Pharmacokinetic and pharmacodynamic modelling for renal function dependent urinary glucose excretion effect of ipragliflozin, a selective sodium–glucose cotransporter 2 inhibitor, both in healthy subjects and patients with type 2 diabetes mellitus

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Aims: To provide a model-based prediction of individual urinary glucose excretion (UGE) effect of ipragliflozin, we constructed a pharmacokinetic/pharmacodynamic (PK/PD) model and a population PK model using pooled data of clinical studies.

Methods: A PK/PD model for the change from baseline in UGE for 24 hours ($\Delta$UGE$_{24h}$) with area under the concentration–time curve from time of dosing to 24 h after administration (AUC$_{24h}$) of ipragliflozin was described by a maximum effect model. A population PK model was also constructed using rich PK sampling data obtained from 2 clinical pharmacology studies and sparse data from 4 late-phase studies by the NONMEM $\$PRIOR$ subroutine. Finally, we simulated how the PK/PD of ipragliflozin changes in response to dose regime as well as patients’ renal function using the developed model.

Results: The estimated individual maximum effect were dependent on fasting plasma glucose and renal function, except in patients who had significant UGE before treatment. The PK of ipragliflozin in type 2 diabetes mellitus (T2DM) patients was accurately described by a 2-compartment model with first order absorption. The population mean oral clearance was 9.47 L/h and was increased in patients with higher glomerular filtration rates and body surface area. Simulation suggested that medians (95% prediction intervals) of AUC$_{24h}$ and $\Delta$UGE$_{24h}$ were 5417 (3229–8775) ng·h/mL and 85 (51–145) g, respectively. The simulation also suggested a 1.17-fold increase in AUC$_{24h}$ of ipragliflozin and a 0.76-fold in $\Delta$UGE$_{24h}$ in T2DM patients with moderate renal impairment compared to those with normal renal function.
Conclusions: The developed models described the clinical data well, and the simulation suggested mechanism-based weaker antidiabetic effect in T2DM patients with renal impairment.

KEYWORDS
ipragliflozin, pharmacodynamics, pharmacokinetics, sodium–glucose cotransporter 2 inhibitor, Suglat, type 2 diabetes mellitus

INTRODUCTION

Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors are a novel class of drug that inhibit the reabsorption of glucose from the kidneys and stimulate urinary glucose excretion, thereby lowering blood glucose levels in patients with type 2 diabetes mellitus (T2DM). Ipragliflozin (Suglat) is a SGLT2-selective inhibitor co-developed by Astellas Pharma Inc. and Kotobuki Pharmaceutical Co., Ltd. for the treatment of T2DM, and has been approved in Japan and Korea. In Japan, use as monotherapy or in combination with antihyperglycaemic agents (metformin, pioglitazone, sulfonylureas, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon-like peptide-1 agonists or insulin) at a 50 mg dose once daily before or after breakfast have been approved. The dosage can be increased to 100 mg once daily if the efficacy of the 50 mg dose is insufficient. In Korea, use as monotherapy or in combination with metformin, pioglitazone or add-on treatment with combination of metformin and sitagliptin have been approved, and the recommended oral dosage is 50 mg once daily before or after breakfast.

In phase I and clinical pharmacology studies in Japanese healthy subjects and patients with T2DM, ipragliflozin was consistently well tolerated, and exposure and urinary glucose excretion (UGE) were found to increase dose-dependently. In a 12-week phase II study, dose-dependent decreases in fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) levels were observed when ipragliflozin was given by once daily administration at 12.5, 25, 50 and 100 mg. In a phase III study in Japanese patients with T2DM (BRIGHTEN Study), ipragliflozin was well tolerated on once daily administration at 50 mg for 16 weeks. Ipragliflozin was superior to a placebo in decreasing FPG and HbA1c levels, with lowering body weight and blood pressure. The long-term safety and efficacy of ipragliflozin have been established in phase III studies in T2DM patients. By contrast, in T2DM patients with moderate renal impairment, a weaker antidiabetic effect was reported.

The pharmacokinetics (PK) of ipragliflozin is characterized by high oral bioavailability (>90%), high protein binding ex vivo (~96%), a major metabolic pathway of glucuronidation by multiple UDP-glucuronosyltransferases and a very low urinary excretion ratio of unchanged ipragliflozin (approximately 1%). The aim of this study was to provide a model-based prediction method for the PK/pharmacodynamics (PD) of ipragliflozin and to determine factors that influence the pharmacological effect on UGE in Japanese patients with T2DM.

METHODS

2.1 Study design

The exposure of ipragliflozin and urine glucose excretion data from the phase I study in healthy subjects (Study A) and the clinical pharmacology studies in T2DM patients (Studies B and C) were used to establish the PK/PD model of ipragliflozin. The PK data from 6 clinical studies (Studies B–G) in T2DM patients were used to develop a population PK (PopPK) model of ipragliflozin. All studies were conducted in accordance with ethical principles based on the Declaration of Helsinki, Good Clinical Practice, and International Conference on...
Harmonization Good Clinical Practice guidelines, and were approved by an institutional review board. All subjects provided written informed consent. The brief summaries of the clinical studies are as follows:

**Study A (CL-0101, NCT01121198, phase I)** was a single-centre, placebo-controlled, single-blind, randomized, sequential-group, dose-escalation study which consisted of 2 parts: single oral dosing in the fasting state and multiple oral administration following food intake (breakfast). In the single-dosing arm, ipragliflozin at a dose of 1, 3, 10, 30, 100 or 300 mg or matching placebo was administered to healthy subjects in the fasting state (n = 48). Blood samples for measurement of plasma ipragliflozin concentration were collected at predose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration. Urine samples were collected for 24 hours before drug administration and 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36, 36–48 and 48–72 hours after administration, and UGE for 24 hours (UGE$_{24h}$) was calculated at and after administration. In the multiple-dosing arm, ipragliflozin at 20, 50 or 100 mg or placebo was administered on Day 1, and after Day 3, subjects received single daily oral doses of ipragliflozin or placebo for 7 days after a standardized meal (n = 36). Blood samples for measurement of plasma ipragliflozin concentration were collected at predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours after administration on Days 1 and 9. Urinary samples were collected for 24 hours before drug administration and 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36, 36–48 and 48–72 hours after administration, and UGE for 24 hours (UGE$_{24h}$) was calculated at and after administration.

**Study B (CL-0070, NCT01023945, Phase II)** was a 2-week, randomized, double-blind, placebo-controlled, parallel group, multiple-dose study that assessed the daily profile of PK and PD in 2TDM patients. Subjects were randomized into 3 treatment groups (placebo or ipragliflozin 50 or 100 mg, once daily of oral dose). Blood samples for measurement of plasma ipragliflozin concentration were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 10, 12 and 24 hours after administration on Day 14. Urine samples were collected for 24 hours before drug administration and 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36, and 36–48 hours after administration on Days 1 and 9, and 48–72 and 72–96 hours after administration on Day 9. From day 3 to day 8, urine collections were conducted every 24 hours. UGE$_{24h}$ was calculated at predose and at every dosing interval.

**Study C (CL-0073, NCT01097681, Clinical pharmacology study)** was an open-label, single-dose study which assessed the effect of renal function on PK, PD and safety. Ipragliflozin was administered as a single oral dose of 50 mg to T2DM patients with normal renal function (estimated glomerular filtration rate [eGFR] $\geq$90 mL/min/1.73 m$^2$), mild renal impairment (eGFR 60–90 mL/min/1.73 m$^2$), and moderate renal impairment (eGFR 30–60 mL/min/1.73 m$^2$). Blood samples for measurement of plasma ipragliflozin concentration were collected at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after administration on Day 1. Urine samples were collected for 24 hours before drug administration and 0–4, 4–10, 10–24, 24–36, 36–48, and 48–72 hours after administration on Day 1, and UGE$_{24h}$ was calculated at predose and after administration on Day 1.

**Study D (CL-0103, NCT00621868, Phase II)** was a 12-week, randomized, double-blind, placebo-controlled, multiple dose study which assessed the dose–response of ipragliflozin. Subjects were randomized into 1 of 5 treatment groups (placebo or ipragliflozin 12.5, 25, 50 and 100 mg at once daily of oral dose). Blood samples for measurement of predose plasma ipragliflozin concentration were collected at 0, 2, 4, 8 and 12 weeks.

**Study E (CL-0105, NCT01057628, Phase III)** was a 16-week, randomized, double-blind, placebo-controlled monotherapy study to assess the efficacy, safety, and tolerability of ipragliflozin. Subjects were randomized into 1 of 2 treatment groups (placebo or ipragliflozin 50 mg at once daily of oral dose). Blood samples for measurement of predose plasma ipragliflozin concentration were collected at 4, 8, 12 and 16 weeks.

**Study F (CL-0121, NCT01054092, Long-term study)** was a 52-week, open-label, uncontrolled monotherapy study to assess long-term safety, tolerability and efficacy of ipragliflozin. Ipragliflozin was given by once daily oral administration at 50 mg, which was increased to 100 mg in subjects who met the dose-escalation criteria at 20 weeks after the start of ipragliflozin treatment. Blood samples for measurement of predose plasma ipragliflozin concentration were collected every 4 weeks from 4 to 52-week assessment visits.

**Study G (CL-0072, NCT01316094, Long-term study with renal impairment patients)** was a 52-week study to assess the long-term safety and efficacy of ipragliflozin. T2DM patients with mild or moderate renal impairment who were currently on diet/exercise therapy alone or in combination with an α-glucosidase inhibitor, a sulfonylurea, or pioglitazone in a constant dosing were randomized in the study. Ipragliflozin was given by once daily oral administration at 50 mg or placebo for 24 weeks under double-blind conditions. At 24 weeks, subjects who are willing to continue participation in the study receive study drug for another 28 weeks in an open label condition. Dose escalation to 100 mg is acceptable if subjects met the dose-escalation criteria at 20 weeks. The data for 24 weeks (before dose escalation) were included in this analysis. Blood samples for measurement of predose plasma ipragliflozin concentration were collected at 8, 16, 24, 32, 40 and 52 weeks.

### 2.2 Assay for plasma levels of ipragliflozin

The concentrations of unchanged ipragliflozin in plasma were measured by liquid chromatography–tandem mass spectrometry. The lower limit of quantification was 1 ng/mL when 0.2 mL plasma was used.

### 2.3 Statistical methods

Descriptive statistics were calculated, including mean, standard deviation and range for continuous variables. Frequencies and percentages were calculated for categorical data. Simulation results were summarized by median and the prediction interval. All statistical data processing and summarization were performed using SAS version 9.1 and R.
the PK/PD relationship of ipragliflozin. Individual AUC 24h of
ance (Q/F), and apparent volumes of distribution in the central (Vc/F)
ADVAN4, the built
constant (Ka), oral clearance (CL/F), apparent intercompartment clear-
model. The model was parameterized by first order absorption rate
2
mation method with interaction using NONMEM version 7.1.0.
The potential of the following factors at baseline to influence Emax
Interindividual variability (n) in Emax or EC50 was not modelled
because only 1 or 2 ΔUGE24h, data per subject were available. For
the residual error, a combination of additive (εabs) and proportional
errors (εprop) was selected based on the objective function values
(OFV).
The potential of the following factors at baseline to influence Emax
and EC50 were then explored: disease state (healthy/T2DM), dosage
effect (single/multiple), food effect (fasted/fed), history of 1 or more
oral antidietetics treatment, disease duration, sex, age, body weight,
body mass index, body surface area (BSA), renal function classification,
urea nitrogen, urinary creatinine, urinary albumin corrected by
creatine, and urinary protein. Addition of covariate candidates was
assessed based on exploratory plots and a decrease in OFV in a
step-wise manner, with a statistical significance of P < .05 and backward deletion applied at P < .001.

2.4 I PK/PD model
AUC of ipragliflozin from time of dosing to 24 h after administration
(AUC24h) was used as an independent exposure variable to establish
the PK/PD relationship of ipragliflozin. Individual AUC24h of
ipragliflozin in Studies A, B and C were calculated by noncompartment
analysis. UGE24h, at predose and after dose were calculated for the
same time interval of AUCs. The relationship between AUC24h of
ipragliflozin and change in UGE24h from baseline (ΔUGE24h) was
described by a maximum effect (Emax) model by NONMEM. The model
was parameterized by Emax and exposure (AUC24h) producing 50% of
Emax (EC50) as follow:

\[
ΔUGE24h (mg) = Emax \frac{AUC24h}{(EC50 + AUC24h)}
\]

Interindividual variability (n) in Emax or EC50 was not modelled
because only 1 or 2 ΔUGE24h, data per subject were available. For
the residual error, a combination of additive (εabs) and proportional
errors (εprop) was selected based on the objective function values
(OFV).
The potential of the following factors at baseline to influence Emax
and EC50 were then explored: disease state (healthy/T2DM), dosage
effect (single/multiple), food effect (fasted/fed), history of 1 or more
oral antidietetics treatment, disease duration, sex, age, body weight,
body mass index, body surface area (BSA), renal function classification,
urea nitrogen, urinary creatinine, urinary albumin corrected by
creatine, and urinary protein. Addition of covariate candidates was
assessed based on exploratory plots and a decrease in OFV in a
step-wise manner, with a statistical significance of P < .05 and backward deletion applied at P < .001.

2.5 I Population PK model
To obtain individual AUC of ipragliflozin from plasma trough concen-
tration, a PopPK model was constructed using nonlinear mixed effect
modelling by NONMEM. The base model for the PK of ipragliflozin
was developed using the sequential concentration–time data from 2
clinical pharmacology studies in T2DM patients (studies B and C). A
2-compartment model with first order absorption, implemented in
ADVAN4, the built-in subroutines in NONMEM, was used as the base
model. The model was parameterized by first order absorption rate
constant (K0), oral clearance (CL/F), apparent intercompartment clear-
ance (Q/F), and apparent volumes of distribution in the central (Vc/F)
and peripheral (Vp/F) compartments (TRANS4). Interindividual variabil-
ity (n) for all the PK parameters and the residual random error (ε) were
assumed to be log-normal and proportional, respectively.

This base model was then utilized as a prior for the analyses of
trough concentration data from the 4 late-phase studies (studies
D–G) using NONMEM SPRIOR subroutine. The degree of freedom
(v) of omega (Ω) prior (the degree of informativeness about Ω) was
set to N − λ, where N is the number of patients utilized to establish
the prior model and λ is the number of parameters. Covariates were
explored for CL/F regarding the following variables: age, sex, body
weight, body mass index, BSA at baseline, aspartate amino transferase,
alanine amino transferase, alkaline phosphatase, serum albumin, total
protein (TPRO), total bilirubin (TBIL), GFR, and food effect at each
assessment visit and treatment visit. Addition of covariate candidates
was assessed by a stepwise manner, with statistical significance of
P < .05 and backward deletion applied at P < .001.

2.6 I Model evaluation
Models were evaluated by assessing goodness-of-fit (GOF) plots. Pred-
itive performance of the final PopPK model was evaluated by visual
prediction check (VPC) with using individual demographic data from
887 T2DM patients in the analysis dataset. Robustness of the final
PK/PD and PopPK models was assessed by nonparametric bootstrap.

2.7 I Simulation
The steady-state PK/PD profiles of ipragliflozin at once daily adminis-
tration of 12.5, 25, 50 and 100 mg were simulated for 887 Japanese
patients with T2DM enrolled in the 6 clinical studies (Studies B–G).
AUC24h, was calculated using individual post-hoc CL/F from the final
PopPK model and UGE24h, was simulated by the final PK/PD model.
The effect of renal function on the exposure of plasma ipragliflozin
was also investigated.

2.8 I 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 PHARMA-
COLOGY,27 and are permanently archived in the Concise Guide to
PHARMACOLOGY 2017/18.28

3 I RESULTS
3.1 I Demographics and laboratory variables
A summary of demographic and clinical laboratory variables for sub-
jects administered placebo or ipragliflozin is presented in Table 1.
Estimated GFR (mL/min/1.73m2) was calculated using the Modification
of Diet in Renal Disease study equation modified for Japanese
patients with chronic kidney disease,16 and GFR (mL/min) corrected
by individual BSA was used for modelling. BSA was calculated by the
Du Bois equation.17
| Study Subjects | Study A Phase I Healthy volunteers n = 84 (60/24) | Study B and C Clinical pharmacology T2DM patients n = 53 (43/10) | Study D, E, F, and G† Phase II, III T2DM n = 834 (652/182) | Total in T2DM n = 887 (695/192) |
|---|---|---|---|---|
| Number (active/placebo) PK/PD variables | | | | |
| Sex n (%) | Male 84 (100.0%) 37 (69.8%) 569 (68.2%) 606 (68.3%) | | | 606 (68.3%) |
| | Female 0 (0.0%) 16 (30.2%) 265 (31.8%) 281 (31.7%) | | | 281 (31.7%) |
| Age category n (%) | <65 y 84 (100.0%) 34 (64.2%) 563 (67.5%) 597 (67.3%) | | | 597 (67.3%) |
| | ≥65 y 0 (0.0%) 19 (35.8%) 271 (32.5%) 290 (32.7%) | | | 290 (32.7%) |
| Renal function n (%)† | Normal (eGFR>90 mL/min/1.73 m²) 58 (69.0%) 22 (41.5%) 296 (35.5%) 318 (35.9%) | | | 318 (35.9%) |
| | Mild (eGFR 60 to <90 mL/min/1.73 m²) 26 (31.0%) 21 (39.6%) 445 (53.4%) 466 (52.5%) | | | 466 (52.5%) |
| | Moderate (eGFR 30 to <60 mL/min/1.73 m²) 0 (0.0%) 10 (18.9%) 93 (11.2%) 103 (11.6%) | | | 103 (11.6%) |
| | Severe (eGFR<30 mL/min/1.73 m²) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) | | | 0 (0.0%) |
| Age (y) Mean (SD) | 25.4 (5.2) 59.3 (10.4) 58.7 (10.1) 58.7 (10.1) | | | 58.7 (10.1) |
| | Range (20–41) (34–75) (26–86) (26–86) | | | (26–86) |
| Body weight (kg) Mean (SD) | 64.08 (5.26) 69.06 (11.89) 68.14 (12.13) 68.19 (12.11) | | | 68.19 (12.11) |
| | Range (51.4–80.1) (45.6–100.8) (41.5–128.0) (41.5–128.0) | | | (41.5–128.0) |
| BMI (kg/m²) Mean (SD) | 21.59 (1.55) 25.78 (3.14) 25.60 (3.62) 25.62 (3.59) | | | 25.62 (3.59) |
| | Range (18.5–25.8) (20.0–33.9) (19.1–40.6) (19.1–40.6) | | | (19.1–40.6) |
| BSA (m²) Mean (SD) | 1.758 (0.086) 1.744 (0.183) 1.731 (0.178) 1.732 (0.178) | | | 1.732 (0.178) |
| | Range (1.56–2.03) (1.35–2.14) (1.28–2.47) (1.28–2.47) | | | (1.28–2.47) |
| GFR (mL/min)†‡ Mean (SD) | 101.28 (15.68) 84.28 (29.29) 84.50 (23.49) 84.46 (23.91) | | | 84.46 (23.91) |
| | Range (72.2–153.0) (29.8–169.8) (24.1–175.4) (24.1–181.5) | | | (24.1–181.5) |
| Total protein (g/dL) Mean (SD) | 6.73 (0.31) 7.19 (0.47) 7.28 (0.40) 7.27 (0.40) | | | 7.27 (0.40) |
| | Range (5.8–7.5) (6.1–8.3) (5.8–9.1) (5.8–9.1) | | | (5.8–9.1) |
| Total bilirubin (mg/dL) Mean (SD) | 0.76 (0.23) 0.81 (0.33) 0.81 (0.31) 0.81 (0.31) | | | 0.81 (0.31) |
| | Range (0.4–1.3) (0.4–2.7) (0.2–3.6) (0.2–3.6) | | | (0.2–3.6) |
| FPG (mg/dL) Mean (SD) | 92.6 (5.1) 156.0 (40.2) 169.1 (37.7) 168.3 (37.9) | | | 168.3 (37.9) |
| | Range (83–110) (84–255) (73–342) (73–342) | | | (73–342) |
| HbA1c (NGSP) (%) Mean (SD) | 5.11 (0.19) 8.05 (1.45) 8.08 (0.82) 8.08 (0.87) | | | 8.08 (0.87) |
| | Range (4.8–5.6) (5.8–14.0) (6.3–11.4) (5.8–14.0) | | | (5.8–14.0) |

†In study G, eGFR during placebo run-in period were summarized as the baseline values

‡eGFR corrected by individual BSA were summarized

AUC<sub>24h</sub>, area under the concentration–time curve from time of dosing to 24 h after administration; BMI, body mass index; BSA, body surface area; C<sub>trough</sub>, plasma trough concentration; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; PK/PD, pharmacokinetic/pharmacodynamic; SD, standard deviation; T2DM, type 2 diabetes mellitus; UGE<sub>24h</sub>, change in urinary glucose excretion for 24 hours
3.2 Exploratory assessment of PD

A total of 686 UGE_{24h} data from 137 subjects (84 healthy subjects and 53 T2DM patients) were collected at predose, after the first dose, during multiple doses and after the last dose. A dose-dependent increase in UGE was observed after single and multiple doses both in healthy subjects and T2DM patients. UGE_{24h} was generally higher in patients with T2DM than in healthy subjects and dependent on renal function.\textsuperscript{3-5} Scatter plots of (A) UGE_{24h} at baseline (UGE_{24h, base}) vs FPG at baseline, (B) absolute UGE_{24h} after dose vs AUC_{24h}, (C) ΔUGE_{24h} vs AUC_{24h} and are presented in Figure 1. In the exploratory plots, a total of 177 measurements after first and last doses that have corresponding exposure values (AUC_{24h}) were plotted. T2DM patients with high FPG levels (>~180 mg/dL) had significant UGE before ipragliflozin treatment. UGE is known to be determined by plasma glucose levels and renal function,\textsuperscript{18,19} which could explain the correlations among ΔUGE_{24h}, FPG and GFR observed in the studies (Figure 2). ΔUGE_{24h} in T2DM patients was generally dependent on both FPG and GFR except for some patients with very high baseline UGE_{24h} (UGE_{24h, base}) who appeared not to follow the trend. As ΔUGE_{24h} depends on both FPG and GFR, a hybrid parameter, FAC, which is a product of FPG and GFR, was calculated and used as a predictor of UGE_{24h, base}, UGE_{24h}, and ΔUGE (Figure 3). The plots clearly suggested that ΔUGE_{24h} of patients with zero or minimal UGE_{24h, base} depends strongly on FAC, whereas ΔUGE_{24h} of patients with significant UGE_{24h, base} was roughly constant regardless of FAC. The apparent threshold of FAC for UGE_{24h, base} was about 16 000 to 18 000, which is consistent with the threshold at which glucose appears in urine being at a plasma glucose level of 160–180 mg/dL\textsuperscript{18,19} when subjects have normal GFR of around 100 mL/min. Based on the exploratory plots, 18 000 was used as the threshold for FAC in further modelling.

3.3 PK/PD model

A total of 155 ΔUGE_{24h} data points from 111 subjects (65 healthy subjects and 46 T2DM patients) were included in the analysis. UGE_{24h} values that have no corresponding AUC_{24h} as the same collection interval were excluded from the analysis. Additionally, data for low doses (1 and 3 mg) were also excluded from analysis because no significant effects on UGE were observed throughout the evaluation period.

A PK/PD model for ΔUGE_{24h}, with AUC_{24h} of ipragliflozin was described by an E_{max} model. The parameter estimates in the final model are shown in Table 2. Based on the exploratory assessment, FPG and GFR were preset as covariates of E_{max} as products of power functions (Equation 2). The covariate exploration for E_{max} and EC_{50} elucidated that only a threshold for FAC was significant as an additional covariate for E_{max} (Equation 3). Other laboratory variables and background demographic factors had no significant impact on E_{max} or EC_{50}.

\[
\text{if FAC} \leq 18\,000: E_{max} = 72.3 \times \frac{\text{FPG}}{100^{1.37}} \times \frac{\text{GFR}}{90^{0.623}} \\
\text{if FAC} > 18\,000: E_{max} = 107
\]

E_{max} was 72.3 g/24 h for subjects with the reference FPG of 100 mg/dl and the reference GFR of 90 mL/min. The fixed effect model indicates E_{max} depends on FPG and GFR up to a threshold value (18,000) of FAC (Equation 2), and then E_{max} becomes constant at 107 g/24 h (Equation 3). EC_{50} for glucose excretion effect was 1590 ng·h/mL. The residual error of ΔUGE_{24h} was ±352 mg and 19.8% (when E_{max} = 72 g/24 h, it is approximately ±14 g) for additive
and proportional errors, respectively. The residual error of the final model was comparable to the interindividual variability (IIV) of ΔUGE24h assessed in placebo patients (±20 g).

### 3.4 PopPK model

First, a total of 534 plasma ipragliflozin concentrations from 43 patients in studies B and C were adopted to develop the prior model of the PopPK model. The structural PK model of ipragliflozin was a 2-compartment model with first-order absorption, and IIV of PK parameters were assumed to CL, Vp, and F considering change in OFV and η correlation between parameters.

Next, a total of 3714 trough concentration measurements from 630 patients in studies D, E, F and G were utilized with the developed prior model. In the late phase studies, only trough plasma concentration data were available, therefore, for IIV of PK parameters in the base model, only that of CL/F was assumed because it was unable to appropriately evaluate all η in the prior model. The covariate correlation based on the step-wise (P < .05) and the backward deletion (P < .001) revealed that GFR, TPRO, TBIL and BSA were significant covariates on CL/F. The fixed effect model for the covariates suggests that CL/F increases with increasing GFR and BSA, and decreases with increasing TPRO and TBIL, as described in Equation 4.

\[
CL/F (L/h) = 9.47 \times (GFR/90)^{0.233} \times (TPRO/7.0)^{0.417} \times (TBIL/0.8)^{-0.0681} \times (BSA/1.7)^{0.610} \tag{4}
\]

The parameter estimates for the final PopPK model are presented in Table 3. Estimated population means of Ka, CL/F, Vc/F, Q/F and Vp/F were 6.38 h⁻¹, 9.47 L/h, 39.4 L, 6.63 L/h and 68.1 L, respectively. The change in OFV from the base model was −252.044, and the IIV of CL/F decreased from 26.8 to 23.4%, and the shrinkage for η CL/F in the final model was 2%. The residual error in plasma ipragliflozin concentration was 24.8%.

### 3.5 Model evaluation

In the final PK/PD model, GOF plots suggest acceptable model fittings (Figure S1). The predicted mean and the 95% confidence interval in VPC plot shows that Emax curve is reproducible (Figure S2). In the final PopPK model, GOF plots also suggest acceptable model fittings. The conditional weighted residuals showed no trend against time, visit or dose (Figure S3). And, the model enables to predict individual AUC24h reliably (Figure S4). VPC plots demonstrated that the final PopPK model well reproduced the observed data regardless of dose (Figure 4). The success rate of bootstrap runs was 100% of 300 runs for both the PK/PD model and PopPK models. The summary statistics of the bootstrap estimates were consistent with the parameter estimates of the final model, suggesting the robustness of the estimates.
3.6 | Simulation

Simulated median and the 95% prediction interval (2.5th–97.5th percentiles) of \( \text{AUC}_{24h} \) and \( \Delta \text{UGE}_{24h} \) at steady state for each treatment are summarized in Table 4 and Figure 5. The effect of renal function on the exposure of plasma ipragliflozin at steady state was also investigated with once daily administration at 50 mg (Table 5). The simulation suggested a 1.17-fold increase in \( \text{AUC}_{24h} \) of ipragliflozin and a 0.76-fold change in \( \Delta \text{UGE}_{24h} \) in T2DM patients with moderate renal impairment (eGFR: 30 to <60 mL/min/1.73m²) compared to those with normal renal function.

4 | DISCUSSION

The developed PK/PD model described the relationship between the individual plasma ipragliflozin exposure (\( \text{AUC}_{24h} \)) and \( \Delta \text{UGE}_{24h} \) as a pharmacological effect of ipragliflozin. The PopPK model was
developed in order to assess the individual AUC24h in patients with T2DM from sparse PK samples. In a previous publication, we described increase in UGE using an Emax model predicted by AUC24h and the initial excretion level (E0).20 In the model, however, the impact of renal function on UGE was not considered, thus the Emax need to be estimated separately for healthy subjects and patients with T2DM. The new model established in this article provides the mechanism-based pharmacological effect of SGLT2 inhibitor both healthy subjects and patients with T2DM in 1 model by taking into consideration the individual FPG and GFR.

In healthy individuals, about 180 g of glucose (calculated as the primitive urine production of 180 L/24 h times the normal FPG level of 100 mg/dL) is filtered daily at the renal glomeruli and nearly 100% of filtered glucose is reabsorbed at the renal tubules.19 In other words, both FPG and GFR are determinative factors of UGE. SGLT2 is expressed at the renal proximal tubules and accounts for over 90% of renal glucose reabsorption.21 When the blood glucose level is higher than the maximum capacity of reabsorption (approximately 180 mg/dL), glucose is then excreted into urine. Beyond the threshold, urinary glucose increases in a linear fashion with increasing plasma glucose level.18,19 SGLT2 inhibitors lower the maximum capacity of glucose reabsorption.

The relationship between FPG, GFR and UGE are clearly indicated by the observed clinical data taken from patients with ipragliflozin in studies A, B and C, which are schematically presented in Figure 3. The figure shows that the threshold value for reabsorption at baseline used in the PK/PD modelling (FPG × GFR = 18 000 or 180 g/24 h) is physiologically adequate if considering the pharmacological effect of SGLT2 inhibitors. As obvious based on the mechanism, the maximum effect on UGE of SGLT2 (ΔUGE24h) never exceeds filtered glucose.

TABLE 4  Simulated area under the concentration–time curve from time of dosing to 24 h after administration (AUC24h) of ipragliflozin and change in urinary glucose excretion for 24 hours (ΔUGE24h) at steady-state in each treatment

| Treatment        | AUC24h (ng·h/mL) | ΔUGE24h (g) |
|------------------|------------------|-------------|
| 12.5 mg daily    | 1354 (807–2194)  | 51 (30–91)  |
| 25 mg daily      | 2709 (1615–4387) | 70 (42–120) |
| 50 mg daily      | 5417 (3229–8775) | 85 (51–145) |
| 100 mg daily     | 10834 (6458–17550)| 95 (57–162) |

Median (2.5th–97.5th percentile) are presented for simulated n = 887 data for each treatment
Therefore, $E_{\text{max}}$ of $\Delta UGE_{24h}$ was parameterized by product of FPG and GFR in this article. In the PK/PD analysis, the estimated $E_{\text{max}}$ was 140 g/24 h in Japanese T2DM patients with the reference FPG (160 mg/dL) and GFR (90 mL/min). A comparable $E_{\text{max}}$ for empagliflozin (120 g/24 h) was reported in T2DM patients with a mean FPG of 8–9 mmol/L (144–162 mg/dL).22 The $E_{\text{max}}$ of these SGLT2 inhibitors are estimated to be about 40–50% compared to total amount of filtered glucose (288 g: FPG 160 mg/dL × primitive urine production: 180 L/24 h). The absence of complete inhibition of urinary glucose reabsorption was also found even under the condition with almost no SGLT2 activity expected to be remained in empagliflozin and dapagliflozin studies.22,23 The incomplete inhibition mainly attributes to contribution of reabsorption by SGLT1 expressed in the luminal membrane of the late proximal tubule.24,25

The final PopPK model indicates fixed effects of BSA, GFR, TPRO and TBIL as statistically significant covariates on ipragliflozin exposure. GFR is thought to be a dominant factor to affect ipragliflozin exposure, whereas the other covariates will cause only 10% or less change in the exposure. Despite the negligible urinary excretion of unchanged ipragliflozin, renal function significantly influences ipragliflozin exposure. Both the descriptive comparison of assessed AUC as well as simulation by the final PopPK model indicate about 20% higher exposure in moderate renal impairment patients with T2DM.5 Although GFR has been recognized as a dominant factor affecting ipragliflozin exposure, there is some uncertainty for the application of the model to the T2DM patients with severely impaired renal function who have not been studied in the clinical studies.

By contrast, the PK/PD model suggests that glucose excretion effect almost reaches the maximum level at above 50 mg daily dose of ipragliflozin. Based on the established PK/PD model, it is suggested that any excessive drug effect cannot be expected in renal impairment patients due to the higher exposure caused by renal impairment. In addition, lower GFR in renal impairment patients results in lower urinary filtrated glucose; therefore, the drug effect ($\Delta UGE_{24h}$) by ipragliflozin is lower. Our model well described the result of the lower UGE in renal impairment patients with T2DM found in study C.5 Furthermore, the lower decrease in FPG and HbA1c by ipragliflozin was confirmed in the long-term study in renal impairment patients (study G).9 Recently, de Winter et al. reported a dynamic PK/PD model for HbA1c decreasing effect of canagliflozin.26 In this report, GFR was a significant covariate of $E_{\text{max}}$ and the outcome was simulated by normalized HbA1c level at baseline. The results are consistent with our findings, and it also supports our assumption that UGE effect by SGLT2 inhibitor must link directly to the clinical outcome.

The developed PK/PD and PopPK models enables to provide individual response of increase in UGE by ipragliflozin. The relationship between the pharmacological effect ($\Delta UGE$) and the long-term clinical outcomes, i.e. FPG or HbA1c, will be further modelled in future articles.

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CONTRIBUTORS

All authors were involved with drafting and revising this article. M.S., A.K. and T.K. planned this analysis, and M.S. conducted the analysis. J.T. contributed data verification and the creation of tables and figures. S.Y. was a lead statistician who was responsible for data handling of each study. K.K. was a study leader for ipragliflozin and contributed to the planning and conduct of the clinical studies. E.U. was a project manager of ipragliflozin and contributed to mapping of the development strategy.

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