THE LANCET
Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Minja LT, van der Feltz I, Manyama C, et al. Delpazolid in combination with bedaquiline, delamanid, and moxifloxacin for pulmonary tuberculosis (PanACEA-DECODE-01): a prospective, randomised, open-label, phase 2b, dose-finding trial. *Lancet Infect Dis* 2025; published online July 8. https://doi.org/10.1016/S1473-3099(25)00289-0.

A prospective, randomised, open-label phase 2b dose-finding trial of delpazolid for pulmonary tuberculosis: DECODE

Supplementary Materials

Table of Contents

The PanACEA consortium – list of contributors

The authors would like to acknowledge the members of the data safety monitoring board (Prof. Robert Horsburgh Jr., Prof Andrew Nunn, Prof. Gary Maartens).

Further, we would like to acknowledge the team from TECRO Research for invaluable data management, and FHI for clinical monitoring support.

The Pan African Consortium for the Evaluation of Anti-tuberculosis Antibiotics (PanACEA) comprises of the following individuals and institutions:

LMU University Hospital, Munich, Munich, Germany (Michael Hoelscher, Julia Dreisbach, Larissa Hoffmann, Norbert Heinrich, Alia Razid, Krista Stoycheva, Alexa Dierig, Anna Jarchow-MacDonald, Ivan Norena, Laura Paramo, Rebekka Astudillo, Erlandy Basson, Anna-Lisa Behnke); University of St Andrews, St Andrews, United Kingdom (Derek Sloan, Wilber Sabiiti, Stephen Gillespie); Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands (Lindsey te Brake, Elin Svensson, Chaima Mouhdad, Simon Koele, Rob Aarnoutse, Jodie Schildkraut, Martin Boeree, Ralf Stemkens, Isabella van der Feltz); UCL Centre for Clinical Microbiology, University College of London, London, UK (Anna Bateson, Robert Hunt, Timothy McHugh, Leticia Muraro Wildner, Priya Solanki); University of California San Francisco (Patrick Phillips, Xue Gong, Brian Aldana), MRC Clinical Trials Unit at UCL, London, UK (Angela Crook); University of Cape Town, Cape Town, South Africa (Rodney Dawson, Kim Narunsky); University of Stellenbosch, Cape Town, South Africa (Andreas Diacon, Veronique de Jager, Sven Friedrich); University of the Witwatersrand, Johannesburg, South Africa (Ian Sanne, Mohammed Rassool); The Aurum Institute, Johannesburg, South Africa (Gavin Churchyard, Modulakgotla Sebe, Heeran Makkan, Lucia Mokaba, Namhla Madikizela, John Mdluli, Jane Sithole, Robert Wallis, Trevor Beattie); NIMR-Mbeya Medical Research Centre, Mbeya, Tanzania (Nyanda Elias Ntinginya, Chacha Mangu, Christina Manyama, Issa Sabi, Bariki Mtafya, Lilian T. Minja, Ombeni Chimbe, Beatrice Ngaraguza); Ifakara Health Institute, Dar es Salaam, Tanzania (Francis Mhimbira, Benno Mbeya, Tresphory Zumba, Nyasige Chibunu, Mohamed Sasamalo); Swiss Tropical and Public Health Institute, Basel, Switzerland, University of Basel, Basel, Switzerland (Klaus Reither, Levan Jugheli) ; Kilimanjaro Clinical Research Institute, Moshi, Tanzania (Gibson Kibiki, Hadija Semvua, Stellah Mpagama, Alphonce Liyoyo); Centre de Recherches Médicales de Lambaréné, Gabon (Bayode Romeo Adegbite, Ayola Akim Adegnika, Martin Peter Grobusch); Amsterdam University Medical Centers (Martin P. Grobusch, Bayode Romeo Adegbite); Makerere University, Kampala, Uganda (Bruce Kirenga), Instituto Nacional de Saúde, Marracuene, Mozambique (Celso Khosa, Isabel Timana), College of Medicine, Blantyre, Malawi (Mariott Nliwasa, Madalo Mukoka).

Bio-analytical methods

Quantitative analysis was performed using a Waters Acquity H class ultra-performance liquid chromatographic (UPLC) system consisting of a quaternary pump, flow-through needle cooled autosampler, and column oven, coupled to a Xevo TQ-S micro Tandem Mass Spectrometer (Waters, Etten-Leur, The Netherlands). Chromatographic separation was carried out with either an Acquity UPLC HSS T3 column (1.8 µm 2.1 x 100 mm) for assessment of bedaquiline, desmethyl-bedaquiline, delamanid metabolite DM-6705, moxifloxacin and delpazolid, or an Acquity UPLC CSH C18 column (1.7 µm 2.1 x 50 mm) connected to a Acquity UPLC CSH C18 1.7 µm VanGuard pre-column for quantification of bedaquiline, desmethylbedaquiline and delamanid. The mobile phase for both methods consisted of a gradient with 0.1% formic acid in water and 0.1% formic acid in acetonitrile with a flow rate of 0.3 mL/min. The autosampler temperature was set at 10 °C. Post-injection the needle was washed with a mixture of water and methanol (80:20% v/v). The mass spectrometer was used in the positive ion electrospray ionization mode using multiple-reaction monitoring (MRM). The system was controlled using Masslynx software (version 4.1, Waters, Etten-Leur, The Netherlands). Quantification was carried out using the TargetLynx application.

Sample work-up was carried out in 96-wells format and performed on ice because of delamanid instability at room temperature. Protein precipitation as sample preparation was performed by adding 200 µL of the precipitation reagent (drug internal standards dissolved in methanol) to 50 µL of plasma. After vortex-mixing for 2 minutes, centrifugation was applied at 4865x g for 5 minutes at 10 °C. Subsequently, the sample was split; 75 µL of sample was transferred to a vial for analysis of either bedaquiline, desmethyl-bedaquiline, DM6705, moxifloxacin, delpazolid (method 1) and/or bedaquiline, desmethyl-bedaquiline, delamanid (method 2).

Method validation was performed in accordance with the "Guideline on bioanalytical method validation" of the European Medicines Agency (EMA). Overall accuracy of five concentration levels measured in 5-fold ranged from 93 to 102% for delpazolid, 96-102% for bedaquiline, 96-102% for desmethyl-bedaquiline, 93-102% for moxifloxacin, 93-101% for pyrazinamide, 90-101% for delamanid and 94-103% for DM-6705. Overall precision of five concentration levels measured in 5-fold ranged from 2.2 to 5.6% for delpazolid, 2.2-6.0% for bedaquiline, 1.9-8.0% for desmethyl-bedaquiline, 1.2-2.8% for moxifloxacin, 2.4-5.2% for pyrazinamide, 1.7-2.6% for delamanid and 3.0-5.1% for DM-6705. Final calibration ranges (from lower to upper limit of quantification) were 0.01-30 mg/L for delpazolid, 0.025-10 mg/L for bedaquiline, 0.0075-3.0 mg/L for desmethyl-bedaquiline, 0.040-15 mg/L for moxifloxacin, 0.15-60 mg/L for pyrazinamide, 0.0030-3.0 mg/L for delamanid and 0.0015-0.55 mg/L for DM-6705.

Additional methods and results PK-PD modelling

Data management was performed in R version 4.1.3 [1] utilizing specialized packages such as Xpose4, which was used to make Visual Predictive Checks (VPCs) and other plots. The model was developed in NONMEM 7.4.1 [2] using LAPLACE INTER for both the population PK model and the PK-PD model. Computations were performed on the high-performance cluster managed by the Radboudumc Applied Pharmacometrics group. The development process was documented using PsN and the Pirana run record system [3].

Model selection was based on the difference in objective function value (ΔOFV), goodness-of-fit plots, VPCs, precision in parameter estimates and scientific plausibility. A difference in OFV between two nested models is approximately $\chi 2$ -distributed. A difference in OFV ≥3.84 is thus significant at the 5% level ($p < 0.05$).

Population PK

Delpazolid (DZD) PK was well-described by a two-compartment model with first-order absorption and first-order elimination. The addition of a transit compartment for absorption did not improve performance. Typical bioavailability was fixed to 1, rendering all disposition parameters relative to the absolute bioavailability. Models with a proportional, additive and combined proportional and additive error were tested to describe residual variability. An additive error on top of a proportional error improved performance only if it was very small, but not when taking a value that could be explained with a logical relation to the lower limit of quantification (LLOQ) (for instance √LLOQ/2). For this reason, only a proportional error was chosen.

Base model parameters were central volume of distribution (V2), peripheral volume of distribution (V3), clearance (CL), intercompartmental clearance (Q), absorption constant (Ka) and bioavailability (F). Lognormal interindividual variability (IIV) was included on peripheral volume of distribution. For Ka and F, log-normal inter-occasion variability (IOV) was implemented, with occasion 1 (OCC1) representing the predose sample and occasion 2 (OCC2) all samples after dosing. The same variance was assumed for the two occasions, which is standard for IOV implementation. Estimating separate variances for the two occasions did not improve the model fit. A strong negative correlation between IOV in Ka and F was detected, meaning that slow absorption and high bioavailability are connected. The correlation was bordering the limit (-1) when implemented as an OMEGA block, hence it was included in the final version of the base model as a scaling parameter (-1.33), translating to a 100% negative correlation with IOV for Ka being 33% higher (standard deviation scale) than IOV on F.

The absolute bioavailability of DZD is expected to be very high, around 90% when administered with food. This means that the estimated IOV in F probably also represents other processes, e.g. deviations in reported and actual dosing times. Including the IOV in F was strongly favoured by the data; a model with IIV in V and CL instead of the IOV in F had a difference in objective function value (ΔOFV) that was 138 points higher and was sensitive to initial estimates (prone to local minima in parameter estimation). Including IIV in CL and V2 in addition to the IOV in F did not improve model fit significantly and the estimated IIV variabilities were very small. When additional DZD PK data from other studies becomes available, the variability structure of the model should be reassessed to potentially enable inclusion of more IIV parameters.

Out of the 420 PK observations, 78 were below the limit of quantification (BLQ), equalling 18.6%. These observations were handled using the M3 method [4], generally regarded as most appropriate way of handling BLQ values [5,6]. With M3, observations above the lower limit of quantification (LLOQ) are treated as continuous data and observations below the LLOQ are treated with likelihood-based methods (assessing the likelihood for a BLQ observation to be truly below the LLOQ) [5].

After development of the base model, covariate testing was performed. Allometric scaling using fat-free mass (FFM), with a typical FFM of 58 kg (TVFFM) for a 70 kg individual, was applied to all volume and clearance terms using fixed exponents of 0.75 (for clearance) and 1 (for volume). FFM was calculated using weight, height and sex.[7] The inclusion of allometric scaling significantly improved the model fit to the data, with FFM scaling (ΔOFV 41.042) improving the model fit more than weight scaling (ΔOFV 12.951). Subsequently, predetermined covariate relationships, which are specified in Table S3, were tested. A p-value of 0.05 or lower was considered statistically significant.

The only covariate relations identified as significant at the 0.05 level were sex on bioavailability (estimate of effect 0.248, p=0.00682, ΔOFV 7.312) dose on bioavailability (estimate of effect0.292 for 800 mg dose and 0.148 for 1200 mg dose, p=0.0279, ΔOFV 7.161). There was no clear biological explanation for the sex difference in bioavailability and the estimate of the effect was uncertain (RSE 61%). Regarding the effect of dose on bioavailability, compared to 400 mg, the effect of a dose of 800 mg was higher than that of a dose of 1200 mg which is unrealistic, and the parameter estimates were uncertain (RSE 43 and 94%). Hence, neither of these relationships were included in the final popPK

model. The age range in the included population was limited (older participant 57 years) and the proportion of participants living with HIV was only 14%. That this analysis does not identify relationships should not be seen as proof of no influence of these factors since the findings may be a result of limited power.

Parameter estimates of the final model are shown in Table S4. Visual Predicted Checks (VPCs) are shown in Figure S4 and S5. Goodness of fit plots are shown in Figure S6. $AUC_{0\text{-}24}$ and C_{max} were derived from the developed DZD PK model. As C_{min}, the model-predicted concentration at 24 hrs was selected for patients with once daily dosing (arm 2, 3 and 4) and the predicted concentration at 12 hrs for patients receiving 800 mg twice daily =. An overview of derived PK parameters is presented in Table S5.

Population PD

The modified intention to treat (MITT) population and all time to positivity (TTP) data from just before start of treatment and during the 16 weeks of treatment were used for the analysis. Details on handling of TTP data from participants that interrupted treatment are specified in Table S6.
For two participants interrupting treatment permanently, the TTP data in the period after they stopped was removed. Contaminated TTP results (n=225) were excluded from the analysis. A total of 2312 TTP results were included, of those 1041 and 909 quantitative results with censoring at 42 and 25 day, respectively. The baseline bacterial load did not differ between the arms (main manuscript Table 1).

Linear and bilinear mixed-effects models were fitted to log10-transformed TTP data, applying the censoring limit of 42 days (standard, selected for diagnostic purposes) or 25 days (suggested to have better properties for quantitative analysis) [8]. Bilinear models were clearly better than linear models in describing the data ($p < 0.001$). The node point of the bilinear model was estimated at 7-8 days. Censoring at 42 days resulted in overprediction of quantitative results week 4-8, and underprediction of the proportion negative samples after week 8. Applying an upper limit of quantification (ULOQ) at day 25 resulted in a satisfactory fit to the data demonstrated by the VPCs, hence this censoring limit of 25 days was selected. The culture results above the ULOQ were included in the model fit and handled by the M3 method, in which the likelihood for the sample to truly be above the limit of quantification, given the model, is estimated. There is always a small number of false negatives in results, i.e. negative MGIT results from participants that are known to have TB. To account for this, we calculated the % negatives at baseline and included it in the model. This fixed probability for false negative samples was calculated to 2.7% (4 samples above limit of quantification of 147 available at baseline). The residual error model was additive on log-scale. The model fit is shown in Figure S7. Covariate evaluation was performed based on scientific plausibility. Disease-severity parameters were tested on the baseline bacterial load and on steepness of the slopes of bactericidal activity. The Ralph-score (radiological quantification of lung involvement), in SUDOCU found to correlated to the second slope of bactericidal activity, was not statistically significant here)[9]. There was a significant negative correlation between individual intercept (representing baseline bacterial load) and slope 1 steepness (-58%), but inclusion of this element made the model unstable with unreliable parameter estimation. Hence it was decided to not include this effect before the exposure-response analysis, but rather just conduct sensitivity analysis by adding the correlation again in the final model.

Exposure-response analysis

In addition to the PK metrics $AUC_{0\text{-}24}$, C_{max} and C_{min}, having or not having DZD, and DZD total daily dose were evaluated as predictors of slope steepness. A steeper slope should be interpreted as a faster (i.e. better) treatment response. The effect was tested as being the same on both slopes or of separate magnitude on the first and second slope. A linear relation was first assumed, with more complex relationships (like Emax models or linear+constant functions) considered if the linear relation

suggested a relationship. An overview of the results of the testing is provided in Table S7 with the selected relation in bold. The selected relation predicts that a maximum effect is reached at a DZD $AUC_{0\text{-}24}$ of 50 mg*h/L.

The parameters of the final model were generally estimated with good precision and are listed in Table S8. The parameter precision was obtained from the $Covariance function in NONMEM. The exposure effect was further investigated with a log-likelihood profiling for a better determination of the 95% confidence interval, allowing for non-symmetric uncertainty. The interval was determined to 0.03 – 0.60, just short of including 0 and thereby again demonstrating statistical significance on the 95% level.

Supplementary safety results

Serious and Higher-Grade Adverse Events

A total of two grade 3 and one grade 4 adverse events were reported among all participants in the study. The grade 4 event occurred in a participant in arm 3 (D800) who was diagnosed with diabetic ketoacidosis and assessed as not related to study drugs. The remaining two grade 3 serious adverse events (anaemia and gastritis) occurred in two participants in arm 5 (D800BD) and assessed as possibly related to delpazolid. The two individuals had relatively high delpazolid exposures as shown in Figure S9 below.

Oxazolidinones, including linezolid, are known to cause mitochondrial toxicity when used for prolonged duration. Adverse events related to mitochondrial toxicity, including bone marrow suppression and the resulting anaemia, are associated with trough (C_{min}) drug concentrations in previous studies [10,11]. However, our study suggests drug exposure over time represented by AUC is a key determinant of delpazolid toxicity. This may be explained by the shorter half-life of delpazolid; rapid clearance, as reported previously [12] and observed in this study, minimizes the time at which delpazolid is at a steady (and quantifiable) minimum concentration.

Ethics Committees, Regulatory Authorities and Approvals of the study

Tanzania		**Ethics committee**	**Approval number**	**Amendment approval number**
Sites	National Institute for Medical Research – Mbeya Centre	Mbeya Medical Research and Ethics review Committee (MMREC)	SZEC-2439/R.A/V.1/105	SZEC-2439/R.C./V.1/57
	Ifakara Health Institute	Ifakara Health Institute Institutional Review Board (IHI-IRB)	IHI/IRB/No: 11-2021	IHI/IRB/AMM/No: 02-2022
	Kilimanjaro Christian Research Institute	Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC)	No. 2513	Approval letter dated 21 Feb 2022
National approval		Medical Research coordinating Committee (MRCC)	NIMR/HQ/R.8a/Vol.IX/3649	NIMR/HQ/R.8b/Vol.I/1022
Regulatory approval		Tanzania Medicines and Medical Devices Authority (TMDA)	TMDA 0020/CTR/0008/02 Authorization number: TZ22CT0002	BD.59/62/18/6
South Africa		**Ethics committee**	**Approval number**	**Amendment approval number**

Sites	The Aurum Institute Clinical HIV Research Unit - Witts	WITS Human Research Ethics Committee	200910B	200910B
Germany				
Sponsor		Ethics Committee of the Medical Faculty of the Ludwig-Maximilians-University (LMU)	20-0812	20-0812

References

1. R Core Team R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing, Vienna, Austria* 2022.
2. Beal SL, Boeckmann AJ, and Bauer RJ (eds) NONMEM 7.4 Users Guides. Gaithersburg, MD, USA: ICON plc; 1989–2018.
3. Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. *CPT Pharmacometrics Syst Pharmacol* 2013; **2**(6): e50.
4. Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn* 2001; **28**(5): 481-504.
5. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. *AAPS J* 2009; **11**(2): 371-80.
6. Irby DJ, Ibrahim ME, Dauki AM, et al. Approaches to handling missing or "problematic" pharmacology data: Pharmacokinetics. *CPT Pharmacometrics Syst Pharmacol* 2021; **10**(4): 291-308.
7. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet* 2005; **44**(10): 1051-65.
8. Dufault SM, Davies GR, Svensson EM, et al. Analysis of time-to-positivity data in tuberculosis treatment studies: Identifying a new limit of quantification. *medRxiv* 2024.
9. Heinrich N, Manyama C, Koele SE, et al. A prospective, randomised, open label phase 2b dose-finding trial of sutezolid in combination with bedaquiline, delamanid and moxifloxacin for pulmonary tuberculosis: SUDOCU. *Lancet Infect Dis* 2025
10. Cattaneo D, Orlando G, Cozzi V, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. *Int J Antimicrob Agents* 2013; **41**(6): 586-9.
11. Song T, Lee M, Jeon HS, et al. Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis. *EBioMedicine* 2015; **2**(11): 1627-33.
12. Kim JS, Kim YH, Lee SH, et al. Early Bactericidal Activity of Delpazolid (LCB01-0371) in Patients with Pulmonary Tuberculosis. *Antimicrob Agents Chemother* 2022; **66**(2): e0168421.

Table S1. Display of Time to Culture Conversion in liquid media

Table S1A: Summary of baseline culture results by randomized treatment arm

Baseline		Arm 1: D0 (N=15)	Arm 2: D400 (N=15)	Arm 3: D800 (N=15)	Arm 4: D1200 (N=16)	Arm 5: D800BD (N=15)	Overall (N=76)
MGIT result	Positive	15 (100%)	15 (100%)	15 (100%)	16 (100%)	15 (100%)	76 (100%)
LJ result	Negative	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)	1 (6.7%)	2 (2.6%)
	Positive	14 (93.3%)	15 (100%)	15 (100%)	16 (100%)	14 (93.3%)	74 (97.4%)

Table S1B: ITT population

Summary statistic [1]	Arm 1: D0 (N=15)	Arm 2: D400 (N=15)	Arm 3: D800 (N=15)	Arm 4: D1200 (N=16)	Arm 5: D800BD (N=15)
25th quantile	42.0 days	42.0 days	49.0 days	42.0 days	49.0 days
50th quantile (median)	56.0 days	56.0 days	49.0 days	56.0 days	63.0 days
75th quantile	84.0 days	63.0 days	63.0 days	59.5 days	70.0 days
Converted by Week 0	0.0%	0.0%	0.0%	0.0%	0.0%
Converted by Week **8**	60.0%	73.3%	64.1%	75.0%	46.7%
Converted by Week 10	66.7%	86.7%	92.8%	87.5%	80.0%
Converted by Week 12	80.0%	100.0%	100.0%	100.0%	86.7%
Converted by Week 16	93.3%	100.0%	100.0%	100.0%	93.3%

Data from ITT population.

Table S1C: Adequate Adherence population

Summary statistic	Arm 1: D0	Arm 2: D400	Arm 3: D800-OD	Arm 4: D1200	Arm 5: D800-BD
25th quantile	42.0 days	42.0 days	49.0 days	42.0 days	49.0 days
50th quantile (median)	56.0 days	52.5 days	49.0 days	56.0 days	63.0 days
75th quantile	84.0 days	63.0 days	63.0 days	63.0 days	77.0 days
Converted by Week 0	0.0%	0.0%	0.0%	0.0%	0.0%
Converted by Week **8**	60.0%	71.4%	69.2%	71.4%	36.4%
Converted by Week 10	66.7%	85.7%	92.3%	85.7%	72.7%
Converted by Week 12	80.0%	100.0%	100.0%	100.0%	81.8%
Converted by Week 16	93.3%	100.0%	100.0%	100.0%	90.9%

Data from adequate adherence (AA) population.

[1] Please note, 'converted by week x' shows the Kaplan-Meier estimate of the proportion converted by day corresponding to end of each week, e.g. Week 2 = Day 14.

Table S2. Hazard Ratios for Time to Culture Conversion In Liquid Media

Table S2A: ITT population

Summary statistic [2]	Arm 1: D0 (N=15)	Arm 2: D400 (N=15)	Arm 3: D800-OD (N=15)	Arm 4: D1200 (N=16)	Arm 5: D800-BD (N=15)	All DZD (N = 61)
Unadjusted hazard ratio (95% CI)	1.00 (Reference)	1.81 (0.86, 3.81)	1.78 (0.83, 3.82)	1.87 (0.89, 3.93)	1.06 (0.50, 2.24)	1.53 (0.84,2.76)
Adjusted hazard ratio[1] (95% CI)	1.00 (Reference)	1.74 (0.82, 3.71)	1.74 (0.79, 3.81)	1.81 (0.77, 4.22)	1.16 (0.52, 2.58)	1.55 (0.83,2.91)

Data from ITT population. CI=confidence interval.

Table S2B: AA population

Summary statistic	Arm 1: D0 (N=15)	Arm 2: D400 (N=14)	Arm 3: D800-OD (N=13)	Arm 4: D1200 (N=14)	Arm 5: D800-BD (N=11)	All DZD (N = 61)
Unadjusted hazard ratio (95% CI)	1.00 (Reference)	1.81 (0.85, 3.88)	1.87 (0.86, 4.07)	1.78 (0.83, 3.83)	0.90 (0.40, 2.05)	1.48 (0.81, 2.69)
Adjusted hazard ratio[1] (95% CI)	1.00 (Reference)	1.72 (0.80, 3.74)	1.80 (0.82, 3.98)	1.67 (0.69, 4.02)	0.98 (0.41, 2.35)	1.50 (0.78, 2.83)

[1] Analysis has been adjusted for: gender, age, BMI, HIV status, baseline culture (using time to positivity)

*11/15 participants in the D800BD arm presented adequate adherence (2 participant non eligible and 2 participants inadequate adherence). This could explain the lower HR trend in comparison with the other arms.

Table S3. Covariate relationships evaluated in popPK model

Parameter	Covariates
Clearance	Body size metrics, age, HIV-status
Volume of distribution (central)	Body size metrics, sex
Bioavailability	Sex, dose[1], HIV-status

[1] *Parametrised as FDOSE = 1 for dose 400 mg, FDOSE = 1+THETA(8) for dose 800 mg and FDOSE = 1+THETA(9) for dose 1200 mg*

Table S4. Final PK model parameter estimates

Parameter	Estimate	RSE (%)
Absorption constant Ka (h-1)	1.27	11
Central volume of distribution V2 (L)	75.4	7.3
Peripheral volume of distribution V3 (L)	10.6	20.7
IIV V3 (CV %)	40	19.2
Intercompartmental clearance Q (L/h)	4.0	30.8
Clearance CL (L/h)	38.1	4.8
Scaling factor IOV F to IOV Ka	-1.47	5
Proportional error	0.339	6
IOV bioavailability (F) (CV%)	61.5	6.5

Delpazolid final PK model parameter estimates for a person with FFM of 58 kg. All parameters are relative to bioavailability F, e.g. CL is CL/F. IIV=interindividual variability. IOV=inter-occasion variability. CV=coefficient of variation. RSE=relative standard error.

Table S5. Delpazolid PK parameters AUC_{0-24}, C_{max} and C_{min} per arm

Arm	Dose	AUC_{0-24} (mg/L*h)	C_{max} (mg/L)	C_{min} (mg/L)
		Median (minimum-maximum)		
2 (n=15)	400 mg	10.1 (6.86-20.5)	3.78 (2.92-4.45)	0.00296 (0.000437-0.459)
3 (n=14)*	800 mg	28.6 (15.1-76.7)	7.72 (5.78-13.9)	0.00948 (0.000439-0.810)
4 (n=16)	1200 mg	47.0 (11.8-94.0)	13.7 (9.56-19.7)	0.00240 (0.000215-0.291)
5 (n=15)	2x800 mg	68.5(28.8-198)	9.16 (7.56-13.5)	0.00400 (0.000157-0.564)

* This arm started with 15 participants but one was withdrawn from the study prior medications prior to PK sampling and thus not part of the MITT population

Table S6. Participants with treatment interruption and handling of their data in PK-PD analysis.

ID	Interruption	Action
203010	Stopped study treatment before PK sampling	Not part of MITT
203011	Paused study treatment week 3-4	Include all TTP
203021	Stopped study treatment week 14	Exclude TTP week 15-16
204011	Stopped study treatment week 13	Exclude TTP week 14-16

Table S7. Results exposure-response analysis.

Effect	**ΔOFV (p-value)**	**Parameter estimate (RSE%)**
Having DZD, effect same both slopes	0 (~ 1)	Towards zero bound
DZD total daily dose linear, effect same both slopes[1]	0 (~ 1)	Towards zero bound
DZD AUC_{0-24} linear, effect same both slopes[2]	0 (~ 1)	Towards zero bound
Having DZD, effect only slope 2	-2.068 (0.15)	0.228 (105%)
DZD total daily dose linear, effect only slope 2[1]	-1.483 (0.22)	0.225 (106%)
DZD AUC_{0-24} linear, effect only slope 2[2]	-3.282 (0.070)	0.138 (97%)
DZD AUC_{0-24} EMAX, effect only slope 2	-4.213 (0.12)	EMAX 0.635 (53%) EC50 54.2 (76%)
DZD AUC_{0-24} linear with max effect at 50 mg/L*h, effect only slope 2[3]	**-5.018 (0.025)**	**0.273 (53%)**
DZD C_{max} linear, effect only slope 2[4]	-3.509 (0.061)	0.208 (52%)
DZD C_{max} linear with max effect at 11 mg/L, effect only slope 2[5]	-4.17 (0.041)	0.275 (95%)
DZD C_{min} linear, effect only slope 2[6]	0 (~ 1)	Towards zero bound

*[1] Parametrised as (1+DDOSE/1600*THETA(5)) where 1600 is the highest used dose*

*[2] Parametrised as (1+AUC/36.0*THETA(5)) where 36 is the median AUC_{0-24} across arms 2-5*

*[3] Parametrised as AUC2 = AUC, IF(AUC>50) AUC2=50, (1+AUC/36.0*THETA(5)) where 36 is the median AUC_{0-24} across arms 2-5.*

*[4] Parametrised as (1+CMAX/8.3*THETA(5)) where 8.3 is the median C_{max} across arms 2-5*

*[5] Parametrised as CMAX2 = CMAX, IF(CMAX>11) CAMAX2 =11, (1+CMAX/8.3*THETA(5)) where 8.3 is the median C_{max} across arms 2-5*

*[6] Parametrised as (1+CMIN*THETA(5))*

DZD = delpazolid; RSE= relative standard error. Bold highlighting shows the final model.

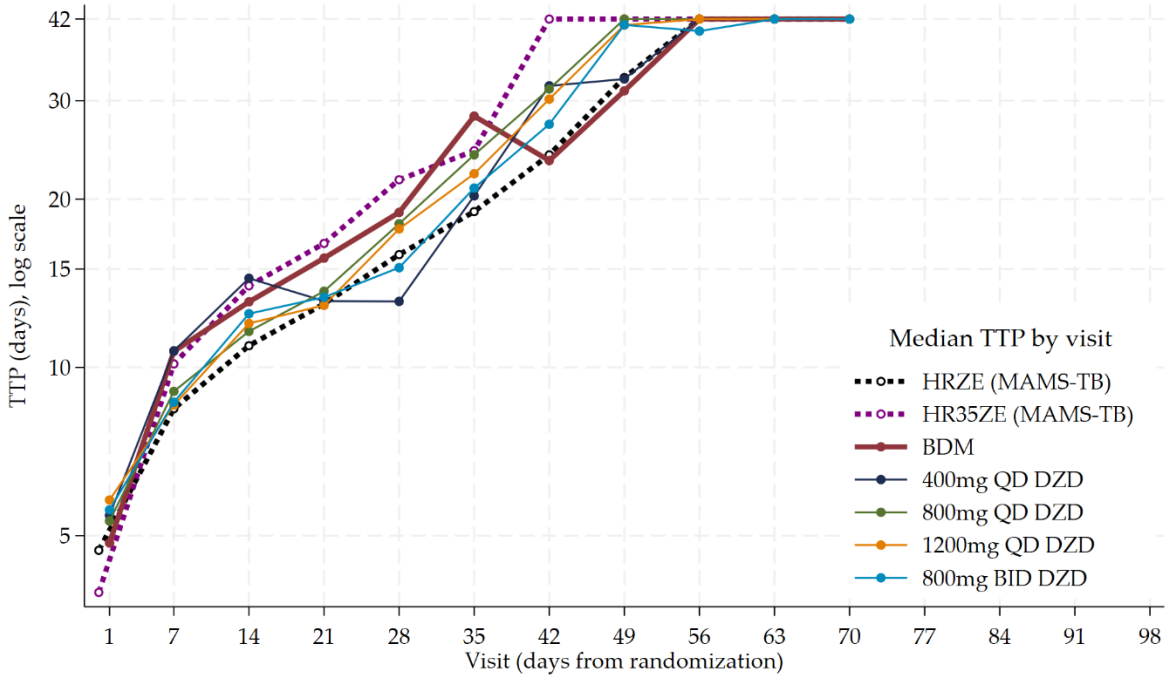
Table S8. Final PK-PD model parameter estimates

Parameter	Estimate (RSE %)	Interindividual variability [CV%] (RSE %)
Baseline bacterial load [log10TTP]	2.12 (0.9)	5.4 (13)
Slope 1 [log10TTP*day-1]	0.0352 (8.2)	29.3 (17)
Slope 2 [log10TTP*day-1]	0.0093 (9.8)	44.0 (19)
Node [days]	7.58 (11)	
Delpazolid exposure effect []¹	0.273 (53)	
Baseline negative culture chance²	0.0272 (fixed)	
Additive error [log10TTP]	0.12 (6.0)	

*¹ Parametrised as AUC2 = AUC, IF(AUC>50) AUC2=50, (1+AUC/36.0*THETA(5)) where 36 is the median AUC_{0-24} across arms 2-5, and AUC_{0-24} is in the unit of mg/L*h.*

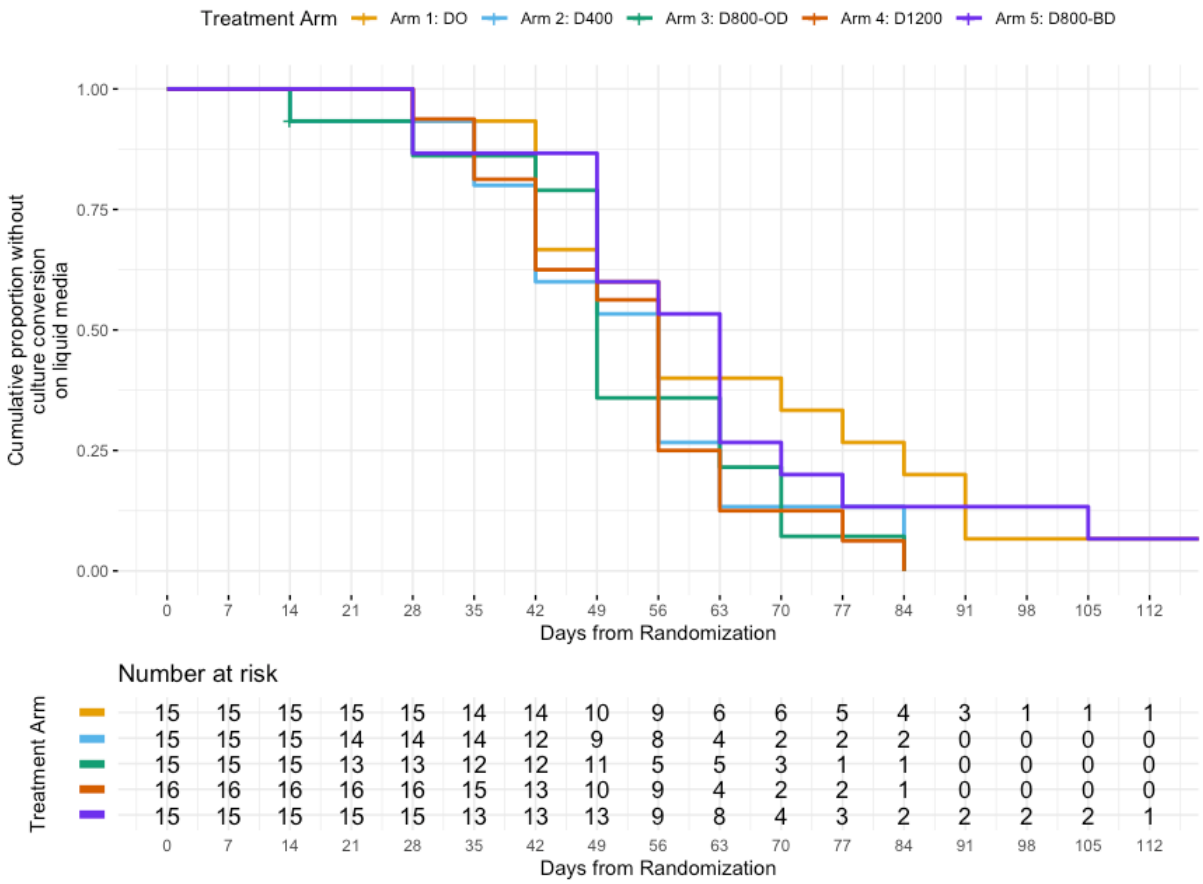
² Determined as the percentage of culture results above limit of quantification at week 0 of treatment.

Figure S1. Median MGIT TTP per arm over time, including historical control from MAMS-TB.



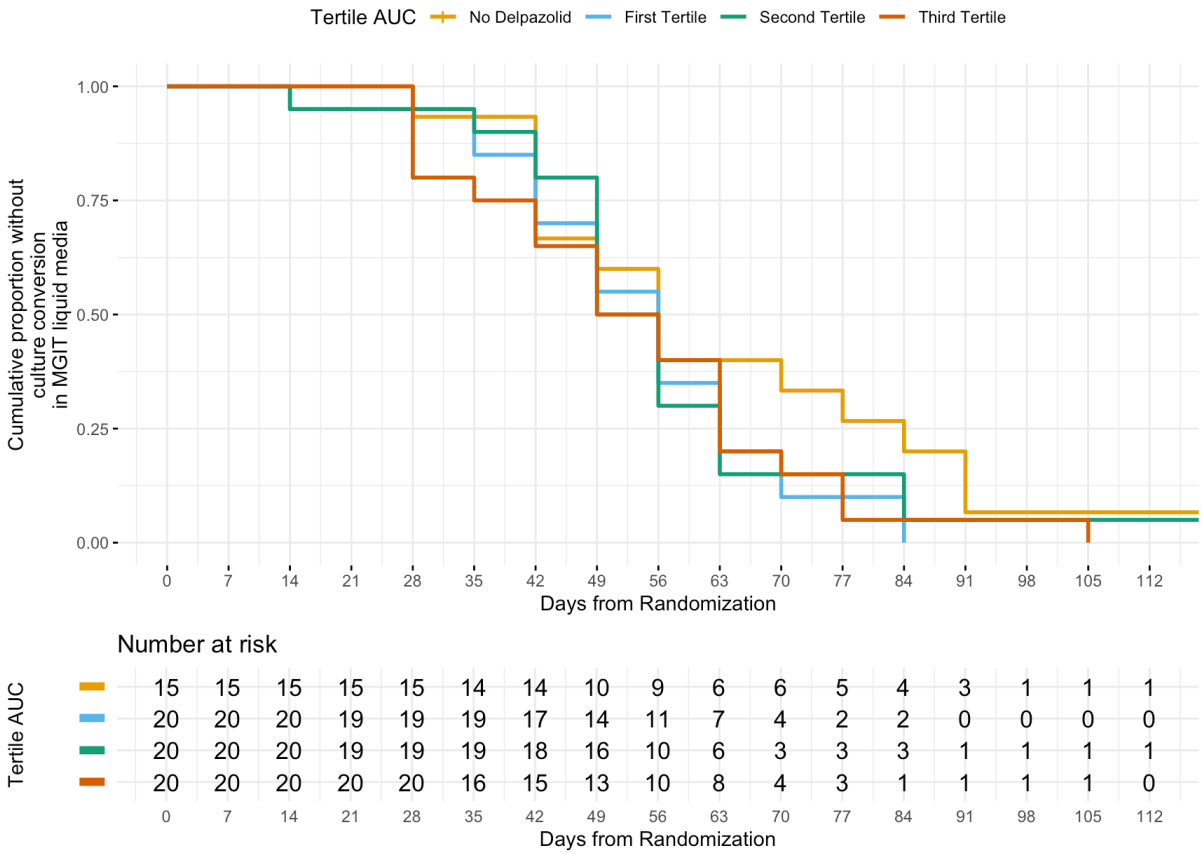
TTP=time to positivity. HRZE=isoniazid, rifampicin (35= dose of 35 mg/kg), pyrazinamide, ethambutol. BDM=bedaquiline, delamanid and moxifloxacin. QD=once daily, BID=twice daily.

Figure S2. Time to sustained sputum culture conversion per arm



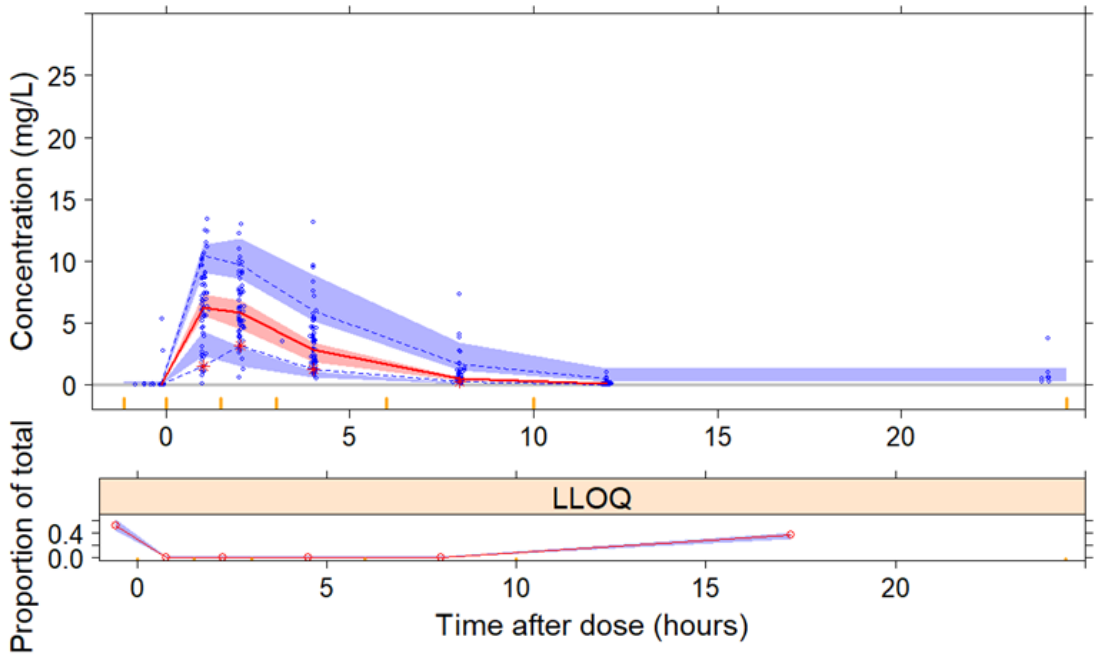
Kaplan – Meier plot of time to culture conversion in liquid media over time per arm in the ITT population; numbers at risk in table below. OD=once daily, BD=twice daily.

Figure S3. Time to sustained sputum culture conversion per exposure tertile



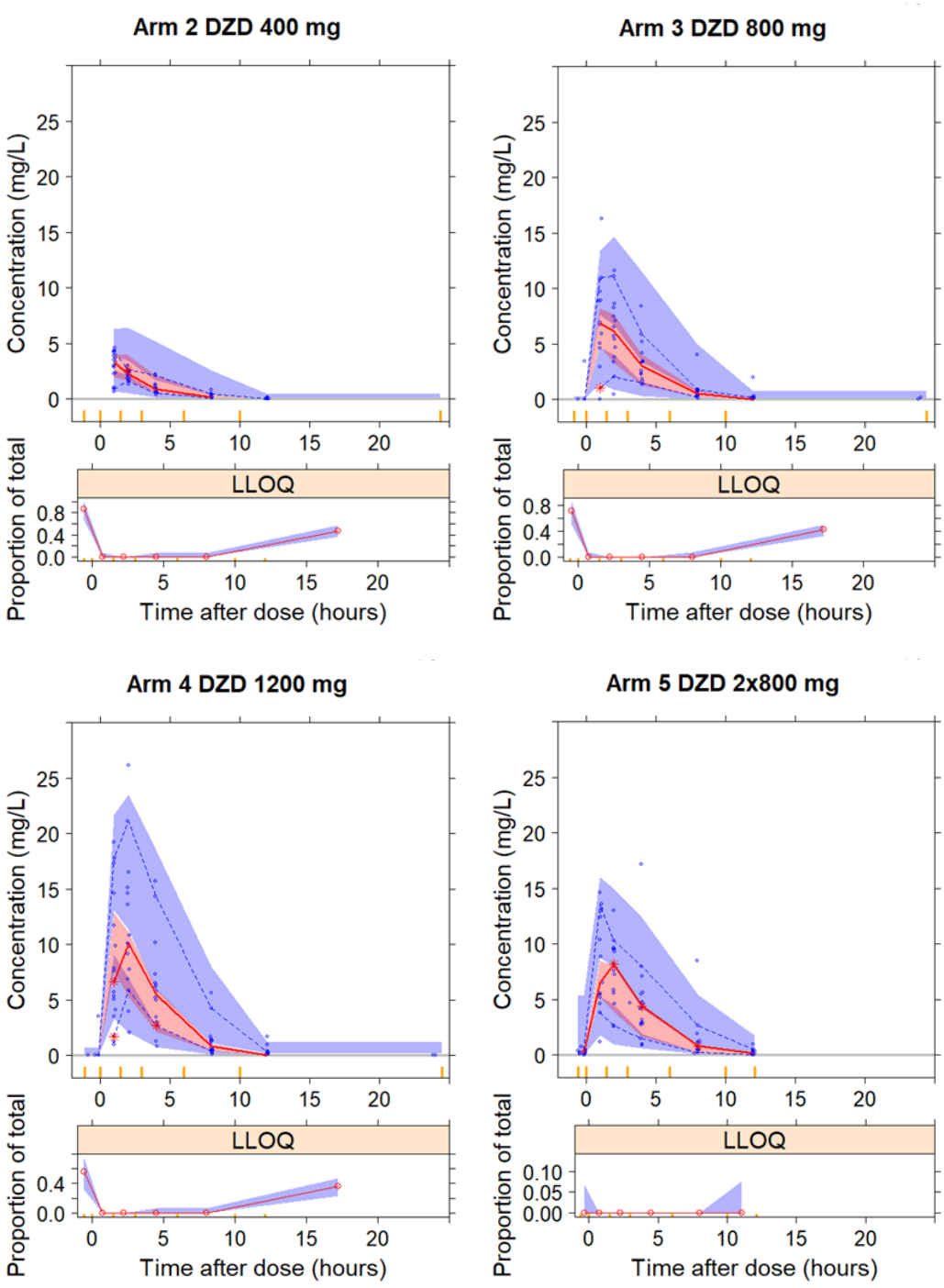
Kaplan – Meier plot of time to culture conversion in liquid media over time per exposure tertile in the ITT population; numbers at risk in table below.

Figure S4. Visual predictive check of the final model



Prediction corrected visual predictive check of the final delpazolid PK model, showing the observed 2.5th, 50th, and 97.5th percentiles (lines) and their corresponding model prediction 95% confidence intervals (shaded areas). Blue dots are the observed concentrations. Lower panel shows the proportion of samples below the lower limit of quantification (LLOQ).

Figure S5. Visual predictive check of the final model, stratified by arm



Visual predictive check of the final delpazolid PK model, stratified by arm showing the observed 2.5th, 50th, and 97.5th percentiles (lines) and their corresponding model prediction 95% confidence intervals

(shaded areas). Blue dots are the observed concentrations. Lower panel shows the proportion of samples below the lower limit of quantification (LLOQ).

Figure S6. Goodness of fit plots

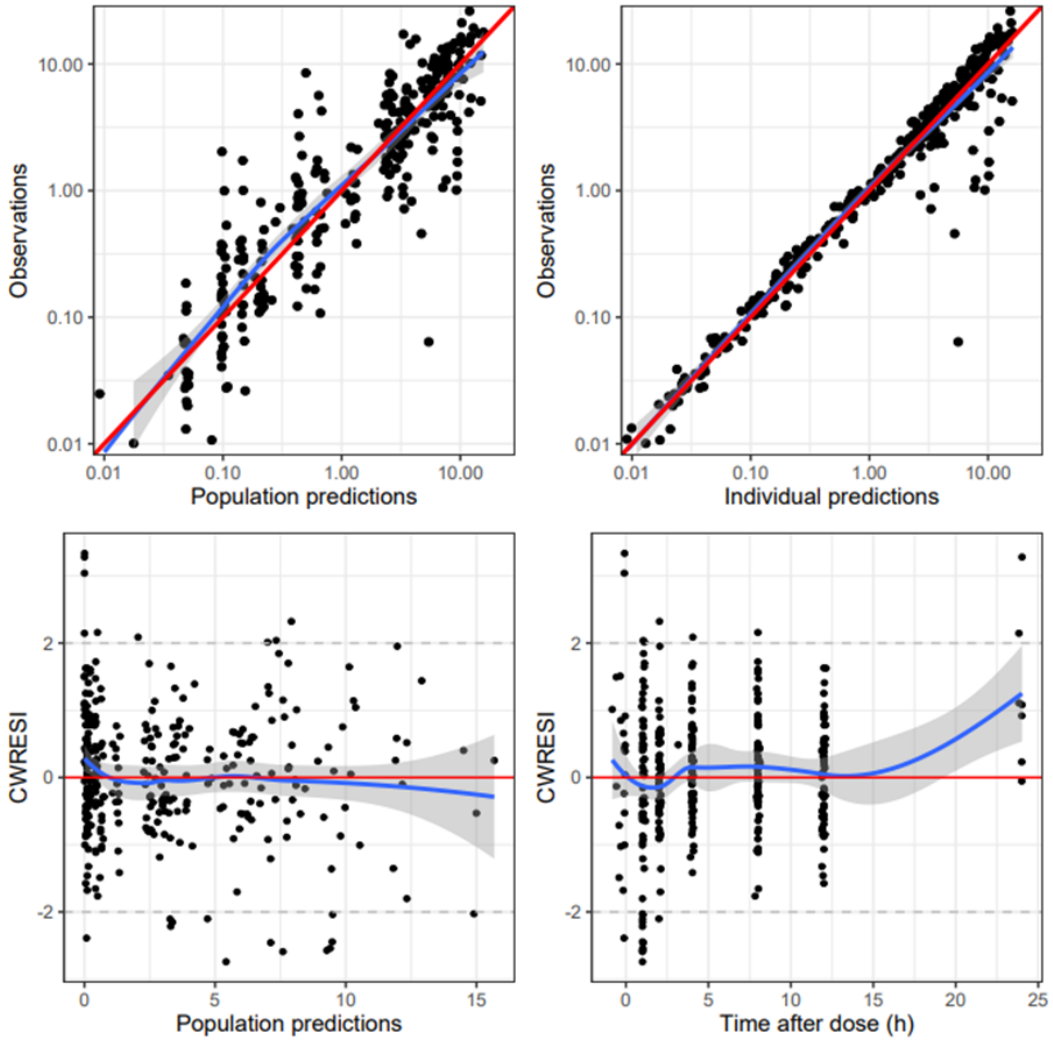


Figure S4. Goodness of fit plots of the final delpazolid PK model showing predictions vs observations, and residuals vs time and predictions (black dots). The blue lines aresmoothed LOESS regressions with their 95% confidence interval shown as grey areas. CWRESI =conditional weighted residuals with interaction.

Figure S7. Visual predictive check of TTP base model

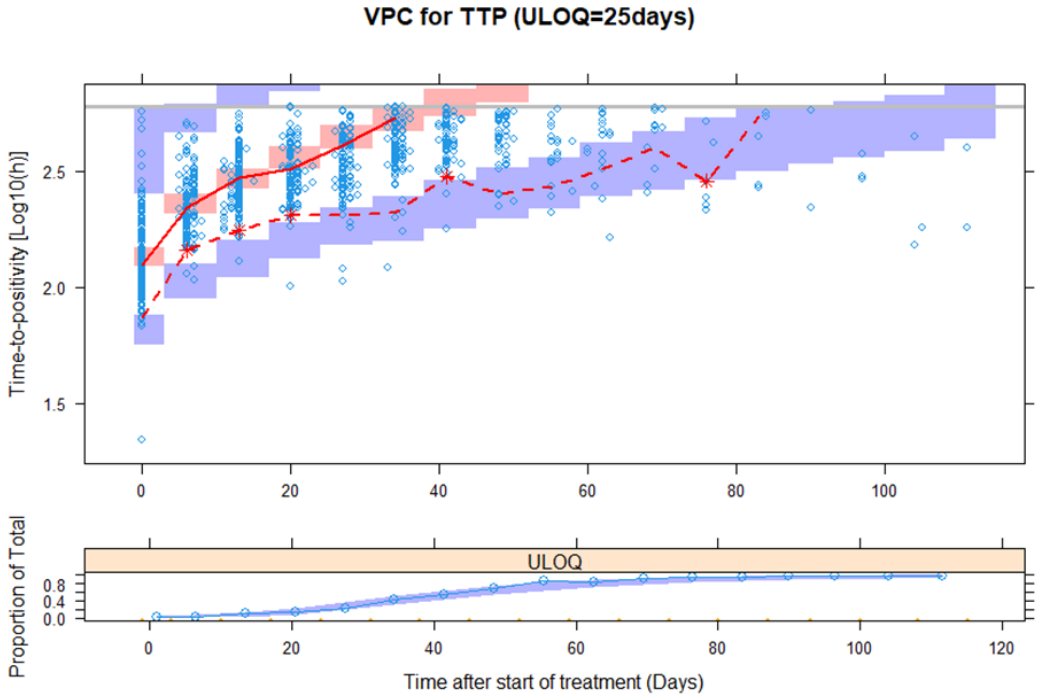


Figure S7. Visual predictive check of TTP base model, showing the observed 2.5th, 50th, and 97.5th percentiles (lines) and their corresponding prediction 95% confidence intervals (shaded areas). The blue dots are the observed TTP values. Lower panel showing the proportion of samples above the upper limit of quantification (ULOQ, 25 days).

Figure S8. Model-predicted delpazolid exposure effect

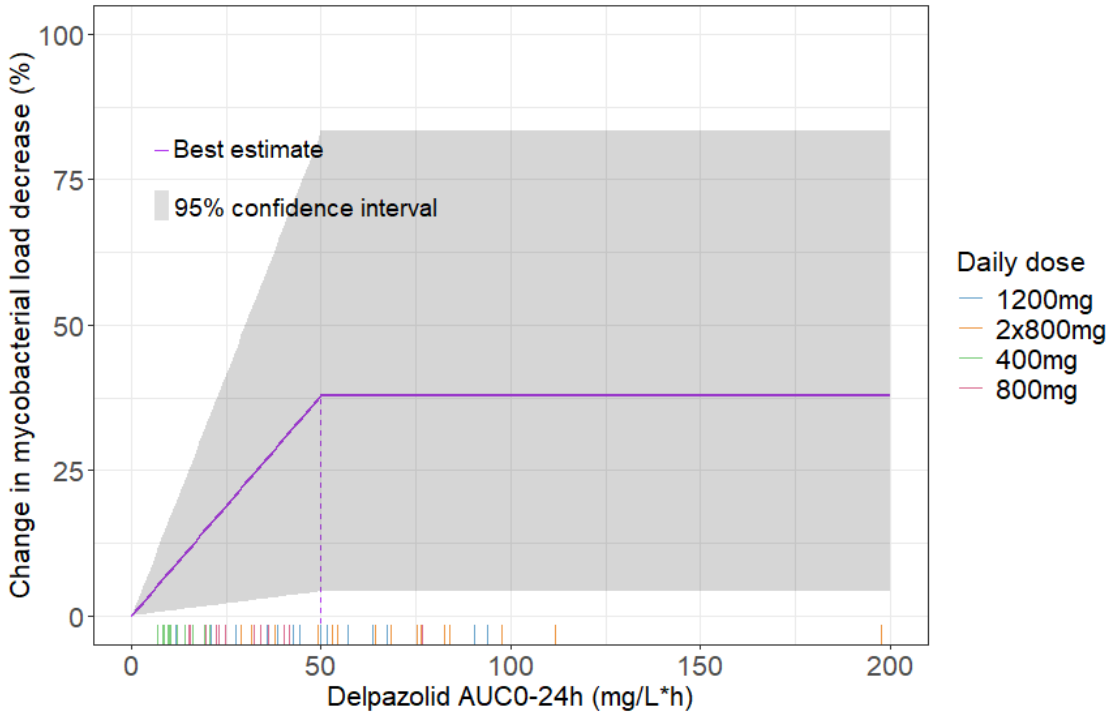


Figure S9. AUC_{0-24}, C_{max} and C_{min} of SAEs possibly related to delpazolid