Bayesian borrowing for paediatric extrapolation: The DINAMO study

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1 Boehringer Ingelheim Pharma GmbH & Co. KG

Outline

- The DINAMO trial
- Bayesian analysis using pharmacometric modelling
- Additional Bayesian analysis using robust MAP priors
- Study results
- Summary

The DINAMO trial

Bayesian borrowing for pediatric extrapolation: The DINAMO study

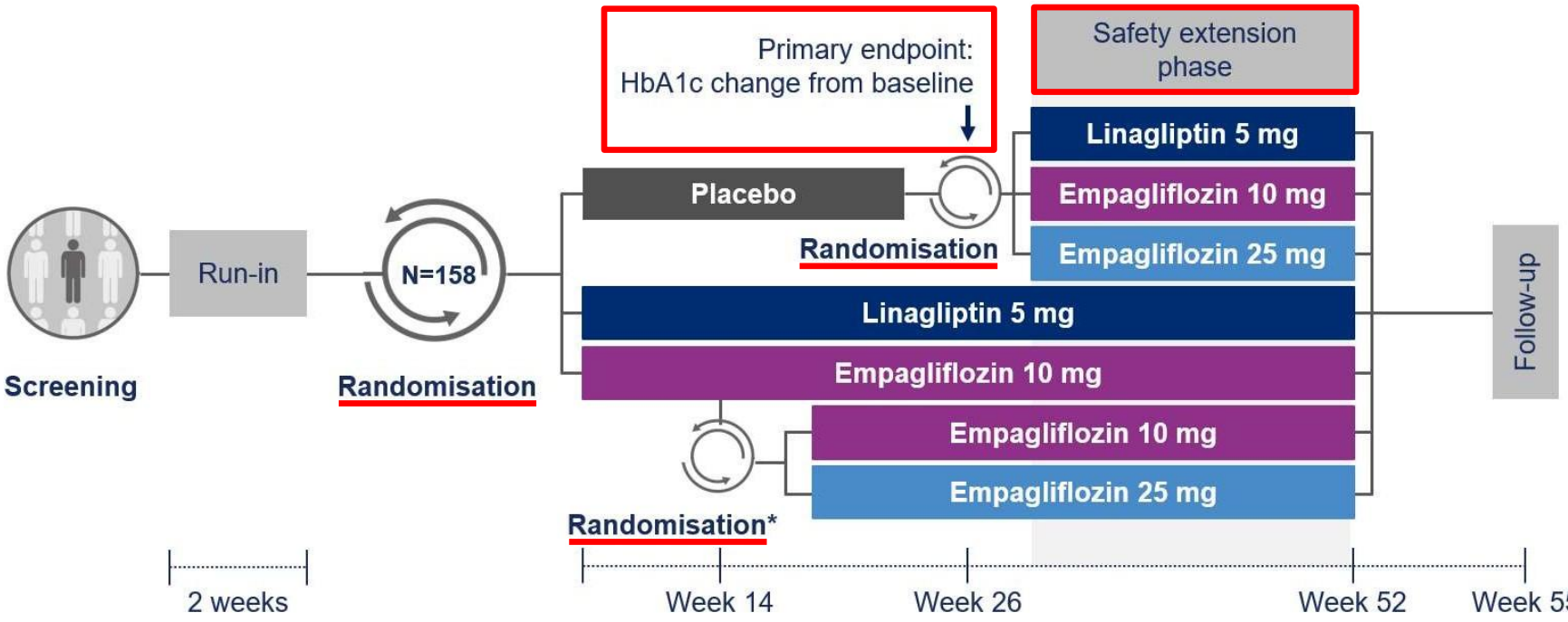
Background

- The worldwide increase in overweight and obesity in children and adolescents has led to an upsurge in T2D in young people[1, 2]
- Clinical course of youth-onset T2D is more aggressive than in adults[3]
- SGLT2 inhibitor empagliflozin and DPP-4 inhibitor linagliptin are well-established treatments for adults with type 2 diabetes mellitus (T2D)
- Lack of oral treatments for T2D in youth, only oral metformin and injected insulin generally approved until recent approval of GLP-1 analogues
- To overcome this limitation, the DIabetes study of liNAgliptin and eMpagliflozin in children and adOlescents (DINAMO) trial was conducted
- Main objective of the DINAMO trial: to assess the efficacy and safety of a dosing regimen with empagliflozin, with potential dose increase from 10 to 25 mg, and linagliptin 5 mg, both compared with a shared placebo group

1. Nolan CJ, Damm P, Prentki M. *Lancet* 2011;378:169-81; 2. Lawrence JM *et al. JAMA* 2021;326:717-27.;
3. Al-Saeed AH *et al. Diabetes Care* 2016;39:823-9

DINAMO study design

- To compare the efficacy and safety of empagliflozin versus placebo, and linagliptin versus placebo, in children and adolescents (aged 10−17 years) with T2D[1]



*Re-randomisation at Week 14 for participants not achieving HbA1c <7% at Week 12

1. Laffel LM *et al. Lancet Diabetes Endocrinol* 2023;11:169-81.
HbA1c, glycated haemoglobin; T2D, type 2 diabetes.

Primary analysis and supplementary Bayesian analysis

- Primary endpoint: Change in HbA1c from baseline to week 26
- Primary analysis: ANCOVA model with baseline HbA1c as a continuous covariate, and with categorical covariates for treatment and age group
- Stand-alone inference with 85% planned power
- Potential underpowering: After recruitment was completed, high standard deviation was observed in early blinded data
- Reopening recruitment wasn‘t considered best option
- Study team proposed supplementary Bayesian analysis
  - Power gain through borrowing of historical data
  - Dedicated SAP prepared and approach discussed with FDA prior to planned read-out

ANCOVA: analysis of covariance

Supplementary Bayesian analysis

- Direct borrowing from adult data to pediatric population not possible: Exchangeability assumption violated

Main approach

- Pharmacometric (PMx) model for change in HbA1c(%) in empagliflozin / linagliptin used to leverage data from trials in adults
- Assumption: Conditional exchangeability between adults / children with T2D treated with empagliflozin / linagliptin, after exposure-response adjustment

Additional analysis

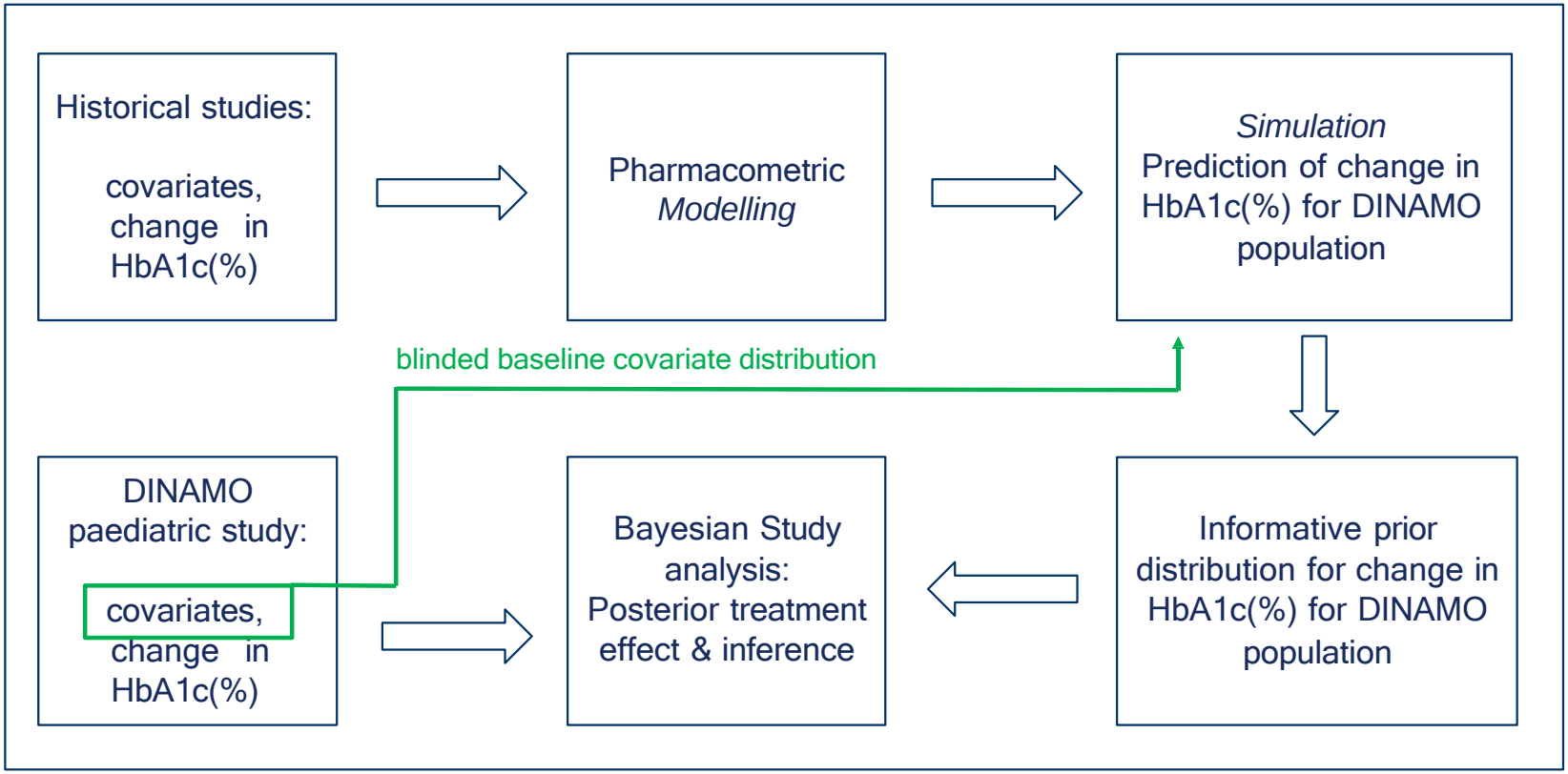
- Robust MAP prior analysis based on data in children with T2D treated with drugs with same mechanism of action
- Assumption: Exchangeability between children with T2D treated with dapagliflozin and empagliflozin / sitagliptin and linagliptin

MAP prior: meta-analytic predictive prior (Schmidli et al. 2014)

Bayesian analysis using pharmacometric modelling

Bayesian borrowing for pediatric extrapolation: The DINAMO study

Supplementary Bayesian analysis: overview



Bayesian borrowing for pediatric extrapolation: The DINAMO study

Model for empagliflozin*

- PK data on >5,000 patients from 14 studies
  - adult data and limited data on adolescents
- Population PK model fitted to data
  - Two-compartment model with sequential zero-first order absorption and fixed allometric scaling of all clearance and volume parameters
- Population PK model used to predict the area under the concentration-time curve at steady state (AUC_{ss})
- PK-PD data on >6,000 patients from 10 studies including placebo patients
- PK-PD model fitted to the data
  - Turnover exposure-response model was developed to describe HbA1c
  - Similar exposure-response relationship in adults and pediatrics supported by UGE assessment

UGE: urinary glucose excretion

* Same approach applied to linagliptin data

Robust mixture prior approach

- Model for placebo-corrected treatment effect (change in HbA1c(%)) θ_I
- Prior distribution of treatment effect (robust parametric mixture distribution)

$$p_I(\theta_I) = w_I Norm(\mu_I, v_I^*) + (1 - w_I) Norm(\mu_I, \sigma_I^2)$$

Weight of informative part of mixture prior.
Elicited with experts from trial steering committee.
$w_I = 0.65$ for empagliflozin and linagliptin agreed with FDA

Mean of informative part of mixture prior.
Calculated as mean of 5,000 means from PK-PD simulation for DINAMO population.

Variance of informative part of mixture prior.
Simulation based, with limit $ESS_{ELIR} \leq 100$ set by expert elicitation.

Variance of robust part of mixture prior.
Unit-information prior: ESS_{ELIR} equal to 1 for robust component.

- Posterior distribution of treatment effect calculated from prior and summary statistics of covariate-adjusted treatment effect in DINAMO

I: treatment group of interest, i.e. empagliflozin or linagliptin; ESS: Effective sample size; ELIR: Expected local information ratio (Neuenschwander et al. 2020)

Additional Bayesian analysis using robust MAP priors

Robust MAP prior analysis for linagliptin*

- Prior based on paediatric data in T2D from other DPP-4 inhibitors
- Two studies with Januvia (sitagliptin) were identified

Januvia 100mg[2] HbA1c change at Week 20	95	0.23		95	0.06		-0.17 (-0.62, 0.28)
Januvia 100mg[3] HbA1c change at Week 20	113	0.09		107	-0.23		-0.33 (-0.70, 0.05)

Predict treatment effect in DINAMO from historical data, assuming moderate between trial heterogeneity

Robust component of prior

Prior: $p_L(\theta_l) = 0.47Norm(-0.25, 0.17^2) + 0.11Norm(-0.23, 0.32^2) + 0.42Norm(-0.23, 2.12^2)$

- Posterior distribution of treatment effect calculated from prior and summary statistics of covariate-adjusted treatment effect in DINAMO

FDA, Statistical Review and Evaluation, NDAs 201280, 201281, 208026

* Same approach applied to empagliflozin data

Study results

Bayesian borrowing for pediatric extrapolation: The DINAMO study

Bayesian analysis* based on exposure-response data - empagliflozin

	Mean	SD	P2.5%	P5%	Median	P95%	P97.5%	Prob. superiority
Prior (exposure-response based)	-1.01	1.37	-4.37	-3.46	-1.01	1.43	2.34	0.885
Likelihood (DINAMO data)+	-0.84	0.33	-1.50	-	-	-	-0.19	-
Posterior distribution	-0.945	0.207	-1.34	-1.27	-0.949	-0.605	-0.524	>0.999

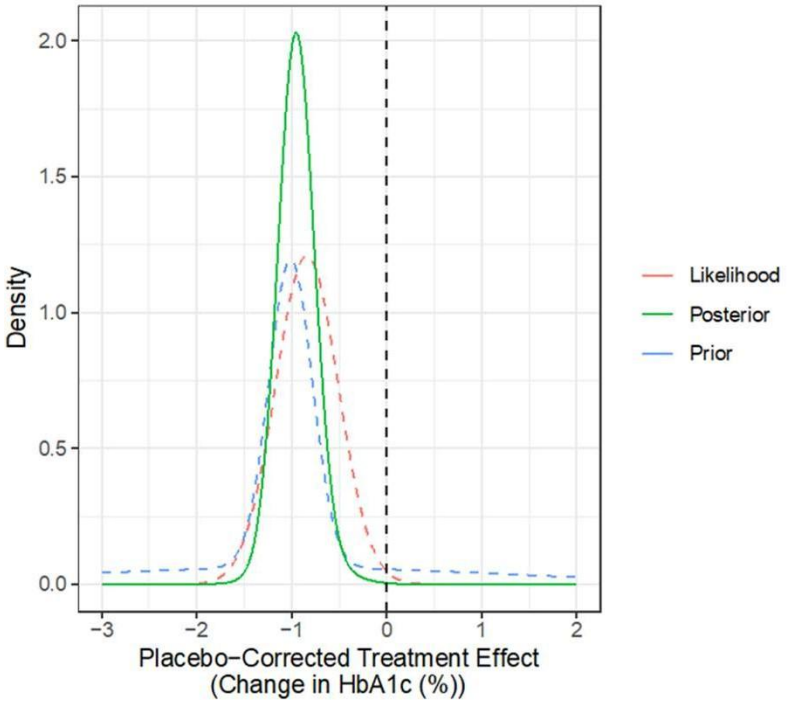
+ From DINAMO primary analysis, adjusted mean, SE and 95% confidence interval (p=0.0116)

- The primary DINAMO analysis confirmed superior efficacy
- Bayesian Borrowing analysis confirmed evidence for clinically meaningful efficacy
  - Overall probability for superiority >0.999, point estimate -0.945
  - 95% credible interval (-1.34, -0.524)

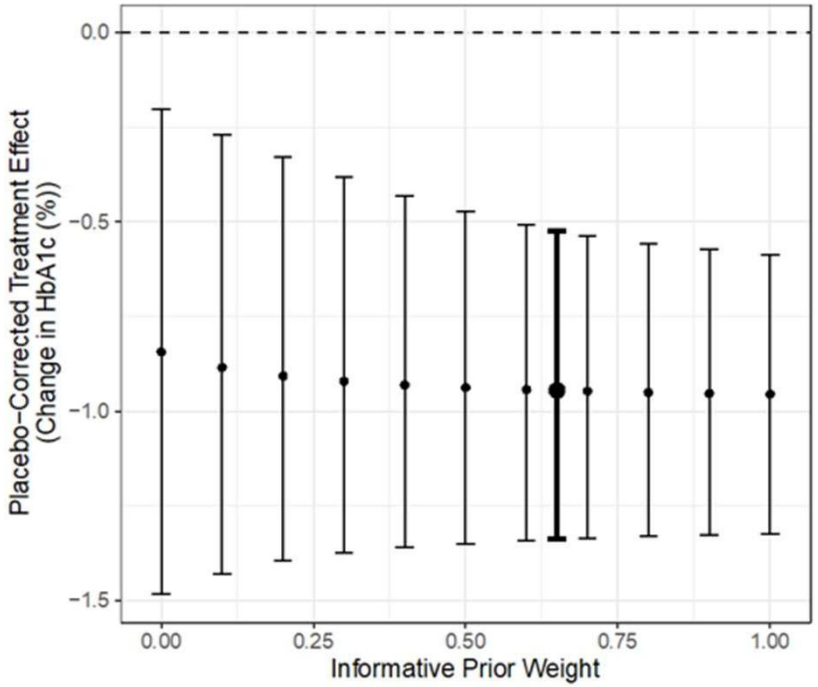
SD: standard deviation; Pn%: percentile; Prob.: probability

* Performed in R with the RBesT package (Weber et al. 2021)

Bayesian analysis based on exposure-response data - empagliflozin



Assessment of prior-data conflict



Sensitivity tipping point analysis for weight of prior (Best et al. 2021)

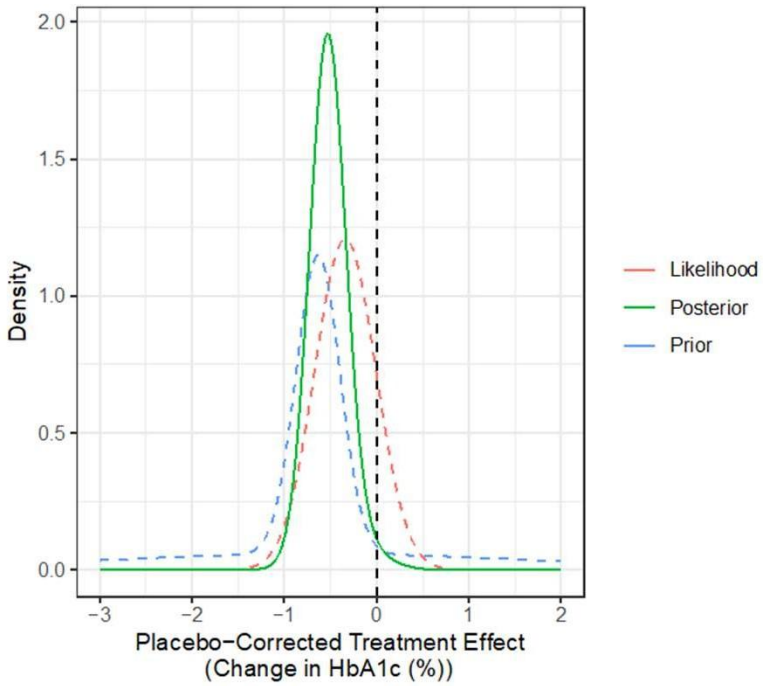
Bayesian analysis based on exposure-response data - linagliptin

	Mean	SD	P2.5%	P5%	Median	P95%	P97.5%	Prob. superiority
Prior (exposure-response based)	-0.635	1.42	-4.12	-3.18	-0.635	1.91	2.85	0.859
Likelihood (DINAMO data)*	-0.34	0.33	-0.99	-	-	-	0.30	-
Posterior distribution	-0.514	0.219	-0.919	-0.854	-0.523	-0.151	-0.052	0.982

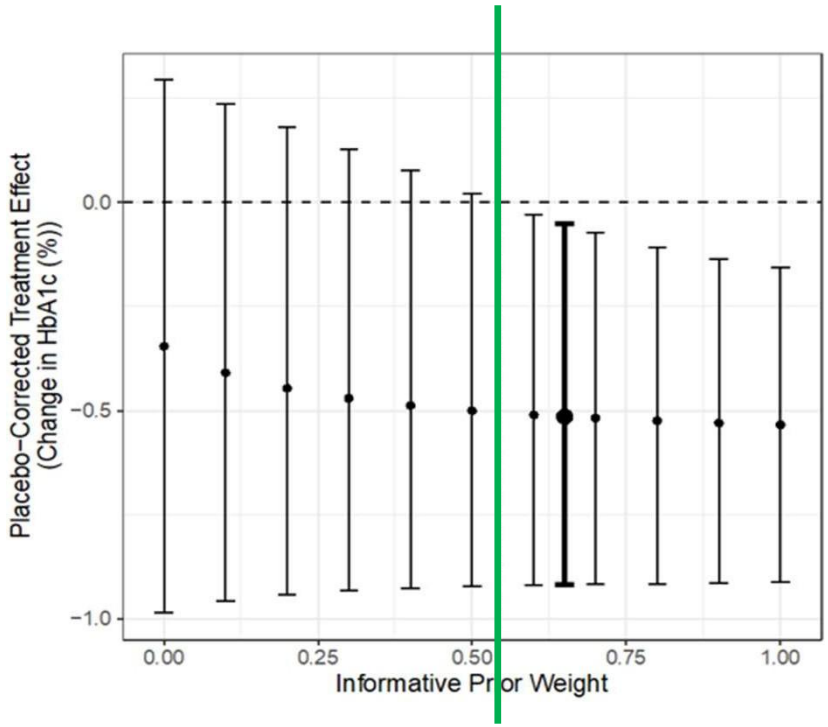
* From DINAMO primary analysis, adjusted mean, SE and 95% confidence interval (p=0.2935)

- The primary DINAMO analysis did not confirm superior efficacy
- Bayesian Borrowing analysis provided evidence for superior efficacy
  - Overall probability for superiority of 0.982, point estimate -0.514
  - 95% credible interval (-0.919, -0.052)

Bayesian analysis based on exposure-response data - linagliptin



Assessment of prior-data conflict

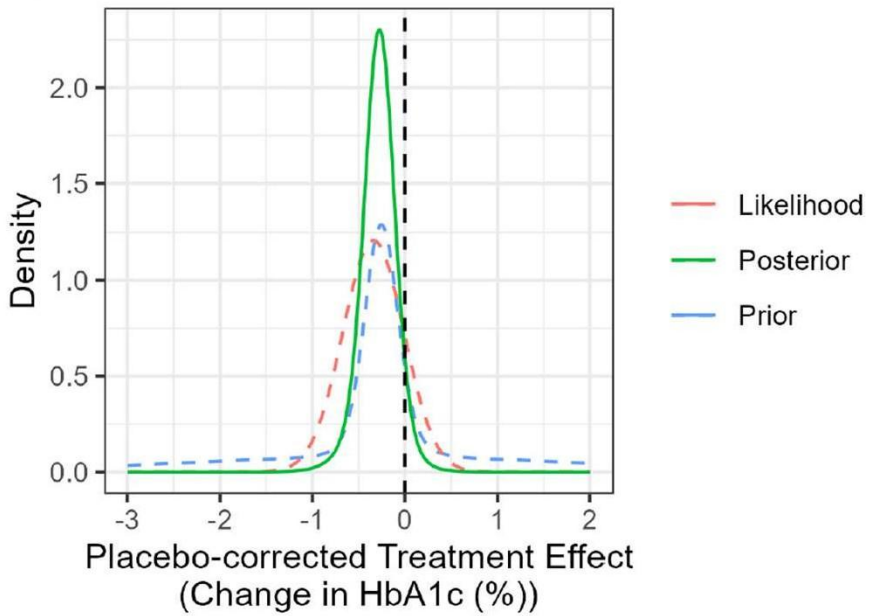


Sensitivity tipping point analysis

Tipping point w=0.542

Bayesian analysis based on robust MAP prior - linagliptin

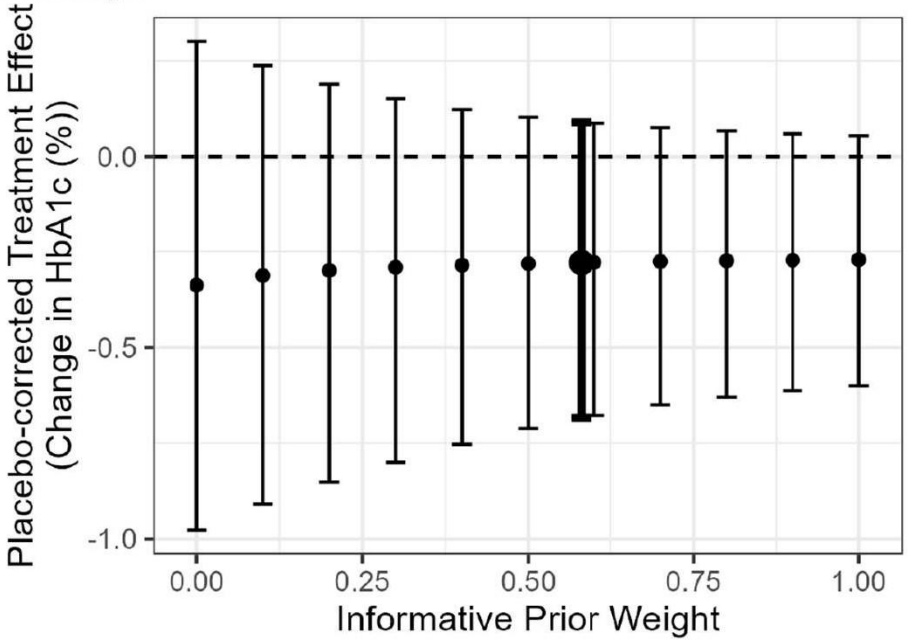
Figure 5: Linagliptin placebo-corrected treatment effect distributions



Source Statistical Reviewer's Analyses

Assessment of prior-data conflict

Figure 6: Linagliptin placebo-corrected treatment effects and 95% equal-tailed credible intervals for different weights



Sensitivity tipping point analysis

FDA, Statistical Review and Evaluation, NDAs 201280, 201281, 208026

Summary

Bayesian borrowing for pediatric extrapolation: The DINAMO study

Summary

- DINAMO showed that an empagliflozin dosing regimen provided clinically and statistically meaningful reductions in HbA1c in youth with T2D
- Bayesian Borrowing analysis confirmed evidence for clinically meaningful efficacy of empagliflozin
- Pharmacometrics-enhanced Bayesian borrowing combines advantages of mechanistic modelling of differences between adults & youth with advantages of partial extrapolation through Bayesian Dynamic Borrowing
- Additional Bayesian analysis used paediatric trial data from drugs with same mechanism of action

Additional information available

Randomized Controlled Trial > Ther Innov Regul Sci. 2025 Jan;59(1):112-123.
doi: 10.1007/s43441-024-00707-5. Epub 2024 Oct 7.

Pharmacometrics–Enhanced Bayesian Borrowing for Pediatric Extrapolation – A Case Study of the DINAMO Trial

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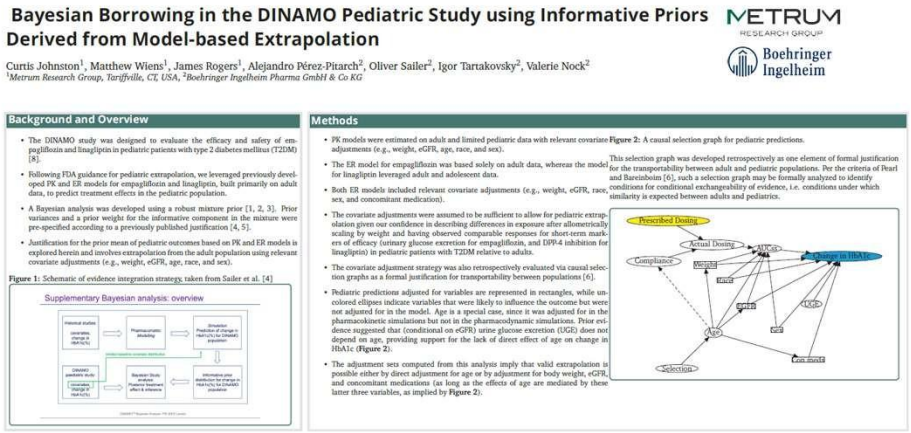
Affiliations + expand

PMID: 39373938 PMCID: PMC11706882 DOI: 10.1007/s43441-024-00707-5



Bayesian Borrowing in the DINAMO Pediatric Study using Informative Priors Derived from Model-based Extrapolation

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Background and Overview

- The DINAMO study was designed to evaluate the efficacy and safety of empagliflozin and linagliptin in pediatric patients with type 2 diabetes mellitus (T2DM) [8].
- Following FDA guidance for pediatric extrapolation, we leveraged previously developed PK and ER models for empagliflozin and linagliptin, built primarily on adult data, to predict treatment effects in the pediatric population.
- A Bayesian analysis was developed using a robust mixture prior [1, 2, 3]. Prior variances and a prior weight for the informative component in the mixture were pre-specified according to a previously published justification [4, 5].
- Justification for the prior mean of pediatric outcomes based on PK and ER models is explored herein and involves extrapolation from the adult population using relevant covariate adjustments (e.g., weight, eGFR, age, race, and sex).

Figure 1: Schematic of evidence integration strategy, taken from Sailer et al. [4]

Supplementary Bayesian analysis: overview

Methods

- PK models were estimated on adult and limited pediatric data with relevant covariate adjustments (e.g., weight, eGFR, age, race, and sex).
- The ER model for empagliflozin was based solely on adult data, whereas the model for linagliptin leveraged adult and adolescent data.
- Both ER models included relevant covariate adjustments (e.g., weight, eGFR, race, sex, and concomitant medication).
- The covariate adjustments were assumed to be sufficient to allow for pediatric extrapolation given our confidence in describing differences in exposure after allometrically scaling by weight and having observed comparable responses for short-term markers of efficacy (urinary glucose excretion for empagliflozin, and DPP-4 inhibition for linagliptin) in pediatric patients with T2DM relative to adults.
- The covariate adjustment strategy was also retrospectively evaluated via causal selection graphs as a formal justification for transportability between populations [6].
- Pediatric predictions adjusted for variables are represented in rectangles, while uncolored ellipses indicate variables that were likely to influence the outcome but were not adjusted for in the model. Age is a special case, since it was adjusted for in the pharmacokinetic simulations but not in the pharmacodynamic simulations. Prior evidence suggested that (conditional on eGFR) urine glucose excretion (UGE) does not depend on age, providing support for the lack of direct effect of age on change in HbA1c (**Figure 2**).
- The adjustment sets computed from this analysis imply that valid extrapolation is possible either by direct adjustment for age or by adjustment for body weight, eGFR, and concomitant medications (as long as the effects of age are mediated by these latter three variables, as implied by **Figure 2**).

Figure 2: A causal selection graph for pediatric predictions.

This selection graph was developed retrospectively as one element of formal justification for the transportability between adult and pediatric populations. Per the criteria of Pearl and Bareinboim [6], such a selection graph may be formally analyzed to identify conditions for conditional exchangeability of evidence, i.e. conditions under which similarity is expected between adults and pediatrics.

Disclosure

- The DINAMO trial (NCT03429543) was funded by the Boehringer Ingelheim (BI) and Eli Lilly and Company Alliance

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