
*Creating and Using a Physiological Model to
Evaluate GPR119 Agonism as a Diabetes
Therapy*

*David Tess, Pfizer PDM
and Rebecca Baillie, Rosa & Co., LLC*

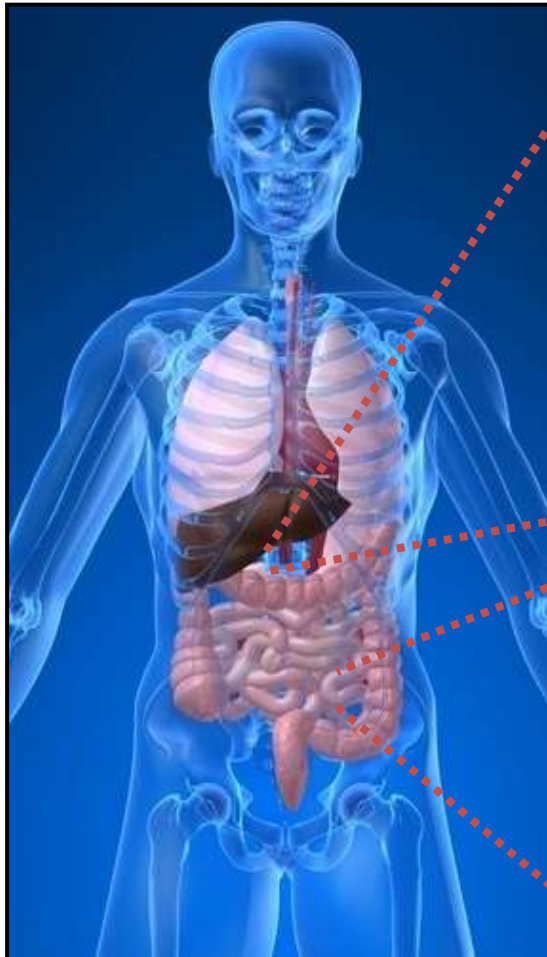
Diabetes

- Complex disease with multiple interacting systems
- Co-administered drugs
- Difficult to get drug approval
 - Other drugs on market
 - Cardiovascular impact
 - Efficacy can cause adverse events



GPR119: Class A GPCR

Two Sites of Action For Better Glycemic Control



Pancreas (islets):

- Increases intracellular cAMP
- Augments glucose-stimulated insulin secretion (direct effect)

Intestines (enteroendocrine cells):

- Increases secretion of gut peptides
 - GLP-1
 - GIP
 - PYY } incretins indirect effect

Why a Mechanistic, Physiological Model?

- Clarify mechanism of action
- Identify drivers of clinical response
- Evaluate drug class before clinical studies
- Address complexity in a quantitative manner
- Analyze mechanistic patient variability
- Comparative efficacy of competitor's drugs
- Optimize compound characteristics
- Identify limitations of animal models
- Set first-in-human dose

Physiological Model Goals

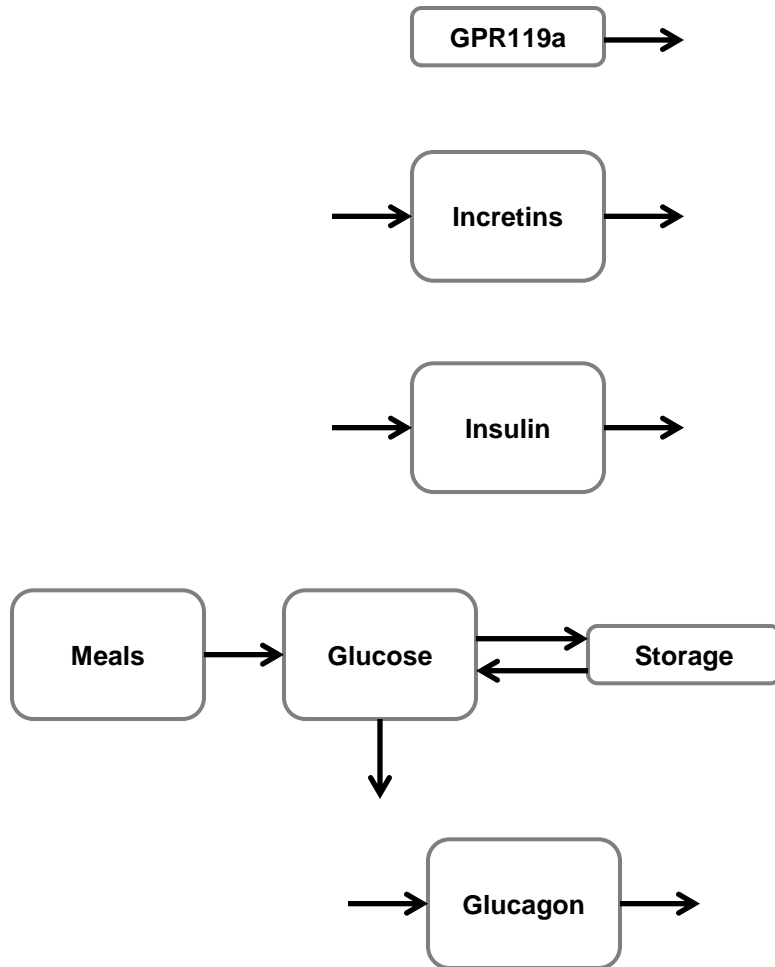
- Evaluate potential of GPR119 agonism as a diabetes therapy
 - Can GPR119 agonism provide comparable glucose control to current therapies (*e.g.* sitagliptin or exenatide)?
- Understand the relative contributions of direct and indirect action of GPR119a on glucose control
- Develop an internal knowledgebase of systems pharmacology model
- Serve as a platform for future target evaluations

Physiological Model Constraints

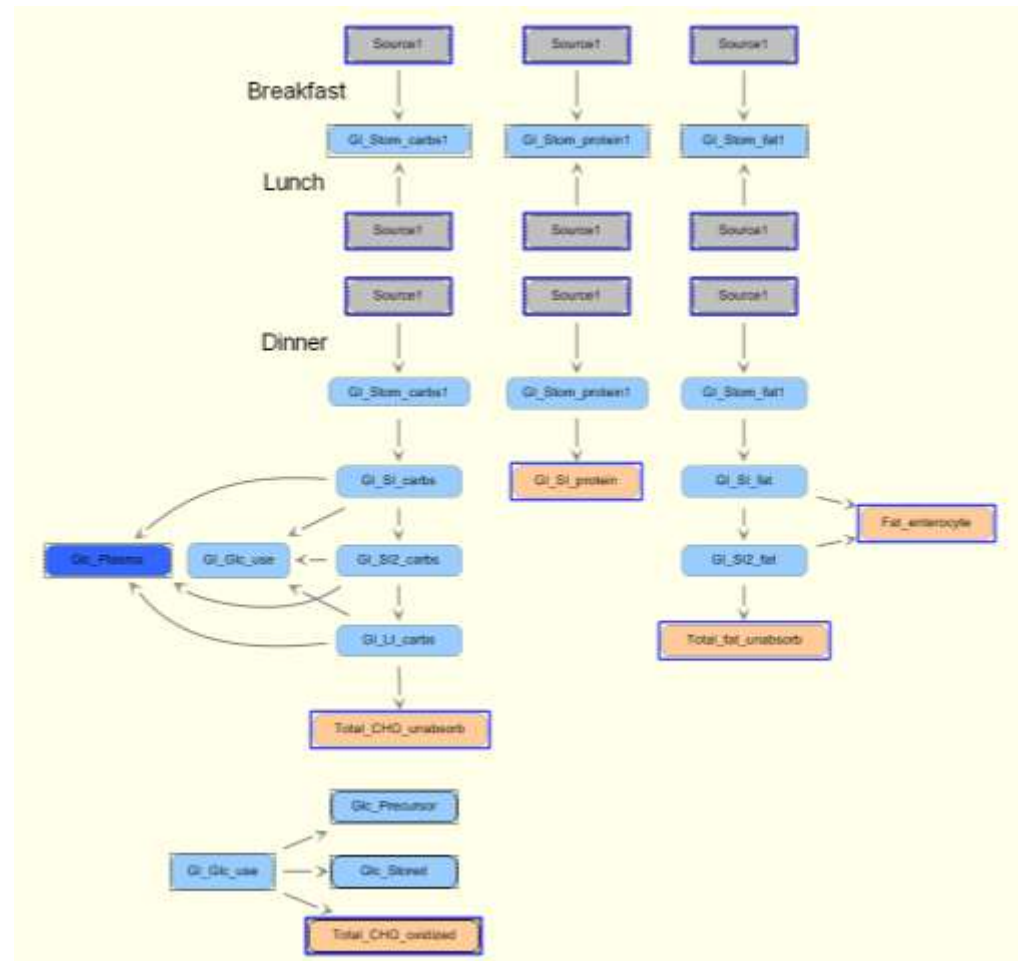
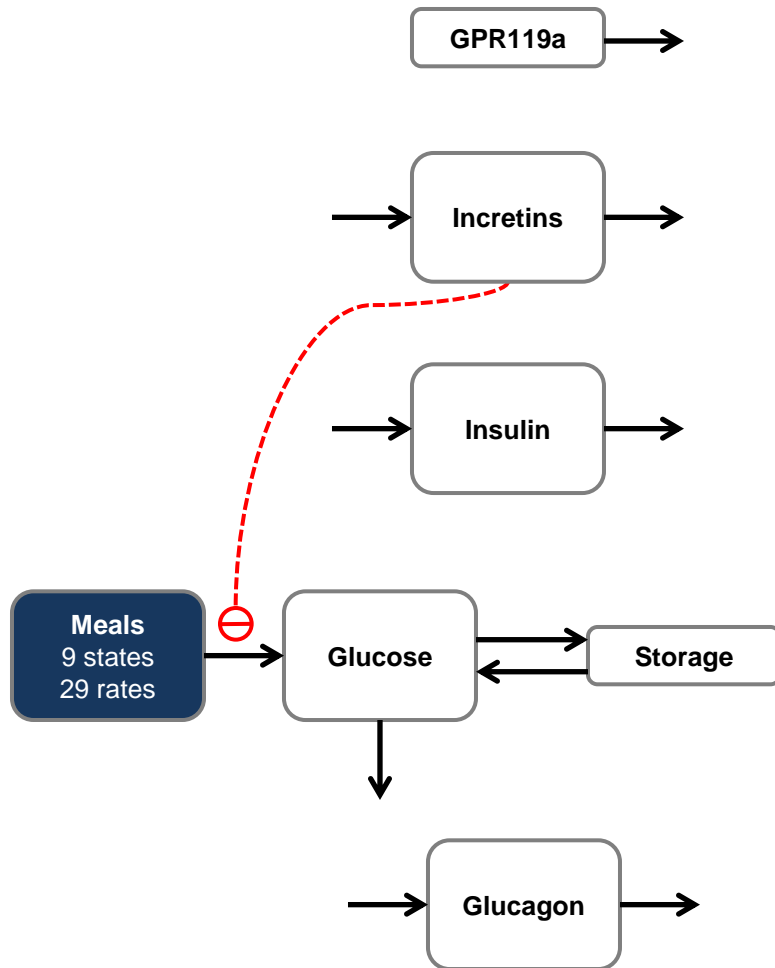
- A mass balance model of glucose metabolism
 - Sedentary lifestyle
 - Energy homeostasis (± 100 kcal/day)
 - No starvation; overnight fasting only
 - Proteins and fat utilization assumed

- Subchronic model (≤ 12 weeks)
 - No long-term disease progression or reversal by therapies

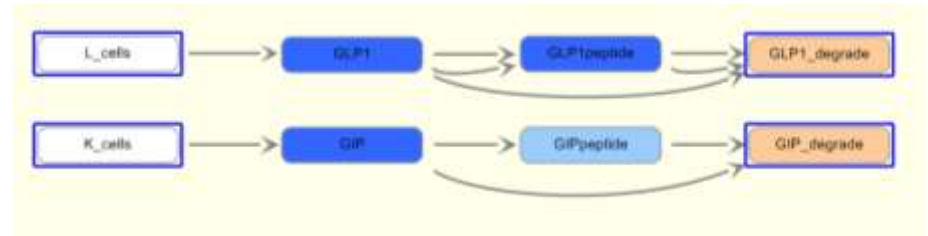
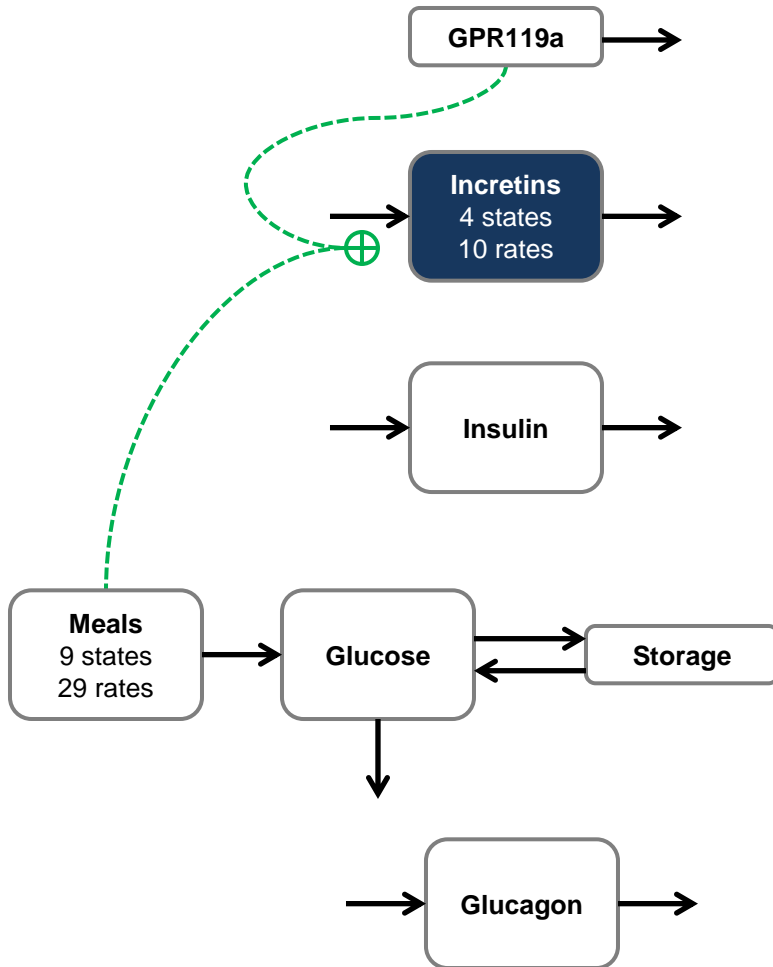
Model Modules



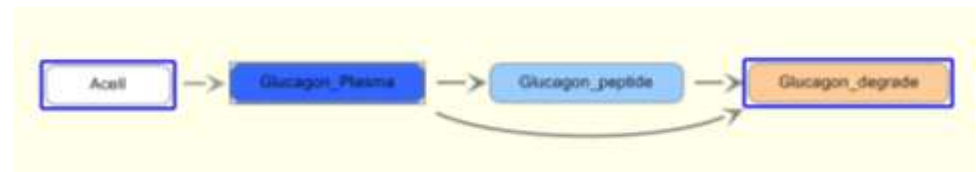
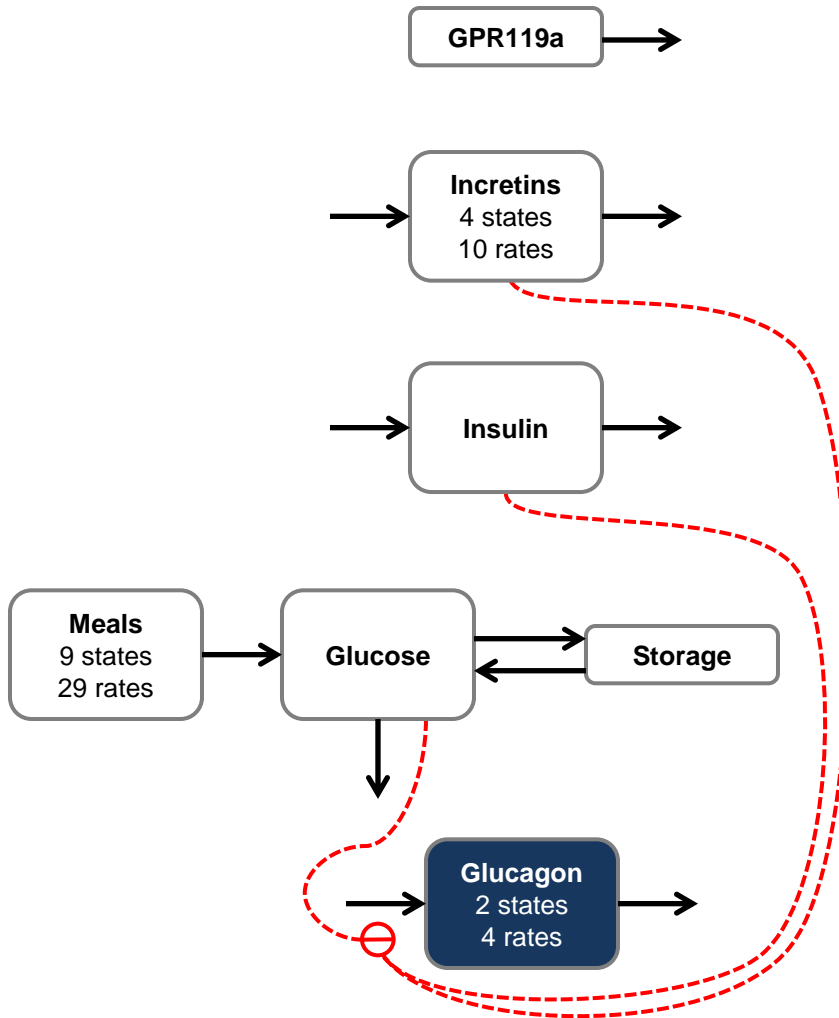
Glucose Absorption



Incretins



Glucagon



Model Calibration

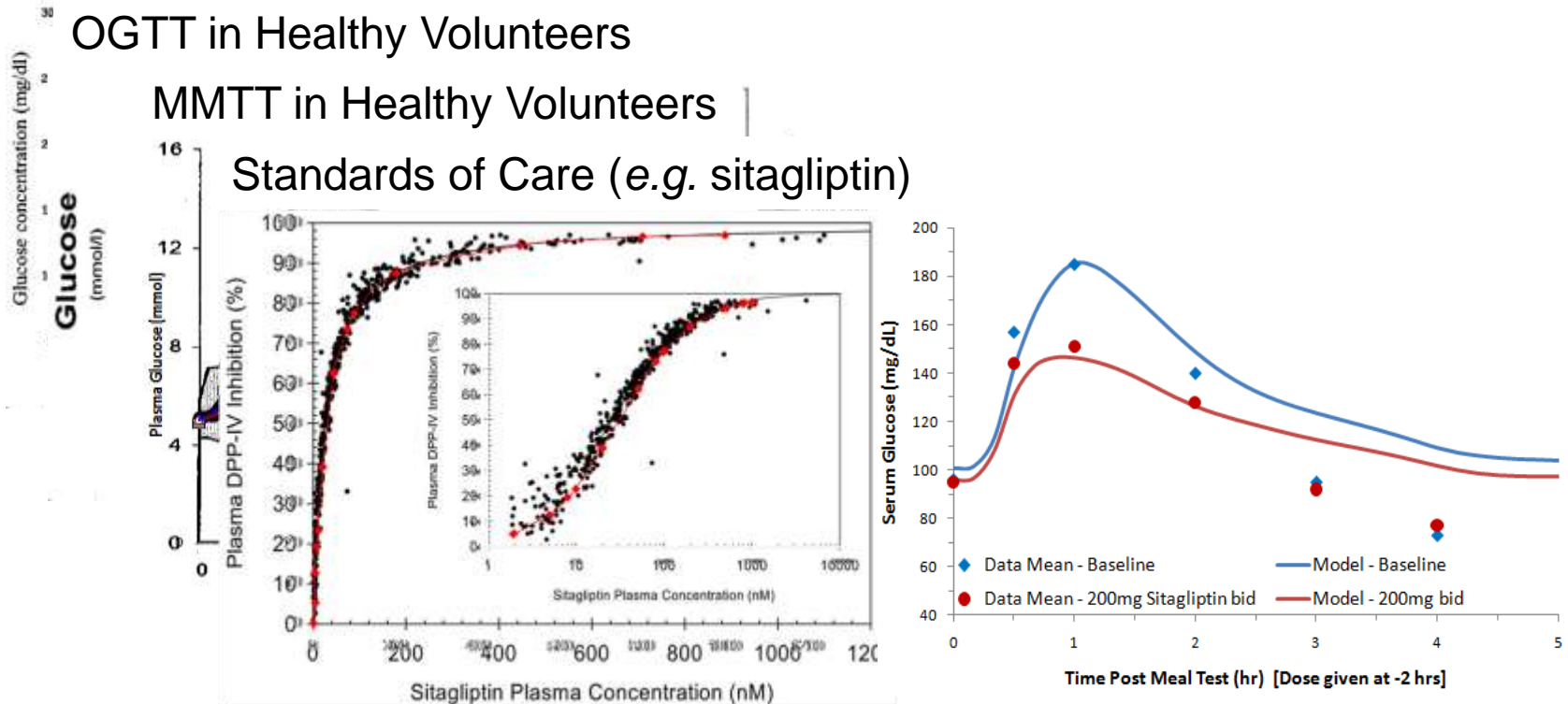
- The model was calibrated with hundreds of literature citations
- Approximately 10% withheld for final validation

IVGTT in Healthy Volunteers

OGTT in Healthy Volunteers

MMTT in Healthy Volunteers

Standards of Care (e.g. sitagliptin)



GPR119a Parameterization

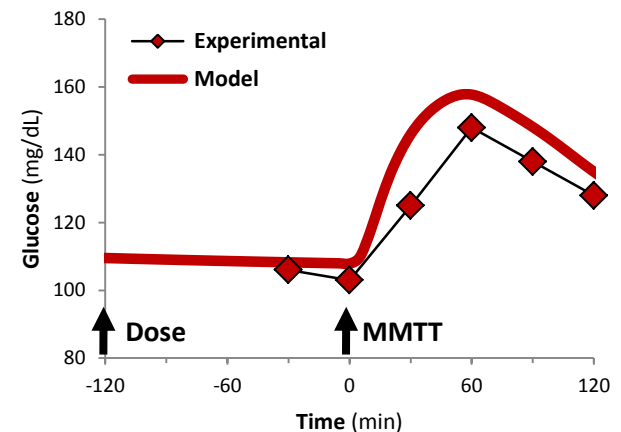
- Data reported for GPR119 agonism are sparse
- Metabolex described clinical results at ADA conferences^{1,2}
MBX-2982 results are the only available GPR119a clinical data
 - Single and multi-dose PK
 - Mixed meal tolerance (MMTT)
 - Glucose lowering
 - Total GLP-1
- These data were used in our model to evaluate GPR119a

¹ Roberts, B., et al. (2009). "American Diabetes Association 69th Annual Scientific Sessions," New Orleans, LA, USA, 5–9 June, Abstract 164-OR.

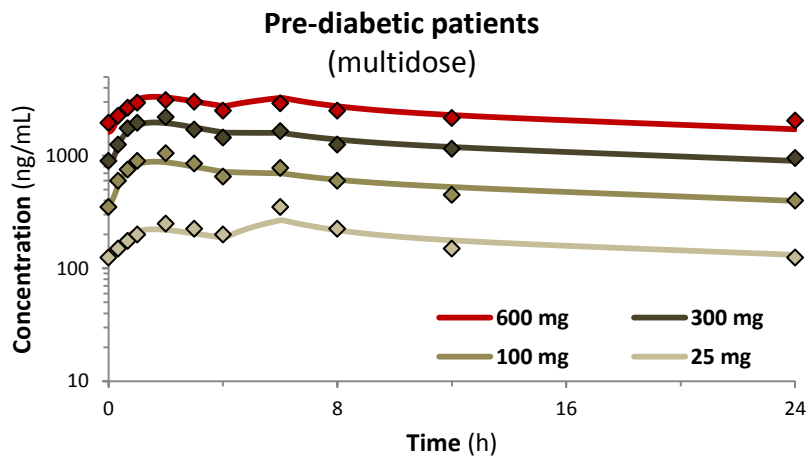
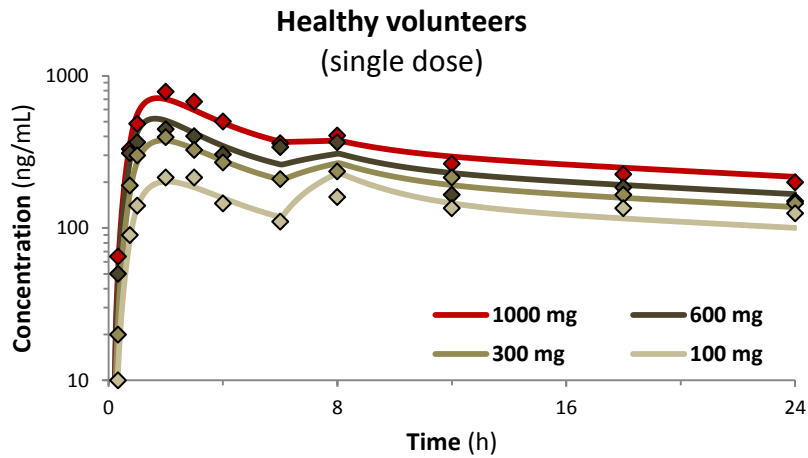
² Roberts, B., et al. (2010). "American Diabetes Association 70th Annual Scientific Sessions," Orlando, FL, USA, 25–29 June, Abstract 603-P.

MBX-2982 Data Limitations

- Unknown demographics of study volunteers and patients
 - Model virtual patients selected to approximate reported fasting plasma glucose
- Unknown composition of the MMTT
 - Assumed an 8 oz Ensure Plus® challenge
 - Glucose absorption parameters modified to better fit reported glucose excursion

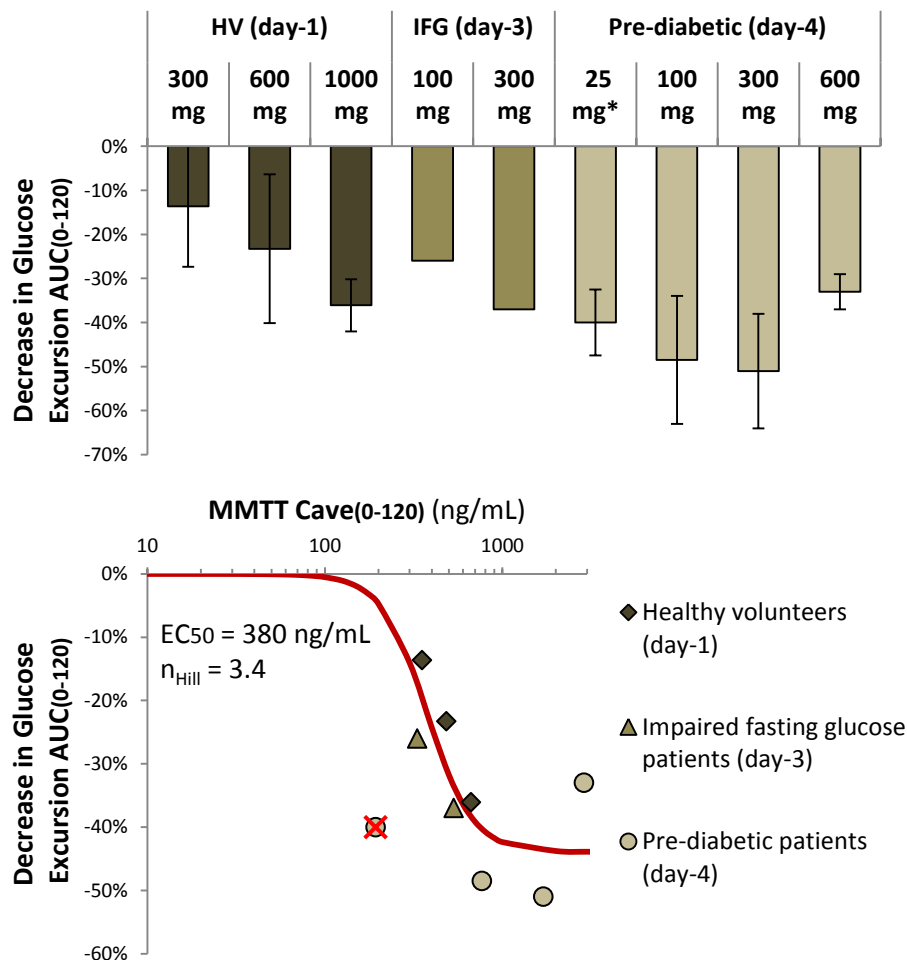


MBX-2982 Pharmacokinetics



- 2-compartment oral kinetics
- Dose independent clearance, volume, and intercompartmental rates
- Dose dependent absorption rate and extent

MBX-2982 Pharmacodynamics



➤ MBX-2982 mixed meal tolerance test (MMTT) glucose excursion lowering provided a concentration-effect relationship to establish an effective EC₅₀

- multiple studies of various populations and study lengths

➤ Both sites of GPR119 agonism (β and L cells) were assumed to have equivalent potencies (EC₅₀) and Hill coefficients (n_{Hill})

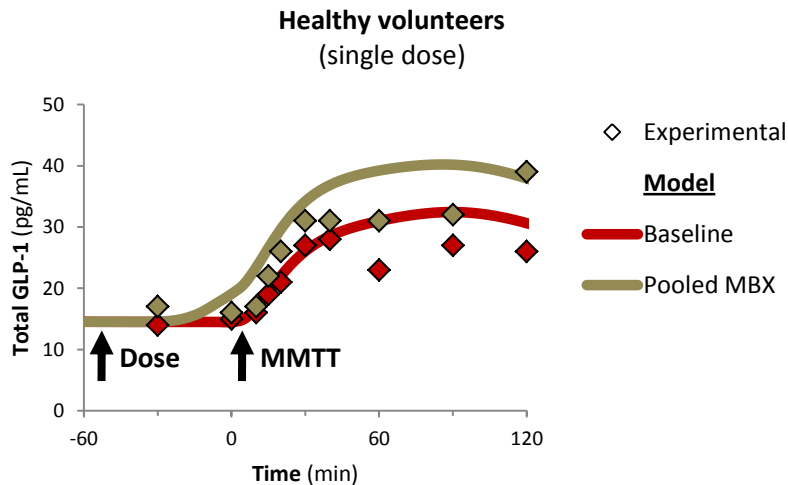
GPR119a Mediated GLP-1 Secretion



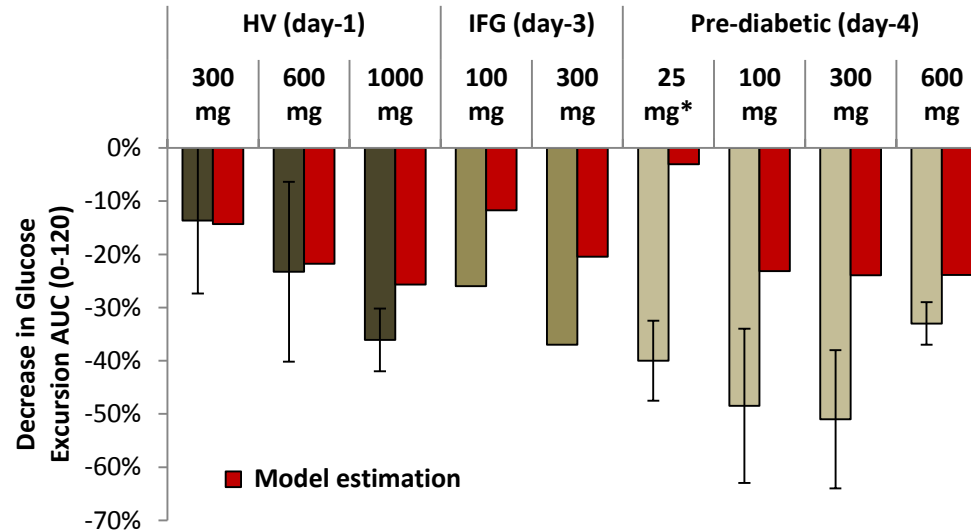
$$k_{in} = k_{basal} + k_{nutrients} \cdot [\text{nutrients}] + \frac{E_{max} \cdot [\text{GPR119a}]^n}{EC_{50}^n + [\text{GPR119a}]^n}$$

- In the model, GPR119a mediated GLP-1 secretion parameterized as additive to the basal- and nutrient-dependent secretion rates
 - [nutrients] represents the amount of carbohydrates and fat in the intestines

- GPR119 agonism is predicted to maximally stimulate basal incretin secretion by 1.8-fold based on the observed postprandial elevation in total GLP-1 during a MMTT following a single dose of MBX-2982 in healthy volunteers (pooled 300, 600, 1000 mg)



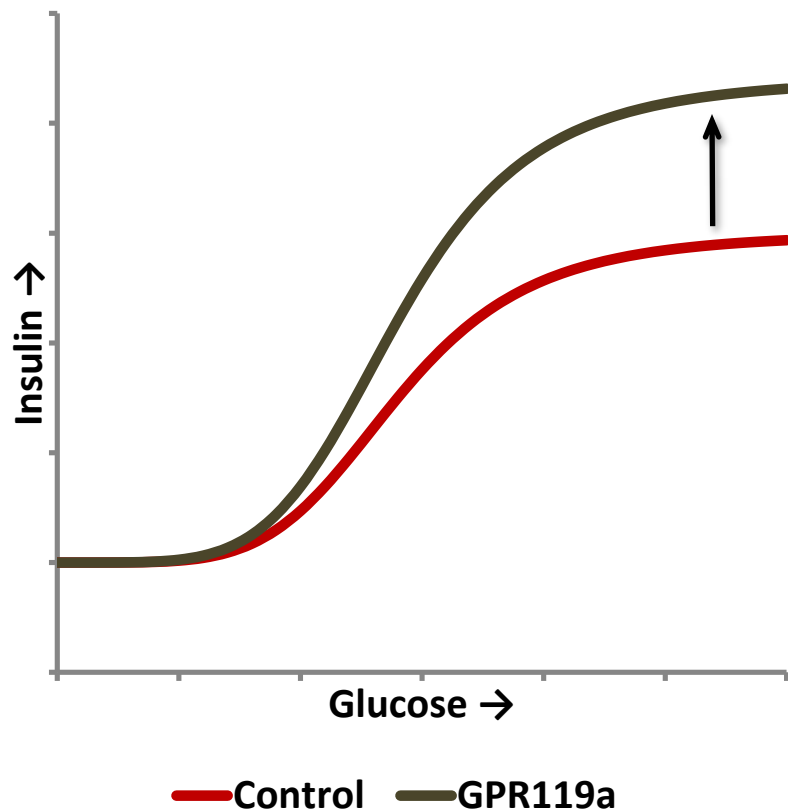
GPR119a Mediated GLP-1 Secretion



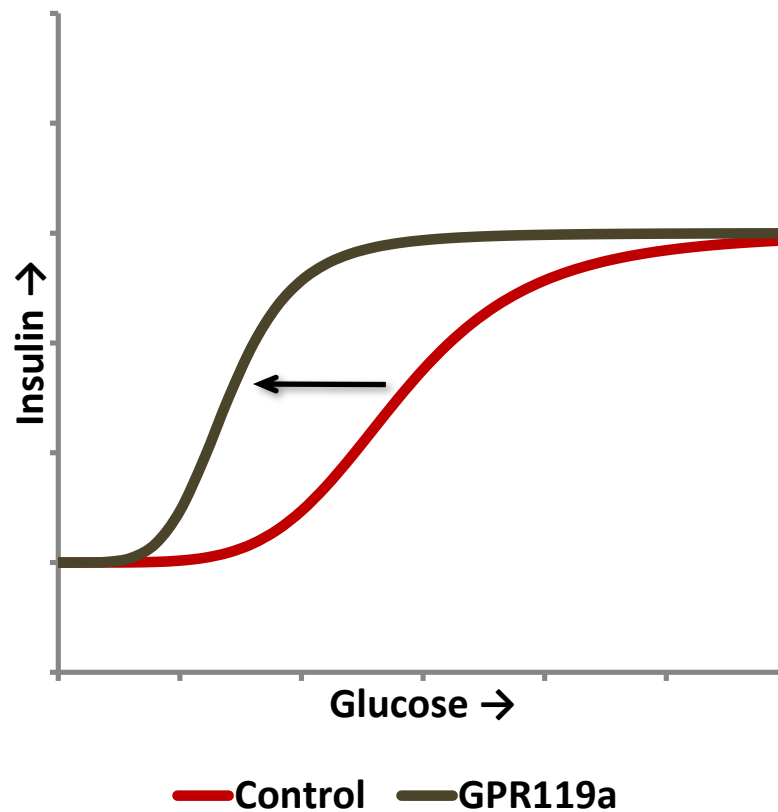
- While GPR119a mediated GLP-1 secretion contributes substantially to glucose lowering, it does not give explanation to all the glucose lowering
- The difference was parameterized through the direct influence of GPR119 agonism on GSIS

GSIS Potentiation & Shift

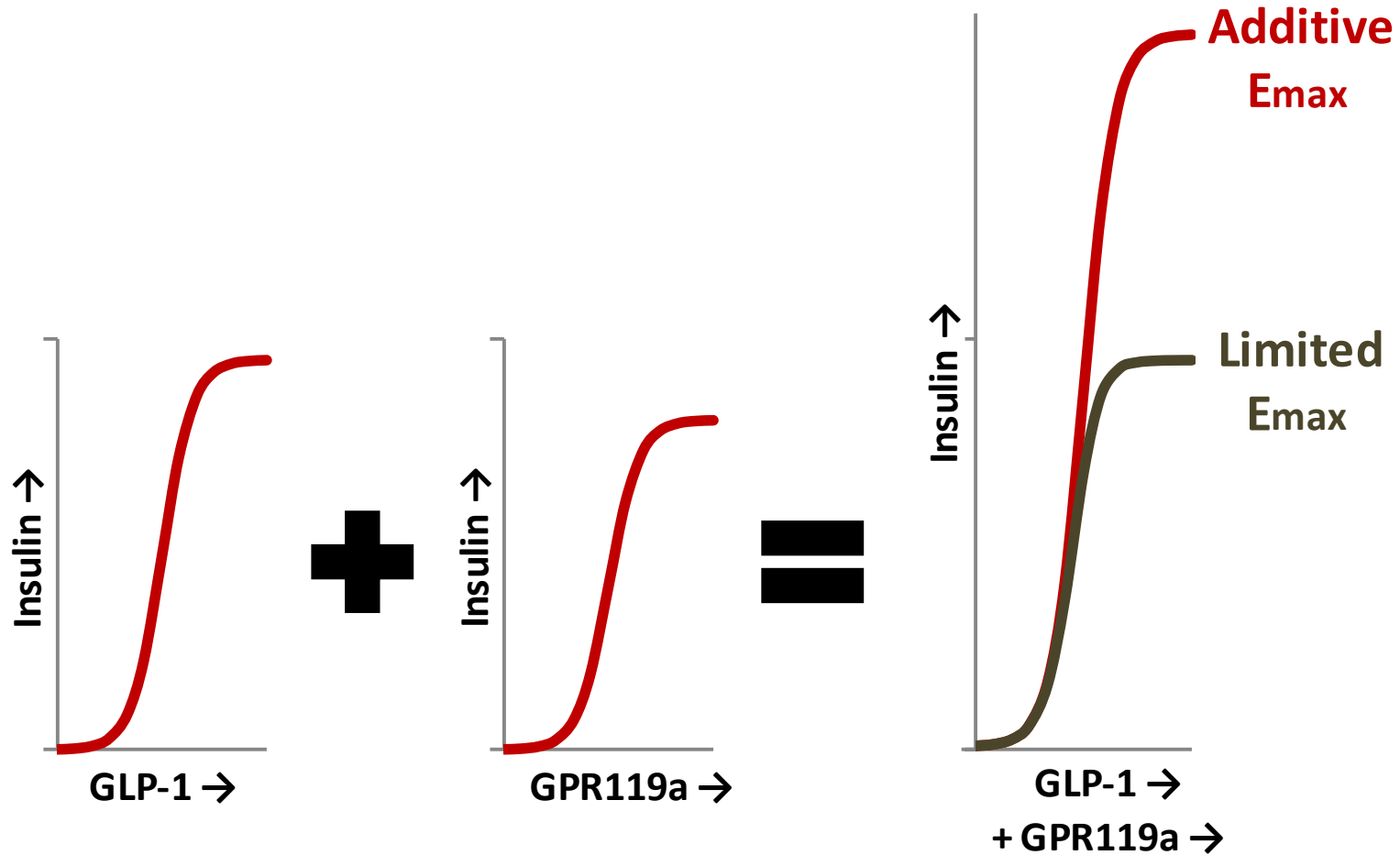
GSIS E_{max} Potentiation



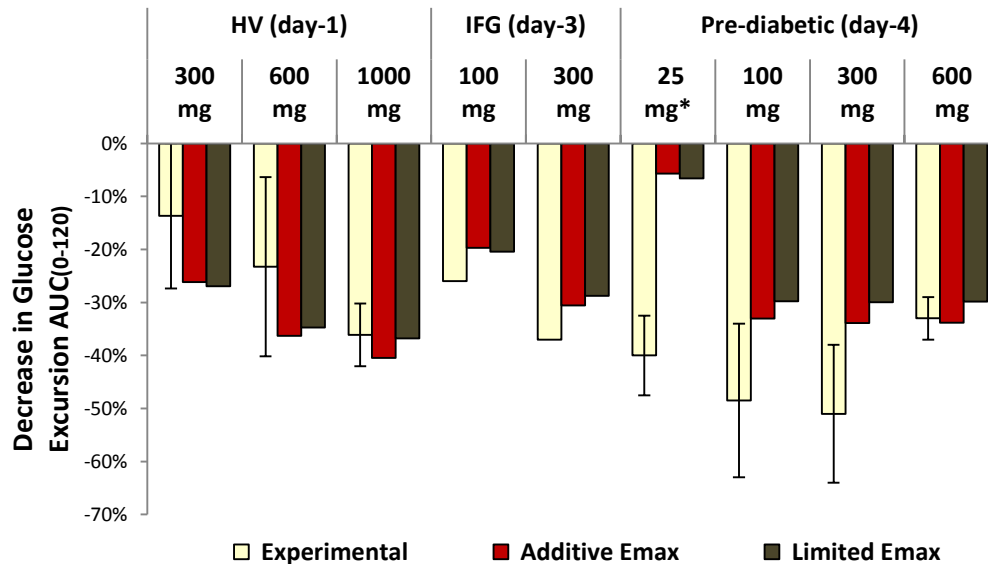
GSIS EC₅₀ Shift



GPR119a & GLP-1 Additivity

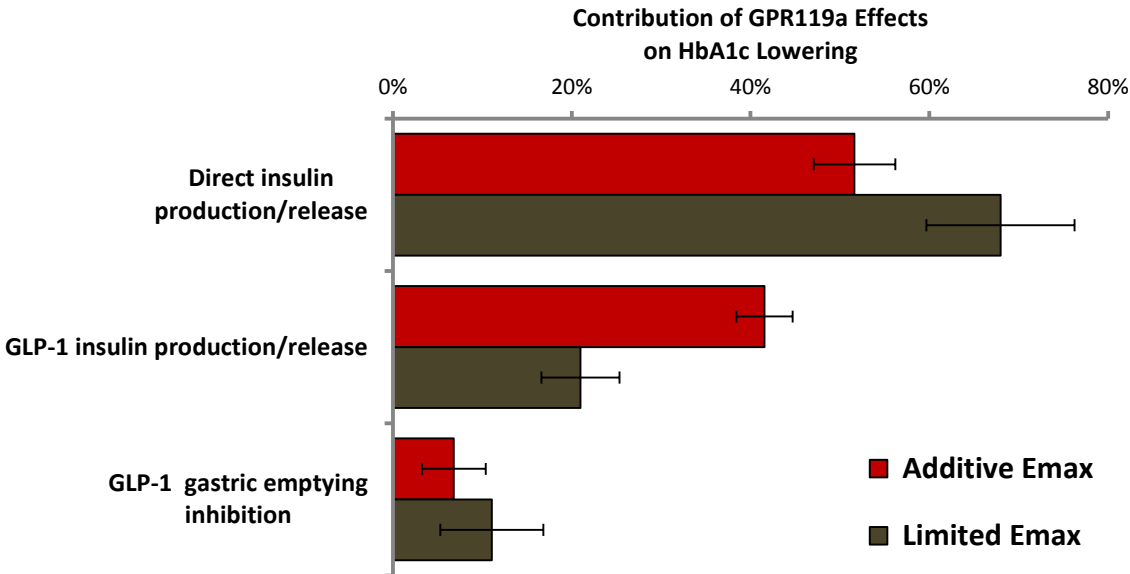


GPR119a Mediated GSIS



- Emax of potentiation and shift effects on GSIS were parameterized to best fit the MBX glucose lowering
- The additive and limited Emax hypotheses have different parameters

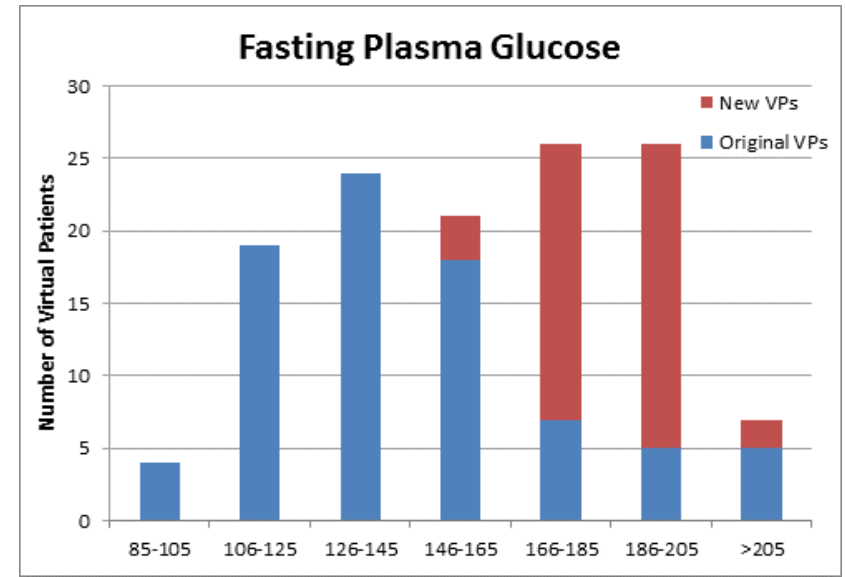
Contributions of GPR119a Effects on HbA1c Lowering



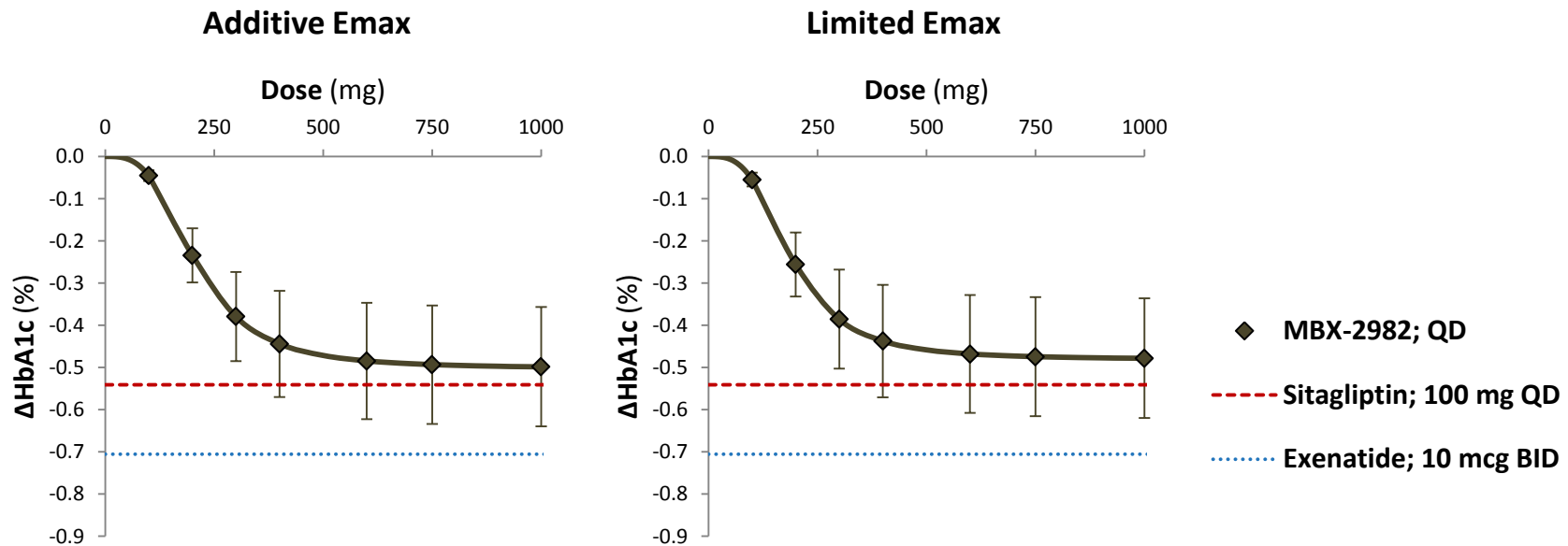
- Direct and indirect actions of GPR119 agonism equally contribute to glucose control

Virtual Patient Demographics

- 2003 NHANES database
- Age: 20-85 years
- Height: 142-187 cm
- Weight: 64-155 kg
- Body mass index: 20-60
- HbA1c: 5-11 %
- Fasting plasma glucose: 89-230 mg/dL
- Fasting plasma insulin: 17-448 pM

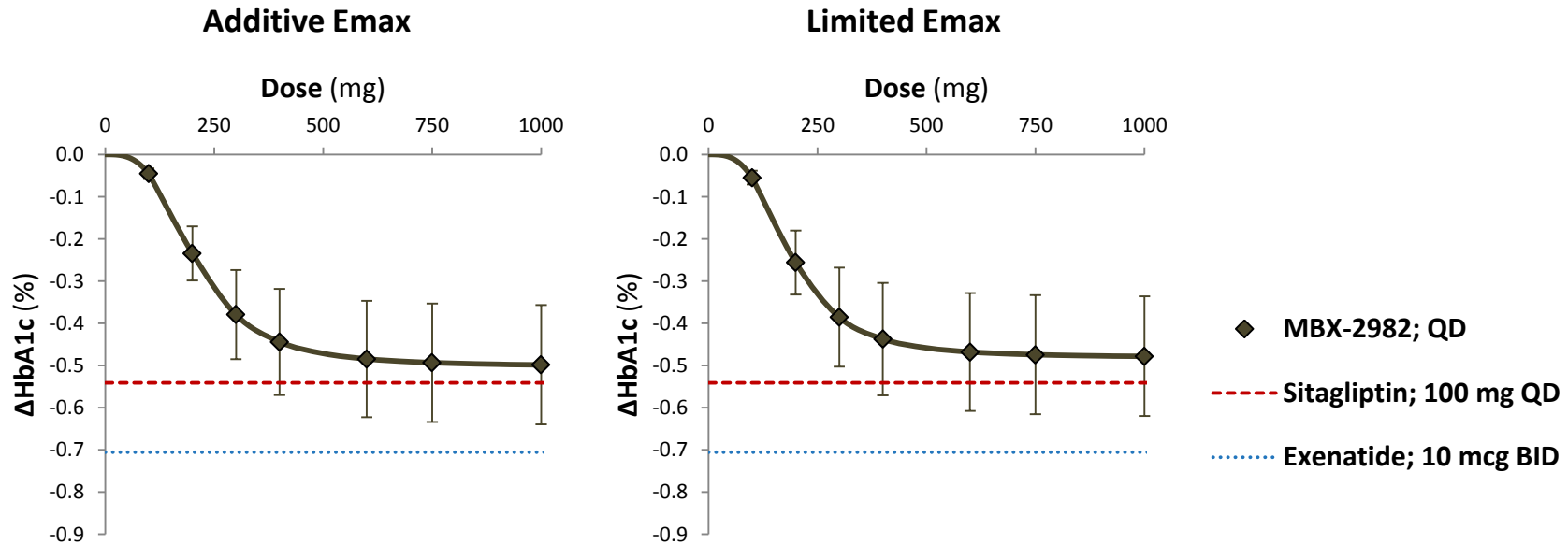


Target Population Outcome



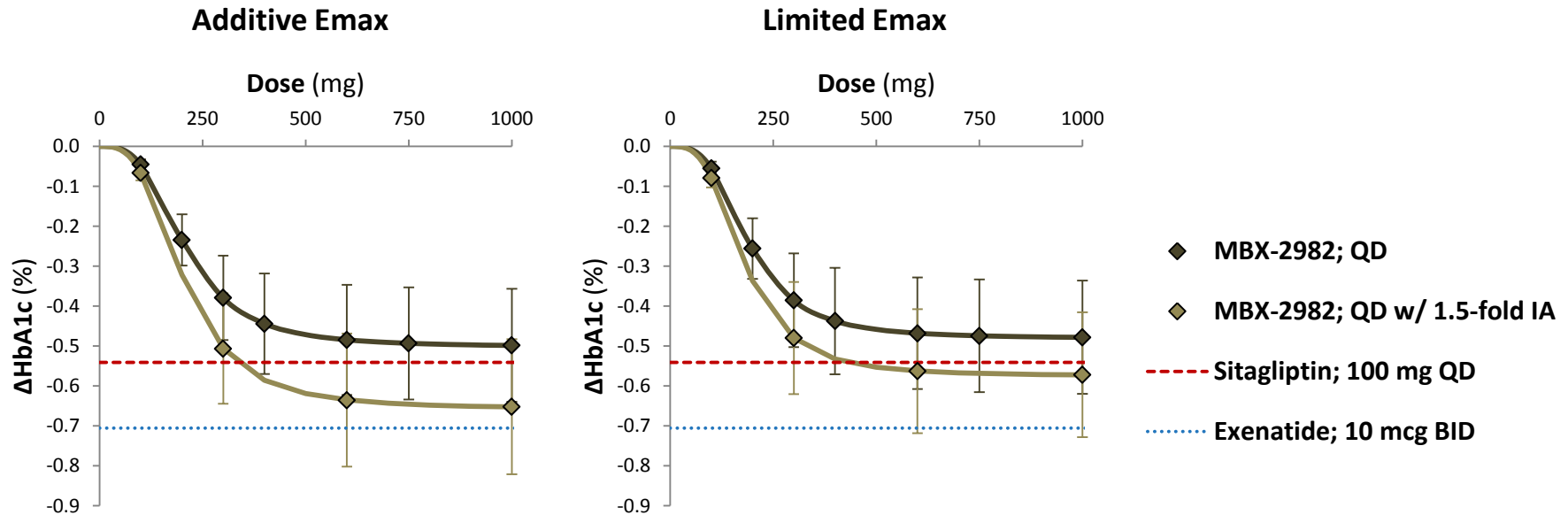
- MBX-2982 forecast to only achieve sitagliptin-like HbA1c lowering in type 2 diabetics

Target Population Outcome



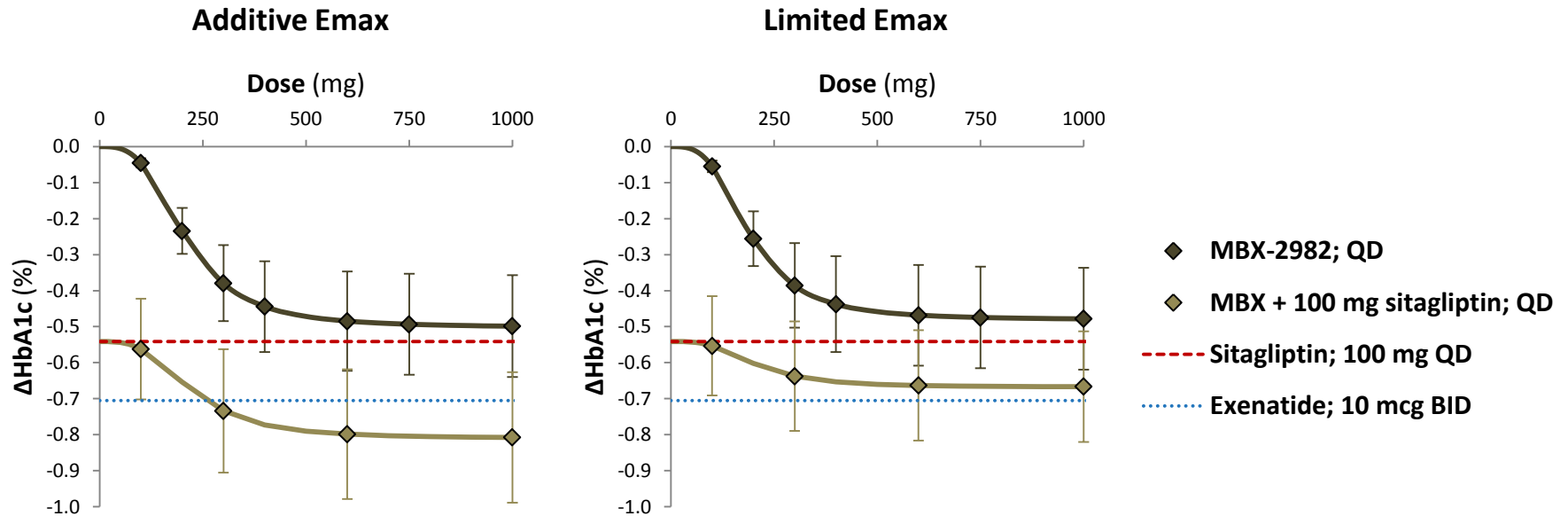
➤ What if higher intrinsic activity is achievable?

Target Population Outcome



- What if higher intrinsic activity is achievable?
- Exceed sitagliptin- and approach exenatide-like HbA1c lowering in Type 2 diabetics

Combination Therapies



- Allows exploration of combination therapies
- Model suggests that understanding the additivity of GPR119a and GLP-1 may be of critical importance to this mechanism's commercial viability

Conclusions

- Systems approach was used to create a predictive model of GPR119 agonism, without clinical data
- Even with sparse data, we could quantify the relationship between the GPR119 agonism E_{max} and likely human outcome
- Predicted results from chronic trials (HbA1c) using subchronic model results (average plasma glucose)
- Used modeling analysis to better assess potential for GPR119 agonism as a diabetes target

Observations

- Systems pharmacology models allow forecasting of late stage (phase II & III) outcome from early signs of efficacy (preclinical and phase I)
- Systems models have significant initial resource requirements, yet provide unique insights
- Their benefit-to-resource ratio improves with each additional utilization

Acknowledgments



➤ Pfizer

- Tristan Maurer
- Danny Chen

➤ Rosa & Co., LLC

- Jim Bosley
- Christina Friedrich
- Ron Beaver

➤ JDesigner

- Herbert Sauro
U of Washington
- Frank Bergman
Caltech