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

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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 SGLT1i and SGLT2i on gastrointestinal (GI) and kidney glucose metabolism and to evaluate the benefits of SGLT1i.

Methods: PK and mechanisms of action for SGLT1i and SGLT2i were added to a Diabetes PhysioPD™ Research Platform. The Platform included glucose and insulin metabolism in the liver, pancreas, kidney, GI and peripheral tissues. Changes in the pathophysiology expected from a SGLTi compound are included in the system, including SGLT1i inhibition of GI glucose absorption and SGLT1/2i inhibition of kidney glucose reabsorption. The Platform was qualified in accordance with Rosa’s Model Qualification Method and was calibrated against published data for SGLT2 inhibitors including empagliflozin and canagliflozin. Virtual Patients (VPs) representing different diabetes disease progression and levels of kidney function were simulated with each drug.

Results: Simulated treatment with SGLT1/2i showed higher A1c reduction in VPs with high baseline FPG and high glomerular filtration rate. Addition of SGLT1i to SGLT2i resulted in an greater reduction of A1c for all VPs. Simulated co-administration of SGLT1i with DDP4 inhibition resulted in increased GLP-1 and significantly reduced A1c levels.

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 a significant benefit to glucose lowering and drug efficacy. This research contributed to the benefit risk analyses for a dual SGLT1/2i. Clinical studies are planned to validate the efficacy benefits.

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