Development of a Mega Population Pharmacokinetic (PK) Model of an Antibody-Drug Conjugate (ADC) Platform

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Objectives: ADCs developed using a platform share the same antibody technology: protease-labile linker and potent anti-cancer toxin. The similarity of ADC structures from this platform may result in comparable PK properties. The goal of this analysis was to develop a mega model that simultaneously describes antibody-conjugated toxin data from multiple ADCs in this platform, and assesses differences and similarities of PK parameters among different ADCs.

Methods: Clinical conjugated toxin data of multiple ADCs were obtained from several Phase 1 or 2 studies. Population PK models for each ADC were developed, and then various features of these models were combined in one mega model. A series of mega-models starting from the model that had all compound-specific parameters up to the model that had common parameters for all compounds were developed. Visual predictive checks (VPC) were used to assess ability of the models to predict PK for each ADC. Influences of body weight, gender, and dose on model parameters were evaluated.

Results: A unified model (two-compartment model with parallel time dependent clearance and Michaelis-Menten elimination, clearance and volume increasing with weight, and clearance mildly increasing with dose) described conjugated toxin PK of all ADCs. Michaelis-Menten elimination had only minor effect on PK. Time-dependence of clearance had no effect beyond the first dosing cycle. The model with all parameters except clearance shared by all ADCs provided reasonable conjugated toxin predictions and VPC plots for all ADCs. This model can be applied in the exposure-response analysis to evaluate key safety events in the future.

Conclusions: A developed population mega-model successfully described conjugated toxin PK of all ADCs. The model will be applied to predict properties of ADCs under development and propose optimal dosing regimens.