

A Systems Approach to Accelerating the Pharmaceutical Industry Pipeline:

Competitive Preclinical and Clinical Modeling in Diabetes Drug Development

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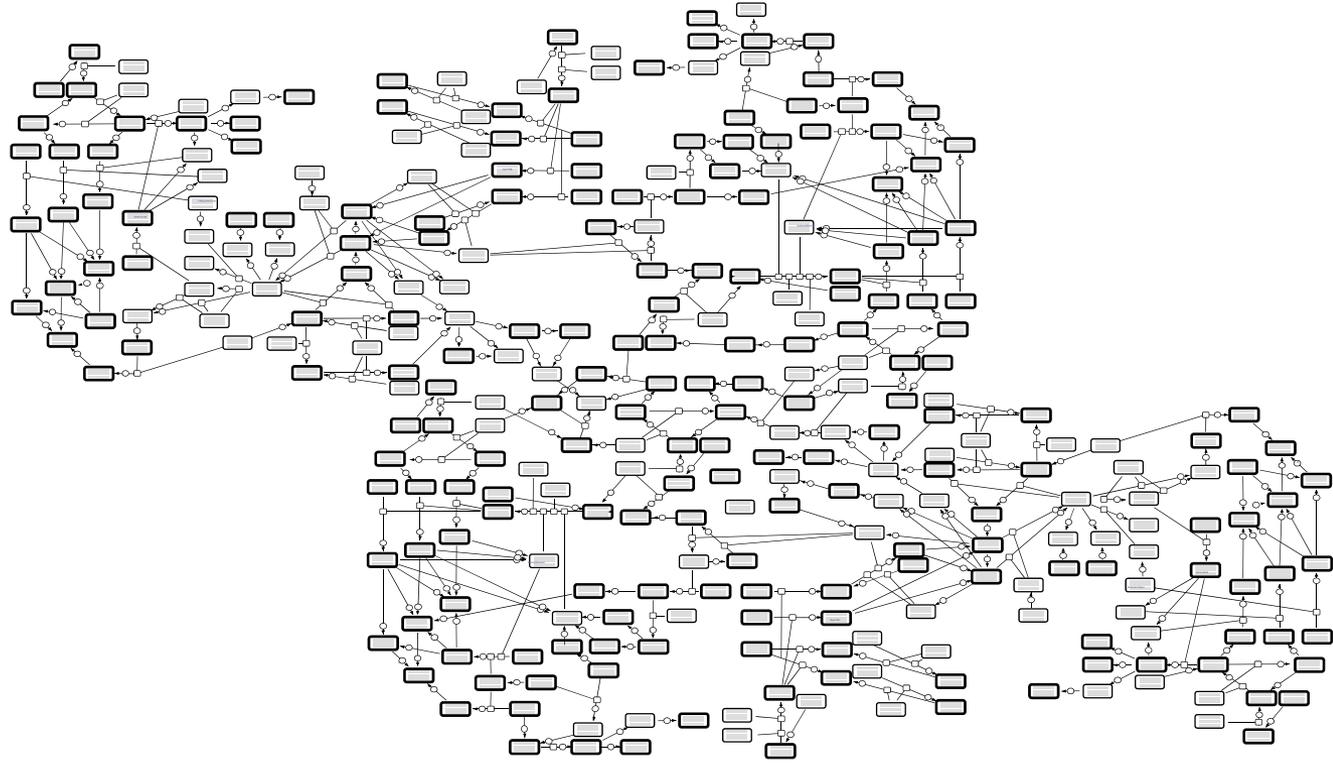
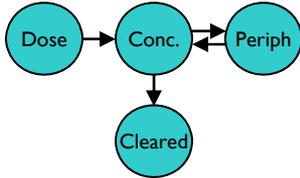
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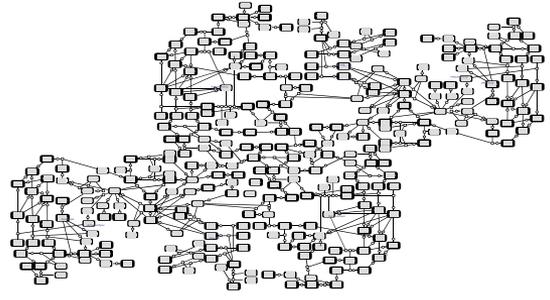
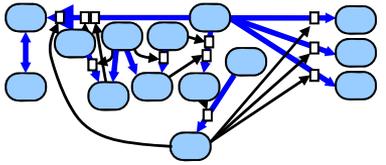
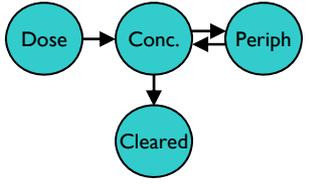
Models that help understand physiology, disease, drug action, and trial designs vary widely in scale and purpose.

PK/PD and Dose-Response Models

Very Large-Scale Mechanistic Models

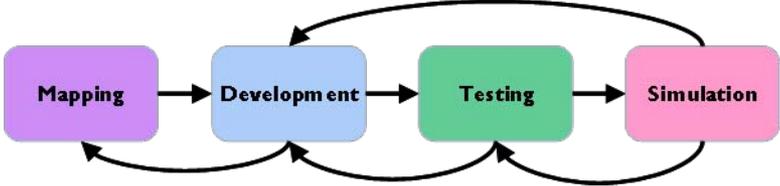
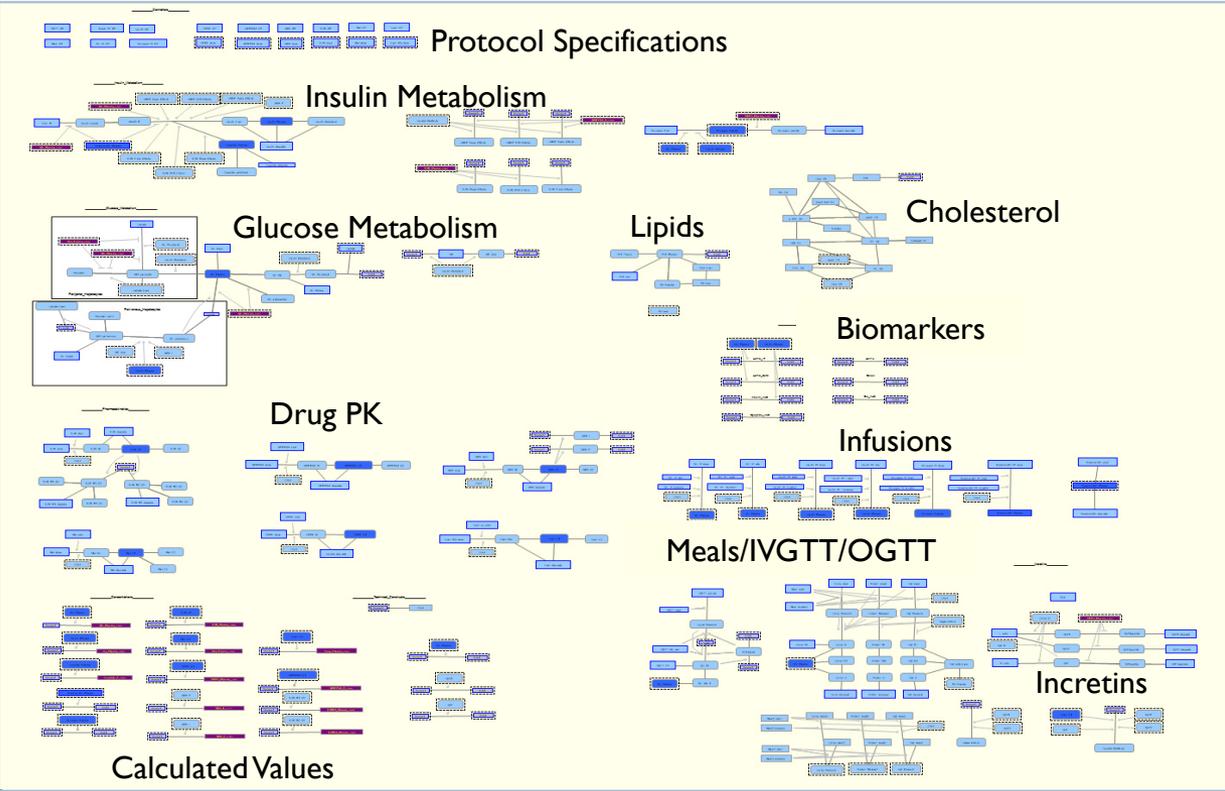


Each scale of model has different strengths and weaknesses.

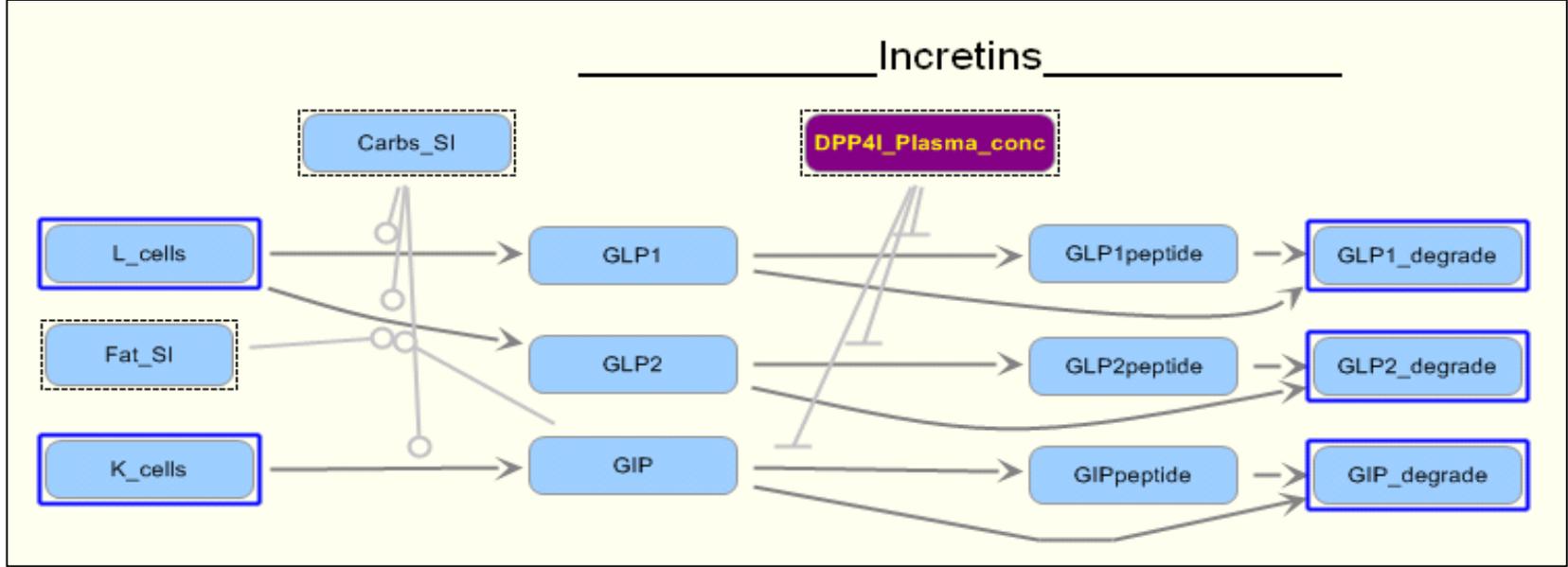


- | | | |
|----------------------------|-------------------------------------|-------------------------------|
| ▶ Narrowly targeted | ▶ Decision-focused | ▶ Broadly applicable |
| ▶ Few physiologic insights | ▶ Mechanistically insightful | ▶ Physiologically sound |
| ▶ Require human data | ▶ Exploits nonclinical data | ▶ Can use nonhuman data |
| ▶ Lower cost | ▶ Detail & cost focused on decision | ▶ Significant investment |
| ▶ Statistically rigorous | ▶ Useful for trial simulation | ▶ Not statistically tractable |
| ▶ Phenomenological | ▶ Not general purpose | ▶ Difficult to modify |

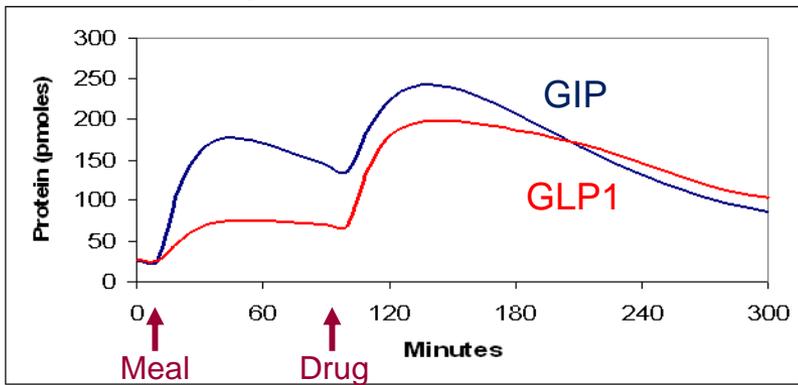
Pfizer & Rosa created the Medium Scale Pfizer Diabetes Model with physiology targeted at addressing program decisions.



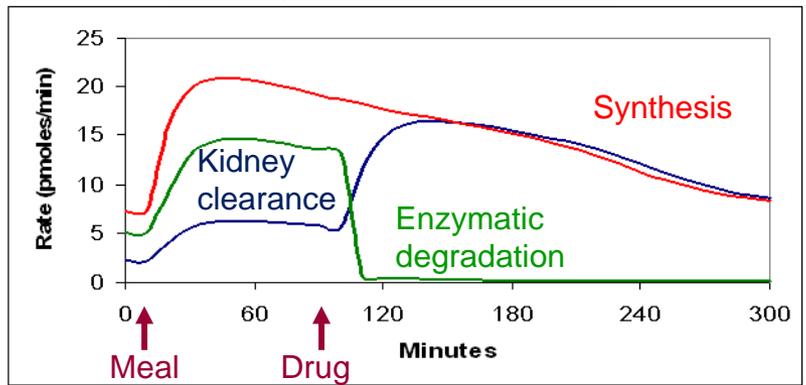
The model represents relevant pathways and drug actions at a level required to address the specific questions.



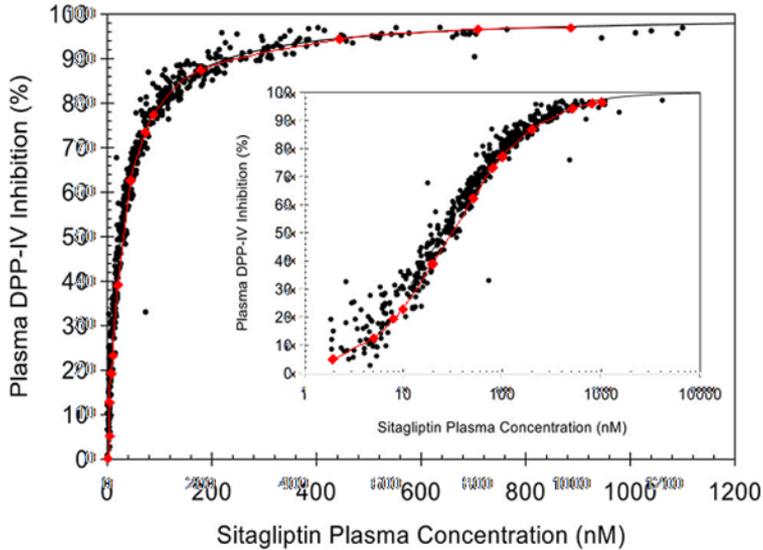
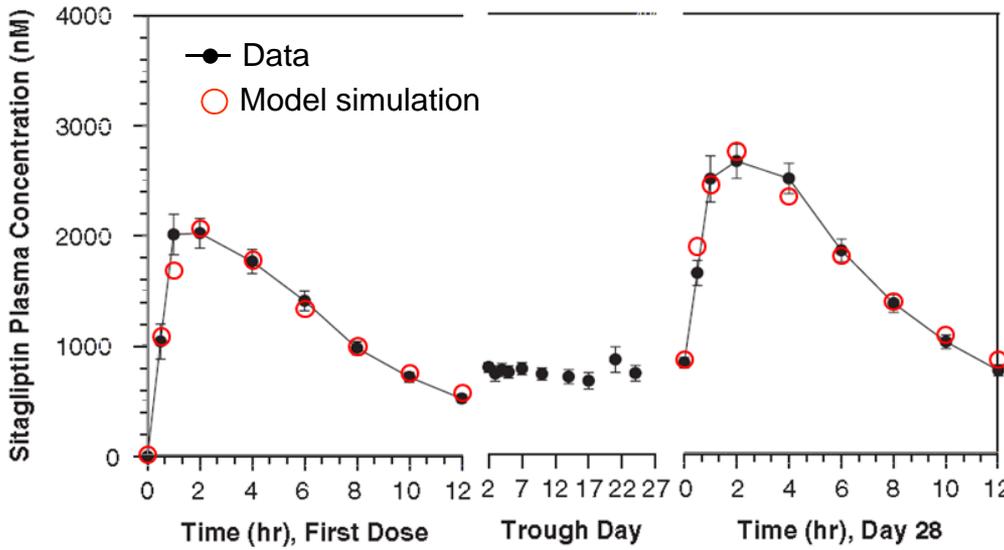
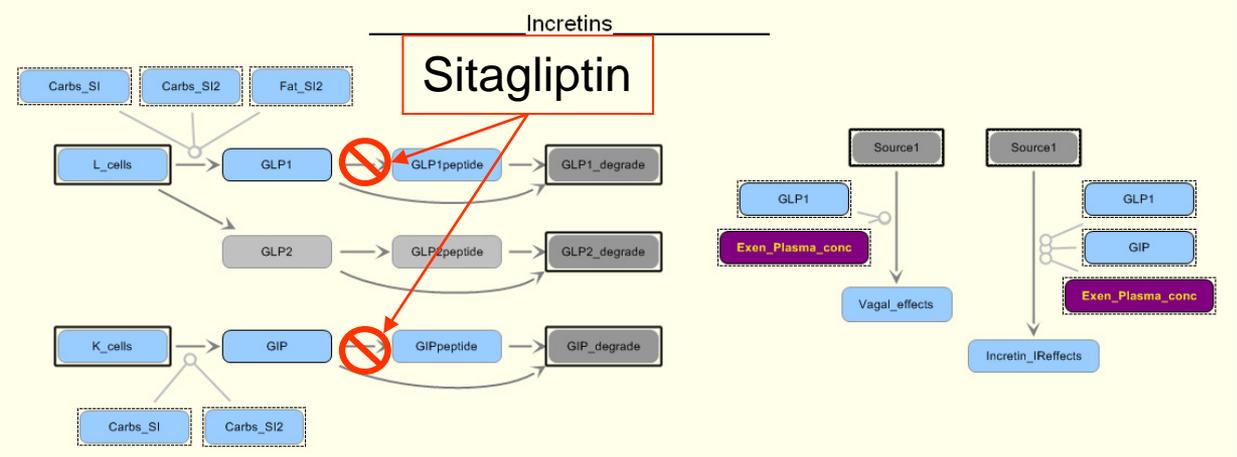
Changes in incretin amounts



Changes in incretin flux

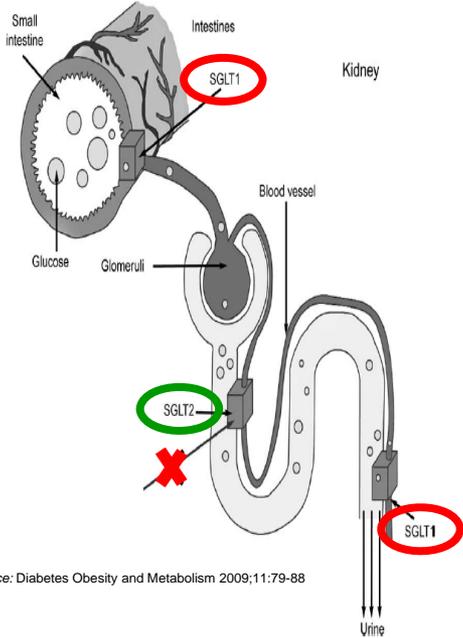


Including drug PK and drug action allowed both component and whole body testing of the model. This built trust in model.



Herman et al. 2005

Additional targets and mechanism of action were added to the Pfizer Model as needed.



Source: Diabetes Obesity and Metabolism 2009;11:79-88

SGLT2 inhibitors promote Urinary Glucose Excretion Leading to:

- Plasma Glucose (PG) Lowering
- Weight Loss
- Favorable Blood Pressure Lowering

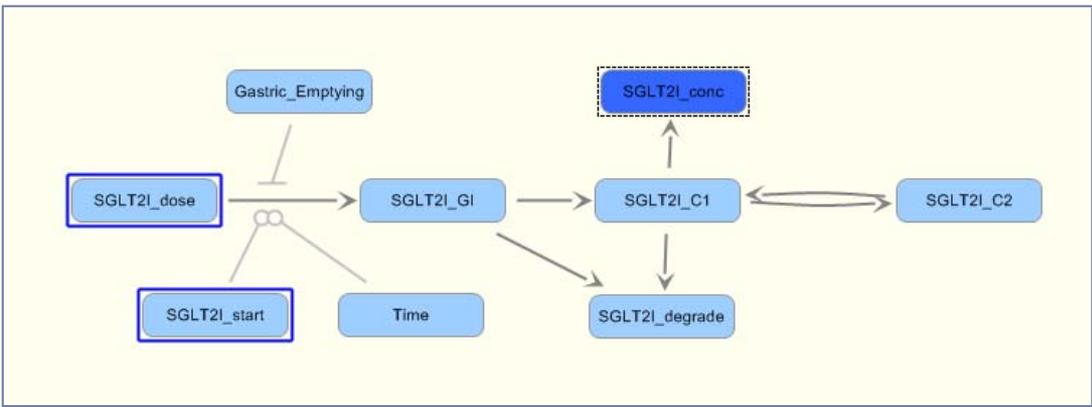
Urinary Glucose Excretion (UGE) provides a readily accessible mechanism based biomarker for clinical assessment

$$\frac{\partial C(x, t)}{\partial t} = \underbrace{-v \frac{\partial C(x, t)}{\partial x}}_{\text{advection/flow}} - \underbrace{\frac{V_{max} C(x, t)}{C(x, t) + K_m(1 + I/K_i)}}_{\text{reabsorption}} \tag{1}$$

SGLT2 inhibitor PK and MOA were rapidly incorporated into and tested in the Pfizer Diabetes model.

$$UGE = GFR \int_0^t K'_m \cdot LambertW \left(\frac{PG(t) \cdot e^{\frac{PG(t)}{K'_m} - \frac{V'_{max}}{K'_m}}}{K'_m} \right) dt$$

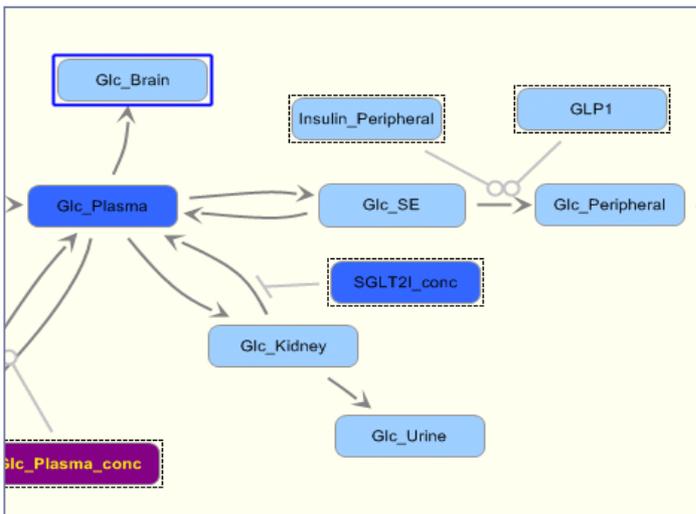
SGLT2 inhibitor PK model accounts for fed/fasted state.



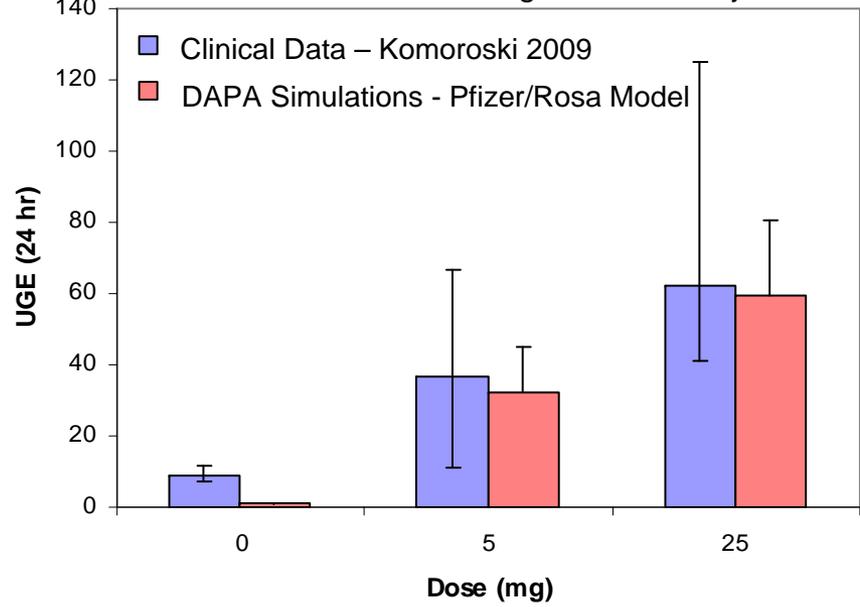
The Pfizer Diabetes Model was used to simulate chronic SGLT2i dosing in T2DM patients and healthy subjects.

The Model includes approximately 60 virtual patients, and more are currently being developed.

SGLT2 inhibitor PD action is based upon public data.



Simulations of chronic dosing in T2DM Subjects



The Pfizer Diabetes Model is a medium-scale, targeted physiological model which yielded significant program impact.

- ▶ Collaborative development over a period of a few months
- ▶ Model accepted, adopted, and used by expert modelers and the clinical team
- ▶ Physiology is focused on and impacted program-relevant decisions
- ▶ More easily-understood model scale, for better regulatory discussions
- ▶ Rapid additions to the model allow use with new drug classes and targets
- ▶ Model represents selected targets well, but does not contain all targets

The same SGLT2I mechanism was modeled using a very large mechanistic model (Entelos).

- ▶ **Integrate:**
 - ▶ Available data on Pfizer Internal Candidate
 - ▶ Physiological Understanding of the Mechanism of Action
 - ▶ Published Public Data on other SGLT2 compounds

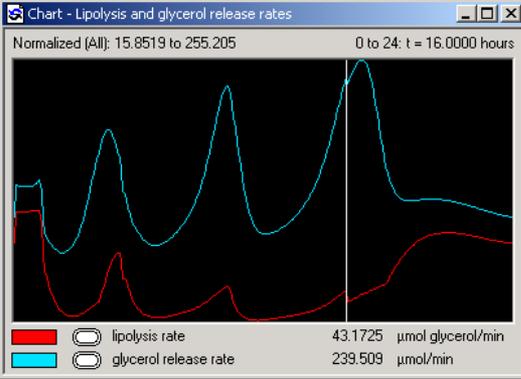
- ▶ **Within an Entelos Based Systems Model to improve :**
 - ▶ Clinical Trial Design
 - ▶ Doses
 - ▶ Dosing Regimens

Entelos Overview – SGLT2i

Systems Modeling used to predict human response and improve decision making throughout pipeline.



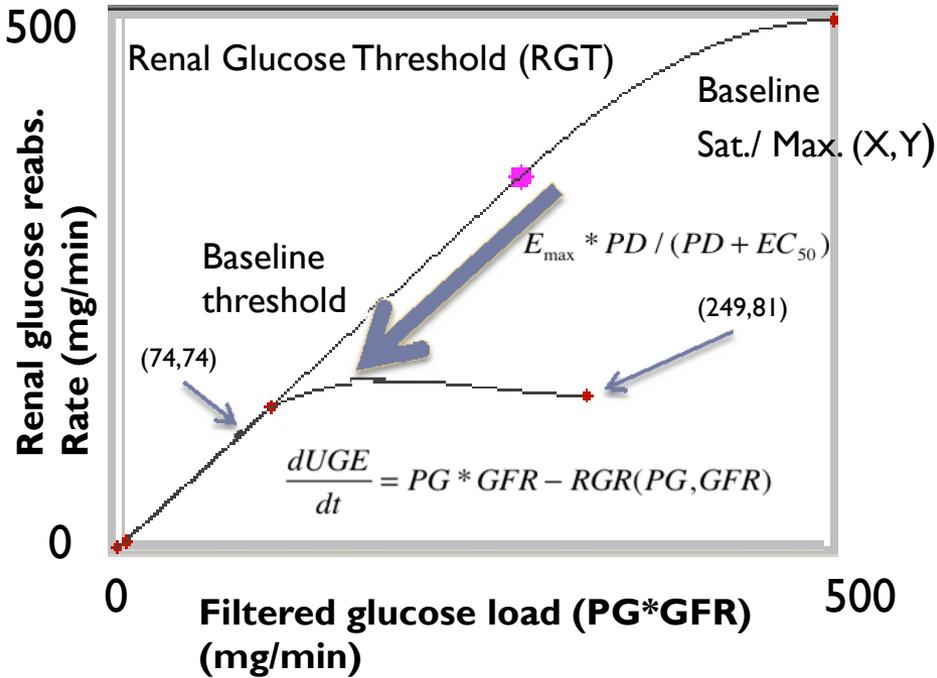
Comment:
The glucokinase regulator of hepatic glucose uptake has a high affinity for its substrate, but is only a moderate activator of insulin release (Pagliasotti 1998). In liver tissues, there is a high concentration of nutrient to metabolize and phosphoenolpyruvate carboxylase and phosphoenolpyruvate carboxykinase are active.



Qualitative relationship between plasma glucose and urinary glucose excretion

- Urinary glucose appearance is a function of:
 - GFR: Glomerular Filtration Rate
60 – 135 ml/min
 - RGT: glucose reabsorption threshold
Baseline Threshold 200 – 275
Baseline Saturation 375 – 450
Baseline Maximum 295 - 360
 - Plasma glucose
- In T2D virtual patients, the impact of variability in GFR and RGT on SGLT2 inhibitor efficacy was explored
 - An increase in RGT (i.e., increased SGLT2 expression) was generally required to eliminate UGE in untreated T2D virtual patients

Renal Glucose Reabsorption Rate

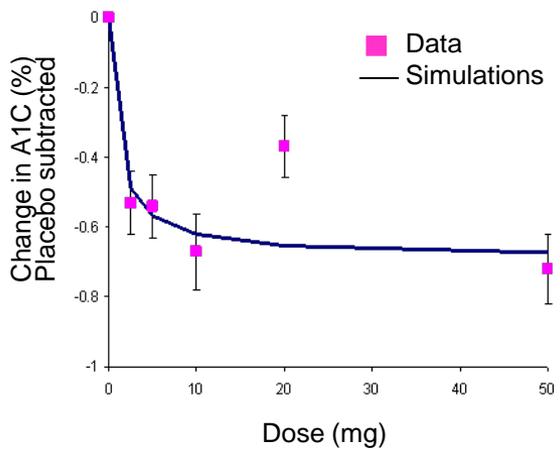


$$\frac{dUGE}{dt} = \begin{cases} PG(t) < RGT, & 0 \\ PG(t) > RGT, & GFR(PG - RGT) \end{cases}$$

Initial PD representation in model tuned to DAPA

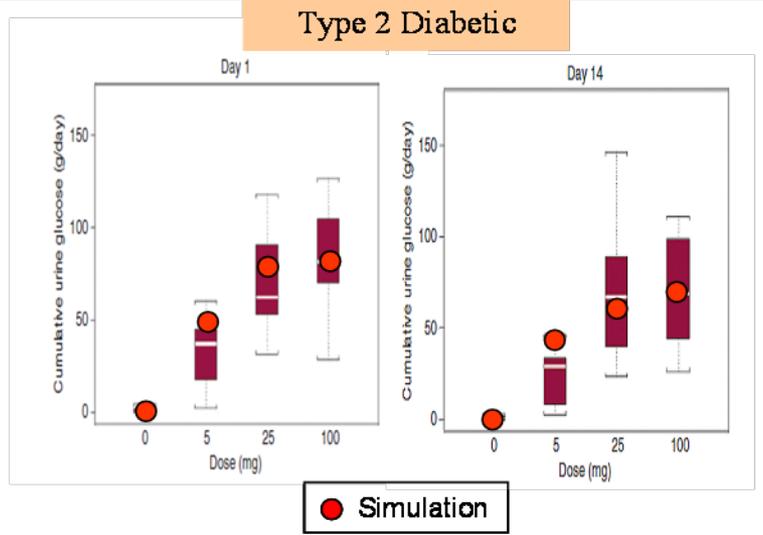
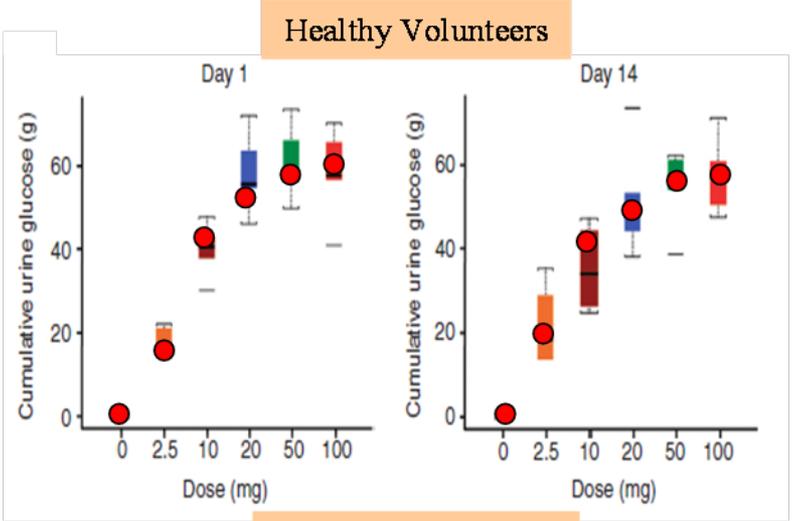
- Methods**
- Clinical data from Komoroski, 2009a,b (SAD/MAD in healthy subjects and T2D patients)
 - Clinical trial protocols, including meal timing and composition, were implemented
 - For HNV, n=1 virtual patient
 - For T2D, n=98 virtual patients prevalence weighted for GFR

This representation was validated using publicly disclosed information on the PK and UGE profile for a competitor SGLT2 inhibitor in both HV and T2D patients in studies spanning from single dose to multiple dose trials and with different meal protocols ^{5,6,7}



- Summary**
- Acute and chronic UGE predictions were generally consistent with observed data in HNV (upper figures) and T2D patients (lower figures)

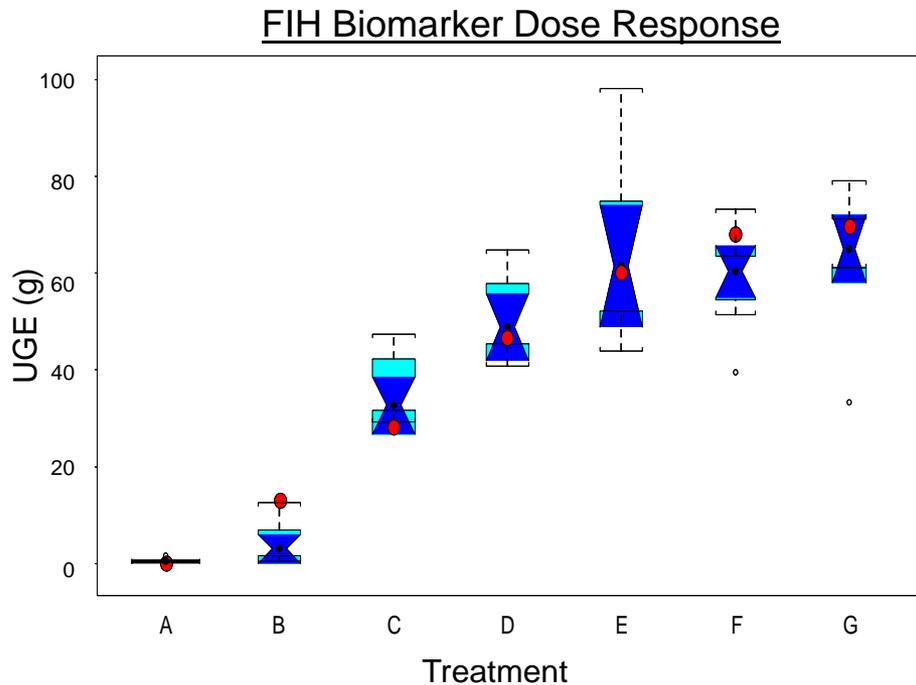
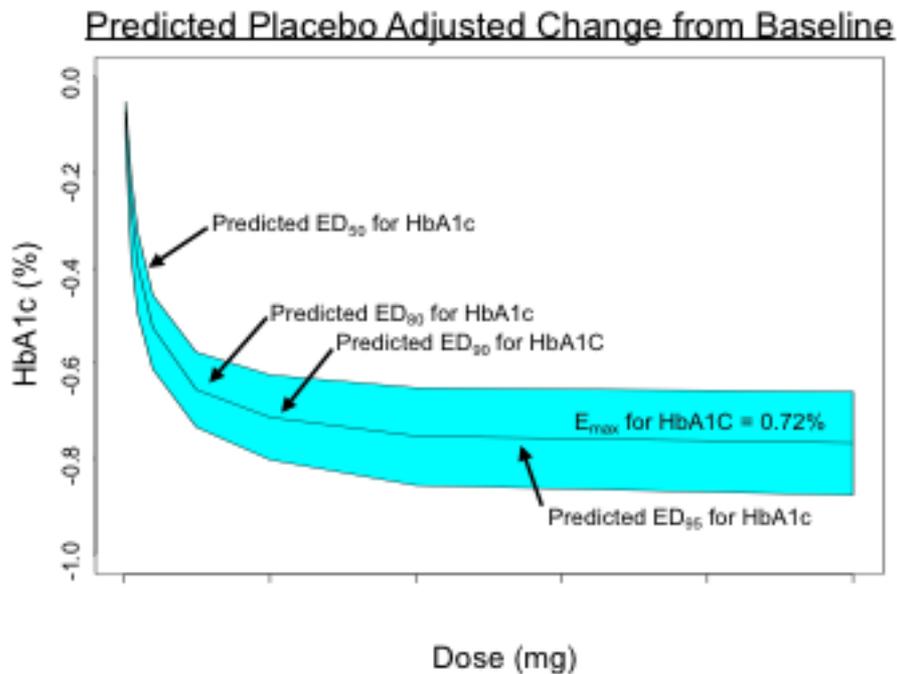
Published Clinical Data and Simulation Results



Internal Pfizer Candidate

- ▶ **Model Design (Based on FIH data):**
 - ▶ Study Design: Dosing Protocol, Meals, HV Characteristics incorporated into Physiolab Platform.
 - ▶ PK: As soon as internal candidate PK became available, popPK parameters included in platform representation.
 - ▶ PD: Drug potency (EC50), and maximal effect (Emax) tuned in “real time” to match observed exposure-response characteristics (24 hr UGE, time course UGE).
- ▶ **Model Prediction:**
 - ▶ FIH parameterized Model
 - ▶ HV Derived Model used to simulate T2D 12 week studies

FIH UGE Response



Summary - Modeling Approaches

SGLT2 / Systems Pharmacology Modeling (Entelos)

- Design Lean / Informative Phase I Program
- Update “real time” PK and PK/PD during the course of the FIH Trial
 - Analysis Provided Dose Rationale and Design for Dose Ranging Studies
 - Combine Phase IIa and IIb
 - Generate / test in silico quantitative hypotheses for differentiation from Competitor SGLT2i

Medium Scale Systems Pharmacology Modeling (Undisclosed Targets; Rosa)

- Agile collaborative development Approach
- Model accepted, adopted and used by Expert Modelers and clinical team
- Physiology focused on and impacted program relevant decisions
- Model scale allows ease of use for regulatory decision making
- Straight forward approach for adding new drug classes and targets
- Model represents selected targets well, but does not contain all targets

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- Ron Beaver
- Paul Brazhnik

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