A Quantitative Systems Pharmacology Model of Glucose Responsive Insulin

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Objectives: Predict the efficacy and safety of a basal glucose responsive insulin (GRI) compared to insulin glargine in a T2DM clinical outcome trial. GRI is an insulin modified to create an additional clearance pathway through an off-target receptor which is competitively inhibited by endogenous glucose. When glucose is low, GRI clearance is increased, less GRI is available, thus reducing additional glucose clearance to avoid hypoglycemia.

Methods: The Merck Diabetes QSP model represents important processes in glucose homeostasis using 11 physiological modules, 6 dynamic state variables, and 35 parameters. The QSP model was calibrated to the glargine arm of a 52 wk study in T2DM [1] using fasting plasma glucose (FPG), HbA1c, and confirmed hypoglycemia event rate (model glucose<55 mg/dL) for 100 random virtual patients. GRI was assumed equipotent to glargine, with additional off-target Michaelis-Menten clearance with competitive glucose inhibition. The GRI off-target affinity was designed for a DClearance, between glucose of 80-300 mg/dL, of 0% (glargine), 12%, 30%, 50%, or 70%, corresponding to a maximum off-to-on-target clearance ratio of 0, 0.45, 1.5, 3.9, and 13, respectively. The insulin titration algorithm was from [1], except upper FPG target was 80, 100, 120, or 140 mg/dL. All 20 combinations of GRI DClearance and FPG target were simulated in the same 100 virtual patients for 52 weeks.

Results: The week 52 mean QSP simulation outputs (Figure) show that GRI outperformed glargine on both HbA1c and hypoglycemia. GRI with 50% DClearance and 120 mg/dL FPG target achieved similar HbA1c (~6.8%) as glargine with a 80 mg/dL FPG target, but had 1/3 lower hypoglycemia rate. Alternatively, GRI with 70% DClearance and a 80 mg/dL FPG target achieved similar hypoglycemia (~2.5 events/person/year) as glargine with a 100 mg/dL FPG target, but had 0.2% lower HbA1c.

Conclusions: QSP simulations demonstrated that GRI outperformed glargine on both glucose lowering and reducing hypoglycemia, albeit at the expense of a higher cost-of-goods.

Figure. GRI QSP simulations: mean results of 100 virtual patients at week 52 in a cross-over study with different GRI glucose responsiveness and FPG targets. The starting mean HbA1c was 8.3%.