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Predicting late-phase outcome from early-phase findings using a model-based approach

Application to Type 2 Diabetes Mellitus

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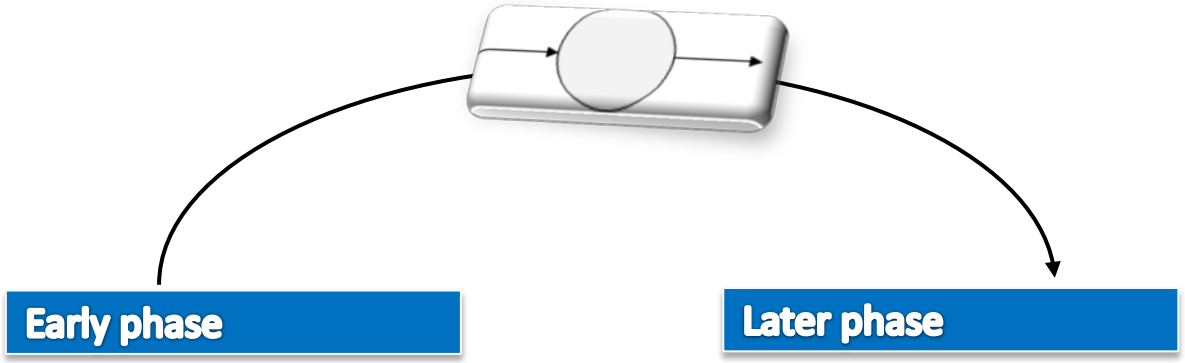
Background
Predicting the next phase in development

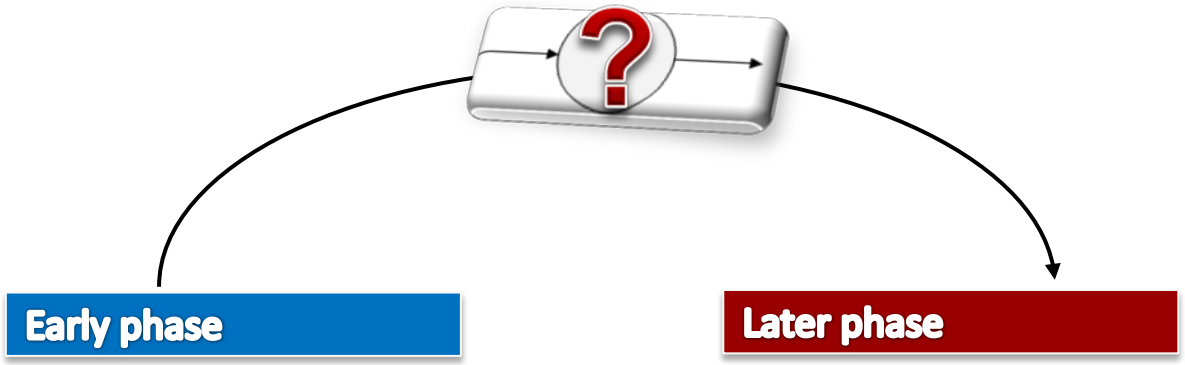
Prediction of later phase from early phase data

⇨ Same biomarker in early and later phase
(or later phase biomarker calculation of early phase biomarker)



Background
Predicting the next phase in development

What if biomarkers are not the same?



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Background
Diabetes Mellitus

- Chronic disease with malfunctioning glucose control
- High blood glucose leads to nerve, kidney, and eye damages as well as cardio-vascular disease
- Glycation reactions occur proportional to level of blood glucose

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Background
Biomarkers in Diabetes Mellitus

- Chronic disease with malfunctioning glucose control
- High blood glucose leads to nerve, kidney, and eye damages as well as cardio-vascular disease
- Glycation reactions occur proportional to level of blood glucose

Early biomarkers: Glucose (and insulin)

Later biomarker: Glycosylated haemoglobin (HbA1c)

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Background
Biomarkers in Diabetes Mellitus

Glucose (and insulin):

- Fast biomarker
- Highly variable
- Sensitive to food intake, circadian rhythm, etc.

- Typical use: phase 1
- Controlled diet settings
- Study duration: < 24 hrs

HbA1c:

- Turn-over 2-3 months – life-spans of RBC
- Less variable
- Less sensitive

- Typical use: phase 2 and 3
- Normal diet settings
- Study duration: > 12 weeks

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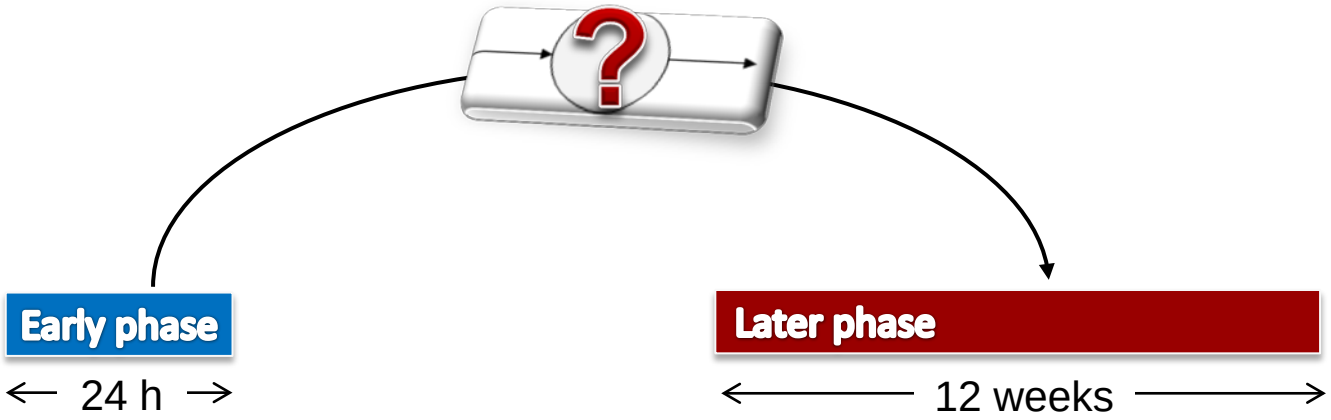
Question

Can we use semi-mechanistic models to predict a later phase where HbA1c is measured for 12 weeks from an earlier phase where glucose is measured for 24 hours?



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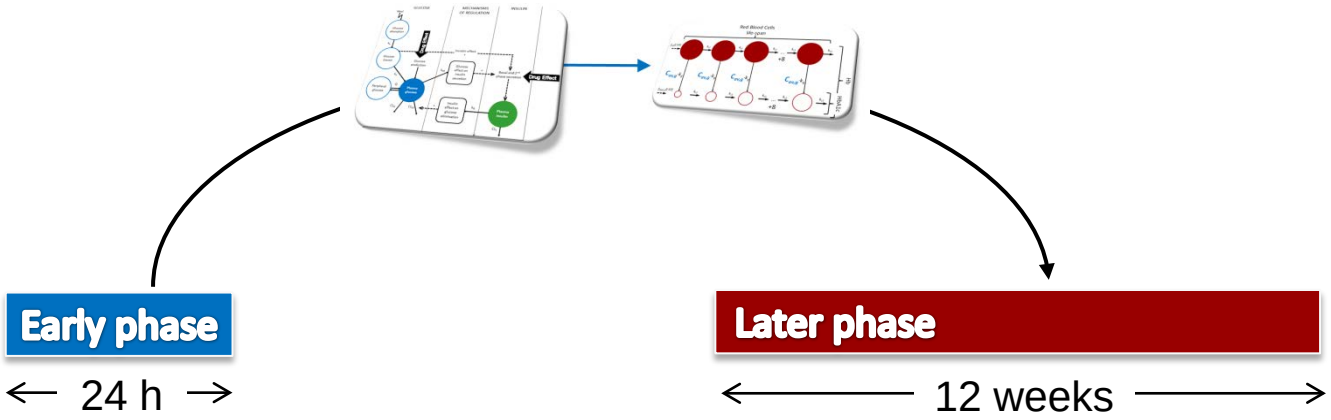
Method
Models for bridging biomarkers

Model describing glucose, daily variations and drug effects:
Integrated glucose-insulin (IGI) model[1, 2]

Model linking glucose to glycation of red-blood cells:
Integrated glucose-RBC-HbA1c (IGRH) model[3]



[1]Jauslin PM *et al* (2011) J Clin Pharmacol. 51: 153-64.
[2] Silber HE et al (2007) J Clin Pharmacol. 47: 1159-71.
[3]Lledo R *et al* (2010) PAGE 19: abstr: 1783.

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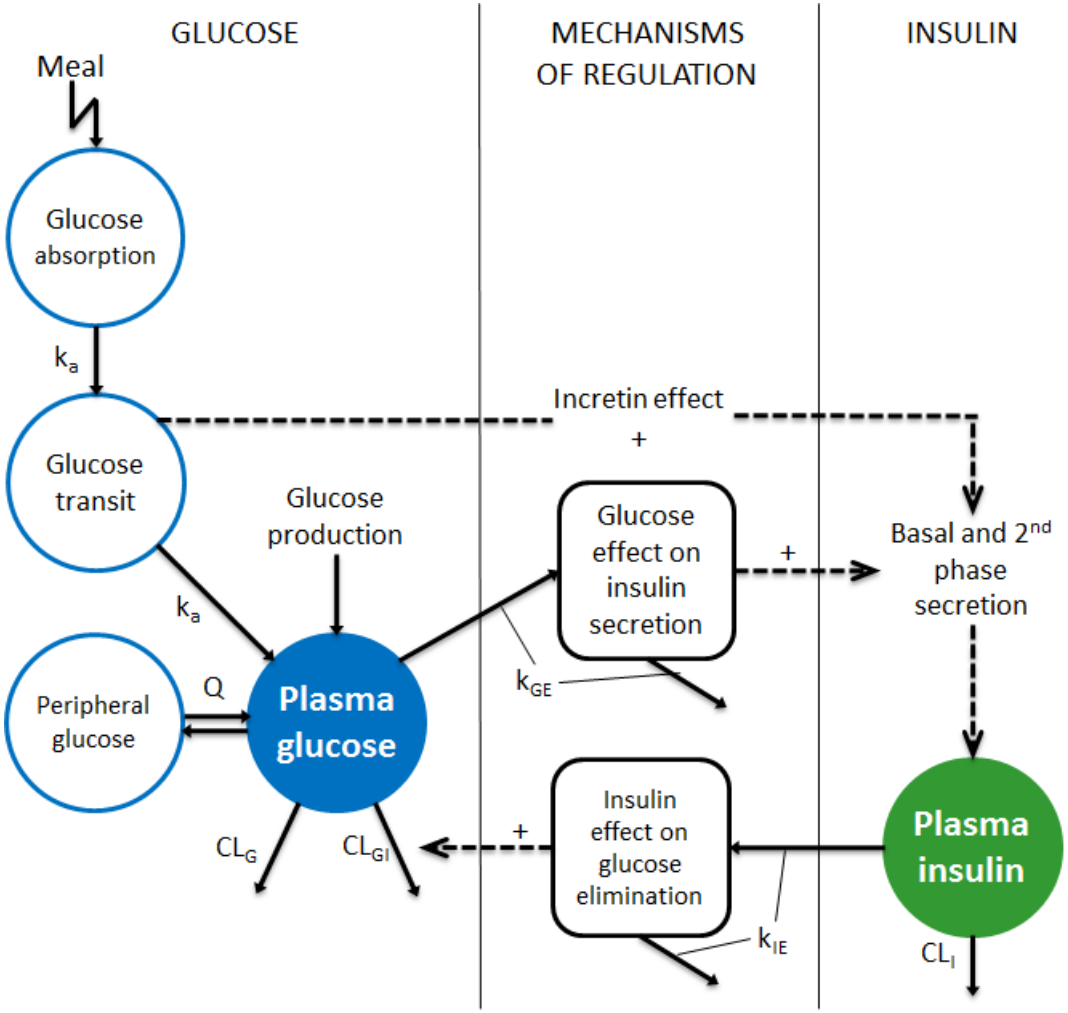
Method
Integrated Glucose-Insulin (IGI) Model



System-specific parameters

E.g. distribution of glucose in peripheral tissue

Study-specific parameters

E.g. baseline glucose and insulin

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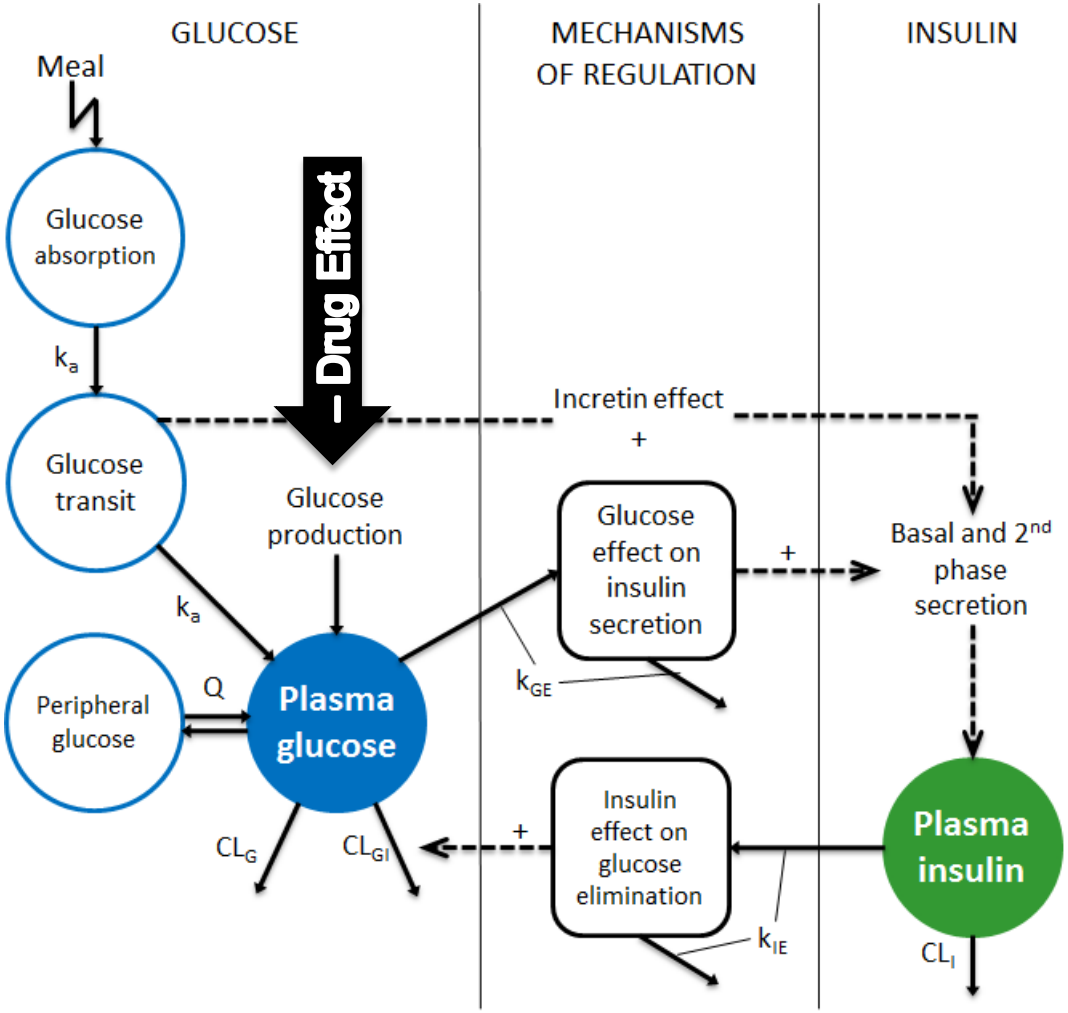
Method
Integrated Glucose-Insulin (IGI) Model



Drug effects can be added on parts of the model supported by mechanism of action.

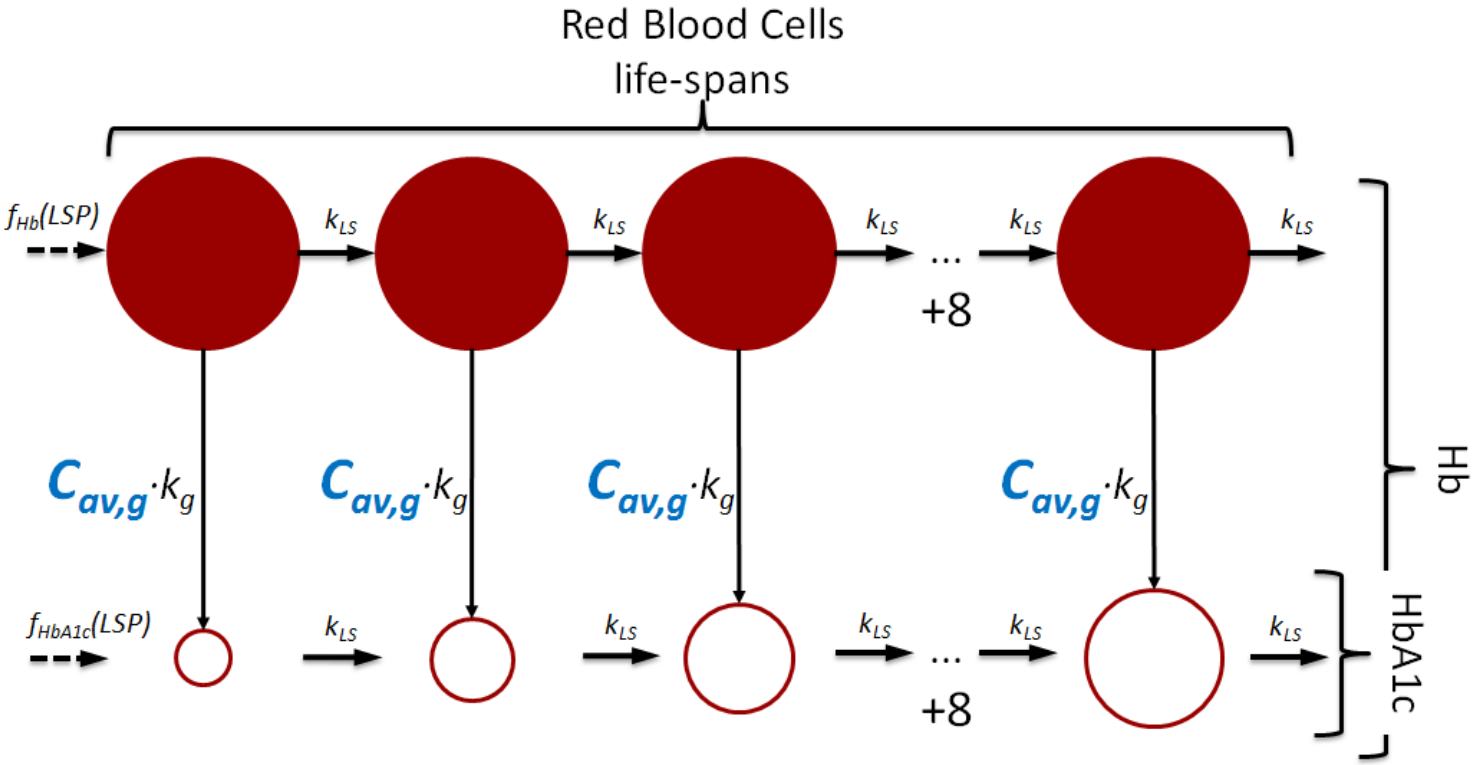
Glucokinase Activator (GKA)

+ insulin secr.

- glucose prod.

Method
Integrated Glucose-RBC-HbA1c (IGRH) Model

The IGRH model describes HbA1c as a function of average glucose concentrations and red blood cell life-spans, with RBC LS dependent on $C_{av,g}$



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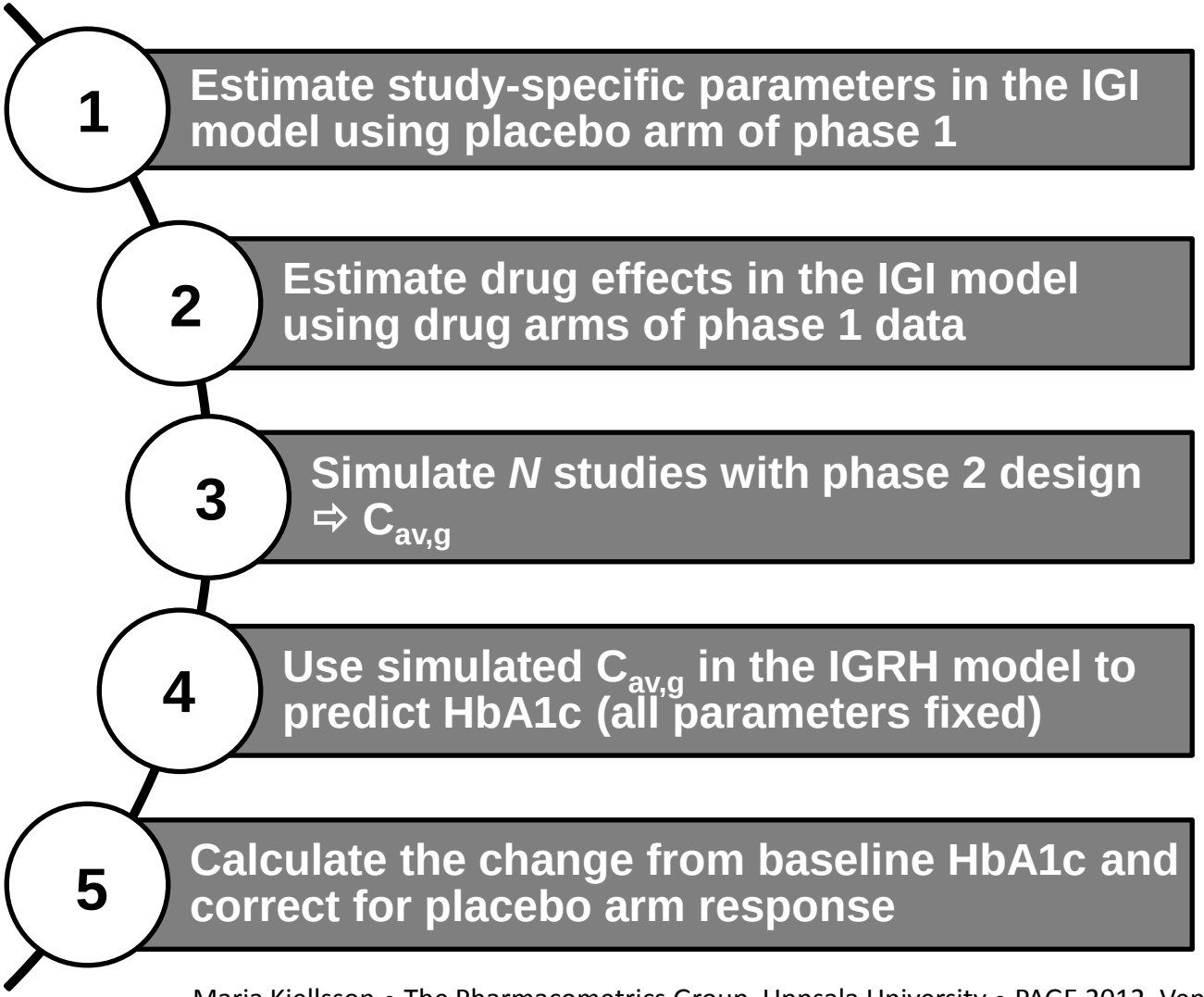
Method
Bridging approach



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Method
Available data/design

Data
Phase 1, PKPD:

- Measurements: **glucose** and **insulin**
- Meal tolerance tests
- Study duration: 1 week (3x24h)
- 59 Type 2 diabetics

- Parallel 7 arms (placebo, 10-200 mg QD/BID of GKA)

- FPG = 151 (24) mg/dL
- No metformin

Design
Phase 2, dose finding:

- Measurements: **HbA1c**
- Normal diet
- Study duration: 12 weeks
- 210 Type 2 diabetics

- Parallel 6 arms (placebo, 25-100 mg QD/BID of GKA)

- FPG = 177 (34) mg/dL
- Add-on to metformin

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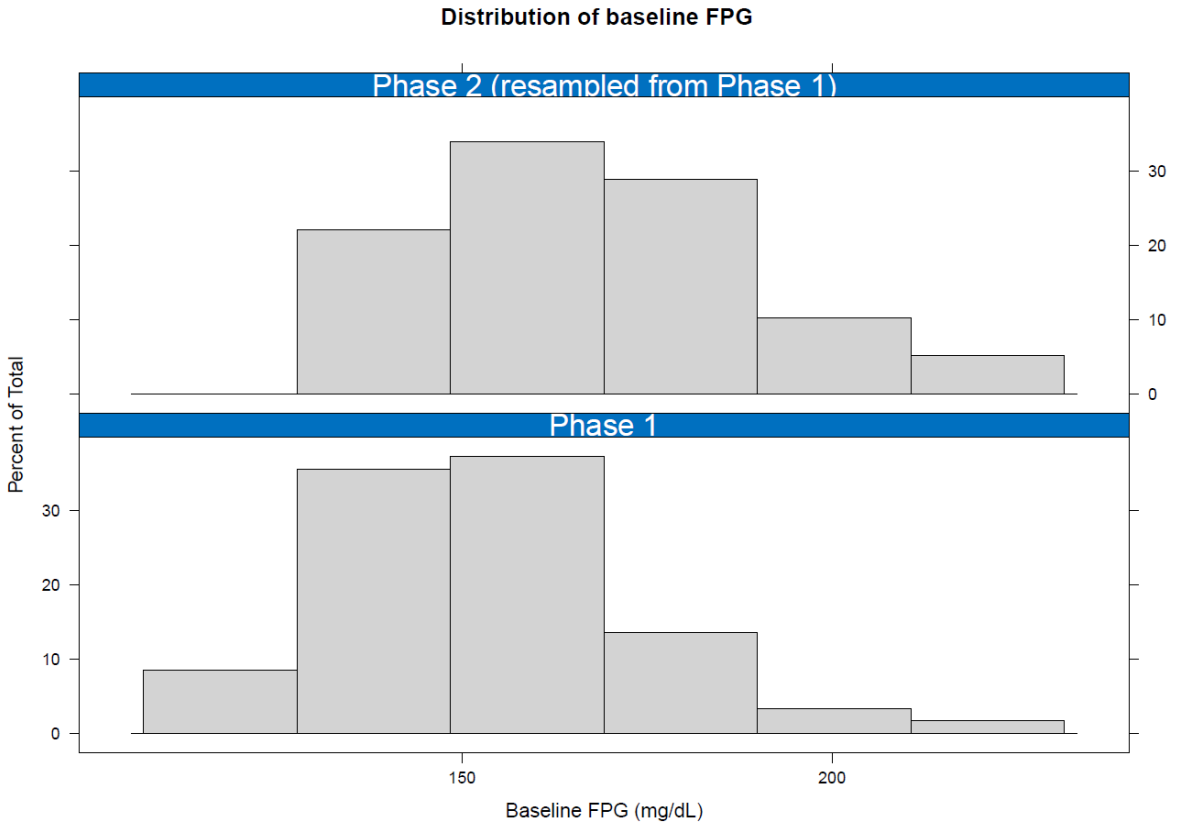
Method
Create Ph2 population from Ph1 data

Sample with replacement from baseline FPG in Phase 1 study (mean: 151) to mimic baseline FPG distribution of Phase 2 study (mean: 177).



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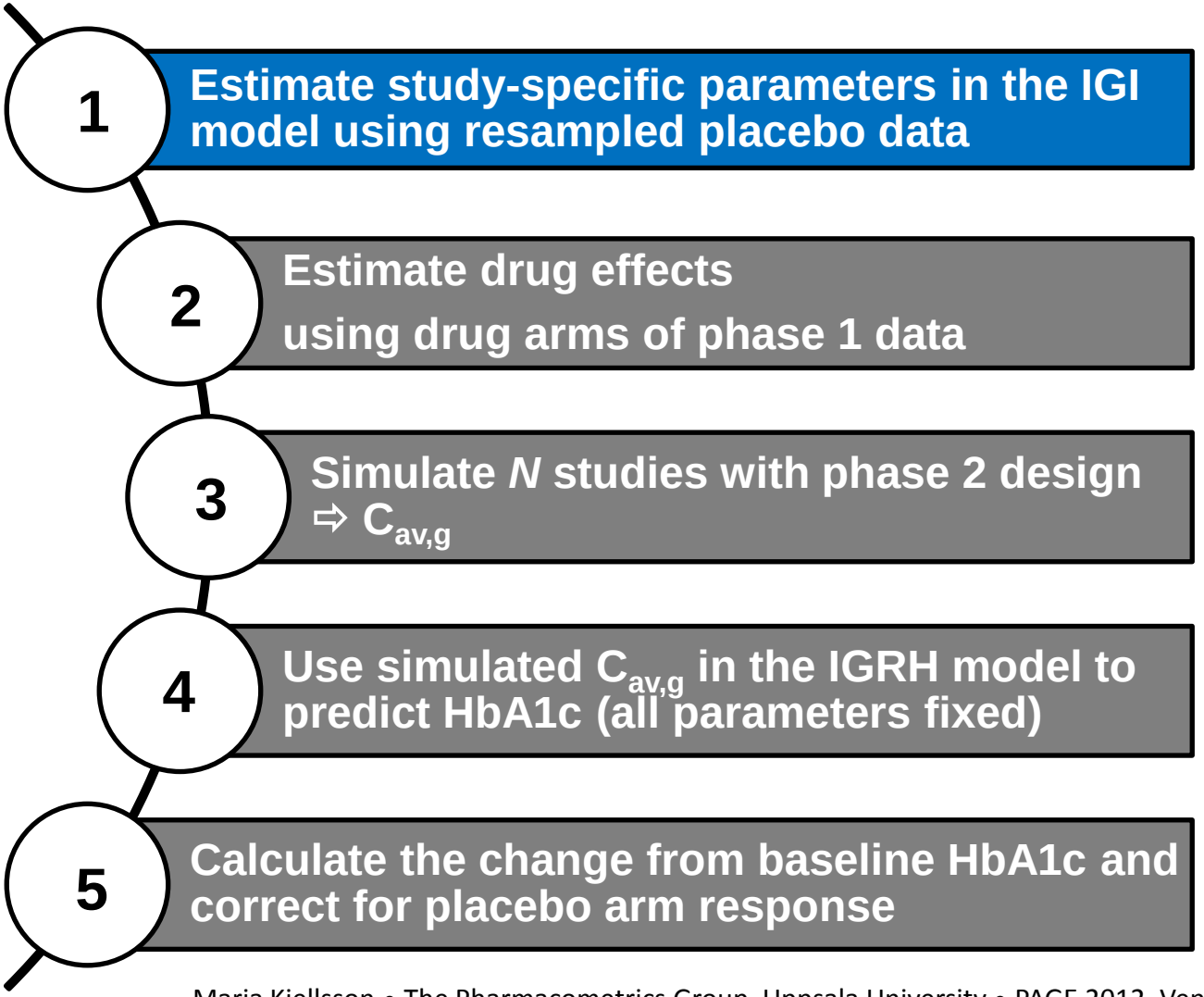
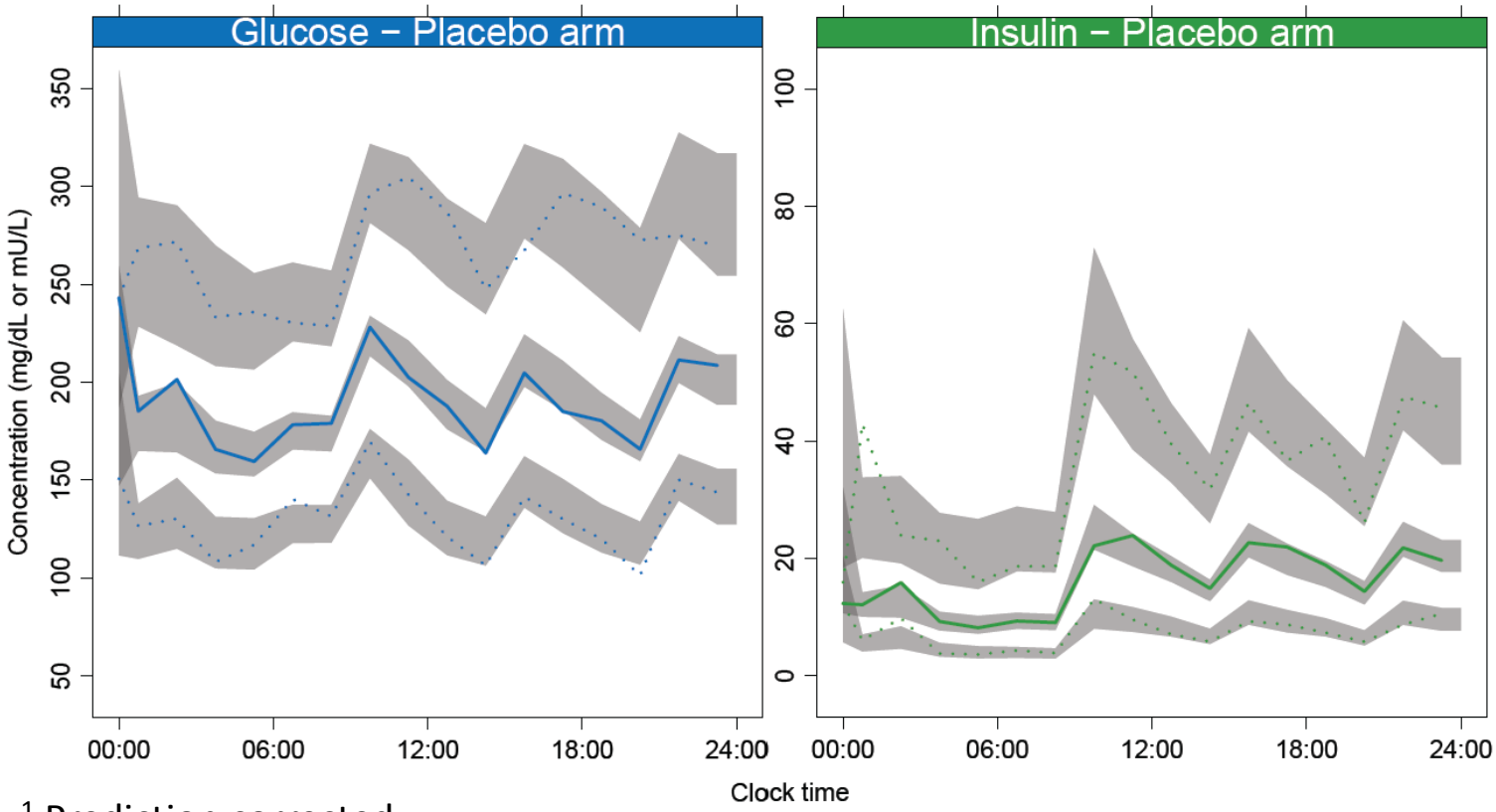
Results
Step 1 – Placebo model



Results
Step 1 – Placebo model

pVPC[1] of daily glucose and insulin for placebo arm



[1] Prediction corrected

Bergstrand M et al (2011) AAPS J, 13: 143-51

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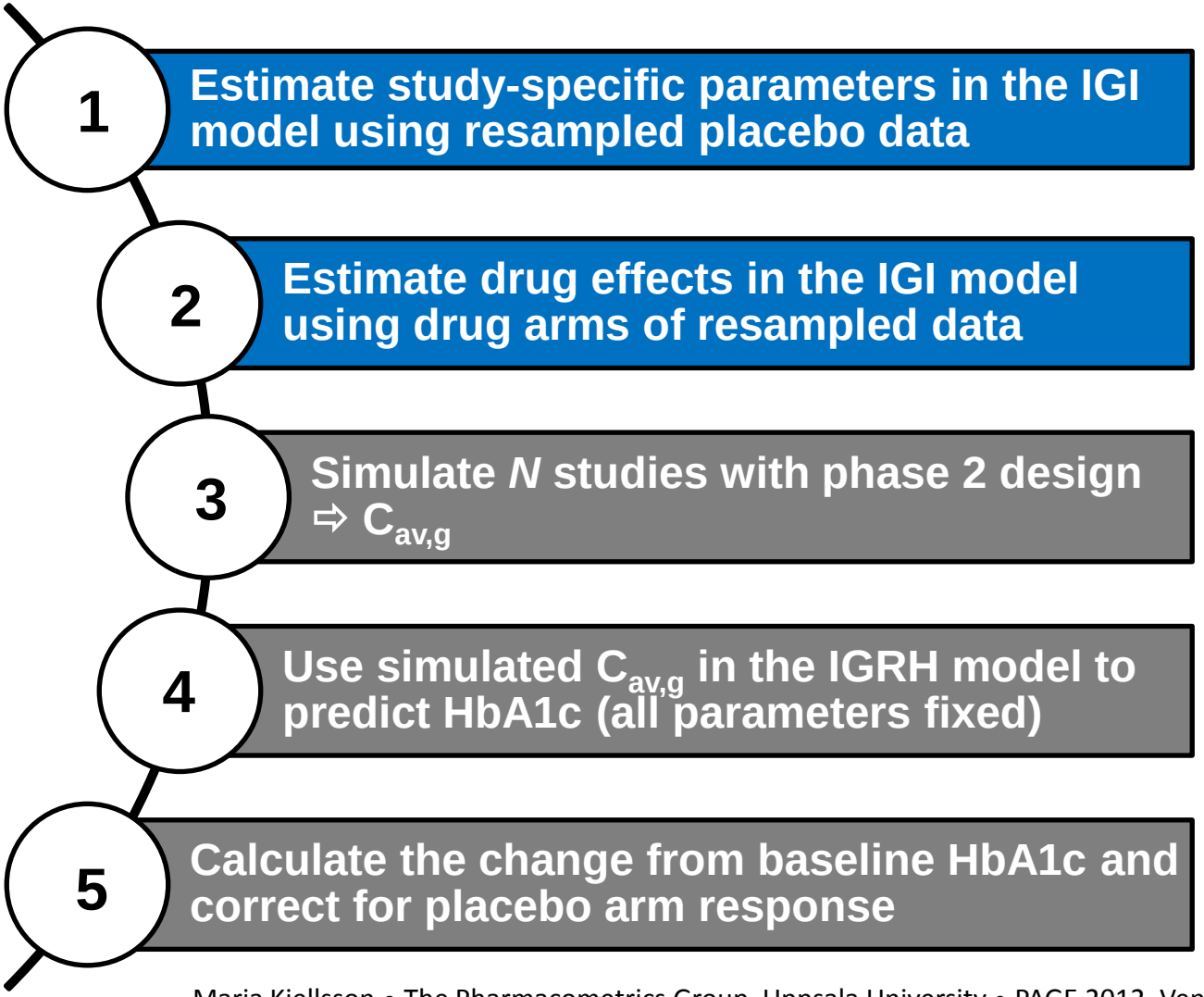
Results
Step 2 – Drug effects



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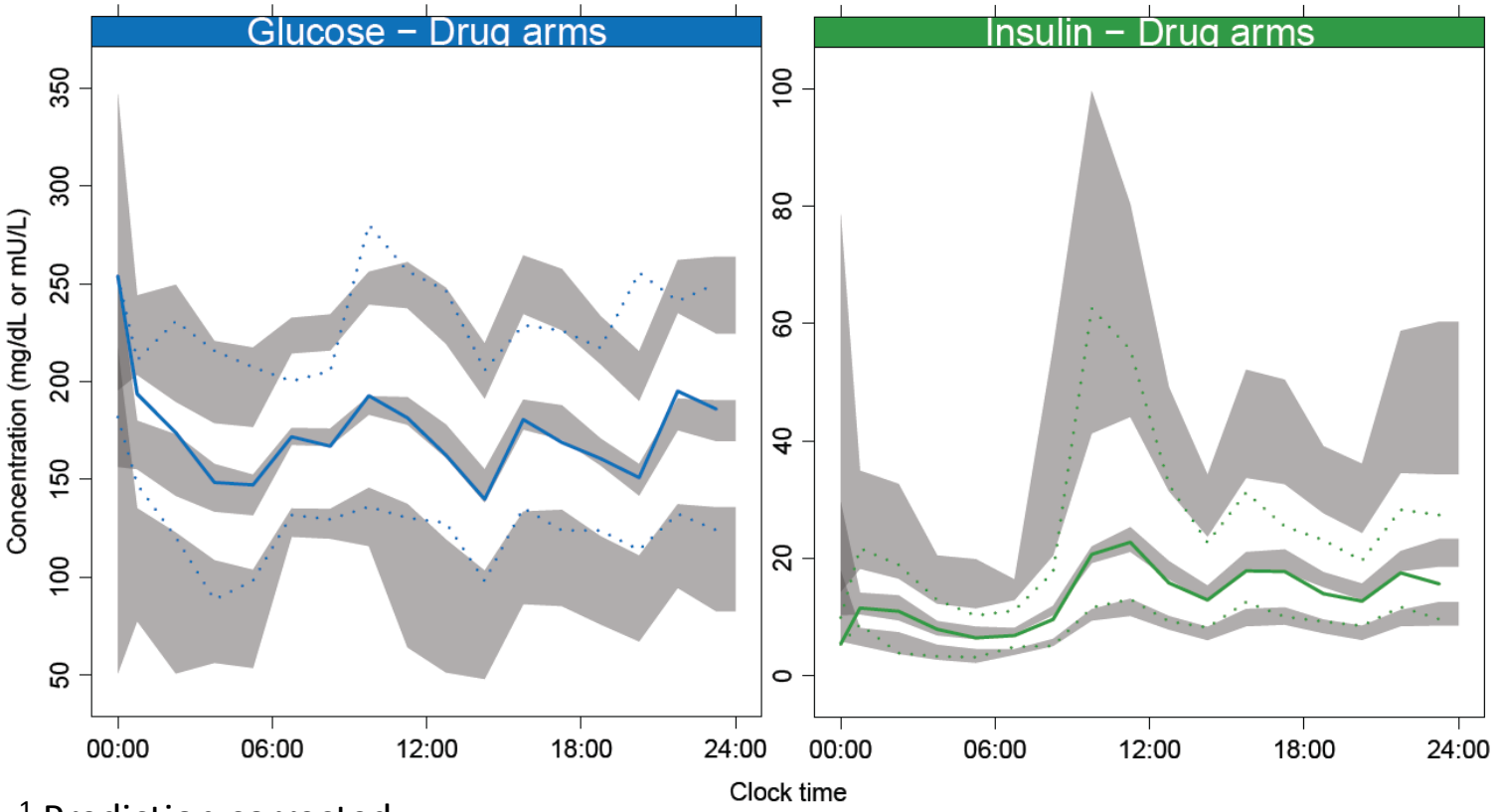
Results
Step 2 – Drug effects

pVPC[1] of daily glucose and insulin for drug arms



[1] Prediction corrected

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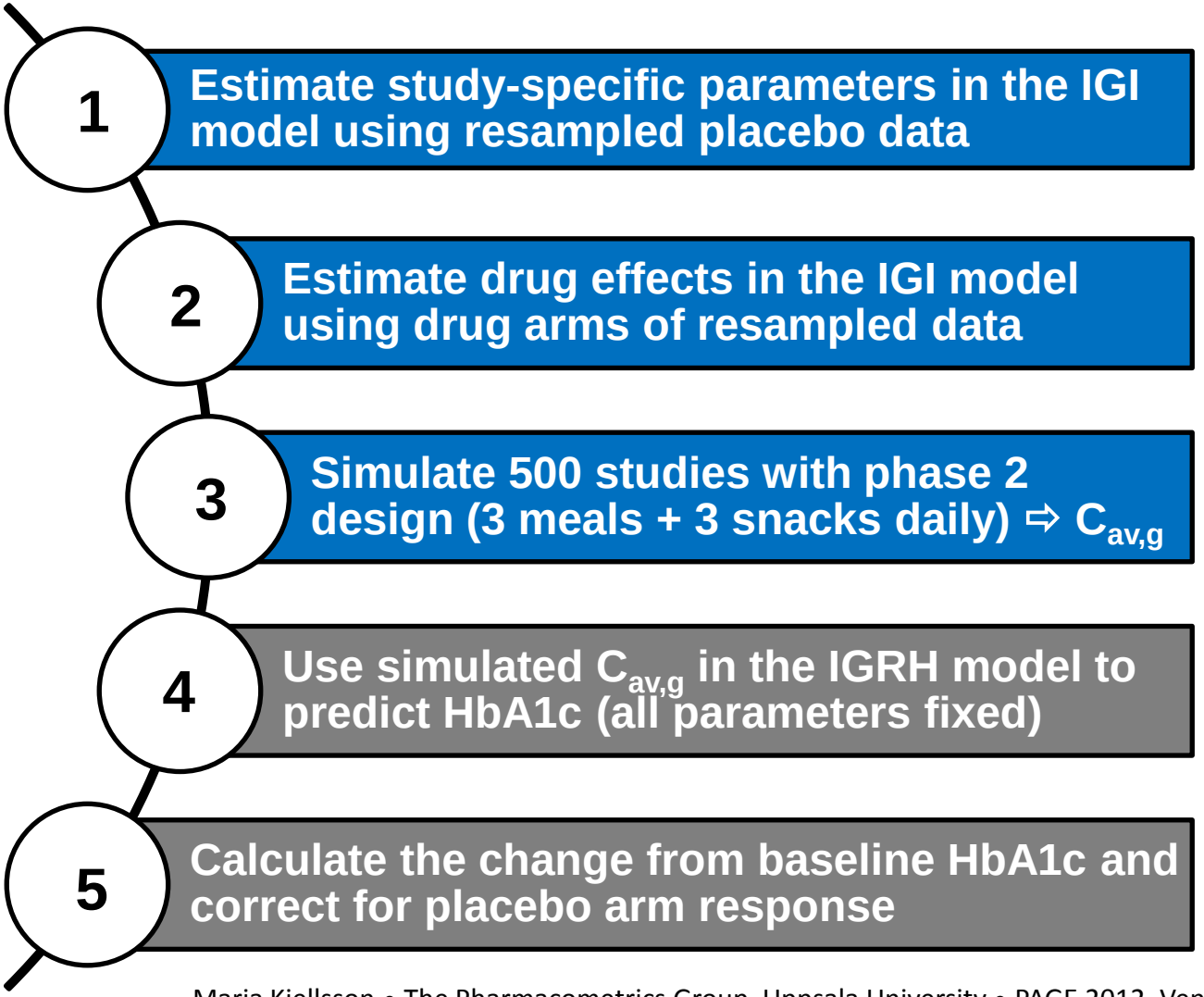
Results Step 3



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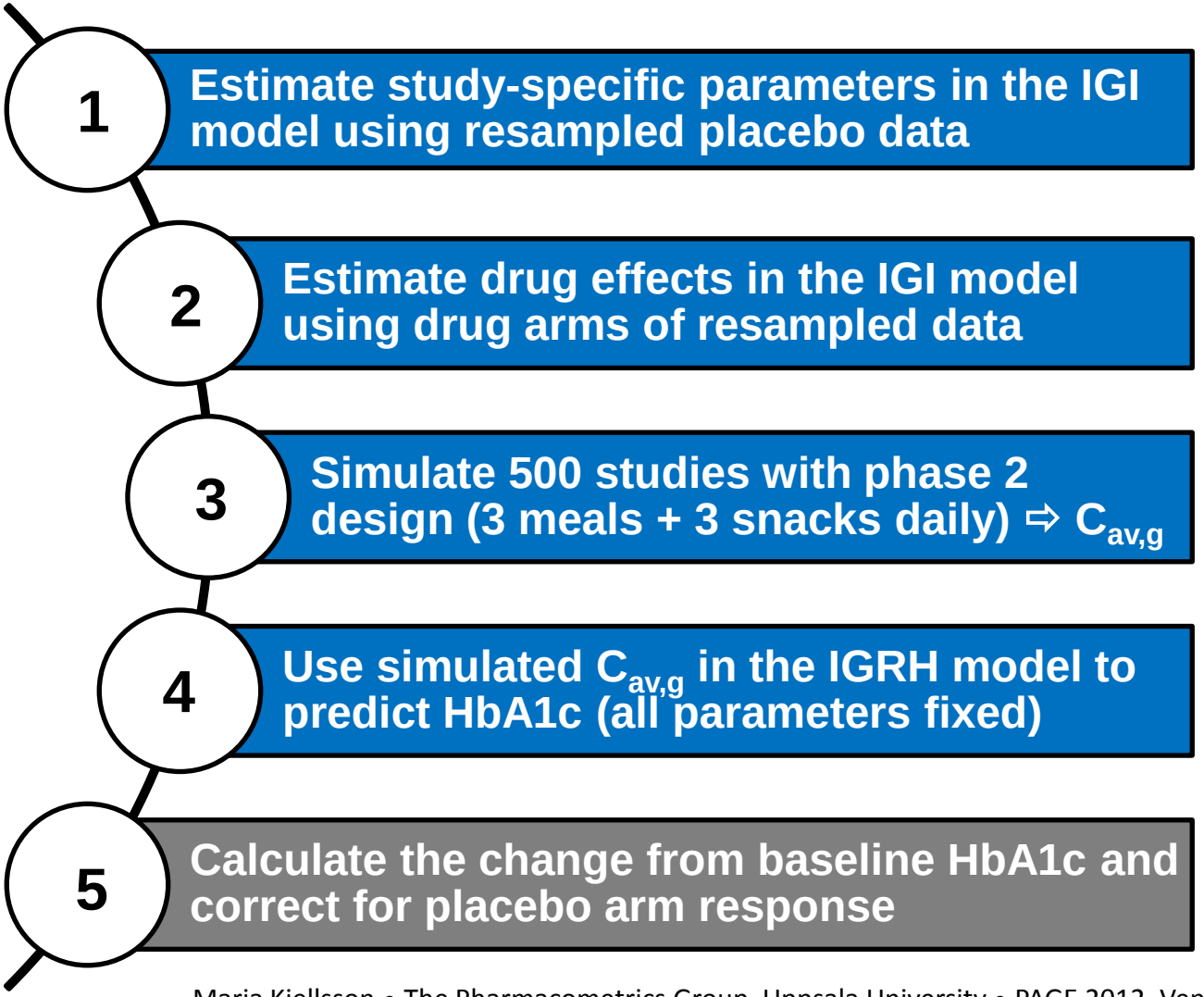
Results Step 4



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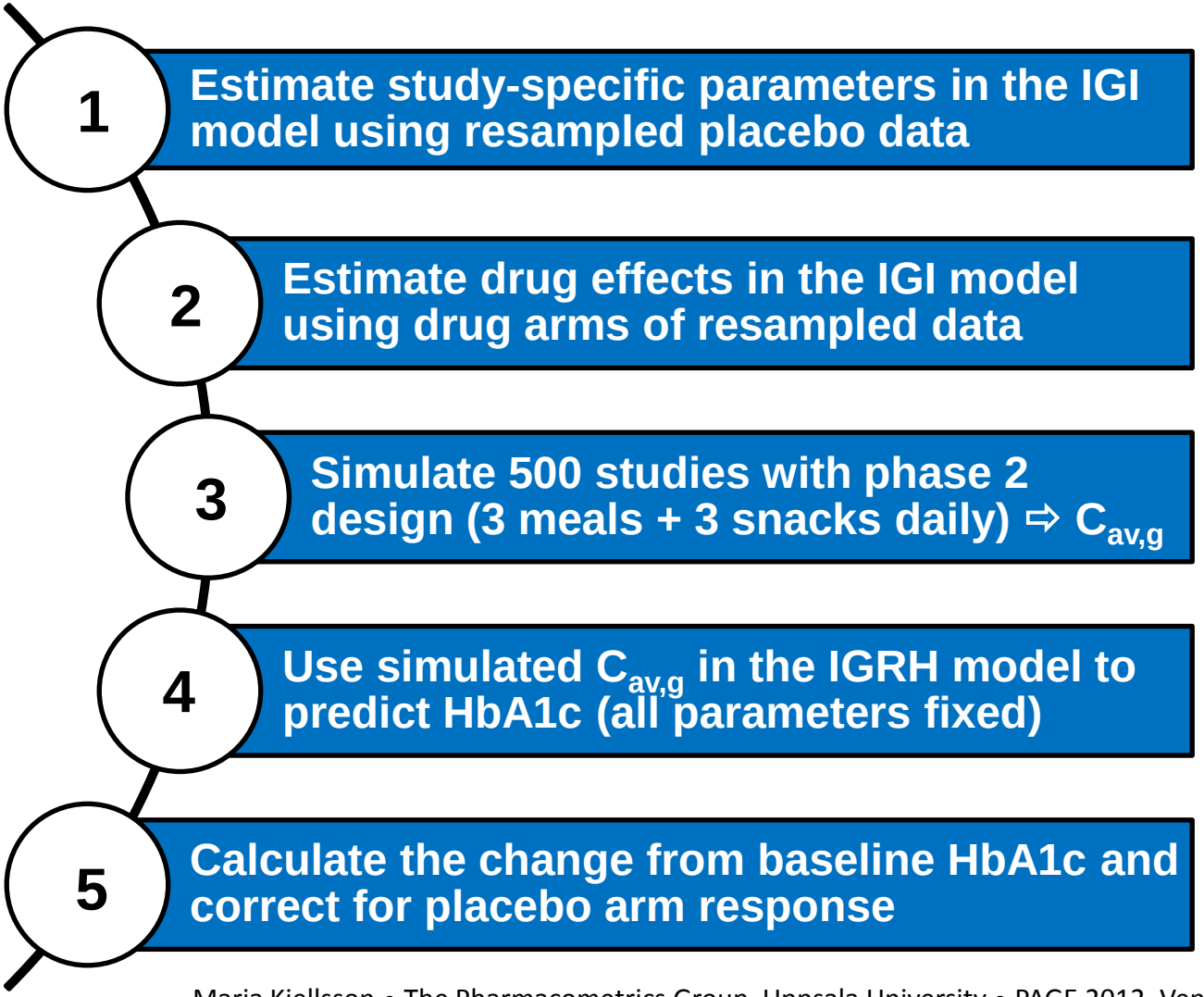
Results Step 5



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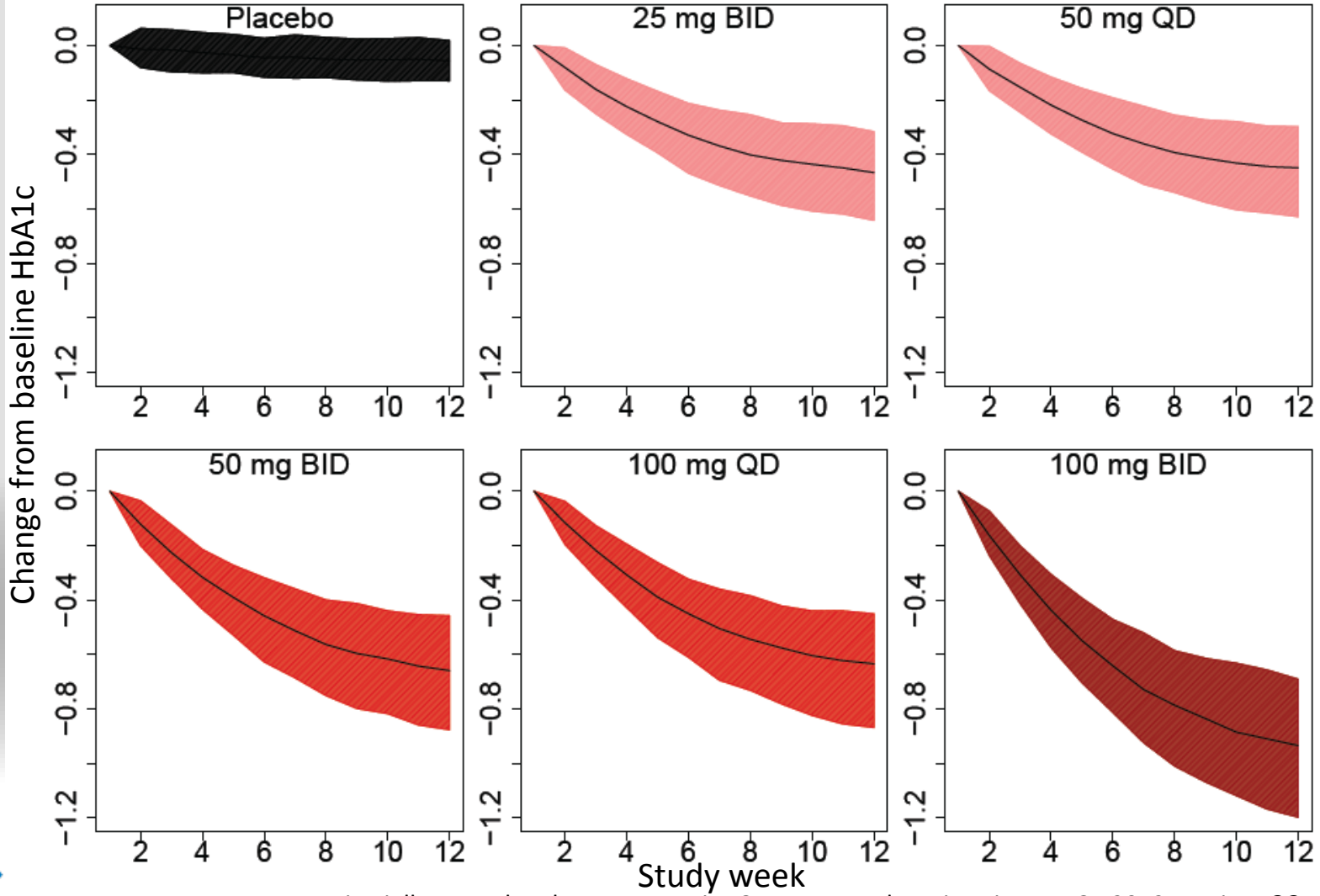
Results

Step 5 - Longitudinal HbA1c predictions



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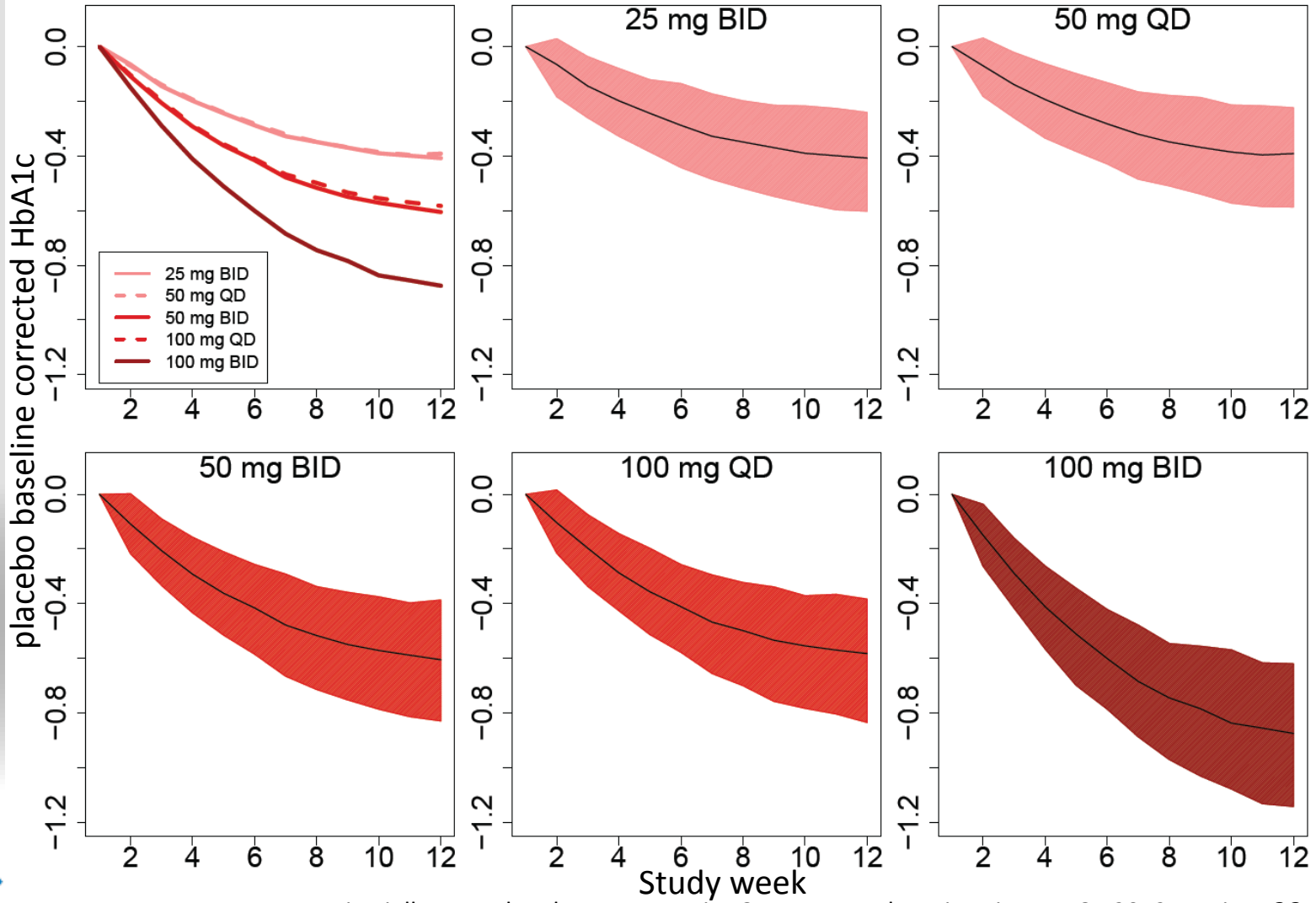
Results
Step 5 - Corrected HbA1c predictions



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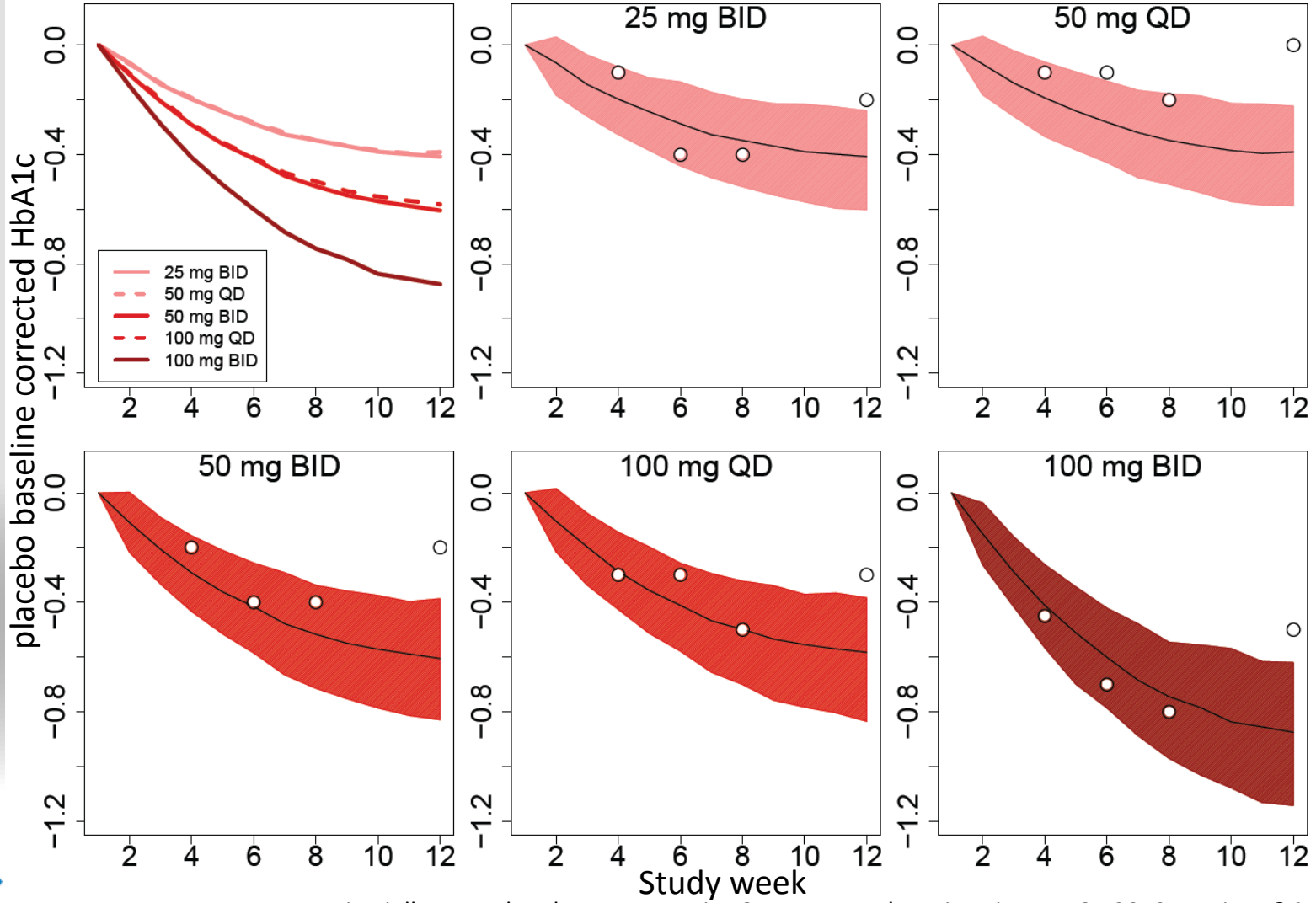
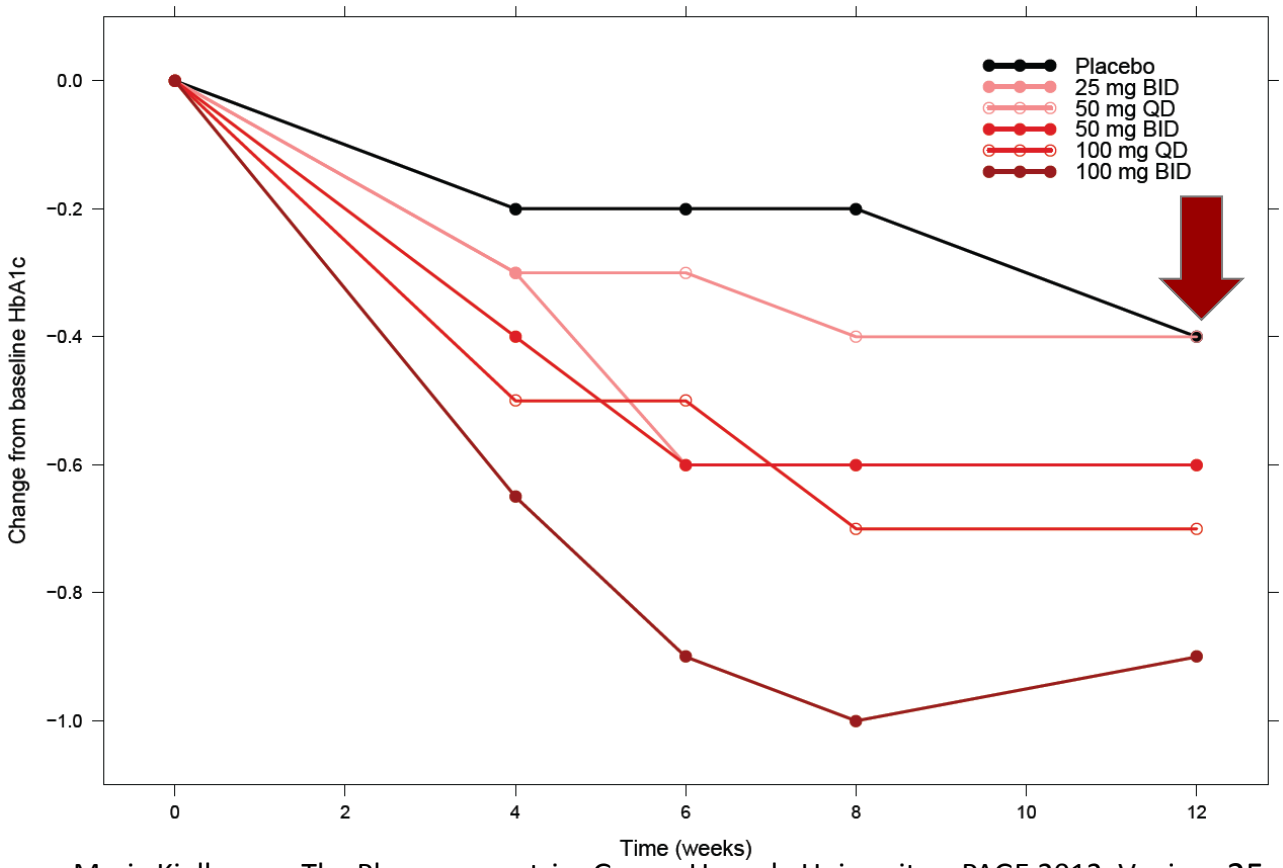
Results

Step 5 - Corrected HbA1c predictions



Results
Actual phase 2 outcome

Hazard of looking at change from placebo!



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Concluding remarks

The model-based approach to predict the dynamic HbA1c up to 12 weeks using information gained in earlier provocation study with glucose and insulin measurements was proven to reasonably well predict the outcome.

Despite ignoring

- Add on to metformin – potential overlap of mechanism
- Disease progression model
- Drop-out and deviations from protocol (e.g. change in diet)

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Acknowledgement

This work was performed with funding from Roche within the DDMoRe project, funded by the Innovative Medicines Initiative.

Acknowledgement: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from Academic and SME partners.

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