What was known

- Previous studies with sodium-glucose co-transporter 2 inhibitors as adjunct-to-therapy in type 1 diabetes (T1D) are promising therapeutic options. The efficacy and safety of empagliflozin has been evaluated in 2 phase 3 trials (EASE-2 and EASE-3). EASE-2 included a unique, low 2.5 mg dose, which demonstrated glycemic benefits without an observed increase in the risk of certain diabetic ketonuria.

- In trials of empagliflozin for T1D, efficacy and safety are established based on phase 3 development across clinical and clinically relevant dose range, so empirical and simulation approach to generate additional evidence for the individual patient is pursued and accepted by regulatory authorities in specific situations.

What’s new

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

BACKGROUND

- Although treatment of type 2 postprandial glucose intolerance that include each dose in the application are expected to obtain drug approval. The Food and Drug Administration Act of 1992 (FDAA) has defined a good and adequate well-controlled investigation and confirmatory evidence.

- Empagliflozin 10 and 25 mg was evaluated in 2 phase 3 trials, randomized double-blind, placebo-controlled (EASE-2 and EASE-3) and conducted with T1D patients.

- EASE-2 was a 26-week phase 3 trial that included empagliflozin 2.5, 10 and 25 mg and placebo for 3 months in adult T1D participants.

- Therefore, to add to the understanding of efficacy for the low dose of empagliflozin in patients with T1D and simulation and strategic approach to generate additional confirmatory evidence of efficacy and investigate factors that drive the variability to response to treatment is highly justified and supported by regulatory authorities.

OBJECTIVES

- The objective of the exposure-response modeling study in T1D was to:
  - Simulate the placebo corrected HbA1c change from baseline to up to 52 weeks in the study population for the placebo and empagliflozin 2.5 mg dose that did not investigate in a clinical trial.
  - Characterize the empirical exposure-HbA1c relationship independent of data from EASE-2.
  - Assess the impact of covariates on the exposure-response relationship for glycated haemoglobin (HbA1c).

METHODS

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

Data/study population

- The analysis was developed by input data from EASE-2 (10 week study that included empagliflozin 10 and 25 mg treatment arm) and EASE-3 (6 week study empagliflozin 2.5 mg). No placebo patients were included.

- A reference patient was described as male, NOC of insulin, baseline total daily dose (LDD) 0.8 U/kg, BMI 25.1 kg/m2, and baseline body weight 75 kg.

Model development

- The applied population PPK model using phase 3 data (data on file) confirmed the structural model (2 compartment for skeleton developed from phase 3 data) and adequately described the phase 3 data in patients with T1D.

- The effect of empagliflozin exposure on changes in HbA1c of T2DM was best described by a direct response model, and the model developed was capable to calculate the time course of HbA1c across each treatment arm for the doses used to initially validate the model (internal evaluation).

- Drug effect was characterized on by empirical exposure model driven by AUC50 (Figure 2), with time-dependent linear placebo.

- Individual residual validation (ICV) for baseline HbA1c and Emax were 7% and 2% respectively, and the proportional and residual random variability estimates (CV%) and standard deviation were 4.85 and 0.11 respectively.

RESULTS

- The exposure-response model accuracy and positive correlation of time and dose-related changes of HbA1c in EASE-2, is not studied in the model development.

- The external model validation demonstrated the utility of the developed model to predict hypothesis outcomes in populations similar to the EASE-3 population reliably.

- In the external simulating model and simulation approach, provided additional evidence of efficacy for empagliflozin 2.5 mg in EASE-3 population, independent of data from EASE-2. Simulations showed a median (95% CI) placebo-adjusted HbA1c change from baseline of Week 2 of -0.30% (−0.44%, −0.16%) and -0.29% (−0.43%, −0.15%).

- This is an example for high impact analyses as defined by Moshahidy et al. illustrating how pharmacometric analyses can be utilized to create further evidence of efficacy and substantiate clinical findings.

CONCLUSIONS

- The exposure-response model successfully predicted the time course and dose-related changes of HbA1c in EASE-2, is not studied in the model development.

- The external model validation demonstrated the utility of the developed model to predict hypothesis outcomes in populations similar to the EASE-3 population reliably.

- In the external simulating model and simulation approach, provided additional evidence of efficacy for empagliflozin 2.5 mg in EASE-3 population.

- Simulations showed a median (95% CI) placebo-adjusted HbA1c change from baseline of Week 2 of -0.30% (−0.44%, −0.16%) and -0.29% (−0.43%, −0.15%).

- This is an example for high impact analyses as defined by Moshahidy et al. illustrating how pharmacometric analyses can be utilized to create further evidence of efficacy and substantiate clinical findings.