Mechanisms of Topical Bruton Tyrosine Kinase Inhibitor PRN473 in Immune-Mediated Skin Disease

Yan Xing, Katherine A. Chu, Jyoti Wadhwa, Wei Chen, Jiang Zhu, Jin Shu, Matthew C. Fouke, Natalie Loewenstein, Phillip Nunn, Kolbot By, Pasit Phisavongsa, David Goldstein, and Claire L. Langrish

Principia Biopharma Inc., A Sanofi Company, South San Francisco, CA, USA

INTRODUCTION

Bruton Tyrosine Kinase

• Bruton tyrosine kinase (BTK) is a promising target in immunology because of its expression in B cells and immune cells that have essential downstream signaling for B-cell receptor, Fc receptors, and other innate pathways (Figure 1).

Figure 1. BTK Plays a Critical Role in Innate and Adaptive Immunity

INNATE IMMUNITY ADAPTIVE IMMUNITY

• The role of innate immune cells is underappreciated in immune-mediated dermatological disease (Figure 2).

Figure 2. Multiple BTK-Dependent Cells Are Active in Skin Inflammation†

Systematic Pharmacology: BTK Occupancy

• BTK occupancy in whole blood

274 ± 95
IC50
0.25% PRN473
1% PRN473
ICG mast cell degranulation and β-hexaminidase release
1130 ± 510

• In vivo, PRN473 inhibited B-cell activation and FcR signaling in monocytes and mast cells, and in the absence of cytokines or effects and had functional effects on baseline, epidermal growth (Table 1).

Figure 6. Dose-Dependent Inhibition in IgE Antibody-Mediated Mouse Passive Cutaneous Anaphylaxis (PCA) With Single Application of PRN473

CONCLUSIONS

• Preclinical studies of PRN473 provide a strong biological basis for targeting skin innate immune cell responses with a rapid onset of action with once-daily topical administration and minimal systemic exposure

• PRN473 effectively inhibited IgG (FcγR) and IgE (FcεR) signaling equivalent to topical systemic accumulation, suggesting that localized exposure to PRN473 provided the major role for the efficacy (data not shown)

• Preclinical studies of topical BTK occupancy with single and multiday doses of topical PRN473 2% or with single application of PRN473 2% IgE PCA mouse model

• Topical BTK occupancy with multiday topical PRN473 2%-4% in the PCA mouse model

REFERENCES


ACKNOWLEDGMENTS

Principia Biopharma Inc., A Sanofi Company, South San Francisco, CA, USA. All studies were performed by the Authors. All efforts were made to ensure that all methodologies and materials were used appropriately and consistently for the research and development efforts.

DISCLOSURES

CORRESPONDING AUTHOR

Yan Xing, Ph.D., Head of Early Drug Development, Principia Biopharma Inc., A Sanofi Company, South San Francisco, CA, USA. Email: Yan.Xing@Principia.com

Presented at the 29th annual congress of the European Academy of Dermatology and Venerology (EADV) virtual from October 29-31, 2020