

Modeling HbA1c dynamics in type II diabetes mellitus in patients treated with lixisenatide

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Status and Problem

Lixisenatide is a new prandial GLP-1 receptor agonist used in type II diabetes mellitus (T2DM) (Bolli et al. 2013). The aim of this work was to develop a model for lixisenatide that enables to describe and predict glycosylated haemoglobin (HbA1c) up to 2 years.

Apart from most recent models based on mean plasma glucose, most of published HbA1c models relate HbA1c to fasting plasma glucose (FPG) (de Winter 2006, Samtani 2010). These models are not suitable for lixisenatide, which is known to act both on FPG and on post prandial glucose (PPG). Consequently there was a need for developing specific models to account for lixisenatide effect on PPG; 2 types of PD-models were investigated.

The first model (Wilkins et al., 2013) is the extension of the published models of Ribbing et al. (2010) and Samtani (2010), giving a long-term description and prediction of the effect of lixisenatide in T2DM, in terms of FPG, HbA1c, fasting serum insulin (FSI), insulin sensitivity, and beta-cell mass (BCM). The effect of PPG on HbA1c is described implicitly. The second model, based on the first model, explicitly accounts for PPG; it requires a sub-model developed for long-term evolution of morning 2H-glucose excursion (GLUEX), defined as the difference between FPG and PPG.

Pharmacometric Approach

A population approach, non-linear mixed effects modeling, was used. Modeling and simulation were performed in Monolix, using the SAEM estimation method. Model comparison was guided by AIC criterion, goodness of fits plots and precision of parameter estimates.

Data were composed of FPG, HbA1c, FSI and GLUEX values, collected from phase II and III clinical studies DRI6012, GetGoal-S, GetGoal-Mono, GetGoal-X, PDY10931 (used for model development) and morning arm of study GetGoal-M (used for external validation), including a total of 2470 patients, with profiles spanning 0 to 840 days.

FPG, FSI, BCM and insulin sensitivity were described by semi-mechanistic turn-over models (detailed in Wilkins et al. 2013), as well as HbA1c. GLUEX was described by an empirical model, because of the relatively low number of GLUEX data (3015 meal tests overall).

Results

Model 1 (Wilkins et al., 2013):

HbA1c synthesis was described by a FPG-dependent term, by a non-FPG dependent term, depending on HbA1c level (Monnier et al. 2003) and impacted by a lixisenatide effect, by a standard of care effect (H_{SOC}) and by an elimination term using on a lower physiological HbA1c level (H_{low}). Covariates were identified on $H_{in,FPG}$, $H_{in,NonFPG}$, H_{SOCmax} : observed HbA1c and FPG baselines, Gender, Race. On average, 20µg lixisenatide dose reduces the FPG contribution by 12% and the non-FPG contribution by 30%.

$$\frac{dHbA1c}{dt} = (H_{in,FPG})_i \cdot FPG_{i,t} + (H_{in,NonFPG})_i \cdot (1 + \theta_{CH} \cdot HbA1c_{i,t}) \cdot (Eff_H)_{i,t} + H_{SOC_i} - H_{out} \cdot HbA1c_{i,t} \cdot (1 - \frac{H_{low}}{HbA1c_{i,t}})$$

Model 2 (see Fig.1):

In the empirical GLUEX model, a disease progression of +0.12 mmol/L per month was identified, as well as a constant "standard-of-care" effect of -1.2 mmol/L, and an additional constant drug effect of -2.9 mmol/L on average. HbA1c synthesis was described by a FPG-dependent term, by a GLUEX dependent term, depending on HbA1c level, and by an elimination term using lower limit H_{low} . Observed FPG and HbA1c baselines, and Asian race, were identified as covariates for $GLUEX_0$, $ED_{50,G}$, k_{DPG} , $H_{in,FPG}$ and $H_{in,GLUEX}$. GLUEX reduction accounted for about 2 times more than FPG reduction in the decrease of the HbA1c synthesis rate induced by 20µg lixisenatide.

$$GLUEX_{i,t} = GLUEX_0 - \frac{E_{max,G} \cdot Dose_{i,t}}{ED_{50,G,i} + Dose_{i,t}} + k_{DPG,i} \cdot t + G_{SOC(t>0)} + \varepsilon_{GLUEX,i,t}$$

$$\frac{dHbA1c}{dt} = (H_{in,FPG})_i \cdot FPG_{i,t} + (H_{in,GLUEX})_i \cdot (1 + \theta_{CH} \cdot HbA1c_{i,t}) \cdot GLUEX_{i,t} - H_{out} \cdot HbA1c_{i,t} \cdot (1 - \frac{H_{low}}{HbA1c_{i,t}})$$

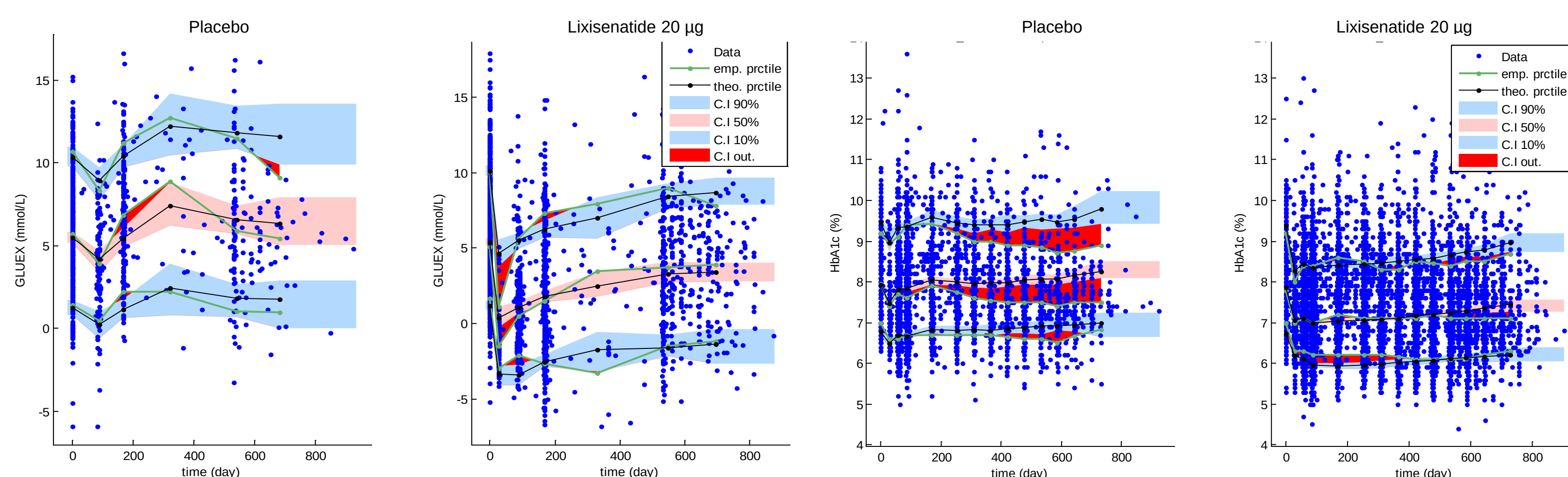


Fig. 2. Visual predictive check for GLUEX and HbA1c for model 2, on the complete (development + external) dataset

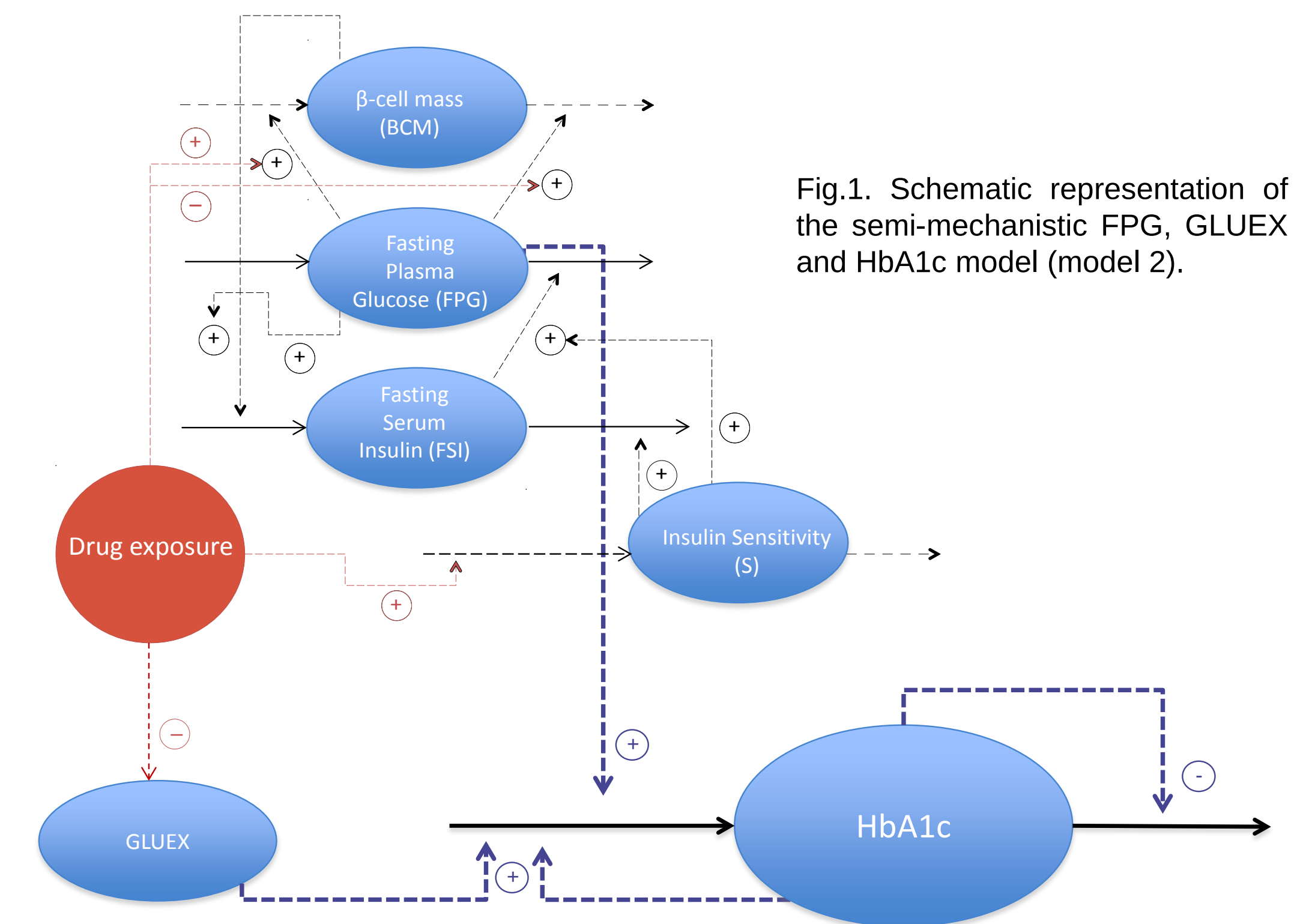


Fig.1. Schematic representation of the semi-mechanistic FPG, GLUEX and HbA1c model (model 2).

Models performances (Fig.2) :

- GLUEX model: globally acceptable despite high residual error & under-prediction in early months for external study GetGoal-M
- HbA1c models (1 & 2): diagnostics graphs & VPC: correct for $t < 200$ days, but over-prediction after, especially in the placebo arm & in external study GetGoal-M (right censoring effect)

Comparison of the two HbA1c models:

- Residual error: smaller in model 2
- VPC slightly better for model 1
- Comparison on validation study GetGoal-M: mean square errors smaller in model 1 for population predictions, but smaller in model 2 for individual predictions, both on all observations and on days 90 or 168
- Similar HbA1c predictions the first months, but higher disease progression with the GLUEX-HbA1c model (Fig.3)

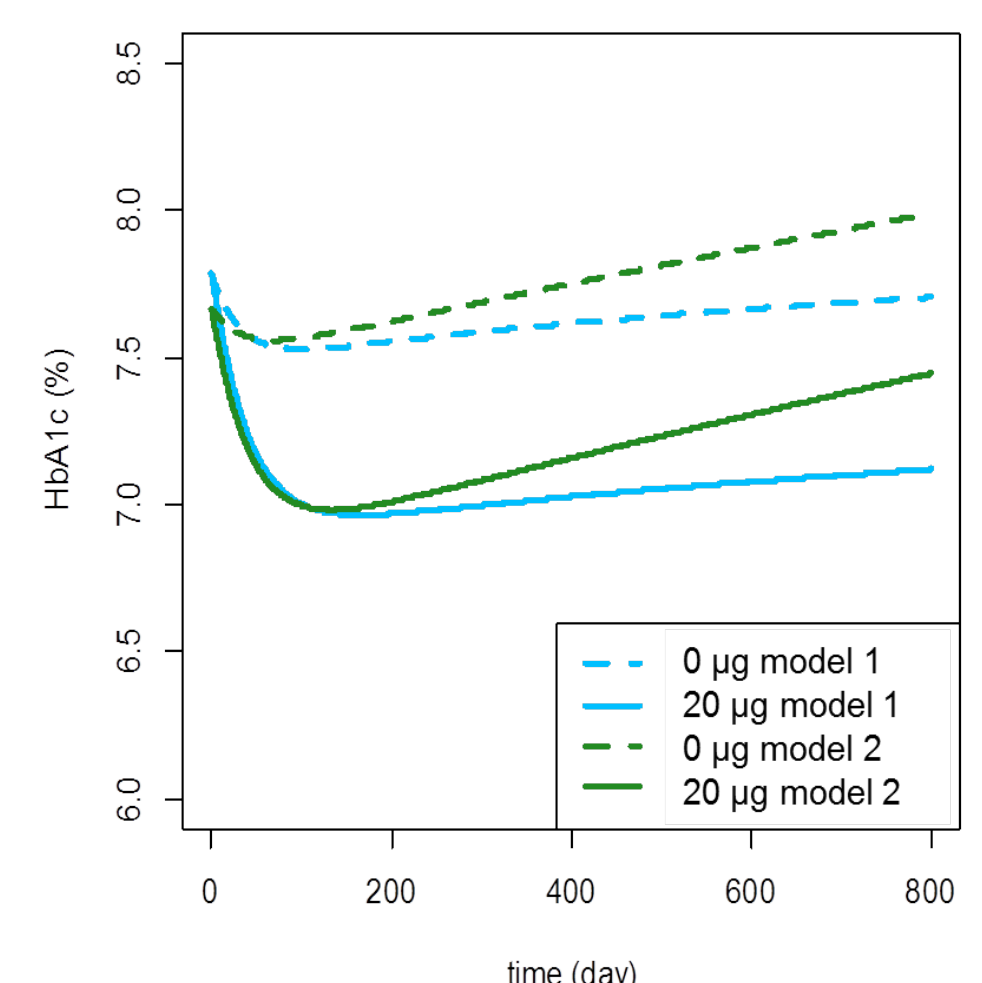


Fig.3. HbA1c predictions for a typical Caucasian patient, with model 1 and 2

Conclusions & Critical Impact

- Up to 24 weeks duration, the 2 models enable the proper description of the therapeutic reduction of HbA1c in lixisenatide treated patients in discriminating the relative contribution of lixisenatide effects on FPG and on PPG (implicitly or explicitly).
- Comparing the 2 models performances shows mixed results, as model 2 seems better for describing and adjusting data but could be slightly less robust than model 1 for predicting. However, model 2 has the advantage to be more mechanistic, by describing lixisenatide effect on GLUEX, and then to confirm the greater impact of GLUEX reduction on HbA1c reduction than FPG reduction.
- This extended model of disease progression in T2DM adequately predicts HbA1c therapeutic changes of a prandial GLP-1 receptor agonist, lixisenatide, up to 24 weeks duration. As predictive tool, the model may be used for the design of a new lixisenatide phase III study or to predict HbA1c results for a new GLP1 agonist using assumptions or early results on FPG and 2H-glucose excursion.

Acknowledgements & References

Studies were funded by **SANOFI**. Model 1 was developed in collaboration with the **SGS Exprimio NV**.

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