Two targets TMDD model described nonlinear pharmacokinetics of a bispecific antibody for Fibroblast Growth Factor Receptor 1/βKlotho Complex in humans

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Objectives: BFKB8488A is a bispecific antibody for membrane proteins Fibroblast Growth Factor Receptor 1 (FGFR1) and βKlotho (KLB) that has agonistic activity on the FGFR1/KLB receptor complex. In a single ascending dose (SAD) study in humans, BFKB8488A exhibited a more than dose-proportional increase in exposure after subcutaneous administrations. The objective of this work was to develop a target-mediated drug disposition (TMDD) model to describe nonlinear pharmacokinetics of BFKB8488A.

Methods: Plasma samples were collected from overweight but otherwise healthy individuals in the SAD study after subcutaneous (3 mg to 681 mg) and intravenous (45 mg) administrations. Intensive plasma concentration samples from 52 subjects were analyzed using non-linear mixed-effects modeling using NONMEM 7.3. Various structures of TMDD models were evaluated for their performances in explaining observed pharmacokinetic profiles.

Results: The complex pharmacokinetic profile of BFKB8488A was described with a two compartment model with TMDD. In a current model, subcutaneous absorption was described by two parallel pathways, and the TMDD component consists of two targets with the following approximations: (1) quasi-equilibrium approximation with no elimination to describe binding to one target and (2) Michaelis-Menten equation to describe elimination through the other target. The estimated binding constants (Kₐ) were similar for these two targets. On the other hand, the estimated inter-individual variability (IIV) of two targets was distinct from each other; total amount (Rₜₒₜ) of the first target had large IIV (CV~100%), while the inclusion of IIV on Vₘₐₓ of the second target did not improve the model fit. These results indicated that BFKB8488A may bind to two targets with similar binding characteristics but with different physiological distributions or expressions.

Conclusions: A two targets TMDD model successfully described the nonlinear pharmacokinetic profiles after a single administration of BFKB8488A. Further work will be needed to refine model structures with pharmacokinetic profiles after multiple administrations.