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ORIGINAL ARTICLE

Population pharmacokinetic modelling of febuxostat in healthy subjects and people with gout

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Aims: To investigate and characterise the pharmacokinetics of febuxostat and the effect of the covariates of renal function and body size descriptors on the pharmacokinetics of the drug.

Methods: Blood samples (n = 239) were collected using sparse and rich sampling strategies from healthy (n = 9) and gouty (n = 29) subjects. Febuxostat plasma concentrations were measured by a validated high-performance liquid chromatography method. Population pharmacokinetic analysis was performed using NONMEM. A common variability on bioavailability (FVAR) approach was used to test the effect of fed status on absorption parameters. Covariates were modelled using a power model.

Results: The time course of the plasma concentrations of febuxostat is best described by a two-compartment model. In the final model, the population mean for apparent clearance (CL/F), apparent central volume of distribution (Vc/F), apparent peripheral volume of distribution (Vp/F), absorption rate constant (ka) and apparent intercompartmental clearance (Q/F) were 6.91 l h^{-1}, 32.8 l, 19.4 l, 3.6 h^{-1} and 1.25 l h^{-1}, respectively. The population parmater variability (coefficient of variation) for CL/F, Vc/F and Vp/F were 13.6, 22 and 19.5%, respectively. Food reduced the relative biovailability and ka by 67% and 87%, respectively. Renal function, as assessed by creatinine clearance, was a significant covariate for CL/F while body mass index was a significant covariate for Vc/F.

Conclusions: Renal function and body mass index were significant covariates. Further work is warranted to investigate the clinical relevance of these results, notably as renal impairment and obesity are common occurrences in people with gout.

KEYWORDS
clinical pharmacology, febuxostat, gout, hyperuricaemia, population pharmacokinetics, rheumatology

The authors confirm that the Principal Investigator for this paper is Professor Richard Day and that he had direct clinical responsibility for the study subjects.

1 | INTRODUCTION

Febuxostat is used to treat gout by reducing serum urate concentrations.[1–7] It inhibits the two isoforms of xanthine oxidoreductase (XOR), namely xanthine dehydrogenase (XDH) and xanthine oxidase (XOD, also abbreviated as XO).[8–10] The pharmacokinetics of febuxostat have been examined primarily in subjects without gout using standard noncompartmental analysis[11–21] and more recently by compartmental analysis using a two-staged approach.[22] Febuxostat is rapidly absorbed in healthy subjects under fasting conditions and extensively cleared by phase I (~35%, oxidation) and phase II (~40%, glucuronidation) metabolism, with febuxostat-glucuronide and unchanged drug (1-6%) being excreted in the urine.[12,15] Plasma concentration declines steeply by up to 100-fold over the dosage interval (24 h).[15,22] The maximum plasma concentrations (C_{max}) and time (T_{max}) to achieve the peak concentrations of febuxostat were similar between male and female healthy subjects.[11,14–16,21,22] The apparent clearance of the drug tended to be lower in females compared to males, but this difference was diminished when the apparent clearance was normalised for body weight.[22] The pharmacokinetic data derived from studies in healthy subjects are characterised by large coefficients of variation,[23] warranting further investigations to identify possible causes of this variability. In healthy subjects, food was found to reduce the rate but not the extent of absorption ($AUC_{0\text{-}48h}$).[17] Mild (Child–Pugh class A) and moderate (Child–Pugh class B) hepatic impairment did not affect the pharmacokinetics of the drug.[14] By contrast, reports of the effect of renal function on the pharmacokinetics of febuxostat have been discordant.[18,24–26] An effect of renal function on the apparent clearance of febuxostat is unexpected because only a small proportion of febuxostat is eliminated unchanged in the urine. The pharmacokinetics of febuxostat have been examined using both one-compartment[24] and two-compartment[25] population pharmacokinetic models. Details and differences between these models[24,25] are described in Supporting Information Table S1). The influence of renal function on the apparent clearance of febuxostat differs between these pharmacokinetic models.[24,25] Renal function had no effect on the apparent clearance of febuxostat in the one-compartment model.[24] By contrast, there was a significant effect of creatinine clearance, as a measure of renal function, on the apparent clearance of febuxostat in the two-compartment model.[25] Furthermore, body weight influenced both the apparent clearance (CL/F) and the apparent volume of distribution (Vd/F) of febuxostat in the one-compartment model.[24] By contrast, with the two-compartment model, body weight was a significant covariate for the apparent clearance of febuxostat only[25] (Supporting Information Table S1). The description of the two-compartment model is limited,[25] however, as the study was only presented in an abstract form and had deficiencies, such as a large residual coefficient of variation (71%), lack of a value of the intercompartmental clearance (Q, L h^{-1}) and an estimated absorption rate constant (ka) of 13 h^{-1} corresponding to a half-life of absorption of 0.053 hours (3 minutes), a value that is biologically implausible given that febuxostat achieves maximum plasma concentration between 0.5 and 1.5 hours post-dose under fasting conditions.[15]

What is already known about this subject

- The pharmacokinetics of febuxostat has been derived mainly from healthy subjects.
- The pharmacokinetics parameters of febuxostat are characterised by large between-subject variability.
- The impact of renal function on the apparent clearance of febuxostat and body size descriptors on both the apparent clearance and apparent volume of distribution is uncertain.

What this study adds

- The pharmacokinetics of febuxostat are best described by a two-compartment model with first-order absorption and elimination.
- Creatinine clearance and body mass index are significant covariates on the apparent clearance and volume of distribution of febuxostat, respectively.

The objectives of the present work were first to examine the pharmacokinetics of febuxostat using population modelling techniques and data from individuals with and without gout. Second, we aimed to investigate the influence of the covariates of renal function on the apparent clearance (CL/F) and body size descriptors on both the CL/F and apparent central volume of distribution (Vc/F) of febuxostat.

2 | METHODS

2.1 | Study populations and blood sampling

Data from two clinical studies were used in the analysis: study A, a single-dose pharmacokinetic-pharmacodynamic (PK-PD) study of febuxostat (80 mg) in healthy subjects, and study B, a multisite, open label, prospective PK-PD study of febuxostat in patients with gout. The studies (SVH 15/276 and SVH 16/22) were approved by the Human Research Ethics Committee of St Vincent's Hospital, Sydney and registered on the Australian New Zealand Clinical Trials Registry (ACTRN 12617001346369 and ACTRN 12616000959471). All study participants provided oral and written consent. The study A cohort were administered a single dose of febuxostat (80 mg) under fasting conditions.[22] Blood samples (5 ml each) were collected from each subject immediately before drug

administration and at the following time points after administration: 1, 3, 6, 9, 24 (±2), 31 (±1), 48 (±2), 72 (±2), 96 (±2) and 102 hours. In study B, subjects with gout were administered a range of doses (40-160 mg/day) of febuxostat in a treat-to-target approach in real clinical settings. Up to four blood samples per patient per dose level were collected at steady state at least 7 days after commencing and/or changing the dose of the drug at 1 (±0.25), 6 (±2), 10 (±2) and 24 (±2) hours post-dose.

2.2 | Bioanalysis

Blood samples were vortexed and plasma separated and kept at −20 °C until analysis. Plasma concentrations of febuxostat were measured using a validated HPLC method with fluorescence detection.[27] The lower limit of quantification (LLQ) of this method was 0.005 μg mL^{-1}. Serum creatinine concentrations were determined by the Jaffe method[28–30] at local pathology laboratories; this assay is subject to routine validation for precision and accuracy.

2.3 | Population modelling

2.3.1 | Software

Population pharmacokinetic analysis was performed by nonlinear mixed-effects modelling using NONMEM version 7.4.1.[31] Wings for NONMEM (WFN version 7.4.1[32]) was used as a DOS-based interface to NONMEM. First-order conditional estimation with interaction (FOCEI) was used to fit models. Post-processing NONMEM outputs and generating graphs were conducted using R software version 3.4.[33]

2.3.2 | Modelling strategy

One- and two-compartment models with first-order absorption with and without lag time were evaluated to determine the base structural model. The elimination phase was assumed to follow first-order kinetics. Additive, proportional and combined (additive and proportional) residual error models were evaluated. All detectable plasma concentrations of febuxostat were included as continuous data, including points below the limit of quantification (BLOQ), which was shown to improve the stability of population pharmacokinetic models.[34] Between-subject variability (BSV) was modelled on pharmacokinetic parameters using a log-normal distribution.

2.3.3 | Covariate modelling

Covariates of renal function on the apparent clearance and body size descriptors on both the apparent clearance and apparent central volume of distribution (Vc/F) were examined in a univariate selection process using a power model (Equation 1).

$$\theta = \theta_{pop} \times (Cov/Cov_{median})^{\theta cov} \quad (1)$$

The effect of renal function was assessed in terms of baseline estimated glomerular filtration rate (eGFR), as estimated by the Chronic Kidney Disease-Epidemiology [CKD-EPI] Equation 2009[35]), on-treatment eGFR (as estimated by CKD-EPI 2009[35] and Modified Diet Renal Disease (MDRD]),[36] with and without adjustment for body surface area, and on-treatment creatinine clearance as estimated by the Cockcroft-Gault equation (Equation 2), with and without adjustment for ideal body weight.[37]

$$CrCL = [(140 - age) \times WT \times F]/(Scr \times 0.8136) \quad (2)$$

where CrCL is creatinine clearance (mL min^{-1}), F is 1 if male and 0.85 if female, age is in years, WT is weight (kg) and Scr is serum creatinine (μmol l^{-1}).

$$\text{CrCL adjusted for ideal body weight (IBW)} = [(140 - age) \times IBW \times F]/(Scr \times 0.8136)$$

where the IBW is calculated as follows:
females IBW = 45.5 kg + 0.9 kg/cm for each cm >152 cm
males IBW = 50 kg + 0.9 kg/cm for each cm >152 cm

Body size descriptors were assessed as body weight, lean body weight (LBW) as calculated by the Boer equation[38] (Equation 3a,b), body mass index (BMI) and body surface area (BSA) as estimated by the Du Bois formula[39] Equation 4).

Boer equation:

$$\text{For males} = 0.407 \times WT + 0.267 \times HT - 19.2 \quad (3a)$$

$$\text{For females} = 0.252 \times WT + 0.473 \times HT - 48.3 \quad (3b)$$

where WT is body weight (kg) and HT is height (cm).

Du Bois formula:

$$BSA = 0.007184 \times WT^{0.425} \times HT^{0.725} \quad (4)$$

The effect of food on ka and oral availability (F) was examined since subjects in study B were allowed to take febuxostat with or without food. A common variability on oral availability (FVAR) approach was tested which employs a common random effect for oral availability that allows parameters affected by oral availability (CL/F, Vc/F, Q/F and Vp/F) to have a shared common source of variability.[40–43] This approach consequently aims to stabilize models by accounting for an important source of correlation between the apparent clearances and volumes, and thereby reducing the unexplained between-subject variability in these parameters.

Significant covariates were examined in a classic forward addition (P value of .05) followed by backward elimination at a higher threshold (P < .01, equivalent to an absolute change in the objective function value of 6.63.[44]

Model selection and predictive performance

Model selection was based on the change in the objective function value, a minimum drop of objective function value (OFV) of −3.84, equivalent to a *P* value of .05, biological plausibility and precision of parameter estimates and subjective criteria.[43–47] The following diagnostic plots were used to assess the predictive performance of the model: observed concentration (Cobs) versus population predicted value (PRED), Cobs versus individual predicted value (IPRED) and conditional weighted residual error (CWRES) versus time after the dose. The extent of shrinkage was evaluated by post hoc Bayesian estimate-based diagnostics. The final model was evaluated using a prediction-corrected visual predictive check (pcVPC). In pcVPC, a total of 1000 replications of the original data set were simulated by NONMEM using the final model to generate the expected concentrations and 95% prediction intervals. The observed data were overlaid on the prediction intervals and compared visually.

3 | RESULTS

3.1 | Subject characteristics

A total of 39 participants were recruited in study A (healthy young subjects, n = 9) and study B (patients with gout, n = 30). Cohort B was older, on multiple medications, and had comorbidities and reduced renal function compared to the healthy subjects (Table 1). A total of 239 samples (study A n = 92 samples and study B n = 147 samples) were collected from the participants, of these 13 samples had concentrations of febuxostat below the limit of quantification (BLOQ < 0.005 μg mL^{-1}). Most of the pharmacokinetic data were derived from febuxostat 80 mg (n = 179 samples, 75%). The contribution of the other doses (40, 120, and 160 mg/day) to the data sets was therefore small.

3.2 | Base model

A two-compartment model with first-order absorption provided a better description of the data compared to a one-compartment model (ΔOFV = 266.367). The residual error was best described by a proportional residual error model. A summary of the pharmacokinetic model building steps is given in Supporting Information Table S2. Inclusion of the BLOQ data (13 samples), as observed, improved the performance of the model (Supporting Information Table S2) compared to removing them from the dataset. In the base model, all parameters were estimated with high precision (≤20% standard error [SE]; Table 2). Shrinkage was low (<37%) except for Q/F and the Vp/F (Table 2). The BSV for all parameters was retained in the base model.

TABLE 1 Summary of the characteristics of the study subjects

Characteristics	Study A (n = 9)	Study B (n = 30)
Population	Healthy subjects	Gout patients
Gender	Males = 6, females = 3	Males = 24, females = 6
Age (year)	26.2 ± 4.9	62.1 ± 13.4
Weight (kg)	69.5 ± 12.1	98.1 ± 28.5
Body mass index (kg m^{-2})	24.0 ± 2.7	34.2 ± 9.6
Lean body mass (kg)	53.2 ± 8.2	63.3 ± 13.0
Body surface area (m^2)	1.9 ± 0.4	2.1 ± 0.3
Baseline serum creatinine (μmol L^{-1})	78.2 ± 7.2	126.5 ± 41.7
On-treatment serum creatinine (μmol L^{-1})	78.2 ± 7.2	128.8 ± 47.2
Baseline eGFR (CKD-EPI 2009 equation, mL min^{-1} 1.73 m^{-1})	115.3 ± 8.4	57.8 ± 27.9
On-treatment eGFR (CKD-EPI 2009 equation, mL min^{-1} 1.73 m^{-2})	115.3 ± 8.4	58.0 ± 29.0
On-treatment eGFR (MDRD equation, mL min^{-1} 1.73 m^{-2})	101.3 ± 8.4	54.8 ± 28.3
On-treatment eGFR (CKD-EPI 2009 equation, mL min^{-1})	120.1 ± 17.0	69.4 ± 35.7
On-treatment eGFR (MDRD equation, mL min^{-1})	105.8 ± 15.7	67.0 ± 33.9
On-treatment creatinine clearance (Cockcroft-Gault, mL min^{-1})	120.7 ± 20.7	83.0 ± 43.2
On-treatment creatinine clearance corrected for ideal body weight (Cockcroft-Gault, mL min^{-1})	113.5 ± 19.5	56.3 ± 31.1
Febuxostat mean dose (mg)	80	89.2
Comorbidities	Nil	Hypertension (58%), hypercholesterolaemia (46%), diabetes (27%), chronic kidney disease (35%), coronary artery disease (15%) and heart failure (12%)
Cotherapies		Diuretics (23%), aspirin (0%)

Note: Data are presented as mean ± SD.

Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiology equation;[35] MDRD, modified diet renal disease;[36] SD, standard deviation.

TABLE 2 Population pharmacokinetic parameter estimates of febuxostat by final model

	Estimate	SE% for the estimate
CL/*F* (θ_1)	6.91	6.0
Covariate TCrCL (θ_6)	0.52	11.0
Vc/*F* (θ_2)	32.8	10.0
Covariate BMI (θ_7)	0.996	17.6
Q (θ_3)	1.25	13.9
Vp/*F* (θ_4)	19.4	11.9
ka (θ_5)	3.62	29.3
Covariate food on oral availability	−0.667	7.5
Covariate food on ka	−0.869	5.7
BSV (shrinkage %)		
BSV-CL/F (θ_1)	13.6 (37.4)	34.8
BSV-Vc/F (θ_2)	22.0 (35.4)	45.8
BSV-Q (θ_3)	-	-
BSV-Vp/F (θ_4)	19.5 (58.2)	52.8
BSV-ka (θ_5)	-	-
BSV-FVAR	27.7 (21.2)	25.4
RUV-CV% (shrinkage %)	39.9 (10.1)	6.1

Abbreviations: BMI, body mass index (kg m^{-2}); BSV, between-subject variability; CL/*F*, apparent clearance (L h^{-1}); FVAR, common variability on oral availability; ka, absorption rate constant (h^{-1}); Q, intercompartmental clearance (L h^{-1}); RUV, residual unexplained variability; TCrCL, on-treatment creatinine clearance (mL min^{-1}); Vc/*F*, apparent central volume of distribution (L); Vp/*F*, apparent peripheral volume of distribution (L).

The final model is described below:

$$F = \text{TVF} \times \text{FVAR, where FVAR} = \text{EXP (ETA)}$$
$$\text{CL}/F = \theta_1 \times (\text{TCrCL}/99)^{0.52}$$
$$\text{Vc}/F = \theta_2 \times (\text{BMI}/30.6)^{0.996}$$

where TVF is the typical population estimate of the absolute oral availability, which is unknown and thus is set to 1 such that CL/*F* and Vc/*F* are apparent oral parameters.

3.3 | Covariates

In the forward univariate selection of covariates, renal function as assessed by on-treatment creatinine clearance (TCrCL, mL min^{-1}) was the most significant covariate for the apparent clearance of febuxostat. The use of baseline MDRD, and on-treatment MDRD, CKD-EPI and eGFR resulted in smaller improvements in the model compared to the on-treatment creatinine clearance. BMI was a significant covariate for the apparent central volume of distribution (Supporting Information Table S2). Body weight was also a significant covariate on the apparent clearance of febuxostat (Supporting Information Table S2). However, it was excluded during the forward addition and backward deletion steps. The inclusion of TCrCL and BMI in the model reduced the coefficient of variation on the apparent clearance and apparent central volume of distribution by 31% and 29%, respectively (Table 2 and Supporting Information Figure S1). The full model including common variability on oral availability approach, fed status on ka and *F*, TCrCL on CL/*F*, and BMI effect on Vc/*F* resulted in the highest reduction in the OFV. Food reduced the oral availability and absorption rate constant by 67% and 87%, respectively. When BSV was re-investigated after inclusion of covariates, it was found that removing BSV on Q/*F* and ka had no negative impact of model fit. All aforementioned covariates were retained in the model during the backward elimination step (Supporting Information Table S2). The population parameter values of the final model are reported in Table 2. All pharmacokinetic parameters were estimated with good precision (% SE < 30%) (Table 2). The diagnostic plots for the final model are depicted in Figure 1.

The final model is described below:

$$\text{F} = \text{TVF} \times \text{FVAR, where FVAR} = \text{EXP}\,(\text{ETA})$$

$$\text{CL}/\text{F} = \theta_1 \times (\text{TCrCL}/99)^{0.52}$$

$$\text{Vc}/\text{F} = \theta_2 \times (\text{BMI}/30.6)^{0.996}$$

where FVAR is between-subject variability on oral availability, TVF is the typical population estimate of the absolute oral availability, which is unknown and thus is set to 1 such that CL/*F* and Vc/*F* are apparent oral parametes, θ_1 and θ_2 are the population means for CL/*F* and Vc/*F*, respectively, CL/*F* is the apparent clearance of febuxostat (l h^{-1}), FVAR is common variability on the oral availability of the drug,

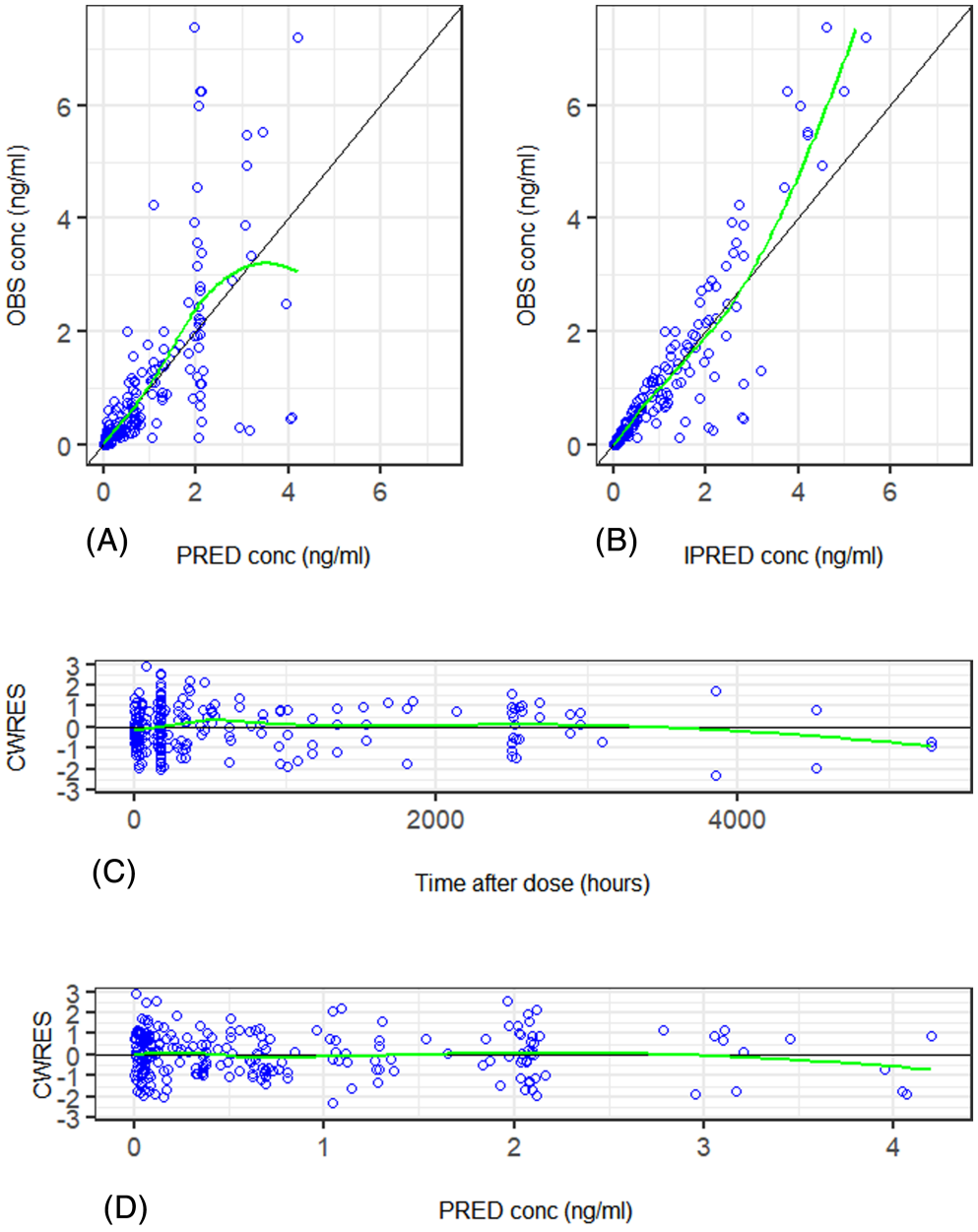

FIGURE 1 Scatter plots of the goodness of fit for the final model. (A) Observed plasma concentration of febuxostat (OBS) versus predicted plasma concentrations of febuxostat (PRED). (B) Observed plasma concentration of febuxostat (OBS) and individually predicted plasma concentrations of febuxostat using Bayesian estimations (IPRED). (C) Conditional weighted residuals (CWRES) versus time after dose. (D) Conditional weighted residuals (CWRES) versus predicted plasma concentrations of febuxostat (PRED)

Vc/*F* is the apparent central volume of distribution (L), TCrCL is the on-treatment creatinine clearance as calculated by the Cockcroft-Gault equation (mL min^{-1}) and BMI is the body mass index (kg m^{-2}).

The observed concentrations of febuxostat versus the individually predicted (IPRED) concentrations using Bayesian estimation showed improvement compared to the model predicted concentrations (PRED). Scatter plots of conditional weighted residuals (CWRES) versus the predicted concentrations (PRED) and the time after dose (TAD) were randomly distributed (Figure 1). The pcVPC of the final model resulted in a good description of the observed data (Figure 2).

4 | DISCUSSION

The time course of the plasma concentrations of febuxostat was best described by a two-compartment model. This is consistent with our previous report, which demonstrated that febuxostat has mean initial and terminal half-lives of 2 and 14 h, respectively, with 81% of febuxostat being eliminated from plasma in the first 9 h post-dose.[22] The inclusion of the observed plasma concentrations of febuxostat that were below the limit of quantification (BLQ) (n = 13 samples) improved the performance of the model, which is in line with reports in the literature that including the BLQ data, as reported by the assay regardless of the lower limit of quantification, improved the performance of population models.[34]

The population estimate of CL/*F* by the present model was 6.91 l h^{-1}. This value was slightly greater than that reported for healthy Chinese subjects (5.3 Lh^{-1}),[17,20] but less than that found for healthy African Americans (10.5 l h^{-1})[11,12,14–16,18–20] and for Japanese subjects who had gout or were hyperuricaemic (9.9 l h^{-1}).[48] The mean value of the Vc/*F* estimated by the present model was

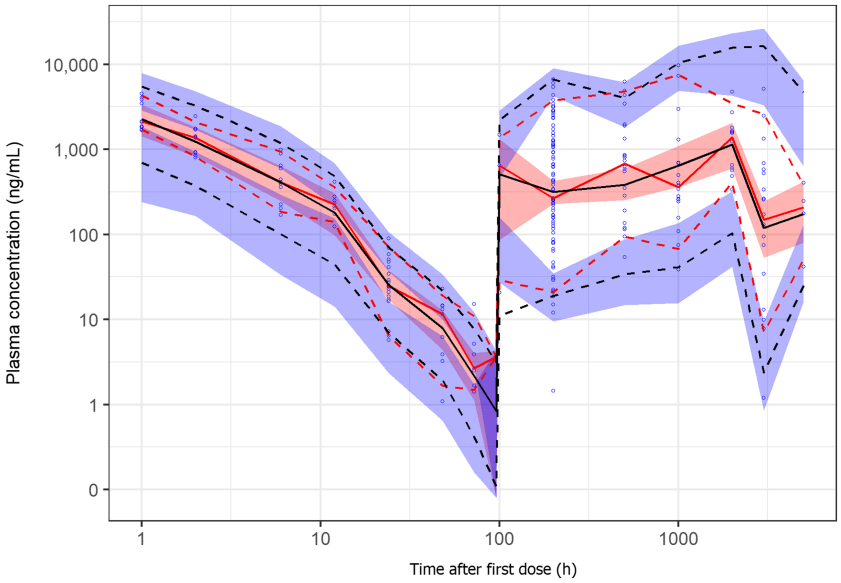

FIGURE 2 Prediction corrected visual predictive check of the final model (black) and observed (red) data. The *x* axis is a logarithmic scale. The solid lines are the median and the dashed lines are the 2.5th and 97.5th percentiles of simulated data from the model. Shaded bands represent the 90% confidence intervals of the median and 2.5th and 97.5th prediction intervals from the final model.

32.8 l. This value was similar to the mean value of Vc/*F* of 32.2 l estimated by the published two-compartment model.[25] The mean value of Vp/*F* (19.4 l) estimated by the present model was comparable to the value estimated by the published two-compartment model (22.2 l).[25] Furthermore, the mean value of ka estimated by the full model was 3.62 h^{-1}, which is in line with the value assumed (ka = 2.18 h^{-1}) by Hirai et al[49] and the one-compartment model (ka = 2.52 h^{-1}).[24]

In the present study, a heterogeneous population comprising healthy subjects and typical patients with gout allowed the influence of a wide span of renal function and body weight values to be examined. In the present model, the on-treatment creatinine clearance, as estimated by the equation of Cockcroft-Gault, and body mass index were significant covariates for the apparent clearance and apparent central volume of distribution of febuxostat, respectively.

The impact of renal function on the apparent clearance of febuxostat in the present study was significant despite published data indicating that only 1-6% of febuxostat is excreted unchanged in the urine. Febuxostat glucuronide, which compromises about 40% of the dose, is also excreted by the kidneys. However, it is well established that acyl glucuronides of many drugs are readily cleared by the kidneys and therefore may accumulate in renal impairment.[50] Subsequent in vivo hydrolysis of the glucuronides may then regenerate the parent compound, which reduces the overall apparent clearance of the parent drug. This process of glucuronidation and hydrolysis to release the parent drug is called futile cycling and is a known feature of drugs that are cleared predominantly by forming acyl glucuronides.[50] However, we neither determined the plasma concentrations of febuxostat glucuronide to test this hypothesis nor noted the classical "delayed" peaks in individual profiles, particularly in view of the sparse sampling, which often characterise acyl-glucuronde futile cycling. The clinical relevance of the present results warrants further investigations.

It was of note that a greater influence of renal function was observed when the on-treatment creatinine clearance was used as the estimate for renal function as opposed to eGFR (as estimated by the CKD-EPI 2009 and MDRD equations). The possible reason is that the creatine clearance but not eGFR is scaled to body weight, which was also a significant covariate of the apparent clearance but was removed during the forward addition and backward deletion steps.

In the present study, food reduced the oral availability of the drug by 67%. In the study by Khosravan et al,[13] food was associated with a 50% reduction in C_{max} and a 20% reduction in $AUC_{0\text{-}24}$ in healthy subjects. By contrast, in the study by Liu et al,[17] the authors examined the plasma concentrations of febuxostat in healthy subjects for a longer period of time (48 h, $AUC_{0\text{-}48}$) and found a negligible effect of food on the extent of absorption. In the present study, we expected that food would lower the rate, but not the extent, of absorption of febuxostat. However, in patients with gout the blood samples were collected over a dosage interval of 24 h at steady state and thus food effects on the extent of absorption were observed over this interval. Although the effect of food on the oral availability and absorption rate constant using the common variability approach improved model predictions, there were still some underestimations of the high concentrations of plasma febuxostat by the final model. However, the pcVPC showed a good description of the data. None of the study participants were on any medication that was known to affect the pharmacokinetics of febuxostat. It has been reported in the literature that polymorphisms in uridine diphosphate (UDP)-glucuronosyltransferase (UGTs) (namely the six and 28 variants) reduced the apparent clearance of febuxostat by 22%.[51] Analysis the DNA of patients for possible interactions between variant UGTs and the apparent clearance of the drug was not undertaken in the present study. It is therefore not known whether any polymorphisms in UGTs could have confounded the results of the present study[51] or the two previously published population pharmacokinetic models.[15,24] There was only one subject in study B

who had hepatic impairment (Child-Pugh grade A). Mild and moderate hepatic impairment (Child-Pugh grades A and B) had no effect on the pharmacokinetics of febuxostat.[14]

5 | CONCLUSION

Renal function had an effect on the apparent clearance of febuxostat. Body mass index was a significant covariate of the apparent central volume of distribution. Further work is warranted to investigate the clinical relevance of these results, notably as renal impairment and obesity are common occurrences in people with gout.

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COMPETING INTERESTS

All authors declare no conflict of interest.

CONTRIBUTORS

All authors contributed to the inception and design of the study, and the writing of the present manuscript. Additionally, B.K., A.Y.A., D.F. and J.K.D. were involved in the data analyses and modelling. Each author contributed to important intellectual content during drafting and/or revision of the manuscript and accepts accountability for the overall work.

DATA AVAILABILITY STATEMENT

We do not have permission from the Ethics Committee or research subject participants to share the study data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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