Center for Tuberculosis
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PREDICTIVE VALIDITY OF POPULATION MODELS FOR LINEZOLID EXPOSURE AND TOXICITY IN ZENIX

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BACKGROUND

Despite approval of the bedaquiline, pretomaind, and linezolid (starting dose of 1200 mg daily) (BPaL) regimen for 6 months against extensively drug resistant (XDR) based on favorable efficacy results from the Nix-TB study[1] (NCT02333799, N = 104), that showed 89% success, the dose and duration of linezolid for the treatment TB remains controversial because of safety concerns.

ZeNix[2] (NCT03086486, N=179), a successor of Nix-TB, was conducted and found that efficacy of the BPaL regimen can be generally maintained while reducing toxicity, through a lower daily dose and/or shorter duration of linezolid.

We've developed pharmacokinetic (PK) and toxicodynamic models based on the Nix-TB study to predict the time course and extent of linezolid-induced toxicity (peripheral neuropathy (PN) and anemia) and provided alternative dosing regimens to manage toxicities.[3] Here, we assess the predictive validity of the models and dosing recommendations using the new data from ZeNix.

METHODS

In ZeNix, all participants received bedaquiline and pretomanid. Participants were randomized to receive one of the following linezolid regimens: **Group 1**: 1200 mg QD for 26 weeks, **Group 2**: 1200 mg QD for 9 weeks, **Group 3**: 600 mg QD for 26 weeks, and **Group 4**: 600 mg QD for 9 weeks. All dosage adjustments were used in our analysis.

Prediction-based (not shown) and simulation-based diagnostics were used to assess predictive power of models from Nix-TB on the data from ZeNix. Models were refitted to the combined data from ZeNix and Nix-TB and reassessed for consistency with the totality of the data.

Model simulations were compared to rates of investigator-reported adverse events in each trial.

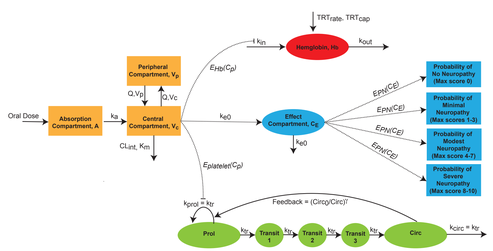

Fig. 1 Final structural pharmacokinetic/toxicodynamic model from analysis of Nix-TB study.[3]

Linezolid toxicity in TB is generally related to extent and duration of linezolid exposure.

Analysis of Nix-TB and ZeNix trials confirm that 1) most peripheral neuropathies reversed and 2) pretreatment and week 4 hemoglobin levels might be useful to guide early dose adjustments to prevent anemia.

RESULTS

- 179 ZeNix participants (45, 45, 45, and 44 in Group 1, 2, 3, and 4 respectively) were included in the analysis. 70 (39%), 65 (36%), 34 (19%), 10 (6%) participants were from Russia, South Africa, Georgia, and Moldova, respectively.

Linezolid PK

- Linezolid PK in ZeNix was well predicted by the two-compartment model with nonlinear elimination developed with data from Nix-TB.

Table 1 Model predicted steady state PK parameters for the ZeNix population. Median (5th - 95th percentile) are reported.

Linezolid regimen	$AUC_{0\text{-}24}$ (mgh/L)	C_{min} (mg/L)	C_{max} (mg/L)
600 mg once daily	95 (51-164)	0.5 (0.08-1.9)	9.2 (6.5-13.2)
1200 mg once daily	255 (126-535)	2.1 (0.2-10.7)	20.4 (14.1-33.9)

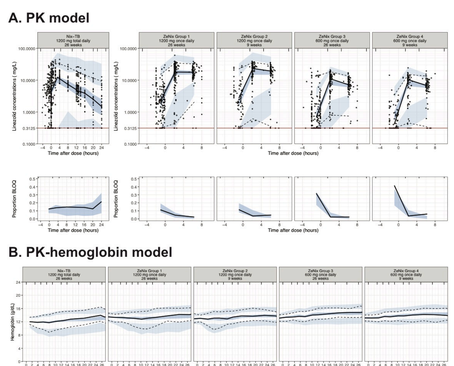

Fig. 2 Visual predictive checks of refined population models that included data from ZeNix and Nix-TB trials.

RESULTS

PK-PN

- In ZeNix, PN in South Africa was successfully predicted with the model from Nix-TB, but overpredicted for participants from other regions. Accounting for region differences in pretreatment PN and the maximum effect of linezolid on PN improved model refit (Fig. 2).
- Time to reversed PN in the ZeNix trial was accurately predicted by the Nix-TB model (Fig. 3). In ZeNix, 73% of modest to severe PN reversed to minimal or normal scores within 6 months in the 1200 mg linezolid groups 100% in the 600 mg groups.
- Model simulations showed that predicted proportions of patients with at least a minimal scores were consistent with the observed rates of investigator-reported PN in the trials (Fig. 4)

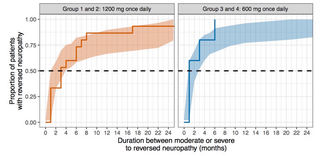

Fig. 3 Reversibility of PN in the ZeNix trial was predicted by PK-PN model developed with Nix-TB trial data. Solid line: observed. Shaded area: 95% PI.

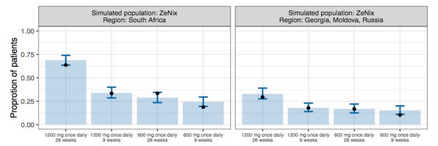

Fig. 4 PK- PN model predicted rates of investigator-reported PN. Bar: proportion with at least a minimum score. Error bar: 95% CI. Point: Observed in trial.

PK-Hemoglobin (anemia)

- The hemoglobin model developed with Nix-TB predicted temporal distributions of hemoglobin in ZeNix (Fig. 2)
- The Nix-TB model's[3] finding that Hb change after 4 weeks of treatment was superior to linezolid trough concentrations for predicting anemia was not recapitulated in terms of the ROC AUC but did manifest in the precision-recall (PR) AUC, which emphasizes prediction of positive cases: (Fig. 5)
- Model simulations showed that predicted proportions of patients with Grade 1 or higher anemia were consistent with observed rates of investigator-reported anemia in the trials (Fig. 6)

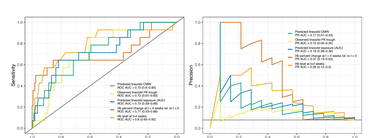

Fig. 5 ROC and PR curves for univariate models that predict investigator-reported anemia

References: [1] Conradie et al. NEJM. 2020. [2] Conradie et al. NEJM. 2022. [3] Imperial et al. CID 2022

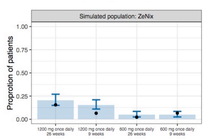

Fig. 6 PK-hemoglobin model predicted rates of investigator-reported anemia. Bar: proportion with at least a Grade 1 AE. Error: 95% CI. Point: Observed in trial