An Evaluation of Three Semi-mechanistic PK/PD Models for Predictive Performance of Long-term HbA1c via Short-term Glycemic Changes for a Glucagon Receptor Antagonist in Type 2 Diabetes Patients

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Sponsored by Eli Lilly and Company

PAGANZ; Melbourne, Australia; Feb 14 – 16, 2024

OBJECTIVES

1. Build three PK/PD models adapted from literature (ADOPT[1], FFH[2], FHH[3]) using glucagon receptor antagonist (GRA) PK, glucose, and HbA1c data from a 4-week Phase 1 trial[4] (Placebo, 5 mg once daily (QD), 30 mg QD, 60 mg QD, 90 mg QD)
2. Compare three PK/PD models for their ability to predict long-term HbA1c using GRA data from a 24-week Phase 2 trial[5] (Placebo, 2.5 mg QD, 10 mg QD, 20 mg QD)

CONCLUSIONS

1. The FHH model performed the best among the three PK/PD models, and it could be useful in predicting long-term HbA1c for GRA at 24 weeks from short-term glucose and HbA1c data in a 4-week trial.
2. The FHH model consists of a transit compartment structure, which is useful in modeling long delays between glucose and HbA1c. It also has a non-linear relationship between glucose and HbA1c.
3. Fasting glucose, which is a short-term biomarker required for the formation of HbA1c in the FHH model, is frequently collected in early-phase trials. This allows for application of the FHH model in Type 2 diabetes drug development without adding burden to Phase 1 studies.

METHODS

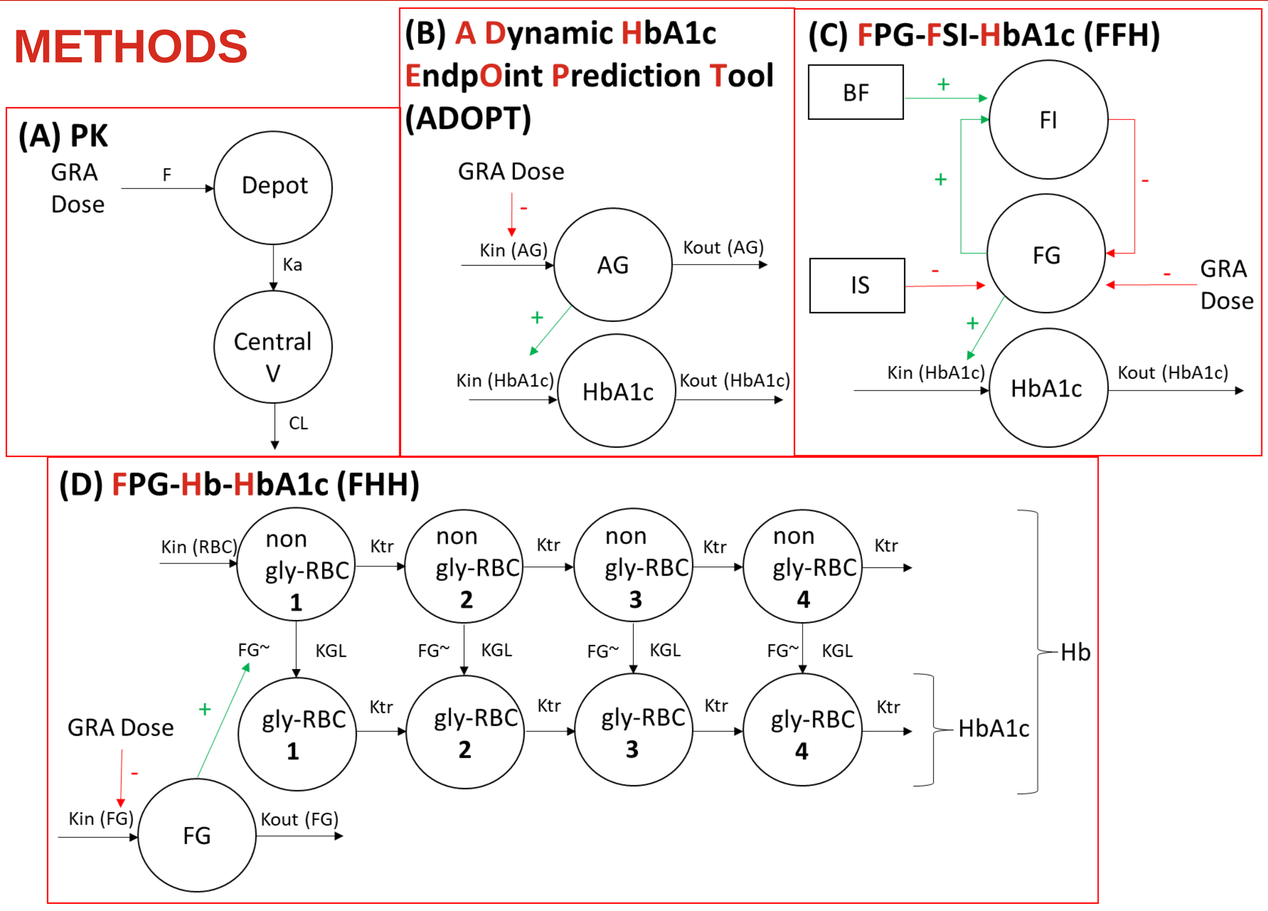

Figure 1. Schematic representation of: **(A)** PK model of GRA, **(B)** A Dynamic HbA1c EndpOint Prediction Tool (ADOPT) model, **(C)** FPG-FSI-HbA1c (FFH) model, **(D)** FPG-Hb-HbA1c (FHH) model.
Green arrows indicate stimulation whereas red arrows indicate inhibition.
Abbreviations: AG = average glucose. BF = β-cell function. CL = clearance. Depot = depot compartment. F = absolute bioavailability. FG = fasting glucose. FI = fasting insulin. gly-RBC = glycated red blood cell compartment. GRA = glucagon receptor antagonist. Hb = hemoglobin. HbA1c = glycated hemoglobin. IS = insulin sensitivity. Ka = absorption rate constant. KGL = glycosylation rate constant. Kin = input rate constant. Ktr = transit rate constant. Kout = output rate constant. non gly-RBC = non-glycated red blood cell compartment. V = volume of distribution.

MODELS

POPULATION PK MODEL OF GRA

- 1-compartment model: first-order oral absorption and elimination

ADOPT MODEL

- Indirect response model: average glucose (AG) and HbA1c compartments

FFH MODEL

- Indirect response model: fasting glucose (FG), fasting insulin (FI) and HbA1c compartments
- Homeostatic feedback between FG and FI
- β-cell function (BF) stimulated FI production and insulin sensitivity (IS) inhibited FG production

FHH MODEL

- Transit compartment model: four non-glycated and four glycated red blood cell (RBC) compartments
- HbA1c formation described through the life-span of RBCs, and driven by FG in a non-linear relationship

INHIBITORY EFFECT OF GRA ON GLUCOSE FORMATION

- GRA reduced hepatic glucose output[5,6] -> inhibited AG/ FG formation (Imax model used)

METHODS

MODEL DEVELOPMENT AND SELECTION

- Model building was performed with relevant short-term biomarkers in Phase 1 trial (plasma concentration of GRA, AG, FG, FI, HbA1c, hemoglobin).
- Model development was based on objective function value (OFV) change ($p < 0.05$, $\Delta OFV > -3.84$), model parameter physiological plausibility and precision, goodness-of-fit plots, visual predictive checks, and shrinkage < 30%[7].
- Both forward covariate selection ($p < 0.01$, $\Delta OFV > -6.64$) and backward covariate elimination ($p > 0.001$, $\Delta OFV < 10.8$) was conducted stepwise[7].
- A sequential modeling approach was used to fit the post-hoc PK parameters with the relevant PD biomarkers (NONMEM v7.5.0 with FOCE-I method[8]).

COMPARISON OF MODEL PERFORMANCE

1. Population PK/PD simulations of 1000 patients per dosing regimen group were performed with final model parameters. Mean change from baseline HbA1c (ΔHbA1c) at Week 24 were compared between observations and simulations.
2. Mean prediction error (MPE) for bias and root mean squared error (RMSE) for precision[9] were calculated using observations and post-hoc model estimates of ΔHbA1c. Lower absolute MPE and RMSE values correspond to smaller bias and greater precision, respectively.

RESULTS

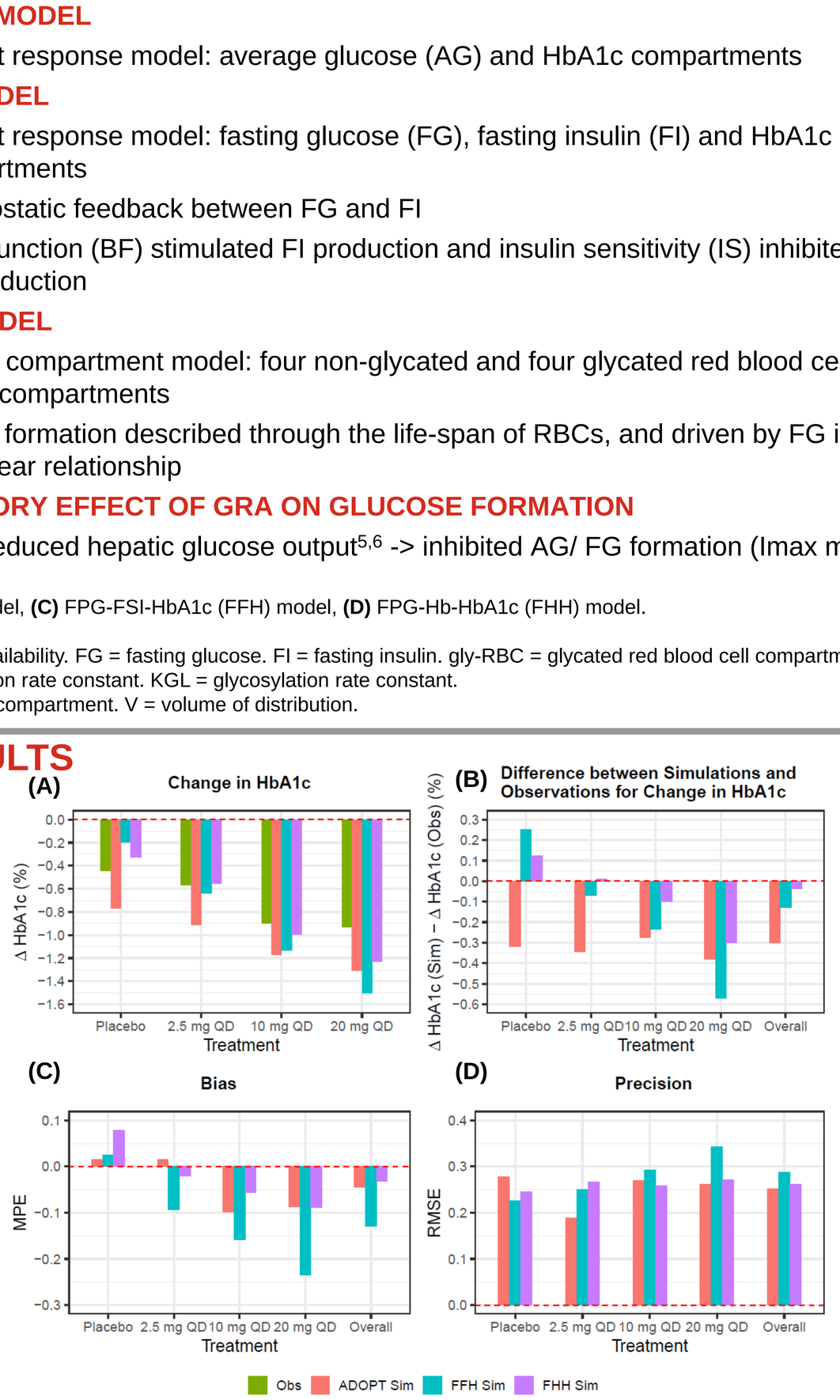

Figure 2. Model performance metrics between observations and simulations of:
(A) Change in HbA1c, **(B)** Difference between Simulations and Observations for Change in HbA1c, **(C)** Bias, **(D)** Precision. Number of patients (observations) in each treatment group in Phase 2 trial:
Placebo [n=26], 2.5 mg QD [n=32], 10 mg QD [n=35], 20 mg QD [n=40].
Abbreviations: ΔHbA1c = change from baseline HbA1c. MPE = mean prediction error.
Obs = observations. QD = once daily. RMSE = root mean square error. Sim = simulations.

- FHH model predicted closely the mean ΔHbA1c across all four dose groups, had similar MPE and RMSE estimates as compared to the other two models, and was the best-performing model overall (**Figure 2**).

DISCUSSION

- The transit compartment model structure is useful in modeling long delays observed between the short-term biomarker (FG) and long-term HbA1c. The non-linear relationship between glucose and HbA1c accounts adequately for the glycation effect of FG on HbA1c.
- The over-estimation of the reduction in HbA1c by both the ADOPT model and FFH model could be due to the systematic over-estimation of the placebo effect on AG and over-estimation of the glycation effect of FG on HbA1c, respectively.

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Software Citations: NONMEM v7.5.0 (ICON plc, Dublin, Ireland)

Disclosures: Karen Schneck, Lai San Tham, Parag Garhyan are employees and stockholders of Eli Lilly and Company.