A prospectively validated translational meta-model framework for *in silico* prediction of dose-ranging Phase 2B tuberculosis regimen outcomes

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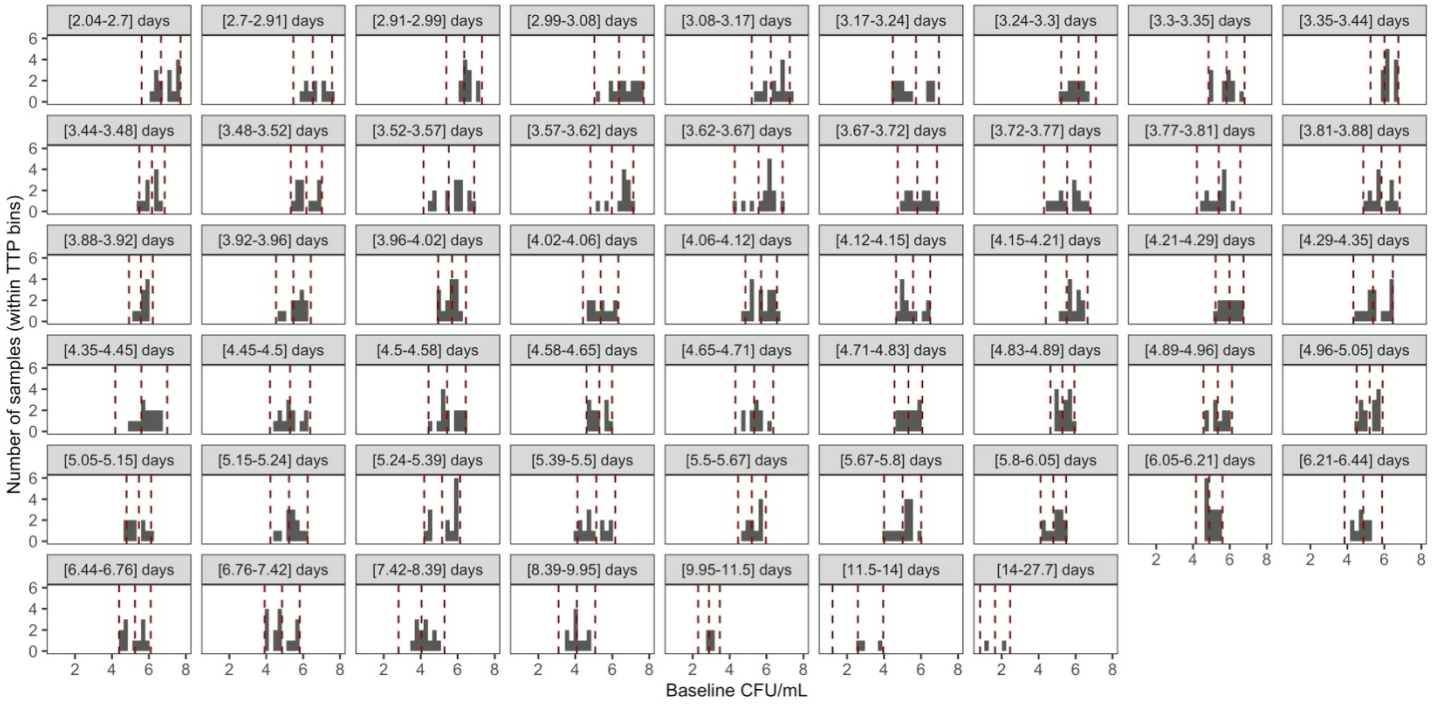
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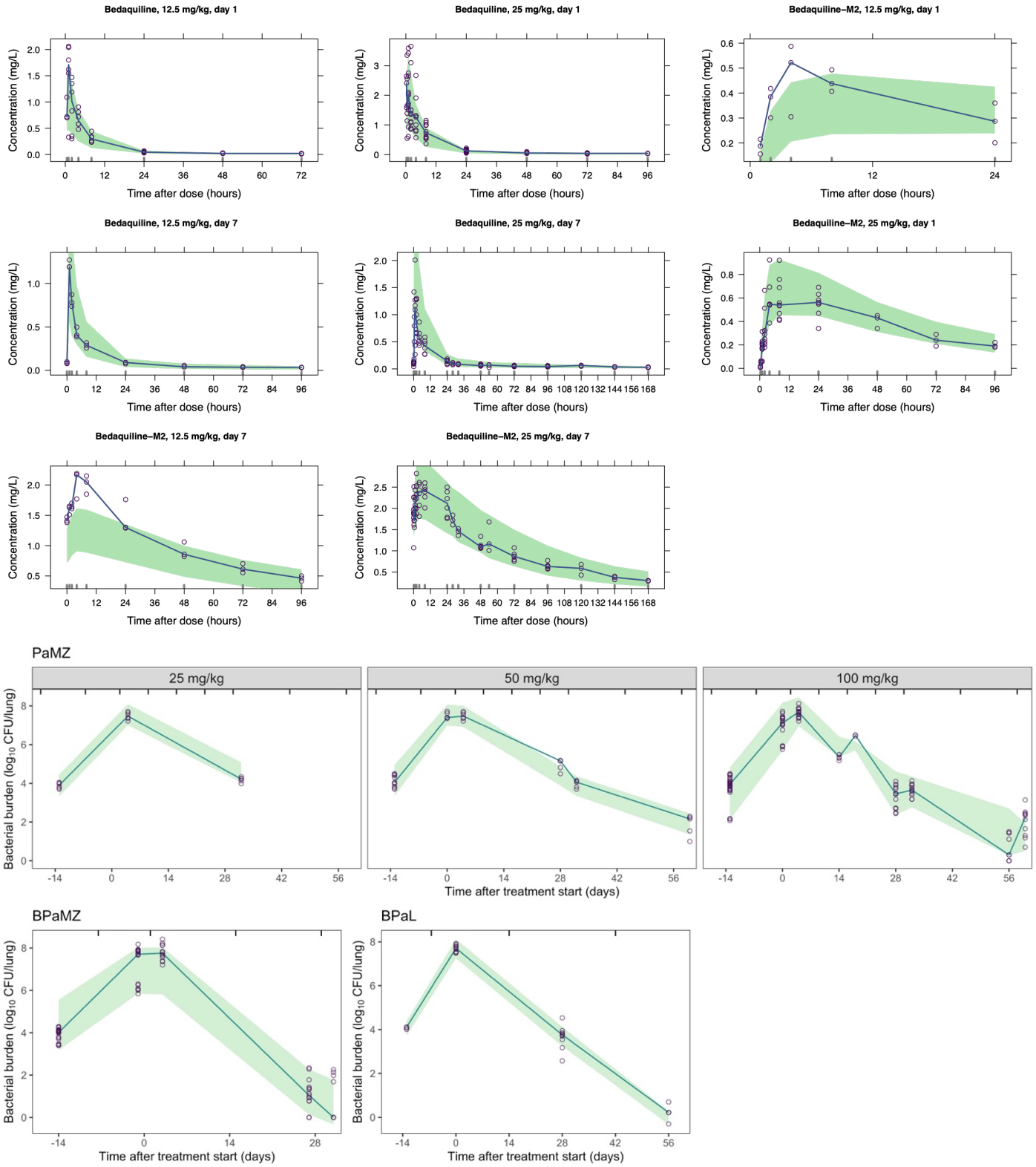
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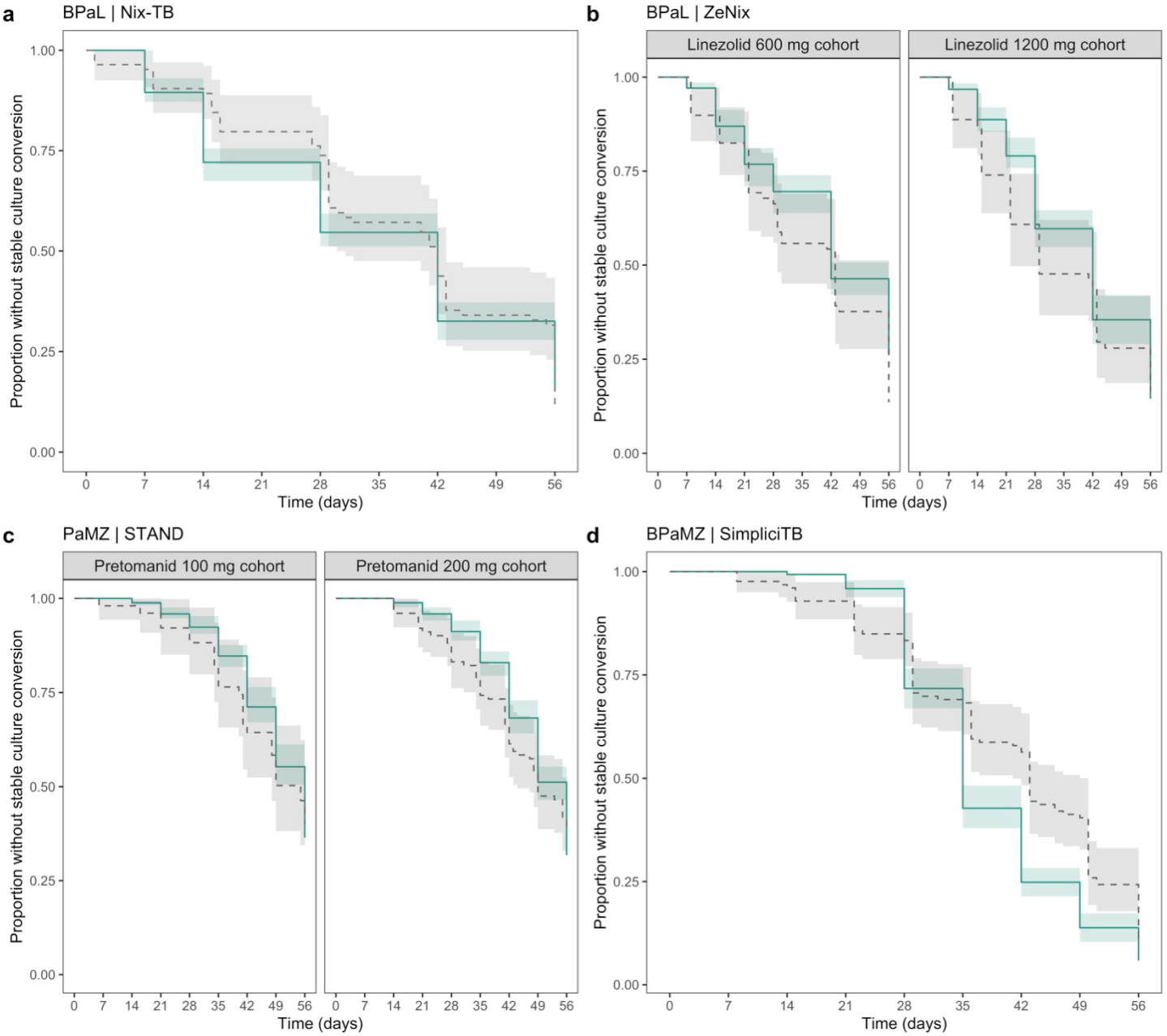
Supplementary Figure 1. Individual-level baseline CFU and TTP pairs from eight tuberculosis clinical trials used in biomarker conversion. Each panel shows the distribution of baseline CFU within a TTP bin (each containing approximately 2% of observations; bin range indicated above each panel). Dashed lines represent the mean (center line) ± standard deviation (outside lines).

Abbreviations: CFU, colony-forming units; TTP, time to positivity



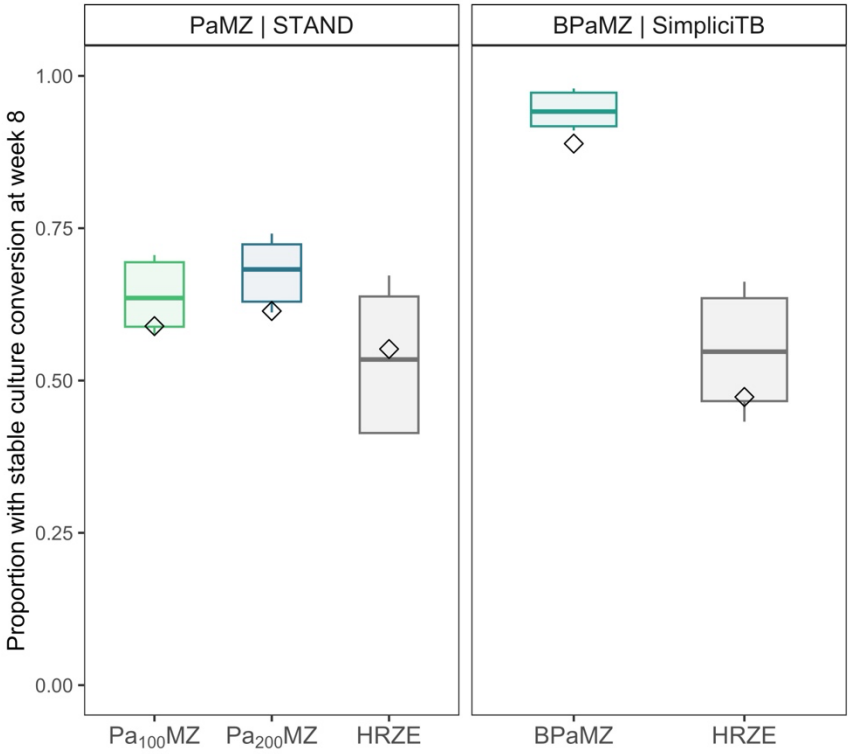
Supplementary Figure 2. Visual predictive checks of bedaquiline mouse pharmacokinetic models (top) and mouse pharmacokinetic-pharmacodynamic models (bottom) used for back-translation of clinically evaluated regimens in historical tuberculosis trials. Open circles and solid lines represent observed data and the medians of the observed data, respectively. Shaded areas represent the 95% prediction intervals.

Abbreviations: B, bedaquiline; CFU, colony-forming units; L, linezolid; M, moxifloxacin; M2, bedaquiline metabolite M2; Pa, pretomanid; Z, pyrazinamide



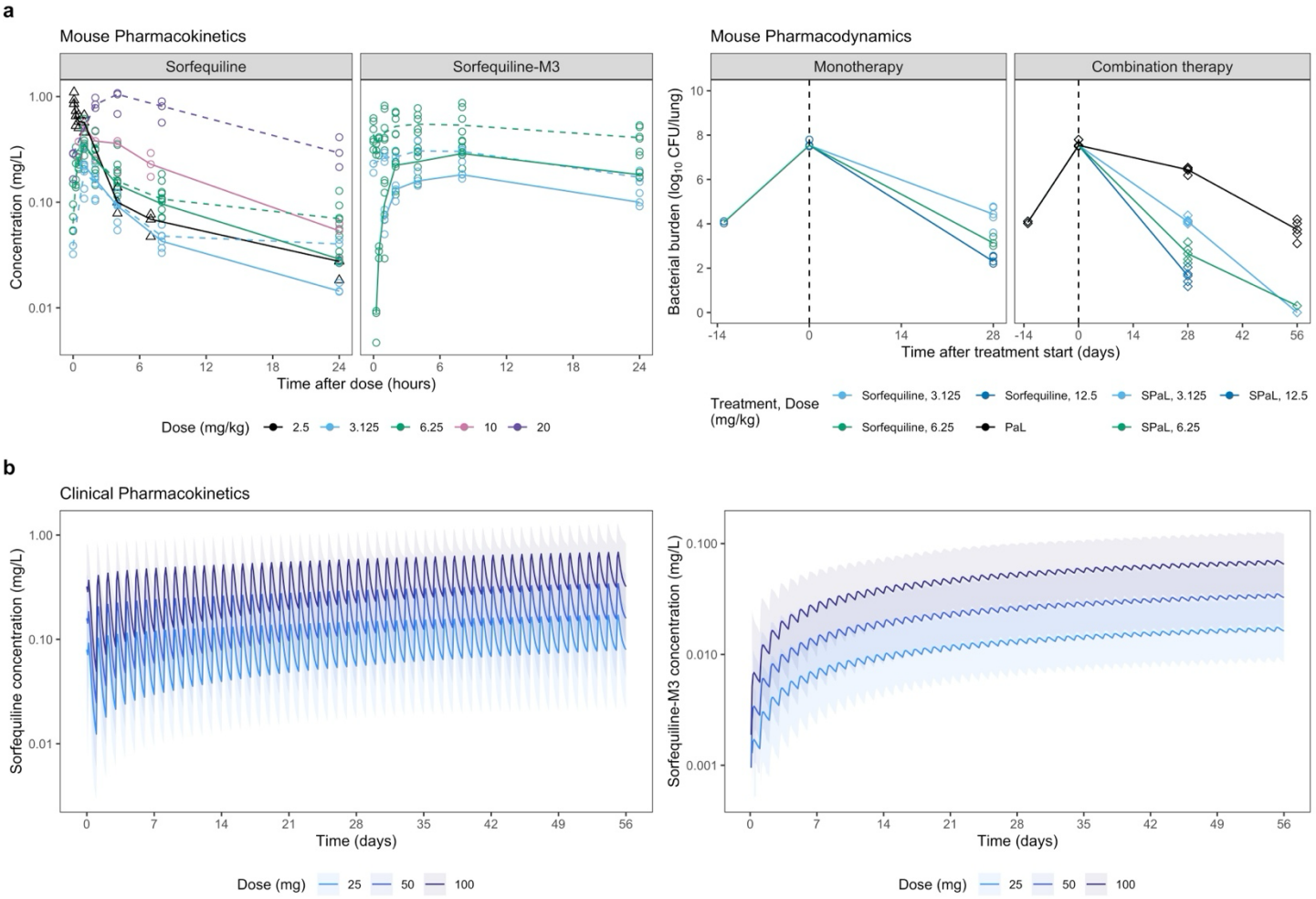
Supplementary Figure 3. Back-translation of clinically evaluated regimens in historical tuberculosis trials. Retrospective validation through back-translation of three regimens evaluated in historical trials to finalize Iteration 1 of the translational meta-model framework: **a,** BPaL in the Nix-TB trial (NCT02333799), **b,** BPaL in the ZeNix trial (NCT03086486), **c,** PaMZ in the STAND trial (NCT02342886), and **d,** BPaMZ in the SimpliciTB trial (NCT03338621). Predicted proportions of patients without stable culture conversion over time were compared with observed clinical trial outcomes. Solid lines represent predicted medians, and shaded areas represent the 2.5th to 97.5th percentiles of the predicted medians. Dashed lines represent observed Kaplan–Meier estimates, and shaded areas represent their 95% confidence intervals.

Abbreviations: B, bedaquiline; L, linezolid; M, moxifloxacin; Pa, pretomanid; Z, pyrazinamide



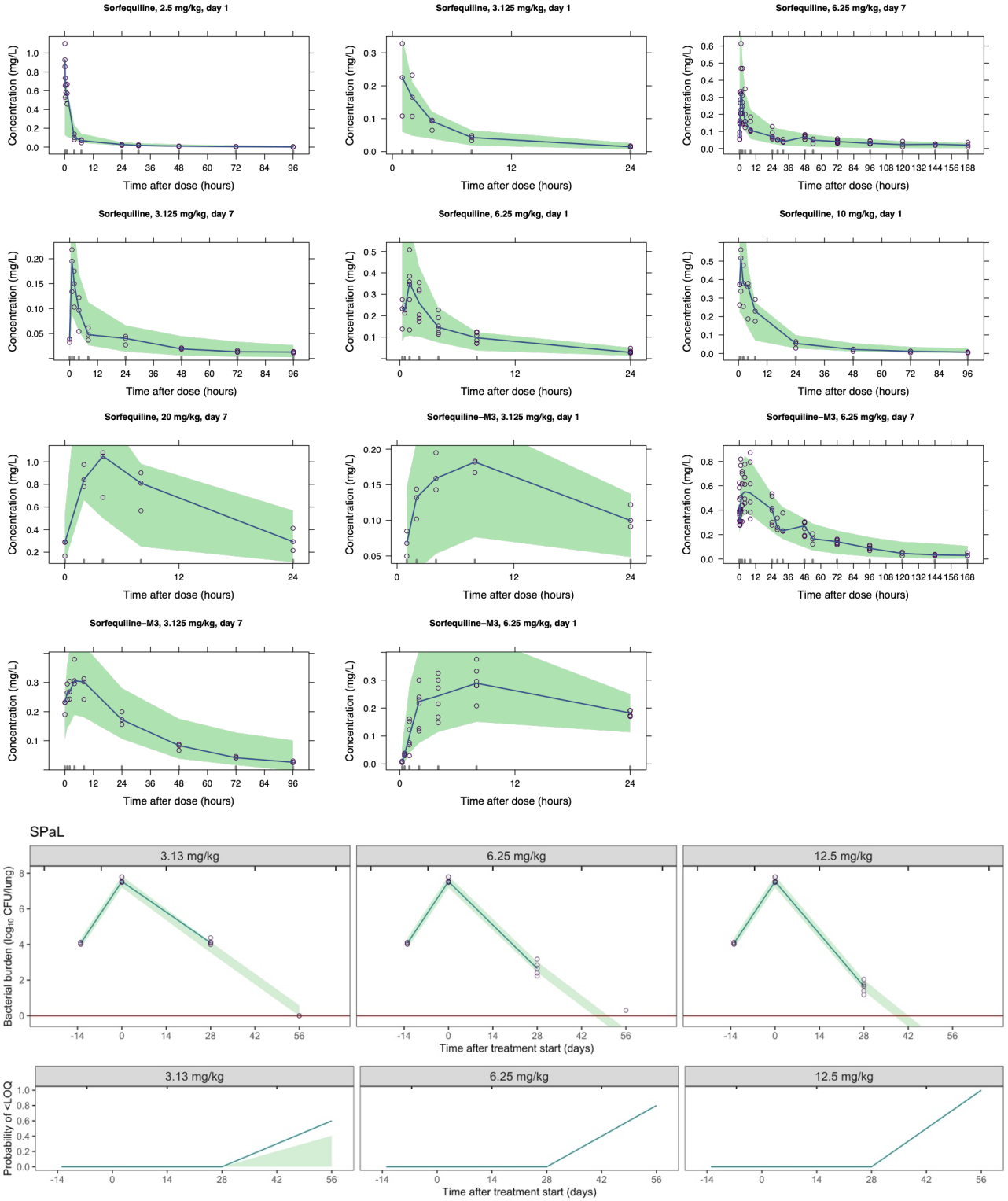
Supplementary Figure 4. Back-translation of clinically evaluated regimens relative to the HRZE control in the STAND and SimpliciTB trials. Predicted proportions of patients with stable culture conversion at week 8 for PaMZ and BPaMZ, and baseline-matched observed proportions for HRZE from TBTC Studies 29 and 29X, were compared with observed clinical trial outcomes. Participants from TBTC Studies 29 and 29X were resampled 200 times by matching baseline characteristics to those in the HRZE control arm of the STAND and SimpliciTB trials, respectively, based on (1) the combination of cavitation status and baseline TTP quartile and (2) the distribution of each combination observed in each trial. Boxes and whiskers represent the 2.5th to 97.5th percentiles and the range of the predicted or resampled medians, respectively. Open diamonds represent observed clinical trial data.

Abbreviations: B, bedaquiline; E, ethambutol; H, isoniazid; M, moxifloxacin; Pa, pretomanid; Pa_{100}, pretomanid 100 mg; Pa_{200}, pretomanid 200 mg; R, rifampin; TBTC, Tuberculosis Trials Consortium; TTP, time to positivity; Z, pyrazinamide.



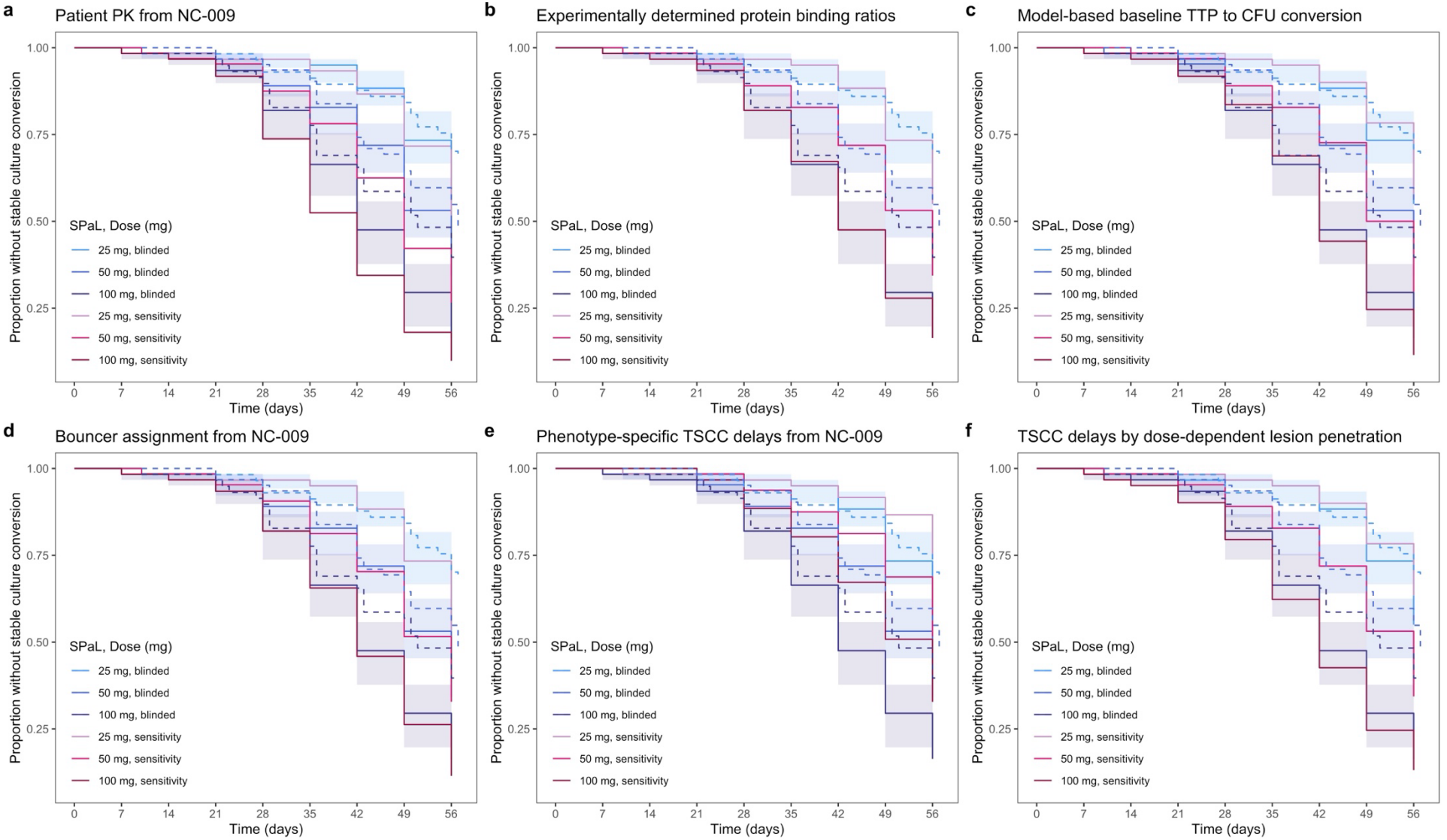
Supplementary Figure 5. Preclinical and clinical data for sorfequiline and M3 metabolite used for blinded prediction of SPaL regimen outcomes in the Phase 2 NC-009 trial. a, Plasma concentrations over time of sorfequiline and M3 in BALB/c mice (left), and lung CFU over time with sorfequiline as monotherapy or in combination with pretomanid and linezolid in BALB/c mice (right). In the left plot, solid and dashed lines represent concentrations after a single dose and after 7 days of multiple doses, respectively. **b,** Simulated plasma concentrations over time of sorfequiline and M3 using population pharmacokinetic models from healthy subjects. Solid lines represent predicted medians, and shaded areas represent the 2.5th to 97.5th percentiles of the predicted medians.

Abbreviations: CFU, colony-forming units; L, linezolid; Pa, pretomanid; S, sorfequiline

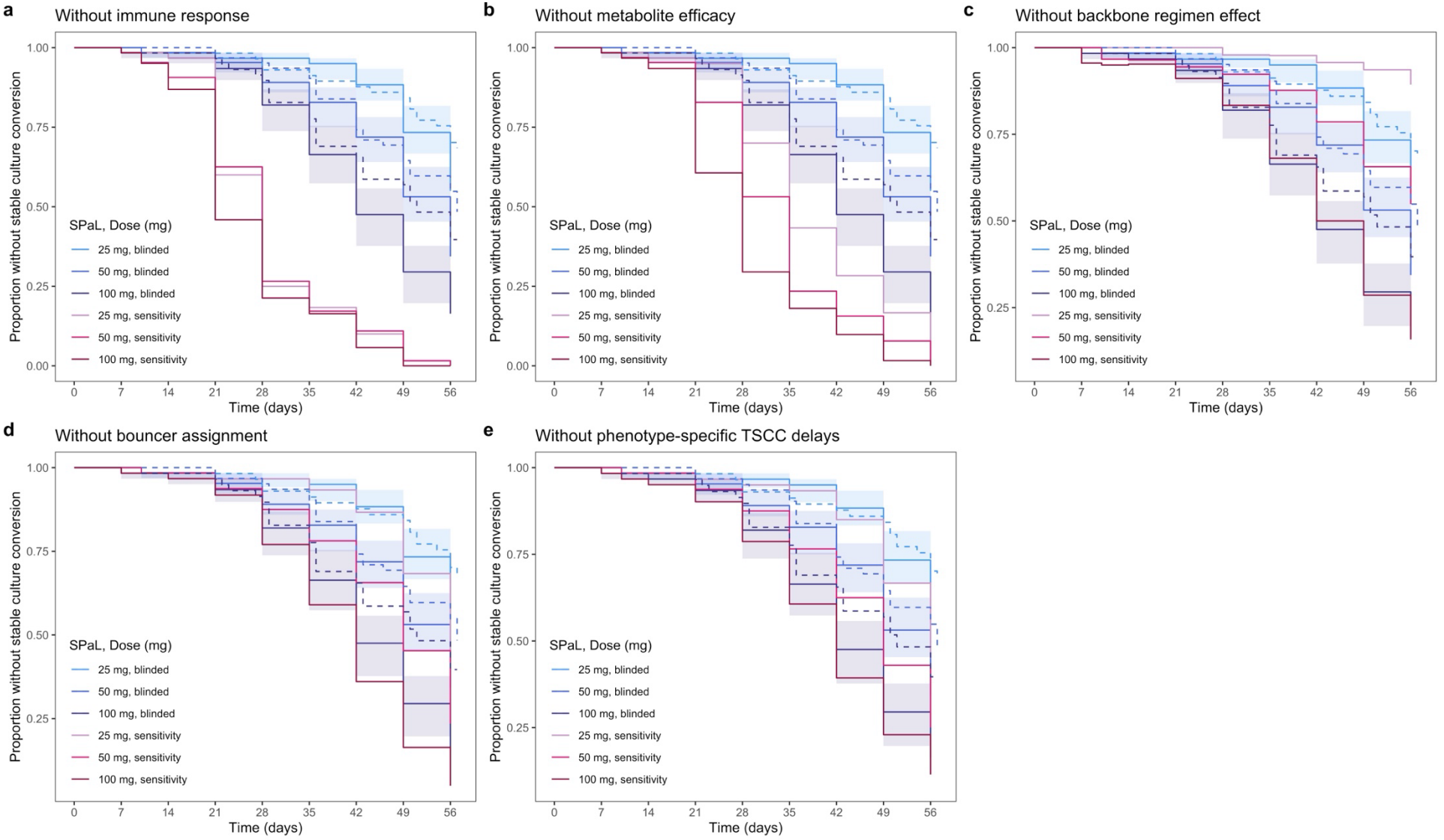


Supplementary Figure 6. Visual predictive checks of sorfequiline mouse pharmacokinetic models (top) and SPaL mouse pharmacokinetic-pharmacodynamic models (bottom) used for blinded predictions of SPaL regimen outcomes in the Phase 2 NC-009 trial. Open circles and solid lines represent observed data and the medians of the observed data, respectively. Shaded areas represent the 95% prediction intervals. Horizontal red lines indicate the lower limit of quantification.

Abbreviations: CFU, colony-forming units; L, linezolid; LOQ, limit of quantification; Pa, pretomanid; S, sorfequiline

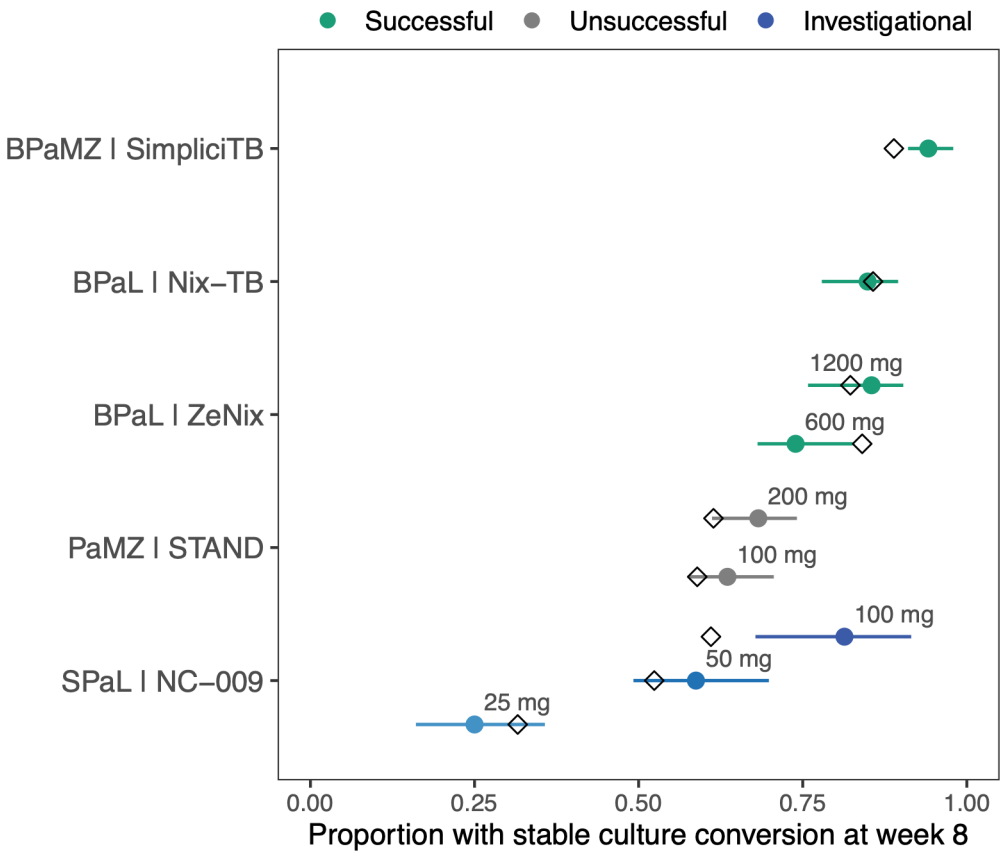


Supplementary Figure 7. Sensitivity analyses for blinded predictions of SPaL regimen outcomes in the Phase 2 NC-009 trial. Predicted proportions of patients without stable culture conversion over time under alternative assumptions for **a**, clinical PK, **b**, protein binding ratios, **c**, baseline TTP to CFU conversion, **d**, bouncer assignment, **e**, phenotype-specific TSCC delays, and **f**, dose-dependent TSCC delays. Solid lines represent predicted medians, and shaded areas represent the 2.5th to 97.5th percentiles of the predicted medians. Dashed lines represent observed clinical trial data. Abbreviations: CFU, colony-forming units; L, linezolid; Pa, pretomanid; PK, pharmacokinetics; S, sorfequiline; TSCC, time to stable culture conversion; TTP, time to positivity



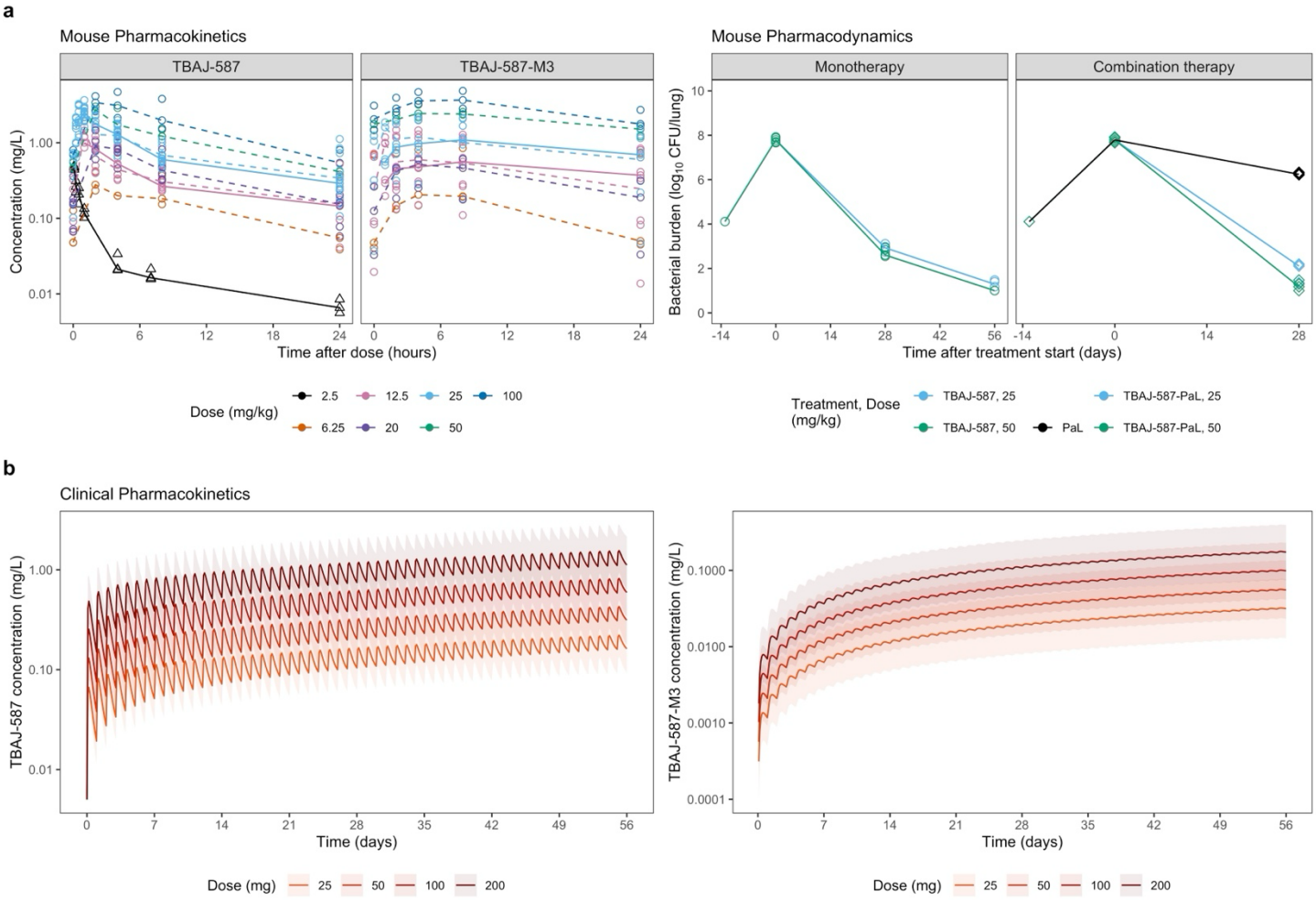
Supplementary Figure 8. Contribution of individual framework components to blinded predictions of SPaL regimen outcomes in the Phase 2 NC-009 trial. Predicted proportions of patients without stable culture conversion over time with the exclusion of **a**, immune response, **b**, metabolite efficacy, **c**, PaL backbone regimen effect, **d**, bouncer assignment, and **e**, phenotype-specific TSCC delays. Solid lines represent predicted medians, and shaded areas represent the 2.5th to 97.5th percentiles of the predicted medians. Dashed lines represent observed clinical trial data.

Abbreviations: L, linezolid; Pa, pretomanid; S, sorfequiline; TSCC, time to stable culture conversion



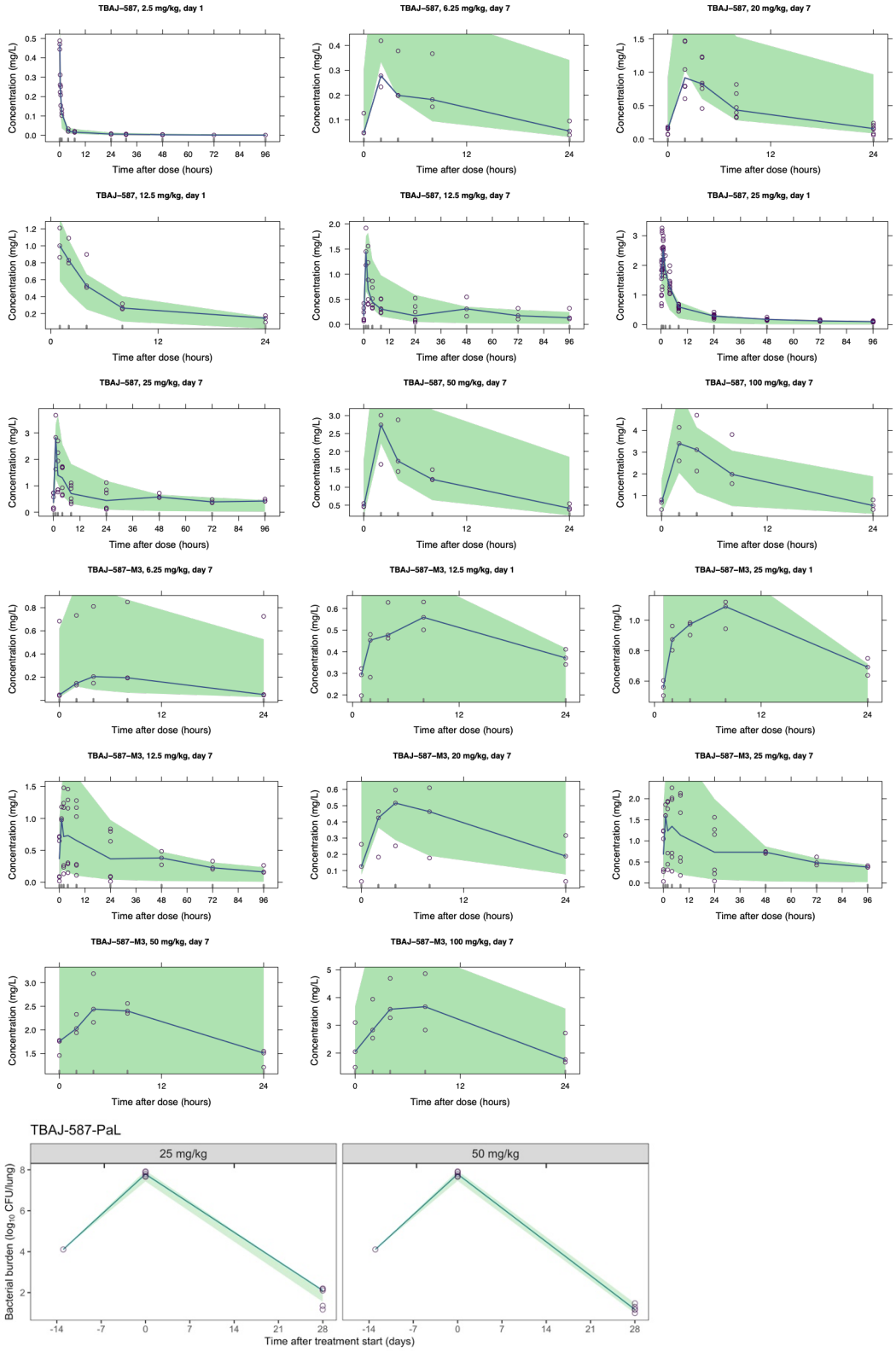
Supplementary Figure 9. Validation of the translational meta-model framework for quantitative prediction of the Phase 2B primary endpoint. Predictions were generated using Iteration 2 of the translational meta-model framework. Predicted proportions of patients with stable culture conversion at week 8 were compared with observed clinical trial outcomes for BPaL in the Nix-TB and ZeNix trials, PaMZ in the STAND trial, BPaMZ in the SimpliciTB trial, and SPaL in the NC-009 trial. Filled circles represent predicted medians, and horizontal lines represent the ranges of the predicted medians. Open diamonds represent observed clinical trial data. Dose labels indicate linezolid doses in ZeNix, pretomanid doses in STAND, and sorfequiline doses in NC-009.

Abbreviations: B, bedaquiline; L, linezolid; M, moxifloxacin; Pa, pretomanid; S, sorfequiline; Z, pyrazinamide.



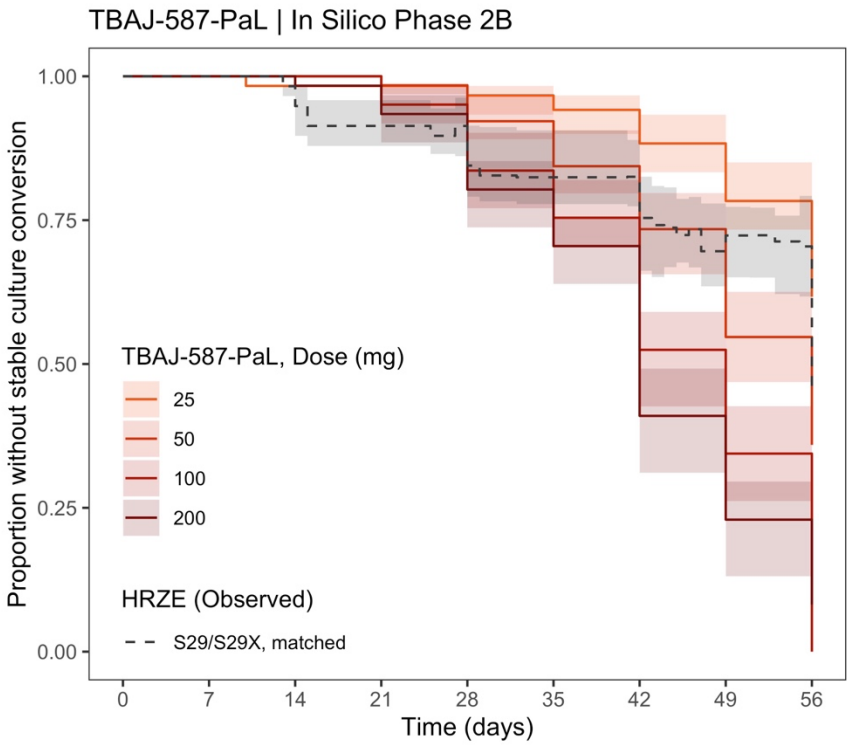
Supplementary Figure 10. Preclinical and clinical data for TBAJ-587 and M3 metabolite used for prospective prediction of TBAJ-587-PaL regimen outcomes. a, Plasma concentrations over time of TBAJ-587 and TBAJ-587-M3 in BALB/c mice (left), and lung CFU over time with TBAJ-587 as monotherapy or in combination with pretomanid and linezolid in BALB/c mice (right). In the left plot, solid and dashed lines represent concentrations after a single dose and after 7 days of multiple doses, respectively. **b,** Simulated plasma concentrations over time of TBAJ-587 and M3 using a population pharmacokinetic model from healthy subjects. Solid lines represent predicted medians, and shaded areas represent the 2.5th to 97.5th percentiles of the predicted medians.

Abbreviations: CFU, colony-forming units; L, linezolid; Pa, pretomanid



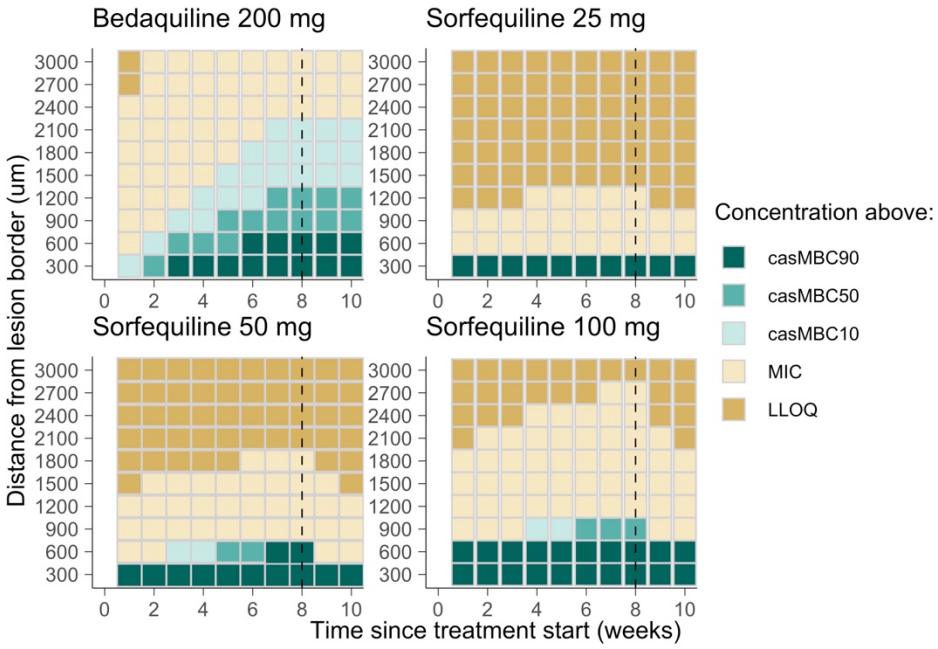
Supplementary Figure 11. Visual predictive checks of TBAJ-587 mouse pharmacokinetic models (top) and TBAJ-587-PaL mouse pharmacokinetic-pharmacodynamic models (bottom) used for prospective prediction of TBAJ-587-PaL regimen outcomes. Open circles and solid lines represent observed data and the medians of the observed data, respectively. Shaded areas represent the 95% prediction intervals. Horizontal red lines indicate the limit of quantification.

Abbreviations: CFU, colony-forming units; L, linezolid; LOQ, limit of quantification; Pa, pretomanid



Supplementary Figure 12. Prospective prediction of dose-ranging TBAJ-587-PaL regimen outcomes compared with baseline-matched observed outcomes of the HRZE control from TBTC Studies 29 and 29X. Participants from TBTC Studies 29 and 29X were resampled 200 times by matching baseline characteristics to those in the HRZE control arm of the Phase 2 NC-009 trial based on (1) the combination of cavitation status and baseline TTP quartile and (2) the distribution of each combination observed in the Phase 2 NC-009 trial. Solid lines represent predicted medians, and shaded areas represent the 2.5th to 97.5th percentiles of the predicted medians. Dashed lines represent baseline-matched observed HRZE outcomes.

Abbreviations: E, ethambutol; H, isoniazid; L, linezolid; Pa, pretomanid; R, rifampin; TBTC, Tuberculosis Trials Consortium; Z, pyrazinamide



Supplementary Figure 13. Target attainment of bedaquiline and sorfequiline as a function of time from treatment start and caseum depth. The dashed black line indicates therapy completion at 8 weeks. Color-coded shaded tiles represent concentrations achieved at a given time and depth into caseum.

Abbreviations: casMBC90, casMBC50, casMBC10, minimum concentration to kill 90%, 50%, and 10% of bacteria residing in the caseum; LLOQ, lower limit of quantitation; MIC, minimum inhibitory concentration

Supplementary Table 1. Input data and models used for back-translation, forward validation, and prospective application of the translational meta-model framework for quantitative prediction of Phase 2B tuberculosis regimen outcomes.

Component	Regimen dependence	Iteration 1				Iteration 2
		Back-translation			Forward validation	Prospective application
		BPaL (Nix-TB, ZeNix)	PaMZ (STAND)	BPaMZ (SimpliciTB)	SPaL (NC-009)	TBAJ-587-PaL
Immune	Drug-agnostic	Zhang et al.[1]	Zhang et al.[1]	Zhang et al.[1]	Zhang et al.[1]	Zhang et al.[1]
PK						
Mouse PK	Drug-specific	Ernest et al.[2]	Ernest et al.[2]	Ernest et al.[2]/ Table S3	Li et al.[3], Figure S5[a]/ Table S9	Li et al.[3], Figure S10[a]/ Table S15
Clinical PK	Drug-specific	Imperial et al.[4]	Salinger et al.[5]	Svensson et al.[6]	Lombardi et al.[7] /Table S9	Leding et al.[8]
PD						
Mouse PK-PD	Drug-specific	Strydom et al.[9]/ Table S4	Goh et al.[10]/ Table S4	Goh et al.[10]/ Table S4	Figure S5[11]/ Table S9	Figure S10[12]/ Table S15
Metabolite efficacy	Drug-specific	NA	NA	Table S2[a]/ Table S4	Table S2[a]/ Table S9	Table S2[a]/ Table S15
Biomarker conversion						
Baseline TTP-CFU	Drug-agnostic	Magombedze et al.[13]	Figure S1[b]	Figure S1[b]	Figure S1[b]	Figure S1[b]
Bouncer assignment	Drug-agnostic	Nix-TB, ZeNix/ Table S5	Nix-TB, ZeNix/ Table S5	Nix-TB, ZeNix/ Table S5	Nix-TB, ZeNix/ Table S5	NC-009/ Table S13
Patient phenotype	Drug-agnostic	Nix-TB, ZeNix, SimpliciTB/Table S7	PaMZ/ NA[e]	Nix-TB, ZeNix, SimpliciTB/Table S7	Nix-TB, ZeNix, SimpliciTB/Table S7	NC-009/ Table S14
Lesion coverage	Drug-specific	NA	NA	NA	Bustion et al.[14]/ Table S10[d]	NA
Clinical observations used for evaluation		NCT02333799[9,15], NCT03086486[9,16]	NCT02342886[10,17]	NCT03338621[10,18]	NCT06058299[c]	NA

Inputs are presented as data source/model sources; for previously published models, only the model reference is shown.

[a] Unpublished data provided by Johns Hopkins University.

[b] Data were used directly for conditional sampling.

[c] Obtained from TB Alliance via personal communication.

[d] The lesion coverage component was applied as a sensitivity analysis.

[e] No phenotype effect was observed for PaMZ; therefore, no phenotype-specific adjustment was applied.

Abbreviations: B, bedaquiline; CFU, colony-forming units; L, linezolid; M, moxifloxacin; NA, not applicable; Pa, pretomanid; PD, pharmacodynamics; PK, pharmacokinetics; S, sorfequiline; TTP, time to positivity; Z, pyrazinamide

Supplementary Table 2. *In vitro* MICs of parent compounds and active metabolites against *Mycobacterium tuberculosis* H37Rv.

Compound	Active metabolite	MIC, parent (ug/mL)	MIC, metabolite (ug/mL)	MIC ratio
Bedaquiline	M2	0.03	0.25	8
Sorfequiline	M3	0.002-0.0039	0.0078	3
TBAJ-587	M3	0.0078	0.03	4

MICs were determined using the 7H11 agar proportion method.
Abbreviations: MIC, minimum inhibitory concentration.

Supplementary Table 3. Mouse PK model parameters used for back-translation of the BPaMZ regimen.

	Bedaquiline	Bedaquiline-M2
Parameter	**Estimates (RSE%)**	**Estimates (RSE%)**
CL/F (L/h)	0.0305 (4.4)	0.00833 (4.7)
V_C/F (L)	0.155 (5.7)	0.228 (14.4)
Q_1/F (L/h)	0.0062 (11.5)	0.0439 (27.1)
V_{P1}/F (L)	0.784 (12.4)	0.212 (12.8)
Q_2/F (L/h)	0.0443 (43.8)	-
V_{P2}/F (L)	0.106 (17.0)	-
K_a (h^{-1})	2.14 (12.6)	-

Abbreviations: CL/F, apparent clearance; Ka, absorption rate constant; PK, pharmacokinetic; Q_1/F, apparent inter-compartmental clearance between central and first peripheral compartment; Q_2/F, apparent inter-compartmental clearance between central and second peripheral compartment; RSE, relative standard error; V_C/F, apparent central volume of distribution; V_{P1}/F, apparent first peripheral volume of distribution; V_{P2}/F, apparent second peripheral volume of distribution

Supplementary Table 4. Mouse PK-PD model parameters used for back-translation of clinically evaluated regimens in historical tuberculosis trials.

Regimen (Trial)	Drug	Parameter	Estimates (RSE%)
BPaL (Nix-TB, ZeNix)	Linezolid	EC_{50} (mg/L)	0.647 (1.6)
		E_{max} (day^{-1})	0.235 (3.4)
		Rate to effect compartment (day^{-1})	12.6 (0.3)
	BPa	Effect (day^{-1})	0.121 FIX[a]
PaMZ (STAND)	Pretomanid with MZ	EC_{50} (mg/L)	0.0476 (0.02)
		$E_{max, 0\text{-}28D}$ (day^{-1})	0.391 (0.2)
		$E_{max, 28\text{-}56D}$ (day^{-1})	0.219 (24.9)
BPaMZ (SimpliciTB)	Bedaquiline	$EC_{50, bedaquiline}$ (mg/L)	0.0435 FIX[b]
		$EC_{50, bedaquiline\text{-}M2}$ (mg/L)	0.348 FIX[b,c]
		$E_{max, 0\text{-}28D}$ (day^{-1})	0.321 (16.6)
		$E_{max, 28\text{-}56D}$ (day^{-1})	0.118 (16.6)
	PaMZ	Effect (day^{-1})	0.212 FIX[d]

[a] BPa effect was estimated based on pooled BPa data.

[b] Bedaquiline EC_{50} was fixed to the value estimated from the mouse monotherapy PK-PD model.

[c] EC_{50} of bedaquiline-M2 was calculated as 8-fold that of bedaquiline based on the ratio of MIC values in the H37Rv strain, reflecting the difference in *in vitro* potency between bedaquiline and bedaquiline-M2.

[d] PaMZ effect was estimated based on pooled PaMZ data.

Abbreviations: B, bedaquiline; EC_{50}, half-maximum effective concentration; E_{max}, maximum efficacy; L, linezolid; M, moxifloxacin; MIC, minimum inhibitory concentration; Pa, pretomanid; PD, pharmacodynamic; PK, pharmacokinetic; RSE, relative standard error; Z, pyrazinamide

Supplementary Table 5. Incidence of TTP bouncers and associated delay in time to stable culture conversion in the Nix-TB and ZeNix trials.

Trial	TTP bouncers, n (%)	TSCC difference in bouncers (days)
Nix-TB	18 (20.9)	14 [12 - 25]
ZeNix	25 (19.1)	20 [14 - 28]
Total	43 (19.8)	17 [14 - 27]

Data are expressed as median [25th to 75th percentiles] unless otherwise indicated.
TTP bouncers were defined as participants who reverted to culture positivity after an initial negative result prior to stable culture conversion. TSCC difference was defined as the difference between the observed time to stable culture conversion and the time of the first negative culture result.
Abbreviations: TSCC, time to stable culture conversion; TTP, time to positivity

Supplementary Table 6. Multivariable hazard ratios for delayed culture conversion in BPa-backbone regimens.

Variable	BPa-backbone regimens	
	Hazard ratio (95% CI)	p-value
Age (per 10-year increase)	0.90 (0.84 - 0.97)	0.005
Bilateral cavitation (vs. No/Unilateral)	0.83 (0.69 - 0.99)	0.04
Baseline TTP (per 1-unit increase)	1.03 (1.02 - 1.04)	<0.001

Abbreviations: B, bedaquiline; CI, confidence interval; Pa, pretomanid; TTP, time-to-positivity

Supplementary Table 7. Delays in time to stable culture conversion by baseline patient phenotype, derived from BPa-backbone regimens.

Baseline patient phenotype	Delay in time to stable culture conversion
Easy-to-treat (age < 45 years with no bilateral cavitation)	No delay
Hard-to-treat (age < 45 years with bilateral cavitation or age ≥ 45 years)	1 week

Abbreviations: B, bedaquiline; Pa, pretomanid

Supplementary Table 8. Predicted and observed hazard ratios for stable culture conversion by week 8 compared with the HRZE control regimen in the STAND and SimpliciTB trials.

Trial	Experimental regimen	Control regimen	Hazard ratio (95% CI)	
			Predicted	Observed
STAND	Pa100MZ	HRZE	1.32 (0.79 - 2.21)	1.23 (0.75 - 2.01)
	Pa200MZ	HRZE	1.49 (0.89 - 2.49)	1.29 (0.84 - 1.97)
SimpliciTB	BPaMZ	HRZE	3.93 (2.72 - 5.68)	4.09 (2.92 - 5.72)

Predicted hazard ratios were estimated using predicted outcomes for the experimental regimens compared with baseline-matched observed outcomes for the standard-of-care HRZE regimen from TBTC Study 29/29X. Participants from TBTC Study 29/29X were resampled 200 times by matching baseline characteristics to those in the HRZE control arm of the STAND and SimpliciTB trials, respectively, based on (1) the combination of cavitation status and baseline TTP quartile and (2) the distribution of each combination observed in each trial. Abbreviations: B, bedaquiline; CI, confidence interval; E, ethambutol; H, isoniazid; M, moxifloxacin; Pa100, pretomanid 100 mg; Pa200, pretomanid 200 mg; R, rifampin; TBTC, Tuberculosis Trials Consortium; TTP, time to positivity; Z, pyrazinamide.

Supplementary Table 9. Model parameters used for blinded predictions of SPaL regimen outcomes in the Phase 2 NC-009 trial.

	Sorfequiline	Sorfequiline-M3
Parameter	**Estimates (RSE%)**	**Estimates (RSE%)**
Mouse PK		
CL (L/h)	0.0141 (9.7)	0.00389 (10.3)
V_C (L)	0.173 (13.5)	0.0264 (19.5)
Q_1 (L/h)	0.00813 (17.0)	0.0116 (43.1)
V_{P1} (L)	2.51 (25.5)	0.016 (29.6)
Q_2 (L/h)	0.0177 (14.0)	-
V_{P2} (L)	0.227 (19.8)	-
K_a (h^{-1})	4.38 (31.1)	-
F	0.468 (10.1)	1 FIX
Mouse PK-PD in combination with PaL		
EC_{50} (mg/L)	0.106 (0.3)	0.318 (-)[a]
$E_{max,\ 0\text{-}28D}$ (day^{-1})	0.288 (0.5)	
$E_{max,\ 28\text{-}56D}$ (day^{-1})	0.0593 (13.5)	
PaL effect (day^{-1})	0.205 FIX[b]	
Clinical PK		
CL/F (L/h)	10.5 (10.7)	47.3 (33.5)
V_C/F (L)	204 (21.6)	58.6 (141)
Q_1/F (L/h)	19.3 (10.3)	3210 (18.6)
V_{P1}/F (L)	414 (8.5)	13100 (5.42)
Q_2/F (L/h)	24.4 (6.1)	92.9 (24.6)
V_{P2}/F (L)	16300 (10.5)	22000 (9.93)
K_a (h^{-1})	0.239 (25.8)	0.348 (191)
K_a ratio, Fed to Fasted	1.72 (49.8)	0.934 (100)
MTT (h)	0.596 (48.0)	8.35 (29.2)
MTT ratio, Fed to Fasted	2.18 (75.2)	0.723 (29.7)
MTT ratio, Suspension to Tablet	0.698 (42.8)	0.793 (60.6)
F ratio, Fed to Fasted	1.96 (56.3)	-

[a] EC_{50} of sorfequiline-M3 was calculated as 3-fold that of sorfequiline based on the ratio of MIC values in the H37Rv strain, reflecting the difference in *in vitro* potency between sorfequiline and sorfequiline-M3.
[b] PaL effect was estimated based on pooled PaL data.
Abbreviations: CL/F, apparent clearance; EC_{50}, half-maximum effective concentration; E_{max}, maximum efficacy; F, bioavailability; Ka, absorption rate constant; L, linezolid; MTT, mean transit time; Pa, pretomanid; PD, pharmacodynamics; PK, pharmacokinetics; Q_1/F, apparent inter-compartmental clearance between central and first peripheral compartment; Q_2/F, apparent inter-compartmental clearance between central and second peripheral compartment; RSE, relative standard error; S, sorfequiline; V_C/F, apparent central volume of distribution; V_{P1}/F, apparent first peripheral volume of distribution; V_{P2}/F, apparent second peripheral volume of distribution

Supplementary Table 10. Delays in time to stable culture conversion by baseline patient characteristics, derived from BPa-backbone regimens with lesion penetration-informed sorfequiline dose adjustment.

Baseline patient characteristics	Delay in time to stable culture conversion		
	25 mg	**50 mg**	**100 mg**
age < 45 years with no cavitation	No delay	No delay	No delay
age < 45 years with unilateral cavitation	No delay	No delay	No delay
age < 45 years with bilateral cavitation	3 weeks	1 week	No delay
age ≥ 45 years with no cavitation	1 week	1 week	1 week
age ≥ 45 years with unilateral cavitation	3 weeks	1 week	1 week
age ≥ 45 years with bilateral cavitation	3 weeks	1 week	1 week

Abbreviations: B, bedaquiline; Pa, pretomanid

Supplementary Table 11. Pre-specified assumptions and corresponding sensitivity analyses for blinded predictions of SPaL regimen outcomes in the Phase 2 NC-009 trial.

	Assumption	Sensitivity analysis
PK		
Clinical PK	PK in patients comparable to healthy volunteers	Individual patient-level PK from the NC-009 trial used
Protein binding ratio	$f_{u,human/mouse}$ set to 1 given very low f_u in both species	Experimentally determined values used
Biomarker conversion		
Baseline TTP-CFU	Conditional sampling from clinical TTP-CFU pairs appropriate	Published model-based equation used
Bouncer assignment	Assignment based on prior BPaL trial observations applicable	Assignment based on NC-009 trial observations
Patient phenotype	TSCC delays consistent with prior BPa-backbone regimens	SPaL-specific phenotype-based TSCC delays used
Lesion coverage	TSCC delays not adjusted for lesion penetration	TSCC delays adjusted by dose-dependent lesion penetration

Abbreviations: B, bedaquiline; CFU, colony-forming units; $f_{u,human/mouse}$, fraction unbound ratio between humans and mice; L, linezolid; Pa, pretomanid; PK, pharmacokinetics; S, sorfequiline; TSCC, time to stable culture conversion; TTP, time to positivity

Supplementary Table 12. Population pharmacokinetic model parameters for sorfequiline and M3 in patients from the Phase 2 NC-009 trial.

	Sorfequiline	Sorfequiline-M3
Parameter	**Estimates (RSE%)**	**Estimates (RSE%)**
CL/F, Male living without HIV (L/h)	3.37 (8.8)	20.1 (5.4)
CL/F, Male living with HIV (L/h)	4.27 (15.3)	23.0 (13.0)
CL/F, Female living without HIV (L/h)	5.73 (7.6)	24.9 (8.3)
CL/F, Female living with HIV (L/h)	10.8 (16.1)	35.8 (16.5)
V_C/F (L)	148 (13.0)	17900 (3.6)
V_C/F ratio, Living with HIV to without HIV	1.802 (30.2)	1.239 (46.0)
V_C/F ratio, Female to Male	-	1.363 (24.7)
Q_1/F (L/h)	21.9 (9.8)	-
V_{P1}/F (L)	1000 (7.5)	-
Q_2/F (L/h)	5.21 (12.0)	-
Q_2/F ratio, Female to Male	2.04 (32.0)	-
V_{P2}/F (L)	4060 (10.7)	-
K_a (h^{-1})	0.645 (19.5)	0.837 (17.1)
MTT (h)	1.53 (10.9)	-

Abbreviations: CL/F, apparent clearance; F, bioavailability; HIV, human immunodeficiency virus; Ka, absorption rate constant; MTT, mean transit time; Q_1/F, apparent inter-compartmental clearance between central and first peripheral compartment; Q_2/F, apparent inter-compartmental clearance between central and second peripheral compartment; RSE, relative standard error; V_C/F, apparent central volume of distribution; V_{P1}/F, apparent first peripheral volume of distribution; V_{P2}/F, apparent second peripheral volume of distribution

Supplementary Table 13. Incidence of TTP bouncers and associated delay in time to stable culture conversion in the Phase 2 NC-009 trial.

Trial	TTP bouncers, n (%)	TSCC difference in bouncers (days)
NC-009	68 (22.7)	14 [7 - 21]

Data are expressed as median [25th to 75th percentiles] unless otherwise indicated.
TTP bouncers were defined as participants who reverted to culture positivity after an initial negative result prior to stable culture conversion. TSCC difference was defined as the difference between the observed time to stable culture conversion and the time of the first negative culture result.
Abbreviations: TSCC, time to stable culture conversion; TTP, time to positivity

Supplementary Table 14. Delays in time to stable culture conversion by baseline patient phenotype, derived from the SPaL regimen in the Phase 2 NC-009 trial.

Baseline patient phenotype	Delay in time to stable culture conversion
Non-severe (No AFB 3+ and no bilateral cavitation)	No delay
Severe (AFB 3+ and/or bilateral cavitation)	2 weeks

Patient phenotype was defined by disease severity as specified in the NC-009 trial.[19]
Abbreviations: AFB, acid-fast bacilli; L, linezolid; Pa, pretomanid; S, sorfequiline

Supplementary Table 15. Model parameters used for prospective prediction of TBAJ-587-PaL regimen outcomes.

	TBAJ-587	TBAJ-587-M3
Parameter	**Estimates (RSE%)**	**Estimates (RSE%)**
Mouse PK		
CL (L/h)	0.079 (13.5)	0.0847 (19.7)
V_C (L)	0.12 (19.9)	0.00009 (25.1)
Q_1 (L/h)	0.047 (13.7)	0.212 (21.6)
V_{P1} (L)	2.39 (21.3)	0.315 (17.8)
Q_2 (L/h)	0.164 (13.4)	-
V_{P2} (L)	0.71 (15.2)	-
K_a (h^{-1})	0.551 (28.1)	-
F_{diff}[a]	2.83 (15.0)	1 FIX
FD_{50} (mg/kg)	75.5 (13.0)	-
GAM	2.4 (18.8)	-
Mouse PK-PD in combination with PaL		
EC_{50} (mg/L)	0.0934 (0.4)	0.374 (-)[b]
$E_{max,\ 0\text{-}28D}$ (day^{-1})	0.291 (0.01)	
$E_{max,\ 28\text{-}56D}$ (day^{-1})	0.102 (-)[c]	
PaL effect (day^{-1})	0.236 FIX[d]	

[a] $F = F_{diff} * (1 - DOSE^{GAM} / (DOSE^{GAM} + FD_{50}^{GAM}))$

[b] EC_{50} of TBAJ-587-M3 was calculated as 4-fold that of TBAJ-587 based on the ratio of MIC values in the H37Rv strain, reflecting the difference in *in vitro* potency between TBAJ-587 and TBAJ-587-M3.

[c] $E_{max,\ 28\text{-}56D}$ was derived from the ratio of $E_{max,\ 0\text{-}28D}/E_{max,\ 28\text{-}56D}$ from the TBAJ-587 mouse PK-PD model in combination with PaL in J4 strain (not shown).

[d] PaL effect was estimated based on pooled PaL data.

Abbreviations: CL/F, apparent clearance; EC_{50}, half-maximum effective concentration; E_{max}, maximum efficacy; F, bioavailability; F_{diff}, maximum relative bioavailability; FD_{50}, dose at which bioavailability is reduced by 50%; GAM, Hill coefficient; Ka, absorption rate constant; L, linezolid; MTT, mean transit time; Pa, pretomanid; PD, pharmacodynamics; PK, pharmacokinetics; Q_1/F, apparent inter-compartmental clearance between central and first peripheral compartment; Q_2/F, apparent inter-compartmental clearance between central and second peripheral compartment; RSE, relative standard error; S, sorfequiline; V_C/F, apparent central volume of distribution; V_{P1}/F, apparent first peripheral volume of distribution; V_{P2}/F, apparent second peripheral volume of distribution

Supplementary Table 16. Framework inputs used for prospective application of the translational meta-model framework to investigational regimens in Phase 2 trials.

Component	Iteration 2			
	ACTG A5409/RAD-TB		TBTC Study 38/CRUSH-TB	
	BPaU	**BPaO**	**BMZD**	**BMZRb**
Immune	Zhang et al.[1]	Zhang et al.[1]	Zhang et al.[1]	Zhang et al.[1]
PK – Clinical PK	Table S17	Strydom et al.[9]	Svensson et al.[6]	Svensson et al.[6]
PD – Mouse PK-PD	Table S17	Table S17	Table S17	Table S17
Biomarker conversion				
Baseline TTP-CFU	Figure S1[a]	Figure S1[a]	Figure S1[a]	Figure S1[a]
Bouncer assignment	Table S13	Table S13	Table S13	Table S13
Patient phenotype	Table S7	Table S7	Table S7	Table S7

[a] Data were used directly for conditional sampling.

Abbreviations: B, bedaquiline; CFU, colony-forming units; D, delamanid; M, moxifloxacin; O, TBI-223; Pa, pretomanid; PD, pharmacodynamics; PK, pharmacokinetics; TTP, time to positivity; U, sutezolid; Z, pyrazinamide

Supplementary Table 17. Regimen-specific model parameters used for prospective prediction of investigational regimens in Phase 2 trials.

Trial	Regimen	Model	Drug	Parameter	Estimates (RSE%)
ACTG A5409/RAD-TB	BPaU	Mouse PK-PD	Sutezolid	EC_{50} (mg/L)	0.024 (3.0)
				E_{max} (day^{-1})	0.175 (0.1)
				Rate to effect compartment (day^{-1})	1.41 (0.3)
			BPa	Effect (day^{-1})	0.121 FIX[a]
		Clinical PK	Sutezolid	CL_{int} (L/h)	166.7 (16)
				K_m (mg/L)	1.56 (42)
				V_C (L)	491.8 (26)
				Q (L/h)	100.1 (23)
				V_P (L)	559.2 (18)
				K_a (h^{-1})	0.91 (35)
				F_{1800}	0.59 (17)
	BPaO	Mouse PK-PD	TBI-223	EC_{50} (mg/L)	1.44 (<0.1)
				E_{max} (day^{-1})	0.254 (0.1)
				Rate to effect compartment (day^{-1})	15.2 (0.6)
			BPa	Effect (day^{-1})	0.121 FIX[a]
TBTC Study 38/CRUSH-TB	BMZD	Mouse PK-PD	Bedaquiline with MZD	$EC_{50,\ bedaquiline}$ (mg/L)	0.0435 FIX[c]
				$EC_{50,\ bedaquiline\text{-}M2}$ (mg/L)	0.348 FIX[c,d]
				E_{max} (day^{-1})	0.318 (<0.1)
	BMZRb	Mouse PK-PD	Bedaquiline with MZRb	$EC_{50,\ bedaquiline}$ (mg/L)	0.0435 FIX[c]
				$EC_{50,\ bedaquiline\text{-}M2}$ (mg/L)	0.348 FIX[c,d]
				E_{max} (day^{-1})	0.323 (<0.1)

[a] BPa effect was estimated based on pooled BPa data. [b] F was fixed to 1 for all doses except 1800 mg. [c] Bedaquiline EC_{50} was fixed to the value estimated from the mouse monotherapy PK-PD model. [d] EC_{50} of bedaquiline-M2 was calculated as 8-fold that of bedaquiline based on the ratio of MIC values in the H37Rv strain, reflecting the difference in *in vitro* potency between bedaquiline and bedaquiline-M2.

Abbreviations: B, bedaquiline; CL_{int}, intrinsic clearance; D, delamanid; EC_{50}, half-maximum effective concentration; E_{max}, maximum efficacy; F, bioavailability; K_a, absorption rate constant; K_m, Michaelis-Menten elimination constant; M, moxifloxacin; MIC, minimum inhibitory concentration; O, TBI-223; Pa, pretomanid; PD, pharmacodynamic; PK, pharmacokinetic; Q, inter-compartmental clearance; Rb, rifabutin; RSE, relative standard error; U, sutezolid; V_C, central volume of distribution; V_P, peripheral volume of distribution; Z, pyrazinamide

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