A simulation study for clinical efficacy of an anti-ORAI1 antibody (DS-2741a) on atopic dermatitis using quantitative systems pharmacology (QSP) modeling for preclinical-to-clinical translation

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Introduction & Objectives

- Atopic dermatitis (AD) is a complex disorder characterized by immune-mediated skin inflammation and epidermal barrier dysfunction.
- ORAI1, a pore-forming subunit of calcium release-activated calcium (CRAC) channels, is essential for activation of T cells and other immune cells in AD.
- A novel humanized anti-ORAI1 antibody DS-2741a was developed to ameliorate AD by suppressing CRAC-mediated cell immune activation.
- Clinical efficacy in AD patients is difficult to predict from preclinical studies due to lack of mouse models relevant to clinical outcome.
- To overcome this translational gap, a QSP model was developed to assess the potential clinical efficacy of DS-2741a in virtual patients (VPs).
- Simulations of DS-2741a efficacy after s.c. dose were compared to dupilumab, an anti-IL-4 receptor antibody approved for AD treatment.

Materials & Methods

A mechanistic QSP model of AD was developed to evaluate the potential clinical efficacy of DS-2741a.

- The QSP model represents AD pathophysiology including keratinocyte, neuron and relevant immune cell and mediator dynamics, skin barrier function, clinical outcomes, and drug pharmacokinetics (PK) (Figure 1).
- The Eczema Area and Severity Index (EASI) score, a standard clinical outcome based on redness, thickness, scaling, and lichenification, was mechanistically associated with cells, cytokines, and biological functions (Figure 2).

Results: Model Qualification

- A cohort of VPs was created to span the range of EASI responses to dupilumab observed in clinical trials (Figure 3).
- A prevalence weighted virtual population (VPop) using this VP cohort reproduced the mean and distribution of EASI responses reported in Simpson 2016 (Figure 4).

Results: Simulations of DS-2741a Efficacy

DS-2741a is expected to be more efficacious than dupilumab

- Clinical trials of various doses of DS-2741a compared to 300 mg dupilumab QW or Q2W were simulated in the VPop (Figure 5).
- All doses of DS-2741a simulated showed superior efficacy compared to dupilumab.
  - Approximately 60% of the VPs treated with DS-2741a achieved EASI-90.
  - Response time was faster with DS-2741a compared to dupilumab.

Results: DS-2741a Differentiation

- While most VPs responded better to DS-2741a treatment than dupilumab, a few showed opposite behavior (Figure 6).
- VPs with stronger dupilumab responses had higher Th2-cytokines while VPs with stronger responses to DS-2741a had higher non-Th2 associated cytokine expression (Figure 7).
- Additional analysis further supported the strong contribution from non-Th2 cytokines in VPs with weak response to dupilumab (Figure 8).
- This is consistent with AD literature demonstrating a contribution of non-Th2 cells and cytokines to chronic AD pathophysiology4,5 (Figure 9).

Conclusions

- QSP modeling provided an early indication of the potential for DS-2741a as a novel therapeutic agent in AD.
- Simulations suggest that DS-2741a could show faster response and more efficacy than dupilumab in a broad spectrum of AD patients.
- QSP modeling and research was regarded in-house as an alternative investigation to preclinical animal model and was leveraged to prioritize the product toward clinical trial.

References:

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