Received: 20 August 2021 | Revised: 21 November 2021 | Accepted: 10 December 2021

DOI: 10.1111/cts.13221

ARTICLE

Imeglimin population pharmacokinetics and dose adjustment predictions for renal impairment in Japanese and Western patients with type 2 diabetes

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Funding information
Sponsored by Sumitomo Dainippon Pharma, Co., Ltd., Metavant Sciences and Poxel SA

Abstract

Imeglimin is an orally administered first-in-class drug to treat type 2 diabetes mellitus (T2DM) and is mainly excreted unchanged by the kidneys. The present study aimed to define the pharmacokinetic (PK) characteristics of imeglimin using population PK analysis and to determine the optimal dosing regimen for Japanese patients with T2DM and chronic kidney disease (CKD). Imeglimin plasma concentrations in Japanese and Western healthy volunteers, and patients with T2DM, including patients with mild to severe CKD with an estimated glomerular filtration rate (eGFR) greater than 14 ml/min/1.73 m^2 were included in a population PK analysis. PK simulations were conducted using a population PK model, and the area under concentration-time curve (AUC) was extrapolated with power regression analysis to lower eGFR. The influence of eGFR, weight, and age on apparent clearance and of dose on relative bioavailability were quantified by population PK analysis. Simulations and extrapolation revealed that the recommended dosing regimen based on the AUC was 500 mg twice daily (b.i.d.) for patients with eGFR 15–45 ml/min/1.73 m^2, and 500 mg with a longer dosing interval was suggested for those with eGFR less than 15. Simulations revealed that differences in plasma AUCs between Japanese and Western patients at the same dose were mainly driven by a difference in the eGFR and that the plasma AUC after 1000 and 1500 mg b.i.d. in Japanese and Western patients, respectively, was comparable in the phase IIb studies. These results indicate suitable dosages of imeglimin in the clinical setting of T2DM with renal impairment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Imeglimin is a first-in-class oral agent for the treatment of type 2 diabetes (T2DM) and is excreted unchanged into urine. A Japanese phase IIb study found that

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1000 mg b.i.d. was optimal in Japanese population, and phase III studies confirmed significant glucose lowering effect. A Western phase IIb study found an optimal dose of 1500 mg b.i.d.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study addressed the key determinants of imeglimin pharmacokinetics (PKs), recommended doses for patients with renal impairment, and what drives the different optimal doses between Japanese and Western patients with T2DM.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Renal function significantly impacts imeglimin PKs. Recommended doses for patients with renal impairment have been proposed for exposure matching. Differences in estimated glomerular filtration rate (eGFR) comprised the key driver for different optimal doses at which estimated exposures were similar between Japanese and Western patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Doses of imeglimin could be reduced based on eGFR. Exposure responses seemed similar between Japanese and Western patients.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by β-cell dysfunction and peripheral insulin resistance leading to hyperglycemia.[1–3] Early intervention with a combination therapy aimed at increasing insulin secretion and decreasing insulin resistance has improved the prognosis of patients with newly diagnosed T2DM.[4]

Imeglimin (hydrochloride salt) is a novel oral antidiabetic drug used to treat T2DM. The novel imeglimin structure and proposed mechanism of action have established it as the first in a class of new tetrahydrotriazines.[5] The mechanism of imeglimin action involves dual effects of amplified glucose-stimulated insulin secretion with preserved β-cell mass, and the enhanced insulin action. These have the potential to inhibit hepatic glucose output and improve insulin signaling in both the liver and skeletal muscle. The underlying mechanism of imeglimin at the cellular and molecular levels might involve the correction of mitochondrial dysfunction, which is a characteristic feature of T2DM pathogenesis.[6–9] Three recently completed pivotal phase III trials in Japan (monotherapy, TIMES 1; combination therapy, TIMES 2; and add-on insulin, TIMES 3) have generated evidence that imeglimin significantly lowers blood glucose levels at a dose of 1000 mg b.i.d. and that it is generally safe, tolerable, and does not induce hypoglycemia.[10–12]

Imeglimin is not metabolized; it is eliminated unchanged in the urine.[10,13] Thus, a dosage reduction might be required for patients with renal impairment. Plasma elimination half-life of imeglimin was 13.0 h with protein binding ratio of 1.2%–6.4% in healthy volunteers.[13] Renal transporters, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, and MATE2-K are involved in its tubular secretion in the kidneys,[13] but the clinical pharmacology study revealed that concomitant administration of an inhibitor of these transporters, cimetidine, showed no clinically relevant effect on imeglimin pharmacokinetics (PKs).[14] Japanese[15] and Western[10] phase IIb studies have found that the minimum doses required for maximal effects are 1000 and 1500 mg b.i.d., respectively, and a slight increase in gastrointestinal adverse events was observed at the highest dose of 1500 mg b.i.d. and 2000 mg b.i.d., respectively.

Here, we characterized the PK properties of imeglimin to identify covariates of clinical relevance using a population PK analysis. We simulated imeglimin exposure in patients with T2DM with chronic kidney disease (CKD) using a population PK model and power regression model between the area under concentration-time curve (AUC) and the estimated glomerular filtration rate (eGFR), to derive a suitable dosing regimen for patients with T2DM with eGFR below 45 ml/min/1.73 m^2. Plasma exposure was compared between Japanese and Western patients with T2DM to determine the cause of the apparent differences in optimal doses between the phase IIb studies of Japanese[15] and Western[10] patients.

METHODS

Clinical studies

Plasma concentration data from 11 clinical studies were used in the population PK analysis (Table 1). Table S1 describes details of the study design and other information, such as time points for blood sampling and study

TABLE 1 Clinical studies included in population PK analysis

Study	Participants for PK analysis (*N*)	Imeglimin dose	Formulation/ dosing conditions before PK sampling	PK data (*n*)	Ref
Single and multiple ascending doses	Japanese HVs (36) Western HVs (6000, 8000 mg only) (12)	500, 1000, 1500, 2000 mg, day 1 single dose, days 4–10 b.i.d. Single dose only: 4000, 6000, 8000 mg	Conventional tablet, fasted (fed: 1500 mg day 4 morning dose only)	Intensive (1148)	–
Western renal impairment	Western HVs and patients with renal impairment (50)	1000 mg q.d. (days 1–8), 500 mg b.i.d. (days 1–7) and 500 mg on day 8	Capsule, fasted	Intensive (1362)	–
Japanese renal impairment	Japanese HVs and patients with renal impairment (24)	1000 mg single (500 mg for patients with severe impairment)	Optimal tablet, fasted	Intensive (318)	–
T2DM with renal impairment	Western patients with T2DM with renal impairment (38)	1500 mg q.d., 500, 1000 mg b.i.d. for 28 days	Optimal tablet	Intensive (407)	–
Western phase IIa (003)	Western patients with T2DM (39)	2000 mg q.d., 1000 mg b.i.d. for 28 days	Capsule, fed	Intensive (653)	5
Western phase IIa (004)	Western patients with T2DM (60)	500, 1500 mg b.i.d. for 8 weeks	Capsule, fed	Intensive (695)	5
Western phase IIb	Western patients with T2DM (283)	500, 1000, 1500, 2000 mg b.i.d. for 24 weeks	Conventional tablet, fed	Sparse (1432)	10
Japanese phase IIb	Japanese patients with T2DM (222)	500, 1000, 1500 mg b.i.d. for 24 weeks	Optimal tablet, fed	Sparse (1842)	15
Japanese phase III monotherapy (TIMES 1)	Japanese patients with T2DM (103)	1000 mg b.i.d. for 24 weeks	Optimal tablet, fed	Sparse (399)	11
Japanese phase III combination (TIMES 2)[a]	Japanese patients with T2DM (690)	1000 mg b.i.d. for 52 weeks	Optimal tablet, fed	Sparse (2625)	12
Japanese phase III add-on insulin (TIMES 3)[a]	Japanese patients with T2DM (106)	1000 mg b.i.d. for 16 weeks	Optimal tablet, fed	Sparse (316)	10

Abbreviations: b.i.d., twice daily; HVs, healthy volunteers; *N*, number of individuals; *n*, number of PK data; PK, pharmacokinetic; q.d., once daily; T2DM, type 2 diabetes mellitus.

[a]Used in external evaluation.

registration numbers. The independent ethics committees/institutional review boards approved the studies, and all patients and healthy volunteers provided written informed consent to participate. Capsules, conventional, or optimized tablet formulations were used in various clinical studies. Multiple plasma samples were collected in all studies after a single oral dose of 500–8000 mg, multiple oral doses of 500–2000 mg b.i.d., and/or 1000–2000 mg q.d. Six of the eight studies that included patients with T2DM were used to develop the population PK model. The remaining two phase III studies (TIMES 2 and TIMES 3) comprised one in which oral antidiabetic agents in various classes were combined and another that included add-on therapy to insulin. The data from these studies were not available during model development. When these data became available, they were used for external evaluation of the final PK model for imeglimin. Among the 11 studies, two included Japanese or Western patients with renal impairment, and one included patients with T2DM and renal impairment at CKD grade 3b (G3b) (30 to <45 ml/min/1.73 m^2) and G4 (15 to <30 ml/min/1.73 m^2). In the current analysis, eGFR was derived based on the three-variable Japanese[16] and CKD-EPI[17] equations used for Japanese population and Western population, respectively. Plasma concentrations of imeglimin were measured using a validated liquid chromatography with tandem mass spectrometry method with a lower limit of quantitation of 10 ng/ml, as described previously.[14,18] Concentrations expressed as hydrochloride salts were converted to concentrations of imeglimin base (molecular weight ratio: 0.810) before analysis.

Population PK analysis

The population PK analysis was implemented using the first-order conditional estimation method in NONMEM

version 7.3.0 (ICON Development Solutions). Automation and post-processing were achieved using Perl-speaks-NONMEM (PsN) version 4.8.1 (Department of Pharmacy, Uppsala University, Uppsala, Sweden). NONMEM output data were managed and processed using R version 3.3.3 (R Core Team). R and the included xpose4 package version 4.6[19] were used for goodness of fit (GOF) analyses, model evaluation, and generation of descriptive statistics. The structural models that were considered included two- and three-compartment models with first-order absorption and terms/models that can manage potential absorption delays. Interindividual variability (IIV) was exponentially included in the PK parameters. Covariances between IIVs were also evaluated. Residual unexplained variability was evaluated using an additive error model on a log-transformed scale. Considering the impact of renal impairment on imeglimin renal clearance and dose-disproportional absorption observed in clinical pharmacology studies,[13] eGFR was incorporated in the model as a structural covariate on apparent clearance (CL/F) and dose as that on bioavailability (F) and absorption rate constant (k_a). Formulation (capsule, conventional tablet, and optimal tablet) and food intake condition (fasted, semi-fasted, fed, fed with high fat food, and no special instruction) were evaluated as structural covariates as well on absorption-related parameters (lag time for first-order absorption, F, and k_a), as a slight decrease in maximum plasma concentration (C_{max}) and prolonged time to C_{max} (T_{max}) were observed in some food effect studies (shown in the package insert). Structural covariates were retained in the model if they were statistically significant and provided biologically reasonable parameter estimates. Once the structural model was established, age, sex, body weight, and ethnicity (Japanese or mostly White patients) were tested as nonstructural covariates on CL/F parameters and apparent volume of distribution parameters, and ethnicity on absorption parameters, using the following equations:

$$\theta_{\mathrm{Cov}_m} = \left(\frac{\mathrm{Cov}}{\mathrm{Cov}_{\mathrm{ref}}}\right)^{\theta_m} \tag{1}$$

$$\theta_{\mathrm{Cov}_m} = \left\{ \begin{array}{ll} 1 & \text{if } \mathrm{Cov} = \mathrm{Cov}_{\mathrm{ref}} \\ 1+\theta_m & \text{if } \mathrm{Cov} \neq \mathrm{Cov}_{\mathrm{ref}} \end{array} \right\} \tag{2}$$

where $\mathrm{Cov}_{\mathrm{ref}}$ is the reference value for covariate m, to which the covariate model was normalized. The total effect of covariates on parameter P was then the product of n covariate terms according to:

$$\mathrm{TVP}_i = \theta_p \times \prod_{m=1}^{n} \theta_{\mathrm{cov}_m} \tag{3}$$

where i is an individual, TVP_i is the i^{th} typical parameter value, given the covariate values of i, and θ_p is the population typical parameter value for a person with typical (reference) covariate values. Nonstructural covariates were assessed using the stepwise covariate model building procedure,[20–22] which consists of forward selection ($p < 0.01$) and backward elimination ($p < 0.001$) steps.

Model evaluation was based on an inspection of graphical diagnostics, including GOF plots and prediction-corrected visual predictive checks (pcVPCs),[23] and changes in the objective function value provided by NONMEM. To evaluate the predictive performance of the model, plasma concentration profiles were simulated 500 times using doses and covariate data from the analysis dataset. Stratification using the following eGFR range ensured that the model performed adequately across important subgroups of patients with CKD; stage G1, eGFR greater than or equal to 90; stage G2, 60 to less than 90; stage G3, 30 to less than 60; and stage G4, 15 to less than 30 ml/min/1.73 m^2. The final population PK model was also externally evaluated using data from the following phase III studies[10]: a 52-week study of imeglimin monotherapy or combined with oral antidiabetics in various classes (TIMES 2)[12]; and a 16-week study of imeglimin as an add-on to insulin therapy (TIMES 3). The parameters were not re-estimated. GOF plots and pcVPCs were generated by superimposing simulated data on the observed data from the two studies.

PK simulation in patients with moderate to severe renal impairment

Individual PK parameters and plasma concentration-time profiles were simulated using the final population PK model to evaluate imeglimin plasma exposure in Japanese patients with moderate to severe renal impairment (CKD stages G3 and G4). The exposure simulations were performed assuming the formulation of the phase III studies and dosing under nonfasting conditions. The AUC for 24 h at steady state ($AUC_{24,ss}$) was calculated as the free base imeglimin concentration using the following equation:

$$\mathrm{AUC}_{24,\mathrm{ss}} = \frac{F \times \mathrm{DailyDose} \times S}{\mathrm{CL}} \tag{4}$$

where F is the relative bioavailability, CL is imeglimin clearance, and S is the free base/salt ratio (0.810). Japanese patients were sampled randomly with replacement from the Japanese phase IIb[15] and phase III (TIMES 1)[11] studies to generate 1000 covariate vectors (referred to as reference patients), where most of them had CKD stage G2 and a few had CKD stages G1 or G3a (45 to <60 ml/min/1.73 m^2). The reference patients were duplicated with

the eGFR being replaced by that sampled from a uniform distribution with minimum and maximum values set to the limits of the CKD stages. This resulted in 1000 patients with CKD stages G3a, G3b (30 to <45 ml/min/1.73 m^2), and G4. Considering that mean age advances along with CKD stage, the age in individual samples was increased by 5.5 years for CKD stage G3a and 7.8 years for CKD stages G3b and G4, based on published data derived from Japanese patients with CKD.[24–26]

Extrapolation of AUC to lower eGFR

To predict $AUC_{24,ss}$ in Japanese patients with T2DM with eGFR below 15 ml/min/1.73 m^2, power regression analysis of individual CL/F against eGFR was conducted, using Origin 2020b (OriginLab Corporation) with Equation 5, which can be translated to Equation 6 as follows:

$$CL/F = \alpha \times eGFR^{\beta} \quad (5)$$

$$\log\left(AUC_{24,ss}\right) = \log\left(\frac{DailyDose \times S}{\alpha}\right) - \beta \times \log\left(eGFR\right) \quad (6)$$

where α is the y-intercept adjustment parameter and β is the slope parameter in the log-log regression model.

Individual empirical Bayes estimates of CL/F at an imeglimin dose of 500 mg q.d. were generated from three studies that included patients with severe renal impairment (CKD stages G1–G5: n = 24, 20, 35, 29, and 4, respectively). Because two of these three studies included the Western population that were generally heavier than the Japanese population (median body weight: 77.4 and 106 vs. 71.8 kg), the estimated CL/F was adjusted with median weight differences from the Japanese study, using the obtained covariate model (Equation 9 in the Results section). The $AUC_{24,ss}$ was simulated in 1000 virtual Japanese patients with eGFR sampled from uniform distribution ranges of 8–15 or 5–8 ml/min/1.73 m^2, using slope (β), intercept and the standard deviation of the residuals estimated by the regression analysis, which should include variability derived from the distribution of age, body weight, and IIV by undetermined factors. Simulated $AUC_{24,ss}$ at 500 mg q.d. was summarized by eGFR ranges to compare with the reference $AUC_{24,ss}$.

Estimation of AUC and exploration of exposure responses in Japanese and Western phase IIb studies

Based on the final population PK model, individual empirical Bayes estimates of $AUC_{24,ss}$ for Japanese and Western patients from phase IIb studies[10,15] were calculated and summarized for each treatment group. The mean change from baseline in observed HbA1c after 24 weeks of treatment was plotted against the mean $AUC_{24,ss}$ estimated for each treatment group in each study.

PK simulation of Japanese and Western patients with T2DM

To evaluate the impact of differences in eGFR and body weight on the difference in PK between Japanese[15] and Western[10] phase IIb studies, individual PK parameters and plasma concentration-time profiles were simulated using the final population PK model. A total of 1000 Japanese patients were generated, assuming the same covariate distribution as found in the Japanese phase IIb[15] and phase III[11] studies, and 1000 Western patients were generated assuming the same covariate distribution as found in the Western phase IIb study.[10] The 1000 sampled Western patients were used twice to generate the general covariate structure for 1000 Western patients, respectively, with a similar eGFR (scenario i), and eGFR and body weight distribution (scenario ii) for the Japanese reference population. Covariate values of Western individuals in scenarios i and ii were adjusted by mean differences in eGFR (+15.24 ml/min/1.73 m^2) and body weight (+17.5 kg) between the Western phase IIb study[10] and Japanese patient (phase IIb[15] and TIMES 1[11]) studies.

RESULTS

Population pharmacokinetic analysis

A total of 867 individuals (745 patients with T2DM) and 8256 imeglimin plasma concentrations were included in the population PK analysis. The eGFR in the patients with T2DM ranged between 14.1 and 138 ml/min/1.73 m^2. Table 2 summarizes the characteristics of these individuals.

The imeglimin population PK was described by a two-compartment model with first-order absorption with a lag time and first-order elimination from the central compartment. Table 3 shows the parameter estimates of the final population PK model. The IIV terms were supported on k_a, F, central volume of distribution (V_c), peripheral volume of distribution, and CL with a correlation between CL and F. Dose nonlinearity was described by an inhibitory maximum effect (E_{max}) function for F (Equation 7) and a power function for k_a (Equation 1).

$$F_{Dose} = \left(1 - \frac{Dose}{Dose + D_{50}} + \frac{1000}{1000 + D_{50}}\right) \quad (7)$$

TABLE 2 Baseline characteristics of individuals included in population PK analysis or in external evaluation

	Phase I		Phase II		Phase III (TIMES 1)		(TIMES 2/TIMES 3)	
Characteristics	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Age, year	57	20–75	59	20–75	63	34–80	59	21–83
Body weight, kg	73.0	42.4–148	80.9	35.6–135	69.1	42.5–124	68.6	39.0–135
eGFR, ml/min/1.73 m^2	77.6	14.1–152	83.8	42.6–138	72.8	47.2–106	76.1	48.6–135
	N	**(%)**	***N***	**(%)**	***N***	**(%)**	***N***	**(%)**
Male/female	93/67	58.1/41.9	313/291	51.8/48.2	87/16	84.5/15.5	576/220	72.6/27.4
Japanese/Westerners	60/100	37.5/62.5	222/382	36.8/63.2	103/0	100/0	796/0	100/0
CKD stage G1	62	38.8	247	40.9	10	9.7	139	17.5
CKD stage G2	30	18.8	318	52.6	77	74.8	606	76.1
CKD stage G3a	14	8.8	37	6.1	16	15.5	51	6.4
CKD stage G3b	21	13.1	1	0.2	0	0	0	0
CKD stage G4	29	18.1	0	0	0	0	0	0
CKD stage G5	4	2.5	0	0	0	0	0	0

Note: Westerners comprised mostly of Whites, 12 Black or African Americans, 8 Asians, 2 Native Hawaiians, and 1 other.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; *N*, number of individuals; PK, pharmacokinetic.

A linear function where CL/F increases with increasing eGFR up to 120 ml/min/1.73 m^2 was included as a structural covariate for CL/F. This function was centered around the median eGFR in the evaluated population ($eGFR_{ref}$: 81.4 ml/min/1.73 m^2).

$$CL/F_{eGFR} = \begin{cases} 1+\left(120-eGFR_{ref}\right)\times\theta_{CL/F,eGFR} & \text{if } eGFR_{baseline}\geq 120 \\ 1+\left(eGFR_{baseline}-eGFR_{ref}\right)\times\theta_{CL/F,eGFR} & \text{if } eGFR_{baseline}<120 \end{cases} \quad (8)$$

Formulation was a structural covariate of the absorption lag time (ALAG) and k_a. Longer ALAG and smaller k_a in fed condition (Equation 2) were in accordance with the clinical pharmacology study results showing no change in AUC and reduced C_{max} with prolonged T_{max} in the fed condition. Additional significant covariates were age and body weight on CL/F (Equations 9 and 10), body weight on V_c/F (Equation 1), and age (Equation 1) and Japanese ethnicity (Equation 2) on inter-compartmental clearance.

$$CL/F_{WT} = \left(\frac{WT}{WT_{median}}\right)^{\theta_{CL/F,WT}} \quad (9)$$

$$CL/F_{Age} = \left(\frac{age}{age_{median}}\right)^{\theta_{CL/F,Age}} \quad (10)$$

The final covariate model is described by Equations 1–3 and 7–10. Figure 1 shows the impact of the major covariates. Summary of the key covariate modeling process and the stepwise covariate model building procedure on the base PK model for imeglimin were summarized in Table S2 and S3.

Standard GOF plots for the final model (Figure S1) revealed no evident bias in the model fit. As the shrinkage for IIV appears to be high (40%–60%) in the final model, which is thought to be driven by imbalanced study design and data limitation in some studies, cautious interpretation of diagnostics based on empirical Bayes estimates is necessary.

Unstratified and stratified pcVPCs according to CKD stages (Figure 2) adequately described the observed concentrations. External evaluation shows that the model provides an adequate description of the data from the two phase III studies (TIMES 2 and TIMES 3; Figure S2). This suggests that the model is fit-for-purpose in predicting the imeglimin PK in Japanese patients with T2DM. Further model updates using these data were not considered given the good predictive performance of the model, similarity in the covariates' distribution between these studies and included phase II/III studies, that no additional participants with CKD stages G3b/4/5 were available, and that no significant drug-drug interactions (DDIs) are expected from concomitant drug use. No model misspecification was evident based on the GOF plots (Figure S2).

Predicted AUC in patients with renal impairment

Table 4 summarizes the $AUC_{24,ss}$ simulated by the CKD stage and its ratio to the median of the Japanese

TABLE 3 Parameter estimates from the final population PK model of imeglimin

Parameter, unit	Typical values	RSE (%)	Shrinkage (%)
Absorption rate constant, k_a, h^{-1}	0.144	4.42	
Absorption lag time, ALAG, h	0.229	11.0	
Relative bioavailability, F	1	(FIX)	
Apparent clearance, CL/F, L/h	66.9	1.70	
Apparent central distribution volume, V_c/F, L	142	5.65	
Apparent inter-compartmental clearance, Q/F, L/h	15.9	7.27	
Apparent peripheral distribution volume, V_p/F, L	374	6.56	
Covariates effect	**Typical values**	**RSE (%)**	
Dose at 50% maximal F, D_{50}, mg	2410	13.0	
eGFR on CL/F, $\theta_{CL/F, eGFR}$	0.00951	3.60	
Capsule formulation on ALAG[a]	2.45	16.0	
Conventional tablet formulation on ALAG[a]	0.719	28.6	
Capsule or conventional tablet formulation on k_a[a]	0.298	15.4	
Fasted or semi-fasted on ALAG[b]	−0.449	12.4	
Fasted or semi-fasted on k_a[b]	0.389	27.2	
Dose on k_a, $\theta_{ka, Dose}$	−0.138	20.5	
Age on CL/F, $\theta_{CL/F, Age}$	−0.343	12.6	
Body weight on CL/F, $\theta_{CL/F,WT}$	0.388	13.4	
Age on Q/F	−0.859	16.0	
Japanese on Q/F	−0.291	17.7	
Body weight on V_c/F, $\theta_{Vc/F,WT}$	0.802	22.6	
Variability	**Typical values**	**RSE (%)**	**Shrinkage (%)**
Interindividual variability of k_a (CV)	0.228	12.6	55.7
Interindividual variability of CL (CV)	0.461	6.53	46.1
Interindividual variability of F (CV)	0.529	7.40	48.7
Correlation CL/F	0.821	7.34	
Interindividual variability of V_c (CV)	0.645	7.21	44.2
Interindividual variability of V_p (CV)	0.605	8.04	62.4
Proportional RUV (CV)	0.359	7.05	12.5
Proportional phase I RUV (CV)	0.190	4.08	9.59
Proportional predose RUV (CV)	0.505	3.49	6.36

Note: The RSE for interindividual variability and residual error parameters are reported on approximate standard deviation scale. Reference patient: Western patients with weight, 77.35 kg, eGFR, 81.4 ml/min/1.73 m^2, age, 59 years.

Abbreviations: CL, clearance; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; RSE, relative standard error; RUV, residual unexplained variability; V_c, central distribution volume; V_p, peripheral distribution volume.

[a]Effect of formulation is relative to that of optimized tablet formulation.

[b]Effect of fasting or semi-fasting condition at the time of dose is relative to that of nonfasting condition with a regular meal or a high-fat meal, or the condition of no specific instructions regarding meal times.

reference group. The median $AUC_{24,ss}$ in CKD stages G3b and G4 was 1.7- and 2.2-fold, respectively, larger than that in the reference population treated with 1000 mg b.i.d. Reducing the dose to 500 mg b.i.d. in CKD stages G3b and G4 resulted in median exposure that was similar to the reference population administered with 1000 mg b.i.d.

The individual CL/F and $AUC_{24,ss}$ after 500 mg q.d. are plotted against eGFR with a regression line in Figure 3a (Equation 5) and in Figure 3b (Equation 6), respectively.

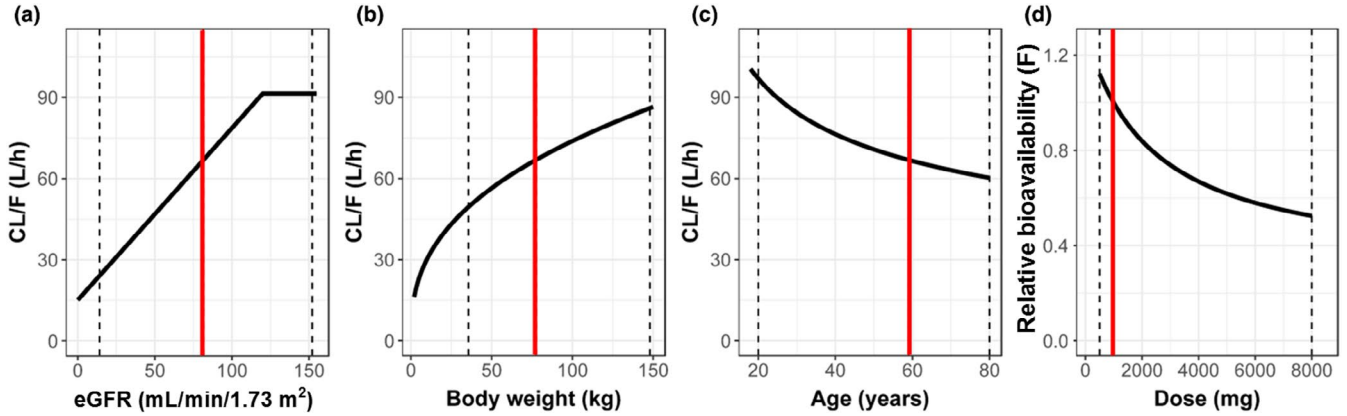

FIGURE 1 Impact of key covariates on imeglimin pharmacokinetics (PKs). Impact of (a) estimated glomerular filtration rate (eGFR) on apparent clearance (CL/F), (b) body weight on CL/F, (c) age on CL/F, and (d) dose on relative bioavailability (*F*). Bold line represents covariate effects on imeglimin PK parameters in the final PK model plotted changing one covariate at a time. Other covariates set to the reference values in the model were age 59 years, body weight 77.35 kg, eGFR 81.4 ml/min/1.73 m^2, and imeglimin 1000 mg. Vertical red line indicates reference value of covariate and vertical dashed black lines indicate observed range of covariates in the PK analysis dataset

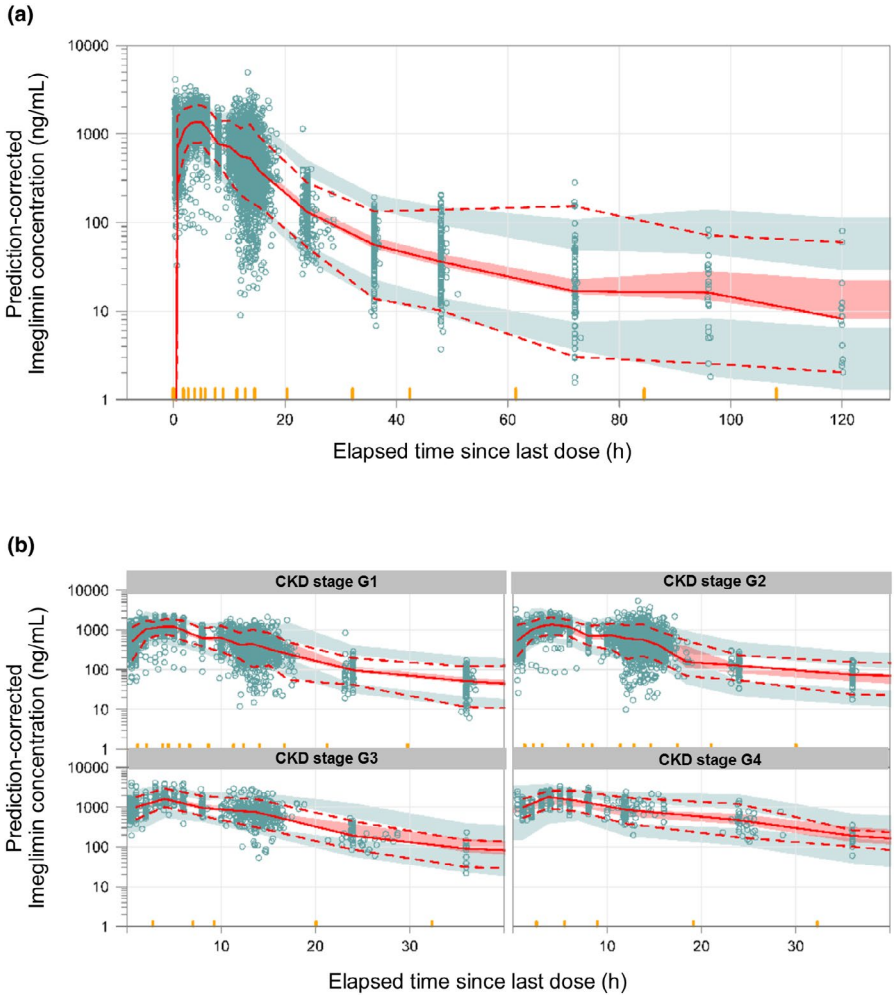

FIGURE 2 Prediction-corrected visual predictive check of imeglimin plasma concentrations versus elapsed time since last dose based on 500 simulated datasets for (a) all analyzed data and (b) data stratified by estimated glomerular filtration rate range, chronic kidney disease (CKD) stages G1, greater than or equal to 90; G2, 60 to less than 90; G3, 30 to less than 60; G4, 15 to less than 30 ml/min/1.73 m^2. Circles represent prediction-corrected observations. Solid and dashed lines represent medians and 5th and 95th percentiles of prediction-corrected observations. Shaded red and green areas represent 95% confidence interval of medians and 5th and 95th percentiles predicted by the model. Yellow tick marks indicate binning edges. *Y* axis is restricted between 1 and 10,000 ng/ml

The relationship between log-transformed $AUC_{24,ss}$ and log-transformed eGFR was linear. The slope ($-\beta$) and intercept of the linear regression line were −0.709 and 2.20, respectively, with an adjusted R^2 of 0.686. The median and 95% prediction interval of the simulated $AUC_{24,ss}$ at 500 mg q.d. in patients with an eGFR of 8–15 or 5–8 ml/

TABLE 4 $AUC_{24,ss}$ and its ratio to reference in patients with renal impairment and Western patients with changes in eGFR and body weight

		Japanese reference	CKD stage G3a	CKD stage G3b	CKD stage G4
Age, years		62 (32, 83)	68 (38, 89)	70 (40, 91)	70 (40, 91)
Weight, kg		68.8 (35.6, 124)	68.8 (35.6, 124)	68.8 (35.6, 124)	68.8 (35.6, 124)
eGFR		72.6 (47.2, 138)	52.5 (45.0, 60.0)	37.6 (30.0, 45.0)	22.4 (15.0, 30.0)
1000 mg b.i.d.	$AUC_{24,ss}$	27 (13, 55)	36 (19, 71)	45 (23, 92)	60 (32, 120)
	$AUC_{24,ss}$ ratio	1 (0.48, 2.0)	1.3 (0.71, 2.6)	1.7 (0.85, 3.4)	2.2 (1.2, 4.4)
500 mg b.i.d.	$AUC_{24,ss}$	15 (7.3, 30)	20 (11, 39)	26 (14, 47)	33 (18, 69)
	$AUC_{24,ss}$ ratio	0.56 (0.27, 1.1)	0.74 (0.39, 1.4)	0.95 (0.51, 1.7)	1.2 (0.66, 2.5)
		Japanese reference	**Western reference**	**Western similar eGFR**	**Western similar eGFR and weight**
Age, years		62 (32, 83)	59 (20, 75)	59 (20, 75)	59 (20, 75)
Weight, kg		68.8 (35.6, 124)	85.8 (54.0, 135)	85.8 (54.0, 135)	68.5 (36.7, 118)
eGFR		72.6 (47.2, 138)	92.8 (47.3, 125)	77.6 (32.2. 110)	77.6 (32.2, 110)
2000 mg b.i.d.	$AUC_{24,ss}$	46 (23, 96)	37 (18, 75)	42 (20, 88)	45 (22, 95)
	$AUC_{24,ss}$ ratio	1.6 (0.81, 3.4)	1.3 (0.65, 2.7)	1.5 (0.72, 3.2)	1.6 (0.79, 3.4)
1500 mg b.i.d.	$AUC_{24,ss}$	37 (17, 75)	29 (14, 59)	34 (16, 71)	37 (18, 76)
	$AUC_{24,ss}$ ratio	1.3 (0.62, 2.7)	1.0 (0.51, 2.1)	1.2 (0.57, 2.5)	1.3 (0.64, 2.7)
1000 mg b.i.d.	$AUC_{24,ss}$	28 (13, 55)	22 (11, 43)	25 (12, 50)	27 (13, 55)
	$AUC_{24,ss}$ ratio	1 (0.47, 2.0)	0.77 (0.38, 1.6)	0.9 (0.43, 1.8)	0.98 (0.47, 2.0)

Note: Age, weight, and eGFR are shown as medians (min, max). $AUC_{24,ss}$ and $AUC_{24,ss}$ ratio are shown as medians (2.5th and, 97.5th percentiles). Japanese reference population was randomly sampled from a Japanese phase IIb study and a phase III monotherapy study (TIMES 1) conducted in Japan, where most patients had CKD stage G2 (73%) and a few had CKD stage G1 (13%) or CKD stage G3 (14%) renal function.

Abbreviations: $AUC_{24,ss}$ ratio, ratio of individual simulated imeglimin area under the curve for 24 h at steady-state$_s$ against median simulated $AUC_{24,ss}$ in the Japanese population receiving 1000 mg b.i.d.; $AUC_{24,ss}$, area under the plasma concentration-time curve for 24 h at steady state as free base $AUC_{24,ss}$ (μg h/ml); b.i.d., twice daily; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2).

min/1.73 m^2 were 28.3 (14.4–55.0) and 42.3 (21.4–78.7) μg h/ml, respectively (Figure 3c).

Estimated AUC and exposure responses in Japanese and Western phase IIb studies

The mean $AUC_{24,ss}$ (standard deviation) estimated for the patients in the Japanese phase IIb study[15] who were treated with 1000 and 1500 mg b.i.d. for 24 weeks was 26.8 (7.34) and 38.6 (10.7) μg h/ml, respectively. The $AUC_{24,ss}$ values at the same doses in the Western phase IIb study[10] were 23.2 (7.45) and 30.9 (9.81) μg h/ml, respectively. The mean $AUC_{24,ss}$ of patients treated with 1000 mg b.i.d., which was the optimal dose in the Japanese phase IIb study, was close to that of patients treated with 1500 mg b.i.d., which was the optimal dose in the Western phase IIb study.

The mean observed change in HbA1c from baseline after 24 weeks of treatment was plotted against estimated $AUC_{24,ss}$ for the Japanese[15] and Western[10] phase IIb studies (Figure S3). The observed changes in HbA1c were close at 1000 and 1500 mg b.i.d. in the Japanese and Western studies, respectively.

Impact of body weight and eGFR on PKs in Japanese and Western patients with T2DM

Table 4 summarizes the simulated $AUC_{24,ss}$ in the resampled Japanese and Western patients and their ratios to the median $AUC_{24,ss}$ of the Japanese population treated with imeglimin 1000 mg b.i.d. The median eGFR and median body weight were 1.28- and 1.25-fold higher in the Western patients than in the Japanese reference group, respectively. The simulated $AUC_{24,ss}$ in Western and Japanese reference patients treated with 1500 and 1000 mg b.i.d., respectively, were similar. The simulations showed that ethnicity did not affect the PK of imeglimin when accounting for differences in body size and eGFR distributions between Japanese and Western patients.

DISCUSSION

Imeglimin is a potential option for treating T2DM, because, unlike other antidiabetic drugs, it has the dual effects of improving pancreatic β-cell function and enhancing insulin action.[6–9,27] As imeglimin is not metabolized but excreted unchanged in urine,[10,13] dose adjustment is crucial for treating patients with T2DM with moderate to severe renal impairment. This is the first study to characterize the population PK of imeglimin. Specifically, we analyzed data from 11 phase I to phase III clinical studies that involved Japanese and Western patients with T2DM and recommended imeglimin dosing regimens for Japanese patients with renal impairment as well as T2DM.

The population PK model established herein accurately described the PK characteristics of imeglimin (Table 3, Figure 2). The findings showed that body weight and age impacted the imeglimin CL/F, but eGFR was the covariate that had the largest impact (Figure 1). Because imeglimin plasma exposure after oral administration was lower than expected according to dose-proportionality, the effect of dose on F was incorporated into the model (Figure 1). We then predicted suitable dose regimens for patients with renal impairment and compared plasma exposure between Japanese and Western populations using the final model (Table 4).

The eGFR has been recommended as a marker of renal function in clinical practice and it is commonly used to diagnose CKD. In this study, the CKD-EPI equation for Western individuals[17] and the three-variable Japanese equation for the Japanese individuals[16] were used to derived eGFR, as each equation has been shown to fit the measured GFR well in each population, recommended by guidelines,[28,29] and used in clinical setting for each population. The eGFR values were standardized to a body surface area of 1.73 m^2, to estimate the impact of renal impairment and that of body size separately as covariates on CL/F during model development. Dose adjustment based on the category of eGFR standardized to a body surface area of 1.73 m^2 was considered sufficient, as the expected magnitude of the impact of body weight on CL/F was much lower than that of eGFR (Figure 1). The simulated $AUC_{24,ss}$ at 1000 mg b.i.d. for CKD stage G3a and at 500 mg b.i.d. for CKD stage G3b plotted against nonstandardized eGFR suggested that most of the $AUC_{24,ss}$ in patients with CKD stage G3a with nonstandardized eGFR less than 45 ml/min and most of $AUC_{24,ss}$ in patients with CKD stage G3b with nonstandardized eGFR greater than or equal to 45 ml/min were in the reference $AUC_{24,ss}$ range (Figure S4). The generally safe profile of imeglimin and its ability to reach E_{max} at 1000 mg b.i.d. also suggested that more stringent dose adjustments based on nonstandardized eGFR were not required.

Imeglimin was generally well-tolerated in Japanese patients with T2DM at the doses of 1000–1500 mg b.i.d. after 24- or 52-week administrations.[10–12,15] Thus, the median $AUC_{24,ss}$ and $C_{max,ss}$ in Japanese patients with T2DM treated with 1000 mg b.i.d. was set as the target exposure for deriving dose recommendations in patients with renal impairment in addition to T2DM. As the distribution of the demographic data was similar among these studies, populations randomly sampled from the Japanese phase IIb study and TIMES 1 were set as the reference, and three test populations with CKD stages G3a, G3b, and G4 based on eGFR were defined for simulations. Simulations of $AUC_{24,ss}$ and $C_{max,ss}$ (data not shown) for the reference and test populations (Table 4) indicated a need to reduce the dose for patients with eGFR below 45 ml/min/1.73 m^2. The selected doses were 1000 mg b.i.d. for patients with CKD stage G3a and 500 mg b.i.d. for stages G3b and G4. The same dosing recommendation was selected based on $C_{max,ss}$ (data not shown). The dose of 1000 mg b.i.d. in patients with CKD stage G3a was also supported with the safety results in this population (37 patients at 1000 or 1500 mg b.i.d.) in phase IIb[15] and phase III[11] studies. The safety and efficacy at the reduced dose levels in patients with CKD stages G3b and G4 were partially supported with the safety results of 4-week study in Western patients with T2DM at CKD stage G3b or G4 at the doses of 500 mg or 1000 mg b.i.d. or 1500 mg q.d. and await confirmation in a 52-week postmarketing study.

One limitation of this study is the absence of PK data for patients with eGFR below 14 ml/min/1.73 m^2 (the lowest was 14.1). Extrapolation was required for AUC prediction in patients with eGFR below 15 ml/min/1.73 m^2. Considering that imeglimin is predominantly eliminated in urine as unchanged drug (97% of total radioactivity excreted in the urine was unchanged imeglimin),[10,13] the contribution of nonrenal clearance should be minimal. Thus, extrapolation with power regression analysis proceeded under the assumption that no imeglimin would be cleared if the eGFR was zero, which provided a conservative dosing proposal. The power model (Figure 3a, bold red line) predicted a similar CL/F to that based on the final population PK model (Figure 3a, dashed black line) within an eGFR range equal to or above 15 ml/min/1.73 m^2. The extrapolated CL/F using the power model in the eGFR range below 15 ml/min/1.73 m^2 generated lower values than those based on the final population PK model.

Imeglimin is a substrate of the renal transporters, OCT2, MATE1, and MATE2-K, and its renal clearance (35.4 L/h) is much higher than eGFR, indicating that it is actively secreted into urine.[13] Recent analysis, using creatinine, which is also a substrate of these renal transporters, suggested that their activity deteriorates disproportionally with decreasing GFR and that the CL of the transporter substrate/GFR ratio

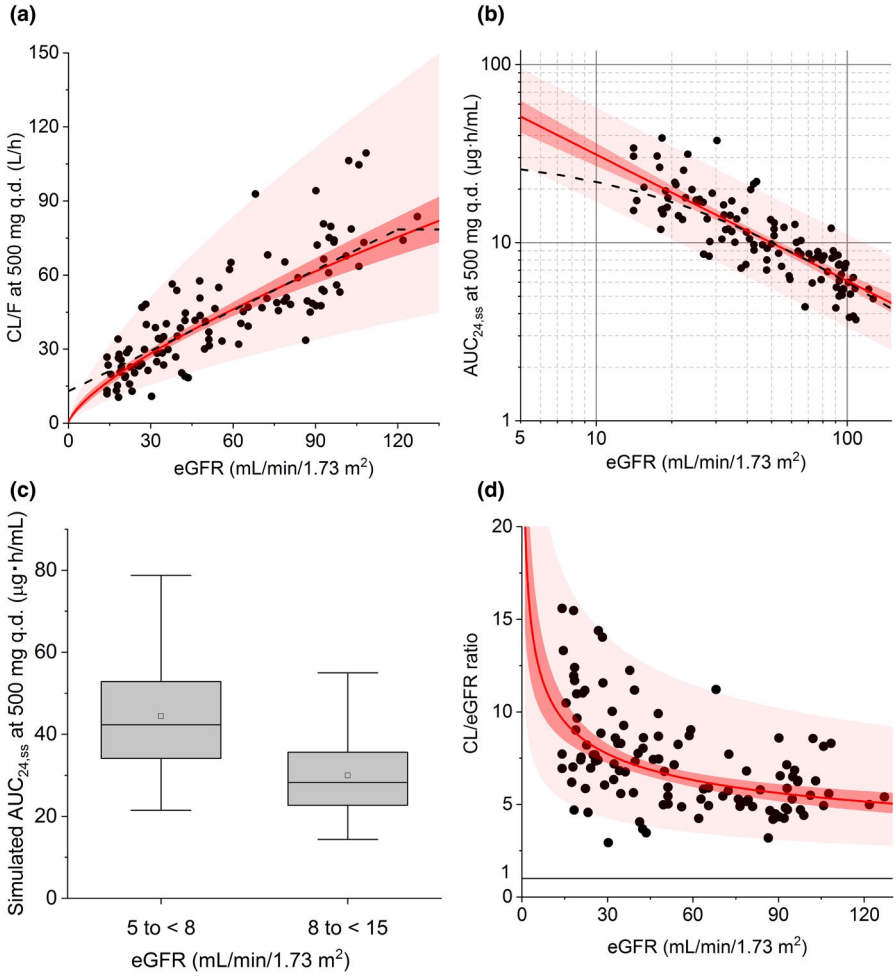

FIGURE 3 Prediction of clearance and area under imeglimin plasma concentration-time curve (AUC) in patients with renal impairment. (a) Relationship between apparent clearance and estimated glomerular filtration rate (eGFR). (b) Derived plots of AUC for 24 h at steady state ($AUC_{24,ss}$) after 500 mg q.d. versus eGFR. (c) Box plots of simulated $AUC_{24,ss}$. (d) Derived plots of clearance (CL)/eGFR ratio versus eGFR. Imeglimin CL was calculated with bioavailability (*F*) value (=0.492) determined based on the percentage of radioactivity excreted in urine after oral administration of radiolabeled imeglimin in mass balance study (0.439) after adjustment by dose (1000 to 500 mg) using the inhibitory maximum effect function for *F* in population pharmacokinetic (PK) model (Equation 7). Symbols and dashed black lines represent individual predicted values and predicted population means based on population PK model. Bold red lines represent regression line with power model and derived lines. Shaded dark and light red areas represent 95% confidence intervals of regression line and 95% prediction intervals, respectively. Boxes indicate interquartile range of simulated AUC in virtual patients with eGFR in each range with medians shown as horizontal line. Squares and whiskers represent means and 95% prediction intervals, respectively

is higher at a lower eGFR.[30] The profile of the imeglimin CL/eGFR ratio plotted against eGFR, together with a translated regression line from Figure 3a (Figure 3d) was similar to that of creatinine described by Takita et al.,[30] suggesting that imeglimin renal clearance decreases disproportionally in relation to the decrease in eGFR (slower decrease in secretory, than filtration clearance). That is, imeglimin renal clearance should be much higher than eGFR, other than in advanced oliguria or anuria. Imeglimin showed inhibition potential on OCT1, OCT2, and MATE1 in in vitro studies.[13] However, a clinical DDI study with metformin, probe substrate of OCT2, MATE1, and MATE2-K, revealed that there is no clinically relevant DDI[18] and increase in serum creatinine was not observed even after dosing up to 2000 mg b.i.d. in healthy volunteers and up to 1500 mg b.i.d. in Japanese patients with T2DM.[15] The simulated $AUC_{24,ss}$ in patients with eGFR ranging from 8–15 or 5–8 ml/min/1.73 m^2 treated with imeglimin 500 mg q.d. was 28.3 and 42.3 μg h/ml, respectively (Figure 3c), whereas that for the reference population was 27 μg h/ml at 1000 mg b.i.d. Therefore, we propose that 500 mg q.d. (or longer dosing intervals) of imeglimin would be an appropriate dosing regimen for Japanese patients with T2DM with renal impairment when the eGFR is below 15 ml/min/1.73 m^2. The safety at these AUC range was supported by the safety results in Japanese patients with T2DM in a phase IIb study[15] at the dose of 1500 mg b.i.d. for 24 weeks with geometric mean (coefficient of variation percentage [CV%]) of estimated $AUC_{24,ss}$

of 37.7 (28.9) μg h/ml (73 patients) and those in Western patients with T2DM at CKD stages G3-G5 at the doses of 500 mg b.i.d, 1500 mg q.d, or 1000 mg b.i.d. for 4 weeks with geometric mean (CV%) of observed $AUC_{24,ss}$ of 28.8 (32.0), 27.5 (50.9), or 57.2 (53.2) μg h/ml at respective doses (13, 12, or 13 patients, respectively). Further information will be obtained in a 52-week postmarketing study.

In this population PK analysis, the estimated $AUC_{24,ss}$ after dosing with imeglimin 1000 mg b.i.d. was smaller in the Western than in the Japanese phase IIb study (23.2 vs. 26.8 μg h/ml). Demographic data indicated that patients in the Western study had a higher weight (87.5 vs. 69.9 kg) and eGFR (89.5 vs. 75.2 ml/min/1.73 m^2) than those of patients in the Japanese study. To clarify the impact of eGFR and body weight on the difference in the estimated $AUC_{24,ss}$ values between Japanese and Western patients, the $AUC_{24,ss}$ was simulated in a Western population with either the same mean eGFR or the same mean eGFR and mean body weight as the Japanese reference population (Table 4). These simulations showed a 21% smaller $AUC_{24,ss}$ in Western patients than in Japanese reference populations. This difference would decrease to 11% if the Western patients had the same mean eGFR as Japanese patients and would further decrease to only a 3.6% difference if Western patients had the same mean eGFR and body weight as Japanese patients. Therefore, eGFR is the main driver of the observed differences in imeglimin exposure between Western and Japanese patients. Imeglimin was generally safe and well-tolerated with a slight increase of gastrointestinal adverse events at 1500 and 2000 mg b.i.d. in the Japanese and Western phase IIb studies, respectively, and the mean changes from baseline in HbA1c after 24 weeks of treatment as well as their corresponding plasma imeglimin exposure were similar between Japanese and Western patients after the administration of the optimal doses in the corresponding studies (1000 and 1500 mg b.i.d. in the Japanese and Western phase IIb studies, respectively; Figure S3), suggesting a similar exposure-safety and exposure-efficacy relationships between Japanese and Western patients with T2DM.

In conclusion, population PK analysis of multiple imeglimin clinical studies could describe the specific characteristics of imeglimin PKs. We identified eGFR, body weight, and age as the major covariates of imeglimin plasma clearance, and the administered dose was the major covariate of the imeglimin fraction absorbed. Dosing regimens for Japanese patients with CKD in addition to T2DM were recommended based on simulated $AUC_{24,ss}$. The recommended dose for patients with eGFR 15–45 ml/min/1.73 m^2 is 500 mg b.i.d. and a longer dosing interval would be required for patients with eGFR below 15 ml/min/1.73 m^2, considering a prolonged elimination half-life. The main driving factor in imeglimin plasma exposure differences observed between Japanese and Western phase IIb studies was the eGFR. Correlations between changes from baseline in HbA1c and predicted $AUC_{24,ss}$ were close in these two populations, suggesting no notable difference in exposure-response relationship.

CONFLICT OF INTEREST

Y.T., A.K., and D.N. are employees of Sumitomo Dainippon Pharma Co., Ltd. E.H., G.W., Q.X.O., and E.M. were paid consultants working with Sumitomo Dainippon and Poxel during the population pharmacokinetic analysis and simulations. F.M. and S.B. are employees of Poxel and may own stocks or stock options.

AUTHOR CONTRIBUTIONS

Y.T., Q.X.O., E.M., E.H., A.K., and D.N. wrote the manuscript. Y.T., E.H., F.M., and S.B. designed the research. Y.T., E.H., Q.X.O., E.M., F.M., G.W., and S.B. performed the research. Y.T., Q.X.O., E.M., G.W., and D.N. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Tomita Y, Hansson E, Mazuir F, et al. Imeglimin population pharmacokinetics and dose adjustment predictions for renal impairment in Japanese and Western patients with type 2 diabetes. *Clin Transl Sci*. 2022;15:1014-1026. doi:10.1111/cts.13221