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TITLE: Application of a physiologically based model incorporating drug-specific PK modules to support optimization of GLP-1 receptor agonist combination therapies for type 2 diabetes

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Purpose
GLP-1 receptor agonists, such as exenatide, have shown significant promise for the treatment of type 2 diabetes. However, their small size and potential degradation by dipeptidyl peptidase-4 (DPP-4) requires twice-daily dosing or formulation modifications for extended release to maintain therapeutic concentrations for adequate glycemic control. Here, we utilize a physiological PK/PD modeling approach to establish optimal plasma concentration profiles for treating type 2 diabetes with GLP-1 receptor agonists in combination with biguanides, sulfonylureas, and DPP-4 inhibitors. The utility of this model-based approach for rational drug development and clinical trial design will be explored.

Methods
A physiological model incorporating glucose metabolism, incretin/insulin secretion, and meal- and glucose-tolerance tests was created to analyze the effects of therapeutic interventions on virtual patients with type 2 diabetes. A pharmacokinetic model for each type of drug was included in the larger model and linked to the mechanistic action.

Results
Baseline model parameters were selected to provide healthy and diabetic virtual patients with physiologically relevant fasting plasma glucose levels and post-prandial glucose excursions eliciting appropriate two-phase insulin release following mixed meals and oral glucose challenges. Simulation results for BID dosing of GLP1-receptor agonists with biguanides or sulfonylureas were compared with published clinical data to calibrate model parameters. Subsequently, the model was used to explore how changes in the combination treatment regimen (e.g., inclusion of DPP-4 inhibitors) as well as drug release profiles (e.g., extended release formulations of GLP-1 receptor agonists) affect therapeutic efficacy. The 2-hour post-prandial glucose and fasting plasma glucose levels were chosen as metrics to compare the relative efficacy of the combination therapies. Mechanistic insights into potential adverse reactions, including hypoglycemia and nausea, following treatment will also be discussed.

Conclusion
Physiological models incorporating drug-specific PK modules can be used to guide the design and optimization of combination therapies which are increasingly used in the treatment of diseases ranging from diabetes to cancer. In addition to providing a framework for examining the mechanistic effects of combination therapies using approved drugs and regimens, the model described here can guide the design of novel drug formulations or combination therapy strategies with improved efficacy for patients with type 2 diabetes.