Population Pharmacokinetics and Pharmacodynamics (PK/PD) of AMG 416 in Chronic Kidney Subjects With Chronic Kidney Disease (CKD) and Secondary Hyperparathyroidism (sHPT) Receiving Hemodialysis

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Objectives: AMG 416 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 AMG 416 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 exploring the interplay between treatment and both markers.

Methods: Serum iPTH and cCa concentration-time data were collected from 3 clinical studies following the administration of AMG 416 as single or multiple intravenous doses (2.5 to 60 mg). Population PK/PD modeling of AMG 416 was performed using NONMEM 7.2. A semi-mechanistic model, implementing allosteric activation, was used to describe the relationship between AMG 416, iPTH and cCa (Figure 1). Impact of relevant covariates (weight, sex, race, age, phosphorus, time on dialysis and vitamin D) was evaluated using forward/backward selection. The model performance was evaluated using standard goodness-of-fit plots and prediction-corrected visual predictive checks (pcVPC).

Results: The interaction between AMG 416, iPTH and cCa was well described by the model. Estimates of turnover half-lives of iPTH and cCa were 0.25 hr and 21.66 hours, respectively. The estimated cooperativity constant was 4.94 confirming allosteric activation effects of AMG 416 on CaSR. The extent of inter-individual variability in model parameters was low to moderate (5-61%). No covariates were identified as significant predictors of PD variability. pcVPC confirmed the predictive ability of the model. Simulations suggested that at steady-state maximum AMG 416 concentration (72.11 ng/mL), mean CaSR occupancy was increased by approximately 10%, resulting in mean relative PTH suppression of approximately 60-70%.

Conclusions: The current model incorporates the major components of the PTH/Ca homeostatic system, and describes the AMG 416 allosteric activation effects of CaSR. Dose adjustment by relevant covariates was deemed unwarranted.
Figure 1. Semi-mechanistic PK/PD Model Structure

- **Compartment 1** ($V_1, C_1$)
- **Compartment 2** ($V_2, C_2$)
- **Compartment 3** ($V_3, C_3$)

**Equations and Parameters**

- $K_{in, iPTH}$ and $K_{out, iPTH}$: the zero-order production rate of PTH and the first-order elimination rate constant for iPTH, respectively
- $\rho_0$: the Ca/CaSR occupancy at baseline
- $\lambda$: a constant determining the strength of the effect of changes in $\rho$ on iPTH production
- $K_{in, Ca}$ and $K_{out, Ca}$: the zero order production rate of Ca and the first order elimination rate for Ca, respectively
- $S$: the slope relating changes in iPTH from baseline to Ca production
- $K_i$: the equilibrium dissociation constant for AMG 416 at the CaSR
- $K_D$: the equilibrium dissociation constant for Ca at the CaSR
- $\alpha$: the cooperativity constant
- $C_p$: the AMG 416 plasma concentration