Pharmacometrics-enhanced Bayesian borrowing for paediatric extrapolation – A case study of the DINAMO™ trial

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Outline

- The DINAMO trial
- Supplementary Bayesian analysis
  - Pharmacometric model and simulation
  - Prior generation
  - Statistical inference and operating characteristics
- Study results
- Summary

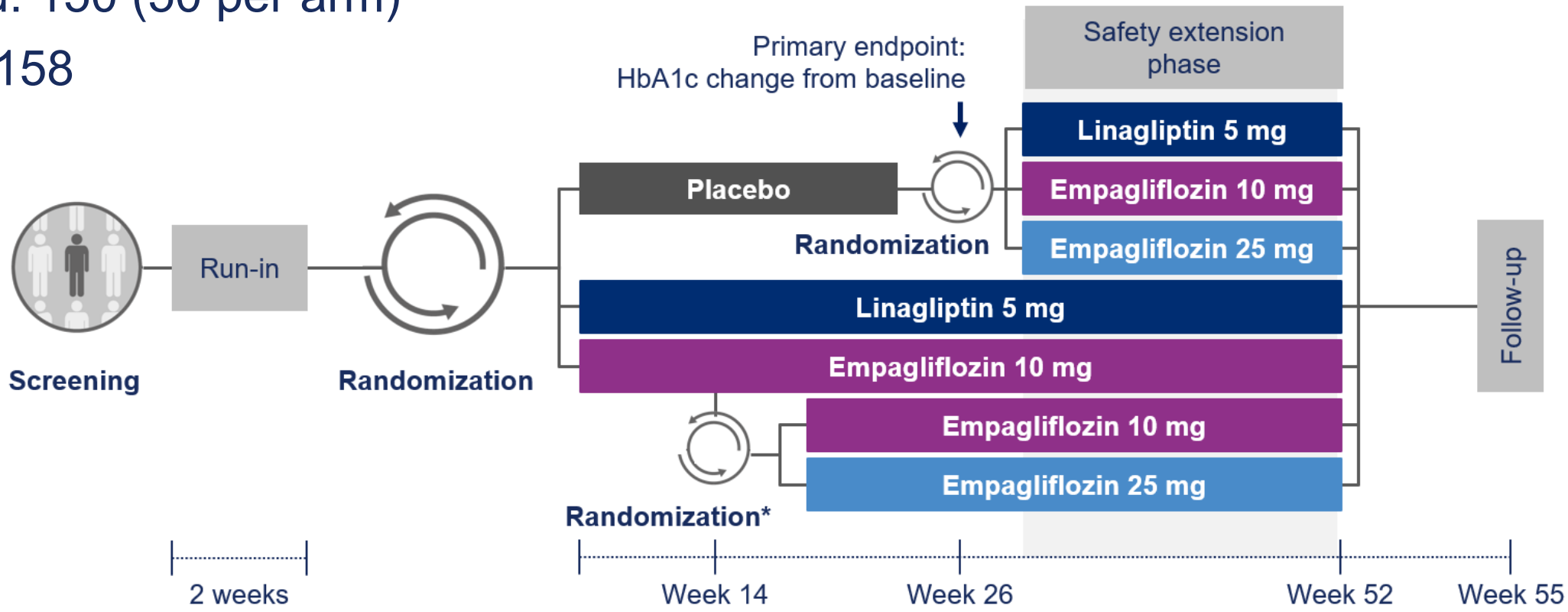
The DINAMO trial

Background

- 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 a single dose of linagliptin 5 mg, both compared with a shared placebo group

DINAMO study design

- N planned: 150 (50 per arm)
- N actual: 158



* Re-randomization at week 14 for participants not achieving HbA1c <7% at week 12

Laffel (2022)

HbA1c, glycated hemoglobin

Planned primary analysis

- Primary endpoint: Change in HbA1c from baseline to week 26
- Primary comparisons:
  - Pooled empagliflozin vs placebo
  - linagliptin vs placebo
- Modified ITT analysis, using multiple imputation for missing data
- The primary endpoint was analyzed by an ANCOVA model with baseline HbA1c as a continuous covariate, and with categorical covariates for treatment and age group

Laffel (2022)

- Stand-alone inference (no extrapolation from data in adults)
  - 85% power at 5% two-sided type I error rate

ANCOVA, analysis of covariance; ITT, intention-to-treat

Background for Bayesian analysis

- After recruitment was completed, high standard deviation was observed in early blinded data
- Need to address potential loss in power

- Reopening recruitment wasn‘t considered as best option
  - Operational feasibility
  - Substantial increase in sample size
  - Substantial delay of study read-out

- Study team proposed supplementary Bayesian analysis
  - Partial extrapolation from adult data keeps original paediatric sample size
  - Novel analysis method developed cross-functionally between Pharmacometrics (PMx), Statistics and Medicine
  - Dedicated SAP prepared and approach discussed with FDA prior to planned read-out

SAP, Statistical Analysis Plan; FDA, Food & Drug Administration

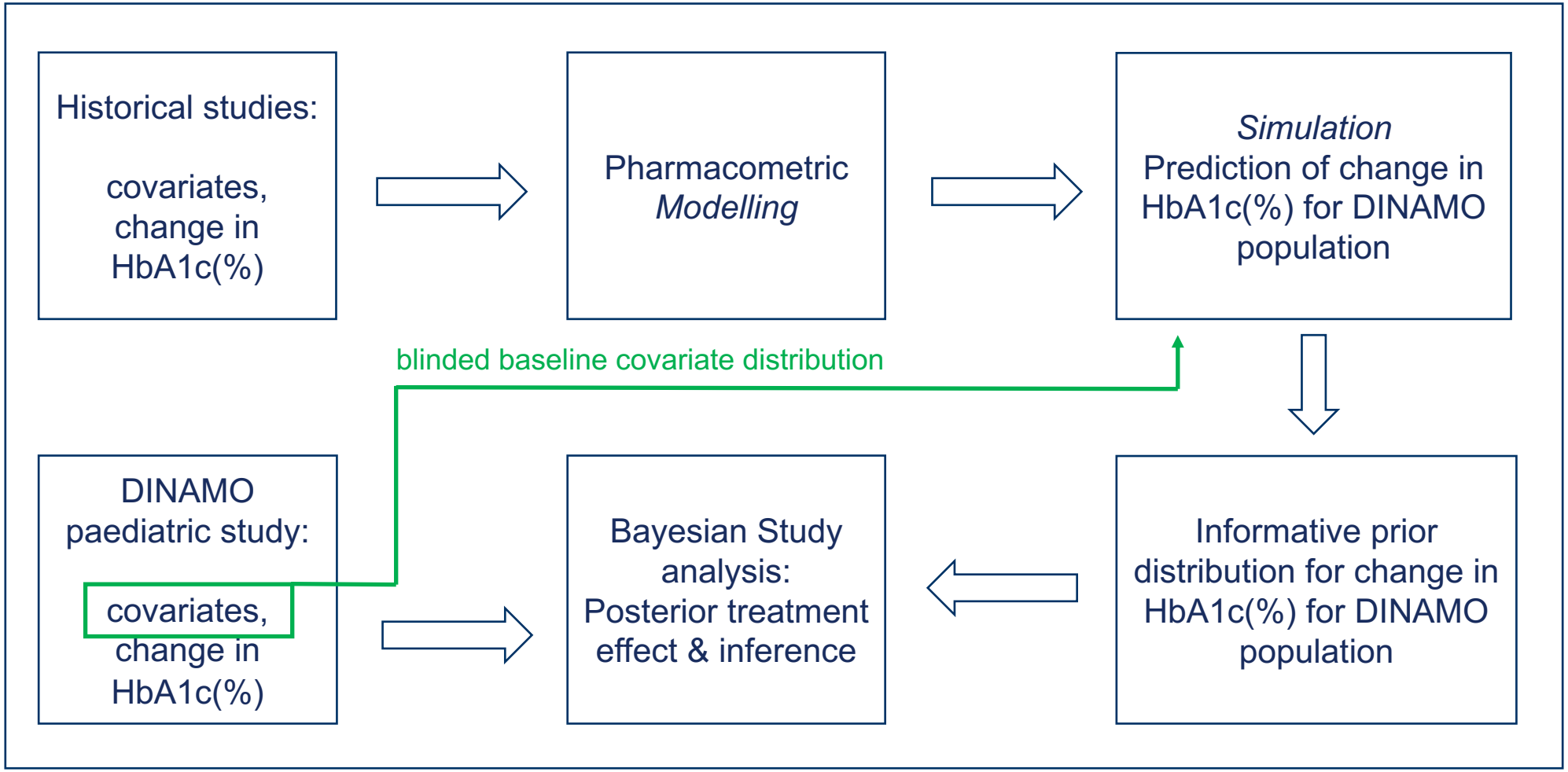
Supplementary Bayesian analysis

Supplementary Bayesian analysis

- Direct borrowing from adult data not possible
  - Exchangeability assumption violated between adults / children with T2D
- Covariate-adjusted dynamic borrowing proposed in literature (Schmidli et al. 2020)
- Regression model based on age does not reflect the mechanistic knowledge about the PK and PD differences between adults and children
- PMx model for change in HbA1c(%) in empagliflozin and linagliptin exists
- Here: PMx enhanced Bayesian borrowing (Fayette et al. 2023) approach used to leverage data from trials in adults

PK, Phamacokinetics; PD Pharmacodynamics

Supplementary Bayesian analysis: overview



Pharmacometric model and simulation

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
  - For empagliflozin only adult data was available for PD model
  - Similar exposure-response relationship in adults and pediatrics supported by UGE assessment

UGE, urinary glucose excretion

* Same approach applied to linagliptin data

Pharmacometric simulations

- 5,000 iterations
- for each iteration:
- Simulate 5,000 patients per treatment arm
  - Patients derived by resampling from the blinded DINAMO data (demographics and background medication)
- Based on allometric scaling of clearances and volumes
  - Physiologic parameters are known to scale with body size
  - To account for this, the principle of allometry is employed in PK models
  - Well-established empiric relationships between body weight and PK parameters (clearences and volumes) are implemented in the PK model
  - Allows for reasonable weight-based characterizations of PK differences

Pharmacometric simulations

- Covariates in pediatric prediction model can adjust for specific population differences
- Generate AUC_{SS} per simulated patient
- Generate longitudinal HbA1c data per simulated patient
- Calculate mean and standard deviation of the placebo corrected HbA1c change from baseline for each treatment group

Prior generation

Robust mixture prior approach

- Model for placebo-corrected treatment effect (change in HbA1c(%)) θ_I
- Using robust parametric mixture distribution
  - Proposed and used before in paediatric partial extrapolation settings*
  - Prior distribution density:

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

  - I: treatment group of interest, i.e. empagliflozin or linagliptin

* Best et al. 2021, FDA 2018

Robust mixture prior approach

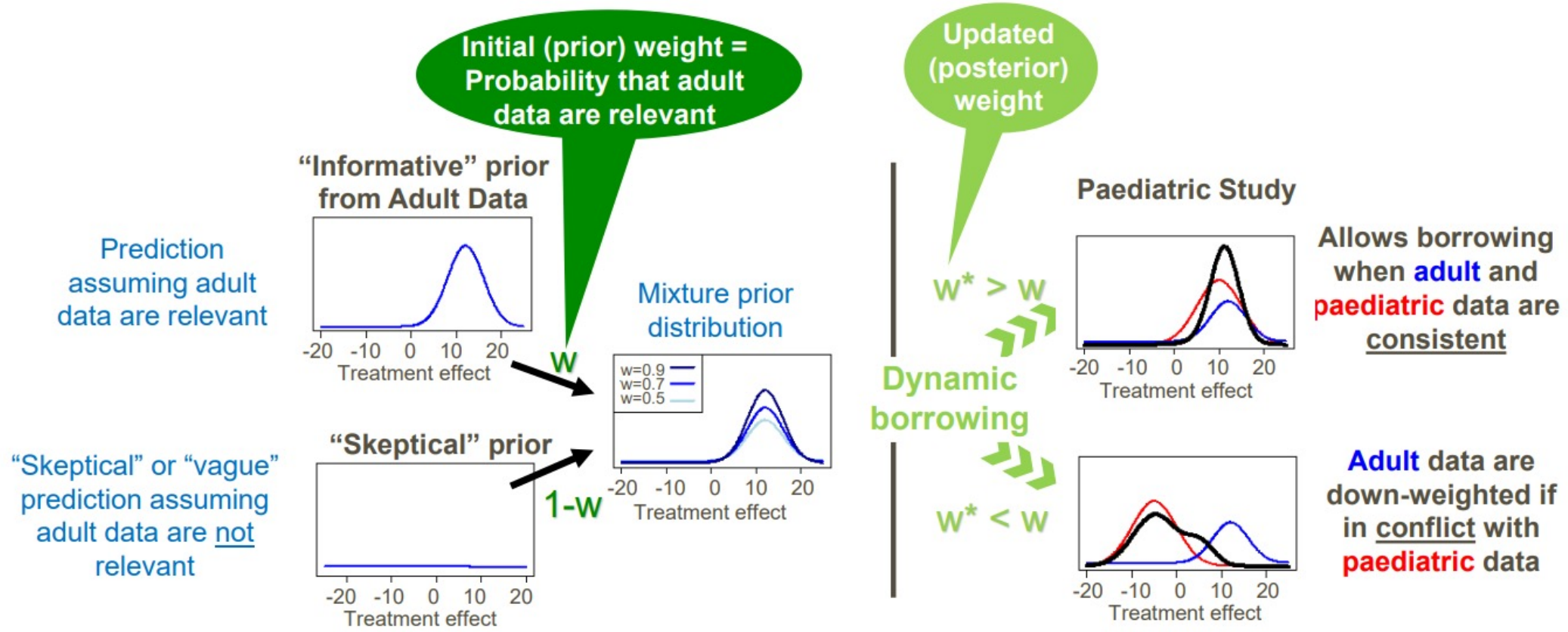


Figure taken from Best & Hammer 2021

Robust mixture prior approach

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

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

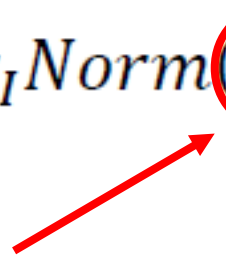
- Weight of informative part of mixture prior
  - Elicited with experts from trial steering committee
  - $w_I = 0.65$ for empagliflozin and linagliptin
  - FDA would allow adjustment of w_I such that prior ESS_{ELIR} (Neuenschwander et al. 2020) equals planned sample size

ESS, Effective sample size; ELIR, Expected local information ratio

Robust mixture prior approach

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

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



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

Robust mixture prior approach

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

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

- Variance of informative part of mixture prior
  - Calculated as sample variance of 5,000 means from PK-PD simulation for DINAMO population
  - Lower limit for v_I^* specified such that informative part of prior corresponds to at most 100 patients per treatment group based on expert elicitation

Robust mixture prior approach

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

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

- Variance of robust part of mixture prior
  - Based on unit-information standard deviation $\sigma_I = 2.3\ (2.1)$ for empagliflozin (linagliptin) vs. placebo
  - ESS_{ELIR} equal to 1 for robust component

Statistical inference and operating characteristics

Statistical inference and operating characteristics

- Posterior distribution of treatment effect calculated from prior and summary statistics of covariate-adjusted treatment effect in DINAMO
- Decision:
  - Lower effects correspond to higher efficacy
  - Compare 97.5% quantile of posterior treatment effect with 0 for each treatment group
- Prior to finalisation of SAP, present probabilities for true / false positive decisions
  - under various assumptions for prior parameters and true efficacy in children
- These operating characteristics informed final choice of prior parameters

Study results

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

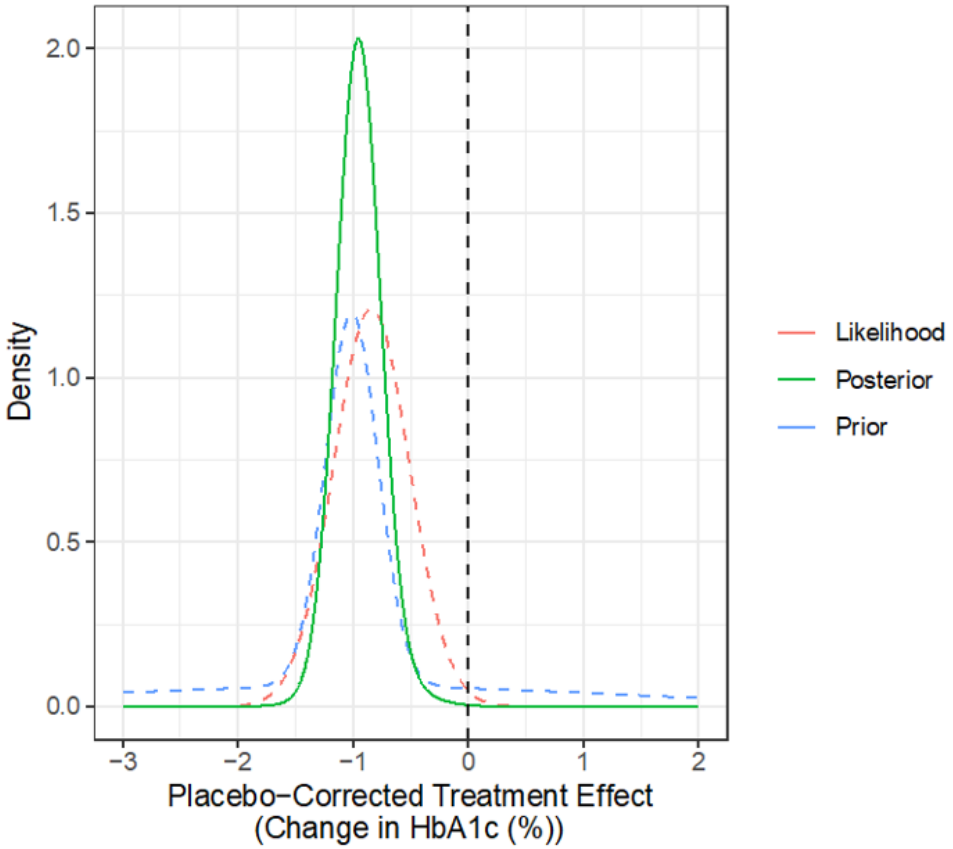
+ From DINAMO primary analysis, adjusted mean, SE and 95% confidence interval (p=0.0116)

- The primary DINAMO analysis confirmed superior efficacy
  - Closely corresponds to Bayesian analysis using an informative prior weight of 0
- 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

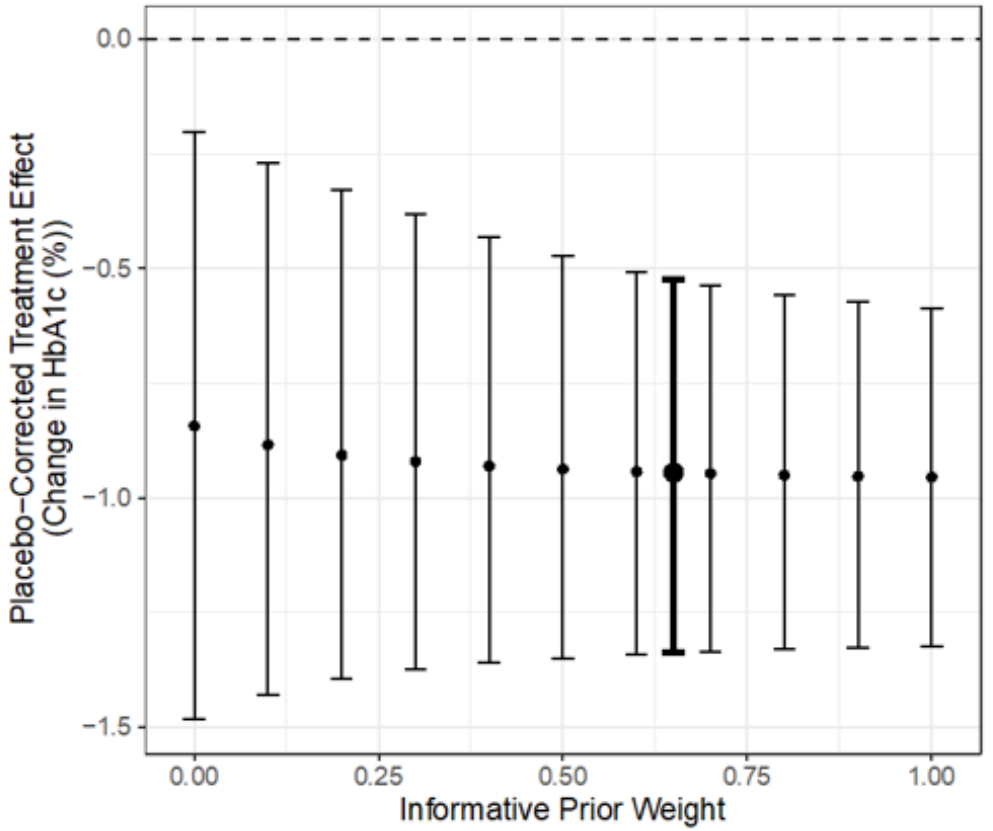
* Performed in R with the RBesT package (Weber et al. 2021)

Bayesian analysis based on exposure-response data - empagliflozin



Assessment of prior-data conflict

Prior/Posterior ESS_{ELIR}: 55/138



Sensitivity tipping point analysis

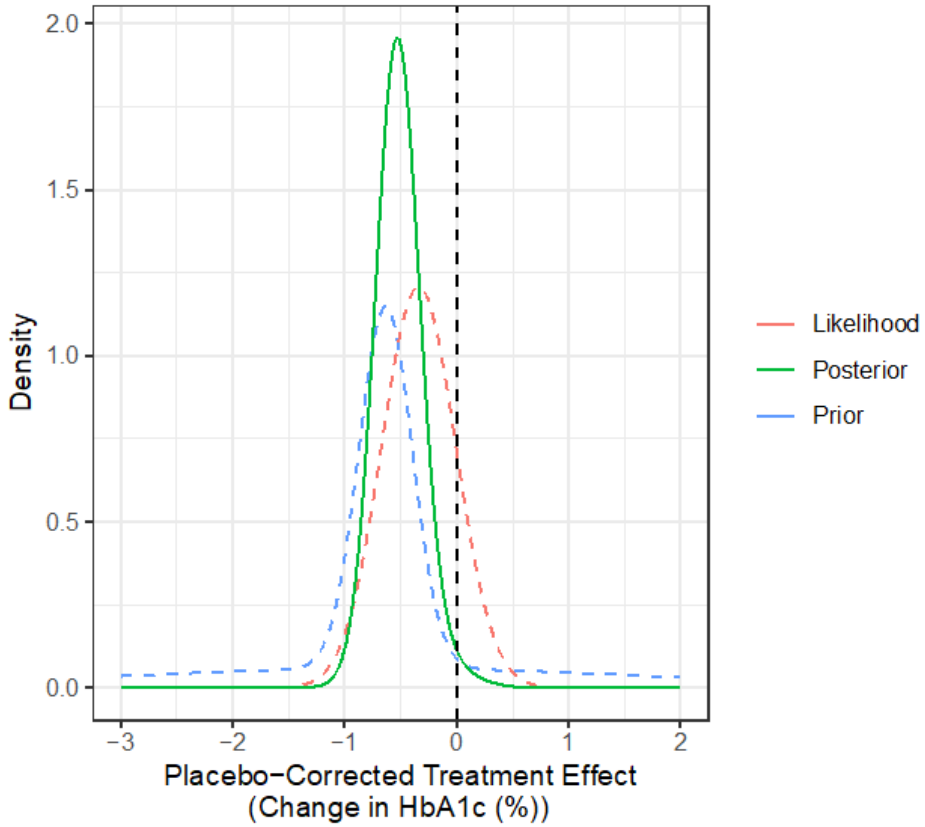
Bayesian analysis based on exposure-response data - linagliptin

	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)

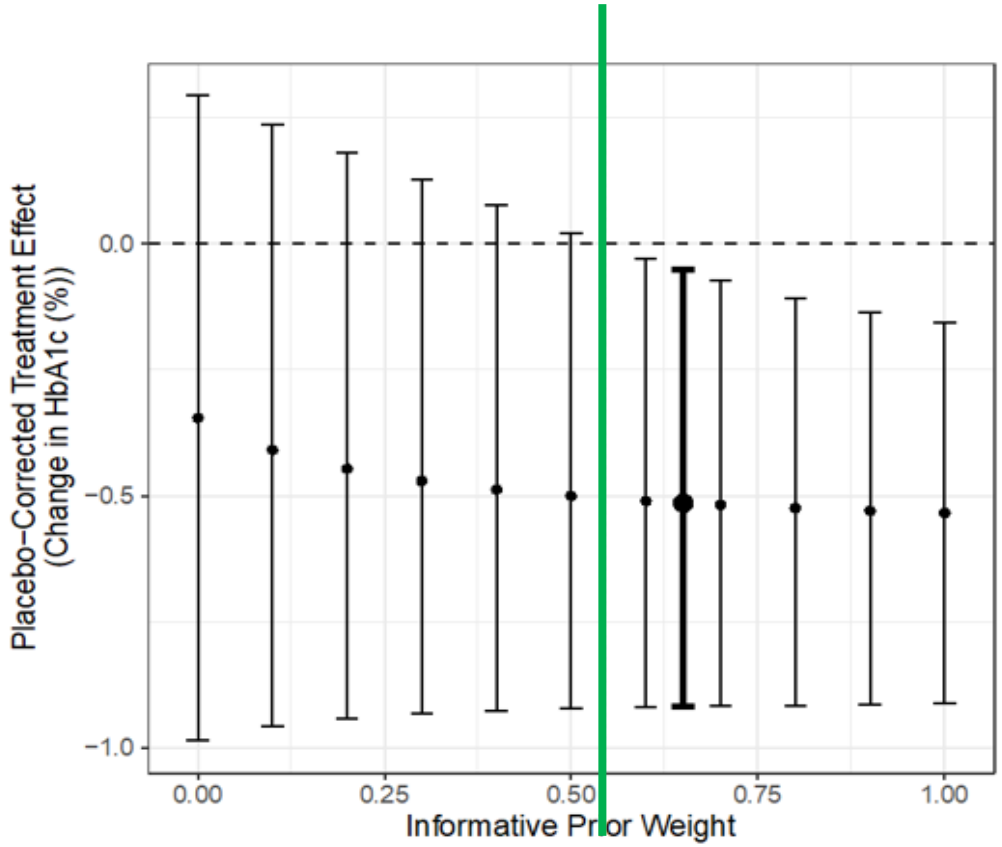
- The primary DINAMO analysis did not confirm superior efficacy
  - Closely corresponds to Bayesian analysis using an informative prior weight of 0
- Bayesian Borrowing analysis provided evidence for superior efficacy
  - Overall probability for superiority of 0.982, point estimate -0.514
  - 95% credible interval (-0.919, -0.052)

Bayesian analysis based on exposure-response data - linagliptin



Assessment of prior-data conflict

Prior/Posterior ESS_{ELIR}: 51/128



Sensitivity tipping point analysis

Tipping point w=0.542

Summary

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
- Transparent quantitative approach to aggregate knowledge about efficacy in adults, limited data in children and assumptions about the relevance of the data in adults for paediatric efficacy

Acknowledgement

- Study participants and their families
- Steering Committee members
- Coordinating and local site study staff who make up the DINAMO Study Group
- BI Study team and the QUIC* team

*Quantitative Data Integration to Enhance Clinical Trials

Disclosure

- The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE)
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