Assessing Sodium-Glucose Co-Transporter Inhibition Using a PhysioPD-Style Model

Rebecca Baillie[1], Michael Weis[1], Hans-Christoph Schneider[2], Ashley Strougo[2], Juliana Oliveira[3], Thomas Klabunde[2], Mike Reed[1]*

*[1]Rosa & Co., San Carlos, CA; [2]Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany; [3]Sanofi US, Bridgewater, NJ. *mreed@rosaandco.com*

Introduction

- Type 2 diabetes (T2D) is a multifactorial, long-term disease which poses challenges for developing efficacious drug therapies. Addition of a second treatment mechanism has proven effective in creating efficacious drug therapies.
- SGLT2 inhibitors have been approved for treatment of T2D, but have limitations in maximum effect. An SGLT inhibitor with both SGLT2 and SGLT1 activity may have additional efficacy when compared to SGLT2 inhibitors alone. Also, inclusion of SGLT1 activity may result in synergy with DPP4 inhibitors such as sitagliptin.
- Quantitative PhysioPD™ modeling can be used to provide mechanistic insight to inform decision making in later drug development stages and trial design.

Objectives

Inhibition of sodium-glucose co-transporter (SGLT) 1 and 2 may provide added benefits compared to a selective inhibition of SGLT2. However, the mechanism and amount of those benefits is not yet fully understood. The objective of this project was to quantify through modeling the inhibition of SGLT1 and SGLT2 on gastrointestinal (GI) and kidney glucose metabolism and to evaluate the benefits of inhibition of SGLT1 and SGLT2 versus pure SGLT2 inhibition.

Methods

A quantitative mechanistic Diabetes PhysioPD™ Research Platforms was used to quantify the effects of SGLT1 vs. SGLT2 inhibition.

- Rosa developed a Diabetes PhysioPD Platform, a quantitative mechanistic model of glucose and insulin metabolism in the liver, pancreas, kidney, GI and peripheral tissues (Figure 2).
- The Platform integrated published and proprietary data for SGLT inhibitors (SGLTi) including canagliflozin, empagliflozin, and sotagliflozin. Changes in the pathophysiology expected from a SGLTi compound were included in the system, including SGLT1i inhibition of GI glucose absorption and SGLT1i and SGLT2i inhibition of kidney glucose reabsorption.
- The Platform was qualified in accordance with Rosa's Model Qualification Method (Figure 1) and was calibrated against published data for SGLT2 inhibitors including empagliflozin and canagliflozin.
- A cohort of 10 Virtual Patients (VPs) representing different type-2 diabetes disease progression and levels of kidney function were simulated with each drug.
- The mechanistic effects of SGLT1 inhibition and the potential interactions with SGLT2 inhibition were evaluated and quantified.

Figure 1. The Platform was qualified according to Rosa's Model Qualification Method[1] (MQM)

Results

A SGLT PhysioPD Platform was developed and qualified, integrating SGLT1 and SGLT2 physiology.

- Platform qualification included evaluation using preclinical and clinical data (Figure 3, Table 1, Table 2) including dietary and drug interventions. Diet interventions included response to fasting, oral glucose tests, and meal tests. Drug interventions included metformin, sitagliptin and SGLT2 inhibitors.

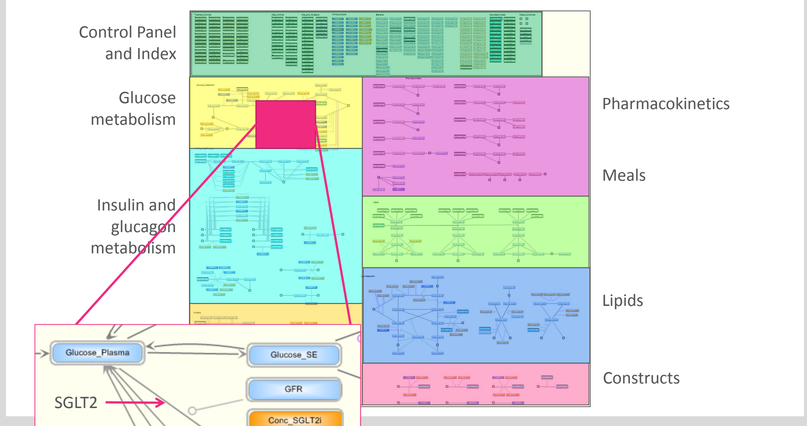

Figure 2. Graphical PhysioMap® of the T2D Platform
Labels indicate areas of metabolism incorporated in the Platform. The Platform software has aliases for the states, allowing connections between all of the sections within the Platform. Enlarged section shows glucose handling by the kidney.

Platform simulations demonstrated the interactions between SGLT1 and SGLT2 function in the kidney.

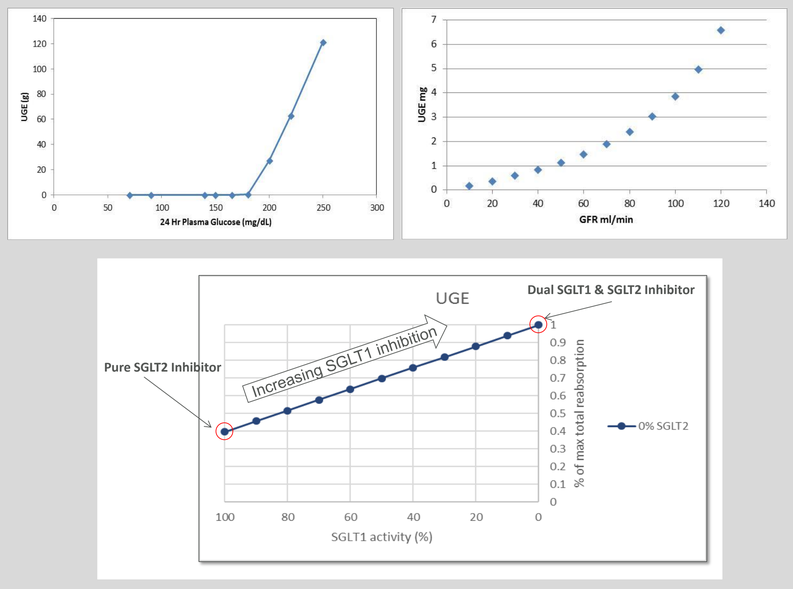

Figure 3. The Platform was used to quantify the impact of SGLT1 inhibition in a dual SGLT1 and SGLT2 inhibitor.
The amount of excreted glucose is determined by both GFR and plasma glucose concentration. Top left: clamped glucose is used to evaluate effects of plasma glucose concentration on urinary glucose excretion (UGE) in a healthy VP. GFR set at 125 ml/min; Top right: Clamped GFR was used to evaluate effects of glomerular filtration on UGE in a healthy VP. Glucose set at 90 mg/dL. Bottom: Blocking both SGLT1 and SGLT2 allows for greater inhibition of kidney glucose reabsorption. The effect of SGLT1 inhibition alone on UGE is minor, but may be significant with co-inhibition of SGLT2. However, these effects on UGE may be affected by delayed glucose absorption in the GI tract when intestinal SGLT1 is inhibited.

Table 1. Baseline comparison of the VP cohort compared with clinical data.

	Clinical Study[3]	VP Cohort*
Fasting plasma glucose (FPG, mg/dL)	172.2 ± 45.3	158 – 160
Fasting plasma insulin (FPI, pM)	NA	25.8 – 27.3
HbA1c %	8.1 ± 1.0	8.4 – 8.7
BMI	33.1 ± 5.7	32.7 – 32.7
Metformin treated	Yes	Yes
Glomerular filtration rate (GFR, ml/min/1.73m^2)	90.0 ± 20.9	90 – 111

*Clinical data is mean ± SD, Simulated data is range of VP cohort (H0-H9)

Table 2. Treatment effects at 12 weeks with 400 mg sotagliflozin treatment.

	Clinical Study[5]	VP Cohort*
Change from baseline in HbA1c %	-0.92 ± 0.873	-0.72 – -1.3
Change from baseline in FPG (range)	-27.1 ± 38.5	-5 – -47
Urinary Glucose Excretion (UGE, g/24h)	+55.6 ± 40.5	+15 – + 48

*Clinical data is mean ± SD, Simulated data is range of VP cohort (H0-H9)

Results

The impact of SGLT1 inhibition on the gastrointestinal tract and incretin production was simulated with and without sitagliptin treatment.

- VPs were treated with sotagliflozin (LX4211) (400 mg qd), sitagliptin (100 mg qd), sotagliflozin and sitagliptin, empagliflozin (25 mg qd), empagliflozin and sitagliptin, or nothing for 28 days.
- GLP-1 Results show a synergistic effect with sotagliflozin and sitagliptin co-administration (Figure 4).

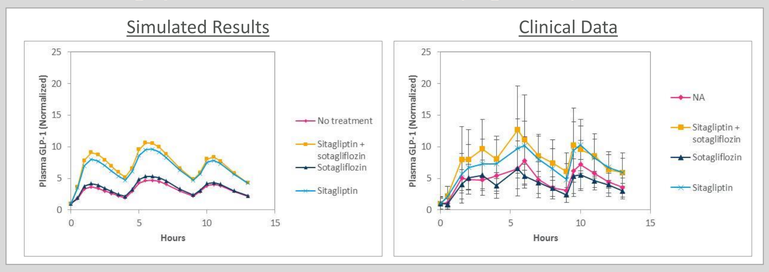

Figure 4. GLP-1 response in a select VP (H2) when treated with sotagliflozin, sitagliptin, or both. Graphs shows active GLP-1 over 13 hours on day 1 of treatment. Left graph shows simulation results. Right graph shows average results from clinical trial[5]. Results in both graphs are normalized to baseline.

Sotagliflozin mechanism synergizes with sitagliptin.

- While empagliflozin and sotagliflozin have a similar urinary glucose, sotagliflozin has a stronger effect on blood glucose. This indicates that SGLT1 mechanisms of action in the intestinal tract have significant effects on plasma glucose (Figure 5).
- These effects could be through a combination of the slowing of gastric emptying and production of intestinal peptides such as GLP-1 and PYY.
- In simulations of sotagliflozin and sitagliptin co-administration, VPs have decreased plasma glucose, insulin, and A1c levels as compared to either drug as a monotherapy. The effects of co-administration of the two drugs appears to be synergistic.

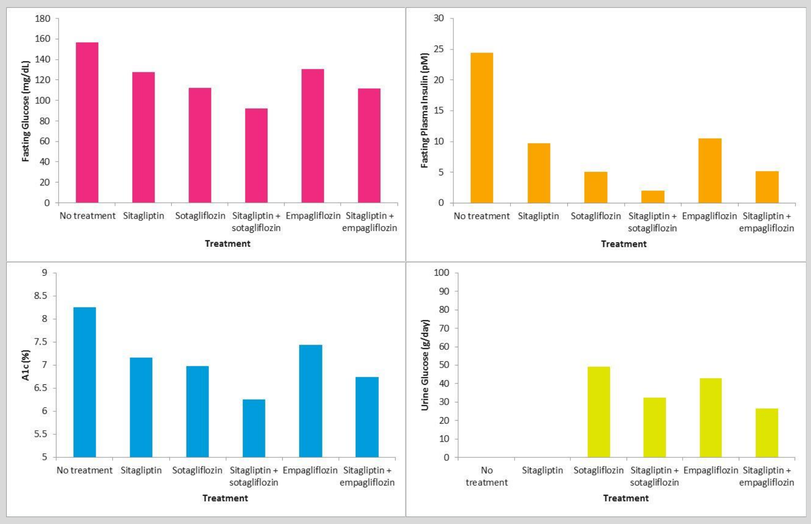

Figure 5. VP (H2) was simulated for 28 days with no treatment or specified drug treatment. Results shown are from day 28 of treatment. Results are mean data for cohort (H3-H9)

Conclusions

- Simulations show that slowing glucose absorption and increased synthesis of incretins by SGLT1i contributes to glucose lowering.
- Co-administration of a DPP4 inhibitor with SGLT1i synergistically reduces A1c levels.
- Modeling research indicates that addition of SGLT1i to an SGLT2i may provide some benefit to glucose lowering and other efficacy markers.
- This research contributed to the benefit risk analyses for a dual SGLT1i and SGLT2i. Clinical studies are planned to validate the efficacy benefits.

References & Disclosures

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Systems Pharmacology 5, 43-53 (MQM)
2. Frank TB, Ravishankar RV, Herbert MS. (2006) Current Proteomics 3, 181-197 (Jdesigner)
3. Rosenstock J, et. al. (2015) Diabetes Care 38(3), 431-438
4. Zambrowicz B. et al. (2013) Clinical Therapeutics 35(3), 273-285
5. Clinical Study Report (Phase II in type-2 patients)

Disclosures: This study was supported by Sanofi-Aventis. CS, AS, JO and TK are employees of Sanofi. RB, MW and MR are employees of Rosa and consultants for Sanofi-Aventis, Germany.

For more information about this work, please contact:
Mike Reed
Rosa & Co., LLC
mreed@rosaandco.com