

Population pharmacokinetics of delamanid in adults treated for rifampicin-resistant tuberculosis: effect of pregnancy

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Background and Objectives

Rifampicin-resistant tuberculosis (RR-TB), a major global health threat,¹ poses increased risks of poor outcomes for pregnant women, particularly in high-Tuberculosis burden countries like South Africa.²

Delamanid is a WHO-recommended drug for the treatment of RR-TB,² however, data describing the pharmacokinetics (PK) of delamanid in pregnant women is currently unavailable.

Delamanid has a terminal half-life of **30-38 hours** and is largely metabolized by albumin into **DM-6705**, the main metabolite, which exhibits a longer half-life of **5-13 days**.³ While DM-6705 does not retain significant pharmacological activity, it has been associated with corrected QT (QTc) interval prolongation.⁴

We aimed to characterize the **population PK** of delamanid and its main metabolite DM-6705 in **adults** treated for RR-TB, and evaluate the **effect of pregnancy**, body size, HIV status, albumin concentrations, co-administered medications and morning versus evening dosing on delamanid exposure.

Methods

We pooled data from two studies in South African adults treated for RR-TB; the BEAT Tuberculosis study⁵ and Impilo study.⁶

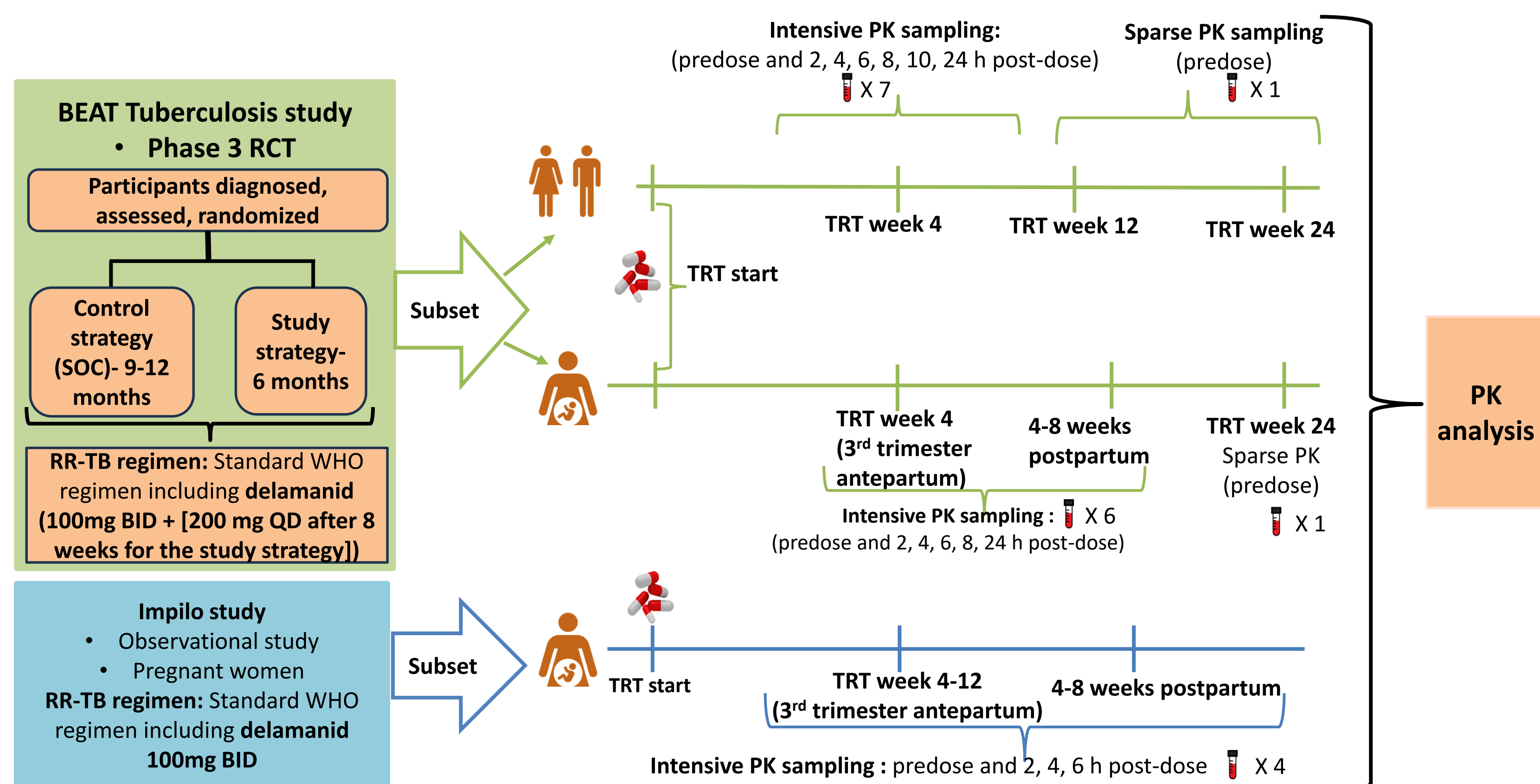


Figure 1. Study protocol. RCT: Randomized Controlled Trial; SOC: Standard of Care; QD: once daily; BID: twice daily; TRT: treatment. Standard WHO RR-TB regimen mainly included; levofloxacin, bedaquiline, clofazimine, linezolid and delamanid.

Non-pregnant females and males were included in the analysis as a control to test the effect of pregnancy in our model since we had few postpartum profiles to represent the non-pregnant state.

We developed a **joint PK model** of delamanid and its DM-6705 metabolite **sequentially**, using NONMEM 7.5.1 (FOCE-I), describing first the parent drug data, and then incorporating the metabolite data.

The residual error of delamanid and DM-6705 observations from the same sample were correlated using the **L2** data item in the NONMEM code.

Results

Table 1. Participant characteristics							
	BEAT Tuberculosis study				Impilo study		Overall
	Antepartum (n=2)	Postpartum (n=3)	Non-pregnant females (n=8)	Males (n=8)	Antepartum (n=5)	Postpartum (n=2)	
Age (years)	25.5 (19.0-32.0)	21 (19-32)	35.5 (25.0-38.0)	36.5 (23-60)	30.0 (28.0-40.0)	35.0 (30.0-40.0)	32.0 (19.0-60.0)
Weight (kg)	59.1 (58.2-59.9)	54.9 (49.8-58.0)	54.1 (37.0-67.6)	52.3 (41.9-55.7)	71.5 (43.0-104)	75.7 (69.0-82.3)	55.5 (37.0-104)
Height (m)	1.58 (1.56-1.60)	1.58 (1.56-1.60)	1.58 (1.54-1.66)	1.73 (1.58-1.88)	1.61 (1.40-1.66)	1.63 (1.61-1.64)	1.60 (1.40-1.88)
BMI (kg/m ²)	23.7 (22.7-24.6)	21.5 (20.5-22.7)	21.3 (15.6-27.4)	17.8 (15.8-19.2)	26.6 (15.6-53.1)	28.7 (25.6-31.8)	21.1 (15.6-53.1)
Albumin (g/L)	27.0 (26.0-28.0)	28.0 (26.0-33.0)	26.5 (20-38)	29.5 (21-38)	29.0 (27.0-29.0)	31 (27-33)	29.0 (20.0-38.0)
HIV positive	1 (50.0)	2 (66.7)	7 (87.5)	2 (25.0)	4 (80.0)	2 (100)	15 (60.0%)
Race							
Black	1 (50.0)	2 (66.7)	7 (87.5)	5 (62.5)	5 (100)	2 (100)	19 (79.2)
White	1 (50.0)	1 (33.3)	1 (12.5)	3 (37.5)	0 (0)	0 (0)	5 (20.8)

Data are represented as median (range) or n (%). No concentrations were below the limit of quantification set at of 0.001 mg/L for both delamanid and DM-6705, quantified by high performance liquid chromatography with tandem mass spectrometry. There were 4 matched antepartum and postpartum profiles. Participants with HIV were commonly treated with dolutegravir-based antiretroviral therapy.

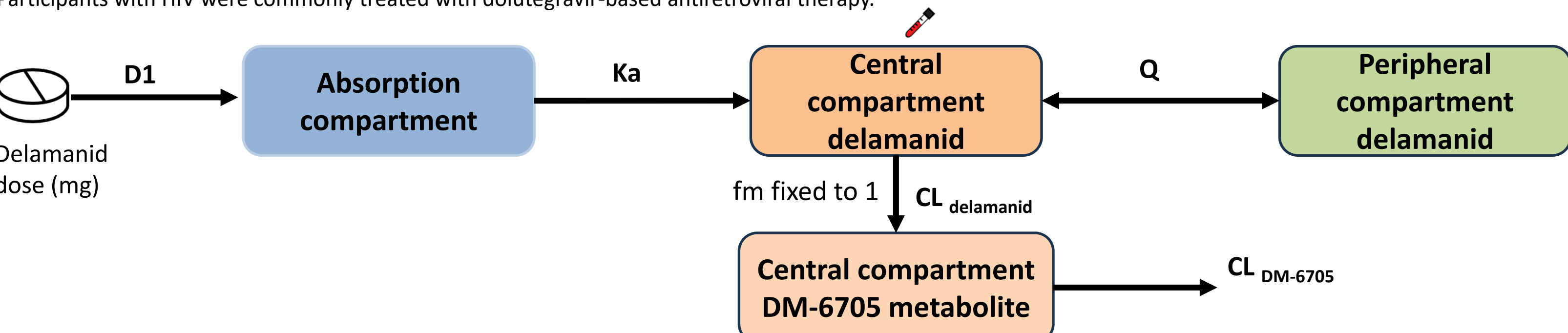


Figure 2. Pharmacokinetic model structure. D1: duration of zero-order absorption; ka: absorption rate constant; Q: intercompartmental clearance; CL: clearance; fm: fraction of delamanid metabolized to DM-6705

• We did not find a significant effect of pregnancy, HIV status, albumin concentrations, co-administered medications, and study difference on the PK of delamanid and its DM-6705 metabolite.

• While including the peripheral compartment of DM-6705 metabolite in the model was significant, the parameter estimates were unstable and therefore were not reported here.

Results

Table 2. Parameter estimates

Parameter	Typical value (95% CI) ^b	Variability %CV (95% CI) ^b
Clearance _{delamanid} (L/h) ^a	33.9 (30.3 – 37.8)	BSV: 27.3 ^c (26.1 – 28.3)
Volume of distribution _{central delamanid} (L) ^a	438 (420 – 453)	
Volume of distribution _{peripheral delamanid} (L) ^a	1360 (1332 – 1383)	
Inter-compartmental clearance _{delamanid} (L/h) ^a	43.7 (40.1 – 48.2)	
Clearance _{DM-6705} (L/h) ^a	160 (147 – 169)	BSV: 45.1 ^c (44.3 – 47.8)
Volume of distribution _{central DM-6705} (L) ^a	3400 (3377 – 3491)	
Duration of zero-order absorption (h)	1.93 (1.43 – 2.31)	BOV: 77.1 ^c (75.4 – 80.1)
Absorption rate constant (1/h)	0.405 (0.351 – 0.719)	BOV: 49.2 ^c (47.1 – 51.4)
Bioavailability, F	1 (fixed)	BOV: 30.3 ^c (28.2 – 33.8)
Effect of evening dose on F (%)	+33.3 (+29.8 – +35.6)	
Scaling factor for BOV of predose occasion (fold) ^d	2.22 (1.87 – 2.65)	
Proportional error _{DLM} (%)	9.25 (7.12 – 10.1)	
Additive error _{delamanid} (mg/L)	0.0321 (0.0221 – 0.0518)	
Correlation RUV delamanid – RUV DM-6705 (%)	43.7 (41.2 – 44.8)	
Proportional error _{DM-6705} (%)	7.26 (6.87 – 7.41)	
Additive error _{DM-6705} (mg/L)	0.00188 (0.00121 – 0.00221)	

^aParameters allometrically scaled by total body weight. The reported values refer to the typical individual in the cohort with a total body weight of 55.5 kg.

^bThe values in the parentheses are empirical 95% confidence interval (CI) computed from standard errors using sampling importance resampling.

^cThe parameter variability was included either as between-subject variability (BSV) or between-occasion variability (BOV), assuming a lognormal distribution, reported here as the percent coefficient of variation (CV) calculated as %CV=√(ω²) × 100, where ω² is the variance.

^dThis is a multiplicative factor increasing the BOV in all absorption parameters for all predose concentrations, which follow an unobserved dose.

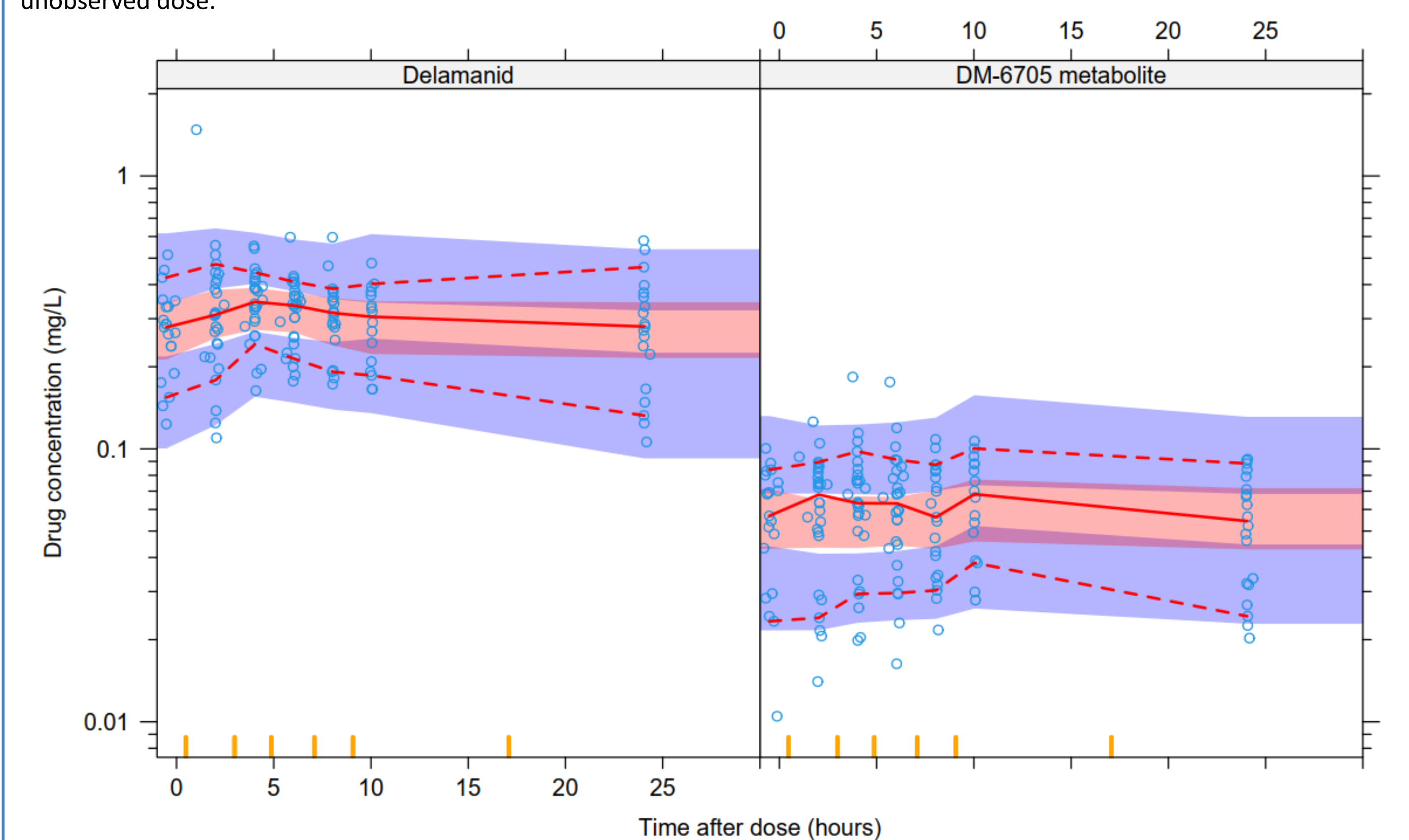


Figure 3. Visual Predictive Check of delamanid and its DM-6705 metabolite concentration versus time after dose with the y-axis plotted in the log-scale. The solid and dashed lines represent the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the model-predicted 95% confidence intervals for the same percentiles. The circles are the observed concentrations.

Conclusions

• Our model shows delamanid and DM-6705 pharmacokinetics are not affected by pregnancy, thus alleviating concerns for dose adjustments in pregnancy, although additional research with a larger sample size of pregnant women is required.

• We observed a higher bioavailability for the evening dose, in line with other studies,^{7,8} possibly attributable to a genuine physiological mechanism or variations in absorption of delamanid influenced by food quantity and composition.

• Total body weight was a better body size descriptor for disposition parameters than fat-free mass, consistent with previous studies.^{7,8}

Acknowledgements

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References

- World Health Organization (WHO), 2023. Global tuberculosis report. 2023:1-57
- World Health Organization (WHO), WHO consolidated guidelines on Tuberculosis module 4: Drug resistant tuberculosis treatment 2022 update. 2022:1-133.
- Y. Liu *et al.*, "Delamanid: From discovery to its use for pulmonary multidrug-resistant tuberculosis (MDR-TB)," *Tuberculosis*, vol. 111, no. April, pp. 20–30, 2018, doi: 10.1016/j.tube.2018.04.008.
- Gler, M.T. *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. *N. Engl. J. Med.* 366, 2151-2160 (2012).
- Conradie *et al.* Building Evidence for Advancing New Treatment for Rifampicin Resistant Tuberculosis (RR-TB) Comparing a Short Course of Treatment (Containing Bedaquiline, Delamanid and Linezolid) With the Current South African Standard of Care. <https://clinicaltrials.gov/ct2/show/NCT04062201>
- Loveday M, Hughes J, Sunkari B, *et al.* Maternal and Infant Outcomes Among Pregnant Women Treated for Multidrug/Rifampicin-Resistant Tuberculosis in South Africa. *Clin Infect Dis.* 2021;72(7):1158-1168. doi:10.1093/cid/ciaa189
- L. Tanneau *et al.*, "Population Pharmacokinetics of Delamanid and its Main Metabolite DM-6705 in Drug-Resistant Tuberculosis Patients Receiving Delamanid Alone or Co-administered with Bedaquiline," *Clin. Pharmacokinet.*, vol. 61, no. 8, pp. 1177–1185, 2022, doi: 10.1007/s40262-022-01133-2.
- X. Wang, S. Mallikaarjun, and E. Gibiansky, "Population pharmacokinetic analysis of delamanid in patients with pulmonary multidrug-resistant tuberculosis," *Antimicrob. Agents Chemother.*, vol. 65, no. 1, 2021, doi: 10.1128/AAC.01202-20.