Mechanistic Model based Assessment of PK/PD Critical Success Factors (CSF) for Next-Generation Ultra-fast Acting Insulins

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Objectives: Exogenously administered insulins aim to mimic the rapid onset of endogenous insulin response to hyperglycemia following meals. Subcutaneous fast-acting insulins are delayed by absorption-rate limited kinetics. To support the definition of “faster onset”, mechanistic PK/PD model-based assessments were conducted to identify the CSF for faster onset of insulin action.

Methods: A population PK model with physiological components (NONMEM 7.3) and a mechanistic model of glucose-insulin dynamics were developed based on published fast-acting meal-time insulin data. Model components were introduced to allow simulations of hypothetical “faster acting” insulins following different mechanisms of subcutaneous absorption. Simulations and sensitivity analyses were implemented in R and Physiolab®. A comprehensive list of PK and glucodynamic parameters were derived from the simulated profiles to evaluate a critical success factor of “> 20% faster”. Time related parameters (e.g., Tmax, Cmax, time to fraction of Tmax) and various fractional area-under-the-concentration (AUC) metrics were examined.

Results: Insulin plasma data were described by a two-compartment model. After subcutaneous administration, zero-order absorption commenced immediately and lasted for ~0.3 hour, followed by first-order absorption of the remaining fraction of dose (>90%). A relationship between body weight and volume of distribution was the only significant covariate detected. To explore hypothetical ultra-rapid insulins, the fraction and duration parameters were allowed to vary systematically based on the mechanism of action. Simulations supported the selection of time to 50% of Tmax and partial AUC in the first 15 to 30 minutes to represent the faster absorption.

The PD model-based simulation following meals with varying amounts of carbohydrate showed that the glucose AUC in the first 2 hours was a sensitive and relevant parameter to represent “faster onset” of action for comparative evaluation.

Conclusions: The PK/PD models described the time-action profiles of fast-acting insulin well. Simulations provided sample size recommendations to meet CSF for next generation fast-acting insulins with 20 to 50% faster absorption and onset of action.