Investigating GPR119 agonist efficacy in a systems pharmacology model of diabetes

Mike Reed¹, Michael Weis², Rebecca Baillie³, Thomas Klambunde⁴, Hans-Christoph Schneider⁵, Markus Rehberg⁶, Lothar Schwink²
¹Rosa & Co., LLC, San Carlos, CA; ²Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

Introduction

- GPR119 receptor agonists are a potential treatment for type 2 diabetes (T2D) that are reported to
  - increase the secretion of incretins with or without food intake
  - increase either glucose-stimulated insulin secretion or glucagon secretion, depending on the glucose level
- However, GPR119 receptor agonists have shown mixed results in clinical settings²

Objectives

The objectives of this work were to
a) integrate GPR119 mechanisms into a quantitative systems pharmacology (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

Methods: Model Qualification

- The GPR119 Research Platform was implemented into a previously-developed diabetes QSP model with the tissues and functions necessary to model metabolism of glucose, amino acids and lipids
- Indirect and direct mechanisms of GPR119 receptor agonism (such as incretin release and enhanced sensitivity on insulin and glucagon secretion), PK, EUC0, and Emax for the agonists were incorporated into the Platform
- Platform behavior was calibrated using public and proprietary pre-clinical and clinical data
- The Platform was qualified in accordance with Rosa’s Model Qualification Method²

Results: Diabetic Virtual Patient

- Obese, T2D, sedentary, diabetic virtual patient (DVP) (HbA1c = 7.2%, fasting glucose = 155 mg/dL) treated with metformin but with low response, mild pancreatic beta cell dysfunction, insulin hypersecretion, and moderate response to sitagliptin (Table 1)

Table 1. Diabetic Virtual Patient (DVP) responds appropriately to sitagliptin

<table>
<thead>
<tr>
<th>Compounds</th>
<th>No Treatment</th>
<th>Sitagliptin 160 mg q.d.</th>
<th>Change from Placebo</th>
<th>Literature</th>
</tr>
</thead>
</table>
| FPG (mg/dL) | 175 | 145 | 11 | 11
| BMI (kg/m²) | 33 | 26 | -7 | -7
| GIP (pmol/L) | 15.7 | 12.6 | -3 | -3
| Glucose (mg/dL) | 126 | 110 | -16 | -16

- Additional testing of DVP showed appropriate response to metformin monotherapy (results not shown)

Results: Monotherapy

- Monotherapy simulation results suggest that the Drug X may have slightly better plasma glucose lowering at select doses compared to the other compounds in the same class

Results: Combination Therapy

- Simulation results suggest that combining a GPR119 agonist with sitagliptin causes higher GLP-1 concentrations and may have superior glucose lowering compared to either monotherapy

Conclusions

- Modification of an existing Diabetes Platform was a rapid and efficient method for comparing a GPR119 receptor agonist and other existing drugs from the same class
- Platform analysis indicated that the direct effects of Drug X contributed approximately 50% of the drugs efficacy
- The new GPR119 receptor agonist (Drug X) showed slight superiority in glucose lowering to existing GPR119 compounds at a lower dose
- GPR119 agonists in combination therapy with sitagliptin may be an effective method for treating Type 2 Diabetes

For more information about this work, please contact:
Mike Reed, PhD, mreed@rosaandco.com