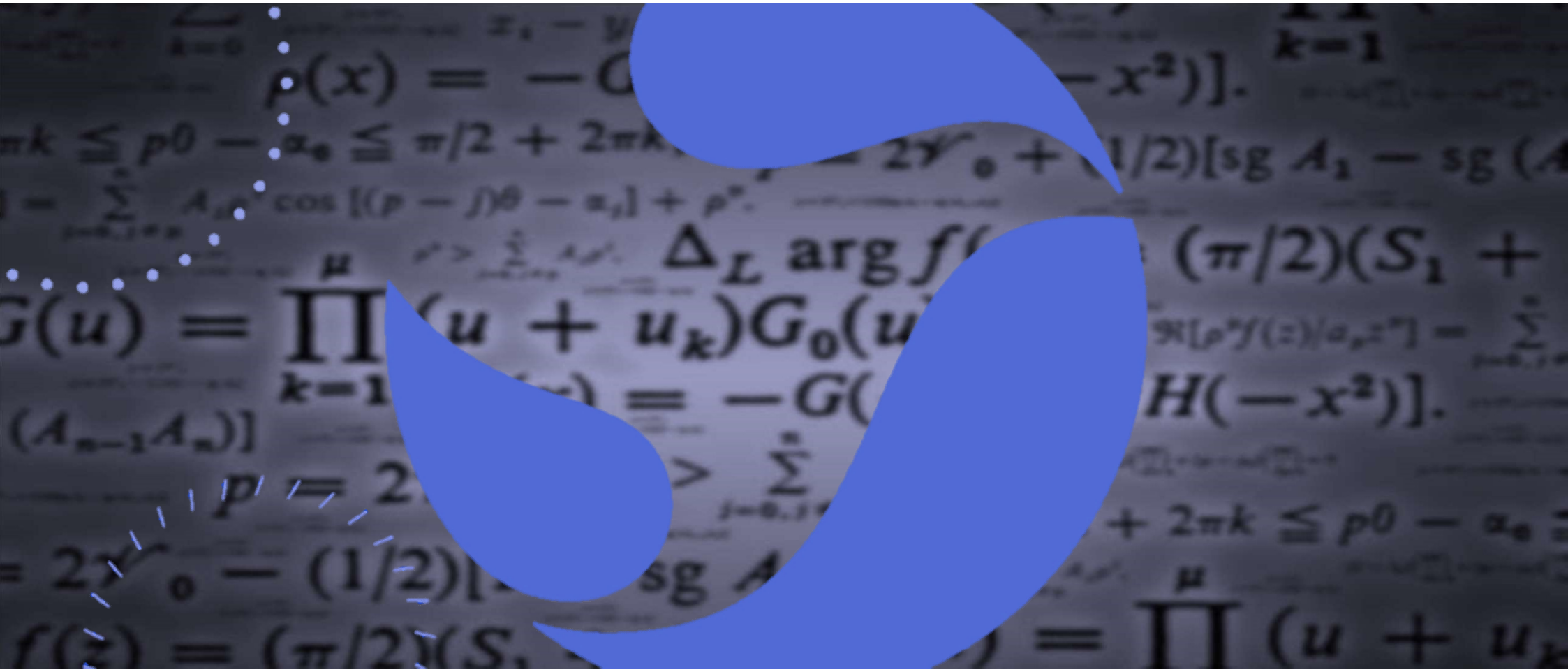

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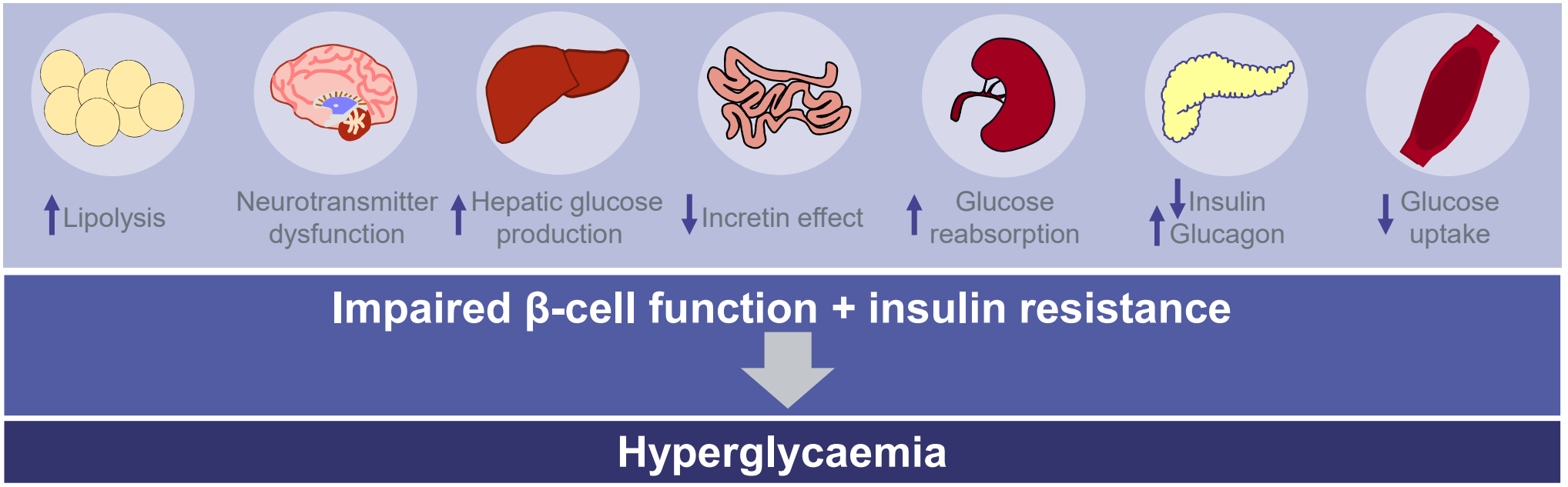
QSP Modeling Support in Development of Novel Diabetes Treatments

Dr. Britta Göbel - Head of Translational Disease Modeling (D-CV and I&I)

A Multitude of Factors Contribute to T2D

- T2D has a complex pathophysiology defined by impaired β-cell function and insulin resistance
- To address individual treatment goals, therapies that target multiple mechanisms are needed



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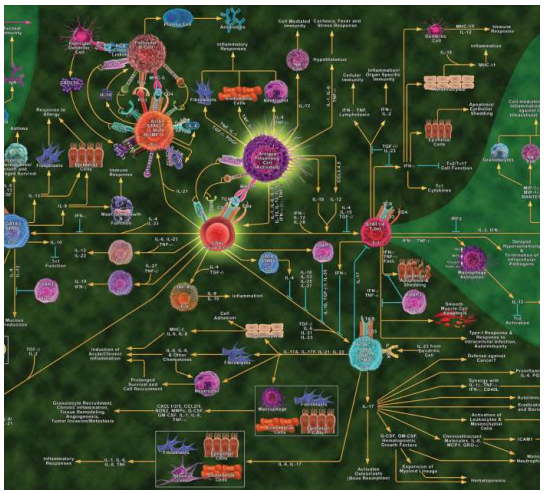
T2D, type 2 diabetes

DeFronzo RA. *Diabetes* 2009; 58: 773–95

Quantitative Systems Pharmacology Modeling

Physiology is complex…



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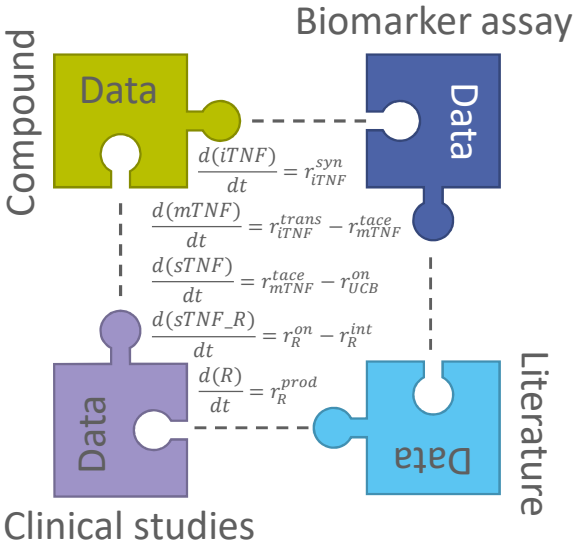
… while data sets are focused snapshots

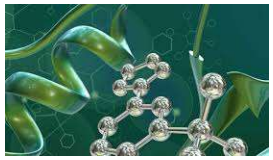


- Quantitative Systems Pharmacology (QSP) modeling is a framework that consistently integrates all available knowledge and data sources to conclude on (patho-)physiological mechanisms and to predict pharmacology in virtual patients

QSP Objectives

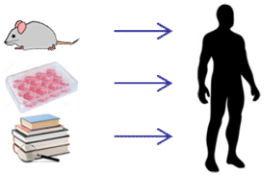
Target Credentialing

- Quantitative understanding of disease biology and mechanistic understanding of drug action



Molecule Design

- Optimal affinity needed for mono-specific or multi-specific modalities
- Compound selection



Translational Modeling

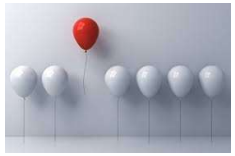
- Translating preclinical to clinical
- Translating healthy volunteer result to patients

Biomarker Identification

- Target engagement biomarkers
- Optimal study design
- Connection of biomarkers to endpoints

Clinical Trial Design

- Efficacy and safety prediction
- Insights responders vs non-responders
- Dose and dosing regimen selection
- Evaluation of drug combinations



Differentiation

- Efficacy / safety comparisons
- Mechanistic understanding of drug action to identify potential differentiating factors

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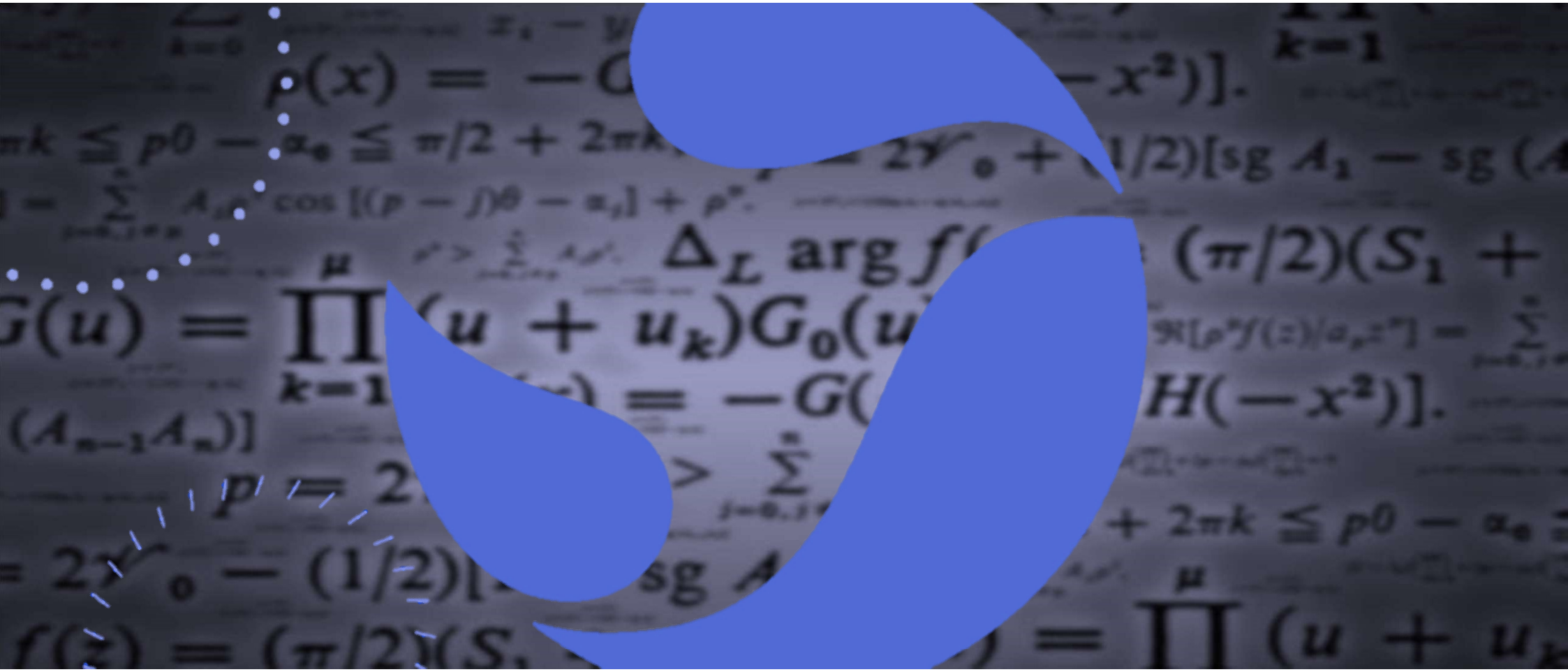

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in collaboration with ROSA

Investigating GPR119 Agonist Efficacy in a Diabetes QSP Model Platform

Introduction and Objectives

Background

GPR119 receptor agonists are a potential treatment for T2D that are reported to

- increase secretion of incretins (basal and food-induced release)
- increase glucose-stimulated insulin or glucagon secretion (depending on glucose level)

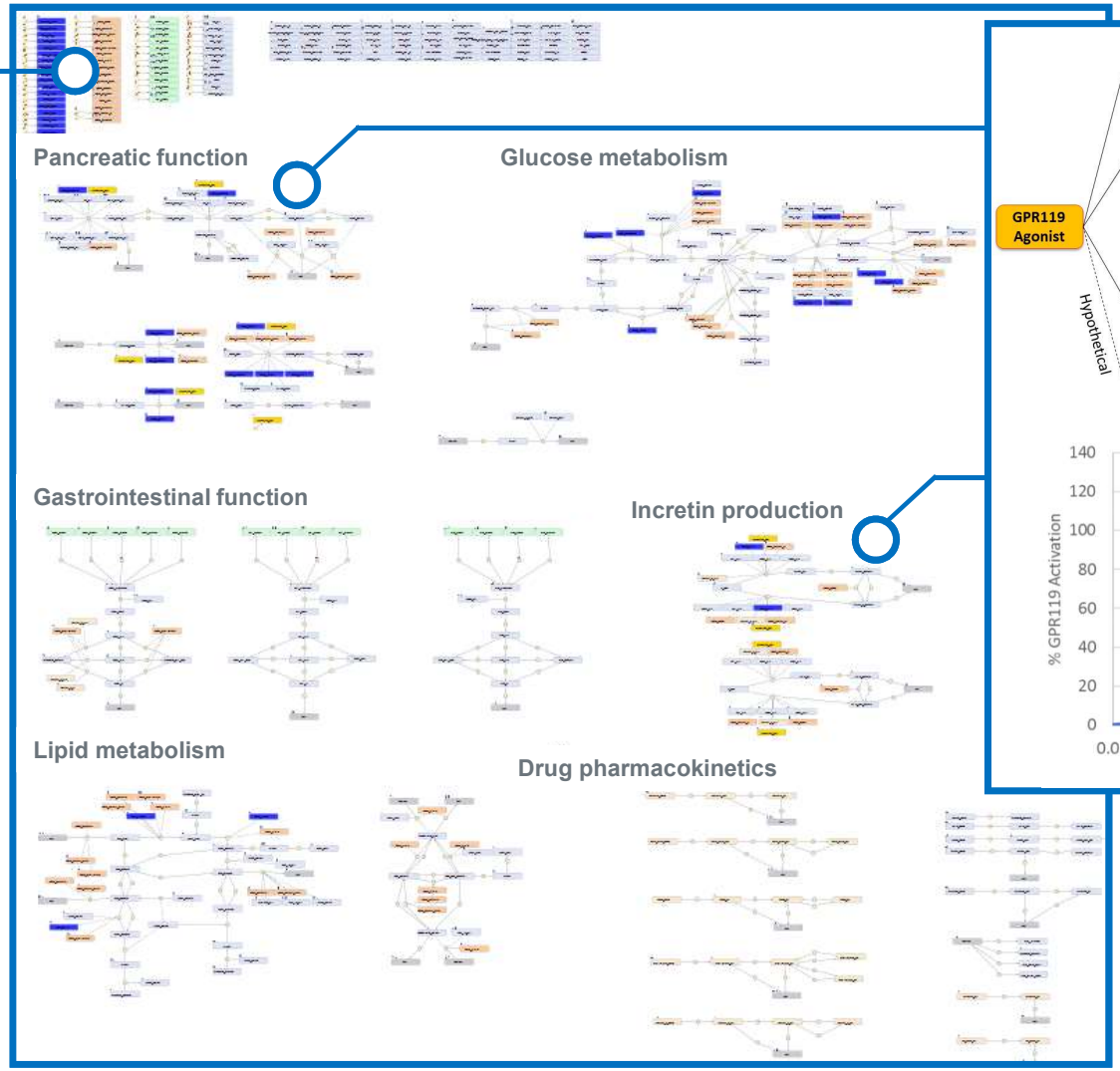
Objectives

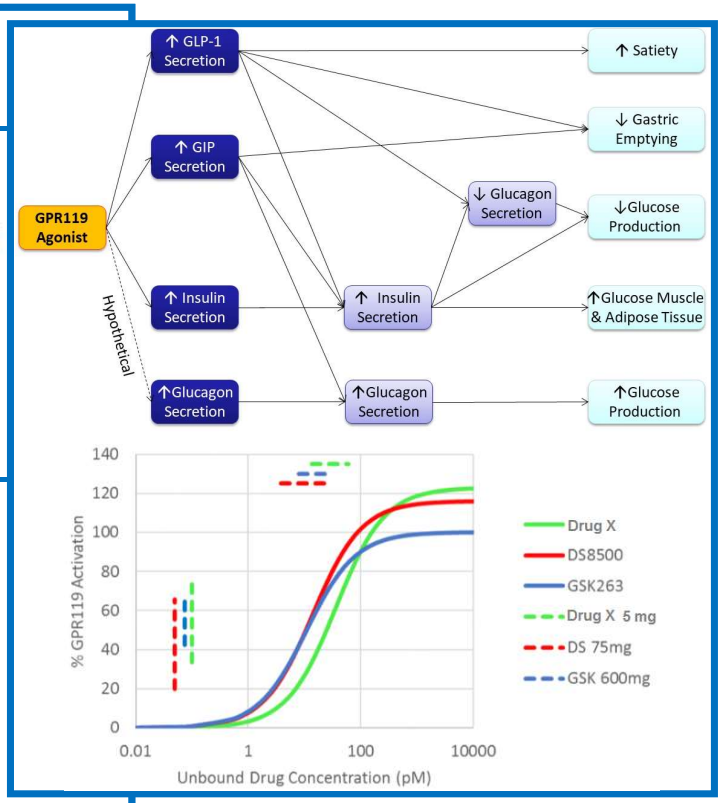
The objectives of this work were to

a) integrate GPR119 mechanisms into a QSP model of T2D
b) compare the efficacy of a new GPR119 receptor agonist with other compounds in the same class
c) increase the mechanistic understanding of the potential efficacy of oral GPR119 receptor agonists to evaluate if GPR119 is an effective target for treating T2D

Mechanistic Model of Incretin Release and Diabetes

Medications	Biomarker
PSN821	Insulin
GSK263	HbA1c
DS-8500	Glucose
Drug X	Glucagon
DPP-IV inh.	GLP-1
	GIP
	C-peptide
	LDL
	HDL
	FFA
	Cholesterin
	Adipose Mass
	TAG





- Medications serve as input, blood biomarker as output

- GPR119 agonism has direct and indirect effects on glucose control

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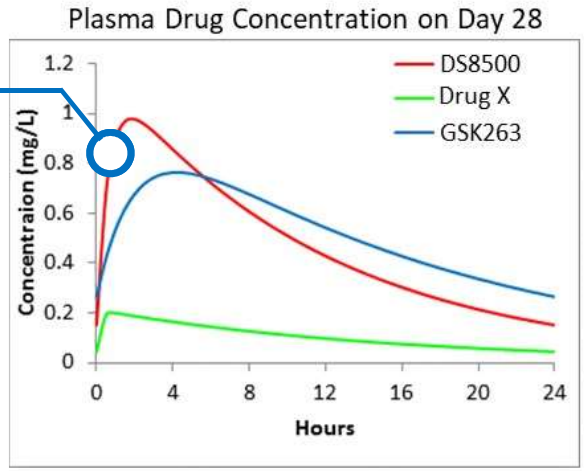
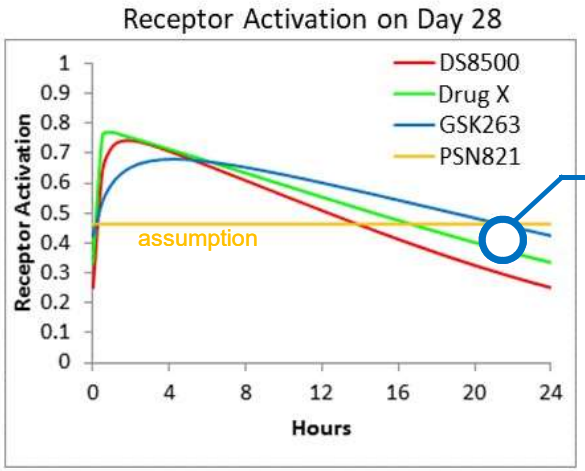
Predicting Plasma Glucose for Monotherapy

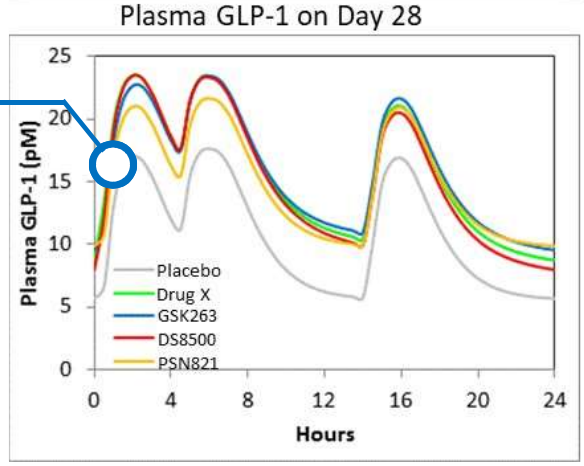
Only 5 mg of Drug X

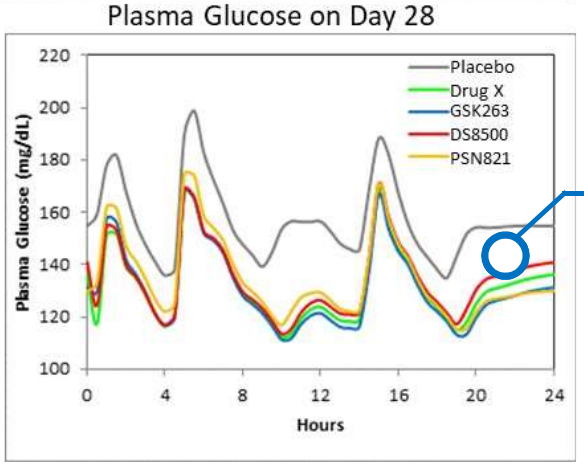




Similar GPR119 activation

Similar GLP-1 secretion





Similar glucose lowering

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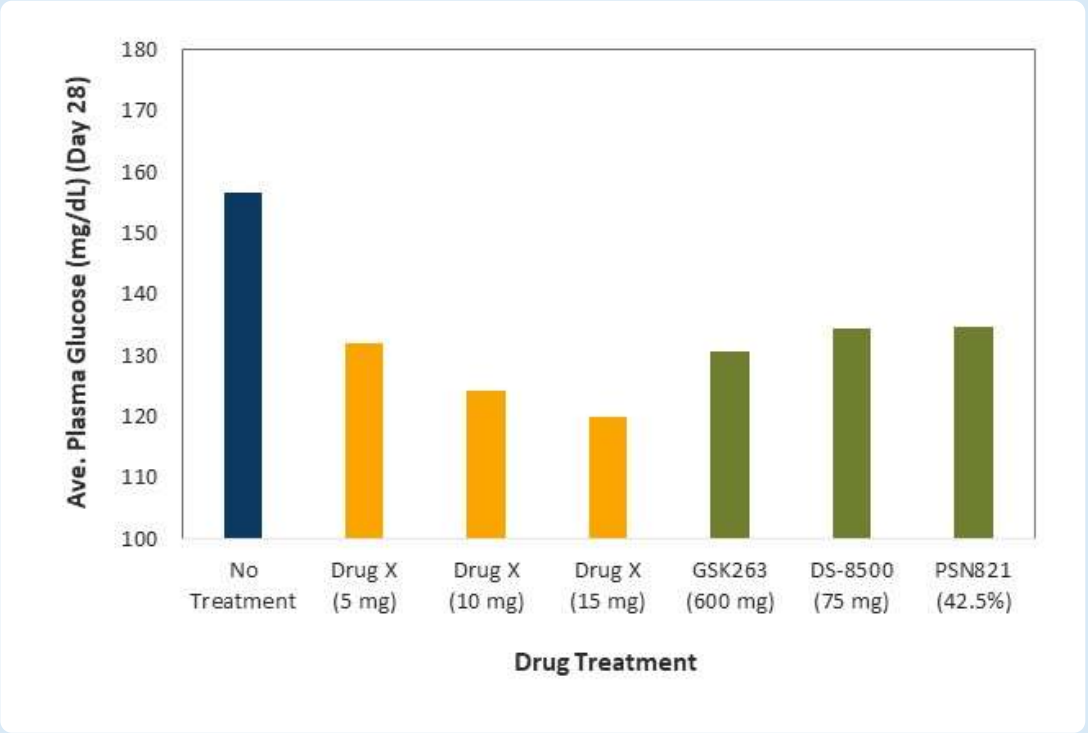
Predicting Plasma Glucose for Monotherapy

What if we use higher doses of Drug X?



- QSP model suggests that higher doses yield better glucose reduction

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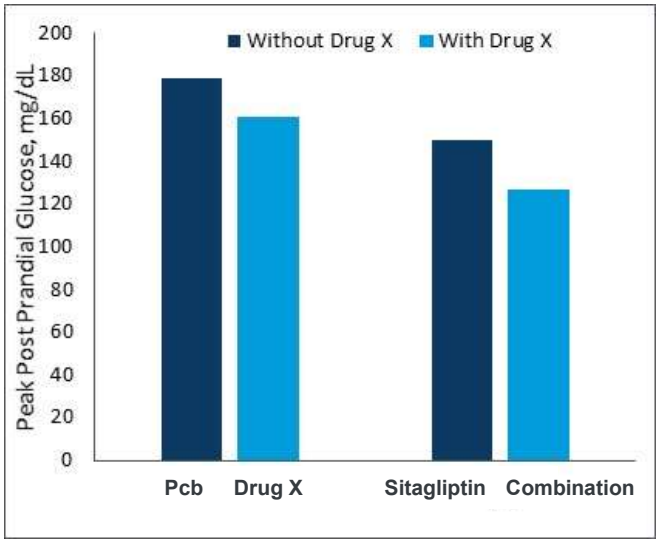
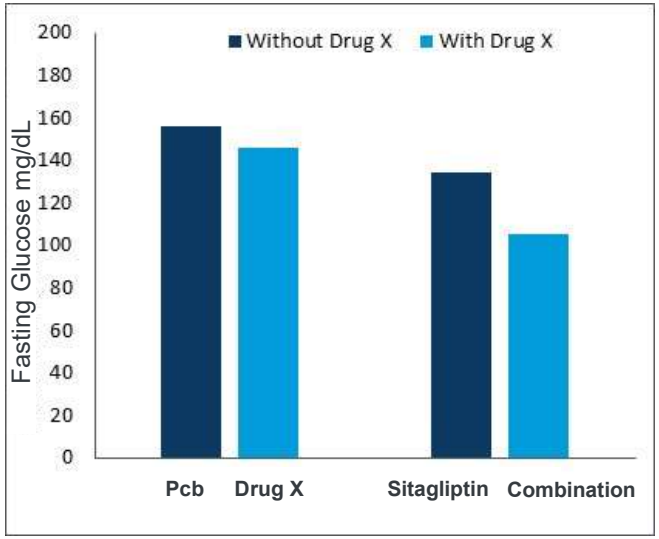
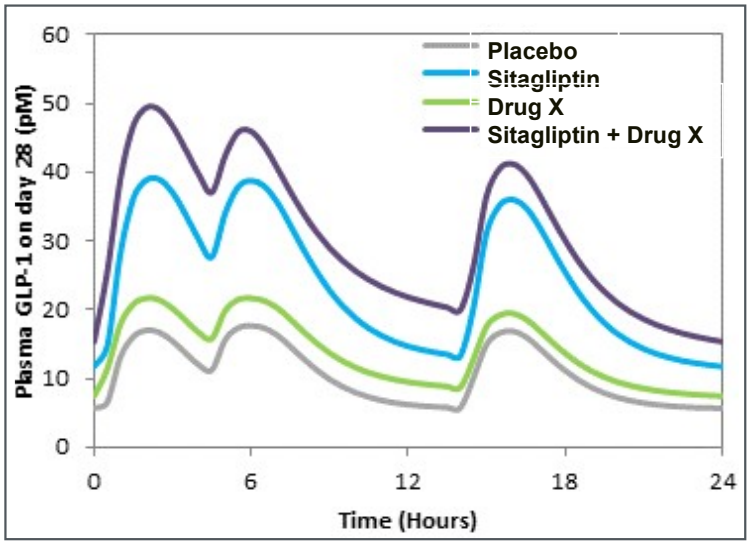
Predicting Plasma Glucose for Combination Treatment







Doses of 2.5 mg qd of Drug X:

- reduce peak post prandial glucose by 20 mg/dL, which is additive to Sitagliptin
- reduce fasting glucose by 10 mg/dL and by additional 30 mg/dL to Sitagliptin (synergistic effect)
- GPR119 agonists in combination therapy with Sitagliptin may be an effective treatment for T2D

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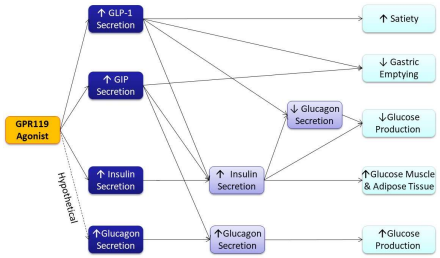
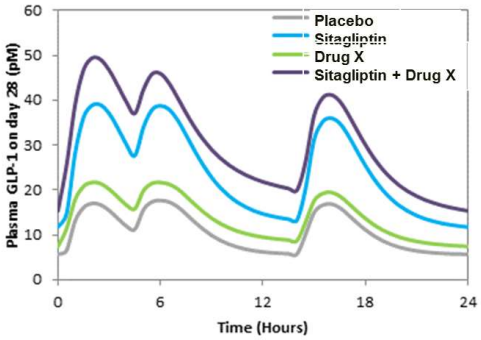
Summary

- Modification of Diabetes Platform was rapid and efficient method for comparing a GPR119 receptor agonist and other existing drugs from the same class
- Platform analysis provides mechanistic explanation for drug efficacy
- QSP model predicts human efficacy of monotherapy and combination therapy at preclinical stage



- The new GPR119 receptor agonist (Drug X) is expected to show better glucose lowering than existing GPR119 compounds at a lower dose
- GPR119 agonists in combination therapy with Sitagliptin may be an effective treatment option for T2D patients



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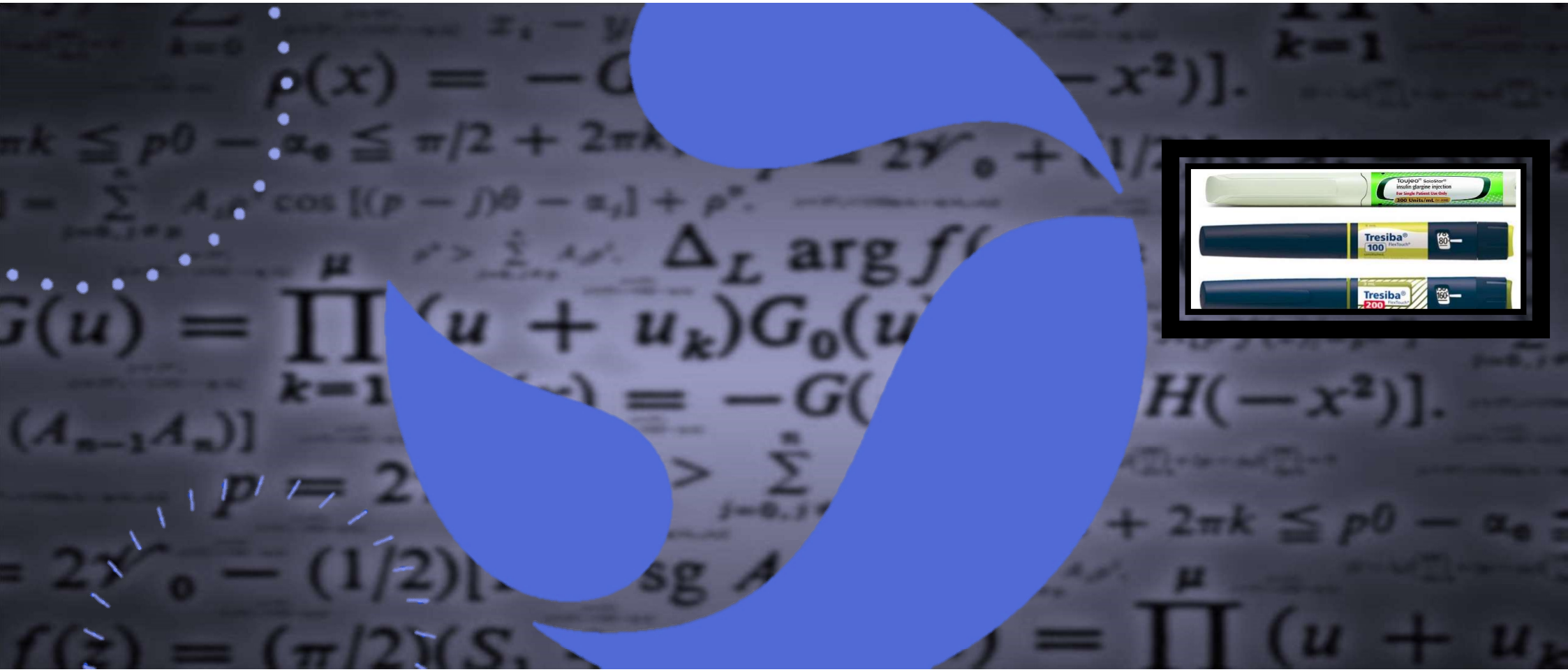

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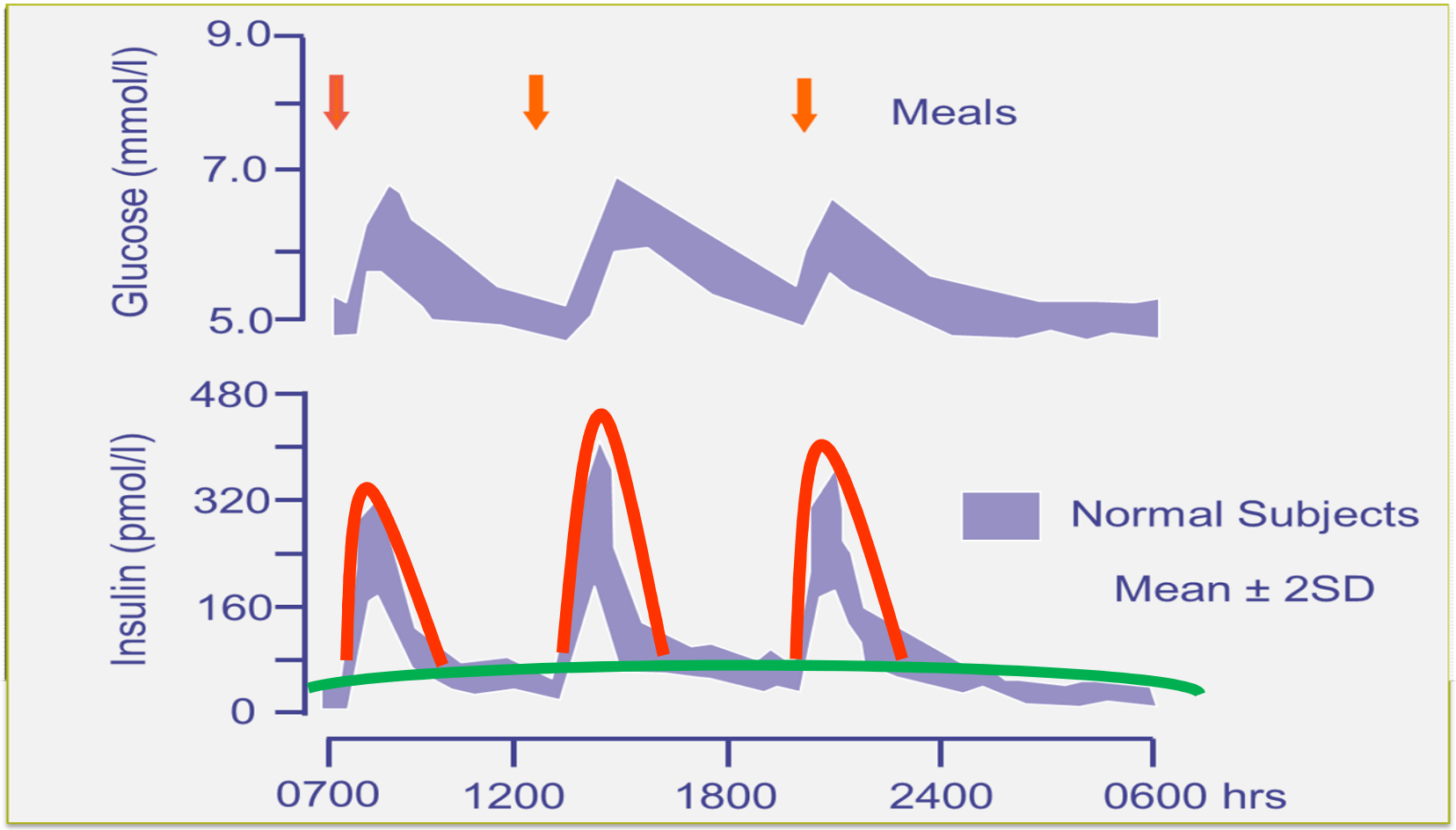
Application of T1D Simulator to Perform Virtual Trial for Toujeo vs Tresiba

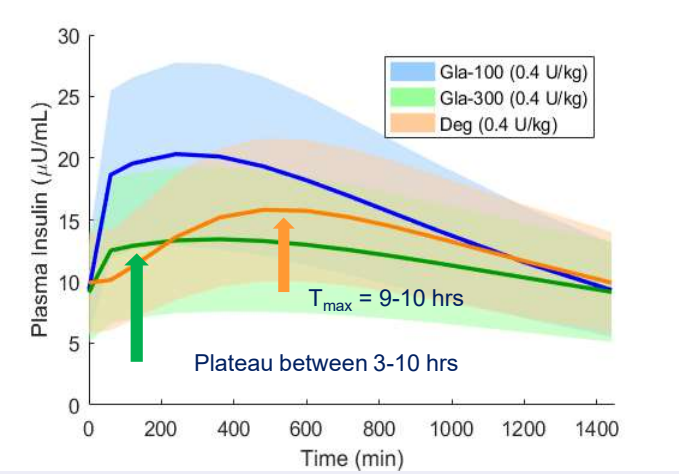
Insulin Basal-Bolus Concept



Virtual H2H CGM Trial Toujeo vs Tresiba

Motivation

- **Clamp study suggests a more flat PK and PD/GIR profile for Toujeo (Gla-300) compared to Tresiba (Degludec) in T1D patients**
- **Clinical study is planned to explore differences of Toujeo vs Tresiba head-to-head (H2H) by CGM**
- **QSP modeling supports optimal CGM trial design**
  - How would differences in PK and clamp PD translate in 24-hr glucose profiles and risk of hypoglycemia for T1D titrated to their individual dose?
  - Injection time selection (morning vs evening dosing)
  - Titration rule selection



Degludec is reported as free (i.e. HSA-unbound) insulin

Input: steady state PK profiles of basal insulins from clinical PK clamp studies in T1D

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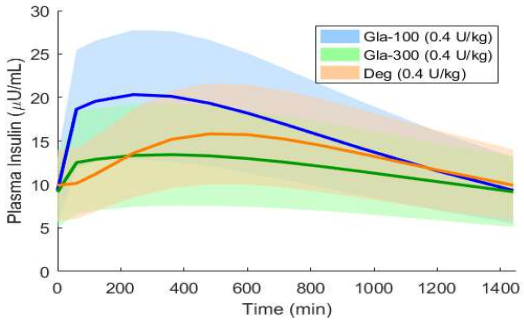
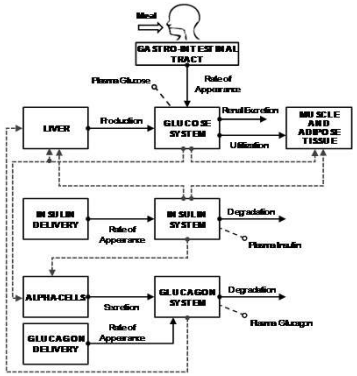
GIR, glucose infusion rate
CGM, continuous glucose monitoring
T1D, type 1 diabetes

Workflow - Virtual H2H CGM Trial Toujeo vs Tresiba



Input: steady state PK profiles of basal insulins from clinical PK clamp studies in T1D

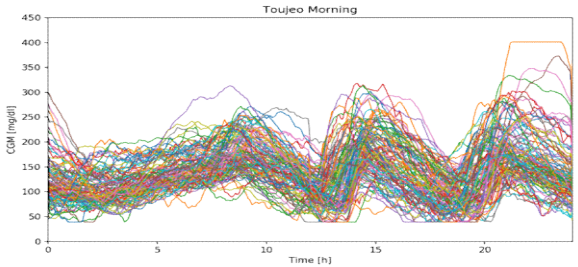
Training



Generation of basal insulin T1D Simulator

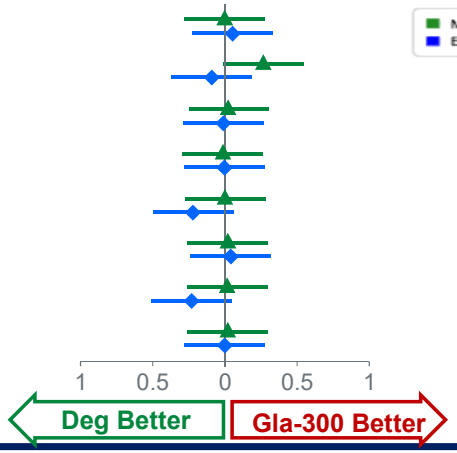
Simulation*

* e.g. 3-meals a day with morning administration of Toujeo and bolus injection for prandial insulin before meal



Output: 24-hr glucose (CGM) profiles for 100 T1D virtual patients for last week of stable dosing of Toujeo (example morning)

Analysis



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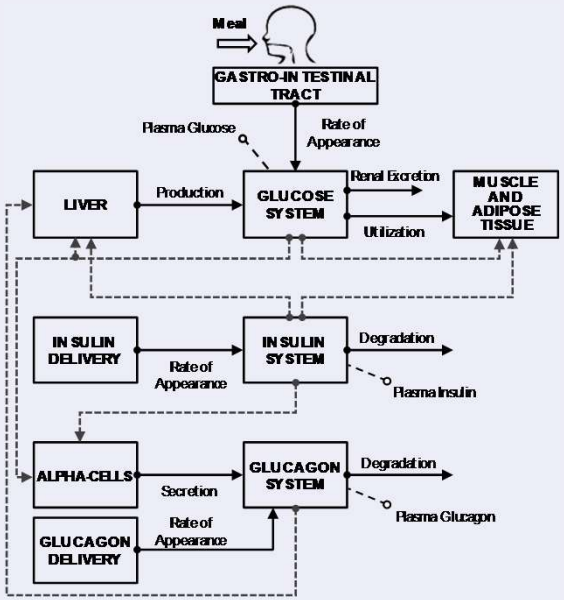
QSP Model - UVA/Padova T1D Simulator

Tool to perform virtual clinical trials for prandial/basal insulins in T1D patients

- **Allows to simulate post-prandial and/or 24-hr glucose profiles of T1D patients after dosing of prandial and/or basal insulin (required input: PK profile of insulin)**
- **Developed by Prof. Cobelli and Dalla Man (Univ. Padova) and Prof. Kovatchev (Univ. Virginia)***
  - Simulator captures the processes involved in glucose-insulin homeostasis. It has been trained by glucose tracer data and allowed the accurate measurements of post-prandial glucose fluxes
- **Approved by FDA (CDRH) in 2008 for pre-clinical testing of certain insulin treatments, including closed-loop**
  - E.g. explore control algorithms for insulin pumps
- **Various successful applications supporting development of novel diabetes drugs**

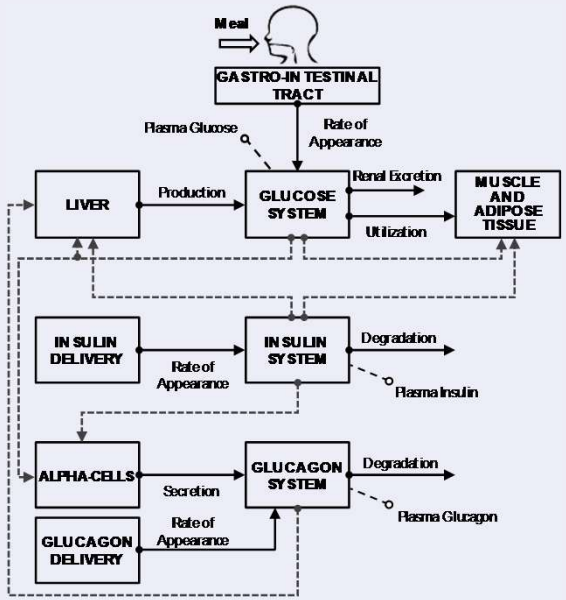


*Kovatchev, et al., J Diabetes Sci Technol, vol. 3, pp. 44–55, Jan. 2009; Dalla Man, et al. , J Diabetes Sci Technol, vol. 8, pp. 26–34, Jan. 2014

QSP Model - UVA/Padova T1D Simulator

Tool to perform virtual clinical trials for prandial/basal insulins in T1D patients

- Thanks to a very rich dataset (triple tracer flux data), the **parameters and their covariance could be estimated**, allowing the model to be used to simulate 24-hr glucose profiles in virtual T1D patients
- **Inter-patient variability** is covered in terms of demographics, insulin and glucose levels, insulin sensitivity and beta-cell function
- **Intra-patient variability** (day-to-day) is included in terms of insulin sensitivity as well as meals composition and timing
- **PK** models describing Toujeo and Tresiba, covering intra- and inter-patient variability, were developed and incorporated into the T1D Simulator

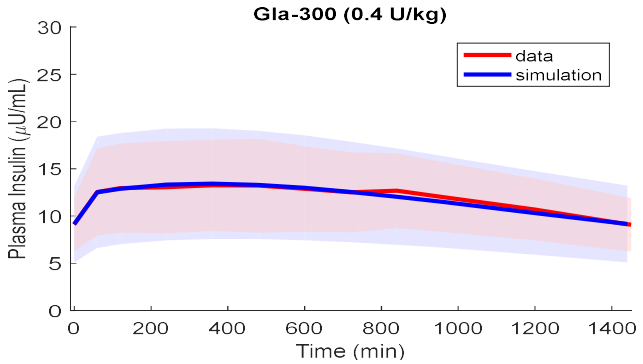


Simulated Insulin Profiles Are in Good Agreement with Clinical Data

Toujeo Data vs. Simulation

Eight days simulations, in which 100 adults were treated with Toujeo (0.4U/kg).

Plasma insulin data of TDR11626 & LPS14858 are compared to simulated insulins at Day 8.

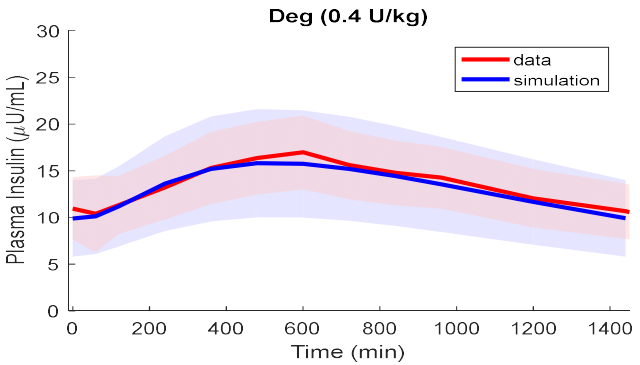


	Data	Simulation	P-value
T_peak (min)	363±230	354±156	NS
Peak (uU/mL)	14.5±4.8	13.8±6.3	NS

Tresiba Data vs. Simulation

Eight days simulations, in which 100 adults were treated with Tresiba (0.4U/kg).

Plasma insulin data of LPS14858 are compared to simulated insulins at Day 8.



Free (active) insulin is obtained by the ratio AUC_{Gla}/AUC_{Deg} = 2.23% of LPS14585 data

	Data	Simulation	P-value
T_peak (min)	565±56	538±97	NS
Peak (uU/mL)	17.0±4.0	16.0±5.8	NS

Larger variability in-silico vs data is likely due to different sample size (N=100 in silico, N<50 within each sub-group of data)

Data are reported as Mean ± SD

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Virtual Clinical Trial Protocol

STUDY DESIGN

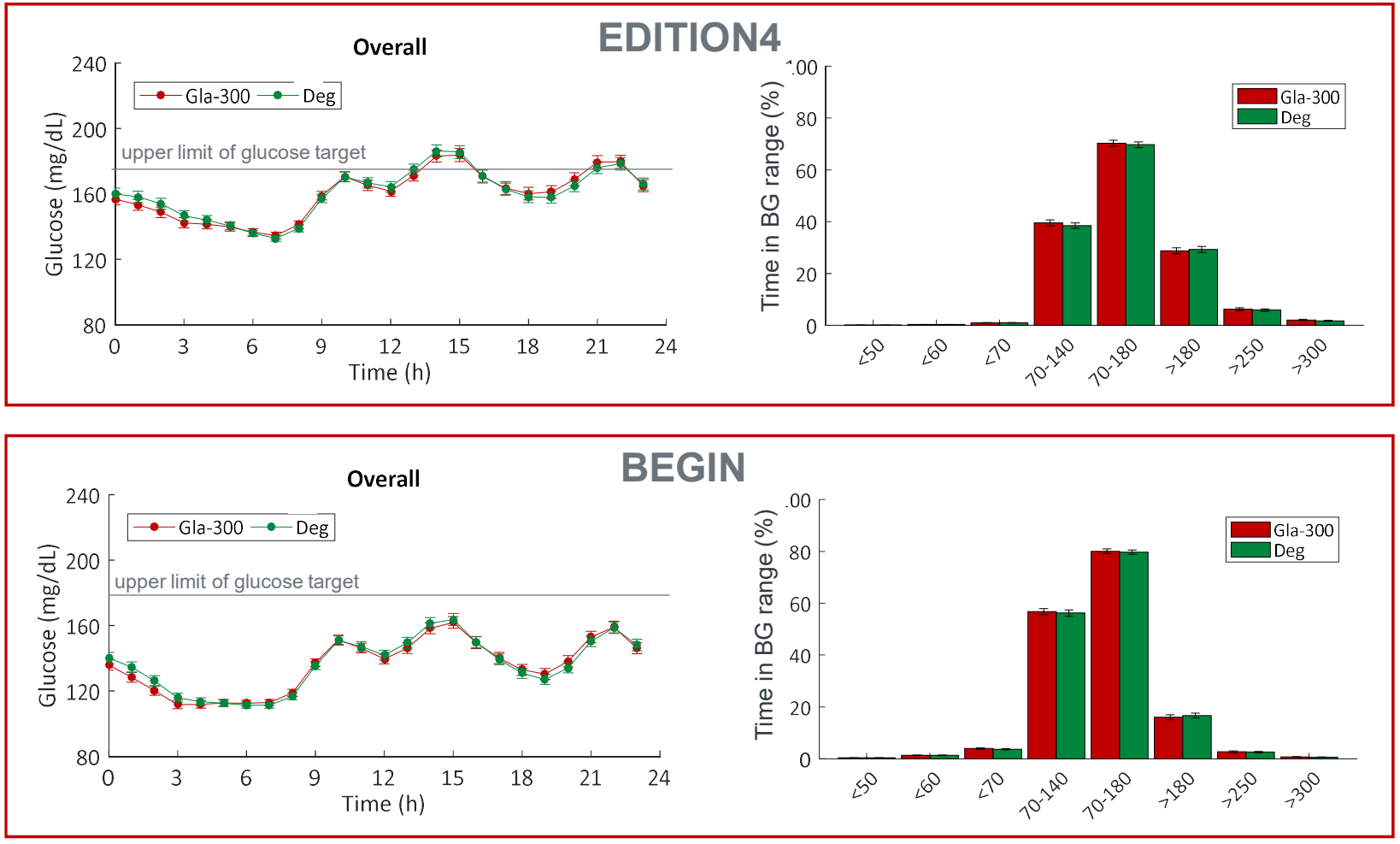
- **Subjects**: 100 T1D adults
- **Duration**: 8 weeks up-titration + 4 weeks stable dosing (profiles of 2 last weeks evaluated)
- **Basal insulin administration**: once-daily injection (morning or evening) of **Toujeo or Tresiba**
- **Meals**: day-to-day variability in time and amount, allow error in carbohydrate estimation
- **Insulin prandial bolus**: optimal (insulin-to-carb ratio + correction factor)
- **Hypoglycemia treatment:** if BG < 65 mg/dL → 16 g of rescue carb

TITRATION RULE

- **Titration rule 1 (from EDITION4 study)**: based on median pre-breakfast BG of the last 3 days (MedBG)
  - Dose increments: 1.5 to 4.5 U
  - BG target: **MedBG in [80-130] mg/dL range**
- **Titration rule 2 (from BEGIN study)**: based on mean pre-breakfast BG of the last 3 days (MeanBG)
  - Dose increments: 2 to 6 U
  - BG target: **MeanBG in [70-90] mg/dL range**
- **Hypo-stop rule** if %time(CGM<50)>2.5% OR %time(CGM<60)>5% OR if %time(CGM<70)>7.5%
  → decrease dose (back to the previous dose)

Titration Rule Selection

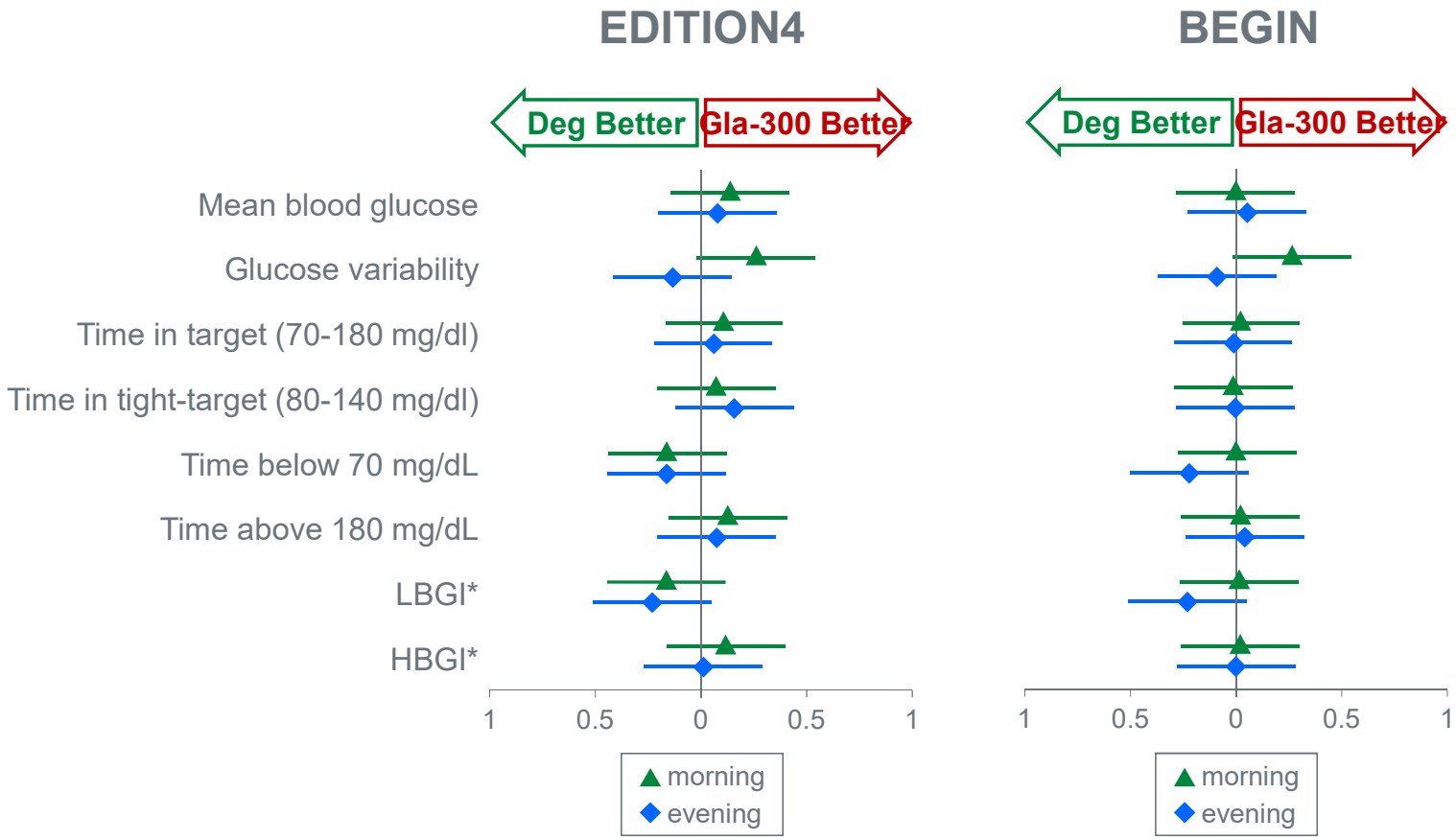
Better glycemic control with BEGIN titration rule



Output: Average 24-hr glucose (CGM) profiles for 100 T1D virtual patients for last weeks of stable dosing

Outcome - *In-silico* H2H Comparison Toujeo vs Tresiba

No statistically significant difference in main CGM-based endpoints



Forest plot to compare CGM-based endpoints for 100 virtual patients receiving either Toujeo or Tresiba treatment

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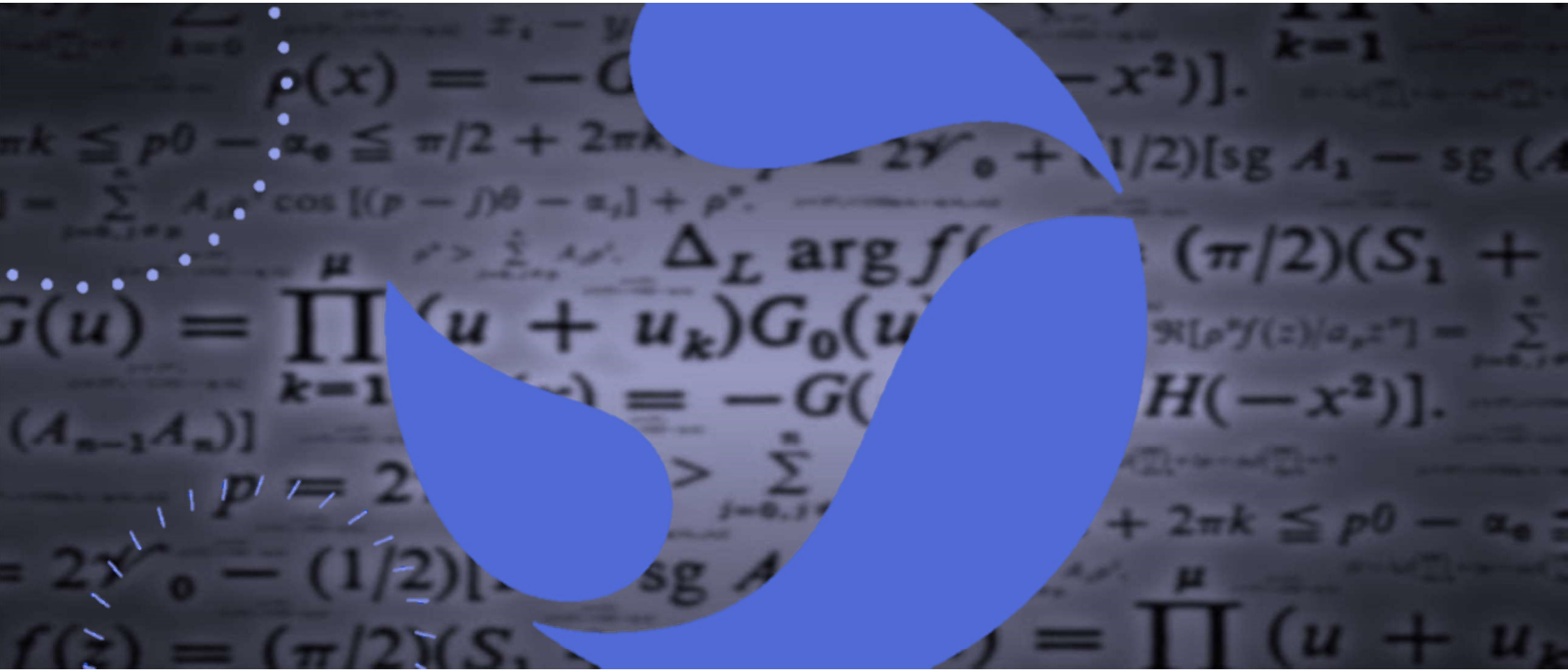
* Low / High Blood Glucose Index

Summary

- **The UVA/Padova T1D Simulator provides a powerful *in-silico* tool to evaluate dosing of novel insulins**
- **PK models describing Toujeo and Tresiba were developed and incorporated into the UVA/Padova T1D Simulator to evaluate their safety and efficacy in basal-bolus therapy**
- **Virtual clinical trials suggest that Toujeo and Tresiba provide overall comparable glucose control in T1D patients under basal-bolus therapy**
- **“BEGIN” titration rule appears providing better - comparable for both basal insulins - glucose control with acceptable risk for hypoglycemic events**
- **Toujeo and Tresiba also seem to provide comparable glucose control regardless of injection time (morning / evening)**



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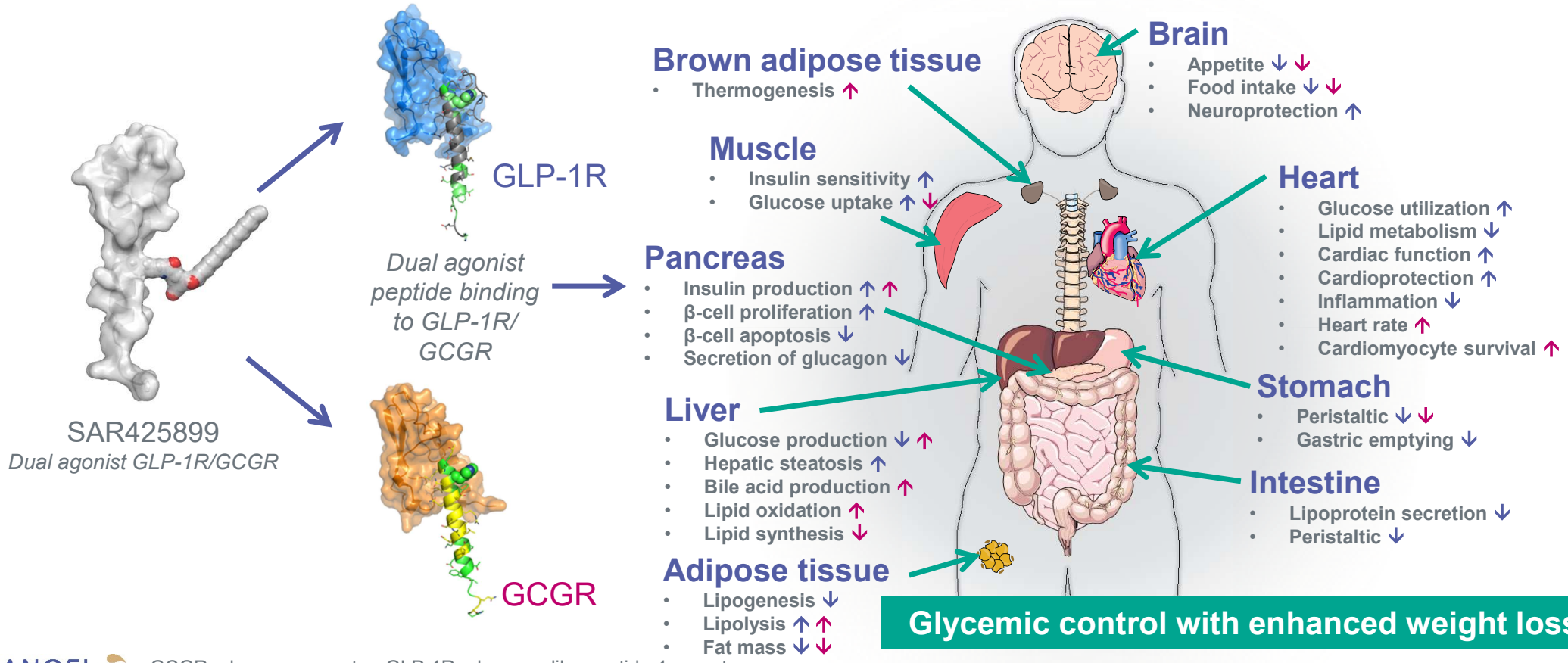
Effects of the Dual GLP-1R/GCGR Agonist SAR425899 on Postprandial Glucose Metabolism in Overweight/Obese Subjects With Type 2 Diabetes

SAR425899: A Dual GLP-1R/GCGR Agonist

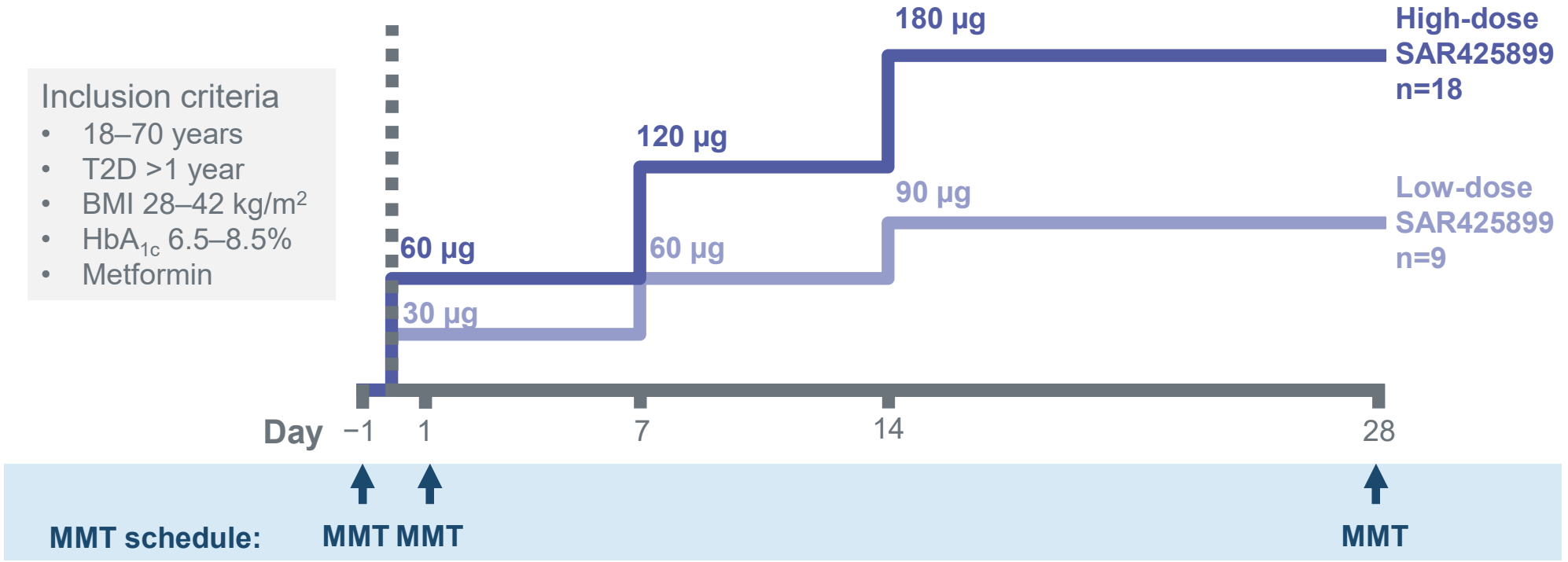
Proposed mechanism of action



GCGR, glucagon receptor; GLP-1R, glucagon-like peptide-1 receptor

Multiple Ascending Dose Trial Design

- Randomized, double-blind, placebo-controlled, Phase I, 4-week study (NCT02411825)



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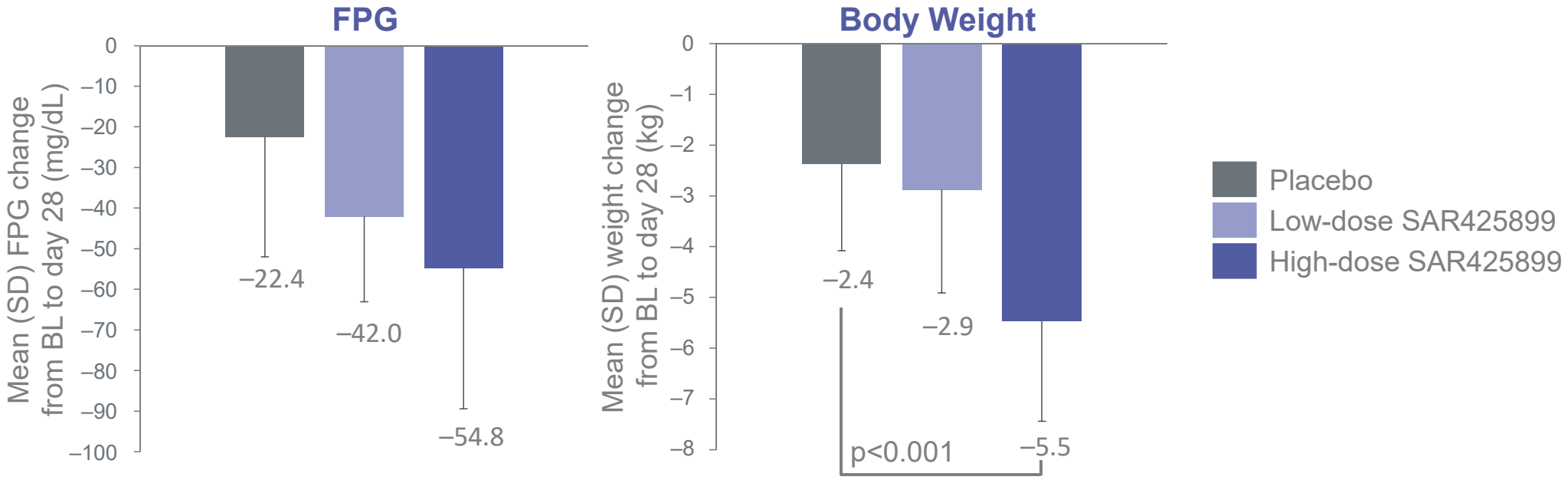
BMI, body mass index; HbA_{1c}, glycated haemoglobin; MMT, mixed meal test, T2D, type 2 diabetes

SAR425899 Phase I Safety and Efficacy: A 4-Week Study

- Subjects treated with SAR425899 demonstrated decreased FPG, PPG and body weight versus placebo
- Safety profile was comparable with that of GLP-1R agonists



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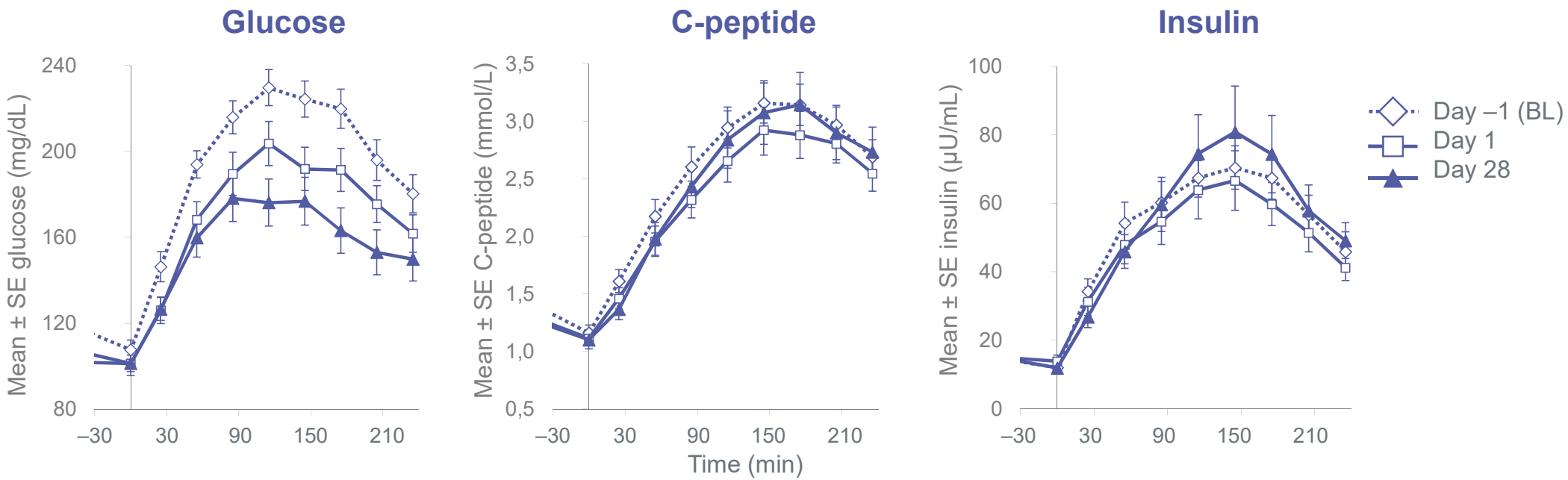
BL, baseline; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; SD, standard deviation

Lindauer K, *et al. Diabetologia* 2016; 59(Suppl 1): S1–581

Minimal Model Inputs From MMT



Glucose Minimal Model[1]	C-Peptide Minimal Model[1]
• **Input:** Insulin, CHO meal dose; **Output:** Glucose → Glucose absorption and insulin sensitivity	• **Input:** Glucose; **Output:** C-peptide → β-cell responsivity
→ Disposition Index = Insulin sensitivity x β-Cell responsivity	

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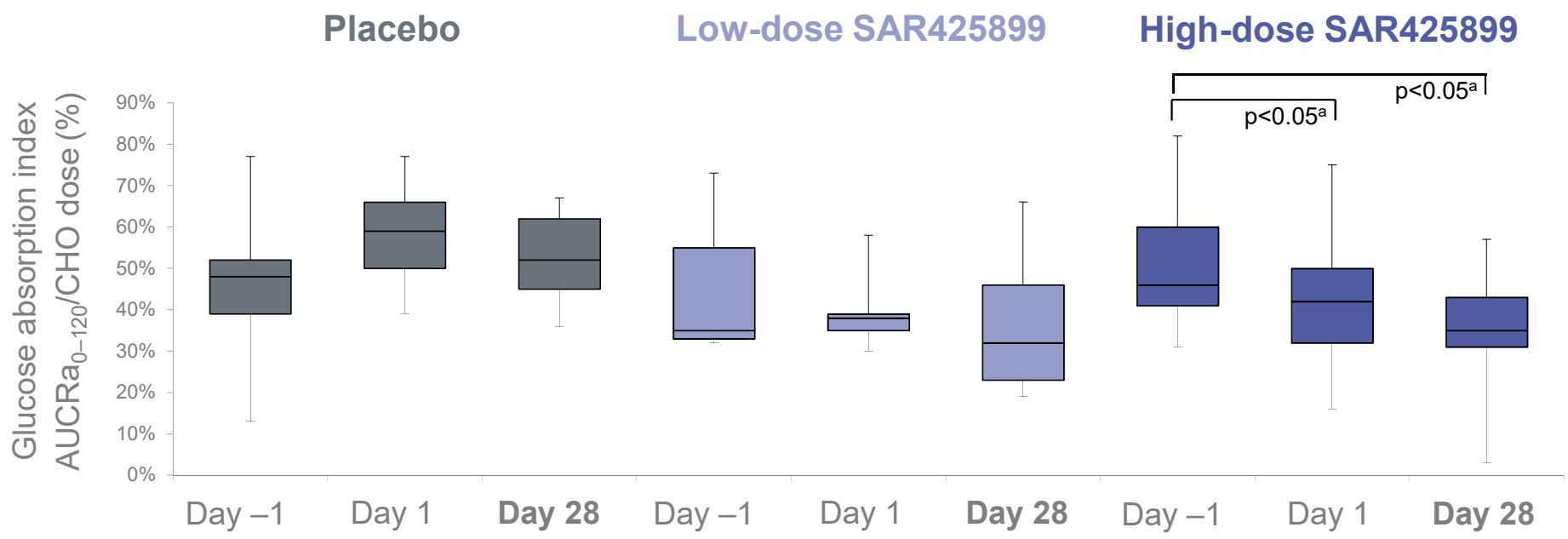
Data shown in this slide are for high-dose SAR425899; BL, baseline; CHO, carbohydrate; MMT, mixed meal test; SE, standard error

1. Cobelli C, *et al. Diabetes* 2014; 63: 1203–12

SAR425899 Delays Glucose Absorption



Median % change from Day –1 to Day 1[b]	29%	–12%	–24%

- High-dose SAR425899 had an acute and sustained effect on glucose absorption

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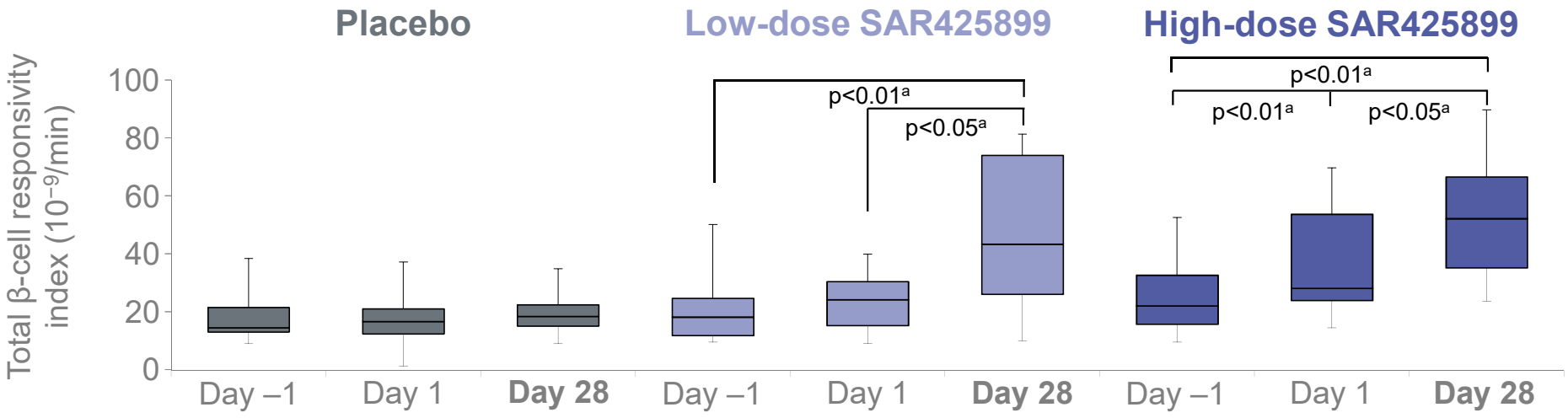
[a] Paired Wilcoxon signed-rank test; [b] Calculated as percent change per subject
$AUCRa_{0–120}$, area under the rate of meal glucose appearance curve between 0 and 120 min, CHO, carbohydrate

SAR425899 Increases β-cell Responsivity



Median % change from Day –1 to Day 28[b]	23%	163%	95%

- At Day 1, a significant increase in β-cell responsivity was observed with high-dose SAR425899
- By Day 28, β-cell responsivity significantly increased with both SAR425899 doses

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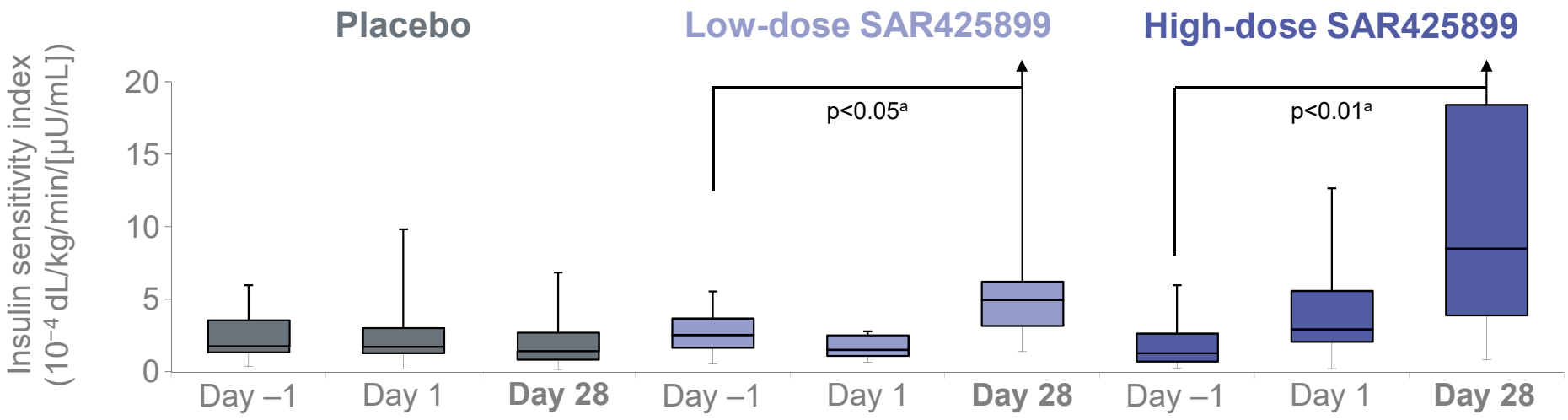
[a] Paired Wilcoxon signed-rank test; [b] Calculated as percent change per subject

SAR425899 Improves Insulin Sensitivity



Median % change from Day –1 to Day 28[b]	12%	104%	262%

- Low- and high-dose SAR425899 improve insulin sensitivity by Day 28

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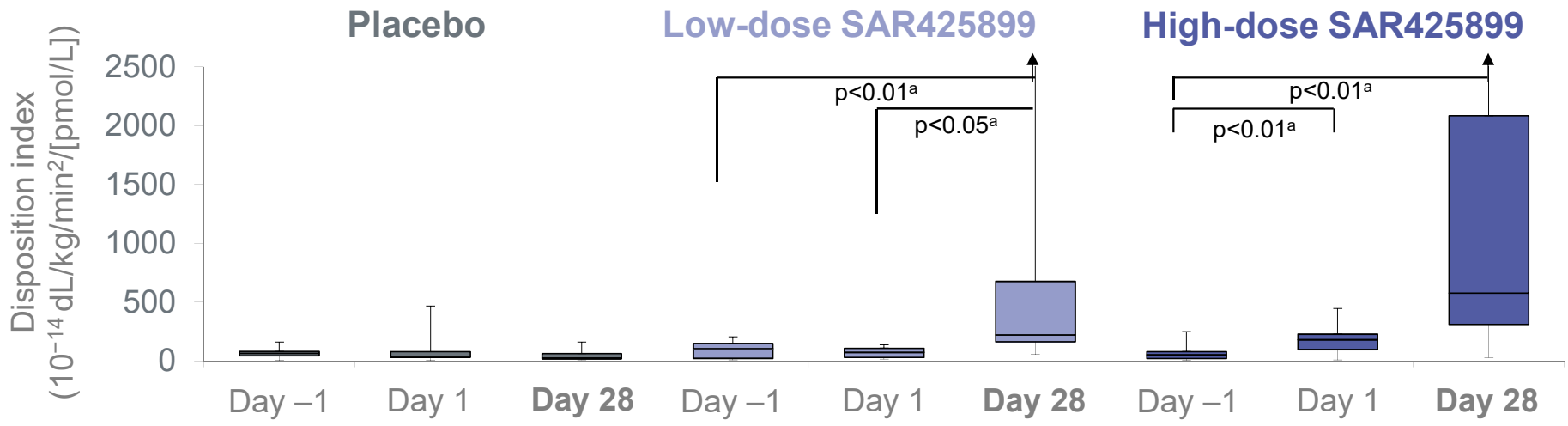
[a] Paired Wilcoxon signed-rank test; [b] Calculated as percent change per subject

SAR425899 Increases Disposition Index, A Measure for β-Cell Responsivity in Relation to Insulin Sensitivity



Median % change from Day –1 to Day 28[b]	16%	408%	657%

- At Day 1, a significant increase in disposition index was observed for high-dose SAR425899
- A significant increase in disposition index was observed by Day 28 for both doses

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[a] Paired Wilcoxon signed-rank test; [b] Calculated as percent change per subject

Conclusions

- After 28 days, SAR425899 improved glycemic control by:
  - significantly delaying glucose absorption
  - significantly enhancing β-cell function
  - significantly improving insulin sensitivity
- A significant increase in the disposition index, an overall indicator of β-cell responsivity in relation to insulin sensitivity, was observed
- Increase in disposition index with SAR425899 appears to be greater than achieved previously with a GLP-1R agonist[1]
- Dual GLP-1R/GCGR agonism with SAR425899 leads to improvement in insulin resistance and β-cell function

SANOFI

GCGR, glucagon receptor; GLP-1R, glucagon-like peptide-1 receptor

1. Visentin R, *et al*. *J Diabetes Sci Technol* 2016: 10; 476–611 (Abstract A110)

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