

Population pharmacokinetics/pharmacodynamics modeling of uric acid formation after xanthine oxidase inhibitor administrations



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BACKGROUND

- Gout is a common inflammatory arthropathy caused by elevated serum uric acid (hyperuricemia), usually due to reduced excretion [1]. There are several categories of drug to lower serum uric acid level, including a xanthine oxidase inhibitor like allopurinol or febuxostat.

STUDY OBJECTIVES

- 1) to characterize the population pharmacokinetics(PK) of a newly developed xanthine oxidase inhibitor in healthy volunteers, 2) to find an appropriate pharmacodynamic(PD) model to explain the metabolic process of uric acid, and 3) finally, to recommend an optimal dose of the drug to treat hyperuricemia or gout patients.

METHODS

Study design

- A dose block-randomized, double-blind, active and placebo-controlled, single and multiple dosing study

Drug administration

- Single Ascending Dose (SAD) study**
 - 10, 25, 50, 100, 200, 400, 600 mg
 - Drug X: placebo - 6:2 (10, 25 mg) or 8:2 (50, 100, 200, 400, 600 mg)
- Multiple Ascending Dose (MAD) study**
 - 100, 200, 400, 600, 800 mg
 - Drug X: febuxostat : placebo - 8:2:2 (100, 200, 400, 600 mg) or 6:2 (800 mg)
 - Once daily for 7 days

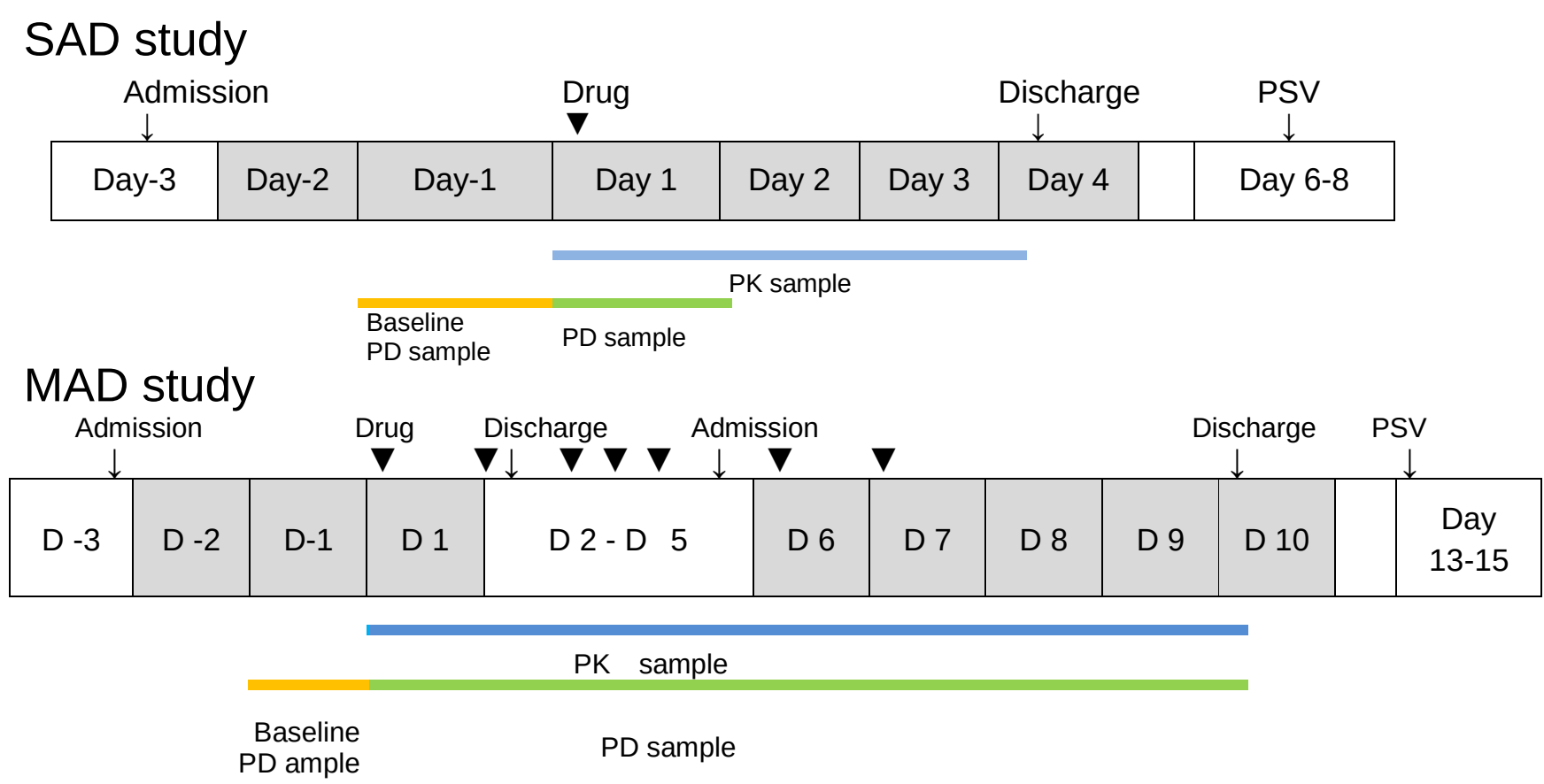


Figure 1. Design of the study

Assessments

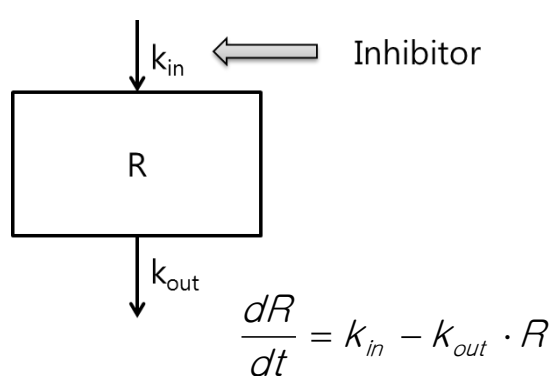
- Analytical Methods(Drug and PD markers concentration measurements)**
 - HPLC-MS/MS
 - Drug concentration in plasma and urine
 - PD markers (uric acid, xanthine, hypoxanthine) in serum and urine
- Population PK and PD dataset**
 - The model building dataset contained 3,116 drug concentration measurements and 2,590 measurements of PD markers
- PK and PD modeling**
 - non-linear mixed effect analysis
 - NONMEM® (version 7.3, ICON development solutions, Ellicott City, MD, USA)

PK modeling

- Compartment with first order absorption and first order elimination
- Evaluation of 1 comp and 2 comp
- Estimation - first-order conditional estimation with interaction
- Screened covariates: age, weight, BMI

PD and PK-PD modeling

- Indirect response model**
 - R: response
 - kin : input or production
 - kout : loss



Model validation

- The standard basic model diagnosis plots, including individual fitting plots, goodness-of-fit plots, and visual predictive check (VPC) plots for plasma concentration were examined to assess model fitting and predictive performance

RESULTS

Demographic characteristics

	Single Ascending Dose study (n=71)	Multiple Ascending Dose study (n=58)
Age (year)	26.6 ± 3.9	26.6 ± 3.6
Weight (kg)	69.7 ± 6.7	68.0 ± 7.3
BMI (kg/m ²)	22.8 ± 1.9	22.5 ± 2.0

Table 1. Demographic characteristics

PK model

- A two-compartment linear PK model with proportional residual error was chosen as the final PK model.
- There was no significant covariate for clearance or volume of distribution
- Goodness-of-fit plots showed a good adequacy between observed and predicted data

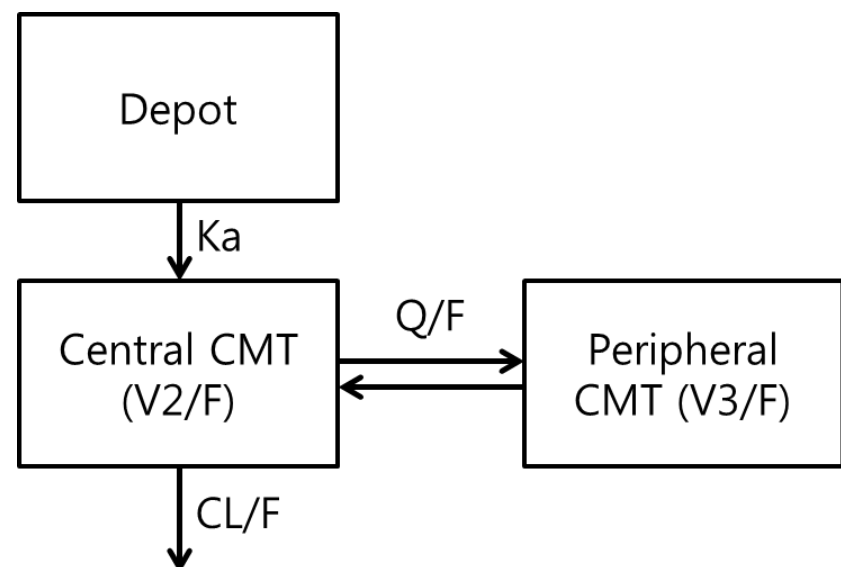


Figure 2. Schematic illustration of two-compartment pharmacokinetic model

Parameter	Population estimate (%CV)*	%RSE
Structural model		
CL/F (L/h)	5.46	3
V2/F (L)	18.5	5
Q/F (L)	1.43	6
V3/F (L/h)	18.3	6
Ka (h ⁻¹)	0.478	4
Variance of interindividual variability		
ω ² CL/F	0.0586 (24.6%)	17
ω ² V2/F	0.171 (43.2%)	25
Residual error (proportional error)		
σ ²	0.535(3%)	3

Table 2. Final pharmacokinetic model parameter estimates

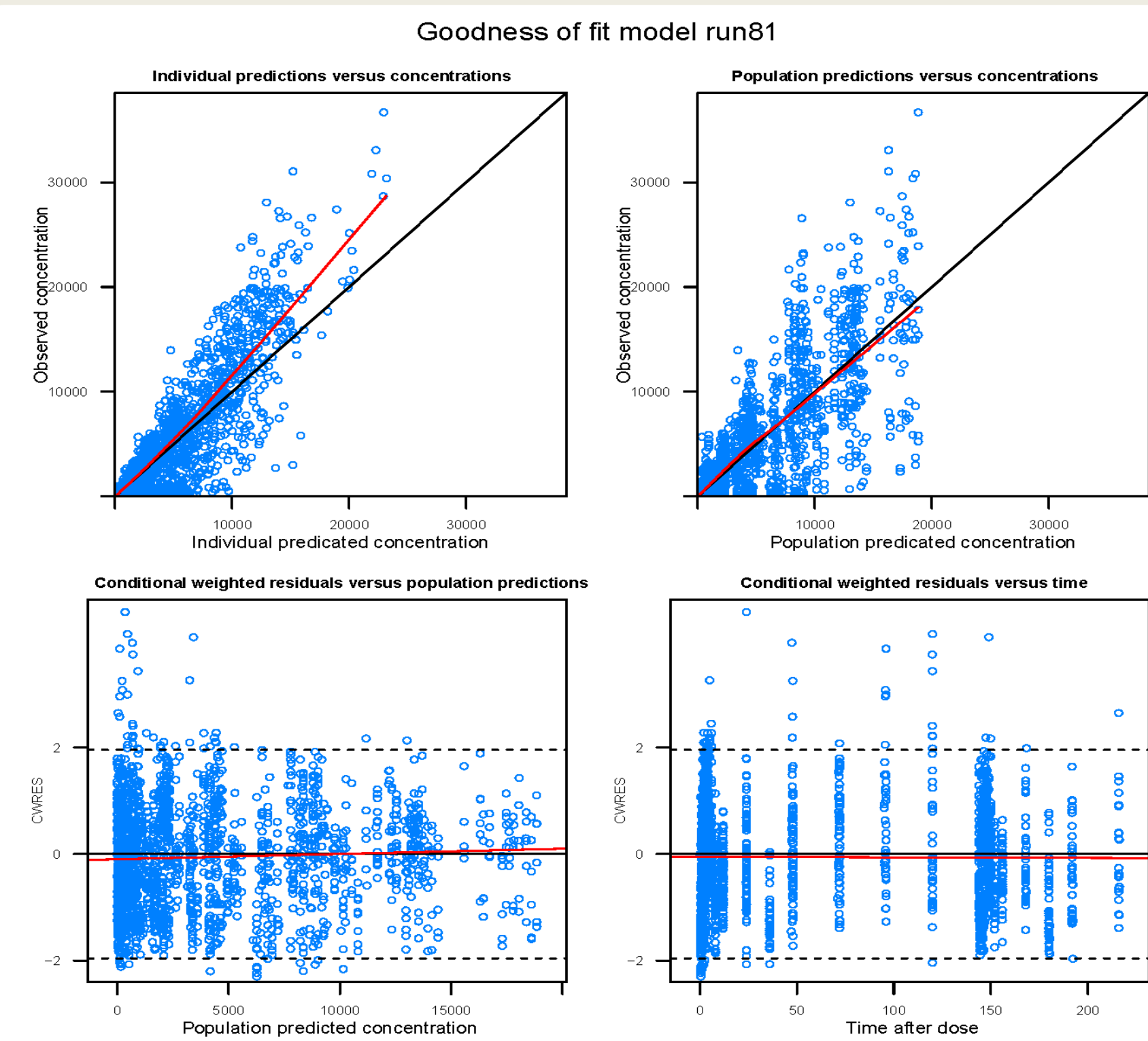


Figure 3. Diagnostic plot of final pharmacokinetic model

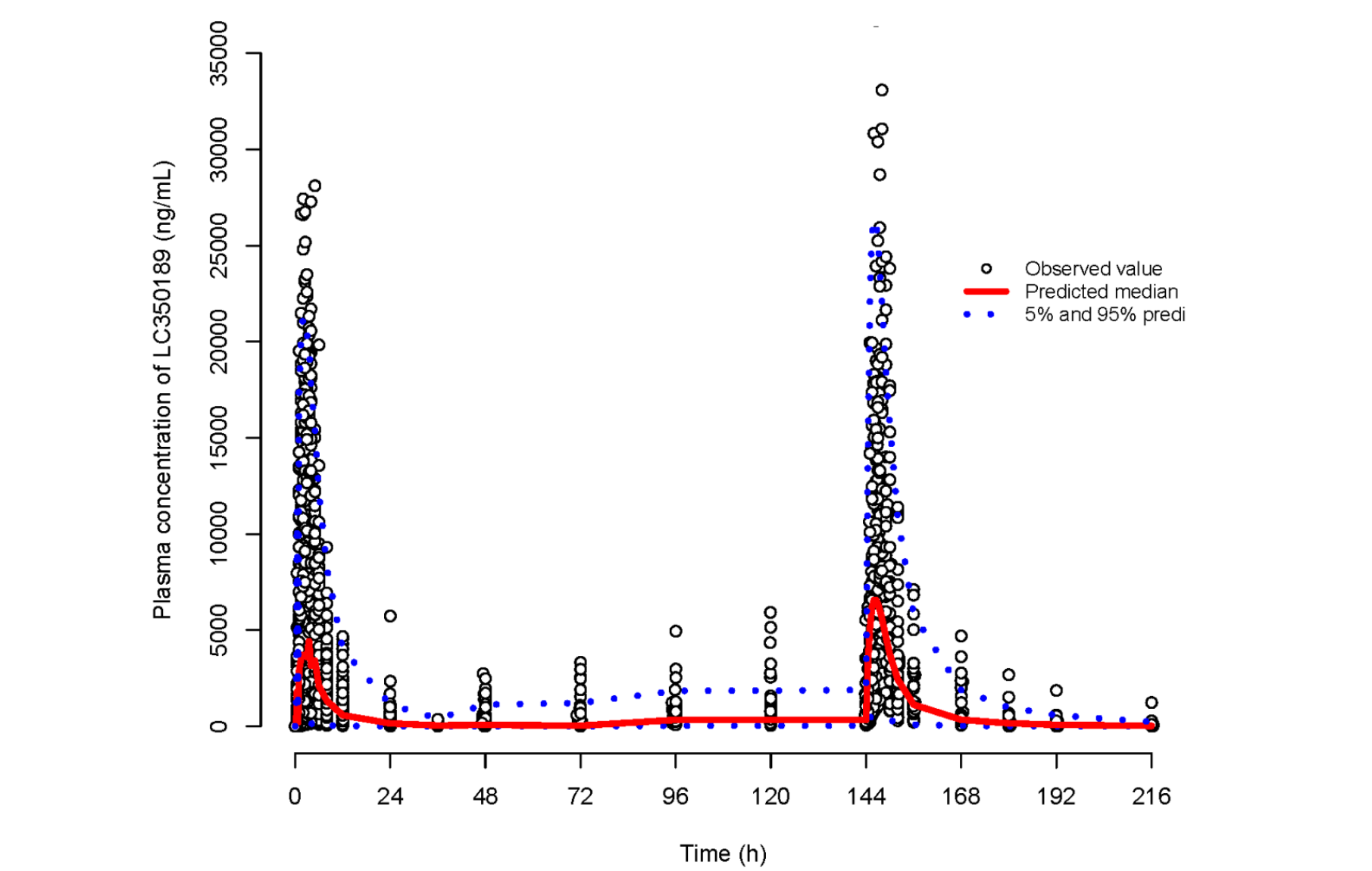


Figure 4. Visual prediction of the final PK model

Baseline PD modeling

- Uric acid formation at baseline was modeled using serum and urine compartments of 3 biomarkers based on known metabolic pathway of uric acid

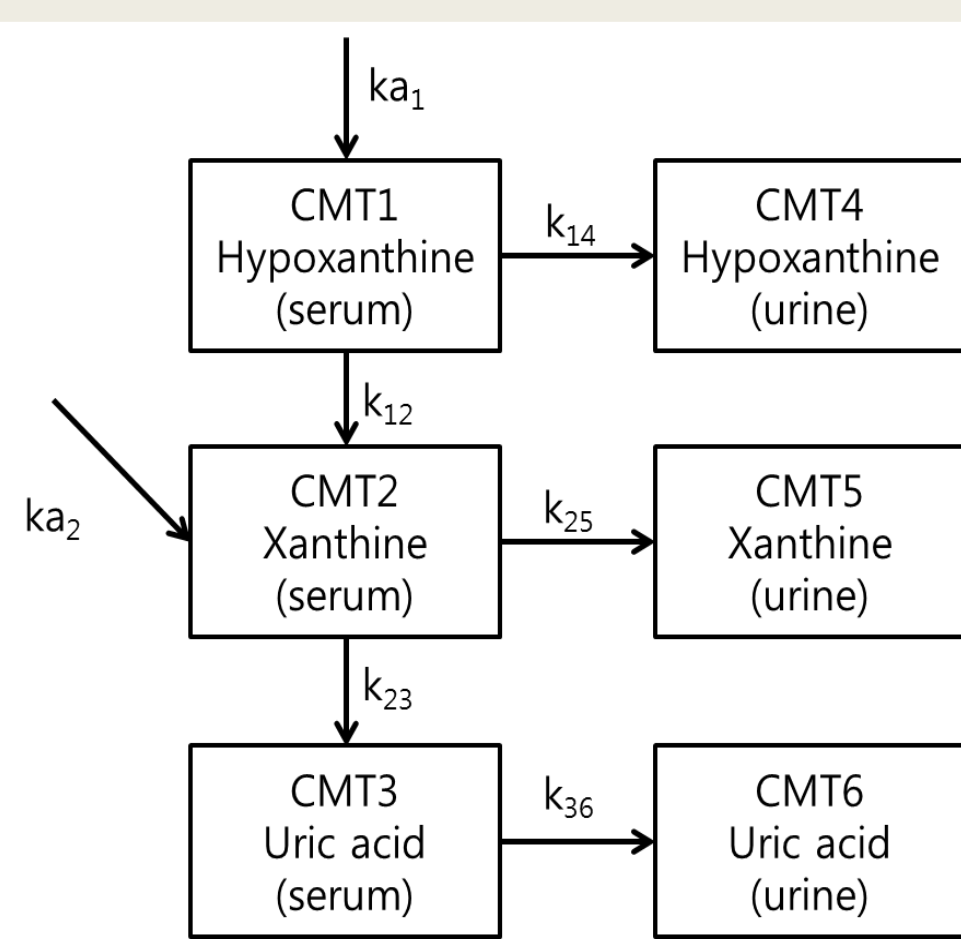
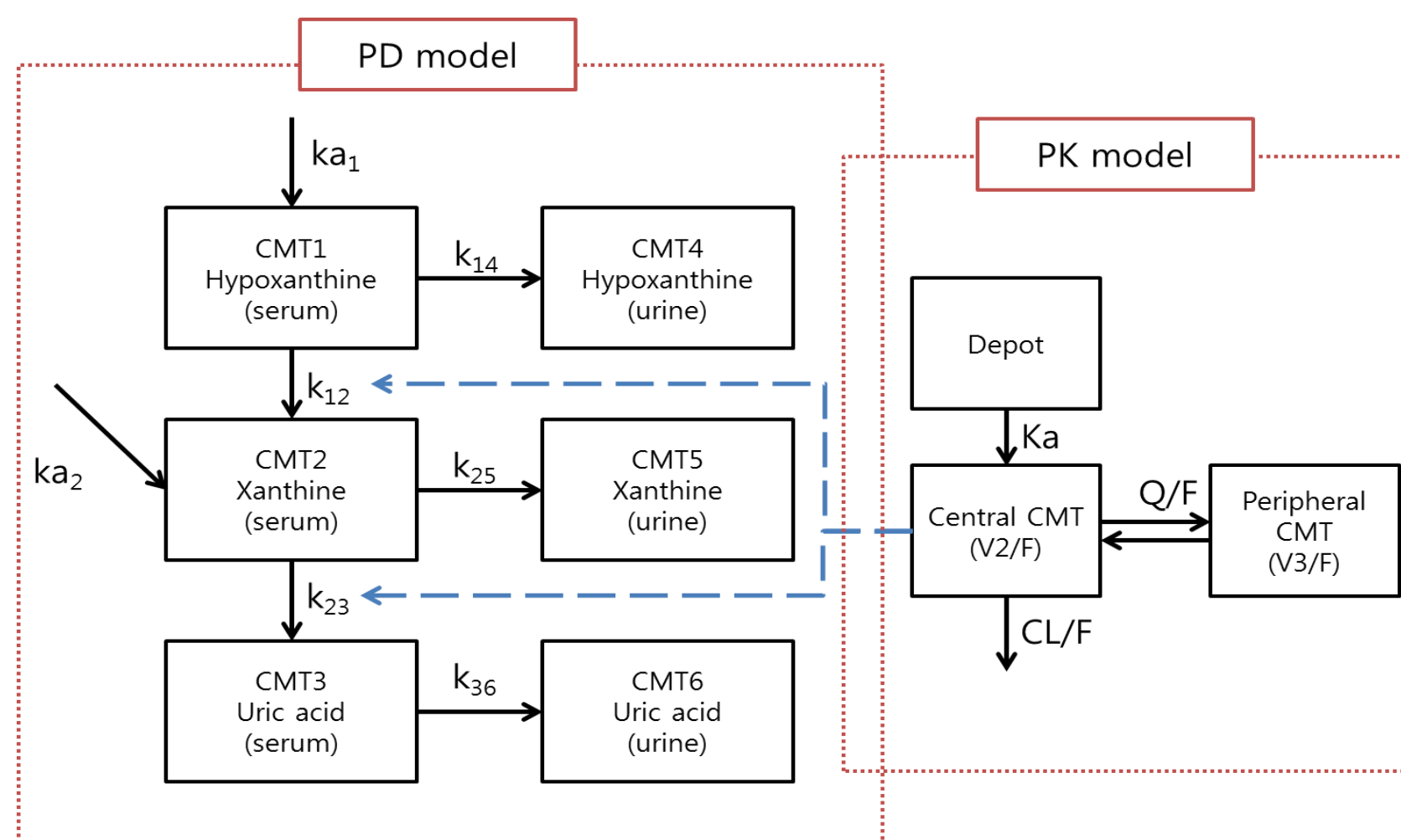


Figure 5. Schematic final pharmacodynamic model for uric acid, xanthine, hypoxanthine

Parameter	Population estimate (%CV)*	%RSE
Structural model		
Ka1 (h ⁻¹)	114	27
Ka2 (h ⁻¹)	55.3	54
K12 (h ⁻¹)	1500000	28
K23(h ⁻¹)	8300000	4
K14 (h ⁻¹)	39900	7
K25 (h ⁻¹)	113000	5
K36 (h ⁻¹)	42900	3
Variance of interindividual variability		
ω ² ka1	0.0392(20%)	33
ω ² k36	0.0427(20.9%)	29
Residual error		
σ ² (CMT1) (proportional)	0.154	9
σ ² (CMT2) (proportional)	0.137	11
σ ² (CMT3) (proportional)	0.00471	19
σ ² (CMT4) (proportional)	0.276	22
σ ² (CMT4) (additive)	2.47	2988
σ ² (CMT5) (proportional)	0.14	13
σ ² (CMT5) (additive)	20	88
σ ² (CMT6) (proportional)	0.113	10
σ ² (CMT6) (additive)	0.91	82

Table 3. Final baseline pharmacodynamic model parameter estimates (SAD study)

PK-PD modeling



CONCLUSION

- We have constructed a PK/PD model of a xanthine oxidase inhibitor using concentrations of the drug in plasma and uric acid, xanthine, hypoxanthine in serum and urine.
- This model will provide us a better understanding about formation of uric acid and is expected to be used to suggest an optimal dosing scheme that could be used in patients with gout or hyperuricemia

REFERENCES

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CONFLICT OF INTEREST

- The authors declare no conflict of interest to disclose.