Simulations of Dulaglutide Phase 3 Studies Using a Quantitative Systems Pharmacology Model of Diabetes

Jeanne Geiser¹, Lai San Tham², Zvonko Milicevic¹

¹Eli Lilly and company, Indianapolis, IN; ²Lilly-NUS Centre for Clinical Pharmacology, Singapore

Objectives: Evaluate quantitative systems pharmacology (QSP) metabolism model predictions for 2 trials of once-weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) dulaglutide conducted in type 2 diabetes (T2D) patients with different baseline disease states.

Methods: A QSP metabolism model of diabetes was developed that describes glucose and insulin fluxes following administration of GLP-1 RA or insulin glargine titrated based on target glucose. Two Phase 3 dulaglutide (DU) studies were simulated using virtual T2D patients (VP) with wide range of insulin secretion and sensitivity which were generated with baseline characteristics matched to the protocol criteria. Study A compared weekly DU to individually titrated daily GL in a 52 week trial [AWARD 2] [1]. Study B compared 1.5 mg QW DU to placebo as add-on to individually-titrated glargine. The predictive performance of the model was evaluated using the observed results from the completed trials.

Results: Study A (250 VPs, 8.1% mean baseline HbA1c) predicted a greater change of HbA1c for 1.5mg DU over GL, agreeing with the observed LS mean difference of -0.45%, 95% CI [-0.60%, -0.29%]. Study B (150 VPs, 8.4% mean baseline HbA1c) predicted a greater change in HbA1c with DU over placebo, agreeing with the observed LS mean difference of -0.77%, 95% CI [-0.97%, -0.56%]). The model predicted well for change in body weight and self-monitored blood glucose (SMBG). However, hypoglycemic event counts were overpredicted compared to the observed, although the difference between treatments was consistent with the observed. This may be attributed to differences between the continuous recording of glucose in simulations versus frequency of reporting in clinical settings.

Conclusions: This QSP model adequately predicted HbA1c, body weight, and SMBG in 2 DU Phase 3 trials in T2D patients for DU and GL. These results give greater confidence in using the model to evaluate alternative pharmacological agents, study designs and patient populations.

References: