Population Pharmacokinetics of Pretomanid

Authors:

David H. Salinger - Certara Inc., Princeton, NJ; under contract with the Bill and Melinda Gates Foundation

Vishak Subramoney - Certara Inc., Princeton, NJ; under contract with the Bill and Melinda Gates Foundation

Daniel Everitt – TB Alliance

(corresponding author) Jerry R. Nedelman – TB Alliance#

Jerry.Nedelman@tballiance.org

ABSTRACT

A population pharmacokinetic (PopPK) model for pretomanid was developed using data from 14 studies in the pretomanid development program: six phase 1 studies, six phase 2 studies, and two phase 3 studies. The final analysis dataset contained 17725 observations from 1054 subjects including healthy subjects and subjects with drug-sensitive (DS), multidrug-resistant (MDR), or extensively drug-resistant pulmonary TB dosed pretomanid in mono or combination therapies for up to six months.

Pretomanid pharmacokinetic behavior was described by a one-compartment model that at a given dose was linear in its absorption and clearance processes but where the rate of absorption and extent of bioavailability changed with dose.

Clearance and volume of distribution scaled allometrically with weight. Apparent clearance in females was 18% less than in males. Among HIV-positive subjects, absent the effect of CYP3A4-inducing antiretrovirals, apparent clearance was 6% higher. Some effects of total bilirubin and albumin were found, but the impacts on exposure were small.

Bioavailability in the fasted condition was about half that in the fed condition. Relative bioavailability decreased with increasing dose in the fasted condition, but not for doses less than or equal to 200 mg in the fed condition. HIV-positive subjects taking efavirenz and lopinavir/ritonavir had exposures that were reduced by 46% and 17%, respectively. There was little evidence for noteworthy effects of regimen partners on pretomanid.

Standard diagnostics indicated that the model described the voluminous, diverse data well, so that the model could be used to generate exposure metrics for exposure/response analyses to be reported elsewhere.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tb*), is the one of the top 10 causes of death and the world's leading cause of death from a single infectious disease. Although globally distributed, in 2017 two-thirds of cases were in eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Less than 10% of cases were in the WHO European Region and the WHO Region of the Americas, combined (1).

First line treatment for TB is a combination of the four drugs rifampicin, isoniazid, pyrazinamide, and ethambutol. TB caused by a strain of *M. tb* with no resistance to these four drugs is called drug-susceptible (DS). In 2017, approximately 558,000 people developed TB that was resistant to rifampicin, of which 82% were also resistant to isoniazid, a condition known as multi-drug resistant (MDR) TB (1). Among the most difficult-to-treat *M. tb* strains are those causing extensively drug-resistant tuberculosis (XDR-TB), defined as MDR-TB with additional resistance to at least one fluoroquinolone and a second-line injectable agent (amikacin, capreomycin, or kanamycin). Among the cases of MDR-TB in 2017, 8.5% were estimated to have XDR-TB (1). Therefore, the need for innovative anti-tuberculosis regimens is great.

Pretomanid (Pa), a new chemical entity of the nitroimidazooxazine class, is under investigation for the treatment of TB. It continues to be studied in defined regimens in

various combinations with partners bedaquiline (B), clofazimine (C), moxifloxacin (M), linezolid (L), and pyrazinamide (Z). These defined regimen combinations include: BPaL in Nix-TB (phase 3, completed; (2)), TB-PRACTECAL (phase 2/3, ongoing; (https://clinicaltrials.gov/ct2/show/record/NCT02589782)); and ZeNix (phase 3, ongoing; (https://clinicaltrials.gov/ct2/show/NCT03086486)); BPaCL and BPaML in TB-PRACTECAL; and BPaMZ in NC-005 (phase 2b, completed; (3)) and SimpliciTB (phase-2c, ongoing; (https://clinicaltrials.gov/ct2/show/NCT03338621)). Across these studies, patients with all types of TB, including DS, mono-resistant, MDR, and XDR are included.

The objective of this work was to develop a population pharmacokinetics (PopPK) model that quantifies the behavior of pretomanid in the diversity of populations represented by the ongoing clinical studies and expected future clinical use.

Characterizing the dose/response relationship of a new drug is a key challenge of drug development (4). PopPK can help to meet this challenge in several ways: identifying covariates that affect PK variability and hence treatment response; deriving PK exposure metrics from sparse data in clinical trials for use in exposure/response modeling; simulating exposures under new dosing regimens (5).

Prior to development of this PopPK model, the pretomanid development program had already identified several notable features of pretomanid PK including: a high-fat, high-calorie breakfast increased the AUC following a single-dose of pretomanid by 88% (6); under fasting conditions, pretomanid exposure increased less than proportionally with dose, with little additional increase after 1000 mg (7); multiple doses of rifampicin,

efavirenz, and ritonavir-boosted lopinavir reduced the AUC of pretomanid by 66%, 35%, and 17%, respectively (8). However, these results were based primarily on studies in healthy volunteers, and they had not been combined into a comprehensive model that accounted simultaneously for other intrinsic and extrinsic factors that might affect PK. Although a PopPK model has previously been developed for pretomanid (9), it was based on two phase 2a studies in 122 DS-TB subjects where pretomanid was administered as monotherapy under fasted conditions. The present work considers 12 additional studies that include phase 2b and phase 3 studies of pretomanid administered as part of multi-drug regimens to a more diverse collection of subjects, 1054 in total, including patients with MDR- and XDR-TB, under fed and fasted conditions (see the next section and Supplementary Tables S1 and S2 for more details on study conduct and subject diversity). Thus, the present work provides a PopPK model more broadly useful for addressing dose/exposure/response relationships of pretomanid.

RESULTS

Data

Data was pooled from six phase-1, six phase-2, and two phase-3 studies. There were 17725 observations from 1054 subjects. 162 HS received single oral doses of pretomanid ranging from 50 to 1500 mg, and 49 received multiple oral doses ranging from 200 to 1000 mg qd for 7 or 8 days. 122 subjects with DS-TB received pretomanid alone at 50 to 1200 mg qd for 14 days. 623 subjects with DS-TB or MDR-TB received pretomanid at doses of 100 mg or 200 mg qd in combination with one or more of bedaquiline, clofazimine, moxifloxacin, and pyrazinamide for 8 weeks to six months. And 98 subjects

with XDR or TI/NR MDR-TB from the Nix-TB study received 200 mg pretomanid qd in combination with bedaquiline and linezolid.

All HS were from North America, and more than 95% of the subjects with TB were from sub-Saharan Africa. No HS were HIV+, but 24% of subjects with TB were. Overall, 65% were male. Median (range) of age and weight were 27 (18 – 50) years and 75 (47 – 102) kg for HS, and 31 (18 – 77) years and 53 (29 – 121) kg for subjects with TB.

See Supplementary Tables S1 and S2 and Figure S1 for more details.

Final Model

The pharmacokinetics of pretomanid was best characterized by a one compartment drug disposition model with absorption lag represented by three transit compartments (Figure S2) that at a given dose was linear in its absorption and clearance processes but where the rate of absorption and extent of bioavailability changed with dose. (Transit compartments are mathematical constructs used to generate a delayed peak in the modeled concentration-time curve, but they do not represent specific physiological compartments (10). The model was parameterized in terms of relative bioavailability (F1), where 200 mg administered with fed status was given the reference value of 1; clearance (CL); volume of distribution (V2); mean transit time (MTT = 3/KTR; where KTR is the first-order rate constant between transit compartments); and first-order absorption (KA).

Inter-individual random effects of the form exp(η) multiplied on all parameters. For F1, KA, and MTT, the η's were normally distributed; for CL and V2, Box-Cox transformations (11) were applied to normal η's to characterize the long-tailed

distributions. (See the final model code in the Supplementary material for more details.) Random effects on F1, KA, and MTT were correlated.

Inter-occasion random effects of the form exp(η), with η's normally distributed and correlated, were multiplied on F1 and CL. Up to three occasions were defined for each trial, depending on trial length and sampling schedule (see Table S1 for details).

The residual error model was a mixture of an additive and a power model (12).

After an exhaustive, pre-specified, search, many intrinsic factors were found to significantly ($p<0.001$) impact model parameters. Clearance and volume of distribution scaled allometrically with weight (13). Apparent clearance in females was 18% less than in males. Among HIV-positive subjects not taking CYP3A4-inducing anti-retrovirals apparent clearance was 6% higher. Some effects of total bilirubin and albumin were found, but the impacts on exposure were small.

Covariates that were considered but not retained as significant in the final model were: age, race, body mass index, metrics of renal function, AST, and ALT. More than 99% of the subjects had normal or only mildly impaired renal function by eGFR.

Regarding extrinsic factors, bioavailability in the fasted condition was about half that in the fed condition. Bioavailability decreased with increasing dose in the fasted condition, but not for doses less than or equal to 200 mg in the fed condition. HIV-positive subjects taking efavirenz and lopinavir/ritonavir had exposures that were reduced by 46% and 17%, respectively. There was little evidence for noteworthy effects of regimen partners on pretomanid.

Some study effects were considered per plan on absorption and bioavailability because phase-1 food-effect studies, with a standard high-fat meal, had found approximate doubling of bioavailability under fed versus fasted conditions, but meal conditions were not strongly controlled in some phase-2 and phase-3 studies. Effects for NC-003 and NC-005 were retained. Other effects for Nix-TB, which was added in a final stage of modeling (see Methods), were found necessary post hoc to achieve an acceptable fit.

The code for the final model is provided in the Supplementary Materials and parameters are provided in Table 1. From these components, the covariate contributions may be reconstructed in detail. Because each of the model parameters F1, KA, MTT, CL, and V2 was allowed a flexible covariate structure, the impact of covariates on exposure is best understood from the simulation results described below.

154 Figure 1 shows prediction-corrected visual predictive checks (14) for the final model
155 indicating a satisfactory fit of the patient data. Predictive checks for other subsets of the
156 data and standard diagnostics (15,16) are included in the Supplementary Materials.
157

Model Application

Simulations incorporating intersubject variability were used to illustrate the effects of various covariate combinations on seven steady-state exposure criteria: average, trough, and maximum concentration ($C_{avg,ss}$, $C_{24h,ss}$, $C_{max,ss}$); time of maximum concentration ($t_{max,ss}$); half-life ($t_{½}$); relative bioavailability (F1); apparent oral clearance and volume (CL/F1, V2/F1); and the mean total absorption time (MTT +1/KA).

The reference subject was a: 55 kg, male, HIV negative, DS-TB subject with baseline total bilirubin (TBIL) of 5 µmol/L and albumin (ALB) of 35 g/L administered 200 mg qd of pretomanid alone in a fed condition to steady state. Departures from these reference conditions that were considered may be seen in the row labels of Figure 2, a forest plot of simulation results for $C_{avg,ss}$. Forest plots and tabular summaries for this and other criteria are provided in the Supplementary Figure S3 and Table S4.

Exposure

Median C_{avg}, C_{max}, and C_{24h} for a reference subject were 2.4, 3.2, and 1.6 µg/mL.

Administration of pretomanid in the fasted condition reduced exposure by about half relative to the reference.

Median C_{avg} was 22% higher in females, 13% lower in HS, and 6% lower in HIV+ subjects relative to the reference.

After the modeling results were reviewed, one group was defined by selecting covariate values that in combination would yield an extremely low exposure: fasting, HIV+, MDR-TB subjects weighing 100 kg, and taking efavirenz. For this group, the median C_{avg} was 0.36 µg/mL and the median C_{24h} was 0.22 µg/mL.

Otherwise, only three groups on 200 mg in the fed condition had median C_{avg} less than 80% of the reference value (i.e., less than 1.9 µg/mL):

- Weight 100 kg: 1.5 µg/mL
- HIV+ and taking efavirenz: 1.3 µg/mL

After the modeling results were reviewed, one group was defined by selecting covariate values that in combination would yield an extremely high exposure: females weighing 35 kg. For this group, the median C_{avg} was 4.0 µg/mL and the median C_{max} was 5.2 µg/mL.

Otherwise, only two categories on 200 mg in the fed condition had median C_{avg} more than 125% of the reference value (i.e., more than 3.0 µg/mL):

- Weight 35 kg: 3.3 µg/mL
- PaMZ regimen: 3.1 µg/mL

Although, per above, in the PaMZ (pretomanid plus moxifloxacin plus pyrazinaminde) regimen pretomanid had median C_{avg} 132% of the reference value, in the BPaMZ (bedaquiline plus PaMZ) regimen in MDR-TB subjects in NC-005, the median C_{avg} was essentially the same as that of the reference value. Nix-TB-related covariates had only small effects: median C_{avg} for TI/NR MDR-TB and XDR-TB subjects was about 15% greater than the reference value. This indicates that bedaquiline and linezolid together had little impact on pretomanid exposure. In the PaM regimen, pretomanid exposure (C_{avg}) was essentially unchanged from the reference value and the BPa and PaZ regimens were found not to impact pretomanid exposure. Thus, overall, there was little evidence for noteworthy effects of regimen partners on pretomanid.

The effect of baseline values of albumin and total bilirubin were retained in the final model, but these had only small effects.

t_{max}

The median t_{max} under reference conditions was 4.25 hours (timepoints on quarter-hour intervals were considered). It varied only ±0.25 hours for all other examined conditions except in study NC-005 where it was 6.5 hours. This was suspected as spurious, but as there were no observations between 4 and 8 hours post dose in that study it could not be readily rejected.

Half life

The median half-life for the reference conditions was 18 hours. For all other conditions, the median half-life was between 10 and 30 hours.

DISCUSSION

Benefits of modeling are said to include simplification of complex systems and integration of diverse data (15, 17). Sometimes the pursuits of these benefits collide. This modeling of the PopPK of pretomanid may represent such a collision. At a given dose, under particular conditions and in a particular population, pretomanid PK can be described by a simple linear one-compartment model, although its late t_{max} requires the added complexity of transit compartments to characterize absorption. Integrating data from 14 studies with a 30-fold range of doses (15 to 1500 mg), varying and even uncertain dosing conditions with respect to food, and various populations (healthy subjects and patients with diverse drug-resistance levels of TB, with and without HIV and comedications for both diseases) led to a final model with 37 fixed-effect and 21 random-effect parameters. The model's simplicity may be difficult to discern in Table 1. Nonetheless, besides the structural simplicity described above, it may be concluded that the only clinically relevant intrinsic and extrinsic associations at the recommended clinical dose of 200 mg are the approximate halving of exposure for fasted conditions relative to fed and in HIV+ subjects taking efavirenz.

As discussed in the Introduction, such a PopPK model is a step in the process of characterizing the relationship between dose and response. One subsequent use of the model is therefore to graduate and interpolate the sparsely collected PK data that went

into the model in order to quantify exposure/response relationships for simultaneously collected clinical data. The model's goodness of fit indicates its aptness for such a purpose.

Another planned application of the model is for decision making about doses in future contexts such as in pediatrics. For such purposes it is important to gain confidence in the model by its ability to predict new data, so-called external validation (15, 16). Such a test of the model is planned when predictions from it will be compared against data arising from the ongoing ZeNix, SimpliciTB, renal impairment, and hepatic impairment studies, as well as a planned relative bioavailability study for the pediatric formulation.

METHODS

Data

Data was pooled from 14 clinical studies: CL-001 and CL-002 (18), CL-003 and CL-009 (19), CL-005 (20), CL-007 (21), CL-010 (22), DMID 10-0058 (https://clinicaltrials.gov/ct2/show/NCT01674218), NC-001 (23), NC-002 (24), NC-003 (25), NC-005 (3), STAND (https://clinicaltrials.gov/ct2/show/NCT02342886), and Nix-TB (2). Details may be found in Table S1.

Observations with missing sample time were excluded from the analysis. Dosing times were not recorded in the four patient studies with dosing durations of eight or more weeks, except for doses administered immediately after trough PK samples. Unrecorded dosing times were imputed based on an assumed, regular pattern of QD dosing, or based on the recorded times of adjacent PK samples.

Data below the quantification limit (BQL) was excluded from the analysis. Only 3.3% of post-first-dose observations were BQL.

Baseline values for covariates were used in dataset construction except for time-dependent histories of anti-retroviral comedications (on/off). For the remarkably few baseline covariate values that were missing, attempts were made to replace the missing value with a screening (or other pre-first-dose) value or to determine a reasonable replacement value. In cases where no reasonable replacement value was found, the covariate was imputed as the median (for continuous covariates) or mode (for categorical covariates) of all subjects within the same study having at least one non-BQL concentration record.

Outliers were identified by visual inspection of the raw data and were excluded. Examples of conditions that might have led to such identification were supposed trough values that were unusually high, as if the samples were collected post-dose and not pre-dose; or values supposedly around t_{max} that were unusually low, as if the sampling time was erroneous. Some outliers were also identified by large values of conditional weighted residuals. These were assessed visually for potential removal.

Winsorization was applied to all continuous covariates to limit the impact of extreme covariate values. For each covariate, values outside of the median plus-or-minus 5 times the standard deviation were censored to the boundary of that range. Only 21 such cases were found out of 9 continuous covariates for 1054 subjects, 0.22% of the total covariate values used.

Modeling methodology

The approximate maximum-likelihood FOCE INTER method of NONMEM Version 7.3 was used for estimating parameters of the models.

Standard methods for population PK model-building and assessment (16) were employed. Model development decisions were based on objective-function values, likelihood ratio tests, parameter plausibility, standard error estimates, and diagnostic checks. More complex models were constructed by successively testing, via backward elimination, terms that contained additional parameters to be estimated. Because there were many such tests, in order to promote parsimony, the additional terms were retained if the chi-square approximation to the likelihood ratio test yielded a p-value less than 0.001. Changes in NONMEM objective function corresponding to p = 0.001 for 1, 2, 3, 4, 5, and 6 parameters are 10.8, 13.8, 16.3, 18.5, 20.5, and 22.5 for the nested models.

Because of the large dataset with multiple disease-state populations, regimen partners, and a variety of covariates, a staged model-building strategy was pre-specified. In this, studies were added to the model in stages with study-groupings selected to best inform a limited set of covariates in each stage. Model-building began before data was available from the Nix-TB study; therefore, it was decided to undertake complete model development from base through final models using data from all the studies *except* Nix-TB. Then data from Nix-TB was added, and a final post-Nix model identified.

The following methodology description contains a mix of the pre-specified modeling and key intermediate decision-making, thus preserving the Results section for description of the final model.

296 **The pre-Nix model**

297 Base-model development began with studies (or arms) in which pretomanid was dosed
298 alone (Studies CL-001, CL-002, CL-003, CL-005, CL-007, CL-009, CL-010, and the two
299 pretomanid-alone arms of DMID 10-0058). The goal was to select the structural model
300 and the roles of four pre-selected covariates (food, dose, disease state (DS-TB and HS),
301 and weight) in it.

302 A one-compartment model with three transit compartments to represent lagged
303 absorption best-represented this data. Covariates included the effect of WT on CL and V
304 and the effects of fed/fasted status and dose on F1, KA and MTT. After diagnostic
305 assessment, further additions to the model included: a two-step CL (with initial and
306 steady state CL), a dose-dependent V2 (possibly as a proxy for concentration-dependent
307 binding), and a generalized power error model (12) of the form:

308 $$Y = F + F^{\theta}\,\varepsilon_1 + \varepsilon_2$$

309 where $\varepsilon_2 \sim N(0,1)$ is the additive error, $\varepsilon_1 \sim N(0,1)$ is the proportional error, and θ is the
310 power. (A value of 1 for θ reverts to the standard additive and proportional error model).

311 An added parameter allowing for an effect on F1 for fed subjects dosed 1000 mg
312 significantly improved model fit. Since the clinical dose was expected to be around 200
313 mg, this step was taken to reduce impact of this odd data.

314 A random effect on the dose effect for fed subjects also significantly improved model fit.

The next step in modeling was to examine potential influences on pretomanid PK of co-administered anti-TB agents bedaquiline, moxifloxacin, pyrazinamide, and clofazimine (BDQ, MOX, PZA, and CFZ). The analysis dataset was augmented with NC-001; NC-003; DS-TB arms of NC-002, NC-005, and NC-006; and the pretomanid + MOX arm of DMID 10-0058. Of most concern with drug interactions were effects on clearance, which might impact bioavailability through first-pass effects. Therefore, possible effects of these four drugs were assessed on clearance and bioavailability.

Because of the varying and/or uncertain fed/fasted conditions in studies NC-002, NC-003, NC-005, NC-006, study indicators were defined as covariates to allow study-specific adjustment to the food effects on F1, KA and MTT as well as effects on the variability of those parameters.

To assess the impact of multi-drug resistant tuberculosis on the PK of pretomanid, the MDR-TB arms of studies NC-002, NC-005, and NC-006 were added to the dataset in this modeling step and the MDR covariate was tested on CL, V2, KA, and F1. In NC-002 and NC-006, MDR patients received PaMZ, as did DS patients. But in NC-005, MDR-TB subjects received BPaMZ, whereas DS-TB patients received BPaZ. The impact of regmen BPaMZ on F1 and CL was also assessed at this step.

Next, the impact of HIV status and anti-retroviral (ARV) drugs on the PK of pretomanid were tested in the model. The effects of efavirenz (EFV) on F1 and CL and the effect of Lopinavir/ Ritonavir LPVr on CL were added to the model (based on previous analysis). Other, less-prevalent, ARVs were planned to be grouped as inducers (INDUC) or inhibitors (INHIB) for testing on CL, but no subjects were on alternative inhibitors.

The effects of age, sex, race, and BMI, were assessed in the next modeling step. So too were baseline values of AST, ALT, total bilirubin, albumin, CrCL, and eGFR on CL and F1 baseline. (Studies of pretomanid in hepatically and renally impaired subjects are ongoing. In two mass-balance studies < 1% of parent drug was excreted in the urine. Nonetheless, renal impairment can affect non-renal aspects of drug absorption, metabolism, and distribution (26).) Additionally, the effect of albumin on V2 was considered based on possible impact on protein binding; and the effects of a high dose (Dose > 200 mg) on Female subjects' CL, KA and MTT were tested based on noted gender differences in half-life at 1000 mg in Study CL-003 that were not seen at lower doses in Study CL-009.

Covariances of inter-individual (IIV) random effects and inter-occasion variability (IOV) on F1 and CL were assessed next.

The final model

The final step of model building commenced with the availability and addition of the Nix-TB study data. Nix-TB introduced two new elements: 1) new disease states (XDR-TB, TI-MDR-TB, and NR-MDR-TB), and 2) a new regimen that included linezolid (not previously examined) as well as bedaquiline. Some ARVs that were inhibitors of CYP3A4 were found, but only in two subjects contributing only three observations, so inhibiting ARVs were not evaluated as a covariate.

The ability of the final pre-Nix model to predict the data from Nix-TB was checked by means of a VPC without re-estimation of parameters. The data was deemed not to be sufficiently well characterized by the model. Additional model-building was necessary.

Model parameters were added to test the impacts of: new disease states (XDR, TI-MDR, and NR-MDR) on CL and V2; and of NIX (study) as a covariate on F1, KA and MTT (since the fed conditions in the study were uncertain); and of NIX (study) as a covariate on CL and F1 (to test the impact of the new regimen BPaL).

After testing, the following were retained: the effect of either XDR-TB or NR-MDR-TB on CL, the effect of XDR-TB on V2, and the effect of study Nix-TB on F1.

This final model candidate was assessed via prediction- and simulation-based diagnostics, but found to be insufficient for prediction of the Nix-TB data in two key ways:

1) For the Week 2, 8 and 16 troughs, the model predicted a steady state, but the trough concentration data diminished over time.

2) For the Week 16 profiles, the model, by design, assumed lognormal distributions for random effects. But the distribution of data appeared to be more skewed than what would be expected under such assumptions.

One possible explanation for the decreasing trough concentrations was the improved health status, including increased body weight, of subjects over time. Examination of the increased body weights showed that very few subjects had greater than 10% increase of body weight by Week 16, and many subjects lost weight. So, changing weight was insufficient to explain the decreasing concentrations.

Covariates were added to allow the CL (or F1) for Nix-TB study patients to increase (or decrease) at Weeks 6 and 12. After testing, only the step-up in CL at Week 6 was found to be significant and was retained.

To attempt to accommodate the longer-tailed distribution, Box-Cox-transformed variability was tested on CL and V2 – with a separate shape parameter for Nix-TB versus other studies. These were found to provide significant improvement to the objective function (about an 88-point improvement in objective function for 4 additional parameters) and to VPCs.

With the addition of the Week 6 step-up in CL and changes in distributions, the effect of disease state XDR or NR-MDR on CL was no longer significantly different from the effect of MDR (including TI-MDR) on CL; and the two parameters were combined into one.

In summary, addition of the effect of disease-state subpopulation XDR-TB on V2 and study Nix-TB on F1 and the variability of F1, plus the four Box-Cox transformed variability shape parameters (for CL and V2 in Nix-TB and non-NixTB studies) constituted the Final Post-Nix Model.

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505

506 **Figure 1 Prediction-corrected visual predictive checks of the final model**

507 Note: Observed and predicted median and 5th and 95th percentiles. Steady state profiles included for
508 studies: NC-002, NC-003, NC-005, and NiX-TB. Steady state troughs included additionally for NC-001
509 and NC-006. Additional VPCs are provided in the Supplementary Materials

510 **Figure 2 Forest plot of simulation results for $C_{avg,ss}$**

511

512 **Table 1 Final Model Parameter Estimates**

THETA terms on fixed-effects	Estimate	Confidence Interval
F1 (Fixed)	1	-
F1~FASTED	0.513	(0.485 - 0.541)
F1~DOSE &FASTED	-0.264	(-0.302 - -0.226)
F1~FED &1000mg	-0.00302	(-0.148 - 0.142)
F1~MOX*PZA	0.925	(0.848 – 1.00)
F1~BDQ*MOX*PZA	1.25	(1.04 - 1.46)
F1~EFV	1.24	(1.03 - 1.45)
F1~HIV	0.789	(0.721 - 0.856)
F1~TBIL (ref=5)	0.0880	(0.0495 - 0.126)
F1~NIX	1.54	(1.28 - 1.80)
KA	1.38 h^{-1}	(1.25 - 1.52)
KA~FASTED	0.482	(0.453 - 0.511)
KA~DOSE	-0.128	(-0.158 - -0.0990)
KA~NC5	0.186	(0.150 - 0.221)
MTT	1.25 h	(1.14 - 1.35)
MTT~FASTED	0.311	(0.293 - 0.329)
MTT~DOSE&FASTED	-0.155	(-0.187 - -0.123)
MTT~NC5	6.95E-07	(-0.0350 - 0.0350)
CL	3.30 L/h	(3.14 - 3.46)
CL~WT (Fixed)	0.75	–

THETA terms on fixed-effects	Estimate	Confidence Interval
SS CL	0.175 L/h	(0.135 - 0.214)
CL~HS	1.16	(1.09 - 1.23)
CL~MOX	0.967	(0.902 - 1.03)
CL~MOX*PZA	0.733	(0.663 - 0.804)
CL~MDR, TI/NR MDR or XDR	1.15	(1.04 - 1.27)
CL~BDQ*MOX*PZA	1.32	(1.12 - 1.51)
CL~EFV	2.17	(1.89 - 2.45)
CL~LPVR	1.14	(1.10 - 1.18)
CL~HIV	0.842	(0.779 - 0.905)
CL~INDUC	1.35	(1.24 - 1.46)
CL~FEMALE	0.837	(0.808 - 0.867)
CL~ALB (ref=35)	0.200	(0.0789 - 0.322)
CL NIX WK≥6	0.466 L/h	(0.285 - 0.646)
V2	90.4 L	(85.8 - 94.9)
V2~WT (Fixed)	1	–
V2~DOSE	0.111	(0.0845 - 0.137)
V2~ MDR or TI/NR MDR	1.44	(1.24 - 1.64)
V2~XDR	1.75	(1.39 - 2.11)
F1 Var ~ NIX	0.919	(0.558 - 1.28)
MTT Var ~ NC3	-0.645	(-1.06 - -0.226)
Box-Cox V2 non-NIX	9.55	(2.25 - 16.9)
Box-Cox V2 NIX	26.0	(-8.54 - 60.5)
Box-Cox CL non-NIX	1.36	(0.733 - 1.99)
Box-Cox CL NIX	2.78	(1.36 - 4.20)
Proportional Error (Variance)	0.548	(0.506 - 0.589)
Additive Error (Variance)	11.5	(5.84 - 17.2)
Error Power	0.795	(0.789 - 0.800)
OMEGA Matrix Terms	**Estimate**	**Confidence Interval**
F1~Dose/Fasted	0.0274	(0.018 - 0.0368)
CL	0.0373	(0.029 - 0.0455)
V2	0.00892	(0.0018 - 0.016)
KA	0.309	(0.252 - 0.366)
KA-MTT	0.0649	(0.00363 - 0.126)
MTT	0.593	(0.475 - 0.71)
KA-F1	-0.0339	(-0.0509 - -0.0168)
MTT-F1	0.00391	(-0.0184 - 0.0262)
F1	0.0227	(0.0136 - 0.0319)
IOC F1	0.0412	(0.0362 - 0.0462)
IOC F1-CL	0.0101	(0.00697 - 0.0132)
IOC CL	0.0185	(0.0155 - 0.0214)

ETA shrinkage (%): 6.6E+01 2.5E+01 5.8E+01 4.2E+01 4.5E+01 4.5E+01 (for dose/fasted-F1, CL, V2, KA, MTT and F1) and 4.2E+01 5.3E+01 4.7E+01 5.2E+01 5.9E+01 6.2E+01 (for inter-occasion F1 and CL; times three occasions); all rounded to two significant digits

EPS shrinkage (%): 1.0E+01 1.0E+01 (for proportional and added error terms)