From In Vitro Efficacy to Long-term HbA1c Response for GLP-1R/GlucagonR Agonism using the 4GI-HbA1c Systems Model

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Introduction

- For the treatment of Type 2 Diabetes (T2DM), high efficacy approaches such as the Glucagon-like peptide 1 (GLP-1)-based therapies are recommended for glucose control [1].
- Prediction of clinical outcome on glucose and Haemoglobin A1c (HbA1c), using early available pharmacokinetic and *in vitro* efficacy information, can be a valuable tool for compound selection and supporting drug development.
- Our previously developed glucose homeostasis QSP model (the 4GI model) is a systems model that quantifies and predicts drug effects on glucose based on in vitro potency and PK information [2,3].
- Average daily glucose levels (Cglc,av) can be used to predict HbA1c using the existing integrated glucose-red blood cell-HbA1c (IGRH) model [4].

Objectives

- Validate the predictive capability of the 4GI model for 24h glucose levels, using continuous glucose monitoring (CGM) data.
- Couple the 4GI model with the IGRH model to predict the long-term longitudinal effect of novel GLP-1 and GLP-1/glucagon therapies on HbA1c.

Methods

- The 4GI systems model was calibrated on CGM data from the cotadutide, a dual GLP-1/glucagon receptor agonist, Phase 2a study (D5670C00011, NCT03244800)[5].
  - System parameters remained fixed, while only parameters related to dietary and lifestyle changes were estimated.
  - Model predicted Cglc,av was compared with calculated Cglc,av from the observed CGM data.
- The predicted Cglc,av was used as input for the IGRH model to predict the effect on HbA1c.
- External validation involved predicting the *in vivo* effect, based on *in vitro* potency information, of both cotadutide and liraglutide (a GLP-1R agonist) on Fasting Plasma Glucose (FPG) and HbA1c for the cotadutide Phase 2b study (D5670C00004, NCT03235050)[6].

Results

- Minimal 4GI model calibration to short-term cotadutide Ph2a CGM data enabled adequate daily average glucose concentration predictions.
- The combined 4GI-IGRH systems model effectively predicted the impact of cotadutide and liraglutide on FPG (RMSPE 5.7%) and change from baseline HbA1c (RMSPE 13%) within a Phase 2b setting.

Successful prediction of Ph2b trial outcome for cotadutide and liraglutide

Compound info

- *In vitro* EC50
- Free Fraction
- PK parameters

Data

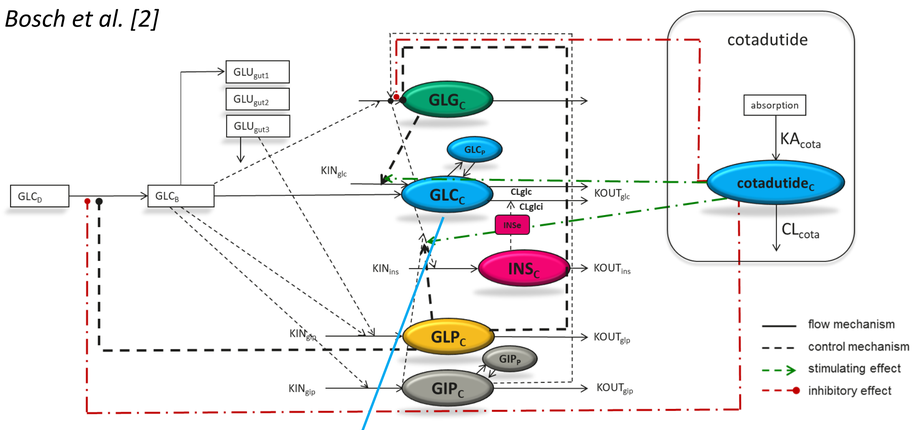
Calibration:
- Ph2a data

External Validation & Prediction:
- Ph2b data

Model

4GI model

Bosch et al. [2]



IGRH model

Lledó-García et al. [4]

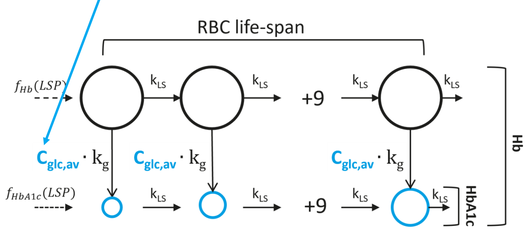
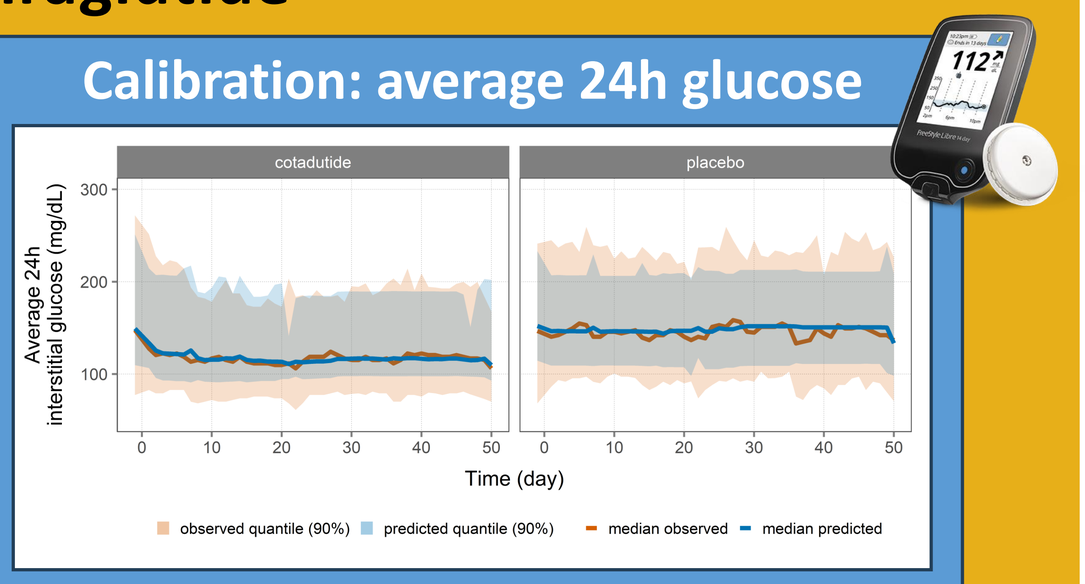
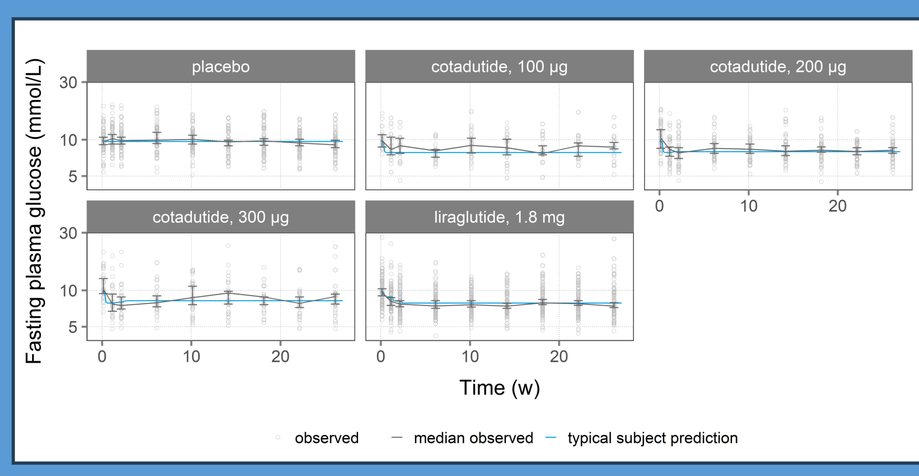


Figure based on Kjellsson et al. [5]

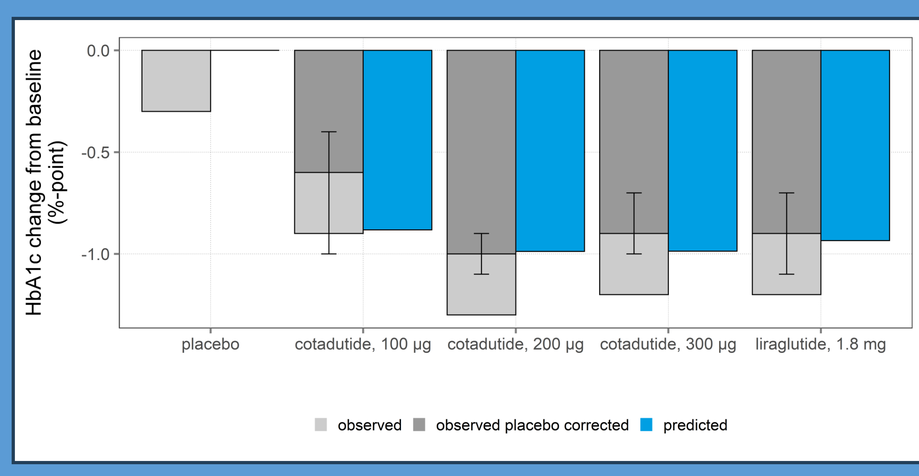
Calibration: average 24h glucose



External Validation: Ph2b FPG



Prediction Ph2b HbA1c



Take a picture for more info

Conclusion

- The 4GI-IGRH systems model was used in cotadutide's clinical development by providing predictive insights into the Phase 2b study prior to its initiation.
- The model accurately anticipated the effects of cotadutide and liraglutide on FPG and HbA1c based on *in vitro* efficacy information.
- This analysis shows the model's potential as a valuable tool in supporting the clinical development of cotadutide, existing and newly developed GLP-1R (/glucagon) agonists.

[1] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019.
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