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ORIGINAL ARTICLE

Urinary glucose excretion after dapagliflozin treatment: An exposure-response modelling comparison between Japanese and non-Japanese patients diagnosed with type 1 diabetes mellitus

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Aims: To assess the dapagliflozin exposure-response relationship in Japanese and non-Japanese patients with type 1 diabetes mellitus (T1DM) and investigate if a dose adjustment is required in Japanese patients.

Materials and Methods: Data from two clinical studies were used to develop a non-linear mixed effects model describing the relationship between dapagliflozin exposure (area under the concentration curve) and response (24-hour urinary glucose excretion [UGE]) in Japanese and non-Japanese patients with T1DM. The effects of patient-level characteristics (covariates; identified using a stepwise procedure) on response was also assessed. Simulations were performed using median-normalized covariate values.

Results: Data from 84 patients were included. Average self-monitored blood glucose (SMBG) at day 7, change from baseline in total insulin dose at day 7, and baseline estimated glomerular filtration rate (eGFR) all had a significant effect on 24-hours UGE, with SMBG being the most influential. Dapagliflozin systemic exposure for matching doses and baseline eGFR was similar between Japanese and non-Japanese patients; however, higher SMBG and a greater reduction in total insulin dose was observed in the Japanese population. When the significant covariates were included, the model fit the data well for both populations, and accurately predicted exposure-response in the Japanese and non-Japanese populations, in agreement with the observed data.

Conclusions: There was no difference in dapagliflozin exposure-response in Japanese and non-Japanese patients with T1DM once differences in renal function, glycaemic control and insulin dose reductions between studies were considered. Therefore, no dose adjustment is recommended in Japanese patients with T1DM.

KEYWORDS

dapagliflozin, exposure-response relationship, SGLT2 inhibitor, type 1 diabetes mellitus

1 | INTRODUCTION

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor that is currently approved for the treatment of patients with type 2 diabetes mellitus (T2DM). Dapagliflozin improves glycaemic control in an insulin-independent manner by blocking the reabsorption of glucose in the proximal tubules in the kidney, resulting in glucosuria.[1] In addition to improved glycaemic control, dapagliflozin has also been shown to reduce blood pressure and body weight.[1] Furthermore, several large clinical studies have shown that SGLT2 inhibitor use

improves cardiovascular and renal outcomes in patients with T2DM and other risk factors.[2–4]

Patients with type 1 diabetes mellitus (T1DM) require lifelong treatment with exogenous insulin following diagnosis. Intensive glycaemic control achieved through increased insulin dosing reduces the risk of micro- and macrovascular complications and their progression.[5,6] However, this often leads to excessive glucose variability, body weight gain, and an increased risk of hypoglycaemia. Frequent episodes of hypoglycaemia negatively impact quality of life, which in turn may lessen patient compliance. Events of severe hypoglycaemia have also been associated with an increased risk of cardiovascular morbidity and mortality, and all-cause mortality in patients with diabetes.[7,8] Clearly, adjunct therapies with insulin-independent mechanisms of action, such as SGLT2 inhibitors, present an opportunity to refine the T1DM treatment paradigm and improve patient outcomes.[6]

Phase 3 investigations in patients with T1DM show that dapagliflozin reduces HbA1c over 24 weeks compared with placebo, without increasing the risk of hypoglycaemia.[9,10] Prior to these large randomized controlled trials of dapagliflozin in patients with T1DM, exploratory studies were conducted to evaluate the safety, pharmacokinetics and pharmacodynamics of dapagliflozin in the target T1DM patient population.

The first trial (NCT01498185) was conducted in the United States, enrolled predominantly Caucasian patients (88.6%), and showed a clear dose- and exposure-response relationship between dapagliflozin (1-10 mg) and 24-hours urinary glucose excretion (UGE) on day 7.[11] A second trial (NCT02582840 Part A) repeated the investigation in Japanese patients with T1DM, and surprisingly did not reveal an exposure-response with dapagliflozin 5 and 10 mg (24 hours UGE values of 115 ± 25 [n = 14] and 115 ± 17 g [n = 14], respectively).[12] It should be noted that while no direct quantitative link has been established between UGE and the lowering of HbA1c, the hypothesis of linking short-term changes in average or fasting plasma glucose to long-term changes in HbA1c has been explicitly modelled in a number of studies.[13–15]

Here, we conducted a pooled population analysis using individual data from the two aforementioned clinical trials to assess the dapagliflozin exposure-response relationship in Japanese and non-Japanese patients with T1DM, and to investigate if any differences in population would necessitate a dose adjustment in Japanese patients. In addition, the effect of patient-level characteristics (covariates) on the relationship between dapagliflozin exposure and 24-hours UGE response was evaluated.

2 | MATERIALS AND METHODS

Pharmacokinetic and pharmacodynamic data from two dapagliflozin clinical trials (NCT01498185[11] and NCT02582840[12]; see Table 1 for summary characteristics) were pooled to develop an exposure-response relationship model between steady-state dapagliflozin exposure measured over a 24-hours period after administration of the dose (area under the concentration curve [$AUC_{0\text{-}24\ h}$]) and 24-hours UGE in Japanese and non-Japanese patients with T1DM (Figure S1 in Appendix S1). In both the non-Japanese and Japanese studies, 24-hours

TABLE 1 Summary of studies and covariates used in the development of the model and the subsequent analysis

	NCT01498185 (non-Japanese study)	NCT02582840 (Japanese study)	Both studies combined
Study description	Randomized, double-blind, 5-arm, parallel-group, placebo-controlled	Randomized, single-blind, 3-arm, parallel-group, placebo-controlled	–
Dapagliflozin doses evaluated (once daily), mg	1, 2.5, 5, 10	5, 10	-
Dapagliflozin PK sampling at day 7, hours	0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24	0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24	-
Treatment duration, days	14	7	-
Women, n (%)	23 (46)	22 (65)	45 (54)
Men, n (%)	27 (54)	12 (35)	39 (46)
Age, years	36.2 ± 13.2 (18, 65)	39 ± 10.2 (22, 60)	37.3 ± 12.1 (18, 65)
Weight, kg	75.6 ± 14.6 (54.7, 115.6)	58.9 ± 9.7 (44.1, 79.2)	68.9 ± 15.2 (44.1, 115.6)
BMI, kg/m^2	24.9 ± 3.5 (19.2, 33.1)	22.8 ± 2.7 (19.3, 31.3)	24.0 ± 3.3 (19.2, 33.1)
Baseline eGFR, $mL/min*1.73\ m^2$	91.1 ± 18 (49.8, 133.8)	94.7 ± 15.4 (66, 129)	92.5 ± 17 (49.8, 133.8)
Baseline HbA1c, %	8.3 ± 0.8 (7, 9.9)	8.1 ± 0.7 (7, 10.1)	8.2 ± 0.7 (7, 10.1)
Baseline total insulin, IU	51.3 ± 30.4 (10, 175)	35.9 ± 13.2 (14, 82)	45.1 ± 25.9 (10, 175)
Day 7 total insulin, IU	43.6 ± 22.8 (13.4, 133)	27.6 ± 13.4 (10, 76)	37.1 ± 20.9 (10, 133)
Day 7 change from baseline in total insulin, %	−6.8 ± 36.3 (−52.6, 120)	−23.1 ± 23.2 (−57.4, 45.8)	−13.4 ± 32.5 (−57.4, 120)
Baseline SMBG, mg/dL	162.2 ± 32.2 (94.9, 234.5)	180.3 ± 40.5 (107, 319.3)	169.5 ± 36.7 (94.9, 319.3)
Day 7 SMBG, mg/dL	144.2 ± 29.7 (79.2, 227.6)	178.4 ± 25.5 (129.4, 236.1)	158.1 ± 32.6 (79.2, 236.1)
Baseline FPG, mg/dL	155 ± 64.9 (50.5, 279.3)	139.2 ± 53.5 (44, 263)	148.6 ± 60.7 (44, 279.3)
Day 7 FPG, mg/dL	125.5 ± 45.5 (52.2, 284.4)	144.5 ± 61.6 (58, 311)	133.2 ± 53.1 (52.2, 311)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; PK, pharmacokinetic; SMBG, self-monitored blood glucose.
Data are mean ± SD (minimum, maximum) unless otherwise stated.

pharmacokinetics of dapagliflozin were assessed at day 7 by the initial sampling scheme that comprised 10 sampling times, including a predose sample and measurements at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose. Dapagliflozin pharmacokinetics have not been shown to possess complex behaviour and are therefore typically described by a two-compartment pharmacokinetic model with first-order absorption and linear clearance[16]; $AUC_{0\text{-}24\ h}$ was evaluated based on non-compartmental analysis performed using Phoenix WinNonlin 6.3 (Japanese study) or Kinetica (non-Japanese).

Full details of the two trials are available in the literature[11,12]; the relevant regional ethics committees approved the studies and all patients provided written, informed consent prior to inclusion in the study. $AUC_{0\text{-}24\ h}$ and 24-hours UGE measurements collected at day 7 were used in the analysis; patients without either day 7 24-hours UGE or pharmacokinetic measurements (i.e. no sample collected) were excluded. The analysis dataset contained a total of 84 patients with paired day 7 24-hours UGE records and steady-state plasma $AUC_{0\text{-}24\ h}$ measurements.

Based on prior knowledge of dapagliflozin and its mechanism of action, certain covariates were selected to assess their impact on exposure-response. In addition to sex, race and age, the baseline values for the following covariates were analysed: estimated glomerular filtration rate (eGFR; calculated using abbreviated Modification of Diet in Renal Disease equation [non-Japanese study], or abbreviated Japanese Society of Nephrology formula [Japanese study]), body weight, body mass index, fasting plasma glucose (FPG), HbA1c, total insulin dose and self-monitored blood glucose (SMBG; average blood glucose level over 24 hours [patients were provided with glucose meters to measure their blood glucose throughout the day]). Day 7 values for the following covariates were also analysed: basal insulin, bolus insulin, total insulin, change from baseline in total insulin, FPG, SMBG, and change from baseline in SMBG.

2.1 | Model development

A non-linear mixed effects model was developed to characterize the relationship between dapagliflozin systemic exposure (plasma $AUC_{0\text{-}24\ h}$ on day 7) and day 7 24-hours UGE, and to evaluate the effects of baseline and day 7 covariates on the 24-hours UGE response. The structure of the base model is defined by the following equation:

$$UGE = UGE_0 + \left[\frac{Emax \times AUCss}{EAUC_{50} + AUCss}\right],$$

where UGE_0 is a regressor taken directly from the data as the 24-hours UGE at day 0, E_{max} is the maximum treatment-induced 24-hours UGE change at steady state (day 7), AUC_{SS} is the observed dapagliflozin $AUC_{0\text{-}24\ h}$ at steady state (day 7), and $EAUC_{50}$ is the $AUC_{0\text{-}24\ h}$ at which half-maximal UGE change is achieved. Random effects for E_{max} and $EAUC_{50}$ variables were not simultaneously estimable because of the data limitations; however, stepwise removal of random effects for each parameter showed that retaining the random effect on E_{max} results in the best overall fit. Constant, proportional and combined residual error models were evaluated. Implementation of day 7 placebo data was necessary to put the UGE observations in the context of a placebo response and justify the use of combined error. Covariates were analysed for correlation with 24-hours UGE, and those with a Pearson's correlation coefficient >0.1 were used in the subsequent stepwise covariate search (*P*-value <0.05 for retention in the model). Meaningful covariates were retrieved using a forward addition process. All covariates were tested one after another separately for the E_{max} parameter and the $EAUC_{50}$ parameter. For the first step, if a covariate improved objective function value (OFV) by >3.84 units (*P*-value <0.05) without increasing uncertainty in other variables, and if the covariate parameter's relative standard error (RSE) was <60%, the covariate was kept in the model; otherwise it was disregarded as insignificant. In the second and third steps, second and third covariates were tested separately using the same quality criteria as described above for the E_{max} parameter and the $EAUC_{50}$ parameter: combinations with %RSE >60% and <3.84 improvements in OFV were excluded. For the last step, the final model was selected from all possible combinations of remaining covariates based on lowest OFV and smallest %RSE, as well as biological plausibility. Model estimation was performed using NONMEM, version 7.3.0 (Icon Development Solutions, Ellicott City, Maryland), with first-order conditional estimation algorithm with interaction (FOCE+I). R version 3.2.4 (R-project, www.r-project.org) was used for the exploratory analysis, NONMEM for postprocessing and goodness-of-fit assessments.

2.2 | Model evaluation

Model quality was evaluated using change in OFV, visual inspection of diagnostic plots, precision of the parameter estimates, shrinkage in empirical Bayes parameter estimates, and decreases in both between-subject variability and residual variability. The criteria for OFV improvements were −3.84 for *P*-value <0.05 and −6.63 for *P*-value <0.01; model variables were considered identifiable if %RSE was <60%, and acceptable shrinkage was considered as <30% for both residual error and random effects.[17] In addition, models were evaluated using a simulation-based visual predictive check (2000 replicates), where the model-predicted distribution (median 2.5% and 97.5% percentiles) of 24-hour UGE at each $AUC_{0\text{-}24\ h}$ bin was overlaid on the observed UGE distribution to visually assess concordance between the model and the clinical data.

Simulations using the final exposure-response model were conducted to explore the 24-hours UGE in patients with differing covariate characteristics based on the four dose levels in the two populations. The simulations were performed using median values for baseline 24-hours UGE and the identified significant covariates for each arm of the studies. Dapagliflozin 1 and 2.5 mg doses were not studied in the Japanese trial, therefore the median dapagliflozin $AUC_{0\text{-}24\ h}$ values from non-Japanese patients were used to simulate these treatment arms in the Japanese population.

3 | RESULTS

3.1 | Analysis of dapagliflozin exposure and study covariates

A graphical comparison of $AUC_{0\text{-}24\ h}$ and the other patient characteristics between non-Japanese and Japanese patients with T1DM is

shown in Figure 1. For a given dapagliflozin dose, the exposure and baseline eGFR were similar in each population. However, higher day 7 SMBG and a greater reduction in total insulin dose were observed in the Japanese population compared with the non-Japanese population. Japanese patients had, on average, 24% higher day 7 SMBG values compared with non-Japanese patients, and their insulin dose was reduced over three times as much by day 7 (−23.1% vs. −6.8% reductions in Japanese and non-Japanese patients, respectively; Table 1).

3.2 | Exposure-response model

The model described the data well, as judged by a visual predictive check plot (Figure 2) and other goodness-of-fit plots (Figures S2-S4). Estimated E_{max} and $EAUC_{50}$ values were 88.1 g/24 h (RSE: 11%) and 45.8 ng/mL*h (40%), respectively. The final model equation, including terms for the significant covariates is described in the supporting information, along with final estimates of all the other variables used in the model (Table S1).

In the final model, % change from baseline in total insulin dose on day 7 and baseline eGFR emerged as meaningful covariates for E_{max}, while day 7 SMBG was identified as the meaningful covariate for $EAUC_{50}$. Further addition of covariates did not result in improvement of parameter estimations or OFV. According to the model, patients with higher SMBG levels, better renal function and greater total insulin dose reduction are predicted to have a more pronounced UGE response to dapagliflozin treatment (Figure 3).

3.3 | Model simulations

The effect size of covariates on predicted dapagliflozin exposure-response was evaluated by simulating mean model predictions of day 7 24-hours UGE within the range of covariate values (Figure 3). The reference simulation was performed using median covariate value estimates calculated from the combined non-Japanese/Japanese dataset. Each of the three meaningful covariates (baseline eGFR, day 7% change from baseline in total insulin and day 7 SMBG) were sequentially varied within the interquartile range.

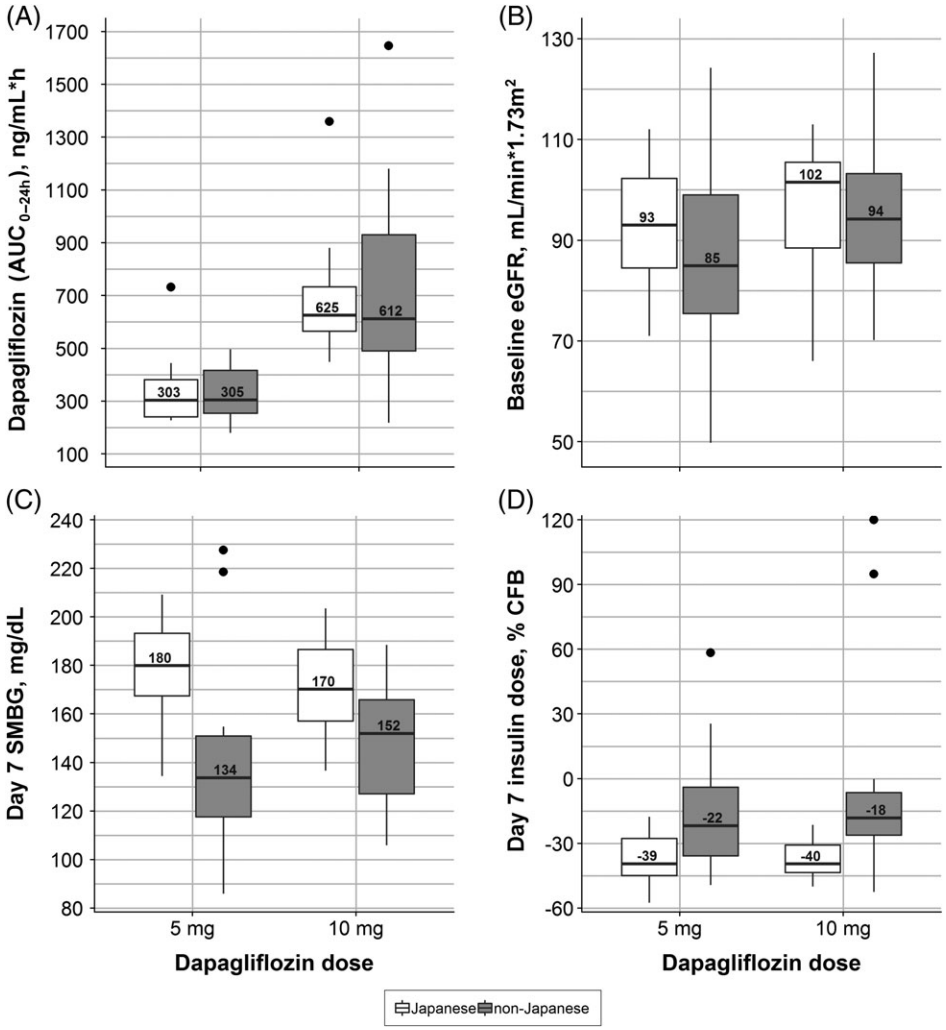

FIGURE 1 Dapagliflozin steady-state area under the concentration curve over a 24-hours period ($AUC_{0\text{-}24\ h}$) and covariates by treatment groups and study population. A, Dapagliflozin $AUC_{0\text{-}24\ h}$. B, Baseline estimated glomerular filtration rate (eGFR). C, Day 7 self-monitored blood glucose (SMBG). D, Day 7% change from baseline (CFB) in total insulin dose. The solid horizontal lines are medians (50th percentile). Bars are interquartile range (IQR). Whiskers represent the range of values no greater than Q1-1.5*IQR and Q3 + 1.5*IQR. Datapoints are outliers. Text within bars denotes median values

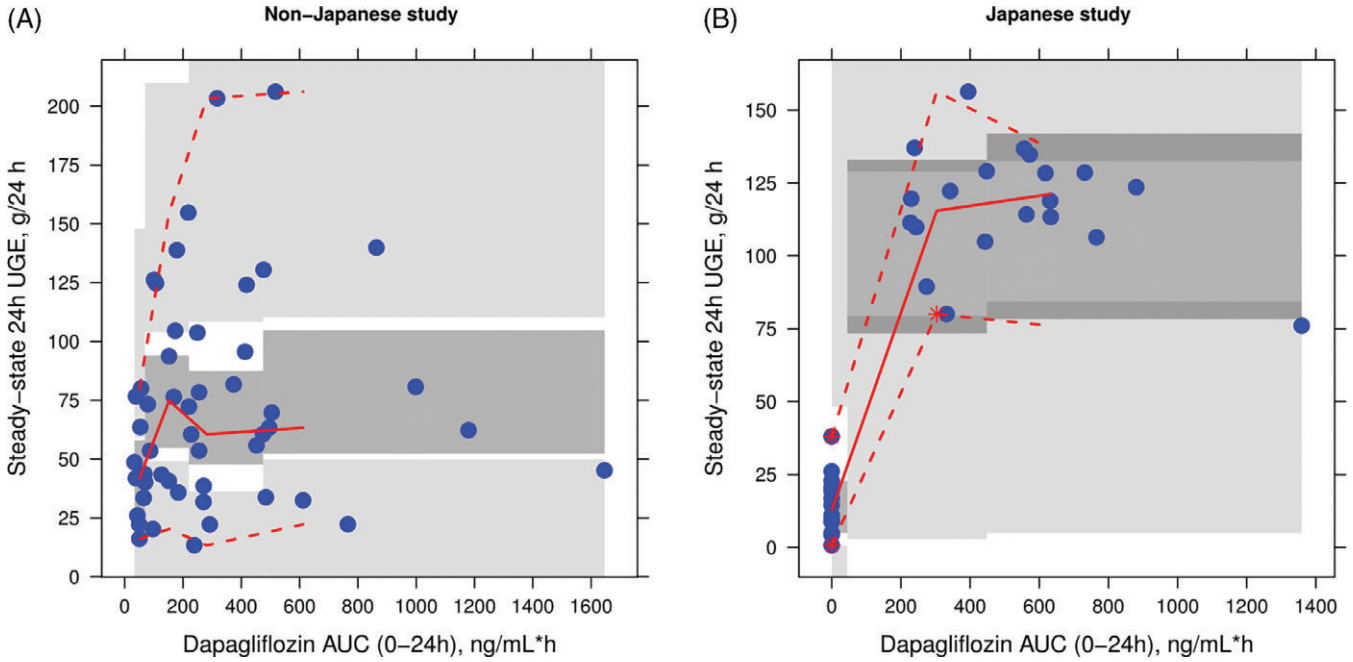

FIGURE 2 Visual predictive check plot of daily urinary glucose excretion (UGE) exposure-response. A, Non-Japanese population. B, Japanese population. Analysis based on the simulations of 2000 samples. Bin widths were chosen based on the number of datapoints per dose per patient cohort. Blue dots: observed 24-hours UGE data; solid red line: median observed 24-hours UGE; dashed red lines: the observed 2.5% and 97.5% percentiles; dark grey shading: a simulation-based 95% confidence interval for the median; light grey shading: 95% confidence intervals for the corresponding model predicted percentiles. Abbreviation: $AUC_{0\text{-}24\ h}$, area under the concentration curve over a 24-hours period

To explain the observed differences in exposure-response (24-hours UGE) between study NCT01498185 (non-Japanese patients) and study NCT02582840 (Japanese patients), simulations using the final exposure-response model were conducted to predict the 24-hours UGE in patients using the median covariate characteristics (Table S3) corresponding to each treatment arm and study. When the patient characteristics from each treatment arm were used to simulate the 24-hours UGE in the two populations, the model predicted the exposure-response in the Japanese and non-Japanese studies. Both of these predictions are in agreement with the respective trial outcomes (Figure 4).

4 | DISCUSSION

The exposure-response model developed in this analysis successfully described the relationship between dapagliflozin systemic exposure

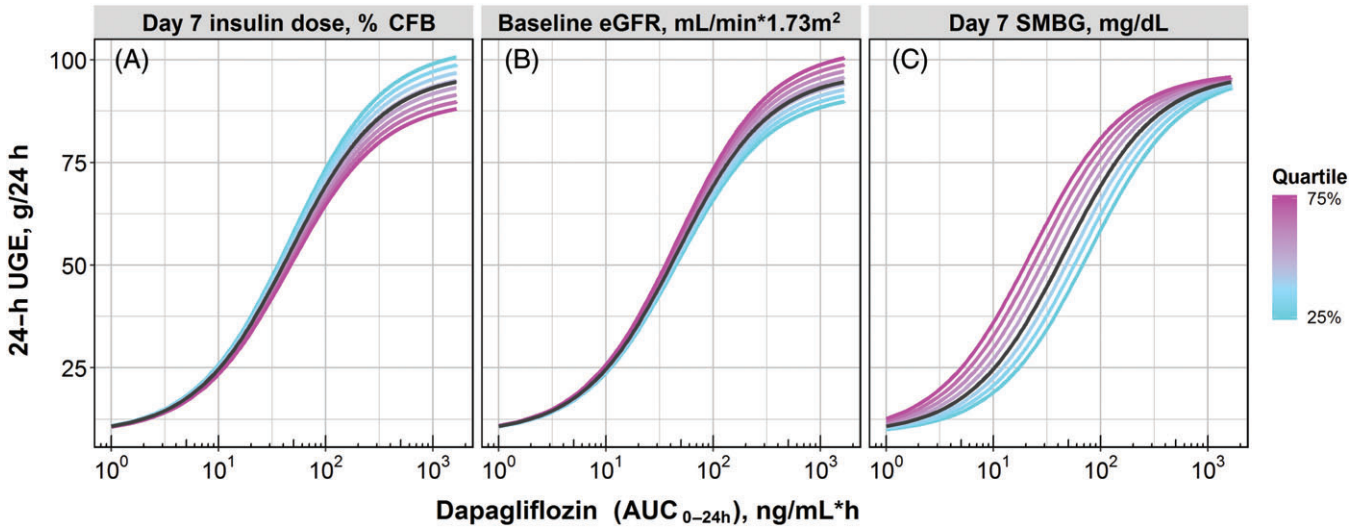

FIGURE 3 Sensitivity of predicted day 7 24-hours urinary glucose excretion (UGE) to the covariate effect size. Mean predicted exposure-response of dapagliflozin on day 7 24-hours UGE in response to variations of A, Day 7 insulin dose, % change from baseline (CFB), B, baseline estimated glomerular filtration rate (eGFR), mL/min*1.73 m^2 and C, Day 7 self-monitored blood glucose (SMBG), mg/dL. Black curves are the median model predictions; coloured curves are the model predictions under variation of a covariate within the interquartile range calculated across the full study population. Abbreviations: $AUC_{0\text{-}24\ h}$, area under the concentration curve over a 24-hours period

and day 7 24-hours UGE response. The exposure of dapagliflozin for matching doses was comparable between Japanese and non-Japanese patients. A covariate analysis of patient-level characteristics revealed day 7 SMBG, baseline renal function, and day 7% change from baseline in total insulin dose are significant determinants of 24-hours UGE response to dapagliflozin treatment.

The covariates were investigated for cross-correlation using Pearson's test, and none showed a significant correlation with a *P*-value <0.05 (Figure S5). While race was also tested as a categorical covariate during the model development process, the predictive power of these models was significantly inferior compared with the final model (%RSE of race parameter >70% and OFV estimated between 660 and 663 compared with an OFV of 641 in the final model), which further consolidates the point that the chosen covariates are responsible for the apparent differences between populations.

According to the final model, patients with higher SMBG levels, better renal function and greater total insulin dose reduction are predicted to have a more pronounced UGE response. Incorporating these characteristics in simulations of the two trials, the model mimics the lack of a clear exposure-response in the Japanese population, while the exposure-response is retained in the non-Japanese population (Figure 4). The observed UGE in the two higher doses of the Japanese population is somewhat underpredicted by the model, possibly because of the presence of an additional factor which further influences E_{max} or $EAUC_{50}$ in the Japanese population. However, taking into consideration a high level of variability in the observed data, we consider the quality of data description to be adequate.

The model structure was selected based on the previous experience of exposure–response modelling of SGLT2 inhibitors in patients with T2DM.[13,18] As 24-hours UGE is a cumulative measurement which reflects the total amount of glucose in the urine accumulated during the day, an integral pharmacokinetic characteristic such as $AUC_{0-24\ h}$ or average concentration was considered more appropriate to use in this analysis than maximum or trough concentration. Log-linear drug effect models were also tested, but the ability of the model to describe experimental data was impaired compared with the sigmoidal maximum effect (E_{max}) model (Figure S4). Initial attempts of base model development included estimation of baseline UGE as a parameter along with E_{max} and $EAUC_{50}$ variables. However, because of the limited number of observations available, this resulted in a substantial increase in %RSE of E_{max} random effect to >300%, even without random effect on baseline UGE. This approach was, therefore, disregarded in favour of implementation of baseline UGE into the model structure as a regressor.

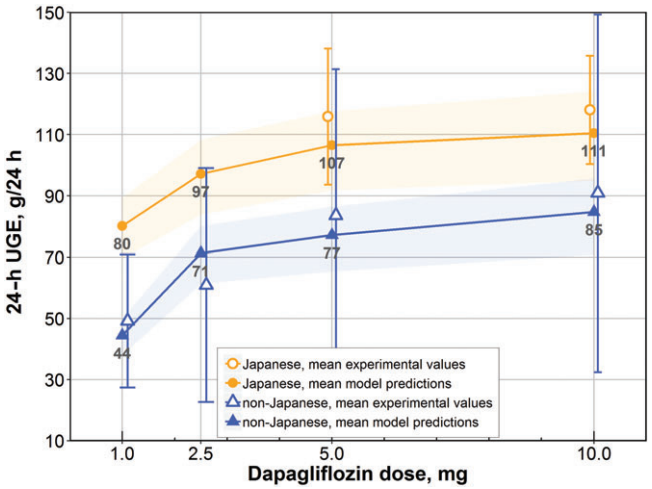

FIGURE 4 Dose-response effect of dapagliflozin on day 7 24-hours urinary glucose excretion (UGE). Shaded areas: simulated interquartile ranges; grey text: simulated 24-hours UGE values for each dosing group in each study; error bars: standard deviation of experimental data

Despite various attempts to improve the shrinkage and %RSE of the E_{max} parameter through the model development process to match the criteria described in the Model development section of Materials and Methods, the best achievable %RSE for ω^2 E_{max} was no less than 90%, with shrinkage between 40% and 50%. This may be explained by the nature of the data; because daily UGE is a cumulative variable measured only once per subject, every subject's UGE measurement could, therefore, be represented by their own E_{max}. To avoid this issue, the data incorporated into the module would have to comprise multiple repeated measurements per single subject. The discrepancy between day 0 and day 7 UGE in the placebo cohort was captured by the residual error, specifically by its additive component, which explains the high value of the corresponding parameter (Table S1). Removing placebo data from the modelling dataset resulted in the proportional residual error model being sufficient for the adequate description of the observed data, but does not lead to any other changes in the final model (Table S2).

While baseline eGFR levels were similar between the studies, % change from baseline in total insulin dose at day 7 was >2 times greater in the Japanese population compared with the non-Japanese population (Table 1). This may have resulted in decreased glucose intake by the tissues and, subsequently, in an overall increase in SMBG and UGE in the Japanese population. This effect was reflected in the model through higher estimated E_{max} in the Japanese versus non-Japanese population. Moreover, in the Japanese population the total insulin dose reduction was similar in the 5 and 10 mg dosing cohort (Figure 1D), resulting in a further increase in SMBG for the 5 mg dosing cohort compared with the respective dosing cohort in the non-Japanese population (Figure 1C). Taken together, higher SMBG levels in Japanese patients resulted in increased sensitivity to dapagliflozin dose, reflected in the model by a lower saturation threshold of $EAUC_{50}$ for the Japanese population, especially in the 5 mg dosing cohort, causing equivalent levels of UGE response in the 5 and 10 mg dosing cohorts.

Our findings complement and align with a similar non-linear mixed-effects analysis comparing the pharmacokinetics and pharmacodynamics of dapagliflozin in patients with T1DM versus T2DM.[18] An exposure-dependent increase in 24-hours UGE was observed with dapagliflozin treatment in both populations. Initially, it appeared that dapagliflozin may be more potent in patients with T1DM; however, after adjusting for baseline FPG, eGFR and 24-hours UGE, the underlying exposure–response relationship of dapagliflozin was similar in T1DM and T2DM.[18] Furthermore, the current analysis showed that, after adjusting for patient characteristics, the exposure–response relationship is the same for Japanese and non-Japanese patients with

T1DM, despite initial differences in UGE response. The significant covariates identified both in our study and the aforementioned analysis[18] correspond to the pharmacology of dapagliflozin action; specifically, 24-hours UGE depends on the amount of glucose filtered by the kidney (the filtered glucose load), which is a product of an individual patient's glucose level (as represented by SMBG and/or FPG) and renal function (eGFR). Taken together, the pharmacological effect of dapagliflozin is clearly dependent upon a patient's overall glycaemic control and renal function.

For a patient starting dapagliflozin treatment, it is plausible that larger insulin dose reductions may coincide with higher glucose levels. It has previously been shown[19] that large insulin dose reductions diminish the glucose-lowering effect provided by dapagliflozin, and erode the potential improvement in glycaemic control sought by the combination therapy. In Phase 3 studies of dapagliflozin in T1DM,[9,10] this is reflected in the patient management protocol by limiting the total daily insulin dose reduction to 20%. However, the insulin dose modifications for the studies in our current analysis were at the discretion of the patient and the physician, and were not proscriptively limited. Therefore, it is probable that had a 20% insulin dose reduction limit been stipulated in the Japanese study, then glucose levels would have remained similar to those in the non-Japanese study (i.e. SMBG levels of ~140 mg/dL), and a clear dose and exposure response would also have been observed in the Japanese population.

In summary, glucosuria in patients with T1DM is strongly dependent on glycaemic control and renal function. The apparent differences between glucosuria in Japanese and non-Japanese patients can be explained by differences in baseline characteristics and insulin titration behaviour in the two studies. Importantly, Japanese and non-Japanese patients with T1DM have similar dapagliflozin exposure-response relationships, and therefore no dose adjustment is recommended in Japanese patients with T1DM.

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CONFLICTS OF INTEREST

V.S. and T.Y. are consultants for AstraZeneca. S.U. and W.T. are employees of AstraZeneca. J.P., R.C.P. and D.W.B. are employees and shareholders of AstraZeneca.

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SUPPORTING INFORMATION

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

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