British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 1072–1081 1072

PHARMACOKINETIC DYNAMIC RELATIONSHIPS

Dynamic population pharmacokinetic–pharmacodynamic modelling and simulation supports similar efficacy in glycosylated haemoglobin response with once or twice-daily dosing of canagliflozin

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Received 17 June 2016; **Revised** 15 September 2016; **Accepted** 12 October 2016

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Keywords Canagliflozin, diabetes mellitus, modelling, pharmacodynamics, pharmacokinetics, simulation

AIM

Canagliflozin is an SGLT2 inhibitor approved for the treatment of type-2 diabetes. A dynamic population pharmacokinetic–pharmacodynamic (PK/PD) model relating 24-h canagliflozin exposure profiles to effects on glycosylated haemoglobin was developed to compare the efficacy of once-daily and twice-daily dosing.

METHODS

Data from two clinical studies, one with once-daily, and the other with twice-daily dosing of canagliflozin as add-on to metformin were used (n = 1347). An established population PK model was used to predict full 24-h profiles from measured trough concentrations and/or baseline covariates. The dynamic PK/PD model incorporated an E_{max} relationship between 24-h canagliflozin exposure and HbA1c-lowering with baseline HbA1c affecting the efficacy.

RESULTS

Internal and external model validation demonstrated that the model adequately predicted HbA1c-lowering for canagliflozin once-daily and twice-daily dosing regimens. The differences in HbA1c reduction between the twice-daily and daily mean profiles were minimal (at most 0.023% for 100 mg total daily dose [TDD] and 0.011% for 300 mg TDD, up to week 26, increasing with time and decreasing with TDD) and not considered clinically meaningful.

CONCLUSIONS

Simulations using this model demonstrated the absence of clinically meaningful between-regimen differences in efficacy, supported the regulatory approval of a canagliflozin-metformin immediate release fixed-dose combination tablet and alleviated the need for an additional clinical study.

DOI:10.1111/bcp.13180

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- A fixed-dose combination tablet of metformin immediate release and canagliflozin may improve patient convenience and compliance to antihypertensive agent therapy. Because metformin immediate release is typically administered twice-daily for patients with type-2 diabetes mellitus, the canagliflozin component was divided to 50-mg and 150-mg twice-daily to provide the same currently approved daily dose (100-mg and 300-mg).

WHAT THIS STUDY ADDS

- This population pharmacokinetic–pharmacodynamic exposure-response analysis establishes a quantitative relationship between canagliflozin exposure and glycosylated haemoglobin response, and demonstrates that differences in canagliflozin dosing regimens would have little to no impact on the HbA1c response.

Tables of Links

TARGETS
SGLT2

LIGANDS
Canagliflozin
Metformin

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

Diabetes is gaining a pandemic status, with a global prevalence in adults of approximately 9% and affecting approximately 415 million people [3, 4]. Metformin, an oral biguanide that reduces hepatic glucose production, [5, 6] is typically the first line of therapy for glycaemic control. Disease progression often necessitates use of combination therapy with other antihyperglycaemic agents (AHA) that can complement the primary treatment for management of hyperglycaemia [7]. Canagliflozin, a selective oral inhibitor of sodium-glucose transporter-2 (SGLT2), has a different mechanism of action than metformin. Canagliflozin is approved in the USA and numerous other countries for the treatment of adult patients with type-2 diabetes mellitus (T2DM). The recommended canagliflozin dose is 100 or 300 mg once-daily (QD), and is indicated as an adjunct to diet and exercise to improve glycaemic control [8–10]. Canagliflozin reduces plasma glucose (PG) in individuals with hyperglycaemia by lowering the renal threshold for glucose excretion (RT_G), thus causing increased urinary glucose excretion [11–13].

The canagliflozin concentration resulting in half maximal reduction (EC_{50}) in RT_G was estimated to be 32 ng ml^{-1} (95% confidence interval [CI]: 19; 45) corresponding to a 90% effective concentration (EC_{90}) of 289 ng ml^{-1} and maximal decrease in RT_G of approximately 64%.[9] In a phase 3 study in patients with T2DM, monotherapy with canagliflozin 100 and 300 mg compared with placebo demonstrated a significant reduction of glycosylated haemoglobin (HbA1c) from baseline (8.0% HbA1c) to week 26 (–0.77%, –1.03% and 0.14%, respectively) [13]. With both canagliflozin doses, reductions in both fasting and postprandial PG levels were observed that were consistent with the observed reductions in HbA1c. The increased efficacy observed with 300 mg canagliflozin was expected, as it provided more sustained maximal decrease in RT_G than 100 mg canagliflozin and also provided an additional, nonrenal effect to lower postprandial PG [14]. Because the pharmacodynamic (PD) effects of canagliflozin-related increases in urinary glucose excretion are dependent on estimated glomerular filtration rate (eGFR), efficacy was reduced in patients with renal impairment due to reduced filtered glucose load [15, 16].

For patients requiring combined treatment with metformin and canagliflozin, the use of a fixed-dose combination (FDC) tablet (comprised of metformin immediate release [IR] and canagliflozin), may improve patient convenience and compliance to AHA therapy. Because metformin IR is typically administered twice a day for patients with T2DM,[5] the FDC was developed to be dosed twice-daily (BID), with the canagliflozin component divided to provide the same 100 and 300 mg total daily dose (TDD) as currently approved for QD dosing (i.e., 50 mg and 150 mg BID) [17]. Comparison of steady-state pharmacokinetics (PK)/PD of canagliflozin administered either QD or BID at the same TDD of 100 and 300 mg in a study in healthy subjects showed that canagliflozin plasma area under the concentration-time curves ($AUC_{0\text{-}24h,ss}$) for the QD *vs*. BID dosing regimens were equivalent. Although, as expected, the steady-state maximum plasma concentration ($C_{max,ss}$) of QD dosing was higher than the corresponding morning $C_{max,ss}$ of the BID regimen in this study; the 24-h mean RT_G for QD and BID regimens at both 100 and 300 mg TDDs were similar [18].

While the short-term PK/PD data suggested similarity between QD and BID regimens given at the same TDD, no long-term study was performed that directly compared the efficacy of different regimens. Three late-stage studies were performed with canagliflozin treatment added on to metformin; two of these studies (12-week study, NCT00642278 [Study1] [19], and 26-week study, NCT01106677 [Study 2] [20] contained QD dosing of 100 and 300 mg *vs*. placebo, whereas a third study (18 weeks, NCT01340664 [Study 3] [21]) contained

50 mg and 150 mg BID doses *vs*. placebo. The placebo-subtracted least square mean reductions in baseline HbA1c seen with 100 mg and 300 mg QD doses in the first two studies (–0.76 and –0.62% for 100 mg QD; –0.92 and –0.77% for 300 mg QD, respectively) were somewhat greater than the corresponding reductions seen with 50 and 150 mg BID doses in the third study (–0.44% and –0.60%, respectively) [19–21]. However, there were differences in other factors between the studies that limited the utility of such cross-study comparisons (most notably baseline HbA1c was lower in the BID study than in the QD studies; Table S1). Therefore, the aim of the current analysis was to develop a robust model-based solution that could account for differences in study populations and, in the absence of directly comparable long-term study results, could assess whether there are differences in the efficacy between QD and BID regimens of canagliflozin at the same TDD. This solution included developing and validating a dynamic population PK/PD model using pooled data from all three studies to characterize the exposure–response relationship of canagliflozin as add-on to metformin on HbA1c-lowering, and performing simulations to compare the effect of QD and BID canagliflozin dosing regimens on HbA1c-lowering using model-based simulations.

Methods

Study populations and data

As this population PK/PD modelling analysis was performed to support the use of an FDC tablet of canagliflozin and metformin, only long-term studies having comparable patient populations with metformin monotherapy as sole background AHA medication and including a placebo dosing arm were used. Studies meeting these criteria were the QD dosing canagliflozin studies (Study 1 [19] and Study 2 [20]) and the BID canagliflozin study (Study 3 [21]) for which patients received canagliflozin or placebo as add-on therapy to metformin monotherapy at randomization. In total, 5764 PD (HbA1c) observations were available for 1347 patients with T2DM, which included 352 patients from Study 1, 717 patients from Study 2 and 278 patients from Study 3.

In Study 1, patients with T2DM received 50, 100, 200 or 300 mg QD, or 300 mg BID canagliflozin, sitagliptin 100 mg QD, or placebo as add-on to metformin for 12 weeks [19]. Blood samples for PD were taken at baseline and at weeks 6, 9 and 12, while PK was sampled predose at baseline and at weeks 3, 6 and 12. In Study 2, patients with T2DM received 100 mg QD or 300 mg QD canagliflozin or sitagliptin (52 weeks), or placebo (26 weeks) as add-on to metformin [20], with PD samples taken at baseline and at weeks 6, 12, 18 and 26. Study 3 included T2DM patients who received 50 mg BID and 150 mg BID canagliflozin or placebo as add-on to metformin for 18 weeks [21], and sampling for PD was done at baseline and at weeks 6, 12 and 18. In all three studies, HbA1c estimation was carried out in the Diabetes Diagnostic Laboratory, University of Missouri School of Medicine using the boronate affinity chromatography method. The studies were conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines, and other applicable regulatory requirements. The study protocol and amendments for all three studies included in this modelling were reviewed by an Independent Ethics Committee or Institutional Review Board, as appropriate, for each site. Written informed consent was obtained from all patients before enrolment.

A population PK model for canagliflozin was developed previously on pooled exposure data comprising a total of 9061 PK samples from 1616 patients, including 5715 PK samples from 245 richly sampled patients and 3346 trough samples from 1371 sparsely sampled patients including those from Study 1 [22]. Because this model was developed primarily on QD dosing data, it was externally validated to adequately predict the 24-h BID dosing profiles in observed in a separate study (Supplementary Figure S1). The individual empirical Bayes estimates for PK parameters obtained from the population PK model for canagliflozin [22] were used to predict individual 24-h canagliflozin exposure profiles in this study. As no canagliflozin PK samples were collected for Study 2 or Study 3, individual 24-h canagliflozin plasma exposure profiles were predicted for patients in those two studies using their baseline covariates and the canagliflozin population PK model [22].

Model development was performed on an internal dataset that pooled the QD dosing exposure–response data from Studies 1 and 2 with baseline characteristics from all treatment arms in Study 3, as well as postrandomization data from the placebo arm in Study 3. The final model developed on the internal dataset was validated on an external dataset consisting of postrandomization exposure–response data from the BID dosing canagliflozin arms of Study 3. The final parameter estimates used for all simulation-based analyses were obtained on the pooled internal and external datasets. The baseline demographics for the pooled internal/external dataset are listed in Table 1.

Population PK/PD model development

A dynamic population PK/PD model was developed by linking the complete 24-h time profile of drug concentrations to the time-profiles for HbA1c. The PK component consisted of a two-compartment population PK model for canagliflozin described earlier [22]. The PD component was based on a well-established turnover model for HbA1c dynamics over time, with a zero-order rate constant (k_{in}) for HbA1c production through haemoglobin glycation (a nonenzymatic and irreversible reaction between haemoglobin and glucose), and a first-order rate constant (k_{out}) for elimination of HbA1c through erythrocyte cell-death [23]. The individual empirical Bayes PK parameter estimates from the population PK model were used to predict individual 24-h plasma exposure profiles, which were linked to the PD component using an E_{max} model.

The population PK/PD analysis was performed using nonlinear mixed effects modelling as implemented in NONMEM 7.2.0 using the FOCE INTERACTION and ADVAN13 algorithms [24]. An efficient method (method of averaging) was developed to solve numerically the ordinary differential equations of the population PK/PD model. This method is described by Dunne *et al*., [25] and was used throughout the analysis. Data set exploration and visualization, as well as

Table 1

Baseline demographics (identical for both the internal and the pooled internal/external datasets)

	Placebo *n* = 301	50 mg QD *n* = 60	50 mg BID *n* = 93	100 mg QD *n* = 346	200 mg QD *n* = 55	150 mg BID *n* = 93	300 mg QD *n* = 339	300 mg BID *n* = 60	Total *n* = 1347
Sex, *n* (%)									
Men	146 (48.5)	31 (51.7)	40 (43)	171 (49.4)	29 (52.7)	44 (47.3)	158 (46.6)	26 (43.3)	645 (47.9)
Women	155 (51.5)	29 (48.3)	53 (57)	175 (50.6)	26 (47.3)	49 (52.7)	181 (53.4)	34 (56.7)	702 (52.1)
Age (years)									
Median	57.0	53.5	58.0	54.0	55.0	58.0	55.0	56.5	56.0
Range	(26.0–80.0)	(33.0–65.0)	(33.0–80.0)	(27.0–78.0)	(31.0–65.0)	(29.0–79.0)	(21.0–77.0)	(32.0–65.0)	(21.0–80.0)
Weight (kg)									
Median	85.0	86.0	87.0	86.0	84.0	89.6	83.0	81.9	85.0
Range	(45.3–164)	(53.0–123)	(55.2–163)	(40.0–188)	(54.0–133)	(51.0–139)	(47.0–168)	(50.8–140)	(40.0–188)
Body mass index (kg m^{-2})									
Median	30.6	31.0	31.1	31.7	30.1	30.7	30.5	30.6	30.9
Range	(19.7–46.6)	(24.9–41.8)	(21.6–55.4)	(19.3–55.3)	(24.9–44.4)	(20.4–53.4)	(18.1–73.0)	(24.2–43.7)	(18.1–73.0)
eGFR (ml min^{-1} 1.73 m^{-2})									
Median	86.0	92.0	85.0	90.0	88.0	86.0	89.0	100	89.0
Range	(49.0–176)	(57.0–150)	(54.0–135)	(45.0–165)	(50.0–143)	(50.0–138)	(55.0–171)	(35.0–150)	(35.0–176)
HbA1c (%)									
Median	7.6	8.0	7.5	7.7	7.4	7.4	7.8	7.5	7.6
Range	(6.0–10.3)	(6.5–10.0)	(6.2–10.1)	(5.5–10.5)	(6.0–9.0)	(5.6–9.8)	(5.6–11.0)	(6.0–9.8)	(5.5–11.0)

BID, Twice-daily; eGFR, estimated glomerular filtration rate; QD, once-daily.

statistical and graphical analyses and diagnostics were performed using R for Windows (Version 3.0.1.).

Physiological considerations, graphical diagnostics and comparison of competing models using the objective function values (OFV) in a likelihood ratio test guided the model development, where a >10.83 points reduction of the OFV (α = 0.001) for one additional parameter in nested models was deemed significant. This significance level was chosen to account for repeated model testing during development. Different implementations of the various model components were tested, such as the implementation of the treatment effects of canagliflozin and placebo (including the effects of diet and exercise counseling) and their dependence on HbA1c at baseline.

Interindividual variability in parameters was regarded as random and was modelled using eta (η) variables (commonly referred to as *random effects*). The individual η-values were assumed to be normally distributed with a mean of zero and an estimated variance (ω^2). The distribution of the individual parameters around the typical population value was assumed to be log-normal for parameters representing physiological properties that can only take positive values to be meaningful, such as HbA1c at baseline, and normal for parameters that can potentially attain negative values, such as the placebo effect. Correlations between random effects were evaluated by means of graphical assessment and tested by inclusion of covariance terms between Interindividual variability parameters in the model. Residual variability was assumed to be random and normally distributed. An additive error model was used to describe the error on log-transformed data.

Covariate effects for age, body weight, body mass index, sex, race and eGFR (calculated according to the MDRD formula) were explored graphically on the empirical Bayes estimates of the η-values in the final structural model, provided shrinkage was sufficiently low (<25%). Thus determined influential covariates were evaluated at α = 0.001 level by a forward inclusion and backward deletion procedure. In order to evaluate the impact of delayed glucose absorption on HbA1c lowering with 300 mg canagliflozin dose only, an additional PD effect for the 300 mg canagliflozin dose strength was also tested.

Model evaluation

The final population PK/PD model was evaluated using both internal and external validation procedures. A visual predictive check (VPC) was performed for internal validation to assess the ability of the model to predict the observed data of Dataset 1 adequately [26]. The final population PK/PD model was externally validated by using it to predict the post-treatment HbA1c observations of BID dosing from Study 3 included in Dataset 2. Prediction of the external HbA1c observations was performed and a VPC was used to assess the quality of the external predictions. Percent prediction errors were calculated as PE% = 100 × (exp (DV)-exp(IPRED) / exp (IPRED), where DV represents the log-transformed observed

values and IPRED represents the log-transformed individual model predictions. Absolute percent prediction errors (|PE|%) were computed to evaluate bias and precision of the model predictions [27]. The compatibility of data and model were assessed by comparing the values of PE% and |PE|% with the 5th and/or 95th percentiles of their posterior predictive distributions (PPD) under the model [28]. The PPD were estimated by repeated simulation and re-estimation/prediction (300 repetitions).

Model-based QD to BID bridging

Potential differences in HbA1c lowering effect between QD and BID canagliflozin dosing regimens were evaluated using the population PK model and final validated dynamic population PK/PD model, respectively, to simulate subject-specific concentration and HbA1c *vs.* time profiles. Simulated subject-specific HbA1c change from baseline profiles were derived from the latter and were used to evaluate the difference in effect between QD and BID canagliflozin dosing regimens for TDD of 100 and 300 mg. The population PK model [22] was used to simulate 24-h steady-state subject-specific PK concentration–time profiles using baseline covariate values from the pooled internal/external dataset (100 simulations per individual subject, for each dose regimen) and by simulating random effects from their estimated distribution (between-subject variation) without incorporating within-subject variability. In this way, for each of the 1347 subjects in the pooled internal/external dataset, 200 different 24-h steady-state concentration–time profiles were simulated, 100 for QD dosing and 100 for BID dosing. The simulated concentration-time profiles were then used in the final dynamic population PK/PD model (i.e. using the final estimated parameter values from Table 2) to produce simulated subject-specific HbA1c profiles. These were simulated using as input, in addition to the simulated concentration–time profiles, subject-specific baseline HbA1c values from the pooled internal/external dataset, and incorporated both between- and within-subject variability, with random effects and within-subject errors simulated from the respective estimated distributions. Moreover, to account for parameter estimation uncertainty in the population PK/PD model, an additional layer of randomness was added by generating for each subject-specific simulated HbA1c profile, a set of model coefficients (fixed effects, only), from the corresponding asymptotic distribution of parameter estimates in the population PK/PD model. This can be regarded as a parametric bootstrap approach to account for parameter estimation uncertainty in simulations. We used only the fixed effects from the population PK/PD model in the parametric bootstrap, as model sensitivity analysis results suggested that the HbA1c predictions were relatively insensitive to variation in the population PK parameters.

The simulated subject-specific HbA1c change from baseline profiles were summarized per dose regimen and time by their respective means and standard deviations. Graphical analyses were used to evaluate the impact of dosing regimen on the mean and variability of the model-derived HbA1c change from baseline. A potential impact of baseline HbA1c on dosing regimen effect differences was evaluated by grouping simulated HbA1c change from baseline profiles according to simulated baseline value intervals.

Table 2

Parameter estimates for the final population PK/PD model as fitted to the pooled internal and external datasets

Parameter	Estimate	Std. Error
$t_{½}$HbA1c (day)	28.2	2.24
Baseline HbA1c (%)	7.72	0.024
Variance of random effect on baseline HbA1c	0.011	0.00044
Ef_p (%HbA1c @ steady-state, Study1)	–0.483	0.062
Ef_p(%HbA1c @ steady-state, Study 2)	–0.330	0.051
Ef_p (%HbA1c @ steady-state, Study 3)	–0.137	0.057
Variance of random effect on Ef_p	0.369	0.026
E_{max}(%HbA1c @ steady-state)	–0.738	0.070
Log(EC_{50}) (Log(ng ml^{-1}))	4.12	0.54
Residual error variance	0.00182	0.00014

Study1: NCT00642278; Study 2: NCT01106677; Study 3: NCT01340664; HbA1c: glycosylated haemoglobin

$t_{½}$HbA1c = half-life of glycosylated haemoglobin turnover = log (2)/k_{out}

Ef_p = effect of placebo + diet and exercise on HbA1c at steady-state for a typical patient (HbA1c at baseline 8.0%)

E_{max} = maximum placebo-corrected HbA1c-lowering effect of canagliflozin at steady-state for a typical patient with HbA1c at baseline of 8.0%

EC_{50} = exposure (C(t)) at which half-maximal effect is reached, the estimate for log(EC_{50}) corresponds to an estimate of 61.6 ng ml^{-1} on the normal scale.

Results

Dynamic population PK/PD model

Of all the models tested during model development, the dynamic population PK/PD model described below provided best fit for the observed HbA1c data of the internal dataset used for model development (see methods section). This model integrated a turnover model for HbA1c [23] with an E_{max} model relating the HbA1c-lowering effect of canagliflozin to the canagliflozin plasma exposure at time t using the following set of structural equations:

$$\frac{dH(t)}{dt} = k_{in} – Ef – k_{out}\, H(t) \quad (1)$$

$$Ef = \left(Ef_c + Ef_p\right) \frac{H(0) – 5}{8 – 5} \quad (2)$$

$$Ef_c = E_{max} \frac{C(t)}{C(t) + EC_{50}} \quad (3)$$

Equation (1) describes the turnover model for HbA1c, where $H(t)$ is the HbA1c (%) at time t, k_{in} and k_{out} are rate parameters related to haemoglobin glycation and red blood cell turnover, respectively, and Ef describes the combined HbA1c-lowering effects of canagliflozin and placebo

treatment. The rate parameter k_{out} was estimated as a half-life by scaling it over log(2) and the rate parameter k_{in} was estimated as the HbA1c (%) at time 0 (baseline) by scaling it over k_{out} (i.e. $k_{in} = H(0) / k_{out}$, see also Table 1).

The term Ef was derived in Equation (2), where Ef_c represents the exposure–response relationship of canagliflozin on HbA1c (Equation (3)) and Ef_p represents the effect of placebo treatment (including diet and exercise counselling) as a step function activated for $t > 0$; these treatment effects were found to be additive. Similar to k_{in}, Ef_c and Ef_p were estimated as scaled by k_{out} in order to render their estimates in Table 1 more readily interpretable in terms of change in %HbA1c from baseline at steady-state. Because baseline glycaemia is known to affect the magnitude of glucose-lowering in response to AHAs, [29] the combined effect parameter Ef was scaled in Equation (2) by the estimated individual HbA1c at baseline, $H(0)$, normalized by a reference baseline HbA1c of 8.0%. In addition, because normoglycaemia is typically associated with HbA1c values of ~5.0% and virtually no reductions in PG are observed in subjects with normoglycaemia who are treated with canagliflozin, this term was corrected for a lower boundary for HbA1c-lowering of 5.0%. This baseline scaling of the treatment effects resulted in a highly significant reduction of the OFV by 305 points (135 points for baseline scaling as such, plus 170 points for correction by a lower HbA1c boundary of 5%).

Equation (3) describes the exposure–response relationship between the HbA1c-lowering effect of canagliflozin, Ef_c, and the canagliflozin plasma exposure at time t, $C(t)$, where E_{max} represented the maximal HbA1c-lowering effect of canagliflozin at steady-state for a subject with a baseline HbA1c of 8.0%, and EC_{50} was the canagliflozin plasma exposure at which the half-maximal effect was reached. Estimating a Hill factor for this E_{max} model did not result in an improvement of the model fit. The final dynamic population PK/PD model as described above by Equations (1)–(3) provided a satisfactory fit to the observed HbA1c data of the internal dataset as per criteria listed under Methods. Figure 1 shows that the dose groups were predicted without significant evidence of bias, most notably 100 mg QD and 300 mg QD doses.

Other than a highly significant effect of baseline HbA1c on efficacy, no covariate effects could be identified on the internal dataset that satisfied the prespecified significance level of $P < 0.001$ (see Methods). The strongest covariate effect found was a power function of eGFR on canagliflozin efficacy as described in Equation (4), yielding a drop of 5.6 points OFV ($P = 0.018$) where E_{max90} (representing the maximum canagliflozin effect for a typical subject with an eGFR of 90 ml min^{-1} 1.73 m^{-2}) was estimated at –0.75% HbA1c and γ was estimated at 0.46.

$$E_{max} = E_{max90}(\text{eGFR}/90)^{\gamma} \quad (4)$$

Because this term did not meet the prespecified significance level, it was not retained in the model.

Model validation

The final population PK/PD model (Equations (1)–(3)) was validated on the internal dataset by a VPC. The VPC plot in Figure 2 shows no major systemic deviation between simulated and observed data, and demonstrated that the model

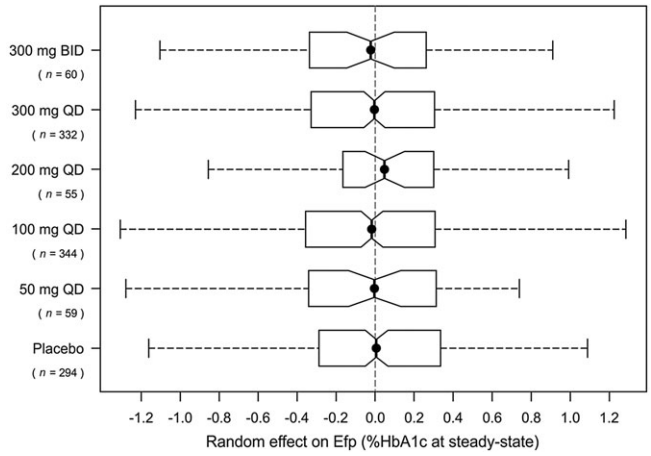

Figure 1

Box plots of the distributions of the random effect on Ef_p per dose group for the fit of the dynamic population PK/PD model on the internal dataset. BID, twice-daily; Ef_p, effect of placebo + diet and exercise on HbA1c at steady-state for a typical patient (HbA1c at baseline 8.0%); HbA1c, glycosylated haemoglobin; PK, pharmacokinetics; PD, pharmacodynamics; QD, once-daily

adequately described in variability in the observed HbA1c data. The model was externally validated by using it to predict the post-randomization the HbA1c observations of the 18-week BID dosing study in the external dataset (see Methods). Figure 3 shows that the model accurately predicted the trends in the external dataset for both 50 mg and 150 mg BID dose levels. The percent prediction errors (PE%) obtained for external validation of the final population PK/PD model remained well within the 5th and 95th percentiles of their corresponding PPD [28] and the absolute percent prediction errors (|PE|%) remained well below the 95th percentile of their corresponding PPD (Table 2).

It follows that the canagliflozin BID dosing HbA1c observations from the external dataset could be predicted with negligible bias and acceptable precision by the model as estimated on the mostly QD dosing data from the internal dataset. Therefore, the dynamic population PK/PD model described by Equations (1)–(3) was retained for all subsequent analyses and model-based simulations. Table 3 lists the final parameter estimates for this model as fitted to the pooled internal and external datasets (comprised of all available observations from studies 1, 2, and 3).

Model-based QD to BID bridging

Based on the HbA1c change from baseline data simulated from the population PK and population PK/PD models (under similar baseline covariate values, including HbA1c, and same study effect), BID and QD dosing at the same TDD were found to be similar in terms of mean HbA1c lowering effect (Figure 4). The differences in HbA1c reduction between BID and QD mean profiles were minimal (at most 0.023% for 100 mg TDD and 0.011% for 300 mg TDD, up to week 26, increasing with time and decreasing with TDD) and not

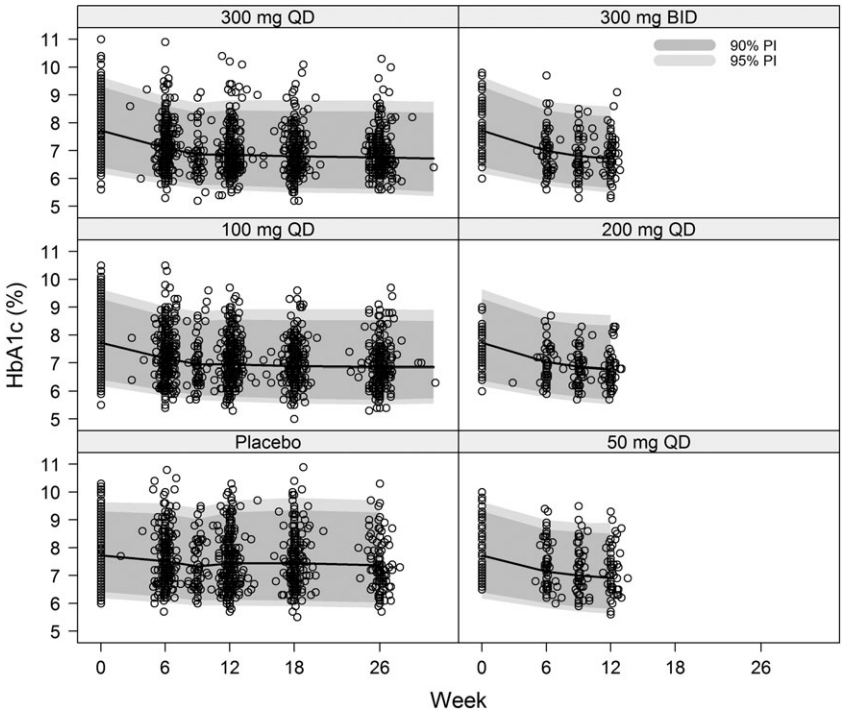

Figure 2

Visual predictive check of the final population PK/PD model on the internal dataset. BID, twice-daily; HbA1c, glycosylated haemoglobin; PD, pharmacodynamics; PI, predicted interval; PK, pharmacokinetics; QD, once-daily

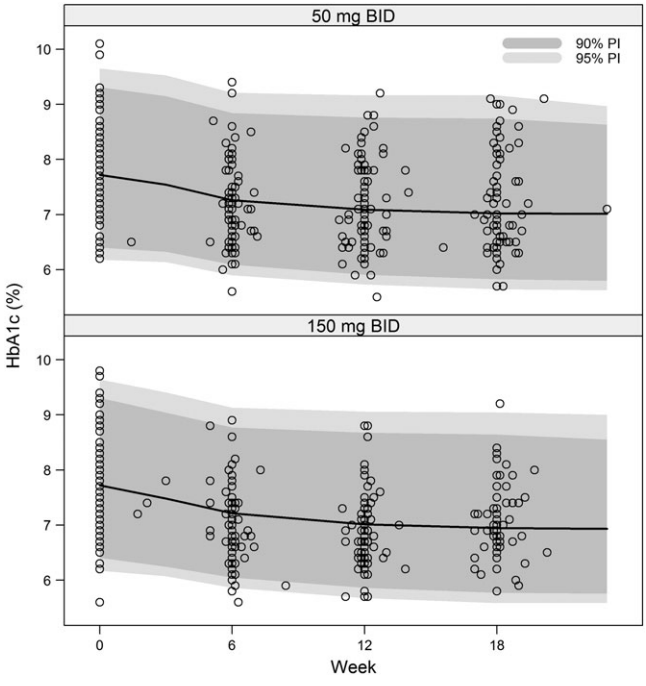

Figure 3

Visual predictive check of the final population PK/PD model on the 50 mg BID and 150 mg BID canagliflozin dosage arms of the external dataset. BID, twice-daily; HbA1c, glycosylated haemoglobin; PD, pharmacodynamics; PI, predicted interval; PK, pharmacokinetics; QD, once-daily

considered clinically meaningful. Similar results were obtained after conditioning on baseline HbA1c.

Discussion

The purpose of this study was to establish a robust relationship between canagliflozin exposure and HbA1c response to compare the effect of BID *vs*. QD canagliflozin dosing regimens in support of the registration of the canagliflozin-metformin IR FDC tablet [30]. To this end, a robust dynamic model was developed by integrating a turnover model for HbA1c [23] with an E_{max} model relating the HbA1c-lowering effect of canagliflozin to its plasma exposure at time *t*. This dynamic model was used to compare the predicted HbA1c response time-courses between QD and BID canagliflozin dosing regimens, and demonstrated that HbA1c change from baseline was similar between QD and BID canagliflozin dosing.

For model development, QD dosing HbA1c data were obtained for the patient population that was comparable to the patient population from Study 3 (18-week BID dosing study) [21]. This dataset included patients from Study 1 (12-week QD dosing study) [19] and Study 2 (26-week QD dosing study) [20] with metformin monotherapy as sole background AHA medication at screening, as well as baseline data from Study 3 (internal dataset). The model was externally validated on postbaseline BID dosing observations from Study 3 (external dataset). Full 24-h plasma PK concentration–time profiles were simulated per patient using a separately developed and

Table 3

PE% and |PE|% for the external validation of the final population pharmacokinetics/pharmacodynamics model on the post-randomization glycosylated haemoglobin observations from the 50 mg and 150 mg BID dosing arms of Study 3(NCT01340664) and the 5th and/or 95th percentiles of their posterior predictive distributions

	Regimen	Median	5th percentile of PPD	95th percentile of PPD
PE%	50 mg BID	–1.1	–2.0	2.1
	150 mg BID	0.0	–2.2	2.2
|PE|%	50 mg BID	4.2	–	6.6
	150 mg BID	4.5	–	6.4

BID, twice-daily; PPD, posterior predictive distributions; PE, prediction error.
Percent prediction errors calculated as PE% = 100 × (exp(DV)-exp(IPRED)) / exp(IPRED), where DV = dependent variable and IPRED = individual prediction; Absolute percent prediction errors (|PE|%) was computed as the absolute value of %PE.

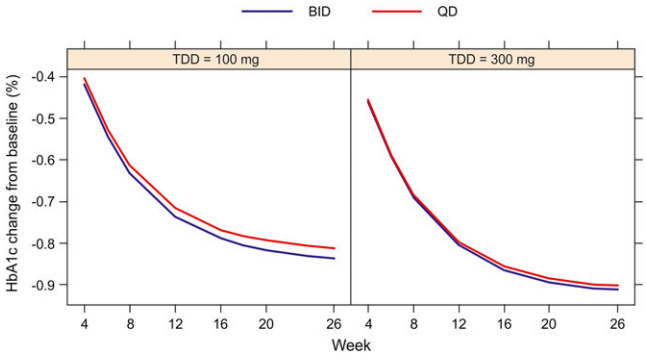

Figure 4

Mean HbA1c change from baseline profiles per regimen and total daily dose derived by averaging out the simulated subject-specific HbA1c change from baseline profiles simulated from the population PK and population PK/PD models. BID, twice-daily; HbA1c, glycosylated haemoglobin; PD, pharmacodynamics; PI, predicted interval; PK, pharmacokinetics; QD, once-daily; TDD, total daily doses

validated population PK model for canagliflozin [22] based on its baseline covariates and, where available, observed plasma trough concentrations (only for Study 1). The final parameter estimates used for simulations were obtained on the pooled internal and external datasets. Table S1 shows adequate consistency between the observed and model-predicted placebo-subtracted least square mean changes from baseline in HbA_{1c} at study visits (last observation carried forward), which is the standard method for comparing study results in diabetes drug development.

The placebo response in diabetes trials is known to be highly variable, including variability within subjects over time, variability between subjects within the same study population, and variability between study populations. Because the mean change in HbA1c in placebo groups is usually small relative to the placebo-subtracted differences in the active treatment arms, it is generally accepted that the placebo-subtracted efficacy is the best measure to use for assessing the efficacy of AHAs. In this model-based analysis we have conformed to this accepted practice by assuming an additive relationship between the placebo effect and the canagliflozin effect in Equation (2).

The HbA1c-lowering efficacy of canagliflozin and placebo treatment was found to be highly dependent on the predicted HbA1c levels at baseline. This is consistent with the finding that patients with higher baseline HbA1c had larger reductions in HbA1c with canagliflozin 100 and 300 mg than those with lower baseline HbA1c [26]. Indeed, it has been demonstrated that, irrespective of drug class, the baseline glycaemic status of patients who have been recruited into clinical trials strongly influence the fasting PG and HbA1c reductions following pharmacological intervention [29]. Other than this highly significant effect of baseline HbA1c on efficacy, no significant covariate effects could be identified on the internal dataset.

Although a covariate effect of renal function (eGFR) on canagliflozin efficacy was expected, [15, 16] it failed to reach statistical significance at the prespecified level ($\alpha = 0.001$), possibly reflecting the patients with moderately impaired renal function in the internal dataset. Given that patients with moderate renal impairment were excluded from the patient population for which the canagliflozin/metformin FDC is indicated, and that the differences in eGFR between the corresponding QD and BID dosing groups were small (Table 1), this was not considered to be a relevant limitation for this study.

In the external validation of the population PK/PD model, the model-predicted that HbA1c profiles agreed well with the observed profiles from the 50 mg and 150 mg BID dosing arms of the external dataset (Study 3). Together with the previous internal model validation, this external validation confirmed the ability of the developed dynamic population PK/PD model to accurately predict HbA1c-lowering for QD as well as BID canagliflozin dosing regimens. A final fit of the dynamic population PK/PD model on the pooled internal and external datasets was performed to obtain parameter estimates that could be used for simulations to compare the predicted efficacy of QD *vs*. BID canagliflozin dosing regimens.

Based on HbA1c change from baseline data simulated from the population PK and PK/PD models, negligible greater than average HbA1c-lowering was predicted for BID over QD dosing regimens (at most 0.023% for 100 mg TDD and 0.011% for 300 mg TDD after 26 weeks of treatment). Such small predicted differences in HbA1c-lowering between QD and BID canagliflozin dosing regimens were not clinically meaningful.

In conclusion, the dynamic population PK/PD model adequately predicted the HbA1c profiles observed in the 18-week canagliflozin BID dosing study (NCT01340664), [21] and showed good agreement between model-predicted and observed reductions in HbA1c for 100 and 300 mg TDDs given as QD and BID dosing regimens. Model-based simulations predicted no clinically meaningful differences in efficacy between QD or BID canagliflozin dosing regimens at either 100 or 300 mg TDD. Therefore, patients on a stable background medication of metformin who switch from canagliflozin taken QD as individual tablets to a single FDC tablet containing metformin and canagliflozin taken as BID should experience similar glycaemic control. The results of this modelling and simulation analysis supported the regulatory approval of the canagliflozin-metformin IR FDC tablet and alleviated the need for an additional clinical trial to directly compare the efficacy of BID *vs*. QD dosing [30].

Competing Interests

All authors are (former) employees of Janssen Research & Development, LLC, and are stock holders of Johnson & Johnson.

The study was sponsored by Janssen Research & Development LLC. Authors thank Eef Hoeben for her work on predicting the PK exposures and Martine Neyens for data management. Shruti Shah, PhD (SIRO Clinpharm Pvt. Ltd.) and Bradford Challis, PhD (Janssen Research & Development, LLC) provided editorial support for this manuscript.

Contributors

W.d.W. was the primary author of both the population PK and PK/PD models for canagliflozin and participated with A. D., X.W.d.T., C.H.H., J.P. and D.P. in the strategic planning and implementation of the modeling and simulation activities presented here. D.D. participated in its design and coordination, and helped with acquisition of data. W.d.W. wrote the initial draft of the manuscript and all authors provided contributions to the text and approved the final manuscript.

All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data and approved submission to this journal. All authors contributed to the data interpretation of the results, development, and review of this manuscript, and confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13180/suppinfo

Figure S1 Visual predictive check for the external validation of the canagliflozin population PK model on the twice-daily dosing study stratified per dose and per dose regimen. The population PK model for canagliflozin as described in [22] was used to simulate 200 databases using the study design and covariate distributions of the external twice-daily dosing study population. Dark grey solid line: median of simulations; light grey solid lines: percentiles of 90% prediction interval; white symbols: observed canagliflozin concentrations. Plasma concentrations are presented on the log scale

Table S1 Comparison of observed and model-predicted placebo-subtracted least square mean changes from baseline in glycosylated haemoglobin at study visits (last observation carried forward)