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ORIGINAL ARTICLE

Population pharmacokinetics of roxadustat in Japanese dialysis-dependent chronic kidney disease patients with anaemia

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Aims: Our objective was to develop a population pharmacokinetic (PK) model to describe roxadustat plasma concentrations in Japanese dialysis-dependent chronic kidney disease (DD-CKD) patients with renal anaemia and to identify the covariate factors that affect exposure of roxadustat.

Methods: In total, 367 patients (male, 256; female, 111) contributing 1285 concentration values from 4 clinical studies were analysed using a nonlinear mixed-effects modelling approach. Candidate covariates included clinical characteristics hypothesized to affect roxadustat clearance and bioavailability, such as demographics, hepatic parameters and concomitant drugs.

Results: The roxadustat PK data in Japanese DD-CKD patients with renal anaemia were well described by a 2-compartment disposition model with first-order absorption and interindividual variability on clearance, central volume of distribution and absorption rate constant. Age was identified as a significant covariate on clearance. PK profiles of haemodialysis and peritoneal dialysis patients were comparable. Eighty-two percent of patients were administered at least 1 phosphate binder (PB). The effect of PBs on roxadustat concentration was modelled as a decrease in bioavailability. Staggered administration of PBs reduced the effect on roxadustat bioavailability. The clinical impact of all covariates on roxadustat PK was mild and manageable as the roxadustat dose was titrated based on haemoglobin level and administered starting from a low dose.

Conclusion: Roxadustat PK in Japanese DD-CKD patients were successfully described by a population PK model. The identified key covariates included coadministration of PBs on the roxadustat bioavailability and age on clearance of roxadustat.

KEYWORDS
chronic kidney disease, dialysis, drug interactions, pharmacokinetics

1 | INTRODUCTION

Chronic kidney disease (CKD) is a growing worldwide public health challenge characterized by the progressive loss of kidney function, resulting in premature death or need for renal replacement therapy. Patients with CKD are at risk of developing various complications, such as cardiovascular disease, bone mineral disorders, eye diseases, infectious diseases and malignancies. Furthermore, the life expectancy is significantly shorter in CKD patients compared with healthy individuals.[1]

CKD is defined as kidney damage, confirmed by a renal biopsy or damage marker, or an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 for >3 months.[2] Haemodialysis (HD) and peritoneal dialysis (PD) are the 2 major dialysis modalities used for providing renal replacement therapy to CKD patients in Japan.[3] Renal anaemia is a common complication of CKD that is associated with left ventricular dysfunction and heart failure, in addition to a reduction in exercise capacity and quality of life.[4]

Hypoxia-inducible factors (HIFs) are key transcription factors that coordinate the physiological response to changes in oxygen levels in the cellular environment.[5] The activity of HIFs is regulated by HIF–prolyl hydroxylase (HIF-PH) enzyme, which trigger proteasomal degradation of HIF.[6,7] Roxadustat is an orally active, HIF-PH inhibitor that promotes erythropoiesis by increasing endogenous erythropoietin.[8] Through the inhibition of HIF-PH, roxadustat stimulates a coordinated erythropoietic response that includes the increase of plasma endogenous erythropoietin levels, regulation of iron transporter proteins and reduction of hepcidin. This results in improved iron bioavailability, increased haemoglobin production and increased red cell mass.[9]

In vitro studies show that roxadustat is a substrate of cytochrome P450 (CYP)2C8 and uridine 5′-diphospho-glucuronosyltransferase-1A9 enzymes, as well as breast cancer resistance protein, organic anion transporting polypeptide-1B1 and organic anion transporters-1 and -3. Roxadustat is predominantly eliminated by phase I oxidation and phase II conjugation (glucuronidation and glycosidation).[10] Furthermore, roxadustat is highly bound to proteins in human plasma (around 99.0%), predominantly albumin.[11] Therefore, dialysis contributes a small fraction of the total clearance.[12]

Roxadustat pharmacokinetics (PK) are affected by phosphate binders (PBs), which are commonly prescribed to CKD patients to treat hyperphosphataemia.[13] Hyperphosphataemia is a widely recognized risk factor for mortality and cardiovascular disease in patients undergoing dialysis.[14] To control hyperphosphataemia, pharmacological treatment with oral PBs is necessary in addition to dietary phosphate restriction.[15] Currently, there are 6 PBs approved for dialysis patients in Japan. There are 2 types of PBs: metal-based binders (calcium carbonate, lanthanum carbonate, ferric citrate hydrate and sucroferric oxyhydroxide); and chemically synthesized polymers (sevelamer hydrochloride and bixalomer).[16] In healthy volunteers, the effect of PBs on roxadustat was observed in drug–drug interaction (DDI) studies; simultaneous administration of roxadustat with sevelamer carbonate and calcium acetate decreased roxadustat's area under the concentration–time curve (AUC) by 67 and 46%, respectively, and maximum concentration (C_{max}) by 66% and 52%, respectively. This effect was attenuated when roxadustat and PB administration occurred with a time lag. The AUC of roxadustat was reduced by 41 and 22%, respectively, when roxadustat was administered 1 hour before or after sevelamer carbonate and by 31 and 14%, respectively, when administered 1 hour before or after calcium acetate. The C_{max} of roxadustat was reduced by 26 and 12%, respectively, when roxadustat was administered 1 hour before and after sevelamer carbonate and by 19% when administered 1 hour before calcium acetate but was not affected when administered 1 hour after.[13] Simultaneous administration of roxadustat with lanthanum carbonate decreased the AUC and C_{max} of roxadustat by 12 and 1.4%, respectively.[17] The precise binding mechanism is still not clear; however, because roxadustat is a weak acid and calcium-based PBs carry the cations, it is likely that an interaction could occur. Sevelamer carbonate is also positively charged, and therefore able to interact with the carboxylic group of roxadustat.[11,13]

Patients were instructed to take roxadustat at least 1 hour before or 1 hour after dosing PBs in the phase III studies based on DDI study results[18–20]; however, this instruction was not given in the phase II study.

To better understand the PK of roxadustat in Japanese patients with anaemia from dialysis-dependent (DD) CKD, we developed a population PK model including covariates such as type of dialysis, PB use and other factors hypothesized to affect the clearance of roxadustat (CL/F) or bioavailability.

What is already known about this subject

- Roxadustat pharmacokinetics in healthy volunteers have been assessed in clinical pharmacological studies. In healthy volunteers, age affects clearance and the relative bioavailability of roxadustat is decreased by the coadministration of phosphate binders.

What this study adds

- A roxadustat population pharmacokinetic model was created to describe the pharmacokinetic profile in Japanese dialysis-dependent chronic kidney disease patients with anaemia. Key factors identified by the model were the effects of coadministration of phosphate binders on bioavailability and age on clearance, respectively. There was no difference in the clearance between haemodialysis and peritoneal dialysis.

2 | MATERIAL AND METHODS

2.1 | Summary of data source

Four studies in Japanese DD-CKD patients were included in the population PK analysis (Table 1). In the phase II study 1517-CL-0304, the

TABLE 1 Clinical studies that evaluate the efficacy of roxadustat

Study number	Patient population	Design	Number of patients (male/female)	Number of samples (male/female)	Number of samples per subject, median (range)	PK sampling schedule	Roxadustat initial dose[a]
1517-CL-0304 (phase II)	Haemodialysis, after ESA washout	Randomized, double-blind (roxadustat arm), open-label (DA arm), active-comparator (DA) study, 24 wk	92 (68/24)	349 (250/99)	5 (1–5)	Weeks 6, 12, 16, 20 and 24 at any time	50, 70 or 100 mg
1517-CL-0308 (phase III)	Haemodialysis, ESA-untreated	Randomized, open-label, uncontrolled study, 24 wk	74 (55/19)	268 (200/68)	4 (1–4)	Weeks 2, 4, 12 and 24 at any time	50 or 70 mg
1517-CL-0307 (phase III)	Haemodialysis, treatment with ESAs (rHuEPO or DA)	Randomized, double-blind, DA-controlled study, 24 wk	145 (97/48)	474 (317/157)	4 (1–4)	Weeks 4, 8, 16 and 24 at any time	70 or 100 mg
1517-CL-0302 (phase III)	Peritoneal dialysis, either on stable ESAs or ESA-untreated	Randomized, open-label, uncontrolled study, 24 wk	56 (36/20)	194 (128/66)	4 (1–4)	Weeks 2, 4, 12 and 24 at any time	ESA-untreated: 50 or 70 mg; ESA-treated: 70 or 100 mg
Total			367 (256/111)	1285 (895/390)	4 (1–5)		

DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent; PK, pharmacokinetics; rHuEPO, recombinant human erythropoietin.

[a]Roxadustat was administered orally 3 times weekly. The initial dose was titrated to a maintenance dose in accordance with the dose adjustment rule.

dose–effect relationship and safety of roxadustat was assessed in patients with renal anaemia undergoing HD after washout of their erythropoiesis-stimulating agent (ESA) treatment. In the phase III study 1517-CL-0308,[19] the efficacy and safety of roxadustat were assessed in patients with renal anaemia undergoing HD who had not been treated with ESAs after starting dialysis. In the phase III study 1517-CL-0307, the efficacy and safety of conversion to roxadustat were assessed in patients with renal anaemia who had been on treatment with ESAs.[20] In the phase III study 1517-CL-0302, the efficacy and safety of roxadustat were assessed in patients with renal anaemia undergoing PD[18] Roxadustat was administered orally 3 times weekly. The initial dose was titrated to a maintenance dose in accordance with an adjustment algorithm based on haemoglobin levels in all studies.[18–20] Study visits for PK sampling were shown in Table 1. Timing of PK sampling as it pertained to HD was not restricted in the studies.

All clinical studies were conducted in accordance with the ethical principles stated in the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonization guidelines, and applicable laws and regulations.

2.2 | Measurement of drug concentrations

Plasma concentrations of roxadustat from all studies were measured at the central laboratory SRL Inc. (Kanagawa, Japan) using a validated liquid chromatography with tandem mass spectrometry method. The lower limit of quantification was 1.00 ng/mL when using 0.05 mL of plasma.

2.3 | Data handling

Plasma concentrations below the quantification limit were treated as 0 and not included in the analysis dataset (15 samples, 1.2%). Observations that appear to be outside the expected distribution were identified by a visual inspection of the dose-normalized concentration data. A total of 4 samples were discarded due to the uncertainty in sampling or dosing time.

2.4 | Statistical models

The statistical model included the random and residual variance models. Population parameters assumed a log-normal distribution:

$$P_i = \theta \times e^{\eta_i}$$

where θ is the typical population value of parameter P, subscript 'i' denotes the i^{th} subject, P_i is the value of parameter P for the i^{th} subject and η_i denotes the deviation for the i^{th} subject's parameter value from the typical value θ.

The random effects η were assumed to have a normal distribution, i.e., $\eta \tilde{N}(0,\omega_P^2)$. ω_P^2 is the variance estimate for interindividual variability (IIV). Residual unexplained variability was described by an additive and proportional residual variance model:

$$Y_{ij} = \widehat{Y_{ij}} + W\varepsilon$$

$$W = \sqrt{\left(\widehat{Y_{ij}} \times \theta_{prop}\right)^2 + (\theta_{add})^2}$$

where Y_{ij} is the j^{th} observation in the i^{th} subject, $\widehat{Y_{ij}}$ is the corresponding model prediction, W is the standard deviation fixed in NONMEM to 1, $\varepsilon \sim N(0,1)$ is a normally distributed random variable with a mean of 0 and variance of 1, and θ_{prop} and θ_{add} represent the proportional and additive errors, respectively.

The significance of added or excluded parameters was tested using the likelihood ratio test. The NONMEM objective function value difference (ΔOFV) between the new and previous models was calculated and compared to a critical value derived from the theoretical χ^2-distribution and significance level α. If ΔOFV exceeded the critical value, the variance was declared to be statistically significant. The α levels for forward selection and backwards elimination were 0.01 (ΔOFV = −6.63, df = 1) and 0.001 (ΔOFV = 10.83, df = 1), respectively.

2.5 | Covariates

The covariates examined are listed in Table 2. Baseline values of demographics (age, sex, body weight and body mass index) and laboratory values were used for the analysis except for dose. A dose effect was tested on CL/F to evaluate the dose linearity of roxadustat. Categorical age (≥65 or <65 y) was tested in addition to continuous age because the IIV of CL/F in the base model changed at around 65 years. Covariates for central volume of distribution (Vc/F) and absorption rate constant (ka) were not tested because of high shrinkage on these parameters.[21]

Daily administration records were used to estimate the influences of concomitant drugs on the PK parameters of roxadustat. To minimize

TABLE 2 List of covariates

PK parameters	Type	List of candidate covariates
Clearance (CL)	Categorical	Age[a], sex, type of dialysis, CYP2C8 inhibitor (clopidogrel), time separation of phosphate binders
	Continuous	Body weight, body mass index, hepatic parameters[b], serum albumin, dose
Bioavailability (F1)	Categorical	Phosphate binders[c], multivalent cation-containing drugs and mineral supplements, oral iron

PK, pharmacokinetics.
[a]Treated as categorical values < or ≥65 years;
[b]aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin;
[c]sevelamer/bixalomer, calcium carbonate, lanthanum carbonate, ferric citrate and sucroferric oxyhydroxide.

the complexity of the analysis, the doses of the concomitant medications were not taken into consideration. The covariance effect of PBs was added to the relative bioavailability as a structural parameter before covariate model development because of their known effect.[22] The influence of PBs on bioavailability was included separately whether time separation of PBs was required or not because it was not required in the phase II study (1517-CL-0304). Sevelamer hydrochloride and bixalomer were grouped due to the same mechanism of action and similar effects on bioavailability and were evaluated as a single covariate. Oral iron and multivalent cation-containing drugs were tested because they potentially chelate with roxadustat to change its bioavailability.

Hepatic parameters (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total protein) and concomitant usage of clopidogrel (CYP2C8 inhibitor) were tested on CL/F because roxadustat is mainly metabolized by the liver as a CYP2C8 substrate. Serum albumin was also tested on CL/F because roxadustat is highly bound to albumin.[11]

Continuous covariate effects were entered into the model using a power model:

$$P_i = \theta_1 \left(\frac{COV}{mean(COV)} \right)^{\theta_2}$$

where θ_1 is the intercept, θ_2 is the slope and COV is the covariate.

The effect of a category was assessed using a proportional change model:

$$P_i = \theta_1 \times \theta_2^{0 \text{ or } 1}$$

where θ_1 is the intercept and θ_2 is the effect of categorical value.

2.6 | Software

The software packages Nonlinear Mixed Effects Modeling (NONMEM) version 7.3 (ICON, Ellicott City, Maryland) and Perl-speaks-NONMEM (PsN) (Uppsala University, Uppsala, Sweden) were used for modelling and simulation. Pirana version 2.9.2 was used as the modelling and simulation workbench for NONMEM. SAS version 9.4 (SAS Institute, Inc.), R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and Rstudio version 0.99.896 were used for data preparation, graphical analysis, model diagnostics and statistical summaries. XPOSE4 (Jonsson & Karlsson, Uppsala) and PsN were used for model diagnostics and bootstrapping. The first-order conditional estimation with interaction method in NONMEM[23] was employed for all model runs.

2.7 | Evaluation of the final model

Bootstrapping was conducted until 1000 minimization results were obtained to successfully calculate the 2.5% and 97.5% tail percentiles (bootstrap 95% confidence interval [CI]). Visual predictive checks were conducted to compare the distributions of the observed and simulated data under the final model ($n = 250$). The concentration–time curve from time 0 extrapolated to infinity (AUC_{inf}) was calculated to evaluate the covariate effect on the exposure:

$$AUC_{inf} = \frac{Dose}{CL/F}$$

where CL/F was adjusted by the covariates such as age and PBs.

2.8 | Nomenclature of targets and ligands

Roxadustat (specific description of ligand): https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=8454

Hypoxia inducible factor prolyl hydroxylases (general description of target): https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=900

3 | RESULTS

3.1 | Analysis dataset

There were 367 patients (male, 256; female, 111) and 1285 concentration values included in the analysis dataset. Mean age, weight and body mass index were 64.4 years, 59.5 kg and 22.8 kg/m^2, respectively, in the pooled dataset. A summary of the patient demographics is included in Table 3. The actual doses titrated based on haemoglobin level ranged from 20 to 250 mg. The number of subjects on concomitant PBs were 79 (sevelamer hydrochloride or bixalomer), 175 (calcium carbonate), 131 (lanthanum carbonate), 59 (ferric citrate) and 17 (sucroferric oxyhydroxide). The number of subjects who received other concomitant drugs is summarized in Table 3.

3.2 | Base model development

Concentration data from HD and PD subjects were analysed simultaneously because the roxadustat concentrations of PD patients were comparable to those of HD patients based on the concentration–time profile plot (Figure 1). Additionally, the type of dialysis was tested as the covariate of CL/F; it was not significant.

The structural model was a 2-compartment disposition model with first-order absorption and lag-time. Interindividual variabilities were supported for CL/F, Vc/F and ka. Shrinkage was low for CL/F (6.9%), but large for Vc/F and ka at 69.2% and 50.7%, respectively.

3.3 | Covariate model development

In the forward selection step, categorized age was selected as a covariate for CL/F. Additionally, concomitant PB (sevelamer/

TABLE 3 Summary of the patient demographics and concomitant drug use

Demographics (mean ± SD)	Phase 2	Phase 3				
	1517-CL-0304 ($n = 92$)	1517-CL-0308 ($n = 74$)	1517-CL-0307 ($n = 145$)	1517-CL-0302 ($n = 56$)	Phase 3 studies pooled ($n = 275$)	All study pooled ($n = 367$)
Age	62.5 ± 8.9	66.2 ± 12.1	64.8 ± 11.6	64.3 ± 10.3	65.1 ± 11.5	64.4 ± 10.9
BMI (kg/m^2)	21.9 ± 2.7	23.4 ± 3.6	22.4 ± 3.6	24.5 ± 3.7	23.1 ± 3.7	22.8 ± 3.5
Weight (kg)	58.1 ± 8.7	61.3 ± 13.6	57.8 ± 12.2	64.0 ± 11.2	60.0 ± 12.6	59.5 ± 11.8
Albumin (g/L)	37.6 ± 2.7	35.6 ± 3.3	37.5 ± 2.9	35.8 ± 4.2	36.7 ± 3.4	36.9 ± 3.3
ALP (U/L)	227.2 ± 94.0	248.1 ± 105.2	248.3 ± 113.4	329.5 ± 177.1	264.8 ± 130.7	255.4 ± 123.5
ALT (U/L)	13.0 ± 7.6	12.9 ± 7.7	11.6 ± 5.4	17.6 ± 9.1	13.2 ± 7.3	13.1 ± 7.3
AST (U/L)	12.2 ± 5.8	15.2 ± 6.3	13.1 ± 5.3	19.0 ± 7.6	14.9 ± 6.5	14.2 ± 6.4
Total protein (g/L)	63.4 ± 4.3	63.0 ± 3.7	64.0 ± 5.0	63.9 ± 5.3	63.7 ± 4.7	63.6 ± 4.6
Numbers of patients used concomitant drugs (%)	**Phase 2**	**Phase 3**				**All study pooled ($n = 367$)**
	1517-CL-0304 ($n = 92$)	**1517-CL-0308 ($n = 74$)**	**1517-CL-0307 ($n = 145$)**	**1517-CL-0302 ($n = 56$)**	**Phase 3 studies pooled ($n = 275$)**	
Sevelamer/bixalomer	34 (37%)	7 (9.5%)	30 (20.7%)	8 (14.3%)	45 (16.4%)	79 (21.5%)
Calcium carbonate	49 (53.3%)	26 (35.1%)	80 (55.2%)	20 (35.7%)	126 (45.8%)	175 (47.7%)
Lanthanum carbonate	38 (41.3%)	16 (21.6%)	54 (37.2%)	31 (55.4%)	101 (36.7%)	139 (37.9%)
Ferric citrate	2 (2.2%)	10 (13.5%)	35 (24.1%)	12 (21.4%)	57 (20.7%)	59 (16.1%)
Sucroferric oxyhydroxide	- (–)	3 (4.1%)	12 (8.3%)	2 (3.6%)	17 (6.2%)	17 (4.6%)
At least 1 phosphate-binder usage during study period	77 (83.7%)	46 (62.2%)	132 (91%)	46 (82.1%)	224 (81.5%)	301 (82.0%)
Oral iron	8 (8.7%)	21 (28.4%)	13 (9%)	11 (19.6%)	45 (16.4%)	53 (14.4%)
Multivalent cation-containing drugs and mineral supplements	14 (15.2%)	16 (21.6%)	39 (26.9%)	20 (35.7%)	75 (27.3%)	89 (24.3%)
Clopidogrel	2 (2.2%)	6 (8.1%)	14 (9.7%)	2 (3.6%)	22 (8%)	24 (6.5%)

ALP, alkaline phosphate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; SD, standard deviation.

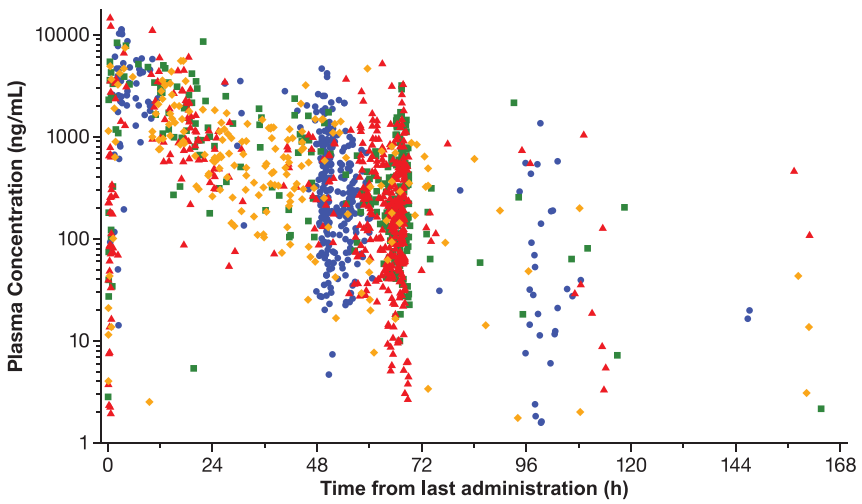

FIGURE 1 Plasma roxadustat concentration versus time elapsed following last administration. Blue circle CL-0304: haemodialysis (P2); green square CL-0308, haemodialysis (P3); red triangle CL-0307, haemodialysis (P3); yellow diamond CL-0302, peritoneal dialysis (P3)

bixalomer, calcium carbonate, lanthanum carbonate, ferric citrate and sucroferric oxyhydroxide) use was selected as a covariate on bioavailability (F1). Other demographic and hepatic parameters had no effects on CL/F. Oral iron, multivalent cation-containing drugs and mineral supplements had no effects on the relative bioavailability. In the backward deletion step, no covariates were deleted.

3.4 | Final model

The PK parameters of the final model are shown in Table 4. A forest plot of intrinsic/extrinsic covariate effects on roxadustat exposure is shown in Figure 4.

If age was ≥65 years, its effect was estimated (0.792) as proportional (20.8% decrease of CL/F). As a result, AUC_{inf} increased by 26.3%.

TABLE 4 Summary of population pharmacokinetic parameters of final model

Description	Estimate	95% CI	RSE (%)	Shrinkage	Bootstrap median	Bootstrap 95%CI
CL/F (L/h)	0.923	0.796–1.05	7.0%		0.914	0.791–1.06
V_c/F (L)	14.6	11.9–17.3	9.5%		14.4	11.6–17.4
Ka (h^{-1})	0.63	0.405–0.855	18.3%		0.639	0.435–0.988
Q/F (L/h)	0.134	0.00601–0.262	48.7%		0.131	0.0551–0.294
V_p/F (L)	2.89	1.59–4.19	23.0%		2.89	1.78–4.64
ALAG1 (h)	0.287	0.273–0.301	2.6%		0.287	0.261–0.388
SBUSE on F1	0.744	0.606–0.882	9.5%		0.739	0.594–0.891
CUSE on F1	0.931	0.799–1.063	7.2%		0.922	0.788–1.060
LUSE on F1	0.969	0.837–1.101	7.0%		0.962	0.835–1.103
FUSE on F1	0.744	0.602–0.886	9.7%		0.737	0.598–0.902
SCUSE on F1	0.837	0.490–1.184	21.1%		0.831	0.478–1.53
No time separation of PBs in phase 2 on F1	0.935	0.888–0.982	2.6%		0.934	0.884–0.986
Age ≥65 y for CL	0.792	0.716–0.868	4.9%		0.791	0.719–0.876
IIV CL/F (%CV)	41.7%	37.6–45.5%	9.6%	6.9%	41.4%	36.9–46.4%
IIV V_c/F (%CV)	22.0%	2.6–31.0%	50.3%	69.2%	22.9%	9.1–37.4%
IIV ka (%CV)	184.1%	154.2–209.8%	15.2%	50.7%	180.3%	144.9–213.4%
Proportional error (CV%)	43.9%	41.3–46.5%	3.1%	12.4%	43.6%	41.0–46.1%
Additive error (ng/mL)	1.88	0.892–2.87	26.8%	12.4%	1.67	0.0188–2.55

ALAG1, lag time for depot compartment; CI, confidence interval; CL, clearance; CL/F, apparent total systemic clearance; CUSE, calcium carbonate; CV, coefficient of variation; F1, bioavailability, FUSE, ferric citrate, ka, absorption rate constant; IIV, interindividual variability; LUSE, lanthanum carbonate; PB, phosphate binder; phase II effect on F1, the additional effect of the phosphate binders due to the uncontrolled intake; Q/F, apparent intercompartmental clearance; RSE, relative standard error; SBUSE, concomitant usage of sevelamer/bixalomer; SCUSE, sucroferric oxyhydroxide; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment.

Modelling demonstrated that PBs decreased the AUC_{inf} of roxadustat by 3% to 25% (calcium and lanthanum carbonate, 3–7%; sucroferric oxyhydroxide, 16%; sevelamer hydrochloride, bixalomer and ferric citrate, 25%). AUC_{inf} of PBs without time separation was 6.5% lower than the phase III studies with time separation. The increase or decrease of AUC_{inf} was not clinically meaningful (no effect boundary range within ±20%).

Basic goodness of fit is shown in Figure 2. The visual predictive checks are shown in Figure 3. These indicate that the final model characterized roxadustat PK well in the studied patients and lacked bias.

4 | DISCUSSION

The objective of this analysis was to develop a population PK model of roxadustat in Japanese DD-CKD patients with renal anaemia and to identify the covariate factors that affect roxadustat PK.

The concentration profile of roxadustat in this patient population was well described by a 2-compartment disposition model with first-order absorption and interindividual variability on CL/F, Vc/F and ka. All PK parameters and their 95% CIs were well estimated except for the relative standard error (RSE) of apparent intercompartmental clearance (Q/F) due to a lack of information regarding the elimination phase. PK sampling was conducted in accordance with the HD schedule (2- or 3-d intervals). Therefore, most PK sampling points were around 48 or 72 hours (Figure 1). The IIV of ka was large (184.1%) because the number of samples in the absorption phase was small compared to the distribution and/or elimination phase.

After adding relevant covariates (age on CL and PBs on relative bioavailability), IIV of ka, RSE of Vc/F and shrinkages of IIV on Vc/F and ka were still large due to the large data variation of the absorption phase.

Population PK parameters were comparable to the bootstrap median. The 95% CIs of all parameters and their bootstrap 95% CIs did not include zero, which means that all parameters were significantly estimated. The sparse sampling and the large concentration variation worsened the bootstrap minimization (success rate was 40%).

The CL/F of roxadustat in Japanese DD-CKD patients was estimated as 0.923 L/h, which is smaller than the CL/F of healthy Japanese volunteers (1.18–1.48 L/h).[17,24] This result is supported by a clinical pharmacological study in renally impaired subjects. The CL/F of roxadustat decreased in subjects with kidney impairment.[25] However, CL/F in Japanese DD-CKD patients was smaller than that of DD-CKD patients (1.36 L/h) in a global study.[26] One possible assumption is the weight of participants; the mean weight of Japanese DD-CKD patients (60.0 kg) is lower than that of the global cohort of DD-CKD patients (75–77 kg), as noted by Rekic *et al*.[26]

Age was a covariate for CL/F. This age effect is supported by the results of a clinical study of healthy young and elderly male and

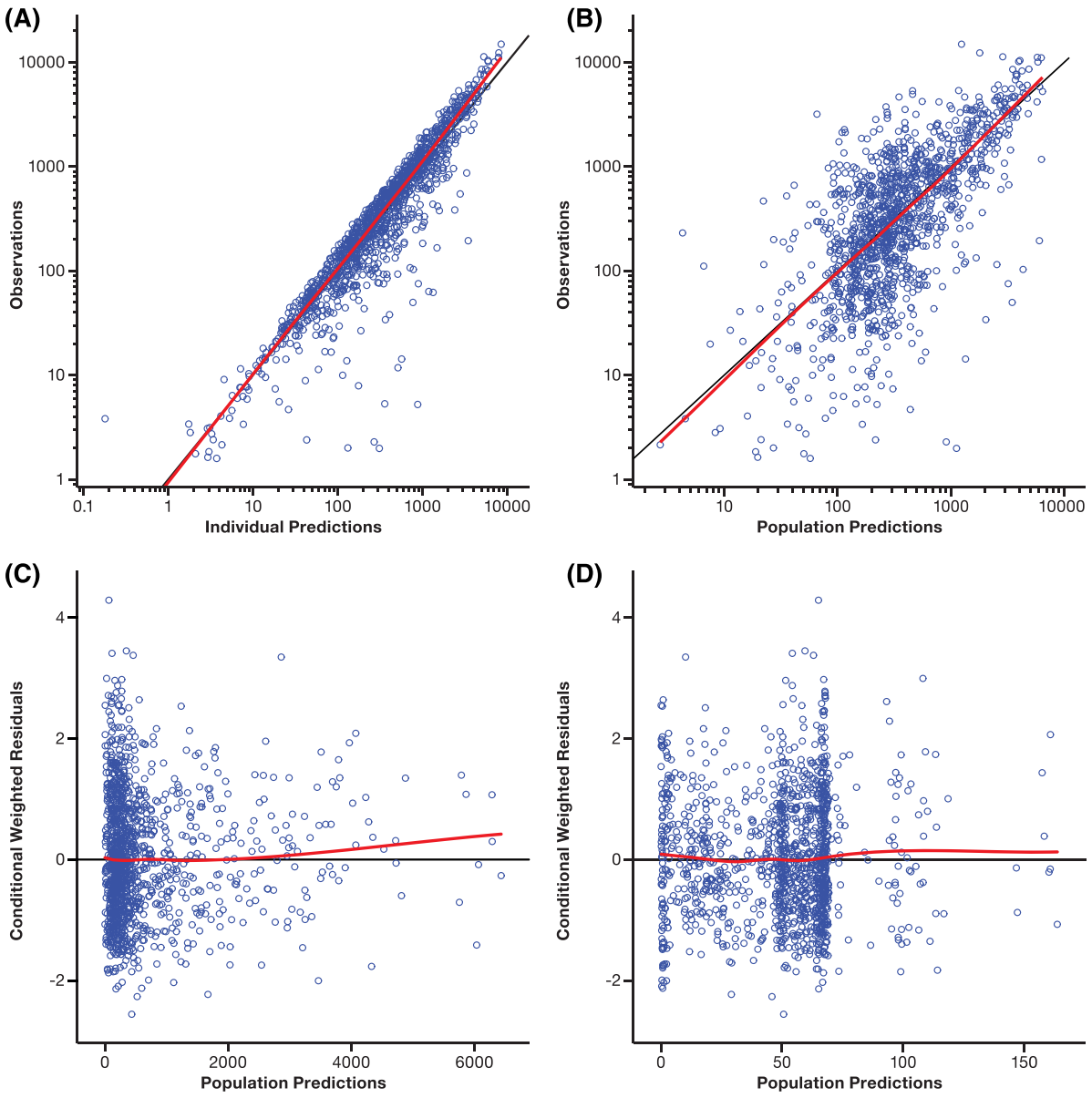

FIGURE 2 Goodness of fit plots. (A) Observed values and individual predicted values, (B) observed values and predicted values, (C) conditional weight residuals and predicted values, (D) conditional weight residuals and time elapsed from dosing. Blue circle: observed data. Red line: trend line

female subjects (data on file); however, age was not significant enough to require a dose adjustment.

No significant difference was observed based on covariate testing between HD and PD patients. The PK profile of roxadustat was not influenced by the type of dialysis.

No laboratory values related to hepatic functions were identified as covariates for CL/F, although liver is the main metabolic pathway of roxadustat. Albumin was also not selected, despite the high binding ratio, although protein binding was different in subjects with liver impairment.[11] Additionally, patients with severe liver impairment were not included in the studies. Concomitant clopidogrel (CYP2C8 inhibitor) was also not identified as a covariate. Dose had no effect on CL/F up to 250 mg, although only 1 patient was administered 250 mg.

At least 1 of the concomitant PBs were administered to 301 patients (82.0% of total). Seventy-seven patients (83.7% in phase II study) were given PBs without time separation, while 224 (81.5% in phase III studies) patients received PBs with time separation (Table 3). The binding effects of sevelamer hydrochloride, bixalomer and ferric citrate on bioavailability were estimated to be larger than other PBs. This result is comparable to the DDI study in which the effect of sevelamer was larger than the effect of calcium acetate.[22] Lanthanum's effect on relative bioavailability is the smallest among PBs and below 10%. This result is also comparable to the DDI study.[17] In addition, the modelling suggests the binding capacity of ferric citrate may be at the same level as sevelamer hydrochloride and bixalomer, although no clinical study was conducted to confirm the DDI of ferric citrate on roxadustat.

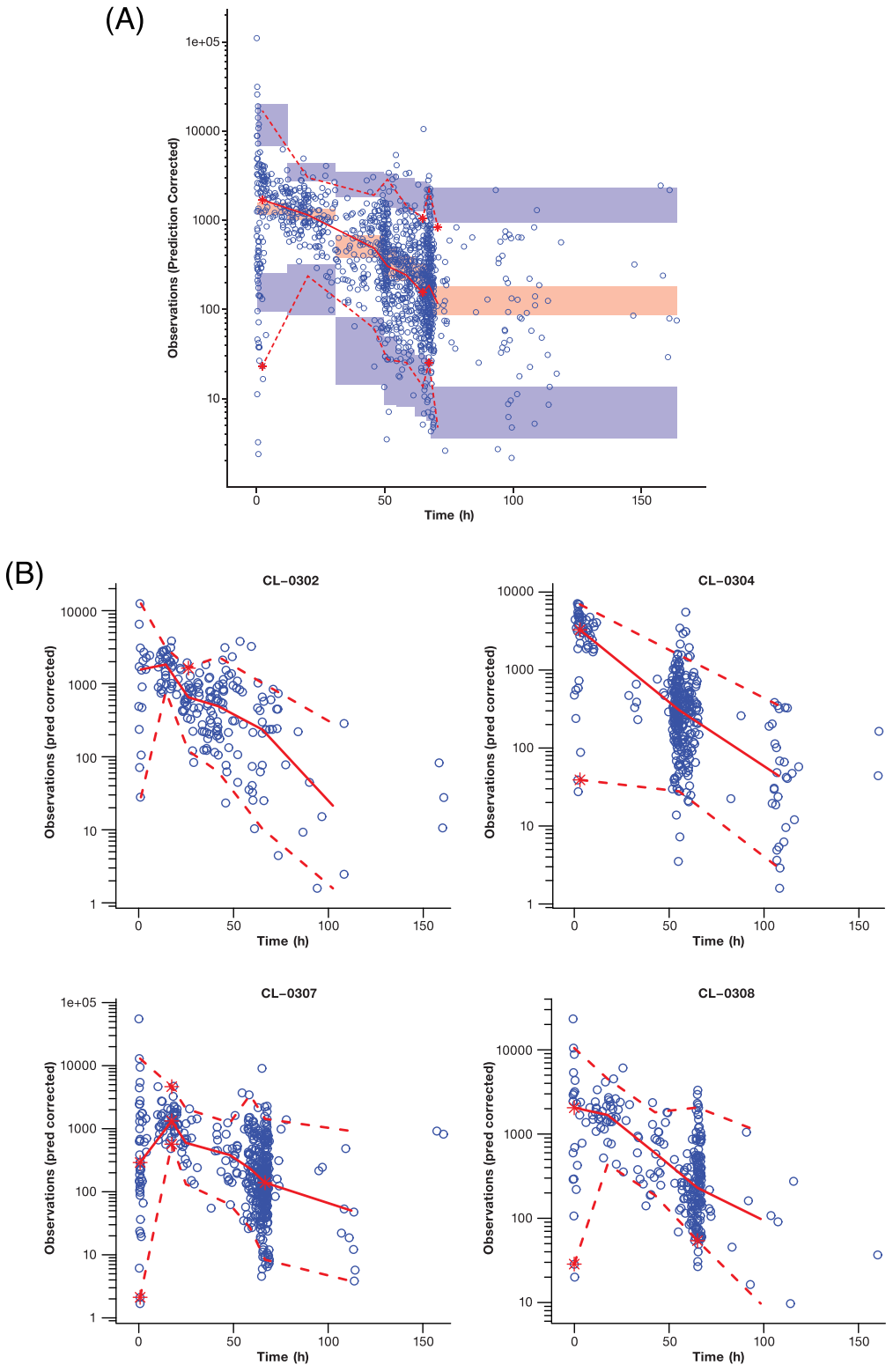

FIGURE 3 Visual predictive check of final model. (A) Pooled, (B) stratified by study. Blue circle: observation. Red solid and dashed lines: 50th and 5th/95th percentiles of the observations. Red shaded areas: the 90% CIs of the simulated median trend. Blue shaded areas: the 90% CIs of the simulated trends at the 5th and 95th percentiles. CI, confidence interval

Time separation of PBs and roxadustat reduced the effect of PBs on roxadustat's bioavailability; this result is supported by findings from the clinical DDI study[22] and a population PK study.[26] Specifically, findings from the clinical DDI study[22] led to a strategy of separating doses of roxadustat and PBs by at least 1 hour in phase III trials of roxadustat in order to minimize the interaction between

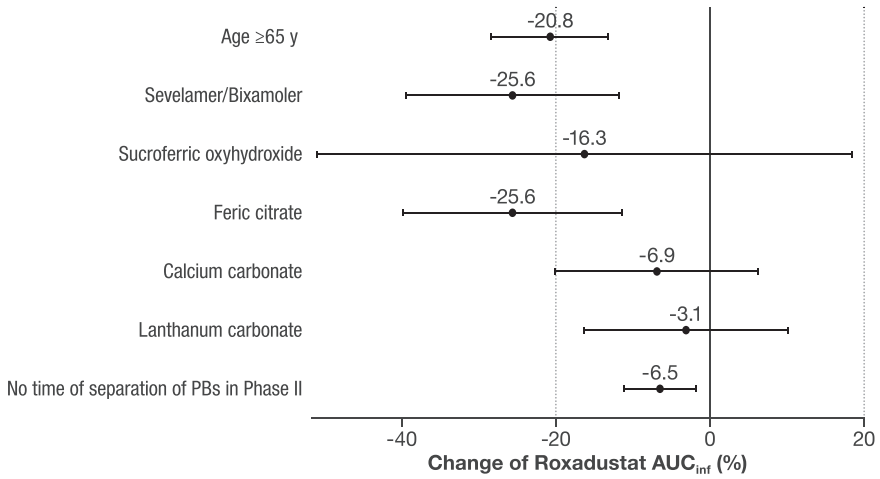

FIGURE 4 Forest plot of intrinsic/extrinsic covariate effect on roxadustat exposure. Mean and its 95% confidence interval were calculated by population pharmacokinetic parameters and standard error. AUC_{inf}, concentration–time curve from time 0 extrapolated to infinity; PBs, phosphate binders

roxadustat and these PBs. In a population PK analysis of phase III studies,[26] the AUC and C_{max} of roxadustat were decreased with PB coadministration, but none of the PBs affected roxadustat exposure more than predefined no-effect boundaries. Based on the findings from the 2 aforementioned analyses, it can be concluded that the staggering strategy (1-h separation) is effective in minimizing the effect of the interaction between roxadustat and PBs.

Because roxadustat was initiated in CKD patients at a relatively low starting dose compared to studied doses in patients in other countries and was titrated to achieve and maintain target haemoglobin levels, the clinical impact of age and PB coadministration on the PK of roxadustat was mild and manageable.

5 | CONCLUSION

The concentration profile of roxadustat in DD-CKD patients with anaemia in Japan was well described by a 2-compartment disposition model with first-order absorption and interindividual variability on CL/F, Vc/F and ka. Key factors contributing to the model were concomitant PB use on bioavailability and age on CL/F. The clinical impact of age and PB coadministration on the PK of roxadustat were mild and manageable.

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COMPETING INTERESTS

A.T. is an employee of Astellas Pharma Global Development, Inc., Illinois, United States. T. Shibata, T. Shiga and K.K. are employees of Astellas Pharma, Inc., Tokyo, Japan. D.G. is an employee of Astellas Pharma Europe B.V., Leiden, Netherlands.

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DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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