Mathematical Modeling of Patient Response and Non-response to Therapy

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Objectives: For novel type 2 diabetes (T2D) drug candidates with promising Phase 1 data, later-stage trial subjects may differ significantly in baseline characteristics and thus may respond differently to therapy. In addition, uncertainty about drug candidate mechanism of action (MOA) may impact the ability to select patients most likely to respond. The purpose of this project was to provide insight into patient characteristics and drug MOA that impact response to therapy in Phase 2 and Phase 3 clinical trials.

Methods: Rosa and Takeda developed a T2D PhysioPD Platform, a quantitative mechanistic model of glucose, insulin, and lipid regulation. This Platform integrated published and proprietary data for TAK-875, a first-in-class GPR40 agonist that was being developed by Takeda. The Platform included a pharmacokinetic model for TAK-875 and a mechanistic representation of TAK-875 pharmacodynamic effects. A diverse cohort of Virtual Patients (VPs) representative of the baseline characteristics of Takeda human trial subjects was developed. The response to TAK-875 treatment was calibrated using Phase 1 clinical data. Subsequently, clinical trial PhysioPD simulations of Phase 2 and Phase 3 trials were conducted in the cohort of T2D VPs, and the results were compared to the clinical data.

Results: Simulation results were consistent with clinical observations across all trial phases and across multiple TAK-875 doses. Mechanistic analysis of the Platform suggested that the TAK-875 mode of action is primarily dependent upon an increase in insulin secretion and suppression of glucagon secretion. Patient beta cell function and insulin resistance at baseline were found to be the primary drivers of response to TAK-875.

Conclusions: PhysioPD Research provided an effective means of extrapolating early TAK-875 clinical trial results to predict late stage trial results in T2D patient populations with different degrees of T2D severity and other baseline characteristics. In addition, the T2D PhysioPD Research Platform helped provide insight into the TAK-875 MOA and patient characteristics most likely to impact efficacy.