

Population Pharmacokinetic Modeling of Linezolid in Plasma and Cerebrospinal Fluid in Adults with Tuberculous Meningitis (LASER-TBM Study)

Noha Abdelgawad (1), Sean Wasserman (2, 3), Mahmoud T. Abdelwahab (1), Angharad Davis (2), Cari Stek (2), Lubbe Wiesner (1), Robert J. Wilkinson (2), Paolo Denti (1)

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Observatory 7925, South Africa

(2) Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa

(3) Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa

Background and Objectives

Tuberculous meningitis (TBM) is associated with severe outcomes, including mortality, despite therapy [1].

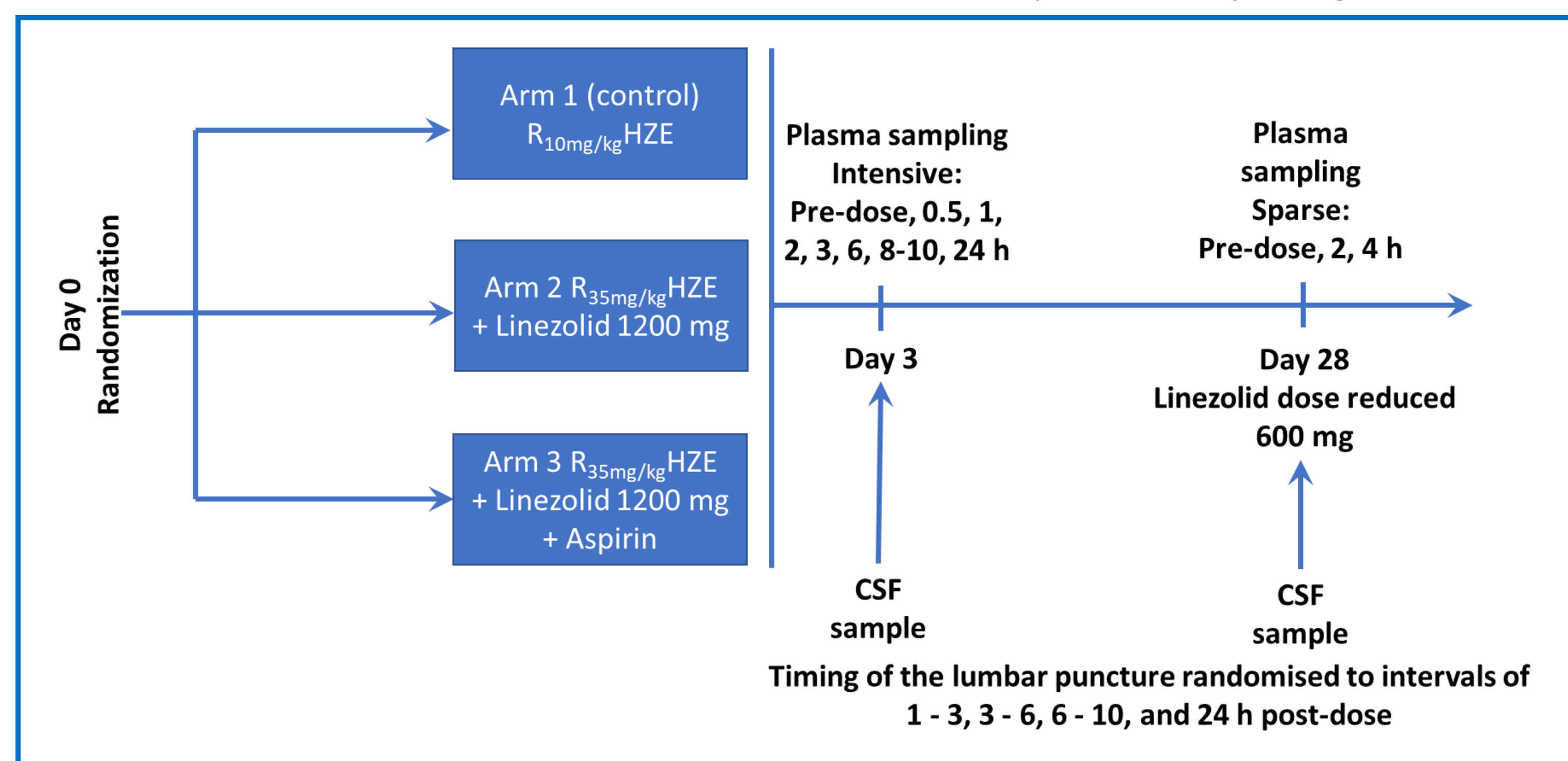
The standard treatment for TBM is similar to pulmonary TB and does not account for drug penetration in the brain. Linezolid-based regimens are being tested for TBM.

We described the linezolid plasma and CSF pharmacokinetics (PK) and investigated the impact of concomitant high-dose rifampicin.

Methods

LASER-TBM is Phase 2b trial to determine the safety of intensified anti-TBM therapy.

HIV+ adults with TBM enrolled from 4 South African hospitals, study design below



Missing heights were imputed with a multiple regression model based on weight and sex from a similar study [2].

The concentrations were modelled with nonlinear mixed-effects modelling in NONMEM® 7.5 using first-order conditional estimation with eta-epsilon interaction.

Results

30 participants received linezolid, providing 247 plasma concentrations and 28 CSF concentrations for the PK analysis.

Table 1: Baseline participants characteristics

N = 30	Median (Min – Max)
Age (years)	40 (27 - 56)
Sex (F/M)	12 (40%) / 18 (60%)
Weight (kg)	59 (30 - 96)
Height (m) ^a	1.61 (1.48 - 1.80)
Fat-free mass, FFM (kg) ^a	45 (30 - 59)
CSF protein (g/L)	1.46 (0.310 – 55.0)

^a Heights and FFM were available for 12/30 (40%) of participants

^b CSF protein was available for 17/30 (57%) of participants

The final plasma model (Figure 1) had transit compartment absorption, one compartment distribution and saturable clearance described by Michaelis-Menten. Clearance and volume were allometrically scaled by FFM.

CSF concentrations were modeled as a separate hypothetical effect compartment, the equilibration $t_{1/2}$ was 3.61 hours and on average the PPC was 38%.

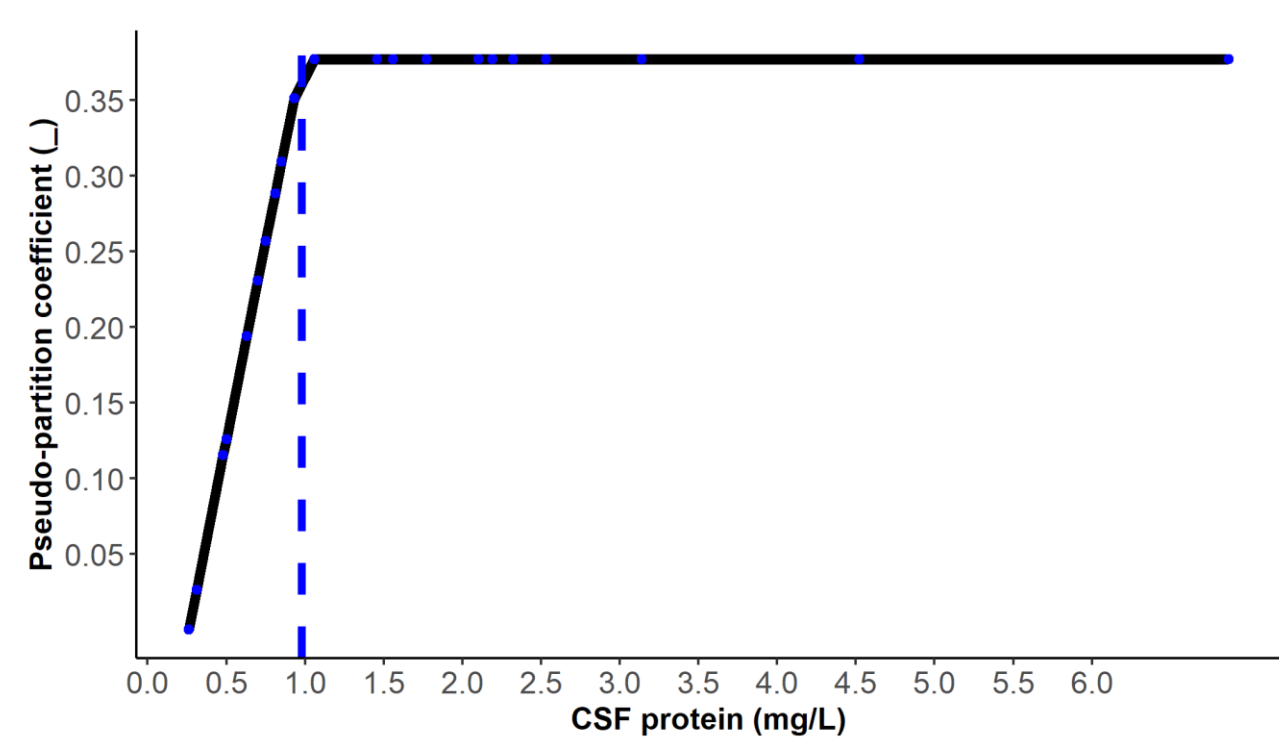
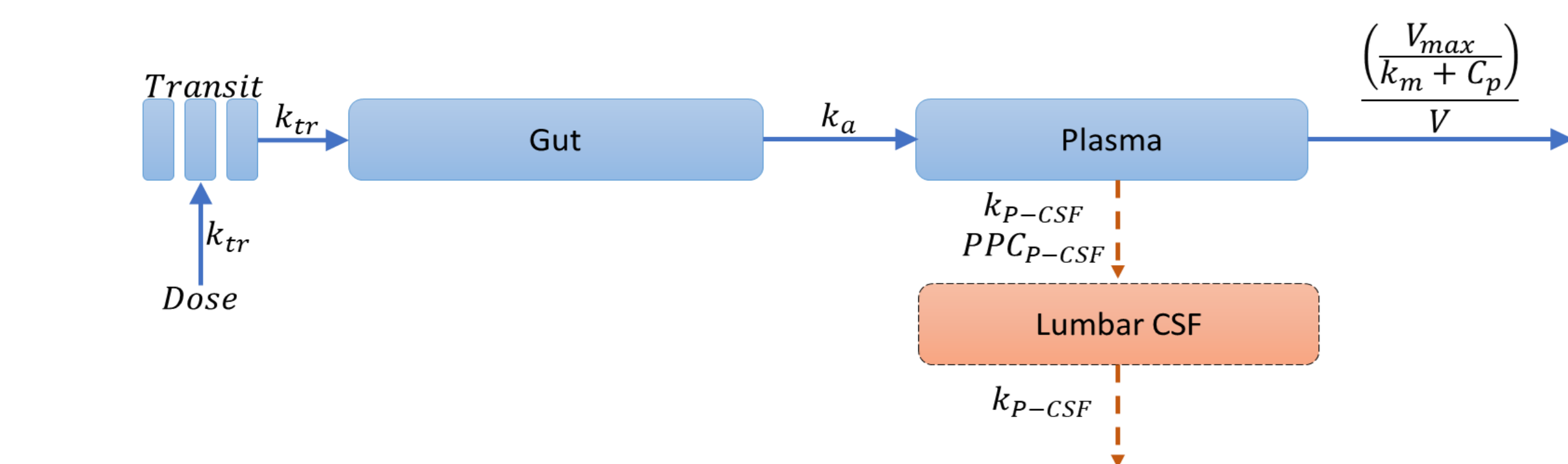


Fig. 2: Relationship between CSF protein and pseudo-partition coefficient (PPC)

For each 0.1 mg/mL unit increase in CSF protein, the PPC increases by 0.0512 until at a value of 0.979 mg/mL CSF protein, there is no increase in PPC with the increase in CSF protein.

Table 2: Parameter estimates

Parameter	Estimate	95% CI ^a
Plasma (Central) compartment parameters		
Saturable clearance, CL_{max} (L/h) ^b	6.82	(5.94 – 7.82)
Michaelis-Menten constant, k_m (mg/L)	33.3	(20.5 – 48.7)
Volume of distribution, V (L) ^b	41.5	(39.1 – 44.0)
Bioavailability, F (.)	1 Fixed	-
Absorption rate constant, k_a (h ⁻¹)	1.21	(0.894 – 1.70)
Mean transit time, MTT (h)	0.234	(0.132 – 0.339)
No. of transit compartments, NN (.)	4.27	(2.02 – 6.92)
Proportional error (%)	19.6	(17.7 – 22.7)
Additive error (mg/L) ^b	0.396	(0.195 – 0.574)
Between-subject variability in CLmax (%)	10.2	(6.32 – 13.0)
Between-visit variability in CLmax (%)	21.5	(16.7 – 26.8)
Between-occasion variability in k_a (%)	94.9	(71.3 – 119)
Between-occasion variability in MTT (%)	133	(96.0 – 169)
CSF (Effect) compartment parameters		
Equilibration rate constant, k_{P-CSF} (h ⁻¹) ^c	0.192	(0.0980 – 0.284)
Pseudo-partition coefficient, PPC (.)	0.377	(0.284 – 0.507)
CSF protein _{max PPC} (mg/mL)	0.979	(0.718 – 1.36)
CSF protein effect on PPC slope (mg/mL ⁻¹)	1.38	(0.799 – 2.08)
Proportional error, CSF (%)	85.8	(68.8 – 97.1)
Additive error (mg/L) ^d	0.02 Fixed	-

^a Values in parentheses are empirical 95% confidence intervals obtained from SIR.

^b The lower limit was fixed to 20% of the LLOQ

^c Equilibration half-life is 3.61 (2.44 – 7.07) hours

^d The estimate of the additive component of the error was not significantly different from its lower boundary of 20% of LLOQ, so it was fixed to this value.

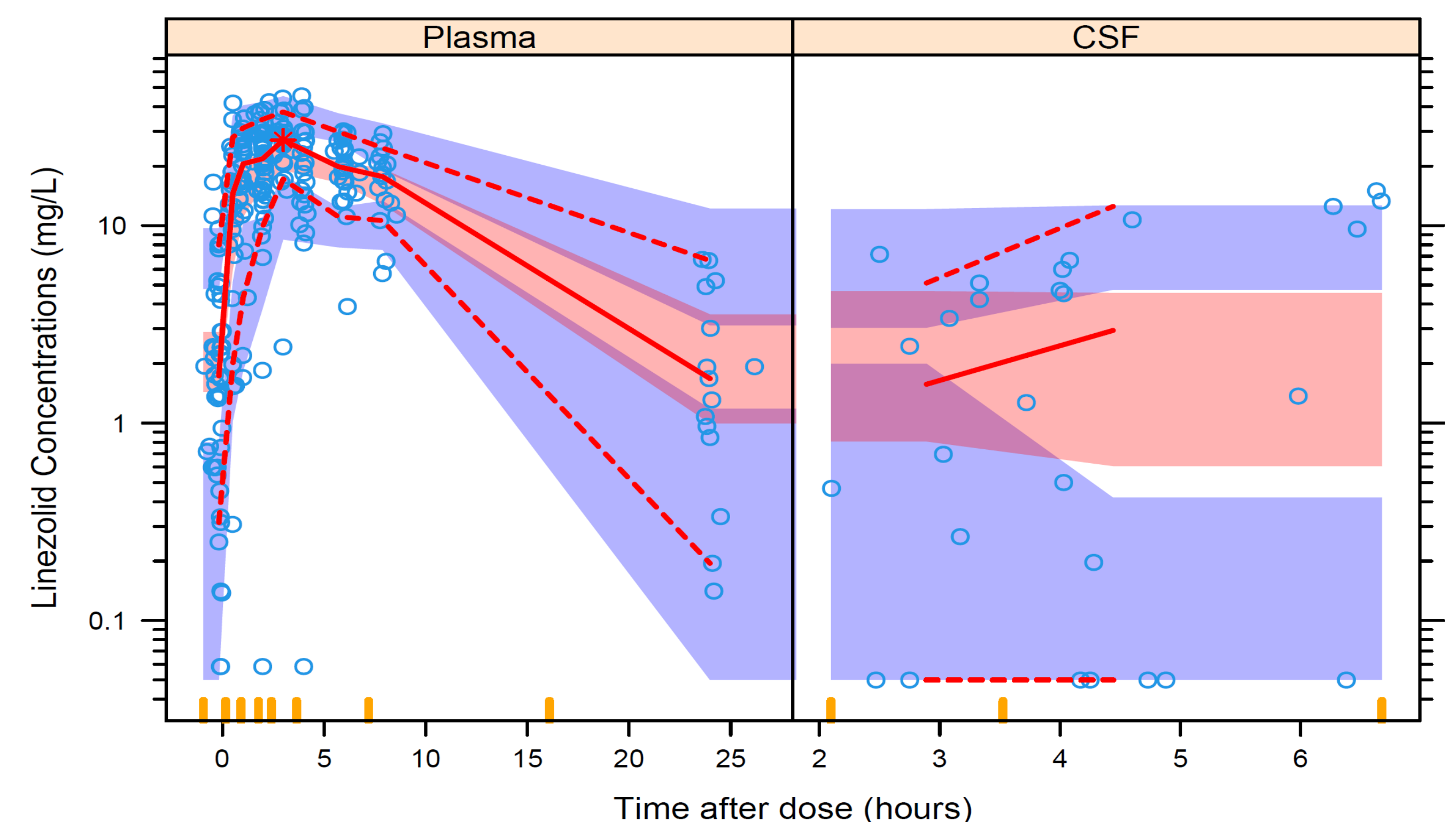


Fig. 3: Visual predictive check (n=1000) linezolid concentrations (mg/L) versus time after dose (h) stratified into plasma and CSF. The circles are the original observations; the solid line and the dashed lines are the median, 5th and 95th percentiles of the observed data; the shaded areas are the 95% confidence intervals of the same percentiles as simulated by the model.

Conclusions

Plasma PK of linezolid is in line with other populations with non-neurological TB [3,4] and CSF concentrations are comparable to those in neurosurgical patients. [5,6].

Linezolid PPC shows that CSF levels are on average 38% of the plasma levels, supporting ongoing clinical evaluation in efficacy trials for TBM. There is a positive correlation between CSF protein levels and the PPC.

Despite co-administration of high-dose rifampicin, linezolid levels were in line with previous reports, providing reassurance for combined use.

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