



Mechanistic Modeling of Glucagon-Like Peptide (GLP-1) Therapeutics Development for Weight Loss Management



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Introduction

Incretin-based therapies targeting hormones such as glucagon-like peptide-1 (GLP-1) have been effective in managing type 2 diabetes (T2D). These hormones play a crucial role in metabolic regulation by stimulating glucose-dependent insulin secretion, inhibiting glucagon release, slowing gastric emptying, and enhancing satiety. Recently GLP-1 receptor agonists (GLP1-RA) have emerged as exciting therapies for weight loss with additional positive effects on metabolic and overall health. Published work has shown the short and long-term effects of caloric intake on both body weight (1) and Glucose metabolism (2,3). Bosch's 4GI model focuses on the interactions between glucose, glucagon, GLP-1, Gastric Inhibitory Polypeptide (GIP), and Insulin but does not account for energy intake, expenditure, or body weight. Hall's energy balance model incorporates weight loss predictions but lacks key glucose regulatory elements like insulin and glucagon. These limitations hinder the ability to capture the full bidirectional relationship between weight loss and glycemic improvements, reducing their utility in assessing combination therapies.

Objective

To predict weight loss and glycemic control with daily three meal intake and GLP-1RA treatment using a QSP model that integrates independent published models simulating weight gain/loss and glycemic control and calibrating it to standard of care GLP-1 receptor agonist Semaglutide trial data in obese T2D patients (5)

Methods

Key considerations for integrating Weight Loss & 4GI model and connecting to GLP-1 RA Therapies

- Glucose-insulin dynamics (4GI model)
 - Fasting plasma glucose, glucagon, GLP, GIP, & insulin
- Energy balance and body weight regulation (EBM model)
- GLP-1 RA drug PK

Pharmacokinetics (PK) modeling

Developed a 2-compartment PK model for Semaglutide as previously described (4)

Pharmacodynamics (PD) modeling

PD outcomes as observed with primary literature (4) were modeled as driven by plasma GLP-1 concentrations Captured dose-dependent effects on:

- Food intake
- Gastric emptying
- Insulin secretion

Body Weight Loss:

Modeled as a key efficacy outcome & calibrated using clinical data across multiple Semaglutide doses (5,6)

HbA1c Dynamics:

Modeled as a key efficacy outcome as seen in weight model. Additionally, we incorporated indirect impact of weight loss via improved insulin sensitivity that improved glycemic control as supported by literature (7) wherein 1 kg weight loss leads to 0.1% reduction in HbA1c

The detailed structure and focus of this integrated approach, along with the clinical endpoints under consideration, are visually represented in Figure 1 and 2.

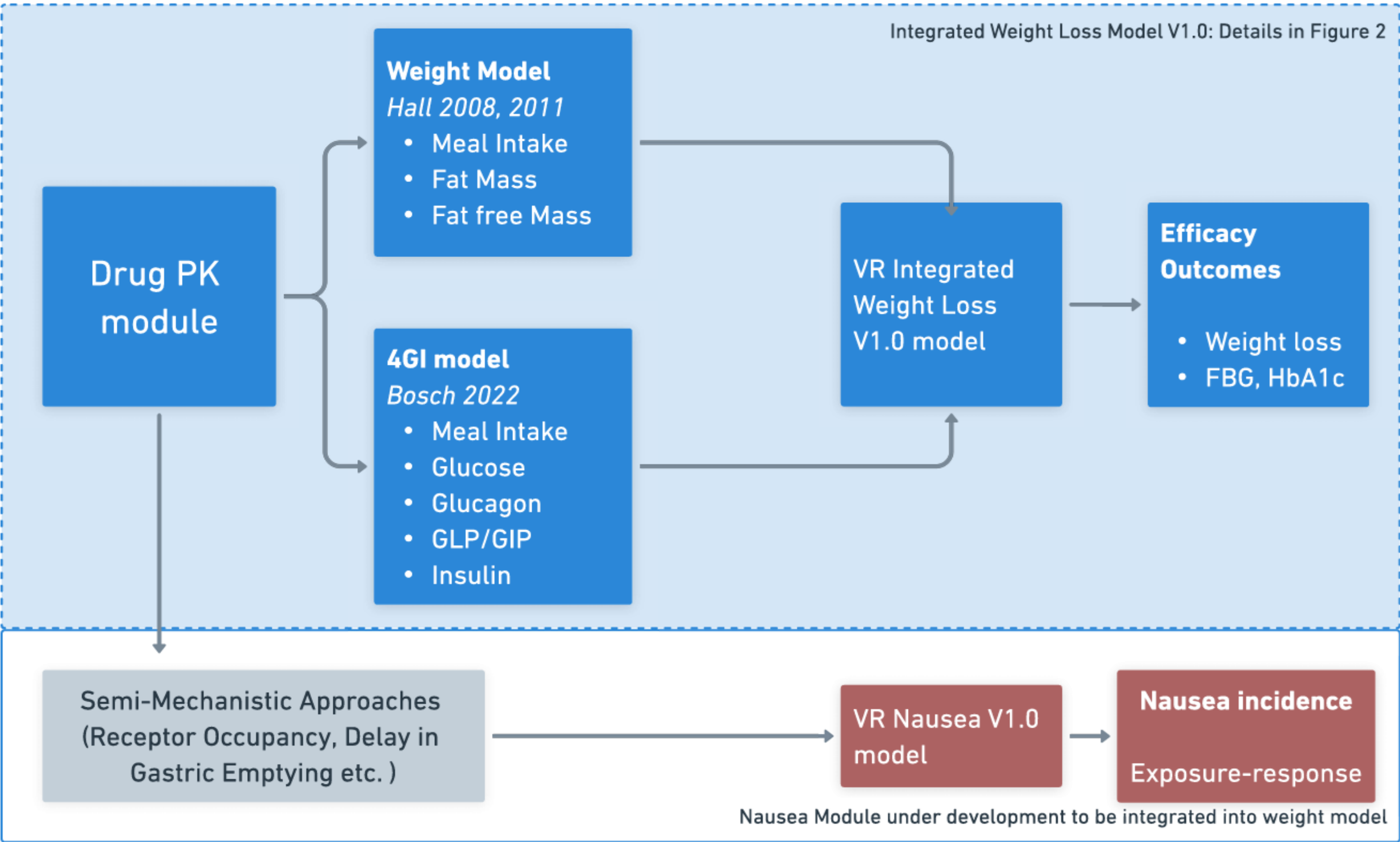


Figure 1. VR Integrated Weight loss model Strategy Roadmap

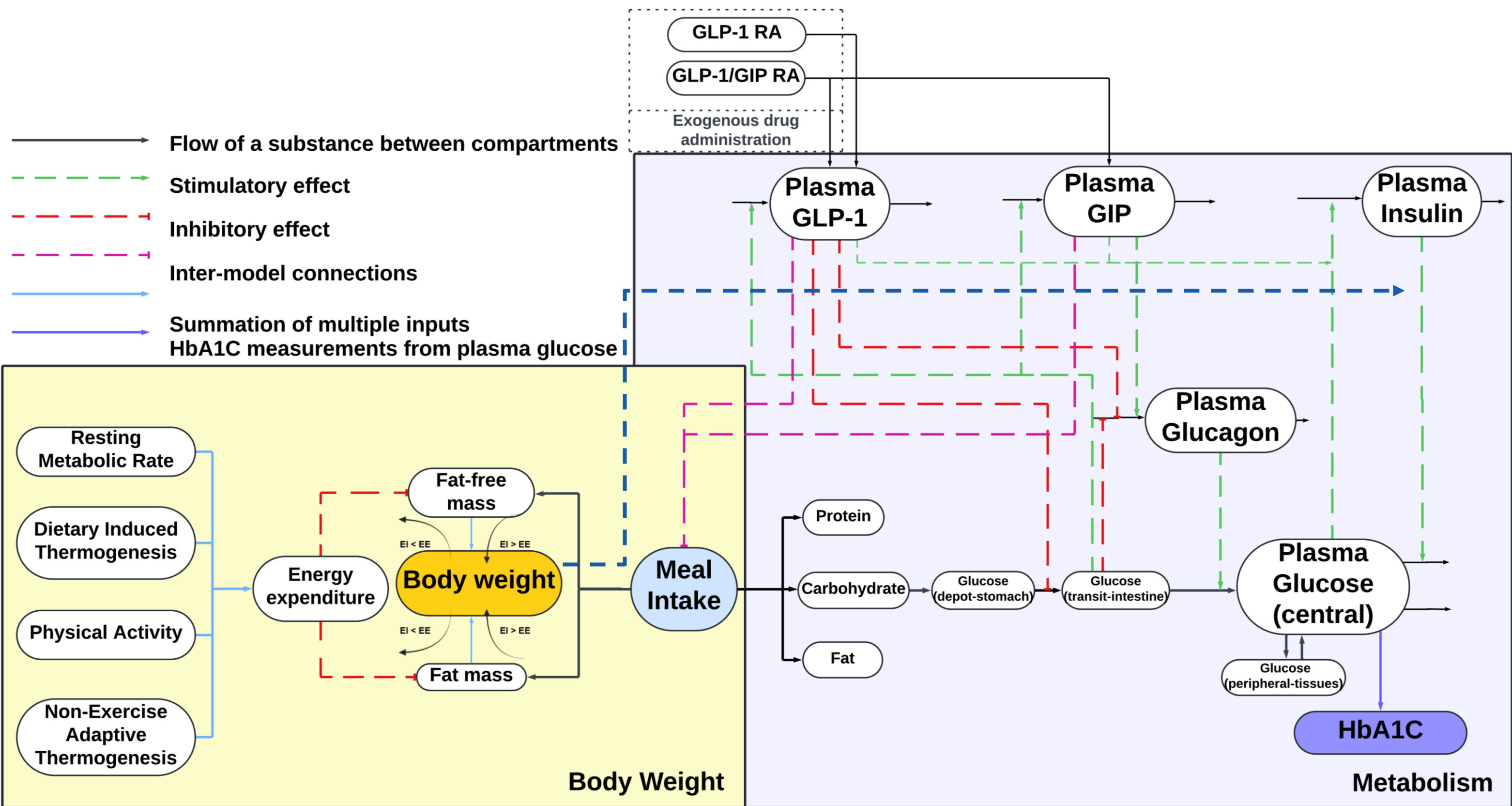


Figure 2. Comprehensive Model Effect Diagram for Integrated Weight Loss model V1.0

Results

The integrated model was tested with once weekly 1mg subcutaneously administered Semaglutide in diabetic obese patients. As seen in Heise et al 2022 (5) patient baseline characteristics, we generated a single virtual patient with baseline weight (92.38 kg), HbA1c (7.71%), fasting plasma glucose (128 mg/dl), fasting plasma insulin (52.4 pmol/L) and fasting plasma glucagon (12.3 pmol/L).

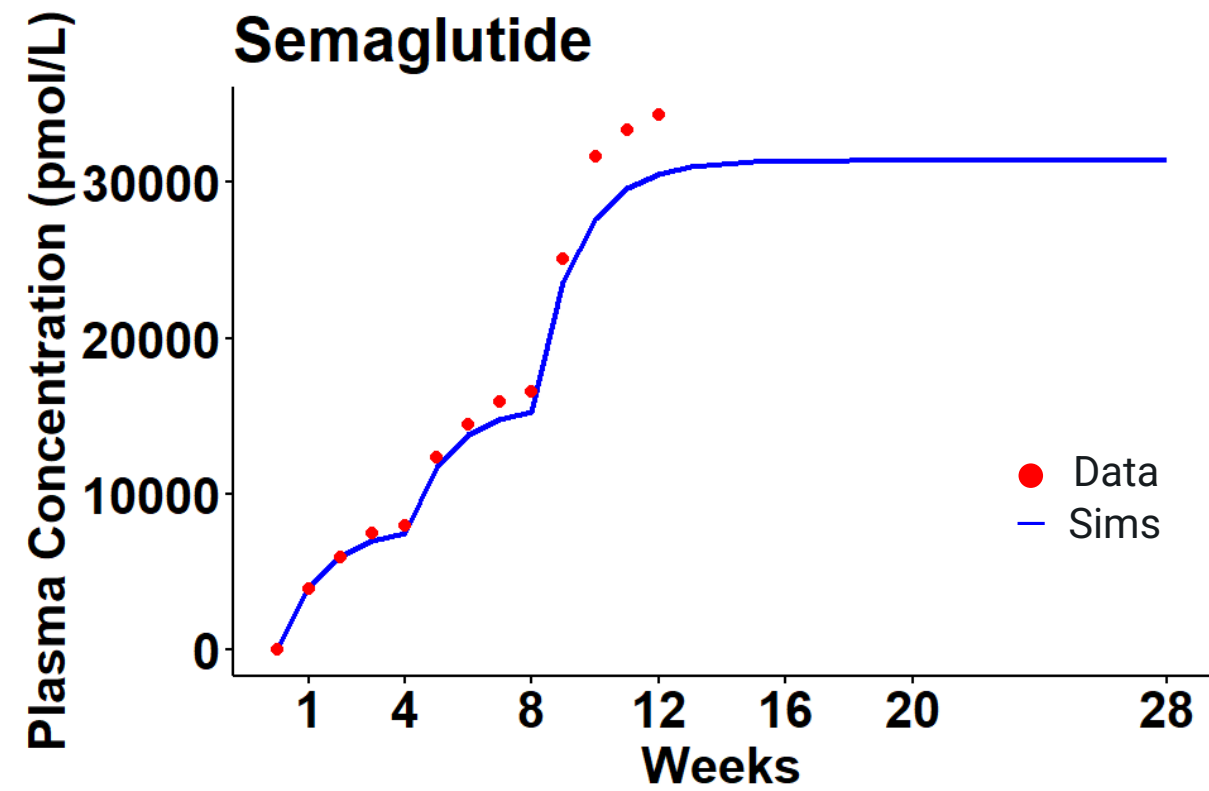


Figure 3. RefVP captures Semaglutide plasma PK as seen in 1mg sc dose (data in red points and sims in blue)

Pharmacokinetic results

The reference diabetic obese virtual patient (refVP) captures the drug PK over 4-week dose escalation starting from 0.25 mg to 1 mg QW dose using the 2-compartment model (Fig. 3). Data was better captured using the 2-compartment model as against the 1-compartment model (data not shown here)

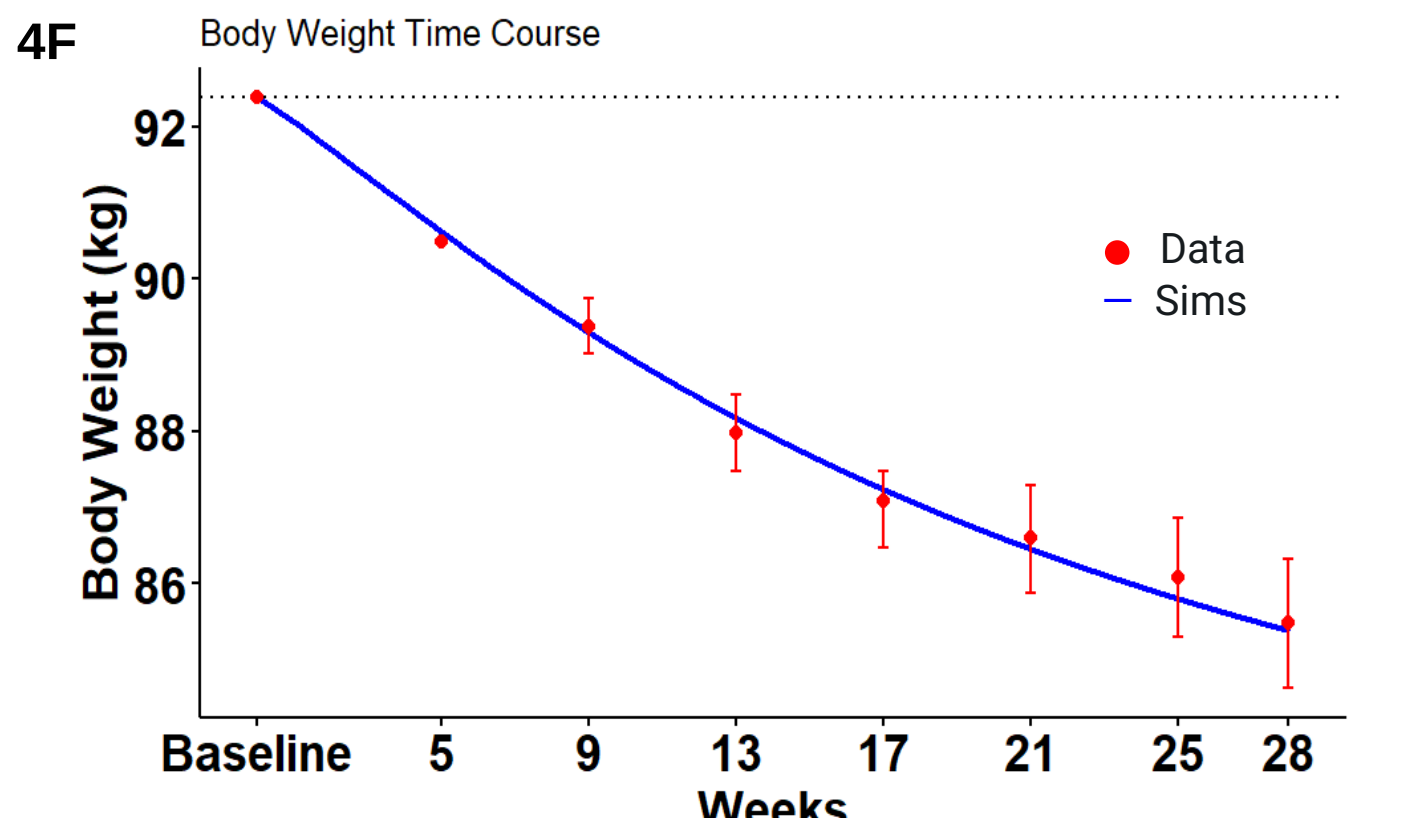
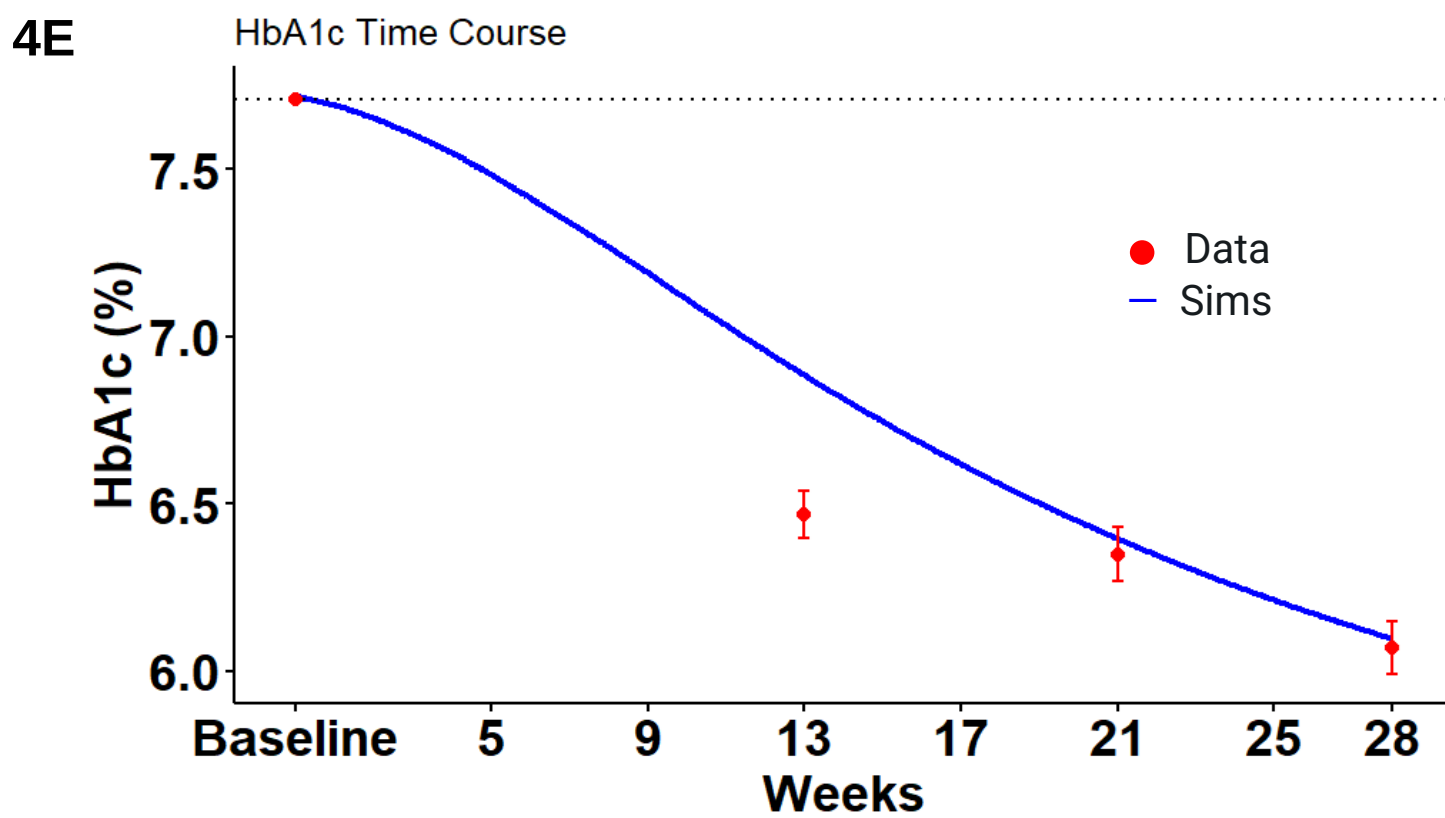
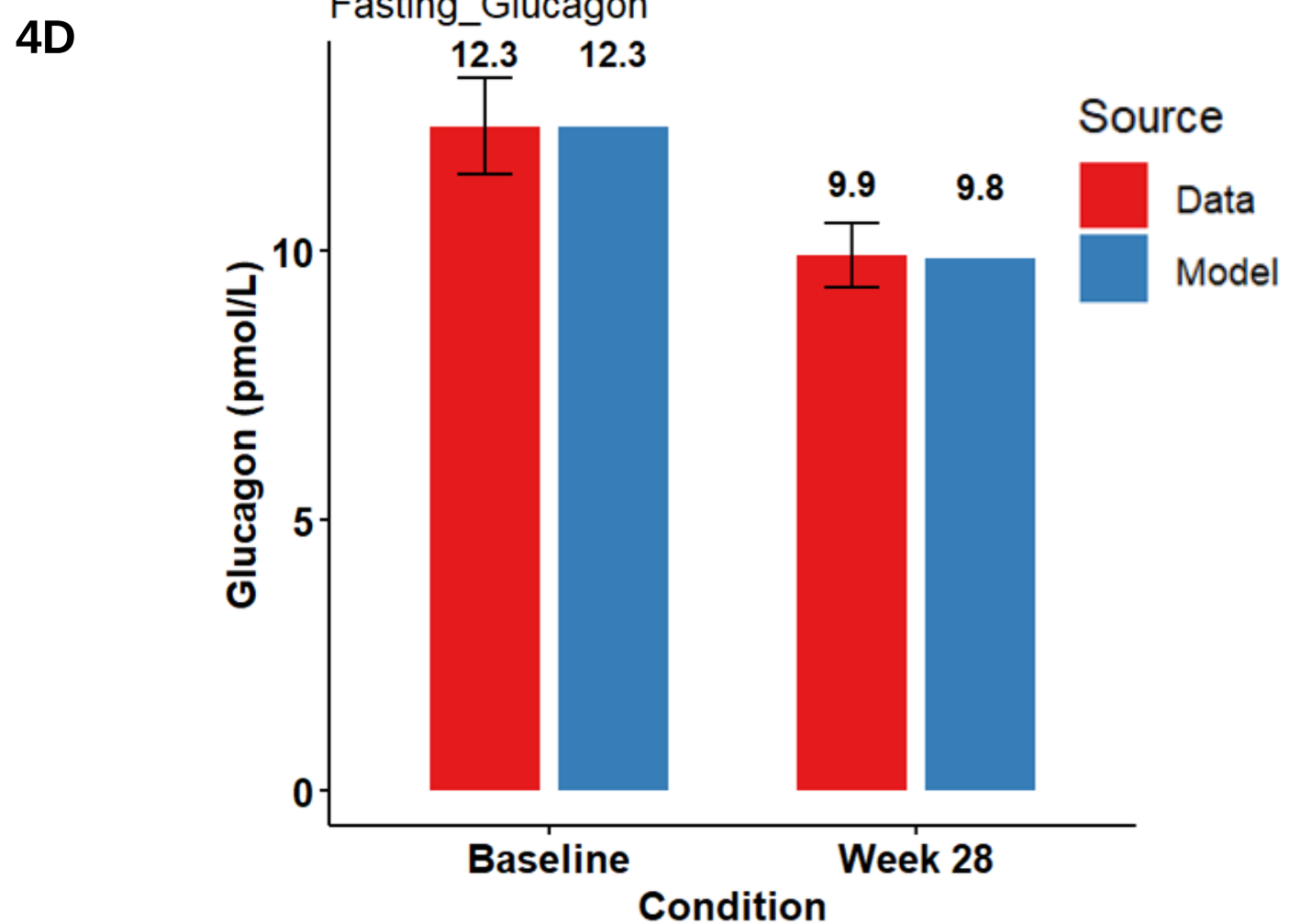
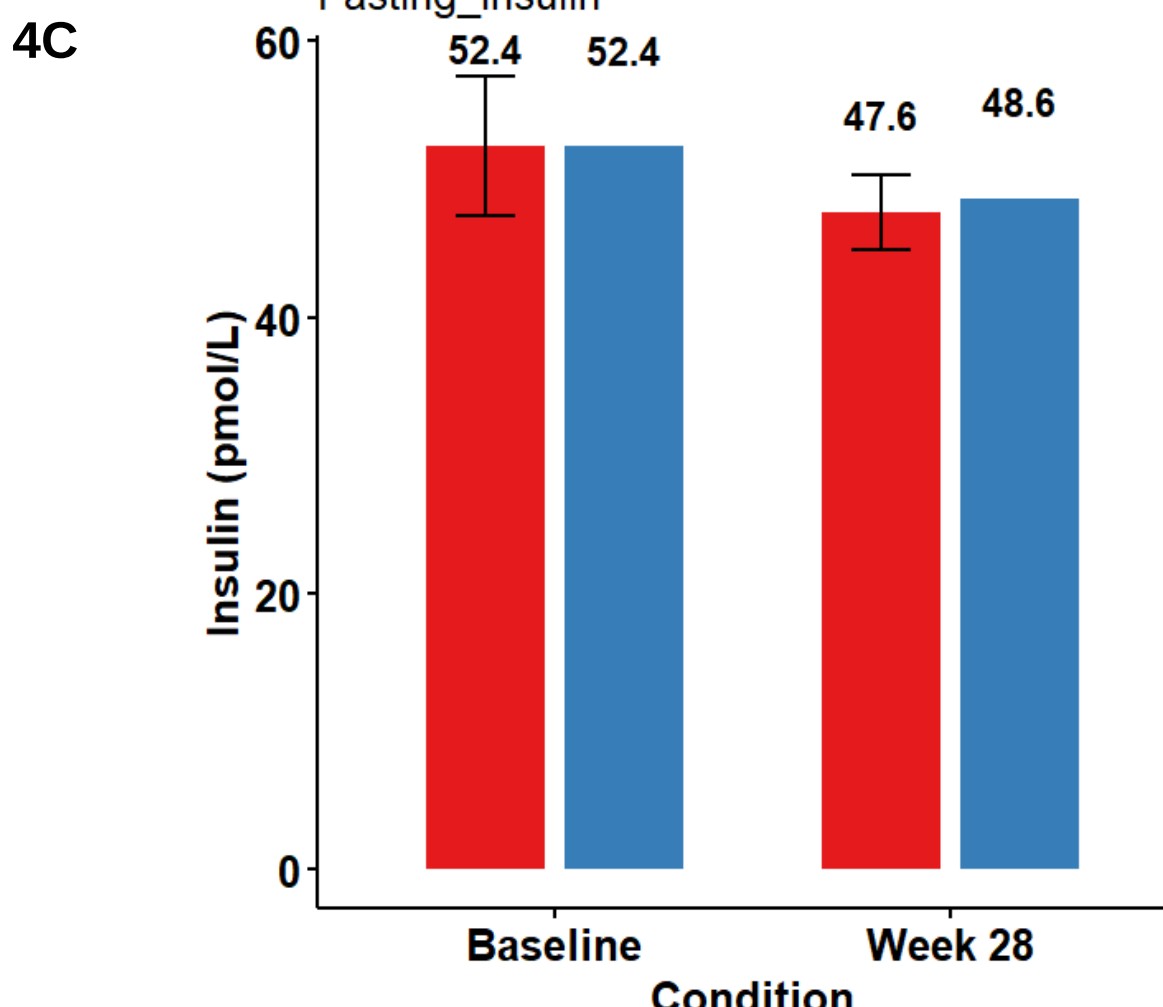
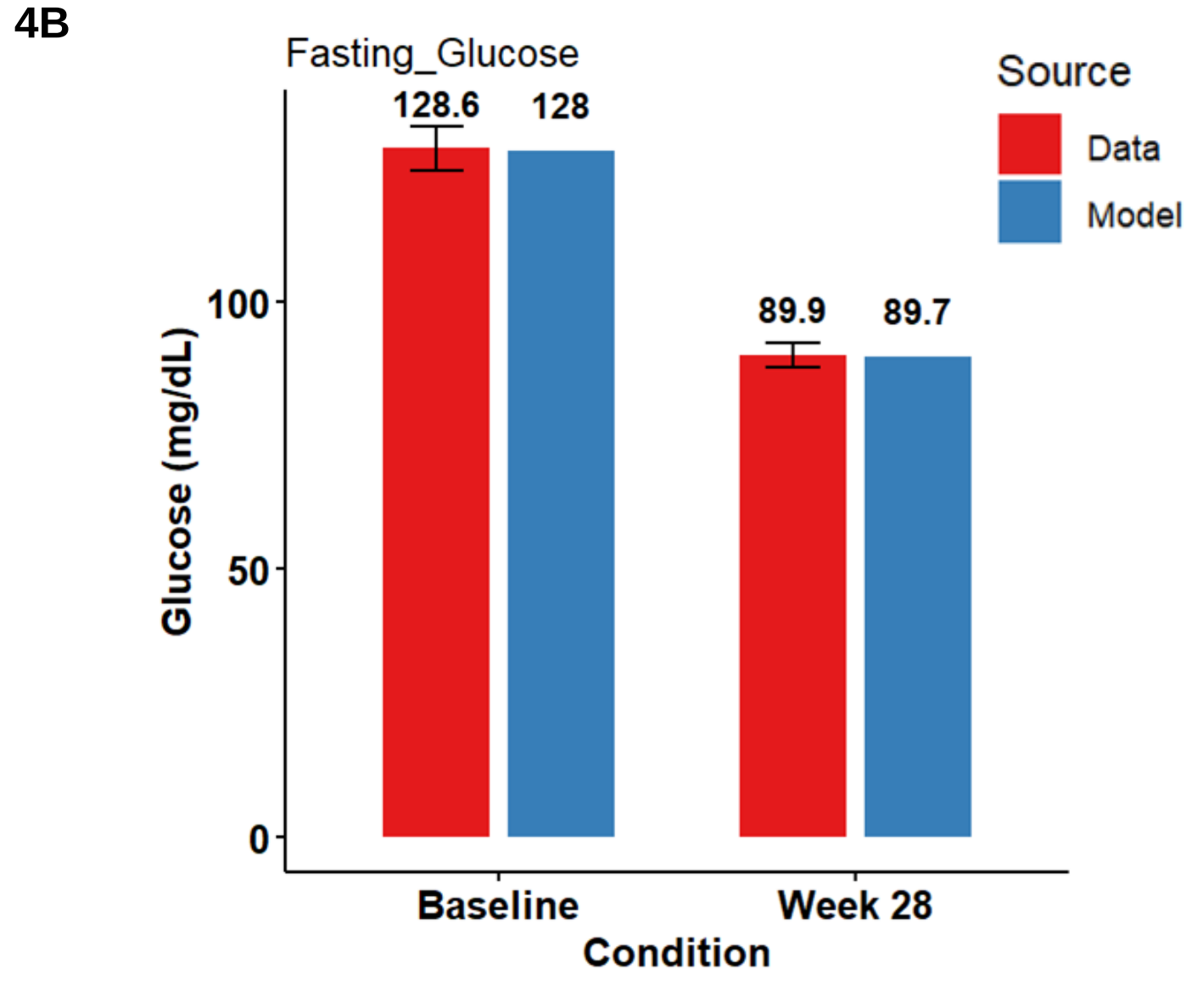
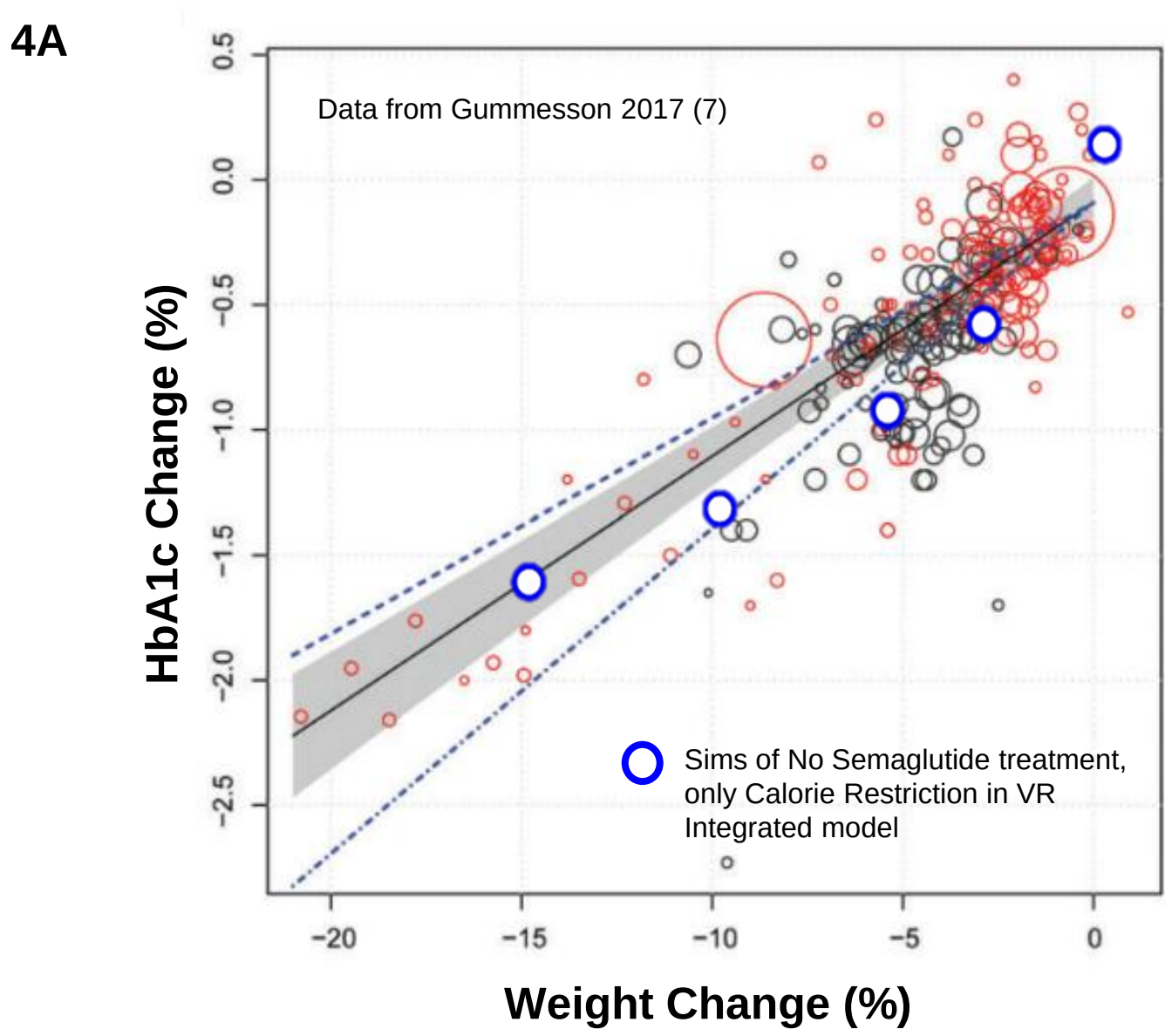


Figure 4. (A) Model well integrates EBM and 4GI models & captures the increased insulin sensitivity to diet-induced weight loss even in the absence of GLP-1RA treatment. RefVP captures glycemic outcomes with Semaglutide treatment - plasma glucose (B), plasma insulin (C), plasma glucagon (D) as well as long term PD outcomes such as HbA1c control (E) and loss in body weight (F)

Pharmacodynamics Outcomes - Efficacy capture

- The integrated model is now capable of predicting no treatment, pure caloric restriction-based weight loss and the dependent improvement in glycemic control (Fig. 4A) as seen in Gummesson et al. 2017 (7)
- The refVP recapitulates the pre & post therapy fasting plasma glucose, insulin and glucagon (Fig. 4B-D) as reported by Heise (5).
- RefVP captures the reduction in HbA1c to 6% over 28 weeks (Fig. 4E), and a 6.9kg decrease in body weight percentage over time with Semaglutide treatment (Fig. 4F).
- Our model thus captures drug PK, PD, and downstream effects on key clinical readouts weight loss, and HbA1c for Semaglutide.

Conclusion

A single RefVP was calibrated to s.c. Semaglutide 1mg using the integrated weight loss model combining the Energy Balance model, the 4GI model and the drug PK module. RefVP captures Sema PK and more importantly both glycemia-related PD outcomes as well as body weight loss in obese T2D patients treated with Semaglutide. In order to improve the utility of the model in drug development, several additional features are being added. In particular, a population approach that enables simulations of clinical trials and virtual populations of non-diabetic obese and diabetic obese people is under development to capture varied responses in specific populations. Further, other drugs in this class including GLP/GIP dual agonists & combinations (e.g. Tirzepatide), are being tested to improve model reliability and enhance the scope of the model application.

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