



Relative bioavailability of delamanid dispersed in water in healthy volunteers

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Background

- Delamanid is a novel antibiotic for drug-resistant tuberculosis, manufactured as 50 mg tablets for adults and 25 mg dispersible tablets for children.
- Dispersible tablets are not yet widely available in programmatic settings.
- Manipulating adult tablets could be feasible for children if changes in bioavailability (F) are controlled, which could then increase access in the field.

We here evaluated the effects of dissolving the delamanid 50 mg tablets to inform its use in children.

Results

24 volunteers (5 male) completed the study. The two methods of administration were not different significantly in either F or the variability in F . The F of dispersed tablets was estimated as 107% of whole tablets, with 90% CI of 99.7-114%, fulfilling the standard 80-125% criterion for bioequivalence.

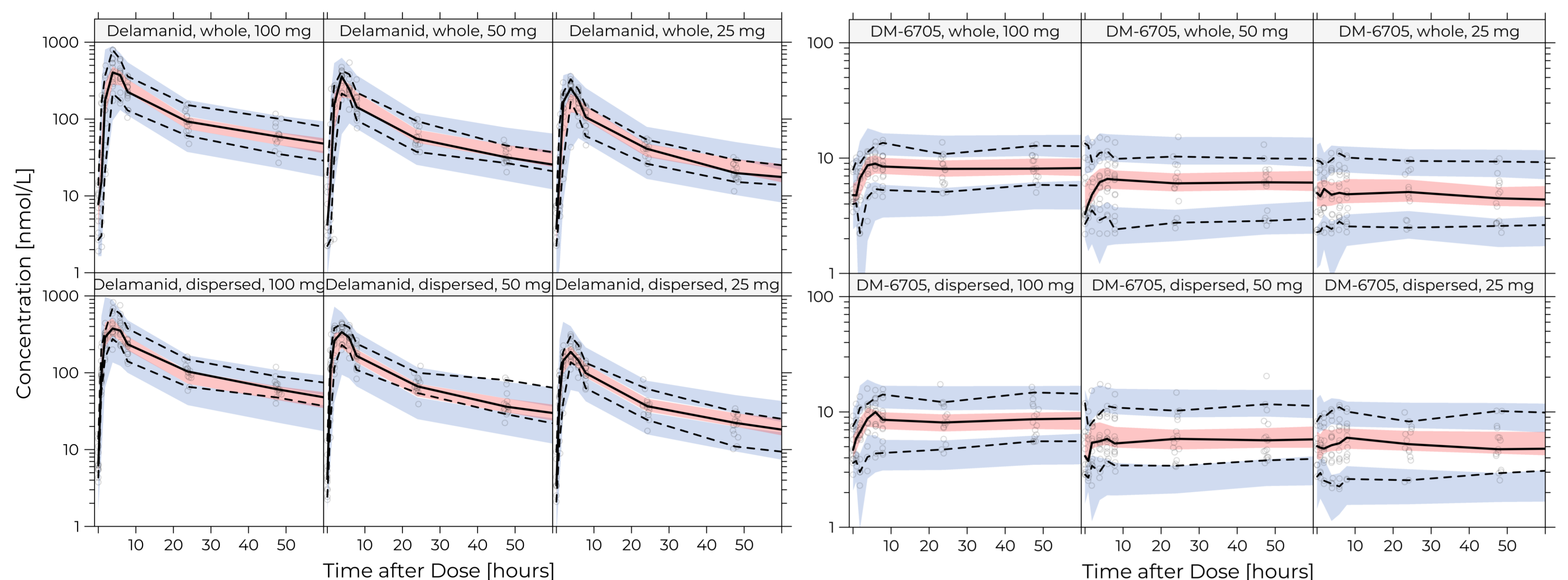
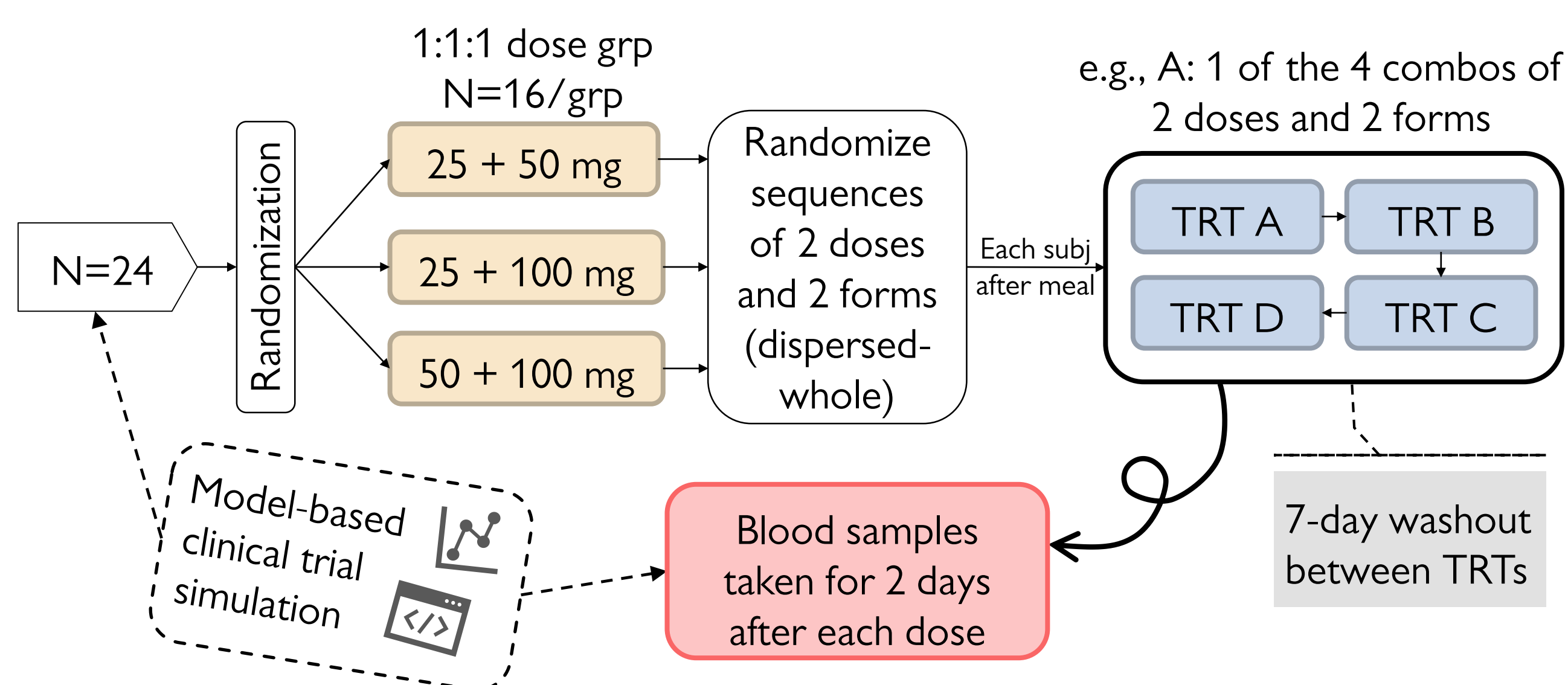


Figure: visual predictive checks of the final updated model with observed (lines) versus simulated (areas) medians (red) and 2.5/97.5th percentiles (blue)

Methods

Phase I single-dose, open-label, randomized 4-period cross-over study



Preparation of dispersed form: 1. allow the tablet(s) to disperse for 5-6mins in 5mL water; 2. add 5-15mL sugar syrup.

Pharmacokinetic (PK) data analysis

- Data:** delamanid and metabolite DM-6705.
- Base model:** the model used in clinical trial simulations with allometric scaling, a pre-final of published model [1].
- Test effect:** dose and form effects on F and absorption rate parameters were tested at significance level of 0.05.
- Evaluation:** 90% confidence interval (CI) of form effect on F was determined with log-likelihood profiling using PsN [2]; precision in other parameters was determined by SIR [3].

Table: PK estimates relative to a healthy participant weighing 60 kg receiving 2x50 mg delamanid whole tablet

Parameter (unit)	Estimate	90% CI	CV %	90% CI
KA (h ⁻¹)	0.812	0.681 – 0.959	49.8 (IOV)	41.0 – 60.0
MTT (h)	1.41	1.25 – 1.57	52.6 (IOV)	45.5 – 60.3
- Dispersing effect on MTT (proportional)	0.494	0.413 – 0.590	-	-
F	1 (fixed)	-	15.5 (IOV)	13.2 – 17.8
- Dose effect of 50 mg on F (proportional)	1.34	1.26 – 1.42	-	-
- Dose effect of 25 mg on F (proportional)	1.74	1.64 – 1.86	-	-
CL _{DLM} /F (L/h)	20.3	19.1 – 21.7	11.3 (IIV)	8.63 – 13.5
Vd _{DLM,central} /F (L)	258	223 – 297	41.1 (IIV)	35.2 – 47.1
Vd _{DLM,peripheral} /F (L)	610	566 – 660	-	-
Q _{DLM} /F (L/h)	34.3	30.3 – 38.5	-	-
f _m	1 (fixed)	-	13.8 (IIV)	10.2 – 17.5
CL _{M1} /F/f _m (L/h)	90.9	83.2 – 98.1	22.0 (IIV)	17.3 – 27.8
Vd _{M1,central} /F/f _m (L)	532	405 – 666	-	-
Vd _{M1,peripheral} /F/f _m (L)	20800	19500 – 22100	-	-
Q _{M1} /F/f _m (L/h)	1800	1700 – 1910	-	-
Proportional error in DLM	24.9%	23.7 – 26.2	-	-
Proportional error in M1	9.70%	9.29 – 10.2	-	-

DLM, delamanid; M1, metabolite DM-6705; KA, absorption rate; MTT, mean transit time; F , bioavailability; f_m, fraction metabolized; CL, clearance; Vd, volume distribution; Q, inter-compartment clearance; IIV, inter-individual variability; IOV, inter-occasion variability.

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- [1] Sasaki T, et.al. Population Pharmacokinetic and Concentration-QTc Analysis of Delamanid in Pediatric Participants with Multidrug-Resistant Tuberculosis. Antimicrob Agents Chemother. 2022 Feb 15;66(2):e0160821.
- [2] Lindbom L, et.al. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005 Sep;79(3):241-57.
- [3] Dosne, AG., et.al. An automated sampling importance resampling procedure for estimating parameter uncertainty. J Pharmacokinet Pharmacodyn 2017 Sep;44:509-520.



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