

Title: Impact of Modeling on GPR119 Agonist Development.

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Objectives and background: GPR119 is a G protein-coupled receptor expressed in beta cells in the pancreas and L cells in the gastrointestinal tract in humans. Activation of the GPR119 receptor causes an increase in intracellular cAMP levels via adenylate cyclase resulting in GLP-1 release from L cells and insulin release by the pancreas. Thus, GPR119 agonists are potential candidates for diabetes therapeutics and are being developed as such by several companies. However, some important aspects of the mechanism of action of GPR119 agonists that are unresolved by current data. For example: How much production and release of GLP-1 can be induced by GPR119? Since GLP-1 also increases glucose stimulated insulin release, is there an interaction between the GPR119 and GLP-1 signaling pathways in pancreas which would limit insulin release? Does GPR119 slow gastric emptying either directly or through GLP-1 release?

We chose to develop a model of GPR119 physiology and pharmacology in relationship to diabetes to address these and other decisions within a GPR119 program. We wanted to understand the relative contributions of direct and indirect action of GPR119 agonists on glucose control, and thus, identify a chemical strategy that maximized efficacy and/or better differentiated GPR119 compounds from competitors. We wanted to translate preclinical data to predict human clinical response for GPR119 agonists, and thus better select doses for first-in-man trials. We wanted a model to help design Proof of Mechanism and Proof of Concept studies for GPR119-based therapies.

Methods: We developed a Physiologically-based model which included insulin, glucose and glucagon metabolism as well as GPR119 MOA and efficacy measures. Meals, infusions, and the physiology and pharmacokinetic models for sitagliptin, exenatide, metformin, and glyburide were also included in the model as both test measures for the model itself, and as comparators for GPR119 agonist compounds. Detailed incretin metabolism and effects were included in this model and will be detailed in this presentation. The model structure and parameters for GLP-1 production, degradation, and metabolic effects were developed and tested based on literature data, specifically targeting the sitagliptin and exenatide literature. The parameters were then further refined using publically available data for GPR119 agonists. Mechanisms were included to address a number of hypotheses for GPR119 effects in gastric emptying and GLP-1 release. Pharmacokinetic information for GPR119 in the model incorporated a PK model, as well as a variety of compound-specific parameters such as potency, intrinsic activity, bound fraction, and molecular weight, to permit easy testing of new compounds and definition of new compound characteristics for medicinal chemistry.

Results: Key metabolites and hormones included in model were glucose, lactate, multi-phase insulin and C-peptide release, incretins and glucagon. Maintenance of energy balance was a primary constraint of the model. The contributions of GLP-1 production, direct insulin release, and potential gastric emptying effects to GPR119 agonist efficacy were quantitatively tested in the model and the results compared to publically available data. An extensive set of tests were performed and documented to ensure the model was suitable for purpose. The potential efficacy and required dose levels of partial and full agonist compounds were evaluated.

Conclusions: Direct effects on GLP-1 release with resulting insulin production or direct effects on insulin production appear to have approximately equal contributions to GPR119 agonist efficacy on glucose homeostasis. GPR119 agonism having no direct effect on gastric emptying is consistent with data and modeling analysis, and the indirect effect through GLP-1 appears to be very limited. The model can be used to evaluate the degree of partial agonism that would yield an acceptable compound. While GPR119 agonists have potential as diabetes therapeutics, both increased direct insulin release and increased GLP-1 release would be necessary to achieve marketable therapeutic potential.