



Sample size estimates for a clinical trial evaluating allometric dosing of miltefosine in children with visceral leishmaniasis in East Africa

Thomas P.C. Dorlo¹, Fabiana Alves², Elin M. Svensson³, Jan H.M. Schellens^{1,4}, Alwin D.R. Huitema⁴

¹ Utrecht University, Utrecht, The Netherlands, ² Drugs for Neglected Diseases initiative, Geneva, Switzerland, ³ Uppsala University, Uppsala, Sweden,

⁴ Netherlands Cancer Institute, Amsterdam, The Netherlands

✉ t.p.c.dorlo@uu.nl

Background

Visceral leishmaniasis (VL) is a fatal neglected tropical parasitic disease and miltefosine is the only oral drug available to treat it. Recent reports indicated increased miltefosine **treatment failure rates** on the Indian subcontinent [1,2]. The only identified risk factor for treatment failure was to have an age <12 years [1]. Treatment failure was most significantly associated with **Time>EC₉₀** [3]. Previously, we have shown extensively that **children were underexposed** to the drug when treated with the conventional miltefosine dosing regimen (2.5 mg/kg for 28 days) [1,3,4]. We therefore developed and published an **allometric dosing algorithm** resulting (theoretically) in a similar miltefosine exposure in children as in adults [3]. A **new exploratory pediatric clinical trial in East African VL patients** is being designed to evaluate the safety and PK of this new dosing algorithm.

Aim

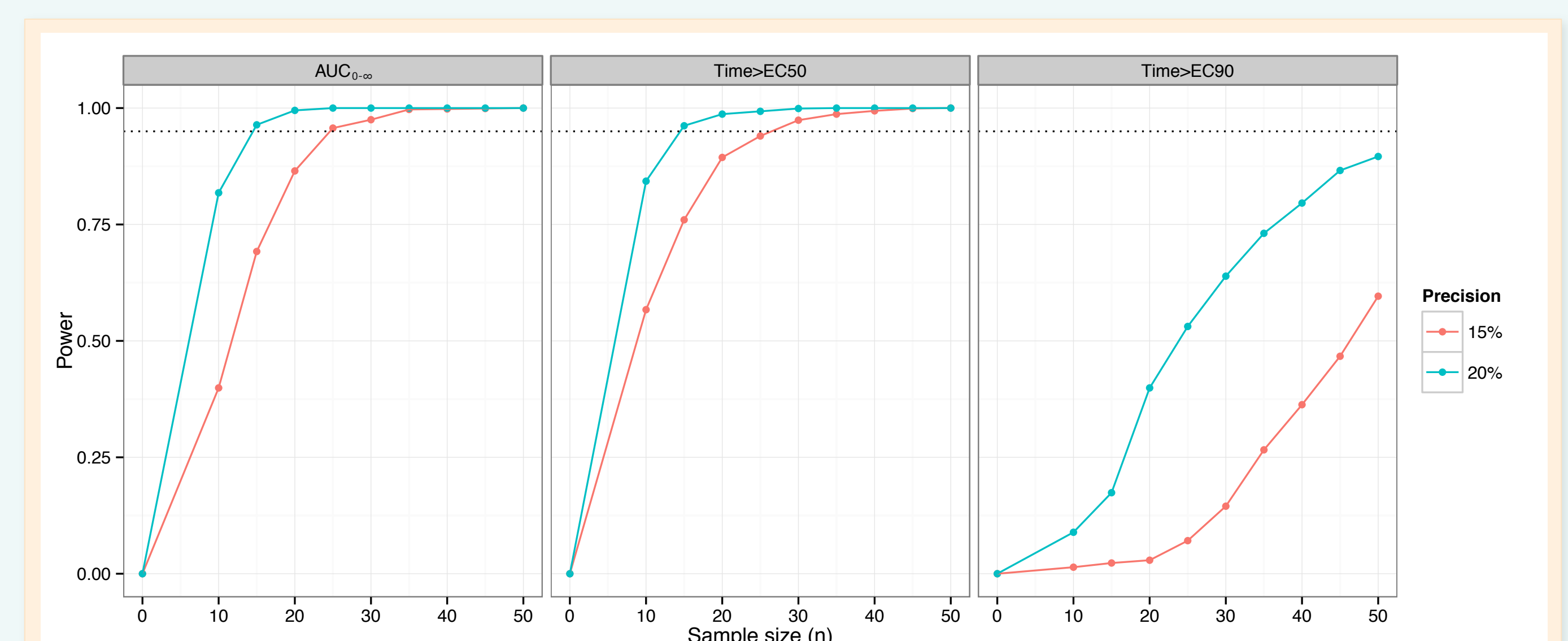
To provide estimates of a minimal sample size for a proposed clinical trial evaluating allometric dosing of miltefosine in children with VL in East Africa, yielding sufficient power for evaluation of clinically relevant PK parameters.

Methods

Anthropometric data from **East African VL patients from Sudan and Kenya** were obtained from a previous clinical trial; total n=972 of whom n=454 pediatric (4-12 years). Miltefosine PK data for the targeted age group (4-12 years) were not available and concentration-time curves for the allometric dosing regimen (28 days) were therefore simulated using a well-established 2-compartment population PK model for miltefosine [3,4,5] and NONMEM 7.3. Secondary PK parameters (e.g. **AUC**, **Time>EC₅₀**, **Time>EC₉₀**) were derived. The **Monte Carlo confidence interval approach** was used to evaluate achieved power for various sample sizes [6]. Clinical trials (n=1000) were simulated with a random sample of pediatric patients (n=10, 15, 20,...50) drawn from the anthropometric database available. The **power** to estimate the confidence intervals (95%CI) of the mean secondary PK parameters in the simulated clinical trials within precision intervals of 15% (85-118%) or 20% (80-125%) of the expected mean in the target population was assessed.

Anthropometric data

Parameter	Median (range)
No. of pediatric patients	454
Age (yrs)	8 (4 – 12)
Body weight (kg)	20 (10 – 40)
Height (m)	1.24 (0.89 – 1.69)
Body Mass Index (kg/m ²)	13.2 (8.53 – 31.0)
Fat-free mass (kg)	17.7 (7.86 – 36.7)
Countries of origin	Sudan and Kenya



Power plotted against sample size with 15% and 20% precision for the secondary PK parameters AUC₀₋₂₈, Time>EC₅₀ and Time>EC₉₀. The dotted line indicates 0.95 power.

Results

For AUC, the sample size minimally required to estimate the **95%CI** within a **15% precision level** with a **power of 0.95** was **25**. For Time>EC₅₀ and similar assumptions this was also 25. For Time>EC₉₀ the sample size required to estimate 95%CI within a 20% precision level (power of 0.95) was >50. With a sample size of 25 the power to estimate the Time>EC₉₀ 95%CI within a 20% precision level was 0.53.

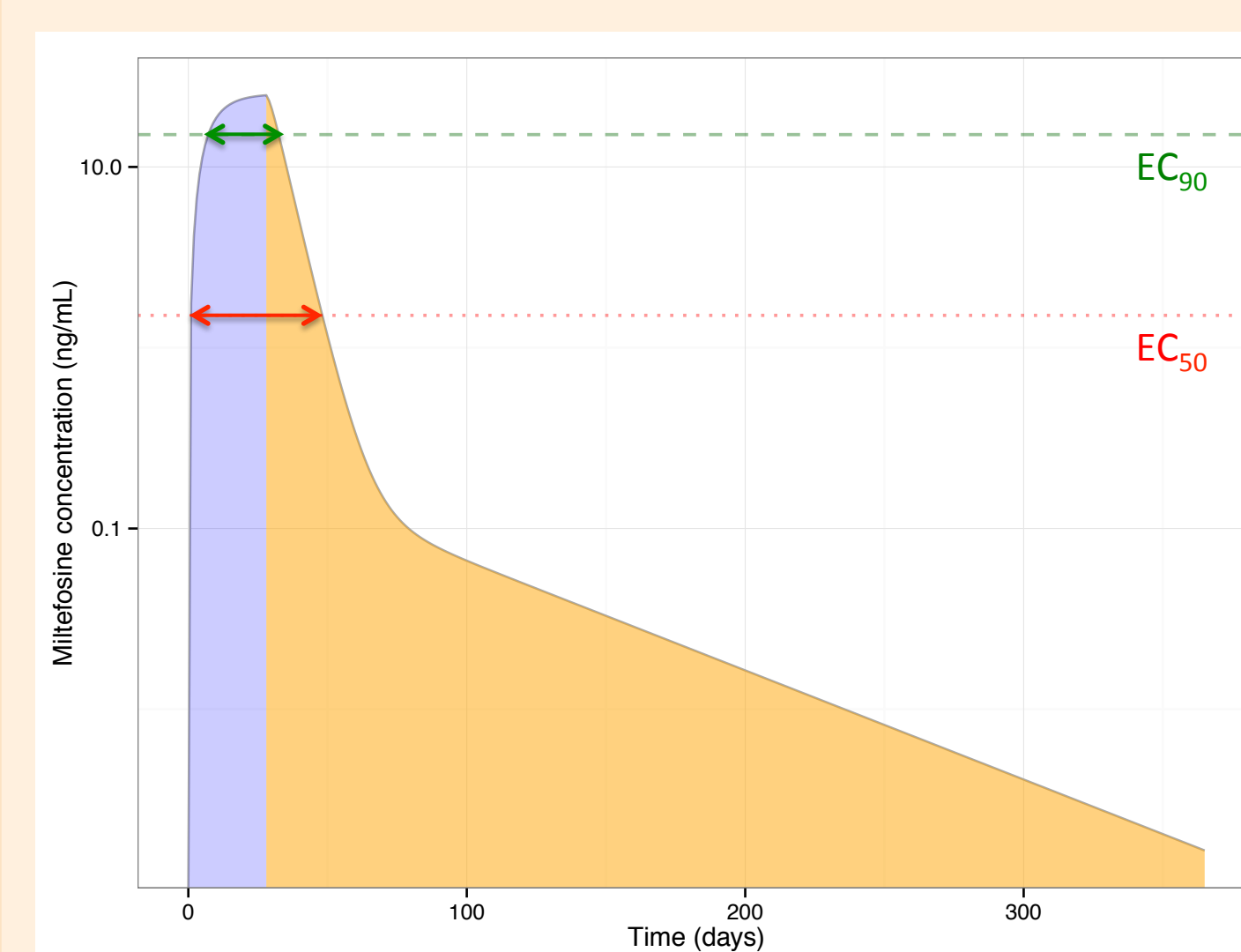
Conclusion

Application of the Monte Carlo confidence interval approach yielded rational and pragmatic estimates of minimally required sample sizes to assess pediatric miltefosine exposure using a novel dosing algorithm and enabled optimization of a planned pediatric population PK trial of miltefosine for VL in East Africa.

PopPK model parameters

Parameter	Estimate	Between-subject variability
Absorption rate (/hr)	0.344	87%
Clearance/F (L/day)	4.85	21.6% ^a
Q/F (L/day)	0.0411	NE
Central volume/F (L)	50.5	11.4% ^a
Peripheral volume/F (L)	2.9	NE

^a BSV of CL and V_c were correlated by 77%. CLs and Vs normalized to a standard FFM of 53 kg.



Typical miltefosine PK curve

A typical miltefosine PK curve for **28 days allometric dosing** (60 mg/day) in a pediatric patient (BW 20 kg). The **blue** area shows the continuous accumulation during treatment, the **orange** area the total AUC. The **EC₅₀/EC₉₀** values used here were obtained from intracellular drug susceptibility tests of East African *Leishmania* isolates. **Time>EC₅₀/Time>EC₉₀** (indicated by the arrows) was model-derived. Not all patients achieve a plasma concentration over EC₉₀ due to BSV and rounding of the dose.

References

1. Sundar et al. Clin Infect Dis. 2012; 55:543-50
2. Rijal et al. Clin Infect Dis. 2013; 56:1530-8
3. Dorlo et al. J Infect Dis. 2014; in press
4. Dorlo et al. Antimicrob Agents Chemother. 2012; 56: 3864-72
5. Dorlo et al. Antimicrob Agents Chemother. 2008; 52:2855-60
6. Ogungbenro et al. Eur J Clin Pharmacol. 2008; 64:705-14