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Quantitative Systems Pharmacology Modeling to Evaluate Clinical Response of an anti-TNFa/anti-Ang2 Bispecific Antibody in Rheumatoid Arthritis

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BACKGROUND: Neovascularization in rheumatoid arthritis (RA) patients has been shown to associate with progression of disease. Increased expression of Angiopoietin-2 (Ang2) may contribute to disease maintenance and progression. An anti-TNFα/anti-Ang2 bispecific antibody (BsAb) was designed to provide the clinical effect of anti-TNF therapies with the additional benefit of neutralizing Ang2 in one single agent.

METHODS: Nonclinical pharmacokinetics (PK) and pharmacodynamics (PD) data following single or repeat-dose were collected from non-GLP and GLP studies in cynomolgus monkeys. PK and PD data were analyzed using Non-Compartmental Analysis (NCA) and a Target-Mediated Drug Disposition (TMDD) model. A quantitative systems pharmacology model (PhysioPD™ model) was constructed to integrate key features of RA pathophysiology with the pharmacological properties of an anti-TNFα approved in RA and the BsAb. The model was used to simulate the effects of the BsAb in virtual patients (VPs) representing relevant biology and explore different hypotheses about TNFα and Ang2 effects in the RA joint.

RESULTS: In cynomolgus monkeys the BsAb exhibited TMDD due to an Ang2 sink at doses lower than 3mg/kg. The RA PhysioPD model predicted that the BsAb has superior clinical response to golimumab in all VPs. VPs with the least anti-angiogenic response to anti-TNFα alone had the greatest additional clinical response from the addition of anti-Ang.

CONCLUSION: Using the RA PhysioPD model the anti-TNFα/anti-Ang2 bispecific antibody was predicted to provide greater clinical response compared to anti-TNFα alone. The RA PhysioPD model is a useful tool for understanding the dynamic interactions between different disease pathways and the effect on clinical outcome.