

Exploring dose-dependent pharmacokinetics of miltefosine in pediatric visceral leishmaniasis patients from East Africa

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BACKGROUND

Conventional 2.5 mg/kg/day dosing of miltefosine was recently shown to be less effective in pediatric VL patients compared to adults in Eastern Africa [1,2]

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An open-label clinical trial with increased mg/kg miltefosine dosing based on an allometric formula was conducted in pediatric VL patients in Uganda and Kenya

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Results of this trial unexpectedly indicated a lower than dose-proportional increase in AUC_{d0-28} and overall lower variability.

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AIM: Characterize nonlinearities in miltefosine pharmacokinetics

METHODS

Data were analyzed in a population approach using FOCE+I in NONMEM (version 7.3.0, Globomax, USA).

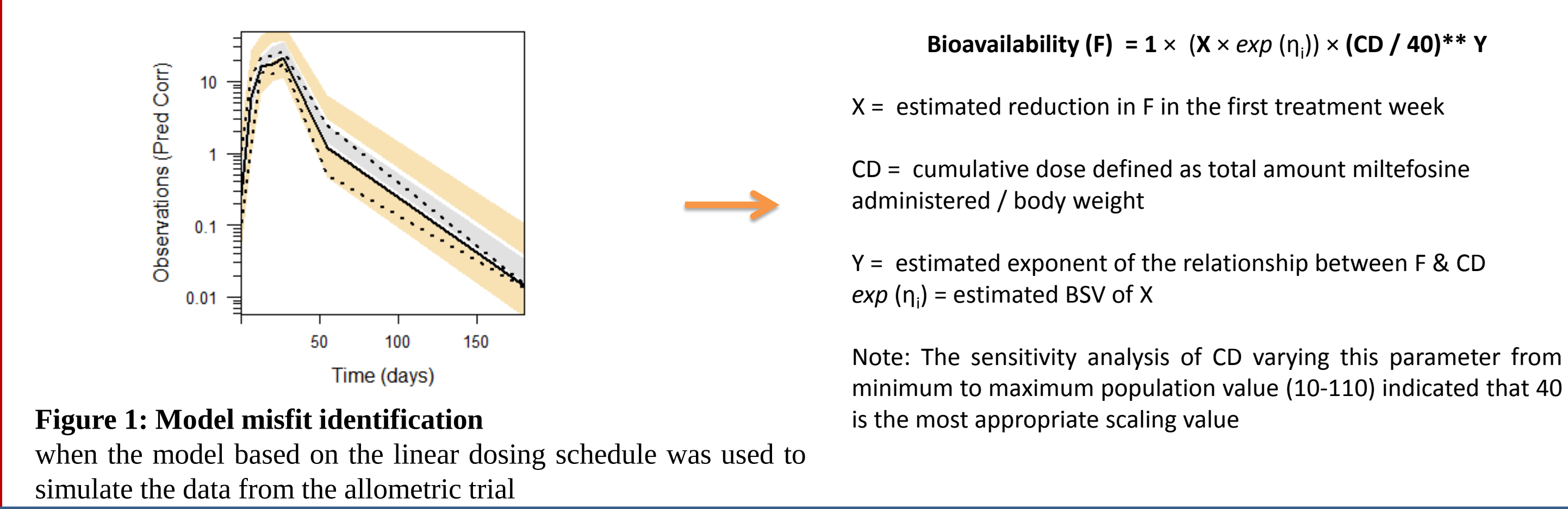
TRIAL 1 Linear dosing schedule
28-day treatment with miltefosine (2.5mg/kg/day)
7 patients from Kimalel (Kenya), 10 from Dooka (Sudan), and 4 from Kassab (Sudan)
PK samples: day 1, 7, 14, 28, 60, 210

TRIAL 2 Allometric dosing schedule [3]
28-day treatment with miltefosine (2.7 to 3.9 mg/kg/day)
21 patients from Kacheliba (Kenya) and 9 form Amudat (Uganda)
PK samples: day 1, 7, 14, 21, 28, 60, 210

PATIENTS

	Number of patients	Gender (% female)	Age (years) Median (range)	Body weight (kg) Median (range)	Height (m) Median (range)
1) Linear Dosing schedule	21	24%	10 (7- 12)	24 (16-34)	1.35 (1.07-1.53)
2) Allometric Dosing schedule	30	27 %	7 (4 - 12)	22 (13-30)	1.25 (0.99-1.45)

RESULTS: PHARMACOKINETIC MODEL



DOSE EFFECT ON MILTEFOSINE BIOAVAILABILITY

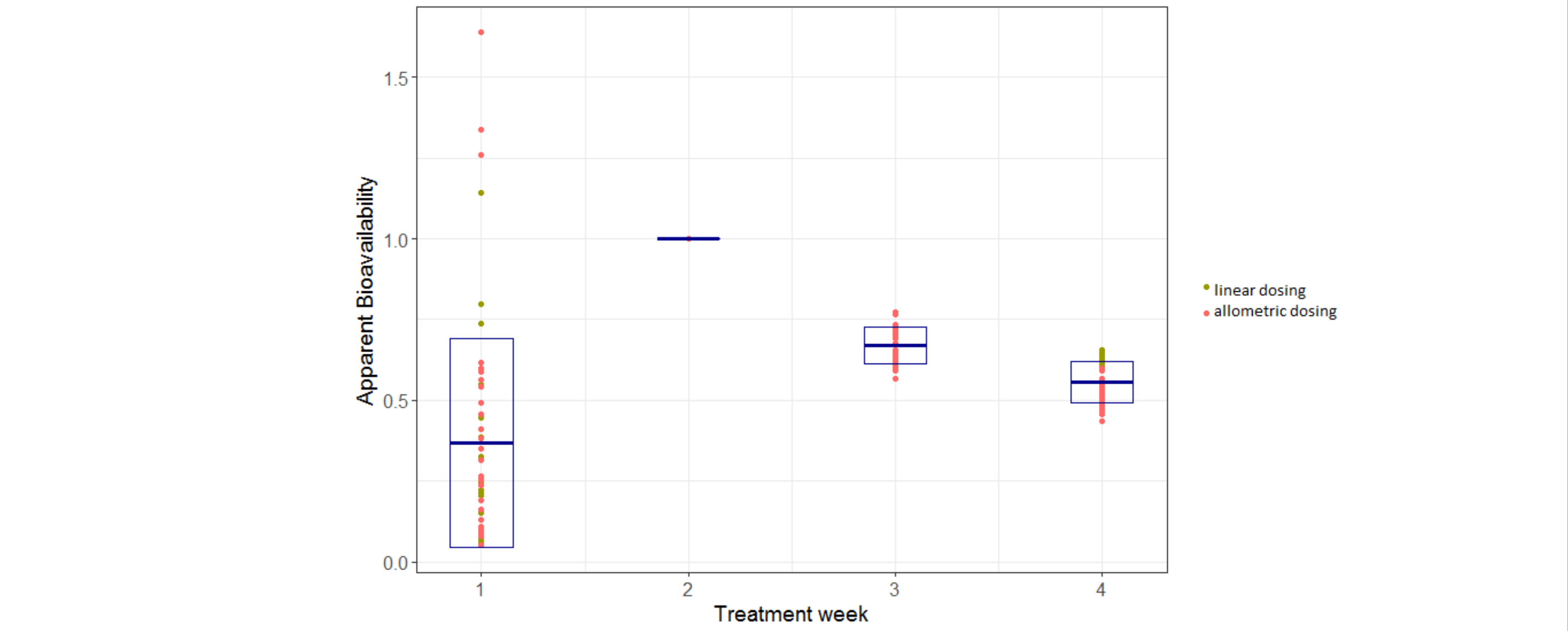


Figure 2: Miltefosine apparent bioavailability (F) over time: two nonlinearities described 1) a decrease in F at the start (ΔOFV -223.9), most likely due to patient initial malnourishment and malabsorption and 2) an effect of the cumulative dose on F in the later phase of treatment (ΔOFV -22)

REFERENCES

[1] T. P. C. Dorlo *et al.*, “Visceral leishmaniasis relapse hazard is linked to reduced miltefosine exposure in patients from Eastern Africa: a population pharmacokinetic/pharmacodynamic study,” *J. Antimicrob. Chemother.* 2017; 72(11):3131–3140.
[2] M. Wasunna *et al.*, “Efficacy and Safety of AmBisome in Combination with Sodium Stibogluconate or Miltefosine and Miltefosine Monotherapy for African Visceral Leishmaniasis: Phase II Randomized Trial,” *PLoS Negl. Trop. Dis.* 2016;10(9):e0004880.
[3] T.P.C. Dorlo *et al.* “Optimal Dosing of Miltefosine in Children and Adults with Visceral Leishmaniasis” *AAC* 2012; 56 7 3864-3872

PARAMETER ESTIMATES

Parameter (unit)	Model Estimated Value (RSE%) [Shrinkage%]	Bootstrap estimates ^a median [CI 5- 95%]
Fixed Effects		
Cl/F (L/day)	2.19 (5%)	2.19 (1.97 – 2.19)
V2/F (L)	21.1 (4%)	20.9 (19.1 -22.95)
KA (/day)	1.64 (19%)	1.64 (1.00 – 2.28)
Q/F (L/day)	0.0211 (9%)	0.0211 (0.016 – 0.025)
V3/F (L)	2.07 (6%)	2.07 (1.81 – 2.33)
F	1 fixed	1 fixed
Decrease F at the treatment start	-0.722 (6%)	-0.721 (-0.816 - -0.627)
Exponent of the CD effect on F	-0.861 (14%)	-0.847 (-1.101 - -0.621)
^b Proportional difference in BSV on Cl	0.25 (48%)	0.28 (0.048 – 0.45)
Inter-individual variability (%)		
Cl	19.5 (16%) [28%]	19.3 (11.4 – 25.1)
Decrease F at the treatment start	86.4 (9%) [2%]	85.3 (21.7 – 101)
Residual Unexplained Variability (%)		
Proportional error	37 (11%) [9%]	36.5 (10.3 – 40.1)

Cl: clearance, V2: volume of distribution in the central compartment, V3: volume of distribution in the peripheral compartment, KA: absorption rate, Q: inter-compartmental clearance, CD: cumulative dose
^a Obtained from 684 bootstrap runs
^b Model estimated proportional difference in BSV in Cl of allometric to linear dosing schedule.

- Allometric dosing in comparison to linear dosing schedule resulted in less variability in Cl among patients
- Linear dosing median AUC_{d0-28} = 315 µg*mL/day (range 248.1-466.4)
- Allometric dosing median AUC_{d0-28} = 363.4 µg*mL/day (range 214.8 – 633.8)

GOODNESS OF FIT

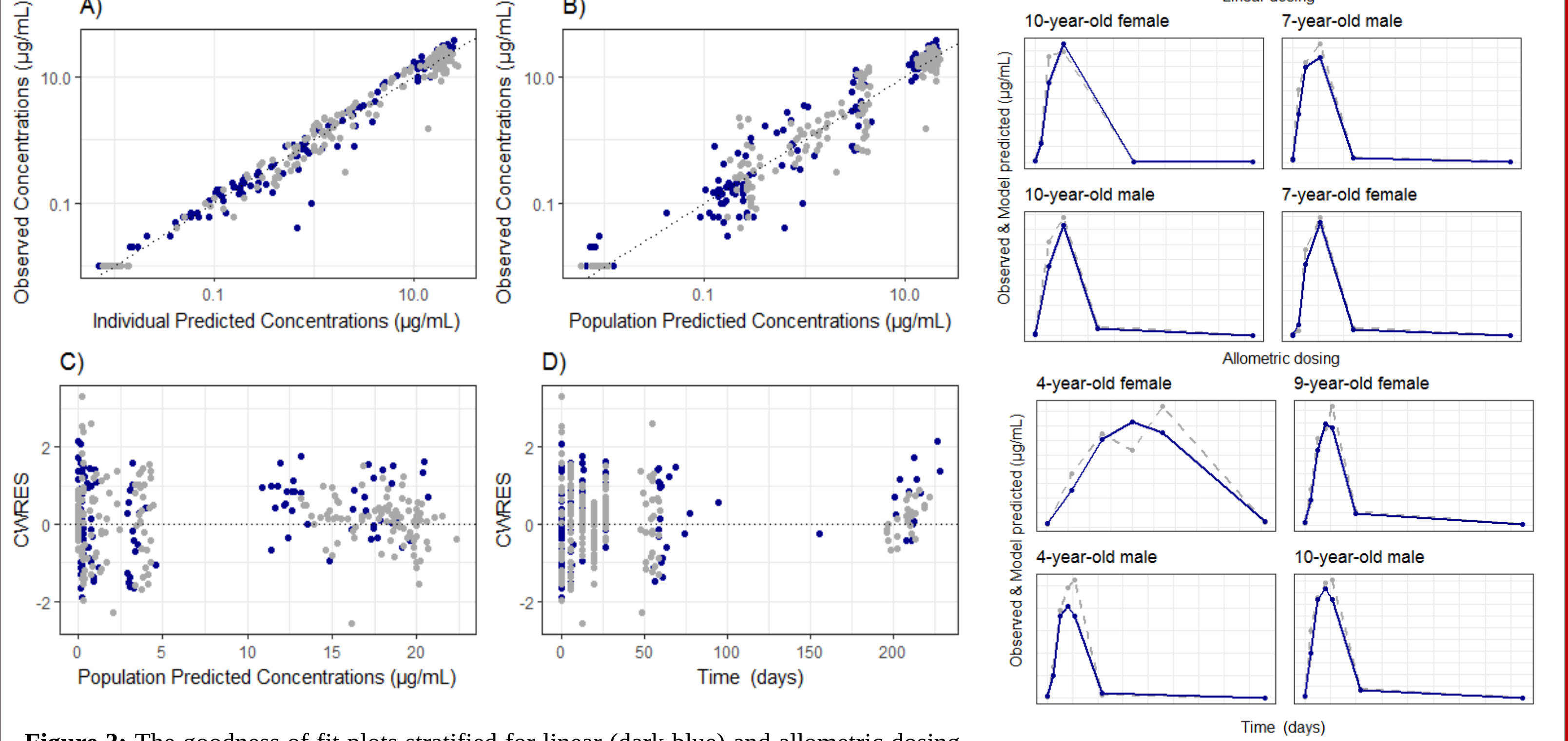


Figure 3: The goodness of fit plots stratified for linear (dark blue) and allometric dosing (grey) A) observed versus individually predicted concentrations, B) observed versus population predicted concentrations, C) conditional weighted residuals versus population predicted concentrations and D) conditional weighted residuals over time

Figure 4: Observed (dashed line) and model predicted (solid line) individual patient PK curves for both trials, representing both sexes and age groups

VISUAL PREDICTIVE CHECK: TRIAL STRATIFIED

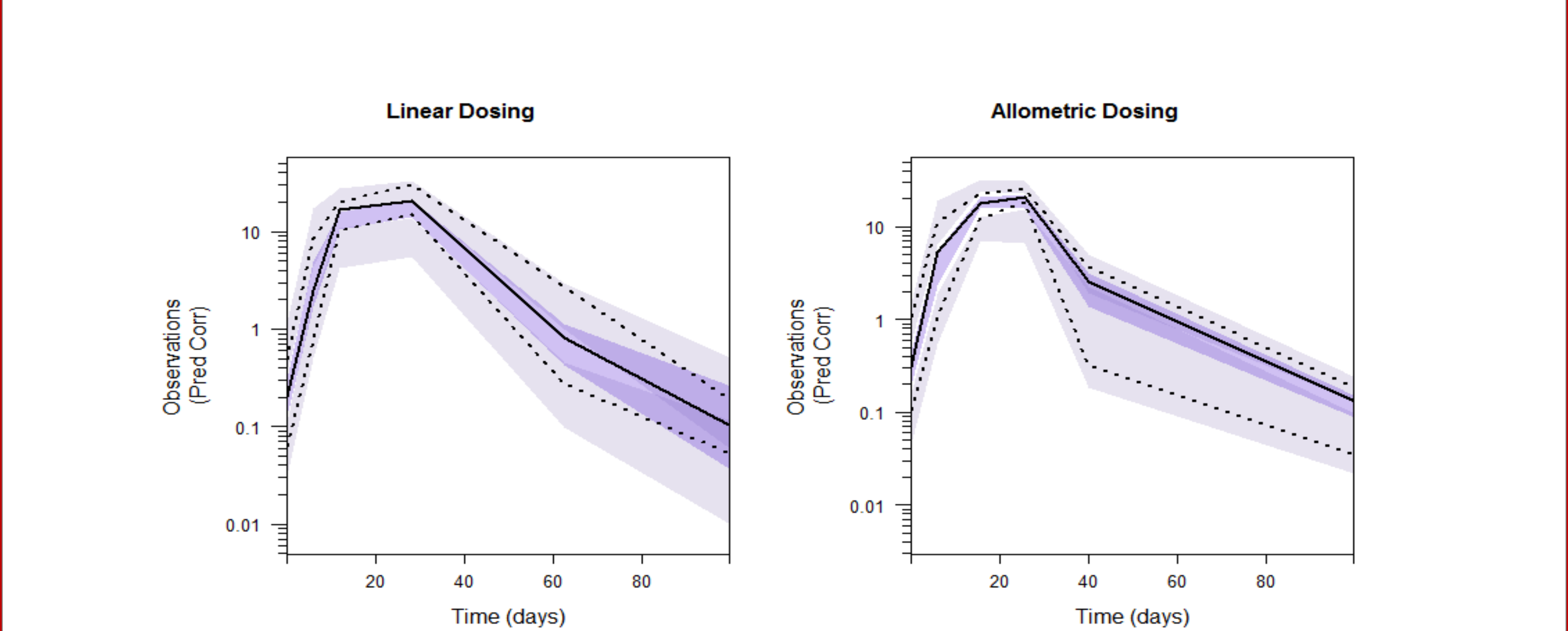


Figure 5: Visual predictive checks (VPC) based on five hundred simulations

CONCLUSIONS

- Miltefosine bioavailability appears to be dose-dependent: increasing the dose does not proportionally increase the total AUC (possibly due to slow accumulation of miltefosine in the gastrointestinal membrane cells and subsequent dose-dependent saturation of paracellular transport, corroborated by the extremely slow absorption rate of miltefosine)
- Nevertheless, allometric dosing in the treatment of pediatric VL resulted in
 - doubled median AUC in the first treatment week
 - less variability in patient PK profiles, characterized by lower BSV on CL.