ORIGINAL ARTICLE

Population pharmacokinetic analysis of peficitinib in patients with rheumatoid arthritis

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Aims: To analyse the population pharmacokinetics (PK) of peficitinib in patients with rheumatoid arthritis (RA) and assess the potential PK covariates to identify the requirement for dose adjustment in RA patients.

Methods: The analysis incorporated 2464 observations from 98 healthy volunteers and 4919 observations from 989 RA patients. A population PK model for peficitinib in RA patients was constructed by a nonlinear mixed effect model using NONMEM with prior information from a healthy volunteer model.

Results: A 2-compartment model with sequential zero- and first-order absorption and lag time was constructed for RA patients. Covariate exploration in the RA patient model revealed that estimated glomerular filtration rate (eGFR) and lymphocyte count had a significant effect on apparent total systemic clearance (CL), which was 91.7 L/h (2.3% relative standard error). Compared with the mean population CL, the model predicted mean changes in CL of 12.3 and −10.7% in patients with observed minimum and maximum lymphocyte count of 500 and 4600 10^6/L, respectively, and mean changes in CL of −17.8 and 16.7% in patients with minimum and maximum eGFR of 36.4 and 188 mL/min/1.73m^2, respectively. The simulated population mean area under plasma concentration–time curve for 24 hours after dosing showed a 1.35-fold increase in patients with severe renal impairment (eGFR 22.5 mL/min/1.73m^2) compared with patients with reference eGFR (91.5 mL/min/1.73m^2).

Conclusion: The population PK model identified eGFR and lymphocyte count as covariates for CL. The magnitude of changes was not considered clinically relevant, indicating no requirement for dose adjustment.

KEYWORDS

population analysis, pharmacokinetics, rheumatoid arthritis

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This manuscript was a nonclinical modelling study, and there was no associated clinical responsibility for patients. As such, there is no Principal Investigator on this publication.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that targets the synovial tissues.[1] The goal of RA treatment is to control disease activity and achieve remission by reducing joint destruction, preventing loss of function, and relieving pain; thereby improving quality of life.[2] Although a great number of biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) have been approved, unmet therapeutic needs in RA remain: 30–40% of patients do not respond to biologics and complete remission is achieved in only 20–25% of patients.[3] Therefore, there is a need to develop new treatments for RA patients who have an inadequate response to existing drugs.

Peficitinib is an oral inhibitor of the Janus kinase (JAK) family of nonreceptor tyrosine kinases (JAK1, JAK2, JAK3 and tyrosine kinase 2), which is a promising therapeutic target for the treatment of autoimmune disorders such as RA.[4–6] The efficacy and safety of peficitinib, as monotherapy or in combination, for treatment of patients with RA has been previously demonstrated in phase 2 and phase 3 randomized, double-blind, placebo-controlled studies.[7–11] Peficitinib has been approved in Japan, Korea and Taiwan as an RA treatment (including prevention of structural joint damage) in patients who have an inadequate response to conventional DMARD therapy.

The pharmacokinetic (PK) characteristics of peficitinib in healthy volunteers were investigated in previous clinical pharmacology studies. These studies showed that peficitinib was absorbed rapidly, as demonstrated by time to maximum observed concentration (T_{max}) of 1.0–1.8 hours, and that food intake increased the area under the plasma concentration–time curve (AUC_{inf}) by 27–36%.[12,13] The mean terminal half-life ($t_{1/2}$) of peficitinib ranged from 2.8 to 12.9 hours,[12] and dose-proportional exposure was demonstrated within the dose ranges studied across single doses (3–300 mg).[12,14] In addition, urinary excretion of peficitinib accounted for 9–15% of the oral dose, and 3 conjugated metabolites were found in plasma and urine (H2: sulfated; H4: methylated; H1: sulfated and methylated).[12,15]

As part of phase 2 and phase 3 studies, data regarding the plasma concentrations of peficitinib in patients with RA were also collected. In this study, a population PK model was constructed to analyse the pooled PK data for peficitinib and to identify significant covariates, with the aim of optimizing the dosing regimen for RA patients based on the magnitude of exposure change under any condition.

2 | METHODS

2.1 | Study design

Table 1 summarizes the designs, including blood sampling times for measurement of plasma peficitinib concentration, of the 5 clinical pharmacology studies[13,16–18] (PK10, PK11, PK12, PK20 and PK27) used for constructing the prior population PK model of peficitinib in healthy volunteers (prior healthy volunteer model) and the 1 phase 2 study[7] (RAJ1) and 2 phase 3 studies[10,11] (RAJ3 and RAJ4) used for

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What is already known about this subject

- The pharmacokinetic (PK) characteristics of peficitinib in healthy volunteers have been reported.
- Although plasma concentrations were collected in phase 2 and phase 3 studies, a detailed investigation of the PK characteristics of peficitinib in patients with rheumatoid arthritis has not been performed, and significant covariates have not been explored.

What this study adds

- We constructed a 2-compartment population PK model for peficitinib in patients with rheumatoid arthritis, with sequential zero- and first-order absorption and lag time, to provide individual post-hoc exposures for further exposure-response analyses.
- Estimated glomerular filtration rate and lymphocyte count were selected as covariates for apparent total systemic clearance, but were not clinically relevant.

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constructing the population PK model of peficitinib for RA patients (RA patient model). All clinical studies were conducted in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practice, and the International Conference on Harmonization guidelines, and were approved by the relevant institutional review boards. All subjects provided written informed consent.

2.2 | Sample measurement

Plasma peficitinib concentrations were measured using validated liquid chromatography–tandem mass spectrometry at LSI Medience Corporation (Itabashi-ku, Tokyo). The lower limit of quantification (LLOQ) was 0.25 ng/mL when 25 μL of plasma was used. The intraday accuracies were within ±15% of the nominal concentration, and the intraday precision did not exceed 15%.

2.3 | Data handling

Missing data or concentrations below the quantification limit were neither imputed nor used for model development. Furthermore, concentrations from renal or hepatic impairment patients were excluded from the healthy volunteer dataset in order to construct a prior model for healthy volunteers with normal renal and hepatic functions. In addition, values taken >48 hours after the last dose of peficitinib in RAJ1, RAJ3 and RAJ4, or <19 hours after the last dose in RAJ1 were excluded because these samples were taken during a time frame for

TABLE 1 Peficitinib clinical studies included in the population PK analysis

Study number	Design	Population	Treatment	Number of subjects [a]	Blood sampling times	Reference
Clinical pharmacology						
PK10 (NCT02586194)	Open-label, single dose, parallel-group comparison	Patients with impaired hepatic function and subjects with normal hepatic function [b]	150 mg	24	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72 h	16
PK11 (NCT02603497)	Open-label, single dose, parallel-group comparison	Patients with impaired renal function and subjects with normal renal function [b]	150 mg	31	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72 h	17
PK12 (not registered)	Open-label, randomized, single dose, 2-way cross over	Healthy volunteers	150 mg	18	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72 h	13
PK27 (NCT02531191)	Open-label, randomized, single dose, 2-way cross over	Healthy volunteers	150 mg	24	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 h	13
PK20 (NCT02760342)	Open-label, single sequence, single dose and multiple dose for 7 days	Healthy volunteers	150 mg	40	Single dose: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 h. Multiple dose: predose on day 2 to 6 and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 h on day 6	18
Phase 2						
RAJ1 (NCT01649999)	Multicentre, placebo-controlled, double-blind, parallel-group, 12-week	Patients with RA; monotherapy	Placebo, 25 mg, 50 mg, 100 mg, 150 mg	221	Trough concentrations for week 1, 2, 4, 8 and 12	7
Phase 3						
RAJ3 (NCT02308163)	Multicentre, placebo-controlled, double-blind, parallel-group, 52-week	Patients with RA and DMARD-IR; concomitant use of DMARDs acceptable	Placebo to 100 mg or 150 mg at week 12, 100 mg, 150 mg, open-label etanercept [c]	295	Trough concentrations for week 4, 8, 12, 28 and 52; postdose concentrations after administration for week 4 or 8	10
RAJ4 (NCT02305849)	Multicentre, placebo-controlled, double-blind, parallel-group, 52-week	Patients with RA and MTX-IR; in combination with MTX	Placebo to 100 mg or 150 mg at week 12 or 28, 100 mg, 150 mg	495	Trough concentrations for week 4, 8, 12, 20, 28, 40 and 52; postdose concentrations after administration for week 4 or 8	11

[a]Total number of subjects who received at least 1 dose of the study drug and provided samples for drug concentrations with analysis points

[b]Patients with renal or hepatic impairment were excluded from the population PK analysis

[c]Patients receiving etanercept were excluded from the population PK analysis.

DMARDs, disease-modifying antirheumatic drugs; IR, inadequate response; MTX, methotrexate; PK, pharmacokinetic; RA, rheumatoid arthritis

which sampling was not scheduled in the protocols and was provided by only a limited number of patients (detailed sampling points are shown in Table 1). In the RA patient dataset, outliers were defined as values greater than the mean + (3 × standard deviation) of log-transformed trough concentrations for each treatment arm of the study. For covariate exploration, baseline measurements of candidate covariates were used; missing baseline values were imputed as the value observed at the closest visit during the treatment period, and value of the LLOQ was imputed if it was below the LLOQ.

2.4 | Population PK model

A population PK model for peficitinib was constructed by a nonlinear mixed-effect model using NONMEM version 7.3 software (ICON, Ellicott City, MD, USA) and Perl-speaks-NONMEM version 4.4.8. Visualization and model diagnostics were performed using R version 3.2.3 and its package Xpose 4 version 4.5.3.[19] Data were analysed using first-order conditional estimation with the interaction option. A 2-compartment model, parameterized in terms of apparent total systemic clearance (CL), apparent intercompartmental clearance (Q), and apparent volume of distribution of the central or peripheral compartment (Vc and Vp, respectively) was proposed to describe the PK of peficitinib in healthy volunteers. The following 5 absorption models were investigated: zero-order absorption (duration, D) with lag-time (ALAG); D without ALAG; first-order absorption (Ka) with ALAG; Ka without ALAG; and sequential zero- and first-order absorption with ALAG. The statistical model included the random and residual variance models. Interindividual variability (IIV) of structural parameters was modelled using an exponential model (Equation 1):

$$P_i = \theta \exp(\eta_i) \tag{1}$$

where θ, P_i and η_i are the population mean of the parameter, parameter P for the i-th subject, and the deviation for the i-th subject's parameter value from the population mean, respectively. η_i is assumed to distribute normally with mean 0 and variance of ω^2. Residual variability was described by a proportional variance model (Equation 2):

$$Y_{ij} = \hat{Y}_{ij}(1 + \varepsilon) \tag{2}$$

where Y_{ij} is the j-th observation in the i-th subject and $\hat{Y}_{ij}$ is the corresponding model prediction. ε is the residual, which is normally distributed with mean 0 and variance of σ^2. This healthy volunteer model was then used as a prior model for the analyses of the RA patients. Using a NONMEM with PRIOR NWPRI option, parameter estimates were obtained using a penalty term on the likelihood function, due to the limited data available for the peficitinib absorption phase in RA patients.[20]

Covariate exploration was undertaken using stepwise forward addition (significance level .01) followed by backward elimination (significance level .001). The relationship between continuous covariates and pharmacokinetic parameters was modelled using a power function centralized by the arithmetic mean of the covariates (mean [cov], Equation 3):

$$P_i = \theta_1 \times (cov_i / mean\,[cov])^{\theta_2} \tag{3}$$

where θ_1 is the population mean parameter of P_i for subjects with the mean value of the covariate, θ_2 is the exponent of the power function, and cov_i is the covariate in the i-th subject. For a categorical covariate, a fractional difference was modelled using a multiplicative function (Equation 4):

$$P_i = \theta_1 \times \theta_3^{cov} \tag{4}$$

where θ_1 is the population mean parameter of P_i for subjects, θ_3 is the coefficient, and cov is the class of covariate (yes: cov = 1, no: cov = 0). In the prior healthy volunteer model, the effect on CL of the following covariates was investigated: age, weight, estimated glomerular filtration rate (eGFR, calculated with the modification of diet in renal disease (MDRD) method[21]), albumin (ALB), alanine transaminase (ALT), aspartate transaminase (AST), serum albumin, alkaline phosphatase (ALP) and total bilirubin (TBIL); the effect of weight on Vp was also investigated. In the RA patient model, the effect on CL of the following covariates were investigated: age, weight, eGFR, ALB, ALT, AST, ALP, TBIL, absolute neutrophil count (ANC), serum creatinine, C-reactive protein, haematocrit, haemoglobin, lymphocyte count, platelets, red blood cells, urate, sex and region (Japan, Korea or Taiwan); the effect of weight, ANC, C-reactive protein, lymphocyte count and weight on Vc was also investigated.

2.5 | Model evaluation

Both the prior healthy volunteer and RA patient models were evaluated using goodness-of-fit (GOF) plots. The predictive performance of the prior healthy volunteer and RA patient models was evaluated by a visual predictive check (VPC) and prediction-corrected VPC, respectively.[22] In the VPC and prediction-corrected VPC, the reproducibility of the final model was assessed by 1000 generated datasets. Robustness was assessed by a 1000 times of nonparametric bootstrap method.

2.6 | Simulation

The effect of eGFR, 1 of the selected covariates, on the AUC was assessed using the final RA patient model. The AUC from 0 to 24 hours after dosing (AUC_{24h}) at steady state with a 150-mg daily dose was calculated by dividing the dose by the model-derived individual *posthoc* CL. Based on simulation of 1000 pairs of CL and eGFR, the mean population CL was calculated at eGFR values of 22.5, 45, 75 and 91.5 mL/min/1.73m^2, which correspond to the medians of the severe, moderate and mild renal function categories and mean observed eGFR obtained in RA patients, respectively.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org,

the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Datasets and demographic summary

The dataset for the prior healthy volunteer model comprised 2464 observations from 98 subjects, and the dataset for the RA patient model comprised 4919 observations from 989 subjects. The demographics and baseline characteristics of each dataset are presented in Table 2 and Table S1.

3.2 | Prior healthy volunteer model

The 2-compartment model with sequential zero- and first-order absorption with lag-time and assuming IIV on CL, Vp, Q, Ka, ALAG, D and relative bioavailability (F) was selected as a base structural model with the lowest objective function value. The covariate exploration

indicated that no candidate covariate met the pre-set inclusion criteria for further investigation ($P < .01$) in the forward addition step; therefore, no covariates were included in the prior healthy volunteer model. The parameter estimates of the prior healthy volunteer model are shown in Table S2. The GOF plots and the VPC plots suggested an adequate predictive performance (Figures S1 and S2). Furthermore, the summary statistics of the 1000 sets of bootstrap estimates were consistent with the parameter estimates of the prior healthy volunteer model (Table S1), indicating the robustness of the estimates.

3.3 | RA patient model

The prior healthy volunteer model was used as prior information to explore fixed effects of structural PK parameters in the RA patient model. However, distribution information from the prior healthy volunteer model was not used for IIV in the RA patient model because the extent of IIV could potentially be different between healthy volunteers and RA patients. After assessing the IIV on all parameters except for absorption, due to limited observations in the absorption

TABLE 2 Patient demographics and baseline characteristics

	Healthy volunteers (*n* = 98)	RA patients (*n* = 1011)
Female, *n* (%)	4 (4.1)	750 (74.2)
Region, *n* (%)		
Japan	98 (100)	957 (94.7)
Korea	-	30 (3.0)
Taiwan	-	24 (2.3)
Age, y		
Mean (SD)	34.7 (12.0)	55.3 (11.8)
Range (min–max)	20–69	20–86
Body weight, kg		
Mean (SD)	64.1 (7.4)	58.1 (12.4)
Range (min–max)	48.8–77.9	29.9–117.4
eGFR, mL/min/1.73m^2		
Mean (SD)	93.85 (13.95)	91.49 (22.27)
Range (min–max)	60.7–130.8	36.4–188.4
Lymphocyte count, 10^6/L		
Mean (SD)	-	1550 (540)
Range (min–max)	-	500–4600
ANC, 10^6/L		5530 (2070)
Mean (SD)	-	1000–15 200
Range (min–max)	-	
CRP, mg/L		
Mean (SD)	-	24.45 (23.00)
Range (min–max)	-	0.1–169.6

ANC, absolute neutrophil count; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease method; RA, rheumatoid arthritis; SD, standard deviation

phase, a 2-compartment model with sequential zero- and first-order absorption and lag-time, with IIV on CL and Vc, was selected as the base RA patient model. The covariate exploration in the RA patient model revealed that eGFR and lymphocyte count had a significant effect on CL.

Based on the covariates included in the final model, the predicted population mean CL ($CL_{pop,j}$) was expressed as follows (Equation 5):

$$CL_{pop,j} = 91.7 \times \left(\frac{eGFR_j}{91.5}\right)^{0.213} \times \left(\frac{\text{lymphocyte count}_j}{1550}\right)^{-0.104} \quad (5)$$

where $eGFR_j$ and lymphocyte count$_j$ represent the eGFR and lymphocyte count, respectively, of the jth subject. The equation for predicted individual CL above indicates that CL tends to decrease in renal impairment patients and in patients with high lymphocyte counts. The model predicted mean changes in CL of −17.8% and 16.7% from the population mean CL in patients with an observed minimum and maximum eGFR of 36.4 and 188 mL/min/1.73m^2, respectively. The model also predicted mean changes in CL of 12.3 and −10.7% from the population mean CL in patients with observed minimum and maximum lymphocyte counts of 500 and 4600 10^6/L, respectively. The effect of eGFR and lymphocyte counts on CL was comparable in magnitude to the remaining IIV for CL caused by other unknown factors (25.7%). The parameter estimates of the RA patient model are shown in Table 3. The GOF and VPC plots suggested an adequate predictive performance (Figures 1 and 2). The summary statistics of the bootstrap estimates were consistent with the parameter estimates of the RA patient model (Table 3), indicating the robustness of the parameter estimates.

3.4 | Simulation for the effect of eGFR on exposure of peficitinib

The simulated population mean AUC$_{24h}$ and 95% CI (2.5th to 97.5th percentiles) for the effect of eGFR are summarized in Table 4 and Figure S3. The simulation suggested a 1.04-, 1.16-, and 1.35-fold increase in AUC$_{24h}$ in patients with mild (eGFR 75 mL/min/1.73m^2), moderate (45 mL/min/1.73m^2) and severe (22.5 mL/min/1.73m^2) renal impairment, respectively, compared with patients with reference eGFR (91.5 mL/min/1.73m^2, the mean observed eGFR obtained in RA patients; Table 4). The trend of increasing AUC$_{24h}$ with decreasing eGFR is illustrated in Figure S3.

4 | DISCUSSION

Phase 3 studies have previously demonstrated the safety and efficacy of peficitinib, a pan-JAK inhibitor, in patients with RA and with an inadequate response to prior DMARD or prior methotrexate treatment.[10,11] This report is the first to analyse the population PK characteristics of peficitinib. Our analysis incorporated 2464 observations from 98 healthy volunteers across 5 phase 1 studies, plus 4919 observations from 989 patients with RA across 1 phase 2 and 2 phase 3 studies. A 2-compartment model with sequential zero- and first-order absorption and lag-time was used for both healthy volunteers and patients with RA. As absorption phase data was limited for patients with RA, we used prior information from the prior healthy volunteer model to construct the RA patient model. Although food intake has previously been shown to increase AUC$_{inf}$ by 27% and

TABLE 3 Peficitinib population pharmacokinetic parameter estimates in the RA patient model

Parameter		Estimate	RSE (%)	Variability [a] (%)	Shrinkage (%)	Summary of bootstrap runs [b]	
						Median	95% CI
Structural PK (θ)	CL (L/h)	91.7	2.3	–	–	91.6	86.8–95.4
	Vc (L)	280	2.3	–	–	279	265–291
	Vp (L)	122	8.5	–	–	122	102–143
	Q (L/h)	10.2	4.9	–	–	10.2	9.11–11.2
	Ka (L/h)	5.83	7.6	–	–	5.82	4.68–6.60
	ALAG (h)	0.132	2	–	–	0.132	0.127–0.137
	D (h)	1.37	4.3	–	–	1.36	1.24–1.47
Covariate	eGFR on CL	0.213	19.4	–	–	0.213	0.135–0.292
	LYM on CL	−0.104	26.9	–	–	−0.104	−0.161 to −0.0476
Random effect for IIV (ω^2)	CL	0.0639	15.3	25.7	12.9	0.0637	0.0474–0.0820
	Vc	0.143	35.7	39.2	48.8	0.144	0.0534–0.230
Residual error	Proportional	0.496	1.6	49.6 [c]	7.7	0.496	0.480–0.511

[a]Inter-individual variability (%) was calculated as follows: $\sqrt{\exp(\omega^2)-1} \times 100$

[b]1000 successful runs for 1000 bootstrap datasets

[c]Variability described as percentage of the estimates multiplied by 100.

ALAG, absorption lag time; CL, apparent total systemic clearance; D, duration; eGFR, estimated glomerular filtration rate; IIV, interindividual variability; Ka, first-order absorption rate constant; LYM, lymphocyte count; Q, apparent intercompartmental clearance; RA, rheumatoid arthritis; RSE; relative standard error, Vc, apparent distribution volume of the central compartment; Vp, apparent distribution volume of the peripheral compartment
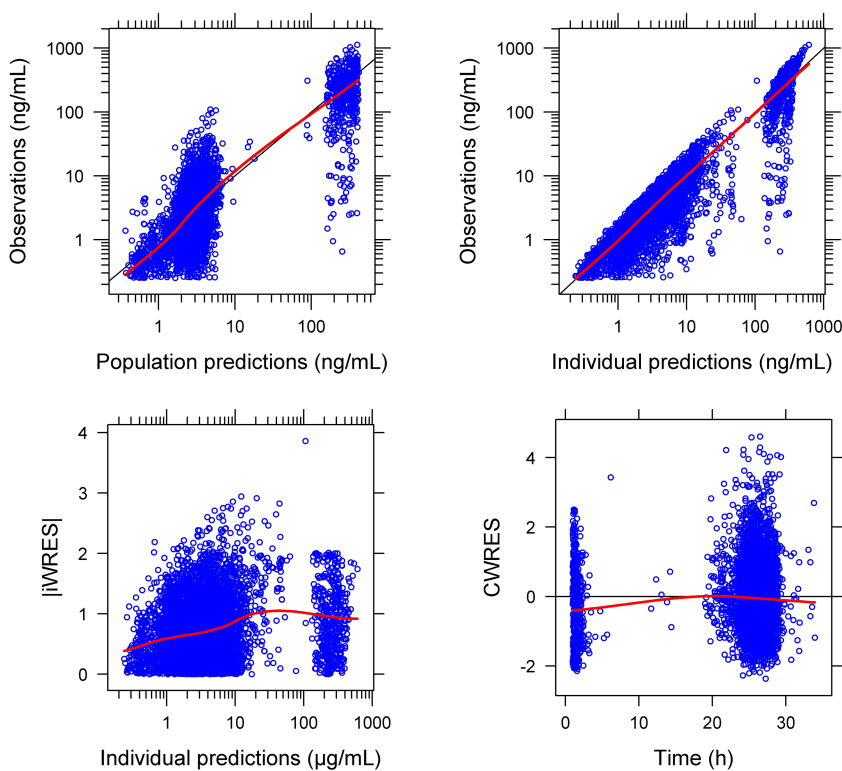
FIGURE 1 Goodness-of-fit plots for the rheumatoid arthritis patient model. |iWRES|, absolute values of individual weighted residuals; CWRES, conditional weighted residuals; red lines, LOWESS smoothing curves; blue circles, observations
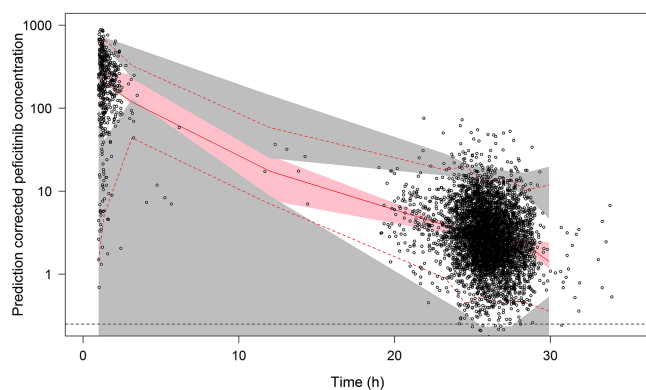

FIGURE 2 Prediction-corrected visual predictive check of the rheumatoid arthritis patient model. Black circles, observations in healthy volunteers; red solid curve and red dashed curves, the median, 2.5th percentile and 97.5th percentile of observations; pink and grey areas, 95% confidence intervals of the median, 2.5th percentile and 97.5th percentile of simulated data; black dashed line, lower limit of quantitation (0.2500 ng/mL)

36%,[12,13] food intake (fasted, high-fat fed, or normal fed) in the phase 1 studies was not included in the models because apparent differences among food conditions were relatively smaller than IIV. In phase 2 and 3 studies, all patients with RA took the study drug in the morning in a fed condition. The relatively large shrinkage of Vc in the RA patient model was probably due to a lack of information regarding the first distribution phase as most PK samples were taken around 24 hours after administration at the trough. Thus, IIV for Vc may be

less reliable. Both the healthy volunteer and the RA patient models provided higher predictions in some subjects/patients mainly for concentrations around the absorption phase (0.25 to 2.5 hours after administration), suggesting that predictions around the absorption phase could be improved. However, the effect of misspecification in absorption phase modelling is limited in the view of obtaining individual *posthoc* exposure (AUC) for 1 of the major purposes of this analysis. As the RA patient model was constructed using PK data from an Asian population, the clinical relevance in other populations is currently unclear and caution should be used when applying this model to non-Asian patients. The greater peficitinib exposure was observed in healthy Japanese compared with Caucasian with unknown reason.[14]

The estimated CL was 83.4 and 91.7 L/h in the prior healthy volunteer and RA patient models, respectively. Following the selection of eGFR as a covariate for CL, the simulated mean AUC was increased by 4, 16 and 35% in patients with mild, moderate and severe renal impairment, respectively, compared with the reference eGFR. However, the simulated results for patients with severe renal impairment have been extrapolated by the model without any actual observations, as patients with eGFR ≤40 mL/min/1.73m^2 (as measured by the MDRD method) were excluded from the study based on the criteria applied in phase 2 and phase 3 clinical trials. The reliability of the simulated results in patients with severe renal impairment therefore needs to be handled cautiously. However, considering that urinary excretion of peficitinib is low (9–17%) in healthy volunteers[12,15] and tolerability was shown in healthy subjects following administration of a single dose up to 450 mg (mean AUC$_{inf}$: 4660 ng·h/mL), the

TABLE 4 Simulated exposure of peficitinib according to renal function

eGFR (min/mL/1.73m^2)	AUC$_{24h}$ (ng·h/mL)	Ratio
91.5 min/mL/1.73m^2 [a]	1636 (1568–1704)	-
75 min/mL/1.73m^2 (mild impairment)	1707 (1633–1785)	1.04 (1.03–1.06)
45 min/mL/1.73m^2 (moderate impairment)	1903 (1771–2039)	1.16 (1.10–1.24)
22.5 min/mL/1.73m^2 (severe impairment)	2205 (1952–2471)	1.35 (1.20–1.52)

Data given as mean (95% CI)

[a]Observed mean in rheumatoid arthritis patients.

AUC$_{24h}$, area under plasma concentration–time curve for 24 hour after dosing; eGFR, estimated glomerular filtration rate

magnitude of the increase was not considered clinically relevant and dose adjustment of peficitinib for patients with renal impairment seems not to be required. This interpretation is consistent with a previous study of patients with renal impairment, which showed that peficitinib exposure was comparable in subjects with and without renal impairment after a single, oral 150 mg dose.[17] Similarly, in a population PK model of upadacitinib, creatinine clearance was identified as a significant covariate for CL, but its effect was not considered clinically meaningful.[23]

Lymphocyte count was also selected as a covariate for CL in our study. It has been reported that population PK models of thymoglobulin, efalizumab and fluconazole also included lymphocyte count as a covariate[24–26]; however, thymoglobulin and efalizumab are both antibodies that block T-cell dependent functions, while the study of fluconazole focused on patients with HIV infection and lymphocyte count was therefore included in the population PK model as a marker of disease severity. Considering the mechanism of action and therapeutic target for peficitinib, the underlying reason for the effect of lymphocyte count on peficitinib CL is unknown. However, the effect is not clinically relevant because the model predicted changes in CL, with the minimum and maximum lymphocyte counts observed in the phase 2 and 3 studies being comparable with the magnitude of the IIV of CL.

Hepatic parameters were not recognized as a statistically significant covariate. A previous study showed that the mean exposure of peficitinib increases in subjects with moderate hepatic impairment; however, no clear relationship between individual measures of hepatic function (albumin and prothrombin time) and individual PK parameters of peficitinib was confirmed.[16] The results of the former clinical study thus seem consistent with the lack of statistically significant hepatic parameters from the covariate exploration.

The convergence success rate of 1000 bootstrap runs was 63.8% in the prior healthy volunteer model. All the convergence failure was due to rounding errors and successful convergence could be achieved by giving appropriate initial values of parameters. Furthermore, comparable medians of the bootstrap estimates were obtained regardless of whether the failure runs were included (data not shown). The low success rate does not suggest low robustness of the prior healthy volunteer model. The robustness was assessed in the RA patient model (bootstrap convergence success rate was 100%). The predictive performance was also assessed by a VPC. Therefore, the obtained

posthoc PK parameters from the final RA patient model are thought to be appropriate to be used as representative individual exposure parameters for future exposure–response analyses.

In conclusion, a population PK model for peficitinib in patients with RA has been constructed using a 2-compartment distribution with lag-time and sequential zero- and first-order absorption. Although eGFR and lymphocyte count were identified as significant covariates for CL in the RA patient model, neither were clinically relevant and no requirement for dose adjustment is suggested.

CLINICAL TRIAL REGISTRATION

NCT02586194 (PK10), NCT02603497 (PK11), NCT02760342 (PK20), NCT02531191 (PK27) NCT02308163 (RAJ3), NCT02305849 (RAJ4), NCT01565655 (RAJ1).

COMPETING INTERESTS

J. Toyoshima, M. Shibata, Y. Kaneko, H. Izutsu and T. Nishimura are full-time employees of Astellas Pharma Inc., Tokyo, Japan. A. Kaibara was a full-time employee of Astellas Pharma Inc., Tokyo, Japan, at the time of analysis. He is currently a full-time employee of Eli Lilly Japan K.K., Tokyo, Japan.

CONTRIBUTORS

J.T. wrote the article. All authors were involved in revising this article. J.T., M.S., T.N. and A.K. planned the analysis, and J.T. conducted the analysis. Y.K. was the lead statistician responsible for data handling for each study. H.I. was the study leader for peficitinib and contributed to the planning and conduct of the clinical studies.

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

REFERENCES

1. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. Wood AJJ, editor. *N Engl J Med*. 2004;350(25):2591-2602.

2. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016;75(1):3-15.

3. Zampeli E, Vlachoyiannopoulos PG, Tzioufas AG. Treatment of rheumatoid arthritis: unraveling the conundrum. *J Autoimmun*. 2015;65: 1-18.

4. Ito M, Yamazaki S, Yamagami K, et al. A novel JAK inhibitor, peficitinib, demonstrates potent efficacy in a rat adjuvant-induced arthritis model. *J Pharmacol Sci*. 2017;133(1):25-33.

5. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis*. 2013;72(Suppl 2): ii111-ii115.

6. Alexander SPH, et al. The Concise Guide to Pharmacology. *Br J Pharmacol*. 2017;174:S1-S446.

7. Takeuchi T, Tanaka Y, Iwasaki M, Ishikura H, Saeki S, Kaneko Y. Efficacy and safety of the oral Janus kinase inhibitor peficitinib (ASP015K) monotherapy in patients with moderate to severe rheumatoid arthritis in Japan: a 12-week, randomised, double-blind, placebo-controlled phase IIb study. *Ann Rheum Dis*. 2016;75(6):1057-1064.

8. Kivitz AJ, Gutierrez-Urena SR, Poiley J, et al. Peficitinib, a JAK inhibitor, in the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate. *Arthritis Rheumatol*. 2017;69(4):709-719.

9. Genovese MC, Greenwald M, Codding C, et al. Peficitinib, a JAK inhibitor, in combination with limited conventional synthetic disease-modifying antirheumatic drugs in the treatment of moderate-to-severe rheumatoid arthritis. *Arthritis Rheumatol*. 2017;69(5):932-942.

10. Tanaka Y, Takeuchi T, Tanaka S, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to conventional DMARDs: a randomised, double-blind, placebo-controlled phase III trial (RAJ3). *Ann Rheum Dis*. 2019;78(10): 1320-1332.

11. Takeuchi T, Tanaka Y, Tanaka S, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan. *Ann Rheum Dis*. 2019; 78(10):1305-1319.

12. Cao YJ, Sawamoto T, Valluri U, et al. Pharmacokinetics, pharmacodynamics, and safety of ASP015K (peficitinib), a new Janus kinase inhibitor, in healthy subjects. *Clin Pharmacol Drug Dev*. 2016;5 (6):435-449.

13. Shibata M, Toyoshima J, Kaneko Y, et al. The bioequivalence of two Peficitinib formulations, and the effect of food on the pharmacokinetics of peficitinib: two-way crossover studies of a single dose of 150 mg peficitinib in healthy volunteers. *Clin Pharmacol Drug Dev*. 2020. https://doi.org/10.1002/cpdd.843

14. Shibata M, Hatta T, Saito M, et al. Pharmacokinetics, pharmacodynamics, and safety of peficitinib (ASP015K) in healthy male Caucasian and Japanese subjects. *Clin Drug Investig*. 2020;40(5): 469-484.

15. Oda K, Cao YJ, Sawamoto T, et al. Human mass balance, metabolite profile and identification of metabolic enzymes of [14C]ASP015K, a novel oral Janus kinase inhibitor. *Xenobiotica*. 2015;45(10):887-902.

16. Miyatake D, Shibata T, Toyoshima J, et al. Pharmacokinetics and safety of a single oral dose of peficitinib (ASP015K) in Japanese subjects with normal and impaired hepatic function. *Clin Pharmacol Drug Dev*. 2019;9(6):699-708.

17. Miyatake D, Shibata T, Shibata M, et al. Pharmacokinetics and safety of a single oral dose of peficitinib (ASP015K) in Japanese subjects with normal and impaired renal function. *Clin Drug Investig*. 2020;40 (2):149-159.

18. Shibata M, Toyoshima J, Kaneko Y, Oda K, Nishimura T. A drug–drug interaction study to evaluate the impact of peficitinib on OCT1- and MATE1-mediated transport of metformin in healthy volunteers. *Eur J Clin Pharmacol*. 2020;76(8):1135-1141.

19. Jonsson EN, Karlsson MO. Xpose–an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Meth Programs Biomed*. 1999;58(1):51-64.

20. Gisleskog PO, Karlsson MO, Beal SL. Use of prior information to stabilize a population data analysis. *J Pharmacokinet Pharmacodyn*. 2002; 29(5/6):473-505.

21. Imai E, Horio M, Nitta K, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol*. 2007;11(1):41-50.

22. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J*. 2011;13(2):143-151.

23. Klünder B, Mittapalli RK, Mohamed M-EF, Friedel A, Noertersheuser P, Othman AA. Population pharmacokinetics of upadacitinib using the immediate-release and extended-release formulations in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I–III clinical trials. *Clin Pharmacokinet*. 2019;58(8): 1045-1058.

24. Admiraal R, van Kesteren C, Jol-van der Zijde CM, et al. Population pharmacokinetic modeling of Thymoglobulin(®) in children receiving allogeneic–hematopoietic cell transplantation: towards improved survival through individualized dosing. *Clin Pharmacokinet*. 2015;54(4): 435-446.

25. Sun Y-N, Lu J-F, Joshi A, Compton P, Kwon P, Bruno RA. Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. *J Clin Pharmacol*. 2005;45(4):468-476.

26. McLachlan AJ, Tett SE. Pharmacokinetics of fluconazole in people with HIV infection: a population analysis. *Br J Clin Pharmacol*. 1996; 41(4):291-298.

SUPPORTING INFORMATION

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