Population Pharmacokinetic and Exposure-Response Analysis of Linagliptin in Pediatric Patients with Type 2 Diabetes Mellitus

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Summary

- Linagliptin is a DPP-4 inhibitor approved for the treatment of type 2 diabetes mellitus (T2DM) in adults.
- Study 1218.91 [1] was a trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with T2DM.
- Models for linagliptin, previously developed with data from adults and adolescents with T2DM, were re-estimated in a Bayesian framework using only the pediatric data from 1218.91 to characterize pediatric pharmacokinetics (PK) and exposure-response (ER) and compare to adults. The ER endpoint of interest was HbA1c.
- Slightly larger but more variable linagliptin exposures were achieved for a 5 mg dose in pediatric subjects relative to adults.
- Pediatric patients achieved a smaller, but highly variable, placebo-adjusted HbA1c decrease relative to adults at week 26 (**Figure 4**).
- The Bayesian estimation approach enabled the characterization of linagliptin PK and ER in a limited sample of pediatric patients, borrowing from what is already known about PK and ER in adults.

Demographics

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

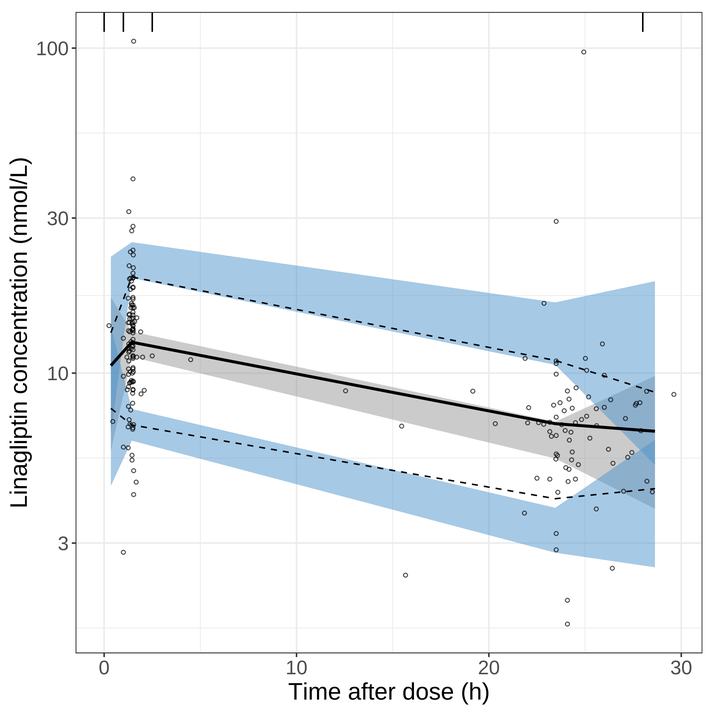
Variable	n	Mean	Median	SD	Min / Max
Study 1218.91					
Weight (kg)	63	103	97.2	28.1	43.1 / 171
Age (years)	63	14.4	14.0	1.84	10.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	63	135	125	34.2	87.2 / 283
DPP-4 Activity (RFU)	63	14900	14700	3440	8930 / 25900
Study 1218.56					
Weight (kg)	23	80.6	74.6	23.4	46.6 / 139
Age (years)	23	14.0	14.0	1.89	11.0 / 17.0
Estimated GFR (ml/min/1.73m^2)	23	136	135	33.6	80.1 / 205
DPP-4 Activity (RFU)	23	8890	9860	6140	981 / 19200
Previous Adults					
Weight (kg)	458	90.6	89.0	15.0	57.0 / 132
Age (years)	458	59.1	60.0	9.08	30.0 / 78.0
Estimated GFR (ml/min/1.73m^2)	458	87.5	82.9	22.8	41.8 / 190
DPP-4 Activity (RFU)	458	12800	12500	3920	1080 / 47500

Methods

- The PK model included 227 observations from 63 patients receiving linagliptin 5 mg once daily. The ER model included 389 total observations from 99 patients receiving linagliptin (N=48) or placebo (N=51).
- The PK model included informative priors using the point and uncertainty estimates from the previous model fit for all parameters except CL/F and V2/F, which used weakly informative priors during estimation.
- The ER model included an informative prior for the AUC_{ss} producing half-maximal inhibitory effect parameter (AUC50), while all other parameters used uninformative priors.
- Monte Carlo simulations were performed to compare population level endpoints for PK (AUCss) and ER (placebo-adjusted HbA1c change from baseline at 26 weeks) in adult and pediatric patients.
- All analyses performed on the Metworx™ computing platform using a suite of open-source tools [2].

Results

Figure 1: PK model: Visual predictive check for linagliptin concentration versus time after dose.



- The PK data was best described by a two-compartment model with first-order absorption and a saturable binding sub-model in the central compartment with covariate effects for sex on CL/F and fixed allometric exponents on CL/F, V2/F, Q/F, and V3/F (**Figure 1**).
- Pediatrics had a lower estimated CL/F in the current model compared to the previously developed adult/adolescent model (median of posterior 81.5 vs 151 L/hr).
- In simulations, pediatric patients had 19.9% higher AUCss values relative to adults; however, the AUCss distributions across the two populations overlapped (**Figure 2**).
- The ER data was best described by a turnover model with a time-varying disease progression component and a maximal inhibition (Imax) linagliptin effect.
- Concurrent insulin use was included as a covariate on baseline HbA1c and disease progression (**Figure 3**).
- The Imax estimate was lower in the pediatric model then the adult/adolescent model (median of posterior: 0.096 vs. 0.141).
- Simulations showed a smaller median placebo-adjusted HbA1c decrease at week 26 in pediatric subjects compared to adults (-0.41% vs. -0.61%) (**Figure 4**).
- 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 model and the current model respectively.

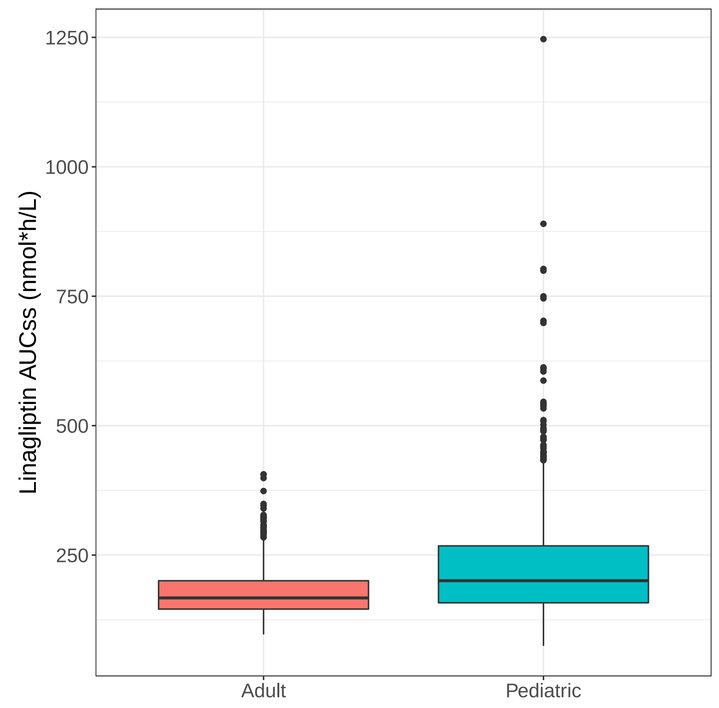


Figure 3: ER model: Visual predictive check for HbA1c change from baseline versus time after first dose; stratified by treatment arm and insulin co-therapy at baseline.

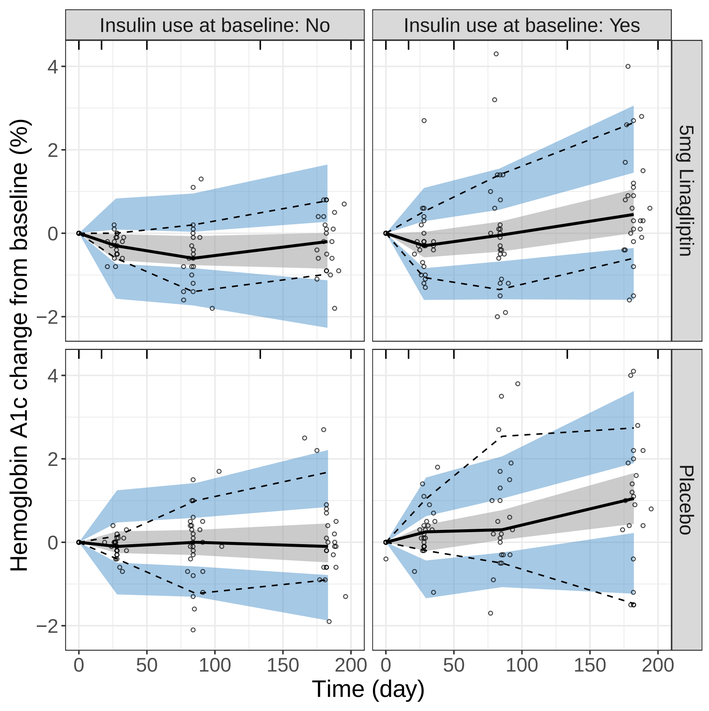


Figure 4: ER model: Box plot of placebo-adjusted HbA1c change from baseline values at 26 weeks after treatment start from Monte Carlo simulations in adults and pediatric patients, using the previous ER model and the current model respectively.

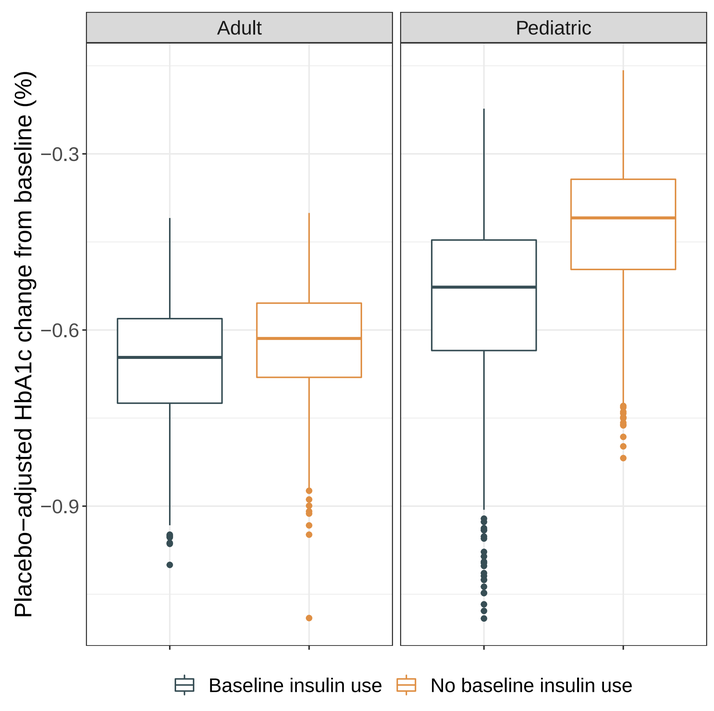
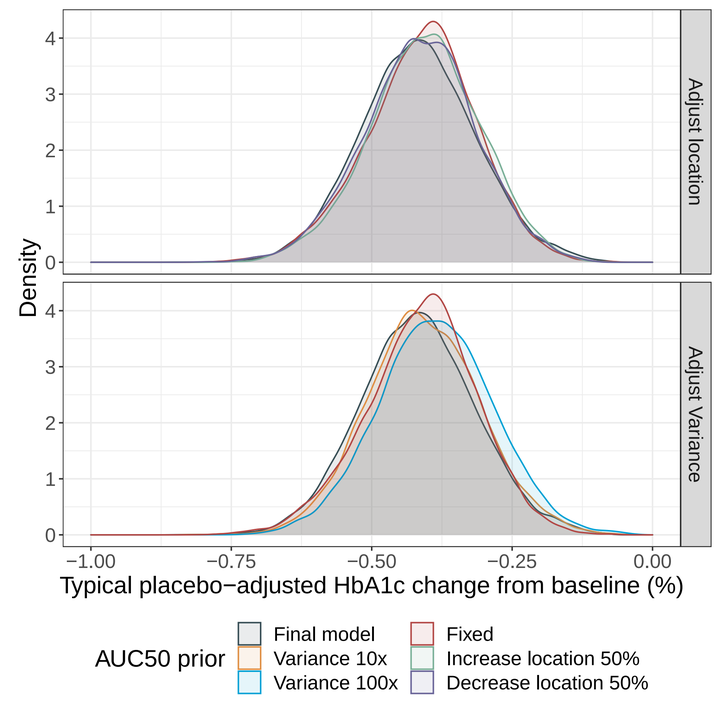


Figure 5: ER model: Impact of AUCss at half-maximal inhibition of HbA1c production rate (AUC50) Bayesian prior variance and scale on typical Imax estimate.



References

[1] Laffel, L.M., Danne, T., Klingensmith, G.J., Tamborlane, W.V., Willi, S., Zeitler, P., Neubacher, D., Marquard, J. and DINAMO Study Group. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *Lancet Diabetes Endocrinol* **11** (2023):169–181.

[2] Try Our Suite of Open-Source Tools. `https://metrumrg.com/try-open-source-tools/`. Accessed: 2022-9-27.

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Presented at the American Conference on Pharmacometrics; 5 November - 8 November 2023 Copies available at: www.metrumrg.com/all-publications