A population-based target-mediated drug disposition model to predict clinical pharmacokinetics of BMS-986090, an anti-CD40 antagonistic domain antibody

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Background: BMS-986090, a dimeric anti-human CD40 V\textsubscript{H} antagonist domain antibody formatted with a human IgG4 Fc tail (dAb-huIgG4), has been developed for the treatment of autoimmune-diseases. Because BMS-986090 does not cross react with monkey CD40, a surrogate anti-monkey CD40 dAb-huIgG4 (BMS-986091), which binds to cynomolgus monkey CD40 with similar affinity to that of BMS-986090 for human CD40, was prepared to facilitate preclinical characterization and subsequent clinical development of BMS-986090.

Objectives: The objective of this analysis was to develop a population-based target-mediated drug disposition model to predict pharmacokinetics of BMS-986090 in first-in-human (FIH) study.

Methods: The analysis included 288 samples of the plasma pharmacokinetics (PK) of BMS-986091 and 196 samples of CD40 receptor occupancy (RO) on peripheral-blood mononuclear cells (PBMC) from 16 cynomolgus monkeys. A two-compartment PK/RO model with first-order absorption and quasi-equilibrium (QE) approximation \textsuperscript{1} for target-mediated drug disposition (TMDD) \textsuperscript{2} was used to describe the observed non-linear PK and the corresponding RO across 3 dose levels (0.5, 5, or 50 mg/kg, subcutaneously or intravenously). The model-estimated parameters were subsequently scaled to predict human PK profile of BMS-986090 over a wide dose range (10-300 mg) in healthy subjects.

Results: The observed exposure and RO in monkeys at all dose levels were adequately described by the population-based QE-TMDD PK/RO model, as suggested by the goodness-of-fit (GOF) and dose-stratified visual predictive check (VPC) plots. The projected human concentration-time profiles of BMS-986090 aligned well with the observed profiles from healthy volunteers enrolled in the phase I study.

Conclusions: The population-based QE-TMDD PK/RO model successfully predicted human PK profiles of BMS-986090.