Orforglipron Weight Loss and Nausea Accurately Simulated with OBESITYsym

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PURPOSE

- The recent availability of effective, GLP-1R agonist (GLP-1RA) based treatments of obesity has provided great benefit to patients
- Understanding the balance between body weight (BW) loss and nausea is paramount in predicting the effectiveness of oral GLP-1RA based medications
- Quantitative systems pharmacology (QSP) modeling can aid in predicting both efficacy and adverse events of compounds, particularly when clinical data are available

METHOD(S)

- OBESITYsym, a QSP model, has been developed to enable simultaneous prediction of BW and nausea due to pharmacologic treatments
- This mechanistic, mathematical model enables prediction of body weight changes, body composition via direct and indirect effects of caloric intake and energy expenditure (1)
- The novel submodel of nausea includes both sensitivity and tolerance, establishing the link between compound exposure, energy balance, and nausea with pharmacokinetic models and compound potency
  - *in vitro* measured GLP-1R potency values (EC50) from the literature were employed for each compound.
  - Compound exposure was predicted utilizing pharmacokinetic models within OBESITYsym
- The model has been **calibrated** with clinical data from compounds **administered both subcutaneously and orally** including **semaglutide** (sema, 2.4 mg QW for 68 weeks (2)), **liraglutide** (lira, 3 mg QD for 56 weeks (3)), **tirzepatide** (tirze, 5, 10, or 15 mg QW for 72 weeks (4)), and **orforglipron** (orfo, 12 and 45 mg QD for 36 weeks (5)) via simulations of phase 2 or 3 clinical trial protocols in a simulated obese population (SimPops) with mean BW of 106.2 kg +/- 14.6 kg.
- Orfo 24 and 36 mg (5) doses (QD for 36 weeks) were used to validate the optimization.

RESULTS

- The simulated clinical responses for all treatments in the SimPops aligned with reported clinical data and were within reported error bounds regardless of the route of administration
- Moreover, the placebo BW and nausea responses were accurately recapitulated across trials (not shown), reflecting the ability for the model to capture both treatment and lifestyle modifications on BW

Efficacy (Weight Loss)

- The model was well calibrated, simulating comparable weight loss over time as was observed in clinical studies for orfo, sema, and lira (Figures B, C)
- Validation was achieved with accurate prediction of weight loss for the 24 mg and 36 mg QD doses (including uptitration, Figure A)

Adverse Events (Nausea)

- The model was well calibrated, simulating comparable nausea incidence as was observed in clinical studies for orfo, sema, and lira (Figures B, C)
- Validation was achieved with accurate prediction of nausea incidence for the 24 mg and 36 mg QD doses (including uptitration, Figure A)

CONCLUSIONS

- There was excellent alignment between the clinical data and the predicted body weight reductions and nausea incidence for 24 mg and 36 mg orfo
- **OBESITYsym can be used to evaluate the efficacy and nausea potential for novel treatments, including oral GLP-1RA and compounds that utilize additional mechanisms to adjust energy balance**

REFERENCES

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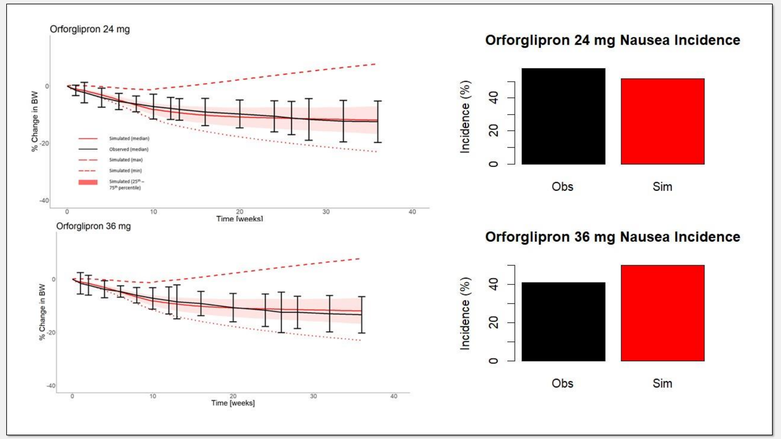
QSP Model Accurately Predicts Efficacy and Side Effects of Weight Loss Drugs

MODEL VALIDATION: ACCURATE PREDICTION OF WEIGHT LOSS AND NAUSEA INCIDENCE FOR ORAL ORFORGLIPRON 24 AND 36 MG

Figure A

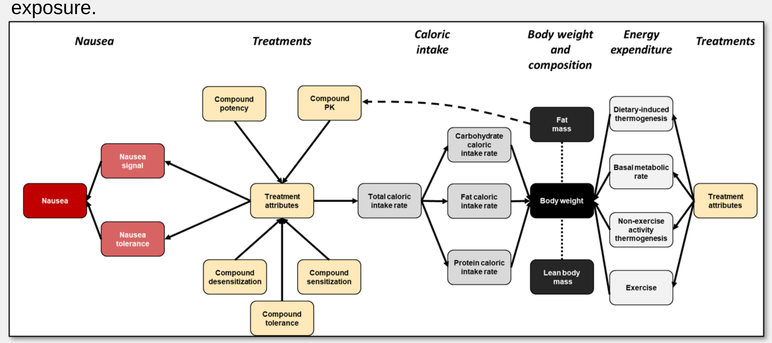
Obese patient population with mean BW of 106.2 kg used for simulation results; Up-titration dosing of oral orforglipron simulated as per the clinical protocol (5)



OBESITYSYM MODEL INCLUDES FUNDAMENTAL MECHANISMS RELATED TO BODY WEIGHT AND NAUSEA

Figure D

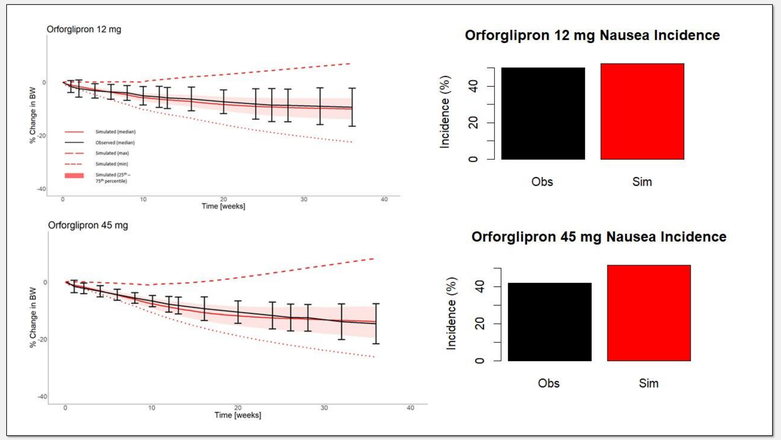
Model calculates how changes in caloric intake and energy expenditure via treatment or environment affect body weight. Monotherapy or combination treatments can be simulated, enabling exploration of complementary mechanisms. Model also includes ability to simultaneously predict nausea sensitivity and tolerance based upon compound exposure.



MODEL CALIBRATION: WEIGHT LOSS AND NAUSEA INCIDENCE ALIGN WITH OBSERVED CLINICAL DATA FOR ORAL ORFORGLIPRON 12 AND 45 MG

Figure B

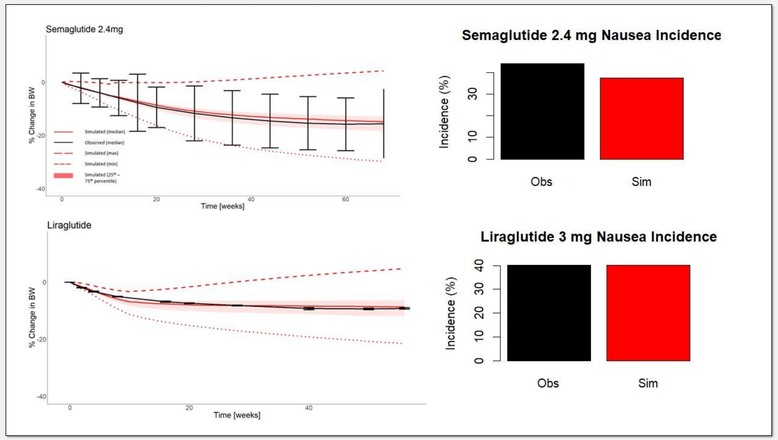
Obese patient population with mean BW of 106.2 kg used for simulation results; Up-titration dosing of oral orforglipron simulated as per the clinical protocol (5)



MODEL CALIBRATION: SUBCUTANEOUS SEMAGLUTIDE AND LIRAGLUTIDE ALIGN WITH OBSERVED WEIGHT LOSS AND NAUSEA INCIDENCE CLINICAL DATA

Figure C

Obese patient population with mean BW of 106.2 kg used for simulation results; Up-titration dosing simulated for both subcutaneous semaglutide and liraglutide as per the clinical protocol (2) and (3), respectively



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