Development of a Disease Model of Bruton’s Tyrosine Kinase (BTK) Inhibition by PRN473 in Rat Collagen-Induced Arthritis (rCIA)

Patrick F. Smith, Dane Karr, Angelina Bisconte, Ron Hill, David Goldstein, Phil Nunn, JO Funk

INTRODUCTION

- PRN473 is a novel inhibitor of Bruton’s Tyrosine Kinase (BTK), a key component of B-cell receptor signaling with potential clinical applications in oncology and autoimmune diseases
- PRN473 is a reversible covalent compound, which is highly selective for the enzyme target, with a long target residence time, and a rapid systemic clearance

RESULTS

- PRN473 was administered orally for 10 days to female Lewis rats with collagen-induced arthritis at doses of 0 (vehicle), 1, 3, 10, 20, and 30 mg/kg QD (n=8/group).
- BTK occupancy was measured in splenocytes at 0, 1, 6, and 12 hours post dose
- PK in animals (n=5/group) were measured at 0, 1, 6, and 12 hours post dose
- The primary measure of PD was the timecourse in rat ankle diameter (AD) changes.
- The PD model and initial parameter estimates were adapted from Liu, et al
- Modeling was conducted using ADAPT II software

- PRN473 demonstrated potent in vitro activity, with an IC50 of 1.8nM in biochemical assays and 8nM in Ramos cells, rapid clearance in animal species (equal to or greater than liver blood flow), and a slow target off-rate in cell based assays
- In the mouse and rat collagen-induced arthritis (CIA) models, PRN473 prevented or reversed the development of arthritis, achieving similar results to dexamethasone
- Our aim was to develop a disease model for PRN473, linking PK, BTK occupancy, and efficacy in the rat CIA model to inform human dose projections

METHODS

- PRN473 was administered orally for 10 days to female Lewis rats with collagen-induced arthritis at doses of 0 (vehicle) 1, 3, 10, 20, and 30 mg/kg QD (n=8/group).
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DISCUSSION

- PRN473 demonstrated potent activity in the rat CIA model
- Despite rapid clearance of plasma concentrations, PRN473 achieves a long duration of on target occupancy
- A 2-compartment PK model linked to an effect site adequately captured the timecourse and disconnect between PK and PD
- An indirect effects model with a transit compartment described the effect of receptor occupancy on ankle diameter changes
- Simulations (not shown) suggest that maintaining BTK occupancy of at least 70% at all times during a dosing interval is necessary to produce maximal drug activity
- This model formed the initial basis of a translational tool to estimate human therapeutic doses, and to select PD-targeted doses for proof-of-concept studies.

REFERENCES