

Population PK/PD modelling and simulation for nedosiran dose guidance in children with primary hyperoxaluria type 1

Pablo Gamallo¹; Steven Zhang²; Verity Rawson²

Aim

- Update a previous nedosiran population PK model with additional data from more pediatric patients and longer exposure
- Derive a nedosiran population PD model based on accurate spot Uox/Cr ratio (from 6 measurements at baseline and 4 at each visit) in patients with PH1
- Perform population PK/PD model simulations to support the proposed dosing regimen for children across age subgroups

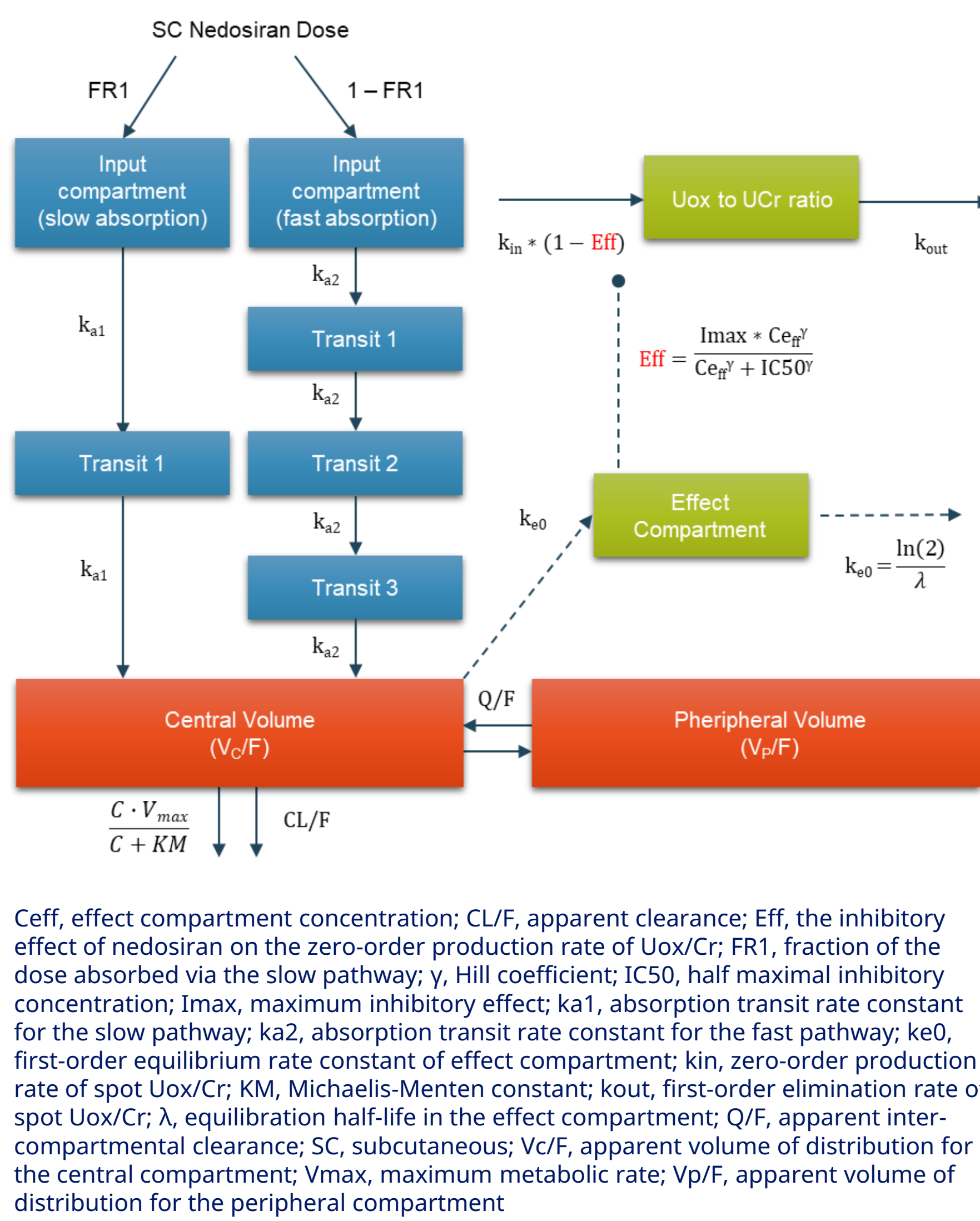
Introduction

- Primary hyperoxaluria is a rare autosomal-recessive disorder resulting in the overproduction of oxalate that leads to recurrent kidney stones and progressive kidney damage [1].
- Nedosiran (Rivfloza®) is a small interfering RNA therapy approved in the US for individuals aged ≥2 years with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (eGFR ≥ 30 mL/min/1.73 m²).
- Nedosiran inhibits oxalate production by silencing lactate dehydrogenase (LDH) mRNA in hepatocytes.
- Building upon prior models [2], a population PK/PD model characterizing the plasma concentration-time profile of nedosiran and its effect on the spot urine oxalate-to-creatinine ratio (Uox/Cr) was developed and validated using data from six clinical nedosiran trials.
- The population PK/PD model was used to assess the effect of covariates on exposure and efficacy response and to perform simulations in paediatric populations.

Methods

- The population PK analysis consisted in updating a previously developed population PK model [2] with the additional plasma PK observations from studies PHYOX8 (NCT05001269) and PHYOX3 (NCT04042402).
- The same prior population PK model structure was considered, a two-compartment with dual transit absorption and parallel linear and nonlinear elimination (Fig. 1). A reassessment of the significant covariates (body weight, eGFR and PH type) identified in the previous PK model was done.
- A population PD model analogous to the previously developed for the 24-hour urine oxalate [2] was contemplated for the spot Uox/Cr. The PD consisted of an indirect model with an effect compartment (Fig. 1) to describe the sustained effect of nedosiran on the reduction of spot Uox/Cr.
- Body weight and eGFR were assessed as continuous covariates on IC50 and Imax. Based on the results reported by Matos et al [3], age was evaluated as a covariate for the baseline spot Uox/Cr.
- The population PK and PK/PD analyses were carried out in NONMEM®, using FOCE-I. GOF plots and VPCs were used to evaluate the Pop-PK and PK/PD models.
- For the PK/PD simulations, a virtual population was generated from the WHO z-scores [4] and the continuous NHANES datasets [5].
- For the paediatric population, the maturation function that describes the increase in glomerular filtration rate with age was included in the derivation of their eGFR [6]. The PK/PD simulations were performed in R with the package mrgsolve [7].

Figure 1: Schematic of the Pop-PK/PD model



Results

- A total of 2087 plasma PK data from 148 participants (85 HVs, 49 patients with PH1, and 14 with PH2), across six clinical studies, contributed to the population PK model (Table 1).
- GOF plots and VPCs (Fig. 2) were used to evaluate the Pop-PK model.
- The updated population PK parameters were comparable to previous estimates [2].
- The effect on the PK exposure, AUC_{tau,ss} and C_{max,ss}, of nedosiran by the identified significant covariates in the population PK model: body weight, PH type/HVs and eGFR, was assessed.
- Body weight in the low and high percentiles showed an increase and a decrease, respectively, in their relative exposures. Moderate renal impairment (eGFR 30 – 59 mL/min/1.73m²) showed an increase in exposure. Mild renal impairment (eGFR 60 – 89 mL/min/1.73m²) and PH type showed no effect on PK exposure of nedosiran.
- The comparison of simulated AUC_{tau,ss} and C_{max,ss} fold changes for different age groups and renal functions is shown in Fig. 3.
- Data from 668 spot Uox/Cr observations of 41 patients with PH1 were utilized for fitting the population PD model (Table 1).
- GOF plots and VPCs (Fig. 2) were used to evaluate the Pop-PK/PD model.
- Age was identified as a significant covariate on the baseline spot Uox/Cr. No other significant covariates were identified for the IC50 and Imax in the population PD model.
- Simulations with the final population PK/PD model showed similar reductions of spot Uox/Cr (Fig. 4 and Table 2) during treatment and similar time to reach the maximum effect in pediatric patients with PH1, across the different age groups and different kidney functions, on the dose regimen of 3.5 mg/kg Q1M, when compared to patients with PH1 aged ≥12 years and weighed ≥50 kg on the dose regimen 170 mg Q1M.

Table 1: Demographics of the participants included in the PK and the PD analyses

Category	Group	Total in PK	Total in PD
All	N	148 (100%)	41 (100%)
Sex	Male	95 (64.2%)	22 (53.7%)
	Female	53 (35.8%)	19 (46.3%)
Age Group	Age 0 to <2 yrs	1 (0.7%)	0 (0%)
	Age 2 to <6 yrs	12 (8.1%)	8 (19.5%)
	Age 6 to <9 yrs	6 (4.1%)	5 (12.2%)
	Age 9 to <12 yrs	5 (3.4%)	5 (12.2%)
	Age 12 to <18 yrs	10 (6.8%)	6 (14.6%)
	Age ≥ 18 yrs	114 (77%)	17 (41.5%)
Race	White	83 (56.1%)	17 (41.5%)
	Asian	29 (19.6%)	8 (19.5%)
	Black or African American	17 (11.5%)	1 (2.4%)
	Multiple	9 (6.1%)	9 (22%)
	Other / Unknown	10 (6.7%)	6 (14.6%)
PH type	HV	85 (57.4%)	0 (0%)
	PH1	49 (33.1%)	41 (100%)
	PH2	14 (9.5%)	0 (0%)
Renal condition	Normal	62 (41.9%)	15 (36.6%)
	Mild impairment	52 (35.1%)	17 (41.5%)
	Moderate impairment	10 (6.8%)	9 (22%)
	Severe impairment	7 (4.7%)	0 (0%)
ESRD	ESRD	17 (11.5%)	0 (0%)
Body weight (kg)	Mean (SD)	67.3 (25.3)	52.1 (26.9)
	Range	[11.1-129.5]	[11.9-115.9]
Age (years)	Mean (SD)	33.3 (18.9)	17.6 (12.8)
	Range	[1.9-73]	[2-46]
BMI (kg/m ²)	Mean (SD)	24.2 (5.5)	21.9 (6.2)
	Range	[14-38.9]	[14-37.2]
eGFR (mL/min/1.73m ²)	Mean (SD)	76.1 (35.9)	80.2 (30.4)
	Range	[3.8-197]	[35-197]

BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HV, healthy volunteer; PH, primary hyperoxaluria; SD, standard deviation;

Figure 2: VPCs for Pop-PK (top) and Pop-PK/PD (bottom)

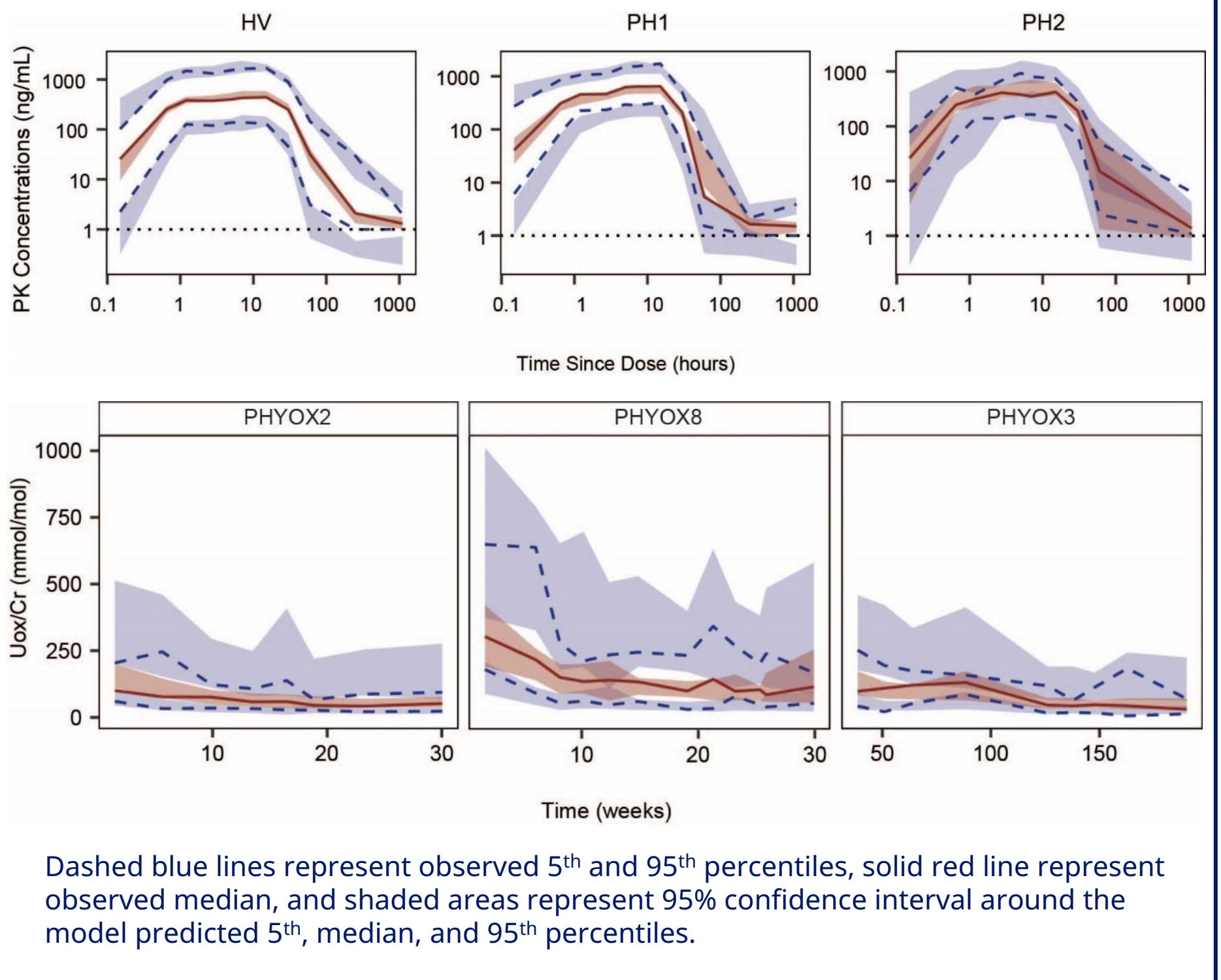


Figure 3: Comparison of simulated fold changes in nedosiran exposures in PH1 patients for different age groups and renal functions

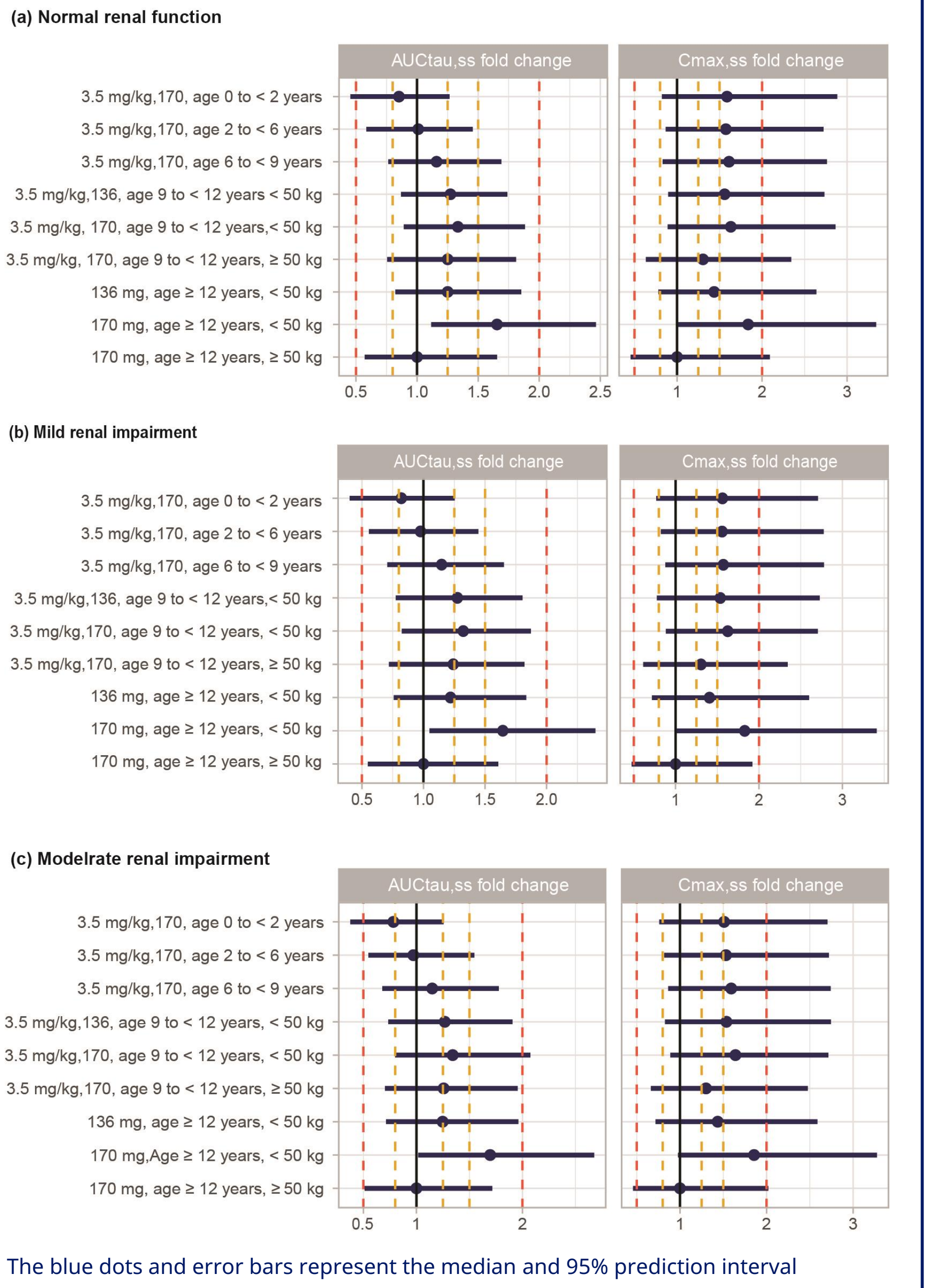


Figure 4: Simulated % change in spot Uox/Cr from baseline in PH1 patients for different age groups and renal functions

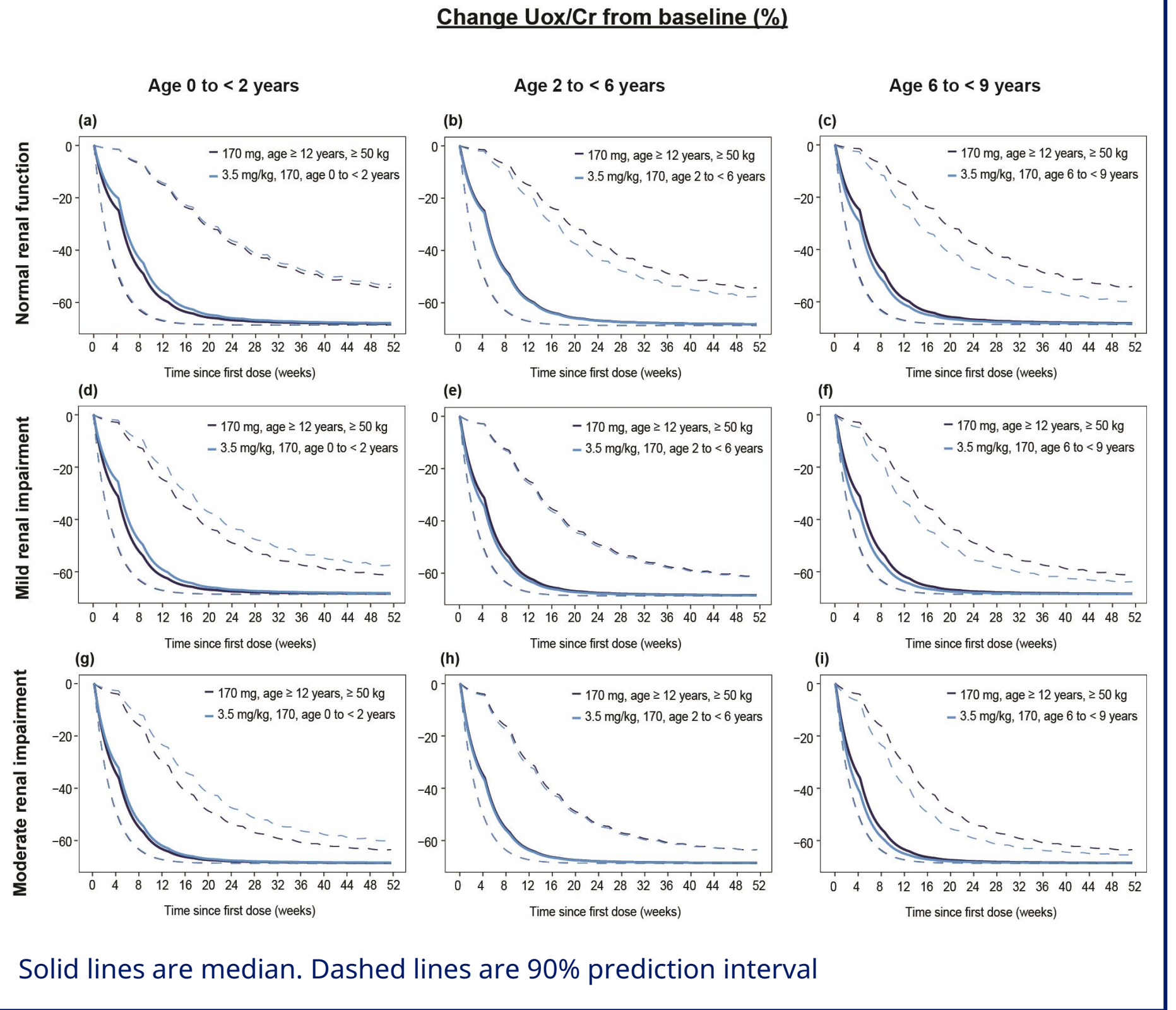


Table 2: Simulated percentage of patients with PH1 reaching 60% Uox/Cr reduction after 26 weeks of treatment

GROUP	Normal renal function	Mild renal impairment	Moderate renal impairment
170 mg, ≥ 12 yrs, < 50 kg	94.9	95.7	98.7
170 mg, ≥ 12 yrs, ≥ 50 kg	78.1	88	91.1
3.5 mg/kg, 0 to < 2 yrs	75.3	83.1	86
3.5 mg/kg, 2 to < 6 yrs	82	88.9	90.7
3.5 mg/kg, 6 to < 9 yrs	88.3	92.3	94.8
3.5 mg/kg, 9 to < 12 yrs, < 50 kg	89.4	93.7	96.9
170 mg, 9 to < 12 yrs, ≥ 50 kg	87.2	92.6	94.7

Normal renal fun.: ≥ 90 mL/min/1.73m²; Mild renal impairment: 60 to 89 mL/min/1.73m²; Moderate renal impairment: 30 to 59 mL/min/1.73m²

Conclusion

- Simulations based on the final population PK/PD model support the 3.5 mg/kg once-monthly dosing regimen in children aged 2 to <12 years with PH1 and relatively intact kidney function (eGFR ≥ 30 mL/min/1.73 m²).
- Extrapolations based on the developed population PK/PD model indicate that the 3.5 mg/kg once-monthly dosing regimen in infants aged 0 to <2 years, with PH1 and relatively intact kidney function, would provide similar spot Uox/Cr reductions as those observed in patients above 2 years. Noted that the PK/PD model has not been validated with clinical data from PH1 patients from 0 to <2 years as these data are being collected in study PHYOX8

References:

¹Novo Nordisk Pharma SA, Madrid, Spain; ²Novo Nordisk Inc., Lexington, Massachusetts, United States
The trials were sponsored by Dicerna Pharmaceuticals, Inc., a Novo Nordisk Company
The authors acknowledge the medical writing assistance of Kati Rehberg.
Presented at the 33rd PAGE meeting, 4-6 June 2025, Thessaloniki, Greece.

(1) Cochat P. et al., N Engl J Med. 2013;369(7):649-58; (2) Zhang S. et al., Br J Clin Pharmacol. 2024;1-14;
(3) Matos V., Am J Kidney Dis. 1999;34(2):e1; (4) World Health Organization. The WHO child growth standards;
(5) National Center for Health. Continuous NHANES;
(6) Anderson BJ, Holford NH. Paediatr Anaesth. 2011;21(3):222-37; (7) Baron K (2024) mrgsolve R package