Predicting End-of-trial Fasting Glucose and HbA1c via Mechanistic PK/PD Modeling based on Longitudinal Type 2 Diabetes Trial Data
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Objectives: The goal of this work was to develop and qualify a mechanism-based drug-disease modeling platform for type 2 diabetes mellitus (T2DM) that links drug-induced changes in fasting serum insulin (FSI) and fasting plasma glucose (FPG) to changes in the well accepted endpoint glycated hemoglobin A1C (HbA1c).

Methods: Patient-level data from a combined database of clinical trials (4,249 patients, 37 arms) following placebo, mono, and combination therapy with metformin, sulfonylurea, thiazolidinedione was used to step-wise develop and qualify a drug-disease model for T2DM in NONMEM v7.3. First, the dynamic interplay between FSI, FPG, and HbA1c was characterized by using cascading turnover models with negative feedback/feed forward mechanisms. Second, disease progression was modeled as a change from the patient’s baseline beta-cell function loss. Finally, a log-linear relationship was used to characterize drug effect(s) following mono and combination therapy at different dose levels and placebo.

Results: This drug-disease model was able to characterize changes in FSI, FPG, and HbA1c as the result of disease progression and/or therapeutic intervention in 4,249 patients receiving single or combination anti-hyperglycemic therapy for up to 104 weeks reasonably well. Body mass index, age, gender, and beta-cell function at baseline were identified as significant covariates for treatment response. In addition, treatment effects on disease progression were found to be additive for these 3 drugs. Longitudinal FSI, FPG and HbA1c data from short- and mid-term duration trials informed the magnitude of treatment effect, while long-term trials (≥52 weeks) informed the effects of underlying disease progression.

Conclusions: A drug-disease modeling platform for T2DM was developed that integrates information on clinically-relevant biomarkers, disease state and progression, treatment effects as well as covariates into a single, unified model. The mechanistic nature of this model allows for evaluation of drugs with novel mechanisms of action on disease progression.