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ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetic Modeling of Canagliflozin in Healthy Volunteers and Patients with Type 2 Diabetes Mellitus

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Abstract

Background and Objectives Canagliflozin is an orally active, reversible, selective sodium-glucose co-transporter-2 inhibitor. A population pharmacokinetic (popPK) model of canagliflozin, including relevant covariates as sources of inter-individual variability, was developed to describe phase I, II, and III data in healthy volunteers and in patients with type 2 diabetes mellitus (T2DM).

Methods The final analysis included 9061 pharmacokinetic (PK) samples from 1616 volunteers enrolled in nine phase I, two phase II, and three phase III studies and was performed using NONMEM® 7.1. Inter-individual variability was evaluated using an exponential model and the residual error model was additive in the log domain. The first-order conditional estimation method with interaction was applied and the model was parameterized in terms of rate constants. Covariate effects were explored graphically on empirical Bayes estimates of PK parameters, as shrinkage was low. Clinical relevance of statistically significant covariates was evaluated. The predictive properties of the model were illustrated by prediction-corrected visual predictive checks.

Results A two-compartment PK model with lag-time and sequential zero- and first-order absorption and first-order elimination best described the observed data. Sex, age, and weight on apparent volume of distribution of the central compartment, body mass index on first-order absorption rate constant, and body mass index and over-encapsulation on lag-time, and estimated glomerular filtration rate (eGFR, by MDRD equation), dose, and genetic polymorphism (carriers of UGT1A9*3 allele) on elimination rate constant were identified as statistically significant covariates. The prediction-corrected visual predictive checks revealed acceptable predictive performance of the model.

Conclusion The popPK model adequately described canagliflozin PK in healthy volunteers and in patients with T2DM. Because of the small magnitude of statistically significant covariates, they were not considered clinically relevant. However, dosage adjustments are recommended for T2DM patients with renal impairment (eGFR ≥60 mL/min/1.73 m^2: 100 or 300 mg/day; eGFR of 45 to <60 mL/min/1.73 m^2: 100 mg/day).

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Key Points

The population pharmacokinetic model adequately described canagliflozin pharmacokinetics in healthy volunteers and in patients with type 2 diabetes mellitus (T2DM).

The magnitude of the statistically significant covariates identified was small and therefore not considered clinically relevant.

Canagliflozin dosage adjustments are recommended for T2DM patients with renal impairment [estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/ 1.73 m^2: 100 or 300 mg/day; eGFR of 45 to <60 mL/min/1.73 m^2: 100 mg/day].

1 Introduction

Diabetes mellitus affects nearly 347 million people worldwide and is estimated to be the seventh leading cause of death by 2030 with type 2 diabetes mellitus (T2DM) accounting for 90 % of these cases. The treatment options available for T2DM focus on reducing insulin resistance, enhancing insulin secretion, or providing exogenous insulin. The inhibition of the sodium-glucose co-transporter plays a pivotal role in increasing the excretion of glucose and lowering blood glucose. The sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a novel therapeutic approach in the management of T2DM. Currently, three SGLT2 inhibitors are approved in the USA and Europe for the treatment of T2DM (canagliflozin, dapagliflozin, and empagliflozin) [1–3].

Canagliflozin, an orally active, reversible, selective SGLT2 inhibitor, is a novel oral hypoglycemic agent approved as an adjunct to diet and exercise in several countries worldwide at 100- and 300-mg doses to improve glycemic control in adults with T2DM [2]. For patients requiring the addition of canagliflozin to metformin therapy or the addition of metformin to canagliflozin, or in those patients already on metformin and canagliflozin, each dosed as separate tablets, the use of a fixed-dose combination tablet comprising metformin and canagliflozin may improve patient convenience and compliance to antihyperglycemic agent therapy [4].

The low-affinity/high-capacity SGLT2 transporter present in the early proximal convoluted renal tubule reabsorbs most of the filtered glucose [5, 6] and a very small amount of glucose is reabsorbed by the high-affinity/low-capacity glucose transporter, SGLT1. Canagliflozin decreases renal glucose reabsorption, thereby increasing urinary glucose excretion and decreasing plasma glucose levels in patients with hyperglycemia. Furthermore, the calories lost in urine (as glucose) may also reduce body weight (WT) [4, 7–10]. In a phase III study, monotherapy with canagliflozin 100- and 300-mg doses resulted in significant ($p < 0.001$) reductions in glycosylated hemoglobin (<7.0 %) from baseline to week 26 vs placebo in patients with T2DM [11].

The pharmacokinetic (PK) profile of canagliflozin is similar in healthy participants and patients with T2DM. Orally administered canagliflozin is rapidly absorbed achieving peak plasma concentrations within 1–2 h [2]. Dose-proportional systemic exposure to canagliflozin has been observed over a wide dose range (50–1600 mg) with an oral bioavailability of 65 %. The apparent terminal half-life was 10.6 h for the 100-mg dose and 13.1 h for the 300-mg dose. Steady state was reached after 4 days, and there is minimal accumulation observed after multiple dosing. The mean steady-state volume of distribution after a single intravenous infusion was 83.5 L in healthy participants, suggesting extensive tissue distribution of canagliflozin. Canagliflozin is extensively bound to plasma proteins (99 %), predominantly to human serum albumin. Approximately 60 and 33 % of the administered dose is excreted in the feces and urine, respectively. Canagliflozin is primarily metabolized by uridine diphosphate-glucuronosyltransferase 1 A9 (UGT1A9) and UGT2B4 to inactive O-glucuronides (M7 and M5) and minimally by cytochrome P450 3A4, and has a very limited potential to cause drug–drug interactions [2].

This article provides a comprehensive summary of the population pharmacokinetic (popPK) analysis, including a covariate search, of canagliflozin. Based on PK data from healthy volunteers and patients with T2DM, a popPK model was developed to improve the understanding of canagliflozin PK and explore possible relationships between patient covariates and PK parameters. The objectives of this analysis were: (1) to develop a popPK model that adequately describes the PK of canagliflozin after oral administration in healthy volunteers and in patients with T2DM; (2) to evaluate the effects of volunteers' demographic characteristics and other covariates on PK parameters of canagliflozin; and (3) to evaluate the clinical relevance of statistically significant covariates and investigate predictive properties of the model.

2 Methods

2.1 Bioanalytical Assay

The validated assays for the quantification of total unchanged canagliflozin (JNJ-28431754) in human plasma

for the clinical studies included in this pooled popPK analysis were based on liquid chromatography coupled to tandem mass spectrometry. The lower limit of quantification (LLOQ) for canagliflozin was 5.00 ng/mL, except for study 9 for which the LLOQ was 1.00 ng/mL. The bioanalytical assay range was from 5.00 to 10,000 ng/mL (all studies included in popPK analysis), except for studies 4 and 9 for which the range was from 5.00 to 5000 ng/mL and from 1.00 to 2000 ng/mL, respectively.

2.2 Study Population and Design

The study population included healthy volunteers from phase I studies and patients with T2DM enrolled in phase II and III studies. Table 1 summarizes study designs, objectives, and enrollment for each study used in this pooled popPK analysis. Each protocol was reviewed and approved by an institutional review board and informed consent was obtained from each volunteer before enrollment in the studies. The studies were conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines, and other applicable regulatory requirements.

The model was developed in steps (i.e., phase I model, pre-final model, external evaluation, and final popPK model). For the phase I model, a total of 5715 PK samples from 245 volunteers across richly sampled phase I studies were used for model development and covariate evaluation on the absorption and distribution parameters (ESM Table 2). Next, the phase I PK dataset was combined with PK data from sparsely sampled phase II and III studies. From this combined dataset, 8813 PK samples from 1526 volunteers were included in the analysis, and covariate effects were explored on the elimination rate constant (k_e) resulting in the pre-final model. The external evaluation dataset contained 174 volunteers that contributed 182 PK samples [from two phase III studies (studies 13 and 14) that were not used to build the model]. The datasets used to build and to evaluate the model were then combined and the final model was re-run on the full dataset (9061 PK samples from 1616 volunteers).

2.3 Population Pharmacokinetic Analysis

The PopPK analysis was performed by non-linear mixed-effects modeling using NONMEM® (ICON plc) Version VII level 1.0, with PREDPP version V level 2.0 with gFORTRAN compiler 4.5.0 [12]. Dataset preparation, exploration, and visualization, as well as statistical and graphical analysis of all NONMEM® output, were performed using R for Windows (version 2.15.3). The first-order conditional estimation with interaction method was used for all analyses. The model was parameterized in

terms of rate constants using the ADVAN4 TRANS1 option in NONMEM. The inter-individual variability (IIV) in PK parameters was regarded as random and was modeled using eta (η) variables. The individual η values were assumed to be log-normally distributed with a mean of zero and an estimated variance (ω^2). Correlations between IIV distributions were evaluated by means of graphical assessment and tested by inclusion of covariance terms between IIV parameters in the model.

Pre-dose samples and PK samples in which corresponding canagliflozin concentrations were below the LLOQ were excluded from the popPK analysis (5.6 % of all samples). Canagliflozin concentrations were excluded from the analysis if the sample date/time was missing, no or insufficient dosing information before sample collection was available, or the time since the last dose was more than 48 h (5.6 % of all samples). Additionally, missing plasma concentration values were treated as missing and were not replaced with imputed values (1.2 % of all samples). Outliers, defined as aberrant observations that significantly deviated from the rest of the observations in a particular individual, were excluded. During model development, 53 outlying data points in 39 patients were identified through the conditional weighted residuals (deviating more than ±6 units) and individual residuals (deviating more than ±2 units). These samples (0.5 % of all samples) were excluded from further analysis because of their disproportional contribution to the residual error.

2.4 Pharmacostatistical Model Development

A popPK model was developed first on the richly sampled phase I data. Extensive covariate analysis was performed on the absorption (absorption rate constant, k_a and lag-time, T_{lag}) and distribution (apparent volume of distribution of the central compartment, V_c/F and distribution rate constant from the peripheral compartment, k_{32}) parameters. These parameters, including the covariance matrix of the random effects were subsequently fixed when fitting the richly (phase I) and sparsely (phase II and III) sampled PK data together.

Once the model built on phase I data was final, the absorption (k_a, D_1, and T_{lag}) and distribution parameters (V_c/F, k_{23}, and k_{32}), including the covariance matrix of the random effects were fixed and the model was re-run on a combined phase I, II, and III dataset (pre-final model). This model was used for covariate analysis on k_e and was subjected to an external evaluation. The evaluation was performed on a subset of data from two phase III studies that were not used to build the pre-final model. Once the pre-final model was evaluated, the datasets used to build and to evaluate the pre-final model were combined and the model was re-run on the full dataset to obtain the final parameters.

Table 1 Summary of study data included in the pooled population PK analysis

Study no.	Study title	Brief description of PK data	Study sample size
1	A Single Blind, Placebo Controlled, Randomized, Sequential, Dose Escalation PK, PD, Safety and Tolerability Study of Canagliflozin	SD in healthy men given 800-, 1200-, or 1600-mg qd canagliflozin oral tablets with 96-h PK profile on day 1	Volunteers enrolled/analyzed: 24/17
2	An Open-Label Drug–Drug Interaction Study to Explore the Effects of Multiple Doses of Canagliflozin on the Pharmacokinetics and Safety of Single Doses of Oral Contraceptive	MAD in healthy women given 200-mg qd canagliflozin oral tablets with 24-h PK profile on day 4	Volunteers enrolled/analyzed: 24/24
3	An Open-Label, Single-Dose Study to Evaluate Canagliflozin Pharmacokinetics, Pharmacodynamics and Safety in Non-Diabetic Patients With Varying Degrees of Renal Function	SAD in non-diabetic renally impaired patients given 200-mg qd canagliflozin oral tablets	Patients enrolled/analyzed: 40/40
4	A Randomized, Double-Blind, Placebo-Controlled, Sequential, Single-Center Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Canagliflozin in Type-2 Diabetes Mellitus	MAD in type 2 diabetic patients given 100-mg qd and 300-mg bid canagliflozin oral tablets with 24-h PK profile on day 27	Patients enrolled/analyzed: 20/20
5	A Single-Dose, Open-Label, Randomized, Two-Way, Cross-Over Study to Assess the Pharmacokinetics and Pharmacodynamics of Canagliflozin	SD in healthy men and women Indian volunteers given 200- and 300-mg qd canagliflozin oral tablets	Volunteers enrolled/analyzed: 16/15
6	A Randomized, Assessor- and Volunteer-Blind, Placebo- and Positive-controlled Study to Evaluate the Photosensitizing Potential of Multiple Oral Doses of Canagliflozin	MAD in healthy volunteers given 100- and 300-mg qd canagliflozin oral tablets with 24-h PK profile on day 4	Volunteers enrolled/analyzed: 24/24
7	A Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study to Evaluate the Multiple Dose Pharmacokinetic and Pharmacodynamic Characteristics of Canagliflozin in Type 2 Diabetes Mellitus	MAD in type 2 diabetic patients given 50-, 100-, and 300-mg qd canagliflozin oral tablets with 24-h PK profile on day 1 and 120-h PK profile on day 7	Patients enrolled/analyzed: 27/27
8	An Open-Label, Randomized, Parallel-Group, Single-Center Study to Evaluate the Single and Multiple Dose Pharmacokinetic and Pharmacodynamic Characteristics of Canagliflozin	MAD in healthy volunteers given 50-, 100-, and 300-mg qd canagliflozin oral tablets with 24-h PK profile on day 1 and on day 9	Volunteers enrolled/analyzed: 27/27
9	Clinical Pharmacology Study of TA-7284 in Patients with Type II Diabetes Mellitus (Multiple Oral Dose)	MAD in Japanese type 2 diabetic patients given 25-, 100-, 200-, and 400-mg qd canagliflozin oral tablets with 48-h PK profile on day 1, trough samples on days 5, 7, 9, 13, and 15, and 72-h PK profile on day 16	Patients enrolled/analyzed: 61/51
10	A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel-Group, Multicenter, Dose-Ranging Study in Patients with Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin	MAD in type 2 diabetic patients given 50-, 100-, 200-, and 300-mg qd, and 300-mg bid canagliflozin oral tablets with trough samples at study weeks 3, 6, and 12	Patients enrolled/analyzed: 320/287
11	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Investigate the Safety and Efficacy of Canagliflozin in Non-diabetic Overweight and Obese Volunteers	MAD in non-diabetic overweight and obese volunteers given 50-, 100-, and 300-mg qd, canagliflozin oral tablets with trough samples at study weeks 3, 6, and 12	Volunteers enrolled/analyzed: 320/250
12	A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Type 2 Diabetes Mellitus with Moderate Renal Impairment	MD in type 2 diabetic patients who have moderate renal impairment given 100- and 300-mg qd canagliflozin for 52 weeks with trough samples at study weeks 3, 12, 26, and 52	Patients enrolled/analyzed: 240/159
13	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in Patients With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise	MD in type 2 diabetic patients given 100- and 300-mg qd canagliflozin for 52 weeks with trough samples at study weeks 6, 12, and 26	Patients enrolled/analyzed: 450/220

Table 1 continued

Study no.	Study title	Brief description of PK data	Study sample size
14	A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin 100 mg and 300 mg Compared with Glimepiride in Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy	MD in type 2 diabetic patients given 100- and 300-mg qd canagliflozin for 104 weeks with trough samples at study weeks 8, 52, 78, and 104	Patients enrolled/analyzed: 1281/455

PK pharmacokinetics, *SAD* single ascending dose, *MAD* multiple ascending dose, *qd* once daily, *bid* twice daily

This final popPK model was used to evaluate the clinical relevance of identified covariates.

Log-transformed plasma concentration-time data were evaluated by a sequence of compartmental models. Different absorption models were tested (e.g., zero- and first-order absorption models, sequential and parallel zero- and first-order absorption) using the first-order conditional estimation with interaction method in NONMEM®, and their results compared. IIV was described using an exponential model. Because the canagliflozin plasma concentrations were log transformed, the residual error was described using an additive error model in the log domain. An extra residual error term was added for data from phase II and III studies to account for the difference in residual variance between richly (phase I) and sparsely (phase II and III) sampled PK data. The final selection of the structural model was based on physiological considerations, goodness-of-fit plots, reduction in minimum objective function value (OFV), and decreases in residual error variance.

2.5 Covariate Analysis

The selected covariates that were assessed included sex, WT, body mass index (BMI), age, estimated glomerular filtration rate (eGFR), fed status, glycemic status (diabetic vs. non-diabetic), encapsulation (over-encapsulated vs. non-encapsulated tablets), dose, genetic polymorphism (carriers of the UGT1A9*3 allele), particle size distribution (PSD), and effect of long-term concomitant medications (substrates of UGT1A9 or UGT2B4). The effect of PSD on PK of canagliflozin was investigated as different active pharmaceutical ingredient lots with their corresponding particle sizes were used in the clinical studies included in this popPK analysis. The PSD (D90, μm) of all batches used in this popPK analysis ranged from 71.0 to 276 μm.

Covariate effects were explored graphically on the empirical Bayes or post hoc estimates of the PK parameters that were estimated with IIV, provided shrinkage was sufficiently low (<30 %). Covariates selected by this method, taking account of known physiological/pharmacological considerations, were subsequently incorporated in the popPK model.

Continuous covariates were included in the model using Eq. 1, where TVP is the typical value of the parameter, and θ_x and θ_y are fixed-effect parameters:

$$\text{TVP} = \theta_x(\text{covariate}/\text{covariate median})^{\theta_y}. \qquad (1)$$

In accordance with the draft US Food and Drug Administration guidance on renal impairment, eGFR was included in the model as a continuous covariate [13].

In the case of categorical covariates, the TVP was allowed to change from category to category by using a different parameter for each category:

$$\text{TVP} = \theta(i),$$

where i is the category.

Selected candidate covariates were formally evaluated for statistical significance by including them in the model one at a time. An OFV change of 10.83 units ($p < 0.001$, chi-squared distribution, one degree of freedom) was used as cut-off value to include a covariate in the popPK model. All covariates that were statistically significant were included in the model at the same time to construct a full model. The final significance of each covariate was evaluated by deleting it from the full model one at a time. To consider exclusion of one covariate in the full popPK model, an increase in minimum OFV of <10.83 units ($p < 0.001$, chi-squared distribution, one degree of freedom) was needed. The covariate resulting in the lowest increase in OFV was removed from the full model first. This process was repeated until all covariates that were not statistically significant were excluded from the model.

Evaluation of clinical relevance of the statistically significant covariates on model parameters, and hence on exposure, was based on area under the curve (AUC) values calculated based on the dose and individual *CL/F*. The individual *CL/F* was derived from the *post hoc* estimated individual V_c/F and post hoc estimated individual k_e,

Table 2 Evaluation of the influence of BMI on k_a and T_{lag} and over-encapsulation (over-encapsulated vs encapsulated tablets) on T_{lag} (phase I data)

	BMI on k_a	BMI on T_{lag}	Over-encapsulation on T_{lag}
Ratio [CI][a]	1.99[b] [1.35–3.32]	2.00[c] [0.98–7.54]	1.93[d] [1.15–3.43]

BMI body mass index, *CI* confidence interval, *n* number of volunteers, k_a first-order absorption rate constant, T_{lag} lag time

[a] Ratio of medians with 95 % CIs, computed using Fieller's theorem with the correlation between numerator and denominator set to zero

[b] Ratio of BMI <24.2 ($n = 82$)/BMI >28.0 ($n = 82$); lower tertile of BMI is 24.2 kg/m^2, while the upper tertile is 28.0 kg/m^2

[d] Ratio of BMI >28.0 ($n = 82$)/BMI <24.2 ($n = 82$); lower tertile of BMI is 24.2 kg/m^2, while the upper tertile is 28.0 kg/m^2

[c] Ratio over-encapsulated ($n = 71$)/non-encapsulated ($n = 174$)

obtained from the final popPK model for the total study population ($N = 1616$), as $CL/F = V_c/F \times k_e$. For each covariate, the dose-normalized AUC values (normalized to a 100-mg dose) were compared at different covariate levels (detailed information on covariate levels are provided in the footnotes of Tables 2 and 6). For each covariate level, median dose-normalized AUCs, 5 and 95 % percentiles were calculated. The ratio of median dose-normalized AUC values with their 95 % confidence intervals (CIs), computed using Fieller's theorem [14] with the correlation between numerator and denominator set to zero (worst case scenario), were calculated for each significant covariate.

2.6 Model Evaluation

The predictive properties of the phase I and final popPK model were illustrated by prediction-corrected visual predictive checks (pcVPCs) [15]. The pcVPCs were constructed based on 1000 simulated replicates of the original dataset. The pcVPCs have time after last dose as the independent variable and are presented both on the linear and log scales. The 5th and 95th percentiles of prediction-corrected observations are depicted, corresponding to a 90 % inter-percentile range (prediction interval). As there was variability in the actual sampling times between volunteers, sampling time binning was performed. The width of each bin was made obvious in the graphs through the width of the square-shaped CIs.

The model was evaluated using an external evaluation dataset, i.e., PK data from two phase III studies that were not used to build the model. Plasma concentrations were predicted using parameter estimates of the pre-final model, fixing the inter-individual and residual random effects to their mean value of zero. The $ESTIMATION command was set as MAXEVAL = 0 and NONMEM was run [12]. A diagnostic plot of the observed versus model-predicted concentrations and a quantile–quantile (QQ) plot of the normalized prediction distribution errors (NPDEs) were generated to determine how well the model was able to predict the external evaluation dataset.

3 Results

3.1 Population Characteristics

In the population from the pooled phase I data, the median age of volunteers was 45 years, and 63 % were men and 59 % were white. The median baseline eGFR was 102 mL/min/1.73 m^2 and 40 % had T2DM. The population from the pooled phase I, II, and III data was also mainly white (71 %) with a median age of 55 years, median baseline eGFR of 87 mL/min/1.73 m^2, and 75 % had T2DM. The proportion of men and women in this dataset was balanced. The detailed demographic and baseline characteristics are outlined in Supplementary material.

3.2 Phase I Population Pharmacokinetic Model

A two-compartment popPK model with a lag-time and sequential zero- and first-order absorption and first-order elimination from the central compartment, with IIV on V_c/F, k_e, k_a, k_{32}, and T_{lag}, provided the best fit to the richly sampled phase I PK data (Fig. 1).

The covariates on the absorption parameters were BMI on k_a, and BMI and over-encapsulation on T_{lag}. Volunteers with lower BMI had faster absorption rates than those with higher BMI. The median k_a value in volunteers with BMI <24.2 kg/m^2 was about two times higher than for those with BMI >28.0 kg/m^2. The median T_{lag} value in volunteers with BMI >28.0 kg/m^2 was about two times higher than in volunteers with BMI <24.2 kg/m^2. An approximately 93 % longer T_{lag} was observed with the over-encapsulated tablet (median T_{lag} of approximately 16 min) compared with the non-encapsulated tablet (median T_{lag} of approximately 8 min) (Table 2). Although T_{lag} was somewhat longer with the over-encapsulated tablets, over-encapsulation had no meaningful effect on the AUC of canagliflozin as the median dose-normalized AUC values were only 6 % higher compared with those of the non-encapsulated tablet (unpublished data).

WT, age, and sex on V_c/F were identified as significant covariates. The effect of these covariates on V_c/F and
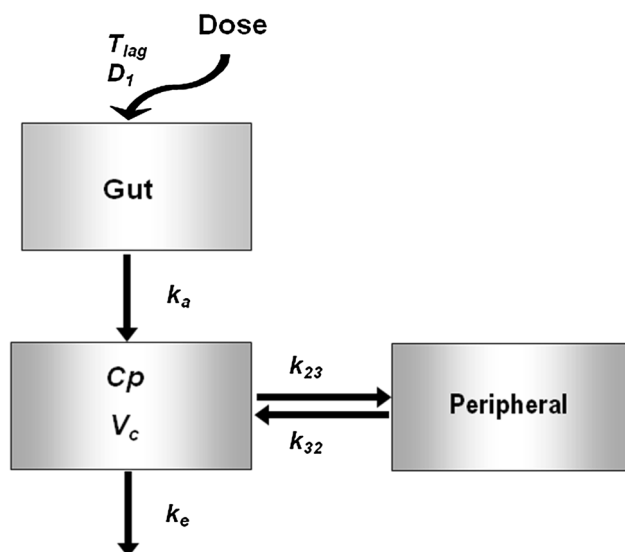
Fig. 1 Model structure of the final population pharmacokinetic model of canagliflozin. A two-compartment disposition model with lag-time and zero-order release in a depot compartment followed by first-order absorption into and first-order elimination from the central compartment was used to describe the plasma concentration vs time profile of canagliflozin. V_c/F apparent volume of distribution of the central compartment, k_a first-order absorption rate constant, k_e elimination rate constant, T_{lag} lag time, D_1 duration of zero-order influx of dose into the gut compartment, k_{23}, k_{32} distribution rate constants to and from the peripheral compartment

hence on AUC was assessed on the *post hoc* estimated median dose-normalized AUC values obtained from the final popPK model, including all significant covariates (i.e., BMI on k_a, BMI and over-encapsulation on T_{lag}, sex, and WT on V_c/F, and eGFR and dose on k_e). The median dose-normalized AUC values were about 22 % higher in women than in men, and approximately 29 % higher in older volunteers (age >60 years) than younger volunteers (age <50 years); and volunteers with WT <78.2 kg had about a 33 % higher AUC than those with weight >95.2 kg.

The parameter estimates presented in Table 3 show that all PK parameters could be estimated from the phase I dataset with adequate precision as expressed by their low relative standard errors (RSE %), ranging from 2 % to 22 %. The IIV on CL/F, V/F, and k_{32} was 20, 15, and 35 %, respectively. The high IIV observed on k_a and T_{lag} was most probably owing to the limited PK data collected around the time to maximum plasma concentrations. The pc-VPCs of the final phase I model revealed acceptable predictive performance of the absorption phase and an over-prediction was observed in the elimination phase (Fig. 2).

3.3 Pre-Final Population Pharmacokinetic Model

The pre-final model constituted the basis for final covariate model development. Shrinkage on IIV for k_e was

acceptable for graphical exploration of covariate effects (~21 %), but was unacceptably high for k_a, T_{lag}, k_{32}, and V_c/F (>55 %). A summary of the covariate testing and the difference in OFV is provided in Table 4. The covariates eGFR, dose, and genetic polymorphism had a significant effect on k_e. No significant effect of age, sex, fed status, race, glycemic status, and concomitant medications on k_e was observed. The effects of PSD and genetic polymorphism on canagliflozin PK were evaluated in the final model, after including all other significant covariates, by forward addition. As shown in Table 4, PSD had no significant effect on k_e, while genetic polymorphism was a significant covariate. As volunteers carrying the UGT1A9*3 allele only represented ~1 % of the total number of volunteers ($N = 1616$) included in this popPK analysis, and as no visual trends could be detected, this covariate was not included in the final popPK model.

3.4 Model Evaluation

The pre-final model, including all statistically significant covariates, was externally evaluated using a subset of data that was not used to build the model. The diagnostic plot of the observed vs model-predicted concentrations and the QQ plot of the NPDEs are provided in Fig. 3. These plots demonstrate that the popPK model of canagliflozin predicts the evaluation dataset adequately, as the trend line of observed vs model-predicted plasma concentrations lies around the line of unity and points in the QQ plot fall approximately along the line of identity.

3.5 Final Population Pharmacokinetic Model

The parameter estimates of the final popPK model are described in Table 5.

The popPK parameters could be estimated with adequate precision as expressed by their low RSE %, ranging from 1 % to 16 %. k_e was estimated at 0.145 h^{-1}, resulting in a CL/F of 14.4 L/h in men and 12.0 L/h in women. The estimated IIV on k_e was low (23 % CV). An additive error model was used to describe the residual variability for the log-transformed data and the residual error was 20.2 % for phase I PK data and 55.9 % for phase II and III sampled PK data.

In addition to the covariates identified on the absorption and distribution parameters, eGFR, dose, and genetic polymorphism were found to be significant covariates on k_e. The additional covariate effect of eGFR accounts for the effect of differences in renal function on canagliflozin clearance, after having corrected for the effect of sex, age, and WT differences on V_c/F. Volunteers with mild (60–89 mL/min/1.73 m^2), moderate (30–59 mL/min/1.73 m^2), and severe (15–29 mL/min/1.73 m^2) renal

Table 3 Parameter estimates of the phase I population PK model

Parameter	Population mean estimate	Relative standard error %	Inter-individual variability (% CV)
V_c/F (L)	99.3	2.0	15
k_e (h^{-1})	0.150	2.1	20
k_a (h^{-1})	3.68	13.7	123
T_{lag} (h) (non-encapsulated tablet)	0.147	9.0	79
D_1 (h)	0.604	8.9	
k_{23} (h^{-1})	0.101	4.8	
k_{32} (h^{-1})	0.0856	3.9	35
V_c/F (L) (female)	82.6	2.7	
T_{lag} (h) (over-encapsulated tablet)	0.262	14.0	
Body weight on V_c/F	0.583	8.5	
Age on V_c/F	−0.167	21.3	
Body mass index on k_a and T_{lag}	1.41	21.6	
Residual variability (%)	22.9	9.7	

For the continuous covariates (body weight and age on V_c/F and body mass index on k_a and T_{lag}), the population mean estimate represents θ_y in Eq. 1

V_c/F apparent volume of distribution of the central compartment, k_a first-order absorption rate constant, k_e elimination rate constant, T_{lag} lag-time, D_1 duration of zero-order input into the gut compartment, k_{23}, k_{32} distribution rate constants to and from the peripheral compartment
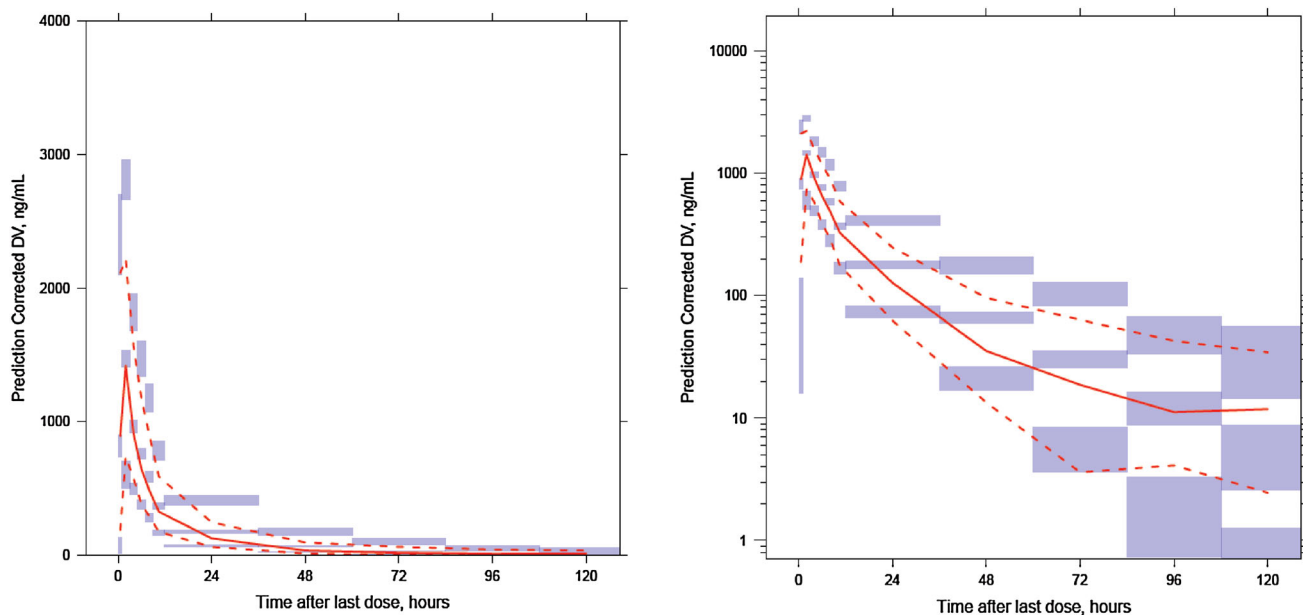

Fig. 2 Prediction-corrected visual predictive checks with 90 % inter-percentile range for the final phase I model. The *solid red line* represents the median prediction-corrected observed plasma concentrations. The *dashed red lines* represent the observed 5 and 95 % percentiles. The 95 % confidence intervals for the corresponding model predicted percentiles are shown as *gray fields*. *DV* dependent variable

impairment had higher median dose-normalized AUC values ($\sim$11, 40, and 29 %, respectively) than volunteers with normal renal function ($\geq$90 mL/min/1.73 m^2) (Table 6).

An additional significant covariate effect of total daily dose on k_e was observed. The median dose-normalized AUC value at 300 mg was approximately 16 and 7 % higher than at 50 and 100 mg, respectively (Table 6). PSD did not appear to affect the PK of canagliflozin, while a significant drop in OFV was observed for the effect of genetic polymorphism on k_e (Table 4). The impact of genetic polymorphism on AUC is presented in Table 6. From this popPK analysis, volunteers ($N = 21$) carrying the UGT1A9*3 allele had somewhat higher

Table 4 Covariate model development phase I, II, and III

Model	Description	n^a	OFV	ΔOFV^b
Base model				
Run525			−8346.8	
Run526	Run525 + covariate effect of eGFR on k_e	1	−8506.9	−160.1*
Run527	Run525 + covariate effect of age on k_e	1	−8397.4	−50.6*
Run528	Run525 + covariate effect of dose on k_e	1	−8385.1	−38.3*
Run529	Run525 + covariate effect of race^c on k_e	1	−8360.7	−13.9*
Run531	Run525 + covariate effect of UGT substrates on k_e	1	−8347.2	−0.3
Run532	run525 + covariate effect of gender on k_e	1	−8353.2	−6.4
Run561	Run525 + covariate effect of fed on k_e	1	−8352.3	−5.4
Run533	Run525 + covariate effect of glycerine status on k_e	1	−8349.6	−2.8
Full covariate model I	Full covariate model with covariate effects of eGFR, age, dose, race on k_e			
Run534			−8552.4	
Run535	Run534 without covariate effect of eGFR on k_e	1	−8448.2	+104.3*
Run536	Run534 without covariate effect of dose on k_e	1	−8515.4	+37.0*
Run537	Run534 without covariate effect of age on k_e	1	−8541.3	+11.2*
Run538	Run534 without covariate effect of race^c on k_e	1	−8551.2	+1.3
Full covariate model II	Full covariate model with covariate effects of eGFR, age, dose on k_e			
Run538			−8551.2	
Run539	Run538 without covariate effect of eGFR on k_e	1	−8441.9	+109.2*
Run540	Run538 without covariate effect of dose k_e	1	−8509.5	+41.7*
Run541	Run538 without covariate effect of age on k_e	1	−8543.2	+7.9
Full covariate model III	Full covariate model with covariate effects of eGFR and dose on k_e			
Run541			−8543.2	
Run542	Run541 without covariate effect of eGFR on k_e	1	−8382.5	+160.7*
Run543	Run541 without covariate effect of dose on k_e	1	−8503.6	+39.6*
Pre-final model	Model with covariate effects of eGFR and dose on k_e			
Run544^d			−8543.1	
Final model	**Final model with covariate effects of BMI on k_e and T_{lag}, over-encapsulation of tablets on T_{lag}, body weight, age and**		**−8516.6**	
Run 549^e	**Gender on V_c/F and eGFR and dose on k_e**			
Run552	Run549 + covariate effect of PSD on k_e	1	−8517.0	−0.5
Run559	Run549+ covariate effect of genetic polymorphism on k_e	1	−8532.4	−15.8*

Bold final model Phase 1, 2 and 3 of population PK analysis

PSD particle size distribution

* Statistical significance at $p < 0.001$

a Number of additional parameters relative to parent model

b Difference in OFV relative to parent model

c Asian versus non-Asian

d Run544 = Run541 with covariance step and initial parameter estimates slightly adapted

e The pre-final model (run544) was re-run on the final NONMEM dataset, resulting in the model (run549)

(about 26 %) exposure (median dose-normalized AUC values) than volunteers not carrying this allele ($N = 700$). No genotype information was available for $N = 895$ volunteers.

In a 12-week, phase II, dose-ranging study in patients with T2DM, administration of canagliflozin at doses ranging from 50 to 300 mg once daily (qd) and 300 mg twice daily (bid) were deemed to be safe and were generally well tolerated. The AUC$_{\tau,ss}$ of 300 mg bid was 93 % higher than the highest recommended dose of 300 mg qd. Given the small magnitude of the effects of sex, age, WT, presence of the UGT1A9*3 allele, or renal function on canagliflozin exposures, they are expected to be well within that of the dose range shown to be safe and well tolerated. Therefore, no dosage adjustment is required on the basis of these factors.

Fig. 3 Goodness-of-fit
diagnostic plots for external
evaluation. **a** The log of the
observed concentrations vs the
log of the model-predicted
concentrations derived from the
population mean parameter
estimates. *Dashed line (black)*
reference identity line, *full line
(gray)* lowess smoother.
Observed and model predicted
concentrations for a typical
patient (i.e., population
prediction) are log-transformed
concentrations. **b** The quantile–
quantile (Q–Q) plot of the
normalized prediction
distribution errors (NPDEs)
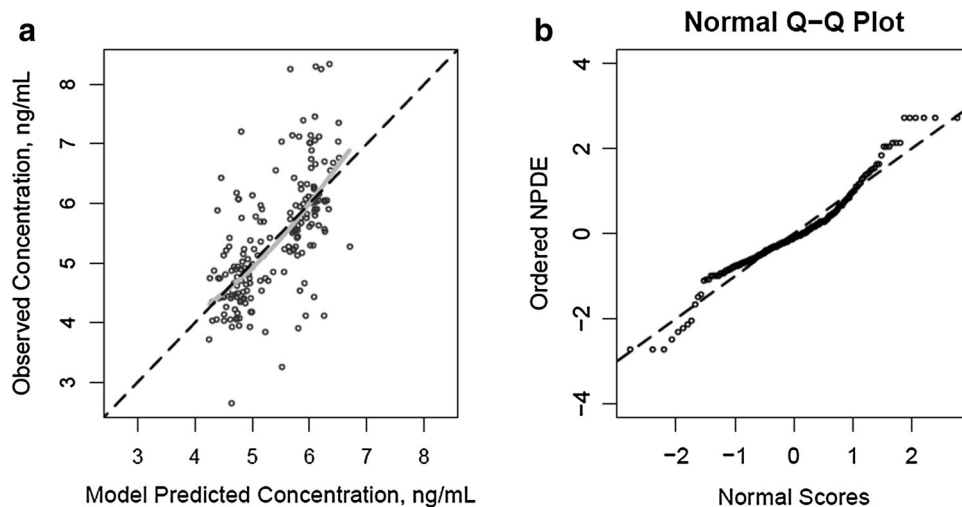
Table 5 Parameter estimates of the final population PK model

Parameter	Population mean estimate	Relative standard error	Inter-individual variability (% CV)
V_c/F (L)	99.3 FIX		15 FIX
k_e (h^{-1})	0.145	1.0	23
k_a (h^{-1})	3.68 FIX		123 FIX
T_{lag} (h) (non-encapsulated tablets)	0.147 FIX		79 FIX
D_1 (h)	0.604 FIX		
k_{23} (h^{-1})	0.101 FIX		
k_{32} (h^{-1})	0.0856 FIX		35 FIX
V_c/F (L) (female)	82.6 FIX		
T_{lag} (h) (over-encapsulated tablets)	0.262 FIX		
Body weight on V_c/F	0.583 FIX		
Age on V_c/F	−0.167 FIX		
Body mass index on k_a and T_{lag}	1.41 FIX		
eGFR on k_e	0.261	9.0	
Dose on k_e	−0.0631	16.2	
Residual variability (%) Phase I	20.2	4.9	
Residual variability (%) Phases II and III	55.9	6.0	

V_c/F apparent volume of distribution of the central compartment, k_a first-order absorption rate constant, k_e elimination rate constant, T_{lag} lag-time, D_1 duration of zero-order input into the gut compartment, k_{23}, k_{32} distribution rate constants to and from the peripheral compartment, *eGFR* estimated glomerular filtration rate, *CL/F* apparent total clearance, *FIX* absorption (k_a, T_{lag}, and D_1) and distribution (V_c/F, k_{23}, and, k_{32}) parameters, including covariate and random effects, were fixed to the values obtained from the model built on phase I data

For the continuous covariates (body weight and age on V_c/F, body mass index on k_a and T_{lag}, and eGFR and dose on k_e), the population mean estimate represents θ_y in Eq. 1. The population mean estimate of the parameters V_c/F, k_e, k_a, T_{lag}, D_1, k_{23}, and k_{32} represents θ_x in Eq. 1

The goodness-of-fit plots suggest that the final model adequately described the observed concentration data (Fig. 4). Overall, the final popPK model characterized well the observed concentrations of canagliflozin in the studies, with good precision on the parameter estimates. The pc-VPCs of the final model (Fig. 5) indicate that the model captured the temporal profile adequately for the whole set of observations.

4 Discussion

A two-compartment popPK model with lag-time and sequential zero- and first-order absorption and first-order elimination with IIV on V_c/F, k_e, k_a, k_{32}, and T_{lag} best fitted the data. The popPK model was parameterized in terms of rate constants instead of primary PK parameters (*CL/F* and *V/F*). In fact, whether the NONMEM control stream is

Table 6 Ratios of dose-normalized AUC values with 95 % CIs for covariates identified on V_c/F and k_e potentially affecting its plasma concentrations

	Age	WT	Sex	Renal function	Daily dose (mg)	Genetic polymorphism
Ratio [95 % CI][a]	1.29[b] [1.23–1.36]	1.33[c] [1.27–1.40]	1.22[d] [1.18–1.28]	1.11[e] [1.07–1.16]	1.16[h] [1.08–1.26]	1.26[j] [1.08–1.44]
				1.40[f] [1.32–1.47]	1.07[i] [1.02–1.12]	
				1.29[g] [1.11–1.48]		

AUC area under the curve, *eGFR* estimated glomerular filtration rate, *CI* confidence interval, *WT* weight, k_e elimination rate constant

[a] Ratio of median dose-normalized (to 100 mg) AUC values with 95 % CIs, computed using Fieller's theorem with the correlation between numerator and denominator set to zero

[b] Ratio of age >60 ($n = 481$)/age <50 years ($n = 533$); lower tertile of age is 50 years, while the upper tertile is 60 years

[c] Ratio of WT <78.2 ($n = 536$)/WT >95.2 kg ($n = 537$); lower tertile of WT is 78.2 kg, while the upper tertile is 95.2 kg

[d] Ratio of women ($n = 847$)/men ($n = 769$)

[e] Ratio of mild ($n = 663$)/normal ($n = 718$)

[f] Ratio of moderate ($n = 209$)/normal ($n = 718$)

[g] Ratio of severe ($n = 18$)/normal ($n = 718$); groups of renal impairment were defined by MDRD-eGFR (mild 60–89 mL/min 1.73 m^2, moderate 30–59 mL/min 1.73 m^2, severe 15–29 mL/min 1.73 m^2); normal ($\geq$90 mL/min/1.73 m^2)

[h] Ratio of 300 mg ($n = 589$)/50 mg ($n = 164$)

[i] Ratio of 300 mg ($n = 589$)/100 mg ($n = 610$)

[j] Ratio of carriers UGT1A9*3 ($n = 21$)/no carriers UGT1A9*3 ($n = 700$)

Fig. 4 Goodness-of-fit diagnostic plots for the final population pharmacokinetic model. *Dotted line* (*black*) reference identity line; *full line* (*gray*) lowess smoother. Observed concentrations, population and individual predictions are log-transformed concentrations. *CWRES* conditional weighted residuals
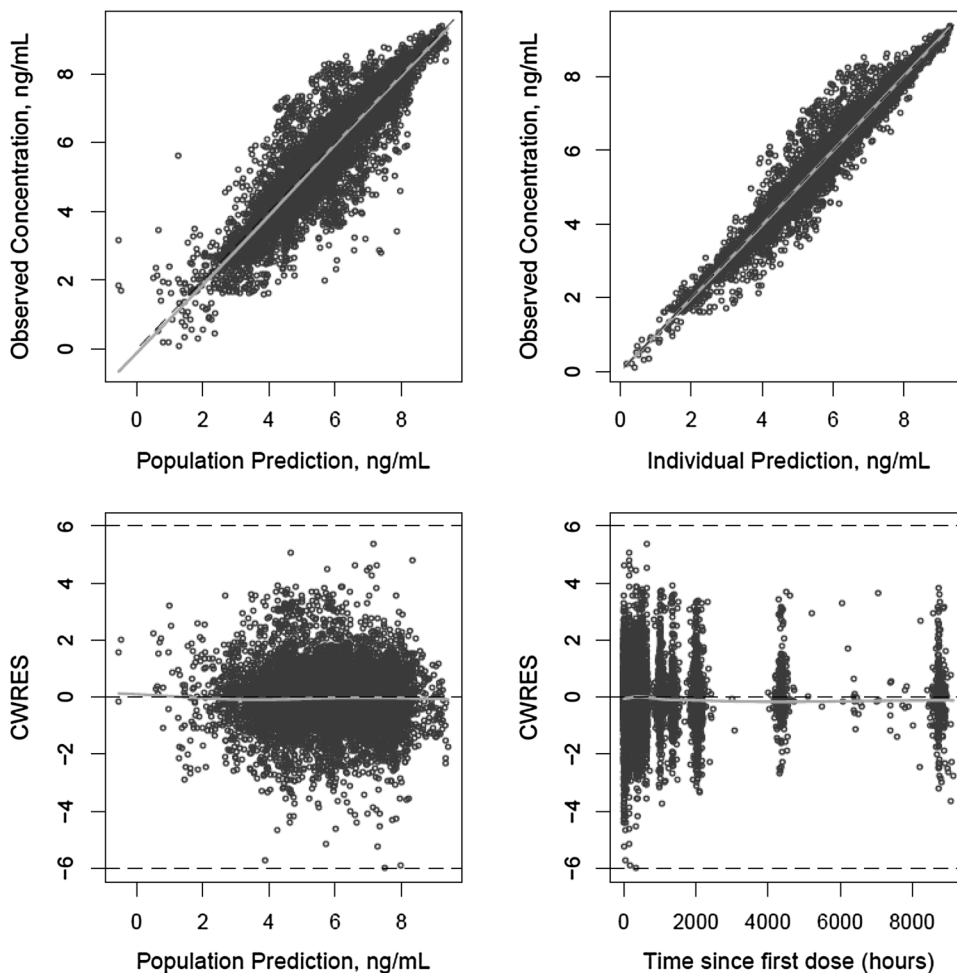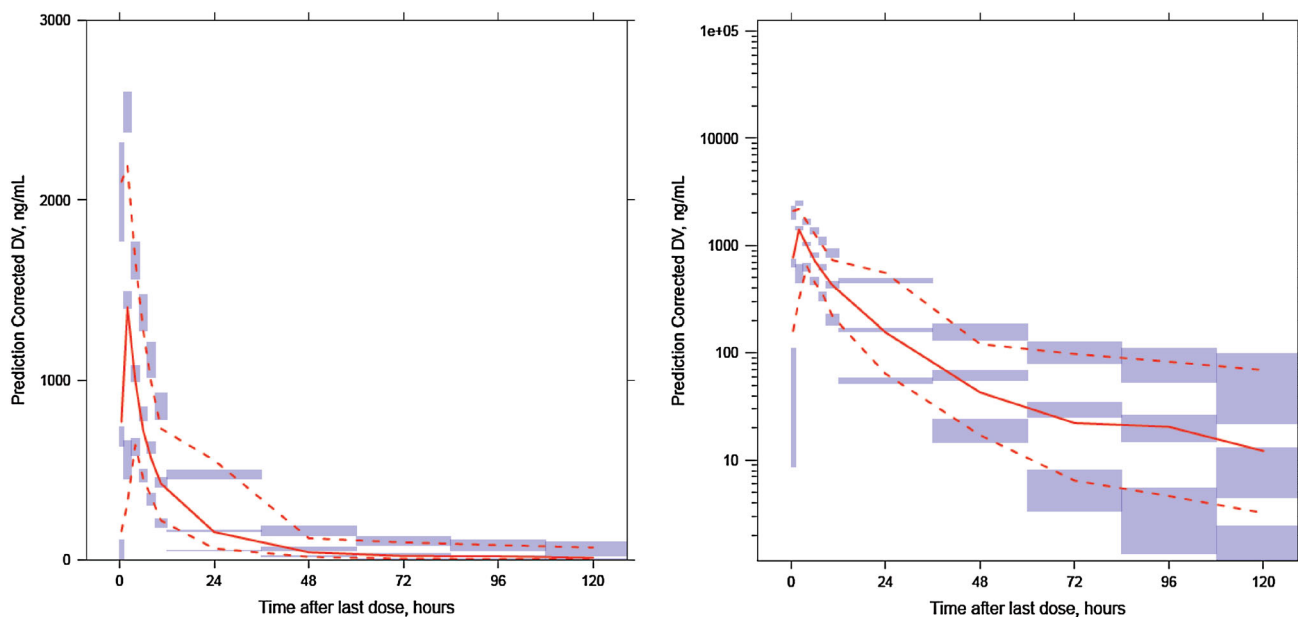
Fig. 5 Prediction-corrected visual predictive checks with 90 % inter-percentile range for the final population PK model. The *solid red line* represents the median prediction-corrected observed plasma concentrations. The *dashed red lines* represent the observed 5 and 95 % percentiles. The 95 % confidence intervals for the corresponding model predicted percentiles are shown as *gray fields*. *DV* dependent variable

specified using rate constants (k_e) or primary PK parameters (*CL/F*, *V/F*), the associated NM-TRAN translator routines (TRANS1 and TRANS3, respectively) ensure that the internal model fitting procedures compute the kinetic equations in terms of rate constants [16–18]. In other words, internally NONMEM always computes the kinetic equations in terms of k_e and, when asked, TRANS3 returns *CL/F* as the product of k_e and *V/F*. It can be demonstrated that, as a result, any covariates evaluated on *V/F* will internally also be evaluated (inversely) on k_e, although that is not apparent from the TRANS3 control stream. This allows for computational dependencies between the covariate effects estimated on *V/F* and those estimated on *CL/F*, which remain hidden for the unsuspecting end user. For the popPK analysis of canagliflozin, we opted for maximal statistical transparency during model development using TRANS1 and explicitly performing the transformation of k_e to the pharmacologically more meaningful *CL/F*, rather than letting TRANS3 perform this transformation implicitly and hidden to the end user.

The popPK model was developed first on the richly sampled phase I data ($N = 245$), which contained the most information on the PK profile of canagliflozin, especially for the absorption and distribution phases. A strong partial inverse correlation was observed between k_a and T_{lag} that might be caused by either a real relationship between k_a and T_{lag} or possibly by insufficient information in the absorption phase to estimate IIV on k_a and T_{lag} independently. Attempts to use a block structure for the IIVs of k_a

and T_{lag} failed, but otherwise the model performed well on the richly sampled data.

As the richly sampled data from phase I was pooled with increasing amounts of sparsely sampled data from phase II and III, which included only pre-dose trough concentrations, the model started to show more and more signs of instability (reported by NONMEM as singular non-positive semi-definite R or S matrices) and eventually failed to minimize altogether. This was accompanied by increasing shrinkage of the random effects on all PK parameters except k_e, which could be attributed entirely to the sparsely sampled patients. This suggested that the lack of information with regard to the absorption and distribution characteristics of canagliflozin for the sparsely sampled patients, increasingly inhibited the model in obtaining unambiguous estimates for the parameters describing these characteristics as more sparsely sampled patients were added to the dataset. Therefore, extensive covariate analyses were performed for the absorption (k_a, T_{lag}, and D_1) and distribution (V_c/F, k_{23}, and k_{32}) parameters on the richly sampled phase I data. The estimates for these parameters as obtained on the richly sampled data, including their covariate relationships and the covariance matrix of their random effects, were subsequently fixed when fitting the pooled richly and sparsely sampled PK data together. This resulted in a stable model fit with a successful covariance step, and allowed a covariate search for k_e on the pooled richly and sparsely sampled data. An additional covariate search for V_c/F on the pooled data was

not feasible because of recurring minimization problems. As noted above, the high shrinkage observed for the random-effects distribution for V_c/F, but not for k_e, when evaluated on the sparse phase II and III PK data, indicated that these data were much less informative for V_c/F than for k_e. Moreover, estimating V_c/F on the sparse data did not significantly improve the model fit, which is to be expected when trying to estimate two PK parameters on just a single, pre-dose, PK time point.

The popPK parameters of the final popPK model could be estimated with adequate precision as expressed by their low RSE %, ranging from 1 to 16 %. The high variability observed on the absorption parameters [k_a (123 % CV) and T_{lag} (79 % CV)] is most probably owing to the limited PK data collected around the time to maximum plasma concentrations. The residual error was 20.2 and 55.9 % for richly (phase I) and sparsely (phase II and III) sampled PK data, respectively. The higher residual error observed for sparsely sampled PK data vs richly sampled PK data was expected as greater variability is commonly observed for data obtained in multicenter phase II and III studies when compared with tightly controlled, single-center phase I studies. The predictability of the model was evaluated by pc-VPC, and the pc-VPC of the final phase I model revealed an acceptable predictive performance in the absorption phase. An over-prediction was observed in the elimination phase but this misspecification disappeared following inclusion of the phase II and III data and the covariate effects on the elimination.

Results from this analysis indicated that participants with WT <78.2 kg are likely to have about 33 % higher median dose-normalized AUC values than participants with WT >95.2 kg. This is to be expected as the volume of plasma and tissue in which canagliflozin can distribute may tend to increase with body size and therefore with WT [19]. Results from this analysis also indicated that dose-normalized AUC values were 29 and 22 % higher in volunteers aged older than 60 years and in women, respectively, owing to the reduced V_c/F [19, 20]. These increases in exposure are not considered to have a clinically relevant effect on the PK of canagliflozin as explained below. Because of the limitations of comparing observed PK parameters between studies conducted in demographically different populations of small numbers of patients, the final popPK model, which incorporates covariates shown to affect canagliflozin PK, was used to predict steady-state canagliflozin $AUC_{24\ h}$ values for a typical population with T2DM for the highest proposed to-be-marketed dose (300 mg qd) and the highest dose studied in long-term clinical studies (300 mg bid). The final popPK model predicted that the mean steady-state canagliflozin $AUC_{24\ h}$ values for the 300-mg qd and 300-mg bid doses were 24,941 ng·h/mL (95 % CI: 24,311–25,571 ng·h/mL) and

54,258 ng·h/mL (95 % CI: 50,623–57,893 ng·h/mL), respectively. Thus, based on these predictions, increases in canagliflozin steady-state $AUC_{24\ h}$ by up to 118 % compared with that for a 300-mg qd canagliflozin dose would not be considered to pose any safety concerns. The absence of safety signals in the 12-week, phase II, dose-ranging study in patients with T2DM treated with canagliflozin 300 mg bid supports this assessment [21]. However, because patients aged 65 years and older may be more sensitive to adverse reactions related to reduced intravascular volume by canagliflozin, correcting this condition prior to initiation of canagliflozin is recommended in patients with volume depletion [2].

A clear relationship between baseline renal function categories and canagliflozin dose-normalized AUC was observed. The median dose-normalized AUC values were about 11, 40, and 29 % higher in volunteers with mild, moderate, and severe renal impairment, respectively, compared with the normal renal function group. These observations are generally consistent with a phase I study conducted in participants with impaired renal function [22]. Similar observations were also made with dapagliflozin. The concentrations of dapagliflozin were increased by 4, 6, and 9 % and its metabolite D3OG by 20, 37, and 52 %, respectively in patients with mild, moderate, and severe renal impairment compared with those with normal kidney function [23]. Empagliflozin showed an increase of 18, 20, and 66 % in patients with mild, moderate, and severe renal impairment [24]. Although systemic exposure to canagliflozin is increased in patients with renal impairment relative to those with normal renal function, the efficacy is reduced in patients with renal impairment owing to the reduced filtered glucose load. In addition, the rate of adverse events (osmotic diuresis, urinary tract infections, and reduced intravascular volume) was slightly higher with 300 mg qd compared with 100 mg qd in participants with stage 3 chronic kidney disease [22, 25]. Therefore, canagliflozin is recommended at a dose of 100 or 300 mg qd for T2DM patients with an eGFR ≥60 mL/min/1.73 m^2, and canagliflozin 100 mg qd is recommended in T2DM patients with an eGFR of 45 to <60 mL/min/1.73 m^2.

The systemic exposure (C_{max} and AUC_∞) of canagliflozin increased dose proportionally following single doses of 50, 100, and 300 mg canagliflozin in healthy volunteers [26]. The final PK parameters were used to estimate the exposure (AUC) for each volunteer who participated in the dose-proportionality study [26] and the AUC values were compared with those calculated by Non-compartmental analysis (NCA) (unpublished data). The mean AUC values estimated by the final model were in good agreement with the AUC values calculated by NCA and therefore, although a significant effect of dose on k_e was observed, the impact

of dose on systemic exposure of canagliflozin is expected to be minimal (data on file).

As canagliflozin is glucuronidated by UGT1A9 and UGT2B4 enzymes, its PK potentially could be influenced by the polymorphism in the genes encoding these drug-metabolizing enzymes. The participants carrying the UGT1A9*3 allele only represented 1 % of the total number of participants included in the popPK analysis and it was observed that participants carrying the UGT1A9*3 allele had higher (about 26 %) dose-normalized AUCs than those without this allele. These findings are consistent with the exposure-pharmacogenomic analysis results, supporting a role for UGT1A9 in the metabolism of canagliflozin [27]. In addition, when considering the safety data from UGT1A9*3 carriers, there appeared to be no increase in the overall incidence of adverse events or in study drug-related adverse events in participants treated with canagliflozin 100 and 300 mg relative to placebo-treated participants. Given the small effect size of this covariate on the PK (AUC) of canagliflozin, the low frequency of the variation in the population, and exposure data from a 300-mg bid cohort in the phase II study (NCT00642278), it was not deemed to be of clinical relevance.

Glycemic status, race, fed status, long-term concomitant medications (substrates of UGT1A9 or UGT2B4), and PSD were not identified as statistically significant covariates affecting the PK of canagliflozin. Therefore, no dose adjustments of canagliflozin are needed based on these factors.

5 Conclusion

The developed popPK model adequately described canagliflozin PK in healthy volunteers and in patients with T2DM. No dose adjustments of canagliflozin are needed based on BMI, body weight, sex, race, and genetic polymorphisms (with respect to the UGT1A9*3 allele). The covariate age (in patients with age-appropriate renal function) and eGFR also had no clinically relevant effect on the PK of canagliflozin. However, because patients aged 65 years and older and patients with impaired renal function (eGFR <60 mL/min/1.73 m^2) may be more sensitive to adverse reactions related to reduced intravascular volume, correcting this condition prior to initiation of canagliflozin is recommended in patients with volume depletion. Based on a phase III program, canagliflozin is recommended at a dose of 100 or 300 mg qd for T2DM patients with eGFR ≥ 60 mL/min/1.73 m^2, and canagliflozin 100 mg qd is recommended in T2DM patients with an eGFR of 45 to <60 mL/min/1.73 m^2.

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