Bridging Disciplines with ICH M15: A Case Study on Assumption Testing for Pharmacometrics-enhanced Bayesian Borrowing

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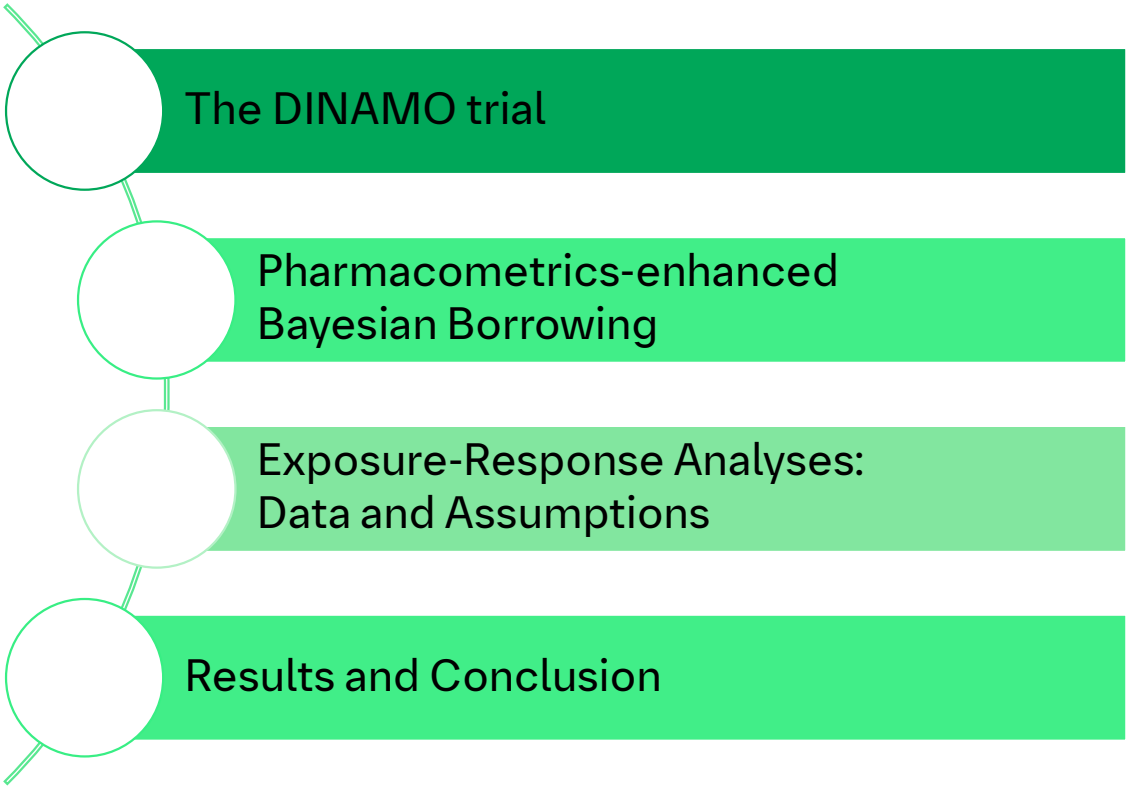
(SC-CRP-18461)

Outline


The DINAMO trial
Pharmacometrics-enhanced Bayesian Borrowing
Exposure-Response Analyses: Data and Assumptions
Results and Conclusion

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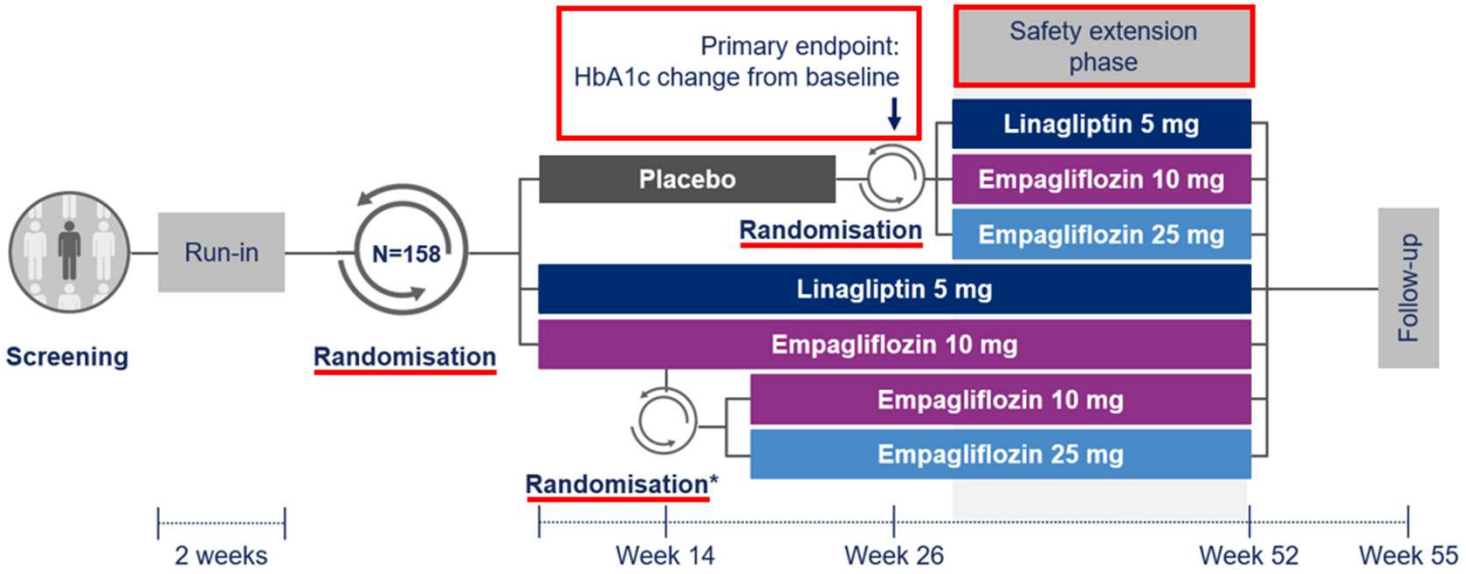
The DINAMO trial

DINAMO™

DIabetes study of
li**NA**gliptin and e**M**pagliflozin
in children and ad**O**lescents

DINAMO study design

- Main objective: 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
- Primary endpoint: Change from baseline in HbA1c after 26 weeks



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

HbA1c, glycated hemoglobin

Laffel LM *et al. Lancet Diabetes Endocrinol* 2023;11:169–81.

After recruitment was completed, high variability was observed in early blinded data

Triggered the need to adress a potential loss in power

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What motivated the application of a Bayesian Analysis?

- 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 to keep the 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 unblinding

Rational for extrapolation

- Comparable PK of linagliptin and empagliflozin in adult and pediatric patients (Phase 1)
- Linagliptin showed comparable PD effects on DPP-4 inhibition, FPG and HbA1c (Phase 1)
- Empagliflozin: Urinary Glucose Excretion (UGE) after 24 h comparable between adult and pediatric patients with T2DM (Phase 1)
  - UGE in adults is sustained over 28 days of treatment
  - Exposure Response curves for UGE and HbA1c in adults follow same shape, with 10 and 25 mg close to maximal effect
- placebo-corrected change from baseline in HbA1c is comparable between the two patient populations despite difference in disease progression

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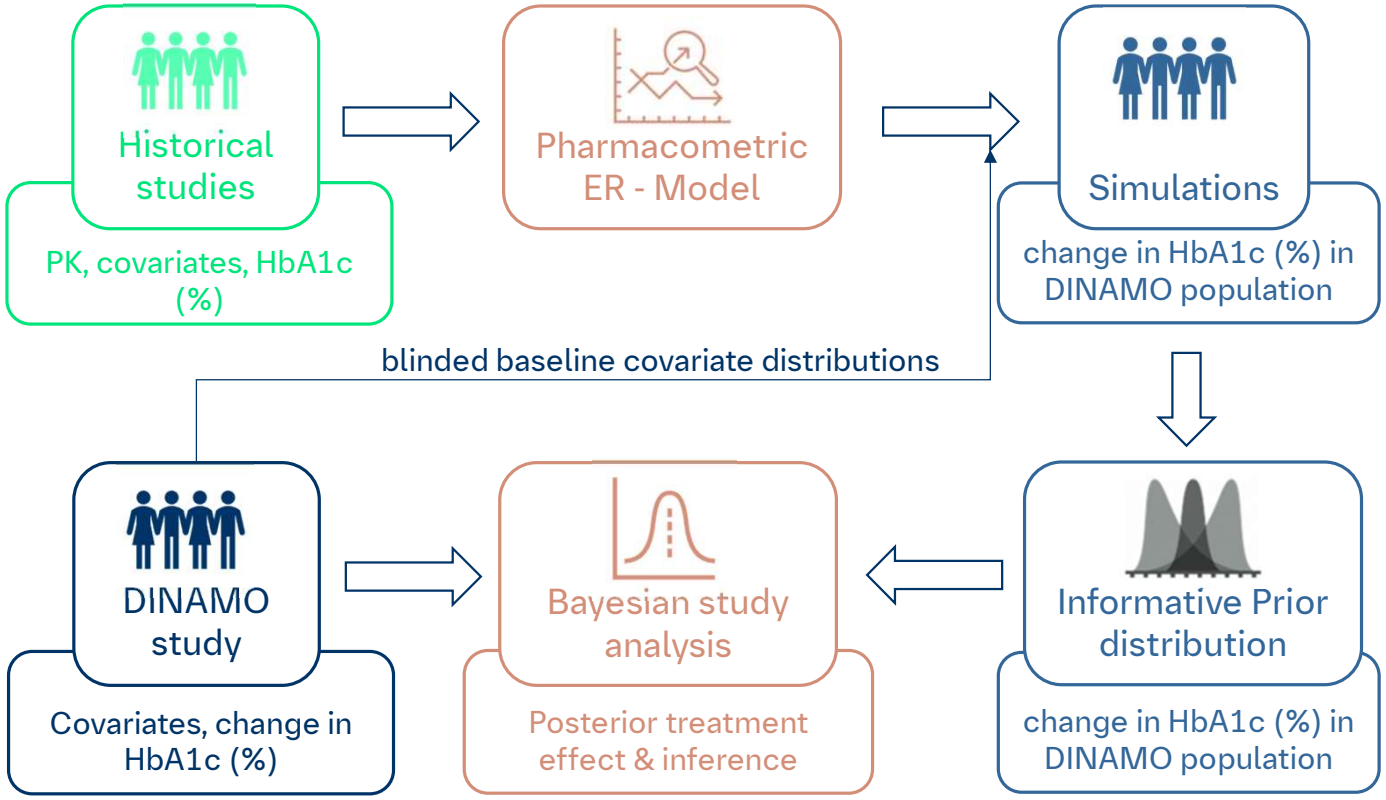
Pharmacometrics-enhanced Bayesian Borrowing

We have worked on a new methodology to borrow data across trials to make drug development more efficient

Pharmacometrics Enhanced Bayesian Borrowing (PEBB):

1. The approach uses historical data to build models to project the outcome of future clinical trials.
2. Thereafter, information is borrowed from these projections to improve the efficiency of clinical trials.

Pharmacometric-Enhanced Bayesian Borrowing



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Robust mixture priors: Dynamic borrowing accounting for potential prior-data conflict

- Prior distribution is a mixture of an informative component based on the PMx model and a weakly informative component ensuring down-weighting of the prior in case of potential prior-data conflict

Key parameter assumptions	Prior effective sample size (ESS*)	Weight of the informative prior component
Impact	Overall contribution of model-based prior to trial analysis	Extent of down-weighting of prior in case of prior-data conflict (robustness)
Planning stage	Elicit & fix prior ESS & weight with trial steering committee and FDA input Consider potential study outcomes under various choices of ESS, weight Calculate type I error rate & power under various choices of ESS, weight	
Reporting stage	Visual inspection of prior-data conflict	Sensitivity analysis of choice of weight

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* ESS ELIR, Neuenschwander et al. (2020)
Mixture prior and sensitivity analysis informed by Best N, Price RG, Pouliquen IJ, Keene ON (2021)

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Exposure-Response Analyses: Data & Assumptions

Data - empaglifozin

- Adult patients with T2DM
- PK: >5000 patients (14 studies*)
- PD: > 6000 patients (10 studies, incl. placebo)
  - Covariates relevant to PK/PD analysis:

- 52 patients receiving empagliflozin 10 or 25 mg; 51 receiving placebo

Covariate	Historical studies % or mean	DINAMO study % or mean (range)
Sex** (% female)	44.7	63.1
Age (years)	56.8	15 (10-17)
Weight (kg)	83.9	98.3 (42.5 – 169)
eGFR (ml/min/1.73 m^2)	84.8	127 (85.2 – 241)
Race (%, white| asian | black)	60.1 | 33.4 | 3.4	46.4 | 3.6 | 32.1
Baseline HbA1c (%)	8.10	8.04 (6-10.7)
Insulin | metformin (%)	6.6 | 75	50 | 90

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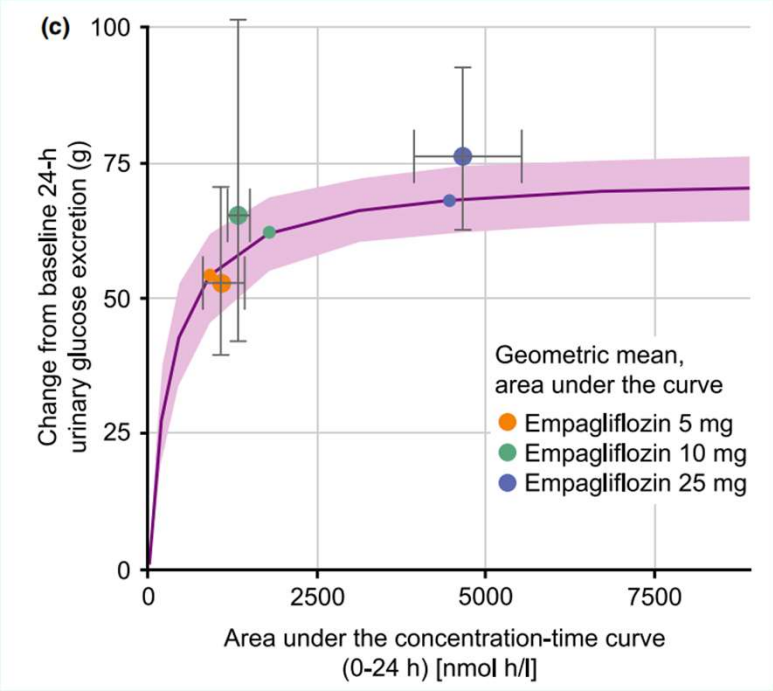
* incl. 1 Phase 1 PK trial in pediatric patients with T2DM | **PK model only

Assumptions (selection)

Justification	New / established	(Non-/) testable	Approach to assess impact
PK and PD is comparable between adults and children placebo-corrected change from baseline in HbA1c is comparable between patient populations despite difference in disease progression			
• Maturation of kidney completed at age of 2 years • Disease progression visible in placebo group	Established (Phase 1)	testable	ER analysis of dinamo data + simulations to compare ER in adults in pediatrics accounting for differences in e.g. eGFR, disease progression
AUC50 value previously estimated for fasting plasma glucose (FPG) in a ER model for FPG/HbA1c applies to updated dataset & model (AUC50 fixed)			
• AUC_{50} established based on 10 phase I-III trials across wide dose range • Comparable AUC50 values found in multiple ER analyses (other data, PD endpoints and populations) • Minor impact on drug effect at 10 and 25 mg expected as AUC50 value corresponds to empagliflozin concentrations at 3 mg	new	testable	Perform sensitivity analyses assessing impact of changes in AUC on model parameters and HbA1c change from baseline

Justification & Evaluation of Assumptions

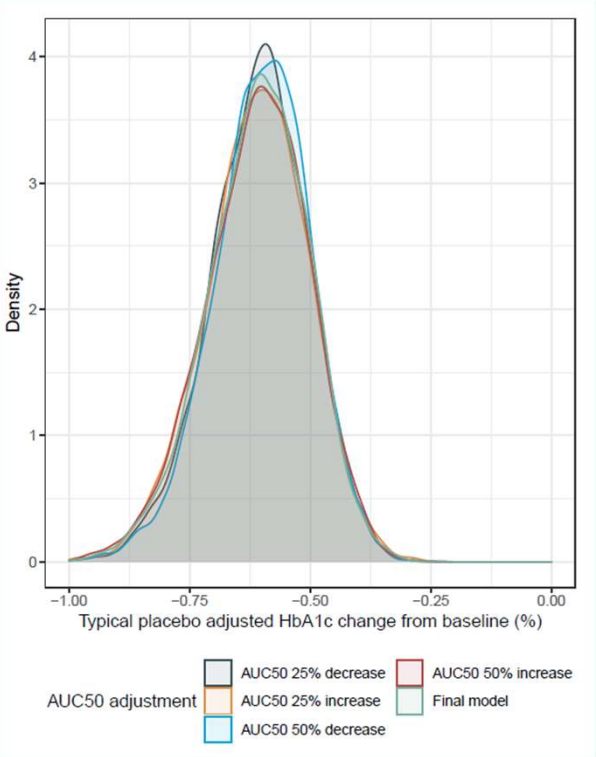
Comparable Exposure-Response (empaglifozin, Phase 1)



Pink line: median of simulations, pink shaded area: 95% CI of simulated median. Small circles: simulated change from baseline in 24-h UGE (adult) at the median 24-h AUC in each dose group simulations. Large circles: gMean change from baseline in UGE (paediatrics) at the gMean 24-h AUC in each dose group. Error bars: 95% CI of the gMeans in each dose group, calculated as gMean 1.96*SE.

Laffel LM *et al. Diabetic Medicine 2018*

Sensitivity analyses AUC50



Posterior distributions for each model of sensitivity analysis. Every 10th interaction across 4 chains is shown for all models. Models were run with 1000 burnin and 2000 sampling iterations.

Cheng et al. ACoP 2023

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Results & Conclusion

Bayesian analysis based on exposure-response data - empagliflozin

	Mean	SD	P2.5%	P97.5%	Prob. superiority
Prior (exposure-response based)	-1.02	1.37	-4.37	2.34	0.885
Likelihood (DINAMO data)+	-0.84	0.33	-1.50	-0.19	-
Posterior distribution	-0.945	0.207	-1.34	-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 of empagliflozin

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Sailer et al. (2025)
Calculation: RBesT package (Weber et al. 2021)
SD, standard deviation; Pn%, percentile; Prob., probability

Bayesian analysis based on exposure-response data - linagliptin

	Mean	SD	P2.5%	P97.5%	Prob. superiority
Prior (exposure-response based)	-0.635	1.42	-4.12	2.85	0.859
Likelihood (DINAMO data)*	-0.34	0.33	-0.99	0.30	-
Posterior distribution	-0.514	0.219	-0.919	-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
- In the linagliptin analysis, the ER model predicted a greater treatment effect (-0.64 %) than was observed in DINAMO (-0.34 %)
- Efficacy criterion met in Bayesian analysis with prespecified weight of informative prior

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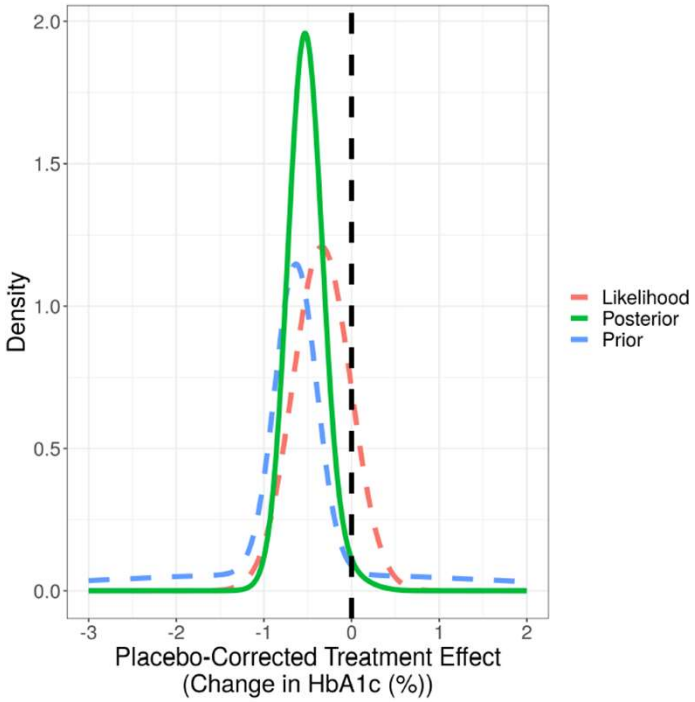
Sailer et al. (2025)
Calculation: RBesT package (Weber et al. 2021)
SD, standard deviation; Pn%, percentile; Prob., probability

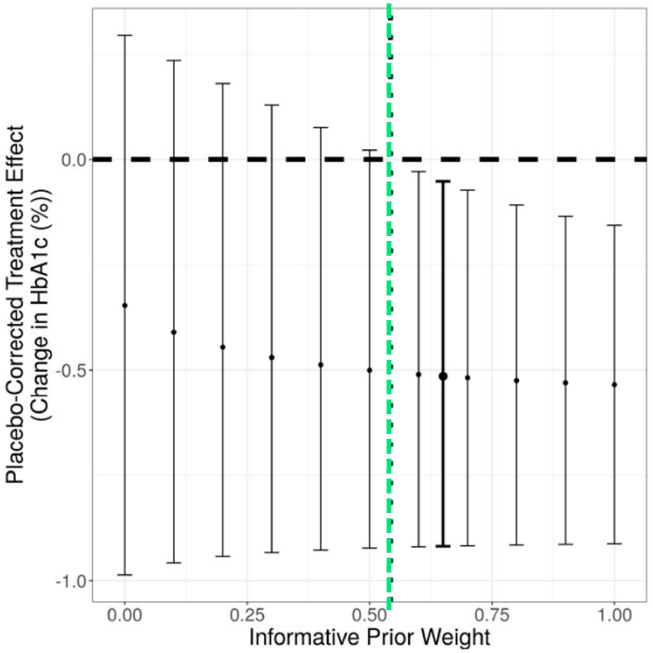
Assumption testing & sensitivity analysis - linagliptin

Assessment of prior-data conflict



Sensitivity tipping point analysis

Tipping point w=0.542



The 95% credible intervals are represented by the ends of line segments. The horizontal dashed line corresponds to the null effect and the green dotted line corresponds to the tipping point threshold. The bold interval corresponds to the pre-specified informative weight of 0.65.

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Summary & Conclusions

- Pharmacometrics-enhanced Bayesian borrowing combines advantages of mechanistic modelling of differences between adults & youth with advantages of partial extrapolation through Bayesian Dynamic Borrowing
- The QUIC team, a collaboration between Biostatistics and Pharmacometrics, enabled timely and efficient discussions with the study team and steering commitee, resulting in the application of the PEBB approach to the DINAMO trial
- Question of Interest, Context of Use, Model Risk and Impact were explicitly adressed during planning and conduct of the analyses
- Questions around model influence and consequence of wrong decision have been implicitly adressed during discussions within the development team and internal decision making
- ICH M15 offers a more structured framework to adress these questions upfront

Acknowledgements

Co-authors of the DINAMO supplementary analysis

- Dietmar Neubacher, Curtis Johnston, James Rogers, Matthew Wiens, Alejandro Perez-Pitarch, Igor Tartakovsky, Jan Marquard, Lori Laffel

Disclosure

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Back-up

Assumption AUC50

sensitivity analyses

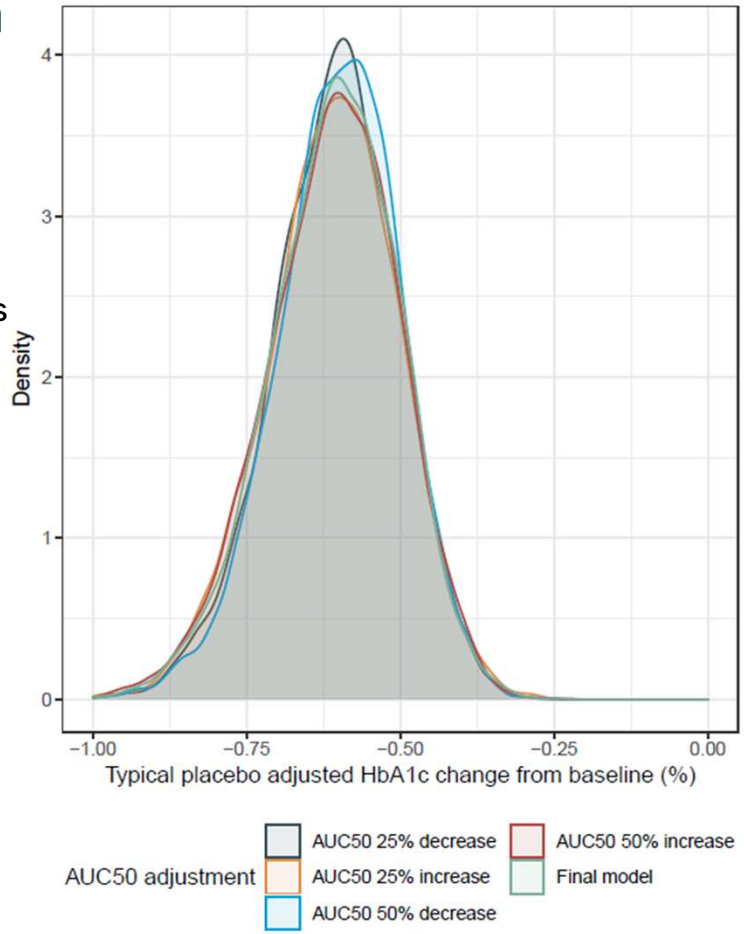
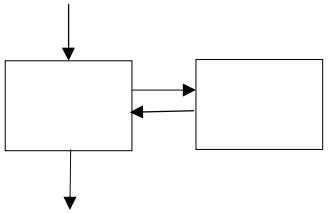


Figure 125: ER model: Impact of AUC50 fixed estimate on typical model predicted placebo-adjusted HbA1c change from baseline at week 26.

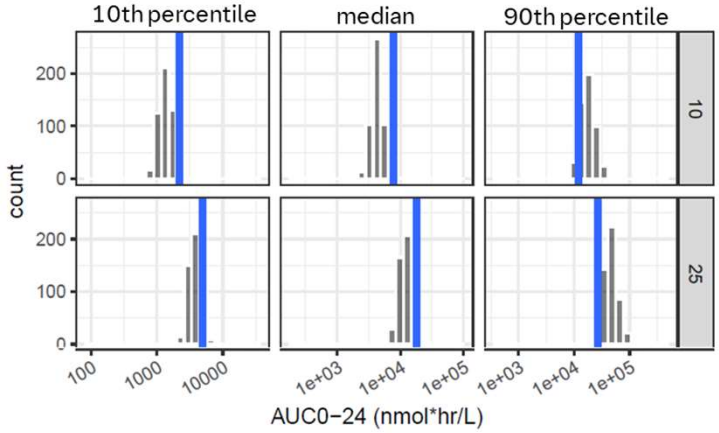
- AUC50 has been established for FPG in a previously developped FPG/HbA1c exposure-repsonse model (10 studies, Phase I-III, dose range: 1-100 mg)
- AUC50 of 703 nM*h corresponds to a dose of approximately 3 mg
- Empagliflozin 10 and 25 mg result in a near-maximal effect in terms of HbA1c lowering
- Negligible impact of fixing AUC50 has been shown during previous sensitivity analyses

Empagliflozin PK and exposure-response model

Population Pharmacokinetic model



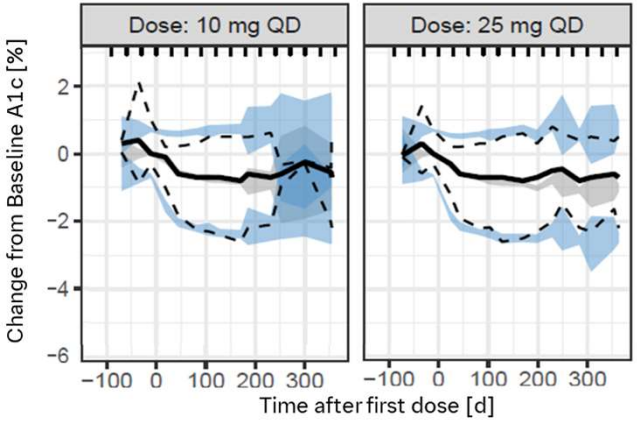
- 2 compartment model
- Sequential zero- and first-order absorption
- Linear elimination



Empagliflozin AUC by dose (last dose only). Solid blue lines: observed percentiles (study 1245.2, 1245.4), grey bars: simulated (n=500). AUC calculated via trapezoidal method

Exposure-Repsonse model

- Turnover model
- Inhibitory drug effect (Imax) on synthesis rate kin
- Placebo / disease effect



Black lines: median, 5th and 95th percentile of observed data. Blue and gray shaded regiosn: 95% predicition interval of corresponding simulated percentiles.

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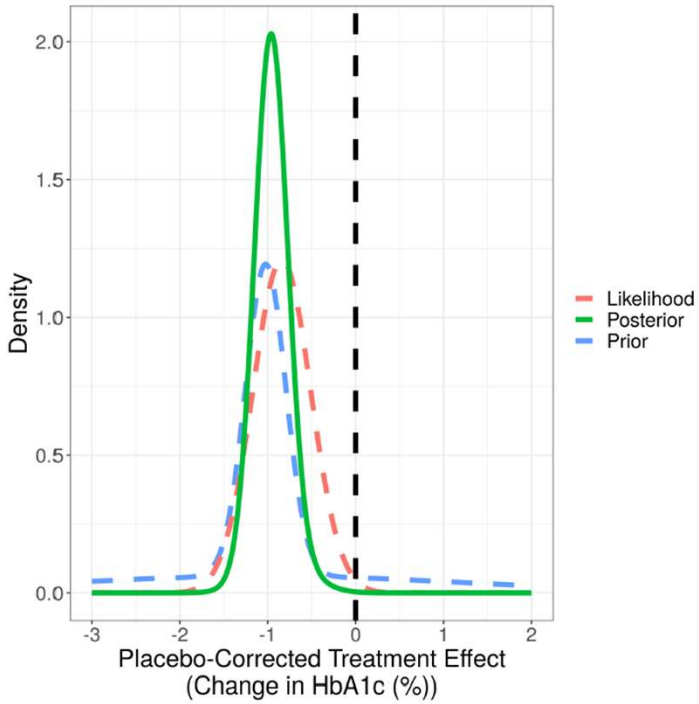
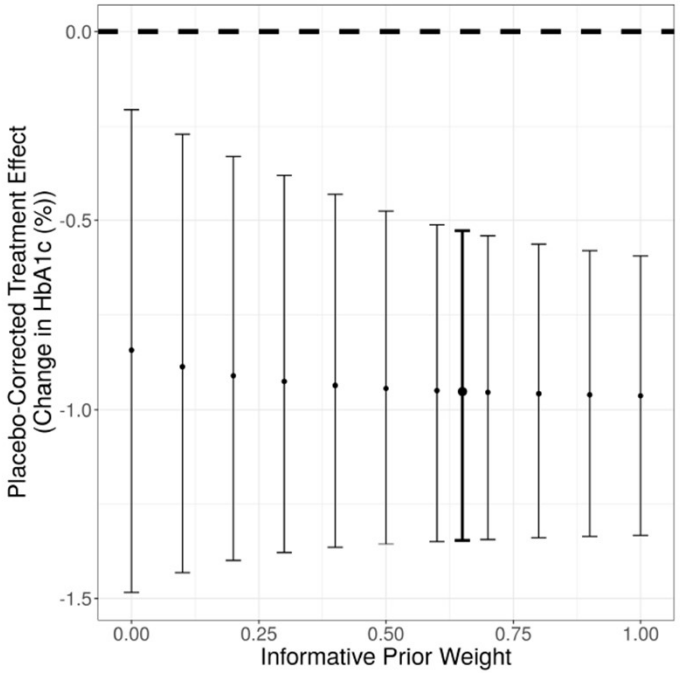
Assumption testing & sensitivity analysis - empagliflozin

Assessment of prior-data conflict



Sensitivity tipping point analysis



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