 31-year-old female patient with XDR-TB and HIV co-infection who had a low BMI of 12.4 kg/m^2, a low albumin of 25 g/L (<lower limit of reference range = 35 g/L), and CD4 count of 328 cells/µL on Screening. After treatment for a superimposed lower respiratory tract infection, she died on Trial Day 55. Autopsy found purulent secretions in the larynx, obliteration of both pleural cavities by adhesions, a large cavity on the right side, and striking mesenteric involvement of lymph nodes by TB, multiple small caseous foci in the spleen, fibrocaseous nodules adherent to the liver capsule, and a hemorrhagic head of the pancreas. The final cause of death was reported as respiratory failure due to severe pulmonary TB. The Investigator and Sponsor considered the event of anemia was probably or possibly related to the trial treatment, respectively, and that the acute severe worsening of the pulmonary TB was not related to the trial treatment.

Patient 4 was a 35-year-old male who had XDR-TB and HIV co-infection, a BMI of 20.8 kg/m^2, and a CD4 count of 168 cells/µL. On Trial Day 51, he reported "coffee-ground" vomiting and severe back pain overnight and developed multi-organ failure and died on Trial Day 53. Autopsy found micronodular cirrhosis associated with hepatitis B virus; microvesicular steatosis and intrahepatic cholestasis; acute hemorrhagic pancreatitis and hemorrhage into mesentery; renal tubules showing evidence of hyperkalemia and urate uropathy; fibrocaseous TB involving predominately left lung, hilar region of right lung, hilar lymph nodes, spleen, and mesenteric lymph nodes; and obliteration of the left pleural cavity and splenic and diaphragmatic adhesions; and the terminal ileum with multiple fibrosis adhesions to mesenteric nodes-subacute obstructions. The Investigator reported that there was a reasonable possibility that the events of acute hemorrhagic pancreatitis, multi-organ failure, and hypoglycemia were possibly related to the trial drug regimen. The Sponsor agreed that the events of acute hemorrhagic pancreatitis and multi-organ failure were possibly related to the trial treatment.

Patient 5 was a 29-year-old female patient with non-responsive MDR-TB who had a BMI of 15.6 kg/m^2 at Screening. On Day 74, she left the hospital and failed to return until Day 83. While at home, she was without trial medication for 8 days, used methamphetamines daily, and developed signs and symptoms of a non-serious community-acquired pneumonia. She was readmitted, developed respiratory distress and died on Trial Day 93. In the Investigator's opinion, the cause of death was probably due to worsening of pneumonia. Transaminitis and sepsis were also reported as fatal. The Investigator and Sponsor considered the sepsis and pneumonia as not related to study drug. The Sponsor assessed the event of transaminitis as unlikely related to the study drug regimen as she developed transaminitis 9 days after trial drug administration was interrupted and alternate causes included methamphetamine abuse, concomitant paracetamol, concurrent infection, respiratory distress, and poor peripheral perfusion.

Patient 6 was a 27-year-old female with XDR-TB, a history of chronic obstructive pulmonary disease (COPD) and ongoing fever. She was HIV negative and had a BMI of 17.1 kg/m^2. On Trial Day 73 she presented to the study center complaining of chest pain (pleuritic and muscular in nature), worsening of her cough, tightness of the chest, and generally feeling unwell. The patient was treated with fluids and antibiotics. She developed worsening pneumonia and septic

shock (secondary to pneumonia) and died on Trial Day 76. Autopsy showed distal destruction of bronchi on the right side and an extensive granulomatous inflammation with central caseation in the right lung, but no viable acid-fast bacilli were seen. The Investigator and Sponsor assessed the events and death as not related to the study drug regimen.

Patient 7 was a 39-year male patient with XDR-TB, HIV co-infection, and a CD4 count of 245 cells/µL. He had culture conversion at Week 4, completed trial treatment, and remained culture negative through his Month 3 post-treatment visit, which was the last time he was seen at the study center. His closest family member reported that he had left home during the month of that visit and could not be contacted. His family was notified about his death that occurred 3 months later. He died at home, and the death certificate stated case of death as natural causes (Note: In South Africa, death due to natural cause means no violence was involved). The Sponsor considered this patient to have died of causes unrelated to the study drug regimen and unrelated to TB.

Patient 8 was a 55-year-old male with XDR-TB and HIV co-infection. At Screening, he had a CD4 count of 67 cells/µL and a viral load of 87 copies/mL. He completed 26 weeks of investigational therapy with negative sputum cultures and relapsed at Month 3 following completion of therapy. After withdrawal from the trial due to relapse, the patient died due to a presumptive diagnosis of thrombotic thrombocytopenic purpura secondary to sepsis, caused by gangrene from peripheral vascular disease, which was considered unrelated to trial treatment regimen by the Investigator and the Sponsor.

7.6 Adverse Events of Special Interest

AESIs for any of the 3 drugs in the BPaL regimen are summarized in Table 35. These were specified in the protocol and identified based on the nonclinical and clinical studies for pretomanid, the product label and investigator brochure for bedaquiline, the product label for linezolid, and literature reports of linezolid long-term toxicity:

- General toxicology and nonclinical safety studies have evaluated the effects of pretomanid on the central nervous, respiratory, and cardiovascular systems and identified target organs of toxicity with adequate margins of safety relative to the expected exposure for the 200 mg/day dose in humans. Based on findings from some of these nonclinical studies, ocular and central nervous system effects (ie, cataracts and convulsions), as well as the potential for testicular effects, were identified for clinical monitoring in clinical studies.
- Bedaquiline labeling contains a black box warning for increased risk of death – as observed in one placebo-controlled trial – and for QT prolongation (Janssen 2018). It also carries a risk of hepatotoxicity; in 2 placebo-controlled studies, aminotransferase elevations ≥3 × ULN were seen in 11/102 (10.8%) bedaquiline-treated patients versus 6/105 (5.7%) placebo patients. Pancreatitis and muscle degeneration were identified in nonclinical toxicology studies.
- Risks of concern identified in linezolid labeling include the following:

- Myelosuppression, with the need to monitor complete blood counts weekly (for the maximum duration of 28 days of drug administration indicated in the label)
- Peripheral and optic neuropathy, which has been seen with treatment extending beyond 28 days
- Lactic acidosis and convulsions

Table 35: Adverse Events of Special Interest Prospectively Identified for Each Component of the Regimen

AESIs	Pretomanid	Bedaquiline	Linezolid
Lens disorders	X[a]		
Testicular toxicity	X[a]		
Convulsions	X[b]		X
ECG QT prolongation	X[c]	X	
Hepatic toxicity	X	X	
Myopathy/rhabdomyolysis		X[d]	
Pancreas-related events		X[d]	
Peripheral neuropathy			X
Optic nerve disorders			X
Myelosuppression			X
Lactic acidosis			X

a. Adverse effects were observed in toxicology studies in rodents.
b. Adverse effects were observed in toxicology studies in rodents and monkeys at high doses.
c. QT effects were observed in vitro and in monkeys.
d. Adverse effects were observed in animal toxicology studies.
AESI=adverse event of special interest

As of 26 March 2018, the majority of AESIs described below had resolved or were resolving, and the proportion of events with outcomes of unresolved or unknown was as expected for an ongoing study with 10 patients (9.2%) completing study treatment at the time of the data cut-off date.

7.6.1 Lens Disorders – of Interest for Pretomanid

In the nonclinical program, cataract development was observed in rats treated with pretomanid 300 mg/kg/day for 3 months and 100 mg/kg/day for 6 months. In a 3-month monkey toxicity study, no ocular abnormalities were detected in any animal during the pretreatment or terminal examination time points. At the end of the 13-week recovery period, however, 2 monkeys treated at high doses (450/300 mg/kg) of pretomanid had bilateral cataracts. The follow-up studies in monkeys treated with pretomanid for 3 and 9 months that involved careful lens examination showed no cataract development.

Because of the earlier rat findings, cataracts and lens disorders were assessed in Nix-TB using slit-lamp examinations with AREDS2 scoring of lens opacities. A standardized MedDRA query (SMQ) for lens disorders was also conducted.

Slit-Lamp Examinations

In the slit-lamp examinations, eyes were scored using the AREDS2 instrument for 3 anatomic areas of the lens in 0.5-point increments on a 0.0 to 4.0 scale, with 0.0 denoting no lens opacity and scores greater than that denoting the presence of lens opacity. Results showed score increases (worsening) of ≥1 from baseline for cortical, nuclear, and posterior subcapsular opacity in 3 (1.7%), 2 (1.1%), and 6 (3.4%) eyes, respectively. Conversely, score decreases (improvement) of ≥1 from baseline were observed in 4 (2.3%), 13 (7.4%), and 0 (0%) eyes, respectively.

An AREDS2 score increase of ≥2 from baseline was observed in 1 patient. The patient was a 50-year-old male who had baseline cortical, nuclear, and posterior subcapsular scores of 0, 1.5, and 0, respectively, in both eyes. At the end of treatment, a subsequent unscheduled visit, and the 3-month post-treatment follow-up, the patient's scores in both eyes were 2.5 (cortical), 0 (nuclear), and 0 (posterior subcapsular). The patient maintained normal distance visual acuity through 3 months following treatment and had a 1-line decrease in vision at the 24-month follow-up exam.

Slit-lamp examinations were also conducted in Studies NC-002, NC-005, and NC-006, which had treatment periods of 2 months, 2 months, and 4 to 6 months, respectively.

In Study NC-002, data were available for 111 eyes in 56 DS-TB patients treated with 100 mg pretomanid-moxifloxacin-pyrazinamide (PaMZ), 160 eyes in 80 DS-TB and MDR-TB patients treated with 200 mg PaMZ, and 108 eyes in 54 DS-TB patients treated with HRZE:

- A score increase of ≥1 from baseline was observed in 1 eye (0.6%; cortical) in the 200 mg PaMZ group, in 1 eye (0.9%; nuclear) in the 100 mg PaMZ group.
- No patient in Study NC-002 had a score decrease or a score increase of ≥2.

In Study NC-005, data were available for 115 eyes in 58 MDR-TB patients treated with bedaquiline-pretomanid-moxifloxacin-pyrazinamide (BPaMZ), 104 eyes in 52 DS-TB patients treated with bedaquiline-pretomanid-pyrazinamide (BPaZ), 104 eyes in 52 DS-TB patients treated with BPaZ using a bedaquiline loading dose, and 116 eyes in 58 DS-TB patients treated with HRZE:

- A score increase of ≥1 from baseline was observed in 1 eye (1.0%; cortical) in the BPaZ group (with no bedaquiline loading dose), and 2 eyes (1.7%; both posterior subcapsular) in the BPaMZ group.
- A score decrease of ≥1 from baseline was observed in 2 eyes (1.9%; both nuclear) in the BPaZ group (with no bedaquiline loading dose) and 3 eyes (2.6%; all cortical) in the BPaMZ group.
- No patient in Study NC-005 had a score change of ≥2.

In Study NC-006, data were available for 123 eyes in 62 DS-TB patients treated with 100 mg PaMZ for 4 months, 132 eyes in 66 DS-TB patients treated with 200 mg PaMZ for 4 months,

147 eyes in 74 DS-TB and MDR-TB patients treated with 200 mg PaMZ for 6 months, and 126 eyes in 63 DS-TB patients treated with HRZE for 6 months:

- A score increase of ≥1 from baseline was observed in 2 eyes (1.6%) in the 100 mg PaMZ group and 1 eye (0.8%) in the 4-month 200 mg PaMZ group (cortical); 3 eyes (2.3%) in the 4-month 200 mg PaMZ group and 4 eyes (2.7%) in the 6-month 200 mg PaMZ (nuclear); and 3 eyes (2.4%), 2 eyes (1.5%), 1 eye (0.7%), and 1 eye (0.8%) for 100 mg PaMZ, 4-month 200 mg PaMZ, 6-month 200 mg PaMZ, and HRZE groups, respectively (posterior subcapsular).
- A score decrease of ≥1 from baseline was observed in 2 eyes (1.6%) in the 100 mg PaMZ group and 3 eyes (2.0%) in the 6-month 200 mg PaMZ group (cortical); 2 eyes (1.6%) in the 100 mg PaMZ group, 1 eye (0.7%) in the 6-month 200 mg PaMZ group, and 2 eyes (1.6%) in the HRZE group (nuclear); and 2 eyes (1.6%), 2 eyes (1.5%), 3 eyes (2.0%), and 1 eye (0.8%) for 100 mg PaMZ, 4-month 200 mg PaMZ, 6-month 200 mg PaMZ, and HRZE control (posterior subcapsular), respectively.
- Three patients in Study NC-006 had an increase of ≥2 in AREDS2 score, and 1 patient had a score decrease of ≥2 from baseline.

Overall, the findings of small percentages of both increases and decreases in AREDS2 scores suggest normal variation in the raters and/or age-related changes, with no evidence for a clinically meaningful adverse effect of pretomanid on the potential for cataract formation.

Standardized MedDRA Query

In Nix-TB, 14 patients (12.8%) reported AESIs related to lens disorders, with the most frequently reported (5.5% of patients) preferred term being visual acuity reduced (Table 36). No event of "cataract" was reported. One patient reported a preferred term specific to the lens of the eye, which was lens disorder (verbatim term AREDS [age-related eye disease] lens grading worse). The onset of lens disorders events was greatest during the time period of >8 to 26 weeks (8.4%) compared with ≤2 weeks (1.8%) and >2 to 8 weeks (0%).

Table 36: Adverse Events in Standardized MedDRA Query for Lens Disorders (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Lens Disorders AESI	**14 (12.8%)**
Preferred term	
Visual acuity reduced	**6 (5.5%)**
Vision blurred	**4 (3.7%)**
Visual impairment	**3 (2.8%)**
Lens disorder	**1 (0.9%)**

AESI=adverse event of special interest

All lens disorder AESIs were either Grade 1 or Grade 2 in severity (Appendix Figure 14), and no event was considered serious. Three events resulted in interruption of study drug, including visual acuity reduced in 2 patients (linezolid only interrupted) and visual impairment in a third patient (entire BPaL regimen interrupted). No lens disorder event led to discontinuation of the treatment regimen or a reduction in study drug dose.

The incidence of lens disorder AESIs in Nix-TB (12.8%) was greater than that in pretomanid-treated patients in the DS-TB pooled dataset (0.9%), which included studies with generally shorter durations of pretomanid exposure (up to 2 months for DS-TB patients vs up to 6 months for Nix-TB patients). However, within the DS-TB dataset, the incidence of these events was greater in HRZE-treated patients than in pretomanid-treated patients (5.2% versus 0.9%). Further, no patient in the MDR-TB or pretomanid-alone pooled datasets reported a lens disorder AESI. The Nix-TB findings for lens disorder events also showed no findings to support a drug-related lens disorder safety signal.

7.6.2 Testicular Toxicity – of Interest for Pretomanid

Testicular toxicity, including seminiferous tubule degeneration, germ cell depletion, and infertility, was observed in rodents (mice and rats) treated with pretomanid, but not in monkeys. Consequently, the potential for such toxicity in humans was explored using the SMQ for fertility.

No AEs in the SMQ for fertility were identified in Nix-TB.

The potential for testicular toxicity was examined in Studies NC-002, NC-005, and NC-006. These studies provided an assessment of serum hormone levels relevant to male reproductive health, including follicle stimulating hormone (NC-002, NC-005, NC-006), luteinizing hormone (NC-002, NC-006), inhibin B (NC-006), and testosterone (NC-002, NC-006). As a whole, these hormone assessments demonstrated an improvement in the underlying hypogonadism, as reflected by increases in the testosterone and inhibin B levels in all treatment arms, which is consistent with improvements in the underlying disease state. In addition, the study comparing two different dose levels of pretomanid (NC-006; 100 mg versus 200 mg) showed no adverse serum hormone effects resulting from doubling the exposure. In conclusion, none of the changes observed suggested testicular damage.

7.6.3 Convulsions – of Interest for Pretomanid and Linezolid

CNS-related effects including convulsions were observed in rodents and monkeys treated with high doses of pretomanid. At the lowest no-effect level, plasma exposure to pretomanid was at least twice that of the human therapeutic dose of 200 mg/day.

The SMQ for convulsions identified 2 patients (1.8%) who experienced AEs in Nix-TB: one with generalized tonic-clonic seizure and the other with seizure. Both events were serious and Grade 3 in severity, and both resolved:

- One patient had a prior history of seizures and experienced the SAE of generalized tonic-clonic seizure 4 weeks after enrollment. The BPaL regimen was interrupted for

7 days for the event of generalized tonic-clonic seizure, and the patient resumed and completed therapy.

- One patient, with HIV co-infection and XDR-TB, experienced a seizure during the week following completion of study treatment. The patient had another seizure approximately 2 months later and underwent surgical removal of a tuberculoma of the right temporal lobe on Day 380, which was positive for molecular and microscopic evidence of *M. tb*, although the tissue was culture negative. The patient remained seizure free following the surgery.

Neither event of seizure was considered related to study drug.

7.6.4 QT Interval Prolongation – of Interest for Pretomanid and Bedaquiline

In vitro cardiovascular studies of pretomanid demonstrated inhibition of hERG with an IC_{50} of approximately ≥17 µM (≥6.1 µg/mL as free drug concentration), which is greater than or equal to a total plasma concentration of 45 µg/mL (pretomanid plasma protein binding 86.4%). In a monkey cardiovascular study, QT prolongation was observed with 150 and 450 mg/kg doses of pretomanid with 8-hour plasma concentrations of 11.2 and 14 µg/mL, respectively. There was no evidence of an interactive effect on QT prolongation when pretomanid was administered with bedaquiline to dogs or with moxifloxacin to monkeys.

Thorough QT Study

In a formal QT study of pretomanid, there was little or no effect of pretomanid at doses of 400 mg (twice the recommended dose in BPaL) or 1000 mg (5 times the recommended dose in BPaL) on ΔΔQTcF. Assay sensitivity was established since the least-squares (LS) mean placebo-adjusted change from baseline in QT with individual corrections (ΔΔQTcI) value for the 400 mg dose of moxifloxacin over 1 to 4 hours post dose was 10.7 msec with a lower confidence limit of 9.5 msec.

The maximum LS mean ΔΔQTcI value for the 400 mg dose of pretomanid administered alone was 2.7 msec, and the maximum LS mean ΔΔQTcI value for the 1000 mg dose of pretomanid was 4.4 msec. The upper limit of the 90% CI did not exceed 4.4 msec for the 400 mg dose or 6.1 msec for the 1000 mg dose, and both were well below the recognized threshold for concern of 10 msec.

Standardized MedDRA Query

In Nix-TB, the SMQ for QT prolongation, 7 patients (6.4%) experienced AESIs which consisted of the preferred terms electrocardiogram QT prolonged (6 patients) and syncope (1 patient). These events had an onset within >2 to 8 weeks (3.7% of patients) and >8 to 26 weeks (2.8%).

Five events were Grade 1 in severity, 1 event was Grade 2, and 1 event (syncope) was Grade 3 and also considered serious. This patient was a 40-year old male with XDR-TB and HIV co-infection who was hospitalized for syncope on Day 155. The patient was standing in a queue when he felt dizzy and fell over; no seizure activity was witnessed, and the patient was noted to

have bleeding from his right ear on transfer to the hospital. Electrocardiogram results at 5 of 7 visits prior to the event of syncope showed low QRS voltage in the limb leads; one reading was normal and another showed nonspecific ST and T wave abnormality. The patient had no QTcB or QTcF value ≥450 msec and no treatment-emergent increase of ≥50 msec in either parameter at any assessed time point. The patient had a history of hypotension and on Screening had a blood pressure of 92/62 mmHg and his heart rate was 94 beats per minute. The event of syncope was considered not related to study drug. See Appendix 10.2.4 for a patient narrative.

No event in the SMQ for QT prolongation resulted in a change in study drug dosing.

7.6.5 Hepatic Toxicity – of Interest for Pretomanid and Bedaquiline

Standardized MedDRA Query

In Study Nix-TB, 40 patients (36.7% of the safety population) reported at least 1 AESI in the SMQ for hepatic disorders (Table 37). The most frequently reported event was gamma-glutamyltransferase increased (16.5%). Of note, 28.6% patients with HIV co-infection had this AESI versus 3.8% of patients without HIV co-infection; this finding was also observed in the broader clinical program including Phase 2 and 3 studies in MDR-TB and DS-TB. The onset of hepatic toxicity AESIs was generally spread across the 26-week treatment period: 12.8%, 14.7%, and 16.8% of patients reported events at ≤2 weeks, >2 to 8 weeks, and >8 to 26 weeks, respectively.

Table 37: Adverse Events in Standardized MedDRA Query for Hepatic Disorders (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Hepatic Disorders AESI	**40 (36.7%)**
Preferred term	
Gamma-glutamyltransferase increased	**18 (16.5%)**
Transaminases increased	**12 (11.0%)**
Alanine aminotransferase increased	**10 (9.2%)**
Aspartate aminotransferase increased	**8 (7.3%)**
Blood alkaline phosphatase increased	**3 (2.8%)**
Drug-induced liver injury	**2 (1.8%)**
Hepatic enzyme increased	**2 (1.8%)**
Hyperbilirubinaemia	**2 (1.8%)**
Hepatic function abnormal	**1 (0.9%)**
Hepatomegaly	**1 (0.9%)**
Jaundice	**1 (0.9%)**
Liver function test increased	**1 (0.9%)**

AESI=adverse event of special interest

The majority of the 65 events identified in the SMQ for hepatic disorders were Grade 1 (20 events) or Grade 2 (25 events); 16 events were Grade 3, and 4 events were Grade 4 (Appendix Figure 14). One hepatic disorder event, transaminases increased, was considered serious; this event was associated with the fatal AEs of sepsis and pneumonia and was considered not related to study drug (Appendix 10.2.1, Patient 5).

The BPaL regimen was interrupted in 8 patients because of hepatic AESIs, which included transaminases increased (5 patients), drug-induced liver injury (2 patients), and hepatic enzyme increased (1 patient). In all 8 patients, the events resolved, and study drug was restarted allowing for completion of the full intended course of therapy. No hepatic disorder AESI led to discontinuation of the treatment regimen.

Across the clinical program, the incidence of hepatic disorder AESIs was greater in Nix-TB (36.7%) than the MDR-TB pooled dataset (14.1%), the DS-TB pooled dataset (pretomanid-treated patients, 18.3%; HRZE-treated patients, 17.9%), and the pretomanid-alone dataset (0.8%). Factors that may influence these results are the severity of the underlying illness, presence of coexisting disease (eg, viral hepatitis infection), number and types of concomitant medications (eg, ART drugs for HIV-positive patients), and alcohol use patterns (FDA 2009). In addition, the mean duration of treatment exposure in Nix-TB (162.6 days, not including interruptions) was longer than the mean duration of treatment with pretomanid in the MDR-TB and DS-TB datasets (62.0 days and 62.5 days, respectively) and the mean duration of treatment with HRZE in the DS-TB dataset (80.0 days).

Laboratory Parameters

Increases in ALT and AST to >3 and ≤5 times the upper limit of normal (ULN) were observed in 6 (5.5%) and 7 patients (6.4%), respectively, and increases in these parameters to >5 and ≤8 times ULN were observed in 5 (4.6%), and 2 patients (1.8%), respectively. An increase in ALT and AST to >8 times ULN was observed in 1 patient (0.9%) for each parameter. Total bilirubin increases to >2 times ULN occurred in 2 patients (1.8%; Table 38). For the majority of patients with treatment-emergent ALT, AST, ALP, and gamma-glutamyltransferase (GGT) abnormalities, the maximum toxicity of any parameter was Grade 1 or 2. Treatment-emergent Grade 3 values for ALT, AST, GGT, ALP, and total bilirubin were reported in 11 (10.1%), 9 (8.3%), 16 (14.7%), 3 (2.8%), and 0 patients, respectively, and treatment-emergent Grade 4 values were reported in 1 (0.9%), 1 (0.9%), 5 (4.6%), 0, and 3 (2.8%) patients, respectively.

Two patients in Nix-TB met laboratory criteria for potential Hy's Law cases:

- The first patient was a 36-year-old female with XDR-TB. On Trial Day 29 she had recurring epigastric pain and weakness, which was reported as an SAE of worsening epigastric pain. This was treated with intravenous hydration and the trial drug regimen was interrupted. Between Week 7 and Week 8 the patient admitted to consuming alcohol, and during Week 8 she had an unremarkable abdominal ultrasound. The study regimen was resumed but then stopped again during Week 10 due to liver enzyme increase. Values for ALT, AST, ALP, and GGT reached peak levels during Week 11 (255 U/L,

329 U/L, 330 IU/L, and 357 U/L, respectively; total bilirubin 56 µmol/L). The values for ALT, AST, and bilirubin rapidly decreased to Grade 1 during Weeks 12 to 13, and the trial drug regimen was resumed. The liver enzyme elevations were observed in the context of alcohol consumption; further, concurrent elevations in GGT and ALP suggest possible cholestasis or hepatic obstruction rather than a primary drug-induced liver injury. Importantly, the hepatic chemistry abnormalities resolved, and the patient completed study drug administration without further dosing interruptions. The abdominal pain resolved during the fourth month after enrollment in the trial. The Investigator considered the event of worsening epigastric pain as possibly related to the trial drug regimen. See Appendix 10.2.4 for a patient narrative.

- The second patient was a 25-year-old male with XDR-TB who had ALT levels increase from a normal value of 19 U/L at baseline to a peak of Grade 3 at 252 U/L during Week 8 and then rapidly decreased to Grade 1 at 50 U/L during Week 12 and a normal value of 41 U/L during Week 20, where it remained within the normal rage through follow-up. The patient's AST levels progressed in a similar way, and total bilirubin rose from a normal value of 21 µmol/L at Week 6 to a Grade 4 value of 46 µmol/L at Week 8 and then back to a normal value of 15 µmol/L at Week 12. ALP was elevated at baseline (Grade 1 at 144 IU/L) and rose to a peak of 237 IU/L at Week 8; values returned to 140 IU/L by Week 12 and within the normal range by Week 16. During this period, the patient had AEs of nausea, intermittent vomiting, elevated urine microalbumin, and anemia. The trial drug regimen was interrupted in Week 8 and resumed in Week 11 and continued to completion with no further clinically significant abnormalities of hepatic chemistry values. See Appendix 10.2.4 for a patient narrative.

The laboratory results across the pretomanid clinical program indicate that hepatotoxicity occurred in all treatment groups but in a higher proportion of patients in Nix-TB, patients with MDR-TB, patients treated with HRZE compared with patients treated with pretomanid alone (Table 38), although studies using pretomanid alone were only 2 weeks in duration. In addition to the 2 cases meeting the laboratory criteria for Hy's Law cases noted above, 7 other potential Hy's Law cases developed in the pretomanid clinical program (4 in pretomanid-treated patients and 3 in HRZE-treated patients).

Appendix 10.3.2 provides additional information based on an analyses of liver-related laboratory values for all 1,168 individuals who were exposed to pretomanid in the clinical development program.

Table 38: Elevated Liver-Related Laboratory (Nix-TB and other Safety Datasets)

	Phase 1 Pool		DS-TB Pools				MDR-TB Pool	Nix-TB
	All Pretomanid N=289 n (%)	Placebo N=35 n (%)	Pretomanid -Alone N=122 n (%)	HRZE N=16 n (%)	All Pretomanid N=656 n (%)	HRZE N=229 n (%)	All Pretomanid N=99 n (%)	BPaL N=109 n (%)
ALT >5 × ULN	0	0	1 (0.8%)	0	45 (6.9%)	10 (4.4%)	6 (6.1%)	6 (5.5%)
AST >5 × ULN	1 (0.3%)	0	0	0	42 (6.4%)	10 (4.4%)	5 (5.1%)	3 (2.8%)
Total bilirubin >2 × ULN	1 (0.3%)	0	0	0	4 (0.6%)	3 (1.3%)	1 (1.0%)	2 (1.8%)
ALT/AST >3 × ULN and total bilirubin >2 × ULN	0	0	0	0	3 (0.5%)[a]	3 (1.3%)[a]	1 (1.0%)	2 (1.8%)

a. 2 additional patients (1 all pretomanid and 1 HRZE) met potential Hy's law criteria based on outside laboratory data that were collected in patient narratives and not recorded in the clinical database.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BPaL=bedaquiline-pretomanid-linezolid; DS=drug-susceptible; HRZE=isoniazid-rifampicin-pyrazinamide-ethambutol; TB=tuberculosis; ULN=upper limit of normal

The cases of liver enzyme elevations in the pretomanid clinical program are confounded by potential hepatotoxicity related to the non-pretomanid components in the regimens studied. Notably, pyrazinamide and bedaquiline were used with pretomanid in several of the regimens in the MDR-TB and DS-TB pooled datasets; both of these drugs have been associated with hepatotoxicity. Factors other than study drugs may have also influenced the observed patterns for hepatic toxicity in the clinical program, including the presence of coexisting and often serious disease, the number and types of concomitant medications, including ART drugs, and alcohol consumption. An additional confounder is the duration of treatment in the different studies, with the longest in Nix-TB.

In Nix-TB, the BPaL regimen was not associated with any sustained hepatic abnormalities that required permanent discontinuation of the therapy. In all cases, liver abnormalities returned to acceptable levels after the regimen was stopped. Thus, it appears that hepatotoxicity in the BPaL regimen is generally reversible with appropriate monitoring and interruption of dosing.

7.6.6 Rhabdomyolysis/Myopathy – of Interest for Bedaquiline

Eleven patients (10.1%) experienced at least 1 AESI in the modified SMQ for rhabdomyolysis/myopathy (Table 39). The most frequently occurring events in this modified SMQ were myalgia (5.5% of patients) and blood creatine phosphokinase increased (4.6%), with all other preferred terms (musculoskeletal pain and myalgia intercostal) reported in 1 patient

each. The onset of these types of events increased slightly over time: 2.8%, 3.7%, and 4.7% for ≤2 weeks, >2 to 8 weeks, and >8 to 26 weeks, respectively.

Table 39: Adverse Events in Modified Standardized MedDRA Query for Rhabdomyolysis/Myopathy (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Rhabdomyolysis/Myopathy AESI	**11 (10.1%)**
Preferred term	
Myalgia	**6 (5.5%)**
Blood creatine phosphokinase increased	**5 (4.6%)**
Musculoskeletal pain	**1 (0.9%)**
Myalgia intercostal	**1 (0.9%)**

AESI=adverse event of special interest

All events in the modified SMQ for rhabdomyolysis/myopathy except 1 were Grade 1 or Grade 2 in severity (Appendix Figure 14); the exception was a Grade 3 event of blood creatine phosphokinase increased. No AESIs in this modified SMQ were considered serious or resulted in a change in study drug dosing. None of the patients with events of blood creatine phosphokinase increased reported other events in this modified SMQ, such as musculoskeletal pain or myalgia.

7.6.7 Pancreas-Related Events – of Interest for Bedaquiline

Pancreas-related events were prespecified as AESIs due to findings in nonclinical toxicology studies of bedaquiline (Janssen 2018). Twenty-two patients (20.2%) experienced at least 1 AESI in the modified SMQ for pancreas-related events, the majority of which were laboratory abnormalities (Table 40). These events tended to occur early in treatment; 11.0%, 7.3%, and 4.7% of patients had onset in ≤2 weeks, >2 to 8 weeks, and >8 to 26 weeks of starting study treatment, respectively.

Table 40: Adverse Events in Modified Standardized MedDRA Query for Pancreas-Related Events (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Pancreas-Related Events AESI	**22 (20.2%)**
Preferred term	
Amylase increased	**9 (8.3%)**
Hyperamylasaemia	**8 (7.3%)**
Lipase increased	**5 (4.6%)**
Pancreatitis	**2 (1.8%)**
Hyperlipaseaemia	**1 (0.9%)**
Pancreatitis Haemorrhagic	**1 (0.9%)**

AESI=adverse event of special interest

Of the 28 events identified, 5 events were Grade 1, 6 events were Grade 2, 15 events were Grade 3, and 2 events were Grade 4 (Appendix Figure 14). The majority of Grade 3 and 4 events were associated with abnormalities in amylase or lipase. Two patients experienced events that were considered serious; the events were pancreatitis and pancreatitis hemorrhagic, both of which were considered by the Investigator to be possibly related to study drug. These SAEs are summarized below (patient narratives are provided in Appendix 10.2.4 and Appendix 10.2.1, Patient 4).

- The first patient was a 38-year-old HIV-positive female with XDR-TB and elevated screening amylase and lipase values of 189 U/L (normal range 28-100 U/L) and 85 U/L (normal range 13-60 U/L), respectively. The patient had no clinical symptoms and received a pancreatitis diagnosis based on an ultrasound report 64 days after the first dose of study drug. Her highest amylase and lipase values were 261 U/L and 129 U/L, respectively. Treatment with BPaL was interrupted because of the event but was resumed shortly thereafter, and the patient completed the course of study treatment without further interruptions or any symptoms suggestive of pancreatitis. During this period her lipase value decreased from 92 to 74 U/L. Given the baseline elevations in amylase, lipase, and hepatic enzymes, including GGT, the lack of symptoms suggestive of pancreatitis, and the reductions in lipase during the last 3 months of uninterrupted study drug treatment, the Sponsor considered it unlikely this patient had pancreatitis caused by the study drug regimen.
- The second patient was the same patient who died and who had hemorrhagic pancreatitis on autopsy. He is described as Patient 4 above in Section 7.5.

Four patients (including the patient with SAE of pancreatitis) had study regimen interrupted. An additional patient had the dose of linezolid reduced for an event of lipase increased.

7.6.8 Peripheral Neuropathy – of Interest for Linezolid

Peripheral neuropathy is a known clinical side effect associated with linezolid (Pfizer 2018). Eighty-seven patients (79.8%) in Study Nix-TB reported AESIs in the SMQ for peripheral neuropathy (Table 41). The most frequently reported (≥2% of patients) preferred terms were peripheral sensory neuropathy (68.8%), neuropathy peripheral (9.2%), paresthesia (4.6%), and hypoesthesia (2.8%). The incidence of onset of these events increased over time, with 4.6%, 21.1%, and 65.4% of patients reporting onset at ≤2 weeks, >2 to 8 weeks, and >8 to 26 weeks of treatment, respectively.

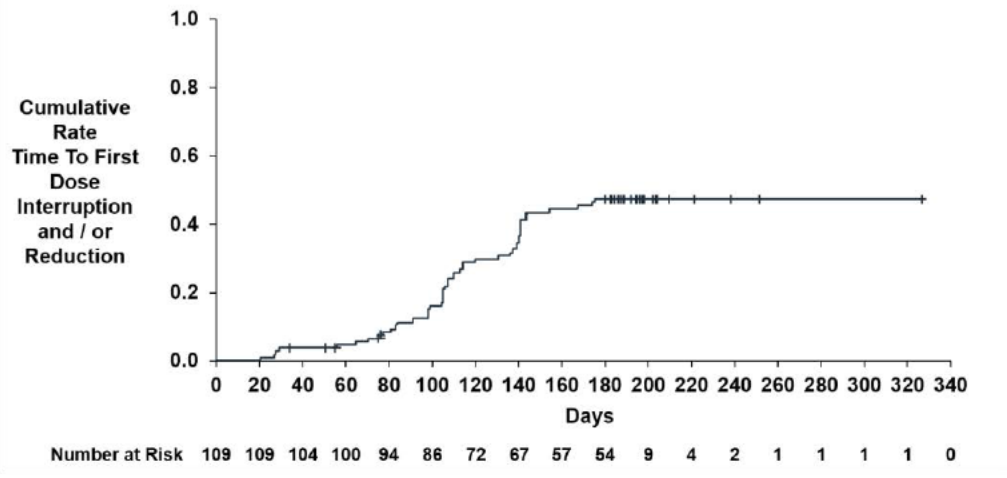
Table 41: Adverse Events in Standardized MedDRA Query for Peripheral Neuropathy (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Peripheral Neuropathy AESI	**87 (79.8%)**
Preferred term	
Peripheral sensory neuropathy	**75 (68.8%)**
Neuropathy peripheral	**10 (9.2%)**
Paraesthesia	**5 (4.6%)**
Hypoaesthesia	**3 (2.8%)**
Peripheral motor neuropathy	**2 (1.8%)**
Burning sensation	**1 (0.9%)**
Hyporeflexia	**1 (0.9%)**
Peripheral sensorimotor neuropathy	**1 (0.9%)**

AESI=adverse event of special interest

The majority of peripheral neuropathy AESIs (96 of 119 events) were either Grade 1 or Grade 2 in severity, 23 events were Grade 3, and no event was Grade 4 or considered serious (Appendix Figure 14). Linezolid dosing changes due to peripheral neuropathy AESIs were common (interrupted for 11 events, reduced for 29 events, and discontinued for 25 events). The rate of dose interruption/reduction showed the greatest increase from approximately Day 80 to approximately Day 140, consistent with the late onset pattern of these events (Figure 12). The entire BPaL regimen was interrupted for 1 event. Fifty-two of the reported events resulted in no change in study drug dosing.

Figure 12: Time to First Dose Interruption or Dose Reduction of Linezolid for Peripheral Neuropathy (Nix-TB)



7.6.9 Optic Nerve Disorder – of Interest for Linezolid

Optic neuropathy is also known clinical side effect associated with linezolid (Pfizer 2018). In Nix-TB, repeated evaluations of visual acuity and color vision were performed. If the Investigator detected a 2 or greater decrease in the lines read on the vision charts from baseline or a loss of 1 or more plates read accurately in color vision, they were to refer the patient to the study center ophthalmologist for further evaluation.

Thirteen patients (11.9%) experienced AESIs in the SMQ for optic nerve disorders (Table 42). The onset of these events was greatest during the period of >8 to 26 weeks: 0.9%, 0%, and 7.5% of patients for ≤2 weeks, >2 to 8 weeks, and >8 to 26 weeks, respectively.

Table 42: Adverse Events in Standardized MedDRA Query for Optic Nerve Disorders (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Optic Nerve Disorders AESI	**13 (11.9%)**
Preferred term	
Visual acuity reduced	**6 (5.5%)**
Visual impairment	**3 (2.8%)**
Amblyopia	**1 (0.9%)**
Optic disc hyperaemia	**1 (0.9%)**
Optic neuritis	**1 (0.9%)**
Optic neuropathy	**1 (0.9%)**
Papilloedema	**1 (0.9%)**

AESI=adverse event of special interest

All events except 1 were either Grade 1 or Grade 2 in severity; one Grade 4 event of optic neuritis was reported (Appendix Figure 14). Two patients experienced events that were considered serious. These SAEs were reported as Grade 4 optic neuritis and Grade 1 optic neuropathy; both were confirmed on retinal examination and started after 16 weeks of study treatment. In both cases, linezolid was discontinued, and the symptoms resolved, with visual acuity returning to baseline levels.

In addition to linezolid discontinuations in the 2 patients above, linezolid dosing was interrupted in 2 patients and reduced in another patient and the BPaL regimen was interrupted in 1 patient with optic nerve disorder AESIs. Of these 4 events resulting in drug interruption or dose reduction, 3 resolved and 1 (visual acuity reduced) had not resolved at the time of data cut-off on 26 March 2018.

7.6.10 Myelosuppression – of Interest for Linezolid

Myelosuppression is another known clinical side effect associated with linezolid (Pfizer 2018).

Standardized MedDRA Query

Events potentially indicative of hematopoietic cytopenias were reported in 51 patients (46.8%) (Table 43), with anemia being the most prevalent (36.7% of patients). The onset of hematopoietic cytopenia-type events was reported most frequently during the periods of >2 to 8 weeks and >8 to 26 weeks (24.8%, and 22.4% of patients, respectively) compared to ≤2 weeks (6.4%).

Table 43: Adverse Events in Standardized MedDRA Query for Hematopoietic Cytopenias (Nix-TB)

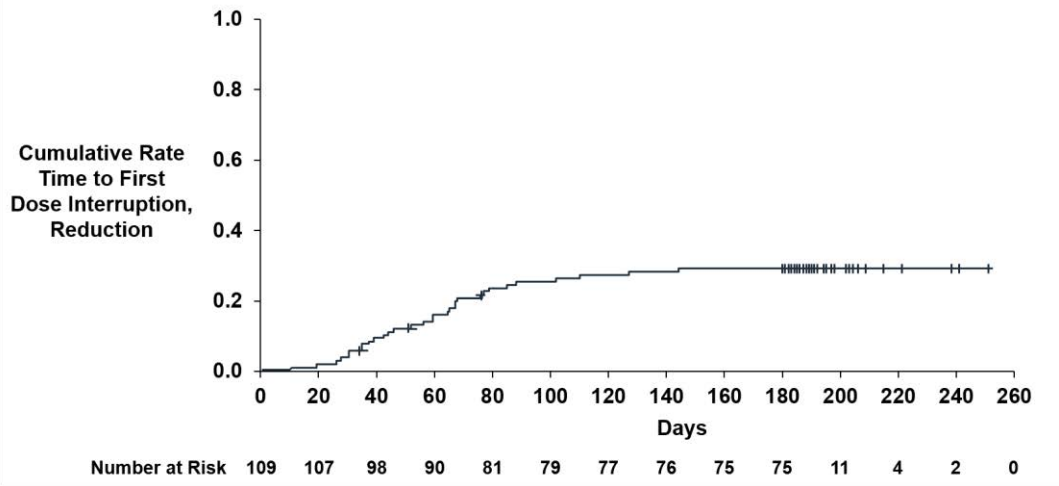
	Nix-TB N=109 n (%)
Patients with any Haematopoietic Cytopenias AESI	**51 (46.8%)**
Preferred term	
Anaemia	**40 (36.7%)**
Neutropenia	**9 (8.3%)**
Thrombocytopenia	**5 (4.6%)**
Bone marrow failure	**3 (2.8%)**
Leukopenia	**2 (1.8%)**
Bicytopenia	**1 (0.9%)**
Lymphopenia	**1 (0.9%)**
Pancytopenia	**1 (0.9%)**

AESI=adverse event of special interest

The majority of the 65 hematopoietic cytopenias AESIs were either Grade 1 (21 events) or Grade 2 (29 events) in severity; 12 events were Grade 3, and 3 events were Grade 4 (Appendix Figure 14). Three patients experienced events that were considered serious; the SAEs were neutropenia (1 patient) and anemia (2 patients), and all were considered related to study drug. For all 3 patients, study drug was interrupted (linezolid only in 1 patient and BPaL in 2 patients), and all 3 SAEs resolved.

Linezolid dosing was interrupted for 20 events, reduced for 13 events, and discontinued for 2 events and an additional 6 events resulted in study drug interruptions (BPaL regimen for 3, drug unspecified for 3). The rate of dose interruption and reduction was greatest from approximately Day 25 to approximately Day 80, consistent with the pattern of onset of these events (Figure 13). Twenty-four events resulted in no change in study drug dosing, and no patient withdrew from the study treatment regimen due to hematopoietic cytopenia.

Figure 13: Time to First Dose Interruption or Dose Reduction of Linezolid for Myelosuppression (Nix-TB)



Hematology Lab Findings

Treatment-emergent abnormalities in hemoglobin, white blood cell (WBC) count, absolute neutrophil count (ANC), and platelet count were primarily Grade 1 or Grade 2. Grade 3 results were reported in 6 patients (5.5%) for decreased hemoglobin, 6 patients (5.5%) for increased WBC count, 4 patients (3.7%) for decreased ANC, and 2 patients (1.8%) for decreased platelet count. One patient (0.9%) had a Grade 4 result, which was for decreased ANC.

Post-baseline shifts of ≥2 toxicity grades in these parameters resulting in a maximum Grade of 3 were observed in 5 patients (4.6%) for decreased hemoglobin, 3 patients (2.8%) for increased WBC count, 3 patients (2.8%) for decreased ANC, and 2 patients (1.8%) for decreased platelet count. One patient had a shift of ≥2 grades to Grade 4, which was for decreased ANC.

7.6.11 Lactic Acidosis – of Interest for Linezolid

Lactic acidosis is another known clinical side effect associated with linezolid (Pfizer 2018). In Nix-TB, 8 patients (7.3%) reported events in the SMQ for lactic acidosis (Table 44). The events were hyperlactacidaemia (3 patients [2.8%]), lactic acidosis (3 patients [2.8%]), acidosis (1 patient [0.9%]), and blood lactic acid increased (1 patient [0.9%]). The frequency of onset of these events increased over time: 0%, 2.8%, and 4.7% of patients reported onset at ≤2 weeks, >2 to 8 weeks, and >8 to 26 weeks, respectively.

Table 44: Adverse Events in Standardized MedDRA Query for Lactic Acidosis (Nix-TB)

	Nix-TB N=109 n (%)
Patients with any Lactic Acidosis AESI	**8 (7.3%)**
Preferred term	
Hyperlactacidaemia	**3 (2.8%)**
Lactic acidosis	**3 (2.8%)**
Acidosis	**1 (0.9%)**
Blood lactic acid increased	**1 (0.9%)**

AESI=adverse event of special interest

Six of the 8 events were either Grade 1 or Grade 2 in severity, 1 event was Grade 3, and 1 event was Grade 4 (Appendix Figure 14). One patient experienced an SAE of lactic acidosis. The BPaL regimen was interrupted for this patient, and the event resolved. Treatment was resumed with linezolid at a lower dose (300 mg QD), and no recurrence of the event was observed through the rest of the treatment period.

For all other lactic acidosis AESIs, study drug was either interrupted (linezolid only for 4 events; BPaL for 2 events; not recorded for 1 event) or discontinued (BPaL for 1 event). All except 1 of the lactic acidosis AESIs resolved. The exception was hyperlactacidaemia in a patient who died from pneumonia and septic shock, which began 2 days after the onset of the hyperlactacidaemia.

7.7 Risk Management

The proposed prescribing information for pretomanid as part of the BPaL regimen includes warnings and precautions to reduce the risks associated with myelosuppression, peripheral and optic neuropathy, and hepatic toxicity.

To reduce the risks associated with myelosuppression, the proposed labeling recommends monitoring of complete blood counts while patients are receiving linezolid as part of the BPaL regimen, and decreasing the dose or interrupting linezolid in patients who develop or have worsening myelosuppression.

To reduce the risks associated with peripheral neuropathy and optic neuropathy, the proposed labeling recommends appropriate monitoring and interruption or adjustment of linezolid dosing. Regarding optic neuropathy, the proposed labeling recommends monitoring of vision function along with prompt ophthalmologic evaluation if a patient experiences symptoms of visual impairment. This is consistent with linezolid prescribing information on long-term use of linezolid.

Bedaquiline, per its label, requires regular monitoring of liver function. The proposed labeling for pretomanid as part of the BPaL regimen also recommends that patients are monitored regularly for symptoms of liver toxicity and with liver function tests at baseline, monthly while on treatment, and as needed. The labeling also proposes guidelines for interrupting treatment

based on liver function test results. Finally, patients are advised to avoid other hepatoxic drugs and alcohol while on treatment.

7.8 Safety Conclusions

AEs in Nix-TB were as expected with the BPaL regimen. Several of the more common AESIs in Nix-TB (eg, peripheral neuropathy, myelosuppression) were uncommon in individuals treated with any pretomanid regimen that did not contain linezolid in the Phase 1 and 2 studies, demonstrating an acceptable safety profile for pretomanid as a single agent. Hepatic toxicities associated with pretomanid in the clinical program overall were reversible with appropriate monitoring and interruption of dosing. Importantly, no patient permanently discontinued therapy because of hepatic toxicities, and those who halted and reinitiated the regimen were able to complete treatment.

Hematologic and peripheral and optic nerve toxicities associated with linezolid in the BPaL regimen were usually reversible with appropriate monitoring and interruption/adjustment of linezolid dosing.

Overall, the safety profile of the BPaL regimen is manageable through dose adjustments of linezolid or interruptions of the regimen, and the majority of patients in Nix-TB were able to complete therapy. The BPaL regimen is a new treatment option offering the potential to cure patients with a life-threatening infectious disease that can spread through a community. While the toxicity profile is significant, this needs to be balanced against the significant individual as well as public health benefit of curing highly resistant TB.

8 BENEFIT-RISK CONCLUSIONS

One of the priorities in accelerating the decline of global TB is technological advancement towards shorter medication regimens for treating TB (WHO 2018a). Treatment for highly resistant TB requires a combination of 5 or more drugs administered for 18 months for longer. For patients who do not tolerate or respond to MDR-TB treatment or those with XDR-TB, the choice of anti-TB drugs is limited. Remaining treatment options are burdensome, prolonged, and toxic. There is an urgent need for a new, defined regimen for highly resistant TB.

The BPaL regimen was developed specifically to 1) shorten treatment duration and simplify drug administration, in order to facilitate treatment adherence; and 2) provide a more effective and better tolerated treatment regimen to curtail the spread of drug-resistant strains of *M. tb*. The regimen meets the need for a new, defined regimen for which highly resistant strains of *M. tb* have little to no resistance. The orally administered, 3-drug BPaL combination with a 6-month treatment duration offers simplified administration, a shorter treatment duration with a manageable safety profile and improved cure rates.

In Nix-TB, 90% of patients with the most difficult-to-treat form of TB responded favorably to the treatment. 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. Efficacy outcomes were very similar in patients either with HIV or without HIV and in patients with either XDR-TB or TI/NR MDR-TB. The results of Nix-TB show a very high rate of overall efficacy not only in the context of a single-arm study, but also when compared with a historical control population. The rate of a favorable outcome in Nix-TB was 6.6-fold higher than the historical control cohort. Together these results show the potential for treatment improvement with the BPaL regimen.

AEs in Nix-TB were as expected with the BPaL regimen and generally manageable through dose adjustments. The data in the larger safety database from all studies in the pretomanid clinical development program raised no additional concerns for pretomanid, compared to Nix-TB. 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. This type of completion rate is similar to completion rates for patients being treated for DS-TB and is greater than generally seen with other treatments for highly resistant TB. Overall, the safety concerns with the BPaL regimen are manageable and the overall benefit to risk is highly positive given the higher efficacy and lower mortality.

The promising results from the Nix-TB study bring hope to patients around the world with highly resistant TB. 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 establishes a standard of care. From the public health perspective, the Nix-TB results offer health care systems a realistic path to scale up an implementable, highly active regimen to markedly decrease the burden of highly resistant TB on health care systems and to decrease the public health care risks associated with further spread of drug-resistant TB.

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10 APPENDICES

10.1 Clinical Development Program

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies)

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
Phase 1: Healthy Adult Subjects				
CL-001	Double-blind, placebo-controlled, dose-escalating, PK and safety study	Pa: 50, 250, 500, 750, 1000, 1250, 1500 mg Placebo (Single dose after overnight fast)	40 (n=4-6/ dose group) 13	• No dose-limiting AEs or effects on ECG, vital signs, or PE. • Moderate serum creatinine elevation.
CL-002	Double-blind, placebo-controlled, multiple-dose, escalating, PK and safety study	Pa: 200, 600, 1000 mg/day Placebo (7 days, QD dosing after overnight fast)	18 (n=6/dose group) 6	• Well tolerated at doses <1000 mg/day. Dosing terminated for 1000 mg/day dose group. • After 5 days' dosing at 1000 mg/day, progressive moderate creatinine elevation: reversed during 7-day washout period. • No consistent effect on BUN. • A planned 1400 mg cohort not enrolled.
CL-003	Open-label, single-dose, food effects and safety study	Pa: 1000 mg (Single dose; dosing within 30 minutes of a high-fat, high-calorie meal or following an overnight fast; 8-day washout separated each dose)	16	• No dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • AEs affecting >1 subject generally occurred more frequently after dosing in the fed condition than the fasted condition, and more frequently among women than men. • Bioavailability 3.5-fold higher when Pa was administered in fed state compared with fasted state.
CL-004	Open-label, single-dose, ADME and safety study	Pa: 873 mg, oral suspension [benzyl-^{14}C]Pa (Single dose after overnight fast)	6	• No dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • ~91% of dose recovered (~65% in urine; ~26% in feces) • Plasma: parent drug and one major metabolite. • Urine: little or no parent drug; multiple major metabolites. • Feces: minimal unchanged parent drug; numerous low-abundance metabolites.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
CL-005	Double-blind, placebo-controlled, multiple-dose, renal PD and safety study	Pa: 800, 1000 mg Placebo (8 days, once daily dosing after overnight fast)	31 (n=21 for 800 mg n=10 for 1000 mg) 16	• No dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • Serum/plasma creatinine levels increased significantly (up to ~40%) during treatment; reversed during 7-day washout period. • No effect during treatment on renal function as evaluated by GFR, ERPF, FF, BUN or UA.
CL-006	Open-label, multiple-dose, drug interaction study with midazolam	Pa: 400 mg (Midazolam 2 mg on Day 1; Pa on Days 4 to 16 after overnight fast; and Pa + midazolam 2 mg on Day 17)	14	• No dose-limiting AEs. • For midazolam, the geometric mean ratio (90% CI) of Day 17 (midazolam+Pa) vs Day 1 (midazolam alone) for C_{max} was 0.84 (0.75, 0.93) and $AUC_{0\text{-}inf}$ was approximately 0.85 (0.74, 0.97). • For the 1-hydroxy midazolam metabolite, the corresponding geometric mean ratio was 1.05 for C_{max} and 1.13 for $AUC_{0\text{-}inf}$.
CL-008	Open-label, single-dose, ADME and safety	Pa: ~1100 mg, oral suspension [imidazooxazine-^{14}C]Pa (Single dose after overnight fast)	6	• No dose-limiting AEs or abnormal laboratory results; no effects on ECG, vital signs, or PE. • ~91% of dose recovered (~53% in urine; ~38% in feces). • Plasma: parent drug. • Urine: little or no parent drug; multiple major metabolites. • Feces: unchanged parent drug; numerous low-abundance metabolites.
CL-009	Open-label, single-dose, food effects and safety study	Pa: 50 and 200 mg (Single dose; dosing within 30 minutes of a high-fat, high-calorie meal or following an overnight fast; 8-day washout separated each dose)	32 (n=16/dose group)	• No dose-limiting AEs. • In the presence of high-fat, high-calorie meal, C_{max} and AUC of the 50-mg dose were increased 1.25 fold and 1.45-fold, respectively, compared to fasted state, whereas for the 200-mg dose, C_{max} increased by 1.73-fold and AUC increased by 1.88-fold when dosed with a meal.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
DMID 10-0058	Randomized, double-blind, placebo and positive control, 5-period, single-dose crossover, single-center study A "Thorough-QT" study	A: Placebo B: Pa 400 mg C: Pa 1000 mg D: MOX 400mg E: Pa 400 mg + MOX 400mg	74	• The upper limit of the 90% CI for QTcI did not exceed 4.4 msec for the 400-mg dose or 6.1 msec for the 1000-mg dose, and both were well below 10 ms. Pa+MOX exceeded 10 msec at multiple time points during the observation period. This was similar to the effect observed with MOX administered alone. • A 2.5-fold increase in Pa dose from 400 mg to 1000 mg resulted in an approximate 2-fold increase in AUC and a 1.8-fold increase in C_{max}. The rate of elimination was independent of dose and the $T_{1/2}$ was approximately 18.5 hours. • Median T_{max} was similar for both Pa doses and occurred approximately 4.5 to 5 hours post-dose. • The PK of Pa was not affected by the co-administration of MOX.
A5306 (Dooley et al. 2014)	Open-label, multicenter trial, completed in 3 sequential phases (Arms) with crossover within each Arm	Arm 1: Pa 200 mg QD for 1 week EFV 600 mg QD for 2 weeks Pa 200 mg + EFV 600 mg QD for 1 week	18	Arm 1: • The median data and geometric mean ratios revealed that, overall, Pa AUC_{0-24h}, C_{min}, C_{max}, and $T_{1/2}$ were significantly lower, and CL/F was significantly greater, when Pa was administered with EFV. However, Pa T_{max} was not changed when Pa was co-administered with EFV. • Overall, there were no significant changes in any of the measured EFV PK parameters when EFV was co-administered with Pa. • No Grade 2 or higher chemistry, hematology, or QTc events were observed. No graded diagnoses were observed on study. No Grade 3 or higher signs and symptoms were reported.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
A5306 (cont.)		Arm 2: Pa 200 mg QD for 1 week LPV/r 400/100 mg BID for 2 weeks Pa 200mg QD + LPV/r 400 mg BID for 1 week	18	Arm 2: • The median data and geometric mean ratios revealed that Pa $AUC_{0\text{-}24h}$, C_{min}, C_{max}, and $T_{1/2}$ were significantly lower, and CL/F was significantly greater, when Pa was administered with LPV/r. However, Pa T_{max} was not changed when Pa was co-administered with LPV/r. • LPV/r concentrations were significantly decreased at 12 hours post-dose when LPV/r was co-administered with Pa. • The median data revealed that LPV/r $AUC_{0\text{-}24h}$, C_{min}, and C_{max} were significantly lower and CL/F was significantly greater, when LPV/r was administered with Pa. However, LPV/r T_{max} and $T_{1/2}$ were not changed when LPV/r was co-administered with Pa. • No Grade 2 or higher hematology or QTc events were observed. No graded diagnoses were observed on study. No Grade 3 or higher signs and symptoms were reported. Two subjects experienced Grade 2 or greater chemistries.
		Arm 3: Pa 200 mg QD for 1 week RIF 600 mg QD for 1 week Pa 200 mg + RIF 600 mg QD for 1 week	16	Arm 3: • The median data and geometric mean ratios revealed that Pa $AUC_{0\text{-}24h}$, C_{min}, C_{max}, and $T_{1/2}$ were significantly lower, and CL/F was significantly greater, when Pa was administered with RIF. However, Pa T_{max} was not changed when Pa was co-administered with RIF. • No Grade 2 or higher chemistry or QTc events were observed. No Grade 3 or higher signs and symptoms were reported.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
Phase 2 Studies: Adult Patients with Pulmonary TB				
CL-007 (Diacon et al. 2010)	Partially double-blinded (blinded as to Pa dose), multiple-dose, EBA, safety, and PK study	Pa: 200, 600, 1000, 1200 mg HRZE (14 days, once-daily dosing after overnight fast)	61 (n=15 or 16/dose group) 8	• Pa treatment produced a measurable decrease in log CFU, with the magnitude of effect equivalent for all doses. • Well tolerated overall. Two SAEs (hemoptysis) occurred (one on Pa and led to discontinuation); both were considered unrelated to study treatment. • No dose-limiting laboratory findings or clinically significant effects on vital signs or PE noted. Clinically significant, possibly treatment-related conduction disorder AEs reported in 2 patients in Pa groups and 1 in HRZE group.
CL-010 (Diacon et al. 2012a)	Partially double-blinded (blinded as to Pa dose), multiple-dose, EBA, safety, and PK study	Pa: 50, 100, 150, 200 mg HRZE (14 days, once daily dosing after overnight fast)	61 (n=15 or 16/dose group) 8	• Pa treatment produced a measurable decrease in log CFU with some evidence of dose dependence. • Well tolerated overall. Two SAEs (pneumonia, pneumothorax [led to discontinuation]) in Pa groups; both were considered unrelated to study treatment. • No dose-limiting laboratory findings or clinically significant effects on ECGs, vital signs, or PE noted.
NC-001 (Diacon et al. 2012b)	Partially blinded (unmasked treatment with HRZE) multiple-dose, EBA, safety, and PK study	Pa 200 mg + BDQ Pa 200 mg + PZA Pa 200 mg + PZA + MOX BDQ alone BDQ + PZA HRZE (14 days, once daily dosing after overnight fast)	15 15 15 15 15 10	• All Pa combinations produced a measurable decrease in log CFU, with the rank ordering for activity being Pa + PZA + MOX combination > Pa + PZA > Pa + BDQ. • Suggestion of higher frequency of AEs leading to discontinuation in Pa + PZA + MOX group (20% vs 6.7% in Pa + PZA or Pa + BDQ groups). • Two SAEs (worsening pulmonary TB, neurocysticercosis) in Pa groups; both were considered unrelated to study treatment.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
NC-002 (Dawson et al. 2015)	Multicenter, open-label, parallel-group, partially randomized based on TB drug susceptibility, with EBA substudy of 15/arm	A: Pa 100 mg + MOX 400 mg + PZA 1500 mg B: Pa 200 mg + MOX 400 mg + PZA 1500 mg C: HRZE D: Pa 200 mg + MOX 400 mg + PZA 1500 mg (8 weeks)	60 (DS) 62 (DS) 59 (DS) 26 (MDR)	• Pa 200+MOX+PZA showed bactericidal activity to a degree that was clinically meaningful in both DS and MDR patients. • The DS treatment group Pa 200+MOX+PZA showed the highest bactericidal activity, followed by that of Pa 100+MOX+PZA, with both groups outperforming HRZE (difference was statistically significant for decline in log CFU count in Pa 200+MOX+PZA group). • The highest incidence of SAEs was reported in the Pa 200+MOX+PZA treatment group (n=7, 11.3%). SAEs were reported for 1 (1.7%), 1 (1.7%), and 0 patients in the Pa 100+MOX+PZA, HRZE, and Pa 200+MOX+ PZA-MDR groups, respectively.
NC-003 (Diacon et al. 2015)	Randomized, open-label, parallel-group, multicenter trial, EBA	A: BDQ 400-200 mg + Pa 200 mg + PZA 1500 mg + CFZ 300-100 mg B: BDQ 400-200 mg + Pa 200 mg + PZA 1500 mg C: BDQ 400-200 mg + Pa 200 mg + CFZ 300-100 mg D: BDQ 400-200 mg + PZA 1500 mg + CFZ 300-100 mg E: PZA 1500 mg F: CFZ 300-100 mg G: HRZE (14 days)	105 (DS) (n=15/arm)	• BDQ+Pa+PZA was associated with the highest estimate of mean EBA, followed by HRZE. • The change from baseline (Day 0) in mean log(CFU) count was greater than 1 for BDQ+Pa+PZA+CFZ, BDQ+Pa+PZA, BDQ+PZA+CFZ. These combination therapies therefore potentially have sterilizing activity in DS-TB when administered over a longer period of time. • The treatment with PZA and CFZ alone was associated with lowest EBA. It is noted that PZA is an essential in combination therapies but has weak EBA when administered alone.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
NC-005	Partially randomized, open-label, parallel-group, multicenter trial, BA	A: BDQ 400-200 mg + Pa 200 mg + PZA 1500 mg B: BDQ 200 mg + Pa 200 mg + PZA 1500 mg C: HRZE D: BDQ 200 mg + MOX 400 mg + Pa 200 mg + PZA 1500 mg (8 weeks)	59 (DS) 60 (DS) 61 (DS) 60 (MDR)	• All treatment groups had statistically significant increases in the BA as compared to HRZE. • The percent of patients who were culture negative at 2 months was higher in all groups as compared to HRZE. • In the MDR group, the BA was higher for PZA-sensitive patients as compared to PZA-resistant patients. • For all serious drug-related, liver-related AEs (excluding deaths), outcome was recovered/resolved. • The proportion of patients with at least one serious liver-related AE was similar across treatment groups except for BDQ 200 mg + Pa 200 mg + PZA 1500 mg where no patients experienced a serious drug-related, liver-related AE.

Table 45: Pretomanid Clinical Development Program (Completed Clinical Studies) Continued

Study	Design	Study Treatments (Treatment Duration)	N	Key Safety/Efficacy Findings
Phase 3 Studies: Adult Patients with Pulmonary TB				
NC-006	Partially randomized, open-label, parallel-group, multicenter trial, BA and long-term relapse-free survival	A: 6 months HRZE/HR	68 (DS)	• Noninferiority was not demonstrated between HRZE/HR and 6Pa200MZ with the upper bound of the 95% CI for the difference in unfavorable assessment being greater than the noninferiority margin of 12%. However, as the trial stopped early it was underpowered. • There were 11 deaths in the PaMZ groups (4 patients on 4Pa100MZ, 3 on 4Pa200MZ, 3 on 6Pa200MZ, and 1 6Pa200MZMDR) and 2 deaths in the HRZE/HR group. 22 patients had SAEs during the treatment period in the PaMZ groups (3 patients on 4Pa100MZ, 8 on 4Pa200MZ, 8 on 6Pa200MZ, and 3 on 6Pa200MZMDR) and 3 patients in the HRZE/HR group. • There were no unexpected safety findings and no apparent differences in AEs between the 4Pa100MZ, 4Pa200MZ, and 6Pa100MZ groups and the HRZE/HR group. The limited number of patients with MDR-TB was not conducive to a comparison and results should be interpreted with caution.
		B: 4 months Pa 100 mg + MOX 400 mg + PZA 1500 mg	65 (DS)	
		C: 4 months Pa 200 mg + MOX 400 mg + PZA 1500 mg	71 (DS)	
		D: 6 months Pa 200 mg + MOX 400 mg + PZA 1500 mg	67 (DS)	
		E: Pa 200 mg + MOX 400 mg + PZA 1500 mg	13 (MDR)	
		Total	284	

ADME=absorption, distribution, metabolism, excretion; AE=adverse event; AUC=area under the concentration-time curve; $AUC_{0\text{-}24h}$=area under the concentration curve from time 0 to 24 hours; $AUC_{0\text{-}inf}$=area under concentration curve from time 0 to infinity; BA=bactericidal activity; BDQ=bedaquiline; BID=twice daily administration; BUN=blood urea nitrogen; CFU=colony-forming units; CFZ=clofazimine; CI=confidence interval; CL/F=oral clearance ; C_{max}=maximum concentration; C_{min}=minimum (trough) concentration; DS=drug-susceptible; EBA=early bactericidal activity; ECG=electrocardiogram; EFV=efavirenz; ERPF=effective renal plasma flow; FF=filtration fraction; GFR=glomerular filtration rate; HRZE=isoniazid-rifampin-pyrazinamide-ethambutol; LPV/r=ritonavir-boosted lopinavir; MDR=multi-drug resistant; MOX=moxifloxacin; PE=physical examination; PK=pharmacokinetic; PZA=pyrazinamide; QD=once daily; QTc=Qt interval, corrected; QTcI=QT interval with individual corrections; RIF=rifampin; SAE=serious adverse event; $T_{1/2}$=half-life; TB=tuberculosis; AE=adverse event; T_{max}=time to maximum concentration; UA=uric acid

Table 46: Pretomanid Clinical Development Program (Ongoing Clinical Studies)

Study	Design	Study Treatment (Treatment Duration)	N	Evaluations
Phase 3 Studies: Adult Patients with Pulmonary TB				
Nix-TB	Pivotal open-label, multicenter study	BPaL regimen: B 400 mg QD for 14 days, then 200 mg TIW + Pa 200 mg QD + L 1200 mg daily (6 months, with option for 9 months if culture positive at 4 months)	Planned: 200 Actual: 109 (n=69 XDR, n=40 TI/NR MDR)	Efficacy, Safety, PK and Tolerability
ZeNix	Randomized, partially blinded (to dose and duration of linezolid), parallel-group study	A: B 200 mg for 8 weeks, then 100 mg for 18 weeks + Pa 200 mg + L 1200 mg B: B 200 mg for 8 weeks, then 100 mg for 18 weeks + Pa 200 mg + L 1200 mg for 9 weeks, then placebo for 17 weeks C: Bedaquiline 200 mg for 8 weeks, then 100 mg for 18 weeks + Pa 200 mg + L 600 mg QD D: B 200 mg for 8 weeks, then 100 mg for 18 weeks + Pa 200 mg + L 600 mg for 9 weeks, then placebo for 17 weeks (QD for 6 months)	Planned: 180 (total XDR, pre-XDR, and TI/NR MDR) Currently recruiting	Efficacy, Safety, PK, and Tolerability

B=bedaquiline; DS=drug-susceptible; EBA=early bacterial activity; HRZE= isoniazid-rifampicin-pyrazinamide; L=linezolid; MDR=multiple drug-resistant; Pa=pretomanid; PK=pharmacokinetics; TB=tuberculosis; TI/NR=treatment-intolerant/nonresponsive; QD=once daily; XDR=extensively drug-resistant

10.1.1 Efficacy Findings from Completed Pretomanid Phase 1–3 Studies

Supporting the Phase 3 results of the Nix-TB Trial, pretomanid has demonstrated antimycobacterial activity as a stand-alone agent in patients with pulmonary TB in 2 Phase 2a studies (CL-007 and CL-010) and in various combinations in 2 Phase 2a studies (NC-001, NC-003), 2 Phase 2b studies (NC-002 and NC-005), and another Phase 3 study (NC-006).

As a single agent, pretomanid showed mycobactericidal activity over 14 days spanning a wide range of doses from 50 to 1200 mg/day: 200, 600, 1000, and 1200 mg/day were tested in CL-007; and 50, 100, 150, and 200 mg/day were tested in CL-010. The bactericidal activity of pretomanid was similar for all doses tested except 50 mg, which showed less activity than the higher doses. In CL-010, patients with pulmonary TB who were administered pretomanid at doses of 200 mg had a mean 1.5-log reduction in CFU from baseline to the end of 14 days of treatment.

As treatment of tuberculosis requires a combination of multiple drugs, pretomanid was also tested in different combination regimens, measuring bactericidal efficacy after 14 days of treatment in NC-001 and NC-003 studies, in order to inform the selection of candidate regimens for later-stage clinical development. All pretomanid-containing arms in these 2 studies showed bactericidal activity. In particular, in NC-001, the PaMZ regimen showed the greatest bactericidal activity, although the small sample size did not allow determination of statistical significance. This combination as well as pretomanid plus bedaquiline plus pyrazinamide (BPaZ) showed daily reductions in CFU counts that were similar to or greater than those in patients administered the standard-of-care 4-drug regimen (HRZE). In NC-003, the combination BPaZ showed the greatest bactericidal activity, followed by that of the standard of care, HRZE.

Several additional regimens were tested over an 8-week treatment period in studies NC-002 and NC-005. In NC-002, patients with DS-TB were treated with either 100 or 200 mg/day pretomanid in combination with moxifloxacin and pyrazinamide (PaMZ); the same combination with 200 mg/day pretomanid was tested in patients with MDR-TB. Results indicated that the bactericidal activity of the 200 mg pretomanid regimen was significantly greater than that of HRZE. In contrast, no significant differences were observed between the 100 mg pretomanid regimen and HRZE.

In NC-005, DS-TB patients were treated with BPaZ with bedaquiline administered as either a loading dose (400 mg/day) for 14 days, followed by 3 TIW at 200 mg/day, or administered consistently at 200 mg/day. Data from this study demonstrated significantly greater bactericidal activity for the BPaZ regimen than for HRZE. The efficacy of the regimen with bedaquiline at 200 mg/day was similar to the efficacy of the regimen with bedaquiline administered as recommended (ie, loading dose and then 3 TIW). In this study, 1 study arm of MDR-TB patients was treated with BPaZ (bedaquiline at 200 mg/day) plus moxifloxacin (BPaMZ). The BPaMZ regimen in MDR-TB patients showed the greatest bactericidal activity and the shortest time to culture conversion among all treatment arms, although conclusions for this population were limited by the absence of a randomized control arm.

The Phase 3 study NC-006 tested the combination PaMZ in patients with DS-TB under 3 different dosing schedules: 6 months with pretomanid at 200 mg/day, 4 months with pretomanid at 100 mg/day, or 4 months with pretomanid at 200 mg/day. An MDR-TB population was also treated with PaMZ for 6 months (pretomanid at 200 mg/day). This study was placed on partial clinical hold in 2015 due to deaths associated with hepatotoxicity. Following investigations, the partial clinical hold was lifted on 17 August 2016. However, due to delays in enrollment and the promising results of other pretomanid-containing drug regimens, TB Alliance chose not to re-open enrollment when the partial clinical hold was removed, but the already enrolled patients (N=284) were followed to the study endpoints. With this reduced sample size, the study failed to demonstrate noninferiority in the efficacy of the PaMZ regimens compared with the efficacy of the standard-of-care regimen (HRZE) at 6 months.

10.2 Patient Narratives

10.2.1 Deaths

Patient 1 (Death; 2 SAEs: disseminated tuberculosis, pulmonary tuberculosis)

This patient was a 34-year-old male who had a HIV co-infection and a prior history notable for heavy alcohol use, but the patient denied current use. The patient's XDR-TB was diagnosed in May 2014, and he received his first administration of trial treatment on (b) (6) Prior treatment for TB included pyrazinamide, ethambutol, moxifloxacin, aminosalicylate sodium, terizidone, clofazimine, ethionamide, capreomycin, and isoniazid. On Screening, the patient had a BMI of 14.6 kg/m^2, an albumin of 27 g/L (<lower limit of reference range = 35 g/L), a CD4 count of 259 cells/µL, and a suppressed HIV viral load of <20 copies/mL on 11 September 2014.

On (b) (6) (Trial Day 34) in the afternoon, the patient complained of dizziness, vomiting, and acute worsening of epigastric pain and was noted to be confused by the nursing staff. The Investigator reported that on (b) (6) the patient developed acute worsening epigastric pain. On (b) (6) the patient died.

On postmortem examination, the patient was noted to be an HIV-positive male with emaciation; bilateral pulmonary TB with cavitation and obliterative fibrosis; pleural fibrosis involving the aorta; and disseminated TB to the spleen, splenunculus, kidneys, and liver. He had hemorrhagic pancreatitis with neutropenic ductulitis, marked iron overload in the liver with microvesicular steatosis, adrenal hemorrhage, and kidneys with acute on chronic pyelonephritis and interstitial fibrosis. According to the autopsy report, the cause of death was severe pulmonary and disseminated TB and emaciation. The Investigator and the Sponsor considered the events of pulmonary TB and disseminated TB not related to trial therapy; the Sponsor considered these events as caused by the disease under study.

Patient 2 (Death; SAE: upper gastrointestinal haemorrhage)

This patient was a 20-year-old female who was HIV negative. The patient had DS-TB in 2008 and 2009, MDR-TB from March 2014 to April 2015, and XDR-TB since 13 April 2015. Previous XDR-TB treatment included aminosalicylate sodium, terizidone, ethionamide, pyrazinamide, ethambutol, clofazimine, isoniazid, capreomycin, moxifloxacin, para-aminosalicylic acid, and levofloxacin. The first dose of trial treatment was given (b) (6) On Screening, the patient had a BMI of 15.4 kg/m^2 and an albumin of 30 g/L (<lower limit of reference range = 35 g/L).

On (b) (6) (Trial Day 43), laboratory results showed hemoglobin of 9 g/dL and platelets 215 × 10^9/L. On (b) (6) (Trial Day 47), the patient experienced nonserious Grade 2 dyspepsia. On the same day, she complained of weakness and vomiting. (b) (6), an intravenous fluid therapy of Ringers Lactate was started in the hospital for vomiting and fluid replacement. On (b) (6) (Trial Day 50), the patient had her Week 7 visit at the trial center, where blood tests were performed which came back later ((b) (6) and showed

hemoglobin of 6.9 g/dL, platelets 45 × 10^9/L, WBC count of 6.5 × 10^9/L, all of which had decreased since the Week 6 visit ([(b) (6)].

On [(b) (6)] the patient received the trial treatment. She complained of shortness of breath that morning and later was seen by the physician at 11:50 AM. She had deteriorated markedly from previous day. The trial center doctor noted deep sighing respiration, respiratory rate of 10, and Glasgow Coma Scale of 4/15. No blood pressure was registered. The patient's abdomen was distended without bowel sounds. Spontaneous respiration stopped while the doctor was with the patient, and no pulse was observed. Cardiopulmonary resuscitation was commenced. There was dark fluid from her mouth with chest compressions, and possible hematemesis. The patient's pupils were fixed and dilated, and cardiopulmonary resuscitation was terminated.

Postmortem findings included severe emaciation and both lungs showing marked apical pleural fibrosis and markedly destroyed and contracted upper lobes. The trachea and bronchi contained mildly bloodstained fluid. Sections of the upper lobes of the lungs showed numerous fibrocaseous nodules and areas of obliterative fibrosis. The esophagus was filled with "coffee grounds," and sections of the esophagus showed loss of surface epithelium distally and invasive candida with an acute inflammatory infiltrate into the wall and ulcerative esophagitis. The liver showed severe non-alcoholic fatty liver disease with focal zone 3 hepatic necrosis, although throughout the trial hepatic enzymes and bilirubin were normal.

The Investigator reported that the event of upper gastrointestinal bleeding, as a cause of death, was possibly related to trial treatment, and that the upper gastrointestinal bleeding was probably linked to the ulcerated esophagitis with invasive candida. The Sponsor considered the event unlikely related to the trial treatment since the autopsy result did not support marrow suppression.

Patient 3 (Death; 2 SAEs: pulmonary tuberculosis, anemia)

The patient was a 31-year-old female with HIV co-infection diagnosed in April 2012. She was diagnosed with MDR-TB from April 2012 to February 2014, with pre-XDR TB in February 2015, and XDR-TB on 26 February 2015. She received her first administration of trial treatment [(b) (6)] She had not been treated for TB since April 2015, but was being treated for HIV at the time of Screening with tenofovir, lamivudine, and lopinavir/ritonavir. At Screening, the patient had a low BMI of 12.4 kg/m^2 and a low albumin of 25 g/L (<lower limit of reference range = 35 g/L). On Screening, her CD4 count was 328 cells/µL and hemoglobin was 11.8 g/L (reference range was 11.6 to 16.2 g/L).

On [(b) (6)](Trial Day 19), the patient had an unscheduled visit to the trial center; she was complaining of weakness and fatigue and noted to be pale, tachycardic, and hypotensive with a functional murmur heard over the left sternal border. The patient's hemoglobin was dropping weekly, but previously she was asymptomatic. The patient's blood results revealed hemoglobin of 8.4 g/dL (reference range of 11.5 to 15.5 g/dL). The entire trial treatment was interrupted due to Grade 2 anemia, with the last dose of trial treatment received on [(b) (6)]

(b) (6). The patient was admitted to the hospital for anemia and was found to have a hemoglobin of 7.3 g/dL (reference range of 12.0 to 15.0 g/dL). On (b) (6) (Trial Day 22), the patient received a blood transfusion of 2 units of red blood cells, and on (b) (6) (Trial Day 23), laboratory blood results after the transfusion showed hemoglobin of 11.8 g/dL. On (b) (6) (Trial Day 29), the patient developed a nonserious superimposed lower respiratory tract infection, which was mild in severity. Symptoms included a cough, shortness of breath, and generalized weakness. On (b) (6) (Trial Day 43), the Investigator decided to re-challenge the trial treatment with a regular dose of bedaquiline and pretomanid but a reduced dose of linezolid (300 mg QD). The patient was started on amoxicillin/clavulanate the same day due to superimposed lower respiratory tract infection.

On (b) (6) (Trial Day 47), the patient was diagnosed with Grade 4 pulmonary TB (acute worsening), which was considered serious. On (b) (6) (Trial Day 50) the patient failed to improve and had an HIV viral load of 8,838 copies/mL. She was further treated with second-line antibiotics azithromycin and metronidazole, fluconazole and nystatin drops for oral candida, and 1 L of intravenous sodium chloride for dehydration. On (b) (6) (Trial Day 55), the patient died. No acute events were reported prior to death; however, the patient had a temperature spike of 39.1°C during the afternoon. The patient had been experiencing ongoing pneumonia (lower respiratory tract infection) and was not improving on second-line antibiotics (azithromycin and metronidazole). The Investigator suspected that the cause of death was overwhelming sepsis or hypoxic cardiac arrest secondary to lower respiratory tract infection at the time of the patient's death.

Postmortem examination found purulent secretions in the larynx and obliteration of both pleural cavities by adhesions with a large cavity on the right side. There were multiple caseous lesions throughout the lung. Other findings included small raised plaques suggestive of candida in the distal third of the esophagus, striking involvement of mesenteric lymph nodes by TB, multiple small caseous foci in the spleen, fibrocaseous nodules adherent to the liver capsule, occasional milliary-type caseous granulomas in the left lobe of the liver, and a hemorrhagic pancreatic head. The marrow appeared cellular with an adequate number of megakaryocytes, abundant myeloid precursors including mature neutrophils, and reduced numbers of erythroid precursors; no erythroid nests and no granulomas were seen.

The final cause of death was reported as respiratory failure due to severe pulmonary TB. The Investigator considered the event of anemia was probably related to the trial treatment and the Sponsor considered the event of anemia as possibly related to trial treatment. The Investigator considered that there was no reasonable possibility that the acute severe worsening of the pulmonary TB was related to the trial treatment and the Sponsor considered the event as not related to the trial treatment.

<u>Patient 4 (Death; 3 SAEs: pancreatitis haemorrhagic, hypoglycaemia, multiple organ dysfunction syndrome)</u>

The patient was a 35-year-old male who had a HIV co-infection. He was diagnosed with DS-TB from February 2008 until September 2012, with MDR-TB from September 2012 until September

2014, pre-XDR TB from September 2014 until October 2014, and XDR-TB since 31 October 2014. The patient's HIV was diagnosed in 2008, and other medical history included chronic active hepatitis B since December 2014. Treatment for TB prior to Screening included moxifloxacin, aminosalicylate sodium, pyrazinamide, ethambutol, and clofazimine. On Screening, the patient had a BMI of 20.8 kg/m^2, an albumin value of 30 g/L (reference range, 35 to 52 g/L), and a CD4 count of 168 cells/µL. He received his first administration of trial treatment on (b) (6)

On (b) (6) (Trial Day 28), laboratory test results showed a white blood cell count 3.9 × 10^9/L, hemoglobin of 9.4 g/L, and a platelet count of 121 × 10^9/L. The Investigator reported a Grade 1 AE of low WBC count (preferred term, leukopenia). The event was considered as probably related to trial treatment by the Investigator. Linezolid was reduced to 600 mg QD. The doses of pretomanid and bedaquiline were not changed.

On Trial Day 42 of study treatment, he experienced Grade 2 nausea and vomiting and Grade 1 left flank pain. Laboratory results showed a lipase level of 24 U/L (within normal limits) and amylase level of 171 U/L (ULN, 100 U/L). On (b) (6) (Trial Day 51), the patient had reported "coffee-ground" vomiting and severe back pain overnight. He was clinically stable but had low blood pressure 66/30 mmHg and mild bradycardia with a pulse rate of 55 beats per minute; therefore, he was started on intravenous fluids. The patient was seen at 7:30 AM, and he was awake, oriented, and pale. He had weak peripheral pulses, cool extremities, and deep abdominal tenderness, and he was more comfortable leaning forward. His hemo-glucose test was 2.1 mmol/L. The ward doctor held the impression that the patient had an upper gastrointestinal bleed (Grade 4) and acute severe pancreatitis (Grade 4). All the medications, including the entire trial treatment, were stopped. The Investigator noted that the results of clinical and laboratory assessment indicated multi-organ failure and reported an additional serious event of hypoglycemia (Grade 4). Local laboratory results included the following: creatinine 204 µmol/L (normal 64 to 104 µmol/L), total bilirubin 18 µmol (5 to 21 µmol), ALT 102 U/L (10 to 40 U/L), lipase 710 U/L (13 to 46 U/L), WBC count 21.93 x 10^9/L (3.92 to 10.40 x 10^9/L), hemoglobin 8.2 g/dL (13.0 to 17.0 g/dL), platelet count 293 x 10^9/L (171 to 388 x 10^9/L), international normalized ratio 3.81 (high), prothrombin time 102.3 sec (30.0 to 40.0 sec), fibrinogen 0.5 g/L (2.0 to 4.0 g/L), and D-dimer 1.22 mg/L (0.00 to 0.25 mg/L). On (b) (6) (Trial Day 53) the patient's blood pressure was 60/30 mmHg, the pulse rate was not recorded, and a hemo-glucose test result was 2.6 mmol/L, which was corrected with 50 mL 50% dextrose intravenously. The patient suddenly deteriorated with a drop in Glasgow Coma Scale and acidotic breathing, and the patient died.

Postmortem examination had major findings of micronodular cirrhosis, hepatitis B virus associated, microvesicular steatosis, and intrahepatic cholestasis; acute hemorrhagic pancreatitis and hemorrhage into mesentery; renal tubules showing evidence of hyperkalemia and urate uropathy; fibrocaseous tuberculosis involving predominately left lung, hilar region of right lung, hilar lymph nodes, spleen, and mesenteric lymph nodes; obliteration of the left pleural cavity and splenic and diaphragmatic adhesions; and the terminal ileum with multiple fibrous adhesions to mesenteric nodes with subacute obstructions.

The Investigator reported that there was a reasonable possibility that the events of acute hemorrhagic pancreatitis, multi-organ failure, and hypoglycemia were possibly related to the trial drug regimen. The Sponsor agreed that the events of acute hemorrhagic pancreatitis and multi-organ failure were possibly related to the trial treatment. The Sponsor assessed the event of hypoglycemia as unlikely related to the trial treatment.

Patient 5 (Death; 3 SAEs: sepsis, transaminases increased, pneumonia)

The patient was a 29-year-old mixed ethnicity female with non-responsive MDR-TB who developed sepsis and worsened pneumonia and died during treatment on Trial Day 93. The patient's medical history included MDR-TB treatment non-responsive since 09 January 2015 and previous DS-TB from 2011 to 2012. She was HIV negative and had a BMI of 15.6 kg/m^2 at Screening. Additional medical history included: intermittent nausea since 2014, chronic suppurative otitis media right ear since 2014, COPD since 2015, intermittent diarrhea since 2015, dyspnea on exertion (Grade 3) since 2016, and fatigue since 2016. Relevant concomitant medications reported included: medroxyprogesterone acetate, pholcodine, salbutamol, oxymetazoline hydrochloride, budesonide, tretinoin, cyclizine, metronidazole, hyoscine butylbromide, and influenza vaccine. At Screening, it was known that she had previously defaulted on TB treatment and abused TIK, a locally manufactured methamphetamine, and Dagga, a form of cannabis. According to the clinic records, she was attending the clinic regularly since December 2015 in the National TB Treatment program, and for more than a year there was no indication of drug abuse. There were 2 periods of 1 week each that she did not attend the clinic. Her urine drug screen at Screening was negative. The Investigator claimed that the patient underwent an intensive counselling by phycologists and social workers during the dry-period, as well as prior to the screening for the Nix-TB trial.

On (b) (6) the patient received her first administration of the trial drug regimen. After her Week 6 visit, a random security check was done in the ward that the patient was admitted to and illicit drugs were found in another patient's room. She admitted that these were her drugs. Her urine drug screen was positive for methamphetamines. About 2 weeks later, the patient was given a pass to leave the hospital to visit her sick child. When she returned to hospital, another urine drug screen was done and was positive for methamphetamines. According to the patient, she had used TIK a few days before leaving the hospital to visit her child. The patient's behavior seemed to improve after counselling. On (b) (6) (74 days after the first administration of trial drug), the patient received her daily dose of the trial drug and then left to attend a funeral. She did not return until (b) (6) and was without trial drug for 8 days.

On (b) (6) (5 days after the last administration of the trial drug while she was off-site), the patient developed signs and symptoms of a nonserious community-acquired pneumonia (Grade 3); no treatment was provided. On (b) (6) (8 days after last administration of the trial drug), the patient took a taxi to the hospital and was brought in to the ward and on arrival she was in a very poor clinical state. The patient admitted that she was using methamphetamines daily for the entire duration (approximately 10 days) that she was at home. On (b) (6) she was transferred to a secondary level hospital where on (b) (6) laboratory results showed

total bilirubin 24 µmol/L, conjugated bilirubin 11 µmol/L, ALT 3314 U/L, AST 6338 U/L (13 to 35 U/L), ALP 123 U/L, GGT 46 U/L (<40 U/L), lactic dehydrogenase 2252 U/L (208 to 378 U/L), white blood cells 7.51 × 10^9/L, neutrophils 84.10%, hemoglobin 9.5 g/dL. Hepatitis B surface antigen and hepatitis C antibody results were negative.

On (b) (6) (16 days after last administration of the trial drug), the patient was discharged from the secondary level hospital with a diagnosis of COPD exacerbation and improving transaminitis, which was likely ischemic in nature. According to the secondary level hospital, there was no evidence of bacterial sepsis, and the patient returned to Brooklyn Chest Hospital later that evening.

On (b) (6) (17 days after last administration of the trial drug), the patient was still very ill, frail, and lethargic. Her blood pressure was not recordable with an electronic blood pressure machine and no manual one was available. Blood cultures (sample collected on (b) (6)) showed no growth after 5 days. Laboratory results showed potassium 5.5 mmol/L, C-reactive protein 68.6 mg/L (<5 mg/L), total bilirubin 23 µmol/L, conjugated bilirubin 11 µmol/L (<3.4 µmol/L), ALP 131 IU/L (30 to 120 IU/L), GGT 56 IU/L (<38 IU/L), ALT 498 IU/L (<35 IU/L), AST 127 IU/L (<35 IU/L), hemoglobin 11.2 g/dL (11.5 to 15.5 g/dL), and white blood cells 26.7 × 10^9/L (4.0 to 11.0 × 10^9/L). Based on the patient's examination and blood results, the pneumonia was most likely bacterial. The Investigator stated that the patient did not improve from a respiratory point of view since referring her to the secondary hospital.

On (b) (6) (18 days after last administration of the trial drug), the Investigator was informed of the patient's passing away the previous night. The patient died with SAEs of worsened pneumonia, sepsis, and transaminases increased. In the Investigator's opinion, the cause of death was probably due to worsening of pneumonia. The Sponsor assessed the event of transaminitis as unlikely related to the entire study drug regimen. The patient had normal liver function up to Week 8 of trial treatment. She developed Grade 4 transaminitis 9 days after trial drug administration was interrupted. Methamphetamines abuse, concomitant paracetamol, concurrent infection, respiratory distress, and poor peripheral perfusion could provide alternative explanations for the event of transaminitis. There was no convincing evidence identified in supporting potential trial drugs (bedaquiline, pretomanid, and linezolid) induced effects. The Investigator and Sponsor considered the sepsis and pneumonia as not related to study drug. The causal relationship between trial drugs and the reported event of transaminitis cannot be established.

<u>Patient 6 (Death; 2 SAEs: septic shock, pneumonia)</u>

The patient was a 27-year-old mixed-race female with XDR-TB who developed worsening pneumonia, hospital-acquired infection (MDR *Escherichia coli*), acute respiratory distress syndrome, and then septic shock (secondary to pneumonia). The patient was HIV negative and had a Screening BMI of 17.1 kg/m^2. The patient's medical history included XDR-TB since 06 January 2017 and DS-TB from 2012 to an unknown date. Other medical history included loss of weight since 2015, COPD since 2016, dyspnea on exertion since September 2016, nausea since November 2016, intermittent vomiting since November 2016, peripheral sensory neuropathy

since December 2016, fever since January 2017, cornea verticillata since an unknown date, and dental abscess from 25 January 2017 to an unknown date in January 2017. On (b) (6) the patient received her first administration of trial drug for XDR-TB.

On (b) (6) (54 days after the first administration of trial drug), the patient experienced a nonserious Grade 1 event of upper respiratory tract infection, and starting from an unknown date in April 2017, the patient experienced a nonserious Grade 1 bronchospasm. On (b) (6) (73 days after the first administration of trial drug), the patient presented to the study center complaining of chest pain (pleuritic and muscular in nature), worsening of her cough, tightness of the chest, and feeling unwell. The patient was started on intravenous normal saline and Ringer's lactate fluids for the dehydration, amoxicillin/clavulanate, and ibuprofen. On (b) (6) (b) (6) (75 days after the first administration of trial drug), the Investigator was contacted by one of the trial nurses informing that the patient was confused and very unwell. The study center could not intubate and ventilate the patient at the Brooklyn Chest hospital. The Investigator immediately contacted the referral hospital, 2 private hospitals, and another government hospital, but none of the hospitals could admit the patient immediately for intubation and ventilation. The patient lost consciousness and died.

The events of worsening pneumonia and septic shock (secondary to pneumonia) were reported as fatal. According to Investigator's assessment, septic shock (secondary to pneumonia) and worsening pneumonia were the causes of death; the Investigator and Sponsor assessed these events and death as not related to the study drug regimen.

The MGIT culture result for Week 8 ((b) (6) Day 57) was still reported as positive. On (b) (6) an autopsy report was received, and findings of note included: Serous cavities examination showed right-sided pleural adhesions. Distal destruction of bronchi on the right side was noted. An extensive granulomatous inflammation with central caseation was present in the right lung, but no viable acid-fast bacilli were seen. Some mild chronic inflammation of the lung parenchyma on the left side with focal edema and changes of mild pulmonary hypertension were seen. On the right side, the lung was shrunken, approximately 9 × 18 × 8 cm, with adherent pleura. On cut surface, there was a loss of the airspaces with a central, pink-black mass surrounded by gelatinous lung parenchyma. The proximal tubules of the kidney showed loss of nuclei indicating acute tubular necrosis, consistent with shock. Bacteriological culture of the lung showed no anaerobic growth after 2 days incubation and isolated 2 organisms: MDR *Escherichia coli* and *Pseudomonas putida*. The *Escherichia coli* culture showed resistance to multiple drugs. The presence of MDR *Escherichia coli* indicated the presence of a hospital-acquired bacterial infection. Mycobacterial Culture Liquid Medium showed negative growth after 42 days of incubation. The probable cause of death was septic shock secondary to acute respiratory distress syndrome secondary to a superimposed hospital-acquired pneumonia. Predisposing factor was a primary *M. tb* infection.

Patient 7 (Death; SAE: death)

This patient died of "natural causes" during follow-up. He was a 39-year old black male patient with XDR-TB and HIV co-infection, with a CD4 count of 245 cells/µL. Medical history

included syphilis, dysphonia, dry skin, and hypoesthesia. On [redacted] the patient received the first administration of trial drug. He culture converted at Week 4, completed trial treatment on [redacted] and remained culture negative until his Month 3 post-treatment visit.

On [redacted] the patient was last seen at the study center for his Month 3 follow-up visit and his sputum culture was negative for *M. tb*. His closest family member (his cousin) reported that he had left home in late September 2017 and could not be contacted. His cousin reported he moved, probably stopped taking his antiretroviral drugs, and did not attend any healthcare facility. She also suspected that he had started using recreational drugs and was drinking alcohol excessively.

On an unreported date, his family was notified about his death that occurred on [redacted] and he was buried on [redacted] He died at home and the death certificate stated case of death as natural causes (Note: In South Africa death due to natural cause means no violence involved). The Sponsor considered this patient to have died of causes unrelated to TB following confirmed negative cultures after completing trial drug therapy, and unrelated to the study drug regimen.

10.2.2 Relapsed Within Month 6 Follow-Up

Patient 8 (relapsed in Month 3 of follow-up; Death; 5 SAEs: thrombotic thrombocytopenic purpura, dry gangrene, sepsis, peripheral vascular disorder, infected skin ulcer)

This patient relapsed with pulmonary TB in Month 3 of follow-up after completing the protocol-specified treatment with the trial treatment. He was a 55-year-old black male patient, who initially had pulmonary DS-TB in 2009, then XDR-TB since 15 October 2015. He received his first dose of trial treatment on [redacted] Prior treatment of his TB included levofloxacin, terizidone, pyrazinamide, amoxicillin/clavulanate, aminosalicylic acid, and clofazimine. Medical history included HIV co-infection October 2015, with a CD4 count of 67 cells/µL and a viral load of 87 copies/mL on Screening. Concomitant medications reported for HIV treatment prior to Screening included efavirenz, emtricitabine, tenofovir disoproxil, abacavir, lamivudine, and nevirapine. The patient received the full 26 weeks of trial treatment with pretomanid, bedaquiline, and linezolid, with the linezolid dose decreased to 600 mg/day during Week 17 due to an AE of peripheral neuropathy. Trough concentrations of the investigational drugs at Week 8 were all above the mean of all patients with Week 8 trough concentrations. During the trial, the patient's ART was abacavir, lamivudine, and nevirapine. Of note, after nearly 6 months of treatment, the patient's viral load was "lower than detectable limit," with a CD4 of 73 cells/µL. The site considered the patient likely an immune non-responder considering his long-term viral suppression and relatively poor CD4 response.

On clinical evaluation [redacted] during the Month 4 of follow-up, the patient was clinically well, but his chest x-ray showed ongoing left-sided infiltrates with a new large left upper lobe cavitation. On [redacted], the patient was seen at the trial center and was complaining of new productive, intermittent cough since [redacted] He was withdrawn

from the trial on (b) (6) and transferred to the National TB Treatment program for further therapy while being followed up for safety assessments according to the protocol.

Prior to Screening (15 October 2015), the patient had documentation from the provincial TB laboratory of a positive culture for *M. tb* resistant to isoniazid, rifampicin, kanamycin, and ofloxacin. On Screening he had a sputum smear positive for acid-fast bacilli, and a Line Probe molecular assay confirmed *M. tb* resistant to isoniazid and rifampicin. Sputum cultures from paired samples were positive prior to initiation of dosing, and at Weeks 1, 2, 4, 6, and 8. Cultures from paired sputum samples were negative at Weeks 12, 16, 20, and 26, with the completion of trial treatment on (b) (6) and at follow-up Month 1 and 2. Sputum samples were confirmed positive for *M. tb* on 3 different dates beginning Month 3 of follow-up on (b) (6) (b) (6)

Isolates from sputum cultures at baseline and at the first positive culture from Month 3 follow-up at the trial central laboratory both determined resistance in liquid culture to ethambutol, isoniazid, kanamycin, moxifloxacin, pyrazinamide, rifampicin, and streptomycin. The MIC values for the trial drugs noted values of 0.12 μg/mL for pretomanid and 0.5 μg/mL for linezolid, both at baseline and at the Month 3 follow-up, and a value of 0.5 μg/mL for bedaquiline at baseline that increased to 4.0 μg/mL at the Month 3 follow-up. Phenotypic drug sensitivity testing found that both the baseline and Month 3 follow-up isolates were resistant to a panel of 17 drugs except for susceptibility to para-aminosalicylic acid and linezolid. Whole genome sequencing at the South African National Institute for Communicable Diseases Laboratory (NICD) in Johannesburg, South Africa of these isolates determined that 1 of the genes relevant to bedaquiline resistance, Rv0678, changed from wild type at baseline to a 138-139 insG variant at the Month 3 follow-up. Whole genome sequencing at the central laboratory determined that the Month 3 follow-up isolate had only 5 single nucleotide polymorphism differences from the baseline isolate. Thus, the patient was considered to have had a relapse of pulmonary TB infection at the Month 3 of follow-up after completion of trial treatment based on both the positive sputum cultures at follow-up and a chest x-ray and symptoms consistent with a pulmonary TB infection.

After withdrawal from the trial due to relapse, the patient died due to a presumptive diagnosis of thrombotic thrombocytopenic purpura secondary to sepsis, caused by gangrene from peripheral vascular disease, which was considered unlikely related to trial treatment regimen by the Investigator and the Sponsor.

Patient 9 (relapsed in Month 2 of follow-up)

This patient relapsed with pulmonary TB in Month 2 of follow-up after completing the protocol-specified treatment with the trial treatment. She is a 21-year-old mixed race female with MDR-TB non-responsive to treatment. She had previous pulmonary DS-TB in 2009, when she completed treatment, and in 2013, when she defaulted in completing treatment. She was HIV negative and had pulmonary MDR-TB with a moderate left pleural effusion unresponsive to MDR-TB treatment that was diagnosed on 09 December 2015. Other history included COPD. She commenced MDR-TB treatment on 10 December 2015 and was deemed a treatment failure

based on sputum samples done on 25 August 2016. She was on the following agents from 10 December 2015: terizidone, pyrazinamide, moxifloxacin, ethambutol, ethionamide, (discontinued on 28 January 2016), isoniazid 600 mg orally QD (discontinued on 16 May 2016), and kanamycin 1 g intramuscularly 5x/week daily (discontinued on 16 May 2016); and clofazimine and para-aminosalicylic acid were added during May 2016. She started BPaL trial treatment on 17 November 2016 and completed treatment on 17 May 2017, remaining on linezolid 1200 mg orally QD throughout the trial. PK samples were available for her at Weeks 2, 8, and 16; her 3 linezolid trough concentrations were all below the limit of quantification, her 3 pretomanid concentrations were all very low but quantifiable, and her 3 bedaquiline and M2 concentrations were somewhat low relative to other patients in the study. This raised a question as to whether her adherence to the drug regimen was not adequate. She withdrew early from the trial on 18 January 2018 due to relapse at 2 months post-treatment.

The patient had cultures positive for *M. tb* complex from baseline to Week 8. She converted at Week 12 and remained culture negative until her Month 2 visit post-treatment completion. At her Month 3 visit (Day 85), she was clinically well with no symptoms of TB, however, had lost weight and had crepitations in the apex of the left lung with wheezing. At a follow-up visit after her Month 3 visit, she had lost 2 kg and had scattered wheezes and crepitations in her left apex on respiratory examination, but still reported no symptoms. These clinical findings were attributed to lung damage and COPD due to many years of TB infection. Her Month 2 follow-up visit sputum sample results then became available, and both were positive for *M. tb* complex. All the following follow-up visits – Month 3 (22 August 2017, Day 279), Month 6 (20 November 2017, Day 369), and unscheduled follow-up visits on 30 November 2017 and 18 January 2018 – yielded cultures that were positive for *M. tb* complex. Her clinical signs and symptoms deteriorated over this time, and she was referred to the local treatment facility for further management of her TB and to start individualized treatment. The patient was withdrawn after completing her Month 6 post-treatment visit and is being followed up for survival outcomes.

Results for extended drug susceptibility tests from the South Africa NICD on 24 November 2017 showed resistance to ethionamide, isoniazid, kanamycin, rifabutin, and rifampicin. MICs to bedaquiline, clofazimine, and delamanid were all considered sensitive. The drug susceptibility test results obtained at the central laboratory confirmed those from NICD for the following drugs: isoniazid, rifampicin, ethambutol, kanamycin, and moxifloxacin. In addition, the Month 2 follow-up isolate was also resistant to pyrazinamide (at 100 μg/mL) and streptomycin (at 1 μg/mL), and MIC testing found MICs of bedaquiline 0.5 μg/mL (sensitive), pretomanid 0.25 μg/mL (sensitive), and linezolid 1 μg/mL (sensitive). Even though no baseline isolate could be tested for comparison to post-treatment isolate, it is clear that the Month 2 follow-up isolate had not acquired resistance to any of the trial drugs. While the lack of a baseline isolates precluded comparison with the positive samples post-treatment by whole genome sequencing, the patient was considered to have relapsed. The patient was referred to start individualized treatment in the National TB Treatment Program.

10.2.3 Relapsed After Month 6 Follow-Up

Patient 10 (relapsed in Month 15 of follow-up)

This patient is 44-year-old black male with XDR-TB who had a relapse at 15 months after completion of the trial drug regimen. He had HIV infection with a CD4 count prior to Screening of 473 × 10^6/L, and a viral load lower than detectable limits. Other medical history included diabetes mellitus, hypertension, gastroesophageal reflux, and previous DS-TB meningitis in 2009 with completed treatment. He was diagnosed with XDR-TB on sputum samples done on 24 April 2013 and was also not responsive to XDR-TB treatment. Prior to enrollment into the trial, he was receiving the following regimen from 14 June 2013 until 03 July 2015: moxifloxacin, capreomycin, terizidone, ethionamide, para-aminosalicylic acid, clofazimine, isoniazid, pyrazinamide, and ethambutol. The patient was screened on 26 June 2015.

He commenced trial drugs on 03 July 2015, which were then temporarily withheld for 30 days due to Grade 3 transaminitis identified on blood samples taken on Screening, which worsened at each subsequent visit. The trial drug was stopped on 31 July 2015. Trial drug recommenced on 30 August 2015 once the patient's transaminase values had halved. He was asymptomatic throughout the period of transaminitis. He was on linezolid 600 mg BID throughout the treatment period. The Week 2 and Week 16 pretomanid and linezolid trough concentrations were around or below the respective population medians. Trial treatment was completed on 27 January 2016, 209 days after starting the trial drugs.

He then relapsed at 15 months on 18 January 2017. The patient had cultures positive for *M. tb* complex from baseline to Week 12. He converted on Week 16 and remained negative until Month 15 of follow-up, with 2 *M. tb* complex-positive cultures obtained that day. The *M. tb* isolated from the patient at baseline and Month 15 follow-up visits were evaluated by drug susceptibility tests and MIC testing at the central laboratory and the South African NICD. Altogether, these tests revealed the baseline and Month 15 follow-up isolates shared the exact same susceptibility profile, with resistance to 13 drugs tested and sensitivity to linezolid, bedaquiline, and clofazimine. Whole genome sequencing and analysis of genes known to be implicated in resistance to some of the drugs confirmed the drug susceptibility test and MIC results. Moreover, the exact same drug-conferring mutations were found in the baseline and follow-up isolates, suggesting the same strain was isolated in both visits. This could not be formally shown, however, as paired whole genome sequencing failed.

At his visit on 18 May 2017, the patient's respiratory examination was remarkable for decreased air entry on the right upper zone with coarse bilateral crepitations, particularly in the right mid-zone and left lower zones. He reported that he felt better than before, however, admitted that he had intermittent pleuritic chest pain for approximately 2 weeks. A repeat x-ray was performed which showed a similar diffuse reticulonodular pattern of infiltrates bilaterally as his Screening chest x-ray. After careful consideration of the available results, the patient was considered to have relapsed. He was started on an individualized regimen at a specialist TB hospital consisting of bedaquiline, delamanid, linezolid, clofazimine, para-aminosalicyclic acid, rifabutin,

pyrazinamide, and moxifloxacin. He was discharged from the hospital after 4 months following 2 consecutive negative sputum cultures.

The patient was seen on 23 January 2018 for a final follow-up visit at Month 24 post-treatment completion. On further follow-up he appeared to be doing well, and his last sputum culture, which was done on 26 March 2018 at the local laboratory, remained negative.

10.2.4 Adverse Events of Special Interest

SAE: syncope

This 40-year old Black male patient with XDR-TB and HIV co-infection was hospitalized for a Grade 3 syncopal event on Day 155. The patient was standing in a queue when he felt dizzy and fell over; no seizure activity was witnessed, although the patient was noted to have bleeding from his right ear on transfer to the hospital. After observation in the hospital, the patient was discharged on Trial Day 162; no discharge summary was available. On return to the study site 11 days after discharge, the patient was found to be hemodynamically stable and fully oriented. Electrocardiogram results at 5 of 7 visits prior to the event of syncope showed low QRS voltage in the limb leads; 1 reading was normal and another showed nonspecific ST and T wave abnormality. Electrocardiogram results at visits following the event included 5 normal readings and 2 readings showing low QRS voltage in limb leads-atypical ECG. The patient had no QTcB or QTcF value ≥450 msec and no increase of ≥50 msec in either parameter at any assessed time point. The event of syncope was considered not related to study drug. Of note, the patient had a history of hypotension and on Screening had a blood pressure of 92/62 mmHg and a heart rate of 94 beats per minute. Of note, he was found to have a complete perforation of the right tympanic membrane (traumatic) 11 days after discharge from the hospital.

Hy's Law (1)

One patient, a 36-year-old HIV-negative female with XDR-TB had a medical history notable for intermittent anxiety, chronic obstructive airway disease, dyspepsia, and insomnia. At her Week 4 visit, she complained of vomiting (Grade 1) and epigastric pain (Grade 2) and was started on lansoprolol, paracetamol, and cyclizine for suspected severe gastritis. She improved but on Day 29 had recurring epigastric pain and weakness. She was treated with intravenous hydration, and the serious AE of abdominal pain upper (verbatim term: worsening epigastric pain) was reported; the study drug regimen was also interrupted. Between Weeks 7 and 8, the patient admitted to consuming alcohol over the weekend. An abdominal ultrasound during Week 8 showed no features of tuberculosis, no biliary duct dilation, or focal liver lesion, and the study drug regimen was resumed.

During Week 10, the study drug regimen was stopped again due to liver enzyme increase, and on Week 12 the study drug regimen was resumed. The patient's abdominal pain resolved during the fourth month after enrollment.

All hepatic clinical chemistry tests were within normal limits at Screening and Baseline. The AST and GGT increased to Grade 1 at Week 2, ALP increased to Grade 1 during Week 4, ALT

increased to Grade 1 during Week 6, and total bilirubin increased to Grade 2 during Week 9. During Week 11, values for ALT, AST, ALP, and GGT reached peaks of 255 U/L, 329 U/L, 330 IU/L, and 357 U/L, respectively. Total bilirubin peaked at a Grade 4 value of 56 µmol/L during Week 11, with a high direct bilirubin of 31 µmol/L and an indirect bilirubin of 26 µmol/L. The values for ALT and AST rapidly decreased to Grade 1 during Weeks 12 to 13, and bilirubin decreased to within normal limits by Week 12 and remained normal through the remainder of the study.

The patient's ALT, AST, ALP, and GGT increased again during Week 20, but the treatment regimen was continued. During Week 20, values for ALT, AST, ALP, and total bilirubin were 115 U/L, 228 U/L, 290 U/L, and 17 µmol/L, respectively. By Week 26, the values were within normal range, except for a slight elevation of ALP: 26 U/L, 27 U/L, 117 U/L, and 6 µmol/L for ALT, AST, ALP, and total bilirubin, respectively. GGT peaked at a Grade 4 value of 620 U/L at Week 22 and decreased to Grade 1 by the end of treatment. The patient's abdominal pain did not return with reintroduction of the study drug regimen, and the hepatic chemistry abnormalities resolved during continued study drug treatment. During the period of hepatic chemistry abnormalities, the patient was treated with concomitant medications that included lansoprazole, metoclopramide, paracetamol, albuterol, Depo-Provera, and tramadol.

When ALT, AST, and total bilirubin were elevated, GGT and ALP were also elevated. This suggests possible cholestasis or hepatic obstruction rather than a primary drug-induced liver injury. The patient admitted alcohol use (at least 1 and a half beers) while out of the hospital on pass, and the elevated GGT suggest that the toxic effects of alcohol may have contributed to the abnormalities. Further, the elevated ALT, AST, and total bilirubin returned to normal while the patient was taking study drug, and the patient later admitted to consuming alcohol.

Per review by the Hepatotoxicity Committee, this event does not qualify as a Hy's law case because the ALP was >2 × ULN, and the R ratio was <5 (actual value 4.1), indicating mixed hepatocellular injury and cholestasis.

Hy's Law (2)

One patient, a 25-year-old HIV-negative male with XDR-TB, had a medical history notable for spontaneous pneumothorax, intermittent hemoptysis, and nausea. The patient's ALT level increased from a normal value of 19 U/L at baseline to a Grade 1 value of 62 U/L at Week 6, peaked at a Grade 3 value of 252 U/L during Week 8, and then rapidly decreased to a Grade 1 value of 50 U/L during Week 12 and then a normal value of 41 U/L during Week 20. Thereafter, the patient's ALT level remained within the normal range through follow-up. The patient's AST levels progressed in a manner similar to ALT, and total bilirubin increased from a normal value of 21 µmol/L during Week 6 to a Grade 4 value of 46 µmol/L during Week 8, and then returned to a normal value of 15 µmol/L during Week 12. Of note, ALP was elevated to a Grade 1 value of 144 IU/L at baseline, increased to a peak value of 237 IU/L during Week 8, and then returned to normal range (126 IU/L) by Week 16.

During the period of liver enzyme elevations, the patient reported AEs of nausea, vomiting, elevated urine microalbumin, and anemia. Concomitant medications during this period included metoclopramide, morphine, pyridoxine, and chloromycetin eye ointment. The study drug regimen was interrupted during Week 8 and was restarted during Week 11. All 3 study drugs in the regimen were continued to completion without further interruption or further clinically significant abnormalities of hepatic chemistry values during rechallenge.

The negative rechallenge suggests effects other than drug-induced liver injury, but may also indicate "adaptation" to the injury during the first exposure. While the peak ALT was >3 × ULN and total bilirubin >2.2 × ULN with ALP <2 × ULN (actual value 1.8 × ULN), the injury pattern was mixed rather than hepatocellular (based on the R value of 3.8) and the peak serum ALT values attained were not as high as would be expected for hepatocellular injury sufficient to result in the rise in serum bilirubin observed. For this reason, this is considered an equivocal Hy's law case.

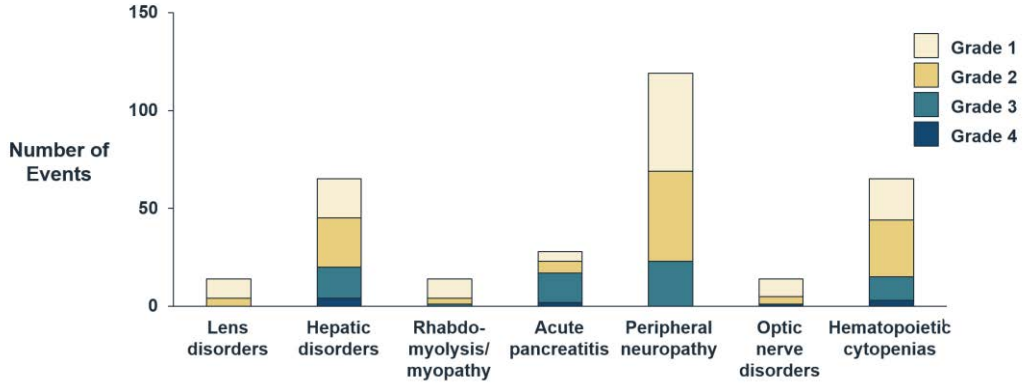
SAE: pancreatitis

The patient, a 38-year-old HIV-positive black female with XDR-TB, had Screening amylase and lipase values of 189 U/L (normal range 28-100 U/L) and 85 U/L (normal range 13-60 U/L), respectively. The patient also had Day 1 pre-dose mild elevations of ALT, AST, and ALP, with GGT >3 times ULN. Her medical history was negative for alcohol use. The patient received a pancreatitis diagnosis based on an ultrasound report 64 days after the first dose of study drug. The patient had no clinical symptoms, and the highest amylase and lipase values were 261 U/L and 129 U/L, respectively. Treatment with BPaL was interrupted because of the event but was resumed shortly thereafter. The patient completed the final 100 days of study treatment without interruptions or any symptoms suggestive of pancreatitis. During this period her lipase value decreased from 92 to 74 U/L. Given the baseline elevations in amylase, lipase, and hepatic enzymes, including GGT, the lack of symptoms suggestive of pancreatitis, and the reductions in lipase during the last 3 months of uninterrupted study drug treatment, it is unlikely this patient had pancreatitis caused by the study drug regimen.

10.3 Additional Safety Information

10.3.1 Severity of Adverse Events of Special Interest

Figure 14: Severity of AESIs Occurring in ≥10% of Patients[a]



a. Based on standardized MedDRA queries.
MedDRA= Medical Dictionary for Regulatory Activities

10.3.2 Additional Analysis of Hepatic Enzyme Elevations

Table 47 summarizes the elevations in ALT, AST, and total bilirubin for all 1,168 individuals who were exposed to pretomanid in the clinical development program (total pretomanid group) and individuals who received non-pretomanid treatment in the Phase 1–3 clinical studies (comparator/control group). The 1,168 pretomanid-treated patients were combined as a total pretomanid group and broken out into 3 categories of exposure: pretomanid alone, pretomanid in combination with other drugs (excluding BPaL regimen), and the BPaL regimen.

Overall, 66 (5.7%) individuals in the total pretomanid group had maximum ALT or AST values >5 × ULN versus 13 (3.8%) in the comparator/control group. Notably, the pretomanid-alone group had fewer of these cases (3 [0.7%]) versus in the pretomanid combination therapy and BPaL groups (57 [9.0%] and 6 [4.8%], respectively). ALP increases >2 × ULN occurred in 2.8% of the total pretomanid group versus 3.8% in the comparator/control group. Regarding potential Hy's law cases (ALT or AST >3 × ULN and bilirubin >2 × ULN), there were no cases in the pretomanid-alone group versus 6 (0.5%) in the total pretomanid group and 3 (0.9%) in the comparator/control group.

The data indicate that hepatotoxicity occurred in all treatment groups but notably in a higher proportion of individuals treated with BPaL, other pretomanid combinations, or comparator (mostly HRZE) compared with pretomanid alone, although studies using pretomanid alone were only 2 weeks in duration. This pattern held with both Hy's law cases and those with ALT or AST >5 × ULN.

Table 47: Elevated Liver-Related Laboratory Parameters (Phase 1–3 Studies)

	Pretomanid-Alone N=411 n (%)	Pretomanid Combination Therapy[a] N=633 n (%)	BPaL[b] N=124 n (%)	Total Pretomanid N=1,168 n (%)	Comparator/ Control[c] N=339 n (%)
ALT or AST >5 × ULN	3 (0.7%)	57 (9.0%)	6 (4.8%)	66 (5.7%)	13 (3.8%)
ALP >2 × ULN	6 (1.5%)	24 (3.8%)	3 (2.4%)	33 (2.8%)	13 (3.8%)
ALT or AST >3 × ULN and total bilirubin >2 × ULN	0	4 (0.6%)	2 (1.6%)	6 (0.5%)	3 (0.9%)
Unique individuals (meeting any of the above criteria)	9 (2.2%)	74 (11.7%)	7 (5.6%)	90 (7.7%)	22 (6.5%)
Study participants	DS	Healthy volunteers DS MDR	TI/NR MDR XDR	Healthy volunteers DS MDR XDR	Healthy volunteers DS MDR

a. Includes pretomanid with any combination of drugs except BPaL.
b. Includes 109 patients from Nix-TB and 15 patients from ZeNix.
c. Includes HRZE, bedaquiline-pyrazinamide-clofazimine, bedaquiline-pyrazinamide, bedaquiline alone, pyrazinamide alone, clofazimine alone, and placebo.
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BPaL=bedaquiline-pretomanid-linezolid; DS=drug-susceptible; HRZE=isoniazid-rifampicin-pyrazinamide-ethambutol; MDR=multi-drug resistant; TI/NR=treatment intolerant/nonresponsive; ULN=upper limit of normal; XDR=extensively drug-resistant