Population Pharmacokinetic (PK) and Exposure-Response (ER) Analysis of Empagliflozin in Pediatric Patients with Type 2 Diabetes Mellitus (T2DM)

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Summary

- Empagliflozin is a potent and highly selective oral sodium-dependent glucose transporter-2 (SGLT-2) inhibitor for the treatment of type 2 diabetes mellitus (T2DM) in adults and pediatrics [1].
- Study 1218.91 was a double-blind, randomized, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a safety extension period up to 52 weeks, in children and adolescents with T2DM.
- Population PK and ER models previously developed for empagliflozin [2] in adults and adolescents were re-estimated in a Bayesian framework to characterize the PK and ER (glycosylated hemoglobin (A1c) lowering) using the pediatric data from Study 1218.91 and assess any differences in relation to adult.
- Similar empagliflozin exposures are achieved for a 10 mg dose in pediatric and adult subjects.
- Pediatric patients achieved a slightly larger, but highly variable, placebo-adjusted A1c decrease relative to adults at week 26 (**Figure 4**: -0.699% vs. -0.528%).
- The Bayesian estimation approach enabled the characterization of empagliflozin PK and ER in a limited sample of pediatric patients and borrowed from what is already known about PK and ER in adults.

Demographics

Table 1: PK model: Comparison of baseline continuous covariates by study.

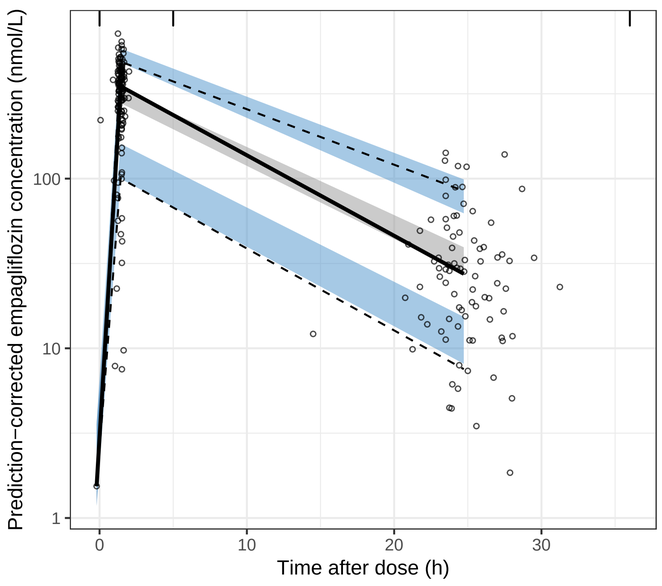
Variable	n	Mean	Median	SD	Min / Max
Study 1218.91					
Weight (kg)	74	96.6	90.0	26.2	42.5 / 169
Age (years)	74	14.5	14.5	1.90	10.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	74	127	125	25.2	89.7 / 241
Study 1245.87					
Weight (kg)	27	96.8	92.0	23.9	61.7 / 143
Age (years)	27	14.1	15.0	1.99	10.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	27	196	190	68.6	88.0 / 424
Previous Adults					
Weight (kg)	4346	84.1	82.4	19.4	38.7 / 175
Age (years)	4346	57.4	58.0	10.1	19.0 / 98.0
Estimated GFR (ml/min/1.73m^2)	4346	85.6	84.4	21.7	15.3 / 334

METHODS

- The PK model included data from 223 observations and 74 patients receiving empagliflozin 10 and 25 mg once daily.
- The ER model included data from 394 observations and 103 patients receiving empagliflozin (N=52) or placebo (N=51).
- The analyses were conducted using Markov chain Monte Carlo (MCMC) Bayesian estimation in NONMEM®.
- The prior distributions were defined from point estimates and uncertainties of the previous adult PK and ER model parameters.
- For PK parameters of primary interest, including CL/F and V2/F, weakly uninformative priors were used for all other ER model parameters.
- The parameter of drug potency for lowering HbA1c was fixed, as in the previous model, while uninformative priors were used for all other ER model parameters.
- Covariate effects of interest were incorporated using a full covariate modeling approach.

RESULTS

Figure 1: PK model: Visual predictive check (VPC) for empagliflozin concentration versus time after dose.



- The empagliflozin PK was well-described by a two-compartment model with sequential zero-order and first-order absorption with covariate effects of sex, age, race, and estimated glomerular filtration rate (eGFR) on CL/F, and fixed allometric exponents on CL/F, V2/F, Q/F, and V3/F (**Figure 1**).
- Individual CL/F estimates were consistent with those of adults from the prior model.
- Simulations of AUCss following the administration of 10 mg once daily empagliflozin demonstrated that adult and pediatric subjects exhibit similar AUCss (**Figure 2**).
- The ER data was adequately described by a turnover model with disease progression (PROG) and AUCss inhibiting the HbA1c synthesis (Kin) through an inhibitory maximum effect (Imax) relationship (**Figure 3**).
- Insulin co-therapy was included as a covariate on the baseline A1c and PROG. The time-varying eGFR and baseline A1c were included as covariates on Imax.
- Simulations showed the placebo-adjusted A1c decrease at week 26 in the pediatric population was larger than that in the adult population (**Figure 4**: -0.699% vs. -0.528%).
- Insulin co-therapy resulted in a larger magnitude of placebo-adjusted A1c decrease in both pediatrics and adults, with the magnitude being larger in pediatrics.
- All adjustments to the variance and location of the prior distribution for AUC50 had minimal impact on the posterior distribution of the model predicted placebo adjusted HbA1c change from baseline at 26 weeks (**Figure 5**).

Figure 2: PK model: Distributions of AUCss values from Monte Carlo simulations in adults and pediatric patients using the previous adult PK model and the current pediatric PK model respectively.

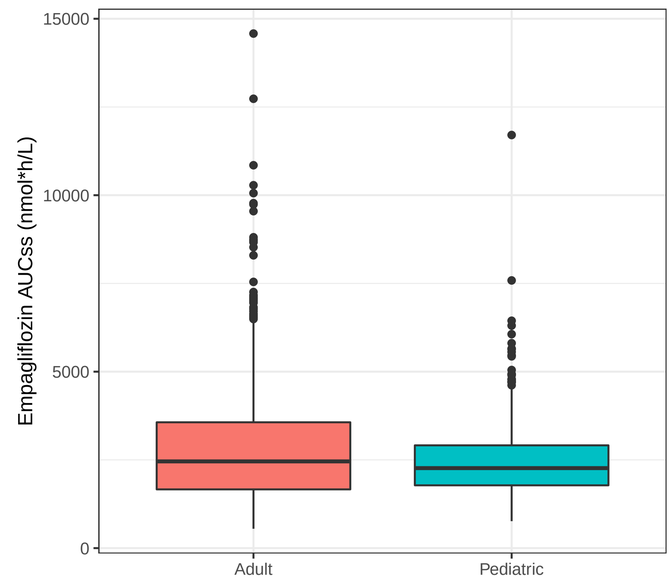


Figure 3: ER model: Visual predictive check (VPC) for HbA1c change from baseline versus time after first dose; stratified by treatment arm and insulin co-therapy at baseline.

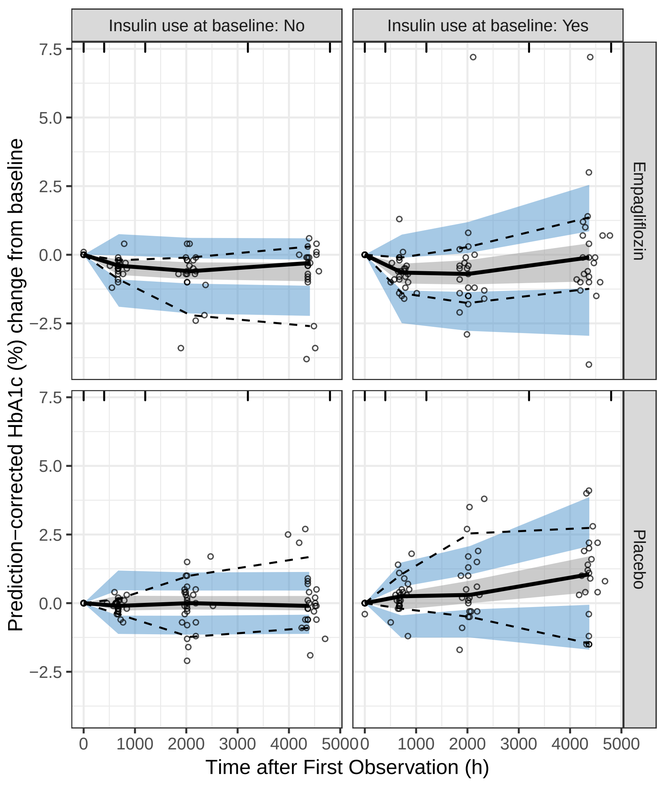


Figure 4: ER model: Box plot of placebo-adjusted HbA1c change from baseline values at 26 weeks after treatment start from Monte Carlo simulations in adults and pediatric patients using the previous adult ER model and the current pediatric ER model respectively.

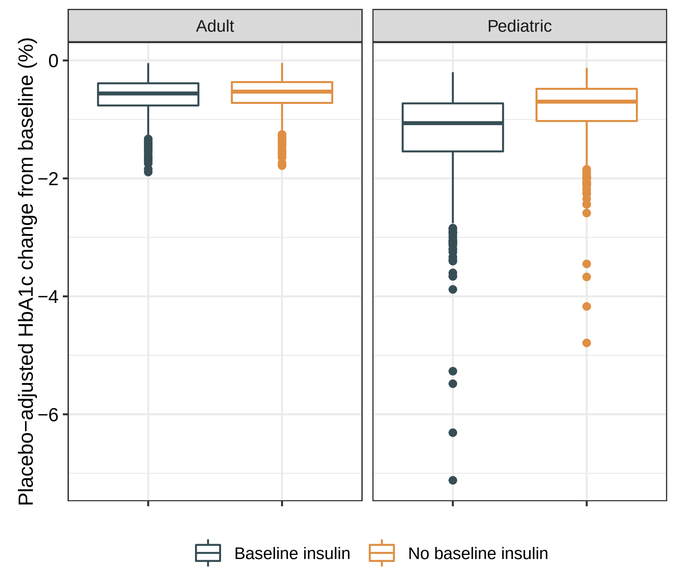
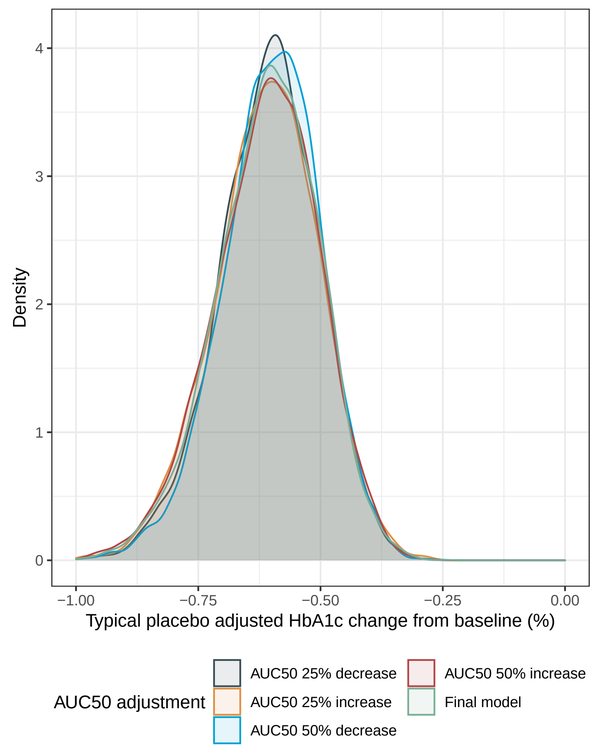


Figure 5: ER model: Impact of AUC_{ss} at half-maximal inhibition of HbA1c production rate (AUC50) Bayesian prior variance and scale on typical placebo-adjusted HbA1c change from baseline values at 26 weeks after treatment start.



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[1] Heise, T., Graefe-Mody, E.U., Hüttner, S., Ring, A., Trommeshauser, D. and Dugi, K.A. Pharmacokinetics, pharmacodynamics and tolerability of multiple oral doses of linagliptin, a dipeptidyl peptidase-4 inhibitor in male type 2 diabetes patients. *Diabetes Obes. Metab.* **11** (2009):786–794.

[2] Metrum Research Group. Empagliflozin Simplified Population PK and Exposure-ResponseModeling for HbA1c. Technical Report c37380422-01, Boehringer Ingelheim Pharma GmbH & Co. KG (2022).

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