Development of a Psoriasis PhysioPD Platform to Evaluate a Novel Therapy and Identify Uncertainties Critical to Efficacy and Competitive Differentiation

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Objectives: To optimize the potential efficacy of a novel therapy for psoriasis and reduce risk for future stages of development by gaining new insights into the pathophysiology of psoriasis.

Methods: Using published and proprietary data, a PhysioPD Platform was built to mechanistically represent the pathophysiology of a single chronic psoriatic plaque. The Platform incorporated a comprehensive set of physiologic processes including: keratinocyte lifecycle and activation; recruitment and activation of immune cells; the production and downstream effects of a variety of cytokines and chemokines; and clinical outcomes related to the PASI score such as redness, scaliness, and epidermal thickness. The Platform was qualified against reported responses to various marketed therapies. Prospective simulations were conducted to evaluate the efficacy of the novel therapy and a sensitivity analysis was conducted to determine which pathways were most critical in regulating plaque healing. To evaluate the impact of target-related uncertainties within these pathways, Virtual Patients were created to define expected best- and worst-case scenarios. Treatment simulations on the Virtual Patients helped to rank the impact of individual uncertainties.

Results: Analysis in the PhysioPD Platform identified key uncertainties related to target expression in immune and skin cells, and to drug distribution and availability in the target tissue. This knowledge, along with the treatment simulations, confirmed that the therapeutic approach is promising and defined the specific conditions under which it would be superior to the standard of care. Analysis in the Platform also helped to identify three follow-up experiments that are the most critical for reducing risk throughout the development process.

Conclusions: Mechanistic modeling is a rigorous approach to understanding the pathophysiology of disease and the abundant biological variabilities that influence drug efficacy. Modeling Platforms are viable for evaluating early-stage drug candidates and reducing risk for late-stage development.