ASCPT Pre-conference Industry Case Study Proposal

Title: Mechanistic and quantitative physiological models for the evaluation and prioritization of dermatology disease targets

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Mechanistic physiological modeling, simulation, and analysis can provide a way to understand and evaluate the interactions between a disease and biological and pharmacological targets. We employed such a systemic approach to guide drug development decisions for repurposing assets for complex dermatologic conditions such as psoriasis, atopic dermatitis (AD) and acne.

As the first stage for a mechanistic model, we developed a biological disease **map** and included mechanisms of action of current standard of care drugs. A model qualification method system documented the design, testing criteria, uncertainties, and other inputs. Literature data were used to design and annotate the **map**, which was critically reviewed by research and development scientists and disease experts. The **map** was used to evaluate drug targets in disease pathways, potential interactions, and relative contributions to efficacy potential, thus informing and enabling the selection and prioritization of drug development targets. Early model development allows us to identify data gaps and biological uncertainties which need further exploration. The **map** provided the foundation for consolidation of historical data and knowledge as well as the basis for further development of quantitative models to evaluate pharmacodynamic endpoints and therapeutic potential.

The **map** for AD was developed into a quantitative pharmacodynamic model. The contributions of skin barrier function, pruritus pathway, and the immune response were integrated to reproduce the disease state and to allow evaluation of clinical endpoints in response to simulated treatments. A model qualification method system documented the design, testing criteria, uncertainties, and other inputs throughout this process as well. Literature data was critically reviewed by scientists and disease experts before being incorporated into the quantitative model.

Validation of the model included testing of this model against qualitative and quantitative data of current standard of care drugs in AD to ensure that appropriate clinical-level responses are reproduced. This type of physiological model will allow prediction of clinical effects due to modulation of different targets and support drug development decisions. Examples for drug development scenarios are ongoing and will be presented.

Keyword(s): systems biology, qualitative, quantitative, dermatology
Conflict of interest statement: EGK, EKH and WC are employees of Stiefel, TW and VD are employees of GSK, and CF and RB are employees of Rosa&Co.