An Integrated Approach to Apply Quantitative Systems Pharmacology Model of Diabetes in Early Phase of Diabetes Research

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Objectives: To incorporate information obtained from different modeling platforms into a quantitative systems pharmacology (QSP) model of diabetes to predict biomarker responses in healthy subjects versus patients with type 2 diabetes mellitus (T2DM) to support candidate screening in early discovery research in diabetes.

Methods: A QSP model of diabetes was developed and used to simulate glucose, HbA1c and weight responses to potential drug candidates targeting key pathways of metabolic dysfunction in healthy subjects and patients with T2DM as the two possible study populations in Phase 1. The parameters and values of PK (clearance and bioavailability) from PBPK modeling in Simcyp (version 15) and PD (Emax and EC_{50}) from PK/PD modeling of preclinical data in NONMEM (version 7) were incorporated in the “drug” modules of the QSP model. The resulting integrated model was used to simulate healthy subject response in Phase 1 study and patient responses in clinical trials.

Results: The QSP model incorporated drug parameters estimated using different modeling platforms and was used to predict the magnitude of glucose response in healthy subjects and in patients with T2DM following treatment of Drug X (Figure 1) targeting one of many pathways in the model. The probability of detecting clinically meaningful response in Phase 1 in the two populations were estimated. Long-term HbA1c and weight response in Phase 2 were simulated over a range of PK and PD parameter values for potential drug candidates in each pathway to inform candidate screening criteria and Phase 1 trial design optimization.

Figure 1: QSP model predicted mean postprandial glucose response to Drug X (left) and the relationship between PK, PD and efficacy (right).

Conclusions: The integrated approach incorporating PK and PD parameters into a QSP model of diabetes is an efficient method to generate clinical responses from different patient populations for trial simulations. The approach maximizes the utility of information and increases cross-functional collaborations in drug discovery research.