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ORIGINAL ARTICLE

Model-based characterization of the relationship between dapagliflozin systemic exposure and HbA1c response in patients with type 1 diabetes mellitus

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Aims: To quantitatively describe the relationship between dapagliflozin systemic exposure and HbA1c response among patients with type 1 diabetes mellitus (T1DM) and assess the potential impact of covariate effects.

Materials and Methods: Individual longitudinal HbA1c data from two phase 3 studies in patients with T1DM (24-week treatment with once-daily dapagliflozin 5 or 10 mg or placebo, with adjustable insulin) were analyzed using a non-linear mixed effect modeling approach. Area under the concentration curve was used to measure dapagliflozin systemic exposure. Baseline HbA1c, estimated glomerular filtration rate, reduction in total insulin dose, baseline glucose concentrations, age, sex, race (Asian vs. non-Asian), and insulin administration method (multiple daily injections vs. insulin pump) were assessed as covariates.

Results: A maximum effect (E_{max}) model identified a positive exposure–response relationship. Model-predicted placebo-corrected HbA1c reductions after 24 weeks for dapagliflozin 5- and 10-mg doses were − 0.42% [95% confidence interval (CI) −0.47 to −0.36) and − 0.45% (95% CI −0.50 to −0.40), respectively; baseline HbA1c was ~8.4%. This was in good agreement with actual observations from both studies. Baseline HbA1c was a significant covariate: patients with higher baseline HbA1c were predicted to have greater HbA1c reductions.

Conclusions: The relationship between dapagliflozin systemic exposure and HbA1c response was successfully described in patients with T1DM. None of the tested covariates affected the efficacy of dapagliflozin to a clinically relevant extent. Therefore, no dose adjustment of dapagliflozin is required in patients with T1DM based on the tested covariates. ClinicalTrials.gov, NCT02268214; NCT02460978.

KEYWORDS

dapagliflozin, dose–response, exposure–response, type 1 diabetes mellitus

1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is characterized by autoimmune destruction of pancreatic β cells, resulting in an impaired ability to produce endogenous insulin.[1] The primary treatment for T1DM remains insulin replacement therapy, usually given as multiple daily injections or as a continuous subcutaneous insulin infusion (insulin pump). Despite proven effects in attaining glycaemic control, insulin therapy has several limitations, including the risk of hypoglycaemia and body weight gain.[2] These limitations often lead to non-adherence regarding the actual insulin dose taken by the patient and, consequently, to poor glycaemic control, which is associated with an increased risk of

microvascular and macrovascular complications and increased mortality.[3–5] According to recent statistics, only 30% of adults with T1DM achieve the HbA1c goal of 7% recommended by the American Diabetes Association.[1] These findings clearly emphasize the need for new treatments—adjuncts to existing insulin therapy for patients with T1DM that will help maintain glycaemic control and potentially reduce unwanted side effects of insulin.[6,7]

Currently, the only adjunct to insulin therapy approved by the US Food and Drug Administration for T1DM is the amylin analogue pramlintide.[8] Other glucose-lowering agents tested in patients with T1DM include glucagon-like peptide-1 receptor agonists,[9] dipeptidyl peptidase-4 inhibitors,[10] and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[11–13] SGLT2 inhibitors, such as dapagliflozin, are an attractive adjunct to insulin treatment for patients with T1DM as they improve glycaemic control independently from insulin by lowering the renal threshold for glucose and increasing urinary glucose excretion. In addition to lowering glucose levels, SGLT2 inhibitors have been shown to have further benefits, including body weight loss, blood pressure reduction, and cardiovascular and renal benefits in patients with type 2 diabetes mellitus (T2DM).[14–17] Dapagliflozin, approved for treatment of T2DM, may also be effective in patients with T1DM. In a short pilot study among patients with T1DM, treatment with dapagliflozin resulted in dose-dependent urinary glucose excretion.[12] Dapagliflozin was also shown to improve glycaemic control during 24 weeks of treatment by significantly reducing HbA1c levels in two phase 3 studies [Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes (DEPICT-1 and DEPICT-2)].[11,18]

While the relationship between dapagliflozin systemic exposure and urinary glucose excretion was well characterized during a previous quantitative assessment,[19] the exposure–HbA1c response of dapagliflozin in patients with T1DM has not yet been described. This analysis used HbA1c data collected during two phase 3 studies of dapagliflozin to quantitatively assess this exposure–response relationship and to explore whether certain covariates have an impact on HbA1c response among patients with T1DM. Such quantitative understanding obtained by describing exposure–response properties of a drug is valuable because it increases knowledge about drug effects in specific patient populations and can be used to inform decisions such as selecting the most appropriate dosing regimen. The main purpose and value of the covariate assessment is to identify potential patients that can benefit most from the treatment.[20]

2 | MATERIALS AND METHODS

2.1 | Data

Data were pooled from two randomized, double-blind phase 3 studies of dapagliflozin in patients with T1DM [DEPICT-1 (ClinicalTrials.gov identifier: NCT02268214) and DEPICT-2 (NCT02460978)] who received dapagliflozin 5 or 10 mg or placebo over 24 weeks (Table S1). All patients were treated with their existing insulin therapy in addition to the study medication. It was recommended that patients reduce their daily insulin dose up to 20% for both basal and bolus insulin the day before or during the first day of treatment with the study medication. Following a recommendation to reduce insulin dose at randomization and subsequently to attempt up-titration, patients were instructed to adjust their insulin doses based on blood glucose measurements, according to their usual practice. Total insulin dose reductions were recorded for each patient and were explored as a covariate in this analysis. Each study was conducted in accordance with the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonisation and the Declaration of Helsinki. All patients provided written informed consent before study participation.

The primary efficacy endpoint for both studies was the change from baseline in HbA1c at week 24. HbA1c data were collected at predose (baseline HbA1c) and week 4, 8, 12, 18, and 24 study visits. HbA1c measurements collected at the protocol-scheduled visits with complete dosing and sampling history for each patient were used in this longitudinal mixed-effects analysis. Steady-state area under the dapagliflozin plasma concentration curve (AUC) was used as an input in the exposure–response model and was estimated during population pharmacokinetic analysis.[21] Dapagliflozin steady-state exposure is constant over time, therefore model-predicted steady-state AUC is an appropriate measure of a patient's systemic exposure at each visit. Details of the population pharmacokinetic model used to derive steady-state AUC for this analysis can be found in the Supporting Information for this article.

2.2 | Model development

A non-linear mixed effect modeling approach was used. In this approach, a mixed-effects model for repeated measures with an exposure–response E_{max} component was used to describe the longitudinal HbA1c data in patients with T1DM. In this model, the HbA1c response at a given visit (k) was dependent on HbA1c at baseline, the placebo effect at the given visit, and the drug effect at the given visit, described by the following equation:

$$HbA1c_k = BL + Placebo_k - Eff_k$$

where BL corresponds to HbA1c at baseline and $Placebo_k$ and Eff_k correspond to the placebo effect and the drug effect at visit k, respectively. The placebo effect was described separately for each study. The drug effect at visit k was described using a maximum effect (E_{max}) function:

$$Eff_k = \frac{E_{\max,k} \times AUC}{EAUC_{50} + AUC}$$

where $E_{max,k}$ is the maximum HbA1c effect at visit k and $EAUC_{50}$ is the exposure (AUC) at which one half of E_{max} is achieved.

The final outputs from the model were a set of five $E_{max,k}$ variables, which correspond to the maximum drug effect at weeks 4, 8, 12, 18, and 24, a set of 10 $Placebo_k$ variables, which correspond to the placebo effect for each study at each visit, and one $EAUC_{50}$ variable.

Between-patient variability for exposure–response variables was evaluated using the log-normal distribution (normal distribution with a mean of 0 and a variance equal to $\omega 2$).[22] Residual variability was modelled using an additive error model.

2.3 | Model selection and validation

Discrimination between models was primarily based on the inspection of graphical diagnostics and changes in the objective function value (OFV) provided by NONMEM (GloboMax, Hanover, Maryland). The adequacy of the models was evaluated using graphical analysis of goodness-of-fit plots and visual predictive checks.[23]

2.4 | Covariate analysis

The covariates assessed in the analysis were selected based on prior knowledge of the mechanism of action of dapagliflozin, previous exposure–response models developed for dapagliflozin in patients with T2DM, and exposure–response models developed for urinary glucose excretion in patients with T1DM. The following covariates were assessed during the modeling analysis: baseline HbA1c, estimated glomerular filtration rate, reduction in total insulin dose at week 24 relative to baseline insulin dose, age, sex, body weight, race (Asian vs. non-Asian), and method of insulin administration (multiple daily injections vs. continuous subcutaneous insulin infusion by insulin pump). All covariates were tested on the dapagliflozin E_{max} and $EAUC_{50}$ variables. None of the patients had missing baseline covariate values.

Baseline average daily glucose levels at weeks 14 and 24 from continuous glucose monitoring (CGM) were explored as a potential covariate. However, they were found to be correlated to baseline CGM values; additionally, these variables were also missing in some patients (11% and 17.5% for CGM at weeks 12 and 24, respectively). For these reasons, CGM was not included in the covariate assessment.

During the covariate analysis, covariates were identified using a stepwise covariate modelling procedure, as implemented within PsN (psn.sourceforge.net). Stepwise testing of linear and power relationships was performed in a forward inclusion (ΔOFV of 6.63; $P < 0.01$ for 1° of freedom) and backward exclusion (ΔOFV of 10.8; $P < 0.001$ for 1° of freedom) procedure. For categorical covariates, ΔOFV at the respective P values may be different depending on the degrees of freedom. Retaining the covariate relationships identified by stepwise covariate modelling was based on the reliability of the variable estimate describing the covariate relationship, and only covariate relationships that exerted a meaningful impact were included in the model.

2.5 | Model predictions

Prediction uncertainty was derived, accounting for model variable uncertainty. In brief, a large set of variable combinations was simulated (n = 10 000) using mean variable values and the covariance matrix. Next, a model prediction (i.e. HbA1c reduction at week 24 predicted for a given AUC value) was derived for each variable combination; this resulted in 10 000 simulated outcomes (HbA1c reduction) that were then used to calculate a median prediction with a 95% confidence interval (CI; calculated as median and 2.5% and 97% quintile of the distribution). Median values of the covariates were used in the simulations. All simulations were performed in R (R-project, www.r-project.org) using the nonmem2R package (https://CRAN.R-project.org/package=nonmem2R).

2.6 | Software

The software package NONMEM version 7.3.0 (GloboMax, Hanover, Maryland) was used in this analysis. Maximum likelihood inference was performed using the conditional first-order approximations (with interaction). PsN version 4.2.0 (psn.sourceforge.net) and R version 3.0 (R-project, www.r-project.org) were used for the exploratory analysis and postprocessing of NONMEM outputs (e.g. to assess goodness-of-fit).

3 | RESULTS

3.1 | Patient characteristics

Data from a total of 1591 patients with T1DM were used in this analysis (DEPICT-1, n = 778; DEPICT-2, n = 813); the number of patients/samples for each arm is shown in Table S2. Baseline characteristics of the patients are presented in Table 1. The median baseline HbA1c across all patients was 8.4% and was similar for both studies (8.4% and 8.3% for DEPICT-1 and DEPICT-2, respectively). There was a wide distribution of age, ranging between 18–75 years, with a median of 43 years. The median body mass index across all patients was 27.3 kg/m^2. Most patients were white and there were slightly more women than men.

3.2 | Pharmacokinetics and pharmacodynamics of dapagliflozin

Dapagliflozin exposure (AUC) and HbA1c response following corresponding doses were similar in both studies. Mean steady-state AUC

TABLE 1 Summary of baseline characteristics of patients with T1DM included in the analysis

	Study		
Characteristic	DEPICT-1 (N = 778)	DEPICT-2 (N = 813)	Combined Studies (N = 1591)
Age, years	43 (18–75)	43 (18–75)	43 (18–75)
Sex			
Female	52.1%	56.0%	54.1%
Male	47.9%	44.0%	45.9%
Body weight, kg	80.8 (46.9–184.8)	76.8 (44.6–159.5)	79.1 (44.6–184.8)
Body mass index, kg/m^2	27.8 (18.2–65.8)	26.9 (18.6–56.6)	27.3 (18.2–65.8)
eGFR, mL/min/m^2	89.7 (33.1–176.9)	89.6 (26.1–178.8)	89.6 (26.1–178.8)
HbA1c, %	8.4 (7.5–10.4)	8.3 (7.5–10.9)	8.4 (7.5–10.9)
FPG, mmol/L	9.84 (1.70–30.87)	9.81 (1.33–26.22)	9.81 (1.33–30.87)
Method of insulin administration			
Multiple daily injections	63.2%	66.1%	64.7%
Insulin pump	36.8%	33.9%	35.3%

Abbreviations: eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; T1DM, type 1 diabetes mellitus.
Data are median (range) unless otherwise noted.

TABLE 2 Summary of dapagliflozin pharmacokinetic and pharmacodynamic characteristics

Study	Dose	Steady-state AUC, ng/mL*h	Placebo-corrected change in HbA1c from baseline at week 24, %
DEPICT-1 (NCT02268214)	5 mg	293.0 (279.3–306.6)	−0.42 (−0.56 to −0.28)
	10 mg	593.7 (559.8–627.6)	−0.45 (−0.58 to −0.31)
DEPICT-2 (NCT02460978)	5 mg	297.4 (280.7–314.0)	−0.37 (−0.49 to −0.26)
	10 mg	590.2 (561.5–618.9)	−0.42 (−0.53 to −0.30)

Abbreviation: AUC, area under the dapagliflozin plasma concentration curve.
Data are mean (95% confidence interval).

and placebo-corrected change in HbA1c from baseline at week 24 for dapagliflozin 5- and 10-mg doses are shown for both studies in Table 2. Mean placebo-corrected change in HbA1c from baseline by study week and stratified by dose is presented in Figure 1. In both studies, dapagliflozin treatment resulted in reduced insulin doses in both 5- and 10-mg treatment arms (see Figure S1).

3.3 | Exposure–response model

A positive exposure–response relationship between the systemic exposure of dapagliflozin and HbA1c reduction in T1DM was identified using an E_{max} model. The entire 24-week HbA1c time course for both dapagliflozin treatment arms was well described by the model. This was judged by goodness-of-fit and visual predictive check plots, which are shown in Figures S2–S5. The model-predicted relationship between dapagliflozin exposure and HbA1c response is presented in Figure 2A. To visualize the level of exposure achieved during both phase 3 studies, density distributions of AUCs for dapagliflozin 5- and 10-mg doses were overlaid in the plot. The developed exposure–response model was used to simulate a relationship between the dapagliflozin dose and HbA1c response (Figure 2B). The derived dose–response relationship was in very good agreement with the clinical data collected during both phase 3 studies (Figure 2).

Among all tested covariates, only baseline HbA1c was found to have an impact on HbA1c reductions with dapagliflozin. According to the model, patients with higher HbA1c baseline were predicted to have greater HbA1c reductions compared with those with lower baseline levels. For example, following treatment with 10 mg dapagliflozin, patients with HbA1c baseline of 7%, 8.4% and 9% were predicted to have −0.34, −0.45 and − 0.50% HbA1c reduction at week 24, respectively. The influence of this covariate on dapagliflozin efficacy is illustrated in Figure 3. In the final model, estimated $EAUC_{50}$ was 31.13 ng/mL*h (95% CI 6.35 to 152.68). Estimated E_{max} at week 24 was 0.48 (95% CI 0.41 to 0.6). Random effects were included on baseline HbA1c and E_{max}. The complete list of all variable estimates from the final exposure–response model is shown in Table S4.

The model-predicted HbA1c responses at week 24 for dapagliflozin 5- and 10-mg doses were – 0.42 (95% CI −0.47, −0.36) and – 0.45 (95% CI −0.5, −0.4), respectively, which was in very good agreement with the observed clinical data. This can be seen in Figure 2B, which shows the derived dose–response relationship (simulated using the final exposure–response model) overlaid with the actual data from both phase 3 studies.

4 | DISCUSSION

The phase 3 DEPICT-1 and DEPICT-2 studies showed statistically significant and clinically relevant reductions in HbA1c among patients with T1DM with dapagliflozin compared with placebo following 24 weeks of treatment. This was accompanied by significant reductions in total daily insulin doses.[11,18] This analysis quantitatively

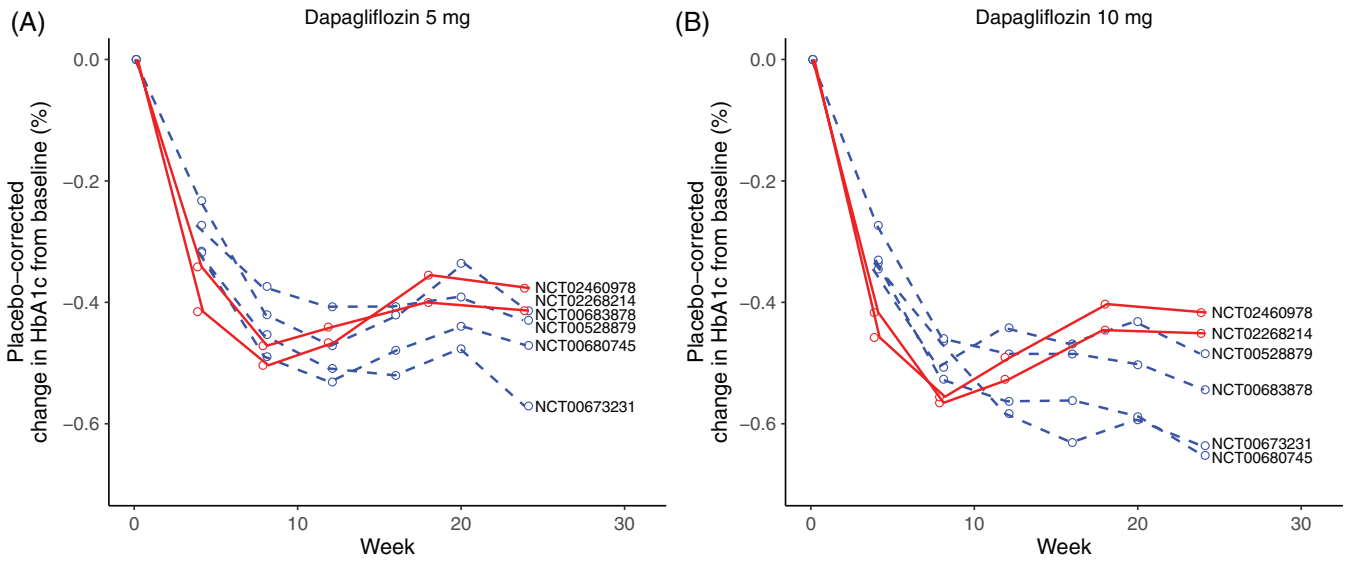

FIGURE 1 Mean placebo-corrected change in HbA1c from baseline over time during treatment with dapagliflozin (A) 5 mg and (B) 10 mg in patients with T1DM or T2DM. The plots show mean last observation carried forward data from the two T1DM studies (NCT02460978 and NCT02268214) and four T2DM studies (NCT00528879, NCT00683878, NCT00680745 and NCT00673231). Details of the T2DM studies, including the type of background medication used and baseline HbA1c for each treatment arm, are presented in Table S3. Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

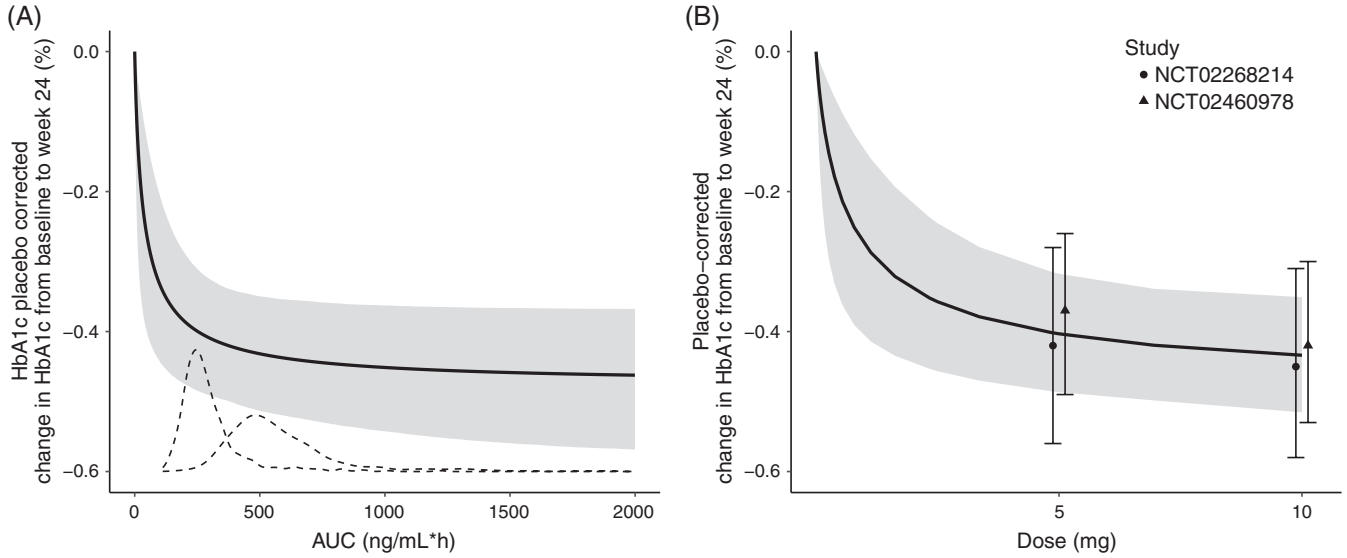

FIGURE 2 (A) Model-predicted exposure–response and (B) derived dose–response relationship for HbA1c reduction with dapagliflozin at week 24. Solid lines and shaded areas correspond to the mean model prediction with 95% CI. The prediction was calculated using baseline HbA1c of 8.4%. Density curves on the exposure–response plot (dashed/dotted lines on the bottom of the plot) correspond to the actual distribution of dapagliflozin exposure (steady-state AUC range used in the analysis) for 5- and 10-mg doses (dashed and dotted lines, respectively), based on individual AUC data from both clinical studies. The actual clinical HbA1c data on the dose–response plot (mean change from baseline, based on a mixed model, with 95% CI) are shown as data points. Abbreviations: AUC, area under the dapagliflozin plasma concentration curve; CI, confidence interval; T1DM, type 1 diabetes mellitus

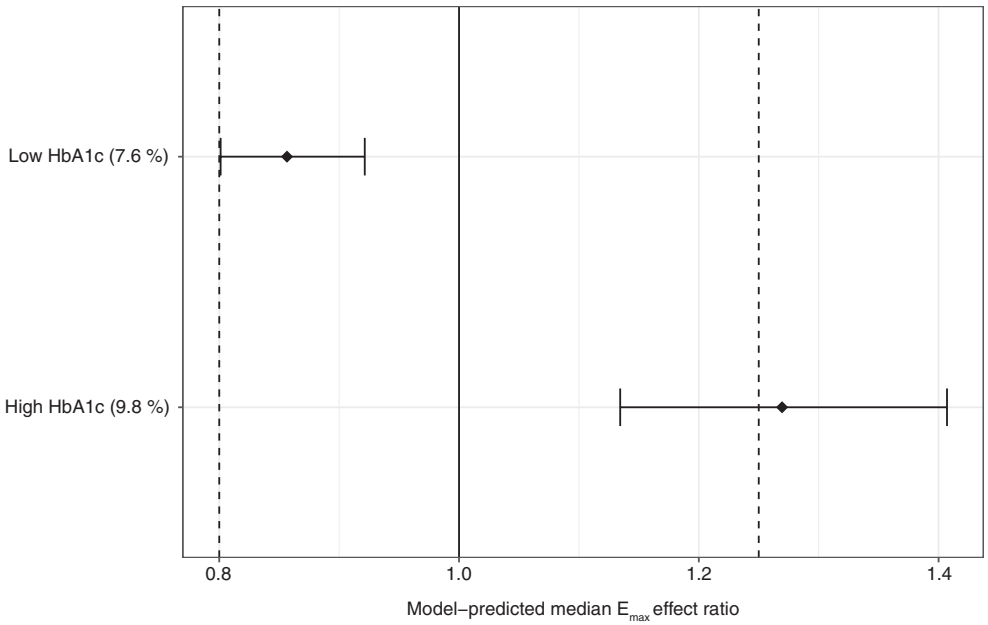

FIGURE 3 Forest plot showing covariate effect on model-predicted dapagliflozin HbA1c efficacy, represented as E_{max} ratio. The solid vertical line corresponds to the reference individual: T1DM patient with baseline HbA1c of 8.4%. E_{max} in patients with lower and higher baseline HbA1c was compared with the reference individual with HbA1c baseline of 8.4%; the symbols represent the median model predicted E_{max} ratio and the whiskers represent the 95% CI

assessed the relationship between dapagliflozin exposure (AUC) and HbA1c response and investigated whether any of the covariates evaluated had a significant impact on HbA1c response in patients with T1DM.

A longitudinal analysis was performed in which the full HbA1c time course, including all data from baseline to week 24, was analyzed. An exposure–response model was successfully developed; although the uncertainty in the $EAUC_{50}$ estimate was high (probably because of limited data available at the low exposures), the model described the data from both phase 3 studies well, as assessed by standard goodness-of-fit and visual predictive check plots. The only covariate that was found to have an impact on HbA1c response with dapagliflozin was baseline HbA1c; patients with higher HbA1c baseline were predicted to have greater HbA1c reductions. This finding is consistent with observed results in the

T1DM clinical studies as well as previous findings in T2DM, where baseline HbA1c has a clear impact on the level of HbA1c reduction by treatment with dapagliflozin and other oral glucose-lowering agents, with greater effects seen among patients with higher baseline HbA1c.[24–27] Interestingly, daily insulin dose reduction was not found to be a significant covariate on dapagliflozin efficacy. This was somewhat surprising because T1DM patients treated with dapagliflozin in both phase 3 studies were observed to have significant reductions in their daily insulin doses[11,18] (Figure S1), which would have an impact on the HbA1c levels. It is anticipated that the overall HbA1c reductions observed in T1DM patients following dapagliflozin or other SGLT2 inhibitor treatment is a combination of a direct effect of the drug (through urinary glucose excretion) and an effect mediated via reduction in insulin dose. The impact of insulin dose reduction on SGLT2 inhibitor efficacy has been previously described in terms of urinary glucose excretion, where T1DM patients who had greater total insulin dose reduction were also observed to have a more pronounced urinary glucose excretion response.[28,29] It is unclear why a similar covariate effect was not identified in the current analysis. One explanation may be that systematic insulin dose reduction data collected in the phase 3 trials were too limited (i.e. not available for every timepoint where HbA1c was measured).

Because it was not possible to "untangle" the combined effect of SGLT2 inhibition and insulin dose reduction on HbA1c levels in the current analysis, it should therefore be highlighted that the developed exposure–response relationship may not reflect the full intrinsic effect of dapagliflozin in T1DM patients. Additional work is needed, for example, using more physiologically based modelling, to fully understand the impact of dapagliflozin on HbA1c efficacy in T1DM patients and the interplay between the drug effect and insulin dose reductions.

This complexity of HbA1c effect in T1DM patients can also have a potential impact when the SGLT2 inhibitor effect is compared between T1DM and T2DM patients. The two major forms of diabetes have rather different management of glycaemia; T1DM patients, who are insulin-dependent, continually adjust doses during the day and from day-to-day, whereas most T2DM patients (even those on insulin) have more stable doses over time. In the case of dapagliflozin, it can be observed that although the HbA1c responses following the same drug doses are comparable between T1DM and T2DM patients, the HbA1c reductions observed among patients with T1DM in both phase 3 studies were within the lower range compared with T2DM patients (Figure 1). For example, the average placebo-corrected HbA1c reduction following 24 weeks of treatment with dapagliflozin 5 mg was −0.40% in a study of patients with T2DM (NCT00683878), with similar baseline HbA1c (8.4%) to that observed in the two T1DM studies described here; this HbA1c reduction was very close to the effect seen in both T1DM studies included in this analysis (−0.37% and − 0.42% in DEPICT-1 and DEPICT-2, respectively). However, for the 10 mg dose, the HbA1c response following 24 weeks of treatment with dapagliflozin was slightly higher in this T2DM study than in the DEPICT-1 and DEPICT-2 studies in patients with T1DM (−0.55% vs. −0.42% and − 0.45%, respectively). The slightly smaller average HbA1c reduction observed among patients with T1DM for 10 mg dapagliflozin can be potentially linked to insulin dose reductions during dapagliflozin treatment, whereas such reductions were not observed in any of the T2DM studies.

Although it was not possible to untangle the combined effect of dapagliflozin and insulin dose reduction on HbA1c response in the current analysis, we believe that there is additional information from T1DM studies that could help us understand this complexity. For example, in both phase 3 T1DM studies, there appears to be a greater difference between dapagliflozin doses with regard to body weight change (that would reflect caloric losses in the urine), than the effect on HbA1c.[11,18] This supports the suggestion that while the 10 mg dapagliflozin dose may have an intrinsically greater effect, its glycaemic efficacy is partly masked by insulin dose changes. A quantitative understanding of the impact of insulin dose changes on HbA1c is yet to be described. Nevertheless, the similarities between patients with T1DM and those with T2DM in terms of HbA1c response to dapagliflozin treatment are clear. Despite their very different clinical situations, patients with T1DM are expected to show comparable benefits from dapagliflozin treatment to those in patients with T2DM.

In conclusion, a positive exposure–response relationship was identified for dapagliflozin, and the developed model successfully described longitudinal HbA1c data among patients with T1DM following 24 weeks of dapagliflozin treatment. According to the model there is a small but consistent difference between 5 mg and 10 mg dapagliflozin doses throughout the treatment duration. Such a relationship provides valuable information that should be taken into account when choosing the "right dose" for T1DM patients. In such a decision, other factors also need to be considered, such as confounding factors of insulin dose reduction on HbA1c efficacy, overall safety and additional benefits of the treatment such as body weight loss and reduction in glucose variability.[11,18] Current results showed that baseline HbA1c was predicted to have an impact on dapagliflozin efficacy; however, the efficacy was not impacted to a clinically relevant extent. Consequently, no dose adjustment of dapagliflozin is required for patients with T1DM in terms of their baseline HbA1c levels. This is an important step in understanding and quantitatively describing the effect of glucose-lowering agents used in patients with T1DM as an adjunct treatment to insulin. Such understanding is crucial when selecting an appropriate treatment regimen for this patient population.

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CONFLICT OF INTEREST

J.P., W.T., M.Å., J.M., E.E., B.H. and D.W.B. are all employees/shareholders of AstraZeneca.

AUTHOR CONTRIBUTIONS

J.P., W.T, M.A and B.H contributed to the study conception and design. All authors contributed equally to the modelling strategy, and were involved in the analysis and interpretation of the data, critically

revised the manuscript for important intellectual content and provided approval of the final manuscript. J.P. performed the modelling analysis and was involved in the writing of the first draft of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

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

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