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

Laffel (2022)

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

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

Laffel (2022)

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

DINAMOTM Bayesian Analysis. PSI 2023 London
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
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, Pharmacokinetics; PD Pharmacodynamics
Supplementary Bayesian analysis: overview

- **Historical studies:**
  - covariates, change in HbA1c(%)  

- **DINAMO paediatric study:**
  - covariates, change in HbA1c(%)  

- **Blinded baseline covariate distribution**

- **Pharmacometric Modelling**

- **Bayesian Study analysis:**
  - Posterior treatment effect & inference

- **Simulation**
  - Prediction of change in HbA1c(%) for DINAMO population

- **Informative prior distribution for change in HbA1c(%) for DINAMO population**

**Diagram notes:**
- Historical studies: covariates, change in HbA1c(%)
- Pharmacometric Modelling
- Simulation: Prediction of change in HbA1c(%) for DINAMO population
- Bayesian Study analysis: Posterior treatment effect & inference
- Informative prior distribution for change in HbA1c(%) for DINAMO population
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 (clearances 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(%)) $\theta_i$

• Using robust parametric mixture distribution
  • Proposed and used before in paediatric partial extrapolation settings*
  • Prior distribution density:

$$p_I(\theta_I) = w_I \text{Norm}(\mu_I, \nu^*_I) + (1 - w_I) \text{Norm}(\mu_I, \sigma^2_I)$$

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

* Best et al. 2021, FDA 2018
Robust mixture prior approach

Prediction assuming adult data are relevant

"Skeptical" or "vague" prediction assuming adult data are not relevant

Initial (prior) weight = Probability that adult data are relevant

Updated (posterior) weight

"Informative" prior from Adult Data

Mixture prior distribution

Paediatric Study

Dynamic borrowing

Allows borrowing when adult and paediatric data are consistent

Adult data are down-weighted if in conflict with paediatric data

Figure taken from Best & Hammer 2021
Robust mixture prior approach

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

\[ p_I(\theta_I) = w_I \text{Norm}(\mu_I, \nu_I^*) + (1 - w_I)\text{Norm}(\mu_I, \sigma_I^2) \]

- 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 $\text{ESS}_{\text{ELIR}}$ (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(%) \( \theta_I \))
• Using robust parametric mixture distribution

\[
p_I(\theta_I) = w_I \text{Norm}(\mu_I, \nu_I^*) + (1 - w_I) \text{Norm}(\mu_I, \sigma_I^2)
\]

• 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(\%)) $\theta_I$
• Using robust parametric mixture distribution

$$p_I(\theta_I) = w_I \text{Norm}(\mu_I, \nu^*_I) + (1 - w_I) \text{Norm}(\mu_I, \sigma_I^2)$$

• 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 $\nu^*_I$ 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(%) \( \theta_i \))
- Using robust parametric mixture distribution

\[
p_I(\theta_i) = w_I \text{Norm}(\mu_I, \nu_I^*) + (1 - w_I) \text{Norm}(\mu_I, \sigma_I^2)
\]

- 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\text{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

<table>
<thead>
<tr>
<th>Prior (exposure-response based)</th>
<th>Mean</th>
<th>SD</th>
<th>P2.5%</th>
<th>P5%</th>
<th>Median</th>
<th>P95%</th>
<th>P97.5%</th>
<th>Prob. superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.01</td>
<td>1.37</td>
<td>-4.37</td>
<td>-3.46</td>
<td>-1.01</td>
<td>1.43</td>
<td>2.34</td>
<td>0.885</td>
</tr>
<tr>
<td>Likelihood (DINAMO data)*</td>
<td>-0.84</td>
<td>0.33</td>
<td>-1.50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.19</td>
<td>-</td>
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<tr>
<td>Posterior distribution</td>
<td>-0.945</td>
<td>0.207</td>
<td>-1.34</td>
<td>-1.27</td>
<td>-0.949</td>
<td>-0.605</td>
<td>-0.524</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

* 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

- 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)

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<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>P2.5%</th>
<th>P5%</th>
<th>Median</th>
<th>P95%</th>
<th>P97.5%</th>
<th>Prob. superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior (exposure-response based)</td>
<td>-0.635</td>
<td>1.42</td>
<td>-4.12</td>
<td>-3.18</td>
<td>-0.635</td>
<td>1.91</td>
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<tr>
<td>Likelihood (DINAMO data)*</td>
<td>-0.34</td>
<td>0.33</td>
<td>-0.99</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.30</td>
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<tr>
<td>Posterior distribution</td>
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<td>-0.919</td>
<td>-0.854</td>
<td>-0.523</td>
<td>-0.151</td>
<td>-0.052</td>
<td>0.982</td>
</tr>
</tbody>
</table>

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

Disclosure

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