



Clofazimine population pharmacokinetics in South African patients with drug resistant tuberculosis

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Background and Objectives

Clofazimine is a repurposed drug which was recently included by WHO in the recommended regimen for **multi-drug resistant (MDR) tuberculosis**.
Despite widespread use, pharmacokinetic (PK) data are scarce and optimal dosing is unknown in patients with drug-resistant TB.

- Long terminal half life ~70 days
- Drug accumulates selectively in the fat cells and reticuloendothelial cells
- High plasma protein binding (> 90 %)

Objectives:

- To characterize the population pharmacokinetics of clofazimine in South African patients with MDR-TB
- Explore the effect of key covariates.
- Investigate different dosing regimens to optimize treatment.

Methods

Study population and sampling

Nested in a prospective multi-center observational study of safety, PK, and resistance to bedaquiline in drug-resistant TB (PROBeX)

A subgroup (n = 22) of patients on 100-mg daily clofazimine underwent rich PK sampling at month 2 after study enrollment, with some patients initiated on the drug prior to study entry.

Blood draws : pre- and 1, 2, 3, 4, 5, 6, 8, and 24 hours post-observed dose.

Model development

NONMEM 7.4.2 (FOCE-I), Pirana, PSN, Xpose

All doses since initiation of clofazimine were individually coded in the dataset, no steady-state assumption

Total body weight, fat-free mass and fat mass ¹(calculated based on empirical formula incorporating sex, height and weight) were tested as body size descriptors for the disposition parameters.

Results

Table 1: Demographics and clinical characteristics (n = 22)

Variable	Median (IQR) or n (%)
Age (years)	29 (20 – 55)
Male sex	11 (50%)
Weight (kg)	55.2 (39.1-79.8)
Body fat (%)	14 (9 – 30)
Clofazimine doses prior to sampling (days)	45 (27-62)
Fast/Fed status	2/20
HIV-1 positive	9 (41%)

Female patients had significantly more body fat than males and their clofazimine concentrations were lower

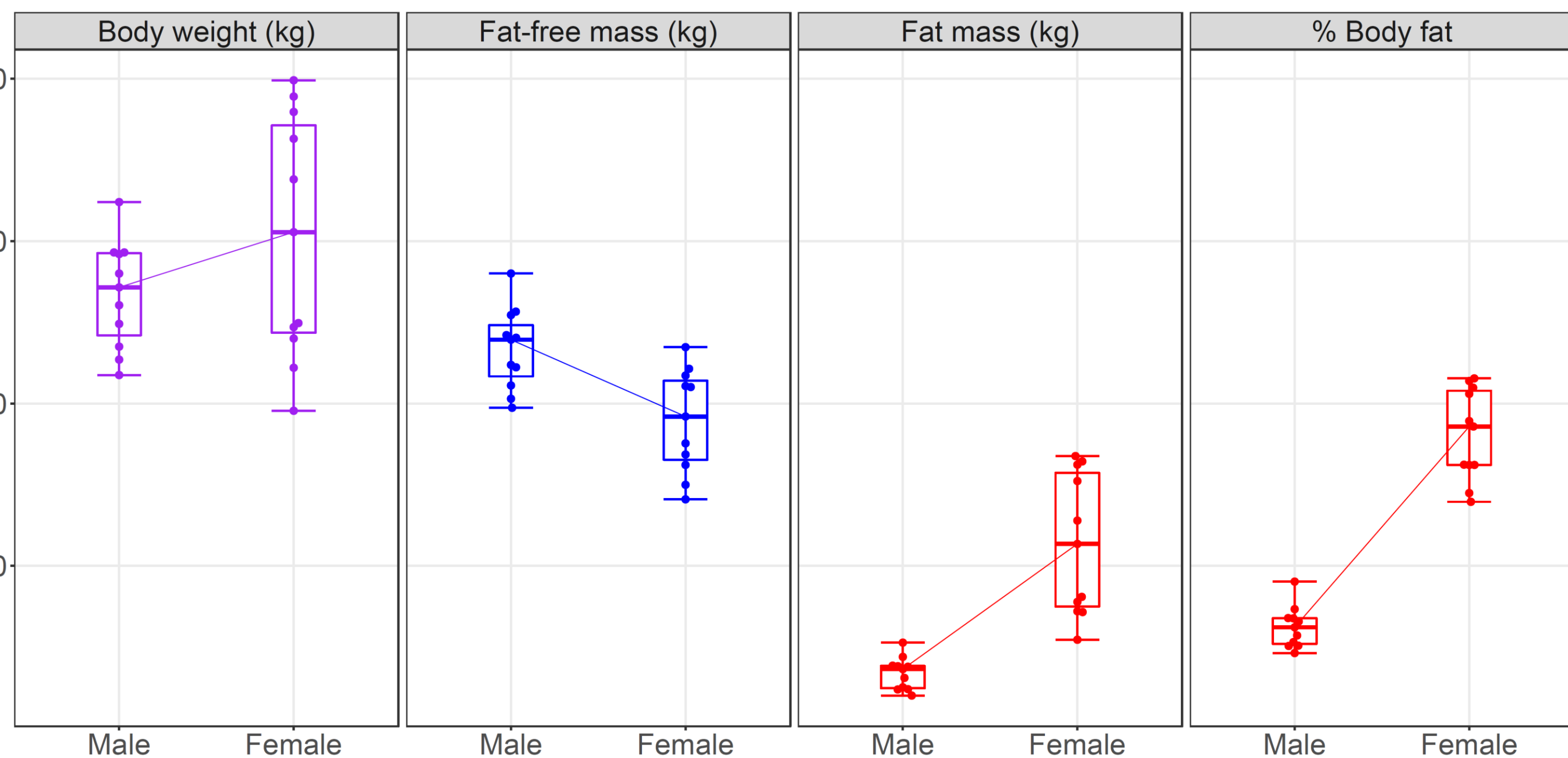


Figure 1: Distribution of different body size composition stratified by sex

A 2-compartment model with transit compartment absorption (no separate ka estimated) fit the data well.

Fat-free mass was significantly better than weight to scale the central volume of distribution and **FAT mass was best to scale peripheral volume of distribution**

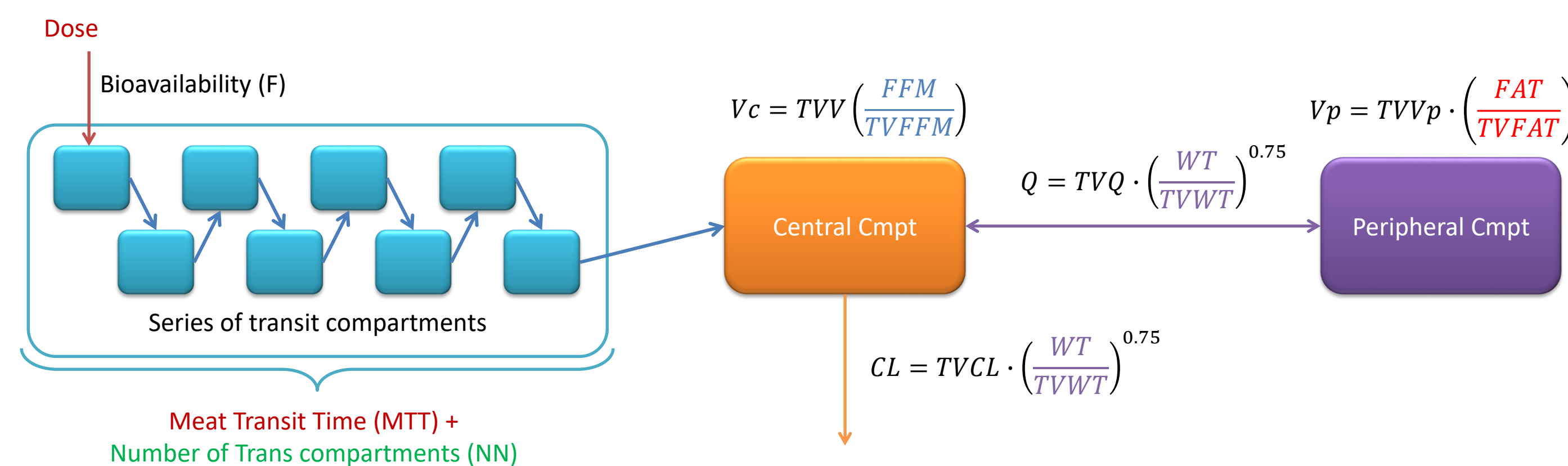


Figure 2 : Structural model with body size descriptors used for scaling

Table 2: Final parameter estimates for clofazimine PK

Parameter	Estimate [95 % CI*]	IIV+ or IOV++ [95% CI*]
CL (L/hr) ^a	9.25 [6.57:12.0]	31.1% ⁺ [13.8:43.7]
V (L) ^a	1090[920:1340]	-
MTT (hr)	1.38[1.06:1.79]	33.9% ⁺⁺ [12.7:51.3]
NN ()	2.88 [1.19:5.74]	
V (L) ^{a,b}	7260 [3120:15000]	
Q (L/hr) ^a	13.6 [3.61;56.1]	
F ()	1 FIXED	23.3% ⁺⁺ [10.0:33.4]
Prop. error (%)	12.7 [11.2:14.4]	-
Add. error (mg/L)	.004 ^d FIXED	-
t _{1/2} β (day) ^c	Overall: 40 – Typical male: 35 - Typical female: 58	

^a Allometric scaling applied. The typical values reported in table refer to typical values of WT (58 kg), FFM (47 kg) and Fat (11 kg)

^b Weakly informative Bayesian prior applied (3960 L with 70% uncertainty)²

^c Estimate of the additive error was not statistically significant from its lower bound (LLOQ/2), thus was fixed to that value

^d Secondary PK parameters derived outside NONMEM

* The precision of the estimates was obtained using sampling importance resampling (SIR) technique using PsN software.

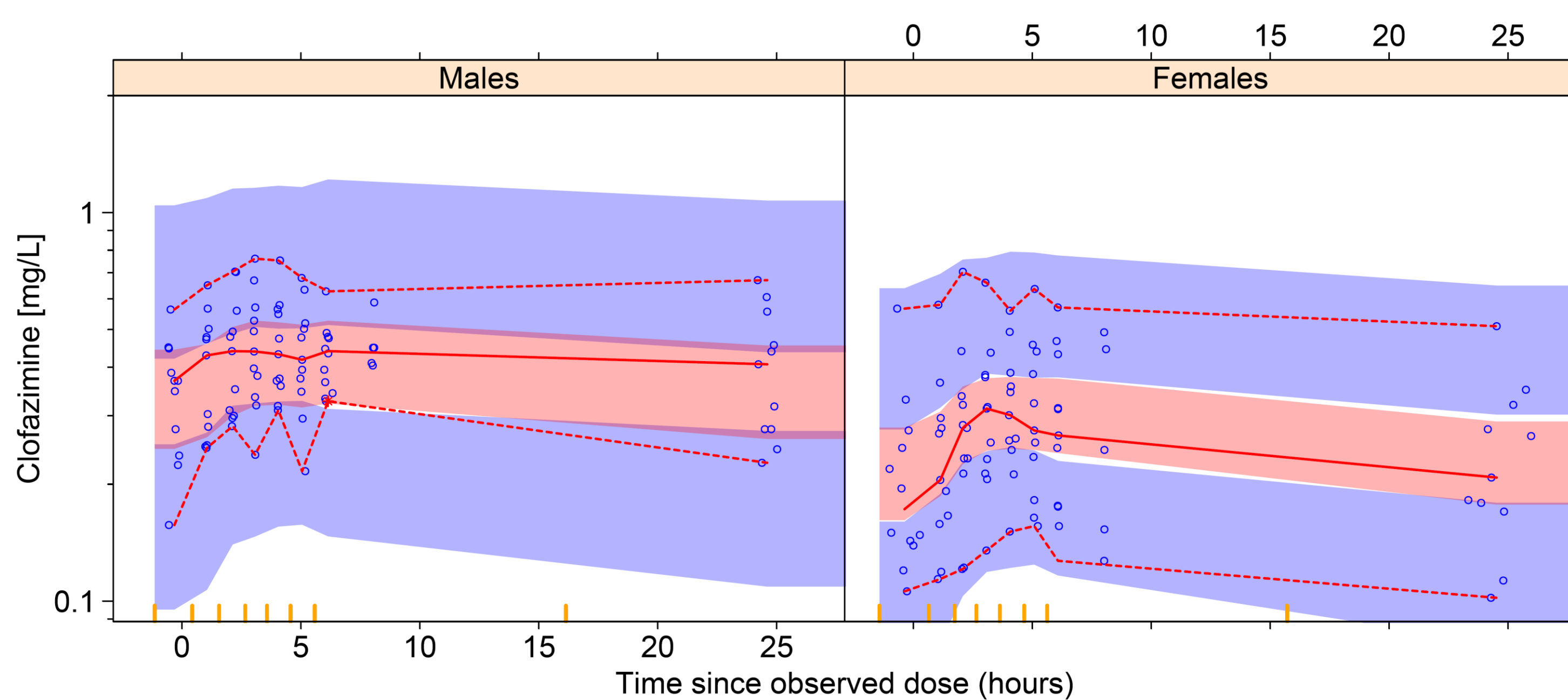


Figure 3: Visual predictive check (log scale). The lower, middle, and upper solid lines are the 2.5th, 50th, and 97.5th percentiles of the observed plasma concentration. The shaded areas are the 95% confidence intervals for the same percentiles, obtained from re-simulations of the same trial.

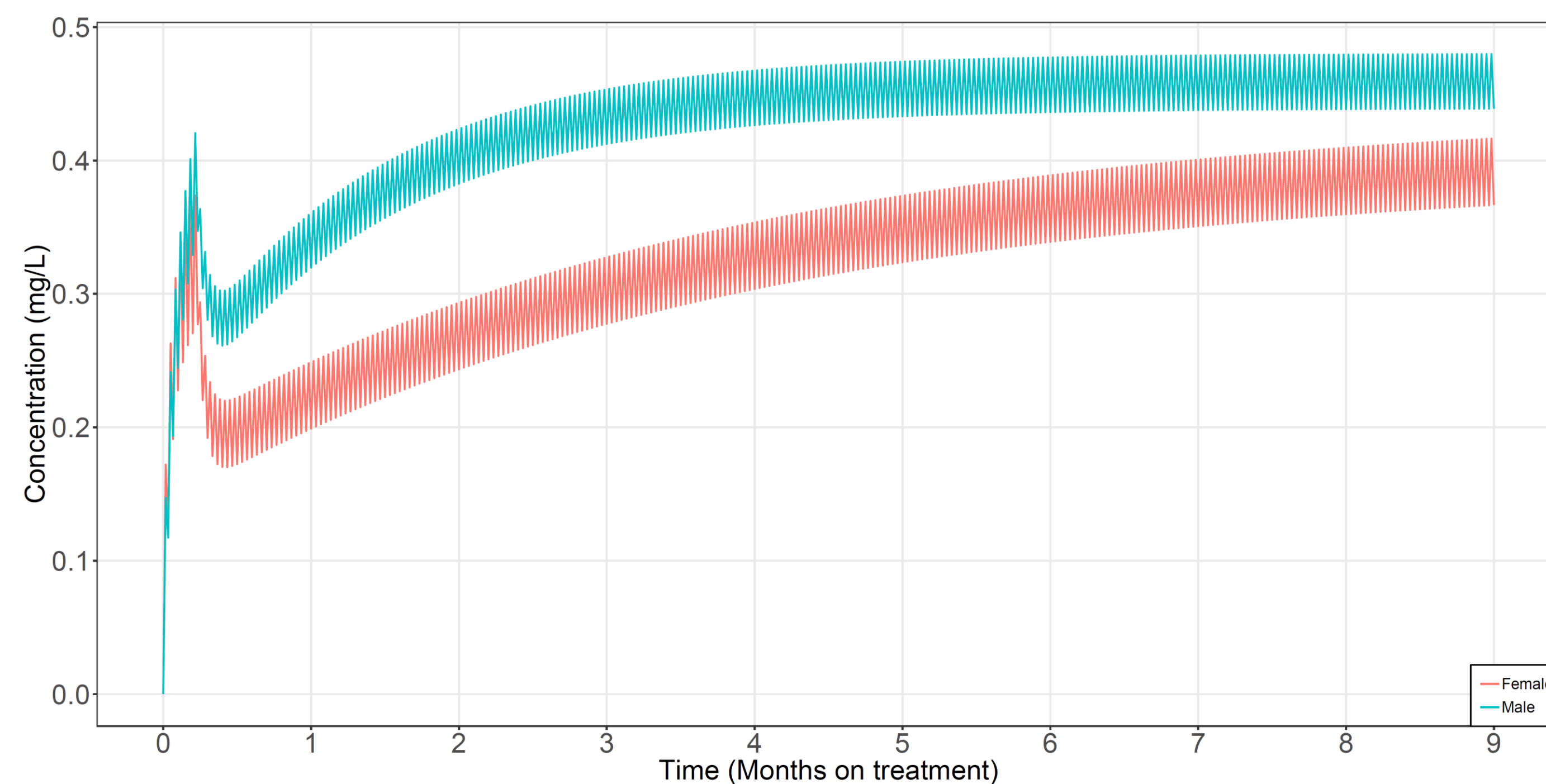


Figure 4: Simulated 200 mg QD loading 1 W + 100 mg QD 37 W maintenance dosing regimen

Conclusions

- Differences in exposure between **males vs females were ascribed to differences in body composition (WT/FFM/FAT)**: females had a higher proportion of body fat, thus a larger peripheral volume of distribution and a longer **terminal half-life**, thus prolonging the number of repeated daily doses necessary to achieve steady state.
- **Female patients in the study had lower concentrations** because at the time of sampling the drug accumulation was lower than in males
- Alternative dosing strategies including a loading phase (possibly depended on body size) are necessary to optimise clofazimine exposure.

References

1. Anderson, B. J., & Holford, N. H. (2008). Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*, 48, 303–332. <https://doi.org/10.1146/annurev.pharmtox.48.113006.094708>
2. Ganesan, S., Sunkara, G., Mcneely, D. & Hughes, D. *Identification of optimal dose and dosing regimen of clofazimine for the treatment of multi-drug resistant tuberculosis (MDR-TB) based on pharmacokinetic modeling*. Poster session presented at The Union World Health Conference on Lung Cancer (2015).