

**A Prospective Population Pharmacokinetic Analysis of Sapropterin Dihydrochloride in
Infants and Young Children with Phenylketonuria**

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ELECTRONIC SUPPLEMENTARY MATERIAL

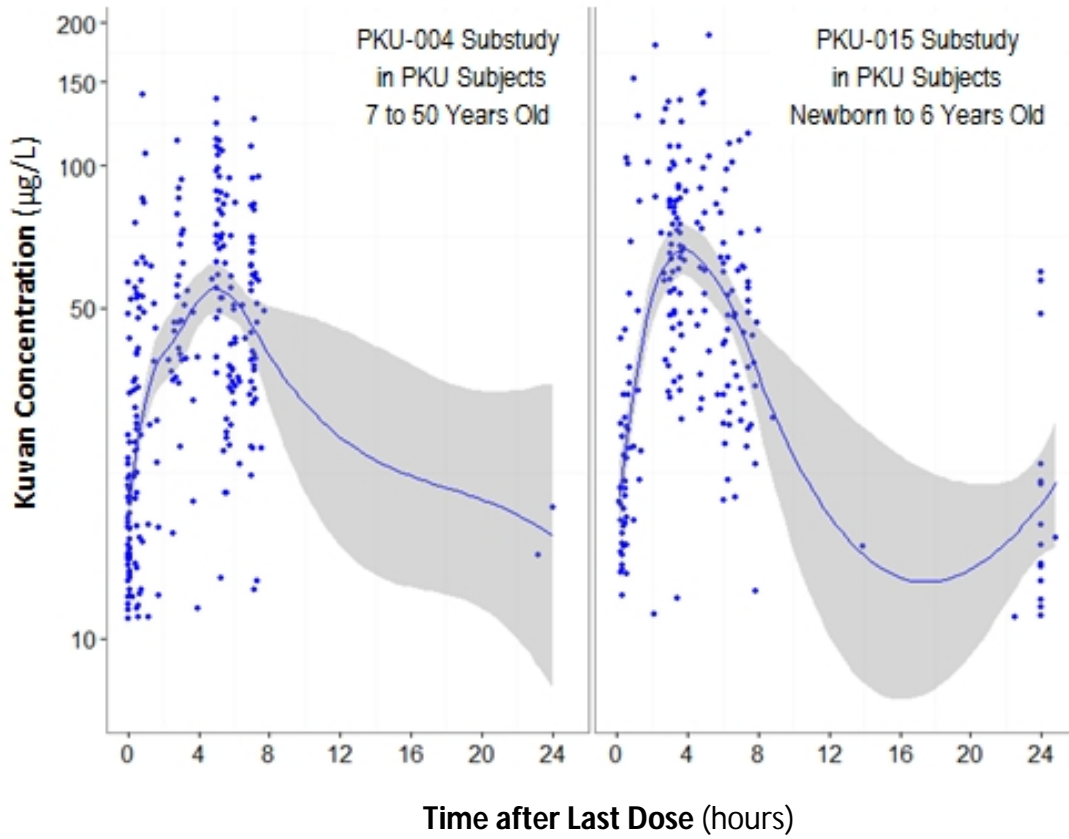


Figure 1S. Concentration-Time Curves, by Study (Population PK Substudy).

Table 1S. List of Covariates Assessed in the Population PK Analysis of Sapropterin.

Covariate	Abbreviation	Unit	Value	Type
Subject Age at baseline	AGE	yr	Numeric	Ratio
Subject Weight	WT	kg	Numeric	Ratio
Subject Height at baseline	HT	cm	Numeric	Ratio
Subject body surface area at baseline	BSA	m ²	Numeric	Ratio
Body mass index at baseline	BMI	kg/m ²	Numeric	Ratio
Subject Gender	SEX	---	1=female 0=male	Categorical
Subject Race	RACE	---		Categorical
Subject Ethnicity	ETHN		0 = Not Hispanic or Latino 1 = Hispanic or Latino	Categorical
Renal Function:				
Creatinine Clearance	CLCR	mL/min	Numeric	Ratio
Hepatic Function:				
Total Bilirubin	TBIL	mg/dL	Numeric	Ratio
Alanine aminotransaminase	ALT	IU/L	Numeric	Ratio
Asparagine aminotransaminase	AST	IU/L	Numeric	Ratio
Disease				
Phenylalanine	PHE	ng/mL	Numeric	Ratio

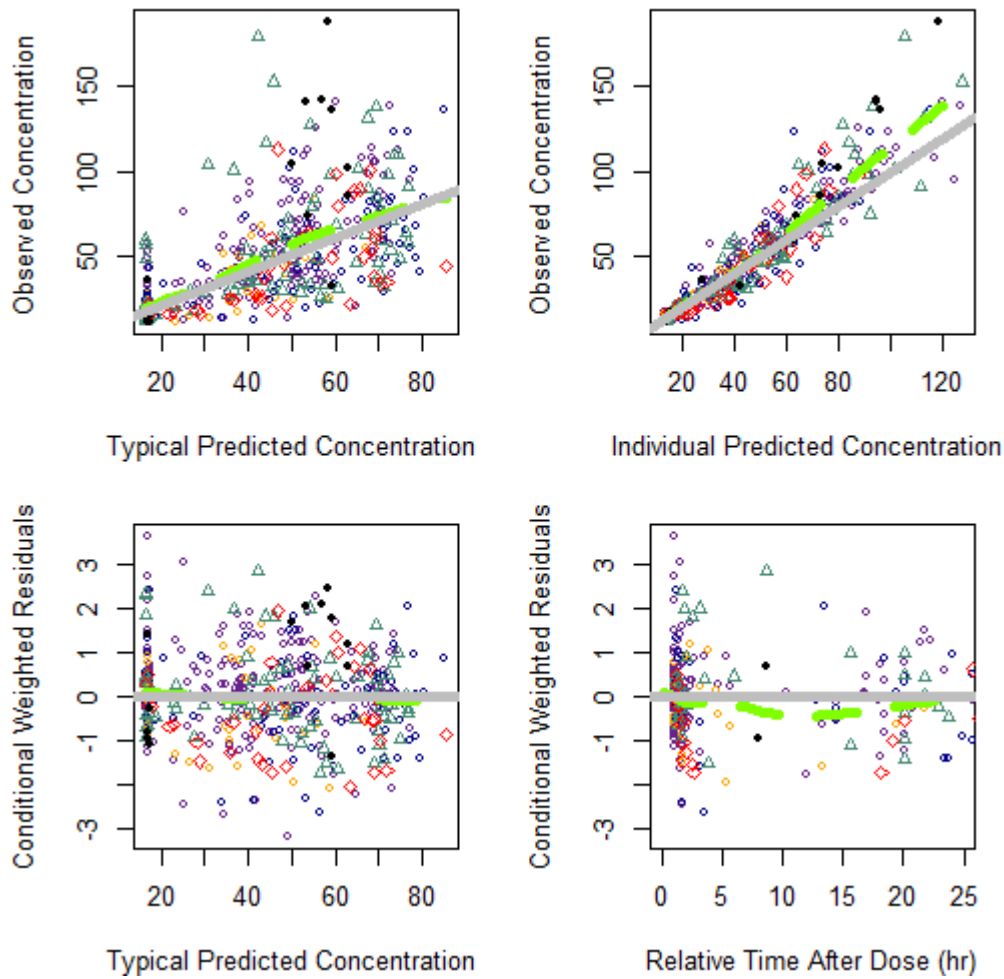


Figure 2S. Basic goodness of fit plots for the final model. Age <1 black filled circles; Age 1 to <2 red open diamonds; Age 2 to <4 aquamarine open triangles; Age 4 to <7 blue open circles; Age 7 to ≤12 orange open diamonds; Age >12 purple open circles; line of unity or identity solid grey line, lowess smooth dashed green line.

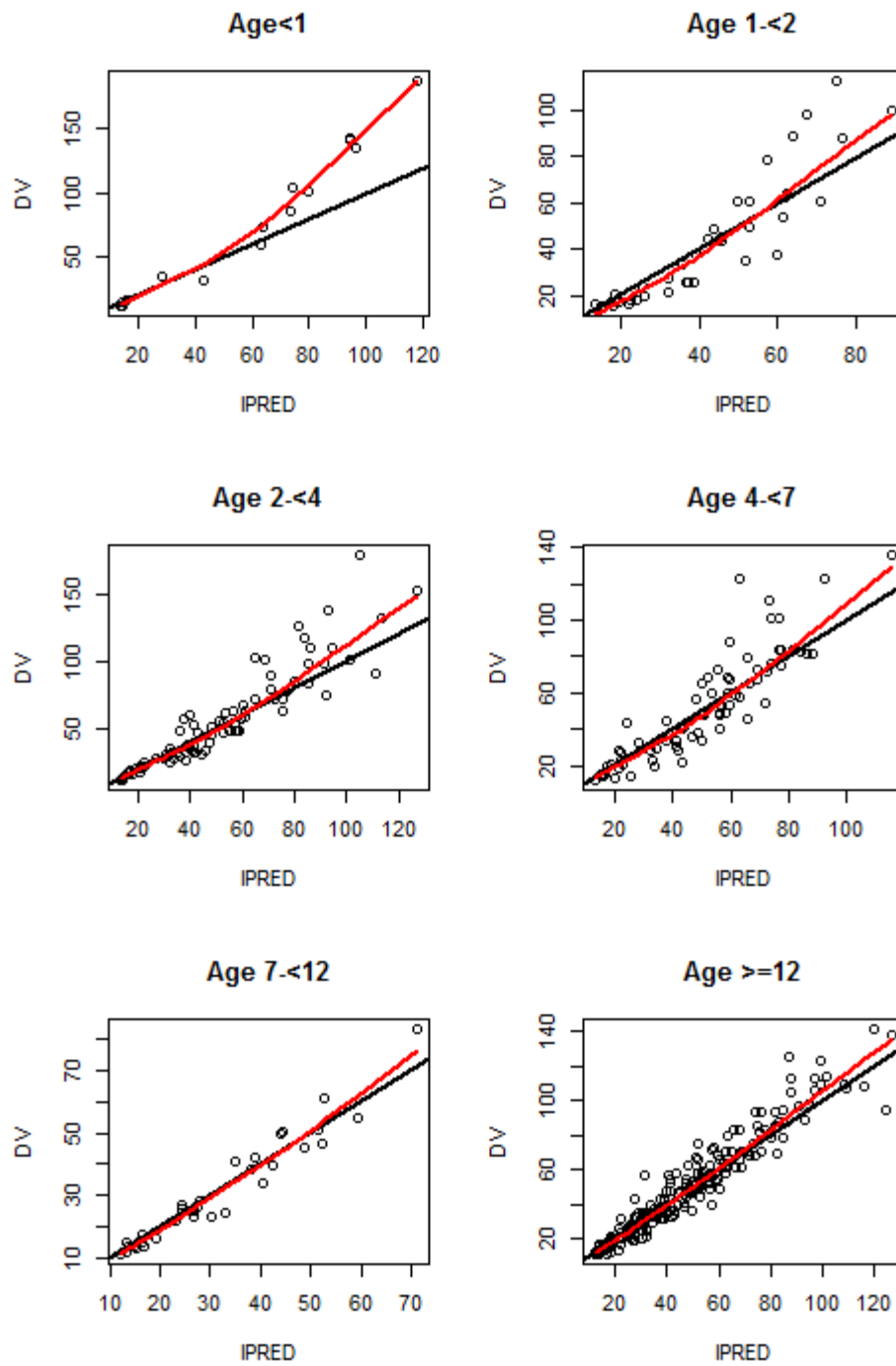


Figure 3S. Observed value (DV) versus individual predicted value (IPRED) by age group. Black line, identity line; red line, lowess smooth line.

Table 2S. Effect of weight on clearance and volume of distribution

Weight (kg)	CL/F (L/hour)	Percent of Reference	V/F (L)	Percent of Reference
5	277.15	10.23	551.95	18.28
15	716.06	26.42	1119.87	37.08
25	1113.33	41.08	1556.10	51.53
35	1488.95	54.94	1932.61	63.99
45	1850.04	68.27	2272.13	75.24
55	2200.28	81.19	2585.58	85.62
65	2541.92	93.80	2879.25	95.34
70 ^a	2710.00	100.00	3020.00	100.00
75	2876.45	106.14	3157.21	104.54
85	3204.96	118.26	3422.23	113.32
95	3528.24	130.19	3676.36	121.73
105	3846.91	141.95	3921.12	129.84
115	4161.48	153.56	4157.70	137.67
125	4472.34	165.03	4387.06	145.27
135	4779.84	176.38	4609.98	152.65
145	5084.25	187.61	4827.08	159.84

a 70 kg is the reference value for weight

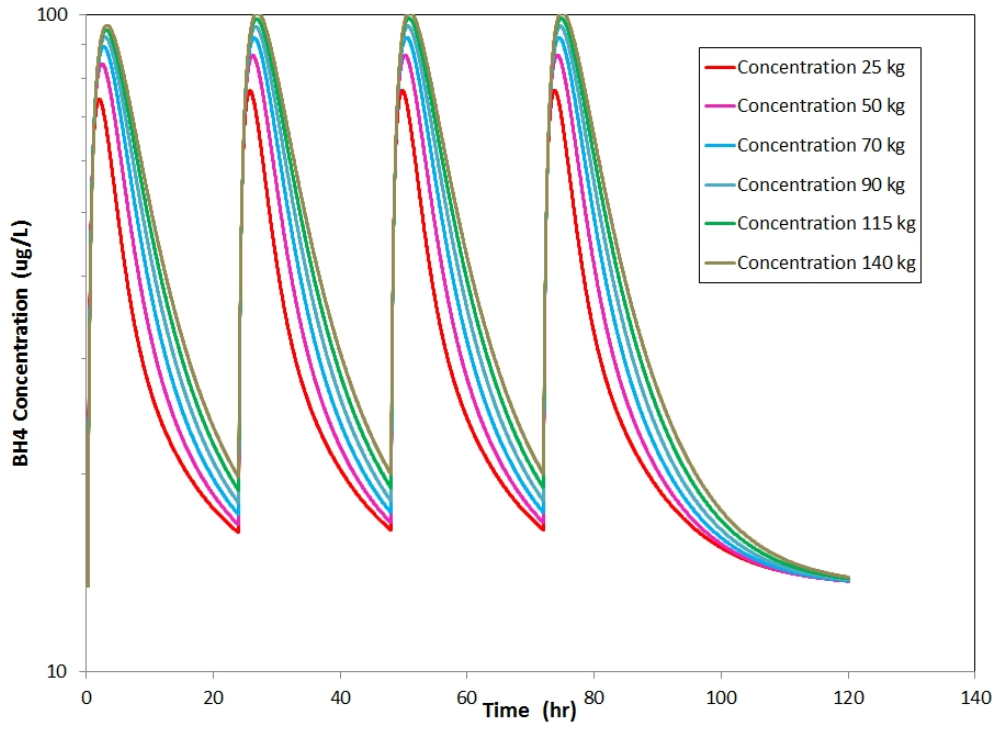


Figure 4S. Simulated Concentration Time Profiles Following Once Daily Dosing of 20 mg/kg.