FDA Introductory Comments

NDA 212862: Pretomanid for the Treatment of Pulmonary Extensively Drug-resistant and Treatment-intolerant/Non-responsive Multidrug-resistant Tuberculosis

Antimicrobial Drugs Advisory Committee Meeting
June 6, 2019

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Introduction

- NDA 212862: Pretomanid tablet, 200 mg
- Applicant: Global Alliance for TB Drug Development, Inc.
- NDA granted priority review
- Currently approved drugs for tuberculosis:
  - Isoniazid
  - Rifampin
  - Ethambutol
  - Pyrazinamide
  - Rifapentine
  - Ethionamide
  - Streptomycin
  - Capreomycin
  - Cycloserine
  - P-aminosalicylic acid (PAS)
  - Bedaquiline

Proposed Indication

- Treatment of Pulmonary Extensively Drug-resistant (XDR) and Treatment-intolerant/Non-responsive Multidrug-resistant Tuberculosis (TI/NR MDR-TB) in combination with bedaquiline and linezolid

Dosing

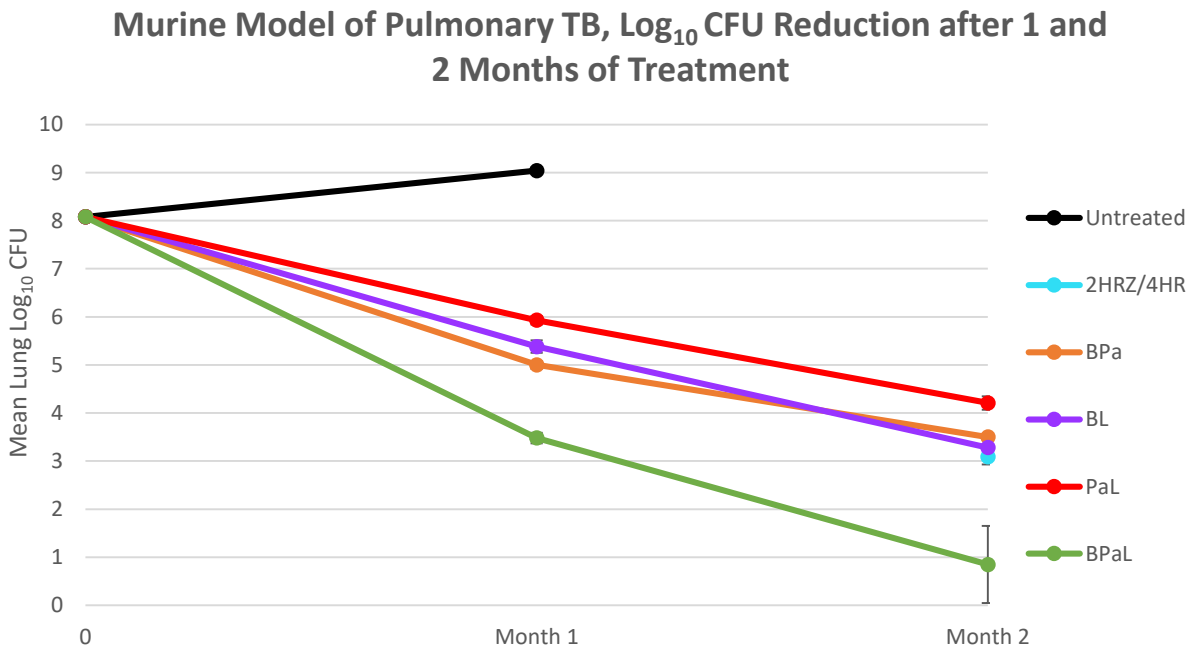
- Pretomanid: 200 mg daily
- Linezolid: 1200 mg daily, with possible reductions to 600 mg daily and then to 300 mg daily if intolerant
- Bedaquiline: 400 mg daily on Days 1 -14 followed by 200 mg 3 times a week for the remainder of the treatment period

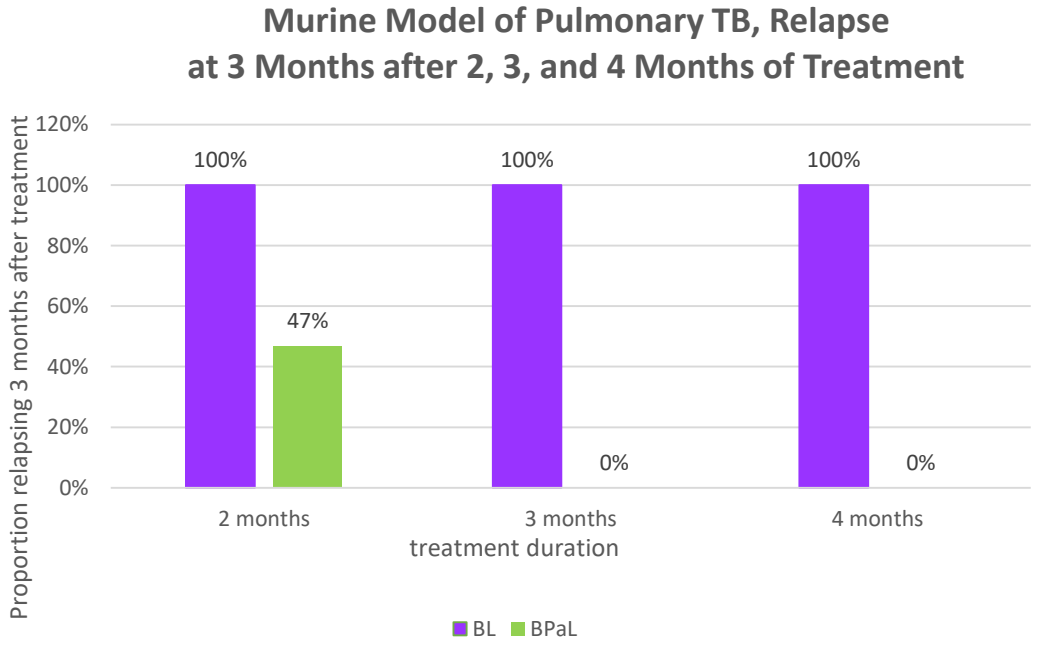
Development Program

Study ID	Title	Status
NC-002	A Phase 2 open-label partially randomized trial of the combination of moxifloxacin , pretomanid, and pyrazinamide after 8 Weeks of Treatment in adults with newly diagnosed smear-positive pulmonary drug-sensitive (DS) or MDR-TB	Completed
NC-005 (not conducted under IND)	A Phase 2, open-label partially randomized trial of the combinations of bedaquiline, moxifloxacin , pretomanid, and pyrazinamide during 8 weeks of treatment in adults with newly diagnosed smear-positive pulmonary DS or MDR-TB	Completed
NC-006 (STAND)	A Phase 3, open-label partially randomized trial of the combination of moxifloxacin , pretomanid, and pyrazinamide after 4 and 6 months of treatment in adults with smear-positive pulmonary DS-TB and after 6 months of treatment in adults with smear-positive MDR-TB.	Completed
Nix-TB	A Phase 3, open-label trial of the combination of bedaquiline, pretomanid, and linezolid in adults with pulmonary XDR-TB or TI/NR MDR-TB.	Ongoing
NC-007 (ZeNix)	A Phase 3, open-label, randomized partially blinded dose/duration-ranging trial of linezolid in combination with bedaquiline plus pretomanid in adults with pulmonary XDR-TB, pre-XDR-TB or TI/NR MDR-TB.	Ongoing
NC-008 (Simplici TB)	An open-Label, Phase 2c, partially randomized trial of a 4-month treatment with a combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) compared to a 6-month control [isoniazid, rifampicin, pyrazinamide, ethambutol)] in adults with smear-positive pulmonary DS-TB and a 6-month treatment of BPaMZ in adults with drug-resistant (DR), smear-positive pulmonary tuberculosis.	Ongoing

Regimen Development

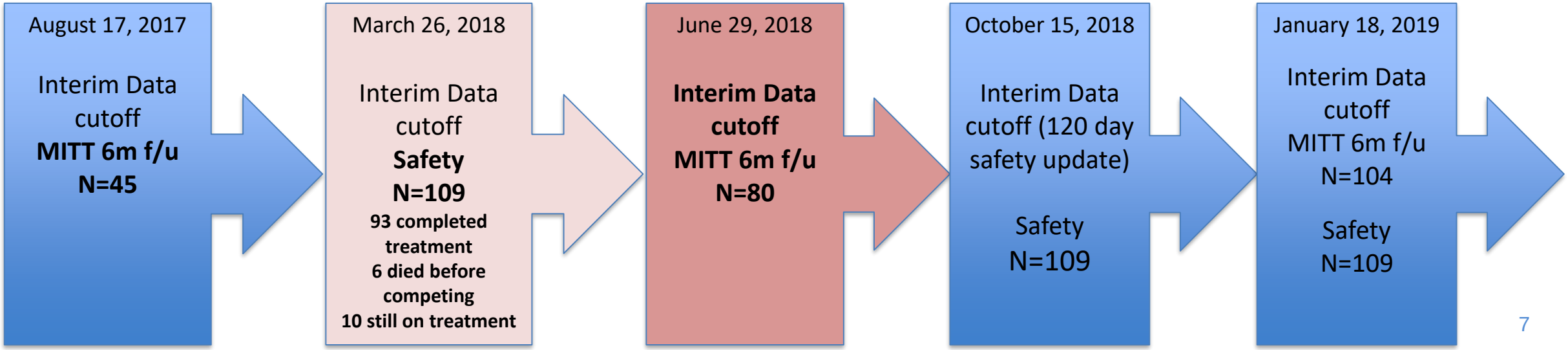
- Contribution of the components in the proposed BPaL regimen was evaluated in
  - *in vitro* experiments
  - in the murine model of pulmonary tuberculosis





Nix-TB

- A single ongoing Phase 3, single-arm, multicenter trial to assess the safety and efficacy of bedaquiline plus pretomanid plus linezolid (BPaL) in patients with pulmonary XDR-TB or TI/NR MDR-TB
- First patient enrolled on April 24, 2015
- Last patient enrolled on November 15, 2017
- Interim analyses every 15 subjects reaching primary endpoint



Efficacy

- Population: XDR-TB and TI/NR MDR-TB, 3 centers in South Africa, 49% HIV positive
- Endpoint: Favorable outcome (absence of bacteriologic failure, relapse, or clinical failure) through follow-up 6 months following end of treatment
- Interim data cutoff, August 17, 2017: MITT N=45
  - 40/45 (88.9%), 95% CI [75.9% to 96.3%]
- Interim data cutoff, June 29, 2018: MITT N=80 (69% XDR-TB)
  - 72/80 (90.0%), 95% CI [81% to 96%]
  - 19/23 (83%) had favorable outcome at 24 months following end of treatment
- Historical control
  - Literature-based favorable outcome for XDR TB: 28%, 95% CI [21% to 34%]
  - Matched historical control favorable outcome for XDR and TI/NR MDR TB:
    - NixTB 39/44 (89%) vs matched control 9/84(11%) RR 64.5, 95% CI [9 to 472], p <0.0001

Safety

- In 19 completed/ongoing trials (3 Phase III, 6 Phase II, and 10 Phase I), 1168/1507 subjects were exposed to pretomanid alone and in combination with other drugs, 124 of them received pretomanid in BPaL regimen for the duration of up to 9 months
  - Nix-TB, n=109
  - ZeNix, n=15 (data cutoff - March 26, 2018); 61 subjects (data cutoff - Oct 15, 2018)

Safety, Pretomanid

- Hepatotoxicity
- Testicular toxicity
- No QT liability
- Cataracts
- Neurotoxicity

Safety, BPaL Regimen

- Hepatotoxicity
- Pancreatitis
- Effect on fertility
- Peripheral and Optic neuropathy
- Myelosuppression
- QT prolongation
- Lactic acidosis

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - **Efficacy** by Daniel Rubin, Ph.D.
  - **Safety** by Elizabeth O'Shaughnessy, M.D.
- Clarifying Questions
- Lunch
- Open Public Hearing
- Question to the committee

Question 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?

  – If yes, please provide any recommendations concerning labeling.
  – If no, what additional studies/analyses are needed?

Presentation of Clinical Efficacy

Antimicrobial Drugs Advisory Committee Meeting
June 6, 2019

Daniel Rubin, PhD
Statistical Reviewer
Division of Biometrics IV, Office of Biostatistics
Office of Translational Sciences, CDER, FDA

Outline

- Study design of Nix-TB
- Study results
- Assessment of historical controls
- Summary and conclusions

Study Design of Nix-TB

- Efficacy assessment was based on Nix-TB because this was the only trial that evaluated the pretomanid regimen and patient population under consideration.

- Patients had extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant/non-responsive multi-drug resistant tuberculosis (TI/NR MDR-TB).

- The study was conducted at 3 study sites in South Africa.

Study Design of Nix-TB

- All patients were treated with bedaquiline plus pretomanid plus linezolid (BPaL).
- Not intended to provide clinical evidence for the contribution of each component.
- Treatment was for 6 months (extended to 9 months per protocol in rare cases).
- The primary endpoint assessment was 6 months after the End of Treatment.

Dosing

- 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.

- Pretomanid: 200 mg once daily.

- Linezolid:
  - Initial protocol: 600 mg twice a day.
  - Amended protocol: 1200 mg once a day.
  - Linezolid could be discontinued, interrupted, or dose reduced while patients remained on bedaquiline and pretomanid. At least 4 weeks of the 1200 mg daily dose of linezolid was to be given before linezolid was discontinued.

Scope of Data Analysis

- The planned sample size of Nix-TB was 200 patients.
- Enrollment stopped after 109 patients were treated. Stopping was due to efficacy results and Applicant preference to instead enroll in ZeNix to refine linezolid dosing.
- Follow-up of the 109 treated patients is continuing.
- The Applicant and FDA agreed that efficacy assessment could be based on the first 45 patients with complete primary endpoint data.
- Efficacy results in this presentation and the backgrounder are based on a June 29, 2018 interim data cutoff, with 81 patients having complete primary endpoint data.
- Efficacy conclusions are not sensitive to the timing of the data cutoff.

Primary Efficacy Analysis

- Primary endpoint: Bacteriologic failure, relapse, or clinical failure through follow-up 6 months after the End of Treatment.

- Primary analysis population: Modified intent-to-treat (MITT) population of all treated patients, with exclusions for late screening failures and other factors.

- Historical control rate: An exact 95% confidence interval was to be formed for the proportion of patients with a favorable outcome. The lower limit was to be compared with a historical rate of 50%.

Code of Federal Regulations on Historical Controls

- *The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).*

Source: 21CFR314.126.

International Conference on Harmonisation E10 on External Controls

- *The inability to control bias restricts use of the external control design to situations in which the effect of a treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized.*

Source: Huitfeldt B et al. Drug Information Journal, 2001;35:1147-1156.

Disposition

- 143 patients signed informed consent
  - 34 screening failures
    - 143-34 = 109 treated patients in the safety population

- June 29, 2018 data cutoff:
  - 81 patients in the intent-to-treat (ITT) population with sufficiently early enrollment to have expected primary endpoint data
    - 80 patients in the modified intent-to-treat (MITT) primary analysis population. 1 ITT patient was excluded due to non-TB death, which was is not recommended but did not affect efficacy conclusions.

Source: Nix-TB Addendum Clinical Trial Report, Figure 6-1.

Demographic Characteristics

Variable	Safety Population (n = 109)	MITT Population (n = 80)
Age (years), mean range	36 (17, 60)	35 (18, 60)
Female	52/109 (47.7%)	38/80 (47.5%)
Trial Center Location in South Africa		
Johannesburg	40/109 (36.7%)	33/80 (41.2%)
Cape Town	57/109 (52.3%)	47/80 (58.8%)
Durban	12/109 (11.0%)	0/80 (0.0%)

Source: Statistical Reviewer

Baseline Disease Characteristics

Variable	Safety Population (n = 109)	MITT Population (n = 80)
HIV-Positive	56/109 (51.4%)	39/80 (48.8%)
Current Tuberculosis Diagnosis		
Extensively Drug-Resistant	71/109 (65.1%)	55/80 (68.8%)
Multidrug-Resistant Non-Responsive	19/109 (17.4%)	12/80 (15.0%)
Multidrug-Resistant Intolerant	19/109 (17.4%)	13/80 (16.2%)
Type of Pulmonary Cavity		
None	17/109 (15.6%)	8/80 (10.0%)
Unilateral	51/109 (46.8%)	43/80 (53.8%)
Bilateral	41/109 (37.6%)	29/80 (36.2%)

Source: Statistical Reviewer

Primary Efficacy Analysis: Favorable Outcomes 6 Months After End of Treatment in the MITT Analysis Population

	Total	XDR	TI/NR MDR
Total Assessable	80	55	25
Favorable	**72/80 (90%)**	49/55 (89%)	23/25 (92%)
Unfavorable	8/80 (10%)	6/55 (11%)	2/25 (8%)
Death	6/80 (8%)	5/55 (9%)	1/25 (4%)
95% CI for Favorable	**81% to 96%**	78% to 96%	74% to 99%

Source: Nix-TB Addendum Clinical Trial Report Dated 01 August 2018, Table 7-24.

Primary Efficacy Analysis

- Strong statistical evidence that the favorable outcome rate for the BPaL regimen exceeds 50% in the setting of Nix-TB.

- Conclusion is robust to the handling of interim analysis and premature study termination. A very conservative 99.9% confidence interval (i.e., the Haybittle-Peto method) yields a favorable outcome rate from 66% to 99%.

- Conclusion is robust to the handling in the analysis of the 34 screen failures and 1 subject considered unassessable due to non-TB death. These exclusions are potentially important for an externally controlled comparison. Even if conservatively imputing unfavorable outcomes for all such patients, the 95% confidence interval yields a favorable outcome rate from 53% to 71%.

Subgroup Results: Favorable Outcomes 6 Months After End of Treatment in the 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%)
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 Results by Linezolid Status: Favorable Outcomes 6 Months After End of Treatment in the MITT Analysis Population

Linezolid Status	BPaL (n = 80)
Initial linezolid dose of 600 mg BID	39/44 (89%)
Initial linezolid dose of 1200 mg QD	33/36 (92%)
Post-baseline linezolid termination due to adverse event	22/23 (96%)
Post-baseline linezolid interruption due to adverse event	37/38 (97%)
Post-baseline linezolid dose reduction	50/54 (93%)

Source: Statistical Reviewer

Selected Secondary Efficacy Endpoints

- Bacteriologic failure, relapse, or clinical failure 24 months after the End of Treatment:
  - Based on enrollment date, only 23 patients were expected to have outcome data.
  - 19/23 (82.6%) patients were successfully treated and remained TB-negative, 3 deaths, 1 relapse.

- Time to sputum culture negative status: Aside from patients who died, all assessable patients were culture negative 16 weeks after enrollment.

- Change from baseline weight 6 months after End of Treatment:
  - 77 patients with weight data.
  - Median weight change = +3.0 kg. Interquartile range from -1.0 kg to 6.7 kg.

Historical Control Rate

- Efficacy conclusions of Nix-TB depended on whether the 50% historical favorable outcome threshold was a reasonable benchmark

- The Applicant provided two analyses to address this issue:
  - Literature review
  - Matched historically controlled comparison

Literature Review

- There were 18 studies with 1731 patients met search criteria for XDR-TB outcomes. We excluded 2 studies in which outcome rates could only be estimated.

- World Health Organization definitions of treatment outcomes for XDR-TB, with success based on cure or completion of therapy.

- Studies were heterogeneous with respect to response rates, mortality rates, timing of assessments, geography, and calendar time of treatment.

- A clinical trial such as Nix-TB potentially may have selected for a less severely ill patient population than literature-based observational studies.

Literature Review

First Author (Year of Publication)	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)	1993-2006	Not available	United States	5/17 (29%)	7/17 (41%)
Dheda (2017)	2008-2012	44%	South Africa	90/203 (44%)	43/270 (16%)
Keshavjee (2008)	2000-2004	0%	Russia	2/29 (7%)	14/29 (48%)
Kim (2008)	2000-2002	0%	South Korea	20/75 (27%)	22/75 (29%)
Kvasnovsky (2016)	2006-2008	62%	South Africa	211/330 64%)	34/330 (10%)
Leimane (2010)	2000-2004	6%	Latvia	4/48 (8%)	18/48 (38%)
Liu (2011)	1996-2009	0%	China	3/48 (6%)	14/48 (29%)
Migliori (2008)	1999-2006	2%	Estonia, Germany, Italy, Russia	14/48 (29%)	22/48 (46%)
Mitnick (2008)	1999-2002	0%	Peru	11/48 (23%)	29/48 (60%)
Mor (2014)	1999-2010	8%	Israel	5/12 (42%)	7/12 (58%)
O'Donnell (2013)	2006-2007	72%	South Africa	48/114 (42%)	25/114 (22%)
Olayanju (2018)	2008-2014	49%	South Africa	69/202 (34%)	27/202 (13%)
Padayatchi (2014)	2009-2011	86%	South Africa	Not available	11/85 (13%)
Pietersen (2014)	2008-2012	41%	South Africa	49/107 (46%)	17/107 (16%)
Tang (2011)	2007-2009	0%	China	5/94 (5%)	14/94 (15%)
Tabarsi (2010)	2004-2007	0%	Iran	3/12 (25%)	5/12 (42%)

Source: Summary of Clinical Efficacy, Table 36.

Literature Review

- Historical treatment success rates from the literature were lower than in Nix-TB.

- A DerSermonian and Laird random effects meta-analysis yielded an estimated historical treatment success rate of 28% with a 95% confidence interval from 21% to 34%. Thus, the upper limit was well below the 50% threshold used in Nix-TB.

- Historical treatment success rates have been low in South Africa. All 6 South African studies in the literature review reported success rates ≤22%, and Nix-TB was conducted entirely in South Africa.

Matched Comparison

- The Applicant additionally conducted a historically controlled matched comparison.

- BPaL group:
  - First 45 patients in Nix-TB with primary outcome data, enrolled in 2015-2016
  - Highest enrolling site was Brooklyn Chest Hospital in Cape Town, South Africa
  - Primary endpoint of unfavorable outcome 6 months after 6-9 months of treatment

- Historical controls:
  - Drawn from 202 patients with newly diagnosed XDR-TB at Brooklyn Chest Hospital in Cape Town, South Africa from 2008-2014 without bedaquiline, linezolid, pretomanid, or delamanid.
  - Primary endpoint: Unfavorable outcome defined per World Health Organization as death, judgment of treatment failure, default, or loss to follow-up 24 months after the start of treatment. Treatment was planned for 18 months or longer.

Matched Comparison

- Individually matched subsamples from the two groups based on propensity scores from the covariates of sex, body weight, and baseline HIV status.
- A ratio of 1:2 of Nix-TB: control patients.
- The statistician responsible for matching was kept blinded to outcomes in both groups throughout the matching process.

Matched Comparison

Baseline characteristic	BPaL (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, Table 40.

Matched Comparison

Favorable outcome		Relative risk	95% CI	p-value
BPaL 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, Tables 41 and 42.

Matched Comparison

- Results were not an artifact of the shorter assessment times in Nix-TB:
  - Favorable outcome rates 24 months after the end of treatment in Nix-TB were 19/23 (82.6%), which were similar to results for the primary endpoint.
- Rates of death 12 months after the start of treatment were also lower in the Nix-TB group compared to the matched historical control group: 9% versus 34%, $p<0.01$.
- It is possible that there were unmeasured baseline differences between patients in Nix-TB and historical controls. The historical group only included newly diagnosed XDR-TB while Nix-TB also included prior treatment failures and patients with treatment intolerant/nonresponsive multidrug-resistant TB.
- Rates of patients screened for Nix-TB were lower than rates of patient treatment in the historical control period at the Brooklyn Chest Hospital, so the entire XDR-TB target population at this hospital may not have been screened.

Summary and Conclusions

- The favorable outcome rate for the BPaL regimen in Nix-TB was convincingly higher than the prespecified historical control rate of 50%.
- The 50% historical control threshold was evaluated from a literature review of previous treatment outcomes for XDR-TB.
- The literature review was supplemented by a matched comparison from an Nix-TB study center. Treatment and control groups were similar on demographic factors and HIV status but those treated with BPaL in Nix-TB had higher favorable outcome rates and lower mortality rates.
- As there was no randomized control group in Nix-TB there remains the possibility that results may have been confounded, but this appears to be a setting in which efficacy can be evaluated using historical controls.

Presentation of Clinical Safety Pretomanid

Antimicrobial Drugs Advisory Committee Meeting

June 6, 2019

Elizabeth O'Shaughnessy, MD

Division of Anti-Infective Products, CDER, FDA

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- Office of Computational Science
  - Peter Glass, MS (Applied Statistics)
  - Rui Li, MD, MS, Clinical Data Specialist
  - Scott G. Runyan, BS, Senior Analyst, JReview Support Team

Outline

- Safety findings for pretomanid alone
  - Animal toxicology studies
  - Two Phase 2 EBA studies
- Adverse reactions associated with bedaquiline and linezolid
- Safety findings for BPaL regimen in the Nix-TB trial (*data cut-off: March 26, 2018*)
  - Common treatment emergent adverse events (TEAEs)
  - Serious TEAEs
  - TEAEs of special interest (hepatic, neurologic, hematologic)
- Interim safety information from ongoing ZeNix trial
- Summary of safety for BPaL regimen

Pharmacokinetic (PK) Highlights - Pretomanid

Absorption	Distribution
• AUC and Cmax increases were approximately dose proportional following doses of 50 mg to 200 mg • AUC and Cmax increases were less than dose proportional following doses of 200 mg to 1000 mg • **Food effect:** PK exposure ↑ with high-calorie, high-fat meal following 200 mg dose; mean C_{max} ↑ 76% mean AUC↑ 88% • **Median T_{max} (range) under fed conditions**: 5 hours (3 – 8 hours) • Steady-state plasma concentrations achieved following 4 to 6 days of 200 mg QD, with 2-fold accumulation	• **Protein binding:** 86.4 %
Metabolism/Elimination	**Excretion/Elimination**
• Extensively metabolized by multiple reductive and oxidative pathways • CYP3A4 plays minor role in metabolism i.e., approximately 20 % based on in vitro studies • Not a substrate of CYP2C9, 2C19, or 2D6	• **Mean $T_{1/2}$:** 17 hours following single 200 mg dose and 16 hours following multiple doses of 200 mg QD • **Human ADME study:** 53% in urine and 38% in feces primarily as metabolites; approximately 1% excreted in urine as unchanged pretomanid
• The effect of renal or hepatic impairment on the PK of pretomanid is unknown • No clinically significant differences in the PK of pretomanid were observed based on sex, body weight, race/ethnicity (Black, White, other), pulmonary TB status, or HIV status.	

Safety Signals in Animal vs. Human Studies of Pretomanid

Safety Signals	Animal Studies – Pretomanid alone	Human Studies – Pretomanid with other antimycobacterial drugs
Neurotoxicity	Convulsions and ataxia in monkeys at 5x human exposure, generally after 60 days of dosing	Convulsions in 2 subjects in Nix-TB trial
Cataracts	Cataracts in rats and monkeys at 7x human exposure No cataracts in rats at 2x human exposure or in monkeys at 5x human exposure	No cataracts in clinical trials: NC-002, NC-005, NC-006, and Nix-TB.
Testicular Toxicity (Infertility)	Spermatocyte degeneration, atrophy of seminiferous tubules, reduced fertility in rats at 1.5x human exposure. Testicular toxicity was associated with infertility (not reversed) in rats at 3x human exposure.	Male hormones in normal ranges in Phase 2 & 3 trials: NC-002, NC-005, NC006 Human Semen Analysis Study is 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 to 5x ULN in rodents and monkeys at exposures similar to human exposure	Hepatic transaminases increased in phase 2 studies of pretomanid alone Hepatic transaminases and DILI observed with pretomanid as part of antimycobacterial regimens in Phase 2 & 3 trials

Two Phase 2 EBA Studies (pooled): Pretomanid Alone x ≤ 14 days

Treatment Emergent Adverse Events	Pretomanid (N=122)	HRZE (N=16)
Any TEAE	***47 (38.5)***	***7 (43.8)***
TEAEs (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)

EBA: Early Bactericidal Activity; HRZE: Isoniazid, Rifampin, Pyrazinamide, Ethambutol

Bedaquiline, SIRTURO® USPI

- **Warnings and Precautions**
  - QT Prolongation
  - Hepatotoxicity
  - Drug Interactions: CYP34A inducers, e.g. efavirenz
  - Increased risk of death
    - unexplained imbalance in deaths in bedaquiline vs. placebo in one study of pulmonary MDR-TB

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1534c9ae-4948-4cf4-9f66-222a99db6d0e

Linezolid, ZYVOX® USPI

- **Warnings and Precautions**
  - Myelosuppression
    - anemia, leukopenia, thrombocytopenia, pancytopenia
  - Peripheral and Optic Neuropathy
  - Serotonin Syndrome with serotonergic drugs
  - Elevation of blood pressure, hypoglycemia, convulsions, lactic acidosis
  - Mortality imbalance
    - Linezolid vs. comparator in one study of catheter-related bloodstream infections

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021130s037,021131s030,021132s035lbl.pdf

Clinical Studies in Pretomanid Safety Database

(Data cut-off, March 26, 2018)

Clinical Trials	No. of Subjects N = 1507	Pretomanid alone or part of combination n= 1168	HRZE or other comparator n= 339
Phase 3: XDR-TB and TI/NR MDR-TB	124	**NixTB: 109** **ZeNix: 15**	NA
Phase 3: DS-TB and MDR-TB (*STAND* Trial)	284	216	68
Phase 2: DS-TB and MDR-TB	347	227	120
Phase 2 EBA: DS-TB	328	212	116
Phase 1	324	289	35

Bedaquiline/ Pretomanid/ Linezolid (BPaL)

- Nix-TB:
  - 109 patients enrolled with XDR-TB or TI/NR MDR-TB
    - 93 (85.3%) completed 6 months treatment (data cut-off, March 26, 2018).
- ZeNix:
  - BPaL - with various doses and durations of linezolid
  - 15 subjects (data cut-off - March 26, 2018); 61 subjects (data cut-off - Oct 15, 2018)

Nix-TB: Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAEs)	BPaL Regimen, Subjects, 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%)
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%)

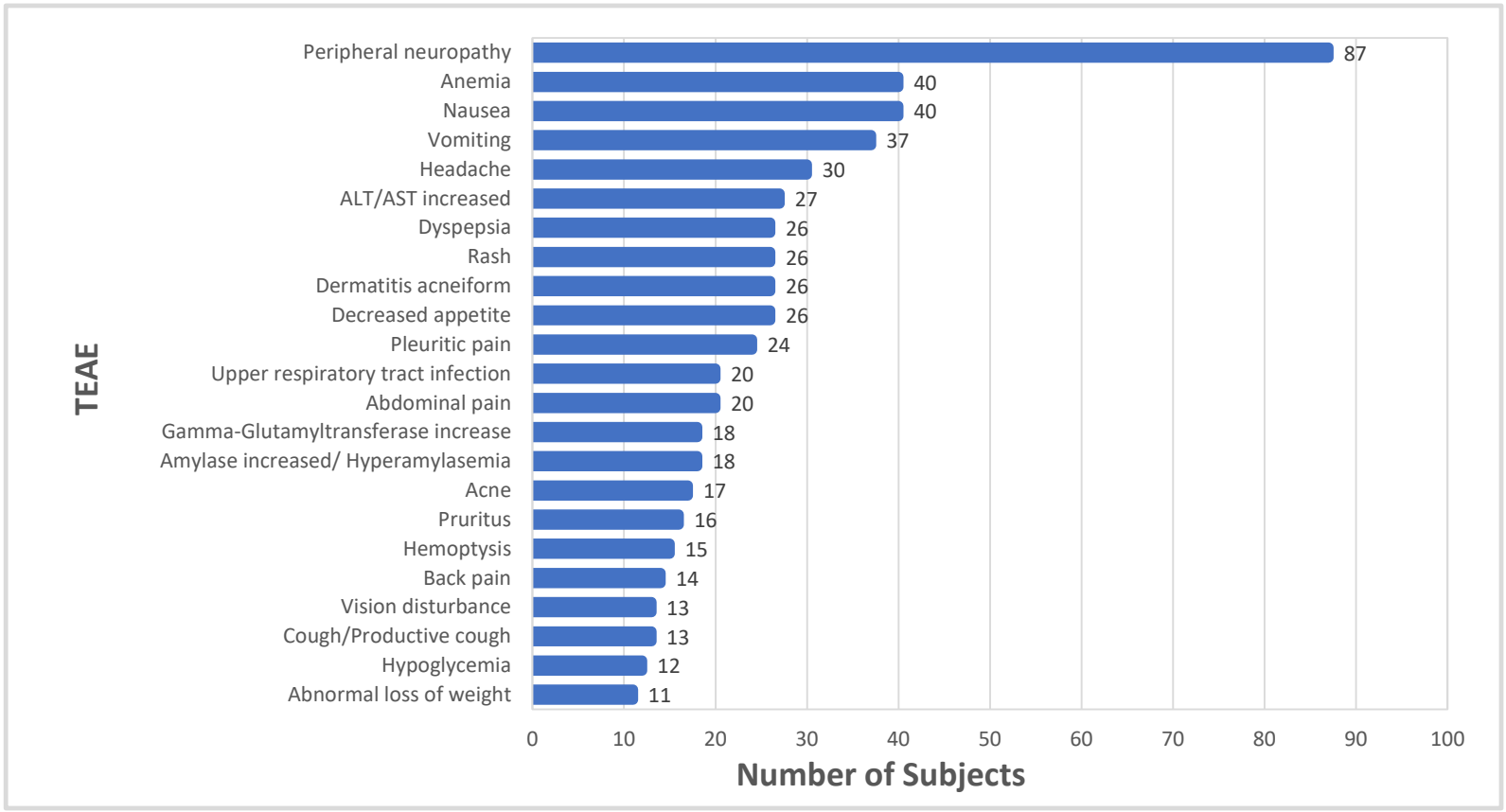
Nix-TB: Deaths

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
M / 34y	XDR/ HIV +	Disseminated Tuberculosis, Pulmonary Tuberculosis, Pancreatitis Hemorrhagic / Severe Pulmonary Tuberculosis and Disseminated Tuberculosis	35
F / 20y	XDR/ HIV -	Upper Gastrointestinal Bleeding/ Upper Gastrointestinal Bleeding	51
M / 35y	XDR/ HIV +	Pancreatitis Hemorrhagic/ Acute Hemorrhagic Pancreatitis	53
F / 31y	XDR/ HIV +	Pulmonary Tuberculosis/ Acute Severe Worsening of Pulmonary Tuberculosis	55
F / 26y	XDR/ HIV -	Septic Shock/ Septic Shock Secondary to Pneumonia	76
F / 29y	TI/NR MDR/ HIV-	Sepsis, Pneumonia/ Worsening Pneumonia	93
M / 38y	XDR/ HIV +	Death/ “Natural causes” characterized as a non-violent death	369
M / 55y	XDR/ HIV +	Sepsis/ Sepsis Secondary to Gangrene from Peripheral Vascular Disease	486

Nix-TB: Serious TEAEs

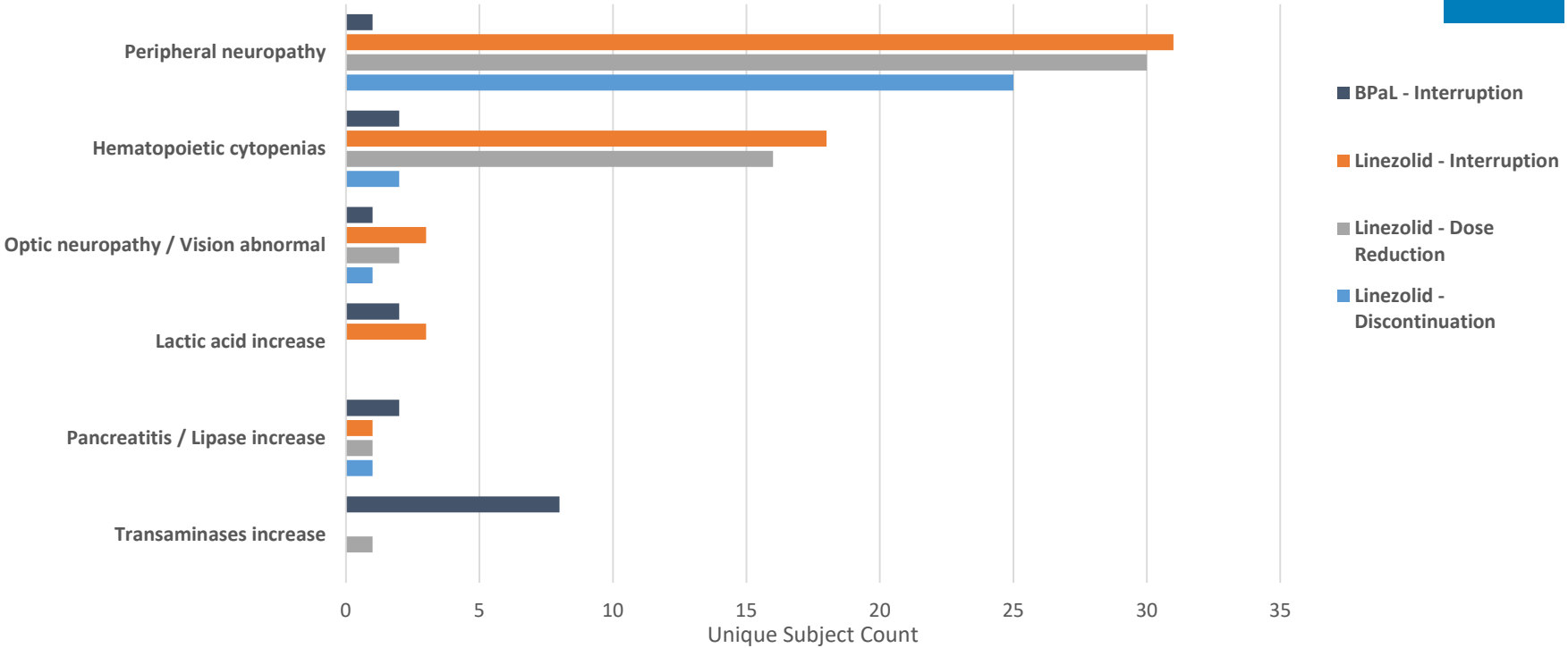
- 19 (17.4%) patients had serious TEAEs
  - 6 patients experienced SAEs leading to death
  - 13 patients had SAEs that resolved or were resolving at data cut-off date.
- SAEs (excluding pulmonary TB) occurring in ≥2 patients included:
  - pneumonia (3, 2.8%), sepsis (2, 1.8%), anemia (2, 1.8%), hypoglycemia (2, 1.8%), pancreatitis (2, 1.8%), optic neuritis/neuropathy (2, 1.8%), seizure (2, 1.8%), and hematemesis (2, 1.8%).

Nix-TB: Treatment Emergent Adverse Events



Footnote: Grouped preferred terms (PTs) and then analyzed with cut-off > 10%.

Nix-TB: Selected Adverse Events Leading to Interruption, Dose Reduction, or Discontinuation of Study Drugs



The groups consist of the following TEAEs: **Peripheral neuropathy** - Peripheral sensory neuropathy, Neuropathy peripheral, Hypoesthesia; **Hematopoietic cytopenias** - Anemia, Neutropenia, Thrombocytopenia, Bicytopenia, Bone marrow failure; **Optic neuropathy / Vision abnormal** - Visual acuity reduced, Optic neuropathy, Optic disc hyperemia, Visual impairment; **Lactic acid increase** - Blood lactic acid increased, Hyperlactacidemia, Lactic acidosis; **Pancreatitis / Lipase increase** - Hyperlipasaemia, Lipase increased, Pancreatitis, Pancreatitis hemorrhagic; **Transaminases increase** - Drug-induced liver injury, Hepatic enzyme increased, Transaminases increased

Nix-TB: TEAEs of Special Interest

- Peripheral neuropathy
- Optic neuropathy
- Myelosuppression
  - Anemia, thrombocytopenia, leukopenia, pancytopenia
- Hepatic enzyme abnormalities
- Pancreatitis
- Lactic acidosis

Nix-TB: Peripheral Neuropathy

Treatment Emergent Adverse Event	BPaL Regimen		
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%)
Hypoesthesia	1 (1.9%)	2 (3.6%)	3 2.7%)
Hyporeflexia	0	1 (1.8%)	1 (0.9%)
Neuropathy Peripheral	5 (9.4%)	5 (8.9%)	10 (9.2%)
Paresthesia	3 (5.7%)	2 (3.6%)	5 (4.6%)
Peripheral Motor Neuropathy	1 (1.9%)	1 (1.8%)	2 (1.8%)
Peripheral Sensorimotor Neuropathy	0	1 (1.8%)	1 (0.9%)
Peripheral Sensory Neuropathy	37 (69.8%)	38 (67.9%)	75 (68.8%)

Nix-TB: Optic Neuropathy

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

Nix-TB: Hematopoietic Cytopenias

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%)***
Anemia	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%)
Anemia and Thrombocytopenia	1 (1.9%)	0	1 (0.9%)
Lymphopenia	0	1 (1.8%)	1 (0.9%)
Pancytopenia	1 (1.9%)	0	1 (0.9%)

Nix-TB: Hepatic Abnormalities

Treatment Emergent Adverse Events	BPaL		
	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
Any TEAE	***16 (30.2%)***	***23 (41.1%)***	***39 (35.8%)***
Transaminases increased	15 (28.3%)	12 (21.4%)	27 (24.8%)
Gamma-glutamyltransferase increased	2 (3.8%)	16 (28.6%)	18 (16.5%)
Blood alkaline phosphatase increased	1 (1.9%)	2 (3.6%)	3 (2.8%)
Drug-induced liver injury	1 (1.9%)	1 (1.8%)	2 (1.8%)
Hyperbilirubinemia	1 (1.9%)	1 (1.8%)	2 (1.8%)
Hepatomegaly	0	1 (1.8%)	1 (0.9%)

Nix-TB: Alanine Aminotransferase (ALT)

	BPaL (N=109); n/N(%)			
	Max. Post Baseline Shift in ALT (U/L) Level Categories			
Baseline	≤ 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)

Nix-TB: Total Bilirubin

	BPaL (N=109); n/N(%)			
	Max. Post-Baseline Shift in Total Bilirubin (µmol/L) Level Categories			
Baseline	≤ ULN	> ULN - ≤ 2xULN	> 2xULN - ≤ 5xULN	> 5xULN
≤ ULN	101 (92.7)	6 (5.5)	2 (1.8)	0
> ULN - ≤ 2xULN	0	0	0	0

Potential Hy's Law Case: Subject 1

- 25 y male, XDR-TB, HIV -
  - ALT ↑, total bilirubin↑ peaked at ~ Week 8
  - Fulfilled biochemical criteria for Hy's law (ALT > 3x ULN and total bilirubin > 2x ULN with alkaline phosphatase < 2x ULN)
  - Hepatitis B, Hepatitis C, urine toxin screen – negative. No alcohol or herbal medications.
  - BPaL regimen interrupted for ~ 3 weeks: ALT↓, Total Bilirubin↓
  - ALT and bilirubin continued to decline after re-challenge BPaL
  - Completed 26 weeks of BPaL treatment

Potential Hy's Law Case: Subject 2

- 36 y female, XDR-TB, HIV –
  - ALT ↑, total bilirubin↑, alk. phos. ↑ peaked at ~ Week 11
  - Alcohol use +
  - BPaL regimen interrupted for ~ 2 wks: ALT↓, Total Bilirubin↓
  - ALT and bilirubin declined after re-challenge BPaL
  - Completed treatment (BPa) at Week 34
    - linezolid discontinued at Week 26 for worsening peripheral neuropathy

Nix-TB: Acute Pancreatitis & Lipase / Amylase Elevations

Treatment Emergent Adverse Events	BPaL , N=109; n/N(%)		
	HIV Negative (N=53)	HIV Positive (N=56)	Total (N=109)
Any TEAE	***8 (15.1)***	***14 (25.0)***	***22 (20.2)***
Amylase Increased / Hyperamylasemia	6 (11.3)	11 (19.6)	17 (15.6)
Lipase Increased / Hyperlipasemia	3 (5.7)	3 (5.4)	6 (5.5)
Acute Pancreatitis	1 (1.9)	2 (3.6)	3 (2.8)

Nix-TB: Lipase Levels

	BPaL, N=109; n/N(%)				
	Maximum Post-Baseline Lipase (U/L) Level Category				
Baseline	<= 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)

Nix-TB: Lactic Acidosis

Treatment Emergent Adverse Events	BPaL, N=109; n/N(%)		
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)
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)

Study ZeNix: Selected Treatment Emergent Adverse Events in BPaL Group
Data cut-off date: Oct 15, 2018

	BPaL Regimen (N=61); n/N(%)
Any TEAE (where PT > 5%)	***51 (83.6)***
TEAEs by Preferred Term	
Peripheral sensory neuropathy	9 (14.8)
Alanine aminotransferase increased	8 (13.1)
Vomiting	7 (11.5)
Anemia	6 (9.8)
Dermatitis acneiform	6 (9.8)
Aspartate aminotransferase increased	5 (8.2)
Nausea	5 (8.2)
Fatigue	4 (6.6)
Hyperkalemia	4 (6.6)
Hypertension	4 (6.6)
Non-cardiac chest pain	4 (6.6)

Summary & Conclusions - BPaL Regimen

- Limited safety database
- Nix-TB: 8 deaths – pneumonia / TB progression, sepsis, acute pancreatitis, or upper GI bleed
- Peripheral sensory neuropathy, anemia, nausea, vomiting, headache, and increased transaminases were common treatment emergent adverse events
- Two potential Hy's Law cases - no progression to serious liver injury
- Neurologic, hematologic, and hepatic adverse events associated with the BPaL regimen were managed with dosing interruptions, dose reductions, or discontinuation of study drug(s)
  - Most adverse events were reversible using this approach; however, peripheral neuropathy may be irreversible in some patients
- Safety findings were similar among HIV-negative and HIV-positive patients

Summary & Conclusions - BPaL Regimen

- If pretomanid is approved, regular monitoring of patients on BPaL for development of optic and peripheral neuropathy, myelosuppression (anemia, thrombocytopenia, leukopenia), QT prolongation (bedaquiline), and hepatotoxicity will be important for patient safety.