



POPULATION PHARMACOKINETICS OF RIMEPORIDE IN HEALTHY VOLUNTEERS AND CHILDREN SUFFERING FROM DUCHENNE MUSCULAR DYSTROPHY (DMD)



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INTRODUCTION

DMD is a rapidly progressive and lethal form of muscular dystrophy affecting male children caused by mutations in the dystrophin gene
Rimeporide is a potent and selective NHE-1 inhibitor which has been shown to be cardioprotective and to improve skeletal muscle phenotype in animal models of DMD
A previously reported PK model [2] was built based on healthy adult data in order to simulate Rimeporide concentrations in young boys suffering from DMD

The aim of this work was to refine the existing Rimeporide PK model after pooling the data coming from adult healthy volunteers studies and from a paediatric clinical study in DMD patients

PATIENTS AND METHODS

Data/study description (Table 1)

In adult healthy volunteers, plasma concentrations after intravenous and oral administrations were obtained from 6 clinical studies gathering in total 156 individuals
In DMD children, Rimeporide was administered orally three-times a day (tid) for 4 weeks to evaluate the PK profile
Plasma concentrations were obtained the first and the last day of treatment
Design of the paediatric trial is depicted in figure 1

Bioanalytical method

2 different bioanalytical methods were used in the adult studies (LOQ=0.1 ng.mL⁻¹) and in the DMD children study (LOQ=25 ng.mL⁻¹)

Covariate analysis

Different covariate were investigated on PK parameters to explain IIV:
- Demographic covariates (age, BW, BMI, LBM...)
- Biochemical covariates (ALT, AST, serum creatinine, glomerular filtration rate (GFR), bilirubin)

N.B: for GFR, DMD disease impacting serum creatinine values, Cystatin C was used to compute of GFR for DMD patients using the Filler formula [3]
Log-transformed data were used for model development

Simulations

Simulations of the PK model were performed in order to investigate PK profiles of adults and DMD patients after one day of administration (150mg/adm, tid)

Model development, model diagnostics and simulations were performed using NONMEM 7.3. and PsN 4.6.0

Table 1: Studies' characteristics

	Adult studies	Paediatric study
Population	Healthy volunteers	DMD patients
Route of administration	Per os and IV	Per os
Doses	From 25 to 600mg /adm qd	From 50 to 300mg /adm tid
Age* (years)	27 [18 – 49]	9 [6 – 11]
Number of individuals	156	20

*reported as median and range [min – max]

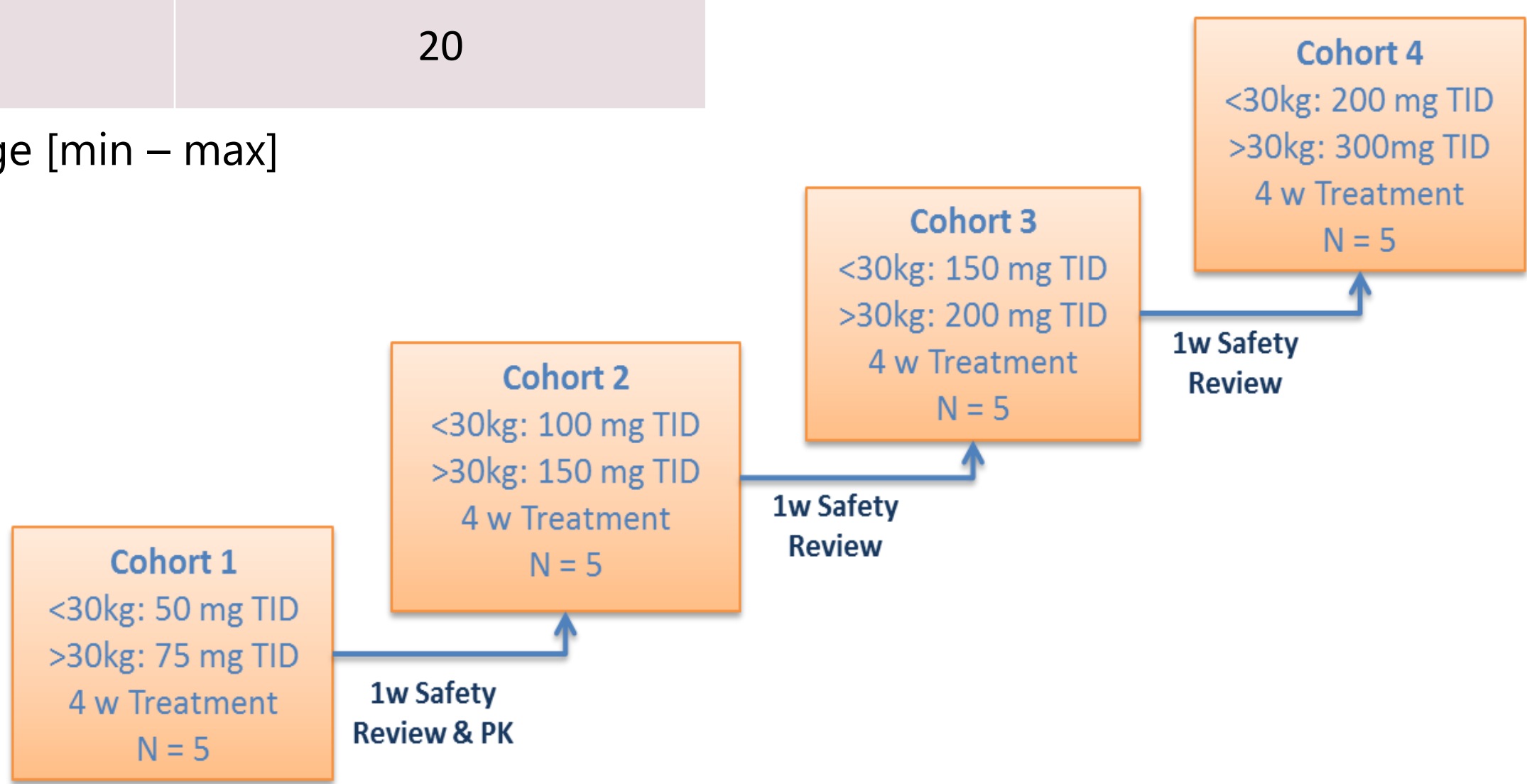


Figure 1: Design of the paediatric study

RESULTS

Model development:

The structure of the refined population PK model for Rimeporide (Figure 1) was:

- a 3-compartment disposition model
- an absorption phase described by 5 transit compartments
- a first-order elimination process

Covariate analysis revealed:

- absorption rate lowered in fed condition
- clearance decreased when GFR was low (confirming the elimination pathway)
- serum creatinine (SCr) increases volumes of distribution (indicating a distribution in muscle tissues, body composition being altered in DMD disease with a loss of muscle mass)

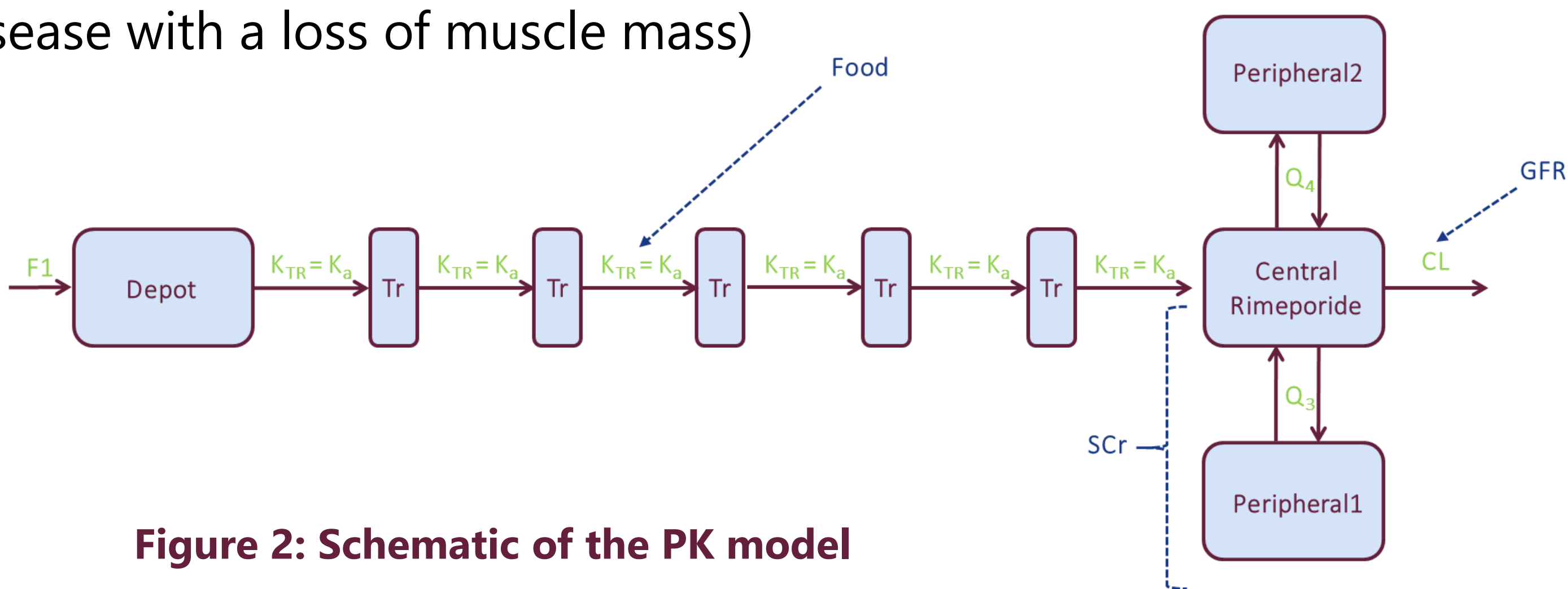


Figure 2: Schematic of the PK model

VPCs and parameter estimates are provided in Figure 3 and in Table 2

Table 2: Estimated parameters of the PK model

Parameter	Units	Estimate (RSE)	IIV in CV% (RSE)	Parameter	Units	Estimate (RSE)	IIV in CV% (RSE)
F1	-	1 fix	-	GFR on CL*	-	+0.29 (14.8)	-
k _{tr} fasted	h ⁻¹	4.12 (5.2)	43.8 (14.0)	k _{tr} fed	h ⁻¹	7.8 (5.4)	-
CL	L.h ⁻¹ .(115) ^{GFR_CL}	19.5 (1.0)	10.4 (15.1)	SCr on Vs*	-	+0.64 (13.4)	-
V _c	L.(93) ^{SCr_Vs}	29.7 (4.8)	28.0 (19.7)	Add Res Err Adult	%	25.7 (1.0)	-
Q ₃	L.h ⁻¹	0.53 (4.0)	-	Add Res Err Children	%	47.1 (6.9)	-
V _{p1}	L.(93) ^{SCr_Vs}	7.13 (3.8)	36.6 (15.3)				
Q ₄	L.h ⁻¹	56.7 (5.5)	-				
V _{p2}	L	41.8 (2.5)	-				

IIV: Inter-individual variability; CV: coefficient of variation; RSE: Relative standard error; RSE are computed from the SIR procedure [4]
*power model

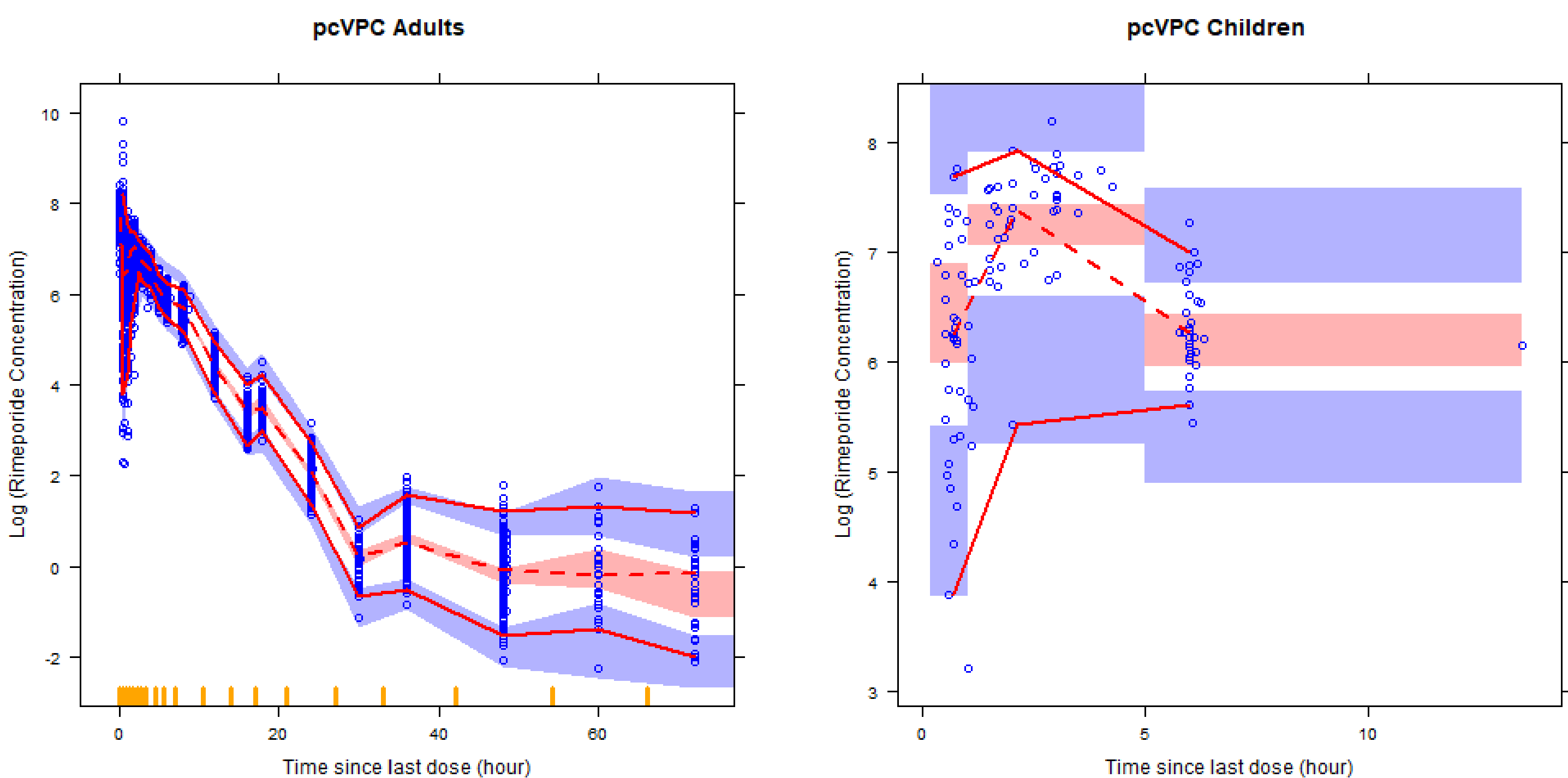


Figure 3: pcVPCs of the PK model in adults HV (left) and in DMD children (right)

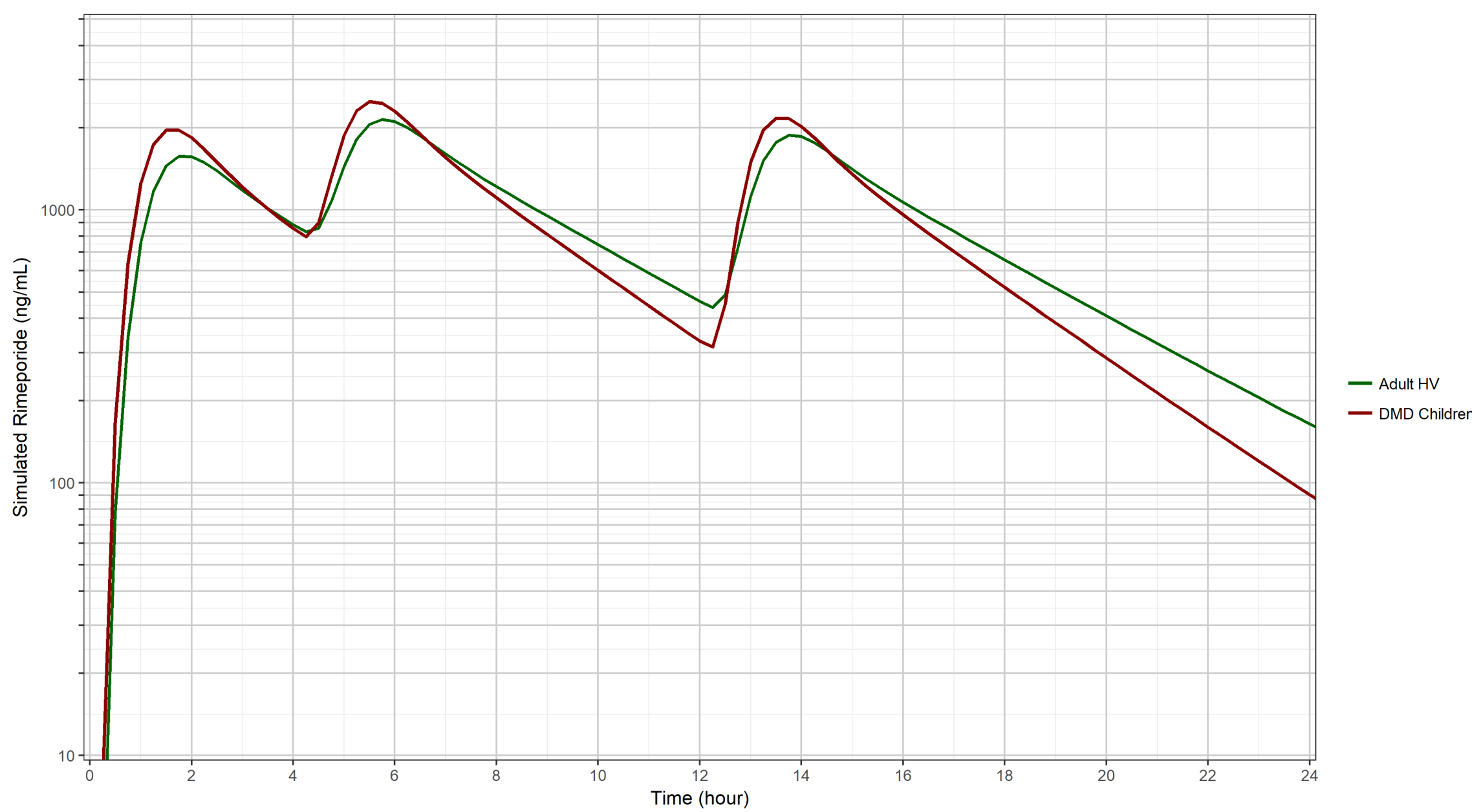


Figure 4: Simulated PK profiles for adults HV and DMD children after administration of 150mg tid

CONCLUSION

The presented PK model built from both adult healthy volunteers and young boys suffering from DMD studies described satisfactorily Rimeporide PK data. Incorporation of serum creatinine levels on distribution process was found to be better than bodyweight in order to explain both adults and DMD children. Rimeporide PK model will be expanded to investigate potential relationships between plasma concentrations and muscle damage biomarkers.

References:

- [1] Mendell et al, Ann Neurol, 2012
- [2] Laveille C. et al. PAGE 26 (2017) Abstr 7177
- [3] Filler et al, Pediatr Nephrol, 2003
- [4] Dosne, AG et al, JPKPD. 2016