

Bayesian borrowing in a pharmaceutical company

Oliver Sailer

09 SEP 2025 | GMDS Jena

Agenda

- Use of data borrowing in clinical development
- Case study 1: Hybrid control arm in a phase 2 study
- Case study 2: Pediatric extrapolation in the DINAMO study
- EFSPi working group on historical data

Use of Bayesian borrowing in clinical development

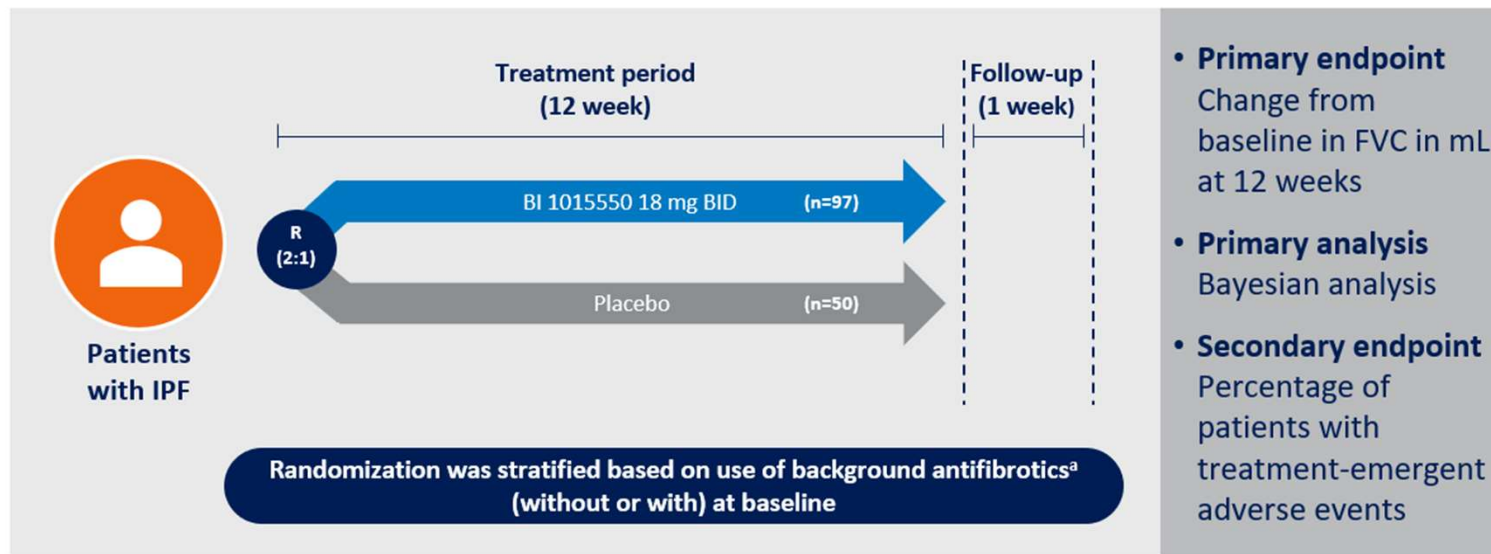
- Bayesian borrowing increasingly popular in clinical development
- Proof of concept trials / phase II: Meta-analytic predictive (MAP) prior based on historical data to reduce placebo arm
 - Baeten et al. (2013): Antiinterleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 382 (9906): 1705-13.
- Pediatric development: Robust meta-analytic predictive (rMAP) prior on treatment effect
 - Maher et al. (2024): Estimating the effect of nintedanib on forced vital capacity in children and adolescents with fibrosing interstitial lung disease using a Bayesian dynamic borrowing approach. *Pediatric Pulmonology* 59:1038-1046.

Use of Bayesian borrowing in the industry

- Rare disease / rare events: Robust MAP prior combining case-control studies
 - Cheuvart et al. (2023): Effectiveness of maternal immunisation with a three-component acellular pertussis vaccine at preventing pertussis in infants in the United States: Post-hoc analysis of a case-control study using Bayesian dynamic borrowing. *Vaccine* 41(40):5805-5812.
- Feasibility issues: Phase III but recruitment during COVID pandemic & low blinded event rate lead to protocol amendment, robust mixture prior borrowing from global population
 - Chen et al. (2024): Efficacy and safety of mepolizumab in a Chinese population with severe asthma: a phase III, randomised, double-blind, placebo-controlled trial. *ERJ Open Res* 2024; 10: 00750-2023

Case Study 1: MAP priors to augment control arm in a phase II study

Phase 2 study investigated the efficacy and safety of BI 1015550 in patients with IPF



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^aReceived a stable dose of nintedanib or pirfenidone for at least 8 weeks prior to screening. BID, twice daily; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis. Richeldi L, et al. *N Engl J Med.* 2022.

Case Study 1: MAP priors to augment control arm in a phase II study

Primary analysis: Bayesian analysis incorporating historical data



Informative priors were chosen for the placebo groups

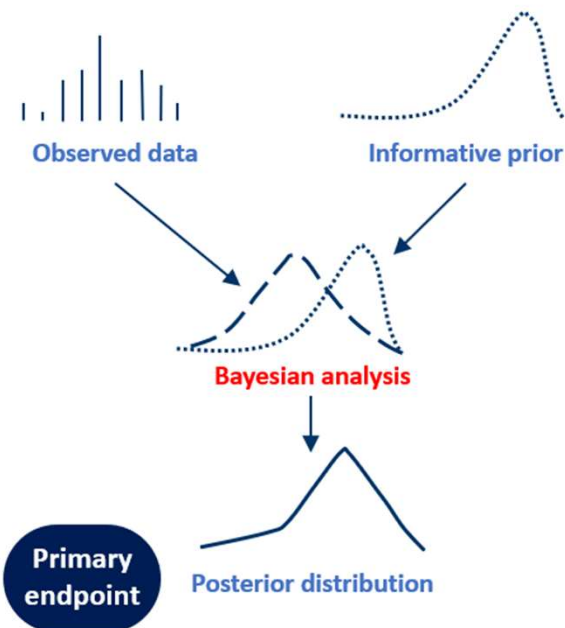


Data from the current trial and prior information were combined via Bayesian analysis to derive posterior distribution for treatment difference



Based on the posterior distribution, the median, 95% credible intervals and probabilities that BI 1015550 were superior to placebo were calculated

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Case Study 1: MAP priors to augment control arm in a phase II study

Historical data for placebo group: stratum **without** background antifibrotics

Study: 12 weeks' placebo

1199.30, TOMORROW

1199.32, INPULSIS-1

1199.34, INPULSIS-2

1199.187, Phase IIIb

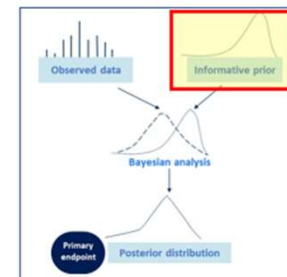
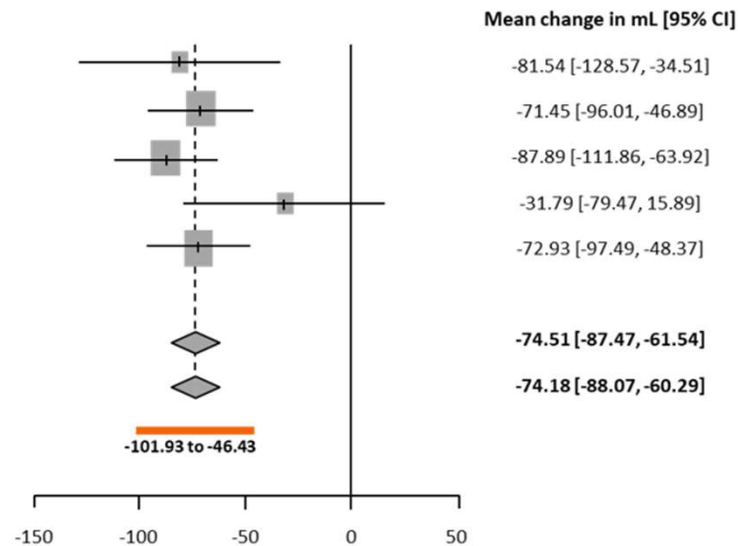
1199.227, INMARK

Fixed effect model

Random effects model

Prediction interval

Heterogeneity: $I^2 = 10\%$,
 $\tau^2 = 25.8471, p = 0.35$



The prior used for analysis was a meta-analytic predictive prior based on Bayesian meta-analysis.

CI, confidence interval; FVC, forced vital capacity.

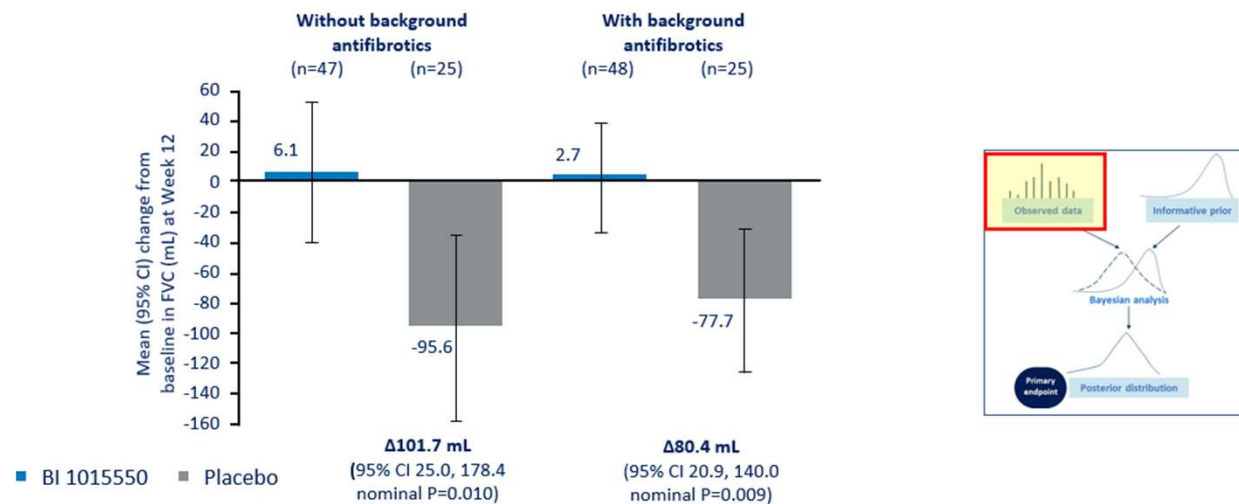
Richeldi L, et al. *N Engl J Med*. 2022.



Richeldi et al. *N Engl J Med* 2022; 386:2178-87. DOI: 10.1056/NEJMoa2201737

Case Study 1: MAP priors to augment control arm in a phase II study

Phase 2 study with BI 1015550: Change in FVC at Week 12 by MMRM analysis



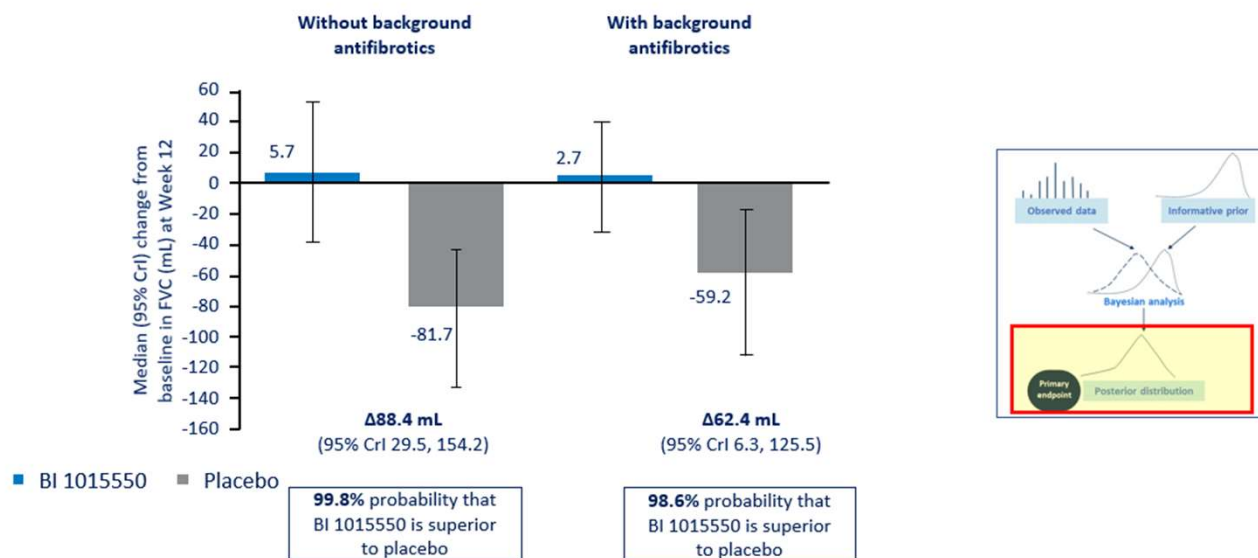
CI, confidence interval; FVC, forced vital capacity; MMRM, mixed model for repeated measures.
Figure taken from the New England Journal of Medicine, Richeldi L, Azuma A, Cottin V, et al., Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis. Copyright © (2022) Massachusetts Medical Society. Reprinted with permission. Richeldi L, et al. *N Engl J Med.* 2022.



Richeldi et al. *N Engl J Med* 2022; 386:2178-87. DOI: 10.1056/NEJMoa2201737

Case Study 1: MAP priors to augment control arm in a phase II study

Phase 2 study with BI 1015550: Change in FVC at Week 12 by Bayesian analysis



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Figure taken from the New England Journal of Medicine, Richeldi L, Azuma A, Cottin V, et al., Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis. Copyright © (2022) Massachusetts Medical Society. Reprinted with permission. Richeldi L, et al. *N Engl J Med*. 2022.

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Boehringer
Ingelheim

Richeldi et al. *N Engl J Med* 2022; 386:2178-87. DOI: 10.1056/NEJMoa2201737

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Case Study 1: MAP priors to augment control arm in a phase II study

This trial used a Bayesian approach that allowed more patients to be randomly assigned to active treatment; because of the use of historical data, this approach reduced the number of patients who were assigned to the placebo group for the 12-week duration of the trial.^{11,12} This strategy may also have facilitated the recruitment and conduct of the trial, in particular during the Covid-19 pandemic.

Case study 2:



Bayesian borrowing for paediatric extrapolation: The DINAMO study

Martin Oliver Sailer¹, Igor Tartakovsky¹

Workshop on Bayesian Statistics in Clinical Development

17th June 2025

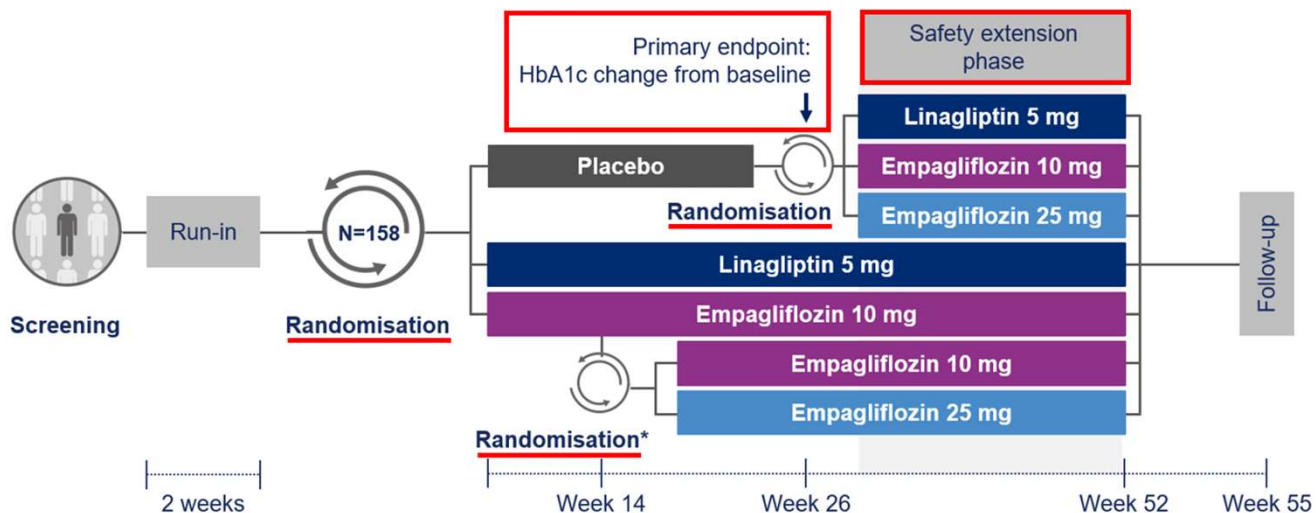
EMA, Amsterdam

¹ Boehringer Ingelheim Pharma GmbH & Co. KG

Case study 2: Pediatric extrapolation

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 T2D¹



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

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

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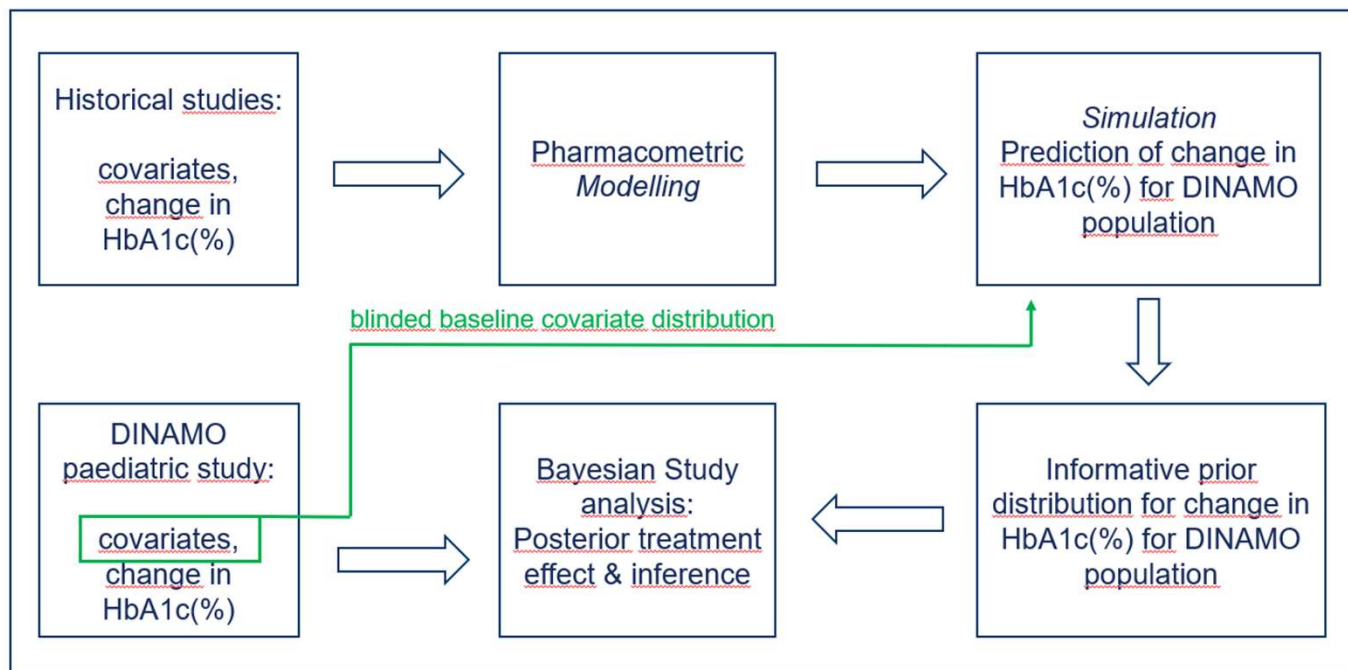
Case study 2: Pediatric extrapolation

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

Case study 2: Pediatric extrapolation

Supplementary Bayesian analysis: overview



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Case study 2: Pediatric extrapolation

- 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

Case study 2: Pediatric extrapolation

Acknowledgement: Co-authors of the Bayesian supplementary analysis

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

Martin Oliver Sailer¹, Dietmar Neubacher², Curtis Johnston³, James Rogers³, Matthew Wiens³, Alejandro Pérez-Pitarch^{4,5}, Igor Tartakovsky⁴, Jan Marquard⁶, Lori M Laffel⁷

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

Curtis Johnston¹, Matthew Wiens¹, James Rogers¹, Alejandro Pérez-Pitarch², Oliver Sailer³, Igor Tartakovsky², Valerie Nock²

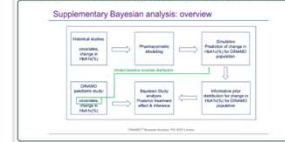
¹Metrum Research Group, Torrville, CT, USA, ²Boehringer Ingelheim Pharma GmbH & Co KG



Background and Overview

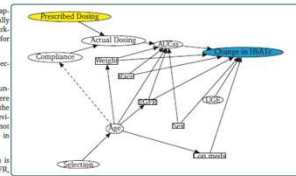
- The DINAMO study was designed to evaluate the efficacy and safety of empagliflozin and insulin in pediatric patients with type-2 diabetes mellitus (T2DM) [8].
- Following FDA guidance for pediatric extrapolation, we leveraged previously developed PK and ER models for empagliflozin and insulin, both 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]



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 insulin leveraged adult and adolescent data.
- Both ER models included relevant covariate adjustments (e.g., weight, eGFR, race, sex, and concomitant medications).
- 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 HbA1c inhibitors for insulin) 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 transpopularity 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) using 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).



Disclosure:

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

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EFSPI/PSI SIG Historical Data

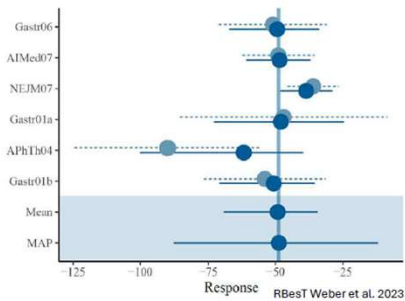
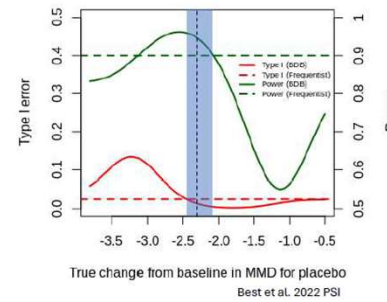


Historical Data Special Interest Group

30+ members from
15+ companies

How to incorporate historical or external data into the design and analysis of clinical trials?

- State of the art Statistical approaches
- Making historical and current data comparable
- Regulatory requirements for acceptance in drug approval



SIG activities:

- Review of methods, sources of historical data and case studies
- Collaborate with experts to refine and extend available methods
- Interact with regulators to understand their requirements
- Provide trainings, workshops and talks
- Promote good practice through templates

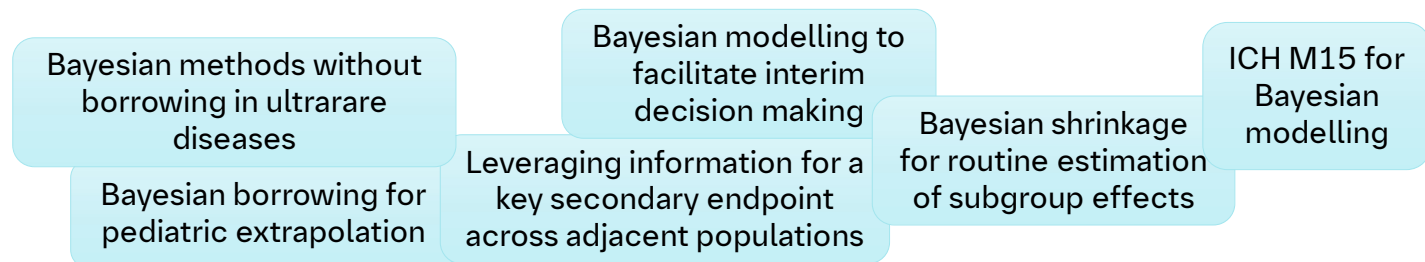
[Historical Data SIG information with materials](#)

Get in touch with the SIG leaders: nicky.x.best@gsk.com or simon.wandel@novartis.com



SIG interaction with regulators

- Ongoing request for CHMP qualification
 - Framework for evaluation and reporting of fully pre-specified Bayesian Dynamic Borrowing
 - For primary analysis of confirmatory RCTs
 - Based on robust Meta-Analytic Predictive (rMAP) prior approach
- Substantial contribution to EMA workshop on the use of Bayesian statistics in clinical development (Amsterdam, 17 June 2025)
- Industry presentations highlighting use cases of Bayesian analysis in various stages of clinical development



Summary

- Bayesian borrowing used in clinical development
- Typically in situations where a fully powered stand-alone RCT is not possible but relevant historical data exists
 - Proof-of-concept trials with external control information
 - Pediatric development following approval in adults
 - Rare diseases / events
- EFSPi/PSI SIG Historical data: Scientific and regulatory exchange on Bayesian borrowing