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

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What was known

- Sodium-glucose co-transporter inhibitors recently tested in phase 3 clinical trials as adjunct-to-insulin therapy are a promising therapeutic option in type 1 diabetes (T1D).
- One of the 2 phase 3 trials (EASE-3) with empagliflozin 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 glycated haemoglobin (HbA1c) benefit from low-dose empagliflozin 2.5 mg that was directly observed in a phase 3 clinical trial was confirmed using this semi-mechanistic, exposure-response model.
- This approach illustrates how pharmacometric analyses can be utilised to simulate untested scenarios 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 U.S. 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 also included a unique low empagliflozin 2.5 mg qd treatment arm.[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 is highly justified and supported by regulatory authorities.[2,4]

OBJECTIVES

- To further characterise the efficacy of the empagliflozin 2.5 mg qd dose, independent of data from EASE-3 (a phase 3 study which investigated this dose).[3]
- Specifically, this semi-mechanistic exposure-response modelling study (M-EASE-1) was performed to simulate 2 scenarios for placebo-adjusted HbA1c change from baseline:
  1. To assess the effect of insulin dose adjustment on HbA1c
  2. To extrapolate the effect on HbA1c lowering in the study population of a 4-week, phase 2 trial (EASE-1) by simulating HbA1c lowering to 26 weeks.

METHODS

Software

- The analysis used non-linear, mixed-effects modelling and was conducted in NONMEM Version 7.4 with first-order conditional estimation with η–ϵ interaction (FOCEI) routine.

Data/study population

- The M-EASE-1 model development was informed by data from EASE-1 (a 4-week phase 2 study, empagliflozin 2.5, 10, 25 mg qd) and EASE-2 (a 52-week study that included empagliflozin 10 and 25 mg qd treatment arms).[3,5]
- Individual predictions of empagliflozin exposure at steady state (AUC_{SS}) were taken from a previous population pharmacokinetic analysis,[6] which was updated to include data from EASE-2 and EASE-3.

Model development

- The exposure-response relationships between longitudinal HbA1c, total daily insulin dose (TDID) and mean daily glucose (MDG) measurements as functions of empagliflozin AUC_{SS} were parametrically modelled in a step-wise fashion:
  1. TDID was described as a function of empagliflozin exposure
  2. The effect of changes in TDID on MDG placebo data was estimated, fixed, and thereafter, the effect of empagliflozin exposure and TDID on MDG for the active dose groups were estimated
  3. Based on this model, individual MDG profiles were derived and parameters affecting the time course of HbA1c were estimated.
- The relationships of the final insulin-MDG and HbA1c models are shown in **Equation 1A** and **1B**, respectively, and a schematic overview of the final model structure is shown in **Figure 1**.

Equation 1

A.

$$TDID_{i,j} = TDID_{t0,i} \bullet Inc_i \bullet \left(1 - \frac{Emax_{TDID,i} \bullet AUC_{SS,i}}{AUC_{50,TDID} + AUC_{SS,i}}\right)$$

$$MDG_{i,j} = MDG_{t0,i} \bullet \left(\frac{TDID_{i,j}}{TDID_{t0,i}}\right)^{\theta_k} + PBO_{MDG} \bullet TIME - \left(\frac{Emax_{MDG,i} \bullet AUC_{SS,i}}{AUC_{50,MDG} + AUC_{SS,i}}\right)$$

B.

$$HbA1c_{i,j} = HbA1c_{t0,i} \bullet \left(\frac{MDG_{i,j}}{MDG_{t0,i}}\right)^{\theta_4} \bullet exp^{\eta_2}$$

In this equation, $TDID_{ij}$ represents the subject's predicted total daily insulin dose for a given subject(i) at a given time(j); $TDID_{t0,i}$ represents predicted baseline insulin dose for a given subject; Inc_i represents a scale parameter reflecting the amplitude for insulin dose adjustment (applies only to EASE-1 during the first week of treatment); $Emax_{TDID,i}$ represents the maximal effect parameter for empagliflozin AUC_{SS} on TDID achieved; $AUC_{50,TDID}$ represents the AUC_{SS} at which half the maximal effect of empagliflozin on TDID is achieved; $AUC_{SS,i}$ represents the individual Empirical Bayes Estimates of AUC_{SS}; $MDG_{t0,i}$ is the baseline MDG for a given subject; MDG_{ij} represents the mean daily glucose, calculated from $AUC_{0\text{-}24,glu,ij}/24$ for a given subject and time; $Emax_{MDG,i}$ represents the maximal effect parameter for empagliflozin AUC_{SS} on MDG achieved; $AUC_{50,MDG}$ represents the AUC_{SS} at which half the maximal effect of empagliflozin on MDG is achieved; η_2 was only estimated for EASE-2; $HbA1c_{t0,i}$ represents the predicted baseline HbA1c for a given subject.

Model evaluation

- For internal and external model evaluation via visual predictive checks, 500 Monte Carlo trial simulation replicates were generated with parameter uncertainty based on both fixed and random effects.
- For internal model qualification, posterior predictive checks including parameter uncertainty for change from baseline and the placebo-adjusted change from baseline in HbA1c (%) at 4 and 26 weeks were performed.
- External model qualification, focused on an out of sample prediction using data from EASE-3 was done.

Simulations

- To assess the effect of insulin adjustment, simulations were based on random samples from the full data set (EASE-1, -2 and -3 populations) with 500 patients per dose group; simulating with and without an empagliflozin exposure effect on TDID (hypothetical stable insulin).
- To simulate the change from baseline in HbA1c after 26 weeks in EASE-1, simulations were based on the study population and the treatment paradigm of this study (18–19 patients per dose group, 1-week stable insulin, then insulin titration).

RESULTS

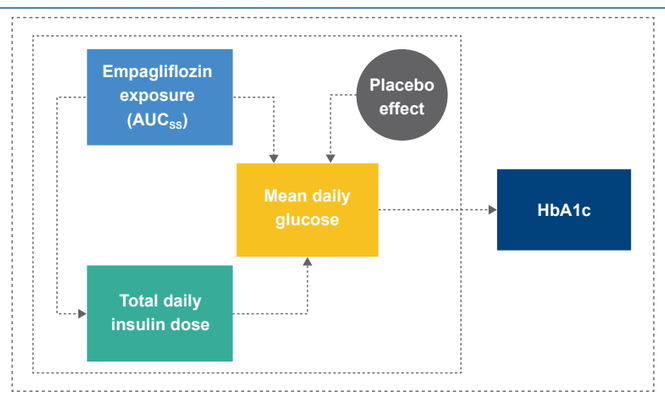
Data/study population

- The study population included 391 males and 405 females. The 95% percentile intervals at baseline were age: 21–69 years, body weight: 55–125 kg, HbA1c: 7.2%–9.5%, total daily insulin dose: 0.37–1.30 U/kg, estimated glomerular filtration rate (eGFR): 57–127 ml/min/1.73 m^2, and MDG: 134–228 mg/dl.
- A reference patient was described as male, receiving multiple injections of insulin, HbA1c=8.1%, eGFR=99 ml/min/1.73 m^2, and baseline body weight=82 kg.

Model development

- Overall, TDID was well described using a direct response Emax function driven by AUC_{SS}.
- MDG was affected by 3 components (**Figure 1**):
  1. Empagliflozin exposure expressed as a direct response Emax function
  2. A linear time-dependent placebo effect
  3. TDID profiles derived from the first model part.

Figure 1: Schematic of the final model structure



AUC_{SS}, area under the plasma-concentration-time curve at steady state; HbA1c, glycated haemoglobin.

- Changes in HbA1c were driven by changes in MDG predicted in the second step.
- Typical key population parameters, inter-individual and proportional and additive residual variability estimates are shown in **Table 1**.

Table 1. Typical key population parameters

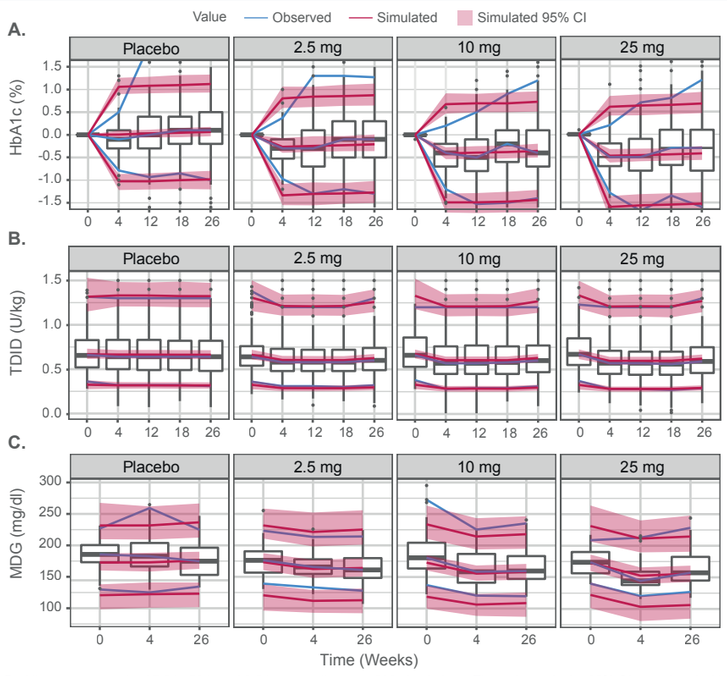
Parameter	
Pharmacodynamic	**Median (95% CI)**
Baseline HbA1c:	8.15% (8.09%, 8.21%)
AUC_{50} for $TDID_{EASE\text{-}1}$:	110 (14.3, 836) nmol•h/l
Emax for TDID:	0.186 (0.145, 0.238)
AUC_{50} for MDG:	370 (83.9, 1630) nmol•h/l
Emax for MDG:	634 (534, 753) mg•day/dl
Inter-individual variability	**CV%**
Baseline TDID	32.0
Emax on TDID	86.0
Baseline MDG	9.51
Emax on MDG	27.8
Residual variability	**CV% (SD)**
TDID	15.6 (0.0316)
MDG	16.0 (0.0316)
Reference patient: Male, eGFR=99 ml/min/1.73 m^2, body weight=82 kg, and cumulative MDG over 24 h; MDG=4266 mg·day/dl	

AUC_{50}, the AUC_{SS} at which half the maximal effect of empagliflozin on $TDID_{EASE\text{-}1}$ and MDG is achieved; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; Emax, maximal effect parameter for empagliflozin AUC_{SS} on TDID and MDG; HbA1c, glycated haemoglobin; MDG, mean daily glucose; SD, standard deviation; TDID, total daily insulin dose.

Model evaluation

- External model evaluation using out-of-sample predictions from EASE-3 indicate that the model adequately captured the time courses of TDID, MDG and HbA1c (**Figure 2A–C**).
- Internal model evaluation with visual predictive checks and posterior predictive checks also showed adequate model performance (results not shown).

Figure 2. External model evaluation by visual predictive check by dose for change from baseline in **A.** HbA1c, **B.** TDID and **C.** MDG

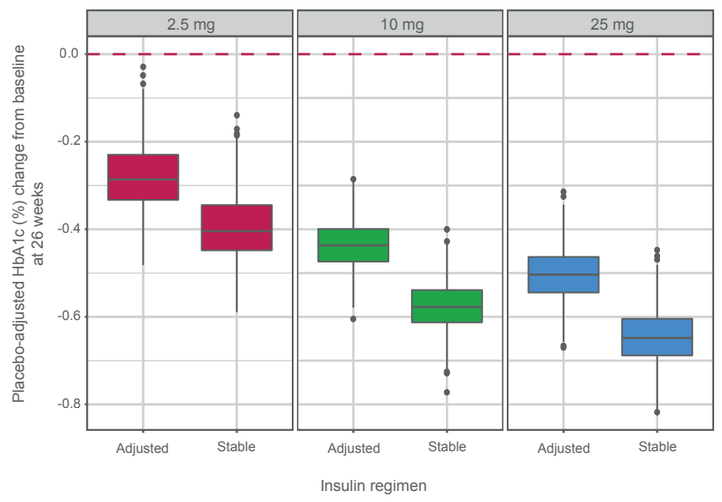


Red lines represent the 97.5th, 50th and 2.5th percentiles over 500 simulations. The red area is the 95% CI associated with these metrics. The interval between the 97.5th and 2.5th percentiles is the 95% prediction interval. Clue lines represent the corresponding observed metrics. Whiskers on box-plots represent 1.5 X interquartile range. The black dots represent observed data falling outside of 1.5 X the interquartile range.
HbA1c, glycated haemoglobin; MDG, mean daily glucose; TDID, total daily insulin dose.

Simulations

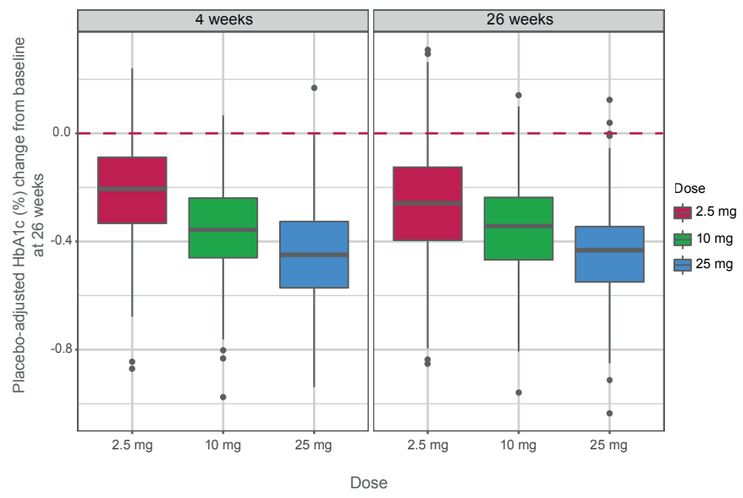
- The simulated median (95% CI) placebo-adjusted HbA1c change from baseline at Week 26 for empagliflozin 2.5 mg qd based on 500 study replicates (each with 500 patients in each treatment arm sampled from EASE-1, EASE-2 and EASE-3 populations) was -0.29% (-0.40%, -0.10%) and -0.40% (-0.53%, -0.23%) with adjusted and stable insulin therapy, respectively (**Figure 3**).
- Simulations of the study population and treatment paradigm of EASE-1 (i.e. 19 patients) showed a median (95% CI) placebo-adjusted HbA1c change from baseline at Week 26 of -0.26% (-0.62%, 0.08%) for patients receiving empagliflozin 2.5 mg qd (**Figure 4**).

Figure 3. Placebo-adjusted HbA1c (%) change from baseline at Week 26 in 500 patients per dose group, grouped by dose and insulin regimen



Distributions represent simulated median values from 500 replicates grouped by dose and insulin regimen. Whiskers represent 1.5 X interquartile range. Black dots indicate simulated data outside of 1.5 X interquartile range.
HbA1c, glycated haemoglobin.

Figure 4. Placebo-adjusted HbA1c (%) change from baseline at Week 4 and 26 in EASE-1, n=18–19 per dose group, grouped by time and dose



Distributions represent simulated median values from 500 replicates grouped by time and dose. Whiskers represent 1.5 X interquartile range. Black dots indicate simulated data outside of 1.5 X interquartile range.
HbA1c, glycated haemoglobin.

CONCLUSIONS

- The semi-mechanistic exposure-response model successfully predicted the time-course and dose-related changes of HbA1c for data used for model development (EASE-1 and -2) and the external evaluation dataset (EASE-3).
- The M-EASE-1 model provided evidence of efficacy for empagliflozin over 26 weeks in the EASE-1 population (median [95% CI] placebo-adjusted change: -0.26% [-0.62%, 0.08%]) and in a hypothetical scenario of adjusted or stable insulin therapy (-0.29% [-0.40%, -0.10%] and -0.40% [-0.53%, -0.23%], respectively).
- The predicted placebo-adjusted median HbA1c change from baseline at 26 weeks was approximately 30% greater in magnitude in the presence of a stable insulin regimen than an adjusted insulin regimen.
- This model predicted the long-term efficacy of the 2.5 mg dose in the EASE-1 population without using available data from EASE-3, thereby creating independent evidence of efficacy in this dose group.
- This modelling and simulation analysis is an example for high impact analyses as defined by Marshall *et al*,[7] illustrating how pharmacometric analyses can be utilised to simulate untested scenarios to create further evidence of efficacy and substantiate clinical findings.

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Disclosures

Rena Eudy-Byrne, Ahmed Elmokadem, Matthew Riggs and Curtis Johnston are employees of Metrum Research Group, who were contracted by Boehringer Ingelheim to perform this analysis. Jan Marquard, Nima Soleymanlou, Valerie Nock, and Karl-Heinz Liesenfeld are all employees of Boehringer Ingelheim.

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