Mechanistic modeling of efficacy and nausea of GLP-1 receptor agonist (RA) Semaglutide and dual GLP-1/GIPRA Tirzepatide in non-diabetic obese patients

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MOTIVATION

- Energy intake changes correlate with body weight loss
- Earlier, the Obesity model predicted weight loss with diet & **mono GLP-1RA** (4A)
- Semaglutide 1mg and Tirzepatide 15mg in non-T2D obese patients had similar energy intake reduction but Tirzepatide patients had more weight loss hypothesized primarily by a larger fat oxidation [1]
- Can our Obesity model
  - Capture the drug-specific, and target class-specific drug responses with mono and dual RA
  - Capture increased weight loss in tirzepatide?

KEY INSIGHTS

- **Increased fat oxidation in tirzepatide** accounts for the additional weight loss compared to semaglutide for a similar reduction in the energy intake (1A-C)
- **Capture of weight loss plateau:** Non-adherence to caloric deficit instructions in clinical weight loss trials (1D) and drug tolerance
- **Population-level nausea incidence** reflects the **delay in gastric emptying (semi-mechanistically captures gut-brain signaling)** caused by GLP-1RA & dual GLP-1/GIPRA (4B & 5B)

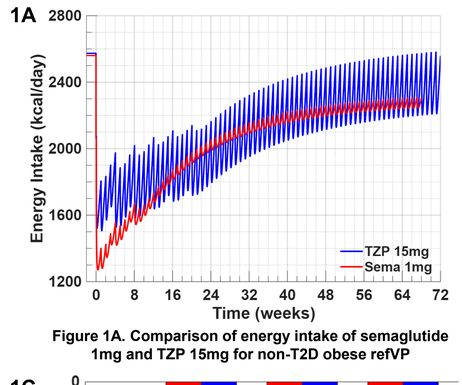

Figure 1A. Comparison of energy intake of semaglutide 1mg and TZP 15mg for non-T2D obese refVP

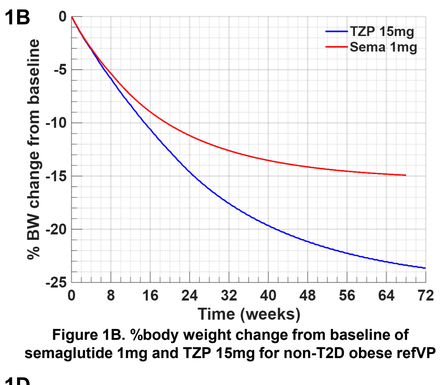

Figure 1B. %body weight change from baseline of semaglutide 1mg and TZP 15mg for non-T2D obese refVP

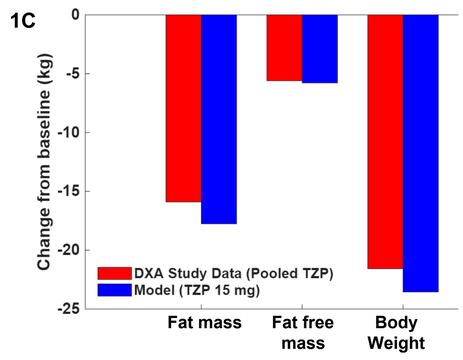

Figure 1C. RefVP captures absolute change in body composition at Week 72 of pooled TZP 5mg, 10mg, and 15mg dose groups of SURMOUNT1 [2]

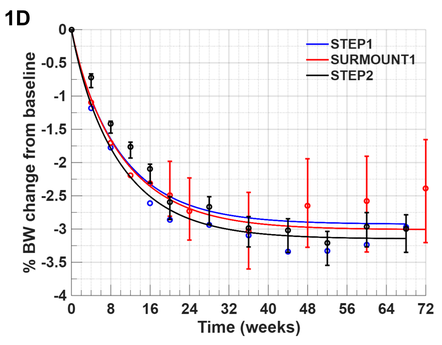

Figure 1D. Non-adherence effect in model captures weight loss plateau in placebo arms of STEP2 (calibration), STEP1 and SURMOUNT1 (validation)

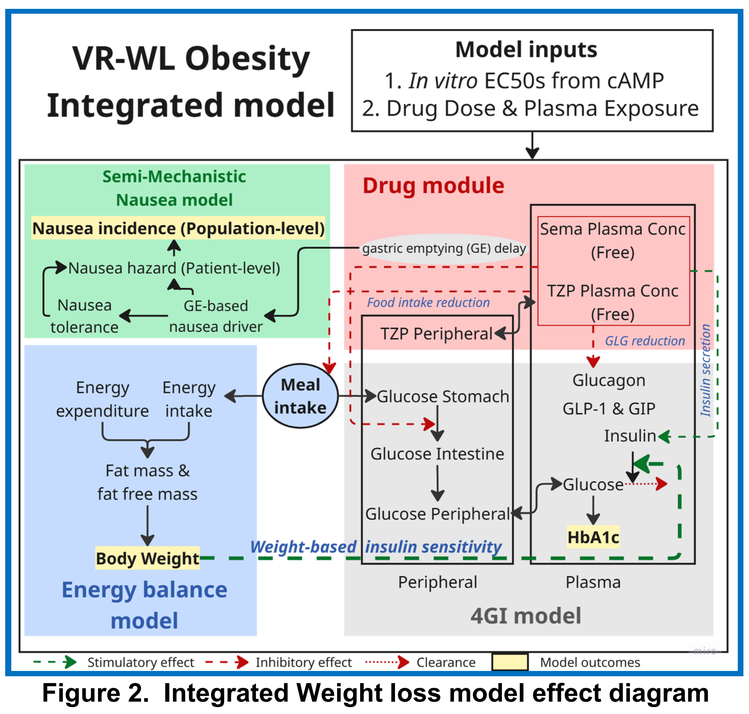

Figure 2. Integrated Weight loss model effect diagram

VPOP WORKFLOW

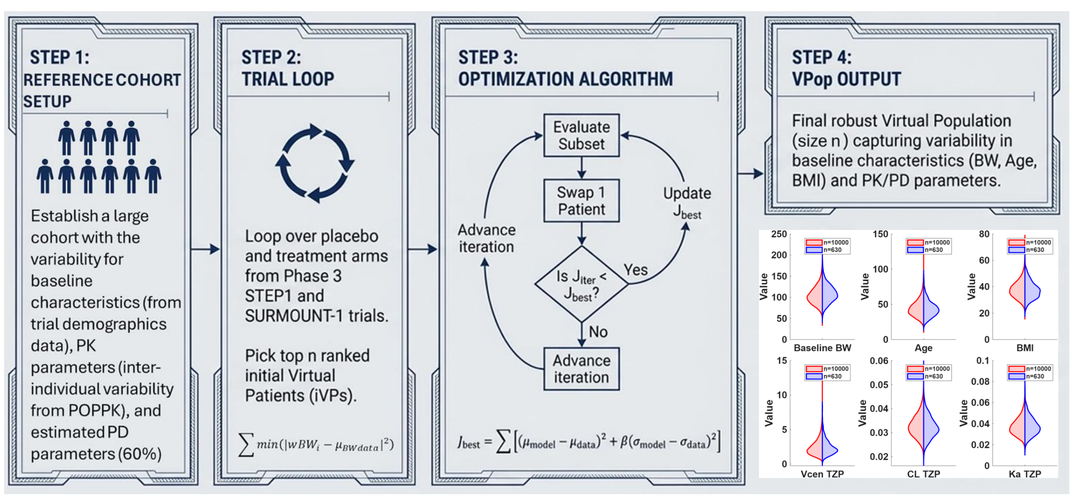

Figure 3. VPOP workflow

APPROACH

- **Literature-based PK module:** semaglutide – Strathe et al., [3], tirzepatide – FDA label [4]
- **Model inputs: *In vitro* EC50 from cAMP assay, and drug PK**
- Weight loss segment modeled based on Hall et al., [5], and glycemic segment modeled based on Bosch et al., [6] and Silber et al., [7]
- Novel population-level nausea incidence modeled as a hazard-based function of drug's plasma exposure and gastric emptying delay

Non-T2D Obese Population – Efficacy & Nausea GLP-1RA Semaglutide (STEP 1)

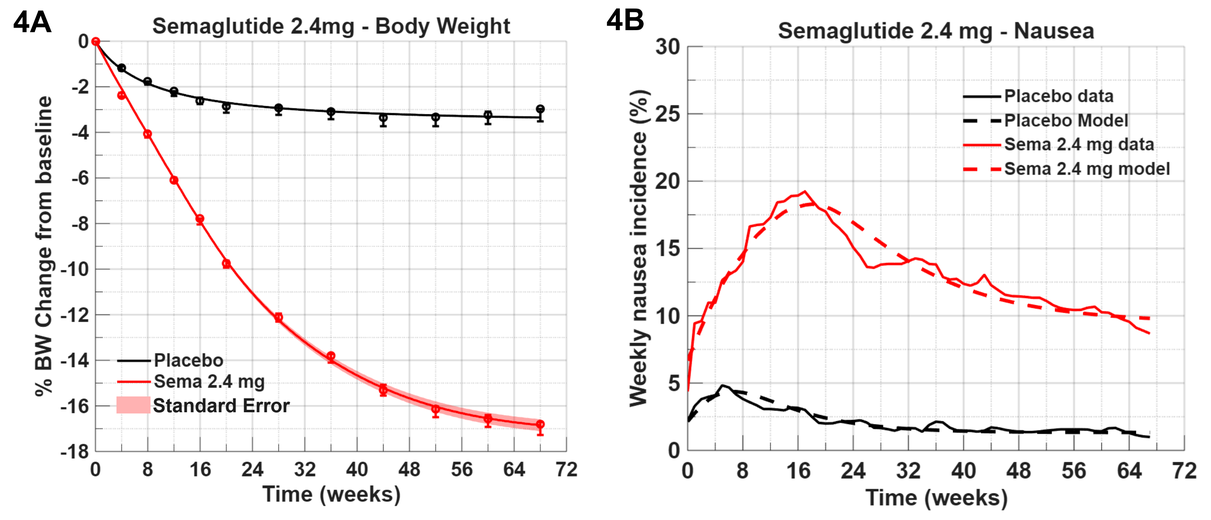

Figure 4. Non-T2D obese VPOP captures (a) long term body weight % loss and (b) % nausea prevalence as reported in STEP 1 for sema 2.4mg QW s.c. dose [8]

Dual GLP-1/GIPRA Tirzepatide (SURMOUNT 1&5)

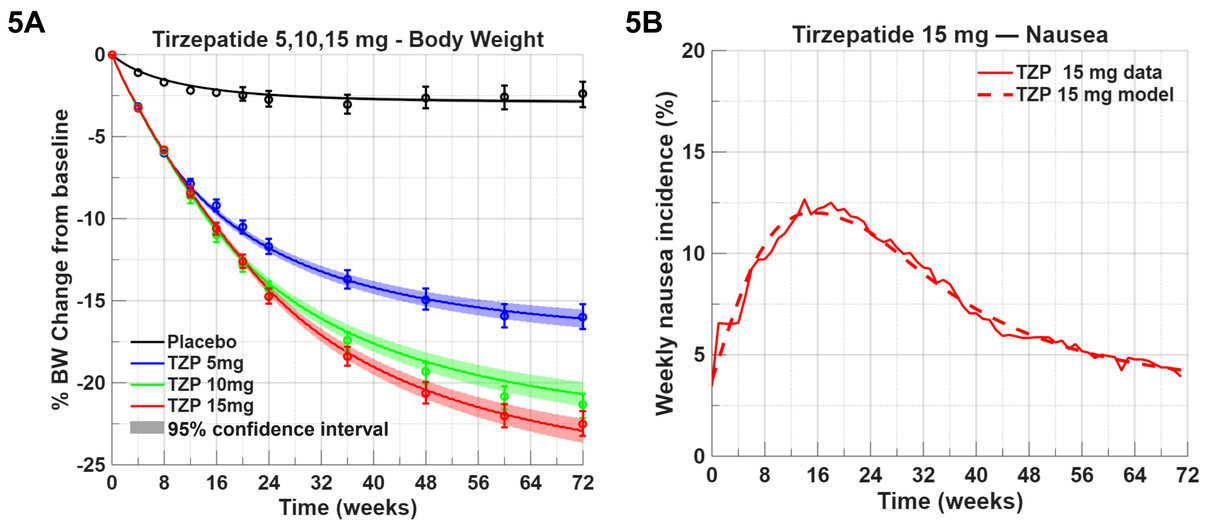

Figure 5. Non-T2D obese VPOP captures (a) long term body weight % loss for TZP 5,10,15 mg QW SC dose (SURMOUNT 1 [9]) and (b) % nausea prevalence for TZP 15 mg QW s.c. dose (SURMOUNT 5 [10])

CONCLUSION

- Model predicts weight loss and nausea in both **mono GLP-1 class** receptor agonist Semaglutide (4A & 4B) and **dual GLP-1/GIP class** receptor agonist Tirzepatide (5A & 5B) in non-T2D obese population
- Model predicts the **additional body weight loss in dual RA** (Tirzepatide) compared to Semaglutide by accounting for the increased fat oxidation
- **Model predicted virtual population** captured the differential responses generated by varying baseline characteristics, drug exposure and PD potencies of the drug, and well captures the breadth of the patient response seen in STEP 1 and SURMOUNT 1 trials.

REFERENCES

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8. Wilding J, et al. (2021)
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STRATEGIC NEXT STEPS IN OBESITY ROADMAP

- Expanding into next-gen target & mechanism addition **(Amylin & GcGR)**
- Predicting efficacy and safety of **combination therapies (GLP/Amylin or Triple agonists)**
- Comparing **Oral vs Subcutaneous** drug PD & safety profiles
- Optimizing dosing & titration strategies for improved therapeutic window
- Modeling fat mass vs **lean mass dynamics, & weight regain** upon treatment withdrawal
- Predicting target engagement across target & non-target tissues & correlating with clinical outcomes