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# Dapagliflozin Pharmacokinetics Is Similar in Adults With Type 1 and Type 2 Diabetes Mellitus

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**Abstract**

Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) and is approved in Japanese patients with type 1 diabetes mellitus (T1DM) with inadequate glycemic control. The objectives of this work were to characterize the dapagliflozin pharmacokinetics (PK) in patients with T1DM, assess the influence of covariates on dapagliflozin PK, and compare dapagliflozin systemic exposure between patients with T1DM and T2DM. Population PK analysis was performed using a nonlinear mixed-effect modeling approach. The analysis included 5793 dapagliflozin plasma concentrations from 1150 adult patients with T1DM (global population), who were on routine insulin therapy, collected from 1 phase 2 (NCT01498185) and 2 phase 3 (DEPICT-1, NCT02268214; DEPICT-2, NCT02460978) studies. Covariate effects were investigated using stepwise covariate modeling. Model-derived area under the concentration-time curve (AUC) in patients with T1DM was compared to AUC in patients with T2DM (using data from historical dapagliflozin studies). The final 2-compartmental model adequately described the dapagliflozin concentrations in patients with T1DM. The estimated apparent clearance was 20.5 L/h. Renal function (measured as estimated glomerular filtration rate), sex, and body weight were identified as covariates, where patients with better renal function, male patients, and heavier patients had lower dapagliflozin systemic exposure. Among the covariates studied, none of the covariates affected dapagliflozin systemic exposure >1.4-fold compared to a reference individual and were therefore deemed to be not clinically relevant. Dapagliflozin systemic exposure was comparable between patients with T1DM and T2DM.

**Keywords**

dapagliflozin, pharmacokinetics, SGLT2 inhibitor, type 1 diabetes, type 2 diabetes

Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) and is currently licensed in many countries worldwide. Dapagliflozin inhibits the sodium-glucose cotransporter 2, which results in reduction of glucose reabsorption from urine. This leads to an increase in urinary excretion of glucose and, consequently, reduction of blood glucose levels.[1] The short-term effects of dapagliflozin (increase in urinary glucose excretion and lowering of plasma glucose) are accompanied by the long-term effects of lowering hemoglobin $A_{1c}$ ($HbA_{1c}$) levels. Because the mode of action of dapagliflozin is independent of insulin, investigations using dapagliflozin for the treatment of patients with type 1 diabetes mellitus (T1DM) and inadequate glycemic control were undertaken in 2 phase 3 studies (DEPICT-1, NCT02268214[2]; DEPICT-2, NCT02460978[3]). Both studies showed a positive benefit of dapagliflozin (5 and 10 mg) on $HbA_{1c}$ as an adjunct therapy to insulin treatment after 26 and 52 weeks of treatment.[2] Consequently, dapagliflozin has been approved for use in T1DM in Japan. No dose adjustments based on different patient characteristics (eg, age or renal function) are required.[4]

The pharmacokinetics (PK) of dapagliflozin has been studied in a wide dose range (0.1-500 mg) in different populations, such as healthy subjects, adults with T2DM, and adolescents with T2DM.[5,6] Single doses of dapagliflozin up to 500 mg and multiple once-daily doses up to 100 mg were, in general, safe and well tolerated in healthy subjects and had a dose-proportional exposure. The peak concentrations of dapagliflozin are usually reached within 2 hours, and

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the terminal half-life is approximately 12.5 hours. There is minimal accumulation observed after multiple dosing (≤1.13-fold).[7] Dapagliflozin is mainly metabolized in the kidneys and liver by UDP glucuronosyltransferase family 1 member A9 to the inactive metabolite, dapagliflozin 3-O-glucuronide.[8] Dapagliflozin does not affect the activity of major drug metabolizing enzymes and transporters (including cytochrome P450 enzymes) and it does not exhibit clinically meaningful interactions with other drugs commonly prescribed to patients with diabetes, including metformin, warfarin, pioglitazone, and sitagliptin.[8] There is no clinically meaningful impact of food on dapagliflozin PK.[8]

A previously established semimechanistic population pharmacokinetic (popPK) model of dapagliflozin included the PK of dapagliflozin 3-O-glucuronide and was, therefore, able to assess the contribution of renal (normal renal function, 40%-55%) and hepatic elimination to the metabolite formation.[9] The analysis also identified creatinine clearance as a covariate on both renal and nonrenal clearance as well as hepatic impairment status on clearance and volume of distribution. In addition, sex was identified as a covariate on dapagliflozin apparent clearance, whereas no impact of race was found.[9] However, none of these covariates were deemed clinically relevant and the simulations from the model indicated that the increase of systemic exposure of dapagliflozin was <2-fold in subjects with mild or moderate renal impairment. The effect of dapagliflozin on $HbA_{1c}$ correlates with the area under the concentration-time curve (AUC),[10] and AUC has, therefore, been selected as the metric of interest for the current analysis.

Diabetes is a disease of inadequate control of blood glucose levels, and type 1 and type 2 subtypes have a different pathophysiology. T1DM is an autoimmune disease, where the body attacks beta cells in the pancreas, which leads to an inability to produce insulin and as a consequence, high glucose levels. In T2DM, high glucose levels are the result of insulin resistance, which may be caused by multiple factors, including obesity and aging.[11] Despite the different pathophysiology of T1DM and T2DM, the PK and efficacy of dapagliflozin are expected to be similar in both types of patients. It is expected that the differences in body weight and renal function (which have an impact on dapagliflozin PK) between patients with T1DM and T2DM may impact their systemic exposure following the same drug doses; however, the underlying PK characteristics are expected to be similar. Indeed, a previous PK analysis by Tang et al[12] indicated that the PK properties of dapagliflozin were similar in patients with T1DM and T2DM. This assessment was, however, based only on the phase 2 data and was conducted using a noncompartmental analysis. The advantage of the present analysis is the inclusion of a much larger T1DM data set, including a global patient population, from multiple countries and with a more diverse distribution of baseline covariates, such as estimated glomerular filtration rate (eGFR), body weight, and race. This was achieved by pooling phase 2 data with data from 2 phase 3 studies. In addition, in the current work, we have applied a model-based approach, which allowed us to achieve a better understanding of dapagliflozin PK in patients with T1DM, including impact of covariates, which could not be assessed with noncompartmental analysis.

## Methods

### Study Design

For the current analysis, studies in patients with T1DM, including PK sampling of dapagliflozin plasma concentrations, were identified and are summarized in Table 1. The clinical studies (NCT01498185[13], NCT02268214,[2] and NCT02460978[3]) were conducted according to the Declaration of Helsinki and Good Clinical Practice and were approved by institutional review boards and independent ethics committees for the participating centers. All patients signed the informed consent before study initiation. The study sites where the clinical studies were performed are provided in the Supplemental Information.

A single phase 2 study (NCT01498185[13]) and 2 phase 3 studies (NCT02268214[2] and NCT02460978[3]) were available for patients with T1DM. In the phase 2 study, patients were treated with either placebo or dapagliflozin (once-daily doses of 1, 2.5, 5, or 10 mg) for 2 weeks, in addition to background insulin therapy. In the phase 3 studies, patients received either placebo or dapagliflozin (once-daily doses of 5 or 10 mg) for 24 weeks, in addition to background insulin therapy. During the studies, patients were advised to adjust their insulin dosing as needed to avoid hypoglycemia. All available PK samples were included in the analysis, given that the dosing records were available and correct and the measurement was above the lower limit of quantification.

Overall, 5793 dapagliflozin plasma concentrations (91%) of the available samples from 1150 patients with T1DM met the inclusion criteria and were used for the current analysis. A complete list of exclusions is available in the Supplemental Information.

### Population Pharmacokinetic Model

*Model Development.* The structural model (2-compartmental model with first-order absorption and lag time) from a previous popPK model established in patients with T2DM and healthy subjects was used as the basis for the current model (see Supplemental

**Table 1.** Summary of Studies Included in the Analysis for Patients With Type 1 Diabetes Mellitus

| Study Number | Study Description | Doses (mg) | Number of Patients | PK Sampling Times | Samples/Patient Median (Range) |
|---|---|---|---|---|---|
| NCT01498185 (MB102072) | Randomized, double-blind, placebo-controlled, parallel-group, exploratory phase 2a | 1, 2.5, 5, and 10 | 54 | Day 7 (before dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h after dosing) | 10 (9-10) |
| NCT02268214, DEPICT-1 (MB102229) | Randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 | 5 and 10 | 566 | Day 1 (60, 90, and 180 min after dosing) and weeks 12, 18, and 24 | 6 (1-6) |
| NCT02460978, DEPICT-2 (MB102230) | Randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 | 5 and 10 | 530 | Day 1 (60, 90, and 180 min after dosing) and weeks 12, 18, and 24 | 6 (1-7) |

PK, pharmacokinetics.

Information).[14] In this model, a combined error model was applied to account for residual variability. Between-subject variability was estimated on the first-order absorption rate constant and apparent clearance (CL/F). No covariates from the original popPK model were included in the development of the base model. Once the base model was successfully developed, the impact of covariates was assessed using a stepwise covariate modeling procedure. The base model parameters were initially estimated using only data from the phase 2a study (NCT01498185) before the phase 3 data were added (NCT02268214 and NCT02460978). The absorption model was reassessed, whereas no further disposition models were evaluated.

*Covariate Assessment.* Prespecified covariates were selected based on physiological plausibility, prior knowledge, and correlation between covariates. Covariates assessed for CL/F included age, sex, race, body weight, and eGFR. Covariates assessed for central volume of distribution (Vc/F) included age, sex, race, and body weight. The Modification of Diet in Renal Disease equation was used for calculating eGFR.[15] Covariates were identified using a stepwise covariate modeling procedure implemented in Perl-speaks-NONMEM (psn.sourceforge.net)[16] to derive statistically significant covariate effects. Stepwise testing of linear and power relationships was performed using forward inclusion (difference in objective function value [ΔOFV] of 6.63, $P < .01$ for 1 degree of freedom [DF]) and backward exclusion (ΔOFV of 10.8, $P < .001$ for 1 DF) procedures.

In addition, the full covariate approach was applied to allow for assessing the impact on CL/F for all statistically significant and nonsignificant covariates in a forest plot. In this approach, all covariates with correlation coefficient ≤0.4 were added as covariates on CL/F. Because the body mass index highly correlated with body weight ($r^2$, 0.84) and age correlated with eGFR ($r^2$, −0.5), these covariates (body mass index and age) were not included. Hence, sex, race, body weight, and eGFR were added as covariates on CL/F.

The impact of these covariates on dapagliflozin systemic exposure (i.e., AUC) was illustrated in forest plots. For this purpose, predicted dapagliflozin AUC for the reference patient (White man with median covariates) was compared with predicted AUC for patients with different sets of covariates (5th or 95th percentile of baseline body weight, 5th or 95th percentile of baseline eGFR, 5th or 95th percentile of baseline age, female sex, different race, etc). Dapagliflozin CL/F was sampled 1000 times using typical value of CL/F and the covariance matrix and was used to derive AUC according to Equation 1. The 90% confidence interval for dapagliflozin AUC was generated from the 5th and 95th percentiles.

$$AUC = \frac{Dose}{CL/F} \quad (1)$$

*Model Selection and Evaluation.* Model selection was based on the inspection of goodness-of-fit plots and changes in the OFV. The ΔOFV between nested models is approximately $\chi^2$ distributed and a difference of −6.635 corresponds to a $P$ value of <.01 for 1 DF. Models were also judged by the plausibility of parameter estimates and parameter precision (fixed effects >30% relative standard error [RSE], random effects >50% RSE[17]).

The simulation-based visual predictive check (VPC) method was used to assess the adequacy of the model. The model was used to simulate 1000 replicates of the analysis data set stratified on study. The 5th, 50th, and 95th percentiles of the simulated and observed data were derived and used for graphical comparison. Prediction-corrected VPCs were used to assess the performance of all doses simultaneously.[18]

*Dapagliflozin Systemic Exposure in Different Subpopulations.* To assess individual model-predicted systemic exposure in different subpopulations, box plots of different subpopulations based on age, sex, race, body weight, and eGFR were explored. In addition, dapagliflozin systemic exposure from the previous T2DM submission was extracted and used for comparison. Information regarding the T2DM submission, including studies used and the popPK model, can be found in the Supplemental Information.

*Software.* The popPK model was established in NONMEM 7.3 (Icon Development Solutions, Ellicott City, Maryland[19]) using Perl-speaks-NONMEM 4.4.8.

## Results

### Patient Population and Exploratory Data Analysis

In total, data from 1150 patients with T1DM were used for model development. As seen in Table S1 and Figure S1, the median age and body weight were slightly higher in the phase 3 studies compared with the phase 2a study. Renal function (measured as eGFR calculated using the Modification of Diet in Renal Disease equation) was comparable in all 3 studies. Most patients in the studies were White (87.7%), followed by Asians (9.0%), whereas the distribution of female and male patients was similar (53.7% and 46.3%, respectively) (Figure S2).

Dapagliflozin plasma concentration–time profiles showed a biphasic decline and were similar across all 3 studies (Figure S3).

### Population Pharmacokinetic Model

The final model was a 2-compartmental model with first-order absorption and first-order elimination. The dapagliflozin first-order absorption rate constant was fixed to the estimate from the previous popPK model (3.0/h; Table S2) due to limited data in the absorption phase. The lag time used in the previous popPK model was removed since it was not supported by the data. The estimated dapagliflozin CL/F was 20.9 L/h, and Vc/F was 87 L. The estimated between-subject variability was low for dapagliflozin Vc/F (16.6%) and intermediate for CL/F (34.1%) and apparent intercompartmental clearance (Q/F, 35.4%). Shrinkage was rather large for dapagliflozin Vc/F and Q/F (≈60%). For residual variability, separate proportional errors were included for the phase 2a (32.3%) and phase 3 studies (37.3%). As seen in Table S2, all dapagliflozin PK parameters were estimated with accurate precision (RSE < 30%).

After the stepwise covariate analysis, eGFR (higher dapagliflozin CL/F with higher eGFR), body weight (higher CL/F with higher body weight), and sex (higher CL/F for male patients) were added as covariates on dapagliflozin CL/F. In addition, body weight (higher dapagliflozin Vc/F with higher body weight), sex (higher Vc/F for male patients), and age (lower Vc/F for higher age) were added for Vc/F. Adding covariates resulted in a decrease in interindividual variability of CL/F (decrease from 36.5 to 34.1), Vc/F (decrease from 24.5 to 16.6), and Q/F (decrease from 38.8 to 35.4). The equations, including the respective covariate relationships for dapagliflozin CL/F and Vc/F, are shown in Equations 2 and 3, respectively.

$$CL/F = CL_{REF}/F \cdot (BWT/BWT_{REF})^{BWT \sim \frac{CL}{F}} \cdot (eGFR/eGFR_{REF})^{eGFR \sim \frac{CL}{F}} \cdot (1 + SEX \sim CL/F) \quad (2)$$

$$Vc/F = Vc_{REF}/F \cdot \left(1 + BWT \sim \frac{Vc}{F}\right) \cdot (BWT - BWT_{REF}) \cdot (AGE/AGE_{REF})^{AGE \sim \frac{Vc}{F}} \cdot (1 + SEX \sim Vc/F) \quad (3)$$

As seen in the prediction-corrected VPCs stratified by study (Figure 1), as well as in the goodness-of-fit plots (Figure S4), no unacceptable trends in the diagnostic plots were observed, indicating that the final popPK model accurately describes the data.

### Inference From popPK Model

The estimates of the full covariate model (Table S4) were very similar to the estimates of the final popPK model. The forest plot (Figure 2) indicated that no individual covariate at either high or low values resulted in changes in systemic exposure of >25% relative to a reference individual (White male patient with median covariates). None of the covariates were, therefore, considered to be clinically relevant.

### Comparing Exposure in Different Subpopulations

Model-predicted dapagliflozin AUC normalized to 10 mg stratified by sex, race, age group, renal function, and body weight is presented in Figure 3. Overall, slightly higher model-predicted dapagliflozin median AUC normalized to 10 mg was observed in female patients compared with male patients (1.2-fold higher), in patients aged >60 years compared with patients aged 40-60 years (1.2-fold), in patients with eGFR <60 mL/min/1.73 $m^2$ compared with those with eGFR >90 mL/min/1.73 $m^2$ (1.4-fold), and in patients

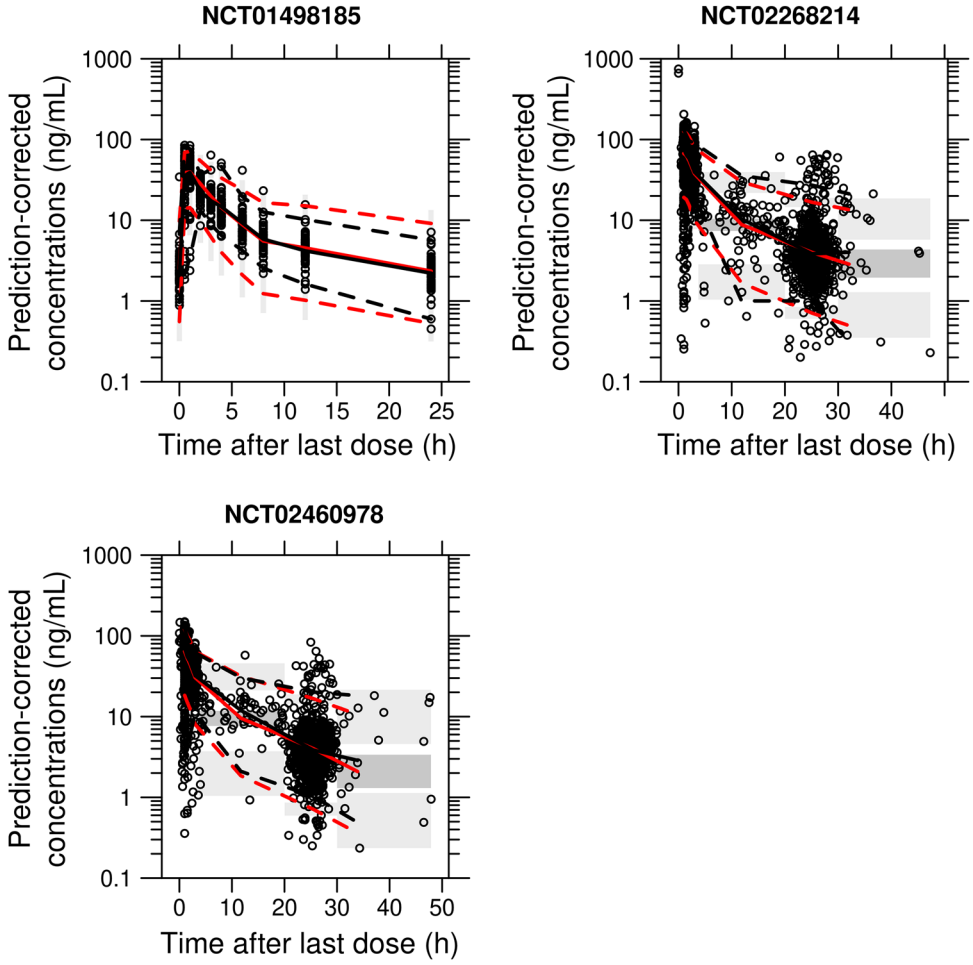


**Figure 1.** Prediction-corrected visual predictive check stratified by study. Lines: 10th, 50th, and 90th percentiles of observed data. Shaded areas: 95% confidence interval around 10th, 50th, and 90th percentiles of simulated data (n = 1000). Circles: Observations. For steady-state observations, time after last once-daily dose is plotted.

with body weight <70 kg compared with those with body weight 70-100 kg (1.2-fold). However, these differences were not deemed clinically relevant since dapagliflozin is well tolerated at much higher exposures (it is safe and well tolerated following single doses up to 500 mg and multiple once-daily doses up to 100 mg). In addition, the distributions (as shown by the box plots in Figure 3) were largely overlapping, indicating no difference between the groups. No difference in dapagliflozin systemic exposure was observed between racial groups.

### Comparison of Systemic Exposure Between Patients With T1DM and T2DM

The observed predose concentration data following administration of the 5-mg and 10-mg dapagliflozin doses in patients with T1DM and T2DM were similar, as shown in Figure S5. Also, as seen in Figure 4, the distributions of the model-predicted dapagliflozin AUC normalized to 10 mg for T1DM and T2DM were largely overlapping. Model-predicted median dapagliflozin AUC normalized to 10 mg was similar in adult patients with T1DM (526 ng • h/mL) compared with adult patients with T2DM (464 ng • h/mL), corresponding to a 1.1-fold higher dapagliflozin systemic exposure in T1DM compared with T2DM.

## Discussion

The aim of the current analysis was to characterize the PK of dapagliflozin in adults with T1DM using data from 1 phase 2a study (NCT01498185) and 2 phase 3 studies (NCT02268214 and NCT02460978). In addition, the analysis sought to identify covariates with a significant impact on PK parameters and compare dapagliflozin systemic exposure between patients with T1DM and T2DM (extracted from a previous analysis).

The established 2-compartmental disposition model with first-order absorption and elimination adequately

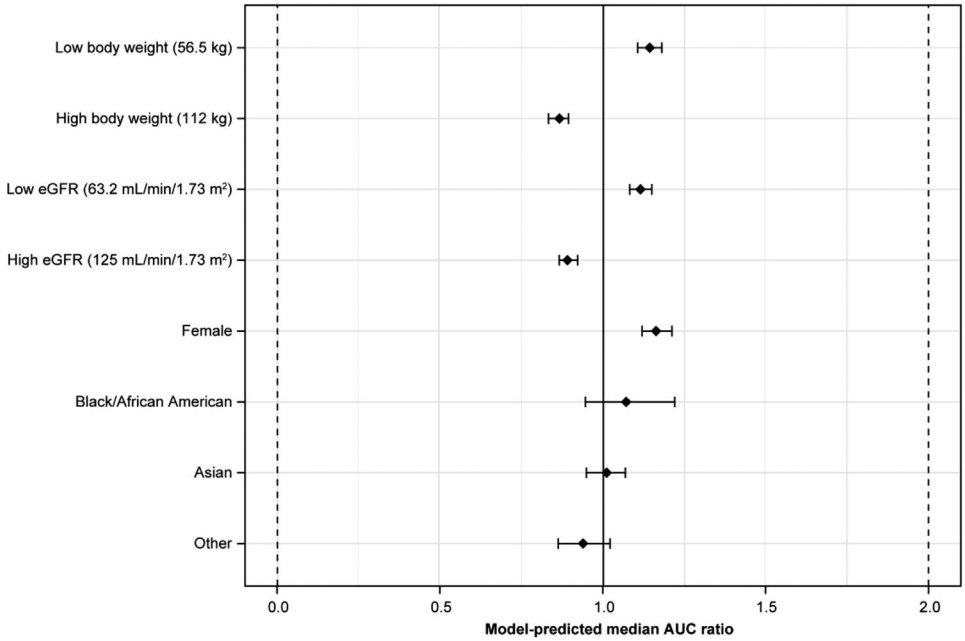


**Figure 2.** Forest plot showing covariate effect of the full dapagliflozin covariate model for model-predicted AUC. The solid vertical line corresponds to the reference individual: White male with body weight of 78.7 kg and eGFR of 88.6 mL/min/1.73 $m^2$. The symbols represent the median model-predicted AUC ratio, and the whiskers represent the 95% confidence interval. "Other" race corresponds to Other, Native Hawaiian/Other Pacific Islander. AUC, area under the concentration-time curve; eGFR, estimated glomerular filtration rate.

described the dapagliflozin plasma concentrations in patients with T1DM. Model diagnostics indicated a good description of the data, and PK parameters were estimated with high precision.

The current analysis showed that body weight, sex, and eGFR had an impact on dapagliflozin systemic exposure. Higher body weight and eGFR were associated with higher clearance and, therefore, lower dapagliflozin systemic exposure. In addition, male patients had lower dapagliflozin systemic exposure compared with female patients. Renal function (creatinine clearance) and sex were previously identified as covariates for dapagliflozin CL/F in patients with T2DM (Supplemental Information). The current analysis is, therefore, consistent with the previous observations and supports the impact of renal function and sex on dapagliflozin systemic exposure, regardless of the underlying disease. Although eGFR and sex were identified as statistically significant covariates, no clinically relevant changes were identified between male and female patients and for the observed eGFR range in the current studies. Therefore, adjustment of the dapagliflozin dose based on sex and eGFR (in the studied eGFR range) was considered unnecessary. It should be highlighted that dapagliflozin was well tolerated following single doses up to 500 mg and multiple once-daily doses up to 100 mg, where exposures were much higher compared to those achieved in the studies included in the current analysis (where the highest dose was 10 mg). In addition, dapagliflozin has a low drug-drug interaction risk; therefore, the exposures observed and expected in patients with T1DM are anticipated to be safe (summary of dapagliflozin characteristics can be found in the European Medicines Agency summary).[20]

For dapagliflozin Vc/F, covariates included body weight (higher Vc/F with increasing body weight), sex (higher Vc/F for male patients), and age (lower Vc/F with increasing age). Body weight was identified for dapagliflozin Vc/F in the previous analysis, whereas sex and age were not identified. Vc/F does not affect AUC but will have an impact on maximum concentration of dapagliflozin. Because the therapeutic effect of dapagliflozin is mainly driven by AUC, our assessment focused on AUC rather than on maximum concentration.

The model-predicted systemic AUC was compared between different subgroups to support the lack of clinically relevant covariates in the current analysis. The comparison indicated no clinically relevant impact of sex, age group, race, or renal function on dapagliflozin AUC (Figure 3). For these reasons, the results from the popPK analysis suggest that no dose adjustments are needed in patients with T1DM.

The study by Tang et al,[12] which included data from the same phase 2 study as in the current article, showed similar exposure in patients with T1DM and T2DM. This finding was confirmed by the similar

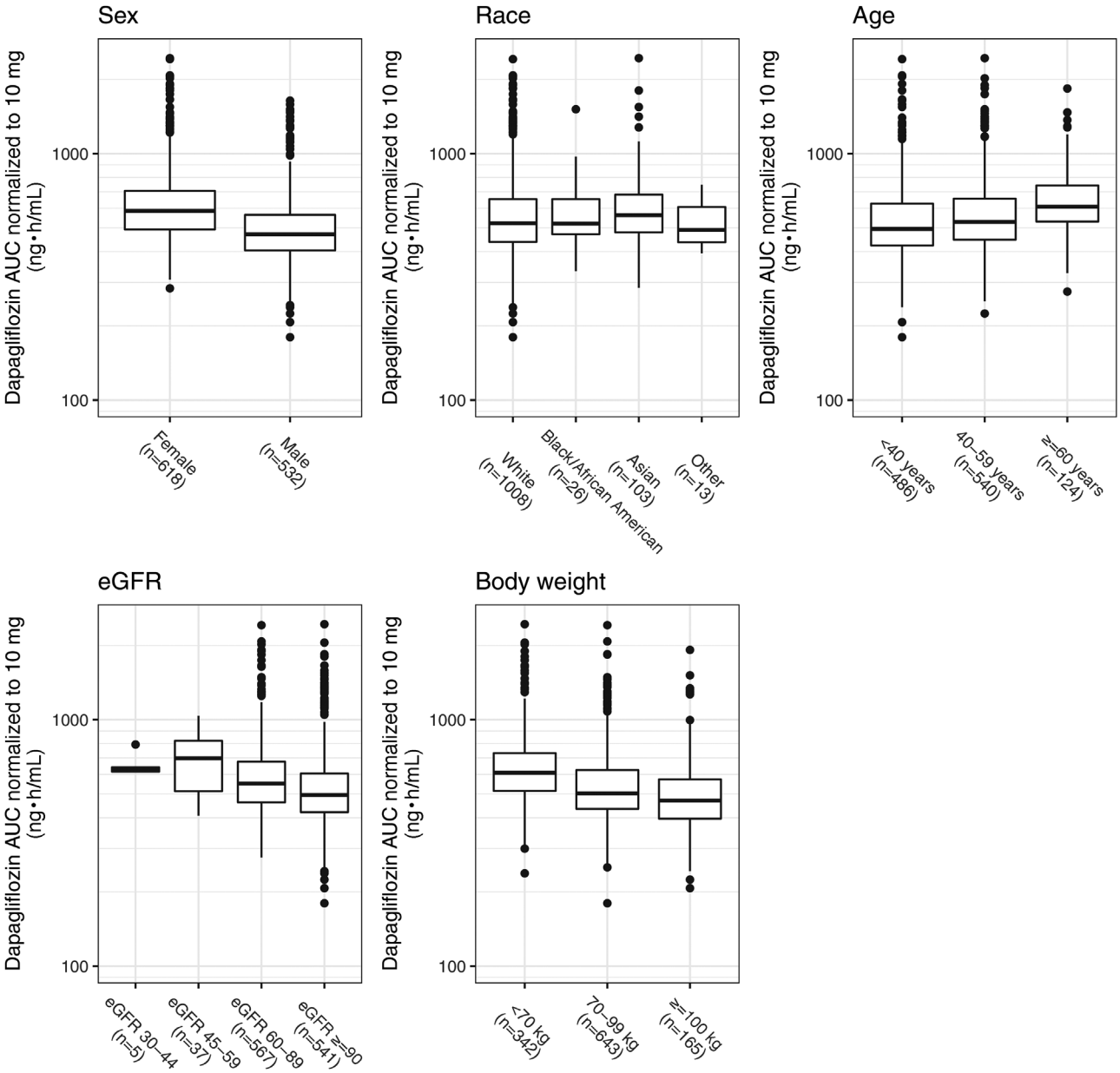


**Figure 3.** Dose-normalized dapagliflozin AUC in T1DM stratified on different covariates. "Other" race corresponds to Other, Native Hawaiian/Other Pacific Islander. Vertical line corresponds to median, boxes represent the interquartile range, whiskers correspond to minimum and maximum (lowest and highest data point excluding outliers, respectively), and datapoints correspond to outliers. AUC, area under the concentration-time curve; eGFR, estimated glomerular filtration rate; T1DM, type 1 diabetes mellitus.

model-predicted AUC in the current analysis, which in addition considered phase 3 data from 1096 patients with T1DM. In addition, the dapagliflozin CL/F in patients with T1DM (20.5 L/h) was similar to a previous estimate in patients with T2DM and healthy subjects (22.9 L/h), further confirming the previous findings. The dapagliflozin CL/F is also in the same range as the previous estimate of 19.5 L/h in adults and adolescents with T1DM.[21] Therefore, this popPK model adequately described dapagliflozin PK in patients with T1DM, exhibiting comparable dapagliflozin systemic exposure between patients with T1DM and T2DM with no PK-attributed reason to adjust dapagliflozin doses in patients with T1DM.

## Conclusions

In conclusion, the PK of dapagliflozin in patients with T1DM was adequately described by the popPK model, and no clinically relevant covariates were identified. Moreover, the identified covariates in patients with T1DM were similar to the covariates identified in

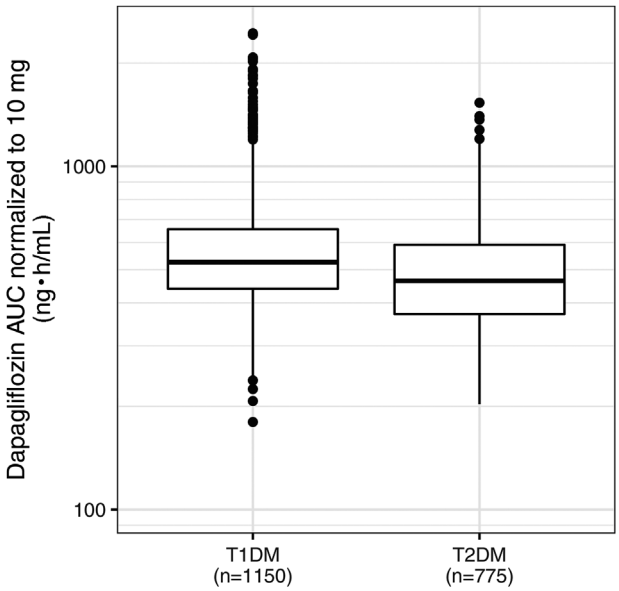


**Figure 4.** Dose-normalized dapagliflozin AUC in patients with T1DM vs patients with T2DM. Vertical line corresponds to median, boxes represent the interquartile range, whiskers correspond to minimum and maximum (lowest and highest data point excluding outliers, respectively), and datapoints correspond to outliers. AUC, area under the concentration-time curve; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

patients with T2DM. Dapagliflozin systemic exposure in patients with T1DM following administration of 5 and 10 mg of dapagliflozin was found to be comparable to the exposure in patients with T2DM receiving the same doses. This finding confirms that the PK properties of dapagliflozin are similar for both patient populations and suggests that there is no PK-attributed reason to adjust dapagliflozin doses in patients with T1DM.

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## Conflicts of Interest

All authors are employees of AstraZeneca and own AstraZeneca stock.

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## Author Contributions

J.M. and J.P. contributed to study design, data analysis, and manuscript preparation. W.T., D.R., B.H., R.C.P., and D.W.B. contributed to study design, data review, and manuscript preparation.

## Data Sharing Statement

The authors confirm that the clinical data supporting the modeling are listed on ClinicalTrials.gov and the details of these clinical studies have been published elsewhere.

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## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.