A Mechanistic PK-Target Occupancy Modeling Approach to Predicting Efficacious Human Dose for an Irreversible BTK Inhibitor
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Objectives: This study aims to develop a predictive model of an irreversible inhibitor of Bruton’s Tyrosine Kinase (BTK) that is known to be pathogenic in murine models of systemic lupus erythematosus (SLE), lupus nephritis (LN) and rheumatoid arthritis (RA) to facilitate the discovery of an efficacious and safe dose for treating human immune diseases.

Methods: A mechanism-based pharmacokinetic-target occupancy (PK-TO) model of a novel, highly selective, irreversible BTK inhibitor was developed based on non-clinical and clinical findings reported in the literature or generated in house. The model was trained with published clinical PK and TO data sets for ibrutinib and CC-292, and further validated with pre-clinical in-vivo observations for in-house compounds including a highly selective development candidate, BI-BTK-1.

Results: The PK-TO model was successfully utilized for identifying a high quality clinical candidate by providing projections of PK-TO profiles and efficacious dose in humans. The PK of BI-BTK-1 was characterized by a one-compartment model with a first-order oral absorption, moderate clearance, moderate volume of distribution and high bioavailability. The target occupancy dynamics was described by explicitly incorporating the irreversible binding mechanism of compound and target kinase along with target turnover into the model. From the model calibration using the reported clinical observations, the first-order half-life of human BTK was estimated to be 50h. The reverse translation of the model from human to mouse demonstrated that the predictions of target occupancy and efficacious dose in mice are in good agreement with in-vivo TO and PD measurements obtained independently, confirming the predictability of the human projection model. The model predicted that oral administration of BI-BTK-1 at 2 mg once a day can achieve a maximum target occupancy level of 95% in human exhibiting therapeutic efficacy.

Conclusions: The developed mechanistic PK-TO model was successfully integrated with the team strategy by providing a quantitative guidance on selecting a high quality clinical candidate for treating BTK-associated autoimmune diseases.