FDA Briefing Document

Pretomanid Tablet, 200 mg
Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

June 06, 2019

The committee will discuss new drug application (NDA) 212862

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The FDA have brought Pretomanid tablets to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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1 Introduction

This briefing document prepared by the FDA for panel members of the Antimicrobial Drugs Advisory Committee describes the safety and efficacy data for pretomanid. The FDA would like the committee to discuss whether the data are adequate to support the safety and efficacy of pretomanid as part of a regimen (B-L-Pa: bedaquiline, linezolid, pretomanid) for treatment-intolerant/nonresponsive multi-drug resistant tuberculosis (TI/NR MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).

2 Background

Pretomanid (also known as PA-824) is not currently marketed in the US or anywhere in the world. In the NDA, pretomanid was evaluated as part of an oral regimen in combination with bedaquiline and linezolid for the treatment of TI/NR MDR-TB and XDR-TB.

3 Product Information

Pretomanid is a nitroimidazooxazine antimycobacterial drug. Each immediate-release tablet contains 200 mg of pretomanid.

4 Regulatory History

Clinical trials of pretomanid (> 14 days of treatment) in various antimycobacterial drug regimens are summarized in Table 8-1.

Pretomanid was granted orphan drug designation and Fast Track designation for the treatment of tuberculosis, and Qualified Infectious Disease Product (QIDP) designation for the treatment of DS-TB, MDR-TB and XDR-TB. The NDA was granted a priority review.

The applicant and the Agency agreed that an interim clinical study report (CSR) providing safety and efficacy data on the first 45 subjects assessed for the primary efficacy endpoint in the ongoing single-arm Phase 3 trial (Nix-TB) in patients with XDR-TB and TI/ NR MDR-TB would be acceptable to support an NDA submission. In addition, the Agency agreed that an addendum to the CSR with updated efficacy and safety data on all 109 enrolled subjects could be included in the initial NDA submission. To support the efficacy outcomes in Nix-TB, the applicant agreed to provide a literature summary and case-matched analysis of historical control data for XDR-TB patients.

Other agreements between the applicant and the Agency included:

- Ophthalmological evaluations for cataract formation would be incorporated in clinical trials of pretomanid dosed for more than 14 days, based on a signal for cataract formation in nonclinical studies.

- The signal for male infertility observed in animal toxicology studies of pretomanid would be further investigated clinically, including evaluations of male hormone levels in clinical trials and a semen analysis study in human subjects.
- Additional hepatic impairment and renal impairment pharmacokinetic (PK) studies would be conducted concurrent with the NDA.

As agreed with the Agency at the pre-NDA meeting, results of the semen analysis study and the hepatic impairment and renal impairment PK studies will not be available until after NDA review.

5 Clinical Pharmacology

Absorption
Pretomanid exposures were approximately dose-proportional over a dose range from 50 to 200 mg. At doses greater than 200 mg, exposure increased in a less than dose-proportional manner. Steady-state pretomanid plasma concentrations were achieved at approximately 4 to 6 days following multiple dose administration of 200 mg and the accumulation ratio was approximately 2. Administration of a 200 mg dose of pretomanid with a high-fat, high-calorie meal increased mean C_{max} by 76% and mean AUC_{∞} by 88% as compared with the fasted state. PK parameters following single and multiple 200 mg doses of pretomanid in healthy adult subjects are summarized in Table 5-1.

Table 5-1. Pretomanid Pharmacokinetic Parameters in Healthy Adult Subjects Under Fasted and Fed Conditions

PK Parameter	Single Dose 200 mg; Fasted	Single Dose 200 mg; Fed	Steady State 200 mg QD; Fasted
C_{max} (µg/mL)	1.1 (0.2)	2.0 (0.3)	1.7 (0.3)
AUC_t(µg•hr/mL)	28.1 (8.0)	51.6 (10.1)	[§]30.2 (3.7)
AUC_{inf} (µg•hr/mL)	28.8 (8.3)	53.0 (10.6)	[#]ND
[*]T_{max} (hr)	4.0 (2.0, 6.0)	5.0 (3.0, 8.1)	4.5 (2.0, 8.0)
Vd/F (L)	180 (51.3)	97.0 (17.2)	[#]ND
$t_{½}$ (hr)	16.9 (3.1)	17.4 (2.8)	[#]ND
CL/F (L/hr)	7.6 (2.5)	3.9 (0.8)	[#]ND

All values are reported as mean (SD); [*] - Median (minimum, maximum); [§] - AUC_{24}; [#] ND = Not determined

Distribution/Elimination

The human plasma protein binding of pretomanid is approximately 86.4 %. Following administration of ^{14}C radiolabeled pretomanid in healthy adult males, approximately 53% of a radioactive dose was excreted in urine and 38% in feces, primarily as metabolites; approximately 1% of the dose was excreted in the urine as unchanged pretomanid.

Metabolism/Drug-Drug Interactions (DDI)

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: CYP3A4 plays a minor role in the metabolism of pretomanid, i.e., up to 20%. Pretomanid is not a substrate of CYP2C9, CYP2C19, and

CYP2D6. Pretomanid is not an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations based on in vitro studies. Pretomanid is not an inducer of CYP3A4 and CYP2C9 at clinically relevant concentrations based on *in vitro* studies.

Transporter Systems: In vitro studies indicate that at clinically relevant plasma concentrations, pretomanid inhibits the OAT3 drug transporter which could result in increased concentrations of OAT3 substrates clinically. No clinical DDI studies have been conducted with OAT3 substrates. However, co-administration of pretomanid with drugs that are OAT3 substrates (e.g., methotrexate) should be avoided.

In vitro studies indicate that at clinically relevant plasma concentrations, pretomanid is not likely to inhibit human OAT1, OCT1, OCT2, OAT1B1, OATP1B3, BCRP, BSEP, P-gp, MATE1, and/or MATE2-K mediated transport. Pretomanid is not likely to be a substrate of OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and/or P-gp transporters.

Clinical DDI Studies

Pretomanid does not inhibit or induce the metabolism of CYP3A4 substrates to a clinically significant extent. In a DDI study with a sensitive CY3A4 substrate, midazolam, co-administration of pretomanid with midazolam resulted in no clinically significant change (i.e., increase or decrease) in the systemic exposure of midazolam or its major metabolite, 1-hydroxy midazolam. Thus, pretomanid may be co-administered with drugs that are substrates of CYP3A4.

Co-administration of pretomanid with rifampin reduced the AUC and C_{max} of pretomanid significantly. Thus, rifampin and other strong CYP3A4 inducers should not be administered with pretomanid.

Co-administration of pretomanid with ritonavir-boosted lopinavir did not significantly affect pretomanid exposure and ritonavir-boosted lopinavir is not likely to cause a clinically significant drug-drug interaction upon co-administration with pretomanid.

Co-administration of pretomanid with efavirenz reduced the AUC and C_{max} of pretomanid. Also, based on the approved bedaquiline labeling, efavirenz is not recommended to be co-administered with bedaquiline. Therefore, efavirenz should not be used with the B-L-Pa regimen.

Specific Populations

Population PK analyses indicate that the PK of pretomanid was not significantly affected by age and race. Body weight, gender, HIV status, and pulmonary TB status affected the PK of pretomanid. However, the overall effect of these covariates on the PK of pretomanid is not deemed to be clinically significant. The PK of pretomanid has not been studied in patients with renal or hepatic impairment.

6 Microbiology

Mechanism of action:
Pretomanid inhibits cell wall biosynthesis via blockage of the oxidation of hydroxymycolate to ketomycolate. Under anaerobic conditions, pretomanid causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species.

In vitro activity:
The pretomanid minimum inhibitory concentration (MIC) range for the drug susceptible (defined as susceptible to first line TB drugs) *M. tuberculosis* (MTB) isolates (n = 68) ranged from 0.005 to 0.48 mcg/mL using the Mycobacterial Growth Indicator Tube (MGIT) system. Against the multidrug resistant (defined as resistant to both isoniazid and rifampicin) MTB isolates (n = 26) and extensively drug resistant (defined as resistant to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin) in addition to multidrug resistance) MTB isolates (n = 6), the pretomanid MIC range was 0.005 to 16 mcg/mL. The isolate with MIC of 16 mcg/mL was resistant to pretomanid.

Resistance:
The *in vitro* frequency of spontaneous resistance to pretomanid (at 2x MIC to 6x MIC) is 10^{-5} to 10^{-7} and similar to isoniazid and delamanid but more frequent than that seen with rifampicin. The mechanism of resistance to pretomanid in MTB includes 5 non-essential genes associated with the bioreductive activation of pretomanid within the bacterium.

In vivo activity:
The *in vivo* activity of pretomanid administered as oral monotherapy was examined in acute, chronic, and latent TB murine infection models by measuring mycobacterial burden. In the lung and spleen, the reduction of bacterial burden (in immunocompetent BALB/c mice), at a pretomanid dose of 25 mg/kg was similar to isoniazid at 25 mg/kg. In the gamma interferon knockout mice, the activity of 100 mg/kg pretomanid was similar to 25 mg/kg isoniazid. In the chronic infection mouse model, 2-3 $\log_{10}$ reduction in bacterial burden is achieved at 12 weeks of treatment with pretomanid (100 mg/kg); however, complete eradication is not achieved with monotherapy.

The activity of pretomanid (Pa, 100 mg/kg), bedaquiline (B, 25 mg/kg), and linezolid (L,100 mg/kg) as monotherapy, in 2-drug combinations, and as a 3-drug combination was evaluated in the murine TB model to demonstrate the contribution of each of the components in the combination (Table 6-1). The standard combination regimen of rifampicin (10 mg/kg), isoniazid (10 mg/kg), and pyrazinamide (150 mg/kg) was used as the comparator. BALB/c mice were infected via aerosol with ~4 .0 $\log_{10}$ CFU of *M. tuberculosis* H37Rv. Oral treatment once daily (5 days/week) was initiated 14 days post-infection. The lung bacterial burden was determined after 1, 2, or 3 months of treatment. Relapse was assessed in some studies by holding the mice for an additional 3 months following completion of treatment. The 3-drug combination of B-L-Pa, achieved a significantly greater CFU reduction than any of the 2-drug regimens (BPa; BL; PaL) ($p<0.02$), at both the 4-and 8-week treatment time points. Additionally, fewer mice treated with the 3-drug combination (B-L-Pa) for 2 or 3 months relapsed compared to 2-

drug combination (BPa, BL). Studies in guinea pigs support the *in vivo* activity of pretomanid.

Table 6-1: The *in vivo* Activity of Pretomanid Monotherapy, and as 2-drug and 3-drug Combinations against MTB in a Murine TB Model.

Regimen	Mean (±SD) Lung Log_{10} CFU count by time point			Proportion (%) relapsing after treatment period (months held post-treatment for assessment)		
	Month 1	Month 2	Month 3	Month 2 (+3)	Month 3 (+3)	Month 4 (+3)
Study Report JHU Study 2015 Experiment 2a-f						
$R_{10}H_{10}Z_{150}$	5.47 ± 0.19	1.43 ± 0.81	NR	NR	NR	NR
Pa_{100}	6.02 ± 0.19	4.57 ± 0.20	NR	NR	NR	NR
B_{25}	4.73 ± 0.20	2.09 ± 0.28	NR	NR	NR	NR
L_{100}	6.81 ± 0.13	5.61 ± 0.25	NR	NR	NR	NR
$B_{25}L_{100}$	4.79 ± 0.17	2.85 ± 0.25	NR	NR	NR	NR
$B_{25}Pa_{100}$	4.57 ± 0.21	1.80 ± 0.82	NR	NR	NR	NR
$Pa_{100}L_{100}$	5.33 ± 0.24	3.34 ± 0.52	NR	NR	NR	NR
$B_{25}Pa_{100}L_{100}$	2.75 ± 0.31	0.00±0.00	NR	NR	NR	NR
Study Report JHU 2014 Experiment 2f-a						
Untreated	9.04±0.03	NR	NR	NR	NR	NR
$R_{10}H_{10}Z_{150}$		3.09 ± 0.16	NR	NR	NR	NR
$B_{25}Pa_{100}L_{100}$	3.48 ± 0.11	0.85 ± 0.80	NR	NR	NR	NR
$B_{25}Pa_{100}$	5.0 0± 0.08	3.50 ± 0.05	NR	NR	NR	NR
$Pa_{100}L_{100}$	5.93 ± 0.09	4.21 ± 0.14	NR	NR	NR	NR
$B_{25}L_{100}$	5.38 ± 0.13	3.28 ± 0.24	NR	NR	NR	NR
Study Report JHU 2016 Experiment 3a						
$R_{10}H_{10}Z_{150}$	5.12 ± 0.14	2.55 ± 0.07	NR	NR	NR	7/15
$B_{25}Pa_{100}L_{100}$	3.10 ± 0.17	0.00 ± 0.00	NR	4/15	1/15	NR
$Pa_{100}L_{100}$	4.28 ± 0.10	2.75 ± 0.52	NR	NR	NR	NR
Study Report JHU Study 2017 3d-1						
$B_{25}L_{100}$	4.87 ± 0.16	2.69 ± 0.30	-	15/15	15/15	15/15
$B_{25}Pa_{100}L_{100}$	3.29 ± 0.09	0.68 ± 0.24	-	7/15	0/15	0/15
Tasneen et al 2016						
Untreated*	6.47± 0.06	-	-	-	-	-
2 $R_{10}H_{10}Z_{150}$/ 4 $R_{10}H_{10}$	3.47± 0.37	1.59± 0.25	0.50± 0.51		13/15	1/20
B_{25}	3.24± 0.25	NR	NR	NR	NR	NR
Pa_{50}	4.57 ± 0.22	NR	NR	NR	NR	NR
L_{100}	4.97 ± 0.26	NR	NR	NR	NR	NR
$B_{25}Pa_{50}$	4.21 ± 0.40	1.62 ± 0.19	0.52 ± 0.36	15/15	10/15	2/20
$B_{25}L_{100}$	2.82 ± 0.15	1.91 ± 0.66	NR	NR	NR	NR
$Pa_{50}L_{100}$	3.23 ± 0.41	1.48 ± 0.12	NR	NR	NR	NR
$B_{25}Pa_{50}L_{100}$	3.28 ± 0.65	0.34 ± 0.41	0.0 0± 0.00	12/15	0/14	0/20

CFU = colony-forming unit; B = bedaquiline; H = isoniazid; L = linezolid; Pa = pretomanid;
R = rifampicin; Z = pyrazinamide; the number shown as subscript next to the drug represents the dose that was tested: Pretomanid (50 mg/kg or 100 mg/kg), bedaquiline (25 mg/kg), linezolid (100 mg/kg); of rifampicin (10 mg/kg), isoniazid (10 mg/kg), and pyrazinamide (150 mg/kg).
Study Report JHU 2015 Experiment 2a-f: Day 0 untreated mean lung log10 CFU counts:7.68±0.27;
Study Report JHU 2014 Experiment 2f: Day 0 untreated mean lung log10 CFU counts:8.08±0.04
Study Report JHU 2016 Experiment 3a:; Day 0 untreated mean lung log10 CFU counts:7 30±0.10.
Tasneen et al 2016: Day 0 untreated mean lung log10 CFU counts: 6.17±0.27.
* no mice remained in the untreated control group at the 2- and 3-month time points

7 Pharmacology/Toxicology

The toxicology program for pretomanid included oral, repeat-dose studies in mice (up to 13 weeks), rats (up to 26 weeks), and cynomolgus monkeys (up to 39 weeks) with reversibility assessment for up to 3 months following termination of dosing, where needed. Genotoxicity was assessed using *in vivo* and *in vitro* assays and reproductive toxicity studies were conducted in rats and rabbits. *In vivo* and *in vitro* phototoxicity studies were also conducted, as well as special studies in rats and monkeys to investigate testicular toxicity. Toxicokinetic evaluations were conducted to characterize the exposure to pretomanid.

Adverse Events of Special Interest

QT prolongation
In conscious male cynomolgus monkeys, using a crossover, 7-day washout design study, pretomanid resulted in either no QT_c prolongation or marginal QT_c prolongation, depending on the formula used to derive the QTc. There were no pretomanid-related ECG changes in monkeys after 90 days of pretomanid with a 4-week recovery period or after 39 weeks with a 12-week recovery period.

Reproductive Toxicity

Fertility
Testicular toxicity was observed in mice and rats in all repeat-dose studies. Sperm motility was decreased in rats after as few as 3 days of dosing. Spermatocyte degeneration/necrosis was observed in the testes after as few as 7 days of dosing. Testicular effects showed evidence of being partially reversible during a 6-month recovery period in rats dosed for 7 days but were irreversible in rats dosed for as few as 14 days. Other findings included increased frequency of abnormal sperm morphology and decreased epididymal sperm counts. Pretomanid did not affect reproductive function in male rats given low daily oral doses (about 0.5x MRHD) for 13 weeks. Testicular toxicity was not a prominent feature in monkeys, but seminiferous tubule atrophy has been observed in a few monkeys at 0.5 to 2x MRHD (based on AUC comparisons).

Female rats dosed daily with oral pretomanid (at a dose about 4x MRHD for two weeks), showed body weight loss, reduced feed consumption, reduced number of estrous stages per 14 days, and a greater incidence of prolonged diestrus. When paired with treated males, the number of days in cohabitation was higher and there was complete infertility, although the reduced fertility may have been due to the effects on spermatogenesis in males.

Embryo-fetal Toxicity
Pretomanid administration to rats during organogenesis (Gestational Day [GD] 7 through 17) resulted in maternal toxicity (reduced maternal body weight and/or body weight gain and feed consumption during the entire dosage period). At high doses, post implantation loss was greater, litters were smaller, the number of live fetuses and fetal body weight were lower, and skeletal development was slowed (delayed ossification in hindlimb

phalanges). In rabbits dosed during organogenesis (GD 7 through 20), maternal toxicity (reduced feed consumption and maternal body weight) was observed at the high dose. No adverse effects on fetal survival, growth, or development were observed at doses about 1.5xMRHD.

Lactation

Administration of pretomanid to nursing dams resulted in the presence of pretomanid in milk at all dose levels. The pretomanid concentration was higher in milk than plasma at each dose level, but it was much lower in plasma of pups than plasma of dams.

Cataracts

Cataracts developed in rats given pretomanid for 13 weeks or for 26 weeks. In the 26-week study, the no-effect level for cataracts was approximately twice the predicted exposure in patients at the MRHD. Cataracts did not develop in monkeys given daily oral doses of pretomanid of 100 mg/kg for 39 weeks. This dose produced an average AUC_{0-24} value more than twice the exposure in patients at the MRHD.

CNS toxicity

In CD-1 mice given high daily oral doses of pretomanid for four weeks, clinical signs included spasms and abnormal spontaneous motor activity. The NOAEL for CNS-related findings was 250 mg/kg for 13 weeks in female CD-1 mice, with AUC_{0-24} values approximately 9 times the predicted exposure in patients at the MRHD.

In monkeys, ataxia and convulsions were observed at high doses given for four weeks. CNS-related clinical signs were not seen in monkeys dosed for 39 weeks at exposures (AUC_{0-24} values) similar to the predicted exposures in patients at the MRHD.

Liver toxicity

Hepatocellular hypertrophy, increased liver weight and increased serum transaminases were seen in mice, rats, and monkeys given daily oral doses of pretomanid at higher dose levels. In CD-1 mice given daily oral doses for 13 weeks, higher mean serum cholesterol concentration, higher serum AST (5x control mean) and ALT (3x control mean) and hepatocellular hypertrophy were seen. In rats given daily oral doses of pretomanid for 26 weeks, minimal centrilobular hepatocellular hypertrophy (and therefore, greater mean liver weight) were seen at ≥30 mg/kg/day, which produced mean AUC_{0-24} values similar to the predicted exposures in patients at the MRHD.

In monkeys given daily oral doses for 39 weeks, there was a reversible, dose-related increase in liver weight in males at all dose levels, (as low as 0.6x MRHD) which was not associated with histopathologic findings.

Carcinogenic Potential

Carcinogenicity studies in rats and mice are ongoing.

8 Overview of Clinical Development Program

Clinical trials of pretomanid in various drug regimens are summarized in Table 8-1.

Table 8-1. Phase 2/3 Studies: Pretomanid-containing Regimens (>14 days of Treatment)

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

In the NDA, the evidence of efficacy of pretomanid is primarily based on the ongoing Phase 3 trial of a B-L-Pa regimen, Nix-TB. The study has completed enrollment of 109 patients and is continuing long-term follow-up. Per agreement with FDA, the applicant provided efficacy data based on the results for the first 45 patients with complete primary outcome assessment data at 6 months after the end of 6-9 months of treatment. Therefore, the review strategy was to first assess outcomes in this subset and then examine updated outcomes from continued follow-up.

Table 8-2. Nix-TB Timeline

Calendar Date	Nix-TB Milestone
April 24, 2015	First patient enrolled.
August 17, 2017	Interim data cutoff. N = 45 patients in the MITT population with primary endpoint data 6 months after the End of Treatment. The applicant and FDA initially agreed that the NDA could be submitted with the efficacy assessment based on this data cutoff.
November 15, 2017	Last of N = 109 patients enrolled.
March 26, 2018	Interim data cutoff. N = 109 patients in the safety population. This data cutoff was used for safety analyses in the NDA submission and advisory committee backgrounder.
June 29, 2018	Interim data cutoff. N = 80 patients in the MITT population with primary endpoint data 6 months after the End of Treatment. N = 109 patients in the safety population. The applicant and FDA agreed that efficacy presentations at the advisory committee would be based on this interim data cutoff.
October 15, 2018	Interim data cutoff for the NDA 120-day safety update. N = 109 patients in the safety population.
January 18, 2019	Interim data cutoff from the NDA 120-day efficacy update. N = 104 patients in the MITT population with primary endpoint data 6 months after the End of Treatment. N = 109 patients in the safety population.

Another Phase 3 trial of a pretomanid containing regimen, NC-006, evaluated the combination of moxifloxacin plus pretomanid plus pyrazinamide for either 4 or 6 months for the treatment of DS-TB and 6 months for the treatment of MDR-TB. After enrolling 284 patients this study was prematurely terminated due to the applicant's view that more promising pretomanid regimens should be developed. The pretomanid regimens in NC-006 did not meet prespecified statistical criteria for demonstrating noninferiority to the randomized control regimen of HRZE for treatment of DS-TB using a noninferiority margin of 12%. There was no control group for patients treated for MDR-TB. The efficacy assessment in the NDA focuses on Nix-TB rather than NC-006 because Nix-TB was the only trial that evaluated the pretomanid regimen and patient population under consideration.

8.1 Study Nix-TB

8.1.1 Study Design

Nix-TB is an ongoing Phase 3, single-arm, multi-center trial to assess the safety and efficacy of bedaquiline plus linezolid plus pretomanid (B-L-Pa) in patients with pulmonary XDR-TB or TI/NR MDR-TB. Diagnosis of TB required documented positive *M. tuberculosis* culture or sputum-based molecular testing within 3 months prior to or at screening.

XDR-TB was defined by documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable drug. TI/NR MDR-TB was defined by resistance to isoniazid and rifampin and documented non-response to treatment with the best available regimen for 6 months or more prior to enrollment, or inability to continue a second-line drug regimen due to documented intolerance to para-aminosalicylic acid, ethionamide, aminoglycosides, or fluoroquinolones. The clinicaltrials.gov identifier for Nix-TB is NCT02333799.

The trial was originally planned with a sample size of 200 patients assigned to B-L-Pa. Enrollment was initiated in April 2015 and stopped in November 2017, with a final sample size of 109 patients. The applicant stopped enrollment due to the observed efficacy results and enrolled patients in an ongoing randomized Study NC-007 comparing doses and durations of linezolid in B-L-Pa regimens. Per agreement with the FDA, the clinical trial report submitted in the NDA summarizes the evidence for efficacy from the first 45 patients who completed the 6-month follow-up after the treatment period or who died or relapsed. An addendum submitted to the NDA provides results from an interim data cutoff of June 29, 2018 that includes primary endpoint data 6 months after the End of Treatment (EOT) for 81 patients.

As all patients in Nix-TB received a B-L-Pa regimen, the trial was not designed to provide clinical evidence for the contribution of pretomanid to the regimen but was meant to assess the efficacy of the three-drug regimen. For the discussion on the contribution of pretomanid to the regimen see section 6, Microbiology.

Patients in Nix-TB were to receive a minimum of 6 months of treatment with B-L-Pa. For patients persistently culture positive between Month 4 and 6 with clinically ongoing TB, treatment could have been extended to 9 months or the patient could have been withdrawn from the trial.

The B-L-Pa dosing regimen included:

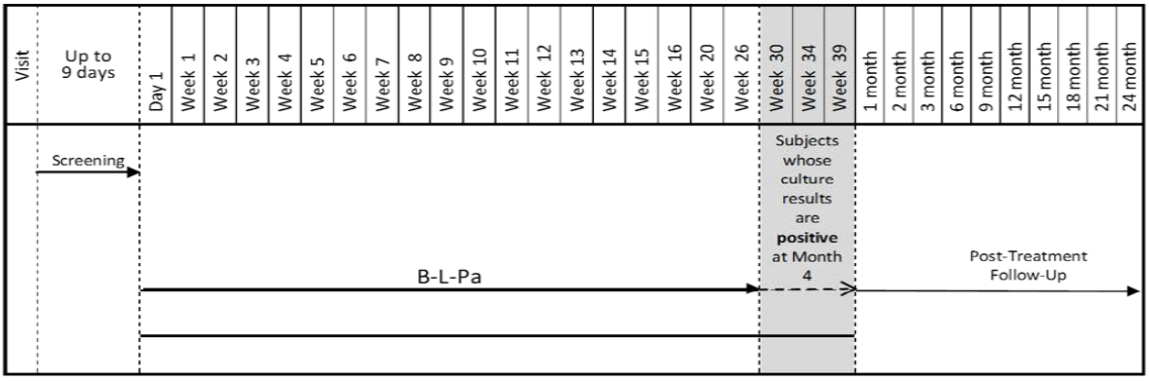
- Bedaquiline: 400 mg once daily for Days 1 to 14 followed by 200 mg 3 times a week for the remainder of the treatment period.
- Linezolid: initially, patients were to receive 600 mg twice a day. The protocol was subsequently amended to begin treatment with 1200 mg once a day. If adverse events developed, the treatment could be interrupted or reduced to either 600 mg or 300 mg once a day. If linezolid toxicity prohibited further treatment, patients could remain on treatment with only bedaquiline and pretomanid if they had

received the initial 1200 mg/day total dose of linezolid for at least the first 4 consecutive weeks of treatment, had negative or trace/scanty smear results and were clinically improving.

- Pretomanid: 200 mg once daily.

The study schedule is outlined in the figure below. Patients were screened within 9 days before receiving the first dose of B-L-Pa. Patients received either 6 months of treatment (Treatment Period) from Day 1 through Week 26, or 9 months from Day 1 to Week 39 based on their response at Months 4-6. Follow-up visits were performed at 1 and 2 months after treatment completion and then every 3 months for 24 months.

Figure 8-1: Schematic of Nix-TB Trial Design



Abbreviations: B-L-Pa, bedaquiline-linezolid-pretomanid.
Source: Nix-TB clinical trial report, Figure 9-1.

Study therapy could be discontinued or the patient could be withdrawn from the trial or treatment period for the reasons listed below. Upon discontinuation of trial treatment, patients were to be referred to a unit specializing in XDR-TB.

- Withdrawal of informed consent or loss to follow-up or noncompliance with protocol.
- Pregnancy.
- Trial treatment halted >35 consecutive days (unless the patient was smear-negative or had trace/scanty smear results and was clinically improving) and the patient received less than 4 weeks of linezolid 1200 mg total daily dose since the start of trial treatment.
- Trial treatment halted for >60 cumulative days in patients on 6 months of trial treatment or > 90 cumulative days in patients on 9 months of trial treatment.
- If the patient had not received at least 4 consecutive weeks of linezolid at a 1200 mg total daily dose after the start of trial treatment and linezolid was:
    - Halted >60 cumulative days in patients on 6 months of treatment or;
    - Halted >90 cumulative days in patients on 9 months of treatment or;
    - Interrupted for >35 consecutive days.

The primary efficacy endpoint was bacteriologic failure, relapse, or clinical failure through follow-up for 6 months after EOT. The following definitions were used:

- Clinical failure (Treatment failure): an unfavorable status at, or before, EOT or failing to attain a culture negativity, or if the patient was withdrawn at or before EOT for clinical reasons including retreatment or changing treatment.
- Bacteriologic relapse (Relapse): failing to maintain a culture negativity or having an unfavorable outcome after EOT in patients who attained culture negative status by EOT and had culture conversion to a positive status with the same *M. tuberculosis* strain. Patients who after EOT were withdrawn for clinical reasons including being retreated for TB or changing from trial treatment were also considered relapsed.
- Bacteriologic failure (Reinfection): failing to maintain culture negative status or having an unfavorable outcome (including being withdrawn for clinical reasons including being retreated or changing from trial treatment for TB after EOT in patients who attained culture negative status by EOT and had culture conversion to positive status with a *M. tuberculosis* strain that was different from the infecting strain at baseline.

Culture conversion required at least 2 consecutive culture negative samples at least 7 days apart. Patients who were unable to produce sputum and were clinically responding well to treatment were considered culture negative at that visit. Culture negative status was achieved when a patient produced at least 2 negative culture results at different visits at least 7 days apart without an intervening positive culture.

Secondary efficacy endpoints included:

- Incidence of bacteriologic failure, or relapse, or clinical failure through follow-up until 24 months after the EOT.
- Time to sputum culture conversion through the Treatment Period.
- Proportion of patients with sputum culture conversion at 4, 6, 8, 12, 16, and 26/39 weeks.
- Change from baseline TB symptoms, weight, and patient-reported health status using the European Quality of Life 5 dimension (EQ5D) questionnaire.

For defining microbiological components of efficacy endpoints, two sputum samples were collected at the following visits:

- Screening; Day 1; Weeks 1, 2, 4, 6, 8, 12, 16, 20, 26; also, 30, 34, and 39 for patients on 9 months of treatment and at any time of early treatment withdrawal.
- During the posttreatment follow-up on Months 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24.

A liquid MGIT culture was used. Speciation to confirm *M. tuberculosis* was performed at baseline and on the first positive culture at EOT or during follow-up for any positive at or after the Month 4 visit.

Other procedures conducted at various study visits included assessment of TB symptoms, patient-reported health status, ophthalmic examinations, vital signs, physical examinations, laboratory safety tests, peripheral neuropathy, and adverse events.

Key inclusion criteria were as follows:

1. Consenting male and female subjects aged ≥ 14 years, weighing ≥ 35 kg, of non-childbearing potential or using effective birth control methods, tested for HIV
2. Having 1 of the following pulmonary TB conditions:
    a. XDR-TB with:
        i. Documented culture positive (for *M. tuberculosis*) results within 3 months prior to screening or *M. tuberculosis* confirmed in sputum based on molecular test within 3 months prior to or at screening;
        ii. Documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable historically at any time prior to enrollment.
    b. MDR-TB documented by culture positive results (for *M. tuberculosis*) within 3 months prior or at screening with documented non-response to treatment with the best available regimen for 6 months or more prior to enrollment;
    c. MDR-TB documented by culture positive (for *M. tuberculosis*) results within 3 months prior to or at screening and unable to continue second-line drug regimen due to a documented intolerance to:
        i. Para-aminosalicylic acid, ethionamide, aminoglycosides or fluoroquinolones;
        ii. Current treatment not listed above that rendered patient eligible for the trial in the Investigator's opinion.
3. Had a chest X-ray (within a year prior to screening) consistent with pulmonary TB;

<u>Medical history:</u>

1. Any condition where participation in the trial compromised the well-being of the patient or could have prevented, limited, or confounded protocol-specified assessments;
2. Abuse of alcohol or illegal drugs;
3. Survival expectancy of less than 12 weeks;
4. Karnofsky score <50 within 30 days prior to screening;
5. Body mass index (BMI) <17 kg/m^2;
6. History of hypersensitivity to any of the trial treatments or related substances;
7. HIV-infected patients with a CD4 count of ≤50 cells/μL; For HIV-infected patients having a CD4 count >50 cells/ μL;
    a. Were being treated/needed to initiate antiretroviral therapy (ART) not compatible with the study regimen.
    b. Could not ensure a 2-week interval between commencing trial treatment and the start of the ART, if not already on ARTs.
8. Had participated in other interventional clinical trials within 8 weeks prior to the trial start;
9. Had significant cardiac arrhythmia requiring medication or risk factors for torsade de pointes or QTcF of >500
10. Females who are pregnant, breastfeeding, or planning to conceive a child during the trial or within 6 months of cessation of trial treatment. Males planning to conceive a child during the trial or within 6 months of cessation of trial treatment;
11. Had peripheral neuropathy of Grade 3 or Grade 4, or, neuropathy of Grade 1 or Grade 2 that was likely to progress/worsen over the course of the trial

Specific Treatments:

12. Concomitant use of medications that affect QT interval or can cause a serotonin syndrome when combined with study treatment
13. Patients previously treated for DS/MDR-TB (with specific exceptions for bedaquiline and/or linezolid as noted below) but treatment was discontinued at least 3 days prior to the first trial treatment administration;
14. Patients received less than 2 weeks of bedaquiline or linezolid prior to enrollment/first administration of trial treatment.

Laboratory Abnormalities:

15. Patients with the following at Screening (repeated testing):
    a. Hypokalemia;
    b. Anemia (hemoglobin <8.0 g/dL);
    c. Thrombocytopenia (<75000/mm^3);
    d. Absolute neutrophil count (ANC) <1000/mm^3
    e. Aspartate aminotransferase (AST) >3 x ULN.
    f. Alanine aminotransferase (ALT) >3 x ULN.
    g. Total bilirubin ≥2 x ULN, or if ≥1.5 up to 2 x ULN when accompanied by an increase in other liver tests (ALT, AST, alkaline phosphatase or gamma-glutamyltransferase).
    h. Direct bilirubin > than ULN;
    i. Serum creatinine level > than 2 x ULN;
    j. Albumin <32 g/L.

8.1.2 Statistical Methodologies

Separate statistical analysis plans were developed for safety and efficacy. Safety analyses were conducted in the safety population that was comprised of all 109 treated subjects.

The analysis plan for efficacy defined the following three analysis populations:

- Intent-to-treat (ITT): All patients excluding late screening failures, those withdrawn from the trial treatment because of ineligibility based on data collected prior to enrollment. However, no patients met these criteria for late screening failure by the June 29, 2018 interim data cutoff.
- Modified intent-to-treat (MITT): The ITT analysis population with additional exclusions related to loss to follow-up or withdrawal after repeated negative cultures, withdrawal from therapy due to pregnancy, death from violent or accidental causes, death from non-TB causes after repeated negative cultures, reinfection with a different strain, or inability to produce sputum at the primary endpoint visit. Patients were not to be excluded from the MITT analysis population after prior determination of an unfavorable outcome.
- Per-protocol (PP): The MITT population with extra exclusions.

The MITT analysis population was the primary efficacy analysis population. However, the ITT, MITT, and PP analysis populations almost completely coincided. Therefore, differences between the analysis population definitions did not impact the interpretation of efficacy results.

The trial Data Safety Monitoring Committee were to meet at least every 6 months while the study was ongoing and review interim analyses performed cumulatively on every 15 patients who completed treatment or were withdrawn early.

There were 4 amendments to the original protocol. Key amendments included changing the linezolid dosing from 600 mg twice a day to 1200 mg once a day, adding allowances for continuing trial treatment without linezolid if patients received at least 4 weeks of the 1200 mg total daily dose, and changing the primary endpoint follow-up from 24 months following EOT to 6 months following EOT. The latter change was implemented to be in line with the other Phase 3 trials and because most relapses were expected to occur within 6 months after the completion of treatment.

For the primary efficacy analysis, the proportion of assessable patients in the MITT population with favorable and unfavorable outcomes were to be presented with exact 95% confidence intervals. The lower bound of the 95% confidence interval for the favorable outcome rate was to be compared with a historical rate of 50%. Please refer to section 8.1.4 for a discussion on historical controls.

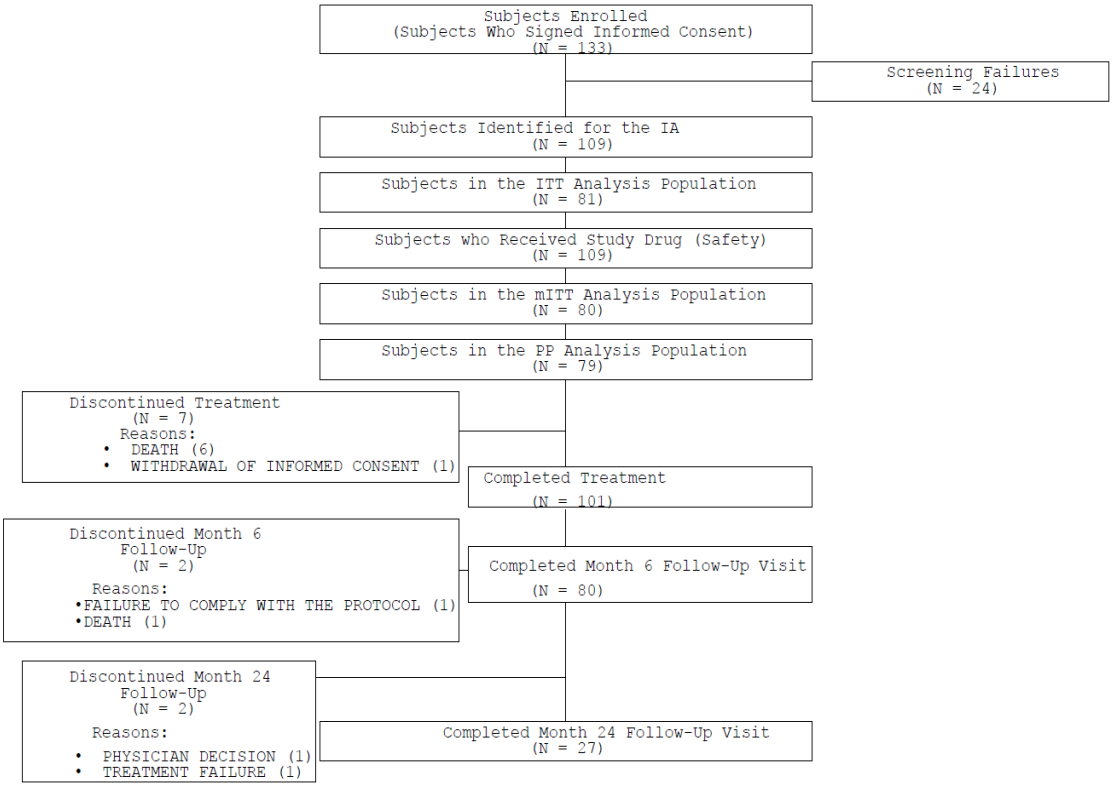
8.1.3 Patient Disposition

The figure below displays the patient disposition. There were 133 subjects who signed informed consent; 24 of these subjects were screen failures and were not treated. Thus, a total of 109 subjects were treated and thereby included in the safety population.

Prior to NDA submission, the applicant and Agency agreed that efficacy could be assessed based on results in the first 45 patients who completed the 6-month posttreatment follow-up or who died or relapsed. All patients in this analysis were enrolled by August 4, 2016, and the interim data cutoff for the analysis was August 17, 2017. The ITT, MITT, and PP analysis populations completely coincided for these first 45 patients.

At the June 29, 2018 interim data cutoff, 81 patients were included in the ITT analysis population. One of the ITT patients was excluded from the MITT primary analysis population due to non-TB death. Exclusion from the MITT population due to death is not generally recommended, and handling of this case in the analysis will be further described in the discussion of efficacy results. One additional patient in the MITT population was excluded from the PP population due to failure to comply with the protocol.

Figure 8-2: Disposition of Patients in Nix-TB



Abbreviations: IA, Interim analysis; ITT, Intent-to-treat; mITT, Modified intent-to-treat; PP, Per-protocol; N, Total number of patients in each category.
Completion status during the 6 Month Follow-up: Excludes those patients prematurely discontinuing trial participation prior to the 6 Month Follow-up period.
Completion status during the 24 Month Follow-up: Excludes those patients prematurely discontinuing trial participation prior to the 24 Month Follow-up period.
Source: Nix-TB addendum clinical trial report, Figure 6-1.

Because outcomes were compared with a historical favorable response rate of 50%, reasons for screening failures may be of greater interest than in a randomized comparison as screening factors can potentially select for differences between the study population and XDR patients reported in the literature. The unique reasons for screening failures are listed in the table below. The table includes both the original reasons for the 24 screen failures as well as reasons for failed rescreening.

Table 8-3: Reasons for Screening Failures in Nix-TB

[1] "9 DAYS SCREENING ELAPSED"
[2] "ACTIVE DRUG USE, INABILITY TO FOLLOW UP"
[3] "ALANINE AMINOTRANSFERASE (ALT) GREATER THAN OR EQUAL TO 5 x ULN (EXC 16)"
[4] "ASPARTATE AMINOTRANSFERASE (AST) GREATER THAN OR EQUAL TO 5 x ULN (EXC 16)"
[5] "CD4 < 50 (EXC 5)"
[6] "CLINICALLY SIGNIFICANT DISEASE OR ABNORMALITY (EXC 1)"
[7] "DUE TO SCREENING WINDOW BEING EXCEEDED"
[8] "EXCLUDED BY OPHTHALMOLOGY ON AREDS2 LENS GRADING"
[9] "FEATURES ARE CONSISTENT WITH RECENT ANTERIOR SEPTAL MYCARDIAL INFARCTION WHICH REQUIRES

FURTHER WORK UP. PRIOR TO ENROLLMENT THEREFORE PARTICIPANT SCREEN FAILED."
[10] "HEMOGLOBIN LESS THAN 8.0 G/DL (EXC 16)"
[11] "MDR-TB- NO DOCUMENTED NON-RESPONSE OR INTOLERANCE (INC 6)"
[12] "MEDICAL MONITOR ADVICED TO EXCLUDE PATIENT ON BASIS OF RAISED PRE-ENTRY LIPASE + AMYLASE, PANCREATITIS"
[13] "PATIENT HAS DRUG SENSITIVE TB AND NO MDR-TB OR XDR TB"
[14] "POTASSIUM 3.0, ALT GRADE 3, AST GRADE3 AND ALBUMIN 3"
[15] "QTCF > 500 (EXC 8)"
[16] "RECEIVED FLUCONAZOLE <30/7"
[17] "RECEIVED TB TREATMENT WITHIN 3 DAYS PRIOR TO STUDY TREATMENT (EXC 15)"
[18] "REPEAT POTASSIUM WAS 3.0MMOL/L"
[19] "SIGNIFICANT PERIPHERAL NEUROPATHY (EXC 10)"
[20] "SPONSOR DECISION PATIENT RECEIVED > 2 WEEKS OF LZD AND BDQ."
[21] "SUBJECT COMPLETED MORE THAN 14 DAYS OF LINEZOLID"
[22] "UNABLE TO ENSURE 2 WEEK INTERVAL BETWEEN COMMENCING STUDY IMP AND START OF COMPATIBLE ART (EXC 5)"
[23] "UNABLE TO SWITCH TO ALLOWED ARTS (EXC 5)"
[24] "USE OF STRONG CYP450 ENZYME INDUCER WITHIN 30 DAYS PRIOR TO ENTRY"
[25] "XDR- NO DOCUMENTED TB TEST RESULTS CONFIRMING (INC 6)"

Source: Statistical reviewer.

The applicant's summary of major protocol deviations from the June 29, 2018 interim data cutoff is presented in the table below. The applicant's clinical trial report states that "The major protocol violations were not considered to have an effect on the overall conclusions related to safety or efficacy." There were 11 patients with eligibility criteria deviations, which were almost exclusively due to previous TB medications not having been stopped a full 3 days prior to the first dose of study therapy.

Table 8-4: Major Protocol Deviations in Nix-TB Based on June 29, 2018 Interim Data Cutoff (Safety Analysis Population)

Variable	Statistic	B-L-Pa (N=109)
Entry Criteria	n (%)	0
Eligibility	n (%)	11 (10.1)
Inclusion/Exclusion Criteria	n (%)	6 (5.5)
Informed Consent	n (%)	8 (7.3)
IMP Administration	n (%)	11 (10.1)
Mycobacteriology Laboratory	n (%)	6 (5.5)
Procedural	n (%)	54 (49.5)
Safety and PK Lab	n (%)	5 (4.6)
Serious Adverse Event	n (%)	1 (0.9)
Visit Schedule	n (%)	27 (24.8)
Other	n (%)	15 (13.8)

Abbreviations: IMP, Investigational medicinal product; n, number of subjects in each category; N, total number of subjects in the relevant analysis population.
Source: Nix-TB addendum clinical trial report, Table 6-2.

Nix-TB enrolled patients from three trial centers in South Africa. The table below displays demographic characteristics for all 109 enrolled subjects in the safety population as well as for the 80 subjects in the MITT primary efficacy analysis population based on

the June 29, 2018 interim data cutoff. Subjects were roughly evenly split between males and females and had an average age of 36 years.

Table 8-5: Nix-TB Baseline Demographics Based on the June 29, 2018 Interim Data Cutoff

Variable	Safety population B-L-Pa (n = 109)	MITT population B-L-Pa (n = 80)
Age (years)		
Mean	36	35
SD	10	10
Minimum	17	18
Median	35	33
Maximum	60	60
Gender		
Female	52/109 (47.7%)	38/80 (47.5%)
Male	57/109 (52.3%)	42/80 (52.5%)
Race		
Black or African	83/109 (76.1%)	59/80 (73.8%)
Mixed race	25/109 (22.9%)	20/80 (25.0%)
White	1/109 (0.9%)	1/80 (1.2%)
Trial Center ID in South Africa		
01 – Johannesburg	40/109 (36.7%)	33/80 (41.2%)
02 – Cape Town	57/109 (52.3%)	47/80 (58.8%)
04 - Durban	12/109 (11.0%)	0/80 (0.0%)

Source: Statistical reviewer.

Approximately half of subjects had HIV at baseline. Approximately two thirds of patients had XDR-TB, with the remaining patients having treatment intolerant/non-responsive MDR-TB.

Table 8-6: Nix-TB Baseline Characteristics Based on the June 29, 2018 Interim Data Cutoff

Variable	Safety population B-L-Pa (n = 109)	MITT population B-L-Pa (n = 80)
Height (cm)		
Mean	166	166
SD	10	11
Minimum	144	144
Median	165	166
Maximum	186	186
Weight (kg)		
Mean	57	57
SD	15	15
Minimum	29	29
Median	55	56
Maximum	112	112
BMI (kg/m^2)		
Mean	21	21
SD	5	5
Minimum	12	12
Median	20	20
Maximum	41	41
CD4 Count (cells/µL, among HIV positive)		
Mean	394	436

Variable	Safety population B-L-Pa (n = 109)	MITT population B-L-Pa (n = 80)
SD	212	217
Minimum	55	85
Median	343	432
Maximum	1023	1023
Karnofsky Performance Score		
= 100	9/109 (8.3%)	8/80 (10.0%)
= 90	50/109 (45.9%)	34/80 (42.5%)
= 80	29/109 (26.6%)	21/80 (26.2%)
= 70	19/109 (17.4%)	16/80 (20.0%)
= 60	2/109 (1.8%)	1/80 (1.2%)

Source: Statistical reviewer.

Table 8-7: Nix-TB Baseline Disease History Based on the June 29, 2018 Interim Data Cutoff

Variable	Safety population B-L-Pa (n = 109)	MITT population B-L-Pa (n = 80)
HIV Status		
Negative	53/109 (48.6%)	41/80 (51.2%)
Positive	56/109 (51.4%)	39/80 (48.8%)
Duration Since HIV Diagnosis (months)		
Mean	4	4
SD	4	4
Minimum	0	0
Median	4	4
Maximum	14	14
Original TB Diagnosis		
DS	11/109 (10.1%)	9/80 (11.2%)
MDR	76/109 (69.7%)	58/80 (72.5%)
XDR	21/109 (19.3%)	12/80 (15.0%)
Not available	1/109 (0.9%)	1/80 (1.2%)
Duration Since Original TB Diagnosis (months)		
Mean	24	22
SD	28	27
Minimum	0.5	0.5
Median	12	17
Maximum	141	141
Current TB Diagnosis		
XDR-TB	71/109 (65.1%)	55/80 (68.8%)
MDR-TB Non-Responsive	19/109 (17.4%)	12/80 (15.0%)
MDR-TB Intolerant	19/109 (17.4%)	13/80 (16.2%)
Duration Since Current TB Diagnosis (months)		
Mean	11	10
SD	16	14
Minimum	0.4	0.4
Median	3	3
Maximum	90	90
Duration Since Positive TB Culture (days)		
Mean	52	55
SD	24	24
Minimum	16	16
Median	49	61

Variable	Safety population B-L-Pa (n = 109)	MITT population B-L-Pa (n = 80)
Maximum	106	106
Type of Cavity		
Unilateral	51/109 (46.8%)	43/80 (53.8%)
Bilateral	41/109 (37.6%)	29/80 (36.2%)
No Cavities	17/109 (15.6%)	8/80 (10.0%)

Source: Statistical reviewer.

Among the 109 patients in the safety population, 101 (92.7%) completed treatment. In only two cases was the treatment duration extended from 6 months to 9 months due to delayed culture conversion, as per protocol. Of the patients with premature treatment discontinuation, 6 cases were due to death.

The starting dose of linezolid was 600 mg BID for 44/109 (40.4%) subjects and 1200 mg QD for 65/109 (59.6%) subjects. Although premature discontinuation of the entire B-L-Pa regimen was uncommon, 30/109 (27.5%) patients discontinued linezolid treatment due to an adverse event, 53/109 (48.6%) interrupted linezolid due to an adverse event at least once, and 69/109 (63.3%) had at least one linezolid dose reduction. These discontinuations, interruptions, and dose reductions were most commonly due to peripheral neuropathy.

Concomitant or rescue TB medications were not allowed in the trial and generally were not used because patients had favorable outcomes with only B-L-Pa.

8.1.4 Efficacy Results

Primary Endpoint

The table below first displays results for the primary efficacy analysis of favorable and unfavorable outcomes at 6 months following the EOT for the first 45 patients with primary outcome data.

The rate of favorable outcomes was 40/45 (88.9%), with a 95% confidence interval (CI) of 75.9% to 96.3%. Because the lower confidence limit of 75.9% greatly exceeded the predefined threshold of 50%, this single-arm study met statistical criteria for declaring efficacy of B-L-Pa. Of the 5 patients with unfavorable outcomes, 4 died. They died between 5 to 8 weeks after initiation of study therapy. The additional patient with an unfavorable outcome relapsed after the EOT and died 69 weeks after the start of study therapy.

The table also displays results for the XDR-TB and MDR-TB subsets. All 8 patients with TI/NR MDR-TB at baseline had favorable outcomes, compared with 32/37 (86.5%) of patients with XDR-TB. No patients were classified as having missing outcomes.

Table 8-8: Primary Efficacy Analysis in Nix-TB (ITT, MITT, and PP Analysis Populations)

	Total	XDR	TI/NR MDR
Total	45	37	8
Unassessable	0	0	0
Total Assessable	**45**	**37**	**8**
Favorable	**40 (89%)**	**32 (86%)**	**8 (100%)**
Unfavorable	**5 (11%)**	**5 (14%)**	**0**
95% CI for Favorable	(**75.9%**, 96.3%)	(71.2%, 95.5%)	(63.1%, 100%)

Abbreviations: CI, Confidence interval; ITT, Intent-to-treat; MDR, Multi drug-resistant; MITT, Modified intent-to-treat; NR, Non-responsive; PP, Per-protocol; TI, Treatment-intolerant; XDR, Extensively drug-resistant.
Source: Nix-TB clinical trial report, Table 11-10.

Table 8-9 shows results from the interim data cutoff of June 29, 2018. A total of 81 subjects were assessed and 80 were incuded in the MITT analysis population. Results are shown for the MITT analysis population (prespecified for efficacy analysis). Of the 80 subjects in the MITT population, 55 subjects had XDR-TB and 25 subjects had TI/NR MDR-TB. The 80 MITT subjects almost completely overlapped with the ITT (81 subjects) and PP analysis populations (79 subjects). The favorable outcome rate of 72/80 (90.0%) was almost identical to that previously seen in the analysis of the first 45 subjects, and the 95% CI for the success rate was 81% to 96%. Of the 8 subjects in this analysis with unfavorable outcomes, 6 were due to death (non-violent or accidental) and 2 were due to posttreatment relapse (1 of whom later died). High rates of favorable outcomes were observed for both the XDR-TB and TI/NR MDR-TB subsets. Hence, this analysis of more complete Nix-TB outcome data continued to provide evidence that the success rate for B-L-Pa was substantially larger than the 50% rate prespecified as the historical control rate threshold.

Table 8-9: Primary Efficacy Analysis in Nix-TB Based on June 29, 2018 Interim Data Cutoff (MITT Analysis Population)

	Total	XDR	TI/NR MDR
N expected	**81**	**56**	**25**
Unassessable	1	1	0
Total Assessable	**80**	**55**	**25**
Favorable	**72 (90%)**	**49 (89%)**	**23 (92%)**
Unfavorable	**8 (10%)**	**6 (11%)**	**2 (8%)**
95% CI for Favorable	81% to 96%	78% to 96%	74% to 99%

Abbreviations: CI, Confidence interval; MDR, Multi drug-resistant; MITT, Modified intent-to-treat; NR, Non-responsive; PP, Per-protocol; TI, Treatment-intolerant; XDR, Extensively drug-resistant.
Source: Nix-TB Addendum Clinical Trial Report Dated 01 August 2018, Table 7-24.

The single ITT patient in this table excluded from the MITT analysis population was classified as "unassessable" by the applicant because he died of natural causes during follow-up. When this patient was included in the analysis with an unfavorable outcome,

the response rate did not change: 72/81 (88.9%) with an exact 95% CI of 80.0% to 94.8%.

One caveat to these analyses is that there were no adjustments for the multiple interim analyses conducted or the fact that the trial was prematurely terminated. In principle, early efficacy stopping can introduce random high biases. However, this was unlikely to affect the interpretation of Nix-TB. A very conservative 99.9% exact CI (i.e., the Haybittle-Peto method of adjusting for interim analysis) for the favorable outcome rate was 66.3% to 98.5% for the analysis of the first 45 subjects and 74.6% to 97.7% for the 80 MITT subjects from the June 29, 2018 interim data cutoff. Thus, even with this correction, the lower confidence limits still greatly exceeded the predefined favorable threshold of 50%.

Because screening failures may select for differences between Nix-TB patients and patients reported in historical literature, another sensitivity analysis considered all 24 screening failures and the unassessable subject to have unfavorable outcomes. With this very conservative method of imputation, the response rate became 72/105 (68.6%) with an exact 95% CI of 58.8% to 77.3%. Thus, handling of screening failures in the analysis did not affect the conclusion that Nix-TB provided evidence for a response rate exceeding the 50% threshold.

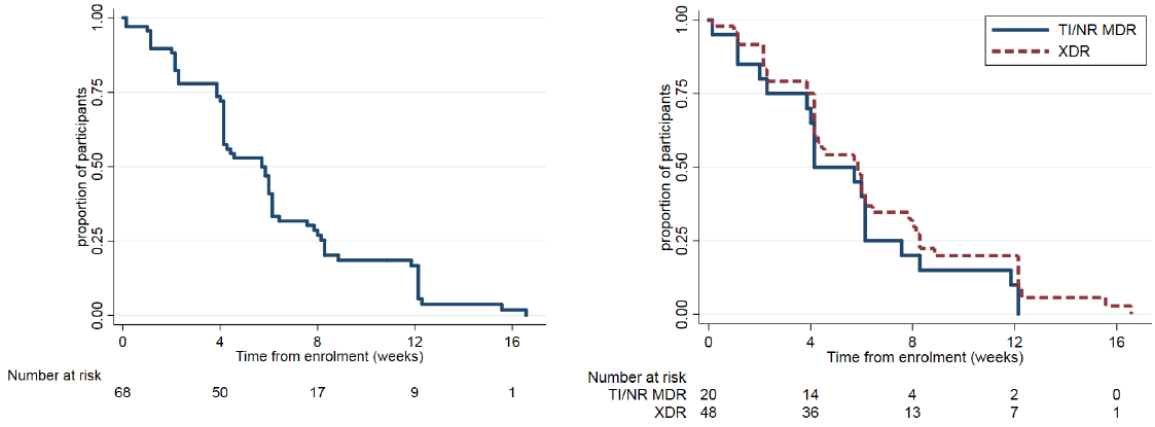
Secondary Endpoints

Results for selected secondary endpoints are shown for the 80 patients in the MITT analysis population from the June 29, 2018 interim data cutoff. These patients all had follow-up data 6 months after the EOT, except in cases of death.

Results are largely unavailable for this ongoing study for the secondary efficacy endpoint of bacteriologic failure, relapse, or clinical failure through 24 months after the end of treatment. At the June 29, 2018 interim data cutoff, there were 23 patients expected to have complete follow-up data, with this expectation based on enrollment before October 20, 2015, and allowances similar to the primary endpoint for visit windows and data entry. Of these 23 patients with data for the 24 month posttreatment secondary endpoint, there were 3 deaths, 1 relapse, and 19/23 (82.6%) subjects were successfully treated and remained TB-negative. Hence, based on the limited available data, the high success rates of B-L-Pa appeared to be maintained over a 24-month posttreatment follow-up period.

The Kaplan-Meier curve is displayed below for the secondary endpoint of time to sputum culture negative status. Aside from the patients who died, all assessable patients were culture negative 16 weeks after enrollment.

Figure 8-3: Time to Sputum Culture Negative Status for Those Positive at Baseline in Nix-TB Based on June 29, 2018 Interim Data Cutoff (MITT Analysis Population)



A **B**

A – Overall Nix-TB study population
B – Stratified by TB type: TI/NR-TB (blue solid line) and XDR-TB (red dashed line) presented separately
Source: Nix-TB addendum clinical trial report, Figure 5-4.

Table 8-10 presents results for Patient Self-Reported Health Status at planned protocol visits. Resolution of symptoms was difficult to interpret without a comparator group.

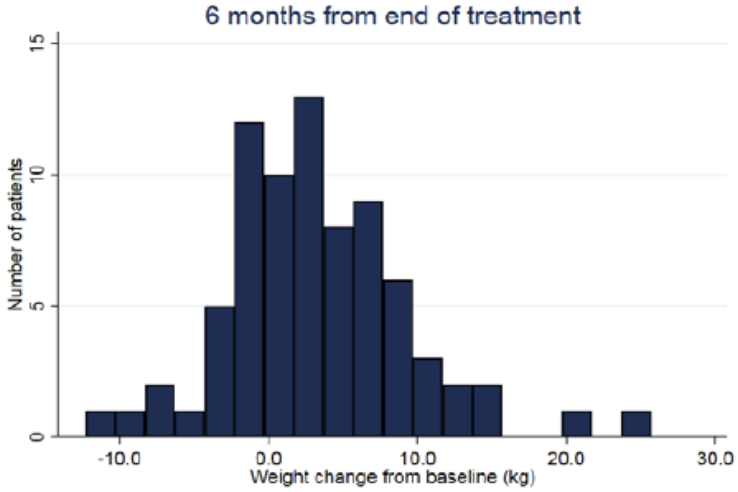
Table 8-10: Patient Self-Reported Health Status at Planned Protocol Visits in Nix-TB Based on June 29, 2018 Interim Data Cutoff (Safety Population)

		Overall			XDR			TI/NR MDR		
	Level	Baseline	Week 8	End of Treatment	Baseline	Week 8	End of Treatment	Baseline	Week 8	End of Treatment
	N enrolled	109	109	109	71	71	71	38	37	38
	N with data*	109	100	100	71	64	64	38	36	36
Anxiety/ Depression	No problems	72 (66%)	84 (84%)	94 (94%)	46 (65%)	52 (81%)	59 (92%)	26 (68%)	32 (89%)	35 (97%)
	Problems	37 (34%)	16 (16%)	6 (6%)	25 (35%)	12 (19%)	5 (8%)	12 (32%)	4 (11%)	1 (3%)
Mobility	No problems	98 (90%)	97 (97%)	85 (85%)	63 (89%)	62 (97%)	53 (83%)	35 (92%)	35 (97%)	32 (89%)
	Problems	11 (10%)	3 (3%)	15 (15%)	8 (11%)	2 (3%)	11 (17%)	3 (8%)	1 (3%)	4 (11%)
Pain/ Discomfort	No problems	64 (59%)	88 (88%)	80 (80%)	44 (62%)	55 (86%)	55 (86%)	20 (53%)	33 (92%)	25 (69%)
	Problems	45 (41%)	12 (12%)	20 (20%)	27 (38%)	9 (14%)	9 (14%)	18 (47%)	3 (8%)	11 (31%)
Self-care	No problems	106 (97%)	100 (100%)	100 (100%)	68 (96%)	64 (100%)	64 (100%)	38 (100%)	36 (100%)	36 (100%)
	Problems	3 (3%)	0	0	3 (4%)	0	0	0	0	0
Usual activities	No problems	99 (91%)	98 (98%)	99 (99%)	64 (90%)	62 (97%)	64 (100%)	35 (92%)	36 (100%)	35 (97%)
	Problems	10 (9%)	2 (2%)	1 (1%)	7 (10%)	2 (3%)	0	3 (8%)	0	1 (3%)
VAS score	mean	82	88	92	80	87	92	84	89	93
	median	88	90	95	90	90	95	85	90	96
	IQR	75 to 95	80 to 100	90 to 100	70 to 95	80 to 99	90 to 100	80 to 95	80 to 100	90 to 100
	range	0 to 100	40 to 100	55 to 100	0 to 100	40 to 100	55 to 100	50 to 100	60 to 100	60 to 100

Note: One patient had a missing VAS score at every time point but filled in all other questions. Therefore, the N with data is one less for the VAS than all other categories.
Source: Nix-TB clinical trial report, Table 9.1.

The secondary endpoint of change from baseline weight (kg) is displayed in the histogram below. Weight change was difficult to interpret without a comparator, but it was visually apparent from the histogram that most subjects gained weight over the study.

Figure 8-4: Histogram of Change from Baseline Weight (kg) at 6 Months Post EOT in Nix-TB Based on June 29, 2018 Interim Data Cutoff (Safety Population, Including Only the 77 Subjects with Weight Data)



Source: Nix-TB addendum clinical trial report, Figure 7-8.

The table below presents rates of favorable outcomes for selected subpopulations. Outcomes were generally favorable across all subgroups considered.

Table 8-11: Nix-TB Favorable Outcomes 6 Months After the EOT by Subgroup Based on June 29, 2018 Interim Data Cutoff (MITT Analysis Population)

Subgroup	B-L-Pa (n = 80)
Age (years)	
<30	22/26 (84.6%)
≥30	50/54 (92.6%)
Gender	
Female	33/38 (86.8%)
Male	39/42 (92.9%)
Race	
Black or African	55/59 (93.2%)
Other	17/21 (81.0%)
Trial Center ID in South Africa	
01 - Johannesburg	32/33 (97.0%)
02 – Cape Town	40/47 (85.1%)
04 – Durban	0/0
HIV Status	
Negative	37/41 (90.2%)
Positive	35/39 (89.7%)
TB Diagnosis at Baseline	
XDR-TB	49/55 (89.1%)
MDR-TB Non-Responsive	10/12 (83.3%)
MDR-TB Intolerant	13/13 (100%)
Weight (kg)	
≥50	48/50 (96.0%)
<50	24/30 (80.0%)

Source: Statistical reviewer.

Efficacy Impact of Linezolid Dose and Intolerance

Although many subjects prematurely discontinued, interrupted, or reduced the dose of linezolid due to adverse events, this did not appear to negatively affect efficacy outcomes in Nix-TB. The table below shows that there were high rates of favorable outcomes irrespective of the initial linezolid dose or post-baseline linezolid intolerance.

Table 8-12: Nix-TB Favorable Outcomes 6 Months After the EOT by Linezolid Status Based on June 29, 2018 Interim Data Cutoff (MITT Analysis Population)

Linezolid status	B-L-Pa (n = 80)
Initial linezolid dose of 600 mg BID	39/44 (88.6%)
Initial linezolid dose of 1200 mg QD	33/36 (91.7%)
Post-baseline linezolid termination due to AE	22/23 (95.7%)
Post-baseline linezolid interruption due to AE	37/38 (97.4%)
Post-baseline linezolid dose reduction	50/54 (92.6%)

Source: Statistical reviewer.

Literature Review of Historical Success Rates

Because the primary analysis in Nix-TB was based on a comparison with a historical success rate of 50%, the efficacy conclusions depended on whether this was a reasonable benchmark. The applicant provided two sets of analyses to address this issue. First, the applicant conducted a literature review of outcomes in patients treated for XDR-TB without pretomanid, bedaquiline, or linezolid, which will be discussed in this subsection. Second, the applicant conducted a matched historically controlled comparison.

The table below displays the World Health Organization-based outcome definitions for XDR-TB patients used in the applicant's literature review.

Table 8-13: World Health Organization Definitions of Treatment Outcomes for XDR-TB Patients

Outcome	Definition
Cure	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failure	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: − lack of conversion by the end of the intensive phase, *or* − bacteriological reversion in the continuation phase after conversion to negative, *or* − evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, *or* − adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up (also indicated as default)	A patient whose treatment was interrupted for 2 consecutive months or more.

Outcome	Definition
Treatment success	The sum of cured and treatment completed.
Conversion (to negative)	Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Source: Summary of Clinical Efficacy, Module 2.7.3, Table 34.

The applicant identified 18 studies with treatment success rate results in their literature review. The following table summarizes results for 16 of these studies and excludes 2 in which the success rates were unknown and could only be bounded.

Table 8-14: Listing of Historical Control References for Study Nix-TB

First Author, Year of Publication, Digital Object Identifier (DOI)	Calendar time of study	HIV Positive in XDR-TB Patients	Study Location	All-Cause Mortality in XDR-TB Patients	Treatment Success Rate (WHO Criteria: Cure or Completion of Therapy) in XDR-TB Patients
Banerjee, 2008, 10.1086/590009	1993-2006	Not available	United States	5/17 (29%)	7/17 (41%)
Dheda, 2017, 10.1016/S2213-2600(16)30433-7	2008-2012	44%	South Africa	90/203 (44%)	43/270 (16%)
Keshavjee, 2008, 10.1016/S0140-6736(08)61204-0	2000-2004	0%	Russia	2/29 (7%)	14/29 (48%)
Kim, 2008, 10.1164/rccm.200801-132OC	2000-2002	0%	South Korea	20/75 (27%)	22/75 (29%)
Kvasnovsky, 2016, 10.3201/eid2209.160084	2006-2008	62%	South Africa	211/330 (64%)	34/330 (10%)
Leimane, 2010, 10.1183/09031936.00003710	2000-2004	6%	Latvia	4/48 (8%)	18/48 (38%)
Liu, 2011, 10.1371/journal.pone.0019399	1996-2009	0%	China	3/48 (6%)	14/48 (29%)
Migliori, 2008, 10.1183/09031936.00028708	1999-2006	2%	Estonia, Germany, Italy, Russia	14/48 (29%)	22/48 (46%)
Mitnick, 2008, 10.1056/NEJMoa0800106	1999-2002	0%	Peru	11/48 (23%)	29/48 (60%)
Mor, 2014, 10.5588/ijtld.14.0192	1999-2010	8%	Israel	5/12 (42%)	7/12 (58%)
O'Donnell, 2013, 10.3201/eid1903.120998	2006-2007	72%	South Africa	48/114 (42%)	25/114 (22%)
Olayanju, 2018, 10.1183/13993003.00544-2018	2008-2014	49%	South Africa	69/202 (34%)	27/202 (13%)
Padayatchi, 2014, 10.1093/jac/dku235	2009-2011	86%	South Africa	Not available	11/85 (13%)
Pietersen, 2014, 10.1016/S0140-6736(13)62675-6	2008-2012	41%	South Africa	49/107 (46%)	17/107 (16%)
Tang, 2011, 10.3109/00365548.2010.548080	2007-2009	0%	China	5/94 (5%)	14/94 (15%)
Tabarsi, 2010, 10.1089/mdr.2009.0073	2004-2007	0%	Iran	3/12 (25%)	5/12 (42%)

Notes: Follow-up periods and treatments differed between studies. Calendar times in some cases referred to years of diagnosis and others included years of follow-up. This table excludes two studies from the applicant's review in which treatment success rates were not available.

Source: Summary of Clinical Efficacy, Module 2.7.3, Table 36.

The italicized text below is taken from the applicant's Summary of Clinical Efficacy, and describes the methodology used in the literature search and the applicant's conclusions.

> *The goal of this literature review was to identify all peer-reviewed articles that report 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 drugs (pretomanid, bedaquiline, and linezolid) or delamanid (delamanid is in the same drug class as pretomanid). In some articles, definitions for treatment outcomes are not specified, but reference is made to the WHO definitions and reporting framework for TB [shown in the table above].*
>
> *One author of this literature review independently performed the search and evaluated the articles according to the search criteria discussed below. A second author and the sponsor assisted in critical assessment of the identified articles to determine which met the criteria for inclusion in this summary. PubMed (www.ncbi.nlm.nih.gov/pubmed) was utilized to identify relevant primary manuscripts and abstracts, excluding reviews and commentaries/editorials. The PubMed database was searched using combinations of the keywords "extensively drug-resistant tuberculosis" and "treatment outcomes." The analysis was restricted to human studies written in English, and placed no limitations on publication date. Articles were included only if the studies (1) reported on adult patients (≥16 years) with XDR-TB; (2) provided details about the treatment regimen and drugs used; and (3) reported treatment results for XDR-TB patients as a specific category of TB. Additionally, articles were excluded (1) if treatment of XDR-TB patients included the use of bedaquiline, delamanid, or linezolid; (2) if the study reported treatment outcome data on ≤10 XDR-TB patients; or (3) the main outcomes reported in the articles were related to the role of surgery. A full-text review was performed for the articles that met the inclusion and exclusion criteria.*
>
> *The articles identified in this literature search are heterogeneous in content and therefore conclusions that can be drawn from the data are limited. The typical definition of XDR TB was resistance to isoniazid and rifampicin and resistance to any of the fluoroquinolones (such as levofloxacin or moxifloxacin) and to at least one of the three injectable second-line drugs (amikacin, capreomycin, or kanamycin), consistent with the WHO definition. However, there were variations in the definition across articles. Differences in procedures were also common. In some articles, the primary aim was to examine outcomes associated with XDR-TB (a major consideration for this report), while in other articles, the primary aim was more tangentially related (e.g., to determine risk factors associated with mortality). In addition, outcomes were often assessed at different time points. Although many articles reported treatment success according to the WHO definition ("cure" and treatment completion), some did not.*
>
> *Eighteen studies that met search criteria and that described outcomes that could be mapped to the standardized WHO outcome of treatment success were identified.*

These studies reported outcomes in 1731 patients. The majority of the patients in these studies came from South Africa (1300 patients from 8 studies), where the Nix TB study was conducted. Rates of treatment success across the South Africa studies were consistent, averaging 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%; two studies reported rates above 50%.

While the applicant did not attempt a formal meta-analysis of the historical data, a DerSimonian and Laird random effects model of the 16 studies in the preceding table yielded an estimate for the historical treatment success rate of 28% for the treatment of XDR-TB with a 95% confidence interval for the success rate from 21% to 34%. This provided some support for the prespecified historical control rate of 50% in Nix-TB being appropriately conservative.

However, limitations of the literature review included the heterogeneity of studies and outcomes, geographic and temporal differences from Nix-TB, and possible selection of patients who would have been ineligible or unenrolled in a clinical trial such as Nix-TB. The use of all-cause mortality was limited by different follow-up times and reporting periods across studies. The outcome of treatment success was standardized to some degree according to WHO criteria, but the timing of assessment was not standardized and was not necessarily comparable to Nix-TB. Nevertheless, the success rates reported in the literature generally were much lower than success rates in Nix-TB. The Nix-TB study would perhaps provide more convincing evidence of efficacy if high success rates were demonstrated over broad geographic areas rather than 3 study sites, and over a longer follow-up period. However, Nix-TB was conducted entirely in South Africa, where success rates in the literature have historically been very low. Overall, the B-L-Pa regimen appeared to provide a greater chance of treatment success than has been observed with XDR-TB treatments in the published literature.

Comparison with Matched Historical Controls

In addition to the literature review, the applicant submitted an analysis comparing B-L-Pa with a matched historical control group. This comparison partially addressed the limitations of the literature review related to heterogeneity and lack of comparability in terms of geography, patient characteristics, and study assessments. Patient-level datasets were not submitted for the matched historical control group.

The Nix-TB population included in the comparative analysis was based on the first 45 patients enrolled in the trial. The historical control group was based on patients from Brooklyn Chest Hospital in Cape Town, South Africa. This was the highest enrolling study site in Nix-TB. Outcomes for this historical cohort have been previously published [Olayanju O. et al. (2018). European Respiratory Journal, Volume 51, Number 5]. The applicant based the analysis on 202 patients from this cohort admitted between January 2008 and September 2014 who were treated for XDR-TB with regimens that did not include bedaquiline, linezolid, pretomanid, or delamanid (as this was in the same drug class as pretomanid).

Treatment outcomes for the Nix-TB group were defined according to the primary endpoint of bacteriologic failure, relapse, or clinical failure 6 months after the EOT. Treatment outcomes for the historical control group were defined according to World Health Organization criteria as modified in [Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, et al. Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults. Int J Tuberc Lung Dis. 2016 Mar; 20(3):290-4.]. An unfavorable outcome was based on death, judgment of treatment failure, default, or loss to follow-up.

Patients in the historical control group were treated with a backbone of para-aminosalicylic acid/clofazimine/capreomycin and second-/fourth-generation fluoroquinolones. The patients in the historical control group had newly diagnosed XDR-TB, while the Nix-TB group also included prior treatment failures.

The assessment times differed between the Nix-TB group and historical control group. For Nix-TB the primary endpoint was defined 6 months after the 6-month treatment period. For the historical control group, the assessment time point was 24 months after the start of treatment, and treatment was planned for 18 months or longer.

The table below shows that the Nix-TB group and historical control groups had similar baseline characteristics with respect to sex, age at diagnosis, weight, and HIV status.

Table 8-15: Baseline Characteristics of the Nix-TB and Control Groups

Baseline characteristic	Nix-TB (n = 45)	Control group (n = 202)	p-value
Sex			0.85
Female	20 (44.4%)	84 (41.6%)	
Male	25 (55.6%)	118 (58.4%)	
Age (years)	Mean = 33.6 SD = 10.0	Mean = 34.7 SD = 11.1	0.49
Weight (kg)	Mean = 57.7 SD = 16.5	Mean = 53.6 SD = 12.8	0.13
HIV status			1.00
Negative	23 (51.1%)	104 (51.5%)	
Positive	22 (48.9%)	97 (48.0%)	
Refused	0 (0.0%)	1 (0.5%)	

Source: Summary of Clinical Efficacy, Module 2.7.3, Table 37.

The next table shows that the rate of favorable outcomes was much higher in the Nix-TB group than the historical control group.

Table 8-16: Comparison of Outcomes Between the Nix-TB and Historical Control Groups

Favorable outcome		Relative risk	95% CI	p-value
Nix-TB group	Control group			
40/45 (88.8%)	27/202 (13.4%)	6.6	4.6 to 9.6	<0.0001

Source: Summary of Clinical Efficacy, Module 2.7.3, Tables 38 and 39.

A secondary analysis performed by the applicant was based on individually matched subsamples from the two groups. Matching was by propensity scores constructed from the covariates of sex, age, body weight, and baseline HIV status. The applicant aimed for a 1:2 ratio of Nix-TB: control patients, but 1 Nix-TB patient did not have a match and 4 had only 1 matched control. Thus, the two subsamples included 44 Nix-TB subjects and 84 control subjects. The applicant reports that the statistician responsible for the matching was kept blinded to outcomes in both the Nix-TB and control groups throughout the matching process.

Table 8-17: Baseline Characteristics of Individually Matched Subsamples

Baseline characteristic	Nix-TB (n = 44)	Control group (n = 84)	p-value
Sex			0.97
Female	19 (43.2%)	38 (45.2%)	
Male	25 (56.8%)	46 (54.8%)	
Age (years)	Mean = 33.7 SD = 10.1	Mean = 32.0 SD = 9.0	0.35
Weight (kg)	Mean = 56.4 SD = 14.4	Mean = 54.0 SD = 13.5	0.36
HIV status			1.00
Negative	22 (50.0%)	42 (50.0%)	
Positive	22 (50.0%)	42 (50.0%)	

Source: Summary of Clinical Efficacy, Module 2.7.3, Table 40.

The subsequent table shows that in the matched subsample, the Nix-TB group had a much higher favorable outcome rate than the historical control group.

Table 8-18: Comparison of Outcomes Between the Individually Matched Subsamples

Favorable outcome		Relative risk	95% CI	p-value
Nix-TB group (n = 44)	Control group (n = 84)			
39 (88.6%)	9 (10.7%)	64.5	8.8 to 472	<0.0001

Source: Summary of Clinical Efficacy, Module 2.7.3, Tables 41 and 42.

The large difference in favorable outcome rates did not appear to be an artifact of a shorter assessment time in Nix-TB. The tables above report assessments for the control group approximately 24 months after the start of treatment. Based on the June 29, 2018 interim data cutoff for Nix-TB, the rate of favorable outcomes 24 months after the EOT was 19/23 (82.6%), which was similar to the success rate seen for Nix-TB in the table above and much larger than the historical control success rate.

The applicant also provided comparisons between Nix-TB patients and matched historical controls for all-cause mortality. All-cause mortality could be objectively measured and was of predominant clinical importance. Rates of death were lower for the Nix-TB subjects than the individually matched historical control subjects at 12 months after the start of treatment (9% versus 34%, $p<0.01$).

Although the differences in outcomes between the Nix-TB group and historical control group were too large to be explained by chance variation, it remained possible that there were systematic differences between the groups other than the TB regimens administered. In particular, the two groups may have differed because it is well-known that subjects enrolled in clinical trials tend to be healthier than general patient populations. Clinical care and follow-up may have differed in a clinical trial setting. The applicant additionally notes that there may have been changes in background care provided to XDR-TB subjects between the enrollment periods of 2015-2016 for the Nix-TB subset and 2008-2014 for the historical control group.

8.2 Summary and Conclusions of Efficacy

The efficacy assessment of the B-L-Pa regimen for the treatment of XDR-TB and TI/NR MDR-TB was based on Nix-TB. Based on the June 29, 2018 interim data cutoff, the rate of favorable outcomes for the primary endpoint of bacteriologic failure, relapse, or clinical failure was 90%, with a 95% confidence interval from 81% to 96%. The lower confidence limit for the success greatly exceeded the prespecified historical control rate of 50%. Results were robust to the handling of screening failures in the analysis or interim analyses.

The 50% historical control threshold rate was evaluated based on a literature review of existing treatment outcomes for XDR-TB. A random effects meta-analysis of published treatment success rates had an upper confidence limit of only 34%. In addition, the high success rates in Nix-TB was observed in South Africa in a patient population with a high rate of HIV infection, where previous studies have reported poor outcomes. This literature review was supplemented by a comparison of Nix-TB outcomes to a matched historical control group from patients at one of the study centers who had been treated for XDR-TB without bedaquiline, linezolid, or pretomanid. The two groups were similar on measured baseline factors such as age, sex, HIV status, and weight, but the patients in Nix-TB treated with B-L-Pa had much greater rates of treatment success and lower mortality rates.

With the monitoring in this clinical trial setting, linezolid intolerance did not appear to adversely affect efficacy outcomes for the B-L-Pa regimen.

Although there remains the possibility that non-randomized comparisons could be confounded, historical controls can provide convincing evidence of efficacy when the outcomes with currently available treatment options are poor and the treatment effect is too large to be easily explained by confounding factors, and this is the most straightforward interpretation of Nix-TB results.

9 Evaluation of Safety

9.1 Safety Summary

Across the clinical development program, 1507 subjects were exposed to pretomanid in 19 completed or ongoing studies: three Phase 3 studies, six Phase 2 studies, and ten Phase 1 studies. Among the 1507 subjects, 1168 (77.5%) were exposed to pretomanid either alone (411 [27.3%] subjects) or in combination with other antimycobacterial drugs (757 [50.2%] subjects).

A total of 124 (8.2%) subjects in the clinical program were exposed to the B-L-Pa regimen, in the ongoing Nix-TB (N=109) and ZeNix (n=15) trials. The safety data cut-off date for the Nix-TB and ZeNix trials was March 26, 2018.

9.2 Methods

The focus of the safety review is the Nix-TB trial. Adverse events of special interest such as hematologic, hepatic, ophthalmic, neurologic, cardiac, dermatologic, and gastrointestinal associated with the B-L-Pa regimen were evaluated. Safety analyses were also presented for pretomanid in pooled Phase 1 studies in healthy subjects and pooled Phase 2 Early Bactericidal Activity (EBA) studies.

9.3 Adverse Event Analysis

Disposition of Study Subjects

In the Nix-TB trial, 93/109 (85%) patients had completed six months of treatment with the B-L-Pa regimen as of the cut-off date of March 26, 2018, Table 9-1. Out of 93 patients, 15 (13.8%) have completed the entire study (6 months treatment and 24 months follow-up). Among 109 patients enrolled, 84 (77.1%) subjects were still participating in the study either in treatment (9 patients) or in post-treatment follow up.

Ten (9.2%) patients discontinued from the study, 7 (6.4%) due to death and 3 (2.8%) for other reasons such as relapse of TB (2 patients) or withdrawal of consent (1 patient). There were eight deaths overall, six patients died while on B-L-Pa treatment and two patients died in the posttreatment period, Table 9-5.

Table 9-1. Study Nix-TB: Disposition of Study Subjects

	B-L-Pa, N=109; n/N (%)
End of Treatment Status	
Completed 6 months	93 (85.3)
Ongoing treatment	9 (8.3)
Discontinued	7 (6.4)
End of Treatment Reason	
Death (i.e., discontinued group)	6 (5.5)
Other (consent withdrawal)	1 (0.9)
End of Study Reason	
Death	7 (6.4)
Other (consent withdrawal, relapse)*	3 (2.8)
TEAEs Leading to Death	
Pneumonia	2 (1.8)
Pulmonary Tuberculosis	2 (1.8)
Disseminated Tuberculosis	1 (0.9)
Multiple Organ Dysfunction Syndrome	1 (0.9)
Pancreatitis†	2 (1.8)
Sepsis	1 (0.9)
Septic Shock	1 (0.9)
Upper Gastrointestinal Hemorrhage	1 (0.9)

Source: Custom Table Builder (R v3.5).
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and AEOUT = FATAL).
* Subject (b) (6) relapsed and was discontinued ("physician/sponsor decision') from study approximately three months before he died from sepsis /gangrene; this subject is listed as discontinued from the study by reason of "Other" Subject (b) (6) is listed in "ongoing treatment " in applicant's initial ISS data and documentation; however, this subject discontinued from the study by reason of 'Other' based on a safety update from the applicant.
†Acute pancreatitis was considered by the reviewer to have contributed to death in two patients, Subject (b) (6) and Subject (b) (6).

Overview of Treatment Emergent Adverse Events (TEAEs)

In Nix-TB, a TEAE is defined as an event that starts or worsens at, or during the time of, first study drug administration up to 14 days after the last study drug administration.

TEAEs occurred in all 109 (100%) patients in the Nix-TB trial, Table 9-2. Nineteen (17.4%) patients experienced at least one serious adverse event (SAE). A maximum severity of either a grade 3/severe (37.6%) or a grade 4/life-threatening (15.6%) TEAE were reported in 58 (53.2%) patients. Linezolid was discontinued due to a TEAE at a higher rate (27 [24.8%] patients) than bedaquiline or pretomanid (any study drug was discontinued by 33 [30.3%] patients). Six (5.5%) patients discontinued the B-L-Pa regimen due to death.

Table 9-2. Study Nix-TB: Overview of Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAEs)	B-L-Pa regimen, n (%)
Any TEAE	***109 (100%)***
Serious TEAE	19 (17.4%)
TEAE by severity	
Life-threatening	17 (15.6%)
Severe	41 (37.6%)
Moderate	43 (39.4%)
Mild	8 (7.3%)
TEAEs leading to discontinuation of any study drug	33 (30.3%)

Treatment Emergent Adverse Events (TEAEs)	B-L-Pa regimen, n (%)
TEAEs leading to discontinuation of linezolid	27 (24.8%)
TEAEs leading to discontinuation of B-L-Pa	6 (5.5%)
TEAEs leading to death	6 (5.5%)

Source: Applicant's Integrated Summary of Safety (ISS) datasets: ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y).

Common TEAEs

Preferred terms (PTs) for similar TEAEs were grouped and then analyzed with a cut-off >5%, Table 9-3. Peripheral neuropathy occurred in 87 (80%) patients and among these patients, peripheral sensory neuropathy was reported in 75 (69%). The next most common TEAEs were anemia and nausea in 40 (37%) patients, each. Elevations in AST and ALT occurred in 27 (25%) patients. Other adverse events occurring in > 20% of patients included vomiting, headache, skin rash, dermatitis acneiform, decreased appetite, and dyspepsia. TEAEs of special interest such as myelosuppression, prolongation of the QT interval, optic neuropathy, peripheral neuropathy, hepatotoxicity, and pancreatitis are discussed in section 9.4.

Table 9-3. Study Nix-TB: Common TEAEs (Grouped) in >5% Subjects – Safety Population

TEAEs by Preferred Term	B-L-Pa (N=109)
Peripheral neuropathy*	87 (79.8)
Anemia	40 (36.7)
Nausea	40 (36.7)
Vomiting	37 (33.9)
Headache†	30 (27.5)
ALT/AST increased§	27 (24.8)
Dyspepsia	26 (23.9)
Rash‡	26 (23.9)
Dermatitis acneiform	26 (23.9)
Decreased appetite	24 (22.0)
Pleuritic pain	20 (18.3)
Upper respiratory tract infection	20 (18.3)
Abdominal pain¶	18 (16.5)
Gamma-Glutamyltransferase increase	18 (16.5)
Amylase increased/ Hyperamylasemia	17 (15.6)
Acne	16 (14.7)
Pruritus	15 (13.8)
Hemoptysis	14 (12.8)
Back pain	13 (11.9)
Vision disturbance±	13 (11.9)
Cough/Productive cough	12 (11.0)
Hypoglycemia	12 (11.0)
Abnormal loss of weight	11 (10.1)
Diarrhea	11 (10.1)
Pneumonia / Lower respiratory tract infection	10 (9.2)
Constipation	9 (8.3)
Gastritis	9 (8.3)
Neutropenia	9 (8.3)
Dry skin	8 (7.3)
Blood lactic acid increased¥	7 (6.4)
Chronic obstructive pulmonary disease	7 (6.4)

TEAEs by Preferred Term	B-L-Pa (N=109)
Pain in extremity	7 (6.4)
Urinary tract infection	7 (6.4)
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)
Lipase increased/ Hyperlipasemia	6 (5.5)
Myalgia	6 (5.5)

Source: OCS Analysis Studio, Custom Table Builder.
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y), MedDRA 20.0.
*Peripheral Neuropathy includes the following PTs: neuropathy peripheral / peripheral sensory neuropathy / paresthesia / hypoesthesia / peripheral sensorimotor neuropathy
†Headache includes: headache / migraine / sinus headache / tension headache
‡Rash includes: rash/ rash pruritic / rash papular / rash maculopapular / rash erythematous / rash vesicular
§ALT /AST Increased includes: transaminases increased / alanine aminotransferase increased / aspartate aminotransferase increased / hepatic enzyme increased / liver function test increased / hepatic function abnormal
¶Abdominal Pain includes: abdominal discomfort / abdominal pain / abdominal pain upper / abdominal pain lower
±Vision Disturbance includes: vision blurred / visual acuity reduced / visual impairment
¥Blood Lactic Acid Increased includes: blood lactic acid increased / hyperlactacidemia / lactic acidosis

Serious TEAEs

Serious adverse events (SAEs) occurred in 19 (17.4%) patients, Table 9-4. Individual patients experienced more than one SAE. Most SAEs occurred after Day 30 of treatment. SAEs (not pulmonary tuberculosis) occurring in ≥2 patients included pneumonia (3, 2.8%), sepsis (2, 1.8%), anemia (2, 1.8%), hypoglycemia (2. 1.8%), pancreatitis (2, 1.8%), optic neuritis/optic neuropathy (2, 1.8%), seizure (2, 1.8%), and upper gastrointestinal hemorrhage/hematemesis (2, 1.8%). Six of the 19 patients who developed SAEs during the trial also died. In the other 13 patients, the SAEs resolved or were resolving at the data cut-off date.

Table 9-4. Study Nix-TB: SAEs by System Organ Class and Preferred Term

System Organ Class/Preferred Term	B-L-Pa (N=109), n(%)
Infections and Infestations	**7 (6.4)**
Pneumonia	3 (2.8)
Pulmonary tuberculosis	3 (2.8)
Sepsis	2 (1.8)
Disseminated tuberculosis	1 (0.9)
Septic shock	1 (0.9)
Tuberculoma of central nervous system	1 (0.9)
Gastrointestinal Disorders	**5 (4.6)**
Abdominal pain upper	1 (0.9)
Hematemesis	1 (0.9)
Pancreatitis (hemorrhagic)	1 (0.9)
Pancreatitis	1 (0.9)
Upper gastrointestinal hemorrhage	1 (0.9)
Metabolism and Nutrition Disorders	**4 (3.7)**
Hypoglycemia	2 (1.8)
Abnormal loss of weight	1 (0.9)
Lactic acidosis	1 (0.9)
Nervous System Disorders	**4 (3.7)**

System Organ Class/Preferred Term	B-L-Pa (N=109), n(%)
Generalized tonic clonic seizure	1 (0.9)
Optic neuritis	1 (0.9)
Seizure	1 (0.9)
Syncope	1 (0.9)
Blood and Lymphatic System Disorders	**3 (2.8)**
Anemia	2 (1.8)
Neutropenia	1 (0.9)
Respiratory, Thoracic and Mediastinal Disorders	**3 (2.8)**
Asthma	1 (0.9)
Dyspnea	1 (0.9)
Hemoptysis	1 (0.9)
Pneumothorax spontaneous	1 (0.9)
Psychiatric Disorders	**2 (1.8)**
Depression suicidal	1 (0.9)
Generalized anxiety disorder	1 (0.9)
Eye Disorders	**1 (0.9)**
Optic neuropathy	1 (0.9)
General Disorders and Administration Site Conditions	**1 (0.9)**
Multiple organ dysfunction syndrome	1 (0.9)
Investigations	**1 (0.9)**
Transaminase increase	1 (0.9)

Source: Custom Table Builder (R v3.5).
Data sets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and AESER = Y)

Deaths

Eight (7.3%) patients died during the Nix-TB trial: 4 males and 4 females aged 20 to 55 years, Table 9-5. Seven patients had XDR-TB and five were co-infected with HIV. Six (5.5%) patients died during the 26-week treatment period with B-L-Pa and 2 (1.8%) deaths occurred posttreatment.

TEAEs leading to death included: pneumonia (2 patients), pulmonary tuberculosis (2 patients), disseminated tuberculosis (1 patient), sepsis or septic shock (2 patients), acute pancreatitis (2 patients), upper gastrointestinal hemorrhage (1 patient), and multi-organ dysfunction (1 patient).

Table 9-5. Study Nix-TB: Summary of Deaths

Subject ID/ Gender/ Age	XDR or TI/NR TB / HIV status	TEAEs leading to Death: Dictionary Derived Term(s) / Verbatim Term	Study Day of Death
(b) (6)* M/35y	XDR/ HIV +	Pancreatitis (Hemorrhagic)/ Acute Hemorrhagic Pancreatitis	53
(b) (6) F/31y	XDR/ HIV +	Pulmonary Tuberculosis/ Acute Severe Worsening of Pulmonary Tuberculosis	55
(b) (6) F/ 26y	XDR/ HIV -	Septic Shock/ Septic Shock Secondary to Pneumonia	76
(b) (6)* M/34y	XDR/ HIV +	Disseminated Tuberculosis, Pulmonary Tuberculosis, Pancreatitis (Hemorrhagic) / Severe Pulmonary Tuberculosis and Disseminated Tuberculosis	35
(b) (6) F/20y	XDR/ HIV -	Upper Gastrointestinal Bleeding/ Upper Gastrointestinal Bleeding	51

Subject ID/ Gender/ Age	XDR or TI/NR TB / HIV status	TEAEs leading to Death: Dictionary Derived Term(s) / Verbatim Term	Study Day of Death
(b) (6) F/29y	TI/NR MDR/, HIV-	Sepsis, Pneumonia/ Worsening Pneumonia	93
(b) (6) M/ 38y	XDR/ HIV +	Death/ "Natural causes" characterized as a non-violent death	369
(b) (6)† M/55y	XDR/ HIV +	Sepsis/ Sepsis Secondary to Gangrene from Peripheral Vascular Disease	486

Source: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and AEDECOD, AESDTH, DTHDY). *In the Nix-TB study report, acute pancreatitis was listed as contributing to death in one patient, Subject (b) (6). Acute pancreatitis is considered by the reviewer to have contributed to death in two patients, Subject (b) (6) and Subject (b) (6)
† Subject (b) (6) relapsed and was discontinued (physician/sponsor decision") from the study approximately three months before he died from sepsis /gangrene.

No deaths were reported in the Nix-TB trial during the period between the original NDA safety data cut (March 26, 2018) and the recently submitted 120-day safety update which has a data cut-off date of October 15, 2018.

9.4 Adverse Reactions of Special Interest and Submission Specific Safety Issues

9.4.1 Hepatobiliary

Hepatic TEAEs occurred in 39 (36%) patients and were more common in HIV-positive patients than in HIV-negative patients, 23 (41%) versus 16 (30%), respectively, Table 9-6. Twenty-seven (25%) patients experienced increases in ALT and/or AST.[1] Increases in GGT occurred mostly in HIV co-infected patients.

Table 9-6. Study Nix-TB: Hepatic Disorders

	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
Any TEAE	***16 (30.2)***	***23 (41.1)***	***39 (35.8)***
Hepatic Treatment Emergent Adverse Event			
Blood alkaline phosphatase increased	1 (1.9)	2 (3.6)	3 (2.8)
ALT increased	6 (11.3)	4 (7.1)	10 (9.2)
AST increased	5 (9.4)	3 (5.4)	8 (7.3)
Drug induced liver injury	1 (1.9)	1 (1.8)	2 (1.8)
Gamma-glutamyltransferase increased	2 (3.8)	16 (28.6)	18 (16.5)
Hepatic enzyme increased	2 (3.8)	0	2 (1.8)
Hepatic function abnormal	0	1 (1.8)	1 (0.9)
Hepatomegaly	0	1 (1.8)	1 (0.9)
Hyperbilirubinemia	1 (1.9)	1 (1.8)	2 (1.8)
Liver function tests increased	0	1 (1.8)	1 (0.9)
Transaminases increased	6 (11.3)	6 (10.7)	12 (11.0)

[1] ALT and /or AST increases includes the following preferred terms: transaminases increased / ALT increased / AST increased / hepatic enzyme increased / liver function test increased / hepatic function abnormal.

	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)

Source: OCS Analysis Studio, Custom Table Builder
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ01NAM = Hepatic disorders SMQ).
A patient may experience more than one adverse event. One patient was reported to have jaundice but was excluded because there was no laboratory evidence of elevated total bilirubin levels on treatment.

Increases in ALT and AST led to either an interruption of the B-L-Pa regimen or linezolid in 8 (7.3 %) patients. Patients were able to restart study drugs without experiencing further clinically significant elevations in ALT and AST.

Maximum post baseline increases in ALT levels to > 3 to ≤ 5x ULN or > 5 to ≤10x ULN were observed in 6 (5.5%) patients, each. Maximum post baseline increases in AST levels to > 3 to ≤ 5x ULN or > 5 to ≤10x ULN were observed in 8 (7.3%) and 2 (1.8%) patients, respectively. Among patients with normal ALT at baseline, maximum post baseline elevations > 3 to ≤ 5x ULN or > 5 to ≤ 10x ULN were observed in 2 (1.8%) and 3 (2.8%) patients, respectively. Total bilirubin increases to >2x ULN occurred in 2 (1.8%) patients. Most of the hepatic TEAEs (57 of 65) resolved or were resolving as of the data cut-off date of March 26, 2018.

Hy's Law Case

One patient (HIV negative) fulfilled the laboratory criteria for Hy's Law, i.e., ALT > 3x ULN, total bilirubin > 2x ULN, and alkaline phosphatase < 2x ULN. The B-L-Pa regimen was interrupted in this patient from Weeks 8 to 11 due to elevated hepatic transaminases (8x ULN) and B-L-Pa was reintroduced with a lower dose of linezolid (due to anemia) during Week 11. ALT declined to near normal range during Week 12 and continued to decline on B-L-Pa treatment to within the normal range at Week 20 and at the EOT, Week 26. Total bilirubin declined to the normal range at Week 12 of treatment. The patient developed anemia during this time; hemoglobin nadir was 8.6g/dL, which improved by reducing the dose of linezolid to 600mg/day. Results for hepatitis B and C and a urine toxin screen were negative. The patient completed 26 weeks of treatment with B-L-Pa regimen without further dosing interruptions. The patient completed the final trial visit at Month 24 and all TEAEs (including optic neuropathy) had resolved.

One patient was a potential Hy's Law case with an elevated ALT >3x ULN, total bilirubin >2x ULN; however, alkaline phosphatase was >2x ULN. ALT and total bilirubin levels increased after eight to ten weeks of treatment, and the levels declined when the B-L-Pa regimen was interrupted. ALT and bilirubin levels continued to decline toward the normal range when the regimen (with a lower dose of linezolid) was reintroduced at Week 12. There was a transient increase in ALT (not bilirubin) at Week 20; however, the overall trend in ALT levels was toward the normal range. Hepatic transaminases and total bilirubin were in the normal range at EOT, Week 34.

Deaths due to hepatotoxicity in other pretomanid-containing regimen

In 2015, there were four deaths due to hepatotoxicity in two pretomanid trials other than the Nix-TB trial; one death in trial NC-005 in a patient treated with the comparator, HRZE and three deaths in trial NC-006 in patients treated with a pretomanid-containing regimen, MPaZ (moxifloxacin (M) 400mg, pretomanid (Pa) 200mg and pyrazinamide (Z)

1500mg). These two trials evaluated antimycobacterial regimens different from the B-L-Pa regimen studied in the Nix-TB trial.

In 2015, Study NC-006 was on partial clinical hold to enrollment of new subjects for all study arms until a possible association of the pretomanid-containing regimen with hepatotoxicity could be examined. There was no significant signal for hepatotoxicity for pretomanid in the nonclinical program and Phase 1 studies in healthy subjects. The 3:1 ratio of liver-toxicity related deaths seen in the study matched the treatment allocation ratio. In 2016, the partial clinical hold was removed after additional monitoring for hepatic adverse events and other safety measures were put in place in study NC-006 and in subsequent clinical protocols (see introduction to section 8).

There were four deaths due to hepatotoxicity in NC-005 and NC-006:

- 3 cases of hepatotoxicity/fatal in the $MPa_{200mg}Z$ arm in Study NC-006
- 1 case of hepatotoxicity/fatal in the HRZE (H: isoniazid, R: rifampin, Z: pyrazinamide, E: ethambutol) arm in Study NC-005

9.4.2 Ophthalmic

Optic Nerve Disorders

Thirteen (11.9%) patients had TEAEs related to Optic Nerve Disorders, Table 9-7. The most frequent TEAE was visual acuity reduced 6 (5.5%). Four (3.7%) patients were diagnosed with abnormalities of the optic nerve:

- Two (1.8%) patients developed optic neuropathy (grade 1) or optic neuritis (grade 4) after four months of treatment and this led to discontinuation of linezolid but not the regimen. Both cases of optic neuropathy resolved.
- One patient was diagnosed with bilateral papilledema two days before the end of study treatment and it resolved two months later; periodic visual acuity and color vision examinations were reported to be normal in this patient during the study.
- One patient with optic disc hyperemia had a dose reduction in linezolid.

Three additional patients had study drug interrupted because of vision abnormalities, which included reduced visual acuity in two patients (linezolid only interrupted) and visual impairment in the third patient (B-L-Pa interrupted). Optic neuropathy /optic neuritis is known to be associated with linezolid.

Most of the TEAEs (9 of 14) associated with optic nerve disorders resolved or were resolving as of the data cut-off date. Three of the four TEAEs that led to a drug(s) interruption or dose reduction had resolved, and one TEAE (visual acuity reduced) was ongoing. There were three TEAEs (visual impairment, visual acuity reduced, and amblyopia) that had not resolved and the outcome for one TEAE was unknown.

Table 9-7. Study Nix-TB: Optic Nerve Disorders

Treatment Emergent Adverse Event	HIV Negative N=53	HIV Positive N=56	Total N=109
Any TEAE	***9 (17.0%)***	***4 (7.1%)***	***13 (11.9%)***
Amblyopia	0	1 (1.8%)	1 (0.9%)
Optic disk hyperemia	1 (1.9%)	0	1 (0.9%)

Treatment Emergent Adverse Event	HIV Negative N=53	HIV Positive N=56	Total N=109
Optic neuritis	1 (1.9%)	0	1 (0.9%)
Optic neuropathy	0	1 (1.8%)	1 (0.9%)
Papilledema (bilateral)	1 (1.9%)	0	1 (0.9%)
Visual acuity reduced	4 (7.5%)	2 (3.6%)	6 (5.5%)
Visual impairment	2 (3.8%)	1 (1.8%)	3 (2.7%)

Source: ISS dataset, applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ04NAM = Optic Nerve Disorders SMQ).

Lens Disorders

Fourteen (12.8%) patients had TEAEs in the Lens Disorders. None of the TEAEs were reported as SAEs. Three events resulted in interruption of dosing of study drugs: "visual acuity reduced" in 2 patients (linezolid interrupted) and "visual impairment" in one patient (entire B-L-Pa regimen interrupted). These three patients overlap with patients listed in Table 9-7. No TEAE associated with lens disorders led to discontinuation of the B-L-Pa regimen.

Table 9-8. Study Nix-TB: Lens Disorders

Treatment Emergent Adverse Event	HIV Negative N=53	HIV Positive N=56	Total N=109
Any TEAE	***8 (15.1%)***	***6 (10.7%)***	***14 (12.8)***
Lens disorder	0	1 (1.8%)	1 (0.9%)
Vision blurred	2 (3.8%)	2 (3.8%)	4 (3.6%)
Visual acuity reduced	4 (7.5%)	2 (3.8%)	6 (5.5%)
Visual impairment	2 (3.8%)	1 (1.8%)	3 (2.7%)

Source: ISS dataset, applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ04NAM = Lens Disorders SMQ).

Clinical studies with pretomanid exposure longer than 14 days have included visual acuity assessments, slip-lamp examinations, and AREDS-2 lens opacity scoring. Consultants from the Division of Ophthalmology and Transplant Products (DTOP) evaluated the submitted data and found no clinically meaningful effect of pretomanid on the potential for cataract formation at the doses and durations studied. Ocular monitoring continues in the pretomanid clinical development program.

9.4.3 Fertility

No TEAEs related to fertility disorders were found in the Nix-TB study. Male reproductive hormone levels were not evaluated in the study.

Based on the testicular toxicity seen in rats, serum male reproductive hormone levels were evaluated in three clinical trials, NC-002, NC005, and NC006. These three trials investigated pretomanid-containing regimens different from the regimen in the Nix-TB trial, Table 8-1. Patients were exposed to pretomanid for 8 to 26 weeks.

Consultants from the Division of Bone, Reproductive and Urologic Products (DBRUP) evaluated the data for the three trials and concluded that the results from NC-002 and NC-005 were insufficient to definitively rule out pretomanid-associated testicular toxicity. A review of the data from Study NC-006 indicated that follicle stimulating hormone

(FSH), inhibin B, and luteinizing hormone (LH) levels remained stable throughout the study period and at the 26- week time-point. Testosterone levels increased with treatment and remained within the normal range at EOT, Week 26. The data for HIV- positive and HIV- negative men were aggregated and this may have resulted in a dilution of a safety signal because hypogonadism is more common in HIV positive men. The male reproductive hormonal data from study NC-006 suggested that pretomanid does not affect the hypothalamic-pituitary axis; however, there was insufficient evidence to definitively rule out a direct pretomanid-associated testicular toxicity. The applicant's planned Human Semen Analysis Study will further evaluate the nonclinical testicular toxicity signal; however, the results will available after this NDA review cycle.

9.4.4 Cardiac

Six (5.5%) patients experienced QT prolongation. Five events of QT prolongation were grade 1 severity, one event was grade 2, and all were asymptomatic. One patient experienced a syncopal episode (grade 3). No patients had QTcF intervals >480 ms. One (0.9%) patient had a post-baseline increase of QTcF of >60 ms. No TEAE resulted in an interruption or dose reduction of a study drug(s). All TEAEs resolved except one adverse event of QT prolongation (mild).

The patient who experienced a syncopal event, reported feeling dizzy and he fell while standing in-line. On examination (not at study site), he had a perforated right tympanic membrane with bleeding from the right ear. ECG and vital signs were not reported and no discharge summary was available. Subsequent ECGs did not show QTc prolongation.

Thorough QT (TQT) Study

A TQT study for pretomanid showed no clinically meaningful increase in QTc after single oral doses of 400 mg and 1,000 mg of pretomanid. Pretomanid was found to have a low risk to prolong the QTc interval at therapeutic exposures. Co-administration of pretomanid 400 mg with moxifloxacin 400 mg did not significantly increase the QTc effects of the combination. Bedaquiline is a known QT prolonging drug (largest mean increase in QTc = 15.7 ms). Linezolid at therapeutic exposures is not associated with a clinically significant risk of QT prolongation. Pretomanid co-administration with other QT prolonging drugs such as bedaquiline may cause small increases in QT interval which would not substantially increase the pro-arrhythmic risk of the combination.

9.4.5 Hematologic

Myelosuppression

TEAEs associated with cytopenias were reported in 51 (47%) subjects, Table 9-9. Anemia, neutropenia, and thrombocytopenia were the most common TEAEs occurring in 40(37%), 9(8%), and 5(5%) patients, respectively, and they occurred more frequently in HIV-positive patients than in HIV-negative patients.

The onset of anemia and other cytopenias occurred most frequently after two weeks of B-L-Pa treatment and were reported in 25%, and 22% of subjects after >2 weeks to 8 weeks, and >8 weeks to 26 weeks of treatment, respectively. Cytopenias led to dosing

interruptions of the B-L-Pa regimen and dosing interruptions, dose reductions or discontinuation of linezolid.

Thirty-four (31%) patients who had normal hemoglobin levels at baseline experienced a decrease in their hemoglobin level below the lower limit of normal (< LLN) during treatment. Fourteen (13%) patients with normal baseline platelet counts experienced decreases in platelets < LLN during treatment. Thirty (28%) patients who had neutrophil counts within the normal range at baseline experienced a decrease in neutrophil counts < LLN on B-L-Pa treatment.

Table 9-9. Study Nix-TB: Hematopoietic Disorders (Cytopenias)

	B-L-Pa		
Treatment Emergent Adverse Event	**HIV NEGATIVE N=53**	**HIV POSITIVE N=56**	**Total N=109**
Any TEAE	***21 (39.6%)***	***30 (53.6%)***	***51 (46.8%)***
Anemia	16 (30.2%)	24 (42.9%)	40 (36.7%)
Bicytopenia *	1 (1.9%)	0	1 (0.9%)
Bone marrow failure	2 (3.8%)	1 (1.8%)	3 (2.7%)
Leukopenia	0	2 (3.6%)	2 (1.8%)
Lymphopenia	0	1 (1.8%)	1 (0.9%)
Neutropenia	2 (3.8%)	7 (12.5%)	9 (8.3%)
Pancytopenia	1 (1.9%)	0	1 (0.9%)
Thrombocytopenia	2 (3.8%)	3 (5.4%)	5 (4.6%)

Source: ISS dataset, ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ11NAM= Hematopoietic Cytopenias SMQ).*Bicytopenia, i.e., anemia and thrombocytopenia.

9.4.6 Neurologic

Peripheral Neuropathy

Eighty-seven (79.8%) patients experienced symptoms and signs of peripheral neuropathy, Table 9-10. TEAEs were mostly equally distributed among HIV-positive and HIV-negative patients. Peripheral sensory neuropathy occurred in 75 (69%) patients, “neuropathy peripheral” in 10 (9%) patients, and paresthesia in 5 (5%) patients. Eighty-two (75%) patients experienced peripheral sensory neuropathy or “neuropathy peripheral”.

Peripheral neuropathy was most likely associated with linezolid. Study drug dosing was interrupted for 11 events (linezolid for 10 events and B-L-Pa for 1 event), dose reduced for 29 events (linezolid for all 29 events), and discontinued for 25 events (linezolid for all 25 events). Sixty-nine of 119 TEAEs resolved or were resolving as of the data cut-off date. There were 31 TEAEs that had not resolved and outcomes for 19 TEAEs were unknown.

Table 9-10. Study Nix-TB: Peripheral Neuropathy

Treatment Emergent Adverse Event	**B-L-Pa**		
	HIV NEGATIVE	**HIV POSITIVE**	**Total**
	N=53	**N=56**	**N=109**
Any TEAE	***43 (81.1%)***	***44 78.6%)***	***87 (79.8 %)***
Burning sensation	1 (1.9%)	0	1 (0.9%)

Treatment Emergent Adverse Event	B-L-Pa		
	HIV NEGATIVE	HIV POSITIVE	Total
Hypoesthesia	1 (1.9%)	2 (3.6%)	3 2.7%)
Hyporeflexia	0	1 (1.8%)	1 (0.9%)
Neuropathy peripheral	5 (9.4%)	5 (8.9%)	10 (9.2%)
Paresthesia	3 (5.7%)	2 (3.6%)	5 (4.6%)
Peripheral motor neuropathy	1 (1.9%)	1 (1.8%)	2 (1.8%)
Peripheral sensorimotor neuropathy	0	1 (1.8%)	1 (0.9%)
Peripheral sensory neuropathy	37 (69.8%)	38 (67.9%)	75 (68.8%)

Datasets: ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and Applicant's SMQ09NAM = Peripheral Neuropathy SMQ).

Seizures

Two (1.8%) patients experienced seizures, Table 9-11. The patient who experienced a tonic/clonic seizure during B-L-Pa treatment had a history of seizures. The other patient completed B-L-Pa treatment and had a seizure at one week post treatment and a second seizure at two months post treatment probably due to a tuberculoma in the right temporal lobe. The patient had no seizures in the 6-month period following neurosurgery to remove the tuberculoma.

Table 9-11. Study Nix-TB: Convulsions

Treatment Emergent Adverse Event	B-L-Pa		
	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
Any TEAE	***1 (0.9%)***	***1(0.9%)***	***2(1.8%)***
Generalized tonic clonic seizure	1 (0.2%)	0	1 (0.9%)
Seizure	0	1 (0.2%)	1 (0.9%)

Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ03NAM = Convulsions SMQ).

9.4.7 Pancreatic

Pancreatitis

Twenty-three (21.1%) patients experienced increases in lipase and/or amylase levels or acute pancreatitis, Table 9-11. Acute pancreatitis was a contributing cause of death in 2 (1.8%) patients; both patients had hemorrhagic pancreatitis confirmed at autopsy. Their risk factors for pancreatitis included HIV/ anti-retroviral therapy (2 patients) and alcohol use (1 patient). One additional patient (HIV +) with no history of alcohol use had a maximum lipase level of 129/UL (normal range 13 - 60 U/L) on B-L-Pa treatment and was asymptomatic and was diagnosed on abdominal ultrasound as having pancreatitis. This patient did not appear to have acute pancreatitis clinically. B-L-Pa was interrupted for ~ 20 days and lipase levels returned to normal ranges following re-challenge with B-L-Pa.

Among patients with normal lipase levels at baseline, elevations post-baseline were observed in 18 (16.5%) patients, and most of the patients had maximum levels ≤ 2x ULN. Four (3.7%) patients had a maximum post baseline elevation in lipase >2 to 5x ULN on B-L-Pa treatment and 1 (0.9%) patient who had a mild elevation in lipase at baseline had elevated lipase levels > 5 to 10x ULN post baseline.

Table 9-12. Acute Pancreatitis

	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
Any TEAE	*8 (15.1)*	*15 (26.8)*	*23 (21.1)*
	7 (13.2)	***13 (23.2)***	***20 (18.3)***
Amylase increased	4 (7.5)	5 (8.9)	9 (8.3)
Hyperamylasemia	2 (3.8)	6 (10.7)	8 (7.3)
Hyperlipasemia	0	1 (1.8)	1 (0.9)
Lipase increase	3 (5.7)	2 (3.6)	5 (4.6)
	1 (1.9)	***2 (1.8)***	***3 (2.8)***
Acute pancreatitis (hemorrhagic)	1(1.9)	1 (1.8)	2 (1.8)
Pancreatitis	0	1(1.8)	1(0.9)

Source: OCS Analysis Studio, Custom Table Builder
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ06NAM = Applicant's modified Acute Pancreatitis (SMQ).

9.4.8 Lactic Acidosis

Eight (7.3%) patients reported TEAEs associated with lactic acidosis. All TEAEs resulted in study drugs being interrupted (7 patients) or withdrawn (1 patient). Linezolid was interrupted for four TEAEs, B-L-Pa regimen for two TEAEs, and study drug(s) was not recorded for one TEAE. All except one TEAE had resolved by the data cut-off date.

Table 9-13. Lactic Acidosis

Treatment Emergent Adverse Event	HIV Negative N=53	HIV Positive N=56	Subjects N=109
Any TEAE	***5 (9.4%)***	***3(5.4%)***	***8(7.3%)***
Acidosis	1 (1.9%)	0	1 (0.9%)
Blood Lactic Acid Increased	0	1 (1.8%)	1 (0.9%)
Hyperlactacidemia	2 (3.8%)	1 (1.8%)	3 (2.7%)
Lactic Acidosis	2 (3.8%)	1 (1.8%)	3 (2.7%)

Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ12NAM= Lactic Acid Acidosis SMQ).

9.5 Phase 1 Pooled Studies

Ten Phase 1 studies included 324 healthy adult subjects (U.S. only) of whom 289 received pretomanid (single and multiple doses) and 35 received placebo. One hundred seventy-four subjects were exposed to a single dose of pretomanid ranging from 50 mg to 1500 mg (with or without other drugs), and 115 subjects were exposed to repeated daily doses of pretomanid ranging from 200 mg to 1000 mg for up to 14 days (with or without other drugs). Sixty-four percent of the subjects who received pretomanid were male and predominantly white (68.2%). The mean time on pretomanid treatment (all pretomanid group) was 17.2 (range 1 to 43) days. The placebo group had a mean time of 5 (range, 1 to 8) days on treatment.

Disposition

Ten (3.5%) subjects in the pretomanid group and no control subjects reported TEAEs that led to permanent discontinuation of pretomanid.

Table 9-14. Phase 1 Pooled Studies: Disposition of Study Subjects

	Single Dose Pretomanid (N=174)	Multiple Dose Pretomanid (N=115)	Placebo (N=35)
End of Treatment Status			
Completed	169 (97.1)	105 (91.3)	32 (91.4)
Discontinued	5 (2.9)	10 (8.7)	3 (8.6)
End of Treatment Reason			
Adverse event	4 (2.3)	0	0
Protocol violation	1 (0.6)	2 (1.7)	0
Physician/sponsor desicion	0	6 (5.2)	2 (5.7)
Subject withdrawal	0	2 (1.7)	1 (2.9)
End of Study Reason			
Adverse event	4 (2.3)	0	0
Protocol violation	1 (0.6)	3 (2.6)	0
Physician/sponsor desicion	0	7 (6.1)	2 (5.7)
Subject withdrawal	2 (1.1)	1 (0.9)	1 (2.9)
TEAE Leading to 'Drug Withdrawn'			
Electrocardiogram QT prolonged	1 (0.6)	0	0
Rash papular	1 (0.6)	0	0
Sinus tachycardia	1 (0.6)	0	0
Ventricular extrasystoles	1 (0.6)	0	0
Blood creatitine increased	0	5 (4.3)	0
Mental status changes	0	1 (0.9)	0

Source: Custom Table Builder (R v3.5)
Datasets Used: Applicant's ISS ADSL (POOL6SFL = Y) and ISS ADAE (TRTEMFL = Y and AEACN = DRUG WITHDRAWN)
In the Single Dose Pretomanid arm, four subjects had an Adverse Event Leading to 'Drug Withdrawn'. These four subjects had an End of Treatment Reason of 'Adverse Event'. In the Multiple Dose Pretomanid arm, six subjects had an Adverse Event Leading to 'Drug Withdrawn'. Five of these subjects had an End of Treatment Reason of 'Physician/Sponsor Decision' and one subject had 'Subject Withdrawal'.

TEAEs

There were no deaths or SAEs in the Phase 1 studies. The most common TEAE (≥ 2%) in healthy adult subjects was headache, 91 (32%) subjects in the pretomanid group versus 8 (23%) in the placebo group. Other adverse events occurring at a rate > 10% and greater than placebo included: nausea in 34 (12%) subjects, contact dermatitis in 33(11%) subjects, and decreases in hemoglobin in 31 (11%) subjects in the pretomanid group.

Table 9-15. Phase 1 Studies: Treatment Emergent Adverse Events (≥ 2%) Pretomanid vs. Placebo - Safety Population

	Pretomanid (N=289)	Placebo (N=35)
Any TEAE	*186 (64.4)*	*14 (40.0)*
TEAEs by System Organ Class / PT (where PTs ≥ 2%)		
Nervous System Disorders	**109 (37.7)**	**8 (22.9)**
Headache	91 (31.5)	8 (22.9)
Dizziness/dizziness postural	25 (8.7)	1 (2.9)
Gastrointestinal Disorders	**70 (24.2)**	**3 (8.6)**
Nausea	34 (11.8)	0
Diarrhea	25 (8.7)	0
Abdominal pain*	18 (6.2)	2 (5.7)
Flatulence	7 (2.4)	0
Vomiting	6 (2.1)	0
Dry mouth	2 (0.7)	1 (2.9)
Investigations	**63 (21.8)**	**4 (11.4)**
Hemoglobin decrease	31 (10.7)	0
Electrocardiogram QT prolonged	12 (4.2)	3 (8.6)
ALT increased/abnormal	7 (2.4)	0
Skin and Subcutaneous Tissue Disorders	**50 (17.3)**	**2 (5.7)**
Dermatitis contact	33 (11.4)	0
Rash / Rash generalized maculopapular	7 (2.4)	2 (5.7)
Pruritus/pruritus generalized	8 (2.8)	0
General Disorders and Administration Site Conditions	**31 (10.7)**	**2 (5.7)**
Fatigue	13 (4.5)	0
Chest pain/Chest discomfort	2 (0.7)	1 (2.9)
Respiratory, Thoracic and Mediastinal Disorders	**19 (6.6)**	**0**
Nasal congestion	7 (2.4)	0
Renal and Urinary Disorders	**11 (3.8)**	**0**
Chromaturia	8 (2.8)	0

Source: OCS Analysis Studio, Custom Table Builder
Datasets Used: Applicant's ISS ADSL (POOL6SFL = Y) and ISS ADAE (TRTEMFL = Y)
*Abdominal Pain includes preferred terms: abdominal pain /abdominal discomfort / abdominal pain upper / abdominal pain lower / gastrointestinal pain (verbatim term: "intestinal cramps").

TEAEs by Pretomanid Dose Category

In the Phase 1 studies, the following pretomanid dose categories were created for analysis of single- and multiple-doses: < 200mg, 200mg, and > 200mg. More than 50% of the subjects in each pretomanid dose category and 40% of patients in the placebo group experienced a TEAE. Headache was the most common TEAE (> 20%) across the three pretomanid dose categories. Headache, dizziness, diarrhea, and chromaturia were the most common TEAEs in the pretomanid 200mg (to be marketed dose) dose category. TEAEs such as hemoglobin decreased, QT prolongation, and ALT / AST increases were reported in subjects who received pretomanid > 200mg. There appeared to be a dose response for increases in ALT and AST; however, a definitive conclusion is limited by the small number of subjects in each of the dose categories. No potential Hy's Law cases were identified in the Phase 1 pooling group.

Severe TEAEs

Grade 3 adverse events were observed in the four subjects on pretomanid treatment and consisted of blood creatine phosphokinase increased (n=1), AST abnormal (n=1), neutrophil count decreased (n=1), and generalized rash (n=1). One additional subject developed a skin rash one day posttreatment.

9.6 Phase 2 Pooled Studies

Two Phase 2 EBA studies of pretomanid were conducted in South Africa. The safety population included 138 adults, 122 patients received pretomanid alone and 16 patients received the standard of care regimen, HRZE, for drug-sensitive TB. The mean age of study subjects was 27 (range,18 to 56) years. Males were 52% of the study population. Race was reported as black (46%) and "other (mixed race)" (54%). Most patients (approximately 88%) were HIV-negative in both pretomanid and HRZE groups.

Patients received pretomanid alone once daily for ≤14 days at doses ranging from 50 to 1,200 mg. The mean number of days on treatment was 13.7 (range, 2 to 14).

Disposition

Seven (5.1%) subjects discontinued from the pooled Phase 2 studies. Four (2.9%) patients discontinued treatment with pretomanid due to a TEAE, 2(1.6%) patients were lost to follow up and one (0.7%) patient withdrew, Table 9-16.

Table 9-16. Phase 2 Pooled Studies: Disposition of Study Subjects

	All Pretomanid (N=122)	HRZE Control (N=16)
End of Treatment Status		
Completed	117 (95.9)	16 (100.0)
Discontinued	5 (4.1)	0
End of Treatment Reason		
Adverse Event	4 (3.3)	0
Subject Withdrawal	1 (0.8)	0
End of Study Status		
Completed	115 (94.3)	15 (93.8)
Discontinued	7 (5.7)	1 (6.2)
End of Study Reason		
Adverse Event	4 (3.3)	0
Lost to Follow-Up	2 (1.6)	1 (6.2)
Subject Withdrawal	1 (0.8)	0

Source: OCS Analysis Studio, Custom Table Builder
Datasets Used: Applicant's ISS ADSL (POOL5SFL = Y).

TEAEs

No deaths occurred in the Phase 2 pretomanid-alone pooling group. Forty-seven (39%) subjects in the pretomanid group (all dose categories) and 7 (44%) in the HRZE group, experienced adverse events, Table 9-17. The most frequently reported system organ classes of TEAEs in the all-pretomanid group were skin and subcutaneous disorders [18(14.8%) patients] and gastrointestinal disorders [13 (10.7%) patients].

TEAEs reported in patients in the pretomanid group and not reported in the HRZE group included skin rash in 10 (8.2%) patients, and headache, dizziness, abdominal pain in 3

(2.5%) patients each. Urticaria was reported in 2 (1.6%) patients in the pretomanid group and in 1 (6.2%) patient in the HRZE group.

Table 9-17. Phase 2 Pooled Studies: Common Treatment Emergent Adverse Events ≥ 2%, Pretomanid vs. HRZE Control – Safety Population

	Pretomanid (N=122)	HRZE (N=16)
Any TEAE	*47 (38.5)*	*7 (43.8)*
TEAEs by SOC/PT (where PTs ≥ 2%)		
Skin and Subcutaneous Tissue Disorders	**18 (14.8)**	**3 (18.8)**
Pruritus*	7 (5.7)	2 (12.5)
Rash†	10 (8.2)	0
Urticaria	2 (1.6)	1 (6.2)
Gastrointestinal Disorders	**13 (10.7)**	**1 (6.2)**
Nausea	5 (4.1)	1 (6.2)
Vomiting	4 (3.3)	1 (6.2)
Abdominal pain‡	3 (2.5)	0
Nervous system Disorders	**6 (4.9)**	**0**
Headache	3 (2.5)	0
Dizziness§	3 (2.5)	0
Respiratory, Thoracic and Mediastinal Disorders	**4 (3.3)**	**2 (12.5)**
Hemoptysis	3 (2.5)	1 (6.2)
Pleuritic pain	0	1 (6.2)
Cardiac Disorders	**4 (3.3)**	**1 (6.2)**
Atrioventricular block first degree	0	1 (6.2)

Source: OCS Analysis Studio, Custom Table Builder
Datasets Used: Applicant's ISS ADSL (POOL5SFL = Y) and ISS ADAE (TRTEMFL = Y)
*Pruritus includes the PTs: pruritus and pruritus generalized. †Rash includes PTs: rash /rash papular/ rash maculopapular. ‡Abdominal Pain includes PTs: abdominal pain/ abdominal pain upper. §Dizziness includes PTs: dizziness / dizziness postural.

TEAEs of interest such as peripheral neuropathy, decreases in hemoglobin, increases in hepatic enzymes, and QT prolongation occurred in 1 (0.8%) subject each in the pretomanid-treated group. No potential Hy's Law cases were identified in the Phase 2 pooling group.

Serious Adverse Events

Hemoptysis was reported in one patient in the pretomanid group and one patient in the HRZE group and pneumothorax was reported in one patient in the HRZE group. The SAEs were related to underlying tuberculosis.

9.7 Summary of Safety

Eight patients died in the Nix-TB study. Adverse events such as peripheral neuropathy, optic neuropathy, hematopoietic cytopenias, acute pancreatitis, seizures, and elevations of hepatic transaminases, total bilirubin, lipase, amylase, and lactic acid were reported during B-L-Pa treatment. Peripheral and optic neuropathies and myelosuppression are known adverse effects of linezolid. In most patients, adverse events were managed by dosing interruptions followed by dose reductions of linezolid or a dosing interruption of the entire B-L-Pa regimen. The subjects who discontinued the B-L-Pa regimen were the 6

(5.5%) subjects who died during the treatment period. All patients who survived were able to resume antimycobacterial therapy to complete study treatment.

There were no additional safety findings of clinical significance in the pooled Phase 1 and Phase 2 trials. There were no deaths or SAEs associated with pretomanid and common TEAEs included headache, nausea, diarrhea, and skin rash. Increases in hepatic transaminases and decreases in hemoglobin were also reported. Overall, pretomanid was generally well tolerated in the pooled Phase 1/2 studies; however, the duration of treatment with pretomanid was short (1 to 43 days) as compared to 6 to 9 months in the Nix-TB trial.

10 Draft Points for Advisory Committee Discussion

- Has the applicant provided substantial evidence of the safety and effectiveness of pretomanid in combination with bedaquiline and linezolid for the treatment of intolerant /nonresponsive multi-drug resistant tuberculosis (TI/NR MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in adults?
    a. If yes, please provide any recommendations concerning labeling.
    b. If no, what additional studies/analyses are needed?