

Development of population pharmacokinetic model of verinurad used for simulations of various dosing scenarios in different populations

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- Introduction
- Verinurad (RDEA3170) is a novel URAT1 inhibitor currently in Phase II development for treatment of chronic kidney disease (CKD).
 - Verinurad lowers serum uric acid (risk factor for CKD [1]), by inhibiting reabsorption of uric acid in the proximal tubule of the kidney [2].
 - Verinurad as mono therapy or combined with a xanthine oxidase inhibitor has been shown to lower serum uric acid in patients with recurrent gout and/or asymptomatic hyperuricemia [3,4,5].
 - In recent studies, verinurad has been administered as an oral extended release formulation with higher bioavailability and no effect of food.
 - Renal function and Asian origin has previously been identified to impact verinurad exposure [6][7].
 - The objective of this work was to integrate pharmacokinetic data from relevant verinurad studies and develop a population pharmacokinetic model for predicting exposure for the two formulations in different populations.

- Methods
- In total 12398 verinurad plasma concentration samples from 419 subjects were obtained from 12 studies (8 Phase I and 4 Phase II).
 - Three of the studies included gout patients (n=144), one study included patients with albuminuria (n=27), one study was a renal impairment study (n=31), and 7 studies were done in healthy volunteers (n=217) (Table 1).
 - A modified release (MR4) formulation was used in 8 studies (n=316) and an extended release (ER8) formulation was used in 4 studies (n=123).
 - Renal function ranged from 12 to 138 mL/min in the pooled population (using estimated glomerular filtration rate (eGFR) with CKD-EPI).
 - Subjects with at least one measurable PK concentration were included in the analysis.
 - Covariates included in the analysis were: renal function, Asian origin, formulation, food status, body weight, and gout.
 - The model of verinurad was developed using NONMEM 7.3.0 and PsN 4.4.8 [8,9].

Table 1: Aggregated subject demographics

Variable	Levels	Value
Age (years)*		43.7 (13.6)
Sex**	Male	410 (97.9%)
	Female	9 (2.1 %)
Weight (kg)*		85.3 (16.1)
Race**	Western (Caucasian/Black/Other)	299 (71.4 %)
	Asian	120 (28.6 %)
Population**	Healthy volunteers	248 (59.2 %)
	Gout/Hyperuricemic	144 (34.4 %)
	Albuminuria	27 (6.4 %)
eGFR (mL/min)*		94.4 (22.2)

(*) mean and standard deviation, (**) number and percent

- Results
- Model structure
- The disposition of verinurad was adequately described by a two-compartmental linear disposition model.
 - The absorption of verinurad required a complex absorption model with three parameters (lag-time, zero order duration and ka).
 - The difference between the MR4 and ER8 formulation was incorporated as a different zero order duration and relative bioavailability (Table 2, Figure 3).

Effect of covariates on verinurad PK

- To adequately describe the observed difference in exposure between westerners and Asian subjects, an additional Asian covariate on F1 was needed.
- Simulations shows that the typical Asian subject has a 1.45-fold higher AUC compared to a non-Asian subject after correcting for renal function and body weight (Figure 1, Figure 2).
- Subjects with moderate renal impairment (eGFR = 60 mL/min) were estimated to have 1.24-fold higher AUC compared with subjects with normal renal function (eGFR = 90 mL/min) (Figure 1).

Figure 1: The predicted effect of Asian origin and renal function on verinurad AUC

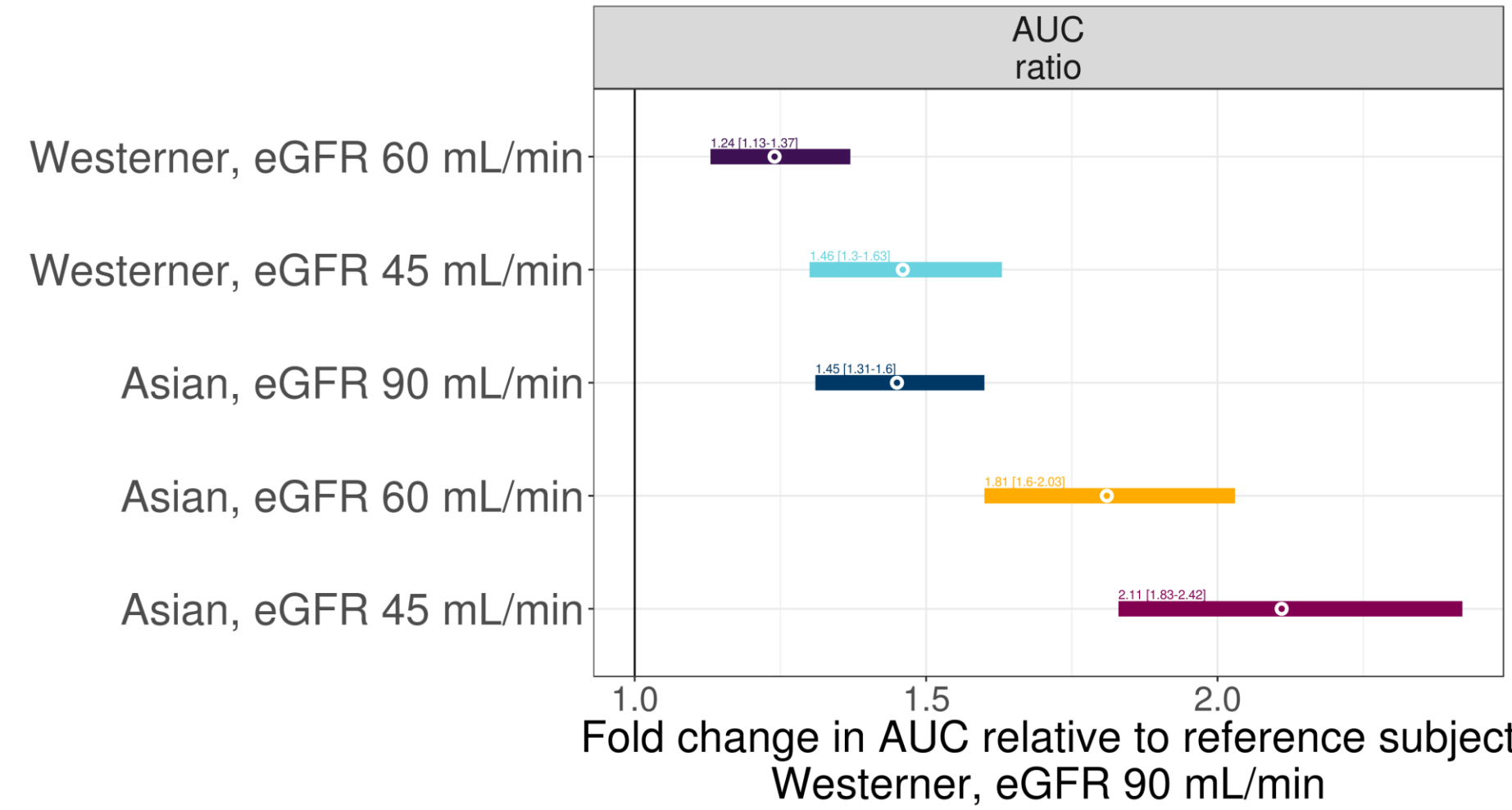


Table 2: Final parameter estimates

Parameter	Description	Estimate	RSE (%)	BSV (CV%)	RSE (%)
CL (L/h)	Clearance	93	2.7	26.8	3.81
V2 (V)	Central volume	314	7.7	35.5	13.7
Q (L/h)	Intercompartmental clearance	149	4.5		
V3 (L)	Peripheral volume	1040	3.8	47.6	5.94
Lag-time (h)	Absorption lag time	0.158	8.2	117	4.77
D1 (h)	Zero order absorption duration	0.156	21.2	59.2	4.81
F1	Bioavailability	1.00 (fixed)		24	7.00
Ka (1/h)	First order rate of absorption	0.606	6.4		
F1 Asian	Fractional difference	1.45	3.81		
F1 ER8	Fractional difference	1.66	4.55		
D1 MR4 fed (h)	Absolute value	2.03	4.0		
D1 ER8 (h)	Absolute value	3.42	3.3		
Residual error	Additive on log scale	0.509	1.95		
eGFR-CL	Power relationship	0.543	12.6		
WT-CL	Allometric scaling	0.75 (fixed)			
WT-Q	Allometric scaling	0.75 (fixed)			
WT-V2	Allometric scaling	1.00 (fixed)			
WT-V3	Allometric scaling	1.00 (fixed)			

Figure 2: Predicted population variability in verinurad AUC after ER8 12 mg in Westerners and Asians for with eGFR=60 mL/min. The lines represent population medians.

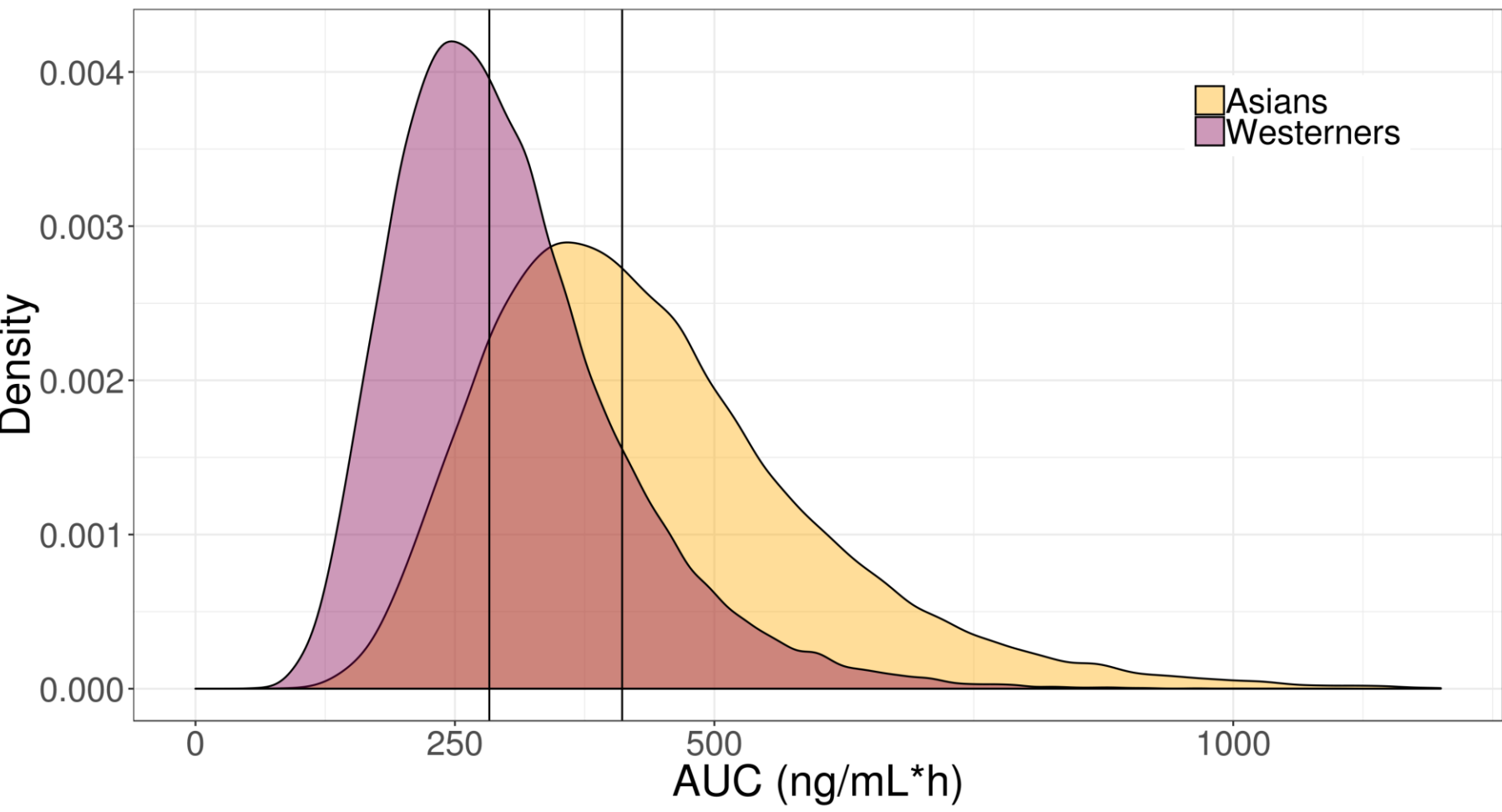
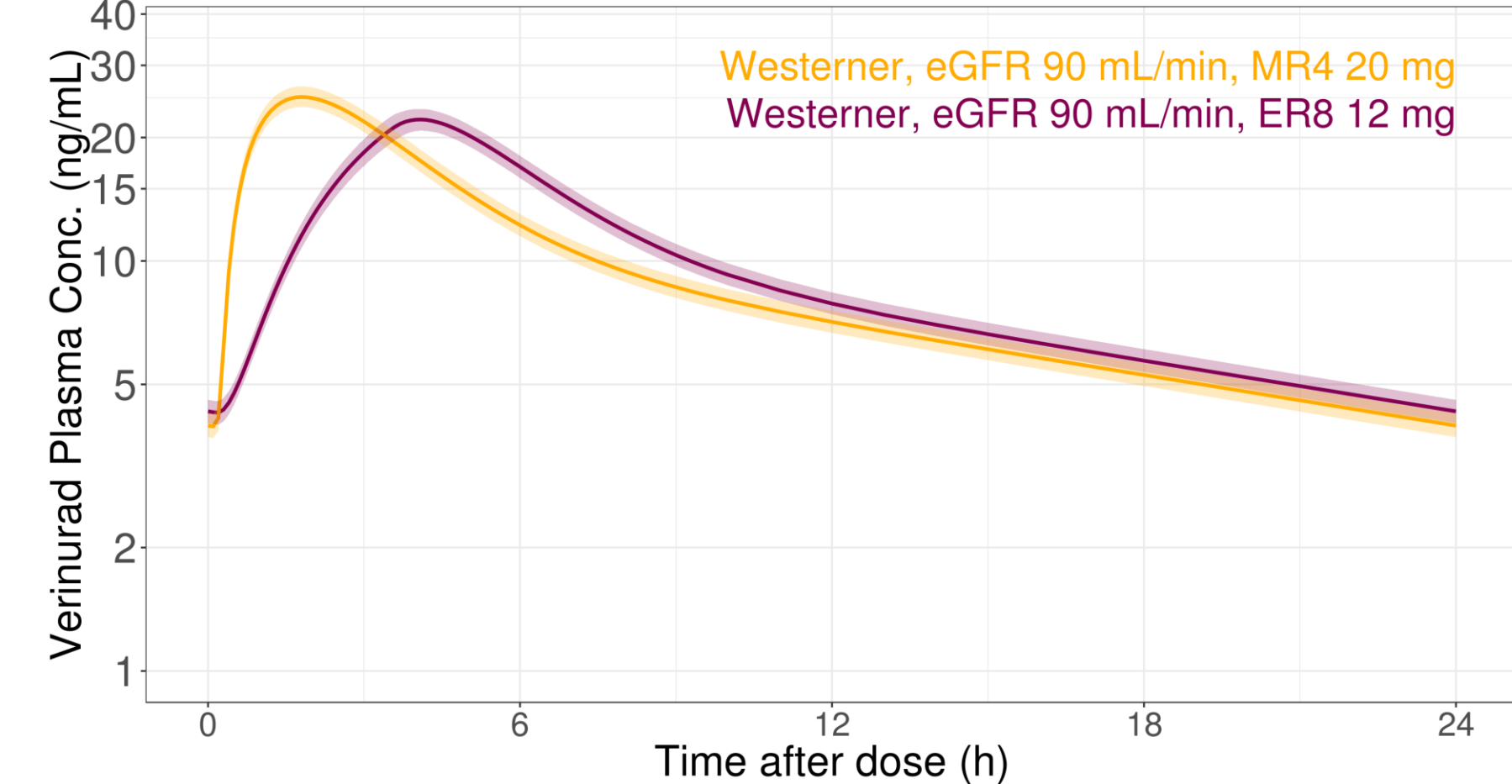


Figure 3: The simulated steady-state profile of an ER8 formulation (purple) compared to a similar dose of MR4 (yellow).



- Conclusions
- A population pharmacokinetic model was developed for verinurad, based on the wide range of data integrated from several studies (different patient populations and drug formulations).
 - The established model allowed simulation of various dosing scenarios and was valuable to support dose selection for the verinurad clinical development program.

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