

A population pharmacokinetic model for ethionamide in South African children; impact on dosing regimen

Henrik Bjugård Nyberg¹, Heather R. Draper², Anthony J. Garcia-Prats²,
Stephanie Thee³, Andrew C. Hooker¹, H. Simon Schaaf², Helen McIlleron⁴,
Anneke C. Hesselning², Paolo Denti⁴

¹ Department of Pharmaceutical Biosciences, Uppsala University, Sweden

² Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, South Africa

³ Department of Pediatrics, Charité University Medicine, Berlin, Germany

⁴ Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa

Background and objective

Ethionamide is used both in first-line and second-line treatment of tuberculosis, including in disseminated tuberculosis and tuberculous meningitis due to its good penetration in cerebrospinal fluid [1]. The current understanding of ethionamide's pharmacokinetics (PK) is limited, especially in children.

The aim of this study was to develop a pediatric population PK model for ethionamide, and suggest an improved dosing over different weight bands.

Methods

- Population pharmacokinetics modelling in NONMEM 7.4
- AUC scaled to model prediction of 750 mg dose in adults 50-70 kg
- Simulation for dose adjustment in weight bands to match target AUC

Study population	
Covariate	Median (range) or count
N	110 + 9 from two studies [3,4]
Age (years)	2.6 (0.25 – 15)
Weight	12.5 (2.5 – 66)
Dose (mg/kg daily)	20 (10 – 25)
Administration	Naso-gastric tube: 82 Oral: 37
HIV ⁺	24 (22 on ART)
Rifampicin	21

Table 1. Characteristics of the study population

Results - Modelling

- One compartment
- Transit absorption [8]
- First order elimination
- Allometric scaling of CL and V
- M6 method for below limit of quantification observations [7]
- HIV co-infection → Lower bioavailability
- Rifampicin co-administration → Higher CL
- Maturation of CL
- Maturation of absorption:
 $K_A = TVK_A * Scale * (1 + e^{-age})$
 $MTT = TVMTT / (Scale * (1 + e^{-age}))$
- NGT → Faster absorption, lower mean transit time (MTT)

Parameter	Estimate (RSE%)	IIV / IOV* CV% (RSE%)
CL	8.88 l/h (4%)	17% (22%)
V	21.4 l (3%)	
CL with RIF	+0.16 (34%)	
PMage ₅₀ (CL)	10.5 months PMA (10%)	
Y _{mat} (CL)	2.6 (30%)	
BIO	100% FIX	25% (17%) *
BIO with HIV	-0.22 (19%)	
MTT Oral	1.07 h (5%)	97% (5%) *
MTT NGT	-0.68 (6%)	
N	2.31 (20%)	
K _A	0.87 (6%)	36% (28%) *
Scale _{Abs.mat.}	1.43 (2%)	
Add error	0.0138 (6%)	
Prop error	0.172 (5%)	

Table 2. Estimates for typical values, Inter-individual (IIV), and inter-occasional variability (IOV) for the ethionamide population PK model. For CL and V, the values refer to a typical 13 kg BW subject.

Results - VPCs

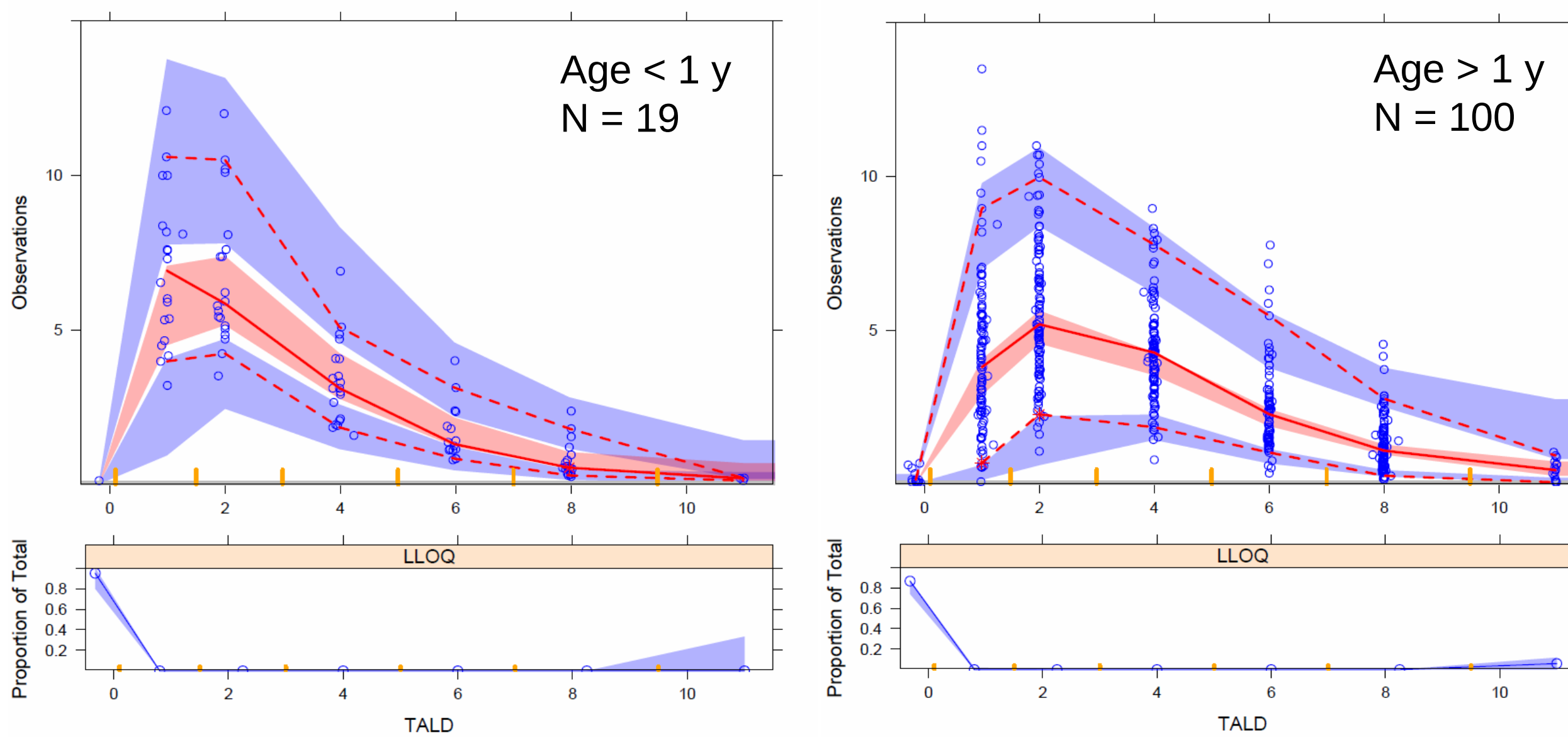


Figure 1. Visual predictive check for subjects under (left) and over (right) one year old.

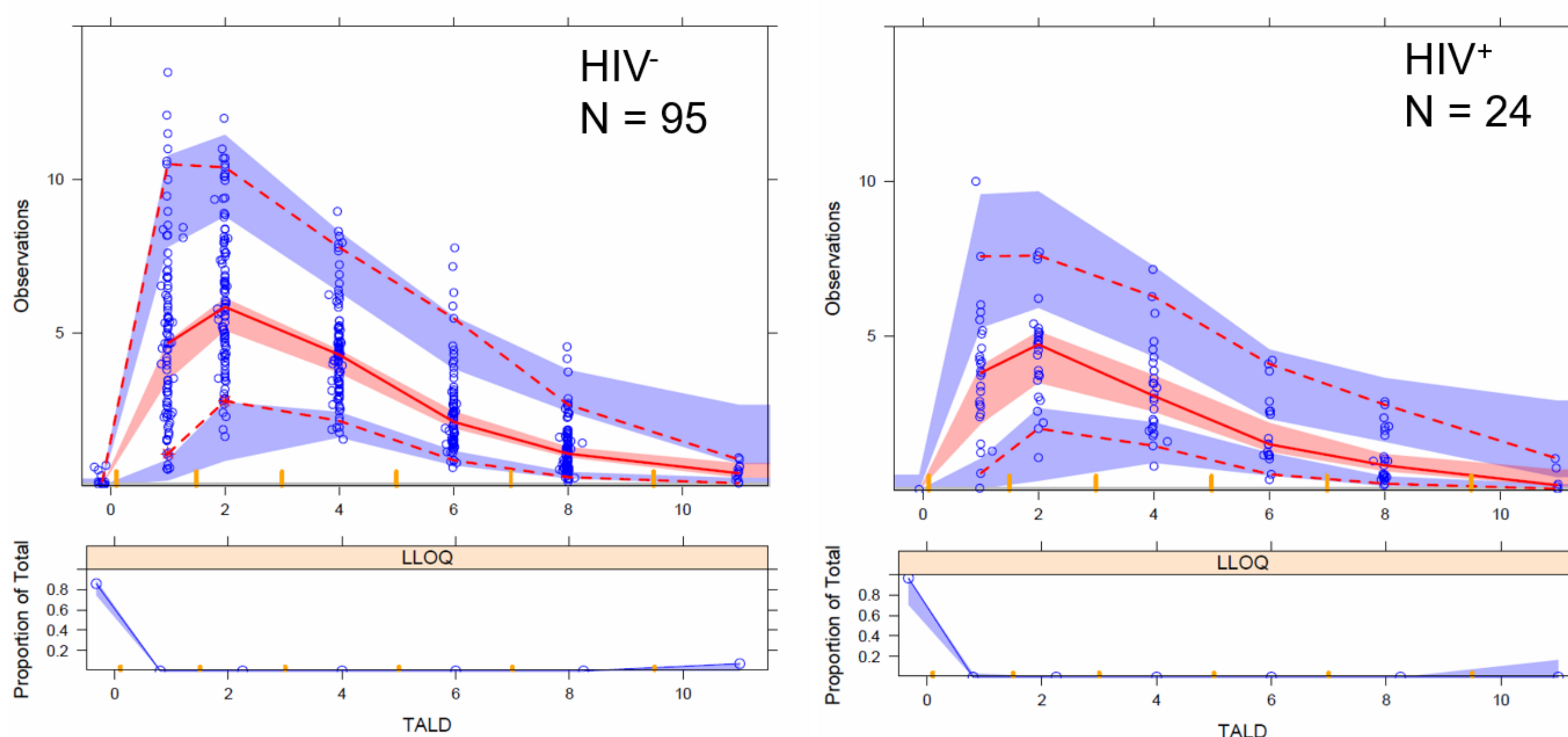


Figure 2. Visual predictive check for HIV negative (left) and HIV positive (right) subjects.

Results - Adjusted dosing

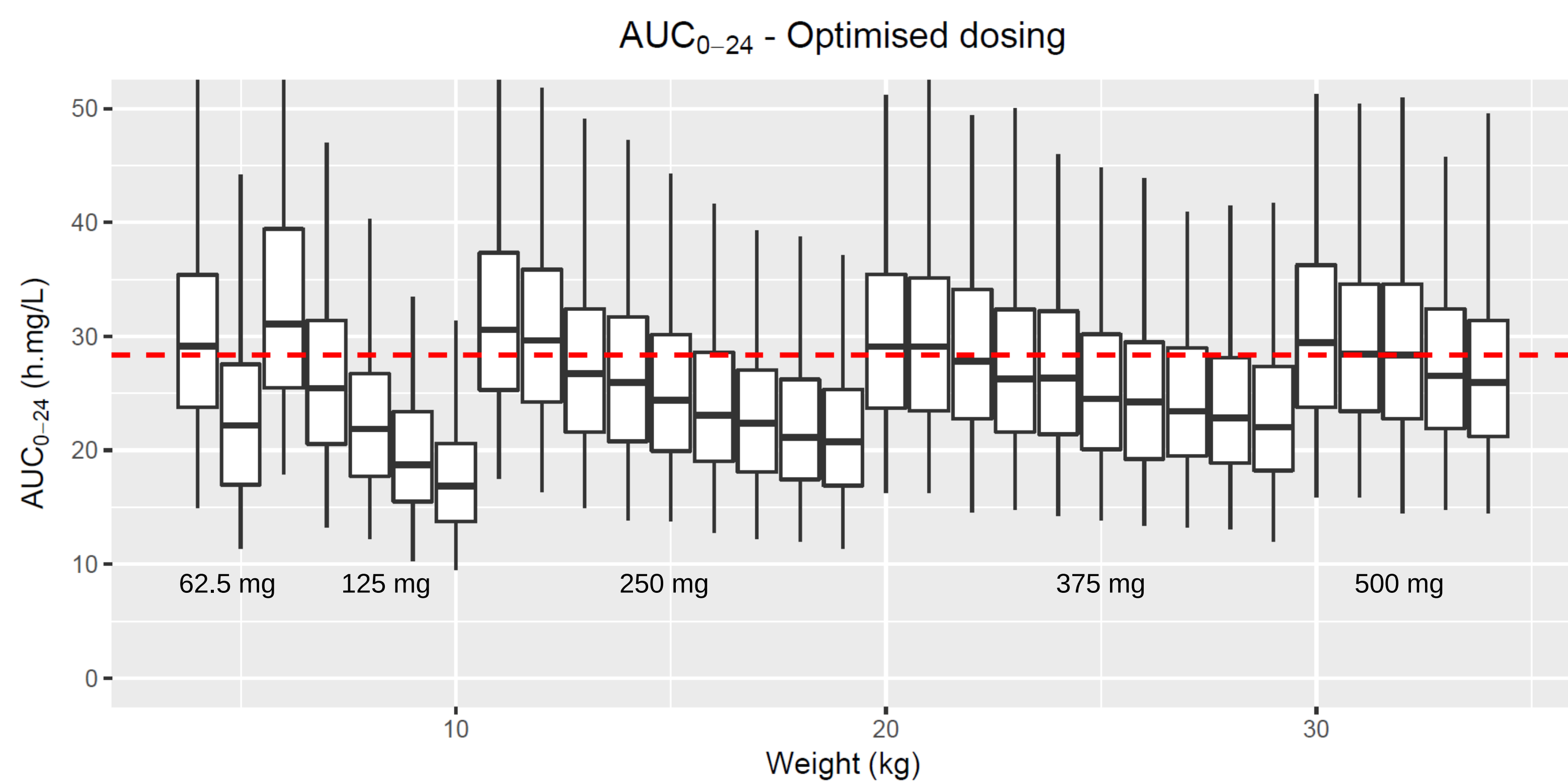


Figure 3. Exposures in different weight bands after suggested dose adjustment. Dashed line is projected adult AUC of 28.4 h*mg/L after 750mg dose.

Conclusions

We propose a model that successfully describes ethionamide pharmacokinetics in children.

With higher ethionamide doses for children in the 8 - 20 kg bodyweight range, and lower doses for children below 5 kg, drug-exposure comparable to adults following a standard oral dose are achieved.

Acknowledgements

We would like to acknowledge the staff and patients who participated in the two studies.

This work received funding from NRF/STINT grant number 101575.

References

- [1] Falzon, D. et al, WHO guidelines for the programmatic management of drug resistant tuberculosis: 2016 update, Eur. Respir. J., 2017, 49(3): 1602308.
- [2] Vale, N., Gomes, P., Santos, H.A, Metabolism of the Antituberculosis Drug Ethionamide, Current Drug Metabolism, 2013, 14, 151-158.
- [3] Denti, P. et al, Levofloxacin Population Pharmacokinetics in South African Children Treated for Multidrug-Resistant Tuberculosis, Antimicrob Agents Chemother. 2018, 62(2).
- [4] Bekker, A. et al, Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO-Recommended Treatment Guidelines, Antimicrob Agents Chemother. 2016, 60(4).
- [5] Beal S., Sheiner L.B., Boeckmann A., & Bauer R.J., NONMEM User's Guides. (1989-2017), Icon Development Solutions, Ellicott City, MD, USA, 2017.
- [6] Keizer, R.J., Karlsson, M.O., Hooker, A., Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol 2013, 2: e50. <http://psn.sourceforge.net/>
- [7] Beal S.L., Ways to fit a PK model with some data below the quantification limit, Journal of pharmacokinetics and pharmacodynamics, vol. 28, 2001, pp. 481-504.
- [8] Savic, R.M., Jonker, D.M., Kerbusch T., and Karlsson, M.O., Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies, Journal of pharmacokinetics and pharmacodynamics, vol. 34, 2007, pp. 711-26.