POPULATION PHARMACOKINETIC ANALYSIS OF LAMIVUDINE IN CHILDREN AGED 5 MONTHS – 18 YEARS

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Background and Objectives

- **Lamivudine is widely used for the treatment of HIV-infected children.**
- **The aim of this analysis is to describe population pharmacokinetics of lamivudine in HIV-infected children and to evaluate $AUC_{0\text{-}24h}$ in HIV-infected children.**

Methods

- **Data was available for 180 children (Table 1).**
- **The model was built in NM 7.3 using two internal datasets and validated with two external datasets (Table 1).**
- **Different absorption models and covariates (bodyweight, height, age) were investigated.**
- **$AUC_{0\text{-}24h}$ was calculated upon each dosing record in the dataset.**

Discussion and Conclusion

- **This is one of the largest population pharmacokinetic analyses of lamivudine performed in children covering a wide age range.**
- **The external validation confirmed the predictive ability of the model.**
- **Especially for children with a bodyweight <15 kg, doses may need reconsideration if a target $AUC_{0\text{-}24h}$ of 8.9 mg·h/L is aimed for.**
- **Because bioavailability may differ between adults and children[6], intravenous data is warranted in order to distinguish between influence of age-dependent changes on bioavailability, clearance and/or volume of distribution.**

Results

- **A two-compartment model with sequential zero order and first order absorption was identified.**
- **Bodyweight (BW) was identified as covariate on both Cl/F and V_2/F (Table 2).**
- **Evaluation of $AUC_{0\text{-}24h}$ showed that currently used doses lead to below target AUC (8.9 mg·h/L in adults) in a large part of children <15 kg.**

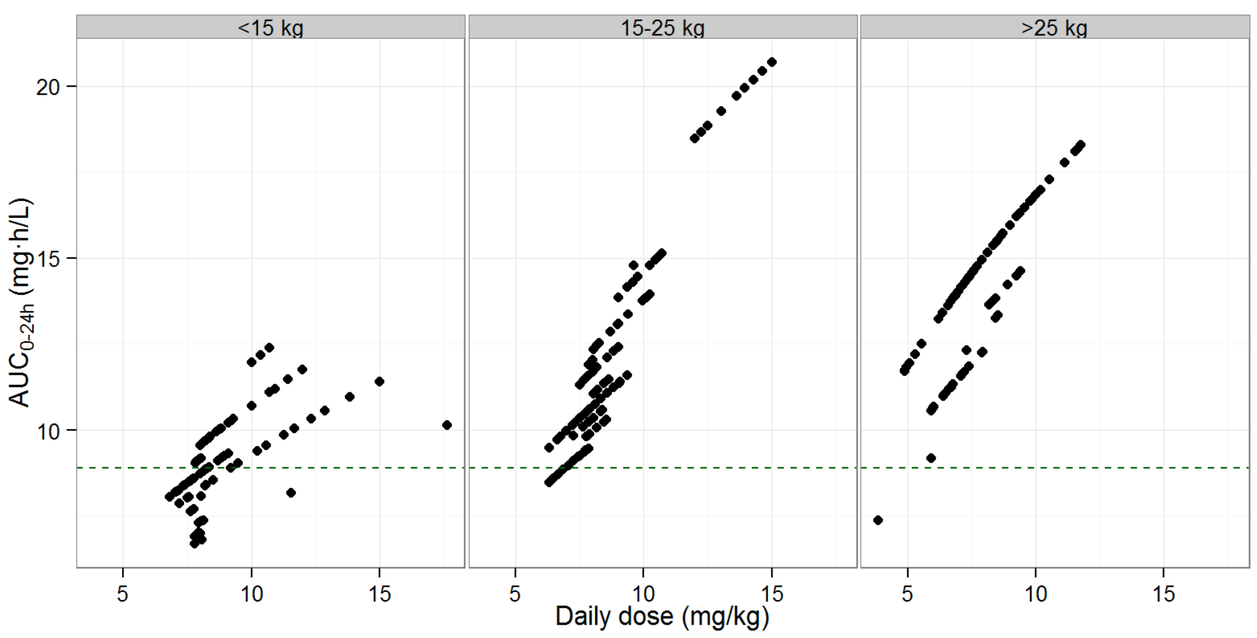

Figure 1. $AUC_{0\text{-}24h}$ versus daily dose administered (mg/kg bodyweight) stratified by bodyweight <15 kg, 15-25 kg and >25 kg respectively, calculated for each dosing record in the dataset. ····· : 8.9 mg·h/L ($AUC_{0\text{-}24h}$ target for adults)

Table 1. Patient characteristics

	Internal dataset 1[1]	Internal dataset 2	External dataset 1[2]	External dataset 2[3-5]	Total
Number of individuals	64	21	24	77	180
Male/female	41/23	7/14	13/11	34/43	95/85
Median age (range; years)	6.95 (0.5-14.9)	7.98 (1.68-17.96)	8.37 (1.57-17.25)	5.79 (0.42-12.84)	6.59 (0.42-17.96)
Median weight (range; kg)	16.25 (3.4-29)	27.8 (10.5-59.2)	30.2 (11-54.1)	17.4 (7.43-60.5)	17 (3.4-60.5)
Median daily dose (range; mg)	120 (60-240)	200 (80-300)	200 (90-300)	150 (60-300)	150 (60-300)

Table 2. Population parameter estimates and bootstrap results (%RSE)

Parameter	Estimate	Bootstrap
Cl/F [L/h]	13.2 (4.2%) * $(BW/16.6)^{0.506\ (20.2\%)}$	13.2 (4.3%) * $(BW/16.6)^{0.524\ (21.9\%)}$
$V_2/F=V_3/F$ [L]	38.9 (7.0%) * $(BW/16.6)^{0.489\ (32.3\%)}$	37.8 (8.4%) * $(BW/16.6)^{0.531\ (34.9\%)}$
Q/F [L/h]	2.02 (13.4%)	2.14 (24.1%)
K_a [h^{-1}]	3.41 (17.3%)	3.16 (37.3%)
D1 [h]	0.847 (10.3%)	0.823 (16.1%)
ω^2 (Cl/F)	37.9% (7.9%)	37.4% (16.3%)
ω^2 (V_2/F)	55.0% (9.0%)	55.9% (19.7%)
ω^2 (D1)	70.4% (10.5%)	72.1% (29.6%)

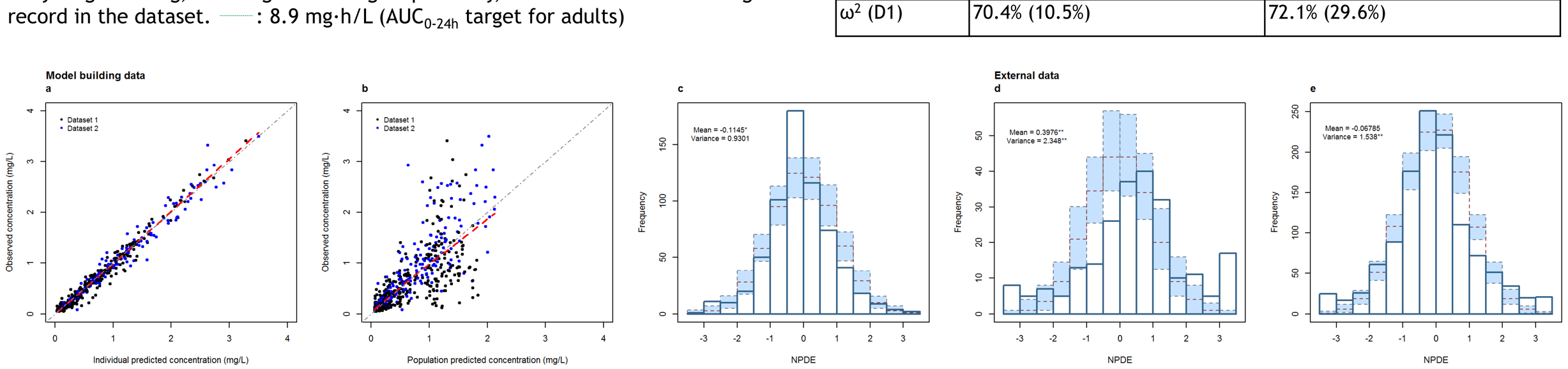

Figure 2. Observed versus individual predicted concentrations and observed versus population predicted concentrations of (a-b) the model building datasets. The histograms show the distribution of the normalized prediction distribution error (NPDE) of the model building datasets (c), external dataset 1 (d) and external dataset 2 (e); mean should be equal to 0, variance should be equal to 1 (p>0.05); *p<0.01; **p<0.001

References

[1]L'homme RFA *et al*, AIDS 2008; [2]Lee M van der *et al*, Antiviral therapy 2006; [3]Bergshoeff A *et al*, Antiviral therapy 2005; [4]PENTA, Antiviral therapy 2010; [5]Musiime V *et al*, Antiviral therapy 2010; [6]EPAR Epivir 150 mg; Conflicts of interests: none