Predicting Phase III Efficacy and Safety in Insulin Response using QSP Modeling

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Objectives: To generate a Diabetes QSP model to facilitate the development of novel insulins for type 1 and type 2 diabetic subjects. To build a model using physiologically based systems pharmacology approaches whereby predictions are drawn from human data and our understanding of the biology of glucose homeostasis and insulin action.

Methods: A detailed Diabetes QSP model of the glucose–insulin system was constructed from literature in the KroneckerBio toolbox in Matlab. The model individually represented the glucose–insulin response for key tissues. It also included endogenous insulin production and glucagon response. The between-subject and within-subject variability in addition to several population parameters were calibrated to the HbA1c, fasting plasma glucose, titrated dose, self-monitored plasma glucose, and hypoglycemic rates from CSRs available from two published Phase III trials—one for type 1 and one for type 2. Type 1 subjects were modeled as having no endogenous insulin production, being insulin resistant, and having an highly attenuated glucagon response. Type 2 subjects were modeled as having attenuated insulin production, being insulin resistant, and having a midly attenuated glucagon response. The calibration of the patient populations using the biology, literature, and CSR data produced good fits across all five of the study endpoints with HbA1c and hypoglycemic rates receiving greater weight in the process.

Results: The resultant Diabetes QSP model reproduces the population mean and population standard deviation behavior for both type 1 and type 2 diabetic populations on insulin glargine treatment for the two studies used for calibration.

Conclusions: Successful calibration of the Diabetes QSP model enables prediction of the efficacy and adverse event profiles of both standard of care and novel insulins, aiding decision making in discovery and development efforts geared to designing improved insulins for the diabetic patient.