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

Renata J. Eudy-Byrne,1 Ahmed Elmakadem,1 Matthew M. Riggs,1 Curtis K. Johnston,1 Jan Marquard,1 Nima Soleymani2,3,4 Valerie Noek,4 Karl-Heinz Liesenfeld4

1Metrum Research Group Tailfifie, CT, USA; 2Boehringer Ingelheim International GmbH, Ingelheim, Germany; 3Boehringer Ingelheim Canada Ltd./Ltée, Burlington, ON, Canada; 4Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

What was known:
- Several previous experimental and computational studies recently tested in vivo pilot clinical trials to adjust to insulin therapy as a promising therapeutic option in type 1 diabetes mellitus (T1D).
- In the case of empagliflozin for T1D, efficacy and safety are established based on phase 3 development across a wide and clinically relevant dose range, simulating and simulation assistance to generate additional clinical evidence, whereas its inclusion to the regulatory authorities is associated with specific situations.

What’s new:
- The glycated haemoglobin (HbA1c) benefit from low-dose empagliflozin is 2.5 mg qd (1.0 mg kg⁻¹ body weight) confirmed through the semimechanistic, exposure-response model. This approach allows the pharmacometric analysis to be utilized to simulate untested scenarios to create further evidence of efficacy and substantiate clinical findings.

OBJECTIVES
- To further characterise the efficacy of the empagliflozin 2.5 mg qd dose, independent of data from EASE-1 (5 weeks of treatment), which investigated the dose,
- To build a model of placebos-adjusted HbA1c change from baseline in the first 26 weeks of treatment
- To assess the effect of HbA1c dose adjustment in the study population of 4 weeks, phase 2 trial (EASE-1) by simulating HbA1c lowering in 26 weeks.

METHODS

Software
- The analysis used non-linear mixed-effects modelling and was conducted in NONMEM Version 7.7 with the first-order conditional estimation with linearisation (FOCE-LIN).

Data/study population
- The M-EASE-1 model development was informed by data from EASE-1 (5 weeks of treatment) and EASE-2 (30-week study with placebo-adjusted 10 and 25 mg (qd) treatment arms). The individual predictions of placebo-adjusted daily glucose (MDG) were taken from a previous study, which was updated to include data from EASE-1 and EASE-2.

Model development
- The exposure-response relationship between longitudinal HbA1c, total daily insulin dose (TDID), and MDG (MDG) measurements of empagliflozin (EII) were pharmacometrically modelled in a stepwise fashion:
  - To define the baseline HbA1c and MDG exposure.
  - To establish the effect of TDID on MDG, placebo in the study population of 4 weeks, phase 2 trial (EASE-1) by simulating HbA1c lowering in 26 weeks.

RESULTS

Data/study population
- The study population included 381 male and 466 female. The 15% percent males at baseline were 21-49 years, body weight 55.1-120 kg.
- The study population was balanced between the treatment arms, receiving multiple injections of insulin (EASE-2:145, EASE-3:150, HbA1c:18-122 mg/dl).
- A reference model was developed to assess multiple injections of insulin (EASE-2:145, HbA1c:18-122 mg/dl) and baseline body weight 94 kg.

Model development
- Overall, TDID was well described using a direct response Emax function driven by
- MDG was affected by 3 components (Figure 1):
  - Empagliflozin exposure by a direct response Emax function:
  - A binary time-dependent placebo effect:
  - Simulations of the site-specific data (EASE-1: 4 weeks, EASE-2: 30 weeks) were performed to estimate the rate of change of HbA1c.

Simulations
- The simulated median (95% CI) placebo-adjusted HbA1c change from baseline at Week 26 was based on 260 study replicates (each with 300 patients in each treatment arm sampled from EASE-1, 260 and EASE-3 placebo-adjusted HbA1c)]
- Sums of the simulation 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 -0.25 (-0.40, -0.10) for patients receiving empagliflozin 2.5 mg qd (Figure 4).

CONCLUSIONS

- The EASE-1 model provided evidence of efficacy for empagliflozin over 26 weeks in the presence of stable insulin regimen (a 1.5% 95% CI: 0.72-2.27 mg/dl placebo-adjusted HbA1c change).
- This model predicted the large efficacy of the 2.5 mg qd in the EASE-1 population without using available data from EASE-3. Hence, creating independent evidence of efficacy in this dose range.
- The modelling and simulation analysis is an essential for high-impact real-world evidence. A semimechanistic exposure-response analysis can be utilized to simulate untested scenarios to create further evidence of efficacy and substantiate clinical findings.

References