A Novel PK-Target Occupancy Link Model for a Covalent and Reversible Inhibitor of Bruton Tyrosine Kinase (BTK)

Dave RA, Smith P, and Karr D

1University at Buffalo, NY, 2D3 Medicine, NJ, 3Principia Biopharma, CA

Objectives: Bruton’s tyrosine kinase (BTK) is a key component of B cell receptor (BCR) signaling and functions as an important regulator of cell proliferation and cell survival in various B cell malignancies. Several small-molecule inhibitors of BTK have shown antitumor activity in animal models and, recently, in clinical studies [1, 2]. Ibrutinib, an irreversible covalent inhibitor, is currently the only FDA approved BTK inhibitor. PRN473 is a covalent and reversible inhibitor of BTK. The overall objective of this study was to develop a PK-BTK occupancy link modeling framework using the data for PRN473 in rats.

Methods: The model was developed using plasma concentration and splenocyte BTK occupancy data for 0.2-5 mg/kg IV and 10-30 mg/kg PO doses of PRN473 in rats. The model was validated using the data for 2 mg/kg IV dose. Plasma concentrations were best captured by a two-compartment model with first order-absorption and linear disposition kinetics. The BTK occupancy was best captured by a model incorporating BTK expression and turnover as well as drug-BTK binding parameters. ID algorithm in ADAPT5 was implemented for model development.

Results: The model was able to reasonably capture both, plasma concentrations and BTK occupancy data, for PRN473. The estimated elimination rate was 10 hr⁻¹, which is consistent with the in vitro evidence of high hepatic metabolism. The estimated values of $k_{on}$ and $k_{off}$ rates were 0.002 ((μg/L)⁻¹×hr⁻¹) and 0.00002 hr⁻¹, respectively. The residual variability in plasma concentrations and BTK occupancy was best described by a combined proportional and additive error model. The model was successfully validated as well.

Conclusion: We successfully developed a novel PK-BTK occupancy link modeling framework using the data for PRN473 in rats, which has application in evaluating PK-target occupancy relationships.

References: