

ORIGINAL ARTICLE

Low-dose empagliflozin as adjunct-to-insulin therapy in type 1 diabetes: A valid modelling and simulation analysis to confirm efficacy

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Abstract

Aim: To confirm the observed reduction in HbA1c for the 2.5 mg dose in EASE-3 by modelling and simulation analyses.

Materials and methods: Independent of data from EASE-3 that tested 2.5 mg, we simulated the effect of a 2.5 mg dose through patient-level, exposure-response modelling in the EASE-2 clinical study. A primary semi-mechanistic model evaluated efficacy considering clinical insulin dose adjustments made after treatment initiation that potentially limited HbA1c reductions. The model was informed by pharmacokinetic, insulin dose, mean daily glucose and HbA1c data, and was verified by comparing the simulations with the observed HbA1c change in EASE-3. One of two empagliflozin phase 3 trials in type 1 diabetes (EASE-3 but not EASE-2) included a lower 2.5 mg dose. A placebo-corrected HbA1c reduction of 0.28% was demonstrated without the increased risk of diabetic ketoacidosis observed at higher doses (10 mg and 25 mg). Since only one trial included the lower dose, we aimed to confirm the observed reduction in HbA1c for the 2.5 mg dose by modelling and simulation analyses.

Results: The simulated 26-week mean HbA1c change was -0.41% without insulin dose adjustment and -0.29% at 26 weeks with insulin dose adjustment. A simplified (descriptive) model excluding insulin dose and mean daily glucose confirmed the -0.29% HbA1c change that would have been observed had the EASE-2 population received a 2.5 mg dose for 26/52 weeks.

Conclusions: The HbA1c benefit of low-dose empagliflozin directly observed in the EASE-3 trial was confirmed by two modelling and simulation approaches.

KEYWORDS

antidiabetic drug, dose-response relationship, empagliflozin, sodium-glucose co-transporter-2 inhibitor, type 1 diabetes

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1 | INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have been proven to be effective for metabolic control and for the prevention of cardiovascular and renal outcomes in patients with type 2 diabetes,¹⁻³ and have also been extensively tested as adjunct-to-insulin therapy in patients with type 1 diabetes as a promising glucose-lowering strategy. Seven phase 3 randomized clinical trials from three clinical development programmes in patients with type 1 diabetes have been completed with SGLT-2 inhibitors: three with sotagliflozin,⁴⁻⁶ two with dapagliflozin^{7,8} and two with empagliflozin.⁹ Collectively, these trials showed consistent HbA1c lowering (mean 0.3%–0.5%) and improvements in “time in range” on continuous glucose monitoring measures without an increase in hypoglycaemia, as well as body weight and systolic blood pressure reductions.¹⁰ A clear dose-dependent causal relationship with the incidence of diabetic ketoacidosis (DKA), however, has been observed in all programmes. Of seven trials, only one (EASE-3) tested a lower dose than those approved for type 2 diabetes to minimize the risk of DKA and still achieved valuable efficacy data.⁹ EASE-3 included a low-dose empagliflozin 2.5 mg arm together with the 10 and 25 mg orally once-daily arms and showed significant gluco-metabolic benefits with the low dose, although slightly lower in magnitude than those observed with higher doses, without an increased risk of DKA.⁹ Lower doses than used in type 2 diabetes were not studied in the sotagliflozin or dapagliflozin programmes for patients with type 1 diabetes.

Based on indirect pharmacodynamic (PD) comparisons, the low-dose SGLT-2 inhibitor approach is supported by findings from a dose-finding study in which the magnitude of urinary glucose excretion associated with 2.5 mg empagliflozin in patients with type 1 diabetes exceeded that observed at the 10 and 25 mg doses observed in patients with type 2 diabetes.¹¹ Traditionally, two phase 3 trials are required for regulatory approval. However, even though two phase 3 trials of empagliflozin were conducted, only one included the 2.5 mg empagliflozin dose. We therefore sought validated and well-established modelling and simulation techniques to characterize drug exposure and clinical endpoint response relationships in empagliflozin trials that were independent from the phase 3 trial that directly tested the low dose. Although such model-informed drug discovery and development (MID3) should not replace all clinical trials, in this particular situation, where efficacy and safety have been established across a wide, clinically relevant dose range, such an approach is supported by health authorities.^{12,13}

We aimed to determine the 26- and 52-week efficacy of empagliflozin 2.5 mg/day in HbA1c lowering by conducting two exposure-response modelling analyses, which were based on individual patient-level data, each using exposure data from two trials (EASE-1¹¹ and EASE-2⁹).

SGLT-2 inhibitors are known to increase circulating ketone levels. As increased beta-hydroxybutyrate (BHB) levels in the presence of predisposing and precipitating factors such as non-adherence, insulin restriction/omission and disordered eating behaviours may be an indicator of DKA risk,¹⁴ a similar analysis to evaluate the

impact of empagliflozin exposure on changes in BHB levels was conducted.

2 | MATERIALS AND METHODS

2.1 | Population pharmacokinetic modelling to derive individual empagliflozin exposure data

To understand the exposure (concentrations) of empagliflozin from administration until complete elimination from circulation (the PK profile), a population PK analysis was conducted based on a previous model.¹⁵ This analysis was performed on the 1241 patients with type 1 diabetes exposed to empagliflozin (excluding the placebo-assigned participants) in the 28-day EASE-1 phase 2 trial,¹¹ the 26-week EASE-3 phase 3 trial⁹ and the 52-week EASE-2 phase 3 trial.⁹ Modelling was based on 6880 plasma concentration measurements with up to 13 samples per visit per participant for those studied in the 28-day EASE-1 trial and up to three samples per visit per participant in the EASE-2 and EASE-3 trials. The model was evaluated by comparing model-predicted concentration time profiles, maximal concentrations and trough concentrations with the corresponding observed values. Additionally, taking between-patient variability and patient-specific factors including renal function and body weight into account, individual patient-level exposures ($AUC_{\tau,ss}$ [area under the plasma concentration time curve at steady state for a dosing interval]) were derived for later input into the exposure-response analyses.

2.2 | The M-EASE-1 (semi-mechanistic) model: determination of the 26-week exposure-response relationship for low-dose empagliflozin with and without insulin dose adjustment

This model investigated the impact of insulin adjustment on HbA1c lowering. It combined the individual $AUC_{\tau,ss}$ obtained in the population PK analysis with data on absolute values of total daily insulin, mean daily glucose and HbA1c over 4 weeks (EASE-1) and 52 weeks (EASE-2) of treatment.¹⁶ In addition to the population PK model-predicted $AUC_{\tau,ss}$, this model included PD outcome data from 796 participants assigned to placebo or empagliflozin in the EASE-1 and -2 trials. In brief, the longitudinal data included 4824 HbA1c measurements, 189 182 records of total daily insulin, 4243 mean daily glucose records obtained by continuous glucose-monitoring measures, and other patient-specific factors including renal function and insulin delivery (multiple daily injections or insulin pump). Exposure-response was described by maximum effect (E_{max}) models for total daily insulin dose and mean daily glucose. Changes in mean daily glucose drove changes in HbA1c, which were linked by a linear model. We simulated the changes in HbA1c assuming that empagliflozin therapy leads to a decrease in total daily insulin dose as observed in our trials, but we also simulated the changes in HbA1c, assuming the patients made no adjustments in their insulin doses.¹⁶

2.3 | The M-EASE-2 (descriptive) model: determination of the 26- and 52-week exposure-response relationship for low-dose empagliflozin in the EASE-2 population

The aim of this analysis was to simulate the effect of empagliflozin 2.5 mg over 26 and 52 weeks of treatment in the EASE-2 study population and to confirm the observed effect on HbA1c at this dose seen in EASE-3. It followed a descriptive modelling approach predicting longitudinal changes in HbA1c from the individual AUC_{T,ss} derived from the population PK model.¹⁷ To enable predictions for the low dose of empagliflozin, the AUC₅₀ (AUC_{T,ss} resulting in the half-maximal effect of an exposure-response relation) from an exposure-response analysis in patients with type 2 diabetes was used to characterize the exposure-response in patients with type 1 diabetes.^{18,19} This assumption was evaluated by sensitivity analyses and further supported by the comparable exposure-response for urinary glucose excretion in the two patient populations.¹⁵ Mean daily glucose was not included in the model.

2.4 | Clinical verification of modelling and simulation approaches

Both modelling approaches were verified by clinical trial simulations using baseline characteristics and study design from the EASE-3 trial. This trial, which included an empagliflozin 2.5 mg dose arm, was not used during model development and hence served as an independent comparator.^{16,17}

In addition to comparing simulated mean change from baseline in HbA1c after 26 weeks of treatment with the observed mean in EASE-3, predictive checks²⁰ were performed based on the clinical trial simulations. For this purpose, distributions of the simulated median change from baseline in the 500 simulated trials were compared with the observed median change from baseline across all time points and dose groups. The model was deemed adequate if the observed median was contained within the distribution of the simulated medians.

2.5 | Exposure-response study to characterize the change from baseline in BHB levels

EASE-2 and -3 included comprehensive BHB monitoring: all participants received a point-of-care device to measure both blood glucose and BHB.⁹ Participants used an electronic diary to record BHB measurements and symptoms suggestive of DKA. During run-in and the first 4 weeks of treatment, patients were advised to test fasting BHB levels daily to provide baseline information irrespective of symptoms, and thereafter 2–3 times per week or in case of any symptoms, regardless of glucose levels. An Emax exposure-response model evaluated the relationship between empagliflozin, placebo and BHB levels at week 26 relative to baseline. It was developed based on data from EASE-3 and qualified by predicting the BHB changes in the EASE-2

TABLE 1 Summary of the empirically observed and simulated mean change in HbA1c for empagliflozin (Empa) 2.5 mg

	EASE-1		EASE-3		Semi-mechanistic model				Descriptive model			
	4 weeks		26 weeks		Variable insulin 26 weeks		Stable insulin 26 weeks		26 weeks		52 weeks	
	Placebo	Empa 2.5 mg	Placebo	Empa 2.5 mg	Placebo	Empa 2.5 mg	Placebo	Empa 2.5 mg	Placebo	Empa 2.5 mg	Placebo	Empa 2.5 mg
Patients analysed	19	19	238	237	500	500	500	500	239	239	239	239
Change from baseline, adjusted mean ^a	-0.18	-0.53	0.20	-0.09	0.07	-0.22	0.07	-0.34	0.12	-0.17	0.23	-0.05
Adjusted mean vs. placebo ^a		-0.35*		-0.28**		-0.29		-0.41		-0.29		-0.29
95% CI ^b		-0.62, -0.09		-0.42, -0.15		-0.42, -0.10		-0.54, -0.23		-0.38, -0.20		-0.38, -0.20

P* = 0.0096; *P* < 0.0001.

^aMeans for EASE-1 are adjusted for baseline HbA1c; means for EASE-3 are adjusted for baseline HbA1c, estimated glomerular filtration rate and pre-existing insulin therapy. Simulations (*n* = 500) for the semi-mechanistic model were based on 500 patients randomly sampled from the joint EASE-1, EASE-2 and EASE-3 study population. Simulations (*n* = 500) for the descriptive model were based on 239 patients randomly sampled from the EASE-2 population.

^b95% CI for the median displayed for the semi-mechanistic and descriptive models.

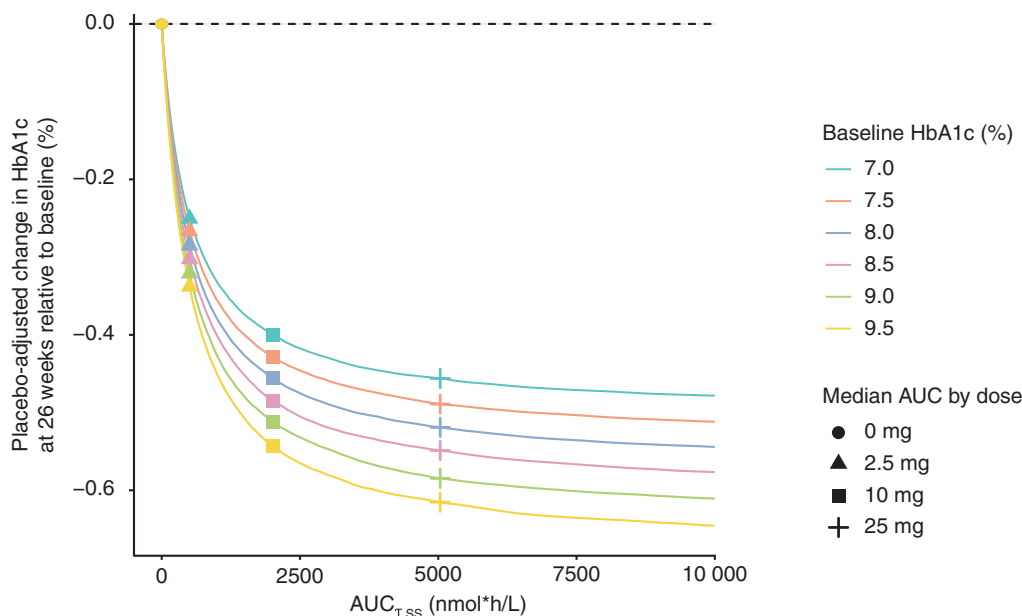


FIGURE 1 Placebo-corrected change in HbA1c at week 26 as a function of empagliflozin exposure at steady state ($AUC_{\tau,ss}$) stratified by baseline HbA1c for a typical patient in the trial population of EASE-2. Simulations were based on the descriptive model. Lines represent simulated median for each respective HbA1c baseline (500 simulations incorporating parameter uncertainty). Symbols denote the simulated median area under the concentration-time curve (AUC) for each dose. Typical subject: male, using multiple dose injections of insulin, estimated glomerular filtration rate = 98 mL/min/1.73 m², baseline patient weight = 82 kg, total daily insulin dose at baseline = 0.660 IU/kg and HbA1c = 8.1%. $AUC_{\tau,ss}$, AUC for a dosing interval at steady state

study population. Simulations were then conducted based on a model including patients from both phase 3 trials ($n = 1518$ patients). The model was verified by predictive checks similar to those detailed in section 2.4 focusing on the change from baseline after 26 weeks of treatment in BHB.

2.6 | Statistical analyses

Assessment of model adequacy and decisions about increasing or decreasing model complexity were driven by the data and guided by goodness-of-fit criteria, including (i) visual inspection of diagnostic scatter plots (eg, observed vs. predicted efficacy endpoints [HbA1c] and residuals vs. linear predictors), (ii) stability of the parameter estimates based on trace plots of the posterior samples, the calculated effective sample size, and the Gelman-Rubin convergence diagnostic (descriptive model only), (iii) plausibility of parameter estimates, and the (iv) precision of parameter estimates. Additionally, the objective function value was used to decide between competing models.

All modelling and simulation analyses were nonlinear mixed-effect analyses using the modelling software NONMEM version 7.3 or greater (ICON Development Solutions, Hanover, MD). Clinical trial simulations based on the M-EASE exposure-response studies were conducted in 239 and 500 patients per dose group in the descriptive and semi-mechanistic models, respectively. For each of the

TABLE 2 External model verification of the simulated change from baseline in HbA1c at week 26 in the EASE-3 study population

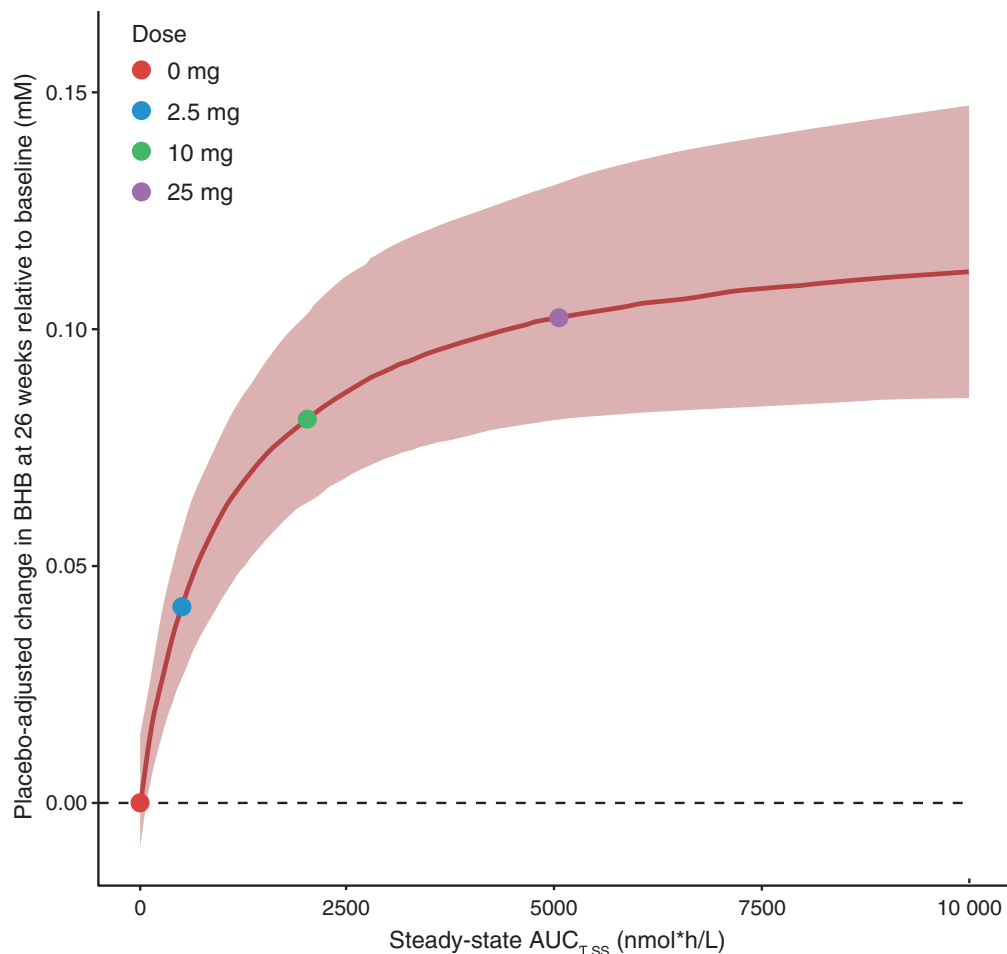
	EASE-3 observed mean \pm SE ^a	Semi-mechanistic model simulated mean \pm SE	Descriptive model simulated mean \pm SE
Empagliflozin 2.5 mg	-0.28 \pm 0.07	-0.27 \pm 0.09	-0.29 \pm 0.05
Empagliflozin 10 mg	-0.45 \pm 0.07	-0.43 \pm 0.07	-0.47 \pm 0.05
Empagliflozin 25 mg	-0.52 \pm 0.07	-0.50 \pm 0.08	-0.53 \pm 0.04

^aAdjusted for baseline HbA1c, estimated glomerular filtration rate and pre-existing insulin therapy.

500 simulated trials, placebo-corrected mean change from baseline and the 95% CI for the mean were calculated.^{16,17}

Patients were sampled, without replacement, for each simulation by sampling from all EASE-2 empagliflozin-treated patients. Additionally, a random sample, without replacement, from the posterior parameter samples estimated by the respective models was used to account for uncertainty in the parameter estimates. Both intersubject and intrasubject (residual error) variability were included. Steady-state exposures for the sampled patients from EASE-2 at a dose of 2.5 mg were generated using the individual specific estimates of the pharmacokinetic variables.

FIGURE 2 Placebo-corrected change from baseline in beta-hydroxybutyrate (BHB) at week 26 as a function of empagliflozin exposure at steady state ($AUC_{\tau,ss}$) for the reference patient. The red line and shaded area represent simulated median and associated 95% CI (500 simulations incorporating parameter uncertainty). Small points denote the simulated median area under the concentration-time curve (AUC) for each dose. Typical subject: male, using multiple dose injections of insulin, estimated glomerular filtration rate = 98 mL/min/1.73 m², baseline patient weight = 81 kg and HbA1c = 8.1%. $AUC_{\tau,ss}$, AUC for a dosing interval at steady state



Investigation of covariates was performed following a full modeling approach. Covariates (Table S1) were selected based on known relations from patients with type 2 diabetes (eg, estimated glomerular filtration rate, weight and sex) and type 1 diabetes specific factors (eg, total daily insulin dose and insulin dose type).

3 | RESULTS

Table 1 summarizes the previously published empiric placebo-adjusted HbA1c projected findings for empagliflozin 2.5 mg from the EASE-1 and EASE-3 studies at 28 days and 26 weeks, respectively, followed by the results of the semi-mechanistic and descriptive model simulated means for 26 and 52 weeks, respectively. Based on the semi-mechanistic model, the placebo-corrected 26-week mean (95% CI) HbA1c change from baseline for patients adjusting insulin was -0.29% ($-0.42, -0.10$). The 26-week estimate (95% CI) for the hypothetical scenario of patients on a stable insulin dose was -0.41% ($-0.54, -0.23$). The estimated 26-week HbA1c change from baseline in the EASE-2 population, when conducting simulations based on the descriptive model, was -0.29% ($-0.38, -0.20$) with an identical change estimated at 52 weeks (-0.29% [$-0.38, -0.20$]). Higher baseline HbA1c values led to greater changes in HbA1c for each of the

2.5, 10 and 25 mg doses (Figure 1, simulations for a reference patient). For a 2.5 mg dose in the EASE-2 study population, this translates to a simulated change from baseline of -0.33% and -0.28% for patients with an HbA1c baseline of 9.0% and 8.0%, respectively. The external model verification of the semi-mechanistic and descriptive models showed that the simulated HbA1c based on the EASE-3 population was consistent with reported EASE-3 trial results for all doses, including the empagliflozin 2.5 mg dose (Table 2, Figures S1 and S2), thereby confirming the adequacy of using the models to simulate untested scenarios.

The population PK model predictions adequately described the observed concentrations both after the first dose and at steady state (Figure S3). Evaluation of the model showed its ability to predict patient drug exposures at steady state. Variability in $AUC_{\tau,ss}$ was primarily affected by renal function, female sex, smoking status and weight, although all of these covariate influences on $AUC_{\tau,ss}$ were of minor magnitude (Figure S4).

The analysis of BHB levels showed a clear exposure-response elevation; however, the increase in BHB was of low magnitude. Median (95% CI) increase at week 26 relative to baseline was 0.032 (0.023, 0.047) mmol/L, 0.074 (0.058, 0.090) mmol/L, 0.113 (0.095, 0.136) and 0.135 (0.113, 0.163) for placebo, empagliflozin 2.5, 10 and 25 mg, respectively (Figure 2). These closely approximated the values directly

observed in the EASE-2 and EASE-3 trials (Figure S5), and with a median BHB of 0.110 mmol/L at baseline, the overall increase was substantially below the cut-off used to identify ketosis events (1.5 mmol/L).

4 | DISCUSSION

Using a large PK database to derive drug exposure combined with the baseline characteristics and outcome measures from the type 1 diabetes empagliflozin clinical trial programme, we were able to determine that the directly observed 26-week mean placebo-corrected HbA1c reduction of -0.28% from baseline in the empagliflozin 2.5 mg arm of the EASE-3 trial was confirmed to be similar in two independent modelling and simulation studies. Specifically, the HbA1c change according to these models was -0.29% at 26 weeks, sustained over 52 weeks, and greater with higher baseline HbA1c. The approach predicted that greater efficacy could be achieved on a stable insulin dose compared with one in which insulin dose was adjusted at the initiation of empagliflozin treatment.

While, in retrospect, the full phase 3 SGLT-2 inhibitor clinical trial programmes for type 1 diabetes could have investigated lower type 1 diabetes-specific effective doses to minimize DKA risk, such an approach was assessed only in one trial within the empagliflozin phase 3 programme, in addition to the evaluation in the phase 2 trial (EASE-1).⁹ Traditionally, two phase 3 trials are required for regulatory approval. However, the US Food and Drug Administration (FDA) Modernization Act permits the determination of effectiveness to be based on “data from one adequate and well-controlled investigation and confirmatory evidence”.¹³ The FDA has also provided guidance on exposure-response relationships that states, “Exposure-response studies can support, or in some cases provide primary evidence for the approval of different doses” of pharmacotherapies that have been investigated at different doses in controlled clinical trials to contribute to existing evidence for substantial efficacy.^{13,21,22} The phase 3 clinical trial programme for empagliflozin, in particular, lends itself very well to the generation of model-informed supportive evidence.

Although the model-informed approach is an accepted method to confirm findings from a clinical trial, there are limitations. First, while the modelling results show the expected efficacy from the clinical trial study population, these results may not be generalizable to the type 1 diabetes general population. Second, assumptions about AUC_{50} in one of the models were conservatively derived from type 2 diabetes studies. The comparability of the exposure-response in patients with type 1 diabetes and type 2 diabetes was previously assessed.¹⁵ Although the maximal urinary glucose excretion was greater in patients with type 1 diabetes compared with patients with type 2 diabetes, the general shape of that exposure-response curve, and importantly its inflection point (AUC_{50}), was very similar between the two patient populations.¹⁵ This assumption was assessed during sensitivity analysis and during the model verification step, which supported the robustness of the assumed prior value. Third, although quantitative BHB levels could be modelled and showed a clear exposure-response relation, DKA events could not be modelled because of low event numbers and an inability to model the

precipitating factors (such as infections or pump malfunction) that appear to represent a component cause for DKA.⁹

The HbA1c benefit and minor blood BHB level elevation from the low-dose empagliflozin 2.5 mg option that was directly observed in a phase 3 clinical trial was confirmed using two modelling approaches from independent studies.

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CONFLICT OF INTEREST

B.A.P. has consulted for Boehringer Ingelheim, Novo Nordisk, Insulet, Sanofi, Abbott and NeuroMetrix; has received honoraria from Medtronic, Johnson & Johnson, Dexcom, Insulet, Novo Nordisk, AstraZeneca, Abbott and Sanofi; and received grants from Boehringer Ingelheim, Medtronic, Novo Nordisk and the Bank of Montreal. J.R. has consulted for, received honoraria from, received grants from, or participated in advisory boards for Eli Lilly and Company, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim and Intarcia. J.S.S. has consulted for DalCor, Diavacs, Dualogics, Esperion, Immunomolecular Therapeutics, Intrexon/ActoBiotics, Orgenesis, Sanofi and Zafgen; has stock ownership/options in Dexcom, Intarcia, Applied Therapeutics, Moerae Matrix and VasoPrep; has received grants from NIAID, JDRF, DRIF and Tolerion; has participated in advisory boards for Adocia, Boehringer Ingelheim and Dance; is on the Board of Directors of Dexcom, Intarcia and Applied Therapeutics; and is Chair of the Strategic Advisory Board of the EU INNODIA consortium. L.M.L. has consulted for Johnson and Johnson, Eli Lilly and Company, Sanofi, Novo Nordisk, Merck, AstraZeneca, Roche, Dexcom, Unomedical-ConvaTec, Insulet, Boehringer Ingelheim and Insulogic. N.S., K.-H.L., D.N., J.T.G., J.M. and V.N. are employees of Boehringer Ingelheim. M.M.R., C.K.J., R.J.E.-B. and A.E. were contracted by Boehringer Ingelheim to perform these analyses.

AUTHOR CONTRIBUTIONS

B.A.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The first draft of the manuscript was written by B.A.P. and V.N., and all authors contributed and were fully responsible for all content and editorial decisions. The authors were involved at all stages of development, and have approved the final version.

DATA AND RESOURCE AVAILABILITY

The co-sponsor of the EASE trials (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents and patient level clinical study data. Researchers are invited to submit inquiries via the Vivli website (<https://www.vivli.org>).

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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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