CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212862Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology / Virology

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA, 505(b)(1)
Application Number(s)	212-862
Priority or Standard	Priority
Submit Date(s)	December 14, 2018
Received Date(s)	December 14, 2018
PDUFA Goal Date	August 14, 2019
Division/Office	Division of Anti-Infective Products (DAIP)/Office of Antimicrobial Products (OAP)
Review Completion Date	August 13, 2019
Established Name	Pretomanid
(Proposed) Trade Name	Pretomanid Tablet
Pharmacologic Class	Nitroimidazooxazine, anti-mycobacterial
Code name	PA-824
Applicant	Global Alliance for TB Drug Development
Formulation	Immediate-release oral tablet
Dosing Regimen	Pretomanid 200 mg daily as part of a regimen with bedaquiline and linezolid
Applicant Proposed Indication/Population(s)	Treatment of pulmonary extensively drug-resistant (XDR) and treatment-intolerant/nonresponsive (TI/NR) multidrug-resistant (MDR) tuberculosis in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Limited Population: Pretomanid Tablet is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.

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Reviewers of Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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Pharmacometrics Reviewer	Eliford Kitabi, Ph.D		Sections: 15.3.1	**Select one:** x_ Authored ___ Acknowledged ___ Approved
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Pharmacometrics Team Leader	Chao Liu, Ph.D		Sections: 15.3.1	**Select One:** ___ Authored ___ Acknowledged x_ Approved
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Clinical Reviewer	Elizabeth O'Shaughnessy, M.D.		Sections: 1, 1.1, 1.2,2, 3,4.1, 7.3,7.4,9,10,11,12 ,13,14, 15	**Select one:** x_ Authored ___ Acknowledged ___ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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Statistical Team Leader	Karen Higgins, Sc.D.		Sections:7	**Select one:** ___ Authored ___ Acknowledged x_ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
OPE= Office of Pharmacoepidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP= Division of Medical Policy
DBRUP= Division of Bone, Reproductive and Urologic Products
DTOP= Division of Transpland and Ophthalmology Products
OTS= Office of Translational Sciences
QT-IRT= QT-Interdisciplinary Review Team

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
BMD	Bone mineral density
BPCA	Best Pharmaceuticals for Children Act
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAIDS	Division of AIDS
DAIP	Division of Anti-infective Products
DMC	data monitoring committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
Hb	hemoglobin
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International Normalized Ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
MTB	Mycobacterium tuberculosis
MGIT	Mycobacterial Growth Indicator Tube
MABA	Microplate-Based Alamar Blue Assay
mITT-E	modified intent-to-treat
micro-ITT	microbiological intent-to-treat
MIC	minimum inhibitory concentration
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
REMA	Resazurin Microtiter Assay
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event
USPI	US prescribing information
WHO	World Health Organization

1 Executive Summary Office Level Concurrence

The Applicant has provided substantial evidence of effectiveness of the pretomanid, bedaquiline, and linezolid (BPaL) regimen and sufficient safety information to support approval in a limited and specific population of patients, adults with pulmonary extensively drug-resistant (XDR-TB) and treatment-intolerant/non-responsive multidrug-resistant tuberculosis (TI/NR MDR-TB). In a single phase 3 clinical trial in patients with XDR-TB or TI/NR MDR-TB, superiority of the BPaL regimen on clinical outcomes was demonstrated compared to historical controls. Supportive information is provided by in vitro studies, murine model of pulmonary tuberculosis, and early bactericidal activity studies.

As the benefit-risk considerations of pretomanid in combination with bedaquiline and linezolid only support its use in a limited population of patients with pulmonary XDR-TB or TI/NR MDR-TB, the NDA is being approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD).

1.1. Product Introduction

Pretomanid is a nitroimidazooxazine antimycobacterial drug. Each immediate-release tablet contains 200 mg of pretomanid. Pretomanid is activated within the *Mycobacterium tuberculosis* (MTB) cells and causes the release of reactive nitrogen species leading to interference with MTB's electron flow and ATP homeostasis under anaerobic non-replicating conditions. In actively replicating MTB, pretomanid affects lipid and protein biosynthesis thereby interfering with cell wall production.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of the effectiveness of the pretomanid, bedaquiline, and linezolid (BPaL) regimen and sufficient safety information to support approval in a limited and specific patient population, adults with XDR-TB or TI/NR MDR-TB. In a single phase 3 clinical trial in patients with XDR-TB or TI/NR MDR-TB, superiority of the BPaL regimen on clinical outcomes was demonstrated compared to XDR-TB historical controls. Supportive information is provided by in vitro studies, murine model of pulmonary tuberculosis and early bactericidal activity studies.

The primary endpoint was a favorable outcome (absence of bacteriologic failure, relapse, or clinical failure) through 6 months following end of treatment (EOT). The trial is ongoing and at the interim data cutoff of June 29, 2019, the rate of favorable outcomes 6 months following EOT was 89% (95/107), 95% CI [81%-96%] in the Intent to Treat (ITT) population. As of the January 18, 2019 interim efficacy data cutoff, 32/38 (84%) patients had favorable outcomes at 24 months following EOT. The lower confidence limit for success greatly exceeded the prespecified historical control rate of 50%. In addition, a comparison was made to the outcomes to a matched historical control cohort and to the outcomes for XDR-TB reported in the literature. For the matched historical control, favorable outcome was 9/84 (11%) compared

to Nix-TB 39/44 (89%), Relative Risk 64.5, 95% CI [9 to 472], p <0.0001. Successful outcomes based on review of the literature for treatment of XDR-TB was 28%, 95% CI [21% to 34%] with regimens that did not contain bedaquiline or linezolid.

The contribution of pretomanid, bedaquiline and linezolid to the BPaL regimen was based on studies in the murine model of pulmonary TB. In three studies, the BPaL regimen achieved significantly greater reduction in bacterial lung burden (bactericidal activity) than the 2-drug regimens (BPa, BL or PaL) at the 8-week treatment time points. In addition, fewer mice treated with the 3-drug combination relapsed (sterilizing activity) compared to the BPa and BL regimens. Supportive information was provided from other studies in murine models that showed the contribution of the 2-drug combinations that contained pretomanid.

As the NDA is being approved under the LPAD pathway, labeling includes appropriate information to reflect approval in a limited population.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 212862, the Applicant is seeking approval of pretomanid in combination with bedaquiline and linezolid for the treatment of adults with extensively resistant (XDR-TB) or treatment-intolerant or nonresponsive multidrug resistant tuberculosis (TI/NR MDR-TB) under the LPAD pathway.

Patients with XDR-TB or TI/NR MDR-TB have low cure and high mortality rates and limited treatment options. Treatment success reported across South African studies average 14%, with a range of 2% to 22%; outside of South Africa, rates of treatment success are variable, ranging from 15% to 60%, with only two studies reporting rates above 50%.[1,2] Current treatment paradigm involves a multi-drug regimen (oral and parenteral) that is individually tailored based on the susceptibility of the *M. tuberculosis* isolate and patients are usually treated with 5 to 8 drugs for up to two years or longer.[3] There is an unmet need for efficacious, safe, simplified and shorter regimens for the treatment of this limited population of patients with XDR- or TI/NR MDR-TB, a serious and life threatening condition.

Due to the rapid development of resistance in MTB with monotherapy, multi-drug regimens are the standard of care for both drug sensitive and drug resistant tuberculosis. As outlined in the guidance on *Codevelopment of Two or More New Investigational Drugs for Use in Combination*, if the individual drugs in the combination cannot be administered separately in clinical trials, and the findings from *in vivo* or *in vitro* models and/or phase 2 trials adequately demonstrate the contribution of each new investigational drug to the combination, Phase 3 trials comparing the combination to the standard of care will generally be sufficient to establish effectiveness. Evaluation of the contribution of the components of a treatment regimen for TB in clinical trials using a factorial design is not ethical or feasible. The evidence for the contribution of the individual components to the proposed BPaL regimen comes from studies in the murine models of pulmonary tuberculosis, in which the three-drug BPaL regimen demonstrated superior bactericidal as well as sterilizing activity compared to two-drug combinations of bedaquiline, pretomanid, and linezolid (BPa, BL, PaL).
The safety and efficacy of the BPaL regimen was demonstrated in an ongoing, phase 3, open-label, noncomparative trial, Nix-TB, of a three-

[1] Mor Z, Goldblatt D, Kaidar-Shwartz H, et al. Drug-resistant tuberculosis in Israel: risk factors and treatment outcomes. Int J Tuberc Lung Dis 2014;18(10):1195-201.
[2] Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 2008;359(6):563-74.
[3] Falzon, D.; Schünemann, H.J.; Harausz, E.; González-Angulo, L.; Lienhardt, C.; Jaramillo, E.; Weyer, K. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur. Respir. J. 2017

Reference ID: 4476823

drug regimen of pretomanid, bedaquiline and linezolid administered orally for 6 months to 109 patients with pulmonary XDR-TB or TI/NR MDR-TB. The regimen includes bedaquiline 400 mg PO once daily Day 1-14, then 200 mg x 3 times per week + pretomanid 200 mg PO once daily + linezolid 1200 mg PO daily. Supportive evidence for the single trial is provided by *in vitro* studies, early bactericidal activity (EBA) studies, and nonclinical studies (murine models of pulmonary TB).

Efficacy Results:

The primary endpoint in the study was treatment failure, defined as bacteriologic failure, bacteriologic relapse, or clinical failure through follow-up until 6 months after the end of treatment. The Agency had agreed to review efficacy data for the first 45 subjects who reached the primary endpoint to support the NDA.

For the agreed to population of 45 patients, the rate of favorable outcomes was 40/45 [89%, 95% CI, 76% - 96%] in the ITT population comprised of all subjects with XDR- TI/NR MDR-TB with sufficiently follow up to allow assessment of the 6-month post-treatment outcome. In these 45 subjects, the ITT population coincided with the Modified ITT (MITT) population and per-protocol (PP) population that were defined with additional exclusions. As of the January 18, 2019 interim efficacy data cutoff, the rate of favorable outcomes for the primary endpoint was 95/107 (89%), 95% CI [81%-94%] in the ITT population of all subjects with sufficient follow up for assessment of the 6-month post-treatment outcome. Of the 12 patients with unfavorable outcomes for the primary endpoint, 7 were due to death, 2 to relapse post-treatment, and 3 to withdrawal, loss to follow-up, or contaminated cultures. At this interim data cutoff timepoint a total of 32/38 (84%) patients had favorable outcomes at 24 months following the end of treatment. High rates of favorable outcomes were observed for both the XDR-TB and TI/NR MDR-TB subsets.

The success rate for BPaL was substantially larger than the 50% rate prespecified as the historical control rate threshold. In addition, a comparison was made to the outcomes in a matched historical control cohort and outcomes for XDR-TB reported in the literature. Matched historical control favorable outcome was 11% compared to 89%, in the Nix-TB trial, Relative Risk 64.5, 95% CI [9 to 472], $p < 0.0001$. A literature-based estimate for successful outcomes for treatment of XDR-TB was 28%, 95% CI [21% to 34%]. While there is a 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. Higher cure rates than either of these controls have been described in some recent observational studies in which bedaquiline and/or linezolid were part of

the treatment regimen; however, it is important to note that these regimens included multiple drugs (≥5) usually including an injectable and treatment was administered for 12-18 months.[4],[5],[6],[7],[8] The BPaL regimen offers the advantage of being an all-oral regimen and is administered for 6 months. Both factors, an all-oral regimen and the relatively short duration of therapy, are major benefits to patients and justify the use of the historical controls to support approval of the BPaL regimen.

Safety Results:

The cutoff date for the safety data in the Integrated Summary of Safety (ISS) was March 26, 2018, which included all 109 patients who had received study therapy. Eight (7.3%) of 109 subjects died, 6 (5.5%) during the 26-week treatment period and 2 (1.8%) during follow-up. Treatment emergent adverse events (TEAEs) leading to death included: pneumonia (2 subjects), pulmonary tuberculosis (2 subjects), disseminated tuberculosis (1 subject), sepsis or septic shock (2 subjects), acute pancreatitis (2 subjects), upper gastrointestinal hemorrhage (1 subject), and multi-organ dysfunction (1 subject). No additional deaths or new safety signals were reported between the original cutoff date March 26, 2018 and the 120-Day Safety Update cut-off date, October 15, 2018.

Significant safety findings associated with the BPaL regimen included optic neuropathy, peripheral neuropathy, myelosuppression, hepatic abnormalities, pancreatitis, lactic acidosis, and QT prolongation. Peripheral sensory neuropathy associated with linezolid, was the most common treatment emergent adverse event (TEAE) and was reported in 75 (69%) subjects; TEAEs related to peripheral neuropathy symptoms captured in standardized MedDRA query (SMQ) of the safety data were experienced by 87 (80%) of patients. Myelosuppression (anemia, leukopenia and thrombocytopenia) associated with linezolid occurred in 51 (47%) subjects. Hepatic TEAEs were reported in 39 (36%) subjects and were more common in HIV-positive 23 (41%) than in HIV negative patients 16 (30%). There was no progression to serious liver disease in

[4] Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J 2017; 49.
[5] Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. Eur Respir J. 2018;52.
[6] Olayanju O, Limberis J, Esmail A, Oelofse S, Gina P, Pietersen E, Fadul M, Warren R, Dheda K. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. Eur Respir J. 2018 May 30;51(5)
[7] Olayanju O, Esmail A, Limberis J, Gina P, Dheda K. Linezolid interruption in patients with fluoroquinolone-resistant tuberculosis receiving a bedaquiline-based treatment regimen. Int J Infect Dis. 2019 Aug;85:74-79
[8] Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821.

Reference ID: 4476823

any patient. One patient fulfilled the laboratory criteria for Hy's law; transaminases and bilirubin improved to normal range after a two-week interruption of the BPaL regimen, and the patient resumed BPaL and completed a full course of treatment. Hepatotoxicity has been reported with other pretomanid-containing regimens (pretomanid, moxifloxacin, pyrazinamide). Mild QT prolongation, associated with bedaquiline, occurred in 6 (5.5%) patients. Lactic acidosis was reported in 8 (7.3%) subjects and was mostly associated with linezolid.

TEAEs were successfully managed by dosing interruptions, dose reductions, or discontinuation of linezolid alone or the entire BPaL regimen. Pretomanid and bedaquiline doses were not adjusted during the trial. Most TEAEs resolved but peripheral sensory neuropathy, was ongoing in 21 (28%) of 75 patients at the safety data cutoff date (March 26, 2018). Pretomanid had no clinically significant effect on the QT interval in a Thorough QT (TQT) study.

In animal toxicology studies of pretomanid, testicular toxicity (irreversible infertility) was noted in male rats. Human male sex hormone levels in clinical trials of pretomanid containing regimens have been within normal ranges. The effects of pretomanid on human spermatogenesis and male fertility in humans are unknown at present. A human semen analysis study will be conducted as a postmarketing requirement (PMR) to investigate the effect of pretomanid on human male fertility.

Overall, the benefit risk considerations are favorable for the BPaL regimen for the treatment of a limited population of patients with XDR-TB or TI/NR MDR-TB, a serious and life-threatening condition with an unmet medical need. While there are uncertainties with use of historical controls, treatment effect seen with the BPaL regimen significantly exceeded the published historical control rates seen in patients treated for XDR-TB without pretomanid, bedaquiline, or linezolid, or in a matched historically controlled comparison. Use of historical controls is appropriate in settings such as XDR-TB, or TI/NR MDR-TB, where the outcomes with currently available treatment options are poor and the treatment effect is too large to be easily explained by confounding factors. Although some recent observational studies suggest higher cure rates with bedaquiline or linezolid containing regimens, the BPaL regimen offers the advantage of being all oral with a 6-month treatment duration, which is much shorter than the currently used 18-24 month regimens which often include an injectable drug. Risk mitigation measures include warnings in labeling regarding risk of hepatic adverse reactions, myelosuppression, QT prolongation, neuropathy, reproductive effects and lactic acidosis. Labeling also includes limitations of use, i.e., pretomanid is not indicated for patients with drug sensitive tuberculosis (TB), latent TB, extrapulmonary TB or MDR-TB that is not treatment intolerant/non-responsive. Additionally, a Medication Guide is included in labeling to inform patients of the risks of the BPaL regimen. The Applicant is required to conduct postmarketing studies to further characterize the safety of pretomanid and to evaluate dosing in patients with hepatic or renal impairment.

Directly observed therapy (DOT) will ensure patient compliance with the BPaL regimen. Patients should be monitored regularly for the development of adverse reactions such as peripheral neuropathy, optic neuropathy, myelosuppression, transaminitis, lactic acidosis, and QT

interval prolongation. Clinical monitoring should include regular neurologic and ophthalmologic (vision and retina) exams. Lipase/amylase levels should be measured if clinically indicated. Male patients should be informed about the possibility of infertility associated with pretomanid until further information is known about its effect on human spermatogenesis. Development of *in vitro* resistance of *M. tuberculosis* to pretomanid will be monitored as a PMR. Additional PMRs include, the ZeNix trial which will provide additional safety data for the BPaL regimen; the SimpliciTB trial, which will provide information on the safety of pretomanid in combination with moxifloxacin, pyrazinamide, and bedaquiline, an animal carcinogenicity study, and PK/safety studies in patients with hepatic and renal impairment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• XDR-TB and TI/NR MDR-TB are serious and life-threatening diseases. • Success rates reported in the literature are low. The reported average cure rate for XDR-TB is 14% in South Africa where the NixTB trial is ongoing. • Treatment success rates as high as 60% have been reported in a small number of studies with bedaquiline-containing multi-drug regimens administered for up to 24 months.	• There is an unmet medical need for the treatment of XDR- and TI/NR MDR-TB. New safe and effective anti-mycobacterial therapies administered for short durations, particularly without parenteral treatment are needed.
Current Treatment Options	• Current regimens are chosen based on the susceptibility results of the *M. tuberculosis* isolate. Treatment can include 5 to 8 antimycobacterial drugs including oral and injectable drugs administered for up to 24 months. • Bedaquiline is the only drug approved as part of a combination regimen for the treatment of MDR-TB in the US.	• The proposed 3-drug regimen (BPaL), offers an advantage over current therapies because it is an all-oral, 3-drug regimen administered for 6 to 9 months versus the 5 to 8 drugs in current regimens, administered for up to 24 months.
Benefit	• The rate of favorable outcomes was 40/45 [89%, 95% CI, 76% - 96%] in the intent-to-treat (ITT) population comprised of all subjects with XDR-	• The 3-drug oral regimen is likely to improve compliance with treatment. • Increased cure rates not only benefit the individual patient with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	TI/NR MDR-TB with sufficiently early enrollment to allow assessment of the 6-month post-treatment outcome. • As of the January 18, 2019, interim efficacy data cutoff, the rate of favorable outcomes for the primary endpoint was 95/107 (89%), 95% CI [81%-94%] in the ITT population at the 6-month post-treatment outcome. At this timepoint, 32/38 (84%) patients had favorable outcomes at 24 months following the end of treatment. • The observed cure rates were significantly higher than the cure rate seen in a historical control cohort of XDR-TB patients and in published clinical outcomes for XDR-TB patients. • The contribution of the components of the BPaL regimen was demonstrated in a murine model of pulmonary tuberculosis.	XDR-TB or TI/NR MDR-TB but could also improve public health outcomes by reducing the transmission of drug-resistant tuberculosis.
Risk	• In the clinical development program, 1168 subjects were exposed to pretomanid either alone (411 [35.2%] subjects) or in combination with other antimycobacterial drugs (757 [64.8%] subjects). • The safety population for the BPaL regimen is limited and includes 124 patients. • TEAEs associated with the BPaL regimen included: peripheral neuropathy, optic neuropathy, myelosuppression (anemia, leukopenia, neutropenia, thrombocytopenia), lactic acidosis, QT prolongation, elevations in hepatic	• An ongoing phase 3 trial, in patients with XDR-TB, Pre-XDR-TB, and MDR-TB should provide additional safety data for the BPaL regimen at various doses and durations of linezolid. • Adverse events associated with BPaL can be monitored with regular assessments for new symptoms & signs and laboratory test abnormalities. • In the Nix-TB trial, risks associated with BPaL were manageable, e.g., peripheral or optic neuropathy and hematopoietic cytopenias or elevated transaminases can be managed by dose reductions, interruptions, or discontinuation of linezolid, or interruptions of the entire BPaL regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	transaminases and bilirubin, skin rash, and gastrointestinal adverse events. • Pretomanid caused testicular toxicity and infertility in male rats. Male hormone levels were within the normal range in the Nix-TB trial and in a phase trial 3 of another pretomanid-containing anti-mycobacterial regimen. The effects of pretomanid on human male fertility is not known.	• Hepatic, hematologic, and most neurologic adverse events were reversible in the Nix-TB trial. • A human semen analysis study will be conducted as a PMR to investigate the effect of pretomanid on human male fertility.

Risk Management		• Directly observed therapy (DOT) is recommended for all patients receiving BPaL to ensure compliance.
		• Regular assessments of neurologic and visual function (linezolid) and measurement of QT interval (bedaquiline) on ECG is essential.
		• Monitoring of full blood count with differential and liver tests at baseline, at 2 weeks, and monthly, at a minimum, is recommended.
		• Lipase/amylase levels should be measured if clinically indicated.
		• Development of *in vitro* resistance of M. *tuberculosis* will be monitored as a PMR.
		• At this time, a REMS is not recommended; labeling including a Medication Guide is sufficient to communicate the risks associated with BPaL.
		• The Applicant will conduct the following studies as PMRs:
		  o Additional safety data for BPaL regimen will be collected in the ZeNix trial
		  o Assessment of hepatic safety of pretomanid in combination with moxifloxacin, PZA, bedaquiline in the SimpliciTB trial
		  o A human semen analysis study to investigate the effect of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		pretomanid on human male fertility. o Animal carcinogenicity study o PK/safety studies in patients with hepatic and renal impairment

2 Therapeutic Context

2.1. Analysis of Condition

Multidrug resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin, the two most effective of the four first-line anti-TB drugs, isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE). Extensively drug-resistant TB (XDR-TB) is a less common form of MDR-TB, that is resistant to isoniazid and rifampin plus any fluoroquinolone and at least one of the three injectable second-line drugs (i.e. amikacin, kanamycin, or capreomycin). Patients who have XDR-TB or treatment intolerant and non-responsive TI/NR MDR-TB, the intended patient population in this NDA, have limited treatment options.

Surveys of worldwide drug resistance indicate that drug-resistant tuberculosis (DR-TB) is an increasing problem.[9] The WHO estimated that there were approximately 558,000 cases of MDR-TB worldwide in 2017; of these, it is estimated that there were 230,000 deaths due to MDR-TB. China, India, Russia, and countries of the former Soviet Union have the highest number of MDR-TB cases in the world.[10] Several African and South East Asian nations also have a high burden of MDR-TB disease. The prevalence of DR-TB in the United States decreased between 1991 and 2006 (3.5 to 1.1 percent) and remained stable between 2005 and 2006 (1.2 percent), even as drug-resistant tuberculosis increased worldwide.[11,12] . MDR-TB disproportionately affects foreign-born individuals and this group accounted for 85% of cases of MDR-TB in the US in 2015.[12]

In a meta-analysis of combined data from 50 different studies including 12,030 adult patients with MDR-TB, a significant association was observed between reduced mortality and use of linezolid, levofloxacin, moxifloxacin, or bedaquiline, as well as use of regimens containing no injectable drug.[8] Although inferences were limited because the data were observational, treatment outcomes were significantly better with use of linezolid, fluoroquinolones, bedaquiline, clofazimine, or carbapenems.

Patients infected with XDR-TB or TI/NR MDR-TB have a high mortality rate and limited treatment options. Treatment success across South African studies averaged at 14%, with a

[9] Zignol M, van Gemert W, Falzon D, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. Bull World Health Organ. 2012 Feb;90(2):111-119D. Epub 2011 Nov 07.
[10] World Health Organization. Global Tuberculosis Report 2017. Available at: http://www.who.int/tb/publications/global_report/en/ (Accessed on November 03, 2017).
[11] Onorato IM, Dansbury KG, Kelly GD, Driver CR, Snider DE Jr, Bloch AB, Cauthen GM. Nationwide survey of drug-resistant tuberculosis in the United States. JAMA. 1994;271(9):665
[12] Trends in tuberculosis--United States, 2007. Centers for Disease Control and Prevention (CDC) MMWR Morb Mortal Wkly Rep. 2008;57(11):281.

Reference ID: 4476823

range of 2% to 22%; outside South Africa, rates of treatment success are more variable, ranging from 15% to 60%, with only two studies reporting treatment success rates above 50%.[13,14] Amongst the most difficult-to-treat *M. tuberculosis* strains are those causing XDR-TB. Current treatment regimens for XDR-TB or TI/NR MDR-TB include a combination of second- and third-line oral drugs with an injectable antimycobacterial drug. The regimen is individually tailored based on the susceptibility pattern of the *M. tuberculosis* isolate, and patients are usually treated with five to eight drugs for up to two years or longer.[3] Poor efficacy, adverse reactions, intolerance, and drug-drug interactions with antiretroviral drugs and other concomitant medications are among the many challenges with antimycobacterial multidrug regimens administered for prolonged periods. Compliance is difficult, and patients endure long hospital stays as treatment has usually been administered in an inpatient setting or more recently in outpatient directly observed therapy (DOT) programs to assure adherence.

There is an unmet need for efficacious, safe, and shorter regimens for treatment of MDR-TB and XDR-TB.

2.2. Analysis of Current Treatment Options

FDA-approved drugs for treatment of tuberculosis include: isoniazid, rifampin, ethambutol, pyrazinamide, rifapentine, ethionamide, streptomycin, capreomycin, cycloserine, p-aminosalicylic acid (PAS), and bedaquiline. Bedaquiline was approved in 2012 to be used in combination with other antimycobacterial drugs for treatment of pulmonary MDR-TB.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pretomanid (PA-824) is a nitroimidazooxazine, currently in clinical development for the treatment of drug-sensitive tuberculosis (DS-TB), MDR-TB, and XDR-TB. Pretomanid is a new molecular entity and is not currently marketed in the US or anywhere in the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-IND meeting with FDA and TB Alliance was held on October 1, 2004 to discuss the adequacy of the completed and planned non-clinical studies to support an IND and the design of phase 1 clinical studies for the treatment of (b) (4) and MDR-TB.

On April 28, 2005, IND 69,580 was opened for pretomanid (PA-824), for the treatment of (b) (4)

[13] Mor Z, Goldblatt D, Kaidar-Shwartz H, et al. Drug-resistant tuberculosis in Israel: risk factors and treatment outcomes. Int J Tuberc Lung Dis 2014;18(10):1195-201.
[14] Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 2008;359(6):563-74.

Reference ID: 4476823

and MDR-TB. Clinical trials of pretomanid (> 14 days) in various anti-mycobacterial drug regimens are summarized in Table 1.

Pretomanid (IND 69,580) was granted orphan-drug designation for the treatment of tuberculosis on July 5, 2007, Fast Track designation for the treatment of tuberculosis on October 22, 2007, and Qualified Infectious Disease Product (QIDP) designation for treatment of DS-TB, MDR-TB and XDR-TB on August 15, 2017.

At the pre-NDA meeting held on June 1, 2018, the applicant and the agency agreed that an interim clinical study report with datasets for the first 45 subjects enrolled and assessed for the primary efficacy endpoint in the ongoing Nix-TB trial would support an NDA submission. In addition, the agency agreed that an addendum to clinical study report (CSR) with updated efficacy and safety data for all 109 subjects in the Nix-TB trial could be included in the initial NDA submission as a stand-alone document. To support the efficacy outcomes in Nix-TB, TB Alliance agreed to provide a literature summary and case-matched analysis of historical control data for XDR-TB patients.

Other agreements between TB Alliance and the agency included:

- Ophthalmological evaluations for cataract formation would be incorporated in clinical trials of pretomanid dosed for more than 14 days because of a signal for cataract formation in animal toxicology studies.
- The signal for male infertility observed in animal toxicology studies of pretomanid would be further investigated clinically, including evaluations of human male hormone levels in clinical trials and a human semen analysis study planned for 2019.
- Additional phase 1 pharmacokinetic studies and studies of pretomanid in patients with hepatic impairment or renal impairment studies could be conducted concurrent with the NDA.

As agreed with the agency at the pre-NDA meeting, results for these studies will be available after the current NDA review cycle except for the studies on cataract formation.

On December 14, 2018, the applicant submitted an NDA for pretomanid as part of regimen with bedaquiline and linezolid for the treatment of XDR-TB and TI/ NR MDR-TB. The NDA received priority review pursuant to section 524A of the FD&C Act (GAIN). However, the Agency also determined that the NDA independently fulfilled the criteria for Priority Review as outlined in the FDA guidance on *Expedited Programs for Serious Conditions – Drugs and Biologics*.

Table 3-1. Phase 2 / 3 studies: Pretomanid-containing antimycobacterial 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

<u>Clinical Hold - IND 69,580</u>

There were four deaths due to hepatotoxicity in two trials, NC-005 (1 death in patient treated with HRZE comparator) and NC-006 (3 deaths in patients treated with a pretomanid-containing regimen), in 2015, Table 9-7. These two trials evaluated antimycobacterial regimens different from the one seeking approval in the current NDA.

The Agency held a teleconference with the TB Alliance on October 1, 2015 to discuss the hepatic deaths and placed a partial clinical hold to enrollment of new subjects for all study arms in Study NC-006 on October 7th, 2015. The partial hold was instituted until a possible

association of the regimen (moxifloxacin, pretomanid, pyrazinamide) with hepatotoxicity could be examined. An FDA hepatologist evaluated the data and concluded that it was highly likely that hepatotoxicity and liver failure were related to the study drug regimen; however, it was not clear which component(s) of the regimen caused hepatotoxicity. There was no 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 clinical development program matched the treatment allocation ratio in the trials. Additional monitoring for hepatic dysfunction and other safety measures were put in place in study NC-006 and in subsequent clinical protocols for other studies to ensure the safety of study subjects. The partial clinical hold on IND 69,580 was removed on August 17, 2016.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

All three study sites participating in the Nix-TB trial in South Africa were inspected by OSI. The FDA Establishment Inspection Report and the documents submitted with that report did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance. The study data are considered reliable in support of the proposed indication based on the OSI inspection. See consult review dated April 22, 2019, by Aisha P. Johnson, M.D., M.P.H., M.B.A., Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, OSI.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No. Impurity specifications are consistent with ICH guidelines.
Sufficient controls to insure safety and efficacy of the commercial product: Yes
Pretomanid Tablet, 200 mg is a white to off-white, oval shaped, uncoated immediate release tablets for oral use. The tablet is debossed with M on one side and P200 on the other side of tablet.

The qualitative and quantitative composition of Pretomanid Tablet, 200 mg on a per tablet basis is provided in Table 4-2. All inactive ingredients are within the allowable Inactive Ingredients (IIG) database limits for an oral solid dosage.

Table 4-1. Qualitative and Quantitative Composition of Pretomanid Tablet, 200 mg

Ingredient/Pharmacopeial standard	Function	%w/w	Weight per Unit (mg)
Pretomanid	Active	(b) (4)	200.0
Lactose Monohydrate, NF			(b) (4)
Microcrystalline Cellulose, NF			
Sodium Starch Glycolate (b) (4) NF			
Magnesium Stearate, NF			
Colloidal Silicon Dioxide, NF			
Sodium Lauryl Sulfate, USP			
Povidone, USP (PVP K30)			
			(b) (4)
Total		100%	800.0 mg

The tablets are packaged in either:

- unit dose blister pack (peel/push) comprising of 20 µm aluminum lidding foil (b) (4) with paper backing, 250 µm clear and transparent PVC film, (b) (4), 1 tablet per blister. The blister pack is placed in an outer carton.
- 60 ml high density polyethylene (HDPE) bottle, 33 mm child resistant polypropylene closure with a (b) (4) liner and an absorbent cotton. The container is sealed with a

paper backed aluminum foil with a clear, heat sealable coating.

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered in Panorama by the Office of Process and Facilities (OPF) on July 19, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

Executive Summary

The nonclinical safety profile of pretomanid was evaluated in safety pharmacology studies (*in vitro* and *in vivo*, in rats, dogs and monkeys), repeat dose toxicity studies (in mice, rats, and monkeys, for up to 39 weeks), fertility and pre- and post-natal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits, and genetic toxicology studies (Ames, *in vitro* chromosomal aberration, mouse lymphoma and *in vivo* rat micronucleus assays). Pharmacokinetics were evaluated in numerous studies *in vitro* as well as in monkeys, rats, dogs, rabbits and mice. Carcinogenicity studies are ongoing. The toxicology findings must be considered relative to the finding that healthy, fed subjects dosed with 200 mg pretomanid had a C_{max} of 1.1 µg/mL, an AUC_t of 52 (µg.hr/mL) and a $T_{½}$ of 17 hours.

Pharmacology

Please refer to the Nonclinical Microbiology section of this review for details on mechanism of action. An *in vitro* secondary pharmacology screen, conducted to assess off target effects, determined that 30 µM pretomanid (about 11 µg/mL) has the potential to interfere with binding to progesterone (40%), thyrotropin releasing hormone (21%), and testosterone (15%) receptors.

Pharmacokinetics

After oral administration, peak plasma concentrations of pretomanid were observed between 1 and 8 hours in rats and 2 to 6 hours in monkeys. AUC and C_{max} were approximately dose-proportional or less than dose proportional. Bioavailability of the PA824 tablet was 37% in fed monkeys and 46% in fasted monkeys, which differed from humans where fed patients showed higher exposures at the same dose. Pretomanid was highly protein bound (80-86% in all species examined) and had wide tissue distribution in rodents. In a study of radiolabeled PA-824 in rats, the highest tissue concentrations were measured in the Harderian gland, liver, renal medulla, adrenal gland, kidney, renal cortex, exorbital lacrimal gland, and spinal cord. Pretomanid concentrations in rat tissues were higher than in blood, but there was minimal partitioning into monkey or human erythrocytes. Pretomanid concentrations in the milk of dosed, lactating dams were about 1.5 times greater than the maternal plasma levels (which were in turn 24- to 31-fold greater than pup plasma pretomanid levels.

Metabolism involves two phases: phase I oxidation, reduction of the nitro group, oxidative deamination, and oxidative-cleavage, followed by phase II glycine conjugation and glucuronidation. Pretomanid was mainly eliminated through metabolism followed by excretion into feces and urine (45% and 26% respectively in rat). Elimination half-life was about 4 hours for the pretomanid tablet in monkeys.

Safety Pharmacology

No significant effects on neurologic or respiratory parameters were observed in rats following single oral 50 mg/kg doses of pretomanid (about 1-2 times the clinic dose based on AUC comparisons). At high doses (4-fold the clinical dose) there was reversibly decreased touch

response, body tone and grooming. *In vitro*, pretomanid inhibited hERG current with an IC_{50} about 6.2 µg/mL. Since pretomanid is 82% protein bound and the IC_{50} was about 6 times the clinical Cmax, this hERG result does not indicate a risk to patients at the clinical dose. In monkeys, QT prolongation was inconsistently associated with pretomanid administration. One study was confounded using ketamine anesthesia, which resulted in QT prolongation predose and in control animals. In conscious monkeys, using raw QT data or data corrected using van de Water's correction formula, pretomanid administration did not result in significant effects on QT. On the contrary, using the Bazett and Fridericia formulae, moderate QT prolongation was observed at all doses tested. The relationship between heart rate and QT varies across species and Van de Water's QTc correction formula was developed based on data from dogs. Bazett' s formula (developed for humans) has been shown to overestimate QT prolongation and there is no validated QT correction formula for use in cynomolgus monkeys. Given the above considerations and since the QT-IRT reviewer, Girish Bende, PhD., agreed that the results of a TQT study showed no clinically meaningful increase in QTc after single oral doses of 400 mg and 1,000 mg of pretomanid, this reviewer's conclusion is that the nonclinical data do not indicate a risk for QT prolongation under the current indicated use.

Repeat-dose Toxicology studies

The reproductive system was identified as a target organ of toxicity in repeat dose studies in mice, rats and monkeys. These effects could relate to pretomanid's affinity for the progesterone and testosterone receptors, although there are no clear mechanistic connections. Testicular toxicity observed in mice and rats resulted in infertility (see Reproductive toxicity) as well as reduced sperm motility, spermatocyte degeneration/necrosis, increased frequency of abnormal sperm morphology and decreased epidydimal sperm counts. In a 13-week mouse study, dose-related changes included oligospermia and bilateral degeneration/atrophy of the seminiferous tubules. The degeneration of the seminiferous tubules ranged from minimal to severe and was evident at doses as low as 0.2 times the MRHD based on AUC comparisons. In a 13-week rat study, the NOAEL for testicular toxicity was similar to human exposures at the MRHD. In a 13-week monkey study pretomanid doses ≥ 150 mg/kg resulted in decreased sperm counts/motility and increased ratio of abnormal sperm, but these doses were also associated with poor general condition (decreased feed consumption and reduced bodyweight). In this study, the NOAEL for testicular toxicity was 50 mg/kg, which was associated with an AUC of 70 µg*h/mL, which is 1.4 times the MRHD. In the 39-week toxicity study in monkeys, the highest dose resulted in slight increases in adrenal, spleen, kidney, testes, and ovary weights (without histopathological correlates) which did not reverse after a 12-week reversibility period. The biological significance of this finding is not apparent, but it may relate to the general poor condition of the animals in this group which received excessive amounts of pretomanid and had a mean 23 % lower bodyweight compared to controls. Cataracts were observed in a few rats at 100 mg/kg in a 26-week study (about 2 times the MRHD based on AUC comparisons) and at 300 mg/kg in a 13-week study (about 8 times the MRHD based on AUC comparisons).

Genetic Toxicology

Pretomanid was not mutagenic or clastogenic as tested in the Ames assay up to 5000 µg/plate, the *in vitro* chromosomal aberration assay in Chinese hamster ovary (CHO) cells up to 1100

µg/mL, the *in vitro* mouse lymphoma assay up to 500 µg/mL and the *in vivo* mouse micronucleus assay, single dose up to 2000 mg/kg/day. PA824 metabolite, M50 was positive for mutagenic potential in the bacterial reverse mutation assay. Two carcinogenicity studies are ongoing.

Reproductive Toxicology
Reduced fertility was observed in male rats given daily oral pretomanid for 13 weeks at 30 mg/kg. At 100 mg/kg, pretomanid was associated with reduced body weight, and complete infertility, associated with testicular atrophy, lower sperm counts, reduced sperm motility, lower serum inhibin B concentration, and higher serum FSH concentration. After a 10-week recovery period, effects on fertility at 30 mg/kg/day showed partial improvement, but at 100 mg/kg/day effects on FSH, inhibin testes/epididymis size, fertility persisted. The NOAEL for fertility effects was 10 mg/kg, about half the clinical exposure based on AUC comparisons. Female rats dosed daily with oral pretomanid 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 at 100 mg/kg/day. When paired with treated males, fertility (conception rate) was reduced at the 30 mg/kg dose and at the high dose there was complete infertility. Reduced fertility appears to be because the effects on spermatogenesis in males since pairs were infertile when high dose males were paired with untreated females.

Pretomanid administration to rats during organogenesis (Gestational Day [GD] 7 through GD 17) resulted in maternal toxicity at the 30 mg/kg and 100 mg/kg doses (reduced maternal body weight and/or body weight gain and feed consumption during the entire dosage period). In the presence of maternal toxicity (100 mg/kg) post implantation loss was increased, the number of live fetuses and fetal body weight were lower, and skeletal development was slowed (reduction in ossified hind limb phalanges). In rabbits dosed during organogenesis (GD 7 through 20) maternal toxicity (reduced feed consumption and maternal body weight) was observed at the 60 mg/kg dose. No adverse effects on fetal survival, growth, or development were observed at this dose (approximately equivalent to the clinical dose based on AUC comparisons). Rats exposed to pretomanid during a prenatal postnatal study showed maternal toxicity (reduced maternal body weight and/or body weight gain and feed consumption) at 60 mg/kg. Pups from dams that experienced maternal toxicity showed a slight delay in the age at which the air-drop righting reflex developed and an increase in basic and fine movement as well as total distance travelled. These changes were observed in the presence of maternal toxicity and are therefore of questionable significance.

RECOMMENDATION
From a pharmacology/toxicology perspective, the applicant has provided sufficient nonclinical safety information on pretomanid to support approval for marketing in the U.S.

5.1. Referenced NDAs, BLAs, DMFs

None

Reference ID: 4476823

5.2. Pharmacology

Primary pharmacology

The IUPAC name for pretomanid is (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)phenyl]methoxy}-6,7-dihydro-5*H*imidazo[2,1-*b*][1,3]oxazine. The CAS registry name is (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine. The applicant has proposed to designate pretomanid a nitroimidazooxazine antimycobacterial drug. The primary pharmacology studies of pretomanid are detailed in the Clinical Microbiology Section of this review.

Secondary Pharmacology

(b) (4) **data report on compound RTI-7 for Research Triangle Institute. Study #1033997.**

Table 5-1: Effect of pretomanid on radioligand binding to progesterone, thyrotropin releasing hormone and testosterone receptors

Target receptor	Species	% inhibition of receptor binding by 30 µM pretomanid
Progesterone PR-B	Human	40%
Thyrotropin releasing hormone	Rat	21 %
Testosterone	Rat	15 %
Glucocorticoid	Human	5 %
Estrogen ER_{α}	Human	-2%
Estrogen ER_{β}	Human	-9%

***In Vitro* Incorporation of [1,2-^{14}C] Acetic Acid into Sterol Precursors in Cryopreserved Hepatocytes from Rats in the Presence and Absence of PA-824.** (b) (4) **Study # 09658.**
De novo cholesterol biosynthesis from acetate was evaluated by incubating cryopreserved plateable rat hepatocytes with [1,2-^{14}**C**]-acetic acid in the presence of up to 30 mcM pretomanid for up to 24 hours. Pretomanid did not inhibit cholesterol biosynthesis in cryopreserved rat hepatocytes exposed to radiolabeled (^{14}**C**-acetic acid).

Safety Pharmacology

Central Nervous System
The effects of PA-824 in the Irwin Test in Sprague Dawley Rats. (b) (4) **Study # SP104-027.**
Oral PA-824 at 50 mg/kg had no effect on gross behavior and physiology in rats observed at 4, 8, and 24 h after dosing. Higher doses (150 and 450 mg/kg) resulted in depression of neural functions including decreased touch response, body tone, and grooming at 4 h postdose. These

Reference ID: 4476823

effects resolved within 24 hours at 150 mg/kg, but piloerection, slightly decreased touch response and slightly decreased grooming were observed 24 h postdose in the animals dosed at 450 mg/kg. PA-824 was formulated in (b) (4) (100 mg/mL) and (b) (4) (100 mg/mL) in (b) (4).

Cardiovascular

Effect of PA-824 and TBA354 on Cloned hERG Potassium Channels Expressed in Mammalian Cells. (b) (4) Test # 110809 (b) (4)

The *in vitro* effects of PA-824 on the hERG (human ether-à-go-go-related gene) channel current (expressed in a human embryonic kidney (HEK293) cell line) were assessed at concentrations up to 100 mcM. Pretomanid inhibited hERG current by 13%, 37%, 64%, and 85% at concentrations of 3, 10, 30, and 100 mcM. The IC_{50} for inhibition of hERG current was 17.3 mcM or about 6.2 mcg/mL

Cardiovascular evaluation of PA824 in conscious cynomolgus monkeys via oral gavage. Study N106361.

Single doses of PA-824 (formulated in (b) (4)) at 50, 150, 450 mg/kg were given by gavage, to 4 male, telemetered (3- to 7-year old) cynomolgus monkeys in a Latin-Square design protocol to assess adverse effects on cardiovascular parameters. QT prolongation was assessed using four different methods. Absolute QT intervals were not statistically different from vehicle at any time point and QT interval prolongations were not statistically significant at any dose level when corrected by the Van de Water's formula. QTc intervals for all groups receiving test article were statistically prolonged (moderately) compared to vehicle when using the Bazett and Fridericia formulae. There is no validated model for correcting the QT in cynomolgus monkeys and the available formulae produce conflicting results. Since The QT-IRT reviewer, Girish Bende, PhD., concluded that the results of a TQT study showed no clinically meaningful increase in QTc after single oral doses of 400 mg and 1,000 mg of pretomanid, the findings in the monkeys are of questionable significance.

2-Week Nasogastric Gavage Toxicity and Toxicokinetic Study with PA-824 in Cynomolgus Monkeys with a minimum 2-Week Recovery Period. Study 7504-110.

Cynomolgus monkeys dosed with 0, 50, 150, 450, and 1000 mg/kg/day of PA-824 (formulated in (b) (4)) for two weeks, by oral gavage showed frank toxicity at doses 450 mg/kg and above including vomiting, hypoactivity, hunched and/or thin appearance, reduced feed consumption and body weight, ataxic behavior, convulsions and feces with a red tinge. Electrocardiographic measurements were recorded on anesthetized monkeys prior to Day 1 and on Days 2, 15, and 28 (recovery phase). ECGs were recorded between 2 to 4 hours postdose for control, 50, and 150 mg/kg/day groups and 5 to 7 hours postdose (the estimated times of Cmax) for the 450 and 1000 mg/kg/day groups. The Day 15 QTc values were 300, 303, 312, 343 and 393 msec at 0, 50, 150, 450, and 1000 mg/kg/day. The NOAEL for QT effects was 150 mg/kg. The $AUC_{(0\text{-}24h)}$ at this dose was 217 µg*h/mL. At the end of recovery, the QTc value (Fridericia) at 450 mg/kg was 296 msec, compared to 270 msec in controls.

Cardiovascular Evaluation in Dogs Given Single Subcutaneous Doses of Pretomanid, Daily Oral Doses of Bedaquiline for 6 Days, or Daily Oral Doses of Bedaquiline for 7 Days with Co-administration of a Subcutaneous Dose of Pretomanid on the Last Day. (b) (4) Study # 1408-010.

Three groups of conscious, telemetered, non-naïve beagle dogs (2/sex/dose) were given either (1) daily doses of bedaquiline vehicle ((b) (4)) on Days 1 through 7 and a dose of pretomanid vehicle ((b) (4)) on Day 7 or (2) daily doses of bedaquiline vehicle on Days 1 through 7 and a dose of 100 mg/kg dose of pretomanid on Day 7 or (3) daily oral doses of bedaquiline at 100 mg/kg on Days 1 through 7 and a dose of pretomanid at 100 mg/kg on Day 7. Mean QT and QTc interval durations observed following the combined administration of 100 mg/kg bedaquiline with 100 mg/kg PA-824 were comparable to the administration of vehicle controls. The heart-rate corrected QT interval was derived from the publication by Miyazaki et al (2002).[15]

Respiratory

The Effects of PA-824 on Respiration Rate and Tidal Volume in Sprague Dawley Rats Study # SPR04-027.

Single doses of PA-824 ((b) (4)) were administered orally by gavage to three groups of 8 male Sprague Dawley rats at 50, 150, and 450 mg/kg and respiratory rate, tidal volume, and minute volume were evaluated before and approximately 4, 8, and 24 h postdose using restrained head-out plethysmography chambers. No significant differences from vehicle were observed with the 50 and 150 mg/kg doses of PA-824 for respiration rate or minute volume but at 450 mg/kg respiration rate and minute volume were decreased by 21-25% at 4, 8, and 24 h postdose compared to control (vehicle).

5.3. ADME/PK

<table>
<tr><th>Type of Study</th><th colspan="2">Major Findings</th></tr>
<tr><td>Absorption</td><td colspan="2"></td></tr>
<tr><td>Pharmacokinetics of PA-824 Formulations After Oral or Intravenous Administration in Male Cynomolgus Monkeys. Study # (b) (4) 7504-115</td><td></td><td>Pretomanid Pharmacokinetic Parameters After Single Oral Gavage or IV Administration of Pretomanid to Cynomolgus Monkeys
<table>
<tr><td>Formulation</td><td>200 mg Tablet (fasted)</td><td>200 mg Tablet (fed)</td><td>45 mg Tablet</td><td>IV</td><td>50 mg Capsule</td></tr>
<tr><td>Dose (mg/kg)</td><td>42</td><td>41</td><td>11</td><td>2.15</td><td>12</td></tr>
<tr><td>T_{max}(h)</td><td>6.0</td><td>5.0</td><td>3.7</td><td>NC</td><td>2.5</td></tr>
</table></td></tr>
</table>

[15] Miyazaki H, Tagawa M. Rate-correction technique for QT interval in long-term telemetry ECG recording in beagle dogs. Exp Anim 2002;51(5):465-475

Type of Study	Major Findings

C_{max}(h)	4.0	3.4	1.2	NC	1.9
AUC $_{(0-\infty)}$ (µg*h/mL)	49	39	12	5.6	17
T ½ (h)	4.6	4.0	3.9	2.8	4.0
CL or CL/F	4.2	6.4	4.5	0.12	3.1
V_d (L)	NC	NC	NC	0.39	NC
F (%)	46	37	42	NA	57

AUCinf = area under the concentration-time curve from time 0 extrapolated to infinity; CL/F = clearance; Cmax = maximum plasma concentration; CM-2 = (b) (4) [redacted]; CMC = carboxymethylcellulose;F = bioavailability; HPβCD = hydroxypropyl-β-cyclodextrin; IV = intravenous; NA: not applicable; NC = not calculated; t½ = half-life; Tmax = time to Cmax; Vz = apparent volume of distribution.

Distribution

Protein Binding of [Imidazooxazine-^{14}C]PA-824 and [Imidazooxazine-^{14}C]TBA-354 in Mouse, Rat, Dog, Monkey and Human Plasma and HSA and BSA. (b) (4) [redacted] (b) (4) [redacted]14648

Protein Binding of [Imidazooxazine-^{14}C]PA-824 and [Imidazooxazine-^{14}C]TBA-354 in Mouse, Rat, Dog, Monkey and Human Plasma and HSA and BSA. (b) (4) [redacted] (b) (4) [redacted]14648

Plasma protein binding of pretomanid (various species)

Concentration (µg/mL)	Plasma Protein Binding (%)					
	Mouse	Rat	Dog	Monkey	Human Plasma	Human HSA
0.5	85.1	79.5	87.0	83.6	86.5	82.9
2	85.5	80.3	87.0	83.3	86.3	82.6
4	85.6	80.5	87.4	83.0	86.5	82.8
12	85.6	79.9	87.1	82.9	86.4	82.4
Average	85.5	80.1	87.1	83.2	86.4	82.7

Determination of *in* vitro blood-to plasma ratio of PA-824 in mouse, rat monkey and human. (b) (4) [redacted] DMPK Study Number: 401951-20171109-BPR&401951-20171207-BPR

Table 5-2: Blood Plasma and erythrocyte binding of pretomanid

	Mouse	Rat	Monkey	Human
$K_{Blood/plasma}$	1.6-1.7	1.3-1.5	0.8-1.0	0.7-0.8
$K_{erythrocyte/plasma}$	2.3	1.6	0.7	0.5

$K_{Blood/plasma}$: Pretomanid Blood to plasma ratio
$K_{erythrocyte/plasma}$: Pretomanid erythrocyte to plasma ratio

Pharmacokinetics, Table 5-3: Concentrations of radioactivity in blood and tissues determined by

Reference ID: 4476823

Type of Study	Major Findings
Absorption, Distribution, Metabolism, and Excretion of [14C]PA-824 Following Administration of a Single Oral Dose to Rats. Study # (b) (4) 7504-127	whole body autoradiography at specified times after a single oral administration of 15 mg/kg [^{14}C]PA-824 to male rats

	µg Equivalents [^{14}C]PA-824/g	
Time postdose	4 hours	96 hours
Adrenal gland	25	0.3
Blood	6.3	0.4
Bone	0.7	BLQ
Bone marrow	8.9	0.1
Cecum	9.5	BLQ
Cecum contents	11	0.2
Cerebellum	16	0.3
Cerebrum	14	0.4
Diaphragm	12	0.4
Epididymis	9.3	0.5
Esophageal contents	0.6	ND
Esophagus	7.5	ND
Exorbital lacrimal gland	19	0.2
Eye	2	0.1
Eye (lens)	1.1	0.2
Fat (abdominal)	3.7	BLQ
Fat (brown)	16	0.4
Harderian gland	37	3.3
Intra-orbital lacrimal gland	18	0.3
Kidney	24	1.7
Large intestinal contents	Nr	0.4
Large intestines	9.3	0.2
Liver	42	0.9
Lung	9.1	0.2
Medulla	16	0.3
Muscle	8.8	0.4
Myocardium	15	0.3
Nasal turbinates	9.0	0.7
Olfactory lobe	11	0.2
Pancreas	20	0.2
Pituitary gland	15	0.1
Preputial gland	15	0.3
Prostate	9.6	BLQ
Renal cortex	23	1.0
Renal medulla	26	2.2
Salivary gland	17	0.2
Seminal vesicle	4.5	BLQ

Type of Study	Major Findings		
	Skin	5.0	0.2
	Small intestine contents	222	0.1
	Small intestine	12	0.3
	Spinal cord	17	0.3
	Spleen	9.0	0.2
	Stomach	11	0.2
	Stomach (gastric mucosa)	17	0.1
	Stomach contents	3.7	BLQ
	Testes	8.3	0.7
	Thymus	8.5	BLQ
	Thyroid	13	0.3
	Urinary bladder	8.1	0.2
	Urine	100	0.1
	Uveal duct	5.4	ND
Metabolism	Metabolism occurred via oxidation at multiple sites, the reduction of the nitro group to an amine, oxidative deamination, and oxidative cleavage to form hydroxy imidazole and 4-trifluoromethoxybenzoic acid, with subsequent conjugation (e.g., with glucuronic acid, glycine, or cysteine) also observed.		

Figure 5-1: Proposed metabolic pathway of [^{14}C] Pretomanid in Rat.

(b) (4)

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>PA-824: Pre and postnatal development toxicity study including maternal function in rats. (b) (4) study# 1408-01</td><td>Table 5-4. Pretomanid excretion into milk
<table>
<tr><td>Pretomanid dose</td><td>7 mg/kg</td><td>20 mg/kg</td><td>60 mg/kg</td></tr>
<tr><td></td><td colspan="3">Concentration (ng/mL)</td></tr>
<tr><td>Milk</td><td>1630</td><td>4070</td><td>17500</td></tr>
<tr><td>Maternal plasma</td><td>1160</td><td>2840</td><td>10700</td></tr>
<tr><td>Pup plasma</td><td>37</td><td>119</td><td>436</td></tr>
</table></td></tr>
<tr><td><u>Rat</u>
Pharmacokinetics, Absorption, Distribution, Metabolism, and Excretion of [14C]PA-824 Following Administration of a Single Oral Dose to Rats. (b) (4) study 7504-127.

<u>Monkey</u>
(b) (4) study # 7504-159.</td><td>Table 5-5: Excretion (urinary, fecal recovery) of [14C]-pretomanid from rats and monkeys
<table>
<tr><td></td><td></td><td>Recovery %</td><td></td><td></td></tr>
<tr><td>Species/Time</td><td>Urine</td><td>Feces</td><td>Cage Rinse</td><td>Total</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Rat (0-96h)</td><td>45</td><td>26</td><td>1.8</td><td>88</td></tr>
<tr><td>Monkey (0-144h)</td><td>30</td><td>27</td><td>8</td><td>68</td></tr>
</table></td></tr>
<tr><td>TK data from general toxicology studies
39-week repeat-dose toxicology and toxicokinetic study with PA-824 in mature cynomolgus macaques, with 12-week recovery period. Study # (b) (4) M962-12

T½ from 7-day monkey study</td><td><u>Monkey</u>
$T_{1/2}$: 3 to 6 hours
Accumulation: No significant accumulation
Dose proportionality: Dose proportional (AUC) or slightly less than dose proportional (C_{max})

Table 5-6: Day 1 pharmacokinetics in monkey 39-week study
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>25</td><td>23</td><td>3.8</td></tr>
<tr><td>50</td><td>52</td><td>5.2</td></tr>
<tr><td>100</td><td>98</td><td>7.7</td></tr>
</table>
Table 5-7: Day 260 pharmacokinetics in monkey 39-week study
<table>
<tr><td>Dose</td><td>AUC</td><td>C_{max}</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>(b) (4) 7504-109</td><td>
<table>
<tr><td>(mg/kg)</td><td>mcg*h/mL</td><td>mcg/mL</td></tr>
<tr><td>25</td><td>32</td><td>3.5</td></tr>
<tr><td>50</td><td>50</td><td>4.9</td></tr>
<tr><td>100</td><td>107</td><td>8.4</td></tr>
</table>
</td></tr>
<tr><td>PA-824: A 3-month oral toxicity study in rats with a 3-month recovery. Study # 1408-002</td><td>
<u>Rat</u>
$T_{1/2}$: 5 to 9 hours
Accumulation: Slight (AUC increased up to 32 %) in 90-day study
Dose proportionality: Approximately dose proportional

Table 5-8: Day 1 pharmacokinetics in 90-day rat study
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>10</td><td>25</td><td>2.0</td></tr>
<tr><td>30</td><td>83</td><td>5.9</td></tr>
<tr><td>100</td><td>203</td><td>14</td></tr>
<tr><td>300</td><td>382</td><td>19</td></tr>
</table>

Table 5-9: Day 90 pharmacokinetics in 90-day rat study
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>10</td><td>33</td><td>2.5</td></tr>
<tr><td>30</td><td>102</td><td>7.9</td></tr>
<tr><td>100</td><td>257</td><td>14</td></tr>
<tr><td>300</td><td>403</td><td>23</td></tr>
</table>
</td></tr>
<tr><td>PA-824: A 13-Week Study to Evaluate Reproductive Function and Lenticular Lesions in Male Cynomolgus Monkeys. Study Number: (b) (4) 269.01</td><td>
Table 5-10: Day 87/88 pharmacokinetics in monkey 13-week study
<table>
<tr><td>Dose (mg/kg)</td><td>AUC_{0-24h} mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>50</td><td>70</td><td>5.8</td></tr>
<tr><td>150</td><td>195</td><td>12.1</td></tr>
<tr><td>300</td><td>267</td><td>16.2</td></tr>
</table>
</td></tr>
<tr><td>TK data from reproductive toxicology studies

Oral (Gavage) Developmental Toxicity and Toxicokinetic Study</td><td>
<u>Rat</u>
Table 5-11: Mean Maternal AUC (Day 18 of gestation), Rat
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>10</td><td>35</td><td>2</td></tr>
<tr><td>30</td><td>106</td><td>7</td></tr>
<tr><td>100</td><td>245</td><td>17</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>of pretomanid in Rats. Study# (b) (4) QTC00004</td><td>Table 5-12: Mean Fetal AUC (Day 18 of gestation), Rat
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>10</td><td>42</td><td>3</td></tr>
<tr><td>30</td><td>123</td><td>8</td></tr>
<tr><td>100</td><td>251</td><td>15</td></tr>
</table></td></tr>
<tr><td>Oral (Gavage) Developmental Toxicity and Toxicokinetic Study of Pretomanid in Rabbits. Study # QTC00006</td><td><u>Rabbit</u>
Table 5-13: Mean Maternal AUC (Day 18 of gestation), Rabbit
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>10</td><td>11</td><td>1.0</td></tr>
<tr><td>30</td><td>37</td><td>2.2</td></tr>
<tr><td>60</td><td>50</td><td>5.0</td></tr>
</table>
Table 5-14: Mean Fetal AUC (Day 18 of gestation), Rabbit
<table>
<tr><td>Dose (mg/kg)</td><td>AUC mcg*h/mL</td><td>C_{max} mcg/mL</td></tr>
<tr><td>10</td><td>10</td><td>0.9</td></tr>
<tr><td>30</td><td>39</td><td>2.7</td></tr>
<tr><td>60</td><td>45</td><td>3.8</td></tr>
</table></td></tr>
</table>

5.4. Toxicology

5.4.1. General Toxicology

Study title/ number: 39-week repeat-dose toxicology and toxicokinetic study with PA-824 in mature cynomolgus macaques, with 12-week recovery period. Study # (b) (4) M962-12.

Key Study Findings

- Frank toxicity (bodyweight reduced by 23%) and reduced appetite at 100 mg/kg
- Increases in adrenal, spleen, kidney, testes and ovary weights without histopathological correlates. Liver weight increase was reversible after 12-week recovery period, but increased organ weights did not reverse in other organs at the 100 mg/kg dose.
- No drug-related QT prolongation

No NOAEL could be determined because of increased relative testes weight and decreased body weight at the lowest dose (25 mg/kg).

Conducting laboratory: (b) (4) (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	25, 50, 100 mg/kg/day
Route of administration:	Oral via nasogastric (NG) intubation
Formulation/Vehicle:	[redacted] (b) (4)
Species/Strain:	*Monkey / Cynomolgus macaques (Macaca fascicularis)*
Number/Sex/Group:	4-7
Age:	Males 5-7 years Females 4.5-6 years
Satellite groups/ unique design:	To evaluate the reversibility of any treatment-related effects, 2 vehicle control/sex and two high dose monkeys/sex were retained for a 3-month drug-free recovery period. To evaluate systemic exposure to the test article, Blood samples were collected on Days 1, 15, 92, and 260 at predose, 1, 2,4, 8, 12, and 24 hr after dosing.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>One high dose animal had a mass in the intrapleural space and died during surgery to remove the mass. The veterinarian concluded this may have been present at the initiation of the study.</td></tr>
<tr><td>Clinical Signs</td><td>Table 5-15: Clinical signs in monkeys dosed with pretomanid for 274 days. (Number of observations/number of animals)
<table>
<tr><td>Pretomanid dose (mg/kg)</td><td>0</td><td>25</td><td>50</td><td>100</td></tr>
<tr><td>Convulsions:</td><td>0/0</td><td>0/0</td><td>0/0</td><td>1/1</td></tr>
<tr><td>Reduced Appetite*</td><td>75/8</td><td>34/5</td><td>67/5</td><td>436/13</td></tr>
</table>
*Number of reduced appetite observations over the dosing period/number of animals

Reduced appetite occurred when the animal was observed to eat less than the typical amount of food (monkey biscuits) for that animal.</td></tr>
</table>

<table>
<tr><td>Body Weights</td><td>Table 5-16: Body weight/bodyweight loss of monkeys dosed with pretomanid for 274 days, with or without a 12-week recovery period
<table>
<tr><td>Day</td><td colspan="2">End of dosing
Day 274</td><td colspan="2">End of recovery
Day 358</td></tr>
<tr><td>Pretomanid dose (mg/kg)</td><td>Body weight (kg)</td><td>Body weight Loss (%)</td><td>Body weight (kg)</td><td>Body weight Loss (%)</td></tr>
<tr><td>0</td><td>6.9</td><td></td><td>7.6</td><td></td></tr>
<tr><td>25</td><td>6.3</td><td>-9%</td><td></td><td></td></tr>
<tr><td>50</td><td>6.1</td><td>-12%</td><td></td><td></td></tr>
<tr><td>100</td><td>5.3</td><td>-23%</td><td>5.4</td><td>-29%</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Ophthalmoscopy</td><td>There were no pretomanid-related effects.</td></tr>
<tr><td>ECG</td><td>QT prolongation was observed prestudy in 4/20monkeys (including one control animal (#005) and in 6/20 animals during the study (including control animal #005). Given the QT prolongation was observed in control animals and during the predosing period, the finding was ascribed to the ketamine anesthetic used to collect ECG measurements. Based on these results, the cardiologist concluded that there were no electrocardiographic findings attributable to treatment with PA-824. Since The QT-IRT reviewer, concluded that the results of a TQT study showed no clinically meaningful increase in QTc after single oral doses of 400 mg and 1,000 mg of pretomanid, the findings in the monkeys are of questionable significance.</td></tr>
<tr><td>Hematology</td><td>Table 5-17: Pretomanid-related effects observed in monkeys dosed for 39 weeks with a 12-week recovery period.
<table>
<tr><td>Pretomanid dose (mg/kg)</td><td>0</td><td>25</td><td>50</td><td>100</td></tr>
<tr><td>Absolute reticulocytes (TH/µL, end of dosing)</td><td>62</td><td>60</td><td>54</td><td>64</td></tr>
<tr><td>Absolute reticulocytes (TH/µL, after 12-week recovery period.)</td><td>68</td><td></td><td></td><td>36</td></tr>
<tr><td>Reticulocytes (%) (end of dosing)</td><td>1.1</td><td>1.1</td><td>1.1</td><td>1.3</td></tr>
<tr><td>Reticulocytes (%) (after 12-week recovery period.)</td><td>1.3</td><td></td><td></td><td>0.7</td></tr>
</table>
This reduction in reticulocytes is of questionable biological significance since it is within the range of historical controls.</td></tr>
<tr><td>Clinical Chemistry</td><td>Creatinine and alkaline phosphatase were increased at all doses, but these increases were not consistently dose-related and significant changes were sometimes within the range of historical controls.</td></tr>
</table>

	While these changes appeared to be pretomanid-related they were of questionable toxicological significance.
Urinalysis	No biologically significant drug-related effects
Gross Pathology	Table 5-18: Gross necropsy findings in monkeys after 39 weeks of pretomanid. (number affected/number examined)

Pretomanid dose (mg/kg)	0	25	50	100
End of dosing				
Thickened ileum	0/6	1/8	2/8	0/9
Thickened jejunum	0/6	3/8	3/8	1/9
Thickened stomach	0/6	5/8	6/8	7/9
Recovery animals				
Thickened stomach	0/2			1/2

Organ Weights

Pretomanid dose (mg/kg)	**0**	**25**	**50**	**100**
End of dosing				
Relative liver weight (Liver/body weight, %)	1.6	1.7	1.9	2.0
Relative adrenal weights (BW, %)	0.009	0.0097	0.01	0.012
Relative kidney weights (BW, %)	0.298	0.295	0.339	0.376
Relative spleen weights (BW, %)	0.089	0.087	0.077	0.092
Relative testes weights (BW, %)	0.58	0.66	0.75	0.78
Relative ovary weights (BW, %)	0.010	0.012	0.013	0.013
Recovery animals				
Relative liver weight (Liver/body weight, %)	1.3			1.3
Relative adrenal weights (BW, %)	0.0068			0.010
Relative kidney weights (BW, %)	0.253			0.334
Relative spleen weights (BW, %)	0.07			0.10
Relative testes weights (BW, %)	0.54			0.81
Relative ovary weights (BW, %)	0.008			0.016

	*Significantly different than the vehicle control, p < 0.01
Histopathology Adequate battery: Yes	Moderate unilateral seminiferous tubule atrophy was seen in one of 4 low dose (25 mg/kg/day) monkeys. Minimal focal seminiferous tubule atrophy was observed in one male at 100 mg/kg/day. Testes histology was normal in recovery animals. At terminal necropsy, thickening of the wall of the stomach and intestinal segments was increased in pretomanid-treated monkeys compared to controls but this thickening did not affect all areas of the gastrointestinal tract uniformly, and did not always correlate with lymphoplasmacytic microscopic infiltrations. Thickening showed evidence of resolving during the recovery period, as it was present only in the stomach of one (of 4) high-dose animals at the end of the recovery period. Although these findings appeared to be treatment-related, they were reversible and lesions of the gastrointestinal tract and chronic gastritis, with mild to marked lymphoplasmacytic cell infiltration of the mucosa and submucosa are common findings in control Cynomolgus macaques. (Chamanza R., et al. Incidences and Range of Spontaneous Findings in Control Cynomolgus Monkeys (*Macaca fascicularis*) Used in Toxicity Studies. Toxicologic Pathology Volume: 38 issue: 4, pages: 642-657)

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

General toxicology; additional studies

Study title/ number: PA-824: A 13-Week Study to Evaluate Reproductive Function and Lenticular Lesions in Male Cynomolgus Monkeys. Study #: (b) (4) 269.01

Key Study Findings *[no more than 3 bullets]*

- Pretomanid doses ≥ 150 mg/kg for 13 weeks resulted in decreased sperm counts and motility and increased ratio of abnormal sperm.
- These doses also resulted in systemic toxicity (decreased food consumption and bodyweight).
- The NOAEL for testicular toxicity was 50 mg/kg, which was associated with an AUC of 70 mcg*h/mL, which is 1.2 times the MRHD

<u>Methods</u>

Dose and frequency of dosing:	50, 150 and 300 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	*Monkey / Cynomolgus macaques (Macaca fascicularis)*

Number/Sex/Group:

Study design

Group	Dose Level (mg/kg)	Number of Animals (Male)	Necropsy (Male)	
			Terminal (day 92)	Recovery (day 232)
1	0	8	4	4
2	50	5	2	3
3	150	5	2	3
4	300	8	4[a]	4

[a] Group 4 terminal animals were euthanized and necropsied 18-37 days after the final dose.

Age:

Satellite groups/ unique design: Animals were included in the study if their baseline semenology data and male reproductive endocrine status were within normal range and if they had no ocular lesions. Animals in the 150 mg/kg group were dosed daily for 13 weeks with 7 days of dose holiday (from days 36 to 42), resulting in a total of 84 dose administrations. All animals in the 300 mg/kg group had a 7-day suspension of dose administration (from days 36 to 42). Additionally, dose administration was discontinued for four animals in the 300 mg/kg group on day 56, 59, or 75; total dose administrations for this group ranged between 47 and 84 days. Dose holidays or dose termination were required as the animals were not eating well and had lost substantial body weight.

Deviation from study protocol affecting interpretation of results: No

Parameters **Major findings**

Mortality

Clinical Signs

Pretomanid-related effects at 150 and 300 mg/kg consisted of hunched posture, ball position, and/or hypoactivity/lethargy. These changes generally disappeared shortly after termination or suspension of dosing.

Decreased food consumption (low or none consumed) was noted frequently in all animals in the 150 and 300 mg/kg groups within 2 to 3 weeks after the initiation of dosing but feeding returned to normal consumption shortly after termination or suspension of dosing.

Food consumption (Number of times observed during the 13-week dosing period), Monkeys

Pretomanid dose (mg/kg)	0	50	150	300
Low Food consumption	1	6	74	90
No food consumption	0	0	41	74

Body Weights

Pretomanid dose (mg/kg)	0	50	150	300
Body weight (Day 91)	6.4	5.9	5.0	5.2
Body weight (Day 231)	6.8	6.9	7.4	5.9

Ophthalmoscopy

No ophthalmologic lesions were observed in any animal.

Semen Analysis

Table 5-19: Occurrences of decreased sperm motility (motility decreased to ≤ 50% of baseline and percent motile spermatozoa ≤ 60%), Monkeys

Group	Animal #	Study Day
150 mg/kg	54	4/5 and 8/9
	30	4/5 and 12/13
300 mg/kg	40	8/9
	42	4/5, 8/9
	44	4/5
	46	4/5
	50	4/5 and 12/13

Table 5-20: Occurrences of decreased total sperm count (decreased to ≤ 50% of baseline and to ≤ 200 x 10^6 /ejaculate), Monkeys

Group	Animal #	Study Day
0 mg/kg	8	8/9
50 mg/kg	22	4/5, 8/9
	26	4/5,8/9
150 mg/kg	54	4/5 and 8/9
	32	8/9, 12/13, 17/18, 26/27
300 mg/kg	38	4/5,8/9
	40	4/5, 8/9
	44	4/5
	46	4/5
	52	4/5, 8/9 and 12/13

Table 5-21: Abnormal sperm ratio (increased to ≥ 200% of baseline and to ≥20% abnormal)

Group	Animal #	Study Day
150 mg/kg	54	4/5
	30	4/5
300 mg/kg	46	4/5

	48	33/34
	50	4/5
	52	4/5

Testicular volume No pretomanid-related effects

5.4.2. Genetic Toxicology

<u>*In vitro* Reverse Mutation Assay in Bacterial Cells (Ames)</u>
Study title/ number: Bacterial Reverse Mutation Assay/ Study G95BC95.501018
Key Study Findings:
- Negative

GLP compliance: Yes
Test system: *S. typhimurium,* Strain TA100; up to 5000 µg/plate; +/- S9]
Study is valid: Yes

Study title/ number: Salmonella/Escherichia coli plate incorporation mutagenicity assay. Study G95BC99.501019
Key Study Findings:
- Negative

GLP compliance: Yes
Test system: *S. typhimurium,* Strains TA98, TA1535, TA1537, WP2uvrA. Up to 5000 µg/plate; +/- S9]
Study is valid: Yes

<u>*In vitro* Assays in Mammalian Cells</u>
Study title/ number: Chromosome Aberration Screening Assay. (b) (4) study AB00CP.331.BTL
Key Study Findings:
- Negative

GLP compliance: Yes
Test system: Chinese hamster ovary cells; up to 360 µg /mL; +/-S9]
Study is valid: Yes

Study title/ number: Chromosome Aberration Screening Assay. (b) (4) study AA75AZ.336.BTL
Key Study Findings:
- Negative

GLP compliance: No
Test system: Chinese hamster ovary cells; up to 1100 µg /mL; +/-S9]
Study is valid: Yes

Reference ID: 4476823

Study title/ number: Evaluation of PA-824 for microbial and mammalian mutagenicity. Study (b) (4) 170-03
Key Study Findings:

- Negative

GLP compliance: No
Test system: L5178Y mouse lymphoma cells, clone 3.7.2.C, heterozygous at the thymidine kinase locus *(tk)*; up to 500 µg /mL; +/-S9]
Study is valid: Yes

<u>*In vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)</u>
Study title/ number: *In vivo* Mouse Bone Marrow Micronucleus Assay with pretomanid. (b) (4) Study 7504-149
Key Study Findings:

- Negative

GLP compliance: Yes
Test system: Mouse, bone marrow micronuclei; single oral doses of 125, 500, 2000 mg/kg, harvested after 24 and 48 hours.
Study is valid: Yes

<u>Other Genetic Toxicity Studies</u>

Genotoxicity study of pretomanid metabolite, M50

Study title/ number: Bacterial Reverse Mutation Assay with confirmatory assay/ (b) (4) Study 8265622
Key Study Findings:

- PA-824 metabolite, M50 was positive for mutagenic potential in the bacterial reverse mutation assay.
- Increased revertants with TA100, TA1535 and WP2uvrA in the presence and absence of S9 mix. Increased revertants with TA98 in the presence of S9 mix and with TA1537 in the absence of S9 mix.
- The carcinogenic potential of M50 is unknown but M50 is found in rat and mouse blood. An assessment of the risk of carcinogenicity from this metabolite will therefore be obtained from the ongoing rat and mouse carcinogenicity studies.

Reference ID: 4476823

Table 5-22: Mean revertant colony counts in *S. typhimurium,* Strains TA98, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA exposed to PA-824

S9 Metabolic Activation	Test Article	Concentration (µg/plate)	TA98	TA100	TA1535	TA1537	WP2*uvr*A
No	M50	625	22.3 ± 11.4	360.3 ± 3.1	38.7 ± 7.0	9.0 ± 3.5	40.3 ± 7.4
No	M50	1250	29.3 ± 12.9	617.3 ± 58.9	41.7 ± 10.0	17.3 ± 5.0	43.0 ± 14.1
No	M50	2500	32.3 ± 2.9	882.7 ± 210.7	53.7 ± 1.5	20.7 ± 3.2	132.3 ± 10.0
No	2-nitrofluorene	1	239.3 ± 28.6	NA	NA	NA	NA
No	Sodium azide	2	NA	1086.3 ± 287.6	982.0 ± 80.1	NA	NA
No	ICR-191	2	NA	NA	NA	1371.0 ± 111.0	NA
No	4-nitroquinoline-N-oxide	1	NA	NA	NA	NA	492.3 ± 124.
Yes	Vehicle (DMSO)	50 µL/plate	20.0 ± 7.8	133.7 ± 13.3	14.7 ± 1.2	7.7 ± 2.9	18.0 ± 5.0
Yes	M50	78	27.7 ± 8.6	227.7 ± 33.5	22.7 ± 8.1	6.7 ± 1.2	15.3 ± 5.7
Yes	M50	156	25.0 ± 9.5	188.0 ± 10.5	20.3 ± 3.5	8.3 ± 4.0	27.3 ± 5.9
Yes	M50	313	22.7 ± 10.1	265.0 ± 1.7	31.3 ± 5.5	12.7 ± 3.8	39.0 ± 8.2
Yes	M50	625	25.3 ± 4.9	379.7 ± 28.4	40.0 ± 6.1	11.3 ± 1.5	33.0 ± 4.6
Yes	M50	1250	31.7 ± 4.0	656.0 ± 27.9	64.3 ± 2.9	13.0 ± 3.0	48.3 ± 6.5

Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Oral (Gavage) Fertility and General Reproduction Toxicity Study of Pretomanid in Rats Study # (b) (4) QTC00007

Key Study Findings

- NOAEL was 10 mg/kg, about half the clinical exposure based on AUC comparisons.
- Complete, irreversible infertility was observed at 100 mg/kg (about 3.5 times the clinical dose based on data from study 1408-002
- Inhibin B levels in males were below LLOQ and FSH levels in males doubled in high dose animals but there were no biologically significant effects on testosterone levels based on the ranges measured in historical control data.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 10, 30, 100 mg/kg/day

Route of administration: Oral (gavage)

Formulation/Vehicle: (b) (4)

Species/Strain: *Rattus norvegicus*/Sprague Dawley

Number/Sex/Group: 25

Satellite groups: A recovery group of 15 males were retained for to evaluate mating/fertility after a 10-week recovery period

Study design: Males were dosed for 70 days prior to cohabitation

through 3 weeks of cohabitation. Females were dosed 15 to 17 days before cohabitation through Day 7 of presumed gestation (DG 7). Day 0 was designated as the day the copulatory plug was sperm positive.
On DS 98 (first day of recovery), 9 or 10 male rats/group were sacrificed, and 15/group were placed into cohabitation with untreated female (Replicate 1) rats, one male rat per female rat, for a maximum of 7 days. On DS 161 (during the tenth week of the recovery phase), male rats were again placed into cohabitation with untreated female (Replicate 2) rats for a maximum of 10 days.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	**Major findings**
Mortality	No drug-related mortality
Clinical Signs	HD (100 mg/kg) urine stained fur, excess salivation, mild dehydration
Body Weights	HD: -18 % (males), -9% (females)
In-life findings	Treated males/treated females Dose (mg/kg): 0, 10, 30, 100 Mating Index (% rats mated): 100, 96, 100, 100 Fertility Index (% pregnant): 92, 96, 64, 0* Day 98 Treated males/untreated females Dose (mg/kg): 0, 10, 30, 100 Mating Index (% rats mated): 100, 93, 93, 93 Fertility Index (% pregnant): 100, 93, 64, 7* Day 161 Treated males/untreated females Dose (mg/kg): 0, 10, 30, 100 Mating Index (% rats mated): 100, 100, 100, 73* Fertility Index (% pregnant): 87, 93, 79, 0*
Necropsy findings	Cesarean section data, treated males/treated females Dose (mg/kg): 0, 10, 30, 100 Ovulations: 15.6, 16.3, 14.3, 12.5* Corpora lutea: 16, 16, 15, Implantations: 15, 15, 13, Nonviable embryos %: 5, 6, 8,

Mean male hormone levels	Table 5-23: Inhibin, FSH and testosterone levels in rats after at least 70 days pretomanid (Day 87) and after a 10-week recovery period,

Day 87

Dose (mg/kg)	0	10	30	100
Inhibin (pg/mL)	103	106	107	LLOQ**
FSH (ng/mL)	8.8	8.4	8.9	18
Testosterone (ng/dL)	162	210	245	244

Day 190 (End of 10-week recovery)

Dose (mg/kg)	0	10	30	100
Inhibin (pg/mL)	103	85	121	LLOQ**
FSH (ng/mL)	7.2	8.4	8.1	17
Testosterone (ng/dL)	253	254	182	309

**LLOQ 75.14 pg/mL
Hormone levels were not evaluated in females

LD: low dose; MD: mid dose; HD: high dose

Embryo-Fetal Development

Study title/ number: Oral (Gavage) Developmental Toxicity and Toxicokinetic Study of pretomanid in Rats. (b) (4) QTC00004

Key Study Findings

- The NOAEL for developmental toxicity was 30 mg/kg due to increased post implantation loss at 100 mg/kg in the presence of maternal toxicity.
- The AUC at the NOAEL was 106 mcg*h/mL, equivalent to about 2 times the clinical exposure.
- NOAEL for maternal toxicity was 10 mg/kg due to reduced feed consumption at 30 mg/kg and above and reduced body weights at 100 mg/kg.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10, 30 and 100 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	*Rattus norvegicus* /Sprague Dawley
Number/Sex/Group:	20
Satellite groups:	Five rats in Group I and twelve rats in each of Groups II through IV were assigned to toxicokinetic sample collection. Three rats from each of Groups II through IV were sacrificed for blood collection at 1 hour, 4 hours, 8 hours and 24 hours after dosage on gestational day 18.
Study design:	Rats were administered pretomanid and/or vehicle once daily on gestational days 7 through 17. Dams were sacrificed on gestational day 21 then caesarean-sections, gross necropsy of the thoracic, abdominal and pelvic viscera were performed.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>There were no drug-related deaths</td></tr>
<tr><td>Clinical Signs</td><td>HD: Increased incidence of sparse hair coat, mild dehydration and urine-stained abdominal fur</td></tr>
<tr><td>Body Weights</td><td>HD: Reduced by 19 % compared to controls</td></tr>
<tr><td>Food consumption</td><td>MD: -10%
HD: -40%</td></tr>
<tr><td>Necropsy findings
Cesarean Section Data
[Implantation Sites, Pre- and Post-Implantation Loss, etc.]</td><td>HD: Mean post implantation loss (%) increased and mean fetal weight reduced compared to controls
<table>
<tr><td>Dose (mg/kg)</td><td>0</td><td>10</td><td>30</td><td>100</td></tr>
<tr><td>Post implantation loss (%)</td><td>4.6</td><td>3.8</td><td>3.5</td><td>13</td></tr>
<tr><td>Fetal body weight</td><td>5.5</td><td>5.6</td><td>5.3</td><td>5.0*</td></tr>
</table>
*Significantly different from concurrent control group value (p≤ 0.01) but just within the lower bound of the historical control range (4.9g) provided by the applicant.</td></tr>
<tr><td>Necropsy findings
Offspring
[malformations, variations, etc.]</td><td>
<table>
<tr><td>Dose (mg/kg)</td><td>0</td><td>10</td><td>30</td><td>100</td></tr>
<tr><td>Mean number of ossification sites in hindlimb phalanges</td><td>6.9</td><td>6.6</td><td>6.4</td><td>5.7*</td></tr>
</table>
*reduced but just within the lower bound of the historical data</td></tr>
</table>

Parameters	Major findings
	(5.65) provided by the applicant.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: Oral (Gavage) Developmental Toxicity and Toxicokinetic Study of pretomanid in Rabbits. (b) (4) QTC00006

Key Study Findings

- The NOAEL for developmental toxicity was 60 mg/kg
- The NOAEL for maternal toxicity was 10 mg/kg due to reduced body weight gain, which was observed at 30 and 60 mg/kg during the dosing period
- No pretomanid-related malformations and variations

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 10, 30 and 60 mg/kg/day

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4)

Species/Strain: *Oryctolagus cuniculus*/New Zealand White [Hra:(NZW)SPF]

Number/Sex/Group: 20

Satellite groups: 18 additional rabbits/group in Group I through IV were assigned to toxicokinetic sample collection and dosed once daily on gestational days 7 through 20. On DGs 7 and 19, a series of blood samples were collected. These rabbits were subsequently sacrificed on DG 20 or 21 following blood sample collection.

Study design: Pregnant rabbits were administered pretomanid and/or vehicle once daily on gestational days 7 through 19. Dams were sacrificed on gestational day 29 then caesarean-sectioned.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	There were no drug-related deaths
Clinical Signs	HD: scant feces

Body Weight (Day20)	HD: -6% compared to controls
Feed consumption (g/kg/day)	HD: Reduced by 40% compared to controls during the dosing period
Necropsy findings Cesarean Section Data	No significant differences between treated and controls. Pregnancies occurred in 19, 19, 20 and 19 rabbits in groups 1 through 4.
Necropsy findings Offspring	No significant differences in malformations and variations between treated and controls

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: Pretomanid: A Pre and Postnatal Developmental Toxicity Study Including Maternal Function in Rats. (b) (4) Study # 1408-019

Key Study Findings

- Maternal toxicity (reduced bodyweight, bodyweight gain, food consumption) observed at the high dose (60 mg/kg)
- Pretomanid measured in milk at levels up to 1.8 times levels measured in plasma of dams.
- Pups exposed to pretomanid through milk had dose-related increases of pretomanid in the plasma as well as significantly increased motor activity (basic movement, fine movement and distance travelled)

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: GD 7 through LD 20 for F0 females

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4)

Species/Strain: *Rattus norvegicus* /Sprague Dawley

Number/Sex/Group: 25

Satellite groups: Toxicokinetics animals (4/dose

Study design: Pretomanid and/or vehicle were administered daily to 25 pregnant female rats/dose via oral gavage at dose levels of 0, 7, 20, and 60 mg/kg/day. Dosing began on GD 7 and continued through lactation day (LD) 20.

Deviation from study protocol No

affecting interpretation of results:

Observations and Results

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td>HD: Reduced Bodyweight gain GD 7 to GD 20.
Reduced food consumption GD 7 to GD 20.
MD: Pretomanid levels in milk higher than levels measured in plasma
LD: Pretomanid levels in milk higher than levels measured in plasma

<table>
<tr><td>Pretomanid dose (mg/kg)</td><td>0</td><td>7</td><td>20</td><td>60</td></tr>
<tr><td>Bodyweight gain GD 7 to 10 (g)</td><td>16</td><td>-9</td><td>-24</td><td>-64*</td></tr>
<tr><td>Bodyweight gain GD 7 to 20 (g)</td><td>116</td><td>+6</td><td>0</td><td>-12%*</td></tr>
<tr><td>Gestational Bodyweight (g)</td><td>298g</td><td>-1%</td><td>0</td><td>-5%*</td></tr>
<tr><td>Food consumption GD 7 to 10</td><td>21</td><td>-5%</td><td>-6%</td><td>-19%*</td></tr>
<tr><td>Food consumption GD 7 to 20</td><td>22</td><td>-8%</td><td>-3%</td><td>-11%*</td></tr>
<tr><td>Plasma pretomanid (µg/mL)</td><td></td><td>1.1</td><td>2.8</td><td>10.7</td></tr>
<tr><td>Milk pretomanid (µg/mL)</td><td></td><td>1.6</td><td>4.1</td><td>18</td></tr>
</table>
*significantly different from control (p<0.01)</td></tr>
<tr><td>F1 Generation</td><td>HD:
-increased time to development of the Air Drop Righting Reflex slightly
-decreased pup weight on lactation day (LD) 21
-increased locomotor activity in female pups

All doses: Pretomanid present in plasma of nursing pups at levels much lower in plasma levels seen in dams at each dose level.

<table>
<tr><td>Pretomanid dose (mg/kg)</td><td>0</td><td>7</td><td>20</td><td>60</td></tr>
<tr><td>Mean male pup weight (g) (LD21)</td><td>63</td><td>62</td><td>61</td><td>58*</td></tr>
<tr><td>Mean female pup weight (g) (LD21)</td><td>60</td><td>60</td><td>58</td><td>56*</td></tr>
<tr><td>Time to achieving Air Drop Righting Reflex (days)</td><td>16.0</td><td>16.1</td><td>16.1</td><td>16.5*</td></tr>
<tr><td>Basic movement (count)</td><td>4226</td><td>4252</td><td>4508</td><td>5077*</td></tr>
<tr><td>Fine movement (count)</td><td>2710</td><td>2742</td><td>2922</td><td>3390*</td></tr>
<tr><td>Total distance (cm)</td><td>7570</td><td>7549</td><td>7972</td><td>8893*</td></tr>
<tr><td>Plasma pretomanid (µg/mL) (LD14)</td><td></td><td>0.04</td><td>0.1</td><td>0.4</td></tr>
</table>
*significantly different from control (p<0.01)</td></tr>
<tr><td>F2 Generation</td><td>No significant findings</td></tr>
</table>

5.4.4. Other Toxicology Studies

none

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Clinical Pharmacology IV and Division of Pharmacometrics) reviewed the relevant information contained in NDA 212862. The clinical pharmacology information submitted in the NDA supports the approval of pretomanid 200 mg tablets as part of the combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary XDR, TI or NR MDR-TB. The review focuses primarily on pretomanid.

Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The evidence of efficacy and safety of pretomanid for the treatment of XDR or TI/NR MDR TB was supported by clinical studies (see sections 7 and 9, respectively). Supportive evidence of efficacy is provided by two phase 2 EBA studies of pretomanid. The review of EBA studies was performed by the clinical pharmacology review team.
General dosing instructions	Administer pretomanid 200 mg orally once daily for 26 weeks with bedaquiline and linezolid: • bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks • linezolid starting at 1200 mg orally once daily for 26 weeks, with dose adjustments for known linezolid toxicities of myelosuppression, peripheral neuropathy, and optic neuropathy • The regimen is to be taken with food
Dosing in patient subgroups (intrinsic and extrinsic factors)	The pharmacokinetics (PK) of pretomanid have not been studied in patients with renal or hepatic impairment.
Labeling	The review team has specific content and formatting change recommendations that were communicated to the applicant and have been addressed.
Bridge between the to-be-marketed and clinical trial formulations	The proposed to-be-marketed product was studied in the Nix-TB trial. Thus, a PK bridging study was not deemed necessary for the proposed to-be-marketed tablet formulation of pretomanid.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Absorption	Following a single 200 mg dose of pretomanid in healthy subjects (N=16) under fed (FDA high-fat, high-calorie meal) and fasted conditions, mean C_{max} and AUC_{inf} increased by 76% and by 88%, respectively, compared with the fasted state.
Distribution	Human plasma protein binding of pretomanid is approximately 86.4% and is independent of drug concentration. Mean (SD) apparent volume of distribution is 97 (17.2) L, when pretomanid is administered under fed condition.
Elimination	Mean (SD) terminal half-life is approximately 17 (2.8) hours in healthy subjects following single dose administration of 200 mg and 16 (1.6) hours following multiple doses of 200 mg QD. Mean (SD) apparent oral clearance is approximately 4 (0.8) L/hr, upon administration of a single dose of 200 mg pretomanid under fed condition.
	Metabolism Pretomanid is metabolized by multiple reductive and oxidative pathways, with no single pathway considered as major. *In vitro* studies using recombinant CYP3A4 demonstrated that this enzyme accounts for approximately up to 20% of pretomanid metabolism.
	Excretion In healthy adult male subjects receiving 1100 mg/91 µCi oral ^{14}C-radiolabeled pretomanid, a mean (SD) of 53 (3.4)% of a radioactive dose was excreted in urine and 37.6 (2.7)% in feces, primarily as metabolites; approximately 1% of the radioactive dose was excreted in the urine as unchanged pretomanid.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Applicant's proposed dosing regimen for XDR or TI/NR MDR- TB, shown below is supported by PK, efficacy and safety data from the clinical trials submitted in the application.

Administer pretomanid 200 mg orally once daily for 26 weeks with bedaquiline and linezolid:

- bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks
- linezolid starting at 1200 mg orally once daily for 26 weeks, with dose adjustments for known linezolid toxicities of myelosuppression, peripheral neuropathy, and optic neuropathy
- The regimen is to be taken with food

Therapeutic Individualization

Extrinsic factors

Drug Interactions

Effect of Other Drugs on Pretomanid:

Efavirenz/Rifampin (CYP3A inducers)

Co-administration of pretomanid with efavirenz or rifampin resulted in a decrease in exposure of pretomanid. Thus, co-administration with strong or moderate CYP3A4 inducers should be avoided.

Also, based on the bedaquiline labeling, efavirenz or rifampin is not recommended to be administered with bedaquiline. Therefore, efavirenz, rifampin or other strong or moderate CYP3A4 inducers should not be used with the bedaquiline-pretomanid-linezolid regimen.

Lopinavir/ritonavir (CYP3A Inhibitor)

Co-administration of pretomanid with lopinavir/ritonavir did not affect exposure of pretomanid. Thus, lopinavir/ritonavir can be co-administered with pretomanid.

Effect of Pretomanid on Other Drugs:

Midazolam (CYP3A4 Substrate)

The co-administration of pretomanid with the CYP3A4 substrate, midazolam, results in no clinically significant effect on the PK of midazolam or its major metabolite, 1-hydroxy-midazolam. Thus, pretomanid can be administered with CYP3A4 substrate drugs.

Transporter mediated interactions: OAT3 substrates

The effect of co-administration of pretomanid on the pharmacokinetics of OAT3 substrates in humans is unknown. However, *in vitro* studies indicate that pretomanid significantly inhibits the OAT3 drug transporter, which could result in increased concentrations of OAT3 substrates (e.g., methotrexate) at clinically relevant concentrations of pretomanid.

The Clinical Pharmacology team recommendation is to monitor for drug-related adverse reactions associated with the OAT3 substrate, and consider dosage reduction, if needed, based on labeling of the co-administered OAT3 drug.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Pretomanid is a nitroimidazooxazine antimycobacterial drug. Pretomanid kills actively replicating *M. tuberculosis*, by inhibiting mycolic acid biosynthesis thereby blocking cell wall production. In addition, under anaerobic conditions, bioreduction of pretomanid generates reactive nitrogen species and results in respiratory poisoning of *M. tuberculosis complex* [see section 8.1.1, Microbiology review for details on mechanism of action].
Active Moieties	Pretomanid
QT Prolongation	No significant QT prolongation effect of pretomanid was detected in the TQT Study; the placebo-corrected change from baseline QTcF (90% confidence interval) values are 1.5 (-0.2, 3.3) and 3.3 (1.6, 5.1) msec with the 400 mg and 1000 mg dose of pretomanid, respectively. In the Nix-TB study, patients received pretomanid-bedaquiline-linezolid regimen for 6 months. No patient had QTcF intervals greater than 480 msec and 1 subject had a post-baseline increase of QTcF of greater than 60 msec.
General Information	
Drug exposure following the therapeutic dosing regimen	**Mean (SD) 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
CL/F (L/hr)	7.6 (2.5)	3.9 (0.8)	ND
$t_{½}$ (hr)	16.9 (3.1)	17.4 (2.8)	16.0 (1.6)

* - Median (minimum, maximum); † - AUC_{96hr}; § - AUC_{24hr}; ND - Not Determined.

Pharmacology	
Healthy vs. Patients	PK samples were collected at Week 16 from 15 patients in the Nix-TB study, where pretomanid was administered as part of the BPaL regimen under fed conditions. The mean (% CV) C_{max} and AUC_{0-24} of pretomanid were 2.6 (27) µg/mL and 45.6 (28.2) µg.hr/mL. The median (range) for T_{max} was 4 (1 – 4.1) hr. Overall, the steady state PK parameters for pretomanid in patients from Nix-TB trial appear to be comparable to that from healthy subjects (see above). Note that this is a cross-study comparison, where pretomanid is given with bedaquiline and linezolid under fed condition in Nix-TB trial versus pretomanid alone in MAD study under fasted conditions.
Dose Proportionality	Pretomanid AUC and C_{max} were approximately dose-proportional following single oral doses ranging from 50 (0.25 times the approved recommended dosage) to 200 mg (approved recommended dosage); at doses greater than 200 mg and up to 1000 mg (5 times the approved recommended dosage), AUC and C_{max} increased in a less than dose proportional manner. There is minimal to no additional increase in AUC and C_{max} at doses greater than 1000 mg to up to 1500 mg.
Food Effect	Administration of a 200-mg dose of pretomanid with a high-fat, high-calorie meal increased mean C_{max} and AUC_{inf} by 76% and 88%, respectively, as compared with the fasted state; see Table above for PK parameters under fed and fasted states.
Volume of Distribution	The mean (SD) apparent volume of distribution after administration of a single oral dose of 200 mg pretomanid orally under fed condition is 97 (17.2) L.
Plasma Protein Binding	Approximately 86.4% and independent of drug concentration
Elimination	
Half-life	The mean (SD) half-life is 17.4 (2.8) hours following single 200 mg dose and 16 (1.6) hours following multiple doses of 200 mg QD in healthy adult subjects.
Metabolism	
Fraction metabolized (% dose)	After oral administration of 1100 mg PA-824 and 91 µCi [^{14}C]-PA-824, the metabolism of [^{14}C]-PA-824 proceeds via a combination of reductive metabolism (approximately 20% to 25% of the dose) and oxidative metabolism. 11 metabolites were identified in plasma, each accounting for less than 10% of the radioactive dose. The trifluoromethoxy benzoic acid glycine conjugate (M11), accounted for approximately 13% of the dose in human excreta; the other metabolites identified either in urine or feces accounted for less than 5% of the radioactive dose. The activity of the metabolites of pretomanid were not

Pharmacology	
	determined/reported by the applicant.
Primary metabolic pathway(s)	*In vitro* studies using recombinant CYP3A4 demonstrated that this enzyme accounts for up to approximately 20% of the metabolism of pretomanid. No primary predominant pathway was identified for metabolism of pretomanid.
Excretion	
Primary excretion pathways (% dose)	A mean (SD) of 53 (3.4) % of a radioactive dose was excreted in urine and 37.6 (2.7) % in feces, primarily as metabolites; [^{14}C]-pretomanid was extensively metabolized and less than 5% of the dose was excreted as unchanged [^{14}C]-pretomanid in the feces and urine.
Interaction liability (Drug as a perpetrator)	
Inhibition/Induction of metabolism	Pretomanid is not an inhibitor or inducer of CYP3A4 substrate drugs based on *in vivo* drug interaction study with midazolam. Pretomanid is not an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations based on *in vitro* studies. Pretomanid is a weak time-dependent inhibitor of CYP2C8 and CYP2C19. Pretomanid was not an inducer of CYP3A4 and CYP2C9 based on *in vitro* studies.
Inhibition of transporter systems	*In vitro* studies indicate that pretomanid significantly inhibits the OAT3 drug transporter which could result in increased concentrations of OAT3 substrates at clinically relevant concentrations of pretomanid. No clinical DDI studies have been conducted with OAT3 substrates. *In vitro* studies indicated that pretomanid has a very low inhibitory interaction potential with the MATE2-K transporter at clinically relevant pretomanid concentrations. Pretomanid does not inhibit human OAT1, OCT1, OCT2, OAT1B1, OATP1B3, BCRP, BSEP, P-gp, and/or MATE1 mediated transport as per in vitro studies.
Interaction liability (Drug as a substrate)	
Metabolism	CYP3A4 accounts for approximately up to 20% of the metabolism of pretomanid. Pretomanid is not a substrate of CYP2C9, CYP2C19, and CYP2D6 based on *in vitro* studies.
Substrate of transporters	*In vitro* studies indicated that pretomanid is not a substrate of OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and/or P-gp transporters.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The pivotal evidence of efficacy of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary XDR or TI/NR MDR TB is

Reference ID: 4476823

from the Nix-TB trial. See Sections 7 and 9 below for further information concerning the results of this trial.

Supportive evidence

The supportive evidence of effectiveness for pretomanid is derived from the findings of two phase 2 EBA studies in DS TB and exposure-response modeling of data from these two studies.

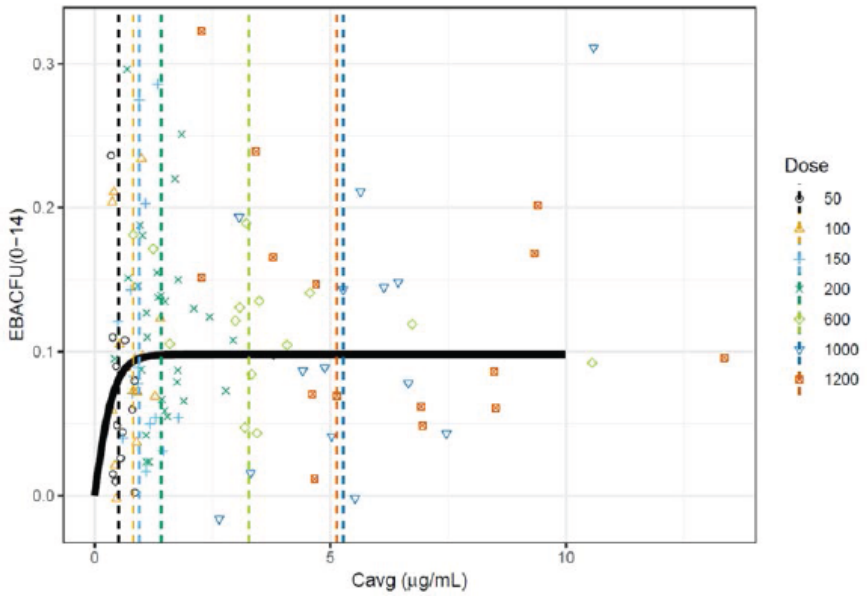
- First phase 2 trial (CL-007) evaluated pretomanid oral doses of 200, 600, 1000, and 1200 mg/day
- Second phase 2 trial (CL-010) evaluated lower pretomanid doses of 50, 100, 150, and 200 mg/day

Exposure-response relationship for Efficacy: EBA in drug-sensitive tuberculosis

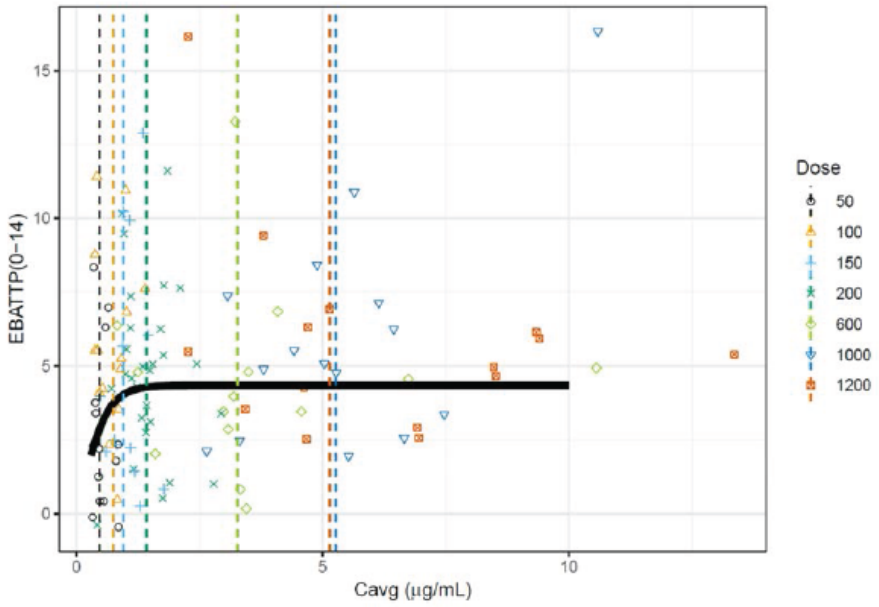
EBA_{CFU} [Change in log_{10}(CFU)/day]; where, CFU is colony forming units and EBA_{TTP} (Change in hours to positivity/day); where, TTP is time to culture positivity, were assessed as efficacy endpoints of pretomanid given over 14 days.

Results from these studies support the 200 mg dose selection, as no further increase in EBA was observed with higher doses as per the results of Study CL-007 and maximum efficacy was demonstrated at the 200 mg once daily dose of pretomanid.

Exposure–response modeling for efficacy was performed by the applicant using data from the EBA studies. At the 100 mg and 150 mg doses, the EBA responses were at 86% and 97% of the plateau. At the 200 mg dose, the EBA response is at the plateau of the dose response curve, and at higher doses, no further increase in response was reported by the applicant (Figure 6-1). For additional details, see Pharmacometrics section 15.3.1.



C_{avg} = steady state average plasma concentration over a dosing interval; $EBA_{CFU}(0\text{-}14)$ = daily rate of change of log-transformed counts of colony-forming units in solid culture over 14 days of treatment
Unit for $EBA_{CFU}(0\text{-}14)$: -[Change in log10(CFU)]/day



C_{avg} = steady state average plasma concentration over a dosing interval; $EBA_{TTP}(0\text{-}14)$ = daily rate of change of time to culture positivity in the mycobacteria growth indicator tube
Unit for $EBA_{TTP}(0\text{-}14)$: -(Change in hours to positivity)/day

Figure 6-1. Pretomanid $EBA_{CFU}(0\text{-}14)$ and $EBA_{TTP}(0\text{-}14)$ versus C_{avg} in Studies CL-007 and CL-010.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

From a clinical pharmacology perspective, the proposed pretomanid 200 mg once daily dosing regimen is acceptable for patients with XDR- or TI/NR MDR-TB. The assessment of the pretomanid dosing regimen is based on two phase 2 EBA clinical studies (see reply to previous question) and that for BPaL treatment regimen is based on the Nix-TB trial (see Sections 7 and 9 below for details). In addition, the relationship between pretomanid exposure and important pretomanid adverse events were explored by the pharmacometrics reviewer. In the reviewer's analyses, pretomanid exposure was not associated with hepatic and hematologic TEAEs; however, it was associated with gastrointestinal (GI) TEAEs. The predicted probabilities of GI TEAEs in patients with typical steady state exposure of 2.4 µg/mL (on 200 mg pretomanid QD) were 7%, 44%, and 59% in patients with TI MDR-TB, NR MDR-TB, and XDR-TB, respectively, indicating that GI disorders were more likely in patients with NR MDR-TB and XDR-TB than those with TI MDR-TB. See section 15.3.1 for the additional details and conclusions for these analyses.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

From a clinical pharmacology perspective, no alternative dosing regimens for pretomanid are deemed necessary based on intrinsic patient factors. This recommendation is based upon the population PK analyses performed by the applicant and reviewed by Pharmacometrics review team (see section 15.3.1). No clinically significant differences in the pharmacokinetics of pretomanid were observed based on sex, body weight, race (Black, White, or other), type of pulmonary TB (TI MDR-TB, NR MDR-TB, or XDR-TB), or HIV status.

For linezolid, dose adjustments were made for known linezolid toxicities of myelosuppression, peripheral neuropathy, and optic neuropathy. See sections 7 and 9 for additional details.

The effect of renal or hepatic impairment on the pharmacokinetics of pretomanid has not been studied.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

<u>Food effect</u>
In the food effect Study CL-009, administration of a 200-mg dose of pretomanid with the FDA high-fat, high-calorie meal increased mean C_{max} and AUC_{inf} by 76% and 88%, respectively, as compared with the fasted state. See section 6.3.1 for PK parameters under fasted or fed conditions and the individual study review (Appendix 15.3.2) for Study CL-009 for details regarding this study.

The approved labeling for bedaquiline states that bedaquiline is to be administered with food. Also, pretomanid was administered under fed conditions in the Nix-TB trial. Thus, the

pretomanid-bedaquiline-linezolid treatment regimen is recommended to be administered with food in the pretomanid labeling.

Drug Interaction Studies

Pretomanid is unlikely to be an inhibitor or inducer of CYP3A4 based on drug interaction studies. However, CYP3A4 inducers reduced the exposure of pretomanid; therefore, concomitant medications which are CYP3A4 inducers should not be co-administered with B-Pa-L regimen.

Drug-interaction liability mediated by major drug transporters is unlikely with pretomanid except with OAT3 substrate drugs.

Clinical Studies

Midazolam (CYP3A4 substrate): In Study CL-006, the applicant investigated the potential interaction of pretomanid with midazolam. A 400 mg (twice the proposed dose of pretomanid) dose of pretomanid QD orally was administered for 14 days, followed by subsequent co-administration of a 2 mg single oral dose of midazolam on day 14. This resulted in a decrease in midazolam mean AUC by 15% and C_{max} by 16 % and an increase in 1-hydroxy midazolam mean AUC by 14 % and C_{max} by 5%. Based on this, pretomanid is not likely to affect the PK of CYP3A4 substrate drugs to a clinically significant extent. Thus, pretomanid can be co-administered with CYP3A4 substrate drugs.

In study A5306, the applicant investigated the potential interaction between steady state pretomanid given at 200 mg once daily and efavirenz 600 mg once daily, lopinavir/ritonavir 400/100 mg twice daily, or rifampin 600 mg once daily.

Lopinavir/ ritonavir (CYP3A Inhibitor): Co-administration of 200 mg pretomanid QD orally with lopinavir/ritonavir 400/100 mg BID for 7 days resulted in a decrease of pretomanid mean AUC by 17% and C_{max} by 13%. Mean AUC and C_{max} of lopinavir was decreased by 14 % and 17 %, respectively, when given with pretomanid. Therefore, ritonavir-boosted lopinavir can be co-administered with pretomanid.

Rifampin (CYP3A4 Inducer): Co-administration of 200 mg pretomanid QD orally with rifampin 600 mg QD for 7 days resulted in a decrease of pretomanid mean AUC by 66% and C_{max} by 53%.

Efavirenz (CYP3A4 Inducer): Co-administration of 200 mg pretomanid QD orally with efavirenz 600 mg QD for 7 days resulted in a decrease of pretomanid mean AUC by 35% and C_{max} by 28%. Mean AUC and C_{max} of efavirenz was decreased by 4 % and 14 %, respectively, when given with pretomanid.

Avoid co-administration of the combination regimen of pretomanid, bedaquiline, and linezolid with rifampin, efavirenz, or other strong or moderate CYP3A4 inducers.

Bedaquiline and Linezolid: The potential for an interaction between pretomanid and other components of BPaL, bedaquiline and linezolid, is low. Bedaquiline is a CYP3A4 substrate

(SIRTURO® label). The results from study CL-006 with midazolam (see above) suggest that a significant pharmacokinetic drug interaction between pretomanid and bedaquiline is unlikely. At the EOP2 meeting held in May 2016, the FDA agreed with the applicant's proposal that no interaction is expected to occur between pretomanid and bedaquiline. Thus, a DDI study between pretomanid and bedaquiline was not conducted.

It is unlikely that pretomanid and linezolid will have an effect on the systemic exposure on each other since linezolid metabolism does not involve CYP450 (ZYVOX® label), and linezolid is not a substrate for the OAT3 transporter that pretomanid inhibits based on *in vitro* studies for pretomanid.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes Mediated DDIs: CYP3A4 accounts for up to approximately 20% of the metabolism of pretomanid. Pretomanid is not a substrate of CYP2C9, CYP2C19, and CYP2D6.

Pretomanid is a time-dependent inhibitor (TDI) of CYP3A4/5; however, in a clinical DDI study with midazolam, pretomanid did not affect exposure of midazolam in a clinically significant manner. Pretomanid is not an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations based on *in vitro* studies. Pretomanid is a weak time-dependent inhibitor of CYP2C8 and CYP2C19. No clinical DDI studies have been conducted with CYP2C8 and CYP2C19 substrates.

Pretomanid was not an inducer of CYP3A4 and CYP2C9 based on *in vitro* studies.

Transporter Mediated DDIs: In vitro studies indicate that pretomanid significantly inhibits the OAT3 drug transporter which could result in increased concentrations of OAT3 substrates at clinically relevant concentrations of pretomanid. No clinical DDI studies have been conducted with OAT3 substrates.

In vitro studies indicated that pretomanid has a very low inhibitory interaction potential with the MATE2-K transporter at clinically relevant concentrations. Pretomanid does not inhibit human OAT1, OCT1, OCT2, OAT1B1, OATP1B3, BCRP, BSEP, P-gp, and/or MATE1 mediated transport at clinically relevant concentrations. Pretomanid is not a substrate of OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and/or P-gp transporters.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

In the NDA, the evidence of efficacy of pretomanid is primarily based on the ongoing phase 3 trial of a BPaL 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.

Another phase 3 trial of a pretomanid containing regimen, NC-006, evaluated the combination of moxifloxacin (400 mg) plus pretomanid (100 mg or 200 mg) plus pyrazinamide (1500 mg) for either 4 or 6 months for the treatment of DS-TB and 6 months for the treatment of MDR-TB. After enrolling 284 of the planned 1500 patients, this study was prematurely terminated due to the applicant's view that more promising pretomanid regimens should be developed. There was no control group for patients treated for MDR-TB. Among randomized assessable DS-TB patients, favorable outcomes for the primary endpoint of bacteriologic failure or relapse or clinical failure 12 months from the start of therapy were reported in the modified intent to treat primary analysis population for:

- 52/60 (87%) patients in the HRZE control group
- 38/57 (67%) patients in the 4 month (100 mg pretomanid) group
- 46/61 (75%) patients in the 4 month (200 mg pretomanid) group
- 43/56 (77%) patients in the 6 month (200 mg pretomanid) group.

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 based on a noninferiority margin of 12% and a hierarchical testing procedure. In the 11 assessable MDR-TB patients treated with the 6-month (200 mg pretomanid) regimen with no control group, favorable outcomes were reported for 10/11 (91%) patients.

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.

Data Sources

Data sources reviewed for Nix-TB included the protocol, statistical analysis plans for efficacy and safety, case report forms, the clinical trial report, and the integrated summary of safety.

Datasets for this NDA submission are available at the following location in the Electronic Document Room: \\CDSESUB1\evsprod\NDA212862\0001\m5\datasets

Data and Analysis Quality

Data and analysis quality were sufficient for review purposes.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Nix-TB Study Design

Trial Design and Endpoints

Nix-TB is an ongoing phase 3, single-arm, multi-center trial to assess the safety and efficacy of bedaquiline plus linezolid plus pretomanid (BPaL) 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 BPaL. 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 BPaL 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. An efficacy summary was also provided by the applicant for an interim data cutoff of January 28, 2019 with primary endpoint data for a total of 107 assessable patients (ITT), including 104 patients in the primary analysis population (MITT).

As all patients in Nix-TB received a BPaL 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.

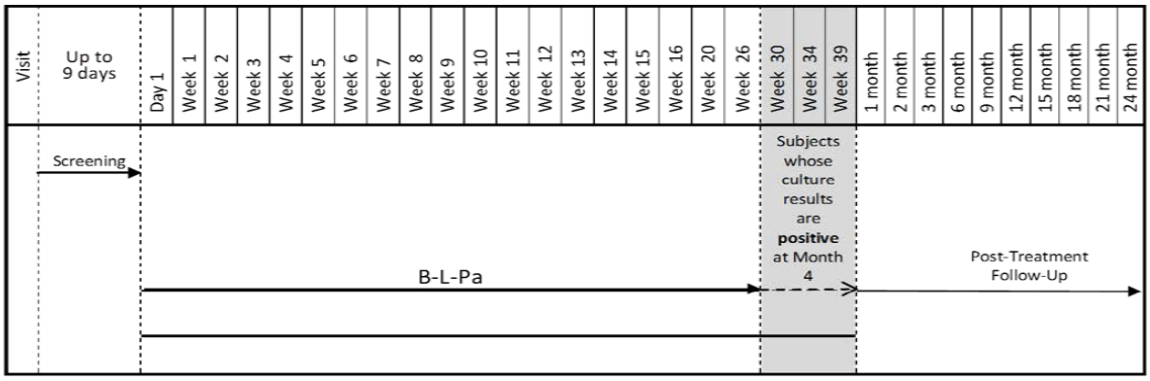
Patients in Nix-TB were to receive a minimum of 6 months of treatment with BPaL. For patients, persistently culture positive between Month 4 and 6 with clinically ongoing TB, treatment could have been extended to 9 months or the patient could have been withdrawn from the trial.

The BPaL 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 BPaL. 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 7-1: Schematic of Nix-TB Trial Design



Abbreviations: BPaL, 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:

- 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.

Upon discontinuation of trial treatment, patients were to be referred to a unit specializing in XDR-TB.

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 by molecular typing.

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.

Inclusion and Exclusion Criteria

Key inclusion criteria were as follows:

1. Consenting male and female subjects aged ≥ 14 years, weighing ≥ 30 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>Exclusion criteria:</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

<u>Specific Treatments:</u>

12. Concomitant use of medications that affect QT interval or can cause a serotonin syndrome when combined with study treatment
13. Patients may have previously been 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 should not receive more than 2 weeks of bedaquiline or linezolid prior to enrollment/first administration of trial treatment.

<u>Laboratory Abnormalities:</u>

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.

Statistical Analysis Plan

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.

7.2.2. Nix-TB Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

Financial certification and disclosure information was submitted for the 40 investigators / sub investigators and study nurse coordinators in the Nix-TB trial and they had no disclosable financial arrangements. See Appendix 15.2 for the Financial Disclosure Form.

Patient Disposition

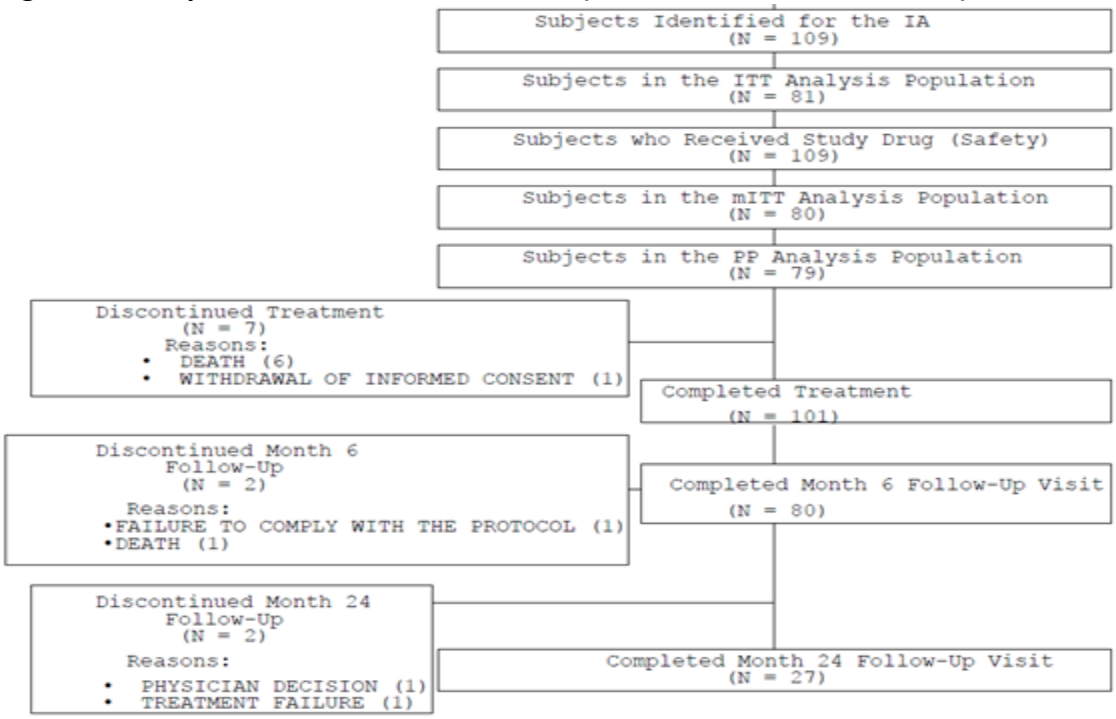
The figure below displays the patient disposition. There were 133 subjects who signed informed consent; 24 of these subjects were screen failures and were not treated. Thus, a total of 109 subjects were treated and thereby included in the safety population.

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.

Efficacy analyses in this review are based primarily on the June 29, 2018 interim data cutoff, at which point 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.

At the January 18, 2019 data cutoff, there were 107 patients in the ITT population and 104 patients in the MITT analysis population.

Figure 7-2: Disposition of Patients in Nix-TB (cutoff date of June 29, 2018)



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 34 screen failures as well as reasons for failed rescreening.

Table 7-1: 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 7-2: Major Protocol Deviations in Nix-TB Based on June 29, 2018 Interim Data Cutoff (Safety Analysis Population)

Variable	Statistic	BPaL (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

Reference ID: 4476823

average age of 36 years. At the January 18, 2019 data cutoff, demographic and baseline disease characteristics for the safety population and MITT population were similar to those from the June 29, 2018 data cutoff.

Table 7-3: Nix-TB Baseline Demographics Based on the June 29, 2018 Interim Data Cutoff

Variable	Safety population BPaL (n = 109)	MITT population BPaL (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 7-4: Nix-TB Baseline Characteristics Based on the June 29, 2018 Interim Data Cutoff

Variable	Safety population BPaL (n = 109)	MITT population BPaL (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

Variable	Safety population BPaL (n = 109)	MITT population BPaL (n = 80)
Maximum	41	41
CD4 Count (cells/µL, among HIV positive)		
Mean	394	436
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 7-5: Nix-TB Baseline Disease History Based on the June 29, 2018 Interim Data Cutoff

Variable	Safety population BPaL (n = 109)	MITT population BPaL (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 (years)		
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

Variable	Safety population BPaL (n = 109)	MITT population BPaL (n = 80)
Duration Since Positive TB Culture (days)		
Mean	52	55
SD	24	24
Minimum	16	16
Median	49	61
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 BPaL 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 BPaL.

The figure below displays the patient disposition in Nix-TB. There were 143 subjects who signed informed consent forms. However, 34 of these subjects were screen failures and were not treated. Thus, a total of 109 = 143-34 subjects were treated and thereby included in the safety population. The first patient was enrolled on April 24, 2015 and the last patient was enrolled on November 1, 2017.

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 BPaL. 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 7-6: 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 7-7 shows results from the interim data cutoff of June 29, 2018. A total of 81 subjects were assessed and 80 were included 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 BPaL was substantially larger than the 50% rate prespecified as the historical control rate threshold. See discussion of the historical control rates in Section 7.3.

Table 7-7. 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 34 screening failures and the unassessable subject to have unfavorable outcomes. With this very conservative method of imputation, the response rate became 72/115 (62.6%) with an exact 95% CI of 53.1% to 71.5%. 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.

The most updated efficacy data are based on an interim data cutoff of January 18, 2019. The table below shows that with107 patients in ITT and 104 patients in the MITT primary analysis population with sufficient follow-up for primary endpoint evaluation, results were very consistent with those from earlier data cutoffs.

Table 7-7: Primary Efficacy Analysis in Nix-TB Based on January 18, 2019 Interim Data Cutoff (ITT and MITT Analysis Populations)

ITT Population	Total	XDR	TI/NR MDR
Total Assessable	107	71	36
Favorable	95/107 (89%)	63/71 (89%)	32/36 (89%)
Unfavorable	12/107 (11%)	8/71 (11%)	4/36 (11%)
Any Death	8/107 (7%)	7/71 (10%)	1/36 (3%)
95% CI for Favorable	81% to 94%	79% to 95%	74% to 97%
MITT Population	Total	XDR	TI/NR MDR
Total Assessable	104	70	34
Favorable	95/104 (91%)	63/70 (90%)	32/34 (94%)
Unfavorable	9/104 (9%)	7/70 (10%)	2/34 (6%)
Any Death	7/104 (7%)	6/70 (9%)	1/34 (3%)
95% CI for Favorable	84% to 96%	80% to 96%	80% to 99%

Source: Nix-TB 120-day update efficacy report, Tables 3.1, 3.2, and 11.1, and statistical reviewer.

Efficacy Results – Secondary endpoints

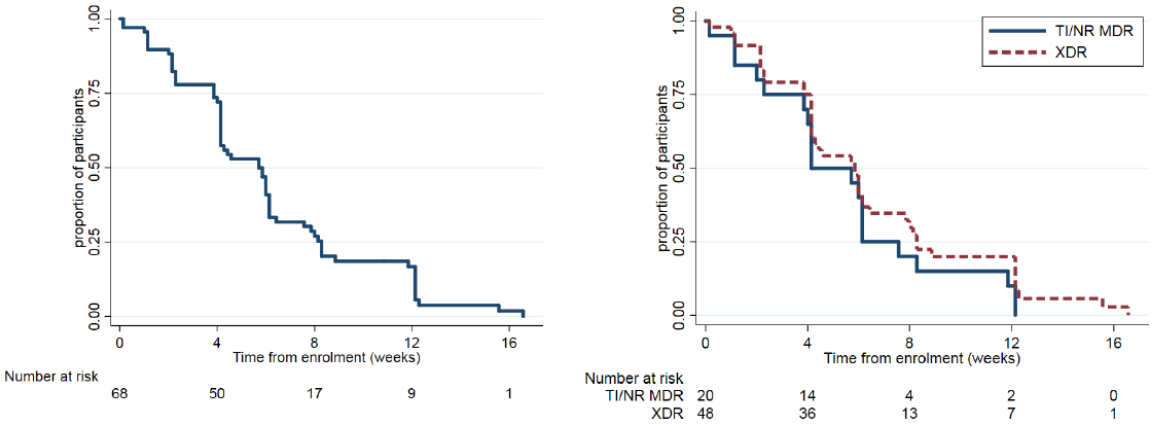
Results for selected secondary endpoints are shown for the 80 patients in the MITT analysis population from the June 29, 2018 interim data cutoff. These patients all had follow-up data 6 months after the EOT, except in cases of death.

Results are largely unavailable for the secondary efficacy endpoint of bacteriologic failure, relapse, or clinical failure through 24 months after the end of treatment as the study is ongoing. At the June 29, 2018, interim data cutoff, there were 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 BPaL seen 6 months posttreatment appeared to be maintained over a 24-month posttreatment follow-up period.

At the January 18, 2019, interim data cutoff, results were available for 38 patients in the MITT analysis population for this secondary endpoint of bacteriologic failure, relapse, or clinical failure through 24 months after the end of treatment. There were 32/38 (84%) patients successfully treated who remained TB negative. Of the 6/38 (16%) patients with unfavorable outcomes, there were 4 deaths and 2 relapses. Thus, secondary endpoint results appeared consistent at this interim data cutoff with those seen at the previous data cutoff.

The Kaplan-Meier curve is displayed below for the secondary endpoint of time to sputum culture negative status, restricting to patients with positive baseline cultures and assessable data. Aside from the patients who died, cultures had almost completely converted to negative status 16 weeks after enrollment.

Figure 7-3: 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 7-8 presents results for Patient Self-Reported Health Status at planned protocol visits. Resolution of symptoms was difficult to interpret without a comparator group.

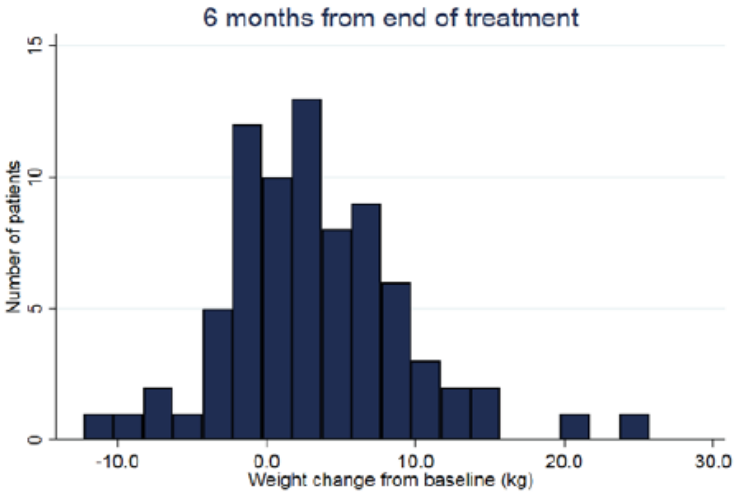
Table 7-8: Patient Self-Reported Health Status at Planned Protocol Visits in Nix-TB Based on June 29, 2018 Interim Data Cutoff (Safety Population)

		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 7-4: 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 7-9: Nix-TB Favorable Outcomes 6 Months After the EOT by Subgroup Based on June 29, 2018 Interim Data Cutoff (MITT Analysis Population)

Subgroup	BPaL (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 7-10: 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	BPaL (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.

Potential for Linezolid Resistance: Dose reduction of linezolid is necessary to reduce adverse reactions however, it is a potential risk factor for the development of linezolid resistance because low doses of linezolid could lead to suboptimal exposure and drive the selection of resistant mutants. Identification of the resistance mutations and clinical factors associated with linezolid resistance is critical to preserve the efficacy of linezolid for the treatment of MDRTB and XDRTB.

Linezolid resistance and treatment failures have been reported in 39 patients (mostly XDR-TB) in South Africa by Wasserman et al.[16] Phenotypic resistance, as defined by a linezolid MIC >1 mg/L, was assessed in patients' isolates using a broth microdilution method. Targeted sequencing of rrl and rplC (genes encoding binding sites) was performed to detect resistance mutations. The authors noted that the background drug regimen at the time of linezolid introduction was probably suboptimal resulting in linezolid monotherapy for prolonged periods of time. Linezolid resistance was detected in 13 (33%) patients after a median duration of 22 months of treatment. The authors note that this observation of resistance occurring late during therapy is reassuring because it confirms linezolid's high barrier to resistance. Despite its high barrier to resistance, with sufficient selection pressure, the emergence of resistance in TB programs is likely to increase with widespread use of linezolid for XDR-TB and MDR-TB. Screening for genotypic resistance should be considered for patients with a positive culture after four months of linezolid therapy to optimize treatment and to avoid the toxicity of ineffective linezolid therapy.

[16] Wasserman S, Louw G, Ramangoaela L, et al. Linezolid resistance in patients with drug-resistant TB and treatment failure in South Africa. J Antimicrob Chemother 2019; doi:10.1093/jac/dkz206

7.3. Review of Historical Success Rates

Literature Review

Because the primary analysis in the Nix-TB trial 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. The definition of cure differed from Nix-TB because it was based on negative cultures after the intensive phase of treatment rather than 6 months after the end of the treatment regimen. Because the Nix-TB favorable outcome definition was more conservative, this difference supported the ability to make comparisons between BPaL outcomes and historical outcomes.

Table 7-11: 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.
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 7-12: 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;
(3) reported treatment results for XDR-TB patients as a specific category of TB.

Additionally, articles were excluded if:
(1) treatment of XDR-TB patients included the use of bedaquiline, delamanid, or linezolid;
Note: The Nix-TB trial was meant to assess whether the entire BPaL regimen given for 6 months adequately treated XDR-TB and TI/NR MDR-TB and not to assess the contribution of pretomanid to an optimized background regimen of 5 or more drugs that included bedaquiline and/or linezolid given for 12-24 months, much longer than the 6-9 months duration for BPaL in Nix-TB.
(2) the study reported treatment outcome data on ≤10 XDR-TB patients;
(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 not enrolled 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, the Nix-TB trial was conducted entirely in South Africa, where success rates in the literature have historically been very low. Overall, the BPaL 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 BPaL 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. However, patient-level datasets were not submitted for the matched historical control group, which limited the ability to reproduce the applicant's results and perform a detailed assessment of the comparability between BPaL and control groups.

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 7-13: 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%)	
TB Diagnosis			<0.01
XDR	37 (82.2%)	202 (100.0%)	
TI/NR MDR	8 (17.8%)	0 (0.0%)	

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 7-14: 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 7-15: 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 7-16: 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 January 18, 2019 interim data cutoff for Nix-TB, the rate of favorable outcomes 24 months after the EOT was 32/38 (84.2%), 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.

7.4. Integrated Review of Effectiveness

Integrated assessments of efficacy across studies were not performed in this review, because Nix-TB was the only trial assessing the BPaL regimen for the treatment of XDR-TB and treatment intolerant/non-responsive MDR-TB.

7.5. Summary and Conclusions of Efficacy

Due to rapid development of resistance in MTB with monotherapy, multi-drug regimens are the standard of care for both drug sensitive and drug resistant pulmonary tuberculosis. Evaluation of drug monotherapies in TB clinical trials is not ethical nor feasible. The evidence for the contribution of the individual components to the BPaL regimen comes from the studies in the murine models of pulmonary tuberculosis, in which the three-drug BPaL regimen demonstrated bactericidal as well as sterilizing activity superior to that of individual components and to the dual combinations of bedaquiline, pretomanid, and linezolid. See Section 8.1.4 for the detailed discussion of the design and results of the nonclinical studies.

The efficacy assessment of the BPaL regimen for the treatment of XDR-TB and TI/NR MDR-TB was based on Nix-TB. Based on the January 18, 2019 interim data cutoff, the rate of favorable outcomes for the primary endpoint of bacteriologic failure, relapse, or clinical failure in ITT population was 89%, with a 95% confidence interval from 81% to 94%. 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

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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 BPaL 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 BPaL regimen.

As all patients in Nix-TB received single arm treatment with a BPaL regimen, the trial was not designed to provide clinical evidence for the pretomanid contribution to the regimen. Rather, the trial was meant to assess whether the entire three drug regimen adequately treated XDR-TB and treatment intolerant/non-responsive MDR-TB. The high success rate in Nix-TB did not directly imply a contribution of pretomanid. For instance, a recent meta-analysis reported success rates of ≥87% for bedaquiline-containing and linezolid-containing regimens for XDR-TB that did not include pretomanid [*Lancet* 2018; 392:821-34]. However, these regimens were constructed based on the individual subject's MTB isolate susceptibility profile and consisted of a minimum of five drugs that had to be given for the duration of a minimum of 12- 18 months, much longer than the 6-9 months duration for BPaL in Nix-TB.

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.

8 Clinical Microbiology Review

8.1. Nonclinical Microbiology

8.1.1. Mechanism of Action

Pretomanid is a bicyclic nitroimidazole, which is activated within the *M. tuberculosis* (MTB) cells by a deazaflavin (F420) dependent nitroreductase (Ddn) resulting in release of reactive nitrogen species such as nitric oxide (NO). Under anaerobic conditions, pretomanid causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species. Under aerobic conditions, pretomanid inhibits cell wall biosynthesis via blockage of the oxidation of hydroxymycolate to keto mycolate. Please see Appendix Section 15.4.1 for studies supporting the mechanism of action.

8.1.2. Antibacterial Activity

Pretomanid is active in vitro against replicating and nonreplicating MTB. The pretomanid MICs vary with the method used for susceptibility testing. The MIC values for pretomanid against quality control MTB H37Rv strain ranged from 0.12 to 0.25 mcg/mL irrespective of the method (BACTEC, Agar dilution or MGIT) or testing laboratory. The pretomanid MIC against the 68-drug susceptible (DS) MTB isolates ranged from 0.005 to 0.48 mcg/mL while against the 26 isolates resistant to both isoniazid and rifampicin (MDR-MTB) and the 6 isolates resistant to any fluoroquinolone and at least one of three second-line injectable (capreomycin, kanamycin, and amikacin) in addition to multidrug resistance (XDR-MTB), the pretomanid MIC ranged from 0.005 to 16 mcg/mL by the agar dilution method. Pretomanid MICs increased 3 to 7-fold in the presence of 50% human serum or 4% human albumin. The bactericidal activity of pretomanid is concentration- and time-dependent. The intracellular activity of pretomanid is similar to isoniazid and lower than rifampicin. For data supporting the *in vitro* activity, please refer to the Appendix Section 15.4.2.

In vitro drug combinations:

An important aspect of the efficacy of the BPaL regimen is understanding the contribution of the individual drugs to the regimen. Checkerboard assays are typically done to determine synergistic effects or contribution of a combination over individual drugs. No *in vitro* studies were conducted to assess the contribution of pretomanid, bedaquiline, and linezolid to the BPaL regimen. However, the activity of the drug combination of bedaquiline and pretomanid (BPa) was compared to the activity of the individual drugs using an inducible Rv0880 overexpression strain (Peterson et al 2016)[17]. The Rv0880 regulon contains a number of target genes that are upregulated when MTB is treated with bedaquiline and leads to a tolerant state. The Rv0880 overexpression strain was treated with 0.3× and 1× MIC of bedaquiline (B) alone and in combination with 0.1× and 0.3× MIC of pretomanid (Pa). The bacterial counts after 7 days of drug exposure was assessed for the Rv0880 overexpressor strain under un-induced (DMSO added) or induced (with anhydrotetracycline) conditions. The activity of the BPa combination was estimated using Excess over Bliss (EOB), which determines whether the combined effect of two drugs is greater or smaller than the independent combination of their individual effects. The EOB estimates were used to determine synergism or antagonism of the tested BPa combination concentrations with un-induced or induced overexpression of Rv0880 (Figure 8-1). The BPa combinations were additive to mildly synergistic at most of the sub-MIC concentrations tested with un-induced Rv0880 overexpression. In contrast, BPa combinations demonstrated strong antagonism when Rv0880 overexpression was induced. The Rv0880-induced samples show that the effectiveness of BPa could be compromised through overexpression of the Rv0880 regulon.

[17] Peterson EJR, Ma S, Sherman DR, Baliga NS. Network analysis identifies Rv0324 and Rv0880 as regulators of bedaquiline tolerance in *Mycobacterium tuberculosis*. Nat Microbiol. 2016 Jun 6;1(8):16078

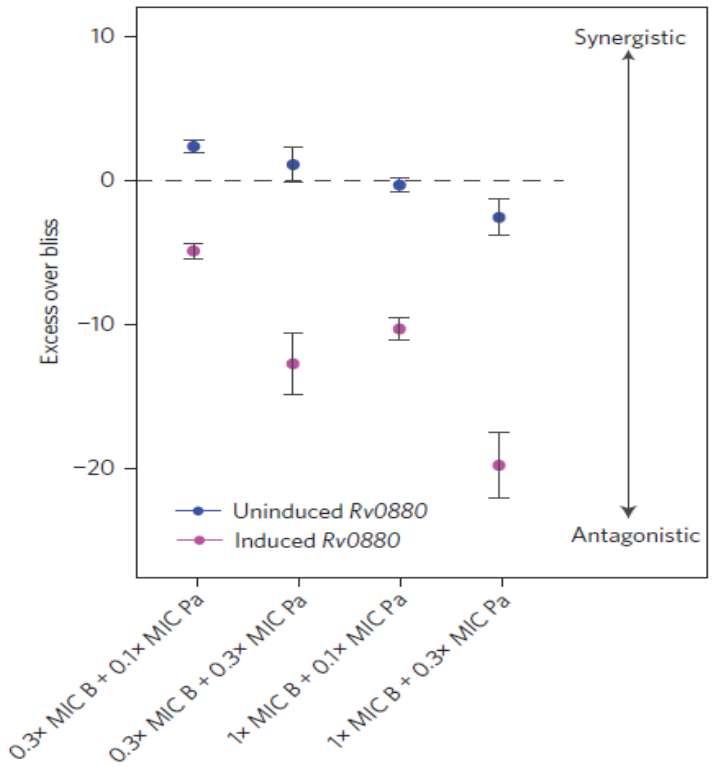

Figure 8-1. Influence of Rv0880 overexpression on EOB estimation of bedaquiline and pretomanid drug combination.

Note: EOB estimation for all bedaquiline and pretomanid (BPa) combinations tested with induced (magenta) and uninduced (blue) Rv0880 overexpression cultures. Error bars represent standard deviation of EOB, estimated from three biological samples. The dashed grey line is at EOB = 0 (additive) and represents a line over and below which BPa combinations are considered synergistic and antagonistic, respectively. This experiment was repeated twice, with reproducible results. B, bedaquiline; Pa, pretomanid. Source: Peterson et al 2016

Reviewer comment: The study is not useful for understanding the contributions of the individual drugs to the BPaL regimen but provides insights into the variable activity of the bedaquiline plus pretomanid combination observed in vitro.

8.1.3. Resistance and Cross-Resistance

The resistance rates for MTB H37Rv to pretomanid at 4x MIC by fluctuation analysis was reported to be 5×10^{-7} mutants/generation which was lower than the rate of isoniazid resistance (4.5×10^{-6} drug resistant mutants/generation) but higher than the rate of rifampin resistance (9.1×10^{-9} drug resistant mutants/generation) (Fortune Pretomanid study 1).

Two other studies evaluated the resistance frequency of MTB H37Rv to pretomanid (Manjunatha *et al* 2006; Haver *et al* 2015)[18,19]. In the study by Manjunatha *et a*l (2006)[18], the *in vitro* frequency of resistance to pretomanid was 6.5 x 10^{-7} after exposure of MTB H37Rv to 6x MIC. The frequency was similar to that observed in the fluctuation analysis. In the study by Haver *et al* (2015)[19], the resistance frequencies were dependent on inoculum and drug concentration (2x MIC to 6x MIC) and ranged from 10^{-7} to 10^{-5}. The frequency rates were similar to isoniazid and delamanid (Fujiwara et al., 2018)[20]. The proposed dosing of 200 mg dose of pretomanid corresponds to concentration of 1.0-1.7 mcg/mL. The predicted mutation frequency at this concentration would be 10^{-6}.

Studies were also conducted to assess resistance development in MTB infected mice (Manjunatha et al 2006; Tyagi et al., 2005; Tasneen et al 2015)[18,21.22]. In the study by Tyagi *et al* (2005)[21], the proportion of isoniazid-resistant CFU and pretomanid-resistant CFU after 8 weeks of isoniazid and pretomanid monotherapy were reported as 2.5 x 10^{-4} and 3.8 x 10^{-3}, respectively. The proportion of bacteria resistant to either drug decreased to <5.0 x 10^{-6}, when the two drugs were dosed in combination. Pretomanid-resistant bacteria with MIC values 100-fold higher than parent strain were observed in the lungs and spleen of mice challenged with MTB H37Rv and treated for 2 weeks with pretomanid (25 and 50 mg/kg) (Manjunatha *et al* 2006)[18]. In the study by Tasneen et al (2015)[22], at 8 weeks of treatment with 300 or 600 mg/kg pretomanid, resistant population accounted for 48% and 80-100% of total CFU, respectively. These studies suggest that combination therapy is necessary to reduce the development of resistance.

<u>Mechanism of resistance:</u>
The mechanism of resistance was initially identified using a *M. bovis* BCG nitroimidazopyran (NAP)-resistant mutant SM3 which was unable to reduce pretomanid (Stover *et al* 2000)[23]. Genetic complementation of this mutant with the *fgd1* gene restored susceptibility of the

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[18] Manjunatha UH, Boshoff H, Dowd CS, Zhang L, Albert TJ, Norton JE, et al. Identification of a nitroimidazo-oxazine-specific protein involved in PA-824 resistance in *Mycobacterium tuberculosis*. Proc Natl Acad Sci U S A. 2006 Jan 10; 103(2): 431-6.
[19] Haver HL, Chua A, Ghode P, Lakshminarayana SB, Singhal A, Mathema B, et al. Mutations in genes for the F420 biosynthetic pathway and a nitroreductase enzyme are the primary resistance determinants in spontaneous *in vitro*-selected PA-824-resistant mutants of *Mycobacterium tuberculosis*. Antimicrob Agents Chemother. 2015 Sep; 59(9): 5316-23.
[20] Fujiwara M, Kawasaki M, Hariguchi N, Liu Y, Matsumoto M. Mechanisms of resistance to delamanid, a drug for *Mycobacterium tuberculosis*. Tuberculosis (Edinb). 2018 Jan; 108:186-194
[21] Tyagi S, Nuermberger E, Yoshimatsu T, Williams K, Rosenthal I, Lounis N, et al. Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother. 2005 Jun; 49(6): 2289-93.
[22] Tasneen R, Williams K, Amoabeng O, Minkowski A, Mdluli KE, Upton AM, et al. Contribution of the nitroimidazoles PA-824 and TBA-354 to the activity of novel regimens in murine models of tuberculosis. Antimicrob Agents Chemother. 2015 Jan; 59(1): 129-35.
[23] Stover CK, Warrener P, VanDevanter DR, Sherman DR, Arain TM, Langhorne MH, etal. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature. 2000 Jun 22; 405(6789): 962-6.

Reference ID: 4476823

mutant to pretomanid (Figure 8-2). The *fgd1* encodes an enzyme that reduces F420 (F420 dependent glucose-6-phosphate dehydrogenase [Fgd1] that is important in nitroreduction of pretomanid.

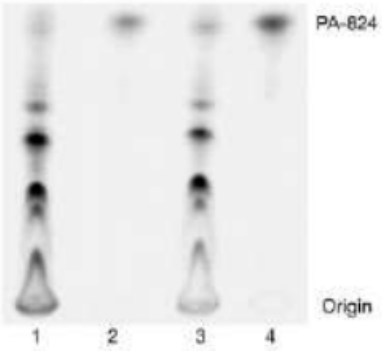

Figure 8-2. Metabolism of ^{14}C-labelled pretomanid.

Note: PA-824 = pretomanid Bacillus Calmette-Guérin (BCG) cells were incubated with labelled drug, and labelled metabolites were recovered from disrupted cells and analyzed by thin-layer chromatography. Lane 1, drug-susceptible BCG parent strain 1102; Lane 2, drug-resistant (DR) mutant strain SM3; Lane 3, strain SM3 transformed with plasmid pMV206-fgd; Lane 4, strain SM3 transformed with control plasmid pMV206. Source: (Stover et al., 2000)

Characterization of pretomanid-resistant *M. bovis* BCG selected *in vitro* by transposon mutagenesis identified mutations in *fbiA* and *fbiB* genes that are involved in the cofactor F420 biosynthetic pathway (Choi et al 2001)[24]. Pretomanid-resistant mutants of MTB H37Rv obtained *in vitro* and *in vivo* were also characterized for presence of the Fgd1 protein using Western blot analysis, and of F420 and its precursor by high-performance liquid chromatography (Manjunatha et al 2006)[18]. The study showed that 20% of the *in vivo*-derived pretomanid-resistant mutants did not produce Fgd1 and 60% were missing cofactor F420; an additional 20% appeared to be wild-type for Fgd1 and F420. To identify the mutation in the Fgd1+/F420+ mutants that was responsible for resistance, a library of pretomanid-resistant mutants was generated using transposon mutagenesis. Four independent mutants had mutations in the Rv3547 gene (*ddn*). Complementation with native Rv3547 resulted in restoration of susceptibility to pretomanid while complementation with the mutated Rv3547 gene (present in the pretomanid-resistant strains) did not restore susceptibility to pretomanid. These genes were also identified during characterization of 183 independent spontaneous pretomanid-resistant mutants of MTB H37Rv (Figure 8-3) (Haver *et al* 2015)[19].

[24] Choi KP, Bair TB, Bae YM, Daniels L. Use of transposon Tn5367 mutagenesis and a nitroimidazopyran-based selection system to demonstrate a requirement for fbiA and fbiB in coenzyme F(420) biosynthesis by Mycobacterium bovis BCG. J Bacteriol. 2001 Dec; 183(24): 7058-66.

Reference ID: 4476823

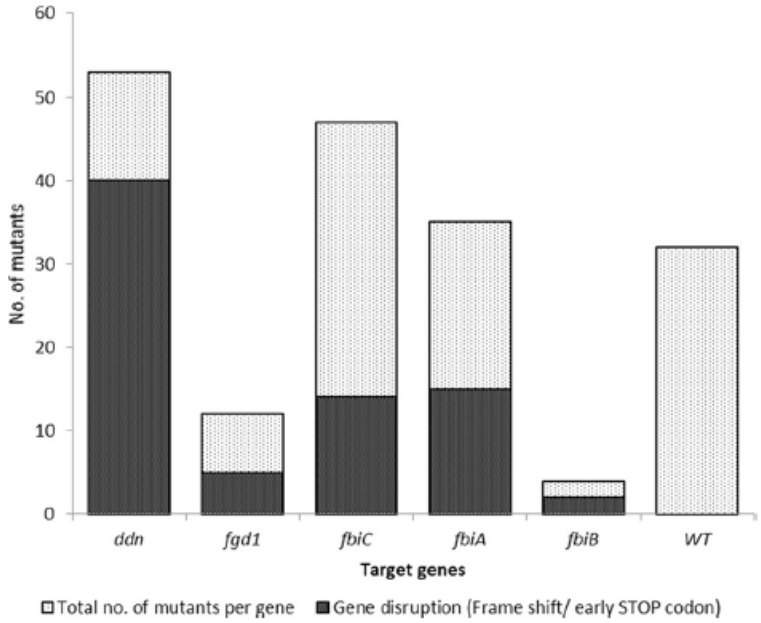

Figure 8-3. Distribution of mutation frequencies to pretomanid among the target genes ddn, fgd1, fbiC, fbiA, and fbiB.

Note: Distribution of mutation frequencies among the 5 target genes. The relative number of genes encoding early STOP codons and out-of-frame insertions and deletions is shown in gray. Source: (Haver et al., 2015)

Mutants resistant to pretomanid have either (a) lost the F420-dependent glucose-6-phosphate dehydrogenase Fgd1, or (b) have disruptions in the biosynthetic genes for cofactor F420, or (c) have lesions in Ddn (Rv3547), the protein that reductively activates the pro-drug in the presence of reduced F420[18, 25, 26, 27]. The MICs of the resistant mutants were several fold higher than the wild-type strains (Table 8-1).

Table 8-1. MICs for various mutants *in vitro*.

Pretomanid-resistant mutant strains	MIC (microM)			
	Pretomanid	NSC4263	Levofloxacin	Isoniazid
H37Rv (wild type)	0.78	1.56	0.78	0.78
T3-MT (FGD- F420+)	>50	25	0.78	0.78

[25] Singh R, Manjunatha UH, Boshoff H, Ha YH, Niyomrattanakit P, Ledwidge R, Dowd CS, Lee IY, Kim P, Zhang L, Kang S, Keller TH, Jiricek J, Barry CE 3rd. Bicyclic nitroimidazoles act as intracellular NO donors and kill non-replicating Mycobacterium tuberculosis. Science. 2008.
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[27] Kidwai S, Park CY, Mawatwal S, Tiwari P, Jung MG, Gosain TP, Kumar P, Alland D, Kumar S, Bajaj A, Hwang YK, Song CS, Dhiman R, Lee IY, Singh R. Dual Mechanism of Action of 5-Nitro-1,10-Phenanthroline against Mycobacterium tuberculosis.Antimicrob Agents Chemother. 2017 Oct 24;61(11).

Reference ID: 4476823

Pretomanid-resistant mutant strains	MIC (microM)			
	Pretomanid	NSC4263	Levofloxacin	Isoniazid
50-5A1 (FGD FbiC-)	>50	25	0.78	0.78
50-14A1 (FGD+ Ddn-)	>50	1.56	0.78	0.78
50-7A2 (FGD+ FbiAB-)	>50	25	0.78	0.78
50-14A1-3547 (50-14A1::Rv3547)	0.78	1.56	0.78	0.78

NSC4263 = investigational drug Source: Kidwai et al 2017

Compound	WT H37Rv MIC (microM)	WT H37Rv MAC (microM)	Mutant 1* MIC (microM)	Mutant 2# MIC (microM)	Mutant 2# MAC (microM)
Pretomanid	0.8	8-16	>100	>100	>500
Metronidazole	>300	62.5	>100	>100	125

* Mutation in genes for biosynthesis of co-factor F420; # mutation in Ddn; MIC= minimum inhibitory concentration; MAC = minimum anaerobicidal concentration after anaerobic incubation for 3 weeks. Source: Kim et al 2009

Reviewer comment: The in vitro resistance rate to pretomanid ranged from 10^{-7} to 10^{-5} to and appears to be concentration-dependent. The resistance frequency rate is similar to delamanid and isoniazid and higher than that for rifampicin. The predicted mutation frequency for pretomanid is 10^{-6} with proposed human dose of 200 mg (based on observed pretomanid resistant mutants in mice with 50 mg/kg dose). Thus, combination therapy would be needed to prevent development of resistance to pretomanid. Five non-essential genes associated with the bioreductive activation of pretomanid within the bacterium were responsible for the mechanism of resistance to pretomanid in MTB. These included ddn, encoding Ddn; fgd1, encoding an enzyme that reduces F420 (F420 dependent glucose-6-phosphate dehydrogenase [Fgd1]); and fbiA, fbiB, and fbiC, encoding the cofactor F420 biosynthetic pathway. Pretomanid-resistant mutants that did not map to the five genes listed above were also observed, indicating that other mechanisms may be involved in the resistance to pretomanid.

Cross-resistance:

To determine whether MTB strains resistant to pretomanid were also resistant to other drugs commonly used to treat TB, a collection of 9 pretomanid resistant mutants (6 from *in vivo* studies and 3 from *in vitro* studies) were tested against a panel of 13 anti-TB drugs (Pretomanid-NCLN-MICRO-005 Study Report). All 9 MTB mutants had been previously characterized and shown to be resistant to high pretomanid concentrations (MIC >16 mcg/mL) but susceptible to bedaquiline (MIC values ranging from 0.25 to 0.5 mcg/mL), and linezolid (MIC values ranging from 0.5 to 1 mcg/mL). All 9 mutant strains except one (BA-036) were resistant to delamanid (Table 8-2). All 9 strains were susceptible to the other anti-TB drugs tested, except for 2 strains (KA_091 resistant to kanamycin and 5A1 resistant to pyrazinamide). The applicant has suggested that mutations to unrelated TB drugs may have been acquired during propagation of the strains in the laboratory. Further characterization of these strains is ongoing.

Table 8-2. Cross-resistance of pretomanid-resistant isolates to anti-TB drugs.

Strain ID	MGIT MIC (µg/mL)			MGIT DST Results (S/R)												
	Pa	BDQ	LNZ	STR	INH	RIF	EMB	MOX	KAN	AMK	CAP	CFZ	DLM	ETH	OFX	PZA
BA_011	>16	0.5	1	S	S	S	S	S	S	S	S	S	R	S	S	S
BA_013	>16	0.25-0.5	0.5-1	S	S	S	S	S	S	S	S	S	R	S	S	S
BA_014	≥ 16	0.5	0.5-1	S	S	S	S	S	S	S	S	S	R	S	S	S
BA_021	>16	0.5	0.5	S	S	S	S	S	S	S	S	S	R	S	S	S
BA_036	>16	0.5	0.5	S	S	S	S	S	S	S	S	S	S	S	S	S
KA_091	>16	0.5	1	S	S	S	S	S	R	S	S	S	R	S	S	S
5A1	>16	0.25	1	S	S	S	S	S	S	S	S	S	R	S	S	R
T3	>16	0.5	1	S	S	S	S	S	S	S	S	S	R	S	S	S
14A1	>16	0.5	1	S	S	S	S	S	S	S	S	S	R	S	S	S

AMK = amikacin; BDQ = bedaquiline; CAP = capreomycin; CFZ = clofazimine; DLM = delamanid; DST = drug susceptibility testing; EMB = ethambutol ETH = ethionamide; INH = isoniazid; KAN = kanamycin; LNZ = linezolid; MGIT = mycobacteria growth indicator tube; MIC = minimal inhibitory concentration; MOX = moxifloxacin; OFX = ofloxacin; Pa = pretomanid; PZA = pyrazinamide; R = resistant; RIF = rifampin; S = susceptible; STR = streptomycin;

All resistant results were repeated at least once. Critical concentrations used: STR = 1 µg/mL; INH = 0.1 µg/mL; RIF = 1 µg/mL; EMB = 5 µg/mL; MOX = 0.25 µg/mL; KAN = 2.5 µg/mL; AMK = 1 µg/mL; CAP = 2.5 µg/mL; CFZ = 1 µg/mL; DLM = 0.06 µg/mL; ETH = 5 µg/mL; OFX = 2 µg/mL; PZA = 100 µg/mL

Source: Pretomanid-NCLN-MICRO-005 Study Report

Reviewer comment: The similar MICs for pretomanid against DS-MTB, MDR-MTB, and XDR-MTB suggest a lack of cross-resistance between pretomanid and common TB drugs. Exceptions were noted for one pretomanid-resistant mutant that was resistant to kanamycin and another that was resistant to pyrazinamide. These two strains are being further characterized. Cross-resistance was observed for drugs from the same class i.e., between pretomanid and delamanid.

8.1.4. Antibacterial Activity in Animal Models

The *in vivo* activity of pretomanid administered as oral monotherapy was examined in several murine models of acute, chronic and latent TB infection (BALB/c, gamma interferon knock-out, C57BL/6, C3HeB/FeJ) and in a guinea pig TB model. These models were used to evaluate monotherapy doses and doses for continuous phase of therapy. 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 and combination with other drugs is needed to prevent resistance development. For additional details on pretomanid monotherapy assessments, please see Appendix Section 15.4.3.

Contribution of the individual drugs to the BPaL regimen:
An important aspect of understanding the efficacy of a combination regimen is to ascertain the contribution of the individual drugs to the combination. Due to rapid development of resistance to monotherapy, it is not possible to obtain clinical data for each drug in the BPaL combination regimen. Therefore, the murine TB model was used to demonstrate the contribution of

pretomanid, bedaquiline and linezolid to the BPaL regimen. The studies that provide support of the activity of the BPaL combination compared to the individual components are described here.

Bactericidal Activity:

JHU study 2015 Expt 2a: The activity of pretomanid (Pa, 100 mg/kg), bedaquiline (B, 25 mg/kg), and linezolid (L, 100 mg/kg) as monotherapies, in 2-drug combinations, and as a 3-drug combination was compared to standard treatment (combination of rifampicin (R, 10 mg/kg), isoniazid (H, 10 mg/kg), and pyrazinamide (Z, 150 mg/kg)) in the murine TB model. Female BALB/c mice were infected via aerosol with mean 4.19 $\log_{10}$ CFU of MTB H37Rv, a drug susceptible strain. Oral treatment (once-daily, 5 days/week) was initiated two weeks post-infection for total of 8 weeks. The addition of pretomanid to linezolid resulted in a greater CFU reduction than effected by linezolid alone ($P<0.01$;Table 8-3). The CFU reduction of the combination of bedaquiline and pretomanid was similar to either drug alone. The 3-drug combination, BPaL, 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. This indicates that each of the components B, Pa, and L contributed significantly to the bactericidal efficacy of the 3-drug regimen. In addition, the 3-drug combination of B, Pa, and L reduced CFU in mouse lungs to undetectable levels by 8 weeks, while RHZ treatment reduced mouse lung CFU to 1.43 $\log_{10}$ following 8 weeks of treatment.

Table 8-3. Mean lung colony-forming unit counts following 1- and 2-month treatment of murine tuberculosis with pretomanid, bedaquiline, and linezolid as monotherapies and in combinations.

Regimen	Mean Lung Log_{10} CFU Count (±SD)	
	4 weeks	8 weeks
RHZ	5.47±0.19	1.43±0.81
Pa	6.02±0.19	4.57±0.20
B	4.73±0.20	2.09±0.28
L	6.81±0.13	5.61±0.25
BL	4.79±0.17	2.85±0.25
BPa	4.57±0.21	1.80±0.82
PaL	5.33±0.24	3.34±0.52
BPaL	2.75±0.31	0.00±0.00

B = bedaquiline 25 mg/kg; CFU= colony-forming unit; H = isoniazid 10 mg/kg; L = linezolid 100 mg/kg; Pa = pretomanid 100 mg/kg; R = rifampicin 10 mg/kg; SD = standard deviation; Z = pyrazinamide 150 mg/kg

Untreated mean lung $\log_{10}$ CFU counts Day -13 = 4.19±0.21; Day 0 untreated mean lung $\log_{10}$ CFU counts = 7.68±0.27.

Source: Adapted from Study Report JHU Study 2015 Expt 2a, Table 2

Study JHU2014Experiment 2f-a: This study used the same experimental design as study JHU2015Expt 2a; however, only 2 drug combinations (BPa, PaL, and BL) were compared to the 3 drug (BPaL) regimen. The lung CFU were determined at 4 and 8 weeks of treatment with 2 drug

combinations (BPa, PaL, BL) and the BPaL regimen. The BPa, PaL, and BL combinations were less active than the BPaL regimen (p<0.0001) (Table 8-4).

Table 8-4. Lung colony-forming unit counts following treatment of MTB-infected mice with combinations of pretomanid, bedaquiline, and linezolid.

Regimen	Mean (± SD) Lung Log_{10} CFU Count by Time Point	
	Week 4	Week 8
Untreated controls	9.04±0.03	
RHZ		3.09±0.16
BPaL	3.48±0.11	0.85±0.80
BPa	5.00±0.08	3.50±0.05
PaL	5.93±0.09	4.21±0.14
BL	5.38±0.13	3.28±0.24

B = bedaquiline; CFU = colony-forming unit; H = isoniazid; L = linezolid; Pa = pretomanid; R = rifampicin; Z = pyrazinamide

Untreated mean lung log_{10} CFU counts Day -13: 4.94±0.04; Day 0 untreated mean lung log_{10} CFU counts: 8.08±0.04.

Day -13, CFU count in lungs 1 day post-infection; Day 0, CFU counts in lungs on first day of therapy. At 4 and 8 weeks, BPaL was significantly more active than BL (p<0.0001). BPa and PaL were significantly less active than BPaL at weeks 4 and 8 (p<0.0001).

Source: Adapted from JHU 2014 Experiment 2f Study Report A Table 2.

Tasneen 2016[28]: The study assessed the contribution of linezolid to regimens containing bedaquiline and pretomanid. The study design was similar to the previous studies (JHU Study 2015 Expt 2a and JHU 2014 Experiment 2f-a). The standard regimen of RHZ reduced the mean lung CFU count by 2.70 log_{10} and by 4.58 log_{10} after 1 and 2 months of treatment, respectively. Linezolid improved the activity of BPa regimen (P<0.01) and the activity of the BPaL regimen was superior to standard regimen at 2 and 3 months of treatment (p<0.001) (Table 8-5). The activity of the 3 drug BPaL combination was superior to the 2-drug combinations (BPa, BL, and PaL) at 2 months (p<0.01), confirming that each component drug contributes to the efficacy of the 3-drug combination.

[28] Tasneen R, Betoudji F, Tyagi S, Li SY, Williams K, Converse PJ, et al. Contribution of Oxazolidinones to the Efficacy of Novel Regimens Containing Bedaquiline and Pretomanid in a Mouse Model of Tuberculosis. Antimicrob Agents Chemother. 2016 Jan; 60(1): 270-7.

Table 8-5. Lung colony-forming unit counts assessed during treatment and relapse rates assessed after treatment of murine tuberculosis with regimens including pretomanid, bedaquiline, and linezolid.

Regimen	Mean (±SD) Lung Log_{10} CFU Count at:			Proportion (%) Relapsing after Treatment for:		
	Month 1	Month 2	Month 3	2 Months	3 Months	4 Months
Untreated	6.47± 0.06	*	*	-	--	
2 months RHZ/ 4 months RH	3.47± 0.37	1.59± 0.25	0.50± 0.51	-	13/15 (87)	1/20 (5)
B	3.24± 0.25					
Pa	4.57± 0.22					
L	4.97± 0.26					
Su	3.85± 0.37					
BPa	4.21± 0.40	1.62± 0.19	0.52± 0.36	15/15 (100)	10/15 (60)	2/20 (10)
BL	2.82± 0.15	1.91± 0.66				
BSu	2.88± 0.07	0.65± 0.50				
PaL	3.23 ± 0.41	1.48± 0.12				
PaSu	1.65± 0.33	0.23± 0.40				
BPaL	3.28 ± 0.65	0.34± 0.41	0.00± 0.00	12/15 (80)	0/14 (0)	0/20 (0)
BPaSu	0.94± 0.14	0.00± 0.00	-	14/20 (70)	1/14 (7)	

B = bedaquiline; CFU = colony-forming unit; H = isoniazid; L = linezolid; Pa = pretomanid; R = rifampicin; Su = sutezolid; Z = pyrazinamide

Untreated mean lung log_{10} CFU counts Day -13: 2.69±0.13; Day 0 untreated mean lung log_{10} CFU counts: 6.17±0.27.

* no mice remained in the untreated control group at the 2- and 3-month time points; Day -13, CFU count in lungs 1 day post-infection; Day 0, CFU counts in lungs on first day of therapy.

Source: Adapted from (Tasneen et al., 2016)

Study JHU 2016 Experiment 3a: This study compared the activity of BL combination to the BPaL regimen and standard RHZ treatment regimen using the same experimental design as previous studies (JHU Study 2015 Expt 2a and JHU 2014 Experiment 2f-a). The addition of Pa to BL improved the activity and reduced the CFU at month 2 by 2.7log_{10} (Table 8-6).

Table 8-6. Lung colony-forming unit counts and relapse rates after treatment with regimens including bedaquiline, pretomanid, linezolid.

Regimen	Time Point				
	Mean Lung Log_{10} CFU Counts (± SD)		Proportion of Mice Relapsing / Mice Held for Assessment		
	Month 1	Month 2	Month 2 (+3)	Month 3 (+3)	Month 4 (+3)
RHZ	5.12±0.14	2.55±0.07	-	-	7/15
BPaL	3.10±0.17	0.00±0.00	4/15	1/15	
BL	4.28±0.10	2.75±0.52			

B = bedaquiline; CFU = colony-forming units; H = isoniazid; L = linezolid; Pa = pretomanid; R = rifampicin; Z = pyrazinamide.
Untreated mean lung log_{10} CFU counts Week -2: 3.94±0.15; Day 0 untreated mean lung log_{10} CFU counts: 7.30±0.10. BPaL was significantly more bactericidal than BL at M1 (p=0.0005) and M2 (p=0.002).
No mice remained in the untreated control group at the 1- and 2-month time points; Week -2, CFU count in lungs 1 day post-infection; Day 0, CFU counts in lungs on first day of therapy.
Source: adapted from Study Report JHU 2016 Experiment 3a Table 2

Study TBI-223-NCLN-041: In this study, the contribution of linezolid to the 3 drug BPaL regimen was assessed. The study design was same as in previous studies assessing the combination regimen. At 4 weeks and 8 weeks of treatment, the BPaL regimen was significantly more active than the BPa regimen (p <0.0001) (Table 8-7).

Table 8-7. Evaluation of bactericidal and sterilizing efficacy of combinations of bedaquiline, pretomanid with linezolid or TBI-223, in a mouse model of tuberculosis.

Regimen	Mean Lung Log_{10} CFU (±SD)		Proportion of mice relapsing after end of treatment at:	
	4 weeks	8 weeks	8 weeks	12 weeks
BPa	5.97±0.34	2.96±0.42		14/15
BPaL	4.48±0.41	1.00±0.90	14/15	7/15
BPAO	4.92±0.40	1.62±0.54	15/15	2/15

B = bedaquiline; CFU = colony-forming unit; L = linezolid; O = TBI-223; Pa = pretomanid; SD = standard deviation.
Untreated mean lung log_{10} CFU counts at Day -15 = 4.66±0.08; Day 0 untreated mean lung log_{10} CFU counts = 8.85±0.15.
Source: Study Report TBI-223-NCLN-041

Study JHU 2017 3d-1 and 3d-2: In this study, the contribution of pretomanid to the 3- drug BPaL regimen was assessed. Comparison of mean CFU counts in groups treated with BPaL and BL regimens showed that the bactericidal activity of BPaL regimen was significantly greater than that of BL regimen at 1 and 2 months, p<0.0001 and p=0.0006, respectively (Table 8-8). Selection of bedaquiline-resistant mutants was assessed at various time points (3 months after 2, 3 and 4 months of treatment) by plating one quarter of the undiluted lung homogenate on 7H11 plates containing 0.125 mcg/ml of bedaquiline. In the infected mice, bedaquiline-resistant colonies were detected (i.e., ≥ 1% of the total CFU isolated) among 8, 5 and 5 mice treated with

the 2 drug JL regimen for 2, 3 and 4 months, respectively, but in none of the mice treated with the 3 drug JPaL regimen, indicating that addition of Pa prevented the selection of bedaquiline resistant mutants.

Table 8-8. Lung colony-forming unit counts and proportions of mice relapsing following treatment of murine tuberculosis with regimens including bedaquiline, pretomanid, and linezolid.

Regimen	Mean lung $\log_{10}$ CFU count (±SD)				Proportion of mice relapsing				
	Week -2	Day 0	Month 1	Month 2	Month 1 (+3)	Month 1.5 (+3)	Month 2 (+3)	Month 3 (+3)	Month 4 (+3)
Untreated	4.06 ±0.05	7.90 ±0.16							
BL			4.87 ±0.16	2.69 ±0.30			15/15	15/15	14/15
BPaL			3.29 ±0.09	0.68 ±0.24			7/15	0/15	0/15
BMZ			1.29 ±0.19		15/15	6/15	1/15		
BPaMZ			1.05 ±0.18		14/15	0/15	0/15		

B = bedaquiline; CFU = colony-forming unit; L = linezolid; M = moxifloxacin; Pa = pretomanid; SD = standard deviation; Z = pyrazinamide
Source: Adapted from Study Report JHU Study 2017 3d-1 and 3d-2 Table 3

Reviewer comment: Relapse is observed, and resistance develops with pretomanid monotherapy. The activity of the BPaL combination regimen was greater than the activity of each drug alone or the 2-drug combination in the murine pulmonary TB models. The reduction in CFU in the lungs with the 3 drug (BPaL) regimen was significantly greater than the 2 drug regimens of BPa, BL or BPa in 3 studies that tested all combinations (p<0.02; p, 0.0001; p<0.01). Some 2 drugs combinations (BPa versus BPaL and BL versus BPal) were tested in additional studies which also demonstrated the significantly improved activity of the 3-drug combination over the 2-drug combination (p<0.0001). The reduction in resistance development was demonstrated with the BPaL regimen compared to the BL regimen.

Relapse/Sterilizing Activity:

Relapse was assessed in 3 studies (Tasneen 2016, TBI-223=NCLN-041 and JHU 2017 3d1-3d2) by holding the MTB infected mice for an additional 3 months following completion of 1 to 4 months of treatment for assessing relapse or the ability of the treatment to sterilize mice. Fewer mice treated with the BPaL combination regimen relapsed compared to two drug regimens (BPa, BL). In the two studies, none of the mice treated with the BPaL regimen for 3 and 4 months relapsed compared to 10-60% relapse in BPa treated mice or 100% relapse in BL treated mice (p <0.01). In one study 7/15 mice relapsed with the BPaL regimen compared to 14/15 mice treated with BPa (p<0.02) (Table 8-5,Table 8-7,Table 8-8).

Additional supportive data for BPa combination using two different murine models:
Supportive data for the bedaquiline plus pretomanid (BPa) combination were obtained in the studies using BALB/c mice (Li et al 2017) [29] and the mouse latent TB models (Laonix et al 2014)[30]. The BALB/c mice were infected by aerosol challenge with 3.5 to 4.0 $\log_{10}$ CFU of MTB H37Rv, and oral treatment was initiated once daily (5 days/week) 14 days post-infection and continued for up to 4 months. Mice were treated with standard RHZ therapy (same dose as previous studies), bedaquiline (B) 25 mg/kg, pretomanid (Pa) 50 or 100 mg/kg, and/or moxifloxacin (M) 100 mg/kg. At the 2- and 3-month time points, the BPa group showed activity similar to the RHZ group (Table 8-9). However, only 1 in 15 mice relapsed in the BPa group compared to the RHZ group 3 months after completion of 4 months of treatment.

Table 8-9. Lung colony-forming unit counts assessed during treatment and proportions of mice relapsing after treatment with bedaquiline and pretomanid-containing regimens, compared.

Drug regimen	$\log_{10}$ CFU count (mean ±SD)			Number relapsing/total number (%)				
	Month 1	Month 2	Month 3	Month 1	Month 1.5	Month 2	Month 3	Month 4
RHZ	4.93±0.22	2.97±0.07	1.05±0.28					5/15 (33)
BPa	5.33±0.26	2.78±0.10	1.39±0.45					1/15 (7)
BPaMZ	1.96±0.25			15/15 (100)	4/17 (24)	0/15 (0)		
BPaZ	2.52±0.19				12/15 (80)	2/15 (13)		
BPaM	4.62±0.27	1.17±0.20	0.16±0.22			15/15 (100)	1/15 (7)	0/15 (0)

B= bedaquiline; CFU = colony-forming unit; H = isoniazid; M = moxifloxacin; Pa = pretomanid; R = rifampicin; SD = standard deviation; Z = pyrazinamide;
Untreated mean lung $\log_{10}$ CFU counts at day 0 = 8.09±0.24.
Source: adapted from (Li et al., 2017)

In the latent MTB infection model, BALB/c and C3HeB/FeJ mice immunized with rBCG30 and then challenged with a low-dose aerosol of MTB H37Rv (Laonix et al 2014)[31]. Pretomanid (50 mg/kg, 5 days/week) had activity comparable to that of INH (10 mg/kg, 5 days/week) at end of treatment (week 8). Pretomanid in combination with bedaquiline (TMC, 25 mg/kg, 5 days a week) was more effective than pretomanid alone (Table 8-10 and Table 8-11).

[29] Li SY, Tasneen R, Tyagi S, Soni H, Converse PJ, Mdluli K, et al. Bactericidal and Sterilizing Activity of a Novel Regimen with Bedaquiline, Pretomanid, Moxifloxacin, and Pyrazinamide in a Murine Model of Tuberculosis. Antimicrob Agents Chemother.2017 Sep; 61(9).
[30] Lanoix JP, Betoudji F, Nuermberger E. Novel regimens identified in mice for treatment of latent tuberculosis infection in contacts of patients with multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2014; 58(4): 2316-21.
[31] Lanoix JP, Betoudji F, Nuermberger E. Novel regimens identified in mice for treatment of latent tuberculosis infection in contacts of patients with multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2014; 58(4): 2316-21.

Reference ID: 4476823

Table 8-10. Lung CFU counts of BALB/c mice.

Regimen or parameter	Strain, mean lung CFU count[a] (log_{10}/lung) ± SD (no. of mice) at:				
	Wk −12	Wk −6	Day 0	Wk 4	Wk 8
Untreated	rBCG30, 2.51 ± 0.13 (4)	rBCG30, 4.87 ± 0.24; H37Rv, 1.04 ± 0.23 (4)	rBCG30, 3.18 ± 0.55; H37Rv, 4.23 ± 0.05 (4)	rBCG30, 3.32 ± 0.43; H37Rv, 3.89 ± 0.69 (4)	rBCG30, 3.47 ± 0.49; H37Rv, 4.30 ± 0.31 (4)
INH				2.62 ± 0.76 (4)	2.49 ± 0.27 (4)
RIF				3.33 ± 0.22 (4)	1.04 ± 0.36 (4)
LFX				4.01 ± 0.28 (4)	3.11 ± 0.31 (4)
MFX				3.60 ± 0.47 (2)	3.18 ± 0.16 (4)
TMC				1.87 ± 0.41 (4)	0.89 ± 0.26 (4)
Pa				3.45 ± 0.36 (4)	2.56 ± 0.28 (4)
PNU				3.33 ± 0.22 (4)	2.59 ± 0.52 (4)
TMC-LFX				2.02 ± 0.21 (4)	0.91 ± 0.37 (4)
TMC-Pa				2.37 ± 0.25 (4)	1.28 ± 0.14 (4)
TMC-PNU				2.36 ± 0.19 (4)	0.80 ± 0.19 (4)
Pa-LFX				3.33 ± 0.20 (4)	1.88 ± 0.41 (4)
Pa-PNU				2.31 ± 0.65 (4)	1.08 ± 0.39 (4)
PNU-LFX				3.72 ± 0.28 (4)	2.58 ± 0.09 (4)
TMC-Pa-PNU				1.01 ± 0.33 (4)	0.00 ± 0.00 (4)
Total	4	4	4	58	60

[a] Week −12 corresponds to the day of aerosol immunization, week −6 corresponds to the day of *M. tuberculosis* challenge, and day 0 corresponds to the start of treatment. The no. of mice is the number initially allocated to each treatment arm; *n* is the number of mice contributing to the mean CFU counts (if *n* is not provided, *n* = the no. of mice initially allocated). CFU counts of rBCG30 were determined from hygromycin-containing plates, and CFU counts of H37Rv were determined from TCH-containing plates. All CFU counts are taken from TCH-containing plates unless otherwise indicated.

Bedaquiline (TMC); pretomanid or PA-824 (Pa); sutezolid (PNU): rifampin (RIF): isoniazid (INH).
Source: Lanoix et al., 2014

Table 8-11. Lung CFU counts of C3HeB/FeJ mice.

Regimen or parameter	Strain, mean lung CFU count[a] (log_{10}/lung) ± SD (no. of mice) at:				
	Wk −12	Wk −6	Day 0	Wk 4	Wk 8
Untreated	rBCG30, 2.56 ± 0.02 (4, *n* = 3)[b]	rBCG30, 5.04 ± 0.19; H37Rv, 0.76 ± 0.16 (4)	rBCG30, 3.88 ± 0.25; H37Rv, 4.32 ± 0.41 (4, *n* = 2)[c]	rBCG30, 2.51 ± 1.42; H37Rv, 4.58 ± 0.57 (5)	rBCG30, 2.62 ± 0.4; H37Rv, 3.78 ± 0.73 (5)
INH				3.53 ± 0.34 (6)	2.87 ± 0.42 (6)
RIF				2.59 ± 0.47 (6)	0.85 ± 0.56 (6)
LFX				3.60 ± 0.66 (6)	3.93 ± 0.50 (6, *n* = 5)[d]
TMC				1.87 ± 0.21 (6)	0.48 ± 0.20 (6)
Pa				3.51 ± 0.65 (6)	2.76 ± 0.32 (6)
PNU				3.47 ± 0.40 (6)	2.60 ± 0.43 (6)
TMC-LFX				1.86 ± 0.36 (6)	0.18 ± 0.28 (6)
TMC-Pa				2.16 ± 0.74 (6)	0.29 ± 0.36 (6)
TMC-PNU				2.09 ± 0.33 (6)	0.72 ± 0.17 (6)
Total	3	4	3	59	58

[a] Week −12 corresponds to the day of aerosol immunization, week −6 corresponds to the day of *M. tuberculosis* challenge, and day 0 corresponds to the start of treatment. The no. of mice is the number initially allocated to each treatment arm; *n* is the number of mice contributing to the mean CFU counts (if *n* is not provided, *n* = the no. of mice initially allocated). CFU counts of rBCG30 were determined from hygromycin-containing plates, and CFU counts of H37Rv were determined from TCH-containing plates. All CFU counts are taken from TCH-containing plates unless otherwise indicated.
[b] One mouse died during the infection procedure.
[c] One mouse died because of cage flooding, and one mouse had no colonies isolated on TCH-containing plates.
[d] The lung homogenate sample was lost when a glass homogenizer broke during the homogenization procedure.

Bedaquiline (TMC); pretomanid or PA-824 (Pa); sutezolid (PNU): rifampin (RIF): isoniazid (INH).
Source: Lanoix et al., 2014

To assess the activity of combinations against resistant strains, BALB/c mice were infected via aerosol with MTB H37Rv pretomanid-resistant mutant (ddn mutation; MIC>16 mcg/mL) (JHU 2017 Expt 3d-1 and 3d-2). Mice were infected with 4.23 log_{10} CFU (high inoculum) and treatment initiated two weeks post-infection with pretomanid alone, or with regimens consisting of bedaquiline (B, 25 mg/kg), pretomanid (Pa, 50 or 100 mg/kg), linezolid (L, 100 mg/kg), moxifloxacin (M, 100 mg/kg), or pyrazinamide (Z, 150 mg/kg) for 4, 8, or 12 weeks. Pretomanid as monotherapy was ineffective in reducing bacterial burden in the lungs at 4

weeks compared to untreated controls. All mice receiving BL or BPaL regimens relapsed at 3 months, suggesting that the combination would be ineffective if resistance to pretomanid develops (Table 8-12).

Table 8-12. Lung colony forming unit counts and proportion of mice relapsing after treatment of a pretomanid-resistant MTB Infection.

Regimen	Mean Lung Log_{10} CFU Count (±SD)		Proportion of Mice Relapsing at:		
	4 weeks	8 weeks	Month 1 (+3)*	Month 2 (+3)*	Month 3 (+3)*
$Pa_{(50)}$	7.34±0.12				
$Pa_{(100)}$	7.26±0.07				
BL	4.54±0.17	2.97±0.28			15/15
$BPa_{(50)}L$	4.68±0.41	3.05±0.28			15/15
$BPa_{(100)}L$	5.31±0.35	3.33±0.09			15/15
BMZ	2.36±0.63	0±0	15/15	2/15	
$BPa_{(50)}MZ$	2.49±0.24	0.08±0.19	15/15	1/15	
$BPa_{(100)}MZ$	2.73±0.46	0±0	15/15	1/15	

B = bedaquiline; CFU = colony forming unit; L = linezolid; M = moxifloxacin; Pa = pretomanid; SD = standard deviation; Z = pyrazinamide. Subscript numbers represent drug doses in mg/kg.
Untreated mean lung log_{10} CFU counts at day -14 = 4.23±0.07; day 0 untreated mean lung log_{10} CFU counts = 7.61±0.19.
*(+3) indicates mice held for an additional 3 months beyond the completion of treatment (e.g., Month 2 (+3) indicates mice were treated for 2 months before being held without treatment for an additional 3 months prior to sacrifice).
Source: JHU 2017 Expt 3d-1 and 3d-2 Study Report Table 4.

Reviewer comment: Relapse is observed, and resistance develops with pretomanid monotherapy. Significantly fewer mice treated with the 3-drug combination (BPaL) for 3 or 4 months relapsed compared to 2-drug combination (BPa, BL) (p<0.01).

8.2. Clinical Microbiology

8.2.1. Assay Descriptions and Methodologies

Microbiological methods in the phase 2 EBA studies:

The diagnosis of pulmonary TB was confirmed by the presence of acid-fast bacilli in the sputum smear using the WHO scale. Rapid tests such as the Cepheid GeneXpert MTB/RIF, or line probe assays (Hain GenoType MTBDR*plus,* GenoType MTBDR*sl*) were used for the detection of resistance to rifampicin, isoniazid, or fluoroquinolones and for identification of MTBC bacteria. Cultures of screening samples were also subjected to rapid tests (non-commercial PCR based test or Becton Dickinson TBc ID, a commercial immunochromatographic assay that detected MPT64 antigen) for identification/ speciation. Pooled overnight sputum samples collected at specified timepoints during the trial were digested and used (1) to inoculate Middlebrook 7H11S medium for quantitative sputum culture (CFU counts per mL of sputum, mean of 4 counts), and (2) to decontaminate and culture in the MGIT system to determine time-to-positivity (TTP; in hours).

The determinations of MIC for the drugs in the phase 2 studies were conducted in the central laboratory ((b) (4)). This laboratory did not validate the MIC methodologies prior to testing the trial isolates and no QC data was collected. Therefore, there is no assurance that the pretomanid MIC values from these studies are valid.

Microbiological methods in the Nix-TB trial:
At screening, a single coached spot sputum was analyzed by smear microscopy for acid-fast bacilli, presence of MTB by culture and Gene Xpert, Hain Assay MTBDRplus or an alternative molecular or antigen-based test to confirm MTB. The MGIT System was used to monitor clearance of MTB in sputum samples from subjects during therapy and to obtain key efficacy endpoints including the incidence of bacteriological failure/relapse, time to culture conversion to negative status, and the rate of change of TTP over time. Speciation of the infecting organism by molecular or antigen-based test to confirm MTB at baseline and at or after 16 weeks of treatment was done at the trial local laboratory. At the central laboratory, the susceptibility testing of MTB isolates at baseline and initial relapse (first positive at EOT or during follow-up) was performed in MGIT liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, and second-line TB drugs including fluoroquinolones and injectables using the critical concentrations recommended by the manufacturer. DNA sequencing analysis of *pncA* gene was performed for the detection of pyrazinamide resistance. The central laboratory also performed susceptibility testing of these isolates to bedaquiline, pretomanid, and linezolid using the validated MGIT method to determine the MIC.

8.2.2. Clinical Microbiology Analyses of Efficacy (micro-ITT population)

The support for the efficacy of pretomanid for the treatment of subjects with XDR-TB and TI/NR MDR-TB as part of a combination regimen with bedaquiline and linezolid is based on data from the ongoing, phase 3 Nix-TB trial. Supportive data come from two phase 2a studies (CL-007 and CL-010) that demonstrates the early bactericidal activity (EBA) of pretomanid as a stand-alone agent in subjects with pulmonary TB. EBA studies measure the fall in CFU or the time to detection in liquid culture. The EBA studies provide support for efficacy but do not reliably predict sterilizing activity. An interim efficacy analysis of patients who completed 6 months of follow-up after end of therapy in the Nix-TB study with database cutoff date of January 18, 2019 was included in the NDA submission.

Phase 2 EBA Studies:
CL-007: The primary objective of this study was to evaluate the EBA of pretomanid administered orally as 200, 600, 1000 or 1200 mg per day for 14 consecutive days, in adults with newly diagnosed, uncomplicated, smear-positive, DS pulmonary TB. Patients (n = 8) who received oral Rifafour®e-275 (standard first-line TB treatment as per the South African TB guidelines) served as controls. The following parameters were calculated: (i) EBACFU: the rate of change of $\log_{10}$CFU in sputum over time, characterized by linear or non-linear regression of $\log_{10}$CFU over time, (ii) EBATTP: the rate of change in TTP (or $\log_{10}$TTP) in the MGIT system during treatment over time.

Reference ID: 4476823

The first-line drug susceptibility testing with the MGIT system revealed that MTB isolates obtained in sputum collections at Day 2 and Day 14 were sensitive to streptomycin, isoniazid, rifampicin and ethambutol, except 2 isolates to streptomycin and 3 isolates to isoniazid. The pretomanid MICs were < 0.1 mcg/mL for 59 of 60 patients for whom data were available.

The mean $\log_{10}$CFU and the change in mean $\log_{10}$CFU over time is shown in Table 8-13 and Figure 8-4, respectively.

Table 8-13. Mean $\log_{10}$ CFU for all treatment groups in study CL-007.

Day	PA-824 200 mg	PA-824 600 mg	PA-824 1000 mg	PA-824 1200 mg	Rifafour® e-275
-2	6.053	6.209	5.905	6.192	5.783
-1	6.592	6.335	6.309	6.057	6.152
1	6.46	6.365	6.077	6.491	5.647
2	6.104	6.179	6.107	6.195	5.161
3	5.924	5.783	5.918	5.955	5.079
4	5.982	5.931	5.772	5.669	4.674
6	5.592	5.44	5.566	5.303	4.783
8	5.415	5.348	5.399	4.919	3.934
10	5.181	5.163	5.306	4.832	4.538
12	4.925	4.854	4.843	4.938	4.398
14	4.861	4.772	4.894	4.846	4.104

Data Source: Section 14.1, Table 25 and Appendix 16.2.1, Listing 36

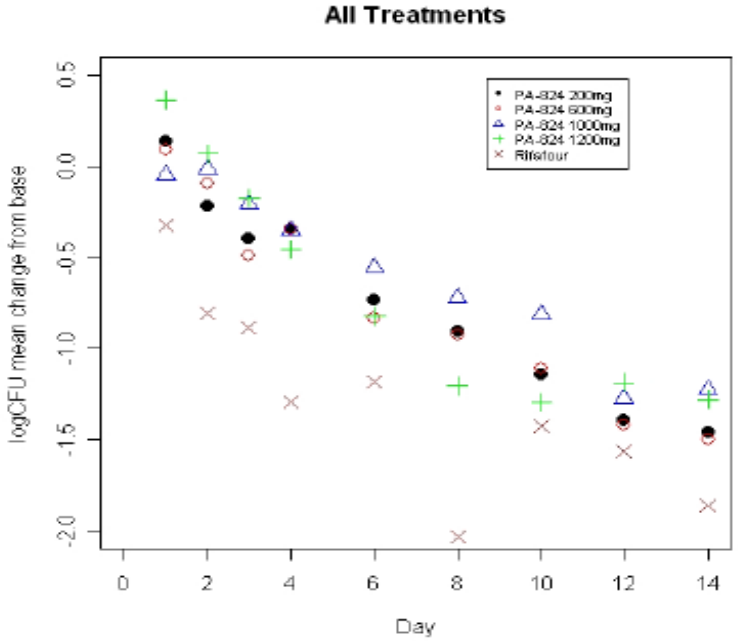


Figure 8-4. Mean $\log_{10}$CFU change from baseline vs. Day: All Treatments.

Reviewer comment: The change in log_{10}CFU at day 14 from baseline values was similar for the pretomanid 200 mg arm and standard HRZE therapy. No significant increase in activity is observed with higher doses of pretomanid.

The rate of change of log_{10}CFU in sputum over time and the rate of change in TTP over time are shown in Table 8-14, and Table 8-15, respectively.

Table 8-14. EBA_{CFU} by study arm and time period in study CL-007.

Dosage	Pretomanid group										Standard treatment group[b]	
	200 mg		600 mg		1000 mg		1200 mg		All groups			
	Mean log_{10} CFU/mL (±SD)	*n*	Mean log_{10} CFU/mL (±SD)	*n*	Mean log_{10} CFU/mL (±SD)	*n*	Mean log_{10} CFU/mL (±SD)	*n*	Mean log_{10} CFU/mL (±SD)	*n*	Mean log_{10} CFU/mL (±SD)	*n*
EBA(0–14)	0.106 (0.049)	12	0.107 (0.053)	14	0.091 (0.083)	15	0.088 (0.084)	11	0.098 (0.072)	52	0.148 (0.055)	7
EBA(0–2)	0.109 (0.487)	15	0.096 (0.226)	13	0.025 (0.340)	15	-0.035 (0.420)	15	0.047 (0.373)	58	0.403 (0.290)	8
EBA(2–14)	0.106 (0.063)	12	0.113 (0.079)	13	0.095 (0.062)	14	0.113 (0.099)	11	0.106 (0.077)	49	0.112 (0.050)	7

Abbreviations: CFU = colony-forming unit; EBA = early bactericidal activity; SD = standard deviation
Source: CL-007 CSR Tables 11.10, 11.14, and 11.16

Table 8-15. EBA_{TTP} by study arm and time period in study CL0007.

Time period (days)	Pretomanid group										Standard treatment group[b]	
	200 mg		600 mg		1000 mg		1200 mg		All groups			
	Mean hr/day (±SD)	*n*	Mean hr/day (±SD)	*n*	Mean hr/day (±SD)	*n*	Mean hr/day (±SD)	*n*	Mean hr/day (±SD)	*n*	Mean hr/day (±SD)	*n*
0–14	3.818 (2.327)	12	4.776 (2.879)	14	4.865 (3.461)	13	4.440 (2.169)	12	4.494 (2.724)	51	9.741 (5.249)	8
0–2	1.115 (15.256)	13	5.788 (12.173)	13	2.795 (9.230)	11	1.400 (7.659)	15	2.721 (11.225)	52	24.125 (12.794)	8
2–14	3.833 (2.954)	11	5.09 (2.768)	13	4.069 (1.916)	12	4.868 (3.224)	12	4.491 (2.718)	48	7.344 (4.660)	8

Abbreviations: EBA = early bactericidal activity; SD = standard deviation; TTP = time to culture positivity
Source: CL-007 CSR Tables 11.21, 11.23, and 11.25

Reviewer comment: The rate of change of log_{10}CFU and rate of change of time to positivity for pretomanid 200 mg monotherapy over time was inferior to standard HRZE therapy.

CL-010: The objective of this study was to determine the EBA of 50 mg, 100 mg, 150 mg and 200 mg once daily doses of pretomanid administered orally for 14 consecutive days, in adult patients with newly diagnosed, uncomplicated, smear-positive, pulmonary tuberculosis. The study design and endpoints were same as CL-007. The study results are shown in Table 8-16.

Table 8-16. EBA_{CFU} and EBA_{TTP} by study arm and time period.

Method	Time Period (days)	Mean (SD) Pretomanid n	50 mg	n	100 mg	n	150 mg	n	200 mg	HRZE n	Activity
EBA_{CFU}	0-14	12	0.063 (0.058)	15	0.091 (0.073)	14	0.078 (0.074)	14	0.112 (0.070)	8	0.177 (0.042)
	0-2	14	0.093 (0.211)	15	0.111 (0.332)	15	-0.009 (0.290)	14	0.160 (0.255)	8	0.470 (0.316)
	2-14	12	0.059 (0.060)	15	0.088 (0.085)	14	0.096 (0.098)	14	0.104 (0.083)	8	0.128 (0.070)
EBA_{TTP}	0-14	13	2.621 (2.534)	14	4.969 (3.644)	15	4.633 (3.687)	16	4.640 (3.447)	8	13.364 (3.979)
	0-2	15	1.483 (8.153)	14	-1.345 (8.586)	15	4.867 (12.755)	13	3.096 (8.202)	8	37.016 (5.639)
	2-14	13	2.958 (2.652)	15	5.744 (3.973)	15	4.594 (5.035)	13	5.391 (3.608)	8	9.422 (4.367)

Abbreviations: CFU = colony-forming unit; EBA = early bactericidal activity; EBA_{CFU} = absolute value of the average daily rate of change of log_{10}(CFU) over the indicated time period; EBA_{TTP} = average daily rate of change in TTP over the indicated time period. HRZE = isoniazid, rifampicin, pyrazinamide, ethambutol; SD = standard deviation; TTP = time to culture positivity

Note that EBA (days 0 to 14) can deviate from the arithmetic sum of EBA (days 0 to 2) and EBA (days 2 to 14) due to missing data points.

Source: CL-010 CSR Tables 11.16, 11.17, 11.18, and 11.19

Reviewer comment: Pretomanid 50 mg per day administered over 14 days may have less EBA and increase in TTP than the higher doses. The EBAs and change in TTP seen with the 200 mg per day pretomanid and the Rifafour®e-275 groups in this study were similar to those observed in study CL-007. The studies support antimycobacterial activity of pretomanid.

NC-001: The objective of this EBA study was to identify multidrug combination therapies containing pretomanid for clinical development. In this study, six parallel treatment groups were studied. Of the six treatment groups, one included a bedaquiline only arm and one included bedaquiline in combination with pretomanid (200 mg) for 14 days. The rate of change of log_{10}CFU and rate of change of TTP over time was slightly better in the arm treated with bedaquiline and pretomanid compared to bedaquiline alone (Table 8-17).

Table 8-17. $EBA_{CFU(0-14)}$ and $EBA_{TTP(0-14)}$ by study arm.

Study Arm	n	Mean (SD) EBA_{CFU}(0-14)	Mean (SD) EBA_{TTP}(0-14)
PaMZ	13	0.23 (0.128)	18.5 (22.58)
PaZ	14	0.15 (0.040)	8.8 (3.47)
BPa	15[a]	0.11 (0.050)	5.9 (2.79)
B	14	0.07 (0.068)	5.4 (3.52)
BZ	15	0.13 (0.102)	10.0 (6.99)
HRZE	10	0.14 (0.094)	11.8 (3.93)

Abbreviations: CFU = colony-forming unit; EBA_{CFU}(0-14) = absolute value of the average daily rate of change of log_{10}(CFU) over Days 0 to 14 based on the bi-linear regression over this period; EBA_{TTP}(0-14) = average daily rate of change in TTP over Days 0 to 14 based on the bi-linear regression over this period; HRZE = combination of isoniazid, rifampin, pyrazinamide, and ethambutol; SD = standard deviation; TTP = time to sputum culture positivity, in hours.

[a] n=14 for EBA_{CFU}(0-14).

Source: NC-001 CSR Table 11.20 and Table 11.21

B = bedaquiline, M = moxifloxacin, Pa = pretomanid

Review comment: The treatment arms did not include a pretomanid only arm. However, the combination of bedaquiline and pretomanid was not antagonistic based on the EBA studies NC-

001, CL-007 and CL0010. No EBA studies were conducted using the BPaL regimen. Hence, the CL0010 study was not useful in assessing the contribution of the individual drugs in the BPaL regimen.

Nix-TB (BPaL): For a description of the clinical study, please see Clinical Efficacy section 7.2.1. Microbiological assessments performed using the MITT population is described here. The subjects with unfavorable response or who were inaccessible are shown in Table 8-18.

Table 8-18. Inaccessible and unfavorable patients at the primary endpoint.

Patient ID	TB type	ITT	MITT	PP	reason	treatment or follow-up
Nix-TB (b) (6)	XDR	unfavourable	unfavourable	unfavourable	confirmed relapse	follow-up
Nix-TB	XDR	*favourable*	*favourable*	**unassessable**	missed >35 consecutive doses	treatment
Nix-TB	XDR	unfavourable	unfavourable	**unassessable**	withdrawal not for treatment failure	treatment
Nix-TB	TI/NR MDR	unfavourable	**unassessable**	**unassessable**	month 6 cultures contaminated	follow-up
Nix-TB	XDR	unfavourable	unfavourable	unfavourable	death, not violent or accidental	treatment
Nix-TB	XDR	unfavourable	unfavourable	unfavourable	death, not violent or accidental	treatment
Nix-TB	XDR	unfavourable	unfavourable	unfavourable	death, not violent or accidental	treatment
Nix-TB	XDR	unfavourable	unfavourable	unfavourable	death, not violent or accidental	treatment
Nix-TB	TI/NR MDR	unfavourable	unfavourable	unfavourable	relapse (not WGS confirmed)	follow-up
Nix-TB	XDR	unfavourable	**unassessable**	**unassessable**	death, not TB related	follow-up
Nix-TB	TI/NR MDR	unfavourable	unfavourable	unfavourable	death, not violent or accidental	treatment
Nix-TB	XDR	unfavourable	unfavourable	unfavourable	death, not violent or accidental	treatment
Nix-TB	TI/NR MDR	unfavourable	**unassessable**	**unassessable**	lost to follow-up	follow-up

Source: Nix-TB study report; XDR = Extensively drug-resistant; MDR = Multidrug-resistant; TI = Treatment-intolerant; NR = non-responsive

Sensitivity analysis was performed on subjects in the MITT population excluding those who were culture negative during the baseline period from screening to week 4 but had documented MTB by culture or molecular test within 3 months prior to screening (Table 8-19).

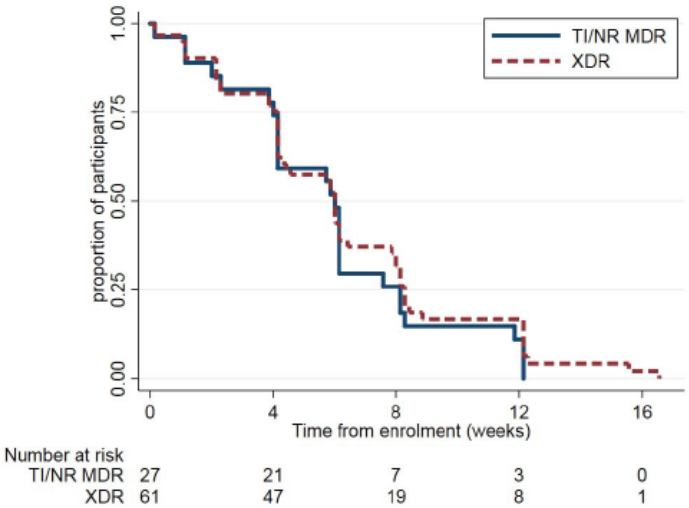
Table 8-19. Primary efficacy analysis excluding patients who were culture negative during baseline period (MITT analysis population).

	All n/N (%)	XDR(n/N)	TI/NR MDR (n/N)
Patients culture negative during baseline period	16/104(15.4%)	9/70 (12.8%)	7/34 (20.5%)
Favorable response	79/88 (90%)	54/61 (89%)	25/27 (93%)
Unfavorable response	9/88 (10%)	7/61 (11%)	2/27 (7%)
Death	6/88 (7%)	5/61 (8%)	1/27 (4%)
Relapse	2/88(2%)	1/61 (2 %)	1/27 (4%)

MITT = Modified intent-to-treat; XDR = Extensively drug-resistant; MDR = Multidrug-resistant; TI = Treatment-intolerant; NR = non-responsive; n = number of subjects with specific response; N = total number of subjects analyzed. Source: Clinical Microbiology Reviewer

The Kaplan-Meier plots stratified by TB type for XDR and TI/NR MDR patients is shown in Figure 8-5. The median time is the time point on the X-axis where the curve meets 0.5 on the Y-axis

(proportion of patients). The overall median time to culture negative status was 6.0 weeks for subjects with XDR TB or TI/NR MDR. The 1 subject (Patient [redacted] (b) (6)) with a positive culture at Week 16 had her trial drug treatment extended by 3 months as allowed in the protocol. At the time of data cutoff, the patient had not yet been followed for the primary endpoint (6 months after EOT). The proportion of subjects with sputum culture conversion to negative status at 4, 8, 12, and 16 weeks is shown in Table 8-26.



Abbreviations: MDR, Multidrug resistant; MITT, Modified intent to treat, NR, Non-responsive, TI, Treatment intolerant; XDR, extensively drug resistant.
Source: Nix-TB study Report 120-day safety update.

Figure 8-5. Time to culture negative status (MITT analysis population).

Table 8-20. Culture conversion negative status at 4, 6, 8, 12, and 16 weeks for subjects positive at baseline (MITT population).

Subject by baseline TB type	Week 4 n/N (%)	Week 8 n/N (%)	Week 12 n/N (%)	Week 16 n/N (%)
XDR	20/61 (33%)	42/61 (69%)	53/61 (87%)	60/61[a] (98%)
TI/NR MDR	6/27 (22%)	20/27 (74%)	24/27 (89%)	27/27[b] (100%)

N = number of subjects in the analysis population, n = number of subjects who culture converted to negative status. [a]5 subjects with XDR died between week 6 and week 16 visits;
[b]1 subject with TI/NR-MDR died by week 16 visit
Source: Clinical Microbiology Reviewer

Of the 32 patients with data for the 24-month endpoint, 4 died during treatment (Nix-TB-[redacted] (b) (6) Nix-TB[redacted] (b) (6) Nix-TB-0[redacted] (b) (6) and Nix-TB[redacted] (b) (6)), 1 relapsed 3 months after EOT (Nix-TB-[redacted] (b) (6)) and discontinued from therapy (died due to sepsis), 1 relapsed 15 months after EOT (Nix-TB-[redacted] (b) (6)), and 26 remained negative.

The pretomanid MICs for baseline MTB isolates from 57 subjects were included in the submission. The lack of baseline MICs for the remaining 52 subjects were either due to (a) absence of MTB positive culture at baseline (16 subjects) and inability to grow the baseline

Reference ID: 4476823

isolates (36 subjects). The pretomanid MICs for the baseline MTB isolates ranged from 0.062 to 1 mcg/mL using the MGIT system. The pretomanid MIC for post-baseline MTB isolates was provided for 4 subjects (subjects (b) (6)). For subject (b) (6) with XDR TB, the postbaseline isolate (month 3 after EOT) showed an increase in bedaquiline MIC from 0.5 mcg/mL to 4 mcg/mL. No increase in pretomanid and linezolid MIC was observed for this isolate. The MTB isolates at baseline and at relapse (month 15 after EOT) from subject (b) (6) with XDR-TB had the same susceptibility profile (resistant to 13 drugs and sensitive to linezolid and bedaquiline, pretomanid; MIC ≤ 0.5 mcg/mL for all 3 drugs). The subject (b) (6) with MDR-TB who relapsed only had MIC data for the isolate at the time of relapse (month 2 after EOT). No baseline isolate MIC was available for comparison. The MIC for the isolate at relapse revealed resistance to isoniazid, rifampicin, ethambutol, kanamycin, pyrazinamide, streptomycin, and moxifloxacin. The MICs for bedaquiline, pretomanid and linezolid were 0.5, 0.25, and 1.0 mcg/mL, respectively. The response for subject (b) (6) for the primary endpoint was not included; however, the pretomanid MICs for the baseline and post-baseline isolates were 0.25 mcg/mL and 0.06 mcg/mL, respectively. The correlation of baseline pretomanid MIC to outcome at 6 months is shown in Table 8-21. Only limited MIC data for 57 of the 104 subjects were included in the primary efficacy analysis. No conclusions can be made with respect to pretomanid MICs contributing to an unfavorable response.

Table 8-21. Relationship of pretomanid MIC to outcome.

TB type	Baseline Pretomanid MIC	Favorable outcome at 6-month follow-up
MDR	0.06	2/2(100%)
	0.12	7/9 (78%)
	0.25	5/5 (100%)
	0.5	1/1 (100%)
	Not tested	17/19 (89%)
XDR	0.06	5/5 (100%)
	0.12	7/9 (78%)
	0.25	17/19 (89%)
	0.5	3/4 (75%)
	1.0	1/1 (100%)
	Not tested	30/33 (91%)

8.2.3. Interpretive Criteria

The MGIT method along with the EpiCenter software was validated prior to using it for measurement of pretomanid, bedaquiline, and linezolid MIC in the Nix-TB trial (Validation of MGIT Method for MIC Testing Report). The validation was performed on 32 strains: MTB H37Rv, 3 laboratory derived linezolid-resistant strains, 8 laboratory-derived bedaquiline-resistant strains, 12 laboratory-derived pretomanid-resistant strains, 5 MDR-TB clinical isolates from the UCL collection, and 3 strains from an external quality assurance program. Ten independent experiments were performed on different dates by 3 different users. The pretomanid MICs are shown in Table 8-22. (b) (4)

[redacted] (b) (4) All 12 laboratory-derived pretomanid-resistant strains had MIC values >16 mcg/mL. In addition, 4 of 8 bedaquiline-resistant mutants also exhibited MIC values to pretomanid ≥ 1 mcg/mL (isolates 141606, 132485,121325, and 132481); 1 MDR clinical isolate (isolate 11:156) also had pretomanid MIC value of 2 mcg/mL. The QC strain H37Rv gave MIC values of 0.125 (n = 2) and 0.25mcg/ml (n = 5) which are within 1 dilution.

MIC testing for pretomanid was performed at the [redacted] (b) (4). Baseline data for the 45 patients in the first interim analysis were included in study report Pretomanid-NCLN-Micro-003. This study also yielded 21 additional MIC values for strain H37Rv. All these H37Rv repeats had a pretomanid MIC of 0.125 mcg/mL (n = 6) or 0.25 mcg/mL (n = 15).

Table 8-22. Summary of pretomanid MIC during MGIT validation.

Strain	Phenotype	PA-824 MIC range	No. Tests	S/R	LZD MIC range	No. Tests	S/R	BDQ MIC range	No. Tests	S/R
H37Rv	Control	≤0.125-0.25	7	S	0.5-1	8	S	≤0.125-0.5	8	S
CB49	LZD-R	0.25	3	S	≥16	4	R	0.5	4	S
3000.1		0.25	2	S	8	3	R	≤0.125-0.25	2	S
7254.1		≤0.125	1	S	8-32	2	R	1	1	?
141606	BDQ-R	1-2	3	R	0.5	4	S	>8	3	R
132485		0.5-1	3	R	0.5	2	S	2-4	3	R
141618		0.25	3	S	1	2	S	4	3	R
121325		1-2	2	R	1	1	S	8	2	R
121749		0.25	2	S	0.5	1	S	>16	2	R
130853		0.25	2	S	0.5	1	S	≤1-2	2	?
130854		≤0.125	2	S	0.5	1	S	≤1-2	2	?
132481		>16	2	R	1	1	S	8	2	R
5A1	PA824-R	>16	3	R	1	2	S	0.25	2	S
KA_008		>16	3	R	0.5-1	2	S	≤0.125-0.5	2	S
BA_013		>16	2	R	0.5-1	2	S	0.25-0.5	2	S
BA_011A		>16	2	R	1	1	S	0.5	1	S
BA_011B		>16	2	R	1	1	S	0.5	1	S
BA_014		>16	2	R	0.5-1	1	S	0.5	1	S
BA_021		>16	2	R	0.5	1	S	0.5	1	S
BA_036		>16	2	R	0.5	1	S	0.5	1	S
KA_059		>16	2	R	0.5	1	S	0.5	1	S
KA_091		>16	2	R	1	1	S	0.5	1	S
T3		>16	2	R	1	1	S	0.5	1	S
14A1		>16	2	R	1	1	S	0.5	1	S
11:156	MDR	2	2	R	0.5-1	2	S	0.25	2	S
11:322		≤0.125	1	S	≤0.5	1	S	≤0.125	1	S
11:191		≤0.125	1	S	1	1	S	0.25	1	S
11:136		0.25	1	S	≤0.5	1	S	0.5	1	S
11:368		≤0.125	1	S	≤0.5	1	S	0.5	1	S
QA2	EQAS	≤0.125	1	S	≤0.5	1	S	0.25	1	S
QA3		≤0.125	1	S	≤0.5	1	S	0.5	1	S
QA5		0.25	1	S	≤0.5		S	0.25	1	S

BDQ = bedaquiline; EQAS = external quality assurance strains; LZD = linezolid; MDR = multidrug-resistant; MIC = minimal inhibitory concentration; QC = quality control

Reviewer comment: The pretomanid MIC range for the QC strain H37Rv was 0.125 to 0.25 mcg/mL. Consistent values were obtained when tested by 3 technicians on different days at the [redacted] (b) (4) *. The QC data for first- or second-line drug was not included from this study. The performance of the MGIT system for pretomanid compared to the reference agar proportion method (Clinical Laboratory Standards Institute (CLSI) document M24-A3, 2018) from multiple laboratories is not available for assessment of proposed critical concentration.*

For MTB, susceptibility is typically based on testing at a "critical concentration" (CC). The CLSI M24-A3 defines the critical concentration as the lowest concentration that inhibits 95% of wild type strains of MTBC that have not been exposed to drug but does not inhibit strains of MTBC considered resistant that are isolated from patient who are not responding to therapy. In 2018, the World Health Organization (WHO) defined critical concentrations as the lowest concentrations that would inhibit growth of 99% of wildtype strains of MTBC *in vitro*.

The pretomanid MIC distribution from preclinical and clinical studies is shown in Figure 8-6. A [redacted] (b) (4)

Correlation of pretomanid MIC and clinical outcome.
In the Nix-TB trial, a favorable outcome was achieved for 48 out of 55 patients from whom baseline pretomanid MIC data was available for analysis. Due to the small number of subjects with baseline pretomanid MIC data and few failures observed so far in the interim analysis of this trial, it is difficult to correlate MIC values and outcome. All available pretomanid MIC in the Nix-TB trial were [redacted] (b) (4) For the 7 subjects with unfavorable outcomes [redacted] (b) (6) , the pretomanid baseline MIC values ranged from 0.12 to 0.5 mcg/mL. For these subjects, the baseline bedaquiline MIC values ranged from 0.12 to 2 mcg/mL, and the linezolid MIC values ranged from 0.5 to 1 mcg/mL. The MIC ranges for the 3 drugs from subjects with favorable versus unfavorable response at 6 months overlapped.

(b) (4)

MIC (µg/mL)

Figure 8-6. Pretomanid MIC distribution against MTB (N=463) by method.

(b) (4)

Reviewer comment: The applicant has proposed that the MGIT and REMA methods for susceptibility testing of pretomanid using a susceptible interpretive criteria of (b) (4) *The Nix-TB trial only used the MGIT testing method after assessing reproducibility of the method in one laboratory. The pretomanid MIC of* (b) (4) *however, it is difficult to evaluate the contribution of pretomanid to clinical outcome when used in a multi-drug regimen and determine if the CC is predictive of clinical response to therapy. The applicant states that the pretomanid dosing in the Nix-TB trial achieves plasma concentration above that required to inhibit isolates with MIC of* (b) (4) *However, it should be noted that plasma concentration may not be completely relevant for breakpoint determinations as MTBC can be present intracellularly and in dormant stages. Based on limited data for QC strain and clinical data to determine clinical relevance of the CC, no susceptibility test criteria will be specified in the label.*

9 Review of Safety

9.1. Safety Review Approach

The objective of this review is to evaluate the safety of the BPaL regimen. The focus of the safety review is the Nix-TB trial in 109 patients with XDR-TB or NR/TI MDR-TB. Safety analyses are also conducted for pooled phase 1 studies of pretomanid alone in healthy subjects, pooled phase 2 (EBA) studies, and pooled phase 3 studies of pretomanid-containing regimens in patients with DS-TB and drug-resistant tuberculosis (DR-TB) across the clinical development program.

Adverse events of special interest such as hematologic, hepatic, ophthalmic, neurologic, cardiac, and gastrointestinal events associated with pretomanid alone or components of the BPaL regimen are evaluated. Recommendations from consultants in the Hepatology/ Office of Surveillance and Epidemiology (OSE), Division of Transplant and Ophthalmology Products (DTOP), Division of Bone, Reproductive and Urologic Products (DBRUP), and the QT-IRT team are summarized.

A data fitness analysis (1/29/19) for the ISS was conducted in the Office of Computational Science (OCS) and data quality was found to be satisfactory.
Clinical study reports and datasets for NDA 212-862 are located at:
\\CDSESUB1\evsprod\NDA212862\0001

Note: This reviewer acknowledges Peter Glass, M.Sc. (Applied Statistics) and Rui Li, Ph.D., in the Office of Computational Sciences (OCS), and Scott G. Runyan, B.S., Senior Analyst, JReview Support Team, for their contribution to several safety analyses presented in this review.

9.2. Review of the Safety Database

Overall Exposure

Across the clinical development program, 1168 of 1507 subjects enrolled were exposed to pretomanid in 19 studies which are either completed or on-going, i.e., 10 phase 1 studies, six phase 2 trials, and three phase 3 trials. Seventeen of the 19 studies in the clinical development program were conducted by the applicant, TB Alliance, and two phase 1 studies were conducted by the National Institutes of Health, Bethesda, MD.

In phase 1 studies, 289 male and female subjects received pretomanid alone as a single dose (50 to 1500 mg) or multiple doses (200 to 1000 mg per day) or in combination with other drugs. These studies evaluated the safety, tolerability, and pharmacokinetics (PK) of pretomanid, and selected drug-drug interactions of pretomanid when administered in combination with efavirenz, midazolam, ritonavir-boosted lopinavir, and rifampin.
Six completed phase 2 studies characterized EBA, safety, PK of pretomanid alone and in

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combination with other antimycobacterial drugs in patients with newly diagnosed DS-TB or MDR- TB. In these phase 2 studies, 122 subjects received pretomanid 50 to 1200 mg/day as a single agent for 14 days, and 417 subjects received pretomanid 100 to 200 mg/day in combination with one or more anti-TB drugs (bedaquiline, pyrazinamide, clofazimine, and moxifloxacin) from 14 days to 8 weeks.

The three phase 3 trials include the ongoing Nix-TB and ZeNix trials of the BPaL regimen and the completed NC-006 which evaluated a different pretomanid -containing regimen [moxifloxacin/pretomanid/pyrazinamide, (MPaZ)] in patients with DS-TB and MDR-TB.

Among 1168 subjects, 411 [35.2%] were exposed to pretomanid alone while 757 [64.8%] received pretomanid in combination with other drugs.
In the Nix TB trial, all 109 (100%) subjects were exposed to the regimen of interest, BPaL. The safety data cutoff for the Nix-TB trial, in the integrated summary of safety (ISS) was Mar 26th, 2018.

The phase 1, 2 and 3 clinical trials which evaluated the safety of pretomanid alone or as part of an anti-TB regimen in healthy subjects and patients with drug sensitive and drug-resistant tuberculosis are summarized in Table 9-1.

Table 9-1. NDA 212-862: Safety Database for Pretomanid - All Studies

Safety Database for Pretomanid[1] N=1507			
Clinical Trials	**Pretomanid alone or part of regimen (n= 1168)**	**HRZE / Other comparator (n=304)**	**Placebo (n= 35)**
Phase 3 trials in patients with XDR-TB and TI/NR MDR-TB and/or pre-XDR-TB			
Nix-TB (BPaL)	109	NA	-
ZeNix (BPaL)	15	NA	-
Phase 3 trial in patients with DS-TB and MDR-TB,			
NC- 006 (MPaZ)	216	68	-
Phase 2 trials in patients with or DS-TB and MDR-TB			
NC- 005 (BPaZ or BMPaZ)	179	61	-
NC- 002 (MPaZ)	148	59	-
Phase 2 trials in patients with DS-TB *Pretomanid alone*			
NC- 003	45	60	-
NC- 001	45	40	-
CL- 010	61	8	-
CL- 007	61	8	-
Phase 1 Studies in Healthy Subjects **(***Pretomanid alone or in various drug combinations***)**			
CL-009	32	-	-
CL-003	16	-	-

Safety Database for Pretomanid[1] N=1507			
Clinical Trials	**Pretomanid alone or part of regimen (n= 1168)**	**HRZE / Other comparator (n=304)**	**Placebo (n= 35)**
CL-001	40	-	13
CL-005	31	-	16
CL-002	18	-	6
CL-008	6	-	-
CL-004	6	-	-
DMID-10-0058 (TQT study)	74	-	-
A5306	52	-	-
CL-006	14	-	-

Source: Adapted from Table 1, Clinical Summary of Safety, Module 2.
DS-TB: Drug sensitive tuberculosis; MDRTB: Multidrug-resistant tuberculosis; XDR-TB: Extensively drug-resistant tuberculosis; BPaL: bedaquiline/pretomanid/ linezolid; MPaZ: moxifloxacin/ pretomanid/ pyrazinamide; BMPaZ: bedaquiline/ moxifloxacin/ pretomanid/ pyrazinamide.

120-day Safety Update

A 120-day safety update submitted on April 5, 2019 contained updated interim safety information on the ongoing Nix-TB and ZeNix trials with a data cutoff date, October 15, 2018. The ZeNix trial is a partially-blinded study evaluating the efficacy, safety, and tolerability of various doses and durations of linezolid in combination with bedaquiline and pretomanid (BPaL) for 26 weeks in patients (planned enrollment: N=180) with either pulmonary XDR-TB; pulmonary tuberculosis resistant to isoniazid, rifamycins, and fluoroquinolones or an injectable (pre-XDR-TB), or pulmonary TI/NR MDR-TB. Safety data from the NixTB and ZeNix trials are reviewed in the addendum to this review, see section 9.9.

Nix-TB Trial

The Nix-TB study was fully enrolled with 109 patients at the time of NDA submission. The safety population in Nix-TB consists of 109 patients: 69 (63%) patients with XDR-TB and 40 (37%) patients with TI/NR MDR-TB. Ninety-seven (89%) patients completed 26 or more weeks of BPaL treatment which includes dosing interruptions.

Treatment duration for BPaL treatment is summarized in Table 9-2.

Table 9-2. Study Nix-TB: Duration of Treatment with BPaL regimen

Duration of BPaL Treatment	BPaL N=109 (100%)
< 8 Weeks	6 (5.5%)
≥ 8 Weeks - < 26 Weeks	6 (5.5%)
≥ 26 Weeks	97 (89.0%)

Source: OCS Analysis Studio, Custom Table Builder
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y)
Cutoffs Used: '8 Weeks' - 56 Days, '26 Weeks' - 181 Days

Exposure to the BPaL Regimen

A total of 21 (19.3%) subjects received more than 27 weeks (>189 days) of treatment with BPaL. The maximum duration of BPaL treatment was 241 days (~8 months), see **Figure 9-1**.
Six (5.5%) patients did not complete 26 weeks of treatment due to death, 5 (4.6%) patients were still on treatment at the data cutoff date*, March 26, 2018,* and 1(0.9%) patient withdrew consent at Week 13. In the 120-day safety update (section 9.9), data for these five subjects' on-treatment were updated to show that all five received >180 days of BPaL treatment.

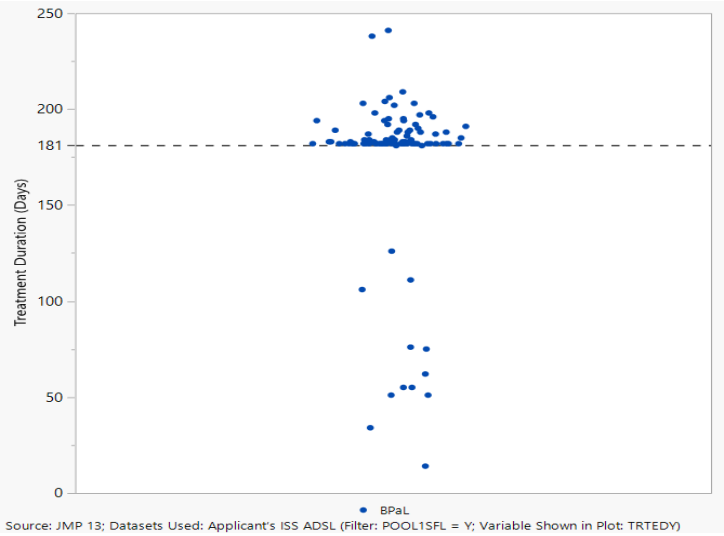

Figure 9-1. Study Nix-TB: Exposure (days) to BPaL regimen

Note: This table shows five ongoing subjects [redacted] (b) (6)) having received less than 26 weeks of treatment. In the 120-day safety update, these patients' data were updated and showed all five received greater than 26 weeks of treatment.

<u>Exposure to Linezolid</u>

Forty-four (40.4%) subjects received linezolid 600mg bid, and 65 (59.6%) patients received linezolid as a once daily dose, 1200mg/day. During the treatment period, TEAE-related dosing interruptions and dose-reductions of linezolid occurred frequently s, for example, 53/109 (48.6%) patients had at least one dose interruption of linezolid. Approximately 33% of patients received a complete uninterrupted 26-week course of linezolid at any dose. The mean duration of exposure to linezolid for a patient in the trial was 23 weeks. Twenty-five (22.9%) patients had at least one interruption of the entire regimen, BPaL. Six (5.5%) patients permanently discontinued the entire BPaL regimen due to death.

When a patient experienced an adverse event believed to be associated with linezolid such as peripheral neuropathy, linezolid dosing was interrupted until the patient improved and linezolid was reintroduced usually at a lower dose of 600 mg per day. Patients continued bedaquiline and pretomanid during the interruption, as per protocol, provided the subject received the initial 1200 mg total daily dose of linezolid for at least the first four weeks and was smear-negative or had trace results and was judged to be clinically improving by the investigator. Exposures to linezolid 600mg bid and 1200mg daily are summarized in Table 9-3.

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Table 9-3. Study Nix-TB: Exposure to Linezolid in Safety Population

		Linezolid Dose		
	Statistic	**600mg BID**	**1200mg/ day**	**Total**
		N=44	**N= 65**	**N=109**
	Subjects	40	63	103
Duration of Treatment* (weeks)	*mean*	23.0	23.0	23.0
	SD	3.6	5.2	4.6
	minimum	15.6	8.9	8.9
	median	24.4	25.7	25.1
	maximum	26.9	37.9	37.8
Uninterrupted full 26-week course at any dose (1200mg/day or lower dose)	*No. subjects (%)*	10 (22.7)	26 (40)	36 (33)
Uninterrupted full 26-week course of 1200mg/daily	*No. subjects (%)*	4 (9.1)	12 (18.5)	16 (14.7)
	Subjects	40	63	103
Cumulative dose (mg) based on planned dose	*Mean ± SD*	193290.0 ± 28184.96	193047.6 ± 43658.05	191341.7 ± 38240.25
	minimum	130800	74400	74400
	median	205200	216000	211200
	maximum	225600	318000	318000
Cumulative dose (mg) based on actual dose	*Mean ± SD*	154065.0 ± 37673.96	161538.1 ± 47081.04	158635.9 ± 43628.42
	minimum	91800	73200	73200
	median	147900	159900	154200
	maximum	220800	318000	318000

Source: Adapted from Nix-TB addendum study report, Table 14.1.9.2, page 229. Subjects who died are excluded from analysis. n: number of subjects in each category; SD: Standard deviation; *Duration of Linezolid (weeks) = (Sum of all study drug administrations – sum of all missed doses)/7.

Relevant characteristics of the safety population

The demographics of safety population (N=1168) who received pretomanid alone or pretomanid in combination with other drugs during the clinical development program are presented in Table 9-4. The mean age of the population was 33 years and 65% were male. The mean body weight was 59kg and BMI 21 kg/m^2 (normal range).

Patients who received the BPaL regimen (n=124) in the Nix-TB and ZeNix trials had similar baseline demographics for age, sex, race, body weight, and BMI to the overall population except for baseline HIV status. Approximately, 47% of the population who received BPaL were HIV-positive as compared to 18% of the total safety population.

Table 9-4. Demographics of Safety Population in Clinical Development Program for Pretomanid

Baseline Characteristic	Pretomanid alone	Pretomanid Combo except BPaL	BPaL Regimen	Comparator/ Control	Total Pretomanid
	N=411	**N=633**	**N=124**	**N=339**	**N=1168**
Age (years), mean	30.1	33.8	36.9	31.6	32.8
Male	248 (60.3)	444 (70.1)	72 (58.1)	234 (69)	764(65.4)
Female	163 (39.7)	189 (29.9)	52 (41.9)	105 (31)	404 (34.6)
Race					
White	197 (47.9)	13 (2.1)	9 (7.3)	31 (9.1)	219 (18.8)
Black	134 (32.6)	436 (68.9)	90 (72.6)	198 (58.4)	660 (56.5)
Asian	3 (0.7)	15 (2.4)	0	5 (1.5)	18 (1.5)
Other	77 (18.7)	169 (26.7)	25 (20.2)	105 (31)	271 (23.2)
Region					
Africa	122 (29.7)	595 (94)	116 (93.5)	294 (86.7)	833 (71.3)
Asia	0	29 (4.6)	8 (6.5)	7 (2.1)	37 (3.2)
Europe	0	9 (1.4)	0	3 (0.9)	9 (0.8)
United States	289 (7(0.3)	0	0	35 (10.3)	289 (24.7)
Weight (KG), mean	69.2	54.8	57	56.2	60.1
BMI (kg/m^2), mean	23.5	19.7	20.6	19.9	21.1
HIV status, n (%)					
Positive	14 (3.4)	135 (21.3)	58 (46.8)	50 (14.7)	207 (17.7)
Negative	107 (26)	496 (78.4)	66 (53.2)	253 (74.6)	669 (57.3)
Unknown	290 (70.6)	2 (0.3)	0	36 (10.6)	292 (25)
CD4 count, cells/µL					
n	14	101	51	40	166
Mean (SD)	523± 207	365± 171	394± 212	469± 238	387± 191

Source: Adapted from Table 8 and Table 9 in Summary of Clinical Safety, NDA 212-862.

The Nix-TB trial was conducted at three study sites in South Africa. Study participants were mostly black (76%) or of mixed race (23%). The population was balanced by sex and HIV status; male patients accounted for 52% of the population and 51% of subjects were coinfected with HIV (baseline mean CD4 count: 343 cells/µL). Mean body weight was 57 ± 15 kg, (range 29 to 112kg), with a mean BMI 20 ± 5kg/m^2 at baseline, i.e., within normal range for an adult.
The mean length of time since diagnosis of XDR-TB or TI/NR MDR-TB prior to enrollment was four months; however, the mean length of time since the original diagnosis of tuberculosis was 24 months. The original diagnosis of tuberculosis was reported as DS-TB in 11 (10.1%) patients,

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MDR-TB in 76 (69.7%) patients, XDR-TB in 21(19.3%) patients, and unknown in one patient.

Clinical Comment: Patients in the Nix-TB trial were infected with M. tuberculosis (regardless of susceptibility) for an average of 24 months (0.5 to 141 months). *Many of the patients had chronic pulmonary tuberculosis manifested by weight loss and low baseline BMI <18.5 kg/m^2 in 43 (39%) patients, and low baseline albumin levels < 3.5g/dL in 29 (27%) patients. Approximately 50% of the patients were co-infected with HIV and were taking concomitant antiretroviral therapy. Tuberculosis with HIV/AIDS increases the potential for adverse events associated with the two diseases and with antimycobacterial and antiretroviral drugs, all of which could confound the assessment of adverse events related to the BPaL regimen.*

Adequacy of the safety database

The data for safety of the BPaL regimen come from 109 subjects in the ongoing Nix-TB trial and additional 15 subjects from the ongoing ZeNix trial. A small safety database of 124 subjects on BPaL and the lack of an active comparator in the Nix-TB trial makes it challenging to assess the safety profile of pretomanid alone and the BPaL regimen. Safety data from 411 healthy subjects in phase 1 studies and 757 subjects who received pretomanid as part of other anti-mycobacterial drug regimens such as pretomanid/ moxifloxacin/ pyrazinamide were used to augment safety data from NixTB and ZeNix. The safety profiles of the other two drugs in the BPaL regimen, bedaquiline and linezolid, are reasonably well established.

Taking all the available safety data into account, the safety database is considered adequate to assess the safety of pretomanid and the BPaL regimen. There are limited treatment options for this life-threatening infection and an unmet medical need for new treatments for XDR-TB and TI/NR MDR-TB; thus, more risk can be tolerated because of the high efficacy of the BPaL regimen.

9.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the NDA submission is satisfactory and there are no major concerns with data integrity. The applicant included statements of Good Clinical Practice (GCP) for each trial. The Integrated Summary of Safety (ISS) dataset was found to be satisfactory in the data fitness analysis.

Categorization of Adverse Events

The method for collecting adverse event data was predefined in the Nix-TB study protocol. Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 in the ISS.

Treatment emergent adverse events (TEAEs) were defined as events that start or worsen at or during the time of first study drug administration, or after the first study drug administration,

up to 14 days after the last study drug administration. TEAEs were classified by maximum severity, drug-relatedness, and treatment/study disposition. Deaths and SAEs were identified and evaluated through case narratives and case report forms (CRFs). Summaries of TEAE incidence were produced to include the most common TEAEs (incidence ≥5%) and SAEs (incidence ≥1%) by MedDRA preferred term (PT). Adverse events of special interest were identified via Standardized MedDRA Queries (SMQs) and included adverse reactions known to be related to components of the BPaL regimen other than pretomanid. SMQs are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development.[32]

In TEAE tabulations, patients are counted only once within each SOC and PT regardless of the number of episodes for a given adverse event. Events of potential drug-induced liver injury with hyperbilirubinemia, also called "Hy's Law" events, were defined as ALT >3x ULN and bilirubin >2x ULN (>35% direct) or ALT ≥3x ULN and INR >1.5, if INR measured.

Adverse reactions associated with the individual drugs in BPaL regimen: bedaquiline and linezolid, and pretomanid were evaluated.

Routine Clinical Tests

Routine clinical evaluations for safety included ascertainment of adverse events through medical history, vital sign measurements and physical examinations, clinical laboratory tests, ECGs, and use of concomitant medications. Patients had periodic evaluations specifically for peripheral neuropathy, a known side effect of linezolid. Slit lamp evaluations for development of cataracts were done in pretomanid clinical trials since 2009 based on a signal in animal toxicology studies. Assessments of visual acuity and color vision were done to evaluate patients for evidence of optic neuropathy, a known adverse-effect of long-term use of linezolid.
In Nix-TB, evaluations were performed at baseline, throughout the 26-week treatment period and the 24 months of follow up. The schedule of monitoring is outlined in Table 9-5.

[32] https://www.meddra.org/standardised-meddra-queries

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Table 9-5. Study Nix-TB: Schedule of Safety Assessments

Period	[a]Screening	Treatment																			9 Months Treatment[b] ONLY			Early Withdrawal	Post Treatment Follow-up Period[c]									
Time of Visit	Up to 9 days prior to	Day1 d	Week 1	Week 2	Week3	Week 4	Week5	Week 6	Week7	Week 8	Week9	Week10	Week11	Week 12	Week13	Week14	Week15	Week 16	Week 20	Week 26	Week 30	Week 34	Week 39		1 month	2 month	3 month	6 month	9 month	12 month	15 month	18 month	21 month	24 month
e Visit Window	N/A	± 3 days																	± 7 days						± 2 weeks									
nformed Consent	X																																	
Demography	X																																	
Medical/Treatm ent History	X																																	
nclusion/Exclu sion	X	X																																
Karnofsky Assessment	X																																	
f HIV Status	X																																	
g CD4 Count	X																																	
h Chest X-Ray	X																																	
Serum or Urine Pregnancy Test	X	X								X										X[j]			X	X										
TB Symptoms Profile	X									X										X[j]			X[j]	X						X				X
Patient-reported Health Status	X									X										X[j]			X[j]	X						X				X
k Slit-lamp Examination	X																			X[j]			X[j]	X			X							
Ophthalmic Examination	X					X				X				X				X	X	X	X	X	X	X			X	X		X				X
Vital Signs	X	X	X	X		X		X		X				X				X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Single 12-Lead ECG	X	X	X			X				X								X		X[j]	X		X[j]	X										
m imited Physical Examination			X	X		X		X		X				X				X	X		X	X					X	X	X	X	X	X	X	X
m Full Physical Examination	X	X																		X[j]			X[j]	X										
n aboratory Safety Tests	X	X	X	X		X		X		X				X				X	X	X	X	X	X	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[o]Trial treatment /Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										
p PK Sampling				X						X								X																
q Early Morning and Spot Sputum	X	X	X	X		X		X		X				X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete/Full Blood Count					X		X		X		X	X	X		X	X	X																	
Peripheral Neuropathy	X					X				X				X				X	X	X	X	X	X	X			X	X		X				X

Source: Adapted from Schedule of Safety Assessments in Nix-TB addendum protocol, section 1.2, page 21.

a. **Sputum Sampling:**
1. Screening (Day -9 to -1): A single spot sputum will be collected at the research site under the coaching and observation of the trial staff.
The following analysis will be performed on this sample:
Smear microscopy for acid-fast bacilli (AFB); Culture for presence or absence of *M. tuberculosis (M.tb)*.; - Gene Xpert, Hain Assay MTBDR plus or an alternative molecular or antigen-based test to confirm *M. tb*;
2. All visits from Day 1 (baseline) up to and including Month 24: Two sputum samples, one early morning brought from home or in the hospital if hospitalized, and one spot at the research site under the coaching and observation of the trial staff (or if hospitalized, in the morning at least 1 hour after the early morning sample) will be collected. If early morning is not available, site should make every attempt to collect two spot samples at least 1 hour apart on site. If sputum samples obtained at Month 4, End of Treatment (Week 26/39) or end of follow-up Month 24 are contaminated, the Subject should return for an unscheduled visit(s) to give additional samples or to document the Subject is not able to produce sputum. The following analyses will be performed on sputum samples at the study lab (lab that receives samples directly from the site):
-Culture for presence or absence of *M.tb.*;
-Speciation (on baseline and first positive at end of treatment or during follow-up or any positive at or after the week 16 visit)
-If MGIT is performed, TTP in liquid medium.
-If participant has received at least 4 consecutive weeks of linezolid at a total daily dose of 1200 mg, and Investigator would like to consider discontinuing linezolid dosing and continuing bedaquiline and pretomanid dosing:
-A smear microscopy for acid fast bacilli (AFB) should be requested by the site and performed at the study lab.
3. First culture positive sample at or following end of treatment: Two sputum samples, one early morning brought from home and one spot at the research site under the coaching and observation of the trial staff (or if hospitalized, in the morning at least 1 hour after the early morning sample) will be collected. If early morning is not available, site should make every attempt to collect two spot samples at least 1 hour apart on site.
Culture for presence or absence of M.tb.;
Extraction of bacterial (M.tb.) DNA for molecular genotyping
Speciation (for initial relapse (first positive at end of treatment or during follow-up) or any positive at or after week 16))
Mycobacteriology Characterization Tests, Performed on:
1. Day 1 (baseline) spot sputum samples (or Screening up to Week 4 if the baseline is contaminated or negative);
2. Confirmed Positive Cultures at or after end of treatment.
The *M.tb.* isolates will be processed at central lab(s) for:
-MIC against bedaquiline, pretomanid and linezolid;
- Drug Susceptibility Testing in liquid culture for rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide, and second-line TB drugs such as fluoroquinolones, and injectables;
- Extraction of bacterial (*M.tb.*) DNA for molecular genotyping;
- Speciation of the infecting organism by molecular/antigen tests
All Day 1 (baseline) *M.tb.* isolates and isolates from positive cultures to be stored at the study microbiology laboratory (or until requested to transfer to the central lab(s) for testing), until trial closure for the applicable study tests. The extracted *M.tb.* DNA and isolates will be stored for
potential further work to validate new assay tools for a maximum of 5 years after trial closure.
b. Visit Schedule: Subjects who are culture positive or revert to being culture positive between month 4 and month 6 visits, will be withdrawn, or will receive a total of 9 months of treatment. (Week 30, 34 and 39 visits should not be done for Subjects who complete study treatment in 6 months). If the duration of treatment is extended due to dose interruptions (e.g., takes participant 8 months to complete 6 months of therapy), Unscheduled visits should be added every 4 weeks through last dose of IMP, then post final treatment visit, follow-up visits should be scheduled. Unscheduled Visits to include: Ophthalmology Examination, Vital Signs, Limited Physical Exam, Laboratory Safety Tests, Con Meds, Adverse Events, Study Medication/Compliance, Early Morning and Spot Sputum and the Peripheral Neuropathy Exam.

9.4. Safety Results

9.4.1. Deaths

Eight (7.3%) of 109 subjects died by the data cutoff date, March 26, 2018; four males and four female subjects between the ages of 20 and 55 years. Seven subjects had XDR-TB and five subjects were co-infected with HIV. Six (5.5%) subjects died during the 26-week treatment period with BPaL and 2(1.8%) deaths occurred post treatment, Table 9-6.

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

Table 9-6. 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(s)	Study Day of Death	Clinical reviewer's assessment of relationship to study drugs
(b) (6) M/34y	XDR/ HIV +	Disseminated Tuberculosis, Pulmonary Tuberculosis, Pancreatitis Hemorrhagic / Severe Pulmonary Tuberculosis and Disseminated Tuberculosis	35	Pancreatitis Hemorrhagic possibly related
(b) (6) F/20y	XDR/ HIV -	Upper Gastrointestinal Bleeding/ Upper Gastrointestinal Bleeding	51	Possibly related
(b) (6) M/35y	XDR/ HIV +	Pancreatitis Hemorrhagic/ Acute Hemorrhagic Pancreatitis	53	Pancreatitis Hemorrhagic possibly related
(b) (6) F/31y	XDR/ HIV +	Pulmonary Tuberculosis/ Acute Severe Worsening of Pulmonary Tuberculosis	55	Unrelated
(b) (6) F/ 26y	XDR/ HIV -	Septic Shock/ Septic Shock Secondary to Pneumonia	76	Unrelated
(b) (6) F/29y	TI/NR MDR/, HIV-	Sepsis, Pneumonia/ Worsening Pneumonia	93	Unrelated
(b) (6) M/ 38y	XDR/ HIV +	Death/ "Natural causes" characterized as a non-violent death	369	Unrelated; completed Rx Day 184
(b) (6) † M/55y	XDR/ HIV +	Sepsis/ Sepsis Secondary to Gangrene from Peripheral Vascular Disease	486	Unrelated; completed Rx on Day 184 and had relapse on Day 266

Source: ISS Dataset: ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL).
† Subject (b) (6) relapsed and was discontinued (physician/sponsor decision') from the study approximately three months before he died from sepsis /gangrene.

<u>Deaths - Case Narratives</u>

Subject (b) (6), M, 35y (acute pancreatitis and multi-organ failure):
This 35-year-old black male with HIV (CD4 168, HIV viral load undetectable), chronic active hepatitis B, anemia, and a drug sensitive TB (dx 3 years prior to study entry), was diagnosed with XDR-TB one year prior to study entry.
Antiretroviral treatment (ART) included emtricitabine, tenofovir disoproxil fumarate, lopinavir, and ritonavir. Anti-mycobacterial drug treatment, prior to enrollment, included moxifloxacin, aminosalicylate, pyrazinamide, ethambutol, and clofazimine. He had no history of alcohol use. At study entry, physical examination was normal. Chest x-ray showed patchy consolidations without cavitations mainly in the left lung.
The patient tolerated the BPaL regimen during the first 3 weeks of therapy. On study Day 25, the patient developed malaise, worsening anemia, and thrombocytopenia; Hb 9.4 g/dL, platelet count 94 × 10^9/L. The dose of the linezolid was reduced from 1200 mg daily to 600 mg daily because of thrombocytopenia.
On study Day 35, hemoglobin declined to 8.4g/dL and platelet count improved to 145 x 10^9. On study Day 42, he developed nausea, vomiting, continuous left flank pain; lipase, amylase, glucose, Hb, WBC, and platelet count were within normal ranges. ALT and AST levels were mildly elevated.
On study Day 51, the patient developed hematemesis (coffee grounds) with backpain, bradycardia, severe abdominal pain, hypoglycemia, and elevated amylase and lipase. He was diagnosed with acute pancreatitis and GI bleed which was treated medically with nasogastric tube, IV fluids, IV ceftriaxone, proton pump inhibitors, vitamin K, anti-emetics, and morphine. Upper GI endoscopy or abdominal ultrasound (US) were not performed.
Laboratory test results showed evidence of renal failure with an increased creatinine level and low GFR, elevated lipase 710 U/L (15x ULN), leukocytosis WBC 22 x 10^9/L, anemia with Hb 8.2g/dL, with evidence of disseminated intravascular coagulation (DIC) (increased prothrombin time/INR, decreased fibrinogen, increased D-dimer). The last dose of BPaL was administered on study Day 51. Prior to death on study Day 53, the patient deteriorated and developed hypotension, hypoglycemia (blood glucose 2.6 mmol/L) treated with IV dextrose.
Autopsy: Significant findings included obliteration of the left pleural cavity, fibro-caseous nodules involving predominately left lung, hilum, spleen, and mesenteric lymph nodes, acute hemorrhagic pancreatitis with bleeding into the mesentery, and micro-nodular cirrhosis. Sections of the kidneys showed foci of chronic inflammation tubular micro-calcifications, some sclerosed glomeruli and hyaline casts. Histopathology of the pancreas showed hemorrhage with focal neutrophilic response, and chronic calcific pancreatitis. There was no evidence of coronary artery disease. The cause of death was hemorrhagic pancreatitis and multiorgan failure.

Clinical Reviewer Comment: The patient was anemic at baseline and hemoglobin and platelet counts further declined while on BPaL. The worsening anemia and thrombocytopenia occurred one week before the event of hematemesis and could have been due to an undetected GI bleed and /or myelosuppression due to linezolid. Myelosuppression (anemia, leukopenia, thrombocytopenia, and pancytopenia) are known side-effects of linezolid. The thrombocytopenia improved when the dose of linezolid was reduced from 600 mg twice daily to 600 mg once daily indicating that linezolid contributed to the adverse event.

Acute pancreatitis is not a labeled adverse event for bedaquiline or linezolid. In clinical trials of linezolid, changes seen in lipase levels without regard to drug relationship, revealed no substantial differences between linezolid and comparators such as cephalosporins, dicloxacillin, and vancomycin. Pancreatitis was reported in animal studies of bedaquiline.
Hypoglycemia was associated with multiorgan failure but hypoglycemia probably was not the immediate cause of the patient's death as it was corrected with IV dextrose before death.
Renal toxicity is not a labeled adverse event for bedaquiline or linezolid. Animal studies and a phase 1 renal study of pretomanid do not indicate that pretomanid causes renal toxicity. Renal impairment in this patient may have been due to HIV and ART (tenofovir) therapy and possibly exacerbated by hypotension.
This patient had evidence of intraabdominal tuberculosis detected at autopsy with infection in the spleen and mesenteric lymph nodes. Disseminated tuberculosis, if found at screening, would have excluded the patient from the Nix-TB study.
Conclusion: The clinical data and autopsy report indicate that the patient's death was caused by acute hemorrhagic pancreatitis, hypotensive shock, and multiorgan dysfunction occurring less than two months after starting the BPaL regimen. There was evidence of acute and chronic pancreatitis on histopathology.
At the time of study entry, the patient was taking lopinavir/ritonavir which is associated with pancreatitis and tenofovir which is associated with renal impairment. However, an association between acute pancreatitis and the BPaL regimen or at least an exacerbation of pancreatitis cannot be excluded because acute pancreatitis occurred while on BPaL treatment.

Subject (b) (6), F/31y (acute worsening of pulmonary TB):
This 31-year-old HIV-positive female with XDR-TB was diagnosed with XDR-TB eight months prior to enrollment in Nix-TB but had not been on any anti-TB drugs for 6 months prior to study entry. ART included tenofovir, lamivudine, lopinavir/ritonavir. An abdominal US showed splenic microabscesses and granulomas consistent with TB. Screening laboratory blood results were within normal limits except for CD_4 count of 328 cells/µL and white blood cell count (WBC) of 14.3×10^9/L).
By study Day 14 of treatment with the BPaL, the patient's Hb and platelet counts had declined to 9 g/dL and 204 x 10^9/L, respectively, and the WBC improved, 6.7 x 10^9/L. Mild myelosuppression was diagnosed and no adjustments to study drugs were made.
By study Day 21, Hb had dropped to a nadir of 6.6g/dL (grade 4 anemia), platelets 121 x 10^9/L, and potassium (K) 3.0 mmol/L. Serum iron, B12, folate and TSH were normal. After a workup patient was diagnosed with myelosuppression related to linezolid. She improved clinically post transfusion of RBCs (Hb 11.8 g/dL and platelets 136 x 10^9/L).
On study Day 29, the patient developed symptoms of a lower respiratory tract infection with WBC 13.8 x 10^9/L, Hb 11.2g/dL, elevations in hepatic transaminases < 2xULN. Total bilirubin and renal function test were normal. No treatment was given. On study Day 36, the patient appeared stable.
On study Day 43, she was re-challenged with bedaquiline/pretomanid/linezolid 300 mg/d (reduced dose). On same day, the patient became ill with a lower respiratory tract infection unresponsive to Augmentin for3 days. On study Day 47, the patient was diagnosed with acute worsening of pulmonary tuberculosis. Augmentin was stopped.

On study Day 50, WBC 16 x 10^9/L and HIV viral load 8,838 copies/mL. She received azithromycin and metronidazole, oxygen, and remained on anti-TB drugs. Chest x-ray showed evidence of pneumonia with bilateral patchy infiltrates. Her overall condition was assessed as *"for palliative treatment*" by the hospital physicians because of failure of maximized intervention for XDR-TB and poor prognosis. Her pneumonia was not improving on azithromycin and metronidazole, and BPaL, and she was emaciated and cyanotic but not jaundiced. On study Day 54, the patient became hypotensive, tachypneic, and body temperature was 36°C. The patient died on Day 55.
Autopsy: The major autopsy findings included extensive cavitation of both upper lobes of the lungs and numerous fibrocaseous lesions, tuberculous lobular pneumonia with early organization, massive mesenteric TB lymphadenopathy, splenic and left lobe of liver TB involvement, hemorrhagic head of pancreas, no pulmonary embolus and bone marrow showing depressed erythroid component. The final cause of death was reported as respiratory failure due to severe pulmonary TB.

Clinical reviewer's comment: This patient had disseminated XDR-TB with multiorgan involvement (lungs, spleen, liver, mesenteric lymph nodes) and a poor clinical prognosis. Disseminated TB, if found at screening, would have excluded the patient from the trial.
The patient was received the BPaL for 17 days before the regimen was interrupted for a two-weeks due to anemia and thrombocytopenia which were probably due to linezolid. The entire BPaL regimen was stopped and laboratory parameters improved following a blood transfusion. She developed worsening pulmonary TB during the interruption interval and she presented with symptoms of a lower respiratory tract infection on Day 29. The $BPaL_{300mg}$ regimen was reintroduced two weeks later.
Autopsy: The worsening bronchopneumonia was due to XDR-TB leading to respiratory failure and death.
Conclusion: This case was a treatment failure of the BPaL regimen. The adverse event of severe worsening of pulmonary TB leading to death was not related to study drugs.

Subject (b) (6), F/ 26y (septic shock secondary to pneumonia):
This 26-year-old HIV negative female, with XDR-TB has been previously treated for DS-TB and rifampicin resistant TB (RR-TB) during the five years prior to enrollment. She was treated with moxifloxacin, kanamycin, ethionamide, terizidone, pyrazinamide, and isoniazid for TB (RR-TB), followed by terizidone, ethambutol, pyrazinamide and clofazimine for XDRTB during the two years prior to enrollment.
Around study Day 35 of BPaL treatment, the patient's sputum smear was positive for *M. tuberculosis* and she developed anemia (Hb 8.9g/dL). The linezolid dosage was changed from 1200 mg to 600 mg daily; anemia resolved on the lower dose of linezolid.
On Day 71 after the first dose of BPaL, she was diagnosed with pneumonia. She was treated with iv fluids, amoxicillin/clavulanate for 2 days; however, she developed worsening pneumonia, hypoxia, hypotension/shock, and hyperlactatemia. The BPaL regimen was continued throughout. Blood cultures were not done/ not reported. Attempts to admit the patient to a facility with ventilator support failed and the patient died on Day 75 of BPaL treatment.

Autopsy: The major findings included extensive granulomatous inflammation with central caseation in the right lung and upper lobe of the left lung consistent with tuberculosis. The right lung was shrunken, with adherent pleura. Lung tissue culture grew multidrug-resistant *Escherichia coli* and *Pseudomonas putida*; however, there were no bacteria on Gram stain and no acid-fast bacilli (AFB) using ZN stain (direct smear). Lung tissue culture did not grow *M. tuberculosis*. Acute tubular necrosis, consistent with shock was observed in the kidneys.
The probable cause of death was septic shock secondary to acute respiratory distress syndrome secondary to a superimposed hospital acquired pneumonia. The predisposing illness was a primary *XDR-TB* infection.

Clinical Comment: The cause of death was respiratory failure and septic shock related to bronchopneumonia. Autopsy revealed extensive granulomatous inflammation with central caseation in the lungs consistent with TB. The adverse event of anemia was probably due to linezolid because anemia reversed when the dose was reduced from 1200mg to 600mg /day. The hyperlactatemia may have been associated with the underlying bronchopneumonia and/or linezolid. Lactic acidosis is listed in Warnings in the linezolid USPI.
Conclusion: This case was a treatment failure of the BPaL regimen. The adverse event of severe worsening of pulmonary TB leading to death was not related to study drugs.

Subject (b) (6), M/34y (severe pulmonary and disseminated TB and acute pancreatitis (hemorrhagic):
This 34-year-old male patient with a history of HIV, heavy alcohol use, dyspepsia, and erectile dysfunction, was diagnosed with XDR-TB five months prior to study enrollment. Medications for the treatment of tuberculosis prior to enrollment included pyrazinamide, ethambutol, moxifloxacin, aminosalicylate sodium, teridizone, clofazimine, ethionamide, capreomycin, and isoniazid. Anti-retroviral treatment was switched from tenofovir, emtricitabine and efavirenz to tenofovir, lamivudine, and nevirapine on study Day 1.
The patient complained of intermittent nausea, epigastric pain and vomiting prior to his enrollment in the trial. He had low body weight of 42kg. HIV viral load was suppressed and CD4 count = 259 cells/ µL. Patient had an elevated GGT, AST, alkaline phosphatase, and low albumin at screening. ALT, bilirubin (direct/indirect), amylase and lipase were normal.
From Day 11 through Day 34 of BPaL treatment, the patient experienced worsening epigastric pain, nausea, and vomiting. On Day 14, his abdominal pain upper was assessed as possibly related to study drugs; however, BPaL was continued and no treatment was reported except for ranitidine (Day 21) and lansoprazole (Day 34). Labs showed an elevated amylase but a normal lipase up to study Day 28. No lipase levels were available beyond Day 28. ALT, AST, alkaline phosphatase, and GGT were elevated. No GI imagining was performed.
On the morning of Day 35, he developed acute worsening of epigastric pain, vomiting, dizziness, and died later that day.
Autopsy: Autopsy findings were emaciation, hemorrhagic pancreatitis with neutropenic ductulitis with extension into the pancreas, bilateral pulmonary tuberculosis with cavitation and AFB positive, and obliterative fibrosis, disseminated TB of the spleen, kidneys and liver, adrenal hemorrhage, marked iron overload in the liver with microvesicular steatosis and unusual ductular proliferative lesion of the portal tracts. There were micro-calculi in the pancreatic

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ducts consistent with prior episodes of pancreatitis. There was evidence of DIC with thrombi in adrenals and liver. There was no evidence of cerebral pathology. Additional sections of the pancreas were evaluated by the pathologist and he noted evidence of obstructive pancreatitis with features of pancreatitis secondary to shock.
The cause of death was determined to be severe pulmonary and disseminated TB and hemorrhagic pancreatitis. The pathologist confirmed that the pancreatitis was not a coincidental finding of the generalized TB and that the acute hemorrhagic pancreatitis was a contributing cause of death.

Clinical comment: This patient died on Day 35 of BPaL treatment due to autopsy-confirmed disseminated tuberculosis and hemorrhagic pancreatitis and shock. Adrenal hemorrhage was also noted which could have caused hypotensive shock/DIC. Lipase levels were normal up to Day 28 but were not available in the week prior to death. There was no evidence of M. tuberculosis infection in the pancreas on autopsy.
Conclusion: This case was a treatment failure of the BPaL regimen. Disseminated TB, if found at screening, would have excluded the patient from the Nix-TB study.
The patient's history of HIV, ART, and alcohol use were risk factors for acute pancreatitis; however, an exacerbation of acute pancreatitis by components of the BPaL regimen cannot be ruled out.

Subject (b) (6), F/20y (upper gastrointestinal bleed):
This 20-year-old, mixed-race female, HIV negative, and history of DSTB diagnosed 7 years prior to enrolment, had failed treatment for MDRTB (dx ~1 year prior to enrollment). She was diagnosed with XDR-TB at approximately four months prior to enrollment. Prior to enrollment XDR-TB treatment included ethionamide, terizidone, levofloxacin, pyrazinamide, ethambutol, clofazimine, isoniazid, PAS and pyridoxine. The patient was diagnosed with pneumonia and was started on Augmentin a week prior to enrollment. Baseline labs were within normal limits.
On Day 43 of BPaL treatment, she had evidence of anemia, Hb 9.0 g/dL. On Day 47 she developed weakness and vomiting and was treated with IV fluids. On Day 50, she had worsening cytopenia, Hb 6.9 g/dL and platelets 45×10^9/L, and she was diagnosed with myelosuppression. The BPaL regimen was continued with no dose reduction in linezolid. Liver function tests were reported as normal throughout the trial.
On Day 51, after BPaL dosing she clinically worsened with shortness of breath, Glasgow coma scale (GCS) 4/15, hypotension, and had a respiratory arrest leading to death.
Autopsy: Severe emaciation; bilateral cavitary TB with destruction of the upper lobes and AFB present; fibrocaseous nodules in upper lobes, AFB negative; acute pulmonary edema; severe non-alcoholic fatty liver disease with focal zone 3 hepatocyte necrosis; ulcerative esophagitis with invasive *Candida*; gastric atrophy with "coffee grounds", chronic superficial gastritis and focal myocyte injury; segment of colon with marked dilation, submucosal fibrosis and smooth muscle injury; erythrophagocytosis of lymph nodes; mild chronic pyelonephritis. There was evidence of peripheral phagocytosis of erythrocytes by macrophages but no evidence of marrow suppression. The cause of death was an upper GI bleed due to ulcerative esophageal candidiasis.

Clinical Comment: This case was a treatment failure of the BPaL regimen in a severely ill patient. The presence of esophageal candidiasis suggests that the patient was immunosuppressed due to her underlying chronic TB. Her complaints of weakness, dyspepsia, and the decreases in Hb from 9.0 g/dL to 6.9 g/dL and decreases in platelets from 215 × 10^9/L to 45 × 10^9/L over a week (Days 43 to 50), should have raised concern about an underlying GI bleed but the results of the blood tests were not available until the day of her death. A dose reduction/discontinuation of linezolid was warranted because of anemia and thrombocytopenia.
Conclusion: The cause of death was an upper GI bleed due to ulcerative esophageal candidiasis. Thrombocytopenia may have contributed to the GI bleed. Linezolid may have contributed to the anemia and thrombocytopenia; however, the pathologist noted that there was no evidence of bone marrow suppression on histopathology. The patient's death was not due to study drugs.

Subject (b) (6), F/29y (worsening pneumonia):
This 29-year-old HIV-negative female with a history of DS-TB (diagnosed 8 years prior to enrollment), was treated for MDR-TB (diagnosed 2 years prior to enrollment) four times during which she defaulted. She had history of illicit drug use with methamphetamine and cannabis. Prior to enrollment, she stopped her XDR-TB treatment in the national TB program because she failed the prescribed regimen, despite adequate compliance.
Physical examination showed blood pressure (BP) 84/60 mmHg, respiratory rate 22 breaths per minute, tachycardia 137/minute, and body temperature 36.2°C. Baseline laboratory values including liver function tests were normal. The sputum MGIT culture was positive for *M. tuberculosis*.
At 74 days after the first dose of BPaL, the patient absconded for approximately 10 days during which time she used methamphetamines. Five days after the last dose of BPaL, the patient developed a respiratory infection and no treatment was provided. At 8 to 9 days after the last dose of BPaL, she was hospitalized with a left-sided pneumonia, hypoglycemia (blood glucose 1.2 mmol/L), and hyperlactatemia. She was treated with IV dextrose, fluids, ceftriaxone, and paracetamol. Laboratory test results showed leukocytosis, neutrophilia, elevated CRP, hyperkalemia, and abnormal liver function tests (LFTs). She was too ill to have a chest X-ray.
At 10 to 11 days after last dose of the trial drug regimen, hepatic transaminases and bilirubin levels continued to worsen, and Hb decreased from 11.1 g/dL to 9.5 g/dL while WBC count improved. Hepatitis B surface antigen and Hepatitis C antibody tests were negative. Laboratory results showed normal WBC and Hb, and elevated total bilirubin 40 µmol/L (5-21 µmol/L), conjugated bilirubin 15 µmol/L, ALT 2105 U/L, AST 1579 U/L, and INR 1.65. At 14 days after last dose, hepatic transaminases were improving. The patient was treated with nebulizers, ipratropium, and prednisolone daily.
Her pneumonia did not improve on IV antibiotics and continuous oxygen and at 17 days after last dose of BPaL, the patient was admitted to the study site hospital for treatment of bacterial pneumonia. Laboratory results showed leukocytosis, neutrophilia, elevated CRP, elevated transaminases and elevated total bilirubin/conjugated bilirubin. Blood cultures were negative. The patient deteriorated and died on the same day. Her family refused an autopsy.

Clinical Comment: This 29-year-old patient died of pneumonia at 18 days after her last dose of BPaL. Elevated transaminases and bilirubin were associated with the fatal event of pneumonia.

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She had normal liver function up to Week 8 of BPaL treatment. She developed Grade 4 transaminitis nine days after BPaL was interrupted. Methamphetamine use, concomitant paracetamol and ceftriaxone, prednisolone, concurrent pneumonia, and poor peripheral perfusion were contributing factors for hepatotoxicity and confound an attribution of hepatotoxicity to the BPaL regimen. BPaL could have contributed to transaminitis and hyperbilirubinemia; however, the reviewer agrees with the investigator and the applicant that a causal relationship between BPaL and the reported adverse event of hepatotoxicity cannot be definitively concluded.

Deaths in the Post Treatment Period

Subject (b) (6), M/ 38y (unknown cause of death, reported as "natural causes"):
This 38-year-old HIV-positive male with XDR-TB had a past medical history which included DS-TB, syphilis, dysphonia, hypoesthesia and dry skin. He achieved sputum culture conversion at Week 4 on BPaL treatment and completed the trial treatment and attended all follow-up visits. At the Month 3 follow-up visit, a sputum culture was negative. At 185 days after the last dose of study drugs, the patient died. The death certificate stated the patient's cause of death was "natural causes" which means, in South Africa, that no violence was involved.

Clinical Comment: This patient with XDR TB responded well to treatment and was culture negative at Month 3 post completion of the six-month BPaL regimen. His death was not related to BPaL.

Subject (b) (6), M/55y (left lower limb gangrene and sepsis):
This 55-year-old HIV-positive male with XDR-TB had a history of DS-TB diagnosed 8 years prior to enrollment. Current ARV treatment included abacavir, lamivudine and nevirapine.
At Week 12, the patient had a sputum culture conversion and remained negative until the two-month follow-up visit. Linezolid dose was reduced to 600 mg daily due to grade 2 anemia. Patient developed mild peripheral neuropathy and was prescribed gabapentin. The patient completed the BPaL regimen on Day 183 (26 weeks). He was noted to have a favorable clinical response at end of treatment. He continued to take gabapentin for mild peripheral neuropathy. However, sputum samples were positive for *M. tuberculosis* on Day 266 and Day 299. The patient was classified as a treatment failure of BPaL and on Trial Day 403 he was withdrawn from the trial due to relapse of XDR-TB.
Microbiological evaluation of the baseline and follow-up (month 3 post treatment) *M. tuberculosis* isolates revealed the follow-up isolate was resistant to bedaquiline and genotypic analysis revealed that the isolates differed by 5 SNPs, confirming relapse with a new *M. tuberculosis* strain.
Peripheral vascular disease was not documented in the patient's history prior to study enrollment; however, on Day 391, the patient presented with a cold, discolored left leg which progressed to ulceration and dry gangrene of the left foot and ankle. The patient did not respond to anticoagulants and antibacterial drugs and he developed hematemesis and epistaxis. On Trial Day 486, the patient died due to a presumptive diagnosis of thrombotic thrombocytopenic purpura (TTP) secondary to sepsis, caused by gangrene from peripheral

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vascular disease. An autopsy was not performed.

Clinical comment: The patient was withdrawn from the trial due to XDR-TB relapse on Day 403, which was approximately three months before his death due to sepsis/gangrene on Day 486. The mild peripheral neuropathy was probably due to linezolid. The clinical reviewer agrees with the investigator that gangrene and sepsis and TTP which led to his death were not related to study drugs. Although the patient relapsed with a new genotype of M. tuberculosis, this case is considered a BPaL treatment failure for the analysis of efficacy.

Summary of Deaths in Nix-TB

Six (5.5%) deaths occurred due to SAEs while on BPaL treatment and two deaths occurred in the post treatment period. The clinical reviewer does not consider these the deaths to be directly related to the BPaL regimen. Most deaths were due to progression of tuberculosis. Two patients ([redacted] (b) (6) and [redacted] (b) (6)) had other potential causes for acute pancreatitis including HIV and ARV therapy and one had a history of heavy alcohol use; however, an association between pancreatitis and the BPaL regimen cannot be excluded as it occurred on treatment. The patient, Subject [redacted] (b) (6), who developed increased transaminases and bilirubin on which progressed to liver failure off treatment also had confounding factors for hepatotoxicity such as recent methamphetamine use, concomitant paracetamol, ceftriaxone, prednisolone, concurrent bacterial pneumonia and poor peripheral perfusion.

ZeNix Trial

No deaths were reported in ZeNix trial of the BPaL regimen at the same data cutoff date of March 26, 2018.

Deaths in the Clinical Development Program for Pretomanid

In the safety database (n=1507) for the clinical development program, 15 (1%) patients died while on treatment with a pretomanid-containing regimen or control regimen. Treatment emergent deaths occurred in Nix-TB trial (6 deaths), study NC-005 (3 deaths), and study NC-006 (6 deaths).

In studies NC-005 and NC-006, the treatment regimens included combinations of bedaquiline (B), pretomanid (Pa), moxifloxacin(M), and pyrazinamide (Z), i.e., BPaZ / BPaMZ, and MPaZ, respectively. The control anti-TB regimen in patients with DS-TB was isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E), i.e. HRZE. Other deaths were related to progression of tuberculosis, pneumothorax, kidney injury, or cancer. In the study NC-006, also known as the "STAND" trial, three patients died due to acute liver failure and these three deaths were considered related to the MPaZ regimen. In study NC-005, one patient who received the HRZE standard of care regimen died due to acute liver failure.

Treatment emergent deaths for the clinical development program for pretomanid other than Nix-TB are summarized in Table 9-7.

Table 9-7. Treatment Emergent Deaths occurring in Clinical Studies NC-002, NC-005, NC-006

Study ID	Subject ID Gender / Age	Drug Regimen	TB / HIV Status	Study Day of Death	Cause of Death Preferred Term / Verbatim Term

Study ID	Subject ID Gender / Age	Drug Regimen	TB / HIV Status	Study Day of Death	Cause of Death Preferred Term / Verbatim Term
NC-005	(b) (6) M / 46	HRZE Control	DS / POSITIVE	44	ACUTE KIDNEY INJURY / ACUTE KIDNEY INJURY
					ACUTE HEPATIC FAILURE / ACUTE LIVER FAILURE
NC-005	(b) (6) M / 34	BPa (200 mg) Z	DS / POSITIVE	23	PNEUMOTHORAX SPONTANEOUS / SPONTANEOUS RIGHT PNEUMOTHORAX
					PNEUMONIA / SUPERADDED PNEUMONIA
NC-005	(b) (6) M / 38	B (loading dose) Pa (200 mg) Z	DS / NEGATIVE	5	PNEUMOTHORAX / RIGHT-SIDED PNEUMOTHORAX
NC-006	(b) (6) F / 39	Pa (200 mg) MZ - 6 months	DS / POSITIVE	163	DEATH / DEATH DUE TO NATURAL CAUSES (CAUSE UNKNOWN)
NC-006	(b) (6) M / 61	Pa (200 mg) MZ - 6 months	MDR / NEGATIVE	34	LUNG CANCER METASTATIC / METASTATIC LUNG CANCER
NC-006	(b) (6) M / 47	Pa (200 mg) MZ - 6 months	DS / POSITIVE	469	ANAL SQUAMOUS CELL CARCINOMA / SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL
NC-006	(b) (6) F / 44	Pa (200 mg) MZ - 4 months	DS / POSITIVE	28	HEPATOTOXICITY / HEPATOTOXICITY
NC-006	(b) (6) M / 21	Pa (100 mg) MZ - 4 months	DS / NEGATIVE	39	ACUTE HEPATIC FAILURE / FULMINANT LIVER FAILURE
NC-006	(b) (6) F / 23	Pa (200 mg) MZ - 4 months	DS / POSITIVE	34	HEPATIC ENCEPHALOPATHY / HEPATIC ENCEPHALOPATHY
					JAUNDICE / JAUNDICE

Source: ISS ADSL and ISS ADAE datasets. DS: drug-sensitive. MDR: multi-drug resistant. bedaquiline (B), pretomanid (Pa), moxifloxacin(M), and pyrazinamide (Z).

Post treatment Deaths

Eighteen patients died during the post treatment follow-up period, Table 9-8. In phase 2 and phase 3 studies, other than Nix-TB, deaths occurring in patients who were off study drugs were mostly due to complications of underlying disease, gastrointestinal bleed, homicide, accident, or unknown cause.

Table 9-8. Deaths in Post Treatment Period in Clinical Studies NC-002, NC-005, NC-006

Study ID	Subject ID Gender / Age	Drug Regimen	TB / HIV Status	Study Day of Death	Cause of Death Preferred Term / Verbatim Term
NC-005	(b) (6) M / 29	BPa (200 mg) Z	DS / NEGATIVE	731	HOMICIDE / HOMICIDE
NC-006	(b) (6) M / 60	Pa (100 mg) MZ - 4 months	DS / NEGATIVE	482	ACCIDENT AT WORK / WORK / FELL FROM BULLDOZER AT WORK
NC-006	(b) (6) M / 45	Pa (200 mg) MZ - 4 months	DS / NEGATIVE	343	NOSOCOMIAL INFECTION / NOSOCOMIAL SEPSIS (PROBABLY RESPIRATORY)
NC-006	(b) (6) M / 45	Pa (200 mg) MZ - 6 months	DS / NEGATIVE	114	PULMONARY TUBERCULOSIS / ACUTE DETERIORATION OF TB CONDITION
					PNEUMOTHORAX / PNEUMOTHORAX
NC-006	(b) (6) M / 51	HRZE Control	DS / NEGATIVE	576	PNEUMONIA / LEFT LOBAR PNEUMONIA
NC-006	(b) (6) M / 31	Pa (100 mg) MZ - 4 months	DS / POSITIVE	305	HAEMATEMESIS / HEMATEMESIS
NC-006	(b) (6) F / 54	HRZE Control	DS / POSITIVE	707	LOWER RESPIRATORY TRACT INFECTION / LOWER RESPIRATORY TRACT INFECTION
NC-005	(b) (6) M / 35	BPa (200 mg) MZ	MDR / NEGATIVE	392	COR PULMONALE / SEVERE COR-PULMONALE
NC-005	(b) (6) M / 35	BPa (200 mg) MZ	MDR / POSITIVE	114	DISSEMINATED TUBERCULOSIS / SEVERE DISSEMINATED TB
NC-005	(b) (6) M / 45	BPa (200 mg) MZ	MDR / NEGATIVE	183	DYSPNOEA / SEVERE DYSPNOEA
NC-005	(b) (6) M / 35	BPa (200 mg) Z	DS / NEGATIVE	508	CIRCULATORY COLLAPSE / DEATH DUE TO CARDIOVASCULAR FAILURE SECONDARY TO SEVERE UPPER GASTROINTESTINAL BLEEDING
					UPPER GASTROINTESTINAL HAEMORRHAGE / SEVERE UPPER GASTROINTESTINAL BLEEDING
NC-005	(b) (6) M / 64	B (loading dose) Pa (200 mg) Z	DS / POSITIVE	403	HIV INFECTION / HIV DISEASE
NC-005	(b) (6) M / 39	HRZE Control	DS / POSITIVE	437	DEATH / DEATH, UNKNOWN CAUSE
NC-005	(b) (6) M / 21	BPa (200 mg) MZ	MDR / NEGATIVE	Unknown	DROWNING / POSSIBLE DROWNING
NC-006	(b) (6) M / 37	Pa (100 mg) MZ - 4 months	DS / NEGATIVE	436	HAEMOPTYSIS / MASSIVE HEMOPTYSIS
NC-002	(b) (6) F / 37	Pa (100 mg) MZ	DS / NEGATIVE	Unknown*	DEATH / DEATH-CAUSE UNKNOWN

Source: ISS ADSL and ISS ADAE datasets. DS: drug-sensitive. MDR: multi-drug resistant. bedaquiline (B), pretomanid (Pa), moxifloxacin(M), and pyrazinamide (Z). *In the Adverse Event (ADAE) dataset, subject (b) (6) has a fatal adverse event 'Death' on study Day 41. In the study report, death was reported due to respiratory failure.

9.4.2. Serious Adverse Events

Serious adverse events (SAEs) occurred in 19 (17.4%) of patients. SAEs (not pulmonary tuberculosis) occurring in ≥2 subjects included pneumonia (3, 2.8%), sepsis (2, 1.8%), anemia (2, 1.8%), hypoglycemia (2. 1.8%), pancreatitis/hemorrhagic pancreatitis (2, 1.8%), optic neuritis/optic neuropathy (2, 1.8%), seizure (2, 1.8%), and upper gastrointestinal hemorrhage/hematemesis (2, 1.8%). Six (32%) of the 19 patients developed SAEs which led to death as described in section 9.4.1. In the other 13 subjects, the SAEs resolved or were resolving at the time of the data cutoff date of March 26, 2018.

Table 9-9. Study Nix-TB: Serious Adverse Events by System Organ Class and Preferred Term

	BPaL (N=109)
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)
HAEMATEMESIS	1 (0.9)
PANCREATITIS	1 (0.9)
PANCREATITIS HAEMORRHAGIC	1 (0.9)
UPPER GASTROINTESTINAL HAEMORRHAGE	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)**
GENERALISED 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)
HAEMOPTYSIS	1 (0.9)
PNEUMOTHORAX SPONTANEOUS	1 (0.9)
PSYCHIATRIC DISORDERS	**2 (1.8)**
DEPRESSION SUICIDAL	1 (0.9)
GENERALISED 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)**
TRANSAMINASES INCREASED	1 (0.9)

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

All SAEs occurred after 14 days of BPaL treatment and approximately 50% of SAEs occurred between Weeks 8 to 26. Following a review of the case narratives for the SAEs, this reviewer considered the following SAEs to be associated with the study drug regimen, BPaL:
Neutropenia (probably related, resolving); pancreatitis hemorrhagic (possibly related, fatal); pancreatitis hemorrhagic (possibly related, fatal), upper gastrointestinal hemorrhage (possibly related, fatal); abdominal pain upper/ gastritis (possibly related, resolved); optic neuritis (related, resolved); multiple organ dysfunction syndrome (unrelated, fatal); optic neuropathy (related, resolved); anemia (probably related, resolved); lactic acidosis (possibly related, resolved); hypoglycemia (possibly related, resolved). Many of these cases are discussed in 9.5. SAEs such as worsening of pulmonary tuberculosis and tuberculoma were associated with underlying disease and are not considered related to the BPaL regimen.
Serious adverse events such as anemia, optic neuropathy/neuritis, and pancreatitis each led to the withdrawal or interruption of study drug(s) in two (1.8%) patients, respectively. Other SAEs leading to interruption or discontinuation of study drug(s) included seizure, hypoglycemia, lactic acidosis, hematemesis, and neutropenia in 1(0.9%) patient, respectively.

9.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the Nix-TB trial, 93 (85.3%) subjects completed six months of treatment with BPaL as of the cutoff date of March 26, 2018, see Table 9-10. Out of 93 patients, 15 (13.8%) subjects completed the entire study i.e., 6 months of treatment and 24 months of follow-up.
Among the 109 patients, 84 (77.1%) are 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%) due to relapse of tuberculosis (2 patients) or withdrawal of consent (1 patient).
The two patients who had relapse of pulmonary tuberculosis completed treatment before they relapsed, and both discontinued from the study; one of them died on Day 486 of sepsis due to gangrene from peripheral vascular disease.
There were 8 (7.3%) deaths overall in the NixTB trial, six patients died while on BPaL treatment and two patients died at Day 369 and Day 486, respectively, in the posttreatment period.

Reference ID: 4476823

Table 9-10. Study Nix-TB: Disposition of Study Subjects

	BPaL, 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 because of 'Other'. Subject (b) (6) (b) (6) is listed in 'ongoing treatment in the applicant's initial ISS data and documentation; however, this subject discontinued from the study because of 'Other' per 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)

9.4.4. Overview of Treatment Emergent Adverse Events

Treatment Emergent Adverse Events

In the NixTB trial, TEAEs occurred in all 109 (100%) patients. Nineteen (17.4%) subjects experienced at least one serious adverse events (SAE). A grade 3 (severe) or grade 4 (life-threatening) TEAE was reported in 58 (53.2%) subjects. Linezolid alone was permanently discontinued due to a TEAE at a higher rate than the entire BPaL regimen, i.e., 27 (24.8%) versus 6 (5.5%) patients. Six (5.5%) patients discontinued the BPaL regimen due to death.

Table 9-11. Study Nix-TB: Overview of Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAEs)	BPaL Regimen. N=109 Subjects n/N (%)
Any TEAE	***109 (100%)***
Serious TEAE	19 (17.4%)
TEAE by worst severity	
Life-threatening	17 (15.6%)
Severe	41 (37.6%)
Moderate	43 (39.4%)
Mild	8 (7.3%)

Reference ID: 4476823

TEAEs leading to discontinuation of any study drug	33 (30.3%)
TEAEs leading to discontinuation of linezolid	27 (24.8%)
TEAEs leading to discontinuation of BPaL	6 (5.5%)
TEAEs leading to death	6 (5.5%)

Source: Adapted from Table 11 in the applicant's Summary of Clinical Safety. Dataset used: ADAE.

Significant Adverse Events

Designated Medical Events (DME) are adverse events reflecting serious medical conditions that may be related to drugs. An evaluation of reported AEs according to CDER's list of Designated Medical Events (DME) was performed to identify subjects who experienced one of the following: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome, Torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation.

In the NixTB trial, QT prolongation, acute pancreatitis, bone marrow suppression, pancytopenia, and seizures were reported; these TEAEs are discussed in section 9.5.

9.4.5. Common Treatment Emergent Adverse Events

Peripheral neuropathy was the most common TEAE, reported in 87 (80%) patients. Among these 87 patients, peripheral sensory neuropathy occurred in 75 (69%) patients. The next most common TEAEs were dermatitis acneiform/ acne and anemia occurring in 41 (38%) and 40 (37%) patients, respectively. Elevations in hepatic transaminases occurred in 27 (25%) of patients. Other adverse events experienced by >20% of patients included nausea, vomiting, headache, skin rash, decreased appetite, and dyspepsia.

Preferred terms (PTs) for common TEAEs were grouped and then analyzed with a cutoff ≥ 5%, see Table 9-12. TEAEs of special interest such as myelosuppression, prolongation of the QT interval, peripheral and optic neuropathy/neuritis, and pancreatitis are discussed in section 9.5. There were no cases of anaphylaxis or anaphylactoid reactions reported in the trial.

Table 9-12. Study Nix-TB: Treatment Emergent Adverse Events (Grouped) in ≥ 5% subjects – Safety Population

TEAEs by Preferred Term ≥ 5%	**BPaL (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)

TEAEs by Preferred Term ≥ 5%	BPaL (N=109)
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)
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

Clinical Reviewer's Comment: Several MedDRA-coded preferred terms (PT) were split in the applicant's analysis of SAEs and TEAEs. Splitting of preferred terms may underestimate a potential safety signal. The applicant noted, in a response to an information request, that PTs were kept separate to be as accurate as possible relative to the verbatim descriptions from the investigators. Linezolid is associated with optic neuropathy and peripheral sensory neuropathy and it appears appropriate to combine PTs, "Optic neuritis"/ "optic neuropathy" and to combine "peripheral sensory neuropathy" / "neuropathy peripheral". The PT, "peripheral neuropathy" was used when the investigator did not specify sensory or motor neuropathy.

TEAEs Leading to Discontinuation of Linezolid or BPaL regimen

Per the protocol for the Nix-TB study, if a subject experienced a suspected linezolid-related toxicity, the dose of linezolid may be reduced or it could be temporarily halted for up to 35 consecutive days. Linezolid 600 mg was administered twice daily to the initial 44 subjects enrolled and the remaining 65 subjects received linezolid 1200 mg once daily, as outlined in a protocol amendment. If temporarily halted, linezolid should generally be restarted at a lower dose; step-down dosing would typically proceed from 1200 mg to 600 mg to 300 mg daily. Linezolid could be restarted at the same dose at the investigator's discretion. If a patient developed toxicity issues associated with linezolid that prohibit further treatment with the drug, the patient could remain on bedaquiline and pretomanid if they received the initial 1200 mg daily dose of linezolid for at least the first 4 weeks of treatment and they were smear-negative or had trace results and judged to be clinically improving by the investigator.

If a patient experienced a suspected toxicity due to bedaquiline and/or pretomanid, the entire BPaL regimen could be halted for up to 35 consecutive days. Treatment with a single drug was not allowed. If a patient remained culture-positive at the Month 4 visit, he/she may have treatment extended to 9 months (with 24 months of follow-up) or be withdrawn from the study.

TEAEs leading to dosing interruptions and dose reductions of study drugs are summarized in Table 9-13. The doses of pretomanid and bedaquiline were not changed during the trial. Linezolid 600 mg was administered twice daily to the initial 44 subjects enrolled and the remaining 65 subjects received linezolid 1200 mg once daily, as outlined in a protocol amendment.

Linezolid was permanently discontinued due to an TEAE in 28 (26%) subjects; there is a difference of one subject between the ADAE or ADEX dataset. BPaL was permanently discontinued in the 6 (5.5%) patients who died on treatment.

Dosing of BPaL or linezolid alone was interrupted due to a TEAE in 20 (18%) and in 48 (44%) patients, respectively. The dose of linezolid was reduced in 43 (39.4%) patients during the treatment period. The doses of pretomanid and bedaquiline were not changed during the trial. Peripheral sensory neuropathy was the most common TEAEs leading to discontinuation, dose reduction, or a dosing interruption of linezolid. Increased hepatic transaminases or drug-induced liver injury (DILI) caused interruption of BPaL in 6(5.5%) and 2(1.8%) patients, respectively.

Table 9-13. Nix-TB: Treatment Emergent Adverse Events Leading to Discontinuation, Dose Reduction or Interruption of Linezolid and BPaL Regimen

	BPaL (N=109)			
	BPaL Interruptions n (%)	**Linezolid Discontinuations n (%)**	**Linezolid Dose Reductions n (%)**	**Linezolid Dose Interruptions n (%)**
Total Subjects	**20 (18.3)**	**28 (25.7)**	**43 (39.4)**	**48 (44.0)**
By Preferred Term				
Peripheral neuropathy*	1 (0.9)	25 (22.9)	30 (27.5)	31 (28.4)
Anemia	2 (1.8)	2 (1.8)	13 (11.9)	16 (14.7)

	BPaL (N=109)			
	BPaL Interruptions n (%)	**Linezolid Discontinuations n (%)**	**Linezolid Dose Reductions n (%)**	**Linezolid Dose Interruptions n (%)**
ALT/AST increased[§]	6 (5.5)	0	1 (0.9)	0
Abdominal pain[¶]	4 (3.7)	0	0	1 (0.9)
Blood lactic acid increased[¥]	2 (1.8)	0	0	3 (2.8)
Thrombocytopenia	1 (0.9)	0	1 (0.9)	2 (1.8)
Vision disturbance[±]	1 (0.9)	0	1 (0.9)	2 (1.8)
Neutropenia	0	0	1 (0.9)	3 2.8)
Hematemesis[Ω]	2 (1.8)	1 (0.9)	0	0
Pancreatitis / Pancreatitis hemorrhagic	2 (1.8)	1 (0.9)	0	0
Vomiting	2 (1.8)	0	0	1 (0.9)
Amylase increased / Hyperamylasemia	2 (1.8)	0	0	0
Bone marrow failure	1 (0.9)	0	1 (0.9)	0
Drug-induced liver injury	2 (1.8)	0	0	0
Nausea	1 (0.9)	0	0	1 (0.9)
Optic neuritis / Optic neuropathy	0	1 (0.9)	0	1 (0.9)
Rash[‡]	0	1 (0.9)	0	1 (0.9)
Lipase increased / Hyperlipasemia	0	0	1 (0.9)	1 (0.9)
Acidosis	1 (0.9)	0	0	0
Bicytopenia	1 (0.9)	0	0	0
Diarrhea	1 (0.9)	0	0	0
Gastritis	1 (0.9)	0	0	0
Generalized tonic-clonic seizure / Seizure	1 (0.9)	0	0	0
Sepsis / Septic shock	1 (0.9)	0	0	0
Hypoglycemia	0	1 (0.9)	0	0
Multiple organ dysfunction syndrome	0	1 (0.9)	0	0
Asthenia	0	0	1 (0.9)	0
Optic disc hyperemia / Papilledema	0	0	1 (0.9)	0
Retinal hemorrhage	0	0	1 (0.9)	0
Gamma-glutamyltransferase increased	0	0	0	1 (0.9)
Gastroenteritis viral	0	0	0	1 (0.9)
Hemoptysis	0	0	0	1 (0.9)
Hypomagnesemia	0	0	0	1 (0.9)

Source: SAS (v9.4) and R (v3.5)
Datasets: Nix-TB ISS-Cut ADEX, Tables reflect the applicant's methodology as used in ISS tables 6.15.1, 6.15.2, and 6.15.3;
Per tables 6.15.1 and 6.15.2 footnotes, BPaL column includes interruptions that occurred simultaneously across all three trial drugs. Linezolid columns include discontinuations/interruptions that occurred in linezolid only, therefore excluding interruptions that occurred also in the other two drugs.
*Peripheral Neuropathy includes: Neuropathy peripheral / Peripheral sensory neuropathy / Paresthesia / Hypoesthesia / Peripheral sensorimotor neuropathy
[§]ALT /AST Increased includes: Transaminases increased / Alanine aminotransferase increased / Aspartate aminotransferase increased / Hepatic enzyme increased / Liver function test increased / Hepatic function abnormal
[‡]Rash includes: Rash / Rash pruritic / Rash papular / Rash maculo-papular / Rash erythematous / Rash vesicular
[¶]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
[Ω]Hematemesis includes: Hematemesis / Upper gastrointestinal hemorrhage

Duration of Treatment Interruptions for Study Drugs

The mean total number of days that dosing was interrupted (sum of all interruptions for a

subject) due to a TEAE was longer for linezolid than for the entire BPaL regimen, i.e., 44.5 days (range 2 to 145 days) versus 19.6 days (range 2 to 48 days), respectively. See Table 9-14.

Table 9-14. Study NixTB: Duration of Treatment Interruption for Study Drugs due to TEAEs

Study Drug(s)	Days [mean (range)] of interrupted treatment	Maximum Duration (Days) Dosing Interruption
Linezolid	44.5 (2-145)	35.5 (2-118)
BPaL regimen	19.6 (2-48)	12.1 (2-30)

The rate of dose interruptions and/or dose reductions of linezolid increased steadily over time from study Day 20 to 150, with a median time to a first dose interruption of approximately 110 days. The rate of dosing interruptions and/or dose reductions was slightly higher in the linezolid 600mg bid group than the 1200mg/day group. Dose interruptions or dose reductions of linezolid due to peripheral neuropathy increased over time and occurred at similar rates in the two dose groups, see Kaplan-Meier graphs, **Figure 9-2** and **Figure 9-3**.

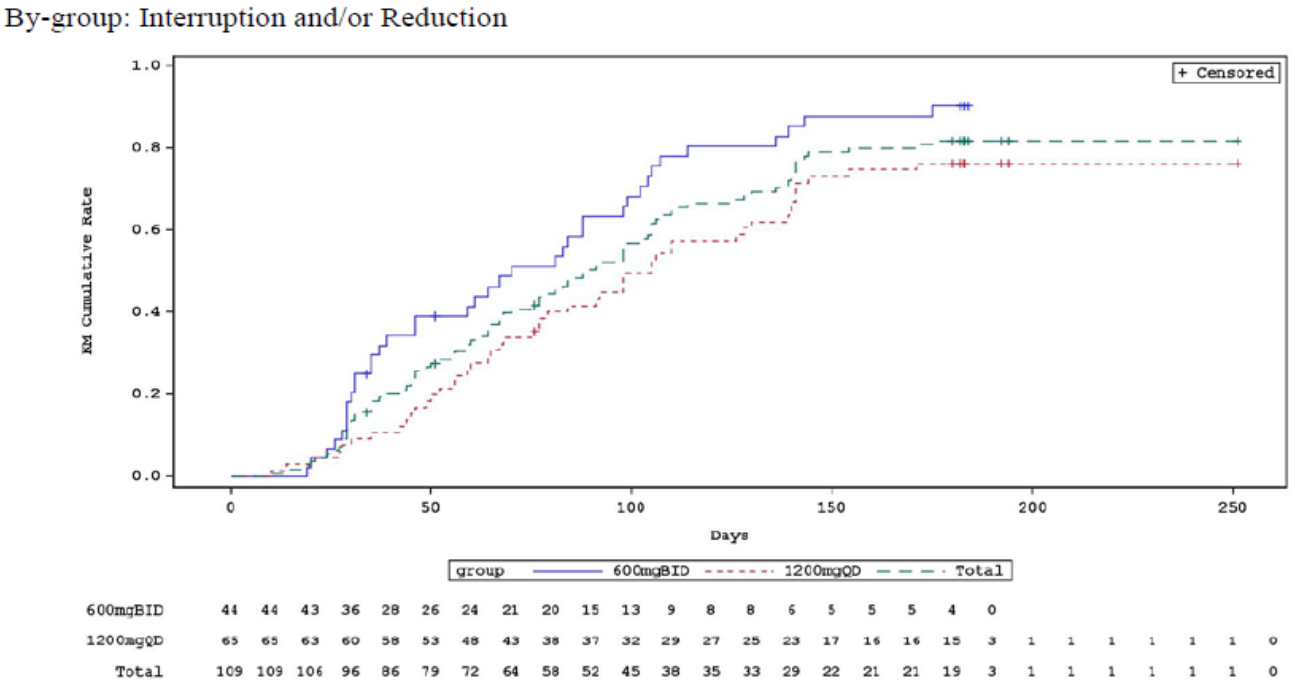


Figure 9-2. NixTB: Kaplan-Meier Curve of Time (Days) to First Dose Interruption and/or Dose Reduction of Linezolid due to an Adverse Event - Safety Analysis Population

Abbreviations: KM, Kaplan-Meier

Time to first interruption and/or reduction (days) = (Date of interruption or reduction - Date of first trial drug administration) + 1. Censored observation: Subjects who do not have a dose interruption and/or dose reduction in linezolid due to an adverse event are censored at the time of premature treatment discontinuation or treatment completion.

Source: Figure 3.1 in ISS; verified by clinical data analyst using JReview v.13.0.

By-group: Interruption and/or Reduction

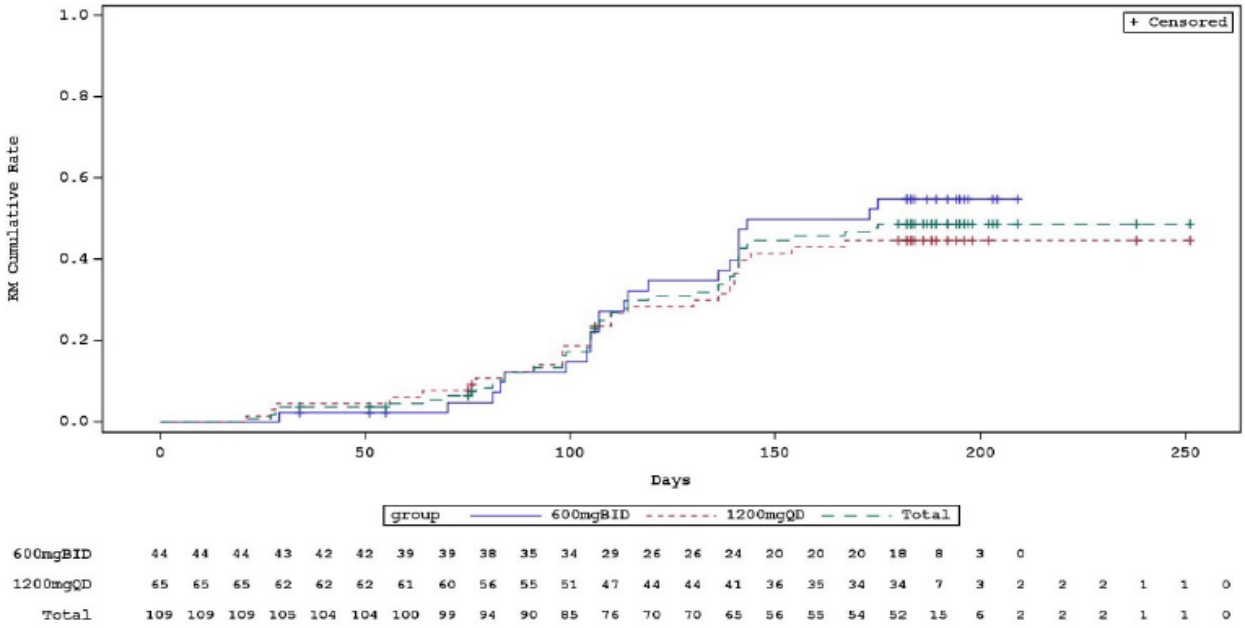


Figure 9-3. NixTB: Kaplan-Meier Curve of Time (Days) to First Dose Interruption and/or Dose Reduction of Linezolid due to Peripheral Neuropathy - Safety Analysis Population

Time to first interruption and/or reduction (days) = (Date of interruption or reduction - Date of first trial drug administration) + 1. Censored observation: Subjects who do not have a dose interruption and/or dose reduction in Linezolid due to an adverse event are censored at the time of premature treatment discontinuation or treatment completion.

Source: Figure 3.1 in ISS; verified by clinical data analyst using JReview v. 13.0.

TEAEs not Resolved

Select TEAEs of interest that were not resolved by the data cutoff date of March 26, 2018 included peripheral neuropathy (mostly sensory neuropathy) in 21 (19.3) patients, myelosuppression (anemia, bone marrow failure) in 3 (2.7%) patients, and QT prolongation (mild) in 1(0.9%) patient.

9.4.6. Laboratory Findings

Analyses of laboratory test results for hematology, chemistry, and hepatology are presented in the following tables. The toxicity grades used in the study are based on National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases Adult Toxicity Table (2007, Draft).

<u>Hematology</u>

Decreases in hemoglobin (Hb), hematocrit (Hct), white blood cell (WBC), and platelet counts from baseline were analyzed using the applicant's laboratory dataset (ADLB). The toxicity grades for these hematologic laboratory parameters were mostly grade 1 or 2 (mild to moderate) severity.

Table 9-15. Study Nix-TB: Treatment Emergent Graded Laboratory Abnormalities - Hematology

Parameter	BPaL N=109			
	Grade 1 / Mild. n/N (%)	Grade 2/ Moderate. n/N (%)	Grade 3/ Severe. n/N (%)	Grade 4/ Life – threatening. n/N (%)
Hemoglobin (g/dL)*	27 (24.8)	26 (23.9)	6 (5.5)	0
Absolute Neutrophil Count (10^9/L)	19 (17.4)	9 (8.3)	4 (3.7)	1 (0.9)
Platelets (10^9/L)	3 (2.8)	1 (0.9)	2 (1.8)	0
White Blood cells (10^9/L)	22 (20.2)	6 (5.5)	6 (5.5)	0

Source: Adapted from Table 8.3.1 in Clinical Summary of Safety.
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and Nix-TB ISS-Cut ADLB. Subjects were counted only once at the highest post-baseline toxicity grade.
*One patient who had Hb nadir of 6.1g/dL (grade 4) at Week 9 and required a blood transfusion is not included; this Hb test may have been performed at a local laboratory as it was not included in the ADLAB dataset.

Hemoglobin (Hb): In the Nix-TB study, approximately 53% of the subjects had Hb levels < LLN at baseline. Thirty-four (31%) patients who had normal Hb/Hct at baseline experienced a decrease in their Hb level and Hct post baseline.

Table 9-16. Study Nix-TB: Baseline to Minimum Post Baseline Shifts in Hemoglobin (g/dL) Value Category

	BPaL regimen (n=109), n/N (%)		
	Min Post-Baseline Hemoglobin g/dL		
Baseline Hemoglobin (g/dL)	**< LLN**	**≥ LLN - ≤ ULN**	**> ULN**
< LLN	58 (53.2)	0	0
≥ LLN - ≤ ULN	34 (31.2)	17 (15.6)	0

Median Hb (g/dL) levels were higher at the end of treatment at Week 26 (Hb 13.6 g/dL) compared to median (Hb 12.0 g/dL) at baseline. The median Hb nadir occurred at Week 7 with Hb 11.75 g/dL. The lowest recorded level in the dataset was Hb 6.6g/dL at Week 9. Patients recovered from anemia with dosing interruptions and dose reductions of linezolid.
Platelet Count: Fourteen (13%) patients with a normal platelet count at baseline experienced decreases in platelets count post baseline. Two (1.8%) patients experienced platelet counts < 50,000 x 10^9/L.
White Blood Cell Count: Thirty-seven (34%) patients who had WBC (10^9/L) within the normal range at baseline experienced a decrease in WBC post baseline.
Absolute Neutrophil Count (ANC): A total of 30 (28%) of patients who had an ANC within the normal range at baseline experienced a decrease in ANC < LLN on BPaL treatment. Eight (7.3%) patients experienced an ANC < 750/mm^3 and 1 (0.9%) patient had an ANC < 500/mm^3.

Liver Tests
The incidence of treatment emergent graded abnormalities for hepatic transaminases, ALT and AST, GGT and, alkaline phosphatase, and total bilirubin are summarized in Table 9-17.
Most abnormal hepatic laboratory values were toxicity grade 1. Grade 3 (3 to 8 x ULN) values

for ALT and AST occurred in ≤ 10% of patients. Grade 3 values for GGT, alkaline phosphatase, and total bilirubin were reported in 16 (14.7%), 3 (2.8%), and 0 patients, respectively. Grade 4 (> 8 x ULN) values for ALT, AST, GGT, alkaline phosphatase, and total bilirubin were reported in 1 (0.9%), 1 (0.9%), 5 (4.6%), 0, and 3 (2.8%) patients, respectively.

Table 9-17. Study Nix-TB: Liver Tests - Toxicity Grades

Laboratory Parameter	Max. Analysis Toxicity Grade	BPaL N = 109, n/N (%)
ALANINE AMINOTRANSFERASE (U/L)	GRADE 1	31 (28.4)
	GRADE 2	15 (13.8)
	GRADE 3	11 (10.1)
	GRADE 4	1 (0.9)
ALKALINE PHOSPHATASE (IU/L)	GRADE 1	27 (24.8)
	GRADE 3	3 (2.8)
ASPARTATE AMINOTRANSFERASE (U/L)	GRADE 1	44 (40.4)
	GRADE 2	14 (12.8)
	GRADE 3	10 (9.2)
	GRADE 4	1 (0.9)
GAMMA GLUTAMYL TRANSFERASE (U/L)	GRADE 1	31 (28.4)
	GRADE 2	20 (18.3)
	GRADE 3	16 (14.7)
	GRADE 4	5 (4.6)
TOTAL BILIRUBIN (µmol/L)	GRADE 1	2 (1.8)
	GRADE 2	1 (0.9)
	GRADE 4	3 (2.8)

Source: JReview, v. 13.0.
Datasets used: ADSL, ADLAB. Toxicity grades: Grade 1/ mild, grade 2/ moderates, grade 3 /severe, grade 4/ life-threatening. Subjects are counted once per highest post-baseline toxicity grade.

Alanine aminotransferase (ALT): Post baseline increases in ALT levels occurred in 44 (40.3%) patients, Table. Maximum post baseline increases in ALT levels to > 3 to ≤ 5x ULN or > 5 to ≤10x ULN were observed in 6 (5.5%) patients in each category. Among subjects with ALT in the normal range at baseline, maximum post baseline ALT elevations >3 to ≤5x ULN or >5 to ≤10x ULN were observed in 2 (1.8%) and 3 (2.8%) subjects, respectively.

Table 9-18. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in ALT Level Category

	BPaL (N=109), n/N (%)			
	Max. Post Baseline Shift in ALT Level Categories			
Baseline ALT	**≤ ULN**	**> ULN - ≤ 3xULN**	**> 3xULN - ≤ 5xULN**	**> 5xULN - ≤ 10xULN**
≤ ULN	43 (39.4)	33 (30.3)	2 (1.8)	3 (2.8)
> ULN - ≤ 3xULN	1 (0.9)	20 (18.3)	4 (3.7)	2 (1.8)
> 3xULN - ≤ 5xULN	0	0	0	0
> 5xULN - ≤ 10xULN	0	0	0	1 (0.9) *

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y). Only subjects that have both baseline and post-baseline tests appear in the table.

Reference ID: 4476823

*One (0.9%) patient, Subject (b) (6), had ALT levels of 106 U/L (2.6 x ULN) at screening and fulfilled enrollment criteria for ALT. However, ALT was 248 U/L (6 x ULN) at baseline and was 229 U/L (5.6 x ULN) on Day 3 of treatment. He had a history of transaminitis associated with use of antimycobacterial drugs. His ALT levels decreased to ≤ 1.5 x ULN while on BPaL treatment.

Aspartate aminotransferase (AST): A total of 12 (11%) subjects experienced elevations in AST levels >3 x ULN postbaseline. Among subjects with AST in the normal range at baseline, maximum post-baseline AST elevations >3 to ≤5 x ULN, > 5 to ≤10 x ULN, and > 10 to ≤20x ULN were observed in 3 (2.8%), 1 (0.9%), and 1 (0.9%) patient(s), respectively.

Table 9-19. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in AST Level Category

	BPaL, N=109, n/N (%)				
	Max Post-Baseline AST U/L				
Baseline AST	**≤ ULN**	**> ULN - ≤ 3xULN**	**> 3xULN - ≤ 5xULN**	**> 5xULN - ≤ 10xULN**	**> 10xULN - ≤ 20xULN**
≤ ULN	27 (24.8)	39 (35.8)	3 (2.8)	1 (0.9)	1 (0.9)
> ULN - ≤ 3xULN	2 (1.8)	29 (26.6)	4 (3.7)	2 (1.8)	0
> 3xULN - ≤ 5xULN	0	0	1 (0.9)	0	0

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y). Only subjects that have both baseline and post-baseline tests appear in the table.

Total Bilirubin: Eight (7.3%) patients with normal baseline bilirubin values had elevations post baseline with 2 (1.8%) patients experienced elevations in total bilirubin levels >2x ULN. These two cases also had elevated ALT >3x ULN and are considered potential Hy's Law cases. See Table 9-20 and Figure 9-4.

Table 9-20. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in Total Bilirubin Level Category

	BPaL (n=109), n/N (%)			
	Max Post-Baseline Total BILIRUBIN (µmol/L)			
Baseline BILI	**≤ ULN**	**> ULN - ≤ 2xULN**	**> 2xULN - ≤ 5xULN**	**> 5xULN**
≤ ULN	101 (92.7)	6 (5.5)	2 (1.8)	0
> ULN - ≤ 2xULN	0	0	0	0

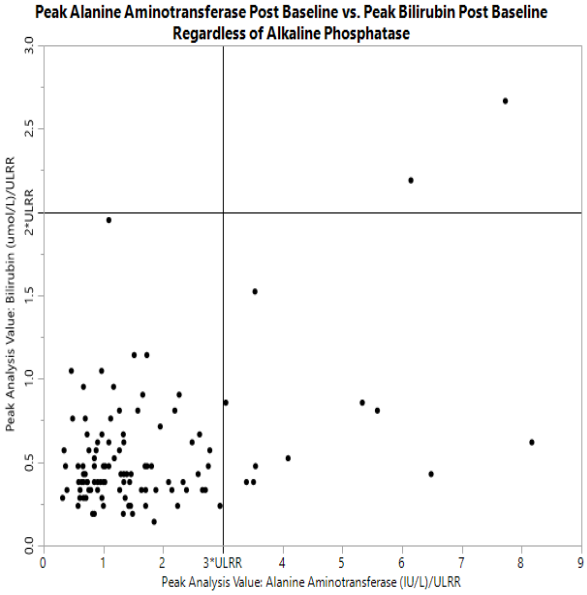
Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y). Only subjects that have both baseline and post-baseline tests appear in the table.

Alkaline phosphatase
Twenty-seven (24.8%) subjects experienced post baseline increases in alkaline phosphatase. Among subjects with alkaline phosphatase in the normal range at baseline, 24 (22%) had a maximum post baseline elevation ≤2x ULN, while elevations >2x ULN were observed in 2 (1.8%) patients. See Table 9-21 and Figure 9-5.

Table 9-21. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in Alkaline Phosphatase Level Category

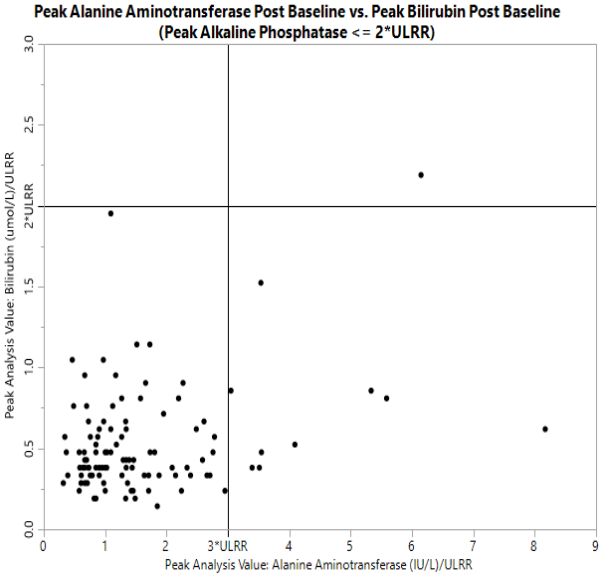
	BPaL (N=109), n/N (%)		
	Max. Post-Baseline Alkaline Phosphatase (IU/L)		
Baseline ALP	**<= ULN**	**> ULN - <= 2xULN**	**> 2xULN**
<= ULN	74 (67.9)	24 (22.0)	2 (1.8)
> ULN - <= 2 xULN	0	8 (7.3)	1 (0.9)

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y)
Only subjects that have both baseline and post-baseline tests appear in the table.



Datasets used: ADSL, ADLAB.

Figure 9-4. Study Nix-TB: Hy's Law Plot - ALT vs Total Bilirubin



Source: Datasets used: ADSL, ADLAB.

Figure 9-5. Study Nix-TB: Hy's Law Plot - ALT vs Total Bilirubin and ALP ≤ 2xULN

Potential Hy's Law Cases

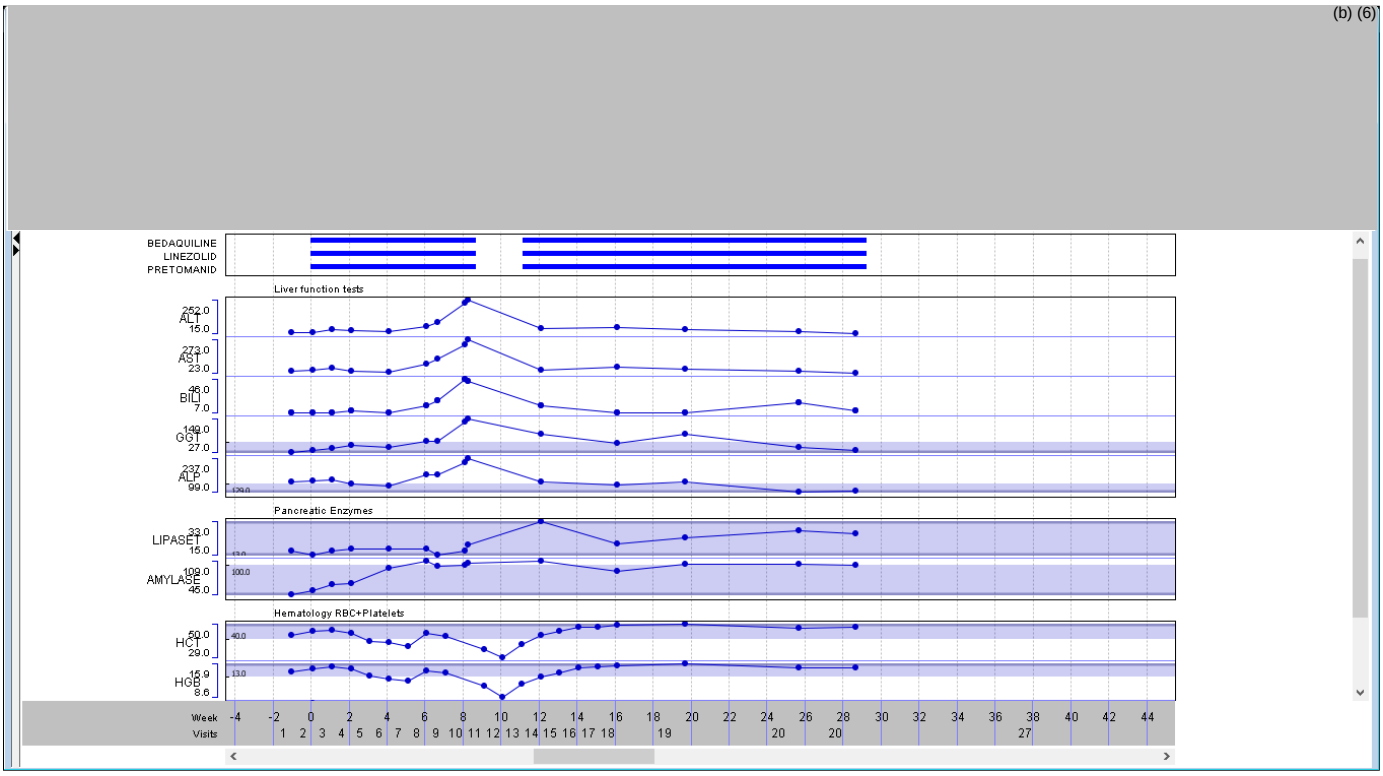
Subject (b) (6) fulfilled the Hy's Law laboratory criteria, ALT > 3 X ULN, total bilirubin ≥ 2 X ULN and alkaline phosphatase <2x ULN. The other patient, Subject (b) (6) had an alkaline phosphatase level >2x ULN and did not fulfill all the criteria for Hy's Law. Case narratives for the two potential Hy's Law cases are summarized below.

Subject (b) (6): This 25-year-old HIV-negative male with XDR-TB had a history of spontaneous pneumothorax, intermittent hemoptysis and nausea. Elevations in hepatic transaminases over time are illustrated in the graphical profile for this patient, Figure 9-6. He had a normal ALT level of 19 U/L at baseline which began to increase around Week 6 of BPaL treatment and peaked at 323 U/L (grade 3) during Week 8. Total bilirubin levels and alkaline phosphatase levels were also increased around Week 8: total bilirubin (max. 46 µmol/L [ULN ≤21 µmol/L] and direct bilirubin (max. 22 µmol/L [0- 5 µmol/L], indirect bilirubin max. 32 (2-17 µmol/L], alkaline phosphatase (max. 324 IU/L [40-129 IU]). Lipase and amylase levels were within normal range throughout the study. The patient was symptomatic with nausea and

Reference ID: 4476823

vomiting probably related to study drugs. His concomitant medications included metoclopramide started just prior to the onset of elevated hepatic transaminases. No alcohol or herbal medicines use were reported. Testing for hepatitis B and C and a urine toxin screen were negative.

The BPaL regimen was interrupted at Week 8 to 11 due to elevated hepatic transaminases and BPaL was reintroduced with a lower dose of linezolid (due to anemia) during Week 11. ALT declined to 50 U/L during Week 12 and declined to within normal range during Week 20. Total bilirubin declined to the normal range by Week 12. The patient completed 26 weeks of BPaL treatment without further dosing interruptions. The patient completed the final trial visit at Month 24 and all TEAEs (including optic neuropathy) had resolved.



Source: JReview, v. 13.0. Datasets used: ADSL, ADLAB.

Figure 9-6. Subject (b) (6): Graphical Patient Profile – Laboratory Tests

Clinical Comment: In Subject (b) (6), Hy's law case criteria are met based on the 2009 FDA Guidance Document in that the peak ALT was >3 × ULN and total bilirubin was >2.2 × ULN with ALP <2 × ULN (actual value 1.8 × ULN).[33] A work up for other causes of hepatoxicity such as Hepatitis B, Hepatitis C, alcohol use, and a urine toxicity screen were negative. There was also a positive dechallenge (total bilirubin improved after the regimen was interrupted) suggesting an association between hepatotoxicity and the BPaL regimen.

[33] 2009 FDA Guidance Document Drug-Induced Liver Injury: Premarketing and Clinical Evaluation. Https://www.fda.gov/downloads/guidances/UCM174090.pdf

Reference ID: 4476823

Subject (b) (6): This 36-year-old HIV-negative patient with MDR-TB and history of COPD, insomnia, and anxiety presented with severe epigastric pain (SAE) due to probable gastritis on Day 27 of BPaL treatment.

During the entire treatment period, there were interruptions in the BPaL regimen for severe epigastric pain, elevations in hepatic transaminases, and peripheral neuropathy (linezolid). Laboratory test results for Hepatitis B and C were not available.

An ALT level was normal at baseline and levels increased between Week 6 to Week 20 peaking at 255 U/L (8x ULN) in Week 10 (~Day 79). Alkaline phosphatase (max. 225 IU/L [35 – 104 IU/L]) and GGT (max. 480 U/L [5 -36 U/L]) levels were elevated during the same timeframe. Total bilirubin (max. 56 µmol/L [ULN ≤21 µmol/L] and direct bilirubin (max. 31 µmol/L [0-5 µmol/L]) levels were elevated from Week 8 to Week 11. On ~Day 73, the BPaL regimen was interrupted due to elevated transaminases and bilirubin.

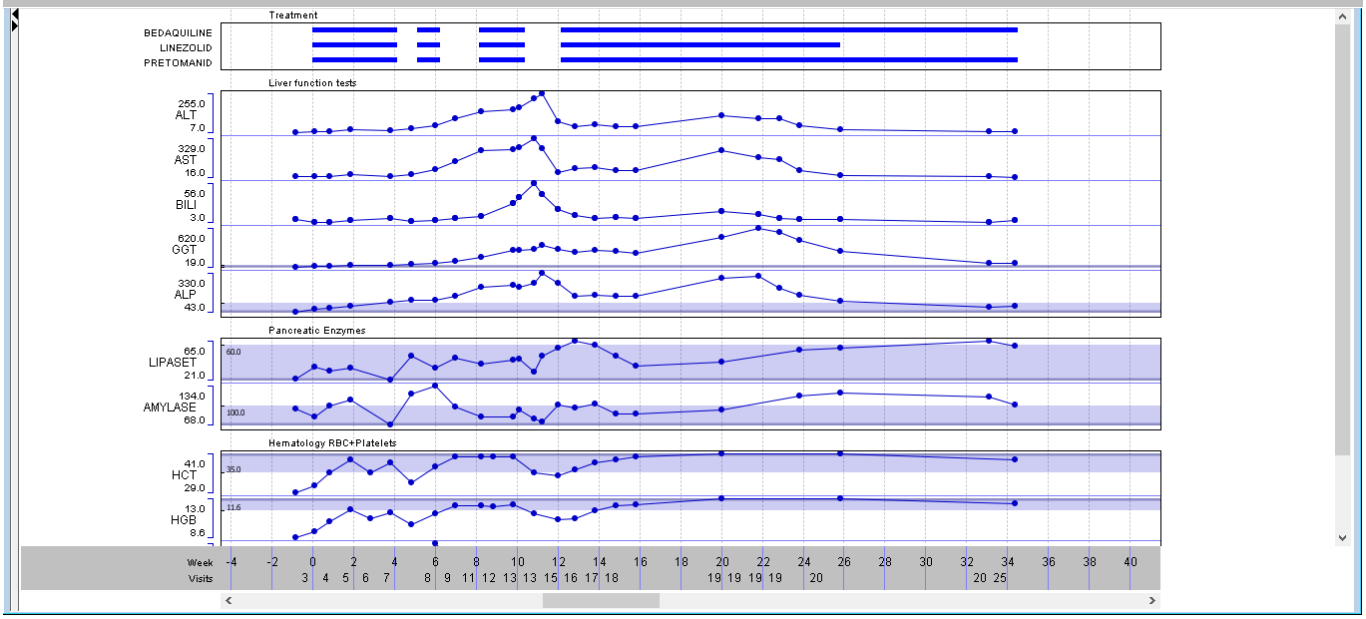
Hepatic transaminases and total bilirubin levels declined to near normal ranges off BPaL and continued to trend downward after restarting BPaL on Day 86 (Week 12). There was a transient increase in ALT (not bilirubin) in Week 20; however, the overall trend in ALT was toward the normal range. GGT was normal at baseline but became elevated from Week 2 through Week 20; the patient consumed alcohol during Week 7 and 8 which probably contributed to the elevations in GGT and ALT/AST. Lipase and amylase levels were in the normal range throughout the study and there was no evidence of pancreatitis.

[On Day 37, when BPaL was reintroduced, linezolid dose was reduced to 600mg /day because the patient had developed peripheral neuropathy. Around Day 140, the dose of linezolid was reduced to 300mg/day for worsening peripheral neuropathy. Linezolid 300mg dose was stopped during Week 26 (Day 180) for worsening peripheral neuropathy].

On Day 241 (Week 34), the participant completed her antimycobacterial treatment with bedaquiline and pretomanid and hepatic transaminases and bilirubin remained in the normal range through the end of therapy in Week 34.

Liver tests over time are illustrated in the graphical profile for Subject (b) (6), see Figure 9-7.

(b) (6)



Source: JReview, v. 13.0. Datasets used: ADSL, ADLAB.

Figure 9-7. Subject (b) (6): Graphical Patient Profile – Laboratory Tests

Clinical Comment: The patient appeared to have a mixed hepatocellular and cholestatic liver injury. The biochemical criteria for Hy's Law case were not met because alkaline phosphatase was > 2x ULN. Elevated alkaline phosphatase levels suggest cholestasis; however, an abdominal ultrasound did not show evidence of biliary duct obstruction or dilation. The patient's alcohol use probably contributed to the increases in transaminases. A contribution of BPaL to hepatotoxicity cannot be ruled out in this case as the transaminases and bilirubin improved after the regimen was interrupted.

In summary, the hepatotoxicity in these two cases was reversible when the dosing of the BPaL regimen was interrupted (positive dechallenge). When the patients were rechallenged, they continued the regimen without experiencing further episodes of hepatotoxicity (negative rechallenge). The consultant hepatologist for the applicant noted that an association between the BPaL regimen and hepatotoxicity cannot be ruled out based on a negative rechallenge because there may have been liver adaptation after the first exposure to the regimen.
A hepatology consult for the Nix-TB trial by John R. Senior, M.D., Office of Surveillance and Epidemiology, is available in DARRTS.

<u>Gamma Glutamyl Transferase</u>

Fifty-four (49.5%) patients had elevations in gamma glutamyl transferase (GGT) post-baseline. Among the patients who had a normal GGT level at baseline, 35 (32.1%) patients had mild elevations (grade 1 or 2) post baseline and 7 (6.4%) patients had elevations >3x ULN.

Table -9-22. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in GGT Level Category

	BPaL (N=109), n/N (%)				
	Maximum Post-Baseline GGT				
Baseline GGT	<= ULN	> ULN - <= 3xULN	> 3xULN - <= 5xULN	> 5xULN - <= 10xULN	> 10xULN
<= ULN	34 (31.2)	35 (32.1)	2 (1.8)	3 (2.8)	2 (1.8)
> ULN - <= 3xULN	0	19 (17.4)	2 (1.8)	5 (4.6)	1 (0.9)
> 3xULN - <= 5xULN	0	1 (0.9)	1 (0.9)	2 (1.8)	0
> 5xULN - <= 10xULN	0	0	1 (0.9)	0	1 (0.9)

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y)
Only subjects that have both baseline and post-baseline tests appear in the table.

Lipase

Among patients with normal lipase levels at baseline, elevations post-baseline occurred in 19 (17.4%) patients and most of them were grade 1 or 2 (< 2x ULN). Four (3.7%) patients had a maximum post baseline elevation in lipase >2 to 5x ULN (grade 3) on BPaL treatment. One (0.9%) patient who had a mild elevation in lipase (grade 1) at baseline experienced elevated lipase levels > 5 to 10 x ULN (grade 4). There were three cases of pancreatitis in the trial which are discussed in section 9.5.7.

Table 9-23. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in Lipase Level Category

	BPaL, N=109, n/N (%)				
Baseline Lipase	Max Post-Baseline LIPASE (U/L)				
	<= ULN	> ULN - <= 2xULN	> 2xULN - <= 3xULN	> 3xULN - <= 5xULN	> 5xULN - <= 10xULN
<= ULN	83 (76.1)	14 (12.8)	3 (2.8)	1 (0.9)	0
> ULN - <= 2xULN	2 (1.8)	5 (4.6)	0	0	1 (0.9)

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y)
Only subjects that have both baseline and post-baseline tests appear in the table.

Most of the elevations in lipase were < 2x ULN and were not associated with pancreatitis. A lipase level of 710 U/L (> 10x ULN) at Week 7 was reported in the case narrative for a patient who died of hemorrhagic pancreatitis and multi-organ failure, but the result was not reported in the laboratory dataset (ADLAB) under scheduled or unscheduled visits, which suggests that the test may have been performed at a local laboratory.

Amylase

Forty-eight (44%) patients experienced elevations in amylase levels post baseline. Among the

patients who had a normal amylase level at baseline, 35 (32%) patients had mild elevations (grade 1 or 2) post baseline. Two (1.8%) patients had a post baseline maximum elevation in amylase of >2 to 5x ULN (grade 3) on treatment.

Clinical Comment: Elevated amylase levels at baseline were not associated with symptoms of pancreatitis and were most likely related to the patients' underlying tuberculosis and/or HIV.

Table 9-24. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in Amylase Level Category

	BPaL (N=109)				
	Maximum Post-Baseline Amylase (U/L)				
Baseline AMYLASE	<= ULN	> ULN - <= 2xULN	> 2xULN - <= 3xULN	> 3xULN - <= 5xULN	> 5xULN - <= 10xULN
<= ULN	25 (22.9)	35 (32.1)	2 (1.8)	0	0
> ULN - <= 2xULN	0	32 (29.4)	6 (5.5)	3 (2.8)	0
> 2xULN - <= 3xULN	0	0	3 (2.8)	2 (1.8)	0

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y). Only subjects that have both baseline and post-baseline tests appear in the table.

Creatinine

Forty-two (38.5%) patients experienced an increase in creatinine from baseline. Among the patients with a normal creatinine at baseline, 42 had increases in creatinine ≤2x ULN. All post baseline elevations in creatinine were severity grade 1 (1.1 to 1.5x ULN) or grade 2 (1.6 to 3x ULN) and one resulted in an interruption in dosing of study drugs.

Table 9-25. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in Creatinine Level Category

	BPaL, N=109, n (%)		
	Max Post-Baseline CREATININE (mg/dL)		
Baseline CREAT	≤ ULN	> ULN - ≤ 2xULN	> 2xULN
≤ ULN	62 (56.9)	42 (38.5)	0
> ULN - ≤ 2xULN	0 (0.0)	5 (4.6)	0

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADLB (POSTBFL = Y)
Only subjects who have both baseline and post-baseline tests appear in the table.

Clinical Comment: Most patients in the trial had normal creatinine at baseline and elevations in creatinine were ≤ 2x ULN post baseline. Patients with creatinine > 2xULN were excluded from the trial per protocol. A safety signal for renal toxicity is not evident in the post baseline creatinine levels. Five patients had creatinine elevations > ULN and ≤ 2x ULN at baseline; therefore, it is not possible to adequately assess safety of the BPaL regimen or pretomanid in patients with renal impairment. In clinical practice, it is highly likely that BPaL regimen will be administered to patients with renal insufficiency, and a study of pretomanid in this patient

group is planned. The applicant will conduct a phase 1, open-label, single-dose study to evaluate the pharmacokinetics and safety of pretomanid in subjects with renal impairment compared to subjects with normal renal function as a postmarket requirement.
The pretomanid label will state that there is no information on the use of pretomanid in patients with renal impairment.

Glucose

Decreases in glucose levels from baseline were reported in 31 (28.4%) patients. Most decreases in blood glucose were grade 1 (mild) with blood glucose in the range, 55 to 64mg/dL. Eleven (11%) patients had grade 2 or grade 3 (mild to moderate) decreases in blood glucose. Among patients with normal blood glucose levels at baseline, 9 (8.3%) developed a grade 2 hypoglycemia (blood glucose: 40 to 54 mg/dL) and 1 (0.9%) subject developed a grade 3 hypoglycemia (blood glucose: 30 to 39 mg/dL). The one event of grade 3 hypoglycemia responded to IV glucose infusion and was associated with acute pancreatitis. There were no patients who experienced grade 4 hypoglycemia (< 30mg/dL).

Table 9-26. Study Nix-TB: Baseline to Maximum Post Baseline Shifts in Blood Glucose Level Category

BPaL (n=109)					
	Max Post-Baseline Glucose Grade – Hypoglycemia				
Baseline Glucose	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0 > 65 mg/dL	57 (52.3)	20 (18.3)	9 (8.3)	1 (0.9)	0
Grade 1 55 to 64mg/dL	11 (10.1)	1 (0.9)	1 (0.9)	0	0
Grade 2 40 to 54 mg/dL	3 (2.8)	0	0	0	0
Grade 3 30 to 39 mg/dL	2 (1.8)	0	0	0	0
Grade 4 < 30mg/dL	0	0	0	0	0

Source: SAS (v9.4) and R (v3.5)
Datasets Used: Applicant's ISS ADSL (POOL1SFL = 'Y') and ISS ADLB (POSTBFL = 'Y', SYMPTM = 'GLUCOSE (mmol/L) – HYPOGLYCEMIA' or ''); mmol/L converted to mg/dL in Table.
Only subjects that have both baseline and post-baseline tests appear in the table. Subjects (b) (6) are also excluded from the above table as these subjects have only hyperglycemic lab results.

Other Chemistry Laboratory Results

Treatment-emergent grade 3 and grade 4 values for other chemistry parameters (sodium, potassium) in Study Nix-TB were infrequent i.e., < 5% of subjects for either grade of any parameter and were < 2% if the changes in glucose levels are excluded.

Reference ID: 4476823

9.4.7. Vital Signs

Mean body temperature was 36.3 °C at baseline and 36.2 °C at EOT. Mean systolic and diastolic blood pressure at baseline were 110 mmHg and 69 mmHg, respectively. Mean changes in systolic and diastolic blood pressure from baseline to EOT were +8 mmHg and +12 mmHg, respectively.

Treatment-emergent increases in blood pressure to grade 2 (systolic ≥160 to <180 mmHg; diastolic ≥100 to <110 mmHg) and grade 3 (systolic ≥180 mmHg; diastolic ≥110 mmHg) were infrequent; increases to grade 2 were observed in 5 patients (4.6%) each for both systolic and diastolic blood pressure and increases to grade 3 were observed 1 patient (0.9%).

Clinical Comment: Overall, the BPaL regimen did not have significant adverse effects on vital signs.

9.4.8. Electrocardiograms (ECGs)

No patient had treatment emergent tachycardia ≥120 beats per minutes or ≥20% increase over baseline. Four (3.7%) patients had a postbaseline heart rate of ≤50 beats per minutes and ≥20% decrease in heart rate from baseline. Five (4.6%) subjects had a treatment-emergent QTcB of >480 msec, and no subject had a treatment-emergent QTcF of this duration. A post-baseline QTcB of ≥500 msec was observed in 1 (0.9%) subject. One (0.9%) subject each had a post-baseline increase of QTcB and QTcF of >60 msec. See section 9.5.9 for further details on QT prolongation.

9.4.9. Immunogenicity

Not applicable.

9.5. Analysis of Submission-Specific Safety Issues

Safety signals from animal studies of pretomanid included neurotoxicity, testicular toxicity, cataract formation, and QT prolongation. TEAEs of special interest related to the BPaL regimen in humans include hepatotoxicity, cataract formation, gastrointestinal events, pancreatitis, lactic acidosis, optic neuropathy, and peripheral neuropathy, myelosuppression, seizures, possible male infertility, and QT prolongation.
The following table summarizes the relevant findings in human trials of pretomanid alone and with other antimycobacterial drugs. Pretomanid alone was studied in two phase 2 EBA (early bactericidal activity) studies, CL-007 and CL-010, in which pretomanid was administered to adult subjects for up to 14 days, see Table 9-53. Most studies, NC-002, NC-005, NC-006, DMID-10-0058, and Nix-TB, studied pretomanid in combination with other antimycobacterial drugs.

Table 9-27. Comparison of Safety Signals in Animal and Human Studies of Pretomanid

Safety Signals	Animal Studies – Pretomanid	Human Studies - Pretomanid

Reference ID: 4476823

Safety Signals	Animal Studies – Pretomanid	Human Studies - Pretomanid
Neurotoxicity	Convulsions and ataxia in monkeys at 5x human exposure	Convulsions reported in 2 subjects with a history of convulsions in Nix-TB
Cataracts*	Cataracts in rats at 2x human exposure	No cataracts in humans in studies of pretomanid, NC-002, NC-005, NC-006, and Nix-TB.
Testicular Toxicity (Infertility)	Spermatocyte degeneration in rats at 1.5x human exposure	Male hormones normal in phase 2 and 3 studies, NC-002, NC-005, NC006. Human Semen Analysis Study planned
QT prolongation	Minimal QT prolongation in monkeys at 15x human exposure	No clinically significant QT Prolongation in TQT study, DMID-10-0058.
Hepatotoxicity	Hepatic transaminases 3-5x ULN at similar human exposure	Hepatic transaminases increased in phase 2 studies of pretomanid alone x 14 days. Hepatic transaminases increased and DILI was reported in phase 3 trials of pretomanid administered with other antimycobacterial drugs.

Source: ADAE dataset and pharmacology/toxicology study reports. Table constructed by this clinical reviewer and pharmacology/toxicology reviewer, Owen McMaster, Ph.D.
**Cataracts were found in rat toxicology studies (pretomanid 100mg/kg x 13 weeks or 300mg/kg x 26 weeks) and initial monkey toxicology studies (450mg/kg x 3 months) but not in repeat monkey toxicology studies (300mg/kg) that had more detailed examinations of the ocular lens.*

Hepatic disorders were reported in clinical trials of pretomanid as part of different antimycobacterial drug regimens and hepatotoxicity is included in the Warnings and Precautions section of the bedaquiline (SIRTURO®) USPI. Myelosuppression, optic neuropathy, and peripheral neuropathy are known to be associated with linezolid and are included in the Warnings and Precautions section of the linezolid (ZYVOX®) USPI.**Error! Bookmark not defined.** QT prolongation is included in Warnings and Precautions section of the bedaquiline USPI. Acute pancreatitis was reported in the Nix-TB trial and is not a labeled adverse reaction for bedaquiline or linezolid and was not reported in animal studies of pretomanid. TEAEs associated with drug-drug interactions with HIV antiretroviral drugs are also of interest. Adverse events of special interest analyzed by baseline HIV status are discussed.

9.5.1. Hepatotoxicity

In the Nix-TB trial, hepatic TEAEs occurred in 39 (36%) subjects, Table 9-28. Hepatic TEAEs were more common in HIV-positive patients than in HIV negative subjects, 23 (41%) versus 16 (30%), respectively. Increases in ALT and/or AST led an interruption of the entire BPaL regimen in 8 (7.3%) patients, see Table 9-13.
In all eight cases, subjects restarted study drugs without experiencing further clinically significant elevations in ALT and/or AST. Two patients were potential Hy's Law cases and one of them fulfilled the biochemical criteria for Hy's Law; the two cases are discussed under hepatic laboratory abnormalities (Section 9.4.6). Elevations in GGT occurred mostly in HIV co-infected subjects. Grade 4 transaminitis (> 20 x ULN) in Subject (b) (6) was associated with pneumonia leading to death (Section 9.4.1).

Reference ID: 4476823

Table 9-28. Nix-TB Hepatic Disorders SMQ by Baseline HIV Status

Treatment Emergent Adverse Events	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
Any TEAE	**16 (30.2)**	**23 (41.1)**	**39 (35.8)**
Blood A kaline Phosphatase Increased	1 (1.9)	2 (3.6)	3 (2.8)
Alanine Aminotransferase Increased	6 (11.3)	4 (7.1)	10 (9.2)
Aspartate Aminotransferase 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 Test Increased	0	1 (1.8)	1 (0.9)
Transaminases Increased	6 (11.3)	6 (10.7)	12 (11.0)

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 list of terms included in the applicant's Hepatic Disorders (SMQ) is provided in Appendix 1 of the ISS SAP.
Subject (b) (6), was reported to have jaundice but there was no laboratory evidence of elevated total bilirubin levels on treatment and the patient is excluded.

One HIV-positive patient, Subject (b) (6), was reported to have jaundice. The patient's ALT and total bilirubin levels were analyzed throughout the 26-week treatment period and total bilirubin level remained within normal range at all scheduled and unscheduled visits indicating that the patient was unlikely to have jaundice while on BPaL. ALT started to increase at Week 4 and reached a max level of 4x ULN at Week 16 and then declined, toward the normal range from Week 18 to 26. Linezolid dosing was interrupted twice (for 2 weeks each time) and bedaquiline dosing was interrupted once (for 2 weeks) during treatment due to elevations in hepatic transaminases. The patient completed a full 26 weeks of treatment and the 6-month follow up visit.

Hepatic TEAEs

A hepatotoxicity signal with use of pretomanid-containing anti-mycobacterial regimens has been identified in study NC-006 (STAND trial). See Sections 3.2 and 9.7.4 for details.
In the Nix-TB trial, the incidence of hepatic TEAEs was similar throughout the 26-week treatment period with a slight duration dependency, i.e., 12.8%, 14.7%, and 16.5% of subjects developed hepatic TEAEs at ≤2 weeks, >2 weeks to 8 weeks, and >8 weeks to 26 weeks, respectively.

Outcomes

Most of the hepatic TEAEs (57 of 65 hepatic TEAEs) were recovered or were recovering as of the data cutoff date, March 26, 2018. Six hepatic TEAEs (increases in transaminases, alkaline phosphatase, and GGT) were not resolved and outcomes for two TEAEs were unknown as of the data cutoff date, March 26, 2018.

Table 9-29. Study NixTB: Outcomes of Hepatic Treatment Emergent Adverse Events

Hepatic TEAEs	Outcomes of TEAEs in Bedaquiline/ Pretomanid / Linezolid Group				
Dictionary Derived Term	**NOT RECOVERED/ NOT RESOLVED**	**RECOVERED/ RESOLVED**	**RECOVERING/ RESOLVING**	**UNKNOWN**	**Total**
ALT Increase	-	11	1	-	12
AST Increase	-	9	-	-	9
Blood Alkaline Phosphatase Increase	1	2	-	-	3
Drug-Induced Liver Injury	-	2	-	-	2
GGT Increase	3	10	3	2	18
Hepatic Enzyme Increase (ALT/AST Increase)	-	2	-	-	2
Hepatic Function Abnormal (ALT/AST Increase)	1	-	-	-	1
Hepatomegaly	-	1	-	-	1
Hyperbilirubinemia	-	2	-	-	2
Liver Function Test Increased i.e., (ALT, AST)	-	1	-	-	1
Transaminases Increased	1	11	1	-	13
Total TEAEs	6	52	5	2	65

JMP Clinical v.6.0. Datasets used: ADAE (TRTEMFL).

9.5.2. Fertility Disorders

No TEAEs related to Fertility Disorders SMQ were found in the Nix-TB study. In animal toxicology studies of pretomanid, testicular toxicity (irreversible infertility) was noted in male rats. Based on the safety signal in rats, male reproductive hormone levels in serum were evaluated in three clinical trials, NC-002, NC-005, and NC-006, see Table 3-1. Male reproductive hormone levels were not evaluated in Nix-TB. The three trials investigated regimens containing pretomanid which were different from the regimen in the Nix-TB. Studies NC-002, NC-005, and NC-006 evaluated anti-mycobacterial drug regimens containing moxifloxacin, pretomanid, and pyrazinamide with or without bedaquiline in patients with DS-TB or MDR-TB. Patients were exposed to pretomanid from 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.

Labeling will note that reduced fertility and testicular toxicity cannot be definitively ruled out in humans. See review by J. Dimitrakoff, M.D., dated 4/15/19 in DARRTS.

Clinical Comment: The potential of pretomanid to cause testicular toxicity in men is unknown at present. The applicant will conduct the planned Human Semen Analysis Study to further evaluate if there is a signal for testicular toxicity in humans as a PMR.

9.5.3. Myelosuppression

Hematopoietic Cytopenias

TEAEs were reported in 51 (47%) patients. 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, see Table 9-30.

The onset of anemia and other cytopenias occurred most frequently after two weeks of BPaL 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. Three subjects experienced cytopenias that were considered SAEs: neutropenia in 1 subject and anemia in 2 subjects which resulted in interruption of one or more components of the regimen, and all resolved. Cytopenias led to dosing interruptions of the BPaL regimen in 2 (1.8%) patients. Dosing interruptions, dose reductions, or discontinuation of linezolid occurred in 18 (16.5%), 16 (14.7%), and 2 (1.8%) subjects, respectively; there is overlap among the subjects in these subgroups as many of the patients who had a dosing interruption restarted linezolid at a lower dose, i.e., 600 mg/day or 300 mg/day.

Thirty-four (31%) patients who had normal Hb levels at baseline experienced a decrease in their Hb 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 BPaL treatment.

Table 9-30. Study Nix-TB: Hematologic Disorders (Cytopenia) SMQ

Treatment Emergent Adverse Event	BPaL		
	HIV NEGATIVE N=53	**HIV POSITIVE N=56**	**Subjects** N=109
Any TEAE	***21 (39.6%)***	***30 (53.6%)***	***51 (46.8%)***
ANAEMIA	16 (30.2%)	24 (42.9%)	40 (36.7%)
NEUTROPENIA	2 (3.8%)	7 (12.5%)	9 (8.3%)
THROMBOCYTOPENIA	2 (3.8%)	3 (5.4%)	5 (4.6%)
BONE MARROW FAILURE	2 (3.8%)	1 (1.8%)	3 (2.7%)
LEUKOPENIA	0	2 (3.6%)	2 (1.8%)
BICYTOPENIA*	1 (1.9%)	0	1 (0.9%)
LYMPHOPENIA	0	1 (1.8%)	1 (0.9%)
PANCYTOPENIA	1 (1.9%)	0	1 (0.9%)

Source: JReview v.12.0. ISS dataset, ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ11NAM = Hematologic Disorders [Cytopenia] SMQ). *Bicytopenia: anemia and thrombocytopenia.

"Bone marrow failure", "pancytopenia" or "bicytopenia" indicating suppression of more than one hematopoietic cell line were reported as TEAEs in 5 (4.6%) patients. RBC (10^9/L), WBC (10^9/L) and platelet count (10^9/L) were analyzed for each patient.
Four of the five patients were confirmed to have cytopenias on further analysis of their laboratory data. Declines in all three cell lines were generally transient and recovered toward the end of treatment except for one patient, Subject (b) (6). Subject (b) (6) experienced declines in RBC, Hb, and platelet count < LLN and died from a GI bleed at Week 7; the patient had other risk factors for GI bleed, see section 9.4.1. Subject (b) (6) had no laboratory evidence of cytopenia on treatment; he died at Week 7 due to worsening pulmonary tuberculosis. Subject, (b) (6), had a borderline low WBC at baseline and throughout the treatment period. Subject (b) (6) ("bicytopenia") had a gradual decline in Hb during the first two months of treatment from 12.3 g/dL at baseline to 6.1 g/dL (grade 3) on Day 64 and required a blood transfusion. Her platelet count declined from 326 x10^9/L at baseline to 108 x10^9/L on Day 64. There was no clinical evidence of bleeding. She was diagnosed with metabolic acidosis (grade 3), gastritis, pancreatitis (grade 2), and anemia (grade 4, life-threatening). The BPaL regimen was interrupted and bedaquiline/ pretomanid (BPa) were reintroduced first and followed by linezolid at a lower dose of 300 mg/day. Her Hb level improved following transfusion on the low linezolid dose. Acute pancreatitis resolved within 2 weeks. By Day 98 (Week 14), Hb level and platelet count had returned to normal.

Clinical Comment: Anemia, leukopenia, neutropenia, thrombocytopenia, and pancytopenia were observed during treatment with BPaL. No patient was withdrawn from the trial due to hematopoietic cytopenias. Myelosuppression is a known adverse reaction associated with linezolid and usually starts after 14 to 28 days of treatment. Linezolid is the most likely cause for most of the hematopoietic cytopenias that were observed on treatment because cytopenias recovered with management strategies such as dosing interruptions of the BPaL or dosing interruptions, dose reductions, or discontinuation of linezolid. Anemia (38%) was the most common cytopenia reported in the Nix-TB trial. One (0.9%) patient developed life-threatening anemia (without evidence of bleeding) and required a blood transfusion. The incidence of anemia with long term treatment with linezolid in published literature ranged from 3 to *69%.*[34,35,36,37,38] *The incidence of thrombocytopenia (4.5%) was low in the Nix-TB trial compared to the reported incidence rates in published literature of 4 to 50% with long term linezolid use*

[34] Anger HA, Dworkin F, Sharma S, Munsiff SS, Nilsen DM, Ahuja SD. Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000-06. J Antimicrob Chemother. 2010 Apr; 65(4): 775-83.
[35] Abbate E, Vescovo M, Natiello M, Cufre M, Garcia A, Gonzalez Montaner P, et al. Successful alternative treatment of extensively drug-resistant tuberculosis in Argentina with a combination of linezolid, moxifloxacin and thioridazine. J Antimicrob Chemother. 2012 Feb; 67(2): 473-7.
[36] Hughes J, Isaakidis P, Andries A, Mansoor H, Cox V, Meintjes G, et al. Linezolid for multidrugresistant tuberculosis in HIV-infected and -uninfected patients. Eur Respir J. 2015 Jul; 46(1): 271-4.
[37] Garazzino S, De Rosa FG, Bargiacchi O, Audagnotto S, Maiello A, Di Perri G. Haematological safety of long-term therapy with linezolid. Int J Antimicrob Agents. 2007 Apr; 29(4): 480-3.
[38] Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK, et al. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. Eur Respir J. 2012 Apr; 39(4): 956-62.

Reference ID: 4476823

for treatment of XDR- and MDR-TB.[39] There was no obvious reason for the low rates of thrombocytopenia.

Onset of TEAEs

The onset of anemia and other cytopenias occurred most frequently beyond two weeks of BPaL treatment and were reported in 25%, and 22% of subjects after >2 to 8 weeks, and >8 to 26 weeks of treatment, respectively. The rate of dose interruptions/reductions was greatest from approximately Day 25 to 80, consistent with the pattern of onset of these events. All except 5 of the 65 reported events in the SMQ for hematopoietic cytopenias resolved or were resolving at the time of data cutoff on 26 March 2018; 3 events had not resolved, and 2 events had unknown outcomes.

9.5.4. Neurologic Disorders

Peripheral Neuropathy

Eighty-seven (79.8%) patients experienced TEAEs in the Peripheral Neuropathy SMQ, Table 9-33. TEAEs were equally distributed among HIV-positive and HIV-negative patients. The most frequently reported TEAEs was peripheral sensory neuropathy 75 (69%), neuropathy peripheral 10 (9%), and paresthesia 5 (5%). Eighty-two (75.2%) patients experienced "peripheral sensory neuropathy" or "neuropathy peripheral" during treatment with BPaL.

Most TEAEs in the peripheral neuropathy SMQ were associated with linezolid. Study drug dosing was interrupted for 32 events (linezolid for 31 events and BPaL for 1 event), dose reduced for 30 events (linezolid for all events), and dosing was discontinued for 25 events (linezolid for all events).

Table 9-31. Study Nix-TB: Applicant's SMQ for Peripheral Neuropathy

Treatment Emergent Adverse Event	**BPaL**		
Preferred Term	**HIV NEGATIVE N=53**	**HIV POSITIVE N=56**	**Subjects N=109**
Any TEAE	*43 (81.1%)*	*44 78.6%)*	*87 (79.8 %)*
BURNING SENSATION	1 (1.9%)	0	1 (0.9%)
HYPOAESTHESIA	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%)
PARAESTHESIA	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 disorders SMQ)

[39] NDA 212862: Applicant's Summary of Linezolid Safety Outcomes from the Literature, Appendix B: Summary of Systematic Reviews and Meta-Analyses of Long-Term Linezolid Use (outside of NixTB trial).

One patient was diagnosed with chronic inflammatory demyelinating polyradiculopathy (CIDP) while on BPaL treatment. Subject (b) (6), a 28-year-old black female (HIV positive, HIV wasting syndrome, XDR-TB) had a normal neurological exam at baseline and was diagnosed with peripheral sensory neuropathy approximately three weeks after starting BPaL regimen. Nerve conduction studies and EMGs were conducted by a neurologist who diagnosed her with grade 3, HIV-related CIDP. The CIDP resolved with an 8-week course of prednisone. The dose of linezolid was reduced due to the peripheral sensory neuropathy and she completed a full 26-weeks of BPaL treatment. Approximately 19 months after EOT, the patient developed an episode of lower limb weakness; it was ongoing at the 24-month final follow up visit and no further details were provided.

Clinical Comment: The patient had symptoms of CIDP at 19 months after she completed BPaL treatment which suggests that CIDP was not related to study drugs; however, the initial episode of peripheral sensory neuropathy associated with CIDP could have been exacerbated by linezolid.

Onset of Peripheral Neuropathy

The peripheral neuropathy TEAEs occurred most frequently beyond two weeks of BPaL treatment and incidence increased over time, Table 9-32. Neuropathy was reported in 5%, 21% and 64% of subjects after ≤ 2 weeks, >2 weeks to 8 weeks, and >8 weeks to 26 weeks of treatment, respectively. The rate of interruption or dose reduction of linezolid also increased over time from approximately Day 20 to Day 150 post treatment, with the greatest increase in the rate of dose interruption/reduction from approximately Day 80 to Day 140, which is consistent with the late onset of neuropathy. The median time to first dosing interruption of linezolid for neuropathy was approximately 110 days or 15 weeks, see Figure 9-3.

Table 9-32. Study Nix-TB: Peripheral Neuropathy (SMQ) on Treatment by Time Interval

PERIPHERAL NEUROPATHY SMQ	Bedaquiline/ Pretomanid/ Linezolid (BPaL), N=109 (100%)					
Dictionary Derived Term	**PRE-TREATMENT**	**ON-TREATMENT UP TO 2 WEEKS**	**ON-TREATMENT >2 - 8 WEEKS**	**ON-TREATMENT >8 - 26 WEEKS**	**ON-TREATMENT >26 WEEKS**	**FOLLOW-UP**
BURNING SENSATION	0	1 (0.9%)	0	0	0	0
HYPOAESTHESIA	0	0	0	3 (2.8%)	0	0
HYPOREFLEXIA	0	0	1 (0.9%)	0	0	0
NEUROPATHY PERIPHERAL	0	0	2 (1.8%)	9 (8.3%)	0	0
PARAESTHESIA	0	1 (0.9%)	1 (0.9%)	3 (2.8%)	0	2 (1.8%)
PERIPHERAL MOTOR NEUROPATHY	0	0	2 (1.8%)	0	0	0
PERIPHERAL SENSORIMOTOR NEUROPATHY	0	0	0	1 (0.9%)	0	2 (1.8%)
PERIPHERAL SENSORY NEUROPATHY	2 (1.8%)	3 (2.8%)	18 (16.5%)	58 (53.2%)	1 (0.9%)	10 (9.2%)
Subjects	2 (1.8%)	5 (4.6%)	23 (21.1%)	70 (64.2%)	1 (0.9%)	12 (11.0%)

JReview v.12.0. Source: ISS ADSL and ADAE datasets. Population pooling flag: POOL1SFL=Y, Treatment-emergent AE Flag = TRTEMFL, applicant's derived variable for study time intervals = APHASE, Peripheral Neuropathy SMQ = SMQ11NAM.

Severity of Peripheral Neuropathy

Moderate or severe peripheral neuropathy was reported in 32% and 22% of patients, respectively. Neuropathic symptoms ranged from mild paresthesia to burning pain in the feet and difficulty walking and /or sleeping, see Table 9-33.

Table 9-33. Severity of Neuropathies associated with linezolid component of BPaL

	Pretomanid-Bedaquiline-Linezolid Regimen (N=109) n (%)
Peripheral Neuropathy	
Life-threatening	0
Severe	24 (22.0)
Moderate	35 (32.1)
Mild	29 (26.6)
Optic Neuropathy	2 (1.8)

Source: Applicant's Table 3 in draft label; data verified by FDA clinical data analyst.

Outcomes for Patients with Peripheral Neuropathy

Most of the peripheral neuropathy TEAEs (69 of 119) resolved or were resolving after adjustments to linezolid dosing as of the data cutoff date, March 26, 2018. There were 31 TEAEs that had not resolved and 27 of these events were related to peripheral neuropathy. Outcomes for 19 TEAEs were unknown or not reported.

Table 9-34. Study NixTB: Outcomes of Peripheral Neuropathy TEAEs

	No. of TEAEs			
Peripheral Neuropathy SMQ Dictionary Derived Term	**Not Recovered/ Not Resolved**	**Recovered/ Resolved**	**Recovering/ Resolving**	**Unknown**
Burning Sensation	-	1	-	-
Hypoesthesia	1	2	-	-
hyporeflexia	1	-	-	-
Neuropathy Peripheral	7	9	-	-
Paresthesia	1	4	-	-
Peripheral Motor Neuropathy	1	1	-	-
Peripheral Sensorimotor Neuropathy	-	1	-	-
Peripheral Sensory Neuropathy	20	45	6	19
Total TEAEs	31	63	6	19

Source: ISS dataset, applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ09NAM = Peripheral Neuropathy)

Clinical Comment: In a prospective multicenter, randomized trial evaluating the efficacy safety and tolerability of linezolid in patients with XDR -TB (Tang, 2015), peripheral neuropathy occurred between 2 to 4 months after starting linezolid, optic neuropathy occurred around 5 to 6 months after starting linezolid, hematologic AEs occurred between 2 weeks and 2 months after starting linezolid treatment, and GI AEs occurred between 2 weeks and 4 weeks after starting linezolid. The findings in the Nix TB trial, are consistent with published literature on long term use of linezolid, with a median time to first dosing interruption of linezolid for peripheral neuropathy of approximately 110 days (~ 15 weeks).

9.5.5. Lens Disorders

Ophthalmologic Evaluations for Cataracts

Fourteen (12.8%) subjects had TEAEs in the Lens Disorders SMQ. None of the them were SAEs. Three events resulted in interruption of study drug, "*visual acuity reduced"* in 2 subjects (linezolid interrupted) and "*visual impairment*" in one subject (entire BPaL regimen interrupted). No TEAEs led to discontinuation of the BPaL regimen.

Table 9-35. Study Nix-TB: Lens Disorders SMQ

TEAE Dictionary Derived Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
	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, SMQ04NAM)

Clinical Comment: Cataracts were found in rat toxicology studies. Following the finding of cataracts in animal studies, clinical studies with pretomanid exposure longer than 14 days have included visual acuity assessments, slip-lamp examinations, and AREDS-2 lens opacity scoring since July 2009. Consultants from the Division of Ophthalmology and Transplant Products (DTOP) evaluated the submitted clinical data and found no clinically meaningful effect of pretomanid on cataract formation at the doses and durations studied. Ocular monitoring continues in the pretomanid clinical development program. See consult review (6/5/19) by William Boyd, M.D., DTOP, located in DARRTS.

9.5.6. Optic Nerve Disorders

Thirteen (11.9%) subjects had TEAEs in the Optic Nerve Disorders SMQ. The most frequent TEAE was reduced visual acuity in 6 (5.5%) patients. Four (3.7%) patients were diagnosed with abnormalities of the optic nerve:

Two (1.8%) patients developed optic neuropathy (grade 1) and optic neuritis (grade 4) after four months of treatment and this led to discontinuation of linezolid but not the regimen. Both cases resolved after approximately one month. One (0.9%) patient was diagnosed with bilateral papilledema two days before the end of study treatment which resolved two months later; the patient had normal visual acuity and color vision examinations during the study. One (0.9%) patient with optic disc hyperemia had a dose reduction in linezolid and recovered.

Three additional subjects had study drug interrupted because of visual abnormalities, which included visual acuity reduced in 2 subjects (linezolid only interrupted) and visual impairment in the third subject (BPaL interrupted).

Table 9-36. Study Nix-TB: Optic Nerve Disorders SMQ

TEAE Dictionary Derived Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109

TEAE Dictionary Derived Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
Any TEAE	***9 (17.0%)***	***4 (7.1%)***	***13 (11.9%)***
AMBLYOPIA	0	1 (1.8%)	1 (0.9%)
OPTIC DISC HYPEREMIA	1 (1.9%)	0	1 (0.9%)
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, SMQ10NAM).

Most of the optic nerve disorders TEAEs (9 of 14) resolved or were resolving as of the data cutoff date, March 26, 2018. Three of the four TEAEs that led to a drug(s) interruption or dose reduction had resolved at the time of data cutoff, March 26, 2018 and one TEAE (visual acuity reduced) was ongoing. There were 4 TEAEs (two visual acuity reduced, and one each visual impairment and amblyopia) that had not resolved at the data cutoff date and the outcome for one TEAE was unknown or not reported.

Table 9-37. Study NixTB: Outcomes of Optic Nerve Disorders TEAEs

OPTIC NERVE DISORDERS SMQ Dictionary Derived Term	NOT RECOVERED/ NOT RESOLVED	RECOVERED/ RESOLVED	RECOVERING/ RESOLVING	UNKNOWN
TOTAL TEAEs	**4**	**8**	**1**	**1**
AMBLYOPIA	1	-	-	-
OPTIC DISC HYPEREMIA	-	1	-	-
OPTIC NEURITIS	-	1	-	-
OPTIC NEUROPATHY	-	1	-	-
PAPILLOEDEMA	-	1	-	-
VISUAL ACUITY REDUCED	2	3	1	-
VISUAL IMPAIRMENT	1	1	-	1

Clinical Comment: Optic neuropathy is a known adverse effect of linezolid. There was a positive dechallenge off linezolid in the four patients with optic neuropathy/neuritis/papilledema, and optic nerve hyperemia.

9.5.7. Pancreatitis, Elevations in Lipase and Amylase

Twenty-two (20.2%) patients experienced at least one TEAE in the pancreatitis SMQ. Lipase levels were elevated in 6 (5.5%) patients. Acute pancreatitis was a contributing cause of death in 2 (1.8%) patients; both patients had hemorrhagic pancreatitis confirmed at autopsy.

Table 9-38. Nix-TB: Acute Pancreatitis SMQ (modified) by Baseline HIV Status

	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
Any TEAE	8 (15.1)	14 (25.0)	22 (20.2)
Modified Acute Pancreatitis (SMQ) TEAEs by Level			
Total	***7 (13.2)***	***13 (23.2)***	***20 (18.3)***
AMYLASE INCREASED	4 (7.5)	5 (8.9)	9 (8.3)

	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
HYPERAMYLASAEMIA	2 (3.8)	6 (10.7)	8 (7.3)
HYPERLIPASAEMIA	0	1 (1.8)	1 (0.9)
LIPASE INCREASED	3 (5.7)	2 (3.6)	5 (4.6)
Total	***1 (1.9)***	***2 (3.6)***	***3 (2.8)***
ACUTE PANCREATITIS (HEMORRHAGIC)	0	2 (3.6)	2 (1.8)
ACUTE PANCREATITIS	1(1.9)	0	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 = Acute pancreatitis (SMQ). A list of terms included in the applicant's modified Acute Pancreatitis (SMQ) is provided in Appendix 1 of the ISS SAP.

Subject (b) (6) (female, 30y, XDRTB, HIV negative) was diagnosed with metabolic acidosis (Grade 3), gastritis, pancreatitis (grade 2), and anemia (grade 4 life-threatening) which required a blood transfusion. Lipase increased from normal baseline 11 U/L to 121 U/L (normal range: 13 to 60 U/L) on trial Day 64. In the 3 weeks prior to this episode, she was diagnosed with gastritis and treated with lansoprazole. For the adverse events on Day 64, the BPaL regimen was interrupted and bedaquiline and pretomanid were reintroduced first, followed by linezolid. Her Hb level improved post blood transfusion and with lowering of the linezolid dose to 300 mg/day. Acute pancreatitis resolved within 2 weeks. By Trial Day 98, the patient's Hb had normalized. She recovered and completed $BPaL_{300mg}$ treatment on Day 189.

Clinical Comment: Risk factors for pancreatitis included HIV+ and ART. An association between acute pancreatitis and the BPaL regimen cannot be ruled out because pancreatitis occurred on treatment.

Subject (b) (6) (XDR-TB, a HIV-positive on ART, history of hepatitis B) with no history of alcohol use had an elevated lipase level 2x ULN and elevated amylase levels > 2x ULN but was asymptomatic. Medications for the treatment of HIV prior to enrollment included efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine, abacavir, nevirapine, and lopinavir/ritonavir. She had a maximum lipase level of 129/UL (normal range 13 - 60 U/L) and maximum amylase level was 261 (ULN=100 U/L) on BPaL treatment but she was asymptomatic and was diagnosed as having pancreatitis on abdominal US. Treatment was interrupted for approximately 20 days and lipase levels returned to normal ranges following a re-challenge of BPaL treatment.

Clinical Comment: There was no significant change in lipase or amylase levels with dechallenge and rechallenge of the BPaL regimen. It is likely that this was a case of low-grade pancreatitis associated with ART and not the BPaL regimen because lipase levels returned to normal following a rechallenge with BPaL. There were other risk factors for elevated lipase and amylase levels, for example, the elevated lipase level may have been associated with subclinical inflammation of the pancreas due to AIDS. The patient's ART regimen contained lopinavir/ritonavir which is known to cause fluctuations in lipase levels and is associated with pancreatitis. Tuberculosis is associated with elevated amylase levels.

There was one case of pancreatitis (hemorrhagic) in the applicant's electronic database. The reviewer found two cases of pancreatitis (hemorrhagic) in the case narratives of patients who died, i.e., Subject (b) (6) and Subject (b) (6) See section 9.4.1.
Lipase and amylase elevations and pancreatitis are associated with HIV infection and are also associated with some ART drugs such as lopinavir/ritonavir and tenofovir; however, one patient, Subject (b) (6), was HIV negative. Lipase and amylase levels also tend to be higher in patients with tuberculosis than in normal controls; however, the differences in levels were still within the normal ranges in one study.[40] Pancreatitis is not listed as an adverse reaction in the bedaquiline or linezolid USPIs. Pancreatitis was noted in animal toxicology studies of bedaquiline[41] and was reported infrequently in humans treated with bedaquiline.
Acute pancreatitis was not reported in other clinical trials of pretomanid as part of other antimycobacterial drug regimens. The BPaL regimen may not have caused acute pancreatitis but the regimen could have exacerbated pancreatitis. Lipase and amylase elevations and acute pancreatitis will be included in the Adverse Reactions section of the pretomanid USPI as an association between these adverse events and BPaL cannot be ruled out.

9.5.8. Skin and Subcutaneous Tissue Disorders

Sixty-one (60%) patients experienced TEAEs. The most frequently reported TEAEs were dermatitis acneiform (23.9%) and acne (14.7%). When PTs for rashes were grouped, the proportion of subjects with skin rashes was 26 (23.9%); rash includes the following PTs: rash / rash pruritic / rash papular / rash maculo-papular / rash erythematous / rash vesicular. Subject (b) (6) developed mild urticaria from Day 72 to 77 and it resolved while on BPaL treatment. All TEAEs were grade 1 or grade 2.

Table 9-39. Study Nix-TB: Skin and Subcutaneous Tissue Disorders SMQ, by HIV Status

TEAE Dictionary Derived Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
Any TEAE	***27 (50.9%)***	***34 (60.7%)***	***61(60.0%)***
ACNE	9 (17.0%)	7 (12.5%)	16 (14.7%)
DERMATITIS ACNEIFORM	13 (24.5%)	13 (23.2%)	26 (23.9%)
DERMATITIS ALLERGIC	0	1 (1.8%)	1 (0.9%)
DERMATITIS ATOPIC	0	1 (1.8%)	1 (0.9%)
DERMATITIS CONTACT	1 (1.9%)	0	1 (0.9%)
RASH	8 (15.1%)	9 (16.1%)	17 (15.6%)
RASH ERYTHEMATOUS	0	1 (1.8%)	1 (0.9%)
RASH MACULO-PAPULAR	0	2 (3.6%)	2 (1.8%)
RASH PAPULAR	0	3 (5.4%)	3 (2.7%)
RASH VESICULAR	0	1 (1.8%)	1 (0.9%)
RASH PRURITIC	0	4(7.1%)	4(7.1%)
URTICARIA	1(1.9%)	0	1(0.9%)

[40] Motswaldi MS, Sekgwana R, Kasvosvel. Tuberculosis alters pancreatic enzymes in the absence of pancreatitis. Afr J. Lab Med 2014; 3(1); 129.
[41] Bedaquiline (SIRTURO®): https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1534c9ae-4948-4cf4-9f66-222a99db6d0e

Reference ID: 4476823

Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y) and SMQ13NAM (modified by reviewer) = Skin and Subcutaneous Tissue Disorders modified SMQ.

In Nix-TB, there were no reports of severe cutaneous skin reactions such as SJS or TEN in the SMQ for severe cutaneous adverse reactions. The cutaneous adverse events did not result in changes to the dosing of BPaL regimen.

9.5.9. QT Prolongation

In Nix-TB, 7 (6.4%) subjects experienced TEAEs in the SMQ for Torsades des Pointes/ QT prolongation, which consisted of the TEAEs i.e., electrocardiogram QT prolonged (6 subjects) and syncope (1 subject), see Table 9-40**.** 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%) subject had a post-baseline increase of QTcF of >60 ms. No TEAE resulted in changes in study drug dosing. All events resolved except for one event of QT prolongation (mild) as of the data cutoff date, March 26, 2018.

The patient who experienced a syncopal event reported feeling dizzy and falling he while was standing in line. There was no reported loss of consciousness. On examination at a local hospital, he had a perforated right tympanic membrane with bleeding from the right ear. No vital signs, ECG or discharge summary were available. At the study site, 11 days later, the patient was stable, ECG showed no evidence of QT prolongation. Some of his ECGs prior to the adverse event showed low voltage in the limb leads and nonspecific ST segment and T-wave abnormalities. Five ECGs during study visits after the syncopal episode were reported as normal and two readings showing low voltage QRS in limb leads.

Table 9-40. Study Nix-TB: Torsades de Pointes/ QT Prolongation SMQ

TEAE	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
Dictionary Derived Term	2 (3.8%)	5 (8.9%)	7 (6.4%)
ELECTROCARDIOGRAM QT PROLONGED	2 (3.8%)	4 (7.1%)	6 (5.5%)
SYNCOPE	0	1 (1.8%)	1 (0.9%)

Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y and SMQ07NAM = Torsade de Pointes/QT Prolongation (SMQ)

Clinical Comment: One patient experienced dizziness leading to a fall which may have been precipitated by a perforated tympanic membrane (TM) and/or a middle ear disorder. The patient did not have true syncope as there was no reported loss of consciousness. There was no reported clinical or ECG evidence that this event was related to QT prolongation.
In the Nix-TB trial, pretomanid was co-administered with bedaquiline, a drug known to prolong the QT interval; therefore, adverse events of QT prolongation cannot be directly attributed to pretomanid exposure. Pretomanid is less likely to have effects on the QT prolongation because a Thorough QT study (TQT) study did not show any clinically meaningful increase in QTc interval.

<u>Thorough QT study (TQT) Study</u>

Study No. DMID-10-0058: A Phase I, Double-Blind, Randomized, Single-Center, Five-Period Crossover Study to Assess the Effects of Single Oral Doses of 400 mg and 1000 mg of PA -824 and 400 mg of PA -824 Plus 400 mg of Moxifloxacin on QTc Interval Compared to Placebo, using Avelox (moxifloxacin) as a Positive Control, in Healthy Male and Female Volunteers Aged 18 to 45 Years.

The applicant evaluated the risk of QT prolongation for pretomanid in a dedicated TQT study and the results were reviewed by the QT-IRT team. The QT-IRT reviewer, Girish Bende, PhD., agreed that the results of a TQT study showed no clinically meaningful increase in QTc after single oral doses of 400 mg and 1,000 mg of pretomanid. Dr. Bende calculated that the predicted QTc effects of pretomanid 200 mg per day with food would be approximately 4 ms in males and 5 ms in females; therefore, pretomanid has a low risk for the QTc interval prolongation at therapeutic exposures.

In the TQT study, co-administration of pretomanid 400 mg with moxifloxacin 400 mg did not significantly increase the QTc effects of the combination. The reviewer noted that co-administration with other QT prolonged drugs such as bedaquiline may cause small increases in QT interval which would not substantially increase the pro-arrhythmic potential of the combination.
Bedaquiline is a known QT prolonging drug (largest mean increase in QTc = 15.7 ms in the SIRTURO® USPI). A TQT study of linezolid at therapeutic exposures was not associated with a clinically relevant risk of QT prolongation.[42] The overall results of the applicant's concentration-QT analysis agree with the FDA's analysis with the mean ΔΔQTcF and upper 90% limit below the 10 ms threshold. *See review by QT-IRT, dated 4/10/2019 in DARRTS.*

9.5.10. Convulsions

In the NixTB, 2 (1.8%) patients experienced seizures. Subject (b) (6) had a history of seizures and experienced a tonic/clonic seizure during BPaL treatment. Subject (b) (6) completed BPaL treatment and had a seizure a week post treatment and a second seizure two months post-treatment due to a tuberculoma in the right temporal lobe. The patient had no seizures in the 6-month period following neurosurgery for the tuberculoma.

Clinical Comment: The two patients had risk factors for seizures i.e., a history of seizures and a temporal lobe tuberculoma, respectively, (see section 9.4.1). Seizures have been reported with use of linezolid in patients who have a history of seizures, and linezolid could possibly have exacerbated seizures in subject (b) (6)*. There was a signal for CNS toxicity i.e., seizures and ataxia in animal toxicology studies with high doses of pretomanid at seven times human exposure and they generally occurred after 60 days of dosing.*

[42] ZYVOX USPI: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=50630775-7f76-413e-9278-ba298dd7f187

Reference ID: 4476823

9.5.11. Gastrointestinal Disorders

Fifty-three (48.6%) subjects experienced treatment emergent gastrointestinal disorders. The TEAEs were relatively evenly distributed among HIV-negative and HIV-positive subjects. Nausea and vomiting occurred in approximately a third of patients and diarrhea occurred in 10% of patients. All the adverse events where either grade 1 or grade 2 severity and there were no reported serious adverse events. Eight TEAEs resulted in the interruption of study drugs.

Table 9-41. Study NixTB: Gastrointestinal Disorders

TEAEs Dictionary Derived Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
Any TEAE	***26 (49.1%)***	***27 (48.2%)***	***53 (48.6%)***
Nausea	23 (43.4%)	17 (30.4%)	40 (36.7%)
Vomiting	16 (30.2%)	21 (37.5%)	37(33.9 %)
Diarrhea	5 (9.4%)	6 (10.7%)	11 (10.1 %)

Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y, SMQ15NAM)

9.5.12. Lactic Acidosis

Eight (7.3%) patients (2 males and 5 females) reported TEAEs in the SMQ for lactic acidosis. The proportion of patients with lactic acidosis was similar in HIV negative and HIV-positive patients. The duration of lactic acidosis ranged from 1 to 18 days. The onset of these TEAEs increased over time with zero events in ≤2 weeks, and 3 (2.8 %) subjects in >2 to 8 weeks and 5 (4.6%) subjects in > 8 to 26 weeks on treatment.

One TEAE of lactic acidosis was an SAE (grade 4/life-threatening), one TEAE of lactic acidosis was grade 3/ severe (Subject (b) (6), HIV negative, $BPAL_{600mg\ bid}$), and the remainder of the TEAEs were grade 1 or 2 severity. All TEAEs resulted in study drugs being interrupted (7 subjects) or discontinued (1 subject). Linezolid dosing was interrupted for three TEAEs, BPaL was interrupted for two TEAEs, and study drug(s) was not recorded for two TEAEs. The patients completed at least 6 months of therapy except for one patient, Subject (b) (6), who died of sepsis.

Subject (b) (6) (TI/MDRTB, HIV positive, $BPaL_{1,200mg}$) developed lactic acidosis (grade 4) which was considered a SAE and the entire BPaL regimen was interrupted. The lactic acid level declined and the patient restarted the regimen with a low dose of linezolid 300 mg/day and completed treatment without further elevations of lactic acid. All TEAEs had resolved except one report of hyperlactacidemia in Subject (b) (6), who died of pneumonia and septic shock two days after developing hyperlactacidemia and the BPaL regimen discontinuation.

Table 9-42. Nix-TB: Lactic Acidosis SMQ

Treatment Emergent Adverse Events	BPaL		
Preferred Term	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%)

Treatment Emergent Adverse Events	BPaL		
Preferred Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
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, SMQ12NAM)

Clinical Comment: The applicant noted that the trial centers did not have the capability to test arterial blood gas parameters such as bicarbonate to confirm the diagnosis of acidosis. No patients were withdrawn from the trial due to lactic acidosis. Lactic acidosis has been reported with linezolid, so it is possible that linezolid contributed to increased lactic acid levels in these patients. One patient with increased lactic acid levels died from sepsis. No subject in the MDR-TB or DS-TB pooled groups in studies NC-005, NC-006 and NC-002, and in the pretomanid-alone pooled studies (CL-007, CL010) reported a TEAE of lactic acidosis. Lactic acidosis is unlikely to be related to pretomanid.
Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation including evaluation of bicarbonate and lactic acid levels, and interruption of linezolid or interruption of the BPaL regimen.

9.5.13. Musculoskeletal Disorders

Five (4.5%) patients reported TEAEs in the SMQ for myopathy/rhabdomyolysis. None of the subjects who developed increased blood creatine phosphokinase (CPK) levels reported symptoms such as musculoskeletal pain or myalgia. No TEAEs were considered serious or resulted in a change in study drug dosing. As of the date of data cutoff, March 26, 2018, 10 of the 14 reported TEAEs had resolved; one TEAE was ongoing, and three adverse events in two subjects had unknown outcomes.

Table 9-43. Nix-TB: Rhabdomyolysis/ Myopathy SMQ (modified)

TEAEs Dictionary Derived Term	HIV NEGATIVE N=53	HIV POSITIVE N=56	Subjects N=109
BLOOD CREATINE PHOSPHOKINASE INCREASED	4 (7.5%)	1 (0.9%)	5 (4.5%)
MUSCULOSKELETAL PAIN	1 (1.8%)	0	1 (0.9%)
MYALGIA	4 (7.5%)	2 (1.8%)	6 (5.5%)
MYALGIA INTERCOSTAL	1 (1.9%)	0	1 (0.9%)

Datasets Used: Applicant's ISS ADSL (POOL1SFL = Y) and ISS ADAE (TRTEMFL = Y, SMQ08NAM)

9.5.14. Hypoglycemia

There were 11 (11%) cases of hypoglycemia in the trial and two episodes of hypoglycemia were related to BPaL. Hypoglycemia occurred in a patient with insulin dependent diabetes mellitus and the other patient developed hypoglycemia associated with acute pancreatitis, sepsis leading to death (see section 9.4.2). These hypoglycemic events are possibly related to use of linezolid in patients with diabetes mellitus taking insulin or oral hypoglycemic agents. Linezolid could have exacerbated hypoglycemia in these two patients.

Clinical Comment: Blood glucose should be evaluated in symptomatic patients who receive BPaL treatment, especially if concomitant medications include hypoglycemic drugs.

9.5.15. Pregnancy

One pregnancy was reported in the Nix-TB trial. Subject (b) (6) experienced an SAE of ectopic pregnancy (grade 3), internal hemorrhage (grade 4), and anemia (grade 4) on Days 241, 252, and 252 of the study, respectively. None of the events were considered related to study drug, and all three adverse events resolved.

Clinical Comment: BPaL has not been studied in pregnancy; therefore, the regimen should be avoided in pregnant women.

9.6. Safety Analyses by Demographic Subgroups

9.6.1. Sex

Overall, the types of TEAEs were similar among males and females but TEAEs occurred more frequently in female patients; however, there was no statistically significant difference for any TEAEs associated with study drugs between the two groups, see Table 9-44. Peripheral sensory neuropathy (> 70%) was the most common TEAE in both groups. TEAEs that occurred at a ≥ 10% difference (arbitrary cutoff) in females versus male subjects were nausea (42% vs. 32%) and vomiting (40% vs. 28%), respectively. ALT increases occurred at a ≥ 10% difference in frequency in male (14%) versus female (4%) subjects.

Table 9-44. Study Nix-TB: Select TEAEs in Males vs. Females, occurring in ≥ 5% subjects – Safety Population

	Female (N=52)	Male (N=57)	Total (N=109)
TEAEs by Preferred Term			
Peripheral neuropathy*	43 (82.7)	44 (77.2)	87 (79.8)
Dermatitis acneiform / acne	20 (38.5)	21 (36.8)	41 (37.6)
Anemia	21 (40.4)	19 (33.3)	40 (36.7)
Nausea	22 (42.3)	18 (31.6)	40 (36.7)
Vomiting	21 (40.4)	16 (28.1)	37 (33.9)
Headache†	16 (30.8)	14 (24.6)	30 (27.5)
ALT/AST increased§	10 (19.2)	17 (29.8)	27 (24.8)
Dyspepsia	15 (28.8)	11 (19.3)	26 (23.9)
Rash‡	12 (23.1)	14 (24.6)	26 (23.9)
Decreased appetite	13 (25.0)	11 (19.3)	24 (22.0)
Pleuritic pain	7 (13.5)	13 (22.8)	20 (18.3)
Abdominal pain¶	8 (15.4)	10 (17.5)	18 (16.5)
Gamma-glutamyltransferase increased	8 (15.4)	10 (17.5)	18 (16.5)
Amylase increased / Hyperamylasemia	6 (11.5)	11 (19.3)	17 (15.6)
Pruritus	10 (19.2)	5 (8.8)	15 (13.8)
Hemoptysis	4 (7.7)	10 (17.5)	14 (12.8)
Back pain	6 (11.5)	7 (12.3)	13 (11.9)

	Female (N=52)	Male (N=57)	Total (N=109)
Vision disturbance[±]	6 (11.5)	7 (12.3)	13 (11.9)
Cough / Productive cough	6 (11.5)	6 (10.5)	12 (11.0)
Hypoglycemia	8 (15.4)	4 (7.0)	12 (11.0)
Abnormal loss of weight	7 (13.5)	4 (7.0)	11 (10.1)
Diarrhea	5 (9.6)	6 (10.5)	11 (10.1)
Pneumonia / Lower respiratory tract infection	8 (15.4)	2 (3.5)	10 (9.2)
Constipation	6 (11.5)	3 (5.3)	9 (8.3)
Gastritis	6 (11.5)	3 (5.3)	9 (8.3)
Neutropenia	6 (11.5)	3 (5.3)	9 (8.3)
Dry skin	2 (3.8)	6 (10.5)	8 (7.3)
Blood lactic acid increased[¥]	6 (11.5)	1 (1.8)	7 (6.4)
Pain in extremity	4 (7.7)	3 (5.3)	7 (6.4)
Arthralgia	3 (5.8)	3 (5.3)	6 (5.5)
Costochondritis	4 (7.7)	2 (3.5)	6 (5.5)
Electrocardiogram QT prolonged	3 (5.8)	3 (5.3)	6 (5.5)
Hypertension	2 (3.8)	4 (7.0)	6 (5.5)
Insomnia	5 (9.6)	1 (1.8)	6 (5.5)
Lipase increased / Hyperlipasaemia	0	6 (10.5)	6 (5.5)
Myalgia	4 (7.7)	2 (3.5)	6 (5.5)

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: ISS ADSL; Filter: POOL1SFL = 'Y'.
TEAEs by Preferred Term - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y'. Percent Threshold: 5%
PTs removed: Upper respiratory tract infection / Chronic obstructive pulmonary disease / Urinary tract infection / Influenza
*Peripheral Neuropathy includes: Neuropathy peripheral / Peripheral sensory neuropathy / Paresthesia / Hypoesthesia / Peripheral sensorimotor neuropathy
[†]Headache includes: Headache / Migraine / Sinus headache / Tension headache
[§]ALT /AST Increased includes: Transaminases increased / Alanine aminotransferase increased / Aspartate aminotransferase increased / Hepatic enzyme increased / Liver function test increased / Hepatic function abnormal
[‡]Rash includes: Rash / Rash pruritic / Rash papular / Rash maculo-papular / Rash erythematous / Rash vesicular
[¶]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

9.6.2. Race

The study population consisted of three race categories, Black African (n=83, 76.1%), Other i.e., mixed race (25, 22.9%), or White, N=1(0.9%). A comparison of adverse events by race did not yield interpretable results because of the uneven distribution of races in the study population.

9.6.3. HIV Status

There were differences in the rate of GGT elevations, dyspepsia, and hemoptysis between HIV-negative and HIV-positive patients. GGT elevations were more common in HIV-positive patients, (29% versus 4%). Dyspepsia (36% versus 13%) and hemoptysis (21% versus 5%) were more common in HIV-negative patients.
Peripheral sensory neuropathy, the most common TEAE in the trial, was reported at similar rates in HIV-negative and HIV-positive patients. Hepatic adverse events (elevations in

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transaminases, ALT, AST, and drug-induced liver injury) were numerically higher in HIV positive patients which would be expected for patients on concomitant antiretroviral therapy. Anemia occurred more frequently in HIV-positive patients (43% versus 30%). A higher proportion of HIV-negative patients experienced GI adverse events such as decreased appetite (28% versus 16%) and nausea (43% versus 30%).

Table 9-45. Study Nix-TB: Select Treatment emergent adverse events by HIV status at baseline in ≥ 5% subjects - Safety population

	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
TEAEs by Preferred Term			
Peripheral neuropathy*	43 (81.1)	44 (78.6)	87 (79.8)
Dermatitis acneiform / acne	22 (41.5)	19 (33.9)	41 (37.6)
Anemia	16 (30.2)	24 (42.9)	40 (36.7)
Nausea	23 (43.4)	17 (30.4)	40 (36.7)
Vomiting	16 (30.2)	21 (37.5)	37 (33.9)
Headache[†]	16 (30.2)	14 (25.0)	30 (27.5)
ALT/AST increased[§]	15 (28.3)	12 (21.4)	27 (24.8)
Dyspepsia	19 (35.8)	7 (12.5)	26 (23.9)
Rash[‡]	8 (15.1)	18 (32.1)	26 (23.9)
Decreased appetite	15 (28.3)	9 (16.1)	24 (22.0)
Pleuritic pain	10 (18.9)	10 (17.9)	20 (18.3)
Abdominal pain[¶]	13 (24.5)	5 (8.9)	18 (16.5)
Gamma-glutamyltransferase increased	2 (3.8)	16 (28.6)	18 (16.5)
Amylase increased / Hyperamylasemia	6 (11.3)	11 (19.6)	17 (15.6)
Pruritus	7 (13.2)	8 (14.3)	15 (13.8)
Hemoptysis	11 (20.8)	3 (5.4)	14 (12.8)
Back pain	8 (15.1)	5 (8.9)	13 (11.9)
Vision disturbance[±]	8 (15.1)	5 (8.9)	13 (11.9)
Cough / Productive cough	5 (9.4)	7 (12.5)	12 (11.0)
Hypoglycemia	6 (11.3)	6 (10.7)	12 (11.0)
Abnormal loss of weight	6 (11.3)	5 (8.9)	11 (10.1)
Diarrhea	5 (9.4)	6 (10.7)	11 (10.1)
Pneumonia / Lower respiratory tract infection	4 (7.5)	6 (10.7)	10 (9.2)
Constipation	6 (11.3)	3 (5.4)	9 (8.3)
Gastritis	6 (11.3)	3 (5.4)	9 (8.3)
Neutropenia	2 (3.8)	7 (12.5)	9 (8.3)
Dry skin	5 (9.4)	3 (5.4)	8 (7.3)
Blood lactic acid increased[¥]	4 (7.5)	3 (5.4)	7 (6.4)
Pain in extremity	3 (5.7)	4 (7.1)	7 (6.4)
Arthralgia	3 (5.7)	3 (5.4)	6 (5.5)
Costochondritis	5 (9.4)	1 (1.8)	6 (5.5)
Electrocardiogram QT prolonged	2 (3.8)	4 (7.1)	6 (5.5)
Hypertension	2 (3.8)	4 (7.1)	6 (5.5)
Insomnia	2 (3.8)	4 (7.1)	6 (5.5)
Lipase increased / Hyperlipasemia	3 (5.7)	3 (5.4)	6 (5.5)
Myalgia	4 (7.5)	2 (3.6)	6 (5.5)

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: ISS ADSL; Filter: POOL1SFL = 'Y'.
TEAEs by Preferred Term - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y'. Percent Threshold: 5%
PTs removed: Upper respiratory tract infection / Chronic obstructive pulmonary disease / Urinary tract infection / Influenza

*Peripheral Neuropathy includes: Neuropathy peripheral / Peripheral sensory neuropathy / Paresthesia / Hypoesthesia / Peripheral sensorimotor neuropathy
†Headache includes: Headache / Migraine / Sinus headache / Tension headache
§ALT /AST Increased includes: Transaminases increased / Alanine aminotransferase increased / Aspartate aminotransferase increased / Hepatic enzyme increased / Liver function test increased / Hepatic function abnormal
‡Rash includes: Rash / Rash pruritic / Rash papular / Rash maculo-papular / Rash erythematous / Rash vesicular
¶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

Clinical Comment: Elevated serum levels of GGT are found in diseases of the liver, biliary tract, and pancreas, and reflect the same spectrum of hepatobiliary disease as alkaline phosphatase.[43] Elevated GGT levels are associated with alcohol use, hepatobiliary disease, and some medications can cause transient elevations in GGT in patients with normal or abnormal hepatic function. The additional burden of ARV drugs and BPaL in the HIV positive group may have led to a higher rate of increased GGT levels as compared to the HIV-negative group. Serum GGT and alkaline phosphatase usually correlate reasonably well; however, blood alkaline phosphatase was elevated in three subjects, 2 HIV-positive subjects and one HIV-negative subject, suggesting that there was relatively little cholestasis among the two groups. For example, in a prospective study that included 1040 nonselected inpatients, 13 percent had an elevated serum GGT activity and only 32% of these subjects had hepatobiliary disease.[44] In the remaining patients, the elevated serum GGT may have been due to alcohol ingestion or medications, which caused a temporary rise in levels but without liver disease.

9.6.4. Body Mass Index and Body Weight

The median BMI (Body Mass Index) was 19.6 kg/m^2 (12.4 to 41.1 kg/m^2) in Nix-TB. TEAEs were analyzed for patients in the following BMI categories: < 18.5, 18.5 to 24.9, 25 to 29.9, and ≥ 30 kg/m^2 representing underweight, normal weight, overweight, and obese patients, respectively. Most of the patients were underweight or normal weight. There was no obvious pattern of increased number of TEAEs in the patients in the < 18.5 kg/m^2 as compared to the 18.5 to 24.9 kg/m^2 category except for an increased TEAEs in the gastrointestinal disorders system organ class as compared to patients in the normal body weight category.

Table 9-46. Study Nix-TB: TEAEs by BMI (kg/m^2) Category

TEAEs by System Organ Class	BODY MASS INDEX (kg/m^2)			
	<18.5 n=43	18.5 to 24.9 n=51	25 to 29.9 n=11	>=30 n=4
NERVOUS SYSTEM DISORDERS	37 (86.0%)	39 (76.5%)	10 (90.9%)	4 (100.0%)
GASTROINTESTINAL DISORDERS	34 (79.1%)	30 (58.8%)	7 (63.6%)	2 (50.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	28 (65.1%)	32 (62.7%)	5 (45.5%)	2 (50.0%)

[43] Friedman LS. Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase. Oct 3, 2018. www.UpToDate.com
[44] Burrows S, Feldman W, McBride F. Serum gamma-glutamyl transpeptidase. Evaluation in screening of hospitalized patients. Am J Clin Pathol. 1975;64(3):311.

Reference ID: 4476823

TEAEs by System Organ Class	BODY MASS INDEX (kg/m^2)			
	<18.5 n=43	18.5 to 24.9 n=51	25 to 29.9 n=11	>=30 n=4
INFECTIONS AND INFESTATIONS	28 (65.1%)	27 (52.9%)	7 (63.6%)	2 (50.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23 (53.5%)	21 (41.2%)	5 (45.5%)	2 (50.0%)
METABOLISM AND NUTRITION DISORDERS	23 (53.5%)	24 (47.1%)	5 (45.5%)	0 (0.0%)
INVESTIGATIONS	19 (44.2%)	24 (47.1%)	5 (45.5%)	1 (25.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	19 (44.2%)	26 (51.0%)	6 (54.5%)	1 (25.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	16 (37.2%)	12 (23.5%)	6 (54.5%)	2 (50.0%)
EYE DISORDERS	10 (23.3%)	17 (33.3%)	3 (27.3%)	3 (75.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (16.3%)	9 (17.6%)	2 (18.2%)	1 (25.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	6 (14.0%)	6 (11.8%)	2 (18.2%)	1 (25.0%)
PSYCHIATRIC DISORDERS	5 (11.6%)	4 (7.8%)	0 (0.0%)	1 (25.0%)
CARDIAC DISORDERS	4 (9.3%)	4 (7.8%)	1 (9.1%)	1 (25.0%)
HEPATOBILIARY DISORDERS	4 (9.3%)	4 (7.8%)	0 (0.0%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	4 (9.3%)	4 (7.8%)	0 (0.0%)	0 (0.0%)
VASCULAR DISORDERS	3 (7.0%)	4 (7.8%)	3 (27.3%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.3%)	5 (9.8%)	2 (18.2%)	1 (25.0%)
RENAL AND URINARY DISORDERS	1 (2.3%)	2 (3.9%)	1 (9.1%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)

JMP Clinical v. 6.0: Datasets used: - ISS ADSL (POOL1SFL), ISS ADAE (TRTEMFL).

TEAEs of special interest, peripheral neuropathy, hepatic disorders and hematopoietic cytopenias, and were evaluated in patients with low body weight, < 50 kg. A larger proportion of patients who weighed < 50 kg experienced peripheral neuropathy and hepatic disorders, as compared to patients ≥ 50 kg to < 80 kg body weight category; however, the number of patients in each weight group is too small to make any definitive conclusions.

Table 9-47. Nix-TB: Hepatic Disorders, Peripheral Neuropathy, Optic Disorders, Lactic Acidosis, and Hematopoietic Cytopenias SMQs - by Body Weight

	< 50kg (N=39)	≥ 50kg to < 80kg (N=62)	≥ 80kg (N=8)	Total (N=109)
Hepatic Disorders (SMQ)	***16 (41.0)***	***23 (37.1)***	***1 (12.5)***	***40 (36.7)***
Gamma-glutamyltransferase increased	4 (10.3)	13 (21.0)	1 (12.5)	18 (16.5)
Transaminases increased	6 (15.4)	5 (8.1)	1 (12.5)	12 (11.0)
Alanine aminotransferase increased	1 (2.6)	9 (14.5)	0	10 (9.2)
Aspartate aminotransferase increased	1 (2.6)	7 (11.3)	0	8 (7.3)
Blood alkaline phosphatase increased	1 (2.6)	2 (3.2)	0	3 (2.8)
Drug-induced liver injury	0	2 (3.2)	0	2 (1.8)
Hepatic enzyme increased	1 (2.6)	1 (1.6)	0	2 (1.8)
Hyperbilirubinemia	2 (5.1)	0	0	2 1.8)
Hepatic function abnormal	1 (2.6)	0	0	1 (0.9)
Hepatomegaly	1 (2.6)	0	0	1 (0.9)
Jaundice	0	1 (1.6)	0	1 (0.9)
Liver function test increased	1 (2.6)	0	0	1 (0.9)
Acute Pancreatitis (SMQ)	***4 (10.3)***	***16 (25.8)***	***2 (25.0)***	***22 (20.2)***
Amylase increased	1 (2.6)	6 (9.7)	2 (25.0)	9 (8.3)
Hyperamylasemia	2 (5.1)	6 (9.7)	0	8 (7.3)
Lipase increased	0	5 (8.1)	0	5 (4.6)

	< 50kg (N=39)	≥ 50kg to < 80kg (N=62)	≥ 80kg (N=8)	Total (N=109)
Pancreatitis	2 (5.1)	0	0	2 (1.8)
Hyperlipasaemia	0	1 (1.6)	0	1 (0.9)
Pancreatitis hemorrhagic	0	1 (1.6)	0	1 (0.9)
Peripheral Neuropathy (SMQ)	***34 (87.2)***	***45 (72.6)***	***8 (100.0)***	***87 (79.8)***
Peripheral sensory neuropathy	30 (76.9)	39 (62.9)	6 (75.0)	75 (68.8)
Neuropathy peripheral	3 (7.7)	5 (8.1)	2 (25.0)	10 (9.2)
Paraesthesia	0	4 (6.5)	1 (12.5)	5 (4.6)
Hypoaesthesia	1 (2.6)	2 (3.2)	0	3 (2.8)
Peripheral motor neuropathy	2 (5.1)	0	0	2 (1.8)
Burning sensation	1 (2.6)	0	0	1 (0.9)
Hyporeflexia	1 (2.6)	0	0	1 (0.9)
Peripheral sensorimotor neuropathy	1 (2.6)	0	0	1 (0.9)
Optic Nerve Disorders (SMQ)	***2 (5.1)***	***10 (16.1)***	***1 (12.5)***	***13 (11.9)***
Visual acuity reduced	0	5 (8.1)	1 (12.5)	6 (5.5)
Visual impairment	1 (2.6)	2 (3.2)	0	3 (2.8)
Amblyopia	0	1 (1.6)	0	1 (0.9)
Optic disc hyperemia	0	1 (1.6)	0	1 (0.9)
Optic neuritis	1 (2.6)	0	0	1 (0.9)
Optic neuropathy	0	1 (1.6)	0	1 (0.9)
Papilledema	0	1 (1.6)	0	1 (0.9)
Hematopoietic Cytopenias (SMQ)	***18 (46.2)***	***32 (51.6)***	***1 (12.5)***	***51 (46.8)***
Anemia	14 (35.9)	25 (40.3)	1 (12.5)	40 (36.7)
Neutropenia	0	8 (12.9)	1 (12.5)	9 (8.3)
Thrombocytopenia	2 (5.1)	3 (4.8)	0	5 (4.6)
Bone marrow failure	3 (7.7)	0	0	3 (2.8)
Leukopenia	1 (2.6)	1 (1.6)	0	2 (1.8)
Bicytopenia	1 (2.6)	0	0	1 (0.9)
Lymphopenia	1 (2.6)	0	0	1 (0.9)
Pancytopenia	0	1 (1.6)	0	1 (0.9)
Lactic Acidosis (SMQ)	***5 (12.8)***	***3 (4.8)***	***0***	***8 (7.3)***
Hyperlactacidaemia	2 (5.1)	1 (1.6)	0	3 (2.8)
Lactic acidosis	2 (5.1)	1 (1.6)	0	3 (2.8)
Acidosis	0	1 (1.6)	0	1 (0.9)
Blood lactic acid increased	1 (2.6)	0	0	1 (0.9)

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: ISS ADSL; Filter: POOL1SFL = 'Y'.
Hepatic Disorders (SMQ) - Dataset: ISS ADAE; Filter: SMQ01NAM = 'Hepatic disorders (SMQ)', TRTEMFL = 'Y'.
Acute Pancreatitis (SMQ) - Dataset: ISS ADAE; Filter: SMQ06NAM = 'Acute pancreatitis (SMQ)', TRTEMFL = 'Y'.
Peripheral Neuropathy (SMQ) - Dataset: ISS ADAE; Filter: SMQ09NAM = 'Peripheral neuropathy (SMQ)', TRTEMFL = 'Y'.
Optic Nerve Disorders (SMQ) - Dataset: ISS ADAE; Filter: SMQ10NAM = 'Optic nerve disorders (SMQ)', TRTEMFL = 'Y'.
Hematopoietic Cytopenias (SMQ) - Dataset: ISS ADAE; Filter: SMQ11NAM = 'Hematopoietic cytopenias (SMQ)', TRTEMFL = 'Y'.
Lactic Acidosis (SMQ) - Dataset: ISS ADAE; Filter: SMQ12NAM = 'Lactic acidosis (SMQ)', TRTEMFL = 'Y'.
A list of terms included in the applicant's SMQs are provided in Appendix 1 of the ISS SAP.

Reference ID: 4476823

9.6.5. Albumin Levels

Approximately 27% of patients in the Nix-TB trial had low albumin levels which is indicative of underlying chronic infection. TEAEs were analyzed by albumin level categories at baseline (< 3.5g/dL (low) and > 3.5g/dL (normal). There were no major differences in the type and number of TEAEs experienced between patients with low and normal albumin levels at baseline, except for abnormal weight loss in the low albumin group which is an expected adverse event.

9.6.6. Age ≥ 65 years and Geographic Location

Analyses of TEAEs with respect to age and geographic region were not conducted because all subjects were younger than 65 years of age and all were from South Africa.

Clinical Comment: In summary, there were no major differences in numbers of patients with TEAEs based on sex, BMI / body weight or low albumin levels. Elevations in hepatic transaminases and anemia occurred more frequently in HIV-positive subjects than in HIV negative which would be expected because of underlying disease and concomitant ART. The clinical pharmacology reviewers found no clinically significant differences in the pharmacokinetics of pretomanid based on sex, body weight, race/ethnicity (Black, Caucasian, other), type of pulmonary TB, or HIV status.

9.7. Specific Safety Studies/Clinical Trials

9.7.1. ZeNix Trial – Interim Results

ZeNix (NC-007) is an ongoing phase 3, randomized, partially blinded (i.e., blinded for linezolid dosing arms), parallel-group trial evaluating the efficacy, safety, and tolerability of different doses and durations of linezolid as part of a 26-week regimen of BPaL in subjects with pulmonary XDR-TB, pulmonary pre-extensively drug-resistant tuberculosis (pre-XDR-TB), or pulmonary TI/NR MDR-TB. The study is being conducted at eight centers across South Africa, Russia, and other countries in Eastern Europe. Interim safety results (cutoff date of October 15, 2018) from the ZeNix trial were included in a 120-day safety update submitted on 4/5/19.
All treatment arms in ZeNix use the same pretomanid dosing (200 mg once daily) as in Nix-TB trial, and one BPaL treatment arm uses the same dosing of linezolid (1200 mg once daily). The other treatment arms use different dosing schemes for linezolid, based on dosing duration (9 weeks versus 26 weeks) or daily dose (600 mg versus 1200 mg).
Bedaquiline is dosed at 200 mg once daily for 8 weeks and then 100 mg once daily; this differs from the bedaquiline dosing used in Nix-TB.

Treatment Emergent Adverse Events
Safety data for 61 patients was submitted. Fifty-one (84%) patients experienced at least one TEAE, Table 9-48. TEAEs are presented using a cutoff rate of ≥ 2. The most common AEs were peripheral sensory neuropathy in 9 (15%) patients, increase ALT in 8 (13%) patients, vomiting in 7 (12%) patients, anemia in 6 (10%) patients, and dermatitis acneiform in 6 (10%) patients.

The type of TEAEs reported in the ZeNix trial are similar to the TEAEs reported in the Nix-TB trial and there are no new safety signals in this interim safety report.

Table 9-48. Study ZeNix: Treatment Emergent Adverse Events (≥ 2%) in BPaL group - Interim results for Safety Population

	BPaL (N=61)
Any TEAE	51 (83.6)
TEAEs by Preferred Term (≥ 2%)	
Peripheral neuropathy*	12 (19.7)
ALT/AST increased[§]	11 (18.0)
Rash[‡]	8 (13.1)
Vomiting	7 (11.5)
Anemia	6 (9.8)
Dermatitis acneiform / Acne	6 (9.8)
Musculoskeletal pain[¶]	5 (8.2)
Nausea	5 (8.2)
Pruritus / Pruritus generalized / Pruritus allergic	5 (8.2)
Fatigue	4 (6.6)
Hyperkaliemia	4 (6.6)
Hypertension	4 (6.6)
Upper respiratory tract infection / Viral upper respiratory tract infection	4 (6.6)
Dermatitis / Dyshidrotic eczema / Eczema	3 (4.9)
Diarrhea	3 (4.9)
Dry skin	3 (4.9)
Dyspepsia	3 (4.9)
Hypophosphatemia	3 (4.9)
Pleuritic pain	3 (4.9)
Stress	3 (4.9)
Arthralgia	2 (3.3)
Blood creatine phosphokinase increased	2 (3.3)
Bronchitis	2 (3.3)
Conjunctivitis allergic	2 (3.3)
Constipation	2 (3.3)
Cough / Productive cough	2 (3.3)
Dermatitis allergic	2 (3.3)
Electrocardiogram t wave inversion	2 (3.3)
Hemoglobin decreased	2 (3.3)
Hemoptysis	2 (3.3)
Headache[†]	2 (3.3)
Herpes zoster / Varicella zoster virus infection	2 (3.3)
Lipase increased / Hyperlipasaemia	2 (3.3)
Muscle spasms	2 (3.3)
Neutropenia	2 (3.3)

	BPaL (N=61)

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: ISS 120 Day ADSL; Filter: POOL2SFL = 'Y'.
Any TEAE - Dataset: ZeNiX 120 Day AE and SUPPAE; Filter: AETRTEM = 'Y'.
TEAEs by Preferred Term (≥ 2%) - Dataset: ZeNiX 120 Day AE and SUPPAE; Filter: AETRTEM = 'Y'; Percent Threshold: 2%.
*Peripheral neuropathy includes: Neuropathy peripheral / Peripheral sensory neuropathy / Paraesthesia / Hypoaesthesia / Peripheral sensorimotor neuropathy / Decreased vibratory sense
[§]ALT/AST increased includes: Transaminases increased / Alanine aminotransferase increased / Aspartate aminotransferase increased / Hepatic enzyme increased / Liver function test increased / Hepatic function abnormal
[‡]Rash includes: Rash / Rash pruritic / Rash papular / Rash maculo-papular / Rash erythematous / Rash vesicular / Nodular rash / Rash macular
[¶]Musculoskeletal pain includes: Musculoskeletal chest pain / Non-cardiac chest pain / Chest pain / Back pain / Neck pain
[†]Headache includes: Headache / Migraine / Sinus headache / Tension headache

Clinical Comment: The ZeNix trial will be requested as a postmarket requirement (PMR) study if the NDA 212862 is approved. The results of this trial will provide additional information on the efficacy and safety of BPaL with various doses and durations of linezolid.

9.7.2. 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. This pooling group also contains the Thorough QT study. 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 mean duration of dosing in the placebo group was 5 (range, 1 to 8) days.

Disposition

Ten (3.5%) subjects in the pretomanid group and no control (placebo) subjects reported TEAEs that led to permanent discontinuation of pretomanid. Five were discontinued due to increased creatinine levels. Serum creatinine was increased in 2.6% subjects in the >200mg pretomanid group and this was investigated in a dedicated phase 1 renal study, CL-005, which found that pretomanid inhibits tubular creatinine secretion rather than affecting glomerular filtration or renal plasma flow, an effect that is not considered clinically meaningful.

Table 9-49. Phase 1 Studies: Disposition of Subjects Pretomanid vs. Control

	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 decision	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

	Single Dose Pretomanid (N=174)	Multiple Dose Pretomanid (N=115)	Placebo (N=35)
Physician/sponsor decision	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 creatinine 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'.

Phase 1 Studies – TEAEs

There were no deaths or SAEs in the phase 1 studies. The most common (≥ 2%) TEAE was headache in 91 (32%) subjects in the pretomanid group versus 8 (23%) subjects in the placebo group. Other AEs occurring in the pretomanid group 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.

Table 9-50. Phase 1 Studies: Common TEAEs (≥ 2%) - Pretomanid vs. Placebo Control - 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

Reference ID: 4476823

	Pretomanid (N=289)	Placebo (N=35)
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").

In the phase 1 studies, the following pretomanid dose categories were studied as single- and multiple-doses: < 200mg, 200mg, and > 200mg. More than 50% of the patients in each pretomanid dose category and 40% of patients in the placebo group experienced a TEAE. Headache was the most common (> 20%) TEAE across the three pretomanid dose categories. Headache, dizziness, diarrhea, and chromaturia were the most common TEAEs in the pretomanid 200 mg (to be marketed dose) category. TEAEs such as Hb 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 about a dose response is limited by the small number of subjects in the dose categories. No potential Hy's Law cases were identified in the phase 1 pooling group.

Table 9-51. Phase 1 Studies: Common Adverse Events (≥ 2%) by Pretomanid Dose Group

	Pretomanid < 200mg (N=20)	Pretomanid 200mg (N=74)	Pretomanid > 200mg (N=195)	Placebo (N=35)
TEAEs by Preferred Term				
Headache	10 (50.0)	15 (20.3)	66 (33.8)	8 (22.9)
Nausea	2 (10.0)	5 (6.8)	27 (13.8)	0
Dermatitis contact	0	0	33 (16.9)	0
Hemoglobin decreased	0	0	31 (15.9)	0
Dizziness / Dizziness postural	1 (5.0)	8 (10.8)	16 (8.2)	1 (2.9)
Diarrhea	4 (20.0)	14 (18.9)	7 (3.6)	0
Abdominal pain[¶]	3 (15.0)	4 (5.4)	11 (5.6)	2 (5.7)
Electrocardiogram QT prolonged	0	0	12 (6.2)	3 (8.6)
Fatigue	0	6 (8.1)	7 (3.6)	0
Rash[‡]	0	1 (1.4)	6 (3.1)	2 (5.7)
Chromaturia	0	8 (10.8)	0	0
Pruritus / Pruritus generalized	0	2 (2.7)	6 (3.1)	0
ALT increased[§]	0	1 (1.4)	6 (3.1)	0
Flatulence	0	4 (5.4)	3 (1.5)	0
Nasal congestion	1 (5.0)	0	6 (3.1)	0
Vomiting	0	3 (4.1)	3 (1.5)	0
AST increased[±]	0	1 (1.4)	4 (2.1)	0
Blood creatinine increased	0	0	5 (2.6)	0
Protein urine present	0	0	5 (2.6)	0
Rhinorrhea	0	1 (1.4)	4 (2.1)	0

Reference ID: 4476823

	Pretomanid < 200mg (N=20)	Pretomanid 200mg (N=74)	Pretomanid > 200mg (N=195)	Placebo (N=35)
Back pain	0	0	4 (2.1)	0
Catheter site pain¥	0	0	4 (2.1)	0
Ecchymosis	0	0	4 (2.1)	0
Hypoaesthesia / Paraesthesia	0	0	4 (2.1)	0
Pain	1 (5.0)	1 (1.4)	2 (1.0)	0
Abnormal dreams	0	3 (4.1)	0	0
Chest pain / Chest discomfort	1 (5.0)	0	1 (0.5)	1 (2.9)
Cough	0	2 (2.7)	1 (0.5)	0
Dry mouth	0	2 (2.7)	0	1 (2.9)
Sinus congestion	0	2 (2.7)	1 (0.5)	0
Vision blurred / Visual impairment	1 (5.0)	0	2 (1.0)	0
Anxiety	0	0	1 (0.5)	1 (2.9)
Feeling hot	1 (5.0)	0	1 (0.5)	0
Pollakiuria	0	2 (2.7)	0	0
Cardiac murmur	0	0	0	1 (2.9)
Chills	0	0	0	1 (2.9)
Dyspnea	1 (5.0)	0	0	0
Excoriation	0	0	0	1 (2.9)
Eye pruritus	1 (5.0)	0	0	0
Lacrimation increased	1 (5.0)	0	0	0
Lymph node pain	0	0	0	1 (2.9)
Musculoskeletal stiffness	0	0	0	1 (2.9)
Palpitations	0	0	0	1 (2.9)
Skin exfoliation	1 (5.0)	0	0	0

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: ISS ADSL (Modified to include dose columns); Filter: POOL6SFL = 'Y'.
TEAEs by Preferred Term - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y'; Percent Threshold: 2% (in any column)
¶Abdominal Pain includes: Abdominal pain / Abdominal discomfort / Abdominal pain upper / Abdominal pain lower / Gastrointestinal pain
‡Rash includes: Rash / Rash generalized / Rash macular / Rash papular
§ALT increased includes: Alanine aminotransferase increased / Alanine aminotransferase abnormal
±AST increased includes: Aspartate aminotransferase increased / Aspartate aminotransferase abnormal
¥Catheter site pain includes: Catheter site pain / Catheter site swelling / Catheter site hemorrhage / Catheter site phlebitis

Severity of TEAEs

Four pretomanid subjects (1.4% of the all-pretomanid group) experienced grade 3 TEAEs. The grade 3 events consisted of blood CPK increased (1 subject in the single-dose pretomanid >200 mg group), AST abnormal (1 subject in the multiple-dose pretomanid 200 mg group), neutrophil count decreased (1 subject in the multiple-dose pretomanid 200 mg group), and rash generalized (1 subject in the multiple-dose pretomanid >200 mg group). One additional patient developed a skin rash one day post treatment.

9.7.3. Phase 2 Pooled Studies

Two phase 2 EBA studies of pretomanid were conducted in South Africa, CL-007 and CL-010, in which pretomanid alone was administered to adult subjects for up to 14 days:

Reference ID: 4476823

CL-007: A Phase 2 Trial to Evaluate the Safety, Tolerability, Extended Early Bactericidal Activity and Pharmacokinetics of 14 Days' Treatment with Four Oral Doses of PA-824 (200, 600, 1000, 1200mg) in Adult Participants with Uncomplicated, Smear-Positive, Pulmonary Tuberculosis.
CL010: A Phase 2, Dose-ranging Trial to Evaluate the Extended Early Bactericidal Activity, Safety, Tolerability, and Pharmacokinetics of PA-824 (50 100, 150, 200mg) in Adult Participants with Newly Diagnosed, Uncomplicated, Smear-Positive, Pulmonary Tuberculosis.

Demographics: The safety population included 138 adults, 122 received pretomanid alone and 16 received the standard of care regimen, HRZE (Rifafour®e-275) 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 (approx. 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 1,200mg. 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 EBA studies. Four (3.3%) patients discontinued treatment with pretomanid due to a TEAE and one (0.8%) patient withdrew, Table 9-52.

Table 9-52. Phase 2 Pooled Studies (CL-007 and CL-010): 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).

No deaths occurred in the pretomanid-alone pooling group. Forty-seven (39%) subjects in the pretomanid group (all dose categories) had TEAEs versus 7 (44%) in the HRZE group, Table 9-53. The most frequently reported (≥10% of subjects) system organ classes of TEAEs in the all-pretomanid group were skin and subcutaneous disorders (14.8%) and gastrointestinal disorders (10.7%).

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

Table 9-53. Phase 2 Studies (CL-007 and CL-010): Common TEAEs ≥ 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.

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.

Table 9-54. Phase 2 Studies (CL-007 and CL-010): Serious Adverse Events by Pretomanid Dose Groups

	Pretomanid < 200mg (N=45)	Pretomanid 200mg (N=31)	Pretomanid > 200mg (N=46)	HRZE Control (N=16)
Any Serious TEAE	1 (2.2)	1 (3.2)	0	1 (6.2)
Serious TEAEs by Preferred Term				

Reference ID: 4476823

	Pretomanid < 200mg (N=45)	Pretomanid 200mg (N=31)	Pretomanid > 200mg (N=46)	HRZE Control (N=16)
HAEMOPTYSIS	0	1 (3.2)	0	1 (6.2)
PNEUMOTHORAX	1 (2.2)	0	0	0

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

9.7.4. Drug-Sensitive and Multi-Drug Resistant Tuberculosis Pooling Groups

In the drug-sensitive tuberculosis (DS-TB) group, 17% of subjects were coinfected with HIV and 38% of subjects were co-infected with HIV in the MDR-TB group. The MDR-TB pooling group represented a population of subjects with pulmonary tuberculosis who, in general, had less severe illness than subjects in the Nix-TB study and more severe illness than subjects in the DS-TB pooling group.

TEAEs

TEAEs for the drug sensitive and multidrug resistant tuberculosis pooling groups are summarized in Table 9-55. SAEs leading to death are described in subsection 9.4.1 and other SAEs are described in section 15.5.

TEAEs for subjects with DS-TB from seven pooled phase 2 /3 studies, i.e., CL007, CL010, NC-001, NC-002, NC-003, NC-005, and NC-006 are summarized in Table 9-55.
In the pretomanid monotherapy group, skin rash (8%) and pruritus (6%) were the most common TEAEs.
In the pretomanid combination therapy group, arthralgia, hyperuricemia / blood uric acid increased (28%), arthralgia (21%), ALT /AST elevations (18%), and nausea (12%) were common (> 10%).
Hyperuricemia/blood uric acid increased (25%), AST/ALT elevations (13%), and generalized pruritus (15%) were the most common (> 10%) TEAEs in the HRZE comparator group. Increased hepatic transaminases and headache were the most common TEAE in the other comparator groups.
Elevated hepatic transaminases occurred in 18% of DS-TB patients treated with pretomanid combinations therapy versus 13% of HRZE controls. The most frequently (≥2% of subjects) reported TEAEs with a maximum grade of 3 (severe) or grade 4 (life-threatening) in the pretomanid-combination therapy group were blood uric acid increased (8%), ALT increased (8%), AST increased (8%), hyperuricemia (5%), and GGT increased (4%).

Multi-Drug Resistant Tuberculosis

TEAEs in patients with MDR-TB subjects in pooled Studies NC-002, NC-005, and NC-006 are summarized in Table 9-55.
Antimycobacterial regimens that were studied included PaMZ, BPaZ, and BPaMZ. The most frequently reported of TEAEs (≥10% of subjects) were hyperuricemia/blood uric acid increased (39%), arthralgia (17%), nausea (14%), vomiting (13%), pleuritic pain (12%), and amylase increased (10%). Hepatic transaminases were elevated in 9% of patients.

Maximum TEAE grades of 3 and 4 were reported in 17% and 6% of subjects, respectively. The most frequently (≥2 subjects [2.0%]) reported TEAEs with a maximum grade of 3 in a subject were AST increased (6%), ALT increased (6%), blood uric acid increased (5%), hyperuricemia (4%), and GGT increased (3%). The most frequently (≥2 subjects [2%]) reported TEAEs with a maximum grade of 4 were AST increased (2%) and ALT increased (2%). Two of these TEAEs were resolving and two were not resolved at the data cutoff date.

Clinical Comment: Arthralgia, elevated blood uric acid levels, and hyperuricemia are associated with pyrazinamide (Rifater® USPI 2018) and to some extent with moxifloxacin (Avelox® USPI, 2016). Hyperuricemia was reported in 1(0.9%) patient treated with BPaL regimen in the Nix-TB study. None of the patients received linezolid in the DSTB and MDRTB pooling groups, therefore the incidence of anemia and other hematopoietic cytopenias was lower than the Nix-TB study.

Table 9-55. Drug-Sensitive and Multi-Drug Resistant Tuberculosis Pooling Groups: Select TEAEs (≥ 2%) – Safety Population

	DS-TB				MDR-TB
	Pretomanid Combination Therapy (N=534)	HRZE Control (N=229)	Pretomanid Monotherapy (N=122)	Comparator (N=75)	Pretomanid Combination Therapy (N=99)
Any TEAE	440 (82.4)	176 (76.9)	47 (38.5)	41 (54.7)	92 (92.9)
TEAEs by Preferred Term (≥ 2%)					
Hyperuricemia / Blood uric acid increased	151 (28.3)	56 (24.5)	0	0	39 (39.4)
Arthralgia	112 (21.0)	33 (14.4)	0	0	17 (17.2)
ALT/AST increased[§]	97 (18.2)	29 (12.7)	1 (0.8)	8 (10.7)	9 (9.1)
Nausea	62 (11.6)	14 (6.1)	5 (4.1)	2 (2.7)	14 (14.1)
Pruritus / Pruritus generalized	45 (8.4)	35 (15.3)	7 (5.7)	0	6 (6.1)
Rash[‡]	47 (8.8)	24 (10.5)	10 (8.2)	2 (2.7)	6 (6.1)
Vomiting	48 (9.0)	19 (8.3)	4 (3.3)	5 (6.7)	13 (13.1)
Headache[†]	43 (8.1)	14 (6.1)	3 (2.5)	8 (10.7)	7 (7.1)
Gamma-glutamyltransferase increased	41 (7.7)	16 (7.0)	0	2 (2.7)	7 (7.1)
Hemoptysis	29 (5.4)	16 (7.0)	3 (2.5)	3 (4.0)	11 (11.1)
Diarrhea	41 (7.7)	6 (2.6)	1 (0.8)	1 (1.3)	7 (7.1)
Abdominal pain[¶]	30 (5.6)	9 (3.9)	3 (2.5)	3 (4.0)	7 (7.1)
Dizziness	33 (6.2)	11 (4.8)	2 (1.6)	0	4 (4.0)
Anemia[¥]	24 (4.5)	14 (6.1)	2 (1.6)	0	1 (1.0)
Pleuritic pain	14 (2.6)	6 (2.6)	0	1 (1.3)	12 (12.1)
Myalgia	22 (4.1)	6 (2.6)	0	0	4 (4.0)
Blood urine present / Hematuria	17 (3.2)	8 (3.5)	0	0	5 (5.1)
Hyponatremia / Blood sodium decreased	18 (3.4)	10 (4.4)	1 (0.8)	0	1 (1.0)
Urinary tract infection	14 (2.6)	6 (2.6)	1 (0.8)	0	4 (4.0)
Peripheral neuropathy*	10 (1.9)	8 (3.5)	1 (0.8)	0	5 (5.1)
Hyperglycemia	17 (3.2)	2 (0.9)	0	0	3 (3.0)
Musculoskeletal pain[¤]	10 (1.9)	7 (3.1)	1 (0.8)	1 (1.3)	3 (3.0)
White blood cell count increased / Leukocytosis	16 (3.0)	4 (1.7)	0	0	2 (2.0)
Pain in extremity	12 (2.2)	3 (1.3)	1 (0.8)	0	5 (5.1)
Blood alkaline phosphatase increased	11 (2.1)	6 (2.6)	0	1 (1.3)	2 (2.0)
Decreased appetite	12 (2.2)	3 (1.3)	0	1 (1.3)	4 (4.0)

	DS-TB				MDR-TB
	Pretomanid Combination Therapy (N=534)	HRZE Control (N=229)	Pretomanid Monotherapy (N=122)	Comparator (N=75)	Pretomanid Combination Therapy (N=99)
Proteinuria	14 (2.6)	4 (1.7)	0	0	0
Electrocardiogram QT prolonged	10 (1.9)	1 (0.4)	1 (0.8)	3 (4.0)	2 (2.0)
Back pain	8 (1.5)	5 (2.2)	0	2 (2.7)	1 (1.0)
Vision disturbance[±]	4 (0.7)	12 (5.2)	0	0	0
Amylase increased / Hyperamylasemia	1 (0.2)	1 (0.4)	0	2 (2.7)	10 (10.1)
Blood glucose increased	9 (1.7)	5 (2.2)	0	0	0
Hypertension	7 (1.3)	4 (1.7)	0	0	2 (2.0)
Pneumonia / Lower respiratory tract infection	7 (1.3)	4 (1.7)	0	0	2 (2.0)
Rales	8 (1.5)	5 (2.2)	0	0	0
Dyspnea	7 (1.3)	3 (1.3)	0	0	2 (2.0)
Hypoalbuminemia	6 (1.1)	5 (2.2)	0	0	0
Conjunctivitis	6 (1.1)	1 (0.4)	0	0	3 (3.0)
Vulvovaginal candidiasis	3 (0.6)	2 (0.9)	0	0	5 (5.1)
Insomnia	4 (0.7)	2 (0.9)	0	0	3 (3.0)
Photophobia	3 (0.6)	1 (0.4)	0	4 (5.3)	1 (1.0)
Pyrexia	5 (0.9)	1 (0.4)	1 (0.8)	0	2 (2.0)
Dyspepsia	3 (0.6)	2 (0.9)	0	1 (1.3)	2 (2.0)
Pain	3 (0.6)	3 (1.3)	0	0	2 (2.0)
Rhinitis	3 (0.6)	5 (2.2)	0	0	0
Constipation	4 (0.7)	1 (0.4)	0	0	2 (2.0)
Oral candidiasis	3 (0.6)	1 (0.4)	0	1 (1.3)	2 (2.0)
Blood pressure increased[Ω]	2 (0.4)	2 (0.9)	0	0	2 (2.0)
Otitis media	3 (0.6)	1 (0.4)	0	0	2 (2.0)
Palpitations	3 (0.6)	1 (0.4)	0	0	2 (2.0)
Electrocardiogram (ECG) abnormality[Δ]	1 (0.2)	1 (0.4)	0	0	2 (2.0)
Pulmonary embolism	1 (0.2)	0	0	0	2 (2.0)
Skin discoloration	1 (0.2)	0	0	2 (2.7)	0
Vertigo	1 (0.2)	0	0	0	2 (2.0)

Source: OCS Analysis Studio Custom Table Builder.
Columns - Dataset: ISS ADSL; Filter: POOL3SFL = 'Y' or POOL4SFL = 'Y'.
Any TEAE - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y'.
TEAEs by Preferred Term (≥ 2%) - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y'; Percent Threshold: 2% in any column
PTs removed: Somnolence / Tooth abscess / Body tinea / Asymptomatic bacteriuria
[§]ALT/AST increased includes: Transaminases increased / Alanine aminotransferase increased / Aspartate aminotransferase increased / Hepatic enzyme increased / Liver function test increased / Hepatic function abnormal
[‡]Rash includes: Rash / Rash pruritic / Rash papular / Rash maculo-papular / Rash erythematous / Rash vesicular / Rash macular
[†]Headache includes: Headache / Migraine / Sinus headache / Tension headache
[¶]Abdominal pain includes: Abdominal discomfort / Abdominal pain / Abdominal pain upper / Abdominal pain lower / Flank pain
[¥]Anemia includes: Anemia / Hypochromic anemia / Microcytic anemia / Iron deficiency anemia / Normochromic normocytic anemia
*Peripheral neuropathy includes: Neuropathy peripheral / Peripheral sensory neuropathy / Paraesthesia / Hypoaesthesia / Peripheral sensorimotor neuropathy
[¤]Musculoskeletal pain includes: Musculoskeletal chest pain / Musculoskeletal pain / Non-cardiac chest pain / Chest pain / Chest discomfort
[±]Vision disturbance includes: Vision blurred / Visual acuity reduced / Visual impairment
[Ω]Blood pressure increased includes: Blood pressure diastolic increased / Blood pressure systolic increased
[Δ]Electrocardiogram (ECG) abnormality includes: Electrocardiogram PR prolongation / Electrocardiogram QRS complex prolonged / Electrocardiogram ST segment depression / Electrocardiogram ST segment elevation / Electrocardiogram T wave amplitude decreased

9.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

9.9. Nix-TB Trial: 120-Day Safety Update

The 120-day safety update report, submitted on April 5, 2019, contained safety data for the ongoing phase 3 studies Nix-TB and ZeNix from the time of study initiation to October 15, 2018 (interim data cutoff date for the safety update). The original NDA safety data cutoff date was March 26,2018.

The updated report included safety data for all 109 patients enrolled in the Nix-TB trial. Of these 109 patients, 101 (92.7%) have completed the protocol-specified 26 weeks of treatment compared to 93 patients (85.3%) at the cutoff for the NDA. A total of 27 patients (24.8%) completed the entire study including the 24 months of follow-up as compared to 15 patients at the time of the safety data cutoff date for the NDA.

Treatment Emergent Adverse Events

There were no new deaths or SAEs (on treatment or post treatment) during the period between the original NDA safety data cut (26 March 2018) and the 120-day safety update data cut (15 October 2018).

Overall, 34 patients (31.2%) experienced a TEAEs that led to permanent discontinuation of any study drug which is an increase by one subject from the original results. Twenty-eight (25.7%) patients permanently discontinued linezolid because of a TEAE, which is a single patient increase from the original results. No subject had the entire regimen permanently stopped due to drug-related toxicity.

The most frequently (≥ 10% of patients) reported TEAEs by preferred term were peripheral sensory neuropathy (69.7%), nausea (36.7%), anemia (36.7%), vomiting (33.9%), headache (27.5%), dyspepsia (23.9%), dermatitis acneiform (23.9%), decreased appetite (22.0%), upper respiratory tract infection (19.3%), pleuritic pain (19.3%), gamma-glutamyltransferase increased (17.4%), acne (15.6%), rash (15.6%), pruritus (14.7%),

hemoptysis (12.8%), back pain (11.9%), hypoglycemia (11.0%), transaminases increased (11.0%), abdominal pain (10.1%), diarrhea (10.1%), and abnormal loss of weight (10.1%).

The types and frequencies of most common TEAEs were the same as, or similar to the types and frequencies of most common TEAEs reported in the original NDA submission.

Treatment Emergent Adverse Events of Special Interest

Hepatic: Three (2.7%) patients (subject (b) (6), subject (b) (6), subject (b) (6)) experienced TEAEs: increase in GGT, increase AST, increase ALT, respectively. None of these events was serious or resulted in a change of study drug dosing and all events resolved.

Skin and Subcutaneous Tissue: Two new skin and subcutaneous tissue disorder TEAEs were reported: macular rash grade 1 and acne, grade 1. The acne resolved and TEAE of macular rash had an unknown outcome at the time of the last reporting period.

Vision and Neurologic Adverse Events: There were no new reports of seizures. Headache was the most frequently reported adverse event was during the period between the original NDA and the 120-Day Safety Update data cutoff date. Two new AEs of headache were reported both were grade 1 and one resolved, and the outcome of the other patient is unknown at the time of last reporting period.

One subject experienced TEAE of visual impairment grade 1 which was described as "reduced distance vision on the right". The event resolved without a change in the study drug dosing. There were three new TEAEs related to peripheral neuropathy: a peripheral sensorimotor neuropathy grade 1 in a patient (Subject (b) (6)) who reported peripheral sensory neuropathy in the original analysis, peripheral sensory neuropathy grade 2 and peripheral sensory motor neuropathy grade 3 in the same patient (Subject (b) (6)). Dosing of study drugs was not changed for these adverse events. At the time of last reporting, the adverse events had not resolved or the outcome was unknown.

Hematologic Adverse Events: One patient (Subject (b) (6)) experienced one new event of thrombocytopenia grade 1 which resolved without a change in the dosing of linezolid.

Laboratory Test Results: The only change in the laboratory data was an increase in the number of patients with an AST level >3 and ≤5 x ULN, from 7 patients (6.4%) to 8 patients (7.3%). The number of patients with the following liver function test abnormalities increased by 1 each in the updated analysis:

- ALT grade 1: from 31 patients (28.4%) in the original analysis to 32 (29.4%)
- Alkaline phosphatase grade 1: from 26 patients (23.9%) to 27 patients (24.8%)
- AST grade 1: from 44 patients (40.4%) to 45 patients (41.3%)

- AST grade 3: from 9 patients (8.3%) to 10 patients (9.2%)
- GGT grade 3: from 16 patients (14.7%) to 17 patients (15.6%)

No additional Nix-TB subjects met the criteria for a potential Hy's law case. The only new changes were increases of 1 or 2 patients with the following abnormalities: grade 1 hyperglycemia, grade one hyperkalemia, grade 1 hypernatremia, and grade 1 hyponatremia. There were no new adverse events of lactic acidosis / lactic acid increased during the reporting period.

Electrocardiogram: The number of patients with a post-baseline increase of >30 msec in QT interval corrected for heart rate (QTcF) increased from 30 (27.5%) patients in the original analysis to 33(30.3%) patients in the updated analysis.

During the period between the original NDA safety data cut and the 120-day safety update data cut, there are no new adverse events such as testicular toxicity, gastrointestinal TEAEs, acute pancreatitis, or QT prolongation. No new pregnancies were reported in Nix-TB trial.

In summary, there were no additional deaths, SAEs, or TEAEs leading to discontinuation of the entire BPaL regimen. No serious liver injury or potential Hy's law cases were reported. There were no novel observations regarding the types and frequencies of TEAEs and the types and frequencies of laboratory findings, vital signs, and ECG abnormalities. The updated safety results for Nix-TB was similar to that observed in the analysis of the NDA.

9.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

The required postmarketing safety studies are discussed in Section 14.

9.11. Integrated Assessment of Safety

Safety data for the BPaL regimen included the NixTB trial (N=109) in the initial submission on Dec 14, 2018 and a 120-day safety update for the trial submitted on April 5, 2019. Supportive preliminary safety data for the BPaL regimen came from the ZeNix trial (N=61).

The main limitations of the safety database are its small size and absence of comparative safety data. There is no uniform standard of care for XDR-TB or MDR-TB and treatment with multi-drug regimens (5 to 8 drugs for up to 24 months) must be individually tailored for each patient based on the susceptibility data for their specific *M. tuberculosis* isolate.

Clinically significant safety risks associated with the BPaL regimen in the NixTB trial were: optic neuropathy, peripheral neuropathy, myelosuppression, hepatotoxicity, QT prolongation, and lactic acidosis.

Peripheral neuropathy, optic neuropathy, myelosuppression, lactic acidosis, are known adverse reactions associated with linezolid. Peripheral neuropathy and myelosuppression increased with the duration of BPaL treatment. The adverse events were successfully managed with dosing interruptions, dose reductions (600mg/day or 300mg/day), or discontinuations of linezolid or dosing interruptions of the entire BPaL regimen. The dose of linezolid was reduced from 1200mg/day to 600mg /day or 300mg/day in 43 (39%) patients due to myelosuppression and peripheral neuropathy; see additional commentary in subsection 9.4.5.
BPaL was not permanently discontinued in any subject except for the patients who died. Peripheral neuropathy usually occurred later in the treatment course than myelosuppression.

Optic Neuropathy: Thirteen (11.9%) patients had vision abnormalities and 2 (1.8%) patients developed optic neuropathy after four months on BPaL treatment. Optic neuropathy was fully reversible when linezolid was discontinued. Visual function, as it relates to optic neuropathy, should be monitored in all patients receiving linezolid as part of the BPaL regimen; if a patient experiences symptoms of visual impairment, prompt evaluation by an ophthalmologist is recommended. The findings in the Nix-TB study are supported by published literature reports which indicate that optic neuropathy is reversible when linezolid is discontinued.[35,45]
Monitoring for cataracts in the clinical program began in 2009 and, thus far, ophthalmological examinations and AREDS2 scores showed no evidence that pretomanid induces cataract formation in humans.

Peripheral Neuropathy: Peripheral neuropathy was reported in 87 (81%) of patients. Peripheral sensory neuropathy was the most common adverse reaction and it increased over the study period. Over 50% of the cases were moderate to severe. The reversibility of peripheral

[45] Koh WJ, Kang YR, Jeon K, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J Antimicrob Chemother2012;67(6):1503-7.

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neuropathy was variable following interruption of linezolid dosing. While receiving linezolid as part of the BPaL regimen, patients should be monitored for symptoms and signs of peripheral neuropathy. Instances of irreversible peripheral neuropathy associated with long term use of linezolid have been reported.[46]

Myelosuppression: Linezolid can cause suppression of all cell lines but is reversible when the drug is stopped or the dose reduced. In the Nix-TB study, myelosuppression associated with linezolid was reversible except for three patients who had ongoing events at the data cutoff date. Complete blood counts should be monitored regularly for example at baseline, at 2 weeks, and monthly while receiving linezolid as part of the BPaL regimen. Interrupting linezolid or decreasing the dose should be done in patients who develop or have worsening myelosuppression.

Hepatotoxicity: Hepatotoxicity, mostly elevated transaminases, were associated with the BPaL regimen. There was no progression to serious liver injury as was observed in the STAND trial. Patients tolerated reintroduction of BPaL and they completed a full course of treatment without further episodes of hepatotoxicity. Regular monitoring of liver tests is important while patients are on BPaL regimen so that treatment can be interrupted, if necessary. Patients with ALT > 3 xULN were not allowed in the trial, therefore the effects of the BPaL regimen on patients with hepatic impairment is not yet known. Regular monitoring for symptoms of liver toxicity and liver tests are important for patients taking BPaL so that an intervention can be made such as interrupting the entire regimen until elevated transaminases decline toward normal. Patients should also avoid other hepatotoxic drugs and alcohol while on treatment.

QT prolongation: QT prolongation is associated with bedaquiline. Mild QT prolongation was reported in Nix-TB trial. ECG monitoring is required for patients on the BPaL regimen. Analyses of TEAEs and ECG results, including analyses based on pretomanid exposure, and the results of the TQT study show no clinically significant increase in QT interval with pretomanid. It is important to monitor serum electrolytes such as potassium, calcium, and magnesium prior to starting BPaL and correct if abnormal. Discontinuation of bedaquiline is warranted if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of greater than 500 ms. Also, if syncope occurs, ECG should be done to detect QT prolongation.

Lactic Acidosis: Lactic acidosis occurred in severely ill patients in the Nix-TB trial; however, lactic acidosis is also associated with linezolid. It is unlikely to be due to pretomanid because it was not reported in other trials of pretomanid-containing regimens. Patients who develop recurrent nausea or vomiting should receive immediate medical evaluation, including evaluation of bicarbonate and lactic acid levels, and the interruption /dose adjustment of linezolid or interruption of BPaL.

[46] Roongruangpitayakul C, Chuchottaworn C. Outcomes of MDR/XDR-TB patients treated with linezolid: experience in Thailand. J Med Assoc Thai 2013; 96(10):1273-82.

Other adverse events of interest included acute pancreatitis which was reported in three patients in the trial. It is not clear whether any of the episodes were associated with the study drugs because patients had other risk factors for pancreatitis including alcohol use, HIV, and antiretroviral therapy such as lopinavir/ ritonavir. Patients who develop abdominal pain during therapy with BPaL should have lipase/amylase levels measured.

Among demographic subgroups, there were no major differences in numbers of patients with TEAEs based on sex, BMI / body weight, or low albumin levels. HIV-positive subjects experienced more elevations in hepatic transaminases and anemia than in HIV negative which would be expected because of underlying disease and concomitant anti-retroviral treatment.

The review of the 120-Day Safety Update (data cutoff date October 15, 2018) for Nix-TB showed results consistent with initial analyses. The applicant reported no new deaths, serious TEAEs, or TEAEs leading to discontinuation of the entire BPaL regimen, or potential Hy's law cases. No novel observations were reported regarding the types and frequencies of TEAEs and the types and frequencies of laboratory findings, vital signs, and ECG abnormalities.

In summary, adverse reactions associated with the BPaL regimen were manageable by temporary discontinuation of the entire regimen or temporary discontinuation followed by dose reduction of linezolid, or permanent discontinuation of linezolid. Most patients in the NixTB trial were able to complete a full 26-week course of therapy. Hepatotoxicity was a safety concern associated with the MPaZ regimen in the NC-006 (STAND) trial. However, in the Nix-TB trial, there was no progression to serious liver injury in any patient. Hepatotoxicity was managed by a temporary interruption of the entire regimen which led to improvement of liver tests in all patients, and resumption of BPaL to complete the 26-week course of treatment. The efficacy of rate of 90% of this oral 3-drug regimen administered for 6-month exceeds the efficacy rate of historical controls and recent studies of bedaquiline-containing regimens administered for up to 24 months in patients with XDR-TB.**Error! Bookmark not defined.** The high cure rates observed with BPaL also have public health implications and should help to decrease transmission of drug-resistant TB.

In view of the limited population of patients in the Nix-TB trial, and the safety concerns with another pretomanid-containing regimen, pretomanid should not be used in other antimycobacterial drug regimens until further data is available. Pretomanid should not be used in regimens to treat drug-sensitive TB as the benefit-risk assessment in this group is entirely different from patients with XDR-TB and TI/NR MDR-TB who have limited or no other treatment options.

10 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was held on June 6th, 2019 to discuss NDA 212862. The following question was posed to the committee:

Has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis?

1. If yes, please provide any recommendations concerning labeling.
2. If no, what additional studies/analyses are needed?

Committee Vote

Yes: 14, No: 4

Summary of the AC discussion

A majority of the Committee members voted "Yes", agreeing that the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis. The Committee members who voted "Yes" stressed that their vote was in support of the drug regimen of the combination of pretomanid with bedaquiline and linezolid and not necessarily pretomanid alone. These committee members also emphasized that patients should be well informed of the risks, and that strict monitoring should be implemented to support safe use, prior to prescribing the regimen of pretomanid, bedaquiline, and linezolid.

The Committee members who voted "No" stated that the applicant had not provided clinical data supporting the contribution of pretomanid to the regimen for the proposed indication. These same Committee members agreed that the Nix-TB trial was lacking in number of participants, diversity, and statistical rigor. One Committee member emphasized that the applicant showed the contribution of pretomanid in mice but failed to provide any clinical evidence to support the contribution of pretomanid to the regimen. Another Committee member noted that the data were difficult to interpret because single-arm studies are vulnerable to bias, comparisons to historical literature or matched historical controls did not include control patients treated with bedaquiline or pretomanid regimens, and the sample size was too small to gather sufficient efficacy and safety data.

Collectively, the Committee members agreed that post marketing surveillance is needed to collect additional safety data for pretomanid as part of the bedaquiline and linezolid regimen. One Committee member commented that Southeastern Asian nations have a high burden of XDR-TB and MDR-TB; therefore, broadening the patient population would better reflect a real-world setting. In addition, the Committee urged the applicant to implement safety monitoring

procedures in future studies of pretomanid as a component of the BPaL, especially in pediatric patients, women, and individuals with underlying liver disease. Lastly, the Committee advised that the labeling for the proposed regimen (pretomanid, bedaquiline, and linezolid) should include complete blood counts and liver function tests at baseline and monitoring during therapy due to reports of hematopoietic cytopenias and hepatotoxicity. One Committee member stressed that the regimen should be prescribed only by clinicians with TB expertise, at least until further safety data are available.

11 Pediatrics

As pretomanid for treatment of tuberculosis has Orphan Disease Designation, the Pediatric Research and Equity Act requirements are not applicable.

12 Labeling Recommendations

12.1. Prescribing Information

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**

Indications and Usage	Pretomanid is (b) (4) indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).
	Limitations of Use: (b) (4) latent or extra-pulmonary Mycobacterium tuberculosis infections, MDR-TB that is not treatment-intolerant or nonresponsive, or drug-sensitive (DS) tuberculosis.
		Limited Population: Pretomanid Tablet is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.
		Limitations of Use:
		• Pretomanid Tablets are not indicated for patients with:
		  • Drug-sensitive (DS) tuberculosis
		  • Latent infection due to Mycobacterium tuberculosis
		  • Extra-pulmonary infection due to Mycobacterium tuberculosis
		  • MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
		Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen

Dosage and Administration		Instructions were added to guide BPaL regimen and linezolid dosing/interruptions and discontinuations due to adverse reactions
Contraindications	(b) (4)	Removed (b) (4) contraindication Refer to the FPI of the companion drugs in BPaL for contraindications
Warnings and Precautions	Hepatotoxicity Myelosuppression Peripheral and optic neuropathy Drug interactions	• Risks Associated with the Combination Treatment Regimen • Hepatotoxicity • Myelosuppression • Peripheral and Optic Neuropathy • QT Prolongation • Drug Interactions • Reproductive Effects • Lactic Acidosis
Drug interactions	(b) (4)	Effect of Other Drugs on Pretomanid • Cyp3A4 Inducers • Lopinavir/ritonavir Effect of Pretomanid on Other Drugs • Midazolam • OAT3 Transporters
Clinical Studies	Results of Nix-TB (b) (4)	Results of Nix-TB at January 18, 2019 data cutoff

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12.2. Patient Labeling

The Medication Guide has been updated to reflect the agreed upon changes in the Full Prescribing Information for Pretomanid.

13 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required.

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14 Postmarketing Requirements and Commitments

Postmarketing Requirements:

1. Conduct a study to evaluate the effect of pretomanid on human semen
    - Final protocol submission: 10/2019
    - Study completion: 09/2023
    - Final report submission: 01/2024
2. Conduct a global surveillance study for a five-year period after the introduction of pretomanid to the market to monitor changes in *Mycobacterium tuberculosis* susceptibility to pretomanid.
    - Final protocol submission: 12/2019
    - First interim report submission: 12/2021
    - Second interim report submission: 12/2022
    - Third interim report submission: 12/2023
    - Fourth interim report submission: 12/2024
    - Study completion: 06/2025
    - Final report submission: 12/2025
3. Conduct a study to evaluate pharmacokinetics and safety of pretomanid in subjects with renal impairment.
    - Final protocol submission: Submitted
    - Study completion: 06/2021
    - Final report submission: 12/2021
4. Conduct a study to evaluate pharmacokinetics and safety of pretomanid in subjects with mild, moderate, and severe hepatic impairment.
    - Final protocol submission: Submitted
    - Study completion: 12/2020
    - Final report submission: 06/2021
5. Conduct the ZeNix trial to evaluate various doses and treatment durations of linezolid plus bedaquiline and pretomanid for treatment of extensively drug-resistant pulmonary tuberculosis
    - Final protocol submission: Submitted
    - Study completion (topline results): 03/2023
    - Final report submission: 07/2023
6. Conduct the SimpliciTB trial to evaluate pretomanid, bedaquiline, moxifloxacin, and pyrazinamide for treatment of drug-resistant pulmonary tuberculosis.
    - Final protocol submission: Submitted
    - Study completion (topline results): 06/2023
    - Final report submission: 10/2023
7. Conduct a two-year rat carcinogenicity study with pretomanid
    - Study completion: 02/2020
    - Final report submission: 08/2020

15 Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):
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 Extensively Drug-resistant Tuberculosis (XDR-TB) or Treatment Intolerant/Non-responsive Multi-Drug Resistant Tuberculosis (MDR-TB).

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **40**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **Zero**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **Zero**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reference ID: 4476823

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Pharmacometrics Review

1.1.1. Population PK analyses

1.1.1.1. Introduction

The applicant developed a population pharmacokinetic model using pooled data from six phase 1 (Studies CL-001, CL-002, CL-003, CL-005, CL-009, and CL-012), six phase 2 (Studies CL-007, CL-010, NC-001, NC-002, NC-003, and NC-005), and two phase 3 studies (NC-006 and Nix-TB). The objectives of the applicant's population PK analyses were:

i. To develop a model that describes the PK data from healthy subjects (HS), drug sensitive (DS-TB) subjects, multidrug resistant (MDR-TB) subjects, multidrug-resistant and treatment intolerant or non-responsive (TIN/NR - MDR) subjects, and extensively-drug-resistant (XDR-TB) subjects

ii. Quantify variation in pretomanid exposure due to the following intrinsic factors: disease state (XDR-TB, TIN/NR MDR-TB, MDR-TB, DS-TB, and HS).

iii. Quantify variation in pretomanid exposure due the following extrinsic factors: dose, fed versus fasted state, concomitant medication.

iv. Generate exposure metrics for use

This review will focus on evaluation of the adequacy of the recommended dose and whether the labelling language is supported by the applicant's findings on the influence of intrinsic and extrinsic covariates on the PK parameters.

1.1.1.2. Methods

Data

Study CL-001 was a randomized, double blind, placebo-controlled, sequential-ascending single dose study that evaluated the safety and pharmacokinetics of pretomanid in healthy adult male subjects. The studied doses and corresponding sample sizes were: 0 mg/Placebo(n=13), 50mg (n = 4), 250 mg (n=6), 500 mg (n=6), 1000 mg (n=6), 1250 mg(n=6) and 1500mg (n=6). Each subject received a single dose after an overnight fast followed by PK sampling at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 30, 36, and 144 hours post dose. Samples from subjects randomized to placebo were excluded from pharmacokinetic analysis.

Study CL-002 was a randomized, double blind, placebo-controlled, sequential ascending, multiple dose study that evaluated safety and PK of pretomanid in healthy male and female subjects. Pretomanid was administered once daily for 7 days after an overnight fast. The studied doses and corresponding sample sizes were 200 mg (n=6), 600 mg (n = 6), 1000 mg (n=

6) and placebo (n=6). Treatment with the 1000mg/day was stopped after 5 days of dosing due to elevation of serum creatinine levels. PK sampling was done at pre-dose each day and at 1, 2, 3, 4, 5, 6, 7, 8, 12 and 16 hours after dosing on days 1 and 7. Additional samples were collected at: 24, 30, and 36 hours after day 7 dosing; daily during washout (days 9 -13) at the time daily dosing would have occurred. Samples excluded from the analysis included subjects assigned to placebo and observations after day 5 in subjects randomized to 1000 mg dose.

Study CL-003 was a randomized open-label, balanced, 2-treatment (Fed or fasted), 2-period, 2-sequence (fed/fasted and fasted/fed), crossover study that evaluated the effect of food on the bioavailability of pretomanid administered orally as a single 1000mg dose. PK sampling was done at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after each dose. An 8-day washout period was allowed between treatments.

Study CL-005 was a double blind, randomized, placebo-controlled, sequential group, ascending multiple dose study that explored the mechanism for the elevation of serum creatinine in healthy subjects. The studied doses and corresponding sample sizes were: 800 mg (n = 21), 1000 mg (n = 10), placebo (n = 16). There were two cohorts of subjects randomized to receive 800 mg (Cohort 1 and 2). The treatments were administered once daily after an overnight fasting for 8 days. PK sampling was done at pre-dose, and at 1, 2, 3, 4, 5, 6, 7, 8, 12, and 16 hours after dose on days 1, 5 (All subjects except cohort 1) and 8. Additional PK sampling was done at 24, 30, 36, 48, 72 and 96 hours after day 8 dosing. Subjects randomized to placebo were excluded from the analysis.

Study CL-009, like CL-003, evaluated the effect of food on bioavailability of pretomanid in healthy subjects. The studied dose was 200 mg taken in a cross-over fashion with or without food (High calorie, high-fat diet). The washout period of 8 days was allowed between treatments. PK sampling was done at pre-dose and then at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after dosing on days 1 and 8.

Study CL-012 was a thorough QT study in healthy subjects to evaluate the QT interval prolongation potential of pretomanid. The studied doses of pretomanid were 400mg (n=74), 1000mg (n = 71) and 400 mg plus moxifloxacin (n = 73). Control treatments were placebo and moxifloxacin. Single doses of study treatments were administered after overnight fasting on days 1, 8, 15, 22, and 29. Subjects randomized to pretomanid treatment received 400mg on occasion 1, 1000 mg on occasion 2, and 400mg plus moxifloxacin on occasion 3. PK sampling were done at pre-dose, 0.25, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, and 96 hours after dose.

Study CL-007 was a phase2a, partial-blind (pretomanid group blinded to dosage), randomized study to evaluate early bactericidal activity (EBA) of pretomanid in adult subjects with newly diagnosed, smear positive DS-TB. The studied doses and corresponding sample sizes were 200mg (n=15), 600 mg (n=15), 1000 mg (n=16), 1200 mg (n = 15). The treatments were taken once daily for 14 days after an overnight fasting. The positive control group received a standard anti-tuberculosis regimen with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE).

Sputum samples for assessment of EBA were collected overnight on days -2, -1, 1, 2, 3, 4, 6, 8, 10, 12, and 14. EBA was measured by counting colony forming units (CFU) per mL sputum on solid media (CFU/mL) and by determining time to positivity (TTP) using the MGIT system (hours). The primary endpoint was the change in logCFU between day 0 and 14 ($EBA_{CFU0-14}$). Another endpoint was change in TTP between day 0 and 14 ($EBA_{TTP0-14}$). PK sampling was done at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 16 hours after dose days 1, 8 and 14.

Study CL-010, like CL-007, was a phase2a, partial-blind, randomized study to evaluate EBA of pretomanid when given alone to adult subjects with newly diagnosed, smear positive DS-TB. The control group received a standard HRZE. The studied doses and corresponding sample sizes were 50 mg (n = 15), 100mg (n = 15), 150 mg (n=15), 200mg (n = 16). The treatments were taken once daily for 14 days after an overnight fasting. The design for collection of sputum and PK samples was the same as in study CL-007.

Study NC-001 was also a phase 2a, partial blind, randomized, parallel group study in adult subjects with newly diagnosed smear-positive DS-TB. Subjects were randomized to different treatment groups as follows: bedaquiline alone (B); bedaquiline (B) + pyrazinamide (BZ); bedaquiline + pretomanid (BPa); pretomanid + pyrazinamide (PaZ); Pretomanid + pyrazinamide + moxifloxacin (PaMZ); HRZE. The studied pretomanid dose was 200 mg. In the PaZ and PaMZ arms pretomanid was taken after overnight fasting. In the BPa arm pretomanid was taken after 4 hours of fasting followed by breakfast and bedaquiline within 30 minutes. PK analysis included data from the pretomanid arms; BPa (n = 15), PaZ (n = 15) and PaMZ (n =15). For PaZ and PaMZ arms PK sampling was done on: days 1 and 8 at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hours post dose; day 14 on 0, 1, 2, 5, 8, and 24 hours post dose. For BPa group PK sampling was done on: Days 1 and 8 at 0, 4, and 8 hours post-dose; day 14 at 0, 1, 2, 5, 8, and 24 hours post-dose. Sputum samples for assessment of EBA were collected overnight on days -2, -1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14. Primary endpoint and measurement of EBA was like for study CL-007

Study NC-002 was another phase 2a study which evaluated EBA of pretomanid in combination with other anti-tuberculosis drugs. It was an open label, partially randomized study to evaluate efficacy, safety and tolerability of PaMZ in subjects with smear positive DS-TB or MDR-TB. Subjects with DS-TB were randomized to 3 treatment groups: Pa 100mg + M 400 mg + Z 1500 mg (n =60, 14 days substudy); Pa 200mg + M 400 mg + Z 1500 mg (n =58, 14 days substudy); HRZE control. Subjects with MDR-TB received Pa 200mg + M 400 mg + Z 1500 mg (n =26, 14 days substudy). PK samples were collected within 2 hours prior to dosing on days 8 – 57. For subjects participating in the EBA sub study additional samples were collected at 1, 2, 5, 8, and 24 hours post-dose on day 14. Sputum samples for measurement of TTP, CFU and determination of sputum culture conversions (SCC) were collected for all subjects at days: -2, -1, 3, 7, 14, 21, 28, 35, 42, 49, and 56. For subjects participating in the EBA sub-study additional sputum samples for determination of SCC and measurement of TTP were collected on days: 1,

2, 5, 9, and 11. EBA was evaluated after 14 days of treatment (In subjects participating in EBA sub study) while sputum culture conversion was evaluated after 56 days.

Study NC-003 was another phase 2a study to evaluate EBA of pretomanid in combination with other anti-tuberculosis agents in subjects with smear positive DS-TB. Subjects were randomized to various combinations of B, Pa, Z and clofazimine (C). The control group received HRZE. The combinations included in the PK analysis were BPaCZ (n = 14), BPaZ (n = 14), BPaC (n = 15). In all combinations pretomanid 200 mg was administered under fed conditions together with other concomitant antitubercular agents. PK sampling was done on: days 1, 2, 3, and 8 at 0, 5, and 10 hours after dose; day 14 at 0, 1, 2, 3, 4, 5, 10, and 16 hours after dose; and on day 15. Sputum samples for assessment of EBA were collected overnight daily from days -2 to 14. Primary endpoint and measurement of EBA was like for study CL-007

Study NC-005 was a phase 2b, 8-week, sputum-culture conversion study in subjects with DS-TB and MDR-TB. DS-TB subjects were randomized to one of two BPaZ arms or HRZE control. Subjects with MDR-TB received BPaMZ. In all treatment arms pretomanid 200mg was tested. Subjects were advised to take the treatments around breakfast time. Since this was an outpatient study, fed versus fasted conditions at time of drug intake was not fully controlled. For all subjects, PK sampling was done pre-dose on days 1, 4, 8, 15, 22, 29, 36, 43, 50, and during the study site visits on days 57 and 70. Fifteen subjects in each arm participated in a PK sub study where on days 14 and 56 samples were collected at 0, 1, 2, 4, 8, and 24 hours post-dose. Overnight sputum samples for measurement of CFU, TTP and time to SCC were collected on days -2, -1, 1, 3, 7, 14, 21, 28, 35, 42, 49, and 56. The primary endpoint was the rate of change in TTP over 8 weeks of treatment $BA_{TTP0-56}$

Study NC-006 was a phase 3 trial to evaluate efficacy and safety of PaMZ in subjects with DS-TB after 4 and 6 months of treatment and in subjects with MDR-TB after 6 months of treatment. DS-TB subjects were randomized to the following treatment groups: Four month treatment with Pa (100 mg) + M (400 mg) + Z (1500 mg) (n = 65); four months treatment with Pa (200mg) + M (400 mg) + Z (1500 mg) (n = 71); six month treatment with Pa (200mg) + M (400 mg) + Z (1500 mg) (n = 67); and six month treatment with HRZE (n = 68). Subjects with MDR-TB were treated with Pa (200mg) + M (400 mg) + Z (1500 mg) (n =13). This was an outpatient study therefore fed or fasted state during drug intake was not controlled. No instructions were given to patients on timing of drug intake relative to meal. Sputum samples for liquid culture to assess presence of bacteria and TTP were collected during screening (days -14 - -1), on the day of treatment initiation, weekly from week 1 – 8, and on week 12, 17, 22, 26. After completion of treatment, follow-up sputum samples were collected on months 9, 12, 15, 18, and 24 or at early withdraw from the study. The primary endpoint was incidence of bacteriologic failure or relapse or clinical failure at 12 months from the start of therapy. Sputum culture conversion at 8 weeks was also considered as a secondary endpoint. PK sampling was done on week 2 and week 8 at the pre-dose time only.

Study Nix-TB is an ongoing phase 3 trial to evaluate safety and efficacy of the bedaquiline + pretomanid + linezolid regimen (BPaL) after 6 months of treatment in subjects with extensively drug resistant TB (XDR-TB) or in subjects who are non-responsive or treatment intolerant to MDR-TB treatment. In this study subjects took pretomanid 200 mg once daily with food for 26 weeks. Bedaquiline was taken as 400 mg once daily for the first 14 days followed by 200 mg once daily from week 2 – 26. Linezolid was taken as 1200 mg/ day (either once or twice daily depending on tolerability). PK sampling was done pre-dose on weeks 2, 8, and 16. Additional samples were collected on week 16 at 0.5, 1, 2, 4, 8, 12, 12.5, 13, 14, 16, 20, and 24 hours post-dose. Sputum samples for liquid culture to assess presence of bacteria and TTP were collected during screening (days -14 - -1), on the day of treatment initiation, weekly from week 1 – 16, and at week 20 and 26. After completion of treatment, follow-up sputum samples were collected at months 1, 2, 3, 9, 12, 15, 18, 21, and 24 or at early withdraw from the study. For patients who needed 9 months treatment (because of positive sputum culture between week 16-26) additional sputum samples were collected at weeks 30, 34, and 39. The primary endpoint of the trial was the incidence of bacteriologic failure, relapse or clinical failure through follow-up until 6 months after the End of Treatment.

Missing data

Dosing times: Where dosing times were missing they were imputed based on assumed regular pattern of daily dosing or based on recorded times of adjacent samples.

BQL samples: Data below limit of quantification were excluded from the analysis.

Observation times: records with missing sampling times were excluded from the analysis.

Covariate values: Missing baseline covariate values were replaced by values at screening. In case no reasonable screening value was available, baseline values were replaced by median of all subjects in the same study having at least one non-BQL record. Baseline values were used during covariate model development.

Reviewers comments: *the applicant's treatment of missing data was considered acceptable as only one subject had missing baseline albumin imputed with median. Two subjects with missing HIV status at baseline had their status imputed based on status of their anti-HIV drug medication.*

Outliers

Pre-dose concentrations that were unusually higher than other pre-dose concentrations were considered to have erroneous sampling time. Similarly, samples at T_{max} that were unusually lower than other T_{max} samples were considered to have erroneous sampling time. These samples were excluded from analysis. Concentrations with unusually high conditional weighted residuals were also excluded from the analysis. Winsorization was applied to all continuous covariates to limit the impact of extreme values. For each covariate, values outside of the

median plus-or-minus 5 times the standard deviation was censored to the boundary of that range.

Reviewer's comments: *The reviewer couldn't find how the applicant pre-defined unusual samples.*

Population PK model building

Population PK model development was done using NONMEM version 7.3. The applicant built the model in several stages guided by objective function values, likelihood ratio test, parameter plausibility, standard error estimates, and diagnostic checks. As a first step, non-compartmental analysis of rich PK datasets (individual or pooled analysis) was used to explore the effect of different covariates on NCA parameters. The identified covariates at this stage (dose, fed vs fasted, body weight, healthy vs DS-TB) were included in the structural form of the base model (See Figure 15-5-1). One and two compartment base models were tested. Base model was developed using all phase 1 studies and two phase 2a studies (CL-007 and CL-010).

```
TVLF1 =   FASTED*log(THETA(4)) +                    # Food effect; = 0 for FED
          (THETA(5) +
          FASTED*THETA(6))*log(DOSE/200) +          # Dose and food×dose
                                                    effects
          log(THETA(12))*HS                         # Disease-state effect

          log(THETA(1)) +
TVLKA =   FASTED*log(THETA(7)) +                    # Food effect
          (THETA(8) +
          FASTED*THETA(9))*log(DOSE/200) +          # Dose and food×dose
                                                    effects
          log(THETA(13))*HS                         # Disease-state effect

TVLCL =   (0.75 + THETA(10))*log(WT/55) +           # Weight effect
          log(THETA(14))*HS                         # Disease-state effect

TVLV2 =   log(THETA(3)) +
          (1 + THETA(11))*log(WT/55) +              # Weight effect
          log(THETA(15))*HS                         # Disease-state effect

TVLQ = log(THETA(16))

TVLV3 = log(THETA(17))
```

Figure 15-5-1. Structural Form of the Base Model Including Covariates Identified through Non-compartmental Analysis

Stage 2 of model building involved exploration of additional covariates as observed in the remaining phase 2 studies (NC-001, NC-002, NC-003, and NC-005) and one phase 3 study (NC-006). The explored covariates at this stage included: Study effects, concomitant anti-tuberculosis agents (bedaquiline, moxifloxacin, pyrazinamide, and clofazimine), MDR-TB, the BPaMZ regimen, HIV status, Concomitant anti-retroviral (Efavirenz and lopinavir/ritonavir), age, race, BMI, sex, renal and hepatic covariates.

Once covariates were identified the model was further improved by adding a covariance structure among inter-individual random effects parameters, and by adding inter-occasion variability (IOV) on F1 and CL.

At stage 3, data from the pivotal Nix-TB trial were included to develop a final model. At this state additional covariates were evaluated, these included: XDR-TB and linezolid co-administration.

1.1.1.3. Results

The initial PK dataset contained 19004 observations from 1056 subjects. After removing the BQL data (5.7%) and outlier concentrations (6.7%), the final population PK analysis dataset contained 17725 observations (7107 HS, 9297 DS-TB, 832 MDR-TB from non-Nix-TB studies, and 489 from Nix-TB study) from 1054 subjects (211 HS, 652 DS-TB, 93 MDR-TB from non-Nix-TB studies, and 98 from nix-TB). Two DS-TB subjects were excluded from the analysis because their concentrations were BQL.

Parameter estimates of the final model are given in Table 15-5-1.

The influence of different covariates on pharmacokinetic model parameters are as given in appendix 1 of the pharmacometrics review.

Table 15-5-1. Final Model Parameter Estimates

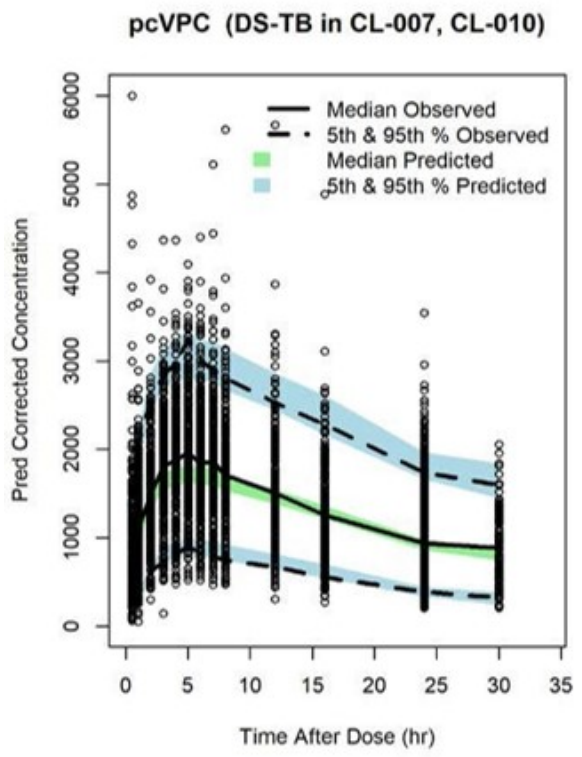
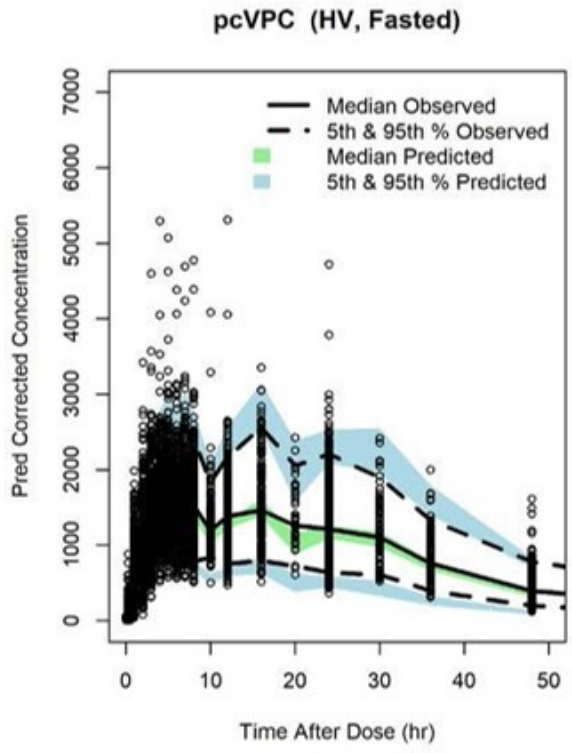
THETA terms on fixed effects	Estimate	Confidence interval	Bootstrap Estimate	Bootstrap Confidence
F1 (Fixed)	1	-	1	-
4 F1~FASTED	0.510	(0.482 - 0.538)	0.513	(0.491 - 0.538)
5 F1~DOSE &FASTED	-0.267	(-0.306 - -0.229)	-0.267	(-0.298 - -0.234)
14 F1~FED &1000mg	-0.0112	(-0.158 - 0.135)	-0.00356	(-0.0638 - 0.062)
16 F1~MOX*PZA	0.904	(0.829 - 0.979)	0.913	(0.810 - 1.03)
22 F1~BDQ*MOX*PZA	1.32	(1.09 - 1.55)	1.34	(1.01 - 1.82)
26 F1~EFV (Fixed)	0.88	-	0.88	–
29 F1~HIV	0.763	(0.701 - 0.826)	0.780	(0.704 - 0.859)
33 F1~TBIL (ref=5)	0.0891	(0.0515 - 0.127)	0.0918	(0.0507 - 0.133)
35 F1~NIX	1.55	(1.28 - 1.82)	1.56	(1.26 - 1.85)
1 KA	1.37 h-1	(1.23 - 1.50)	1.40 h-1	(0.986 - 2.60)
6 KA~FASTED	0.488	(0.459 - 0.518)	0.478	(0.268 - 0.670)
7 KA~DOSE	-0.132	(-0.16 - -0.103)	-0.139	(-0.257 - -0.0186)
19 KA~NC5	0.189	(0.150 - 0.227)	0.179	(0.0873 - 0.273)
9 MTT	1.22 h	(1.11 - 1.32)	1.26	(0.927 - 1.64)
12 MTT~FASTED	0.315	(0.297 - 0.333)	0.307	(0.242 - 0.404)
15 MTT~DOSE&FASTED	-0.161	(-0.192 - -0.129)	-0.174	(-0.374 - -0.0228)
20 MTT~NC5	1.36E-06	(-0.0442 - 0.0442)	1.54E-06	(1.08e-11 - 3.79e-05)
2 CL	3.26 ml/h	(3.10 - 3.43)	3.29 ml/h	(3.17 - 3.42)
CL~WT (Fixed)	0.75	–	0.75	–
11 SS CL	0.166 mL/h	(0.128 - 0.205)	0.170 mL/h	(0.0824 - 0.253)
8 CL~HS	1.16	(1.09 - 1.23)	1.16	(1.10 - 1.24)
17 CL~MOX	0.967	(0.900 - 1.03)	0.969	(0.944 - 0.995)
18 CL~MOX*PZA	0.732	(0.661 - 0.804)	0.733	(0.663 - 0.810)
23 CL~MDR, TI/NR MDR or	1.15	(1.04 - 1.26)	1.16	(1.03 - 1.30)
24 CL~BDQ*MOX*PZA	1.35	(1.14 - 1.56)	1.37	(1.02 - 1.82)
27 CL~EFV (Fixed)	1.53	–	1.53	–
28 CL~LPVR (Fixed)	1.20	–	1.20	–
30 CL~HIV	0.859	(0.797 - 0.920)	0.872	(0.785 - 0.949)
31 CL~INDUC	1.28	(1.18 - 1.38)	1.26	(1.07 - 1.43)
32 CL~FEMALE	0.833	(0.803 - 0.862)	0.830	(0.805 - 0.864)
34 CL~ALB (ref=35)	0.223	(0.103 - 0.343)	0.208	(0.0946 - 0.334)
38 CL NIX WK≥6	0.449 mL/h	(0.271 - 0.626)	0.480	(0.171 - 0.787)
3 V2	89.7 L	(85.1 - 94.2)	90.3 L	(86.6 - 94.6)
V2~WT (Fixed)	1	–	1	–
13 V2~DOSE	0.107	(0.0812 - 0.134)	0.109	(0.0816 - 0.134)
25 V2~ MDR or TI/NR	1.43	(1.23 - 1.63)	1.45	(1.16 - 1.86)
36 V2~XDR	1.75	(1.39 - 2.12)	1.78	(1.34 - 2.64)

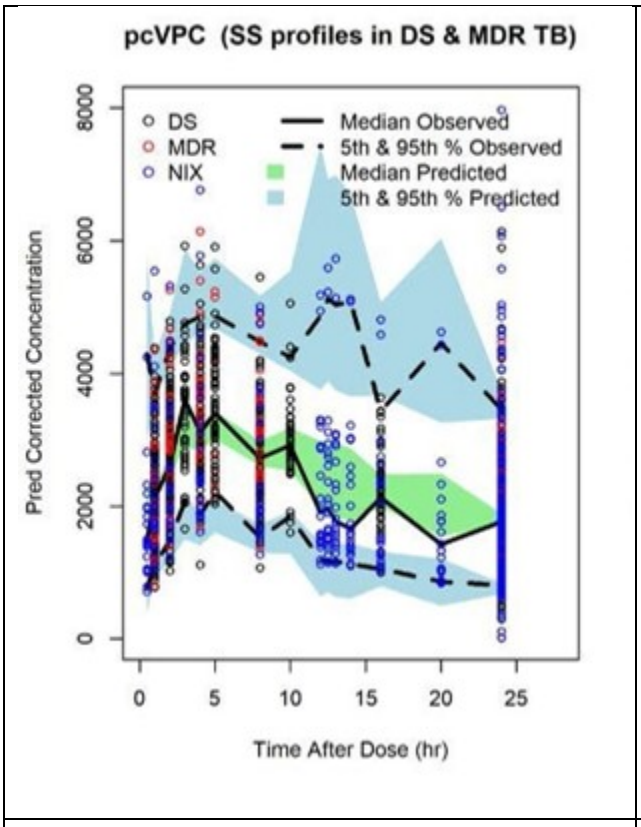
37 F1 Var ~ NIX	0.977	(0.629 - 1.33)	0.880	(0.317 - 1.33)
21 MTT Var ~ NC3	-0.614	(-1.03 - -0.203)	-0.694	(-14.1 - -0.254)
39 Box-Cox V2 non-NIX	9.71	(2.86 - 16.6)	10.2	(4.57 - 75.6)
40 Box-Cox V2 NIX	17.3	(2.29 - 32.4)	17.4	(-43.4 - 53.6)
41 Box-Cox CL non-NIX	1.64	(0.936 - 2.35)	1.62	(0.699 - 2.99)
42 Box-Cox CL NIX	2.74	(1.36 - 4.12)	2.18	(-5.30 - 4.80)
Proportional Error	0.553	(0.512 - 0.594)	0.547	(0.333 - 0.940)
Additive Error (Variance)	11.6	(5.83 - 17.3)	11.4	(0.00180 - 22.5)
10 Error Power	0.794	(0.789 - 0.799)	0.794	(0.755 - 0.83)
			Bootstrap	Bootstrap Confidence
1 F1~Dose/Fasted	0.0270	(0.0174 - 0.0366)	0.0271	(0.0135 - 0.0418)
2 CL	0.0381	(0.0294 - 0.0467)	0.0377	(0.0267 - 0.0482)
3 V2	0.00832	(0.00219 - 0.0145)	0.00778	(0.000661 - 0.0159)
4 KA	0.311	(0.253 - 0.369)	0.307	(0.246 - 0.388)
KA-MTT	0.0747	(0.0120 - 0.137)	0.0596	(-0.0117 - 0.141)
5 MTT	0.605	(0.483 - 0.726)	0.602	(0.458 - 0.789)
KA-F1	-0.0362	(-0.0536 - -	-0.0334	(-0.0519 - -0.0177)
MTT-F1	0.00338	(-0.0196 - 0.0264)	0.00657	(-0.0162 - 0.0321)
6 F1	0.0245	(0.0153 - 0.0336)	0.0235	(0.0113 - 0.0368)
7 IOC.F1	0.0414	(0.0364 - 0.0464)	0.0414	(0.0337 - 0.0509)
IOC.F1.CL	0.00994	(0.00685 - 0.0130)	0.00992	(0.00531 - 0.0147)
8 IOC.CL	0.0187	(0.0158 - 0.0216)	0.0185	(0.0135 - 0.0238)

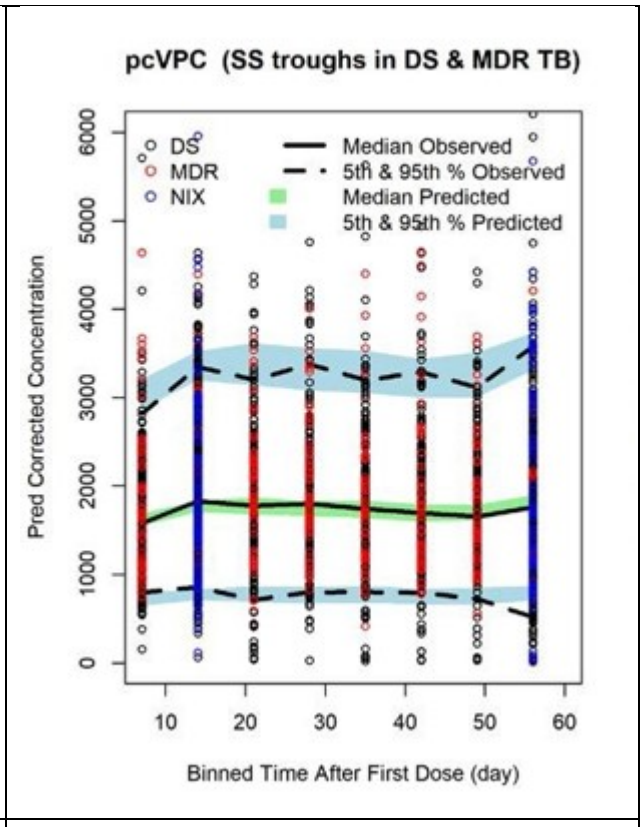
SOURCE: *Applicant's Pharmacometrics Report 2018-01, population pharmacokinetics of pretomanid-modeling report (page 58 of 296)*

The ability of the final model to describe the observed pretomanid concentration -versus -time profiles as evaluated using prediction corrected visual predictive check (pcVPC) is shown in Figure 15-5-2. The figures show that the medians of observed data lie within the prediction intervals.

Figure 15-5-2. Prediction Corrected Visual Predictive Check for the Final Model

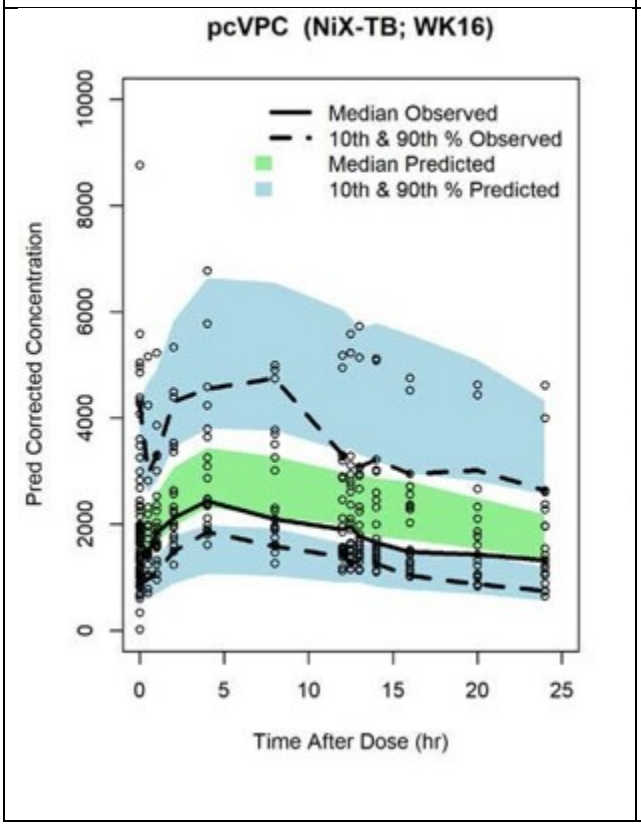
Study CL-007, CL-010	*All phase 1 studies*
	
Phase 2 and 3 studies (Except CL-007, 10, NC001)	*Phase 2 and 3 studies (Except CL-007, 10, NC001)*

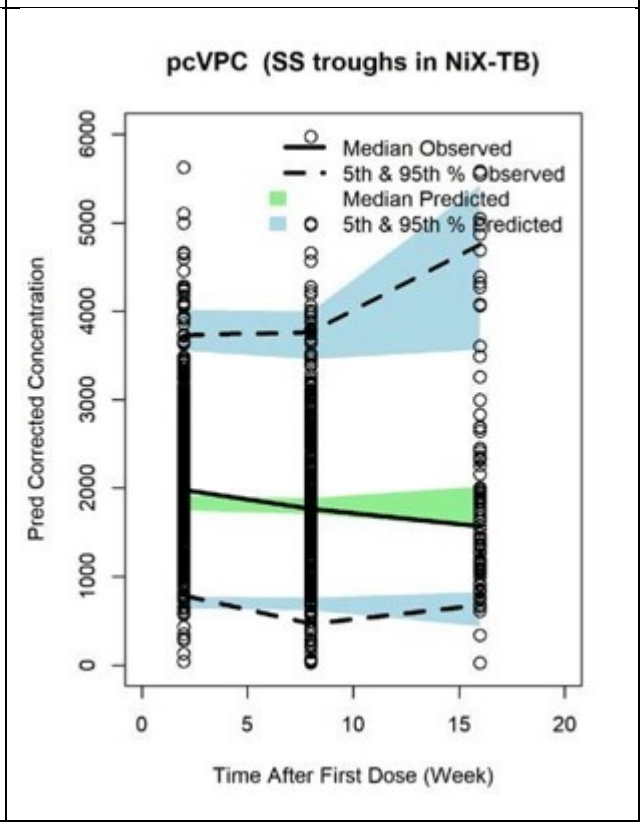




Phase 3 study (Nix-TB)

Phase 3 study (Nix-TB)





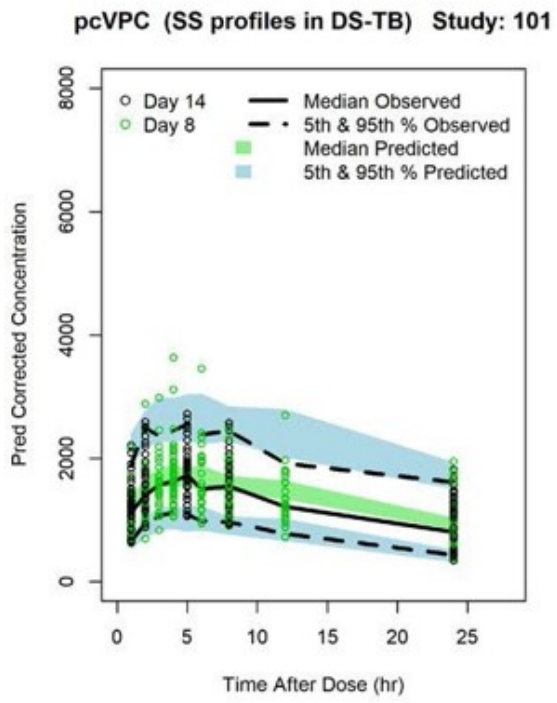
Phase 2 study (NC-001)	
	
SOURCE: Applicant's Pharmacometrics Report 2018-01, population pharmacokinetics of pretomanid-modeling report (page 291 - 296 of 296)	

Figure 15-5-2. Prediction Corrected Visual Predictive Check for the Final Model

<u>Model Application</u>

The applicant performed simulations to illustrate the effect of various covariate combinations. The effects of the covariate combinations were assessed on the following PK parameters: Average concentrations at steady state (C_{avg_ss}), Trough concentration at steady state (C_{24_ss}), Maximum concentration at steady state (C_{max_ss}), time to maximum concentration (T_{max}), steady state half-life ($t_{1/2}$), apparent clearance (CL/F1), apparent volume of central compartment (V2/F1), F1, and mean absorption time (MTT + 1/Ka).

The reference subject was: a 55kg, male, HIV negative, DS-TB subject with baseline TBIL of 5umol/L and ALB of 35 g/L administered pretomanid 200 mg once daily in a fed condition for 8 weeks. A forest plot showing the median and 10th and 90th percentile of C_{avg_ss} for a reference subject and other subjects with different combinations of covariates is shown in Figure 15-5-4. The comparisons between the reference subject and other subjects for other pharmacokinetic parameters are given in forest plots and tables in the appendix 1 of the pharmacometrics review.

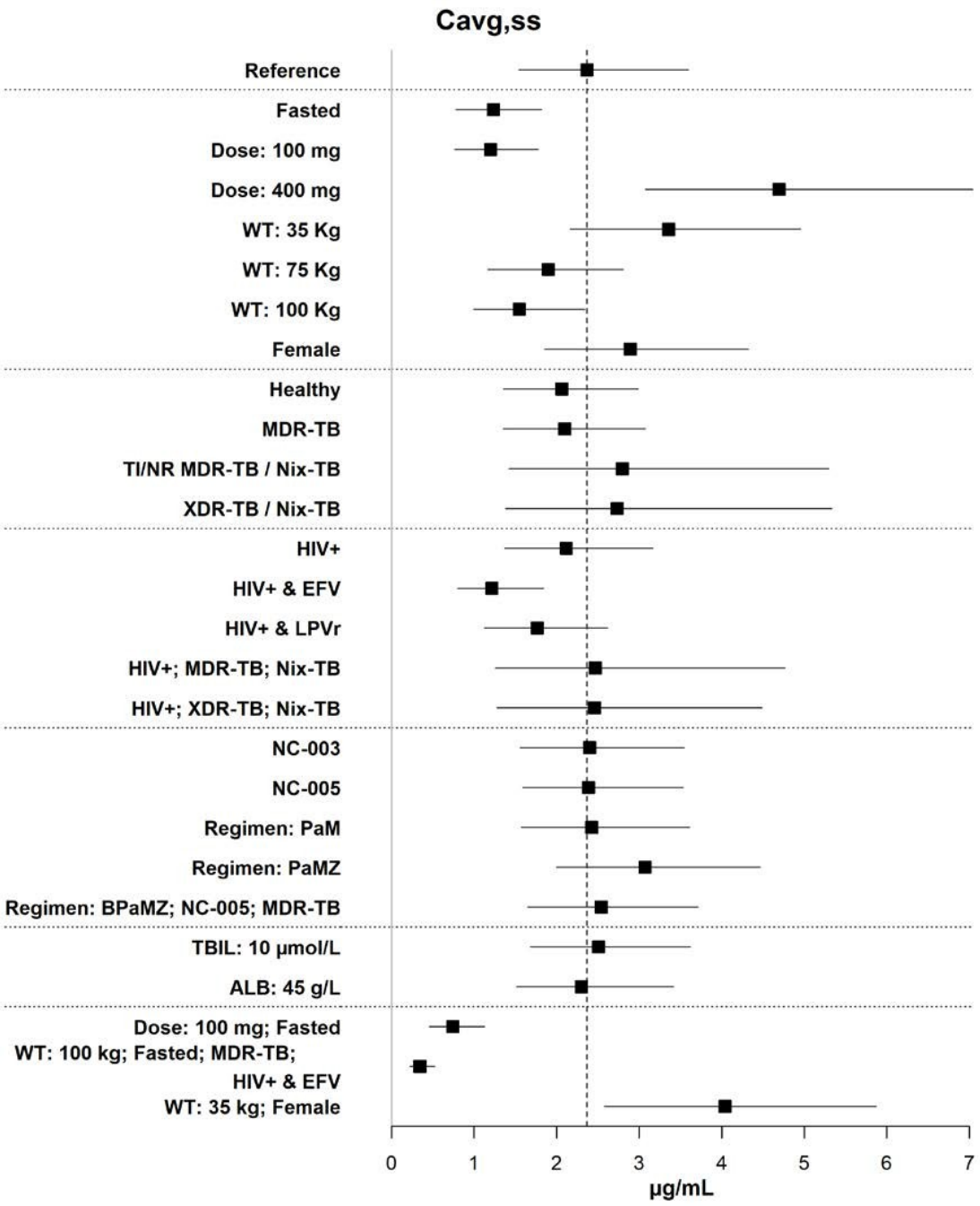


Figure 15-5-4. Forest Plot for Cavg_ss. Vertical Dashed Line = Cavg_ss for a Reference Subject. square points = median for reference and subjects with different combinations of covariates, error-bars = 10th - 90th percentiles

SOURCE: Applicant's Pharmacometrics Report 2018-01, population pharmacokinetics of pretomanid-modeling report (page 62 of 296)

1.1.1.4. REVIEWER'S COMMENTS:

The applicant's population pharmacokinetic model fairly described the observed pretomanid concentrations in different categories of subjects (healthy, DS-TB, MDR-TB and XDR-TB). Simulations from the model show the influence of different covariates (individually and in combination) on pretomanid exposure and therefore support pretomanid label recommendations. Although it is not clear how the applicant pre-defined outlying samples, the model development steps are generally acceptable.

1.1.2. Population PKPD analyses

1.1.2.1. Introduction

The applicant performed exposure-efficacy analysis to provide supportive evidence of effectiveness of pretomanid for treatment of XDR-TB and MDR-TB in subjects who are treatment intolerant or non-responsive to standard treatment of MDR-TB. Data for these analyses were collected in phase 2 and 3 studies. A brief description of the studies is provided in section 1.1.1.2 of pharmacometrics review.

The applicant utilized three efficacy metrics in the exploration of the exposure-efficacy relationships: These were the change in logCFU between day 0 and 14 ($EBA_{CFU0-14}$); the daily percentage change in time to positivity ($EBA_{TTP0-14}$) and Time to Sputum Culture Conversion to negative (TSCC).

Several exposure metrics were evaluated for relationship with efficacy metrics including: dose, trough concentration (C_{min}), maximum concentrations (C_{max}), area under the plasma concentration curve (AUC), and time that the pretomanid concentration is above its minimum inhibitory concentration (TMIC). The relationship between these exposure metrics and different efficacy metrics were explored through scatter-plots and pearson correlation coefficients. In study CL-007, there was no dose-response relationship. In study CL-010, there was statistically significant difference between response ($EBA_{CFU0-14}$ and $EBA_{TTP0-14}$) at 50 mg and the average of response among the other three doses (100 mg, 150 mg, and 200 mg). The Pearson correlation coefficients between different exposure metrics and $EBA_{CFU0-14}$ were small ranging from -0.06 – 0.15. In all other phase 2 studies, the applicant found no consistent trend of relationship between the exposure and efficacy metrics.

The applicant further explored exposure – efficacy relationship by analyzing pooled data from several phase 2 and 3 studies. The exposure metric used for pooled analyses was the model predicted average steady state concentration over a dosing interval (C_{avg}). Other exposure metrics were not explored further because they were correlated with C_{avg} which was considered a better exposure metric.

The objectives of these analyses were to:

1. Explore exposure-response relationship for $EBA_{CFU0-14}$ and $EBA_{TTP0-14}$ using data pooled from phase 2 studies
2. Explore exposure – response relationship for TSCC using pooled data from phase 2 and phase 3 studies
3. Use the discovered exposure-response relationships to extract insight about dosing recommendation for pretomanid.

The applicant performed exposure response analyses in R version 3.4.1

1.1.2.2. Methods

1.1.2.2.1. Exposure – efficacy relationship for $EBA_{CFU0\text{-}14}$ and $EBA_{TTP0\text{-}14}$

Data for these analyses came from treatment arms containing pretomanid in studies CL-007, CL-010, NC-001, NC-002, NC-003, and NC-005. Linear or non-linear mixed effect models were used to fit the longitudinally observed log transformed CFU or TTP data (Log CFU or TTP versus time). The models were used to predict log transformed CFU or TTP at baseline and day 14 which were subsequently used to calculate $EBA_{CFU0\text{-}14}$ and $EBA_{TTP0\text{-}14}$.

The responses ($EBA_{CFU0\text{-}14}$ and $EBA_{TTP0\text{-}14}$) were modelled as functions of pretomanid exposure (C_{avg}) and regimen partners. Nonlinear regression using the *nls* function in R version 3.4.1. was used. The applicant evaluated E_{max} and exponential relationships to describe the dependence of responses on pretomanid exposure. The exponential form was selected because of successful convergence in initial exploration. *Equation 1* shows the exponential relationship between EBA and pretomanid exposure.

Equation 1

$$EBA = Intercept_{regimen} + Change_{regimen} \times \left[1 - e^{-r \times C_{avg}}\right]$$

$$where: Intercept_{regimen} = 0, \qquad i.e.\ at\ Cavg = 0, \qquad EBA = 0$$

1.1.2.2.2. Exposure – efficacy relationship for TSCC

Time to event modeling was used to explore the relationship between exposure (population PK model predicted C_{avg}) and TSCC. Regimen was included in the model as a categorical covariate. Other covariates considered for inclusion were: indicators of disease severity, type of TB, HIV status, baseline TTP, cavitation and BMI.

Data for this analysis came from studies NC-002, NC-005, NC-006, and Nix-TB. Sputum sampling schemes for the different studies are provided in section 1.1.1.2. Patients who did not convert by the end of treatment or loss to follow-up were considered censored after their final observations or end of treatment.

1.1.2.3. Results

1.1.2.3.1. EBA of different pretomanid regimens

EBA of different pretomanid combination regimens were numerically higher compared to EBA of pretomanid alone. EBAs of different pretomanid regimens are given in Table 15-5-2 for $EBA_{CFU0\text{-}14}$ and Table 15-5-3 for $EBA_{TTP0\text{-}14}$.

Table 15-5-2. Summary Statistics of $EBA_{CFU0-14}$ by Regimen

Drugs	*Pa*	*B*	*BPa*	*BPaMZ*	*BPaZ*	*BZ*	*PaMZ*	*PaZ*	*Z*
N	*117*	*14*	*13*	*35*	*125*	*14*	*42*	*14*	*15*
Mean	*0.107*	*0.065*	*0.112*	*0.241*	*0.191*	*0.142*	*0.207*	*0.153*	*0.036*
St. Dev.	*0.074*	*0.068*	*0.051*	*0.109*	*0.071*	*0.101*	*0.115*	*0.040*	*0.044*
Min	*-0.046*	*-0.048*	*0.055*	*0.030*	*0.025*	*0.027*	*-0.025*	*0.102*	*-0.043*
Max	*0.322*	*0.176*	*0.210*	*0.433*	*0.406*	*0.394*	*0.497*	*0.224*	*0.105*
Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 23 of 58)									

Table 15-5-3. Summary Statistics of $EBA_{TTP0-14}$ by Regimen

Study	*Pa*	*B*	*BPa*	*BPaMZ*	*BPaZ*	*BZ*	*PaMZ*	*PaZ*	*Z*
N	*117*	*14*	*15*	*34*	*126*	*15*	*44*	*14*	*15*
Mean	*4.78*	*5.41*	*5.85*	*18.3*	*14.3*	*9.97*	*18.7*	*8.81*	*2.59*
St. Dev.	*3.38*	*3.52*	*2.78*	*10.4*	*8.59*	*6.99*	*14.8*	*3.47*	*1.61*
Min	*-2.06*	*0.0649*	*2.47*	*2.26*	*2.63*	*3.71*	*6.83*	*4.40*	*0.699*
Max	*16.3*	*11.7*	*12.1*	*56.1*	*66.2*	*30.9*	*92.5*	*15.7*	*6.29*
Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 31 of 58)									

1.1.2.3.2. Exposure – efficacy relationship for $EBA_{CFU0-14}$

<u>Pretomanid alone regimen</u>

The exposure-response relationship for pretomanid alone was developed using 115 observations from study CL-007 and CL-010. The relationship between pretomanid C_{avg} and $EBA_{CFU0-14}$ was fairly described by the exponential model as shown by *Equation 1*. However, some observed EBA values were negative, therefore a shift of 0.05 was introduced to all values. The intercept in equation 1 was fixed to log (0.05) instead of 0. Parameter estimates of the model are as given in Table 15-5-4. The pretomanid C_{avg} at which half of maximum response is attained (EC50 = log(2)/r) was estimated to be 0.16µg/mL. However, this EC50 was lower than the minimum of the observed pretomanid concentration (0.33µg/mL), indicating that this EC50 may not be the optimal estimate.

Table 15-5-4. Parameter Estimates for the Model Fitted to Log-transformed $EBA_{CFU0-14}$

```
Parameters:
      Estimate Std. Error t value Pr(>|t|)
D.Pa  1.08540    0.05286  20.534   <2e-16 ***
r     4.25250    1.69783   2.505   0.0137 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.472 on 113 degrees of freedom
```

- *D.Pa = maximum change in response with non-zero values of C_{avg}*
- *r = parameter determining how quickly response changes with increase in Cavg. Log (2)/r = is the value of C_{avg} at which half of D.Pa is attained.*

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 24 of 58)

Figure 15-5-5 shows the fitted curve from the model and the data. Observations from different doses are distinguished by shape and color. Median C_{avg} of each dose is identified by colored vertical lines.

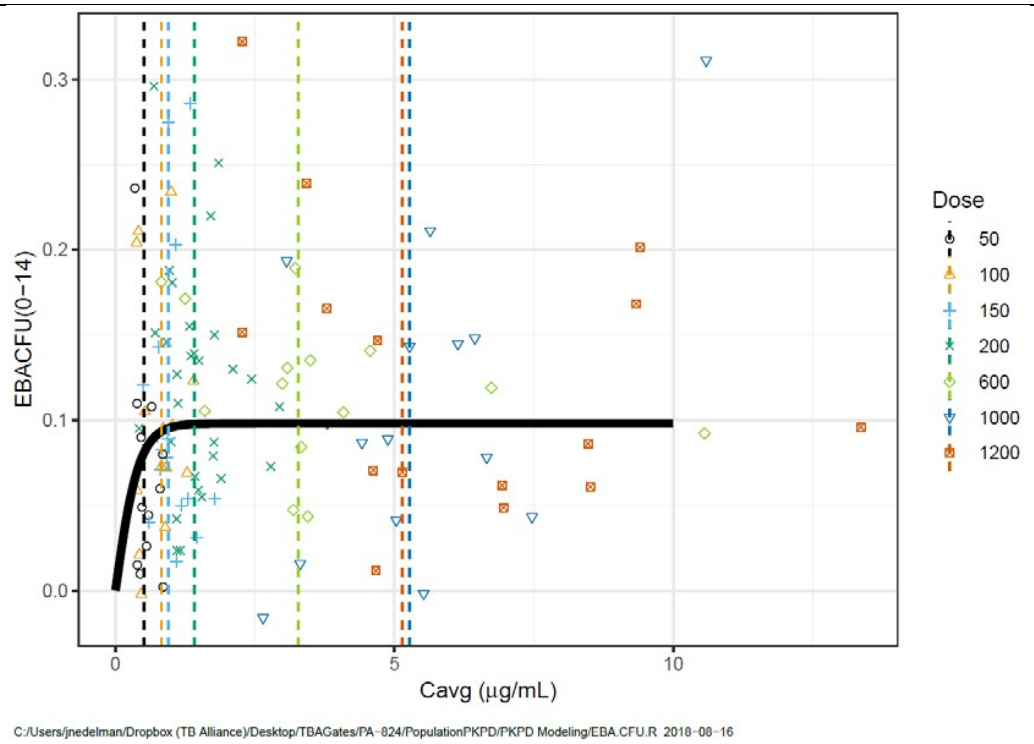


Figure 15-5-5. Fitted Curves and Data for $EBA_{CFU0-14}$ for Pretomanid Alone

Note: Response is shown on original scale, back-transformed from log scale. Unit for $EBA_{CFU0-14}$: -[Change in log10(CFU)]/day

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 25 of 58)

At the dose of 50 mg, the height of the fitted curve is 83% of its plateau. At 100 mg and 150 mg the heights are 95% and 97% of the plateau. For doses of 200 mg and above, the heights are >99% of the plateau.

Combination regimens

To assess the contribution of the BPa combination, the exposure-response relationship for pretomanid in combination regimens was assessed using 268 observations from studies NC-001, NC-002, NC-003, and NC-005. The exposure – efficacy relationship for combination regimen was formulated as shown in *Equation 2*, where:

- B, M, and Z were indicator functions for the presence of bedaquiline, moxifloxacin, and pyrazinamide.
- IZ, IB, and IBZ were parameters for the intercept.
    - IZ was the intercept for PaZ, i.e., Z, and PaMZ. There were no data on MZ alone, so it was assumed that MZ was the same as Z in the absence of Pa.
    - IB was the intercept for BPa, i.e., B.
    - IBZ was the intercept for BPaZ, i.e., BZ, and BPaMZ. There were no data for BMZ, so it was assumed that BMZ was the same as BZ in the absence of Pa.
- DZ, DB, DBZ, DBZM, and DMZ were parameters for the change in the response with nonzero values of C_{avg}, for PaZ, BPa, BPaZ, BPaMZ, and PaMZ, respectively.
- r was a parameter that determined how quickly the response changed as C_{avg} increased. log (2)/r was the value of C_{avg} at which half the maximum change in response was attained.

Equation 2.

$$\begin{aligned}\log(EBA_{CFU0-14} + 0.05) \\ &= [I_Z \times Z \times (1-B) + I_B \times B \times (1-Z) \times (1-M) + I_{BZ} \times B \times Z \times (1-M)] \\ &+ [D_Z \times Z \times (1-B) + D_B \times B \times (1-Z) \times (1-M) + D_{BZ} \times B \times Z \times (1-M) \\ &+ D_{BZM} \times B \times Z \times M + D_{MZ} \times Z \times M \times (1-B)] \times [1 - e^{-r \times C_{avg}}]\end{aligned}$$

Parameter estimates of the model are displayed in Table 15-5-5

Table 15-5-5. Parameter Estimates for the Model Fitted to Log-transformed $EBA_{CFU0-14}$ Including Concomitant Anti-tuberculosis as Covariates.

```
Parameters:
      Estimate Std. Error t value Pr(>|t|)
I.Z   -2.49545    0.09902 -25.203  < 2e-16 ***
I.B   -2.20467    0.10273 -21.461  < 2e-16 ***
I.BZ  -1.76555    0.09901 -17.831  < 2e-16 ***
D.Z    0.88676    0.14694   6.035 5.48e-09 ***
D.B    0.34644    0.15438   2.244 0.025673 *
D.BZ   0.29598    0.10447   2.833 0.004973 **
D.BZM  0.44967    0.11745   3.828 0.000162 ***
D.MZ   0.18277    0.11806   1.548 0.122809
r      4.41011    9.16053   0.481 0.630621
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.3705 on 259 degrees of freedom
```

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 27 of 58)

The intercept parameters indicate activity of regimens not containing pretomanid with the assumption that no placebo effect at zero pretomanid concentration. The change parameters indicate maximum activity achievable at enough pretomanid exposure. The statistically significant positive values of the change parameters for different regimens indicate activity of pretomanid. However, The EC50 (log(2)/r) for pretomanid was poorly estimated because there were no observations with C_{avg} values below the EC50. All observations were on the plateau of response. Figure 15-5-6 shows the fitted curves and the data.

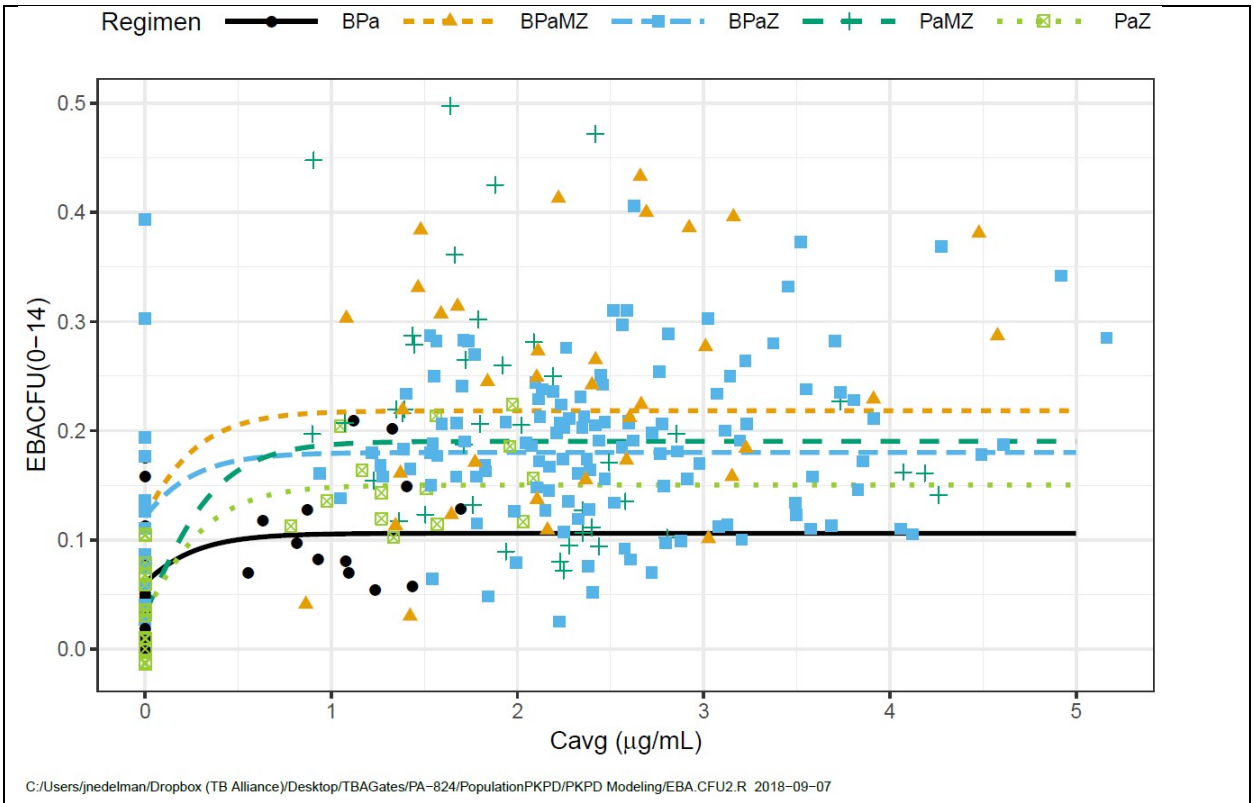


Figure 15-5-6. Fitted Curves and Data for $EBA_{CFU0-14}$ in Combination Regimens

Note: Response is shown on original scale, back-transformed from log scale. Unit for EBACFU (0-14): -[Change in log10(CFU)]/day.

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 28 of 58)

The applicant performed analysis of covariance (ANOVA) to draw inference from the data regarding the contribution of pretomanid activity in different regimens. The ANOVA results are given in Table 15-5-6.

Table 15-5-6. Estimated Differences between Regimens for Log-transformed $EBA_{CFU(0-14)}$

Difference	p-value	Point estimate of difference	95% Confidence Interval for difference
B**Pa** – B	0.010	0.34	0.052 – 0.62
B**Pa**Z – BZ	0.0026	0.29	0.089 – 0.50
BPaZ – PaZ	0.084	0.14	-0.061 – 0.35
BPaMZ – PaMZ	0.10	0.11	-0.058 – 0.28
Note: Confidence intervals and p-values are not adjusted for multiplicity. Unit for $EBA_{CFU(0-14)}$: -[Change in log10(CFU)]/day			

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for

pretomanid (page 30 of 58)

The ANOVA results show that pretomanid has statistically significant contribution to the activity of BPa and BPaZ regimens. The results also show that pretomanid contributes to BPaZ and BPaMZ activity but with marginally significant evidence.

1.1.2.3.3. Exposure – efficacy relationship for $EBA_{TTP0\text{-}14}$

Pretomanid alone

Exposure – efficacy modeling for $EBA_{TTP0\text{-}14}$ was done using 115 observations from CL-007 and CL-010. The data were fitted using the model in *Equation 3*.

Equation 3

$$\log(EBA_{TTP0-14} + 1) = \log(1) + D_{Pa} \times [1 - e^{-r \times C_{avg}}]$$

Table 15-5-7 displays the estimated parameters. The estimated r and hence EC50 (log(2)/r = 0.20 µg/mL) was less than the minimum value of C_{avg} (0.33 µg/mL) among the data.

Table 15-5-7. Parameter Estimates for the Model Fitted to Log-transformed $EBA_{TTP(0\text{-}14)}$

```
Parameters:
      Estimate Std. Error t value Pr(>|t|)
D.Pa  1.67627    0.07536  22.245  < 2e-16 ***
r     3.50239    0.99456   3.522  0.00062 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.6433 on 113 degrees of freedom
```

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 32 of 58)

Figure 15-5-6 shows the fitted curve from the model and the data. At the dose of 50 mg, the height of the fitted curve is 66% of its plateau. At 100 mg and 150 mg the heights are 86% and 93% of the plateau. At 200 mg the height is 99% of the plateau, and at higher doses the heights are >99% of the plateau.

Combination regimens

A total of 275 observations were used for exposure – response analysis for $EBA_{TTP(0\text{-}14)}$. As with $EBA_{CFU(0\text{-}14)}$, both exponential and ANOVA models were used to analyze the data. Results from the exponential model are given in Table 15-5-8, while results from the ANOVA model are given in Table 15-5-9.

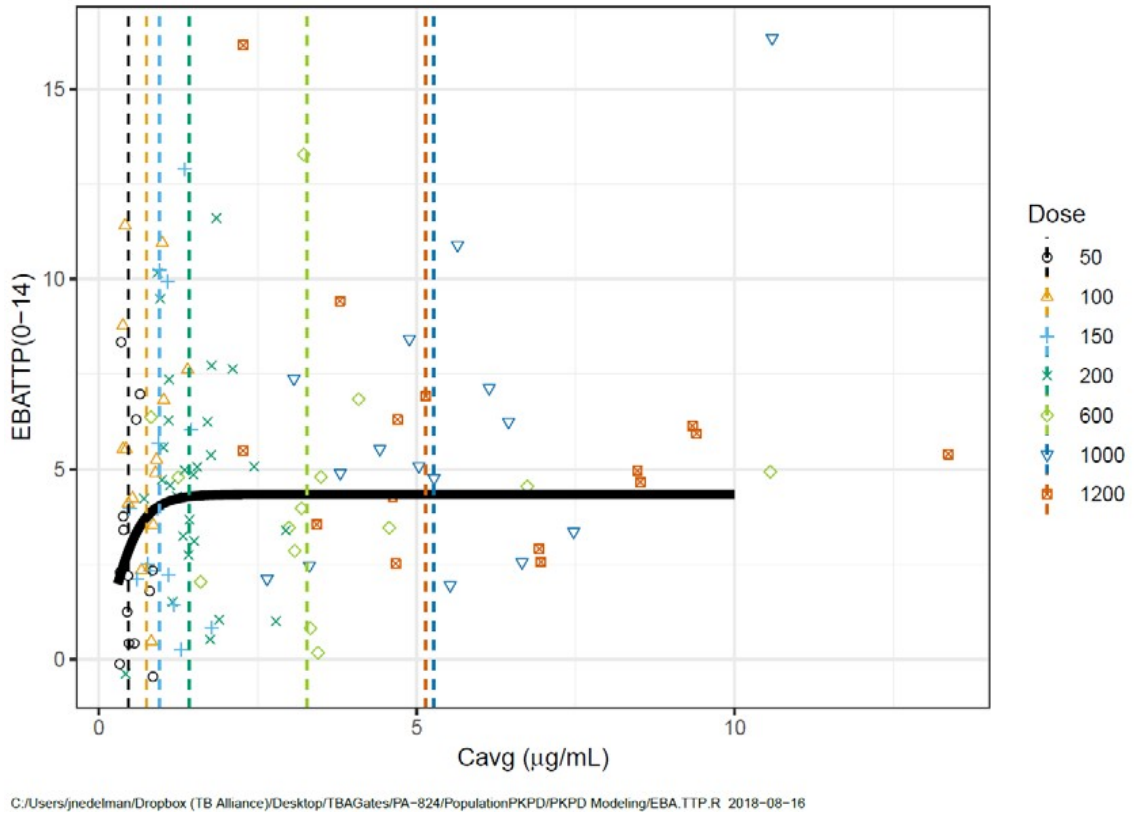


Figure 15-5-7. Fitted Curves and Data for $EBA_{TTP(0-14)}$ for Pretomanid Alone

Note: Response is shown on original scale, back-transformed from log scale. Unit for $EBA_{TTP(0-14)}$: (Change in hours to positivity)/day

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 33 of 58)

Table 15-5-8. Parameter Estimates for the Model Fitted to Log-transformed $EBA_{TTP(0-14)}$

```
Parameters:
       Estimate Std. Error t value Pr(>|t|)
I.Z   8.012e-01  1.321e-01   6.063 4.56e-09 ***
I.B   1.586e+00  1.420e-01  11.173  < 2e-16 ***
I.BZ  2.128e+00  1.321e-01  16.106  < 2e-16 ***
D.Z   1.302e+00  1.914e-01   6.803 6.76e-11 ***
D.B   7.920e-02  1.979e-01   0.400 0.689275
D.BZ  4.123e-01  1.398e-01   2.950 0.003465 **
D.BZM 6.256e-01  1.587e-01   3.943 0.000103 ***
D.MZ  6.564e-01  1.585e-01   4.142 4.63e-05 ***
r     1.568e+01  5.756e+04   0.000 0.999783
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.5118 on 266 degrees of freedom
```

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 37 of 58)

Table 15-5-9. Estimated Differences between Regimens for Log-transformed $EBA_{TTP(0-14)}$

Difference	p-value	Point estimate of difference	95% Confidence Interval for difference
B**Pa** – B	0.34	0.079	-0.30 – 0.46
B**Pa**Z – BZ	0.0017	0.41	0.14 – 0.69
BPaZ – PaZ	0.0013	0.44	0.15 – 0.72
BPaMZ – PaMZ	0.52	-0.0057	-0.24 – 0.23
Note: Confidence intervals and p-values are not adjusted for multiplicity. Unit for $EBA_{TTP(0-14)}$: (Change in hours to positivity)/day			

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 34 of 58)

The results indicate that Pa added significantly to BZ, and that B added significantly to PaZ. There was no evidence of Pa adding to B or B adding to PaMZ.

1.1.2.3.4. Exposure – efficacy relationship for TSCC

A total of 616 non-missing observations were available for time-to-sputum culture conversion analysis, 453 events and 163 censored. Figure 15-5-8 shows Kaplan-Meier plots stratified by regimen. Figure 15-5-9 shows Kaplan- Meier plots stratified by quantile of C_{avg} (lower 10%, middle 80%, upper 10%). And Table 15-5-10 summarizes median time to conversion by regimen and quantile of C_{avg}. The results show that the BPaL regimen had the shortest time to

sputum culture conversion compared to other regimens. The results also show mild relationship between C_{avg} and TSCC.

Table 15-5-10. Median Time to Sputum Culture Conversion by Regimen and Quantile of C_{avg}

Regimen	Median Time to Sputum Culture Conversion (Days) Estimate (95% Confidence Interval)
BPaL	42 (29 – 43)
BPaMZ	43 (35 – 56)
BPaZ	49 (42 – 56)
PaMZ	49 (49 – 56)
Quantile of Cavg	
Low 10%	56 (49 – 83)
Middle 80%	49 (48 – 40)
High 10%	49 (41 – 55)
Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 40 of 58)	

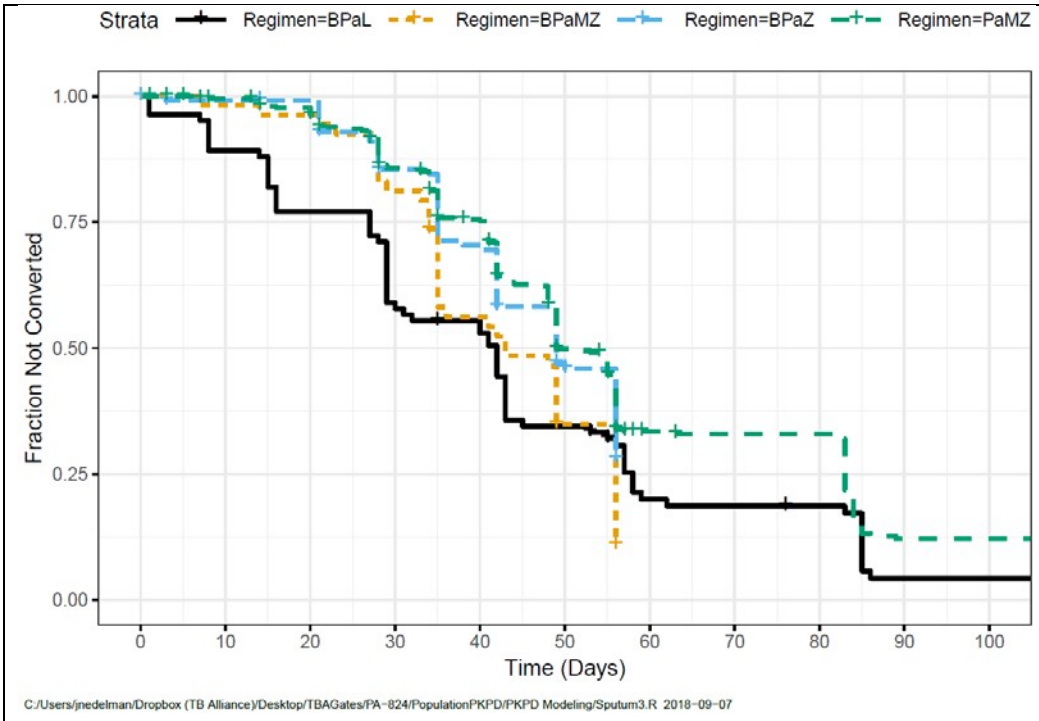


Figure 15-5-8. Kaplan-Meier Plots of Time to Sputum Culture Conversion, by Regimen

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 39 of 58)

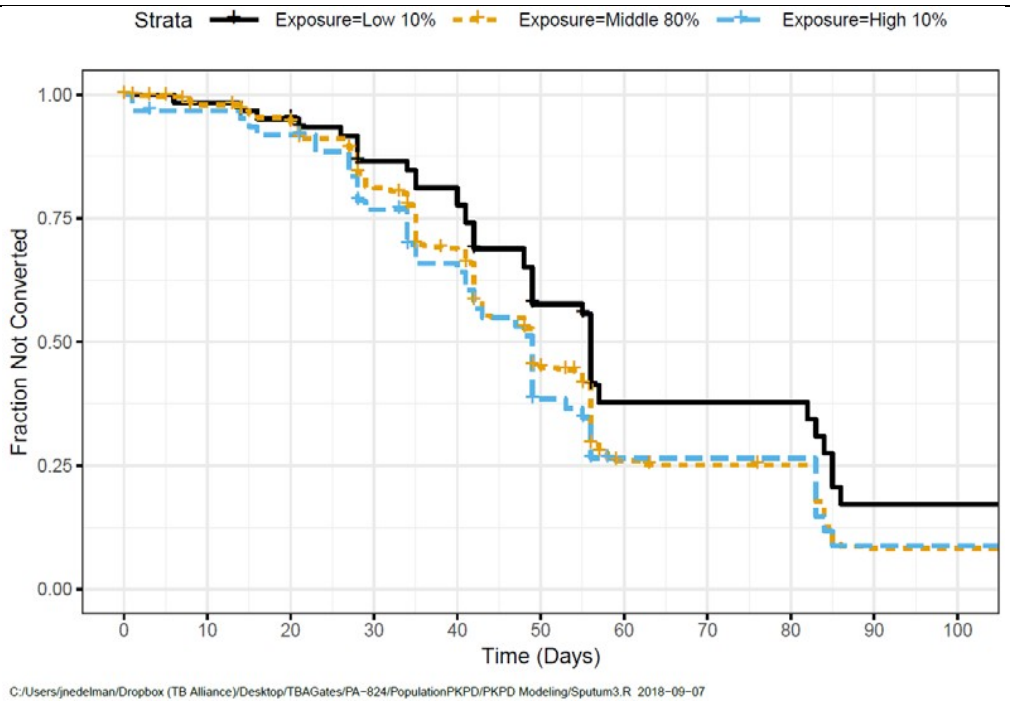


Figure 15-5-9. Kaplan-Meier Plots of Time to Sputum Culture Conversion, by Quantiles of C_{avg}

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 39 of 58)

Cox proportional hazard modeling was used to explore exposure – response relationship for TSCC. In this analysis C_{avg} was centered around its median such that the derived predictor variable was: $dC_{avg} = C_{avg} - 2.4\mu g/mL$. To accommodate for possible nonlinear dependence of the hazard function on dCavg, a cubic spline was used with knots at the quartiles of dC_{avg}: -0.628, 0.038, and 0.966. The applicant tested different covariates, but the final model included C_{avg}, regimens and baseline-TTP (BTTP) as predictors of TSCC. *Equation 4* shows the final log hazard model:

Equation 4

$$\log(hazard) = \log\big(h_0(t)\big) + regimen + Spline(dCavg) + cBTTP + tt(cBTTP)$$

Where:

- $h_0(t)$ = is the baseline hazard that is implicit in the cox-proportional hazards model.
- $regimen$ = is categorical variable with levels BPaL, BPaMZ, BPaZ, and PaMZ.
- $Spline(dCavg)$ = is the spline function in dCavg using six degrees of freedom as described below:

$Spline(dCavg) = x1 + x1.2 + x1.3 + x2.3 + x3.3 + x4.3$ where

$$x1 = dCavg;\ x1.2 = dCavg^2; x1.3 = dCavg^3; x2.3 = \min(0, dCavg + 0.62825)^3;$$

$$x3.3 = \min(0, dCavg - 0.03750)^3;\ x4.3 = \min(0, dCavg - 0.96650)^3;$$

- $cBTTP = \log(BTTP/112)$ where 112 is the median of BTTP
- $tt(cBTTP) = cBTTP \times \sqrt{pmin(time, 60)}$ where pmin returns minima of input values

Table 15-5-11 shows the parameter estimates from the final model and the hazard ratios for the different predictors. The hazard ratios for BPaMZ and BPaZ compared to the BPaL were statistically significantly higher than 1. This implies that at any time during treatment, subjects on BPaMZ and BPaZ are respectively 2.5 and 2 times more likely to have negative sputum culture compared to subjects on the BPaL regimen. These results contradict those reported in Table 15-5-10 because Kaplan-Meier analysis did not account for imbalance in BTTP between the different treatment regimens. Figure 15-5-10 shows the contribution of pretomanid to the log-hazard. Subjects with lower pretomanid concentration have lower contribution to the hazard and therefore lower likelihood to have negative sputum culture at any time during treatment.

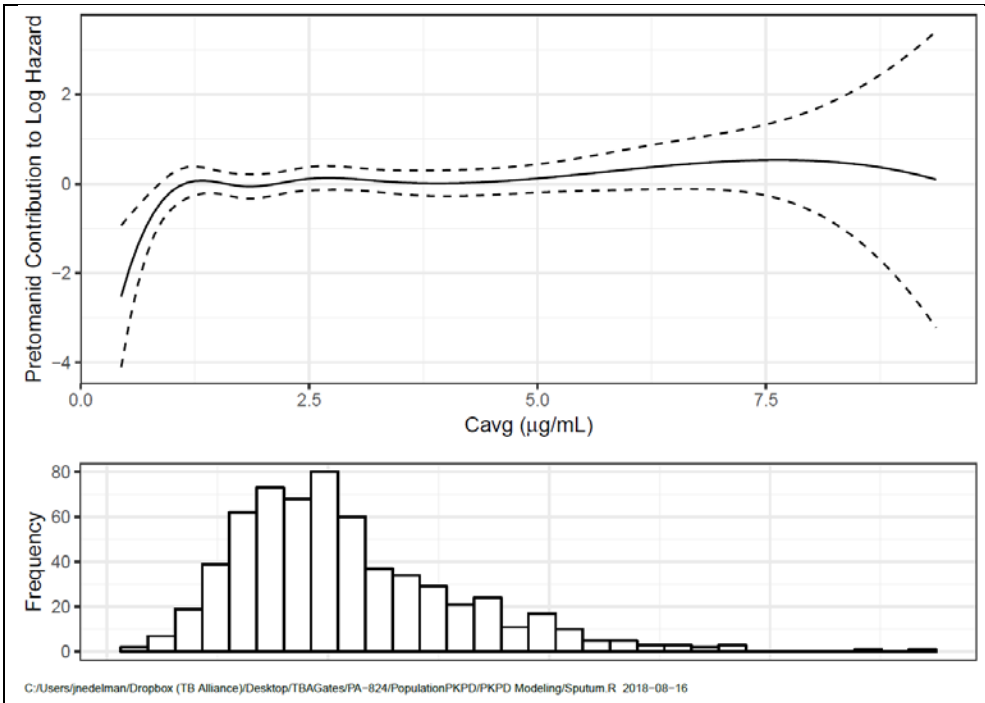


Figure 15-5-10. Contribution to the Log-hazard from Pretomanid Concentration with the Distribution of C_{avg} among Subjects taking the different Pretomanid Containing Regimens.

Subjects with lower pretomanid concentration have lower contribution to the hazard and therefore lower likelihood to have negative sputum culture at any time during treatment.

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 45 of 58)

Table 15-5-11. Summary of Model Parameters for Time to Sputum Culture Conversion

	coef	exp(coef)	se(coef)	z	Pr(>|z|)	
RegimenBPaMZ	0.92768	2.52863	0.22982	4.037	5.42e-05	***
RegimenBPaZ	0.69646	2.00663	0.22141	3.146	0.00166	**
RegimenPaMZ	0.26021	1.29721	0.17102	1.522	0.12812	
cBTTP	3.95873	52.39050	0.48000	8.247	< 2e-16	***
tt(cBTTP)	-0.49786	0.60783	0.07502	-6.636	3.22e-11	***
x1	3.38185	29.42503	1.79619	1.883	0.05973	.
x1.2	4.77024	117.94784	2.32293	2.054	0.04002	*
x1.3	1.96322	7.12224	0.85152	2.306	0.02114	*
x2.3	-2.65975	0.06997	1.36192	-1.953	0.05083	.
x3.3	0.84489	2.32773	0.72827	1.160	0.24599	
x4.3	-0.16251	0.85001	0.20340	-0.799	0.42430	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

	exp(coef)	exp(-coef)	lower .95	upper .95
RegimenBPaMZ	2.52863	0.395471	1.611627	3.967e+00
RegimenBPaZ	2.00663	0.498348	1.300178	3.097e+00
RegimenPaMZ	1.29721	0.770886	0.927769	1.814e+00
cBTTP	52.39050	0.019087	20.449140	1.342e+02
tt(cBTTP)	0.60783	1.645192	0.524717	7.041e-01
x1	29.42503	0.033985	0.870559	9.946e+02
x1.2	117.94784	0.008478	1.242832	1.119e+04
x1.3	7.12224	0.140405	1.342140	3.780e+01
x2.3	0.06997	14.292778	0.004849	1.010e+00
x3.3	2.32773	0.429603	0.558503	9.702e+00
x4.3	0.85001	1.176463	0.570541	1.266e+00

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 44 of 58)

1.1.2.3.5. Application of the Exposure-response Models

The applicant used the final exposure-response models to evaluate the effect of food co-administration on treatment outcome. The following C_{avg} values were considered for subjects administered 200 mg QD:

- Fed50 = 2.37 µg/mL: 50th percentile under fed conditions.
- Fed10 = 1.54 µg/mL: 10th percentile under fed conditions
- Fasted50 = 1.24 µg/mL: 50th percentile under fasted conditions
- Fasted10 = 0.781 µg/mL: 10th percentile under fasted conditions

- Extreme = 0.344 µg/mL: 50th percentile for a combination of covariates that was selected to generate extremely low exposures for a type of subject that might reasonably be expected to receive pretomanid, albeit rarely: a 100-kg male with MDR-TB, HIV+ taking efavirenz, taking pretomanid under fasted conditions. In the PopPK model for pretomanid, clearance increased with weight, was higher for MDR- TB subjects, and was increased by the inducer efavirenz; and bioavailability was less under fasted conditions.

Figure 15-5-11 and Figure 15-5-12 show the fitted exposure/response profiles for $EBA_{CFU(0\text{-}14)}$ and $EBA_{TTP(0\text{-}14)}$. For $EBA_{TTP(0\text{-}14)}$, all five benchmarks are on the plateau of the exposure/response curve. For $EBA_{CFU(0\text{-}14)}$, Fed50, Fed10, and Fasted50 are on the plateau. Fasted10 is only slightly before the plateau (ranging from 96% of the plateau for PaMZ to 99% for BPaZ). The Extreme condition ranged from 74% of the plateau for PaMZ to 92% of the plateau for BPaZ. For the best regimen BPaMZ, the extreme condition achieved a response approximately equal to the plateau condition for the next best regimen PaMZ.

Figure 15-5-13 shows the Kaplan-Meir curves for subjects in different fed conditions. The survival curves for Fed50, Fed10, and Fasted50 are comparable indicating that they are at the plateau of the exposure-response curve. However, the curves for Fed10 and Fed50 are clearly separated to the right indicating delayed response.

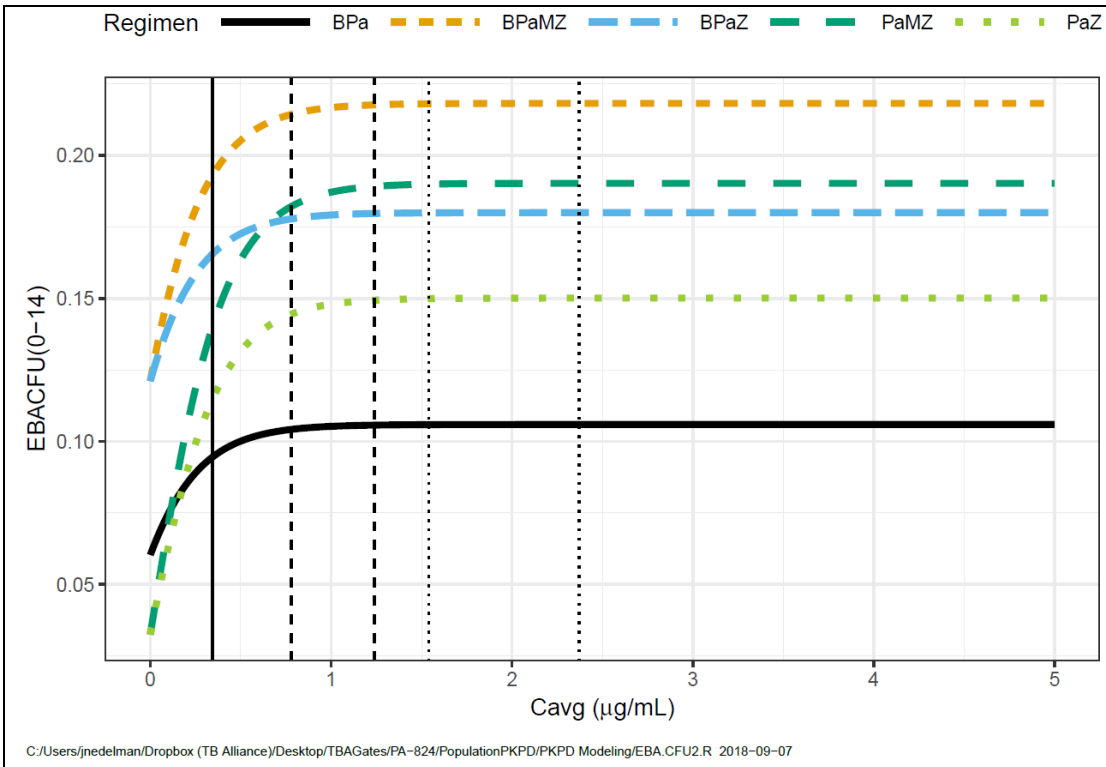


Figure 15-5-11. Exposure Benchmarks in the Exposure/response Relationships for

$EBA_{CFU(0-14)}$

From right to left, the vertical lines show Fed50, Fed10 (dotted lines), Fasted50, Fasted10 (dashed lines), Extreme (solid line)

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 47 of 58)

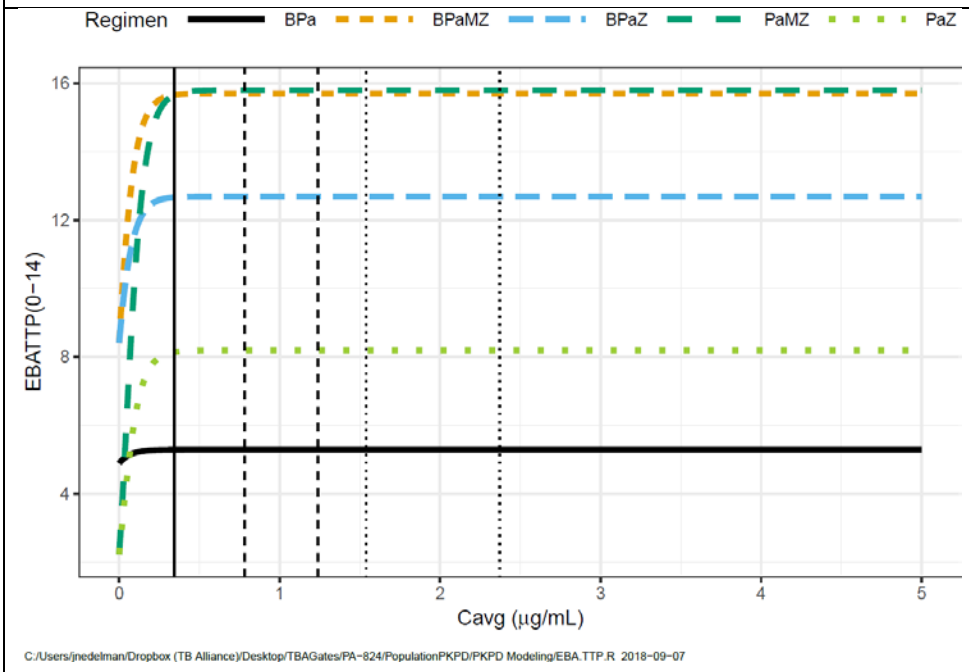


Figure 15-5-12. Exposure Benchmarks in the Exposure/response Relationships for

$EBA_{TTP(0-14)}$

From right to left, the vertical lines show Fed50, Fed10 (dotted lines), Fasted50, Fasted10 (dashed lines), Extreme (solid line)

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 48 of 58)

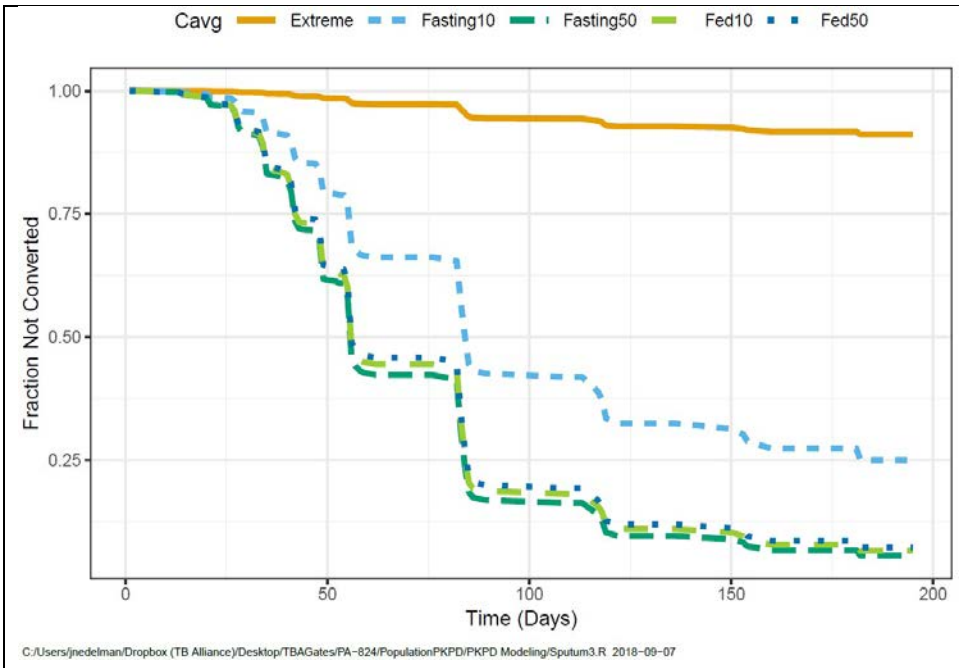


Figure 15-5-13. Exposure Benchmarks in the Exposure/response Relationship for Time to Sputum Culture Conversion

Source: Applicant's Pharmacometrics Report 2018-01, Pharmacokinetics/Efficacy modeling for pretomanid (page 49 of 58)

Based on TSCC, the results show some evidence that some subjects may be at risk of insufficient exposure if pretomanid 200mg is administered under fasting conditions.

1.1.2.4. REVIEWERS' COMMENTS

The applicant's exposure-response analyses fairly described the observed data for the chosen efficacy metrics. The analyses were repeatable and produced the expected results. Simulations from the model show the influence of food on the chosen efficacy metrics and thus support the applicant's label recommendation to administer pretomanid 200mg under fed conditions. The applicant's time to sputum culture conversion analyses indicate that after adjusting for baseline bacterial load, BPaMZ and BPaZ regimens achieved shorter time to sputum culture conversion than the BPaL regimen. The discrepancy between multivariate Cox regression and K-M plot is probably due to the imbalanced distributions of the type of TB that was treated by the different regimens. Subjects receiving BPaMZ and BPaZ regimens were infected with MDR-TB and DS-TB respectively, while subjects on BPaL regimen were infected with XDR-TB or with treatment resistant MDR-TB or intolerant to standard MDR-TB treatment.

1.1.3. Exposure-response analysis for safety.

1.1.3.1. Introduction.

The applicant's exposure – response analysis for safety can be categorized into two types based on the dataset used for those analyses: In the first category, the applicant utilized pooled data from the whole clinical development program to assess association between pretomanid exposure and different metrics for safety. The metrics for safety included the QTc interval, liver enzymes, serum creatinine levels, and reproduction hormones. In the second category, the applicant utilized data from the phase 3 Nix-TB trial to assess association between pretomanid exposure and different adverse events. Three categories of adverse events were assessed, and they were: 1) any grade 3 or grade 4 adverse events observed in the Nix-TB study; 2) The first 5 frequently occurring adverse events including: ALT elevation, Arthralgia, Headache, nausea, and vomiting; 3) Adverse events identified as of special interest for further exploration. These include: Hepatic disorders (standardized medical query, SMQ), lens disorders (SMQ), convulsions (SMQ), fertility disorders (SMQ), severe cutaneous reaction (SMQ), skin and subcutaneous tissue disorder, headaches, and gastrointestinal symptoms. Using the standardized MedDRA query, hepatic disorders included any of the following adverse events terms: *"ELEVATED GGT", "TRANSAMINITIS", "DRUG INDUCED LIVER INJURY", "INCREASED GAMMA-GT", "INCREASED SERUM ALT", "JAUNDICE", "INCREASED GGT", "ELEVATED AST", "ABNORMAL LIVER FUNCTION", "DRUG-INDUCED LIVER INJURY", "ELEVATED GAMMA-GLUTAMYL TRANSFERASE (GGT)", "ELEVATED TRANSAMINASES", "INCREASED GGT GRADE 3", "RAISED ALKALINE PHOSPHATASE", "RAISED ALP", "RAISED ALT", "RAISED AST", "RAISED GGT", "OBSTRUCTIVE HYPERBILIRUBINEMIA", "RAISED LIVER ENZYMES", "RAISED LIVER FUNCTION TESTS (DUCTAL ENZYMES)", "GRADE 3 AST ELEVATION", "RAISED GGT (WORSENING)", "HYPERBILIRUBINEMIA", "ELEVATED ALT", "ELEVATED GGT (GAMMA-GLUTAMYL TRANSFERASE WORSENED)", "RAISED ALANINE AMINOTRANSFERASE", "RAISED ASPARTATE AMINOTRANSFERASE", "HEPATOMEGALY", "ELEVATED (WORSENED) GGT", "RAISED ALANINE AMINOTRANSFERASE (ALT)", "ELEVATED ALANINE AMINOTRANSFERASE (ALT)", "ELEVATED ASPARTATE TRANSAMINASE (AST)", "ELEVATED GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT)", "ELEVATED LIVER ENZYMES - ALANINE TRANSAMINASE (ALT)", "ELEVATED LIVER ENZYMES - ASPARTATE TRANSAMINASE (AST)", "GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT) INCREASED).", "ELEVATED LIVER ENZYMES (GAMMA-GLUTAMYL TRANSFERASE)", "RAISED GAMMA GLUTAMYL TRANSFERASE", "RAISED(ALT)ALANINE AMINOTRANSFERASE", "RAISED GAMMA GLUTAMYL TRANSFERENCE", "RAISED GAMMA-GLUTAMYL TRANSFERASE (GGT)"*

1.1.3.2. Exposure – safety analyses based on pooled data.

The applicant pooled data from phase 2 and 3 studies to perform exposure-response analysis for liver enzymes elevation. The exposure metric was the model predicted C_{avg} while the safety metrics were the maximum fold change from baseline of the log transformed ALP, ALT, AST and bilirubin.

The pooled data were examined in subsets based on duration of pretomanid treatment. The following subsets of data were examined:1) 1 – 2-week treatment (All phase 2 and phase 3

studies); 2) 3 -8 weeks (Studies NC-002, NC-005, NC-006, Nix-TB); 3) 12 -26 weeks (NC-006, and Nix-TB)

For each enzyme linear regression modeling was performed, and regimens were assessed as covariates for the intercept and slope.

Results of the modeling indicated no significant association between pretomanid exposure and elevation of ALT, AST and bilirubin. There was a significant association between pretomanid exposure and ALP elevation from week 12 -26 (NC-006, and Nix-TB). However, the influence of the regimens on the slope were in opposite directions. While the slope was positive for Nix-TB (BPaL), it was negative for NC-006 (PaMZ)

Regarding reproductive hormones, the applicant pooled data from NC-002 (FSH, LH, Testosterone), NC-005 (FSH), and NC-006 (FSH, LH, inhibin B, and testosterone). The applicant found no evidence of any exposure-response relationship.

1.1.3.3. Exposure – safety analyses based on Nix-TB.

The applicant performed a logistic regression modeling to explore association between pretomanid exposure and occurrence or non-occurrence of adverse events. The dataset included subjects who qualified for inclusion in safety population (n = 98). The exposure metric was the population PK model predicted Cavg. Statistically significant associations were found between pretomanid high exposure and occurrence of grade3/4 adverse events, vomiting, and gastrointestinal symptoms. There was no association between pretomanid exposure and all other adverse events observed in the Nix-TB study.

1.1.3.4. Application of the exposure-safety model

Based on exposure – safety models explored using the Nix-TB data, the applicant predicted the probability of occurrence of adverse events at 10th, 50th and 90th percentiles of pretomanid exposure in subjects administered 200 mg dose. The results are given in Table 15-5-12.

Table 15-5-12. Estimated Probability of Occurrence of Adverse Events with BPaL Regimen versus Pretomanid C_{avg}

Adverse event	P-value	Cavg (µg/mL)	Estimate	95% Confidence Interval	95% Confidence Interval
Grade 3/4 adverse events	0.023	1.2	0.404	0.260	0.566
		2.4	0.518	0.413	0.622
		4.8	0.731	0.549	0.858
Alanine aminotransferase increased1	0.564	1.2	0.114	0.044	0.264
		2.4	0.097	0.051	0.178
		4.8	0.070	0.020	0.213
Arthralgia1		1.2	0.037	0.011	0.122

	0.406	2.4	0.045	0.017	0.113
		4.8	0.066	0.024	0.165
Headache1	0.563	1.2	0.295	0.178	0.448
		2.4	0.274	0.191	0.376
		4.8	0.234	0.129	0.389
Nausea1	0.05	1.2	0.259	0.153	0.403
		2.4	0.329	0.237	0.435
		4.8	0.490	0.333	0.650
Vomiting1	0.01	1.2	0.199	0.108	0.339
		2.4	0.291	0.203	0.398
		4.8	0.527	0.353	0.695
Hepatic disorders (SMQ)	0.072	1.2	0.279	0.169	0.424
		2.4	0.343	0.250	0.449
		4.8	0.488	0.333	0.645
Lens disorders (SMQ)	0.991	1.2	0.132	0.061	0.262
		2.4	0.133	0.076	0.221
		4.8	0.133	0.061	0.267
Convulsions (SMQ)	0.296	1.2	0.059	0.009	0.295
		2.4	0.018	0.003	0.095
		4.8	0.002	0.000	0.347
Fertility disorders (SMQ)	1	1.2	0	0	0
		2.4	0	0	0
		4.8	0	0	0
Severe cutaneous adverse reactions (SMQ)	0.813	1.2	0.056	0.018	0.162
		2.4	0.059	0.025	0.133
		4.8	0.067	0.023	0.180
Skin and subcutaneous tissue disorders (SMQ)	0.985	1.2	0.542	0.399	0.678
		2.4	0.541	0.437	0.642
		4.8	0.540	0.394	0.679
Headaches2	0.61	1.2	0.312	0.192	0.464
		2.4	0.294	0.208	0.397
		4.8	0.258	0.148	0.412
Gastrointestinal Symptoms2	0.015	1.2	0.318	0.194	0.476
		2.4	0.430	0.328	0.538
		4.8	0.662	0.479	0.807

BPaL = bedaquiline + pretomanid + linezolid; Cavg = steady state average plasma concentration over a dosing interval; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA query

p-value is for the relationship between Cavg and the probability of the adverse event according to a logistic regression model.

[1] These are all single Preferred Term events. *[2] pre-defined grouping of 2 high level terms (HLT)*
Source: Applicant's summary of clinical pharmacology studies (page 145 of 152)

1.1.3.5. REVIEWER'S COMMENTS:

The Reviewer verified the applicant's exposure-response analyses. The applicant's models were repeatable, and the results were consistent with those reported by the applicant. However, the applicant did not evaluate the influence of concomitant medications, particularly bedaquiline, on the incidence of hepatic disorders. Bedaquiline is known to be associated with increased levels of transaminases compared to placebo. Therefore, the reviewer conducted an independent exposure -vs- hepatic disorders analysis exploring the influence of pretomanid and concomitant medications (bedaquiline and its metabolite (M2) and linezolid). The exposure metrics were the model predicted pretomanid steady state concentration (Cavg) and linezolid, bedaquiline and M2 observed trough concentrations at week 2 (Ctrough). Baseline transaminitis/hyper-bilirubinemia status was explored as a covariate. Baseline transaminitis /hyper-bilirubinemia status was defined as any baseline measure that is higher than the upper limit of normal (grade 1 or higher) of any of the liver transaminases (ALP, ALT, AST, GGT) or bilirubin. Other explored covariates were age, weight, BMI, sex, type of TB (XDR-TB vs MDR-TB), CD4 count, and HIV status. The analysis dataset included a subset of the safety population who had Ctrough data for all the four compounds at week 2 (n = 84). Baseline CD4 count was missing in 27 of 40 HIV non-infected subjects and in 2 of 44 HIV infected subjects. The missing CD4 counts were imputed by median values of respective patient populations (694 cells/mL and 375 cells/mL for non-infected and infected respectively). The following sections provide results from the reviewer's exposure-vs hepatic disorder analyses.

1.1.3.5.1. Correlation between bedaquiline and pretomanid exposure

The reviewer performed collinearity analysis to determine if bedaquiline or its metabolite can be potential confounders of pretomanid -vs-hepatic disorder relationship. Bedaquiline is known to cause elevation of liver transaminases. The results indicated weak correlation between bedaquiline Ctrough at week 2 with pretomanid C_{trough} at week 2 (Pearson correlation = 0.21, p-value = 0.049). However, correlation between bedaquiline Ctrough and pretomanid C_{avg} was marginally significant (Pearson correlation = 0.18, p-value = 0.092). The results indicated no correlation between M2 C_{trough} and pretomanid C_{trough} and C_{avg}. Linezolid C_{trough} had moderate correlation with pretomanid C_{trough} (Pearson correlation = 0.51, p-value = 8.298577e-07)

1.1.3.5.2. Exposure-vs-hepatic-disorder

Among the 84 subjects, 38 (45%) had baseline transaminitis/hyperbilirubinemia and 29 (34%) had hepatic disorder (SMQ) at any time during treatment. Univariate logistic regression

analysis identified pretomanid and bedaquiline as statistically significant predictors of hepatic disorders individually. Other statistically significant univariate predictors were baseline body weight, BMI and CD4 count. The first multivariate logistic regression analysis included pretomanid, bedaquiline, weight and CD4 count. In this model pretomanid and bedaquiline were no-longer statistically significant predictors of hepatic disorder and body weight had marginal significance. The second multivariate logistic regression excluded body weight from the model because of possible collinearity with drug exposures. In this final model pretomanid was not a predictor but bedaquiline and baseline CD4 count had marginal statistical significance. Table 15-5-13 shows results from the reviewer's univariate and multivariate analysis.

Table 15-5-13. Results from Univariate and Multivariate Logistic Regression Analysis of Predictors of Hepatic Disorder (SMQ)

		Univariate		***Multivariate (Including body weight)***		***Multivariate (Excluding body weight)***	
Characteristics	*Predictors*	*Coefficient Estimate*	*P-value*	*Coefficient Estimate*	*P-value*	*Coefficient Estimate*	*P-value*
Pretomanid	*(Intercept)*	*-1.617*	*0.002*				
	Cavg (ug/mL)	*0.317*	***0.038***	*0.151*	*0.369*	*0.221*	*0.192*
Pretomanid	*(Intercept)*	*-1.286*	*0.008*				
	Ctrough (ug/mL)	*0.000*	*0.126*				
Bedaquiline	*(Intercept)*	*-1.554*	*0.003*				
	Ctrough (ug/mL)	*0.615*	***0.048***	*0.298*	*0.425*	*0.584*	***0.082***
Bedaquiline metabolite	*(Intercept)*	*-1.158*	*0.008*				
	Ctrough (ug/mL)	*0.002*	*0.153*				
Linezolid	*(Intercept)*	*-0.919*	*0.013*				
	Ctrough (ug/mL)	*0.038*	*0.314*				
Baseline transaminitis/ hyperbilirubinemia disorder	*No (Reference)*	*-0.932*	*0.004*				
	Yes	*0.613*	*0.186*				
HIV status	*Negative (Reference)*	*-0.969*	*0.006*				
	Positive	*0.602*	*0.199*				
Sex	*Female (Reference)*	*-0.425*	*0.173*				
	Male	*-0.458*	*0.324*				
Age	*(Intercept)*	*0.083*	*0.925*				
	Age (Years)	*-0.020*	*0.396*				
Baseline weight	*(Intercept)*	*1.785*	*0.079*				
	Weight (Kg)	*-0.044*	***0.017***	*-0.036*	***0.090***		
Body-mass-index	*(Intercept)*	*2.080*	*0.093*				
	BMI (Kg/m^2)	*-0.135*	***0.030***				

		Univariate		***Multivariate (Including body weight)***		***Multivariate (Excluding body weight)***	
Baseline CD4 count	*(Intercept)*	*0.473*	*0.411*				
	CD4 count (Cells/mL)	*-0.002*	***0.041***	*-0.002*	***0.045***	*-0.002*	***0.071***
Kanorfsky score	*60 (Reference)*	*15.566*	*0.991*				
	70	*-15.566*	*0.991*				
	80	*-16.259*	*0.991*				
	90	*-16.426*	*0.991*				
	100	*-16.819*	*0.991*				
Type of TB	*MDR Intolerant (Reference)*	*-0.588*	*0.292*				
	MDR Non-Responsive	*0.077*	*0.919*				
	XDR	*-0.105*	*0.867*				

1.1.3.5.3. Exposure-vs- Hematopoietic-cytopenias (SMQ)

Linezolid is the drug in the BPaL regimen that is known to cause myelosuppression. However, the applicant did not evaluate predictors of Hematopoietic-cytopenias (SMQ) among patients exposed to linezolid in the Nix-TB study. According to SMQ the following adverse events terms were used to identify subjects with Hematopoietic-cytopenias at any time during treatment: "ANAEMIA", "NEUTROPAENIA", THROMBOCYTOPAENIA", "LEUCOPENIA", "ABSOLUTE LYMPHOCYTOPAENIA", "NEUTROPENIA", "MYELOSUPPRESSION", "WORSENING ANAEMIA", "SYMPTOMATIC ANAEMIA", "LOW PLATELETS/ THROMBOCYTOPENIA", "PANCYTOPAENIA", "BICYTOPENIA", "SEVERE SYMPTOMATIC ANAEMIA", "THROMBOCYTOPENIA", "ANEMIA", "WORSENED ANAEMIA".

The reviewer assessed different demographic, clinical, and drugs exposures to determine predictors of Hematopoietic-cytopenias (SMQ). Table 15-5-14 shows results from univariate and multivariate logistic regression analysis. The univariate analysis identified statistically marginal influence of pretomanid, type of TB infection (XDR or MDR), and sex on probability of hematopoietic-cytopenia. Linezolid was not identified in both univariate and multivariate analysis. In a multivariate analysis, only XDR-TB was associated with Hematopoietic-cytopenias (SMQ) with marginal statistical significance. The results show that patients with XDR-TB were 3 times more likely to develop Hematopoietic-cytopenias compared to patients with treatment intolerant MDR.

Table 15-5-14. Results from Univariate and Multivariate Logistic Regression Analysis of Predictors of Hematopoietic-cytopenias (SMQ)

		Univariate		***Multivariate (Including body weight)***	
Characteristics	*Predictors*	*Coefficient Estimate*	*P-value*	*Coefficient Estimate*	*P-value*
Pretomanid	*(Intercept)*	*-0.89*	*0.08*	*-1.59*	*0.11*
	Cavg (ug/mL)	*0.30*	***0.06***	*0.29*	*0.10*
Pretomanid	*(Intercept)*	*-0.83*	*0.10*		
	Ctrough (ug/mL)	*0.36*	***0.07***		
Bedaquiline	*(Intercept)*	*0.09*	*0.84*		
	Ctrough (ug/mL)	*-0.06*	*0.82*		
Bedaquiline metabolite	*(Intercept)*	*0.03*	*0.95*		
	Ctrough (ug/mL)	*-0.11*	*0.94*		
Linezolid	*(Intercept)*	*-0.32*	*0.42*		
	Ctrough (ug/mL)	*0.00*	*0.30*		
Baseline cyotepenia	*No (Reference)*	*-0.06*	*0.86*		
	Yes	*0.10*	*0.82*		
HIV status	*Negative (Reference)*	*-0.20*	*0.53*		
	Positive	*0.38*	*0.38*		
Sex	*Female (Reference)*	*0.33*	*0.29*	*-0.30*	*0.56*
	Male	*-0.67*	*0.13*		
Age	*(Intercept)*	*0.99*	*0.24*		
	Age (Years)	*-0.03*	*0.23*		
Baseline weight	*(Intercept)*	*0.94*	*0.29*		
	Weight (Kg)	*-0.02*	*0.28*		
Body-mass-index	*(Intercept)*	*0.58*	*0.55*		
	BMI (Kg/m^2)	*-0.03*	*0.56*		
Baseline CD4 count	*(Intercept)*	*0.30*	*0.57*		
	CD4 count (Cells/mL)	*0.00*	*0.54*		
Kanorfsky score	*60 (Reference)*	*-15.57*	*0.99*		
	70	*16.08*	*0.99*		
	80	*15.28*	*0.99*		
	90	*15.62*	*0.99*		
	100	*15.34*	*0.99*		
Type of TB	*MDR Intolerant (Reference)*	*-0.92*	*0.12*		
	MDR Non-Responsive	*0.41*	*0.61*	*0.31*	*0.71*
	XDR	*1.29*	***0.05***	*1.26*	***0.07***

1.1.3.5.4. Exposure-vs- gastro-intestinal disorders (SMQ)

Pretomanid was identified to be associated with gastro-intestinal (GIT) disorders in the applicant's exposure-vs-safety analyses. However, the applicant did not investigate other factors that might be associated with gastro-intestinal disorders. According to SMQ the following adverse events terms were used to identify subjects with GIT disorders at any time during treatment: "VOMITING", "INTERMITTENT NAUSEA", "NAUSEA", "DIARRHOEA", "INTERMITTENT VOMITING", "VOMITING INTERMITTENTLY", "NAUSEA (INTERMITTENT)", "BILE STAINED VOMITING", "DIARRHOEA- INTERMITTENTLY ", "INTERMITTENT DIARRHOEA", "WORSENING VOMMITING".

The reviewer assessed different demographic, clinical, and drug exposures characteristics to determine predictors of gastro-intestinal disorders. Table 15-5-15 shows results from univariate and multivariate logistic regression analysis. The univariate analysis identified pretomanid, bedaquiline, linezolid, baseline body weight and type of TB to be statistically significant predictors of GIT disorders. However, a multivariate analysis determined pretomanid, and type of TB to be the statistically significant predictors of GIT disorders. The likelihood of GIT disorders was 1.6 times higher for each 1 ug/mL increase in pretomanid exposure. Patients with XDR-TB and non-responsive MDR-TB were about 9 and 16 times more likely to report GIT disorders respectively, compared to patients with treatment intolerant MDR-TB. The predicted probabilities of GIT disorders in patients with typical steady state exposure of 2.4 ug/mL were 7%, 44%, and 59% in patients with treatment intolerant MDR-TB, Non-responsive TB and XDR-TB respectively. The observed proportions of GIT disorders in these patient groups, regardless of pretomanid exposure were 14%, 56% and 50% for with treatment intolerant MDR-TB, Non-responsive TB and XDR-TB respectively.

Table 15-5-15. Results from Univariate and Multivariate Logistic Regression Analysis of Predictors of GIT Disorders

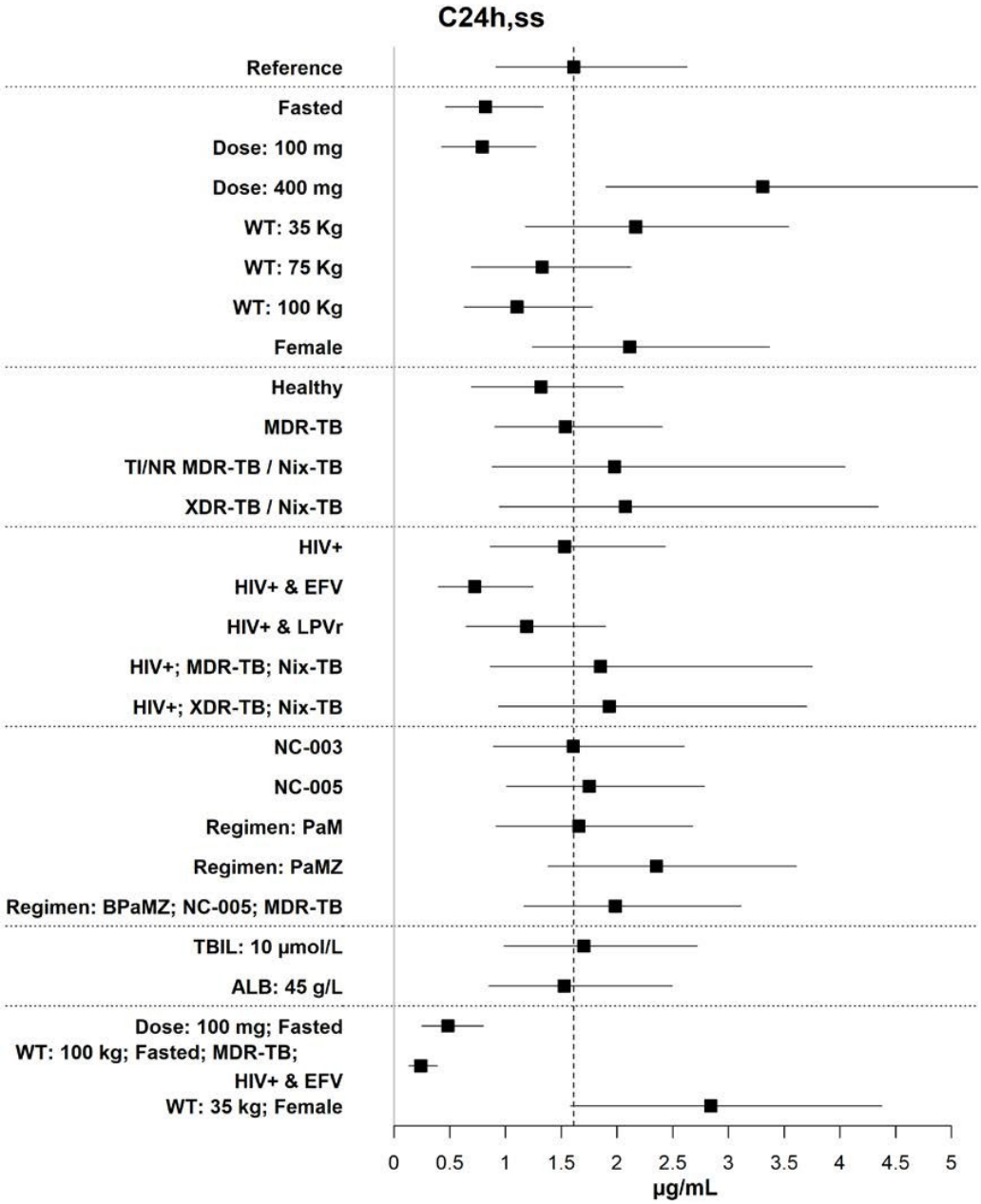
		Univariate		***Multivariate (Including body weight)***	
Characteristics	*Predictors*	*Coefficient Estimate*	*P-value*	*Coefficient Estimate*	*P-value*
Pretomanid	*(Intercept)*	*-1.605*	*0.004*	*-3.29*	*0.15*
	Cavg (ug/mL)	*0.478*	***0.007***	*0.48*	***0.05***
Pretomanid	*(Intercept)*	*-1.619*	*0.005*		
	Ctrough (ug/mL)	*0.616*	***0.008***		
Bedaquiline	*(Intercept)*	*-1.180*	*0.022*		
	Ctrough (ug/mL)	*0.685*	***0.035***	*0.36*	*0.42*
Bedaquiline metabolite	*(Intercept)*	*-0.083*	*0.836*		
	Ctrough (ug/mL)	*-0.452*	*0.748*		
Linezolid	*(Intercept)*	*-0.769*	*0.060*		
	Ctrough (ug/mL)	*0.000*	***0.059***	*0.03*	*0.46*
HIV status	*Negative (Reference)*	*-0.201*	*0.528*		

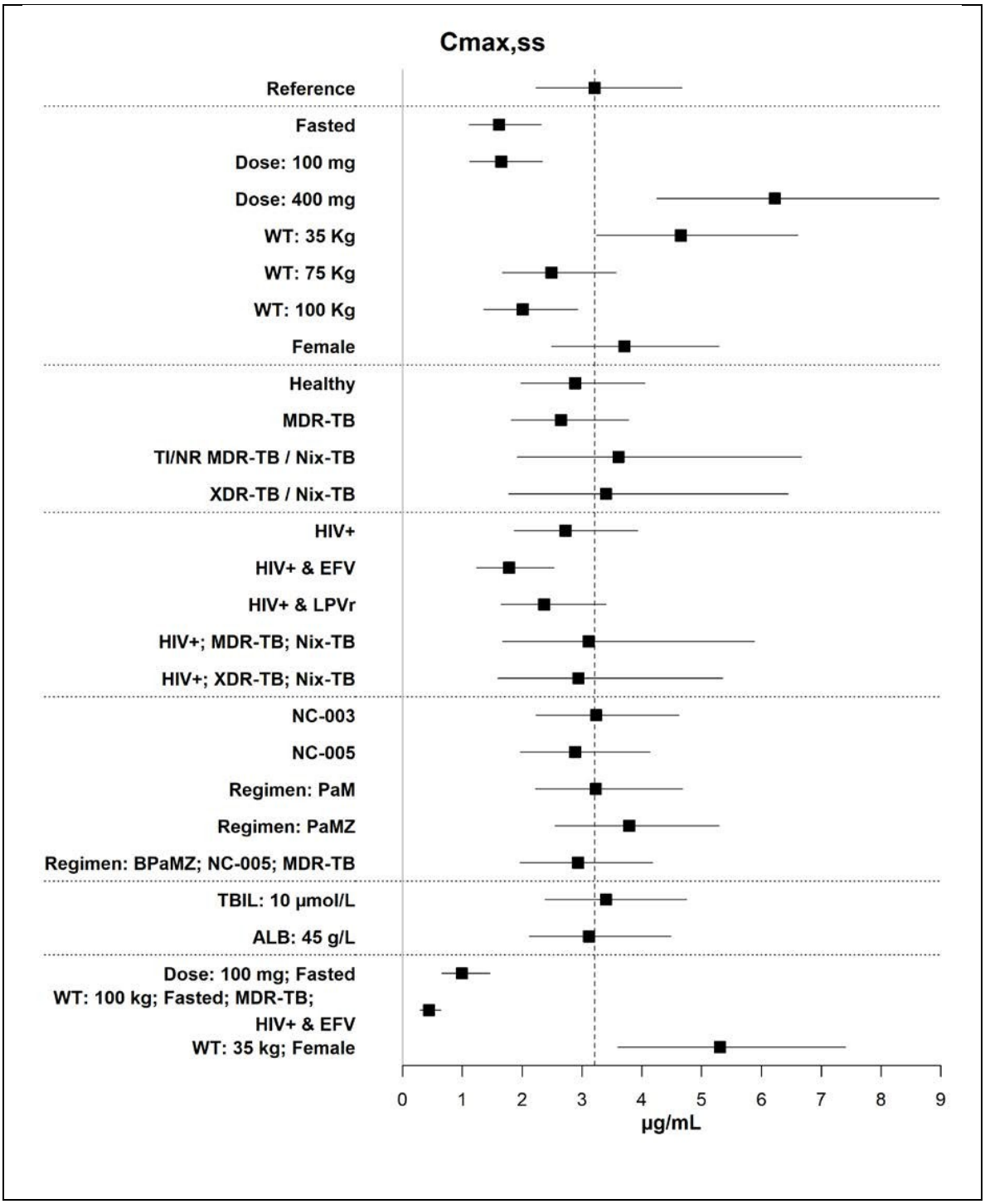
		Univariate		***Multivariate (Including body weight)***	
	Positive	*0.018*	*0.967*		
Sex	*Female (Reference)*	*0.140*	*0.648*	*-0.01*	*0.98*
	Male	*-0.690*	*0.122*		
Age	*(Intercept)*	*0.434*	*0.603*		
	Age (Years)	*-0.017*	*0.439*		
Baseline weight	*(Intercept)*	*2.244*	*0.022*		
	Weight (Kg)	*-0.043*	***0.012***	*-0.02*	*0.45*
Body-mass-index	*(Intercept)*	*1.308*	*0.205*		
	BMI (Kg/m^2)	*-0.072*	*0.146*		
Baseline CD4 count	*(Intercept)*	*-0.431*	*0.425*		
	CD4 count (Cells/mL)	*0.000*	*0.626*		
Kanorfsky score	*60 (Reference)*	*-15.566*	*0.991*		
	70	*16.077*	*0.991*		
	80	*15.661*	*0.991*		
	90	*15.183*	*0.992*		
	100	*14.313*	*0.992*		
Type of TB	*MDR Intolerant (Reference)*	*-1.792*	*0.019*		
	MDR Non-Responsive	*2.043*	***0.026***	*2.78*	***0.01***
	XDR	*1.792*	***0.027***	*2.23*	***0.02***

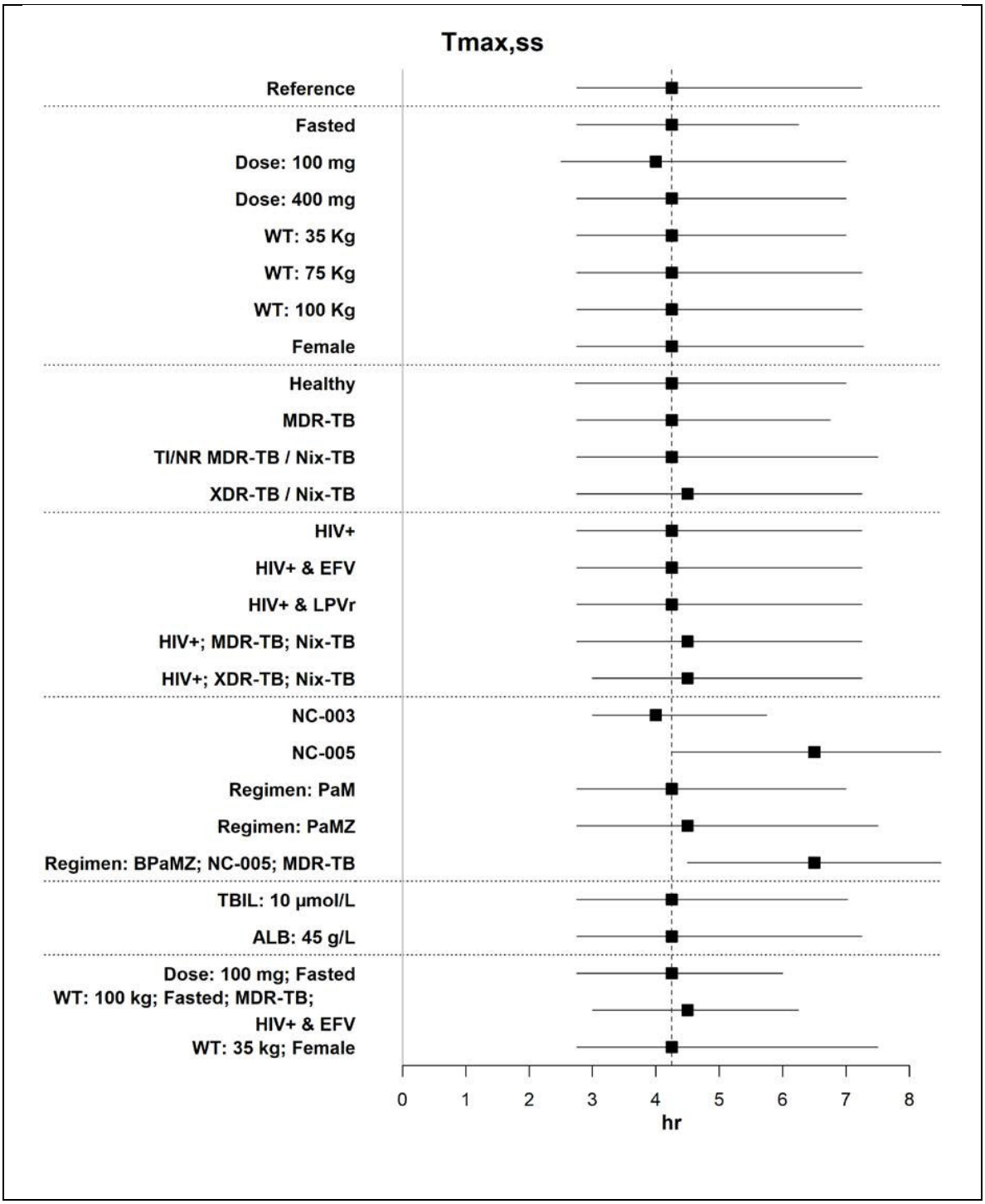
1.1.4. Appendix

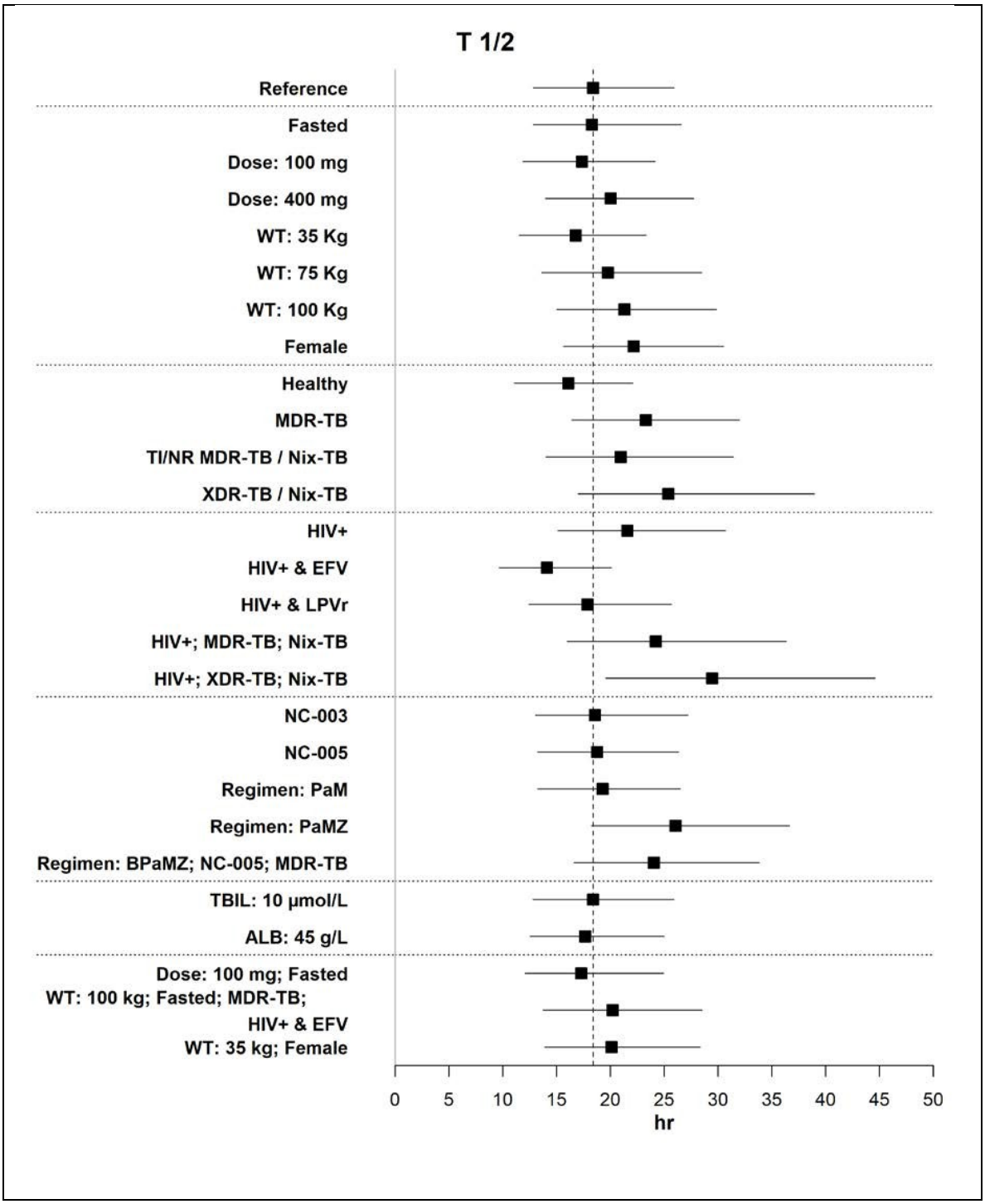
1.1.4.2. Comparisons of different PK parameters between a reference subject and subjects with different covariate combinations

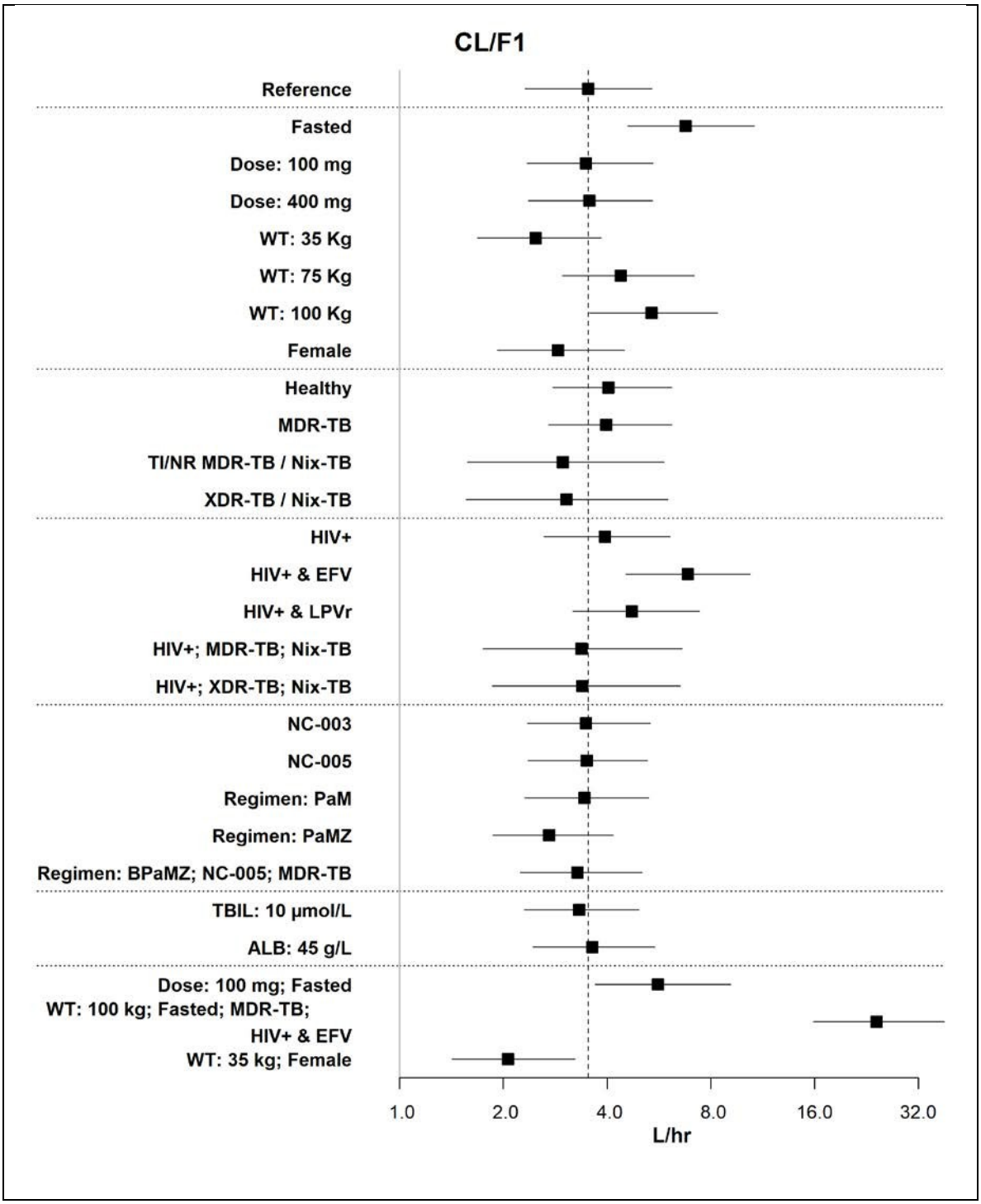
Figure 15-5-14. Forest Plots for C24_ss, Cmax_ss, tmax_ss, CL/F1, V2/F1, F1, and MTT+1/KA

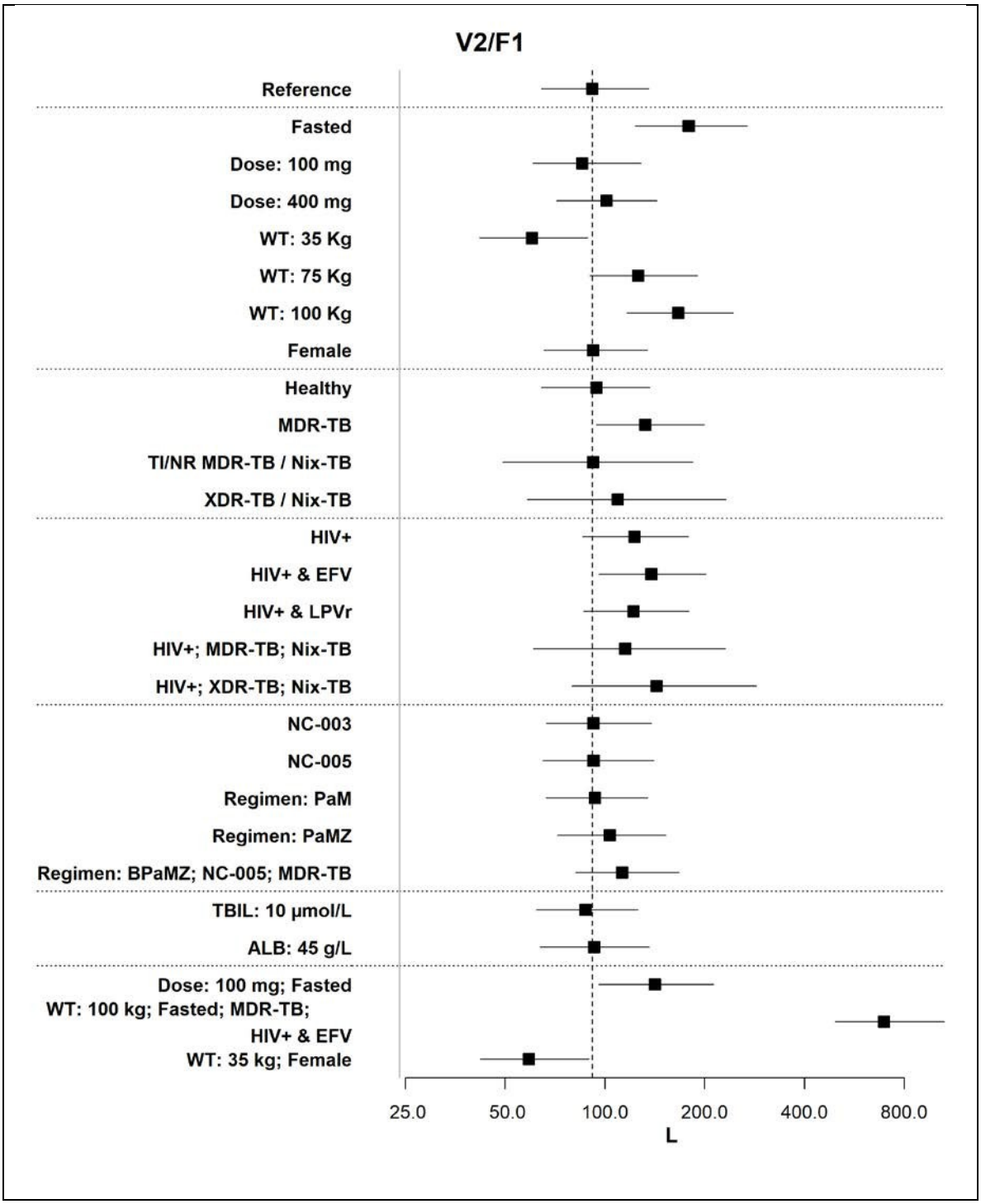


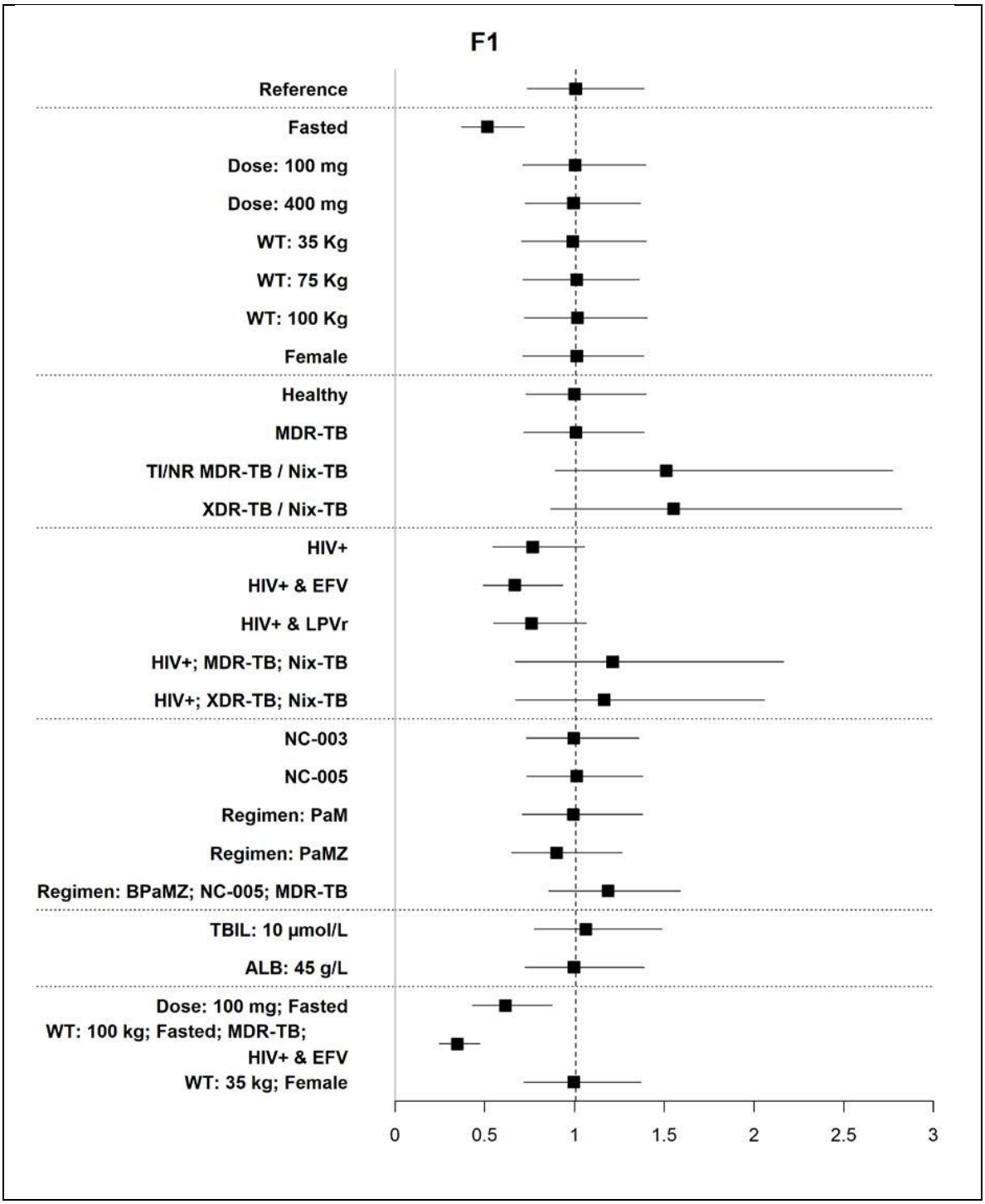

Cmax,ss
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB;
HIV+ & EFV
WT: 35 kg; Female
0
1
2
3
4
5
6
7
8
9
µg/mL

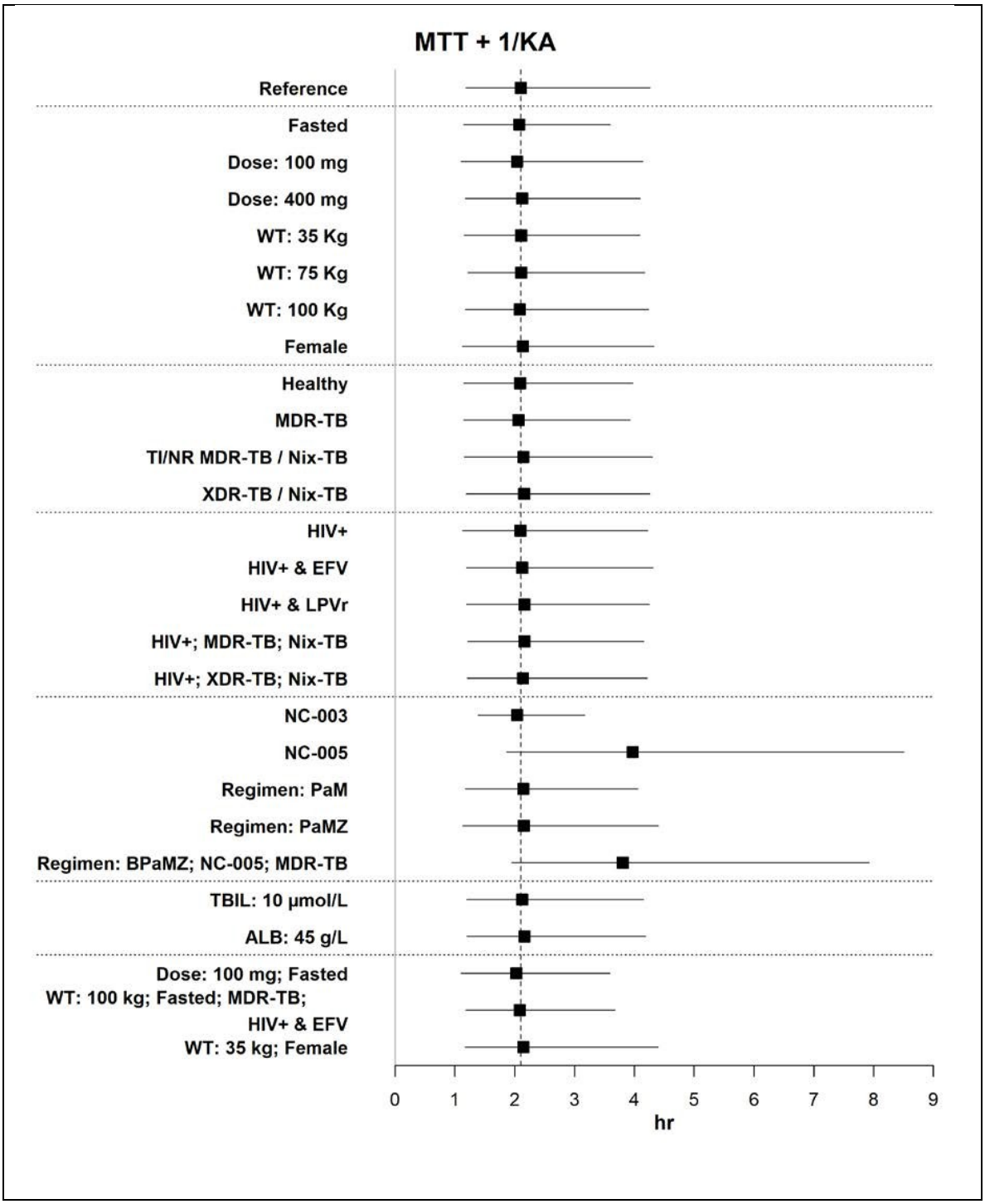

Tmax,ss
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB;
HIV+ & EFV
WT: 35 kg; Female
0
1
2
3
4
5
6
7
8
hr


T 1/2
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB;
HIV+ & EFV
WT: 35 kg; Female
0
5
10
15
20
25
30
35
40
45
50
hr


CL/F1
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB;
HIV+ & EFV
WT: 35 kg; Female
1.0
2.0
4.0
8.0
16.0
32.0
L/hr


V2/F1
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB;
HIV+ & EFV
WT: 35 kg; Female
25.0
50.0
100.0
200.0
400.0
800.0
L


F1
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV
WT: 35 kg; Female
0
0.5
1
1.5
2
2.5
3


MTT + 1/KA
Reference
Fasted
Dose: 100 mg
Dose: 400 mg
WT: 35 Kg
WT: 75 Kg
WT: 100 Kg
Female
Healthy
MDR-TB
TI/NR MDR-TB / Nix-TB
XDR-TB / Nix-TB
HIV+
HIV+ & EFV
HIV+ & LPVr
HIV+; MDR-TB; Nix-TB
HIV+; XDR-TB; Nix-TB
NC-003
NC-005
Regimen: PaM
Regimen: PaMZ
Regimen: BPaMZ; NC-005; MDR-TB
TBIL: 10 µmol/L
ALB: 45 g/L
Dose: 100 mg; Fasted
WT: 100 kg; Fasted; MDR-TB;
HIV+ & EFV
WT: 35 kg; Female
0
1
2
3
4
5
6
7
8
9
hr

Cavg,ss (µg/mL)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	2.37	1.54	3.6	2.5	0.82	2.37	32.8
Fasted	1.24	0.781	1.82	1.28	0.413	1.21	32.3
Dose: 100 mg	1.2	0.765	1.78	1.25	0.403	1.19	32.2
Dose: 400 mg	4.7	3.08	7.04	4.95	1.61	4.69	32.7
WT: 35 Kg	3.36	2.17	4.96	3.48	1.13	3.31	32.4
WT: 75 Kg	1.9	1.16	2.81	1.95	0.648	1.85	33.1
WT: 100 Kg	1.55	0.995	2.34	1.6	0.523	1.52	32.6
Female	2.89	1.86	4.33	3	0.962	2.85	32
Healthy	2.06	1.35	2.99	2.13	0.7	2.02	32.8
MDR-TB	2.1	1.35	3.08	2.17	0.699	2.06	32.2
TI/NR MDR-TB /Nix-TB	2.8	1.42	5.3	3.12	1.66	2.74	53.3
XDR-TB / Nix-TB	2.73	1.39	5.33	3.14	1.72	2.73	54.8
HIV+	2.11	1.37	3.17	2.21	0.71	2.1	32.1
HIV+ & EFV	1.21	0.8	1.84	1.28	0.423	1.21	33.1
HIV+ & LPVr	1.76	1.12	2.62	1.84	0.603	1.74	32.8
HIV+; MDR-TB;Nix-TB	2.47	1.26	4.77	2.83	1.51	2.47	53.2
HIV+; XDR-TB;Nix-TB	2.46	1.28	4.49	2.73	1.41	2.42	51.5
NC-003	2.4	1.56	3.55	2.5	0.81	2.37	32.5
NC-005	2.38	1.59	3.53	2.51	0.803	2.38	32
Regimen: PaM	2.42	1.57	3.61	2.52	0.829	2.39	32.9
Regimen: PaMZ	3.07	2	4.47	3.17	1.01	3.01	31.8
Regimen: BPaMZ; NC-005; MDR-TB	2.54	1.65	3.72	2.64	0.853	2.5	32.4
TBIL: 10 µmol/L	2.51	1.68	3.62	2.63	0.823	2.5	31.3
ALB: 45 g/L	2.3	1.51	3.42	2.39	0.789	2.27	32.9
Dose: 100 mg; Fasted	0.742	0.457	1.13	0.775	0.279	0.728	36
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	0.344	0.219	0.524	0.358	0.12	0.339	33.5
WT: 35 kg; Female	4.04	2.58	5.87	4.16	1.33	3.94	32
C24h,ss (µg/mL)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	1.61	0.915	2.63	1.71	0.697	1.57	40.7
Fasted	0.822	0.462	1.34	0.866	0.348	0.791	40.2
Dose: 100 mg	0.791	0.427	1.27	0.829	0.337	0.76	40.6
Dose: 400 mg	3.31	1.9	5.23	3.49	1.39	3.21	39.9
WT: 35 Kg	2.17	1.18	3.54	2.28	0.96	2.07	42.1
WT: 75 Kg	1.33	0.699	2.13	1.38	0.562	1.26	40.8
WT: 100 Kg	1.1	0.629	1.78	1.16	0.454	1.07	39.2
Female	2.12	1.24	3.37	2.21	0.84	2.05	38.1
Healthy	1.32	0.696	2.06	1.37	0.577	1.24	42.3

MDR-TB	1.54	0.907	2.4	1.61	0.611	1.5	37.9
TI/NR MDR-TB /Nix-TB	1.98	0.881	4.04	2.25	1.34	1.85	59.7
XDR-TB / Nix-TB	2.08	0.945	4.34	2.4	1.45	1.97	60.5
HIV+	1.53	0.862	2.43	1.6	0.619	1.48	38.6
HIV+ & EFV	0.723	0.396	1.25	0.776	0.349	0.696	45
HIV+ & LPVr	1.19	0.649	1.9	1.25	0.51	1.14	40.9
HIV+; MDR-TB;Nix-TB	1.85	0.863	3.75	2.13	1.25	1.77	58.6
HIV+; XDR-TB;Nix-TB	1.93	0.938	3.7	2.16	1.23	1.87	56.7
NC-003	1.61	0.894	2.61	1.7	0.687	1.56	40.5
NC-005	1.75	1.01	2.78	1.86	0.73	1.71	39.3
Regimen: PaM	1.66	0.913	2.68	1.75	0.714	1.59	40.9
Regimen: PaMZ	2.35	1.38	3.61	2.44	0.901	2.28	36.9
Regimen: BPaMZ; NC-005; MDR-TB	1.99	1.16	3.11	2.09	0.796	1.94	38.1
TBIL: 10 µmol/L	1.7	0.988	2.72	1.79	0.71	1.66	39.6
ALB: 45 g/L	1.53	0.849	2.5	1.61	0.663	1.47	41.1
Dose: 100 mg; Fasted	0.484	0.252	0.804	0.513	0.232	0.463	45.1
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	0.239	0.132	0.392	0.253	0.104	0.231	41
WT: 35 kg; Female	2.84	1.58	4.38	2.93	1.14	2.7	38.8
Cmax,ss (µg/mL)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	3.21	2.23	4.67	3.34	0.981	3.2	29.4
Fasted	1.61	1.12	2.32	1.67	0.479	1.6	28.7
Dose: 100 mg	1.65	1.12	2.34	1.71	0.487	1.64	28.5
Dose: 400 mg	6.23	4.25	8.96	6.46	1.88	6.21	29.1
WT: 35 Kg	4.65	3.24	6.61	4.79	1.35	4.61	28.2
WT: 75 Kg	2.49	1.67	3.57	2.56	0.747	2.45	29.2
WT: 100 Kg	2.01	1.36	2.93	2.06	0.603	1.98	29.2
Female	3.71	2.49	5.29	3.82	1.11	3.67	28.9
Healthy	2.88	1.98	4.05	2.98	0.861	2.86	28.9
MDR-TB	2.65	1.82	3.78	2.75	0.801	2.64	29.2
TI/NR MDR-TB /Nix-TB	3.61	1.92	6.67	3.99	2.03	3.46	50.9
XDR-TB / Nix-TB	3.4	1.78	6.45	3.86	2.02	3.33	52.4
HIV+	2.73	1.87	3.93	2.83	0.819	2.72	28.9
HIV+ & EFV	1.78	1.24	2.53	1.84	0.524	1.77	28.4
HIV+ & LPVr	2.37	1.65	3.4	2.47	0.716	2.37	29
HIV+; MDR-TB;Nix-TB	3.11	1.67	5.89	3.52	1.78	3.07	50.5
HIV+; XDR-TB;Nix-TB	**2.94**	**1.59**	**5.35**	**3.26**	**1.6**	**2.92**	**49.1**
NC-003	**3.24**	**2.23**	**4.62**	**3.35**	**0.953**	**3.22**	**28.5**
NC-005	**2.88**	**1.97**	**4.13**	**2.98**	**0.871**	**2.85**	**29.3**
Regimen: PaM	**3.23**	**2.22**	**4.69**	**3.34**	**0.962**	**3.21**	**28.8**
Regimen: PaMZ	**3.79**	**2.55**	**5.29**	**3.89**	**1.13**	**3.73**	**29.1**
Regimen: BPaMZ; NC-005; MDR-TB	**2.93**	**1.97**	**4.18**	**3.02**	**0.896**	**2.89**	**29.7**

TBIL: 10 µmol/L	**3.4**	**2.38**	**4.75**	**3.51**	**0.968**	**3.38**	**27.5**
ALB: 45 g/L	**3.12**	**2.12**	**4.49**	**3.23**	**0.945**	**3.1**	**29.3**
Dose: 100 mg; Fasted	**0.993**	**0.658**	**1.46**	**1.03**	**0.328**	**0.981**	**31.9**
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	**0.44**	**0.298**	**0.643**	**0.457**	**0.135**	**0.438**	**29.6**
WT: 35 kg; Female	**5.3**	**3.6**	**7.41**	**5.43**	**1.56**	**5.21**	**28.7**
Tmax,ss (hr)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	4.25	2.75	7.25	4.71	2.07	4.34	43.9
Fasted	4.25	2.75	6.25	4.46	1.31	4.27	29.4
Dose: 100 mg	4	2.5	7	4.54	1.96	4.19	43.2
Dose: 400 mg	4.25	2.75	7	4.73	1.96	4.39	41.4
WT: 35 Kg	4.25	2.75	7	4.62	2.03	4.27	44
WT: 75 Kg	4.25	2.75	7.25	4.68	1.88	4.36	40.2
WT: 100 Kg	4.25	2.75	7.25	4.7	1.96	4.37	41.7
Female	4.25	2.75	7.28	4.81	2.14	4.42	44.6
Healthy	4.25	2.73	7	4.58	1.93	4.24	42.2
MDR-TB	4.25	2.75	6.75	4.66	1.92	4.32	41.2
TI/NR MDR-TB /Nix-TB	4.25	2.75	7.5	4.8	2.09	4.43	43.5
XDR-TB / Nix-TB	4.5	2.75	7.25	4.8	2.01	4.46	41.8
HIV+	4.25	2.75	7.25	4.75	2.1	4.37	44.1
HIV+ & EFV	4.25	2.75	7.25	4.65	1.99	4.3	42.9
HIV+ & LPVr	4.25	2.75	7.25	4.76	1.96	4.42	41.2
HIV+; MDR-TB; Nix-TB	4.5	2.75	7.25	4.77	1.9	4.44	39.8
HIV+; XDR-TB; Nix-TB	4.5	3	7.25	4.85	2.05	4.5	42.3
NC-003	4	3	5.75	4.28	1.11	4.14	26
NC-005	6.5	4.25	8.5	6.39	1.55	6.19	24.3
Regimen: PaM	4.25	2.75	7	4.67	1.87	4.35	40
Regimen: PaMZ	4.5	2.75	7.5	4.85	2.1	4.47	43.3
Regimen: BPaMZ; NC-005; MDR-TB	6.5	4.5	8.5	6.48	1.51	6.3	23.3
TBIL: 10 µmol/L	4.25	2.75	7.03	4.66	1.83	4.35	39.3
ALB: 45 g/L	4.25	2.75	7.25	4.73	2.04	4.38	43.2
Dose: 100 mg; Fasted	4.25	2.75	6	4.41	1.34	4.21	30.5
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	4.5	3	6.25	4.57	1.39	4.37	30.5
WT: 35 kg; Female	4.25	2.75	7.5	4.78	1.97	4.42	41.3
T 1/2 (hr)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	18.4	12.9	25.9	19.2	6.69	18.4	34.8
Fasted	18.3	12.8	26.6	19.5	11.2	18.4	57.2

Dose: 100 mg	17.3	11.9	24.1	18	5.52	17.2	30.7
Dose: 400 mg	20	14	27.7	20.7	6.88	19.8	33.3
WT: 35 Kg	16.8	11.5	23.3	17.8	12.6	16.6	70.9
WT: 75 Kg	19.8	13.6	28.4	21	8.8	19.8	42
WT: 100 Kg	21.3	15	29.9	22.3	7.15	21.3	32.1
Female	22.2	15.6	30.5	23.2	8.09	22.2	34.8
Healthy	16.1	11.1	22.1	16.7	6.85	15.9	41
MDR-TB	23.3	16.4	32	24.3	8.24	23.3	33.8
TI/NR MDR-TB /	20.9	14	31.4	9200	23800	22.6	2590
Nix-TB				0	00		
XDR-TB / Nix-TB	25.4	17	38.9	2030	31900	27.1	1570
HIV+	21.6	15.1	30.7	22.5	7.24	21.5	32.1
HIV+ & EFV	14.1	9.66	20.1	14.8	5.01	14.1	33.9
HIV+ & LPVr	17.9	12.4	25.7	18.7	6.51	17.8	34.9
HIV+; MDR-TB;	24.2	16	36.3	2270	62800	25.3	2770
Nix-TB				0	0		
HIV+; XDR-TB; Nix-TB	29.4	19.6	44.6	70	945	30.7	1350
NC-003	18.6	13	27.2	20.1	14.8	18.8	73.7
NC-005	18.8	13.2	26.3	19.5	6.44	18.7	33
Regimen: PaM	19.3	13.2	26.5	19.7	6.02	18.8	30.6
Regimen: PaMZ	26.1	18.2	36.6	27.3	8.6	26.2	31.5
Regimen: BPaMZ; NC-005; MDR-TB	24	16.6	33.8	25	7.92	23.9	31.7
TBIL: 10 µmol/L	18.4	12.8	25.9	19.2	6.16	18.4	32.1
ALB: 45 g/L	17.7	12.5	25	18.4	5.96	17.6	32.3
Dose: 100 mg; Fasted	17.3	12.1	24.9	18.2	6.29	17.3	34.6
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	20.2	13.7	28.5	20.9	6.96	20	33.2
WT: 35 kg; Female	20.1	13.9	28.4	20.8	7.04	19.8	33.8
CL/F (L/hr)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	3.52	2.32	5.4	3.71	1.3	3.52	35
Fasted	6.75	4.59	10.7	7.29	2.72	6.88	37.3
Dose: 100 mg	3.47	2.34	5.45	3.71	1.27	3.51	34.2
Dose: 400 mg	3.55	2.37	5.42	3.75	1.3	3.55	34.7
WT: 35 Kg	2.48	1.68	3.85	2.67	0.953	2.52	35.8
WT: 75 Kg	4.38	2.97	7.15	4.79	1.75	4.51	36.6
WT: 100 Kg	5.38	3.56	8.37	5.81	2.1	5.48	36.2
Female	2.88	1.93	4.49	3.09	1.09	2.92	35.3
Healthy	4.04	2.79	6.16	4.36	1.59	4.12	36.5
MDR-TB	3.98	2.71	6.15	4.26	1.47	4.04	34.6
TI/NR MDR-TB /Nix-TB	2.98	1.57	5.87	3.5	2.09	3.04	59.7
XDR-TB / Nix-TB	3.05	1.56	6.02	3.57	2.57	3.05	72

HIV+	3.94	2.63	6.09	4.19	1.42	3.97	33.9
HIV+ & EFV	6.86	4.53	10.4	7.29	2.65	6.88	36.4
HIV+ & LPVr	4.72	3.18	7.42	5.06	1.78	4.78	35.2
HIV+; MDR-TB; Nix-TB	3.37	1.75	6.61	3.9	2.45	3.37	62.9
HIV+; XDR-TB; Nix-TB	3.39	1.86	6.52	3.9	2.43	3.44	62.3
NC-003	3.47	2.35	5.35	3.72	1.29	3.52	34.8
NC-005	3.49	2.36	5.24	3.69	1.28	3.5	34.6
Regimen: PaM	3.44	2.31	5.3	3.71	1.41	3.49	38
Regimen: PaMZ	2.71	1.87	4.16	2.92	1.02	2.77	35.1
Regimen: BPaMZ; NC-005; MDR-TB	3.28	2.24	5.06	3.52	1.26	3.33	35.7
TBIL: 10 µmol/L	3.32	2.3	4.95	3.5	1.18	3.33	33.6
ALB: 45 g/L	3.62	2.44	5.5	3.88	1.4	3.67	35.9
Dose: 100 mg; Fasted	5.61	3.7	9.12	6.11	2.35	5.73	38.4
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	24.2	15.9	38	26.1	9.67	24.6	37
WT: 35 kg; Female	2.06	1.42	3.23	2.24	0.852	2.11	38
V2/F (L)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	91.6	64.4	136	97.7	33.9	93.1	34.7
Fasted	179	123	269	195	108	182	55.6
Dose: 100 mg	85.4	60.7	129	91.5	31.5	87.2	34.4
Dose: 400 mg	101	71.6	143	106	34.6	101	32.7
WT: 35 Kg	60.2	41.9	88.8	64.1	33	60.4	51.5
WT: 75 Kg	126	90	190	136	50.7	129	37.3
WT: 100 Kg	166	117	244	177	59.7	169	33.8
Female	92.1	65.5	135	98.9	43.9	93.7	44.4
Healthy	94.2	64.5	137	99.4	37.2	94.4	37.5
MDR-TB	132	94.2	199	142	49.2	135	34.6
TI/NR MDR-TB / Nix-TB	92.1	49.1	184	10200000	305000000	99.3	2980
XDR-TB / Nix-TB	109	58.4	232	9510	149000	119	1570
HIV+	123	85.6	179	129	43.8	123	33.9
HIV+ & EFV	138	95.9	202	147	54	140	36.7
HIV+ & LPVr	122	86.3	179	129	40.3	123	31.3
HIV+; MDR-TB; Nix-TB	115	60.9	231	116000	303000	123	2600
HIV+; XDR-TB;Nix-TB	143	79.6	287	310	3090	152	997
NC-003	92.4	66.6	138	102	75.2	95.3	73.5
NC-005	92.5	65.1	141	99.2	36.1	94.2	36.3
Regimen: PaM	93.2	66.5	135	98.9	30.5	94.8	30.8
Regimen: PaMZ	104	72	152	109	34.8	105	31.8

Regimen: BPaMZ; NC-005; MDR-TB	113	81.7	168	120	42.1	115	35
TBIL: 10 µmol/L	87.4	62.2	126	91.9	28.2	88.1	30.7
ALB: 45 g/L	92.8	63.8	136	98	35	93.4	35.7
Dose: 100 mg; Fasted	142	95.9	213	151	53.6	143	35.6
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	**695**	**495**	**1060**	**745**	**278**	**709**	**37.3**
WT: 35 kg; Female	**59**	**42.1**	**89.5**	**63.8**	**23.7**	**60.5**	**37.1**
F1							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**Geo-Mean**	**CV%**
Reference	1.01	0.738	1.39	1.04	0.27	1.01	25.9
Fasted	0.514	0.369	0.72	0.536	0.147	0.517	27.4
Dose: 100 mg	1.00	0.712	1.4	1.03	0.27	0.998	26.2
Dose: 400 mg	0.994	0.724	1.37	1.03	0.271	0.996	26.3
WT: 35 Kg	0.992	0.706	1.4	1.03	0.269	0.995	26.1
WT: 75 Kg	1.01	0.712	1.36	1.03	0.258	0.998	25.1
WT: 100 Kg	1.02	0.721	1.4	1.04	0.276	1.01	26.4
Female	1.01	0.713	1.39	1.04	0.262	1	25.3
Healthy	0.999	0.729	1.4	1.04	0.283	1.01	27.1
MDR-TB	1.01	0.717	1.39	1.03	0.268	0.996	26
TI/NR MDR-TB /Nix-TB	1.51	0.892	2.77	1.71	0.815	1.54	47.8
XDR-TB / Nix-TB	1.55	0.867	2.82	1.72	0.836	1.55	48.5
HIV+	0.766	0.545	1.06	0.789	0.209	0.763	26.4
HIV+ & EFV	0.667	0.492	0.936	0.698	0.18	0.676	25.7
HIV+ & LPVr	0.761	0.548	1.07	0.791	0.21	0.765	26.6
HIV+; MDR-TB;Nix-TB	1.21	0.67	2.17	1.34	0.646	1.21	48.1
HIV+; XDR-TB;Nix-TB	1.17	0.671	2.06	1.29	0.59	1.17	45.7
NC-003	0.995	0.73	1.36	1.03	0.254	0.995	24.8
NC-005	1.01	0.732	1.38	1.04	0.272	1.01	26.1
Regimen: PaM	0.992	0.708	1.38	1.02	0.258	0.988	25.3
Regimen: PaMZ	0.9	0.65	1.26	0.932	0.251	0.9	26.9
Regimen: BPaMZ;	1.19	0.856	1.59	1.21	0.297	1.18	24.5
NC-005; MDR-TB							
TBIL: 10 µmol/L	1.06	0.776	1.49	1.1	0.28	1.07	25.3
ALB: 45 g/L	0.996	0.724	1.39	1.04	0.27	1.01	26
Dose: 100 mg; Fasted	0.616	0.432	0.874	0.641	0.187	0.616	29.2
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	0.346	0.247	0.473	0.356	0.0942	0.344	26.5
WT: 35 kg; Female	0.996	0.717	1.37	1.03	0.268	0.997	26
MTT + 1/KA (hr)							
	Median	**10th %tile**	**90th %tile**	**Mean**	**SD**	**GeoMean**	**CV%**
Reference	2.1	1.18	4.27	2.53	1.7	2.19	67.2
Fasted	2.08	1.15	3.6	2.26	1.05	2.05	46.4

Dose: 100 mg	2.04	1.1	4.14	2.42	1.48	2.1	61.2
Dose: 400 mg	2.13	1.18	4.1	2.5	1.47	2.2	58.8
WT: 35 Kg	2.11	1.15	4.09	2.49	1.76	2.16	70.6
WT: 75 Kg	2.1	1.22	4.17	2.47	1.38	2.18	55.7
WT: 100 Kg	2.08	1.18	4.24	2.47	1.48	2.17	59.9
Female	2.14	1.13	4.32	2.56	1.67	2.2	65.3
Healthy	2.09	1.15	3.98	2.46	1.52	2.15	62
MDR-TB	2.06	1.15	3.93	2.43	1.39	2.13	57.4
TI/NR MDR-TB /Nix-TB	2.14	1.16	4.3	2.55	1.61	2.21	62.9
XDR-TB / Nix-TB	2.15	1.19	4.26	2.49	1.41	2.2	56.4
HIV+	2.1	1.13	4.23	2.52	1.61	2.17	63.8
HIV+ & EFV	2.12	1.19	4.31	2.55	1.58	2.22	62.2
HIV+ & LPVr	2.16	1.19	4.25	2.55	1.53	2.24	59.8
HIV+; MDR-TB;Nix-TB	2.16	1.22	4.16	2.49	1.37	2.19	55.3
HIV+; XDR-TB;Nix-TB	2.14	1.21	4.22	2.52	1.52	2.2	60.3
NC-003	2.04	1.39	3.18	2.18	0.752	2.07	34.4
NC-005	3.97	1.87	8.51	4.64	2.8	3.96	60.2
Regimen: PaM	2.15	1.18	4.06	2.47	1.38	2.18	55.9
Regimen: PaMZ	2.15	1.13	4.4	2.55	1.54	2.2	60.5
Regimen: BPaMZ; NC-005; MDR-TB	3.81	1.95	7.92	4.54	2.75	3.9	60.7
TBIL: 10 µmol/L	2.13	1.2	4.15	2.47	1.34	2.19	54.4
ALB: 45 g/L	2.16	1.2	4.19	2.54	1.61	2.21	63.5
Dose: 100 mg; Fasted	2.03	1.1	3.6	2.25	1.08	2.04	47.8
WT: 100 kg; Fasted; MDR-TB; HIV+ & EFV	2.08	1.18	3.68	2.33	1.18	2.1	50.6
WT: 35 kg; Female	**2.14**	**1.17**	**4.4**	**2.53**	**1.45**	**2.21**	**57.2**

15.3.2. Individual Study Reviews

Summary of Bioanalytical Method Validation and Performance
Validated LC/MS/MS (liquid chromatography with tandem mass spectroscopy) methods were used for quantification of pretomanid in human plasma and urine. The analytical method validation and performance were deemed to be acceptable.

Dilution integrity was verified within each clinical pharmacology study when sample dilutions were performed. The sample preparation, stability, analysis accuracy, and precision in each clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and are deemed to be acceptable.

The same was also verified for bedaquiline and linezolid and their relevant bioanalytical methods were also deemed to be acceptable to the review team.

Reference ID: 4476823

Study Number	Study Title
CL-001	Single Ascending Dose Study
CL-002	Multiple Ascending Dose Study
CL 009	Food Effect Study
CL-008	PA-824 Mass balance study
CL-006	Pretomanid (PA-824) and Midazolam Interaction Study
Study A5306	PA-824 drug interaction study with Efavirenz, Ritonavir-Boosted Lopinavir, or Rifampin
CL-007	Early Bactericidal Activity
CL-010	Early Bactericidal Activity
	In vitro Studies

CL-001: Single Ascending Dose Study
A double-blind, placebo-controlled, randomized, single ascending dose study to evaluate the safety, tolerability, and PK of pretomanid in healthy adult male subjects. A total of 53 subjects were enrolled, including 40 who received a single oral dose of pretomanid (50, 250, 500, 750, 1000, 1250, or 1500 mg) and 13 who received placebo. All study treatments were taken following an overnight fast. PK blood samples were obtained for up to 36 hours and at 144 hours during a follow up visit on Day 7 after dosing of pretomanid.

PK results and conclusions: Table 1 summarizes the PK parameter values following single oral pretomanid doses of 50 to 1500 mg.

Reference ID: 4476823

Table 1. Pharmacokinetic Parameters Following Single Oral Dose of Pretomanid in Healthy Adult Male Subjects

Pretomanid Dose	Subjects (N)	Arithmetic Mean (SD)						
		C_{max} (µg/mL)	t_{max} † (hr)	$t_{½}$ ‡ (hr)	AUC_t (µg·hr/mL)	AUC_{∞} ‡ (µg·hr/mL)	CL/F ‡ (L/hr)	Vd/F ‡ (L)
50 mg	4	0.3 (0.12)	5.0 (5, 12)	15.2 (3.04)	5.5 (2.44)	7.5 (3.94)	8.5 (4.67)	173 (73.1)
250 mg	6	1.2 (0.25)	4.0 (2, 5)	14.0 (2.68)	22.0 (4.08)	27.0 (4.31)	9.5 (1.87)	195 (72.1)
500 mg	6	1.6 (0.30)	5.0 (3, 6)	13.5 (1.58)	33.2 (6.60)	41.5 (9.41)	12.6 (3.17)	241 (40.0)
750 mg	6	2.0 (0.46)	5.0 (2, 8)	16.1 (4.45)	45.3 (12.77)	61.4 (19.46)	13.2 (3.90)	299 (93.7)
1000 mg	6	2.8 (0.57)	5.0 (2, 16)	20.0 (3.32)	67.6 (14.40)	101.8 (25.33)	10.4 (2.59)	294 (65.5)
1250 mg	6	2.9 (0.39)	4.0 (3, 12)	18.1 (3.53)	69.4 (11.94)	99.2 (20.98)	13.1 (3.18)	337 (67.9)
1500 mg	6	2.9 (0.49)	4.5 (3, 12)	15.6 (3.07)	73.7 (16.45)	101.2 (28.23)	15.9 (4.78)	346 (79.5)

C_{max} = peak exposure; t_{max} = time to peak exposure; $t_{½}$ = half-life; AUC_t = area under the plasma concentration-time curve from time zero up to last measurable concentration; AUC_{∞} = area under plasma concentration-time curve from time zero to infinity; CL/F = total body clearance after oral dosing; Vd/F = volume of distribution after oral dosing; ‡ = The estimates of $t_{½}$, AUC_{∞}, CL/F, and Vd/F are not reliable, since adequate PK sampling was not performed after the 36 hours post dose and in many subjects the calculated AUC extrapolated was greater than 20 %; SD = standard deviation; † = Median (minimum, maximum).

The median T_{max} for pretomanid was 4 to 5 hours for doses ranging from 50 to 1500 mg. Exposure to pretomanid, based on C_{max} or AUC values, increased in a less than dose-proportional manner with all increasing doses up to 1000 mg. There is a minimal to no additional increase in AUC and C_{max} at doses greater than 1000 mg to up to 1500 mg. The exact reason / mechanism for the less than dose proportional increases in exposure is not known but may be due to saturable absorption of pretomanid resulting in a decrease in bioavailability.

As per the clinical study report from the applicant, dense PK sampling was not performed after the 36-hour PK sampling time point, with only one additional sampling time point at 144 hours post-dose. The reliability of the estimates AUC_{∞}, CL/F, and Vd/F is suspect since the estimated half-life of pretomanid from other PK studies is 18 hours following the clinical dose of 200 mg. Thus, the number of samples in this study after the 36-hour PK sampling time point are not deemed adequate for adequate characterization of these other PK parameters. In addition, the estimate of AUC_{∞} is not reliable, given that in many subjects the extrapolated AUC was greater than 20 %.

CL-002: Multiple Ascending Dose Study

Study CL-002 was a randomized, double-blind, placebo-controlled, sequential multiple ascending dose study that evaluated the safety and PK profile of pretomanid, administered once daily for 7 days to healthy adult male and female subjects. 24 total subjects were enrolled, 18 subjects received pretomanid once daily (QD) at doses of 200, 600, or 1000 mg under fasting conditions, standard meal was ingested 4- and 9-hours post-dose and 6 subjects received placebo. Plasma PK samples were collected up to 13 days. Table 1 summarizes PK parameters observed on Day 1 and Day 7 following administration of pretomanid.

Table 1. Plasma PK Parameters Following Multiple Doses of Pretomanid in Healthy Subjects

Day	Arithmetic Mean (SD) Value				
	AUC_{0-24} (µg·hr/mL)	C_{max} (µg/mL)	t_{max}# (hr)	C_{min} (µg/mL)	$t_{½}$ (hr)
200 mg (N = 6)					
Day 1	15.6 (3.79)	1.0 (0.29)	4.1 (2.0, 5.1)	ND	
Day 7	30.2 (3.71) (3.71)	1.7 (0.29)	4.5 (2.0, 8.0)	0.5 (0.08)	16.0 (1.6)
600 mg (N = 6)					
Day 1	31.6 (7.85)	1.8 (0.45)	5.0 (3.0, 5.0)	ND	
Day 7	70.4 (14.29)	3.8 (0.76)	4.0 (3.0, 4.0)	1.3 (0.33)	15.5 (2.1)
1000 mg (N =6)					
Day 1	34.2 (13.78)	1.9 (0.89)	5.0 (3.0, 8.0)	ND	

AUC_{0-24} = area under the plasma concentration-time curve from zero to 24 hours on Day 1 or Day 7; C_{max} = maximum plasma concentration; C_{min} = minimum (trough) plasma concentration; ND = not determined; SD = standard deviation; $t_{½}$ = half-life; t_{max}= time of peak drug concentration; # Median (minimum, maximum). Day 7 results not available for the 1000 mg dose group since dosing in this group was halted after Day 5 due to adverse events of increased serum creatinine.

Steady state was achieved after 4 to 6 days of dosing for 200 mg and 600 mg, and daily dosing was associated with a mean accumulation ratio for pretomanid of approximately 2 in the 200 mg and 600 mg groups. This extent of accumulation is to be expected based on the observed $t_{1/2}$ of approximately 16 hours in this study.

Exposure to pretomanid increased in a less than dose-proportional manner with the increase in once-daily oral dose from 200 mg to 600 mg. At the single Day 1 dose of 1000 mg there was no further increase in exposure to pretomanid.

CL 009: Food Effect Study

This was a phase 1, randomized, balanced, single-dose, two-treatment, two-period, two-sequence, crossover, open-label study to evaluate the effect of food on the PK of pretomanid tablets in healthy adult subjects. A total of 32 healthy subjects (16 male, 16

female) were randomized to receive a single dose of pretomanid after a 10-hour fast or with FDA recommended high-calorie, high-fat meal. Following an 8-day washout period, subjects were administered another single dose of pretomanid under the opposite conditions. The study was conducted in sequential phases with a single 200 mg dose (4 X 50-mg pretomanid tablets) of pretomanid administered to 16 subjects under fed and fasted conditions in Phase A and a single 50 mg dose of pretomanid as a tablet was administered to 16 different subjects in Phase B. This review focuses only on the applicant's proposed clinical dose of 200 mg pretomanid from Phase A of this study.

PK blood samples were collected pre-dose to up to 96 hours post-dose, and urine collection was also performed at pre-dose and several pre-defined post-dose intervals up to 24 hours following administration of pretomanid.

PK results and conclusions:

Table 1. Pretomanid Pharmacokinetic Parameters Following a Single Dose of 200 mg Pretomanid in Healthy Adult Subjects Under Fed and Fasted Condition

Pharmacokinetic Parameters	Arithmetic Mean ± SD (N = 16)		% Mean Ratio[1]	90% CI[2]
	Fasted Subjects	Fed Subjects		
C_{max} (µg/mL)	1.1±0.2	2.0±0.3	176	165-187
AUC_t (µg.hr/mL)	28.1±8.0	51.6±10.1	188	168-210
AUC_∞ (µg.hr/mL)	28.8±8.3	53.0±10.6	188	168-210
CL/F (L/hr)	7.6±2.5	3.9 ±0.8		
V_d/F (L)	180 ±51.3	97.0 ±17.2		
Tmax (hr)[3]	4.0 (2.0, 6.0)	5.0 (3.0, 8.1)		
$t_{1/2}$ (hr)	16.9 ±3.1	17.4±2.8		

C_{max} = peak exposure; AUC_t = area under the plasma concentration-time curve from zero to last measurable concentration; AUC_∞ = area under the drug concentration-time curve from zero to infinity; CL/F = apparent oral clearance; Vd/F = apparent volume of distribution; T_{max}= time to peak exposure; SD = standard deviation; $t_{½}$ = half-life; CI = confidence interval; [1] % Geometric Mean Ratio = 100*(Fed/Fasted) for ln-transformed parameters; [2] 90% CIs and % geometric mean ratios were calculated based on ln-transformed parameters; [3] t_{max} is presented as median (range).

Upon administration of the 200-mg clinical dose of pretomanid with a high-fat, high-calorie meal, pretomanid C_{max} increased by 76% and AUC_∞ by 88% compared with the fasted state (Table 1).

Note: The final calculation of the % geometric mean ratios to determine food effect of 200 mg pretomanid was performed on PK parameter values in ng/mL, whereas the numbers reported in table above are in µg/mL.

Based on the analysis of urine samples collected in this study, less than 1% of the administered dose of pretomanid was excreted in the urine as unchanged parent drug after pretomanid dosing in either fed or fasted state. A summary of the pretomanid PK parameters in urine can be seen in Table 2 below.

Table 2. Pretomanid Pharmacokinetic Parameters in Urine Following a Single Dose of 200 mg Pretomanid in Healthy Adult Subjects Under Fed and Fasted Condition (N = 16)

Pharmacokinetic Parameters	Arithmetic Mean ± SD** Fasted Subjects	Arithmetic Mean ± SD** Fed Subjects
Cumulative $Ae_{(0-t)}$ (µg)	166.5 ± 91.6	384.3 ± 265.8
CLr (mL/hr)**	7.67 (4.04, 19.57)	8.82(3.69, 39.65)
%dose	0.08 ± 0.05	0.19 ± 0.13

** CLr is presented as Median (range). Renal clearance, defined as $CL_r = Ae_{(0-24)}/AUC_{(0-24)}$ for pretomanid.

Note: As per the discussion among Clin Pharm and Biopharm reviewer, the 50 mg and 200 mg strengths of the pretomanid immediate release (IR) tablets are compositionally proportional. In addition, overall there's no meaningful difference among the 200 mg (50 mg X 4) IR tablets that were administered in food effect study versus 200 mg IR tablet administered in the MAD study. Based on information in these study ISR's, the comparison among these 200 mg pretomanid doses (4 X 50 mg tablets from food effect study; fasted condition versus 200 mg tablet from MAD study; Day 1; fasted) are as follows; mean C_{max} on Day 1 for 200 mg tablet is 1 µg/mL and median T_{max} is 4.1 hr from MAD study versus mean C_{max} for 4 X 50 mg tablet (200 mg dose of pretomanid from IR tablets) is 1.1 µg/mL and median T_{max} is 4.0 hr. The range for T_{max} and SD for C_{max} are comparable too.

Based on cross-study comparison of PK parameters above along with what we have learned from Biopharm reviewer regarding the IR formulation for pretomanid, it appears reasonable to extrapolate information on food effect study results from 50 mg x 4 IR tablets of pretomanid tablets to 200 mg dose (200 mg IR tablet) of pretomanid. Thus, the food effects results hold for the 200 mg pretomanid IR tablet even though Study CL-009 used 4 X 50 mg pretomanid tablets.

CL-008: PA-824 Mass balance study

Study CL-008 evaluated the absorption, metabolism, and excretion following a single dose of [imidazooxazine-^{14}C]-PA-824 in 6 healthy adult male subjects. 1100 mg PA-824 and 91 µCi [imidazooxazine-^{14}C]-PA-824 in oral suspension formulation was administered after a minimum 6-hour fast. Blood, urine and fecal samples were collected pre-dose and up to 22 days post-dose; additional samples were collected weekly for 6 weeks post-dose, if discharge criteria were not met.

A mean (±SD) 53 (±3.4) % of the radioactive dose was recovered in the urine, and 37.6 (±2.7) % of the radioactive dose was recovered in the feces, with 90.6% (range 77.5%-95.4%) of the administered radioactive dose recovered after 21 days.

AUC and C_{max} values were approximately 3 and >20-fold higher, respectively, for total radioactivity in both plasma and blood than for AUC and C_{max} values of parent PA-824 in plasma, which indicates that the majority of circulating total radioactivity was potentially associated with metabolites of PA-824. 11 metabolites identified in plasma including hydroxy-dihydro-pyran ring opened-amino (M27), hydroxy imidazole (M50) and hydroxyl aminooxazine (M52) were accounting for 7.8, 6.3 and 5.1% of radioactivity, respectively. Seven trace metabolites, M10, M13, M20, M28, M31, M48, and M51, were observed in plasma accounting for 0.33% to 2.2% of radioactivity. [^{14}C]-PA-824 was extensively metabolized and <5% of the dose was excreted as unchanged [^{14}C]-PA-824 in the feces and urine. Total radioactivity was slowly eliminated from plasma and whole blood as compared to the elimination of PA-824, indicating that the metabolites are slowly eliminated as compared to that of PA-824.

The metabolism of [^{14}C]-PA-824 proceeds via a combination of reductive metabolism (~20% to 25% of the dose) and oxidative metabolism. In study CL-008 metabolite trifluoromethoxy benzoic acid glycine conjugate (M11), accounted for approximately 13% of the dose in human excreta. M11 acylglucuronides and subsequent transesterification product (M6A) representing 2.3% of the dose in urine and 0.96 % in feces, and (M26), the product of reduction followed by oxidation representing the 2.1% radioactive dose in urine and 1.2% in feces. Metabolite M50, the hydroxy imidazole, represented 2.1 % of the dose in urine.

The applicant had conducted another mass-balance study CL-004 prior to study CL-008. In study CL-004, 6 healthy adult male subjects were administered an oral suspension containing 873 mg PA-824 and 131.5 µCi [benzyl-^{14}C]PA-824. 64.5% of the radioactive dose was recovered in the urine and 25.8% of the dose was recovered in feces primarily as metabolites. In study CL-004, PA-824 was cleaved oxidatively to form the M19 metabolite: 4-trifluoromethoxy benzoic acid, which was the major drug-derived metabolite, representing up to 35% of the radioactivity in plasma at 24 hours post dose. The M19 metabolite was not quantified in Study CL-008 because a different radiolabel was used; however, the M11 metabolite which is the glycine conjugate of M19 was quantified in Study CL-008.

PA-824-CL-006: Pretomanid (PA-824) and Midazolam Interaction Study

This was a phase 1, open-label, multi-dose, two-treatment, two-period study that evaluated the effects of 400 mg (2 X 200 mg oral tablets, i.e., twice the proposed recommended clinical dose of Pa) pretomanid (Pa) on the pharmacokinetics (PK) of CYP3A4 substrate, midazolam (MDZ), 2 mg in 14 healthy adult subjects. All subjects received a single dose of 2 mg MDZ on Study Day 1, followed by a 2-day washout. Following the washout duration, all subjects received 400 mg Pa once daily for 14 consecutive days. On day 14 (Study Day 17), a single dose of 2 mg midazolam was co-administered with 400 mg Pa.

PK blood samples for MDZ were collected pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours after each 2-mg oral dose of MDZ.

The PK endpoints AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for MDZ and 1-hydroxy MDZ were compared between MDZ administered alone versus MDZ co-administered with Pa. The PK parameters of interest are summarized in **Tables 1** and **2** below.

Table 1. Midazolam PK Following Administration of Midazolam Alone and after Co-administration with Pretomanid

	Geometric LS Means		
PK Parameter	**MDZ + Pa**	**MDZ**	**% Mean Ratio (90 % CI)**
C_{max} (ng/mL)	9.05	10.82	83.63 (75.11 – 93.11)
$AUC_{(0-t)}$ (ng*hr/mL)	23.38	27.63	84.61 (74.21 – 96.47)
$AUC_{(0-inf)}$ (ng*hr/mL)	24.47	28.97	84.45 (73.79 – 96.64)

AUC = area under the curve; CI = confidence interval; MDZ = midazolam; Pa = pretomanid; LS = least squares; PK = pharmacokinetics

Table 2. 1-Hydroxy Midazolam PK Following Administration of Midazolam Alone and after Co-administration with Pretomanid

	Geometric LS Means		
PK Parameter	**MDZ + Pa**	**MDZ**	**% Mean Ratio (90 % CI)**
C_{max} (ng/mL)	5.00	4.76	105.23 (93.13 – 118.90)
$AUC_{(0-t)}$ (ng*hr/mL)	12.38	10.86	113.98 (105.53 – 123.09)
$AUC_{(0-inf)}$ (ng*hr/mL)	13.04	11.57	112.68 (103.07 – 123.18)

AUC = area under the curve; CI = confidence interval; MDZ = midazolam; Pa = pretomanid; LS = least squares; PK = pharmacokinetics

The co-administration of pretomanid with the CYP3A4 substrate, midazolam, results in no clinically significant effect on the PK of midazolam or its major metabolite, 1-hydroxy-midazolam.

Study A5306: PA-824 drug interaction study with Efavirenz, Ritonavir-Boosted Lopinavir, or Rifampin

Study A5306 was a three-arm, open label, crossover trial in healthy, HIV-1 uninfected subjects to investigate the potential interaction between steady state Pretomanid (PA-824) given at 200 mg once daily and efavirenz (EFV) 600 mg once daily (Arm 1), ritonavir-boosted lopinavir (LPV/r) 400/100 mg twice daily (Arm 2), or rifampin (RIF) 600 mg once daily (Arm 3). RIF is a potent inducer of cytochrome P450 (CYP) 3A4. EFV is also an inducer of CYP3A4, and LPV/r can inhibit or induce CYP3A.

All drugs were administered orally. There were total 16 subjects in each arm.

Arm 1 (PA-824 and EFV)

Each subject was randomly assigned to receive PA-824 alone or EFV alone followed by EFV plus PA-824 in one of two orders, Treatment 1A and Treatment 1B.

Treatment 1A: Days 1-7: PA-824, 200 mg QD; Days 8-21: Washout; Days 22-35: EFV, 600 mg QD; Days 36-42: EFV 600 mg orally QD plus PA-824, 200 mg QD.

Treatment 1B: Days 1-14: EFV, 600 mg once daily; Days 15-21: EFV 600 mg QD plus PA-824, 200 mg QD; Days 22-35 Washout; Days 36-42: PA-824, 200 mg QD.
Plasma PK profiles over 24 hours were determined for PA-824 at the following time points and compared:
• days 7 and 42 of Treatment 1A
• days 21 and 42 of Treatment 1B
Plasma PK profiles over 24 hours were determined for EFV at the following time points and compared:
• days 34 and 41 of Treatment 1A
• days 13 and 20 of Treatment 1B

Arm 2 (PA-824 and LPV/r)
Each participant was randomly assigned to receive PA-824 alone or LPV/r alone followed by LPV/r plus PA-824 in one of two orders, in Treatment 2A and Treatment 2B.
Treatment 2A: Days 1-7: PA-824, 200 mg once daily; Days 8-21: Washout; Days 22-35: LPV/r 400mg/100mg twice daily; Days 36-42: LPV/r 400 mg/100 mg twice daily plus PA-824, 200 mg QD.
Treatment 2B: Days 1-14: LPV/r 400 mg/100 mg twice daily; Days 15-21: LPV/r 400 mg/100 mg twice daily plus PA-824, 200 mg QD; Days 22-35 Washout; Days 36-42: PA-824, 200 mg QD
Plasma PK profiles over 24 hours were determined for PA-824 at the following time points and compared:
• days 7 and 42 of Treatment 2A
• days 21 and 42 of Treatment 2B
Plasma PK profiles over 12 hours were determined for LPV at the following time points and compared:
• days 35 and 42 of Treatment 2A
• days 14 and 21 of Treatment 2B

Arm 3 (PA-824 and RIF)
Each participant received, in sequential order, PA-824 alone followed by RIF alone followed by RIF together with PA-824.
Treatment: Days 1-7: PA-824, 200 mg QD; Days 8-14: RIF 600 mg QD; Days 15-21: RIF 600 mg QD plus PA-824 200 mg QD.
Plasma PK profiles over 24 hours were determined for PA-824 on days 7 and 21.

Table 1 below shows GMRs of PA-824 when PA-824 is co-administered with either EFV or LPV/r or RIF compared to PA-824 administered alone and associated 90% CIs.

Table 1. Geometric Mean Ratios [With Perpetrator]/[Without Perpetrator] and Associated 90% Confidence Intervals (CI) for PA-824 PK Parameters

Perpetrator	Parameter	N	GMR	90% CI
EFV	AUC_{0-24h} (ng*h/mL)	16	0.654	(0.561, 0.761)
	C_{max} (ng/mL)	16	0.715	(0.616, 0.829)
LPV/r	AUC_{0-24h} (ng*h/mL)	16	0.833	(0.712, 0.975)
	C_{max} (ng/mL)	16	0.867	(0.753, 0.999)
RIF	AUC_{0-24h} (ng*h/mL)	16	0.336	(0.273, 0.415)
	C_{max} (ng/mL)	16	0.466	(0.385, 0.563)

AUC_{0-24h} = area under time concentration curve from 0 to 24 hours after dosing;
C_{max} = maximum plasma concentration

Co-administration of PA-824 with EFV or RIF reduced the AUC and C_{max} of PA-824 significantly. Co-administration of potent inducers of CYP3A4, such as RIF, with Pretomanid should be avoided.
Also, based on the bedaquiline labeling, efavirenz is not recommended to be administered with bedaquiline. Therefore, efavirenz should not be used with the bedaquiline-pretomanid-linezolid regimen.
In Arm 2 LPV/r, PA-824 PK parameters were stratified by three CYP3A5 metabolizer subgroups. In the extensive and slow metabolizer subgroup, there were no significant changes in PA-824 PK parameters when co-administered with LPV/r. In the intermediate metabolizer subgroup, PA-824 $AUC_{0-24h}$and C_{max} were decreased by 40% and 36%, respectively. However, due to small sample size (n=3) for CYP3A5 intermediate metabolizers, changes in PA-824 exposure were not statistically significant. Overall, co-administration of PA-824 with LPV/r did not appreciably affect PA-824 exposure and LPV/r is not likely to cause a significant drug-drug interaction with Pretomanid.
There were no changes in LPV/r or EFV PK parameters when either one was co-administered with PA-824 as compared to when they were administered alone.

CL-007: Early Bactericidal Activity
Study CL-007 was a partially double-blind, randomized study in 69 adult male and female subjects with newly diagnosed, uncomplicated, smear-positive, pulmonary TB. All subjects were randomly assigned to treatment with pretomanid administered orally following an overnight fast at daily doses of 200 mg, 600 mg, 1000 mg, or 1200 mg, or to standard first-line therapy (Rifafour) for TB. Rifafour was administered once daily (each tablet contains rifampicin, isoniazid, pyrazinamide, and ethambutol).
Blood samples were obtained for PK analysis at scheduled time points after dosing on Day 1, Day 8, and Day 14, and at the follow-up visit 14 days after the last dose.
Sputum collections occurred on Days -2, -1, 1, 2, 3, 4, 6, 8, 10, 12, and 14 for assessment of colony forming units (CFU) counting on solid media and time to culture positivity (TTP) in liquid media.

Reference ID: 4476823

The following efficacy variables were assessed for evaluation of efficacy endpoints:

- The change in number of sputum CFU counting on solid media of *M. tuberculosis* (logCFU)
  over time. EBA_{CFU} [change in log10(CFU)/day] is the absolute value of the average daily rate of change of log10(CFU) over days 0 to 14.
- The change in TTP in liquid media over time. EBA_{TTP} (change in hours to positivity/day) is the average daily rate of change of TTP over days 0 to 14.

PK and PD results:

- Pretomanid plasma concentrations increased with dose up to 1000 mg in less than dose proportional manner. The accumulation ratio is approximately 2.
- Early bactericidal activity was demonstrated for all dose levels; however, there was no apparent dose-response relationship. Mean EBA(0-14) values at the four pretomanid dose levels do not differ significantly from each other (Figure 1).
- Because maximum efficacy in this study was achieved at the lowest dose tested (200 mg per day for 14 days), the extended EBA of lower doses was explored in study CL-010 to better evaluate dose-response of Pretomanid (see also review of Study CL-010).

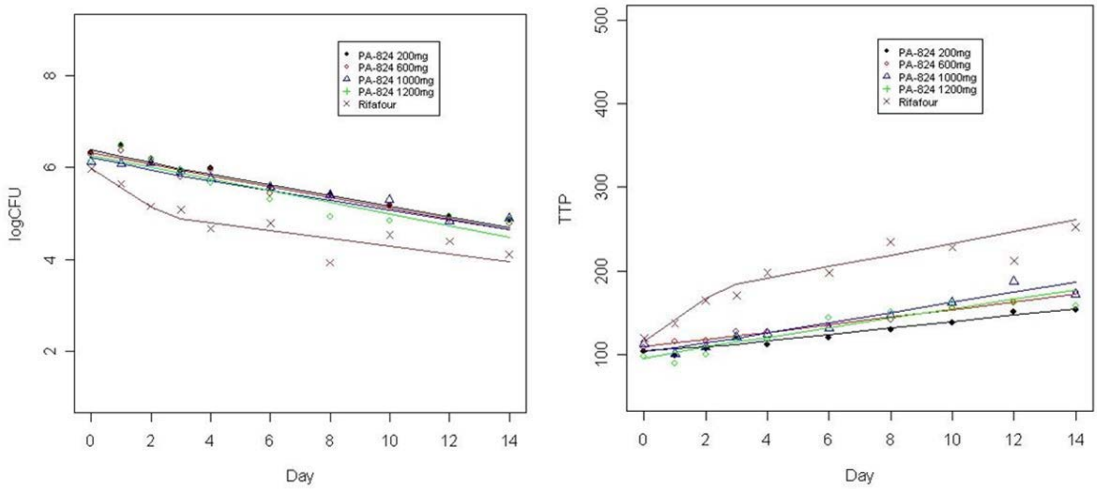


Figure 1. Mean Log-transformed CFU vs Day and Mean TTP vs Day with Fitted Bi-linear Regressions

CL-010: Early Bactericidal Activity

Study CL-010 was a phase 2, dose finding, two-study center, partially double-blinded, randomized clinical study in 69 adult male and female patients with newly diagnosed, uncomplicated, smear-positive, pulmonary tuberculosis (TB). All subjects were randomly assigned to treatment with pretomanid administered orally following an overnight fast at daily doses of either 50 mg, 100 mg, 150 mg or 200 mg., or to standard first-line therapy (Rifafour) for TB. Rifafour was administered once daily (each tablet contains rifampicin, isoniazid, pyrazinamide, and ethambutol).

Blood samples were obtained for PK analysis at scheduled time points after dosing on Day 1 and Day 14, and at the follow-up visit 14 days after the last dose.

Sputum collections occurred on Days -2, -1, 1, 2, 3, 4, 6, 8, 10, 12, and 14 for assessment of colony forming units (CFU) counting on solid media and time to culture positivity (TTP) in liquid media.

The following variables were assessed for evaluation of efficacy endpoints:

- The change in number of sputum CFU counting on solid media of *M. tuberculosis* (logCFU) over time. EBA_{CFU} [Change in log10(CFU)/day] is the absolute value of the average daily rate of change of log10(CFU) over days 0 to 14.
- The change in TTP in liquid media over time. EBA_{TTP} (Change in hours to positivity/day) is the average daily rate of change of TTP over days 0 to 14.

PK and PD results:

- Over the dose range of 50 to 200 mg orally, plasma pretomanid levels increased with dose in an approximately dose-proportional manner with respect to AUC_{∞} (11.9 ± 4.5 µg.hr/mL with 50 mg dose to 38.5 ± 16.6 µg.hr/mL with 200 mg dose). Steady state was achieved at approximately 5 to 7 days following the first dose of pretomanid, and daily dosing for 14 days resulted in accumulation ratios of approximately 2.0. The $T_{1/2}$ was 16.14 ± 5.5 hours and 21.2 ± 6.5 hours for the 50 and 200 mg doses, respectively.
- The C_{max} was 0.47 ± 0.15 µg/mL and 1.18 ± 0.38 µg/mL for the 50 and 200 mg doses, respectively. The median T_{max} was 5 (1 – 12) hours and 6 (2 – 16) hours for the 50 and 200 mg doses, respectively.
- Mean logCFU and TTP vs. Day values at the four pretomanid dose levels are depicted in Figure 1. Based on mean logCFU Change from Baseline over 14 days in Figure 2, there does appear to be a slightly greater efficacy with 200 mg as compared to the lower doses following administration of pretomanid under fasted conditions.
- The results from this study along with that from Study CL-007 support 200 mg as an adequate dose as no further decrease in CFU or increase in TTP values was observed with higher doses per the findings from Study CL-007 (see review of Study CL-007 for additional information); maximum efficacy was achieved at the lowest dose tested (200 mg per day for 14 days).
- Additionally, the applicant pooled the data from EBA studies CL-007 (200 mg and higher doses) and CL-010 (200 mg and lower doses) to further support the dose selection of pretomanid. The results can be seen in Figure 3 and appear to further support the adequacy of the 200 mg dose from an efficacy perspective based on these two EBA studies.

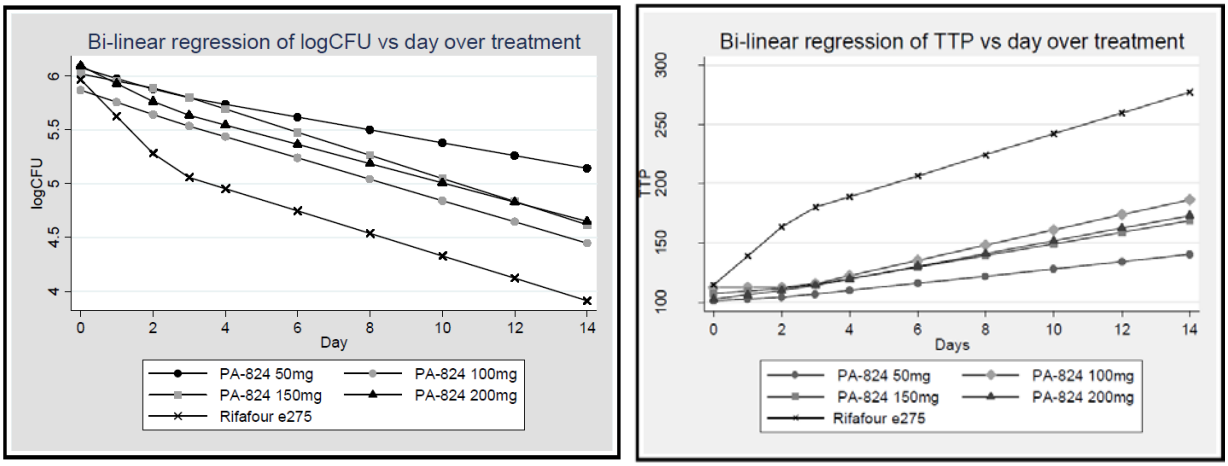


Figure 1. Mean Log-transformed CFU vs Day and Mean TTP vs Day with Fitted Bi-linear Regressions

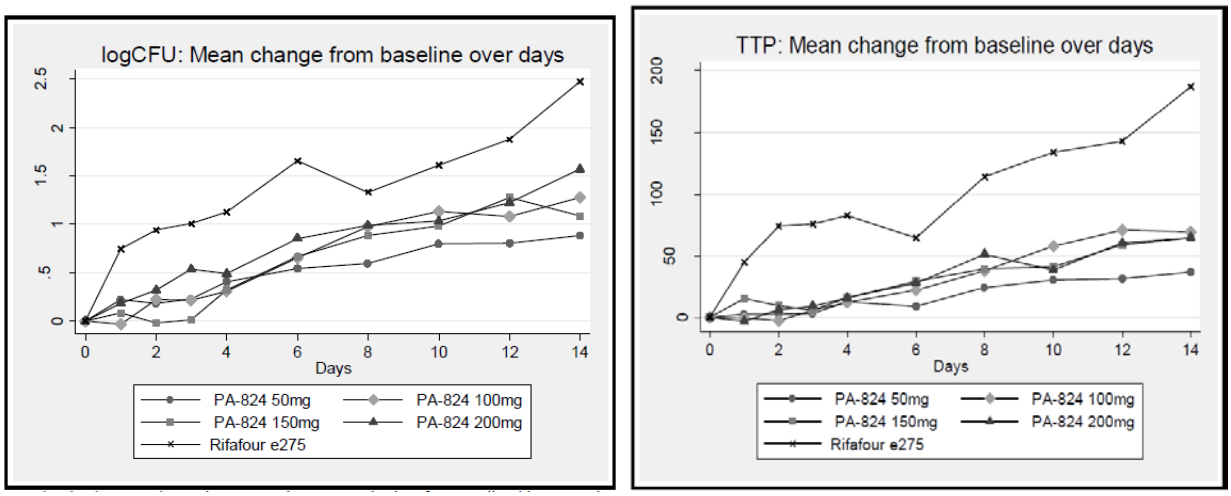
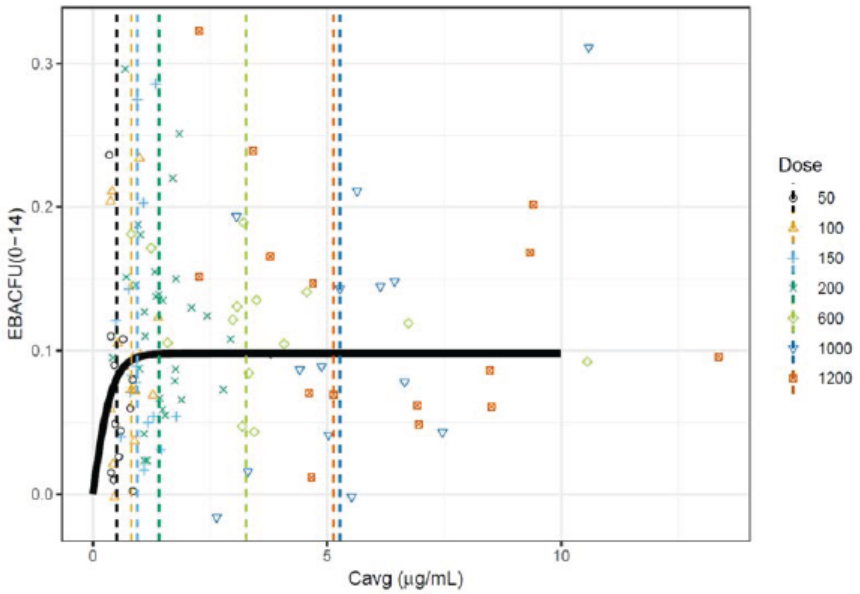
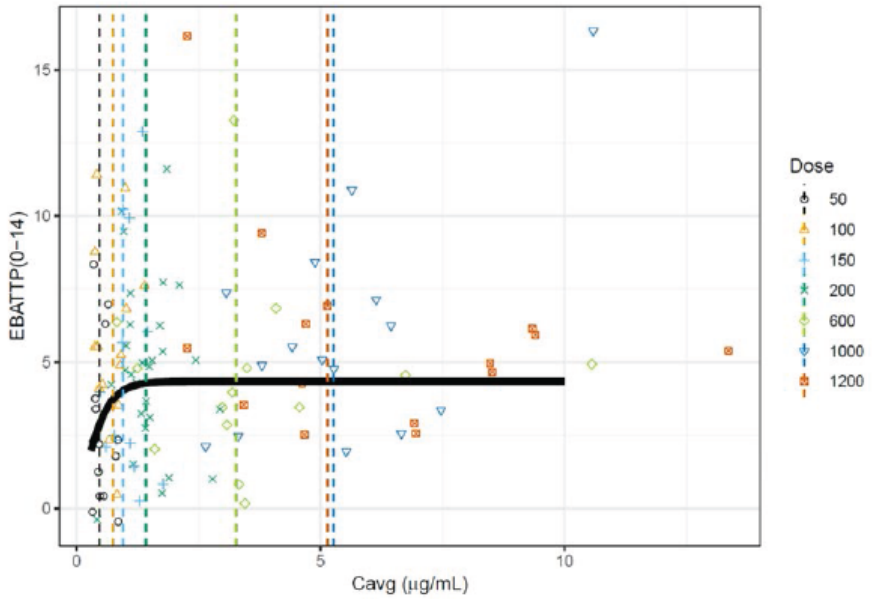


Figure 2. Mean logCFU Change from Baseline vs Day and Mean TTP Change from Baseline vs Day



C_{avg} = steady state average plasma concentration over a dosing interval; EBA_{CFU}(0-14) = daily rate of change of log-transformed counts of colony-forming units in solid culture over 14 days of treatment
Unit for EBA_{CFU}(0-14): -[Change in log10(CFU)]/day



C_{avg} = steady state average plasma concentration over a dosing interval; EBA_{TTP}(0-14) = daily rate of change of time to culture positivity in the mycobacteria growth indicator tube
Unit for EBA_{TTP}(0-14): -(Change in hours to positivity)/day

Figure 3. Pretomanid EBA_{CFU}(0-14) and EBA_{TTP}(0-14)versus C_{avg} in Studies CL-007 and CL-010

In vitro studies

***In vitro* assessment of Pretomanid as a substrate of human OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and P-gp mediated transport**	
Study #	OPT-2018-028
Link#	Application 212862 - 4.2.2.3 Distribution [Study ID - Study Title] -
Objective	*In vitro* study designed to assess if pretomanid is a substrate of Transporters: OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and P-gp
Cell System Used	MDCK-II cells for OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, and BCRP
	MDCK-MDR1 for P-gp
Investigational drug concentration	3 µM, 10 µM, and 30 µM, and 10 µM in presence of reference inhibitor for each transporter
Probe Substrate (concentration)[†]	OAT1: [^{14}H]-p-aminohippurate (2 µM) OAT3: [^{3}H]estrone-3-sulfate (0.1 µM) OCT2: [^{14}C]-metformin (10 µM) OATP1B1: [^{3}H]estradiol-17β-d-glucuronide (2 µM) OATP1B3: [^{3}H]-CCK-8 (2 µM) MATE1: [^{14}C]-metformin (10 µM) MATE2-K: [^{14}C]-metformin (10 µM) BCRP: [^{3}H]-prazosin (2 µM) P-gp: [^{3}H]-quinidine (100 nM)
Reference Inhibitor (concentration)[‡]	OAT1: Probenecid (100 µM) OAT3: Probenecid (100 µM) OCT2: Quinidine (1000 µM) OATP1B1: Rifampicin (100 µM) OATP1B3: Rifampicin (100 µM) MATE1: Cimetidine (100 µM) MATE2-K: Cimetidine (100 µM) BCRP: Ko 143 (1 µM) P-gp: Elacridar (3 µM)
Are controls and control concentrations appropriate?	☑ Yes ☐ No All controls are listed on FDA drug interaction website.

Results and Conclusions: Pretomanid is not a substrate of OAT1, OAT3, OCT2, OAT1B1, OATP1B3, MATE1, MATE2-K, BCRP, and P-gp at clinically relevant concentrations. The key study results are summarized in Table 1.

Table 1. Summary of *In Vitro* Substrate Potential of Pretomanid by Transporters

Transporter	Inhibitor‡	Substrate Potential for Pretomanid	
		Pretomanid (Maximum inhibition ± SD) %; [at 10 µM Pretomanid Concentration]	**Probe substrate†; Inhibition -** (Maximum inhibition ± SD) %
OAT1	Probenecid	ND§	PAH; (92.4 ± 1.3)
OAT3	Probenecid	ND	E3S; (94.3 ± 3.48)
OCT2	Quinidine	ND	Metformin; (101 ± 0.21)
OATP1B1	Rifampicin	ND	E17bGlu; (99.6 ± 0.69)
OATP1B3	Rifampicin	ND	CCK-8; (99.6 ± 0.38)
MATE1	Cimetidine	ND	Metformin; (98.8 ± 0.32)
MATE2-K	Cimetidine	ND	Metformin; (99.4 ± 1.46)
BCRP	Ko 143	ND	Prazosin; (104 ± 0.91)
P-gp	Elacridar	ND	Quinidine; (97.6 ± 0.24)

p-aminohippurate: PAH, Estrone-3-sufate: E3S, Cholecystokinin octapeptide: CCK-8, and Estradiol-17β-d-glucuronide: E17bGlu.

§ - Not determined (ND) due to lack of inhibition of pretomanid transport with respective inhibitors

‡ - Concentrations of inhibitors were per defined in the page 1 of this ISR

† - Concentrations of probe substrates were per defined in the page 1 of this ISR

Assessment of Pretomanid as an Inhibitor of human OCT1, OCT2, OAT1, OAT3, OAT1B1, OATP1B3, BCRP, P-gp, BSEP, MATE1, and MATE2-K mediated transport	
Studies #	OPT-2011-104, OPT-2016-126, and OPT-2011-135
Link#	Application 212862 - 4.2.2.3 Distribution [Study ID - Study Title] -
Objective	To assess if pretomanid is an inhibitor of Transporters: OAT1, OAT3, OCT1, OCT2, OAT1B1, OATP1B3, BCRP, BSEP, P-gp, MATE1, and MATE2-K. ➢ Study OPT-2011-135 was performed to assess IC_{50} values of pretomanid against OAT1, OAT3, OCT1, and OATP1B1 as Study OPT-2011-104 studied only one concentration of pretomanid (15 µM).

Cell System Used	MDCK-II cells for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K
	Caco-2 cells for BCRP
	MDCK-MDR1 for P-gp
	Sf9 membranes vesicle for BSEP
Study (Investigational Drug: concentration or concentration range) and Transporters Studied	Study OPT-2011-104 (Pretomanid concentration: 15 µM): OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, BSEP, and P-gp Study OPT-2016-126 (Pretomanid concentration: 1.02 – 100 µM): MATE1 and MATE2-K Study OPT-2011-135 (Pretomanid concentration: 0 – 300 µM): OAT1, OAT3, OCT1, and OATP1B1
Probe Substrate (concentration)	OCT1: [^{14}C]-metformin (10 µM) OCT2: [^{14}C]-metformin (10 µM) OAT1: [^{14}H]-p-aminohippurate (2 µM) OAT3: [^{3}H]estrone-3-sulfate (0.75 µM) OATP1B1: [^{3}H]estradiol-17β-d-glucuronide (2 µM) OATP1B3: [^{3}H]-CCK-8 (10 µM) BCRP: [^{3}H]-genistein (25 µM) P-gp: [^{3}H]-digoxin (100 nM) BSEP: [^{3}H]-taurocholic acid (1 µM) MATE1: [^{14}C]-metformin (10 µM) MATE2-K: [^{14}C]-metformin (10 µM)
Control Inhibitor (concentration)	OCT1: quinidine (100 µM) OCT2: quinidine (100 µM) OAT1: probenecid (100 µM) OAT3: probenecid (100 µM) OATP1B1: rifampicin (100 µM) OATP1B3: rifampicin (100 µM) BCRP: chrysin (100 µM) P-gp: verapamil (100 µM); ketoconazole (50 µM) BSEP: rifampicin (300 µM) MATE1: Cimetidine (10 µM) MATE2-K: Cimetidine (10 µM)
Are controls and control concentrations appropriate?	☑ Yes ☐ No All controls are listed on FDA drug interaction website.

Reference ID: 4476823

Results and Conclusions: The results are shown below in Table 1. Pretomanid was found to be an *in vitro* inhibitor of OAT3 at clinically relevant concentrations. The overall interpretation of results from Table 1 is that pretomanid does not significantly inhibit any of the other transporters at clinically relevant concentrations.

Based on FDA DDI Guidance 2017, pretomanid presents a very low *in vitro* inhibitory potential on MATE2-K transporters (i.e., $I_{max,u}/IC_{50}$ = 0.022; ≥ 0.02) using the clinically observed mean plasma pretomanid concentration of 2.6 µg/mL.

The reasons for the apparent discrepancy in observed maximal inhibition for OATP1B1 and OCT1 transporters from Studies OPT-2011-104 and OPT-2011-135 are unclear. However, the results from study OPT-2011-135 studied concentrations ranging from 0 to 300 µM. Thus, there doesn't appear to be a significant inhibition interaction potential for pretomanid with OATP1B1 and OCT1 transporters.

Table 1. Summary of *In Vitro* Inhibitory Potential of Pretomanid on Transporters

Transporter	Probe Substrate	Inhibitory Potential	
		Pretomanid (Maximum inhibition) %; [Pretomanid Concentrations]	**Control Inhibitor** (inhibition)%
OCT1	Metformin	(39.2 ± 7.7); [15 µM]§ No Inhibition; [0 – 300 µM]	Quinidine (102 ± 1.0) Quinidine (94.4 ± 2.8)
OCT2	Metformin	(11.2 ± 9.3); [15 µM]	Quinidine (87.1 ± 12.2)
OAT1	p-aminohippurate	(29.7 ± 9.5); [15 µM] § (23.9 ± 9.1); [0 – 300 µM]	Probenecid (89.0 ± 1.0) Probenecid (76.6 ± 4.2)
OAT3	Estrone-3-sulfate	(65.5 ± 6.76); [15 µM] § > 50; [0 – 300 µM]	Probenecid (82.9 ± 2.3) Probenecid (87.2 ± 0.28)
OATP1B1	Estradiol-17β-d-glucuronide	(61.4 ± 9.0); [15 µM] § (13.2 ± 8.8); [0 – 300 µM]	Rifampicin (109 ± 11.1) Rifampicin (89.5 ± 2.7)
OATP1B3	CCK-8	(6.7 ± 8.34); [15 µM]	Rifampicin (92.4 ± 5.9)
BCRP	Genistein	(4.0 ± 3.9); [15 µM]	Chrysin (94.7 ± 4.3)
P-gp	Digoxin	(2.4 ± 2.4); [15 µM]	Verapamil (86.0 ± 3.2) Ketoconazole (100 ± 2.5)
BSEP	Taurocholic acid	(18.4 ± 3.7); [15 µM]	Rifampicin (97.6 ± 0.24)
MATE1	Metformin	*87.7 µM; [0 – 100 µM]	Cimetidine (97.1 ± 1.3)
MATE2-K	Metformin	*45.1 µM; [0 – 100 µM]	Cimetidine (87.2 ± 0.75)

* - IC_{50} Values (µM)
§ - FBS was added as a solubility enhancer in Study OPT-2011-135

Reference ID: 4476823

Study Title: Protein Binding of Pretomanid in Mouse, Rat, Dog, Monkey, Human Plasma, Human Serum Albumin (HSA) and bovine serum albumin (BSA)	
Study #	Study (b) (4) 14648
Link	Application 212862 - 4.2.2.3 Distribution [Study ID - Study Title] -
Objectives	To determine pretomanid plasma protein binding in mouse, rat, dog, monkey, human plasma, human serum albumin (HSA), and bovine serum albumin (BSA)

METHODS

Aliquots of the pretomanid spiking solutions were spiked into plasma to achieve final concentrations as follows:

Species/Matrix	**Pretomanid Concentrations (µg/mL)**			
Mouse, Rat, Dog, Monkey and Human Plasma	0.5	2	4	12
Human Serum Albumin (4% solution in pH 7.4 phosphate buffer; 40 mg/mL)				
Bovine Serum Albumin (0.5% solution in pH 7.4 phosphate buffer; 5 mg/mL)				

Detection technique: RP-HPLC

RESULTS

Table 1. Summary of PA-824 binding to mouse, rat, dog, monkey, human plasma, HSA and BSA

Concentration (µg/mL)	Time Interval (hr)	Mouse Plasma		Rat Plasma		Dog Plasma		Monkey Plasma	
		Average % Bound	RSD[a]	Average % Bound	RSD[a]	Average % Bound	RSD[a]	Average % Bound	RSD[a]
0.5	2	85.05	0.74	79.50	1.14	86.99	0.35	83.55	0.35
2		85.45	0.08	80.33	0.41	87.03	0.29	83.34	0.65
4		85.63	0.30	80.48	0.19	87.41	0.60	83.02	0.09
12		85.56	0.23	79.90	0.30	87.05	0.49	82.93	0.60
Average		85.42		80.05		87.12		83.21	
RSD[§]		0.30		0.55		0.22		0.34	

Concentration (µg/mL)	Time Interval (hr)	**Human Plasma**		**Human Serum Albumin**		Bovine Serum Albumin	
		Average % Bound	RSD[a]	Average % Bound	RSD[a]	Average % Bound	RSD[a]
0.5	2	86.51	0.35	82.92	1.03	27.34	9.84
2		86.26	0.39	82.60	0.35	28.80	4.59
4		86.52	0.43	82.79	0.57	28.42	7.27
12		86.37	0.23	82.36	0.19	29.95	6.10

Average	**86.42**	**82.67**	28.63
RSD§	0.14	0.29	3.76

§RSD = relative standard deviation

CONCLUSIONS

Pretomanid was moderately bound to plasma proteins of all tested species with no major species differences. Among protein binding assessments to proteins, HSA and BSA, pretomanid was weakly bound to BSA. In the concentration range of 0.5-12 µg/mL pretomanid, no concentration dependency of plasma protein binding was observed.

In vitro blood-to-plasma ratio of pretomanid in human

In Studies 401951-20171109-BPR and 401951- 20171207-BPR, the blood-to-plasma ratio ($K_{B/P}$) of pretomanid *in vitro* in whole blood was determined to provide an indication of pretomanid partitioning into red blood cells (erythrocytes). At three concentrations of pretomanid, i.e., 2.5, 5, and 10 µg/mL studied in both studies, the mean $K_{B/P}$ values of pretomanid were reported to be 0.79, 0.73, and 0.83 and 0.66, 0.69, and 0.78 respectively in human whole blood. The erythrocyte-to-plasma ratio ($K_{E/P}$) values were 0.61, 0.49, and 0.68 and 0.31, 0.37, and 0.56 respectively in human whole blood. In conclusion, pretomanid exhibited a low potential for partitioning into human red blood cells.

	***In vitro* assessment of cytochrome P450 enzyme inhibition by PA-824**
Study #	(b) (4)O85102
	Determination of the Inhibitory Potency of PA-824 Towards Human CYP Isoforms
Link	\\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4)085102\ (b) (4)085102-pre-clinical-study-report.pdf
Objectives	Determine if PA-824 is an inhibitor of CYP enzymes
METHODS	
System	

Study	System
Direct inhibition	Human liver microsomes
Time-dependent inhibition	Human liver microsomes

Was an appropriate system used?	☑ Yes ☐ No
Probe substrates	

	Direct inhibition	**Time-dependent inhibition**
Enzyme	Probe substrate	Probe substrates
CYP1A2	Phenacetin	Phenacetin
CYP2C8	Amodiaquine	Amodiaquine

	CYP2C9	Diclofenac	Diclofenac
	CYP2C19	*S*-Mephenytoin	*S*-Mephenytoin
	CYP2D6	Dextromethorphan	Dextromethorphan
	CYP3A4/5	Testosterone	Testosterone
	CYP3A4/5	Midazolam	Midazolam
Were controls appropriate?	☑ Yes ☐ No		
Test drug concentrations	PA-824: 0.1-100 µM		
Were test drug concentrations appropriate?	☑ Yes ☐ No C_{max} for PA-824 ~ ranges from 1.7-5.3 µg/mL (4.7-14.6 µM).		

RESULTS

CYP	Direct inhibition		Time-dependent CYP inhibition	
	IC_{50} (µM)[a]	Maximum inhibition at 100 µM (%)[b]	IC_{50} (µM)[a]	Maximum inhibition at 100 µM (%) [b]
CYP1A2	>100	11	>100	9.8
CYP2C8	>100	29	30	66
CYP2C9	>100	25	>100	32
CYP2C19	>100	47	48	60
CYP2D6	>100	43	83	53
CYP3A4/5	50	65	13	91
CYP3A4/5	>100	33	23	79

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article.

b Maximum inhibition (%) = 100% − Percent solvent control.

CONCLUSIONS:

1. PA-824 directly inhibited CYP3A4/5 with an IC_{50} value of 50 µM for testosterone 6β-hydroxylation and greater than 100 µM for midazolam 1´-hydroxylation. However, both IC_{50} values for testosterone 6β-hydroxylation and midazolam were greater than the highest Cmax value observed clinically (i.e., 14.6 µM). Thus, the potential for a clinically significant DDI between PA-824 and CYP3A4 substrates may be minimal. Nonetheless, an *in vivo* DDI study with midazolam was conducted by the applicant
2. PA-824 directly inhibited CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 with IC_{50} values greater than 100 µM. Thus, there is minimum potential for DDI of PA-824 at clinically relevant concentrations (5-15 µM) with CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 substrates.
3. PA-824 is a time-dependent inhibitor of CYP3A4/5 as a more than 2-fold decrease [from 50 µM (18.4 µg/mL) to 13 µM (4.8 µg/mL)] in IC50 was observed following a 30-minute preincubation.
4. PA-824 is a weak time-dependent inhibitor of CYP2C8 and CYP2C19. However, there is not enough information to evaluate the predicted ratio (R2) of victim drug's AUC in presence and absence of inhibitor as per the *In vitro* metabolism and transporter mediated DDI studies guidance for industry from year 2017 as parameters like KI and K_{inact} were not determined by the applicant, which can help to calculate R2.

Metabolic profile in human hepatocytes	
Study #	7504-133
Link	\\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4) -7504-133 (b) (4) -7504-133-pre-clinical-study-report.pdf
Objectives	To evaluate *in vitro* metabolism of [^{14}C]-pretomanid by human hepatocytes
METHODS	
System	Primary Human Hepatocytes, # of donors n=3
Was an appropriate system used?	☑ Yes ☐ No
Methods	• [^{14}C] PA-824 (5 µM and 50 µM) was incubated with 0.75 x 10^6 hepatocytes/mL suspended in William's E medium at 37°C with 4.8% CO_2 for 0, 60, 120, and 240 minutes. • Metabolites analyzed using HPLC equipped with a radioactivity detector and LC/MS/MS.
Test (substrate or inhibitor) drug concentrations	PA-824 (substrate) 5 µM and 50 µM
Were test drug	

concentrations appropriate?	☑ Yes ☐ No
RESULTS AND CONCLUSIONS	
• Low extent of metabolism PA-824 was observed following *in vitro* incubations with 92-95% of [^{14}C] PA-824 remaining after incubation. • M11 (trifluoromethoxybenzoic acid glycine conjugate) was a major metabolite which represented a maximum of 6.76% or 6.61% of total radioactivity after 240-minutes of incubation with 5 µM or 50 µM [^{14}C] PA-824, respectively. 11 minor metabolites (M8, M10, M19, M20, M36, M37, M38, M40, M42, and M43) were also detected.	

Metabolic stability in human liver microsomes	
Study #	(b) (4) 09645, (b) (4) 08638, 0313251C
Link	\\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4) 09645 (b) (4) 09645-pre-clinical-study-report.pdf \\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4) 08638 (b) (4) 08638-pre-clinical-study-report.pdf \\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4) 0313251c (b) (4) 0313251c-pre-clinical-study-report.pdf
Objectives	To evaluate *in vitro* metabolic stability of PA-824 in human liver microsomes
METHODS	
System	Liver microsomes
Was an appropriate system used?	☑ Yes ☐ No
Methods	The metabolism of PA-824 was examined in 3 different studies: The incubation samples consisted of PA-824, concentrations ranging (1-50 µM), pooled human liver microsomes 0.1, 0.5 and 1.0 mg/mL. Each non-control sample was incubated in the presence of NADPH. The samples were analyzed by HPLC or LC/MS/MS.
Test (substrate or inhibitor) drug concentrations	Study (b) (4) 09645 and study (b) (4) 08638): PA-824 (substrate) concentration 5 µM (2 µg/mL) Study 0313251C: PA-824 (substrate) concentration 1, 2.5, 5, 10, 20, 35 and 50 µM
Were test drug	

concentrations appropriate?	☑ Yes ☐ No
RESULTS AND CONCLUSIONS	
PA-824 is poorly metabolized by microsomal human P450 following all *in vitro* incubations. In studies (b) (4) 9645 and (b) (4) 08638, 77-90 % PA-824 was remaining after 1 hour of microsomal incubation, 61-81% PA-824 was remaining after 2 hours.	

Reference ID: 4476823

Cytochrome P450 phenotyping screen of PA-824 human recombinant CYP (rCYP) enzymes	
Study #	(b) (4) 10605
Link	\\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4) 10605 (b) (4) -10605-pre-clinical-study-report.pdf
Objectives	To evaluate cytochrome P450 phenotyping screen of PA-824 human recombinant CYP (rCYP) enzymes
METHODS	
System	rCYP (CYP3A4, CYP2C9, CYP2C19, and CYP2D6)
Was an appropriate system used?	☑ Yes ☐ No
Methods	PA-824 (1 µM) were incubated with rCYP (0.125 mg/mL). Metabolism of PA-824 at 15, 30, 45, and 60 minutes was assessed by calculating the percentage parent depletion at each timepoint compared to the 0 minute sample. The samples were analyzed by LC/MS/MS.
Test (substrate or inhibitor) drug concentrations	PA-824 (substrate) concentration 1 µM
Were test drug concentrations appropriate?	☑ Yes ☐ No
RESULTS AND CONCLUSIONS	
• Recovery of PA-824 was 79.8% following incubation with rCYP3A4, the results indicated that CYP3A4 plays a minor role in the metabolism of PA-824, i.e., approximately up to 20% metabolism by CYP3A4. • Incubation in the presence of the CYP3A4-specific chemical inhibitor, ketoconazole showed inhibition of pretomanid metabolism, with parent recovery approximately 100%. • Recovery of pretomanid was almost 100% for reactions with CYP2C9, CYP2C19, and CYP2D6, demonstrating that these enzymes are not involved in the metabolism of pretomanid.	

Determination of Induction Potential of PA-824 for CYP P450 Isoforms in Human Hepatocytes	
Study #	(b) (4) 016401-1
Link	\\cdsesub1\evsprod\nda212862\0001\m4\42-stud-rep\422-pk\4224-metab (b) (4) -016401-1 (b) (4) -016401-1-pre-clinical-study-report.pdf
Objectives	Determine if PA-824 is an inducer of CYP enzymes
METHODS	
System and controls	

Study	System	# donors	Incubation time
	Primary human hepatocytes	4	72 hours

CYP	Positive control inducer (concentration)
CYP2E1	Rifampicin, 50 µM Isoniazid, 100 µM
CYP3A4	Rifampicin, 50 µM
CYP2C9	Rifampicin, 50 µM

Method	• Hepatocytes were treated with three concentrations of PA-824 (0.2, 2 and 20 µg/ml), vehicle and positive controls for 72 hours. • At the end of the incubation period, the hepatocytes were washed with PBS. The hepatocytes were then incubated with CYP specific substrates. • The medium was removed and stored at -20 °C prior to LCMS/MS analysis.
Was the study design appropriate?	

Study	Was the study design appropriate?
	☑ Yes ☐ No Variation is high between different hepatocytes donors. Reason for variation is not clear.

Were test drug concentrations appropriate?	Cmax was ~ 1.7-5.3 µg/mL (4.7-14.6 µM).

concentration	Were test drug concentrations appropriate?
0.2, 2, 20 µg/mL	☑ Yes ☐ No

RESULTS AND CONCLUSIONS
RESULTS:

Table 1: CYP Induction with PA-824 (% of positive control Induction)

Concentration µg/mL	CYP3A4		CYP2C9			CYP2E1		
	Donor 2	Donor 4	Donor 2	Donor 4	Donor 5	Donor 3	Donor 4	Donor 5
PA 824 20 µg/mL	0.35	-8.22	17.01	57.11	-9.65	35.13	-22.06	4.58
PA 824 2 µg/mL	-0.07	3.46	23.22	21.14	30.88	48.30	-8.49	70.14
PA 824 0.2 µg/mL	0.27	28.00	23.03	1.84	12.28	107.27	-14.62	34.28

Calculation Based on equation: %of positive control induction = (Sample activity - vehicle control activity)/(Positive control activity-vehicle control activity)*100

CONCLUSION:

CYP	% increase in enzyme activity	Conclusion
CYP2E1	Increase in CYP2E1 activity ranged from approximately 5-107% of positive control at 0.2, 2, and 20 µg/ml PA-824 in three of 4 donors. Increase in activity was not dose dependent.	CYP2E1 induction potential by PA-824 is inconclusive because of high degree of variation in CYP induction results.
CYP2C9	Increase in CYP2C9 activity ranged from approximately 2-57% of positive control at 0.2, 2, and 20 µg/ml in three of 4 donors. Increase in activity was not dose dependent.	Slight increase in CYP2C9 enzyme activity at PA-824 concentration 20 µg/mL (approximately 4-fold higher than clinically relevant concentration).
CYP3A4	Slight increase in CYP3A4 activity ranging from 0.27 – 28% at 0.2, 2, and 20 µg/ml PA-824 in 2 of 4 donors; increase in CYP3A4 activity was not seen at 20 µg/mL PA-824 concentrations (0.35% of control).	Based on results from 2 donors, potential for *in vivo* CYP3A4 induction by PA-824 appears to be minimal.

15.4. Clinical Microbiology Supporting Documents

15.4.1. Mechanism of Action

Pretomanid is a bicyclic nitroimidazole, which is activated within the *M. tuberculosis* (MTB) cells by a deazaflavin (F420) dependent nitroreductase (Ddn) resulting in release of reactive nitrogen species such as nitric oxide (NO) (Figure 15-1)[47,48]. Under anaerobic conditions, NO interferes with electron flow and ATP homeostasis.

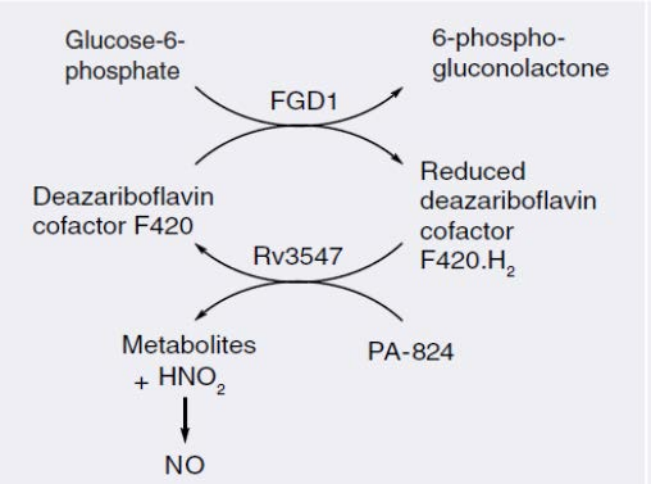


Figure 15-1 Proposed mechanism of reductive activation of pretomanid

Source: Denny and Palmer 2010

A pretomanid–dependent production of HNO_2 by Ddn was observed in the presence of $F420H_2$[49]. A strong correlation between the amount of des-nitro (the major metabolite of pretomanid) formed and anaerobic killing activity was observed (Figure 15-2). The effect of pretomanid on the respiratory complex under hypoxic non-replicating conditions was also manifested by a rapid drop in intracellular ATP levels (Figure 15-3).

[47] Denny and Palmer. The nitroimidazooxanines (PA-824 and analogs): structure-activity relationship and mechanistic studies. Future Med. Chem 2010, 2 (8), 1295-1304.
[48] Gurumurthy et al. Substrate specificity of the deazaflavin-dependent nitroreductase (Ddn) from *Mycobacterium tuberculosis* responsible for the bioreductive activation of bicyclic nitroimidazoles. FEBS J. 2012 January; 279(1): 113–125.
[49] Singh R, Manjunatha U, Boshoff HIM et al. PA-824 kills nonreplicating *Mycobacterium tuberculosis* by intracellular NO release. Science 322, 1392–1395 (2008).

Reference ID: 4476823

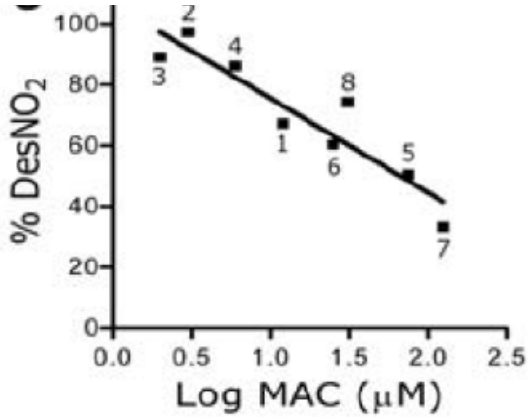


Figure 15-2 Formation of NO and correlation with anaerobic activity.

Source: Singh et al., 2008

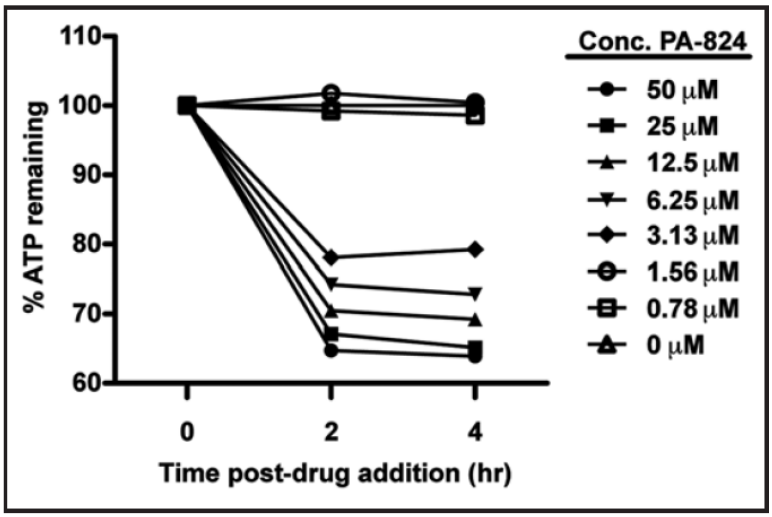


Figure 15-3. Effect of pretomanid treatment on cellular ATP levels on NRP-2 cells.

Note: Intracellular ATP was quantified by using the BacTiter-Glo Microbial Cell Viability Assay Kit (Promega) to measure luminescence. Source. Manjunath et al., 2009

Transcriptional profiling analyses of pretomanid treated cells suggest that inhibition of both cell wall biosynthesis and respiration contribute to the mechanism of action[50]. Several genes involved in cell wall, fatty acid, and respiration, namely, the *fasI* gene, the *efpA* gene, the *iniBAC* operon, the *cyd* operon (*cydA, cydB, cydD* and *cydC*) and the *narGHIJ* genes were upregulated similar to profiles of cell wall inhibitors and cytochrome c oxidase-specific inhibitors like potassium cyanide. Like the respiratory inhibitor cyanide, pretomanid dramatically shifted the predominant isoprenoid quinol/quinone ratio (MK9H2/MK9) in a time and concentration dependent manner and impacts the redox status of the cells.

[50] Manjuanatha U, Boshoff HI, Barry CE. The mechanism of action of PRETOMANID: novel insights from transcriptional profiling. Commun. Integr. Biol. 2, 215–218(2009).

Under aerobic conditions, activated pretomanid inhibits lipid biosynthesis in a dose dependent manner[51]. In the presence of pretomanid, protein synthesis (incorporation of ^{35}S) and lipid synthesis (uptake of ^{14}C-acetate into mycolic acid precursors) were both inhibited in a dose-dependent manner in the *Mycobacterium bovis* BCG strain. Concentrations of ketomycolate decreased with increasing drug, suggesting that pretomanid may inhibit an enzyme or deplete a cofactor involved in the oxidation of hydroxymycolate to ketomycolate.

Reviewer comment: The mechanism of action of pretomanid has been characterized in replicating and non-replicating M. bovis BCG and MTB cells, under aerobic and anaerobic conditions, respectively. Like other mycobactericidal bicyclic nitroimidazoles, pretomanid is metabolically activated within the MTB bacterium by the cofactor F420-dependent deazaflavin-dependent nitroreductase Ddn, resulting in a des-nitroimidazole active moiety. Reduction of F420 is accomplished by the F420-dependent glucose-6-phosphate dehydrogenase, Fgd1. Downstream effects under aerobic conditions include inhibition of cell wall biosynthesis via blockage of the oxidation of hydroxymycolate to ketomycolate. Under anaerobic conditions, bioreduction of pretomanid generates reactive nitrogen species and results in respiratory poisoning.

15.4.2. Antibacterial Activity

<u>Susceptibility test methods:</u>
The BACTEC 960 Mycobacterial Growth Indicator Tube (MGIT) System is a nonradiometric system, which uses an O_2-sensitive fluorescence sensor embedded at the bottom of the culture tubes to monitor mycobacterial growth. The MGIT system is approved for testing of first-line and second-line TB drugs. The configuration of the MGIT system was extended to determine susceptibility testing of MTB to pretomanid, bedaquiline and linezolid in the clinical studies. The standard method for susceptibility testing of MTB recommended by the Clinical and Laboratory Standards Institute (CLSI) is the agar proportion method (CLSI M24 A3 document 2018). Resazurin Microtiter Assay (REMA) and Microtiter Based Alamar Blue (MABA) are broth microdilution assays that use a colorimetric redox indicator. These assays were used in *in vitro* studies for comparison.

Reviewer comment: The REMA and MABA are not FDA approved assays for susceptibility testing of TB drugs but are used in resource-constrained settings. These assays are not standardized for susceptibility testing of MTB.

<u>*In vitro* activity using various methods:</u>

[51] Stover CK, Warrener P, Van Devanter DR et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature 405, 962–966 (2000).

Reference ID: 4476823

The *in vitro* activity of pretomanid against MTB has been studied by a number of groups using several different methods (TBA-354-NCLN-072-A, Stover et al., 2000; Upton et al., 2015; Feuerriegel et al., 2011)[Error! Bookmark not defined.,52,53]

MTB H37Rv strain was used as a control when comparing the activity of pretomanid across studies. The MIC values for pretomanid against MTB H37Rv ranged from 0.12 to 0.25 mcg/mL irrespective of the method (BACTEC, Agar dilution or MGIT) or testing laboratory, except one study (Upton et al., 2015), where the reported MIC value was 0.012 mcg/mL (Table 15-1).

Table 15-1. MTB H37Rv MIC results from *in vitro* studies

Method	MIC (µg/mL)	Reference
BACTEC	0.13	Stover et al., 2000
Agar	0.12	TBA-354-NCLN-072A
MGIT	0.25	Feuerriegel et al., 2011
MABA	0.012	Upton et al., 2015

MABA = microplate-based Alamar Blue assay; MGIT = mycobacterial growth indicator tube; MIC = minimal inhibitory concentration;

The *in vitro* activity of pretomanid against MTB (35 clinical isolates from the NC-006 trial, 2 pretomanid-resistant mutants (14A1 and T3) and MTBH37Rv strain) was compared using MGIT, REMA and Agar proportion methods (Table 15-2). The REMA MIC results were 2- to 4 -folds lower than MGIT results. Where all 3 methods were used, the fold difference between MGIT and Agar proportion ranged from 2 to 8. The well-characterized pretomanid resistant strains displayed MIC >4 mcg/mL by all methods.

[52] Upton AM, Cho S, Yang TJ, Kim Y, Wang Y, Lu Y, et al. *In vitro* and *in vivo* activities of the nitroimidazole TBA-354 against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2015 Jan; 59(1): 136-44.
[53] Feuerriegel S, Koser CU, Bau D, Rusch-Gerdes S, Summers DK, Archer JA, et al. Impact of Fgd1 and Ddn diversity in *Mycobacterium tuberculosis* complex on *in vitro* susceptibility to PA-824. Antimicrob Agents Chemother. 2011 Dec; 55(12): 5718-22.

Reference ID: 4476823

Table 15-2. Comparison of the activity of pretomanid when tested by MGIT, REMA and Agar Proportion.

Isolate/strain	MIC by MGIT (µg/mL)	MIC by REMA (µg/mL)	MIC by agar proportion (µg/mL)	Fold difference (MGIT vs REMA)	Fold difference (MGIT vs agar)
NC-006-0201-004	1	0.25		4	
NC-006-0204-003	0.25	0.125	0.063	2	4
NC-006-0301-015	0.062	0.063		1	
NC-006-0302-642	0.25	0.25		1	
NC-006-0302-655	0.125	0.25		0.5	
NC-006-0305-016	0.125	>4[1]		NA	
NC-006-0305-033	0.125	≤0.031		≥4	
NC-006-0307-008	0.125	0.125	0.031	1	4
NC-006-0309-007	0.125	0.125		1	
NC-006-0310-031	0.125	>4[1]		NA	
NC-006-0313-008	0.125	≤0.031		≥4	
NC-006-0401-001	0.125	≤0.031		≥4	
NC-006-0402-002	0.062	≤0.031	0.016	≥2	4
NC-006-0501-001	0.25	0.25		1	
NC-006-0501-002	0.5	0.5		1	
NC-006-0501-003	0.25	0.125		2	
NC-006-0501-004	0.25	0.063	0.031	4	8
NC-006-0601-004	>16	>4	16	NA	≥1
NC-006-0601-008	0.125	0.063		2	
NC-006-0602-003	0.062	≤0.031	0.031	≥2	2
NC-006-0602-014	0.25	0.063		4	
NC-006-0602-016	0.125	≤0.031		≥4	
NC-006-0701-001	0.125	0.063		2	
NC-006-0702-002	0.062	0.125		0.5	
NC-006-0702-004	0.125	0.063		2	
NC-006-1002-002	1	0.5		2	
NC-006-1003-007	0.5	0.5		1	
NC-006-1003-010	1	0.25	0.25	4	4
NC-006-1003-012	1	0.25		4	
NC-006-1003-018	1	0.25		4	
NC-006-1004-007	1	4		0.25	
NC-006-1004-012	1	0.5		2	
NC-006-1301-006	0.125	0.063	0.063	2	2
NC-006-1301-007	0.125	0.12		1	
NC-006-1301-008	0.125	≤0.031		≥4	
H37Rv	0.125-0.25	≤0.031-0.25	0.031	NA	≥4
14A1	>16	16	8	≥2	≥4
T3	>16	16	>16	≥2	NA

MGIT = mycobacterial growth indicator tube; MIC = minimal inhibitory concentration; NA = not applicable; REMA = resazurin microtiter assay

[1] The culture originally tested by REMA was later found contaminated with NTM bacteria; a new, purified culture was then tested by MGIT only and as a result, a comparison of activity for this isolate across methods is not applicable (NA). MIC range tested by REMA: 4 to 0.03 µg/mL; MIC range tested by MGIT for Nix-TB: 2 to 0.063 µg/mL; MIC range tested by MGIT during Pretomanid-NCLN-MICRO-003: 16 to 0.031 µg/mL.

Source: Pretomanid-NCLN-MICRO-004 Study Report

MIC ranges, MIC_{50} and MIC_{90} values (MIC values at which 50% and 90% of isolates are inhibited, respectively) have been reported using 3 different methods on 98 drug susceptible (DS) MTB isolates, 35 isolates resistant to both isoniazid and rifampicin (MDR-MTB), and 11 isolates resistant to any fluoroquinolone and at least one of three second-line injectable

(capreomycin, kanamycin, and amikacin) in addition to multidrug resistance (XDR-MTB) (Table 15-3). The pretomanid MIC_{90} against 68 DS MTB isolates, 26 MDR MTB, and 6 XDR MTB by the agar dilution method was 0.48 mcg/mL. The pretomanid MIC range against the 68 DS-TB isolates was 0.005 to 0.48 mcg/mL while against the 26 MDR and the 6 XDR-MTB isolates, the pretomanid MIC range was 0.005 to 16 mcg/mL. One isolate, TN 30425, with MIC of 16 mcg/mL was resistant to pretomanid. Sequence analysis of this isolate revealed a mutation in the *fbiC gene* (responsible for F_{420} biosythesis).

Table 15-3. Summary of the activity of pretomanid against MTB DS, MDR, and XDR isolates.

M. tuberculosis resistance phenotype	n	Method	Concentrations Tested (µg/mL)	Pretomanid MIC (µg/mL)[1]			Reference
				MIC Range	MIC_{50}	MIC_{90}	
DS/Monoresistant MTB	13	BACTEC[2]	NA	0.015 - 0.25	0.06	0.13	Stover et al., 2000
	68	Agar dilution	1.92, 0.48, 0.12, 0.04, 0.01, and 0.005	0.005 – 0.48	0.04	0.48	Study Report TBA-354-NLCN-072A
	12	MGIT	1, 0.5, 0.25, 0.125, 0.0625, and 0.0312	≤0.0312 – 0.25	0.125	0.25	Feuerriegel et al., 2011
	4	MABA	NA	0.012 – 0.5	-	-	Upton et al., 2015
Polyresistant/MDR MTB	11	BACTEC	NA	0.03 – 0.25	0.06	0.25	Stover et al., 2000
	26	Agar dilution	1.92, 0.48, 0.12, 0.04, 0.01, and 0.005	0.005 – 16[3]	0.12	0.48	Study Report TBA-354-NLCN-072A
	5	MABA	NA	0.137 – 0.248	-	-	Upton et al., 2015
XDR MTB *M. tuberculosis* resistance phenotype	6	Agar dilution	1.92, 0.48, 0.12, 0.04, 0.01, and 0.005	0.04 – 0.48	-		Study Report TBA-354-NLCN-072A
	1	MABA	NA	0.248	-	-	Upton et al., 2015

DS = drug-susceptible; MABA = microplate-based Alamar Blue assay; MDR = multidrug-resistant; MGIT = mycobacteria growth indicator tube; MIC = minimum inhibitory concentration; MTB = *Mycobacterium tuberculosis*; NA = not available; XDR = extensively drug-resistant

[1]Individual listings were included in Appendix 6.3 and Appendix 6.4 of the NDA submission.

[2] Description of the BACTEC460, agar proportion, MGIT and MABA methods were included in section above.

[3]One MTB isolate was determined to be highly resistant to pretomanid, with an MIC of 16 mcg/mL.

Using the BACTEC radiometric method, the pretomanid MIC against 13 DS- or rifampicin-resistant-MTB isolates and H37Rv strain ranged from 0.015 to 0.25 mcg/mL.

In the MABA method, MIC values were defined as the lowest concentration that resulted in a 90% reduction in fluorescence relative to control. MABA was used to test 4 DS-TB, 1 MDRTB, and 5 XDR-TB isolates mL. The pretomanid MICs against these isolates by MABA method ranged from 0.14 to 0.25 mcg/mL.

The pretomanid MIC range against 12 DS-TB isolates using the MGIT system was <0.03 to 0.125 mcg/mL. Pretomanid MIC values ranged from ≤0.03 to 0.125 mcg/mL against *M. bovis*, *M. africanum*, and *M. pinnipedii* isolates which were similar to the values obtained for MTB isolates. The two *M. canettii* isolates tested had MIC of 8 mcg/mL. Sequencing revealed a *fgd1* mutation (F420-dependent glucose-6-phosphate dehydrogenase) in one of the isolates. The higher pretomanid MIC in the other strain could not be explained as no mutation was detected in the ddn or *fgd1* genes.

Spectrum of activity:
The activity of pretomanid appears to be limited to the MTB complex. Pretomanid is inactive (MICs >128 mcg/mL) against nontuberculous mycobacteria (*M. smegmatis, M. fortuitum, M. phlei, M. kansasii* and *M. avium)*. Pretomanid shows weak activity against *M. ulcerans* (n = 29; MIC_{90} >16 mcg/mL), and *M. leprae* is resistant to pretomanid as it lacks a functional ddn gene.

Pretomanid has been shown to lack activity against other aerobic bacteria and yeast including *E. coli*, *S. aureus*, and *C. albicans*; however, it does display some activity against a small number of Gram-positive and Gram-negative anaerobic bacteria, with MICs in the range of 1 to 32 mcg/mL (Pretomanid-NCLN-MICRO-001).

Effect of serum on the *in vitro* activity of pretomanid:
The activity of pretomanid against replicating MTB H37Rv bacilli in the presence of 0.5-4% human albumin and 0.5-50% human serum was assessed using MABA. The assay was performed in Middlebrook 7H12 and 7H9 supplemented with oleic acid, dextrose, and catalase (OADC) in the presence or absence of human serum or human albumin. Pretomanid exhibited an ~7-fold increase in MIC in the presence of 50% human serum and an ~3-fold increase in MIC in the presence of 4% human albumin (Table 15-4). In another study (Upton et al 2015)[Error! Bookmark not defined.], pretomanid exhibited an ~2-fold increase in MIC in the presence of 4% bovine serum albumin and no change in activity in the presence of 10% fetal bovine serum by MABA assay.

Table 15-4. Effect of serum and albumin on Microplate Alamar Blue Assay minimum inhibitory concentration of pretomanid.

MIC (µM) of pretomanid using the following media:								Source
7H12 medium containing:				7H9 medium +OADC containing:				
Human serum		Human albumin		Human serum		Human albumin		
0.5%	50%	0.5%	4%	0.5%	50%	0.5%	4%	
0.12 (0.04 µg/mL)	0.85 (0.31 µg/mL)	0.20 (0.07 µg/mL)	0.75 (0.27 µg/mL)	0.21 (0.08 µg/mL)	1.39 (0.50 µg/mL)	0.25 (0.09 µg/mL)	0.77 (0.28 µg/mL)	Franzblau et al., 2012

7H12 medium	7H12 medium + 4% Bovine serum albumin	7H12 medium+10% Fetal bovine serum	Source
0.04 (0.014 µg/mL)	0.072 (0.0025 µg/mL)	0.038 (0.014 µg/mL)	Upton et al., 2015

MIC = minimum inhibitory concentration; OADC = oleic acid, dextrose, and catalase

Reference ID: 4476823

In vitro activity of pretomanid against non-replicating MTB:
Several studies have assessed the activity of pretomanid against non-replicating MTB, where the non-replicating state of the bacteria was induced by a variety of stringent culture conditions.

In the study by Stover et al (2000)[Error! Bookmark not defined.], MTB H37Rv containing the luciferase-expressing vector pMV361-*lux* were incubated with test drugs under microaerophilic conditions for 7 days. The cells were then centrifuged and transferred to drug-free media and incubated under aerobic conditions. Bactericidal activity was inferred by growth of culture following transfer to aerobic conditions. Pretomanid and INH reduced bacterial counts at day 4 by ~3 and ~1 $\log_{10}$, respectively (Figure 15-4).

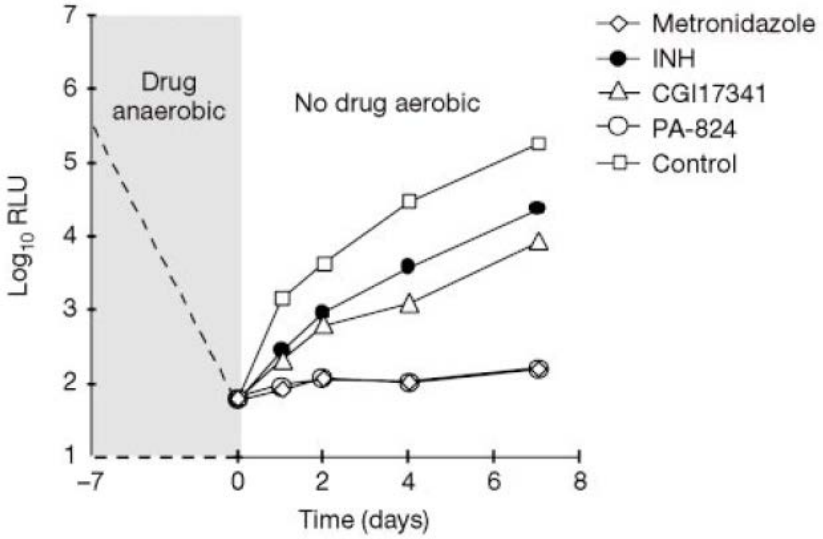


Figure 15-4. Activity of pretomanid on non-replicating MTB H37Rv

Note: INH = isoniazid; PA-824= pretomanid; RLU = relative light units. Source: (Stover et al., 2000).

In another study (Lenaerts et al., 2005)[54], 24-day-old anaerobic cultures of MTB were treated for 96 hours under anaerobic conditions. Pretomanid exhibited concentration-dependent activity, with 85, 89.6, and 93.5% killing at 2, 10, and 50 mcg/mL, respectively (Table 15-5). Rifampicin, gatifloxacin, and moxifloxacin demonstrated concentration-dependent activity, with bactericidal activity of 98.6 to 100% at 10 to 50 mcg/mL. Isoniazid (with activity primarily against replicating bacteria) displayed weak activity against non-replicating bacilli in this assay.

[54] Lenaerts AJ, Gruppo V, Marietta KS, Johnson CM, Driscoll DK, Tompkins NM, et al. Preclinical testing of the nitroimidazopyran PRETOMANID for activity against *Mycobacterium tuberculosis* in a series of *in vitro* and *in vivo* models. Antimicrob Agents Chemother. 2005 Jun; 49(6): 2294-301.

Reference ID: 4476823

Table 15-5. Growth of MTB cultures following 28 days of oxygen depletion after 96 hours of incubation with drugs.

Compound	Concentration (µg/mL)	Log_{10} CFU ± SEM (per mL)	% Growth compared with untreated controls at Day 28[1]
None	-	6.42 ± 0.05	
Isoniazid	2	6.38 ± 0.14	92.8
	10	6.32 ± 0.11	80.4
	50	6.20 ± 0.10	60.6
Rifampicin	2	5.15 ± 0.01	5.2
	10	4.10 ± 0.14	0.5
	50	1.40 ± 0.00	0.0
Gatifloxacin	2	5.27 ± 0.38	9.7
	10	4.29± 0.27	0.9
	50	3.85[2]	0.3
Moxifloxacin	2	5.72± 0.48	32.8
	10	4.13 ± 0.22	0.6
	50	4.56 ± 0.14	1.4
Metronidazole	2	ND	ND
	10	5.58 ± 0.10	14.6
	50	5.38 ± 0.28	10.9
Pretomanid	2	5.61 ± 0.00	15.0
	10	5.43 ± 0.12	10.4
	50	5.24 ± 0.01	6.5

CFU = colony-forming units; ND = not done; SEM = standard error of the mean
[1] Percentage of bacterial growth of drug-treated cultures is compared with growth of untreated controls (represented at 100% growth).
[2] Data are based on a single culture tube.
Source: (Lenaerts et al., 2005)

The activity of pretomanid against non-replicating MTB was also determined using the high-throughput Low Oxygen Recovery Assay (LORA) with a luminescence readout (Cho et al., 2007)[55]. Cultures of MTB H37Rv carrying a lux-expressing plasmid were placed under low oxygen conditions for 10 days, and MIC values were compared with those obtained with aerobic cultures incubated for 7 days. The MIC determined using low oxygen conditions was 1.12 mcg/mL while those under aerobic conditions was 0.22 mcg/mL. Pretomanid was active against both replicating and non-replicating MTB in this assay.

[55] Cho SH, Warit S, Wan B, Hwang CH, Pauli GF, Franzblau SG. Low-oxygen-recovery assay for high-throughput screening of compounds against nonreplicating *Mycobacterium tuberculosis*. Antimicrob Agents Chemother. 2007 Apr; 51(4): 1380-5.

MTB H37Rv was cultured either aerobically or anaerobically in Dubos Tween-albumin broth (DTAB) at pH 5.8 (Piccaro et al., 2013)[56]. Drugs were added to 5-day-old aerobic cultures (A5 in Figure 15-5) or 5-, 12-, or 19-day-old hypoxic cultures (H5, H12 and H19 respectively, in Figure 15-5), and activity was evaluated after 7, 14, and 21 days of incubation. Pretomanid (2 mcg/mL) demonstrated ≥2 $\log_{10}$ CFU decreases in both aerobic and hypoxic cultures at day 21 compared to metronidazole (8 mcg/mL), which was effective against hypoxic cells only. Rifampicin (8 mcg/mL) decreased bacterial counts by ≥2 $\log_{10}$ in aerobic and hypoxic conditions.

	Growth stage and days of exposure											
	A5			H5			H12			H19		
Drug	7	14	21	7	14	21	7	14	21	7	14	21
Rifampin	●	●	●	●	●	●	●	●	●	●	●	●
Isoniazid	●	●	○	○	○	○	○	○	○	○	○	○
Pyrazinamide	○	○	○	○	○	○	○	○	○	○	○	○
Ethambutol	○	○	○	○	○	○	○	○	○	○	○	○
Amikacin	●	●	●	●	●	●	○	○	○	○	○	○
Moxifloxacin	●	●	●	●	●	●	○	○	○	○	○	○
Metronidazole	○	○	○	○	○	○	○	○	●	○	●	●
Nitazoxanide	●	●	●	○	●	●	○	○	●	○	●	●
Niclosamide	○	○	○	○	○	○	○	○	○	○	○	○
PA-824	●	●	●	●	○	○	○	○	●	○	●	●

CFU = colony forming unit; PA-824 = pretomanid; A5 = 5-day-old aerobic cultures; H5, H12, and H19 = 5-, 12-, or 19-day-old hypoxic cultures respectively.
Rapid comparison of antibiotic activities, outlined as 2-$\log_{10}$- CFU decreases.
Symbols: closed circles = ≥2-$\log_{10}$-CFU/mL decrease; open circles = <2-$\log_{10}$-CFU decrease.
Source: (Piccaro et al., 2013)

Figure 15-5. Comparison of antibacterial drug activities as 2-$\log_{10}$ colony forming unit decreases under acidified aerobic and hypoxic conditions.

The activity of pretomanid against MTB under conditions of hypoxia, and under acidic and neutral pH was assessed (Iacobino et al., 2017)[57]. The conditions are stated to simulate the environment of cellular granulomas and caseous, low-oxygen granulomas. MTB H37Rv were cultured for 40 days in Dubos-Tween-Albumin Broth (DTAB) adjusted to pH 5.8 or 7.3, to induce hypoxia for 12 (H12) or 19 (H19) days. Drugs were then added to the cultures and incubated for 7, 14, and 21 days. At day 21, pretomanid demonstrated >2 $\log_{10}$ reduction of non-replicating H12 and H19 bacilli at pH 5.8 and <1$\log_{10}$ reduction at pH 7.3.

Bactericidal Activity:
The minimum bactericidal concentration (MBC) for pretomanid against MtBH37Rv defined as the lowest concentration of the drug that reduced bacterial counts by 99% after incubation

[56] Piccaro G, Giannoni F, Filippini P, Mustazzolu A, Fattorini L. Activities of drug combinations against *Mycobacterium tuberculosis* grown in aerobic and hypoxic acidic conditions. Antimicrob Agents Chemother. 2013 Mar; 57(3): 1428-33.
[57] Iacobino A, Piccaro G, Giannoni F, Mustazzolu A, Fattorini L. *Mycobacterium tuberculosis* is selectively killed by rifampin and rifapentine in hypoxia at neutral pH. Antimicrob Agents Chemother. 2017 Mar; 61(3).

Reference ID: 4476823

under aerobic conditions for 7 days or low oxygen conditions for 10 days compared to initial inoculum was determined[Error! Bookmark not defined.]. Against replicating MTB H37Rv, the MABA MBC (0.02 mcg/mL) was 2-fold the MIC (0.01 mcg/mL) (Table 15-6). Under low-oxygen conditions, the LORA MBC for non-replicating MTB H37Rv (6.3 mcg/mL) was ~7.5 fold the MIC (0.82 mcg/mL).

Table 15-6. Minimum inhibitory concentration and minimum bactericidal concentration values for pretomanid under replicating and non-replicating conditions.

Parameter	MIC or MBC µM
MIC (replicating)	0.04 (0.01 µg/mL)
MBC (replicating)	0.061 (0.02 µg/mL)
LORA (NR) MIC	2.28 (0.82 µg/mL)
LORA (NR) MBC	17.4 (6.3 µg/mL)

LORA = low-oxygen recovery assay; MBC = minimum bactericidal concentration; MIC = minimum inhibitory concentration; NR = non-replicating
Source: Adapted from (Upton et al., 2015)

Similarly, the pretomanid MIC against MTB H37Rv in Middlebrook 7H9 broth was ≤0.125 mcg/mL and the MBC, defined as the lowest concentration of drug that reduced the initial inoculum by ≥99% was 2-fold higher (0.25 mcg/mL) (2018-Pretomanid *In vitro* Anti-TB Activity Study 1).

Time kill experiments were performed to assess the bactericidal activity of pretomanid against MTB H37Rv using Middlebrook 7H9 broth containing 10% OADC (oleic acid, albumin, dextrose, and catalase) and 0.05% Tween 80 under aerobic conditions (JHU 2018-Pretomanid *In Vitro* Anti-TB Activity Study 1). Pretomanid at concentrations of 0.5, 1.0 and 2.0 mcg/mL reduced bacterial counts by 2 to 2.5 $\log_{10}$ by day 3, but no further reduction was observed at day 5 (Figure 15-6). Pretomanid at 2 mcg/mL reduced bacterial counts by 4 $\log_{10}$ at day 5.

Reference ID: 4476823

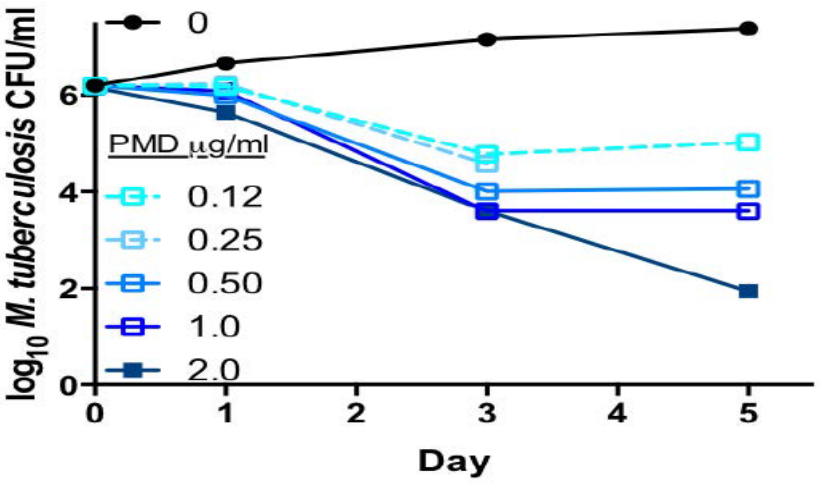


Figure 15-6. Time-kill Assay against *M. tuberculosis* H37Ra in Complete Middlebrook 7H9 Broth containing Tween 80.

The time kill experiments to evaluate the bactericidal activity of pretomanid against MTBH37Rv were also performed under anaerobic conditions (Somasundaram et al., 2013)[58]. Two concentrations of pretomanid were tested (3 and 12.5 mcg/mL). Pretomanid (12.5 mcg/mL) reduced bacterial counts by 2.5 $\log_{10}$ by day 7 and to the limit of detection by day 21 (Figure 15-7). Since the experimentation was performed in non-acid condition, pyrazinamide (PZA) was not active (no change in the log CFU/ml up to day 21).

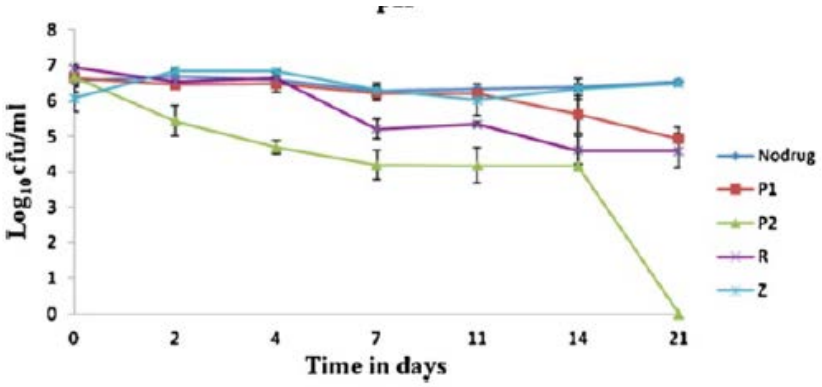


Figure 15-7 Bactericidal activity of pretomanid on MTB H37 RV under anaerobic condition.

Note: P1 and P2: pretomanid at 3 and 12.5 mcg/ml; R: Rifampicin at 1 mcg/ml; Z: Pyrazinamide at 50 mcg/ml. Source: (Somasundaram et al., 2013)

[58] Somasundaram S, Anand RS, Venkatesan P, Paramasivan CN. Bactericidal activity of PA-824 against Mycobacterium tuberculosis under anaerobic conditions and computational analysis of its novel analogues against mutant Ddn receptor. BMC Microbiol. 2013 Oct 1; 13: 218.

In summary, pretomanid exhibits both concentration-dependent and time-dependent bactericidal activity, *in vitro*.

Intracellular Activity:
The intracellular activity of pretomanid was examined using MTB H37Rv infected J774 mouse macrophages (JHU 2018-Pretomanid *In vitro* Anti-TB Activity Study 1). The infected macrophages were exposed to various concentrations of pretomanid and lysed on days 0, 3, and 7 to determine MTB CFU's by plating on Middlebrook 7H11 media. The mean pretomanid concentrations for bacteriostatic and 1-$\log_{10}$ CFU kill over 7 days were approximately 0.54 and 1.2 mcg/mL, respectively (Table 15-7).

Table 15-7. Pretomanid activity against MTB H37Rv Infecting Cultured J774 Mouse Macrophages.

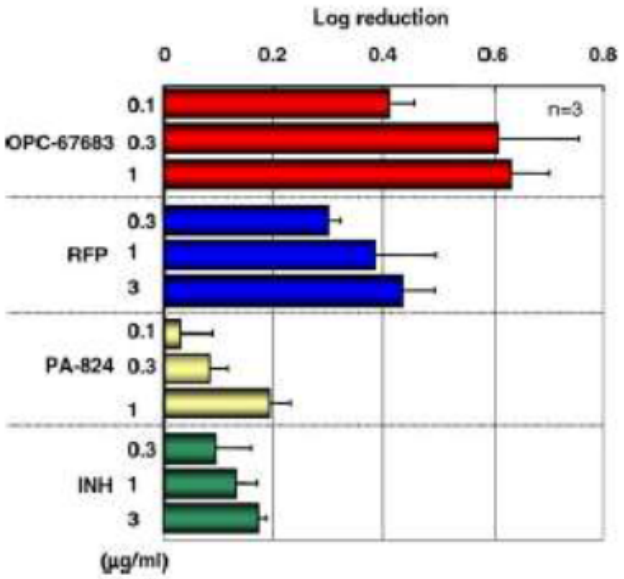
Day	Mean PMD concentration (range) resulting in Δ $\log_{10}$ CFU value of:	
	0	-1
3	1.39 µg/ml (0.824, 2.33)	* (2.605, ∞)
7	0.543 µg/ml (0.412, 0.718)	1.18 µg/ml (0.716, 1.94)

*no mean provided since 1 log kill was not reached on Day 3 in Expt 2

The intracellular activity of pretomanid against MTB H37Rv was also examined using differentiated human THP-1 monocytes (Matsumoto et al 2006)[59]. In this study, pretomanid at a concentration of 1 mcg/mL reduced intracellular bacterial counts by 0.2 $\log_{10}$ (Figure 15-8) similar to 3 mcg/mL isoniazid. Delamanid (OPC-67683, 1 mcg/mL) and rifampicin (3 mcg/mL), reduced intracellular bacterial counts by approximately 0.6 $\log_{10}$, and 0.4 $\log_{10}$, respectively. The MIC values for delamanid, rifampicin, pretomanid, and isoniazid against MTB H37Rv were 0.012, 0.78, 0.2, and 0.1 mcg/mL, respectively.

[59] Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis *in vitro* and in mice. PLoS Med. 2006 Nov; 3(11): e466.

Reference ID: 4476823



INH = isoniazid; PA-824 = pretomanid; RFP = rifampicin
Effect of pulsed exposures of delamanid (OPC-67683), rifampicin, pretomanid and isoniazid on the intracellular growth of MTB H37Rv within THP-1 cells. Infected cells were incubated with test compounds for 4 hours, washed and cultured for 68 hours at 37°C, plated on 7h11 agar, and counted for colonies after 16 days of growth at 37°C. Values represent mean ± standard deviation (n = 3).
Source: (Matsumoto et al., 2006)

Figure 15-8. Effect of exposures to delamanid, rifampicin, isoniazid, and pretomanid.

Reviewer comment: Pretomanid is active in vitro against replicating and nonreplicating MTB. The pretomanid MICs vary with the method used for susceptibility testing. Pretomanid is active against drug-resistant clinical isolates with MIC_{90} of ≤0.48 mcg/mL. The pretomanid MIC values increased 3- to 7-fold in the presence of human serum or albumin. The pretomanid MBCs were 2-fold the MIC values. The bactericidal activity of pretomanid is concentration- and time-dependent. The intracellular activity of pretomanid is similar to isoniazid and lower than rifampicin.

15.4.3. Antibacterial Activity in Animal Models

The *in vivo* activity of pretomanid administered as oral monotherapy was examined in several murine models of acute, chronic and latent TB infection (BALB/c, gamma interferon knock-out, C57BL/6, C3HeB/FeJ) and in a guinea pig TB model. These models were used to evaluate monotherapy doses and doses for continuous phase of therapy.

<u>Monotherapy:</u>
A luminescent reporter strain of MTB H37Rv (10^6 CFU) was used to infect BALB/c mice intravenously and the relative light units (RLU) emitted from lungs and spleens after treatment was measured as a surrogate for CFU quantitation (Stover et al 2000). The reduction in RLU in the spleen and lung tissues in mice treated with 25 mg/kg/day pretomanid was similar to the reduction observed with 25 mg/kg/day isoniazid (Figure 15-9). The RLU were reduced to the limit of detection in lungs and spleens of mice treated with 100 mg/kg pretomanid.

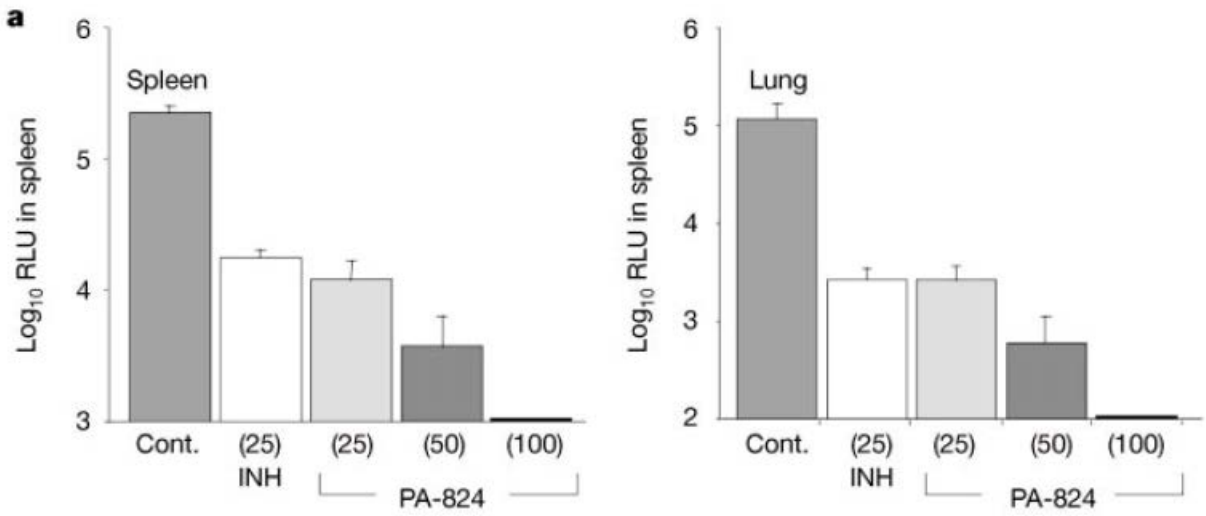


Figure 15-9. *In vivo* activity of pretomanid against MTB in a murine spleen and lung infection model.

Note: INH = isoniazid; PA-824 = pretomanid; RLU = Relative light units. BALB/c mice were infected intravenously with roughly 10^6 CFU of an MTB H37Rv reporter strain for 4 days before daily oral administration of drug at indicated levels (parentheses) for 10 days. Relative light units from surviving MTB reporter strain in in mouse lungs and spleens were determined 10 days after treatment initiation. Source: (Stover et al., 2000)

To determine the minimal effective dose (MED, the lowest dose that prevents development of gross lung lesions and splenomegaly) and minimal bactericidal dose (MBD, the lowest dose that reduces lung CFU burdens by 99% compared to pretreatment controls), BALB/c mice were infected via aerosol with ~10^4 $\log_{10}$ CFU of MTB H37Rv (Tyagi et al 2005)[21]. Oral treatment with pretomanid (doses: 3.125 mg/kg to 200 mg/kg; 5 times a week for 4 weeks) was initiated 24 hours post-infection and lung CFU was determined at the end of therapy. The pretomanid MED was determined to be 12.5 mg/kg (Figure 15-10). At the MED, pretomanid had bacteriostatic activity and dissemination of the infection to the spleen (<10 CFU/spleen) was detected in 5 of 11 mice. No dissemination occurred at doses ≥25 mg/kg. The MBD (100 mg/kg) was 8-fold higher than the MED.

Reference ID: 4476823

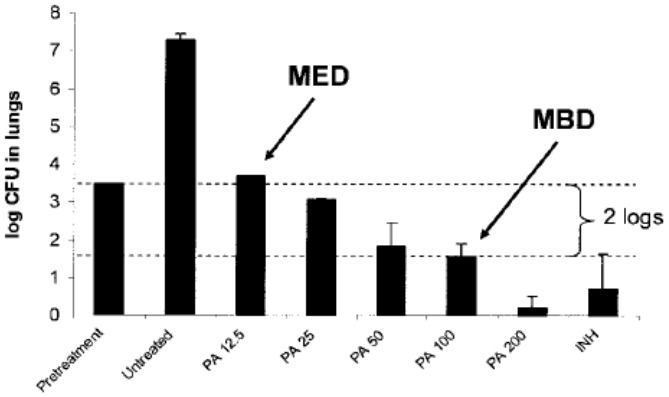


Figure 15-10. Log10 CFU counts in lungs after 1 month of daily treatment with the indicated dose (in mg/kg) of pretomanid or isoniazid (INH).

Note: Arrows denote the minimal effective dose (MED) and the minimal bactericidal dose (MBD). CFU = colony forming unit; PA = pretomanid; INH = isoniazid. Source: (Tyagi et al., 2005)

In the gamma interferon knockout (GKO) mouse model of TB, rapid infection and high lung burdens are observed with low-dose aerosol infection (Lenaerts et al., 2005)[60]. The GKO mice were infected with 50 to 100 CFU of the MTB Erdman strain and oral therapy with pretomanid (50, 100 or 300 mg/kg for 9 days) was initiated 19 days post-infection. pretomanid was formulated either in 0.5% methylcellulose (MC) or in cyclodextrin/lecithin (CM2). A $2\log_{10}$ and $3\log_{10}$ reduction in bacterial burden in the lungs of mice treated with 100 mg/kg and 300 mg/kg pretomanid was observed (Table 15-8). The activity of pretomanid at 100 mg/kg formulated in MC was similar to that of RIF at 20 mg/kg and INH at 25 mg/kg.

Table 15-8. Bacterial numbers in whole lungs and spleens of GKO mice after a 9-day drug treatment regimen.

Treatment regimen[a]	Log_{10} CFU ± SEM	
	Lungs	Spleens
D18, untreated controls	7.16 ± 0.06	5.61 ± 0.38
D28, untreated controls	8.28 ± 0.10	7.14 ± 0.02
D28, INH (25)	5.76 ± 0.11	3.59 ± 0.31
D28, RIF (20)	6.36 ± 0.14	5.14 ± 0.12
D28, moxifloxacin (100)	5.54 ± 0.09	3.25 ± 0.35
D28, moxifloxacin (300)	3.02 ± 0.19	0.90 ± 0.20
D28, PA-824 (50), MC	7.09 ± 0.09	5.35 ± 0.14
D28, PA-824 (100), MC	6.25 ± 0.06	4.89 ± 0.25
D28, PA-824 (300), MC	5.31 ± 0.25	4.24 ± 0.28
D28, PA-824 (50), CM2	6.68 ± 0.11	4.98 ± 0.25
D28, PA-824 (100), CM2	5.70 ± 0.14	3.92 ± 0.10
D28, PA-824 (300), CM2	6.01 ± 0.11	5.54 ± 0.11

[a] D18 and D28, treatment for 18 and 28 days, respectively; values in parentheses are doses (in milligrams per kilogram).

[60] Lenaerts AJ, Gruppo V, Marietta KS, Johnson CM, Driscoll DK, Tompkins NM, et al. Preclinical testing of the nitroimidazopyran PA-824 for activity against Mycobacterium tuberculosis in a series of *in vitro* and *in vivo* models. Antimicrob Agents Chemother.2005 Jun; 49(6): 2294-301.

The activity of pretomanid (100 mg/kg; 5 days a week for 3 weeks) was assessed using acute and chronic TB infection models (Upton et al 2015)[Error! Bookmark not defined.]. In the acute model, pretomanid was bacteriostatic (Figure 15-11). In the chronic model, pretomanid reduced bacterial burdens by 2 $\log_{10}$ CFU compared to the pretreatment controls.

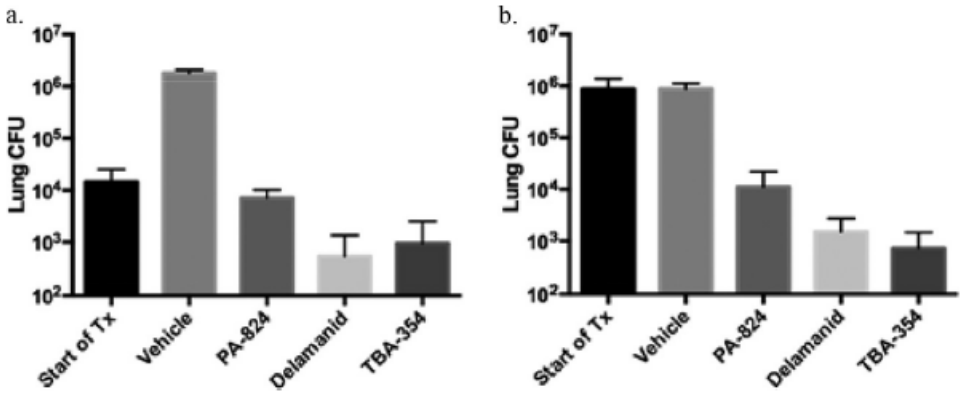


Figure 15-11. Efficacy of pretomanid, delamanid, and TBA-354 against acute and chronic tuberculosis in mice.

Note: Mtb Erdman infection in BALB/c mice. CFU = colony forming unit; PA-824 = pretomanid, Tx = treatment A) Acute infection model: inoculum was determined 3 days after infection. Treatment with vehicle or 100 mg/kg/day each nitroimidazole for 3 weeks, 5 days per week, commenced at day 10 post-infection (start of Tx) and terminated at day 28 post-infection. CFU were determined after a 3-day washout period, and at day 31 post-infection for vehicle- and nitroimidazole-treated mice. B) Chronic infection model: inoculum was determined 4 days post-infection. Treatment with vehicle or 100 mg/kg/day each nitroimidazole for 3 weeks, 5 days per week, started 70 days post-infection (start of Tx) and ended at day 88 post-infection. Colony forming units were determined, after a 3-day washout period, and at day 91 post-infection for vehicle- and nitroimidazole-treated mice. Source: (Upton et al., 2015)

In the immunocompetent C57BL/6 mouse model of chronic TB, mice were infected with 100 CFU of MTB Erdman strain. Oral therapy (pretomanid 100 mg/kg) was administered 5 days per week for 12 weeks. Comparators included isoniazid (INH, 25 mg/kg/day), moxifloxacin (MXF, 100 mg/kg/day), and gatifloxacin (GAT, 100 mg/kg/day). After 12 weeks of treatment, the bacterial burden in the lungs reduced by >3$\log_{10}$ in all treatment groups (Table 15-9). Reduction was also observed in the spleens. Overall, the efficacy of pretomanid was similar to that of comparators. However, complete eradication of the bacterial load (sterilizing activity) was not achieved after 12 weeks of monotherapy with any drug, including pretomanid.

Reference ID: 4476823

Table 15-9. Bacterial numbers in lungs and spleens of C57BL/6 mice after 2, 6, and 12 weeks of drug treatment.

Treatment regimen[a]	Lungs		Spleens	
	Log_{10} CFU ± SEM	n^b	Log_{10} CFU ± SEM	n^b
Start of treatment (untreated controls)	6.88 ± 0.11	5	5.59 ± 0.33	5
Wk 2, untreated controls	5.65 ± 0.24	5	4.40 ± 0.14	5
Wk 2, INH (25)	5.12 ± 0.17	5	3.93 ± 0.20	5
Wk 2, PA-824 (100)	4.71 ± 0.08	5	3.68 ± 0.09	5
Wk 2, gatifloxacin (100)	5.25 ± 0.17	5	4.11 ± 0.18	5
Wk 2, moxifloxacin (100)	4.64 ± 0.13	5	3.50 ± 0.40	5
Wk 6, untreated controls	5.00 ± 0.11	5	3.95 ± 0.15	5
Wk 6, INH (25)	3.79 ± 0.19	5	2.36 ± 0.08	5
Wk 6, PA-824 (100)	3.15 ± 0.09	5	2.64 ± 0.36	5
Wk 6, gatifloxacin (100)	3.79 ± 0.11	5	3.21 ± 0.12	5
Wk 6, moxifloxacin (100)	3.33 ± 0.18	5	1.77 ± 0.18	5
Wk 12, untreated controls	6.00 ± 0.07	6	4.54 ± 0.12	6
Wk 12, INH (25)	2.08 ± 0.16	5[c]	2.07 ± 0.15	5[c]
Wk 12, PA-824 (100)	2.56 ± 0.33	6	2.23 ± 0.11	6
Wk 12, gatifloxacin (100)	2.14 ± 0.13	6	2.31 ± 0.07	6
Wk 12, moxifloxacin (100)	1.75 ± 0.07	6	1.44 ± 0.09	6

[a] Values in parentheses are doses (in milligrams per kilogram).
[b] *n*, number of mice killed per time point.
[c] One mouse died during the treatment regimen due to a drug- or disease-unrelated event.

CFU = colony-forming units; INH = isoniazid; PRETOMANID = pretomanid; SEM = standard error of the mean; Source: (Lenaerts et al., 2005)

In a dose ranging study using the acute MTB infection BALB/c mice model, the highest dose of pretomanid (600 mg/kg) reduced lung burden by 2 logs similar to standard therapy (rifampicin, isoniazid, pyrazinamide (RHZ)) at 4 weeks (Figure 15-12). However, pretomanid-resistant mutants were observed at 8 weeks and found to be cross-resistant to delamanid.

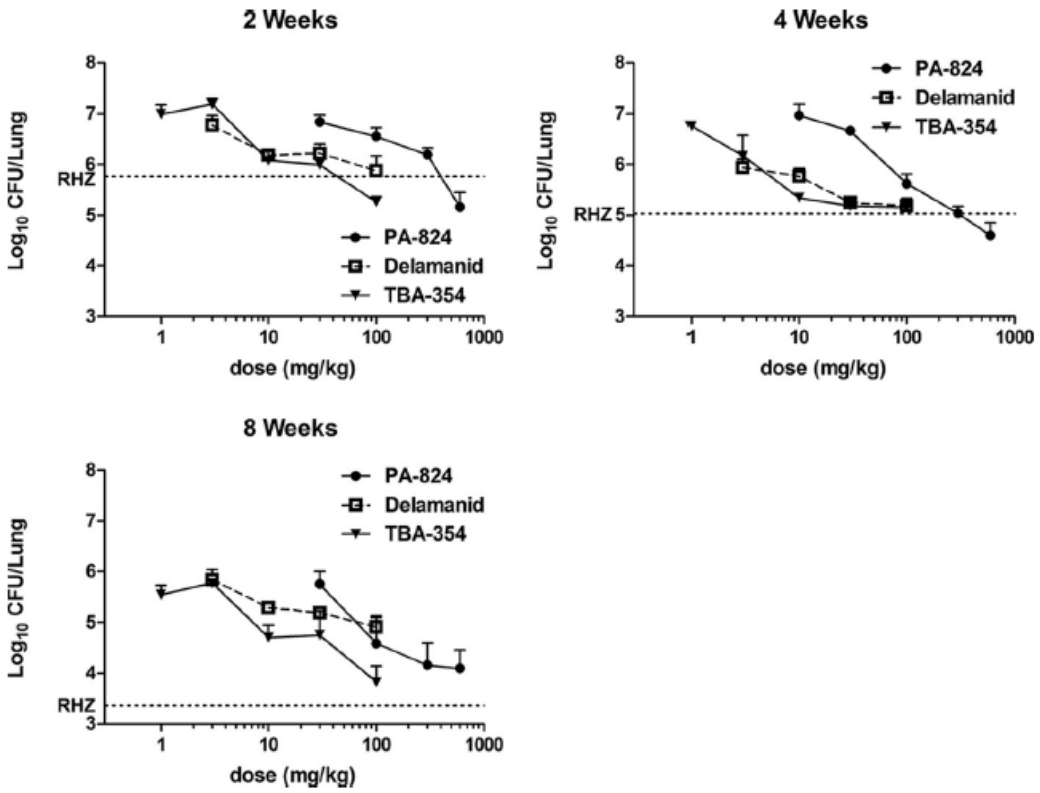


Figure 15-12. Lung log10 CFU counts after 2, 4, and 8 weeks of treatment with increasing doses of nitroimidazoles.

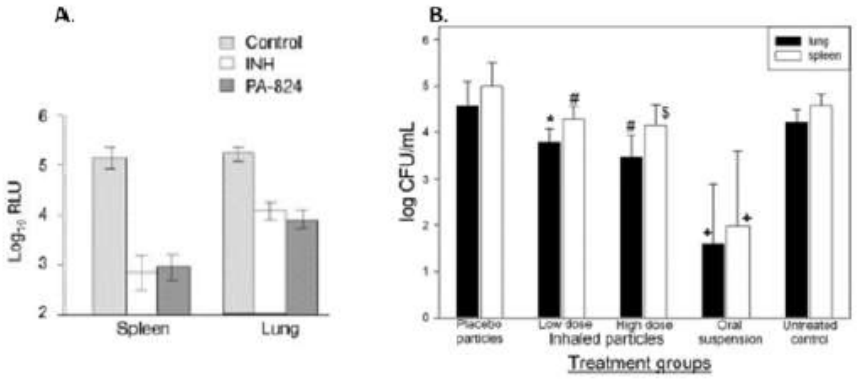
Note: The dotted line represents the mean CFU count for the (rifampicin, isoniazid, pyrazinamide (RHZ)) control group. Error bars represent the standard deviation of the mean. Source: (Tasneen et al., 2015)

MTB-infected guinea pigs develop disease that is considered to resemble the clinical, pathological and immunological nature of human disease. The *in vivo* activity of pretomanid against MTB H37Rv was evaluated in the guinea pig lung infection model in 3 studies (Stover et al., 2000; Garcia-Contreras et al.,2010, and Dutta et al., 2013)[Error! Bookmark not defined., 61, 62]. Guinea pigs (infected via aerosols with 10 CFU of MTB H37RV) were treated 1-month post-infection with 25 mg/kg/day isoniazid or 40 mg/kg/day pretomanid, given orally for 30 days (Stover et al., 2000). Pretomanid reduced bacterial burden in the lungs and spleens to levels comparable to isoniazid (Figure 15-13). Similar results were observed in another study using a comparable experimental design but with an oral suspension of pretomanid (Figure 15-13, Garcia-Contreras et al.,2010). The efficacy of pretomanid as a monotherapy was consistent across the 3 studies (Figure 15-14, Dutta et al 2013). The MTB-infected guinea pigs were not used to

[61] Garcia-Contreras L, Sung JC, Muttil P, Padilla D, Telko M, Verberkmoes JL, et al. Dry powder PA-824 aerosols for treatment of tuberculosis in guinea pigs. Antimicrob Agents Chemother. 2010 Apr; 54(4): 1436-42.
[62] Dutta NK, Alsultan A, Gniadek TJ, Belchis DA, Pinn ML, Mdluli KE, et al. Potent rifamycin-sparing regimen cures guinea pig tuberculosis as rapidly as the standard regimen. Antimicrob Agents Chemother. 2013 Aug; 57(8): 3910-6.

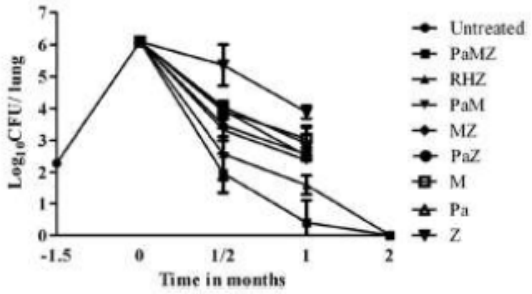
Reference ID: 4476823

assess the BPaL regimen, so the model was not useful to assess the contributions of the individual drugs to the BPaL combination regimen.



CFU = colony forming unit; INH = isoniazid; PA-824 = pretomanid; RLU= relative light unit
A) Guinea pigs were infected with approximately 10 CFU *M. tuberculosis* strain H37Rv by aerosol. After a 30-day incubation period, experimental animals were treated daily with 25 mg/kg of isoniazid or 40 mg/kg of pretomanid orally for 30 days. MTB CFU were determined in lung and spleen tissue 30 days after treatment (60 days post-infection). Note that the y-axis, as originally published, is incorrectly labeled as RLU instead of CFU.
B) Number of viable bacteria (CFU/mL) at necropsy in lung and spleen tissues of infected guinea pigs receiving different pretomanid treatments daily for 4 weeks (average ±standard deviation; n = 6).
+ = significantly lower than any other group ($P < 0.0001$); $ = significantly lower than low-dose group, untreated, control, or placebo ($P = 0.0027$); # = significantly lower than untreated control or placebo ($P = 0.0084$); * = significantly lower than placebo ($P = 0.0074$).
Source: A) (Stover et al., 2000); B) (Garcia-Contreras et al., 2010)

Figure 15-13. Activity of pretomanid in a guinea pig MTB lung infection model after (A) oral and (B) oral vs. inhaled administration.



CFU = colony forming unit; H = isoniazid; M = moxifloxacin; Pa = pretomanid; R = rifampicin; Z = pyrazinamide
Antitubercular activities of the indicated drugs in infected guinea pigs. Animals were infected via aerosol with ~10^2 CFU of MTB H37Rv, and were either left untreated or treated with drugs daily (5 days/week) beginning 6 weeks after infection. Rifampicin at 100 mg/kg once daily; isoniazid at 60 mg/kg once daily; pyrazinamide at 300 mg/kg once daily; pretomanid at 25 mg/kg twice daily; M, moxifloxacin at 90 mg/kg twice daily.
Source: (Dutta et al., 2013)

Figure 15-14 Activities of pretomanid in infected guinea pigs.

Reference ID: 4476823

In the latent MTB infection model, C3HeB/FeJ mice are immunized with a recombinant *M. bovis* BCG strain that overexpresses the 30-kD major secretory protein (rBCG30) which allows for survival of the mice after MTB infection[63]. Mice are infected with MTB H37Rv (100 CFU) via aerosol 6 weeks postimmunization. Treatment was initiated 6 weeks post-infection when the lung burden reached ~4$\log_{10}$ CFU. Pretomanid (50 mg/kg/day) and isoniazid (10 mg/kg/day) demonstrated similar reduction in bacterial lung burden after 1, 2, and 4 months of treatment, compared to untreated control (Table 15-10). In both the isoniazid and pretomanid treatment groups, all mice had positive lung cultures 3 months post-treatment, suggesting sterilization was not achieved with up to 4 months of monotherapy. Although *in vitro* activity is observed against hypoxic MTB cells, pretomanid showed limited activity against latent TB infection in C3HeB/FeJ mice. pretomanid bioavailability within the necrotic lung granulomas was not available.

Table 15-10. Bacillary burden in the lungs of latently infected mice during treatment, and relapse rates.

Group	Mean (±S.D.) $\log_{10}$ CFU count at:					Proportion (%) relapse, assessed 3 months after completion of treatment for:	
	Month −1.5	Month 0	Month 1	Month 2	Month 4	2 months	4 months
Untreated	1.15 ± 0.12	4.24 ± 0.13	4.30 ± 0.16	4.01 ± 0.27	4.12 ± 0.25	N/D	N/D
INH (10 mg/kg)			2.80 ± 0.30	1.92 ± 0.32	1.12 ± 0.33	15/15 (100)	15/15 (100)
RIF (10 mg/kg)			1.93 ± 0.31	0.81 ± 0.2	0 ± 0	15/15 (100)	5/15 (33)
PA-824 (50 mg/kg)			2.41 ± 0.19	1.75 ± 0.22	1.54 ± 0.13	15/15 (100)	15/15 (100)
Total mice	5	5	20	20		45	45

S.D., standard deviation; N/D, not done; INH, isoniazid; RIF, rifampicin.
Data from control groups (untreated, INH and RIF), conducted in parallel with PA-824 treatment, are derived from our recently published study [11].
[a] Mice were immunised via aerosol with a recombinant BCG strain overexpressing the 30-kDa major secretory protein (rBCG30), resulting in mean (±S.D.) implanted lung CFU counts of 3.61 ± 0.07 $\log_{10}$. Six weeks later, the mean lung rBCG30 CFU counts had increased to 5.86 ± 0.18 $\log_{10}$.

Reviewer comment: In a mouse model of acute TB, pretomanid demonstrated a dose-dependent bactericidal activity with a minimum effective dose of 12.5 mg/kg/day and a minimum bactericidal dose (lowest dose capable of reducing lung TB CFUs by 99%) of 100 mg/kg/day. The activity of pretomanid was similar to isoniazid. In the mouse and guinea pig models, the activity of pretomanid monotherapy was similar to isoniazid. Relapse is observed, and resistance develops with pretomanid monotherapy.

15.5. Additional Safety Analyses Tables

<u>SAEs in Drug-sensitive Pooling Group and the Multi-Drug Resistant TB Pooling Groups.</u>
SAEs leading to death such as acute hepatic failure and DILI are described in subsection 9.4.1.

In the DS-TB group, at least 1 SAE was reported in 34 (5.2%) pretomanid subjects, compared with 8 (3.5%) HRZE control subjects and 1 (1.3%) comparator subject. The incidence of serious TEAEs was greater in the pretomanid combination therapy group than in the pretomanid-alone group (6.0% versus 1.6%).

[63] Dutta NK, Karakousis PC. PA-824 is as effective as isoniazid against latent tuberculosis infection in C3HeB/FeJ mice. Int J Antimicrob Agents. 2014 Dec; 44(6): 564-6.

Reference ID: 4476823

Elevated hepatic transaminases were the most common drug-related SAEs in the pretomanid combination therapy group. There were no drug-related SAEs in the pretomanid monotherapy group. The most frequent SAEs in the HRZE control group were pulmonary tuberculosis and hemoptysis in 2 (0.9%) subjects, respectively. There was one SAE of gastroenteritis reported in the comparator group.

Table 15-11. Drug-Sensitive Tuberculosis Pooled Group*: Treatment Emergent Serious Adverse Events

	Pretomanid Combination Therapy (N=534), (n/N%)	HRZE Control (N=229), (n/N%)	Pretomanid Monotherapy (N=122), (n/N%)	Comparator (N=75), (n/N%)
Any SAE	32 (6.0)	8 (3.5)	2 (1.6)	1 (1.3)
SAEs by Preferred Term				
Alanine aminotransferase increased	6 (1.1)	0	0	0
Aspartate aminotransferase increased	6 (1.1)	0	0	0
Pneumothorax	3 (0.6)	0	1 (0.8)	0
Hemoptysis	0	2 (0.9)	1 (0.8)	0
Acute hepatic failure	1 (0.2)	1 (0.4)	0	0
Drug-induced liver injury	1 (0.2)	1 (0.4)	0	0
Gastroenteritis	0	1 (0.4)	0	1 (1.3)
Seizure	1 (0.2)	1 (0.4)	0	0
Acute kidney injury	0	1 (0.4)	0	0
Agranulocytosis	1 (0.2)	0	0	0
Anemia	1 (0.2)	0	0	0
Atrioventricular block second degree	1 (0.2)	0	0	0
Death	1 (0.2)	0	0	0
Dyspnea	1 (0.2)	0	0	0
Epilepsy	1 (0.2)	0	0	0
Hepatic encephalopathy	1 (0.2)	0	0	0
Hepatic enzyme increased	1 (0.2)	0	0	0
Hepatotoxicity	1 (0.2)	0	0	0
Hypersensitivity	1 (0.2)	0	0	0
Jaundice	1 (0.2)	0	0	0
Pericardial effusion	1 (0.2)	0	0	0
Pneumonia	1 (0.2)	0	0	0
Pneumothorax spontaneous	1 (0.2)	0	0	0
Pulmonary edema	1 (0.2)	0	0	0
Vomiting	1 (0.2)	0	0	0

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: ISS ADSL; Filter: POOL3SFL = 'Y'.
Any SAE - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y', AESER = 'Y'.
SAEs by Preferred Term - Dataset: ISS ADAE; Filter: TRTEMFL = 'Y', AESER = 'Y'.

<u>SAEs associated with a pretomanid-moxifloxacin-pyrazinamide regimen ($Pa_{200mg}MZ$) in DSTB</u>

The PaMZ regimen was studied as 4-month or 6 -month regimen versus HRZE to investigate shortening the duration of treatment for DS-TB.

In study NC-002, SAEs in patients treated with PaMZ included agranulocytosis, elevated hepatic transaminases, pneumothorax, AV block, seizure, and dyspnea.
In study NC-005, SAEs in patients treated with PaMZ included elevated hepatic transaminases, and severe anemia; one death due to DILI was reported in the HRZE control group.
In study NC-006 ("STAND" trial), three fatal cases of drug induced liver injury (DILI) were reported in the PaMZ group around Week 4 of treatment; see sections 3.2 and 9.4.1 of this review, clinical review (2015) under IND 69,580, and a hepatology consult review (2015) by Mark Avigan, M.D., OSE, located in DARRTS.

Subjects who experienced SAEs in the DS-TB pooling group are summarized inTable 15-12. Excluding the eight subjects with SAEs leading to death, all SAEs except three SAEs in two patients resolved or were resolving at the data cut-off date.

Table 15-12. Drug Sensitive Tuberculosis Pooled Group: Serious Adverse Events by Study ID and Subject ID

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
CL-007	(b) (6) M / 22 / DS / NEGATIVE	HRZE Control	HAEMOPTYSIS / Hemoptysis	24 / 4	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
CL-007	(b) (6) F / 23 / DS / NEGATIVE	PA (200 mg)	HAEMOPTYSIS / Hemoptysis	9 / 9	MODERATE / RECOVERED-RESOLVED / DOSE NOT CHANGED
CL-010	(b) (6) M / 24 / DS / NEGATIVE	Pa (50 mg)	PNEUMOTHORAX / LEFT PNEUMOTHORAX	3 / 14	MODERATE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-001	(b) (6) M / 23 / DS / NEGATIVE	Pa (200 mg) MZ	NEUROCYSTICERCOSIS / NEUROCYSTICERCOSIS	9 / Missing	SEVERE / RECOVERING-RESOLVING / DRUG WITHDRAWN
NC-002	(b) (6) M / 27 / DS / POSITIVE	Pa (200 mg) MZ	PNEUMOTHORAX / PNEUMOTHORAX	1 / 9	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-002	(b) (6) M / 29 / DS / NEGATIVE	Pa (200 mg) MZ	ATRIOVENTRICULAR BLOCK SECOND DEGREE / CARDIAC ARRHYTHMIA (2ND DEGREE AV BLOCK)	7 / 16	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-002	(b) (6) M / NA / DS / POSITIVE	Pa (200 mg) MZ	AGRANULOCYTOSIS / AGRANULOCYTOSIS	29 / 11	LIFE-THREATENING / RECOVERING-RESOLVING / DOSE NOT CHANGED

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
			HEPATIC ENZYME INCREASED / ELEVATED LIVER ENZYMES	29 / 20	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-002	(b) (6) M / 37 / DS / NEGATIVE	Pa (200 mg) MZ	EPILEPSY / EPILEPTIC SEIZURES	47 / 95	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-002	(b) (6) F / 33 / DS / POSITIVE	Pa (200 mg) MZ	DYSPNOEA / DYSPNOEA	43 / 8	MODERATE / RECOVERED-RESOLVED / NOT APPLICABLE
NC-003	(b) (6) F / 22 / DS / POSITIVE	C	GASTROENTERITIS / ACUTE GASTROENTERITIS	18 / 22	SEVERE / RECOVERED-RESOLVED / NOT APPLICABLE
NC-005	(b) (6) M / 44 / DS / NEGATIVE	HRZE Control	HAEMOPTYSIS / WORSENING OF HAEMOPTYSIS	15 / 2	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-005	(b) (6) M / 46 / DS / POSITIVE	HRZE Control	GASTROENTERITIS / ACUTE GASTROENTERITIS	33 / 12	SEVERE / NOT RECOVERED-NOT RESOLVED / DRUG WITHDRAWN
			ACUTE KIDNEY INJURY / ACUTE KIDNEY INJURY	36 / 9	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
			ACUTE HEPATIC FAILURE / ACUTE LIVER FAILURE	36 / 9	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
NC-005	(b) (6) F / 33 / DS / NEGATIVE	B (loading dose) Pa (200 mg) Z	DRUG-INDUCED LIVER INJURY / DRUG INDUCED LIVER INJURY	22 / 71	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-005	(b) (6) M / 34 / DS / POSITIVE	BPa (200 mg) Z	PNEUMOTHORAX SPONTANEOUS / SPONTANEOUS RIGHT PNEUMOTHORAX	21 / 3	LIFE-THREATENING / FATAL / NOT APPLICABLE
			PNEUMONIA / SUPERADDED PNEUMONIA	21 / 3	LIFE-THREATENING / FATAL / NOT APPLICABLE
NC-005	(b) (6) M / 38 / DS / NEGATIVE	B (loading dose) Pa (200 mg) Z	PULMONARY OEDEMA / PULMONARY OEDEMA	4 / Missing	SEVERE / NOT RECOVERED-NOT RESOLVED / DOSE NOT CHANGED
			PNEUMOTHORAX / RIGHT LUNG COLLAPSE	4 / Missing	SEVERE / NOT RECOVERED-NOT RESOLVED / DOSE NOT CHANGED
			PNEUMOTHORAX / RIGHT-SIDED PNEUMOTHORAX	4 / 2	LIFE-THREATENING / FATAL / DRUG WITHDRAWN

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
NC-005	(b) (6) M / 25 / DS / NEGATIVE	BPa (200 mg) Z	PERICARDIAL EFFUSION / PERICARDIAL EFFUSION	4 / 11	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-005	(b) (6) M / 35 / DS / NEGATIVE	B (loading dose) Pa (200 mg) Z	ALANINE AMINOTRANSFERASE INCREASED / ELEVATED ALANINE TRANSAMINASE	39 / 59	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / ELEVATED ASPERTATE TRANSAMINASE	39 / 44	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-005	(b) (6) M / 35 / DS / NEGATIVE	BPa (200 mg) Z	ANAEMIA / SEVERE ANEMIA	13 / 24	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
			MALARIA / SEVERE MALARIA	13 / 6	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-005	(b) (6) M / 32 / DS / NEGATIVE	B (loading dose) Pa (200 mg) Z	APPENDICITIS / ACUTE APPENDICITIS	32 / 1	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-005	(b) (6) M / 39 / DS / POSITIVE	HRZE Control	PULMONARY TUBERCULOSIS / WORSENING OF PULMONARY TUBERCULOSIS	7 / 21	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
			PULMONARY TUBERCULOSIS / WORSENING OF PULMONARY TUBERCULOSIS	42 / 16	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-005	(b) (6) M / 43 / DS / POSITIVE	HRZE Control	DRUG-INDUCED LIVER INJURY / DRUG INDUCED HEPATITIS	15 / 12	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-006	(b) (6) M / 33 / DS / NEGATIVE	Pa (100 mg) MZ - 4 months	LYMPH NODE TUBERCULOSIS / TB LYMPH NODES (RESISTANT TO RIFAMPICIN)	67 / 263	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-006	(b) (6) F / 26 / DS / NEGATIVE	HRZE Control	INTENTIONAL OVERDOSE / OVERDOSE OF INVESTIGATIONAL PRODUCT (INTENTIONAL OVERDOSE)	82 / 4	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
			SEIZURE / SEIZURE	83 / 1	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG INTERRUPTED
NC-006	(b) (6) F / 23 / DS / POSITIVE	Pa (200 mg) MZ - 6 months	ALANINE AMINOTRANSFERASE INCREASED / ELEVATED LIVER ENZYMES (RAISED ALT)	120 / 115	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
NC-006	(b) (6) F / 39 / DS / POSITIVE	Pa (200 mg) MZ - 6 months	DEATH / DEATH DUE TO NATURAL CAUSES (CAUSE UNKNOWN)	163 / 1	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
NC-006	(b) (6) F / 55 / DS / NEGATIVE	Pa (200 mg) MZ - 6 months	ALANINE AMINOTRANSFERASE INCREASED / ELEVATED LIVER ENZYMES (RAISED ALT)	42 / 56	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / ELEVATED LIVER ENZYMES (RAISED AST)	42 / 67	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-006	(b) (6) M / 35 / DS / NEGATIVE	Pa (200 mg) MZ - 6 months	PNEUMOTHORAX / PNEUMOTHORAX	22 / 8	MODERATE / RECOVERED-RESOLVED / DOSE NOT CHANGED
			PNEUMOTHORAX / PNEUMOTHORAX	38 / 11	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) M / 38 / DS / NEGATIVE	Pa (200 mg) MZ - 4 months	BLADDER MASS / SOLID MASS IN BLADDER	5 / 219	MODERATE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) M / 47 / DS / POSITIVE	Pa (200 mg) MZ - 6 months	ANAL SQUAMOUS CELL CARCINOMA / SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL	174 / 296	LIFE-THREATENING / FATAL / DOSE NOT CHANGED
			URINARY TRACT INFECTION / URINARY TRACT INFECTION	178 / 32	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) F / 44 / DS / POSITIVE	Pa (200 mg) MZ - 4 months	HEPATOTOXICITY / HEPATOTOXICITY	23 / 6	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
NC-006	(b) (6) M / 50 / DS / POSITIVE	Pa (200 mg) MZ - 6 months	ALANINE AMINOTRANSFERASE INCREASED / RAISED ALT	29 / 50	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / RAISED AST	29 / 64	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-006	(b) (6) M / 36 / DS / NEGATIVE	Pa (200 mg) MZ - 4 months	ALANINE AMINOTRANSFERASE INCREASED / ELEVATED ALT	29 / 35	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / ELEVATED AST	29 / 35	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
NC-006	(b) (6) M / 54 / DS / NEGATIVE	Pa (200 mg) MZ - 4 months	NASAL CANDIDIASIS / CANDIDIASIS OF NASAL CAVITY	40 / Missing	SEVERE / NOT RECOVERED-NOT RESOLVED / DOSE NOT CHANGED
			ASPERGILLUS INFECTION / INVASIVE ASPERGILLOSIS OF NASAL CAVITY	40 / Missing	SEVERE / NOT RECOVERED-NOT RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) M / 38 / DS / POSITIVE	Pa (100 mg) MZ - 4 months	HYPERSENSITIVITY / DRUG-INDUCED HYPERSENSITIVITY SKIN REACTION	59 / 9	MODERATE / RECOVERED-RESOLVED / NOT APPLICABLE
NC-006	(b) (6) F / 50 / DS / POSITIVE	Pa (200 mg) MZ - 4 months	ASPARTATE AMINOTRANSFERASE INCREASED / ELEVATED AST	9 / 32	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG INTERRUPTED
NC-006	(b) (6) M / 34 / DS / POSITIVE	Pa (200 mg) MZ - 6 months	SOFT TISSUE INJURY / MULTIPLE SOFT TISSUE INJURIES	194 / 11	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) M / 21 / DS / NEGATIVE	Pa (100 mg) MZ - 4 months	ACUTE HEPATIC FAILURE / FULMINANT LIVER FAILURE	29 / 11	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
NC-006	(b) (6) M / 28 / DS / NEGATIVE	Pa (200 mg) MZ - 4 months	SEIZURE / (ADULT ONSET SEIZURES) EPILEPSY	102 / 6	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
			SEIZURE / (ADULT ONSET SEIZURES) EPILEPSY	147 / 5	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) F / 23 / DS / POSITIVE	Pa (200 mg) MZ - 4 months	HEPATIC ENCEPHALOPATHY / HEPATIC ENCEPHALOPATHY	16 / 19	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
			VOMITING / VOMITING	25 / 10	SEVERE / NOT RECOVERED-NOT RESOLVED / DOSE NOT CHANGED
			JAUNDICE / JAUNDICE	32 / 3	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
NC-006	(b) (6) M / 30 / DS / NEGATIVE	HRZE Control	ACQUIRED HYDROCELE / LEFT HYDROCELE MALE	22 / 32	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) M / 31 / DS / NEGATIVE	HRZE Control	PULMONARY TUBERCULOSIS / CLINICAL DETERIORATION WHILE ON TB TREATMENT	64 / Missing	SEVERE / UNKNOWN / DRUG WITHDRAWN

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
NC-006	(b) (6) M / 45 / DS / NEGATIVE	Pa (200 mg) MZ - 4 months	PULMONARY TUBERCULOSIS / CLINICAL DETERIORATION WHILE ON TB TREATMENT	59 / 138	MODERATE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-006	(b) (6) M / 50 / DS / NEGATIVE	Pa (200 mg) MZ - 6 months	ALANINE AMINOTRANSFERASE INCREASED / ELEVATED ALT	27 / 126	LIFE-THREATENING / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / ELEVATED AST	27 / 126	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN

Source: R (v3 5 1)
Datasets Used: Applicant's ISS ADSL (POOL3SFL = Y) and ISS ADAE (TRTEMFL = Y and AESER = Y)

In the MDRTB group, SAEs were associated with elevated transaminases in patients receiving the BPaMZ regimen, which resolved when the regimen was withdrawn. Other SAEs were associated with underlying tuberculosis or concomitant illnesses. All resolved except for one patient who died from metastatic lung cancer (unrelated to study drugs). Subjects who experienced SAEs in the MDR-TB pooling group are summarized in Table 15-13.

Table 15-13. MDRTB Pooled Studies: Serious Adverse Events by Study ID and Subject ID

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
NC-005	(b) (6) F / 42 / MDR / POSITIVE	BPa (200 mg) MZ	ALANINE AMINOTRANSFERASE INCREASED / RAISED ALT	21 / 8	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / RAISED AST	21 / 8	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-005	(b) (6) M / 56 / MDR / POSITIVE	BPa (200 mg) MZ	HAEMOPTYSIS / HAEMOPTYSIS	30 / 17	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
			PULMONARY ARTERY ANEURYSM / PULMONARY ARTERY ANEURYSM	38 / 236	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-005	(b) (6) F / 48 / MDR / POSITIVE	BPa (200 mg) MZ	ALANINE AMINOTRANSFERASE INCREASED / ELEVATED ALT	31 / 29	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
			ASPARTATE AMINOTRANSFERASE INCREASED / ELEVATED AST	31 / 61	SEVERE / RECOVERED-RESOLVED / DRUG WITHDRAWN
NC-006	(b) (6) M / 61 / MDR / NEGATIVE	Pa (200 mg) MZ - 6 months	LUNG CANCER METASTATIC / METASTATIC LUNG CANCER	17 / 18	LIFE-THREATENING / FATAL / DRUG WITHDRAWN
NC-006	(b) (6) F / 20 / MDR / POSITIVE	Pa (200 mg) MZ - 6 months	MYOCARDITIS / ACUTE MYOCARDITIS	19 / 166	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
			CARDIAC VENTRICULAR THROMBOSIS / LEFT VENTRICULAR APICAL CLOT	19 / 62	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED

Study ID	Subject ID Gender / Age / TB Type / HIV Status	Drug Regimen	Serious Adverse Event Preferred Term / Verbatim Term	Study Day Start / Duration (Days)	Severity / Outcome / Action Taken
			PNEUMONIA / NOSOCOMIAL PNEUMONIA BASED ON WORSENING CONSOLIDATION ON CXR	19 / 10	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED
			LEFT VENTRICULAR DYSFUNCTION / POOR LEFT VENTRICULAR FUNCTION	19 / 166	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
			PULMONARY OEDEMA / PULMONARY OEDEMA	19 / 10	LIFE-THREATENING / RECOVERED-RESOLVED / DOSE NOT CHANGED
NC-006	(b) (6) M / 28 / MDR / NEGATIVE	Pa (200 mg) MZ - 6 months	PNEUMOTHORAX SPONTANEOUS / SPONTANEOUS PNEUMOTHORAX	160 / 119	SEVERE / RECOVERED-RESOLVED / DOSE NOT CHANGED

Source: R (v3 5 1)
Datasets Used: Applicant's ISS ADSL (POOL4SFL = Y) and ISS ADAE (TRTEMFL = Y and AESER = Y)

16 Division Director (Clinical)

I concur with the review.

17 Office Director (OAP)

I have considered the assessements and recommendations expressed by all reviewers in this Multidisciplinary Review of NDA 212862 in determining the regulatory action. No reviewers have identified issues that preclude approval. Pretomanid Tablet will be approved as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug will be indicated for use in a limited and specific population of patients. Labeling including a Medication Guide is described in this Multidisciplinary Review and appended to the Approval Letter. Post-Marketing Requirements and Commitments are described in this Multidisciplinary Review and listed in the Approval Letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FARIBA IZADI
08/13/2019 04:54:57 PM

JOHN J FARLEY
08/14/2019 08:14:37 AM