M-EASE-2: A Modelling and Simulation Study Conducted to Further Characterise the Efficacy of Low-dose Empagliflozin as Adjunctive to InSulin ThErapy (M-EASE) in Type 1 Diabetes Mellitus

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What was known

- Phase 3 clinical trials with sodium-glucose co-transporter inhibitors as adjunct-to-insulin therapy in type 1 diabetes (T1D) are a promising therapeutic option.
- The efficacy and safety of empagliflozin has been evaluated in 2 phase 3 trials (EASE-2 and EASE-3). EASE-3 included a unique, low 2.5 mg dose, which demonstrated glucometabolic benefits without an observed increase in risk of certain diabetic ketoacidosis.
- In the case of empagliflozin for T1D where efficacy and safety are established based on phase 3 development across a wide and clinically relevant dose range, a modelling and simulation approach to generate additional confirmatory evidence on effectiveness is justified and accepted by regulatory authorities in specific situations.

What's new

- The HbA1c benefit from low-dose empagliflozin 2.5 mg that was directly observed in a phase 3 clinical trial was confirmed using this empirical exposure-response model.
- This approach illustrates how pharmacometric analyses can be utilised to create further evidence of efficacy and substantiate clinical findings.

BACKGROUND

- Although traditionally at least 2 pivotal clinical trials that include each dose in the application are expected to obtain drug approval,[1] the Food and Drug Administration Modernization Act of 1997[2] allows determination of substantial evidence of effectiveness to be based on "data from one adequate and well-controlled investigation and confirmatory evidence."
- Empagliflozin 10 and 25 mg qd was evaluated in 2 pivotal phase 3, randomised, double-blind, placebo-controlled trials (EASE-2 and EASE-3) in patients with T1D.[3]
- EASE-3 was a 26-week phase 3 trial that included empagliflozin 2.5, 10, and 25 mg qd or placebo treatment arms.[3]
- Therefore, to add to the understanding of efficacy for the low dose of empagliflozin in patients with T1D, a modelling and simulation approach to generate additional confirmatory evidence of efficacy and investigate factors that drive the variability in response to treatment is highly justified and supported by regulatory authorities.[2,4]

OBJECTIVES

- This exposure-response modelling study, M-EASE-2, was performed to:
  - Simulate the placebo-corrected HbA1c change from baseline up to 52 weeks in the study population of a second phase 3 trial (EASE-2) that did not investigate a 2.5 mg qd dose.[3]
  - Characterise the empagliflozin exposure-HbA1c relationship independent of data from EASE-3.
  - Assess the impact of covariates on the exposure-response relationship for glycated haemoglobin (HbA1c).

METHODS

Software

- The analysis was conducted in NONMEM Version 7.4, applying Markov chain Monte Carlo Bayesian estimation.

Data/study population

- The M-EASE-2 model development was informed by data from EASE-2 (a 52-week study that included empagliflozin 10 and 25 mg qd treatment arms)[3] and EASE-1 (a 4-week phase 2 study, empagliflozin 2.5, 10, 25 mg qd).[5]
- To inform estimation of the exposure-response relationship, despite limited data at empagliflozin 2.5 mg qd, information for AUC_{50} from an exposure-outcome analysis in patients with type 2 diabetes[6] was used to characterise the exposure-response in patients with T1D during parameter estimation.
  - The assumption and rationale to use prior information and use of the linear placebo model are presented in **Table 1**.

Table 1. Key model assumptions

Assumption:	**Emax model was supported by prior information from type 2 diabetes data for AUC_{50} parameter**
Justification	Estimated pharmacodynamic parameters for patients with T1D and type 2 diabetes were overall comparable with only slight differences in Gmax, Imax, and IC_{50}. Those differences led to an increase in UGE in patients with T1D but an overall comparable shape of the exposure-response relationship[7]
Test to assess impact	Evaluate ability of estimated model to capture the time course of HbA1c via out-of-sample predictions into EASE-3. Additionally, the impact of the chosen prior distribution for the AUC_{50} parameter was evaluated via sensitivity analyses focusing on both the variance and location of the prior distribution
Assumption:	**A linear placebo effect over the course of treatment was adequate/appropriate**
Justification	The pre-treatment optimisation phase caused a significant drop of HbA1c until start of treatment that was not maintained over the course of the study and resulted in a similar increase from 4 weeks' post-treatment onwards in all randomisation groups
Test to assess impact	Evaluate ability of estimated model to capture the time course of HbA1c via out-of-sample predictions into EASE-3. Additionally, the stability, identifiability, and overall goodness-of-fit of this model was considered relative to more complex functional forms

AUC_{50}, the AUC_{SS} at which half the maximal effect of empagliflozin on HbA1c is achieved; Gmax, maximum reabsorbed concentration of glucose; IC_{50}, half maximal inhibitory concentration; Imax, maximum inhibition of renal threshold; UGE, urinary glucose excretion; T1D, type 1 diabetes.

- Predictions of empagliflozin exposure based on individual parameter estimates from a previous population pharmacokinetic analysis,[7] which was updated to include data from EASE-2 and EASE-3 (data on file), were used as input for this exposure-response analysis.

Model development

- The effect of empagliflozin exposure on HbA1c was modelled as a direct Emax model including a placebo effect (**Equation 1**), and investigation of the covariate effects was undertaken using a full covariate modelling approach.
  - Primary covariates of interest were predefined based on findings in previously conducted analyses including patient sex and baseline weight, eGFR and HbA1c.
  - Indication-specific factors including daily insulin dose at baseline and insulin dose type (INSDT, multiple daily injections [MDI] versus continuous subcutaneous insulin infusion [CSII]) were also evaluated.

Equation 1

$$Baseline_{HbA1c,i} = \theta_a \cdot \prod_1^m \left(\frac{cov_{mi}}{ref_m}\right)^{\theta_{(m+a)}} \cdot \prod_1^p \cdot \theta^{cov_{pi}}{}_{(p+m+a)} \cdot exp^{\eta_z}$$

$$AUC_{50} = \theta_b$$

$$Emax_i = \theta_c \cdot \prod_1^m \left(\frac{cov_{mi}}{ref_m}\right)^{\theta_{(m+n)}} \cdot \prod_1^p \cdot \theta^{cov_{pi}}{}_{(p+m+n)} \cdot exp^{\eta_s}$$

$$Placebo = \theta_d$$

$$HbA1c_{i,j} = \cdot\ Baseline_{HbA1c,i} - \left(\frac{Emax_i \cdot AUC_{SS,i}}{AUC_{50} + AUC_{SS,i}}\right) + Placebo\ \cdot TIME$$

In this equation, AUC_{50} is the AUC at which half the maximal effect of empagliflozin on HbA1c is seen; $AUC_{SS,i}$ is the individual Empirical Bayes Estimate of empagliflozin exposure AUC_{ss}; $Baseline_{HbA1c,i}$ is the patient-specific predicted HbA1c level at baseline; cov_{mi} is the individual covariate value for the continuous covariate "m", cov_{pi} is the individual covariate value for the categorical covariate "p"; $Emax_i$ is the maximal effect parameter on HbA1c; *Placebo* is an additive placebo effect as a function of time; η are individual-specific inter-subject random effects; ref_m is the population covariate value for the continuous covariate "m".

Model evaluation

- For internal and external model evaluation via posterior predictive checks, 500 Monte Carlo simulation replicates with each using a random sample from the posterior distribution of model parameters were generated.
  - External model qualification focused on an out of sample prediction using data from EASE-3.
- The impact of prior information on HbA1c lowering was investigated via sensitivity analysis (varied informativeness and point estimate).

Simulations

- For trial simulations investigating the effect of empagliflozin 2.5 mg in the study population of EASE 2, 500 Monte Carlo simulation trial replicates with 239 patients were created.
  - Each simulation utilised a random sample from the posterior distribution of model parameters and variability terms (inter-subject and intra-subject variability).
- Simulations to assess the impact of covariates (baseline HbA1c, eGFR, insulin type) on HbA1c lowering were conducted.

RESULTS

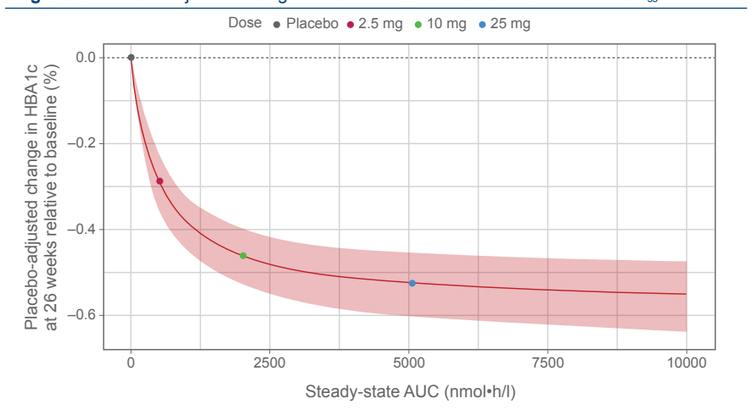
Data/study population

- The study population included 391 males and 405 females. The 95% percentile intervals at baseline were: age 21–69 years, weight 55–125 kg, baseline HbA1c 7.2%–9.5%, and estimated glomerular filtration rate (eGFR) 57–127 ml/min/1.73 m^2.
- A reference patient was described as male, MDI of insulin, baseline total daily dose=0.660 U/kg, HbA1c=8.1%, eGFR=98 ml/min/1.73 m^2, and baseline body weight=82 kg.

Model development

- The applied population PK model using phase 3 data (data on file) confirmed the structural model (2 compartment, first order elimination) developed from phase 2 data[7] and adequately described the phase 3 data in patients with T1D.
- The effect of empagliflozin exposure on changes in HbA1c was best described by a direct-response model, and the developed model was able to accurately capture the time course of HbA1c across each treatment arm for the data used to initially develop the model (internal evaluation).
- Drug effect was characterised by an Emax model driven by AUC_{SS} (**Figure 1**), with a time-dependent linear placebo.
- Inter-individual variance (CV%) for baseline HbA1c and Emax were 7.2% and 38%, respectively, and the proportional and additive residual variability estimates (CV% and standard deviation) were 4.6% and 0.11, respectively.

Figure 1. Placebo-adjusted change in HbA1c at 26 weeks as a function of AUC_{SS}

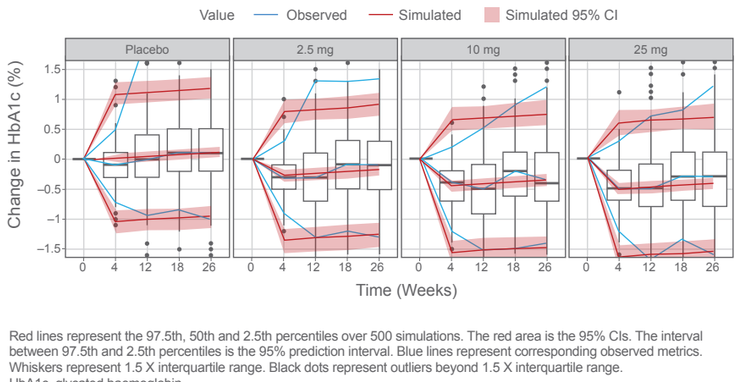


Red line and shaded area represent simulated median and associated 95% CI (500 simulations incorporating parameter uncertainty). Coloured dots denote the simulated median AUC for each dose. Typical subject: male sex, MDI insulin, eGFR=98 ml/min/1.73 m^2, baseline weight=82 kg, baseline total daily dose=0.660 U/kg and HbA1c=8.1%.
AUC, area under the curve; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

Model evaluation

- External evaluation through out-of-sample predictions for EASE-3 indicated that the time courses for HbA1c across treatment arms was adequately captured (**Figure 2**).
- Sensitivity analyses for the AUC_{50} estimate demonstrated that the informative prior on AUC_{50} resulted in conservative estimates of the HbA1c lowering for empagliflozin 2.5 mg (**Figure 3**).

Figure 2. External model evaluation by visual predictive check



Red lines represent the 97.5th, 50th and 2.5th percentiles over 500 simulations. The red area is the 95% CIs. The interval between 97.5th and 2.5th percentiles is the 95% prediction interval. Blue lines represent corresponding observed metrics. Whiskers represent 1.5 X interquartile range. Black dots represent outliers beyond 1.5 X interquartile range.
HbA1c, glycated haemoglobin.

Simulations and covariate effects

- The simulated median (95% CI) placebo-adjusted HbA1c change for a hypothetical empagliflozin 2.5 mg dose in the EASE-2 study population was -0.29% (-0.39%, -0.19%) at Week 26 and -0.29% (-0.40%, -0.19%) at Week 52 (**Figure 4**).
- The distribution of median values at Week 52 across 500 study replicates was small; 96.2% of study replicates showing an HbA1c change of at least -0.20% and 77.2% of the study replicates showed an HbA1c change of at least -0.25%.
- Simulations to illustrate the impact of baseline HbA1c on change in HbA1c were performed; for a 2.5 mg qd dose, a median placebo-adjusted change in HbA1c at 26 weeks relative to baseline of -0.28% versus -0.32% was predicted for a baseline HbA1c of 8.0% and 9.0%, respectively.

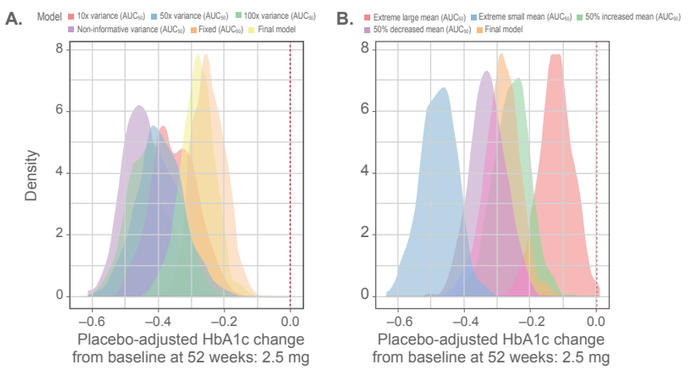
- Moderate effects influencing the placebo-adjusted change of HbA1c at Week 26 relative to baseline were observed for INSDT (CSII vs MDI), baseline HbA1c and baseline eGFR (**Table 2**).

Table 2. Key parameters

Parameter	Estimate	95% CI
HbA1c	**8.14%**	**8.07, 8.22**
AUC_{50}	**498 nmol•h/l**	**296, 819**
Emax	**0.579%**	**0.491, 0.678**
Placebo effect increase	**2.61×10^{-5}%/h**	**1.96×10^{-5}, 3.29×10^{-5}**
Sex – $baseline_{HbA1c}$ (female)	0.988	0.977, 1.00
Sex – Emax (female)	0.984	0.827, 1.17
Sex – placebo (female)	0.727	0.534, 0.971
INSDT – $baseline_{HbA1c}$ (CSII)	1.00	0.988, 1.01
INSDT – Emax (CSII)	0.880	0.737, 1.04
INSDT – placebo (CSII)	1.47	1.10, 1.99
WTB – $baseline_{HbA1c}$	-0.0311	-0.0612, -0.00102
WTB – Emax	0.0555	-0.351, 0.458
eGFR – $baseline_{HbA1c}$	0.0123	-0.0157, 0.0403
eGFR – Emax	0.504	0.116, 0.917
IDB – $baseline_{HbA1c}$	0.0141	-0.00425, 0.0326
IDB – Emax	0.0552	-0.190, 0.300
$Baseline_{HbA1c}$ – Emax	0.999	-0.358. 2.33

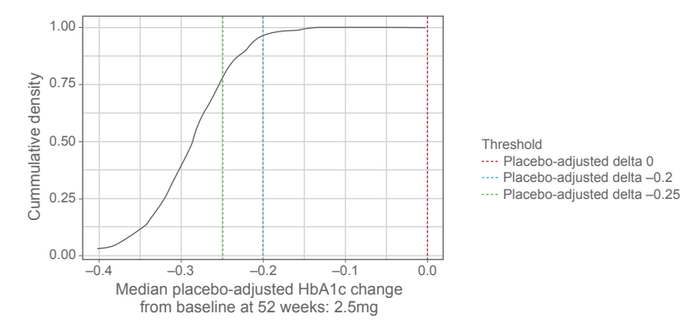
Reference: male, MDI, eGFR=98 ml/min/1.73 m^2, patient weight=82 kg, total daily insulin dose=0.66 U/kg and HbA1c=8.1%.
CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; Emax, maximal effect parameter for empagliflozin AUC_{ss} on HbA1c; IDB, total daily insulin dose at baseline; INSDT, insulin dose type (multiple daily injections vs CSII); WTB, baseline patient weight.

Figure 3. Impact of prior variance (A) and prior mean (B) on predicted placebo-adjusted median HbA1c change from baseline at 52 weeks



Distributions represent simulated median values from 500 replicates including parameter uncertainty for each respective model.
Extreme large mean: 22026 nmol•h/l; Extreme small mean: 0.00005 nmol•h/l.

Figure 4. Cumulative density of the median placebo-adjusted HbA1c change from baseline at 52 weeks



HbA1c, glycated haemoglobin.

CONCLUSIONS

- The exposure-response model successfully predicted the time-course and dose-related changes of HbA1c in EASE-3, a study not included in the model development.
- This external model qualification demonstrated the utility of the developed model to predict hypothetical outcomes in populations similar to the EASE-2 population reliably.
- M-EASE-2, a descriptive modelling and simulation approach, provided additional evidence of efficacy for empagliflozin 2.5 mg qd in the EASE-2 population, independent of data from EASE-3. Simulations showed a median (95% CI) placebo-adjusted HbA1c change from baseline at Week 52 of -0.29% (-0.40%, -0.19%).
- This is an example for high impact analyses as defined by Marshall *et al*,[8] illustrating how pharmacometric analyses can be utilised to create further evidence of efficacy and substantiate clinical findings.

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Disclosures

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