Population Pharmacokinetics and Pharmacodynamics of an Oral Glucagon Receptor Antagonist (LY2409021) in Patients with Type 2 Diabetes Mellitus

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Objectives: LY2409021 is being investigated for the treatment of type 2 diabetes mellitus (T2DM). The objectives of the analyses were to describe the population pharmacokinetics (PK) of LY2409021, evaluate the factors influencing its PK, and quantify the exposure-response relationships for efficacy (fasting plasma glucose [FPG] and glycosylated hemoglobin [HbA1c]).

Methods: Data from a total of 373 healthy subjects and patients with T2DM (7 studies) were combined to develop the population PK model and investigate the effect of predefined covariates. Pharmacodynamic data (FPG and HbA1c) were available from a 24 week phase 2 dose ranging study (N = 264). This PK model was used to predict LY2409021 concentration in a PKPD model to describe the relationship between concentration, FPG and HbA1c simultaneously. All modeling was performed using NONMEM 7.3.0.

Results: A one-compartment model with first order absorption and elimination adequately described the pharmacokinetics of LY2409021. Body weight was the only significant predictor of clearance and volume. A linked indirect response model was used to describe the time course of FPG and HbA1c simultaneously. LY2409021 decreased FPG, with an EC\textsubscript{50} of 1186 ng/ml. Formation of HbA1c was linked to FPG through an indirect response model. The glucose-lowering effect of LY2409021 was constrained such that the HbA1c could not be reduced below a physiological threshold, estimated to be 5.7%. A time-dependent placebo effect on FPG and HbA1c was also included in the model.

Conclusions: A 20mg dose resulted in average steady state concentrations approximately 2-fold higher than EC\textsubscript{50} whilst the 10mg dose resulted in exposure around the EC\textsubscript{50}. Simulations revealed mean reduction in HbA1c of 0.9%-1.4% for doses between 10mg to 20mg and 0.1% for placebo after 26 weeks of treatment from a baseline of 8.0%. Therefore daily doses of 10mg to 20mg of LY2409021 would be effective in achieving clinically significant FPG and HbA1c reductions in patients with T2DM.