Introduction

Bruton’s tyrosine kinase (BTK) plays a role in signaling pathways of the B-cell receptor, Fy receptor and Fc receptor on non-T cell white blood cells and eosinophils and thus represents an attractive target for autoimmune and inflammatory diseases. PRN1008 is a potent, oral, highly selective BTK inhibitor that targets cytokine through a reversible covalent interaction resulting in a slow off rate with prolonged inhibition of the target. PRN1008 has shown efficacy in a rat collagen induced arthritis model with trough BTK occupancy levels of 56% or higher, Prinicipia Biopharma Inc., is developing PRN1008 for the treatment of rheumatoid arthritis and other inflammatory diseases.

Objectives and Methods

Objectives: To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of PRN1008 in single ascending dose (SAD) and multiple ascending dose cohorts (MAD) in healthy, adult volunteers.

Methods: This first-in-human study consisted of two randomized, double-blind, placebo-controlled parts: Part A, 5 SAD cohorts (50-1200 mg) and in Part B, 4 MAD cohorts with 10 days treatment (300 mg and 600 mg QD, 300 mg and 600 mg BID). PRN1008 was administered as a liquid formulation in an inpatient facility. Safety was assessed clinically and by frequent ECG, vital sign and laboratory measurements. PRN1008 PD was assessed by BTK occupancy measured by a fluorescent probe assay.

Design Schematic

• Double blind, placebo controlled trial in 80 healthy volunteers
• Citric acid, liquid, oral formulation
• Evaluated PK, F0, BTK receptor occupancy, safety and tolerability

BTK Occupancy Assay

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Results

• PRN1008 was safe and well tolerated in both parts of the study without clinically significant changes in vital signs, ECG or laboratory measurements.
• In the MAD, treatment emergent adverse events (AEs) were reported by 50-88% of PRN1008-treated subjects, and 50% of placebo-treated subjects, with mild gastrointestinal AEs more common following PRN1008 vs. placebo.
• BTK occupancy ranged from 75% to 90% (mean ± SD) at four hours on day 1, and 84% to 91% at 24 hours on day 10. BTK occupancy declined slowly and persisted at 12 and 24 hours. BTK occupancy at trough (12 or 24 hours) on day 10 ranged from 59% to 80%, at which time plasma PRN1008 concentrations were negligible. A reduction of basal phosphatase activity of up to 73±14.6% (mean ± SD) was observed 4 hours after PRN1008 administration, consistent with BTK pathway inhibition in these cells.

Pharmacokinetics

• PRN1008 was rapidly absorbed following oral administration; maximal plasma concentrations ranged from 43 to 630 ng/mL, 1-2 hours after dosing on day 1 or day 10.
• PRN1008 exhibited approximately dose proportional PK at doses levels above 50 mg with modest PK variability; increases in dose from 600 mg to 1200 mg resulted in no further increase in exposure.
• The half-life of PRN1008 is approximately 3-4 hours, without significant accumulation following multiple dosing.
• Mean PK profiles for SAD (Figure 2) and MAD (Figure 3) are illustrated below:

BTK Occupancy Data

• Despite the fast plasma half life of PRN1008, the PD half life for BTK occupancy is prolonged, consistent with a slow target off-rate.
• Variability in BTK occupancy PD was very low, with intrasubject CV% at each time point 10% or less, suggesting low population variability and consistent PD response.
• The PK/PD profile at a dose of 600 mg QD is illustrated in Figure 6.

Sustained Occupancy Without Sustained Exposure

Safety Data

PRN1008 was safe and well tolerated without changes in vital sign, ECG or laboratory measurements, including LFTs, renal function, hematology, glucose and lipids. In the SAD (data not shown), adverse events were no more frequent than those in the placebo group until the 1200 mg dose level, where all subjects experienced some self-limited, mild or moderate gastrointestinal intolerance. A dose-related increase in gastrointestinal adverse events in both the SAD and MAD, where single doses of 1200 mg and multiple doses of 600 mg had the highest rates. At the dose of 300 mg BID, where BTK occupancy was maintained above 70% for 10 days, few treatment-related adverse events were reported.

Conclusions

PRN1008 was safe and well tolerated after single and multiple day dosing. BTK occupancy with a daily dose of ≥ 300 mg reached therapeutic levels with little variability compared with the variability seen in systemic exposure. These data support further development of the reversible covalent BTK inhibitor PRN1008 for the treatment of RA and other inflammatory and autoimmune diseases.

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