Population Pharmacokinetics and Pharmacodynamics (PK/PD) of Etelcalcetide for Secondary Hyperparathyroidism (sHPT) in Subjects with Chronic Kidney Disease (CKD) on Hemodialysis

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Objectives: Etelcalcetide is a novel calcium-sensing receptor (CaSR) activator currently in development for the treatment of sHPT. The objectives of this analysis were to develop a population PK/PD model relating etelcalcetide exposure to markers of efficacy (intact PTH, iPTH) and safety (corrected serum calcium, cCa); to evaluate covariate effects on PK/PD parameters; and to perform PK-PD simulations to support intravenous TIW administration of etelcalcetide.

Methods: Plasma etelcalcetide, serum iPTH and cCa concentration-time data were collected from 5 clinical studies including phase 1, 2, and 3 clinical trials following the administration of etelcalcetide as single or multiple intravenous doses (2.5 to 60 mg). Population PK/PD modeling of etelcalcetide was performed using NONMEM 7.2. A semi-mechanistic model, implementing allosteric activation, was used to describe the relationship between etelcalcetide, iPTH and cCa (Figure 1). Impact of relevant covariates (weight, sex, race, age, phosphorus, time on dialysis and vitamin D) was evaluated by stepwise forward/backward selection. Model evaluation was based on standard goodness-of-fit plots and prediction-corrected visual predictive checks (pcVPC).

Results: The exposure-response profiles between etelcalcetide, iPTH and cCa were well described by the model. Estimates of the turnover half-lives of iPTH and cCa were 0.36 hr and 23 hours, respectively. The estimated cooperativity constant to 3.41 confirming allosteric activation effects of etelcalcetide on CaSR. The extent of inter-individual variability in model parameters was low to moderate (6-67%). No covariates were identified as significant predictors of PD variability. pcVPC confirmed the predictive ability of the model. Simulations suggested that the titration algorithm is needed to provide effective PTH and minimal Ca lowering.

Conclusions: The current model incorporates the major components of the PTH-Ca homeostatic system, and describes the etelcalcetide allosteric activation effects of CaSR. Dose adjustment by relevant covariates was deemed unwarranted.

Figure 1: Semi-mechanistic PK/PD Model Structure

$K_{in,PTH}$ and $K_{out,PTH}$: the zero-order production rate of PTH and the first-order elimination rate constant for iPTH, respectively

$K_{in,Ca}$ and $K_{out,Ca}$: the zero order production rate of Ca and the first order elimination rate for Ca, respectively

$C_p$: the etelcalcetide plasma concentration

$V_1$, $V_2$ and $V_3$: central compartment, shallow and deep peripheral compartments, respectively