Poster #662

Briquilimab, an Anti-Human c-Kit Antibody, Prevents Epicutaneous Oxazolone-Induced Features of Dermatitis in Mouse Model Expressing Chimeric Human/Mouse c-Kit

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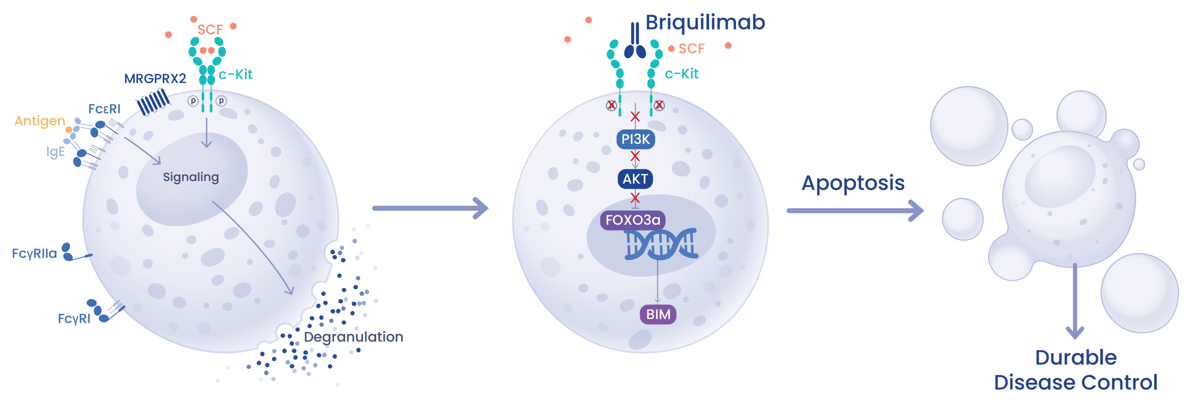
Background

Figure 1. Briquilimab mechanism of action.

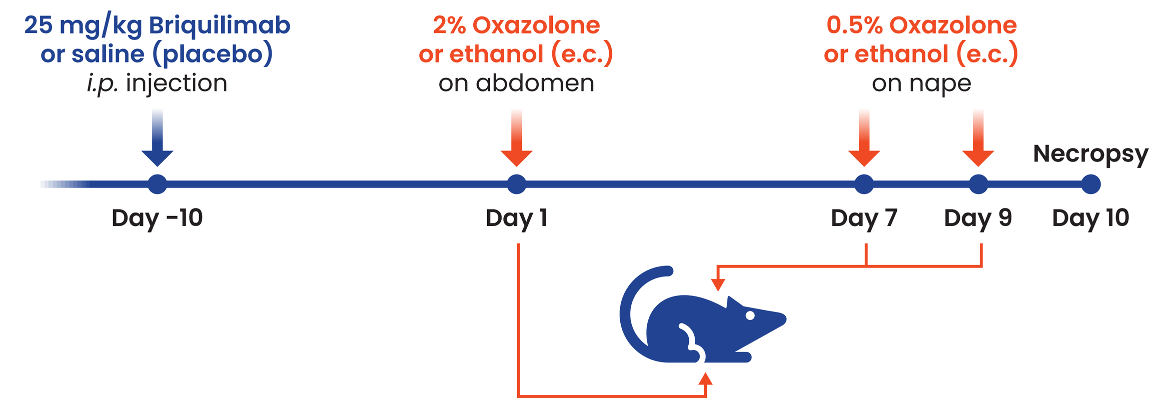


- Briquilimab is a humanized, aglycosylated, c-Kit (CD117) monoclonal antibody that functionally blocks the interaction of SCF and c-Kit, disrupting the critical signal needed for mast cell (MC) survival, leading to MC apoptosis (**Figure 1**).
- A single dose of briquilimab has previously been shown to effectively treat epicutaneous (*e.c.*) house dust mite and *Staphylococcal* enterotoxin B (HDM/SEB)-induced dermatitis in humanized h/mCD117 mice that express chimeric human/mouse CD117 through depletion of mast cells (MCs).
- Haptens, such as oxazolone, represent a distinct class of molecules compared to allergens, characterized by unique physical and chemical properties that enable them to covalently bind to skin proteins and elicit T-cell-mediated immune responses.
- MCs play a crucial role in amplifying and sustaining the inflammatory response by promoting immune cell recruitment, T-cell activation, and tissue damage.
- The present study employed an oxazolone-induced dermatitis model in h/mCD117 mice, to complement previous studies in allergen-induced models, for a comprehensive preclinical evaluation of briquilimab treatment.
- This approach enables the assessment of the versatility and effectiveness of briquilimab-mediated MC depletion in regulating diverse inflammatory pathways involved in skin disorders, thereby advancing its potential as a therapeutic agent across distinct mechanisms of dermatitis induction.

Methods

- In h/mCD117 mice, which express chimeric human extracellular and mouse intracellular domains of CD117, dermatitis was induced through abdominal epicutaneous (*e.c.*) sensitization with 2% oxazolone on day 1, followed by dorsal *e.c.* challenge with 0.5% oxazolone on days 7 and 9.
- Eleven days prior to sensitization, the mice received an intraperitoneal (*i.p.*) dose of either 25 mg/kg briquilimab or saline (placebo).
- A separate control group of h/mCD117 mice received *e.c.* vehicle ethanol instead of oxazolone on days 1, 7, and 9 and received either an *i.p.* dose of 25 mg/kg briquilimab or placebo 11 days prior to the first dermal ethanol application (day 1).

Figure 2. Experimental protocol.



The dermatitis model was induced by e.c. application of oxazolone on days 1, 7, and 9. Briquilimab or placebo treatment was administered 10 days prior to the first e.c. application of oxazolone or ethanol (vehicle control for oxazolone). Necropsy and tissue collection were conducted one day after the final e.c. application of oxazolone or vehicle ethanol.

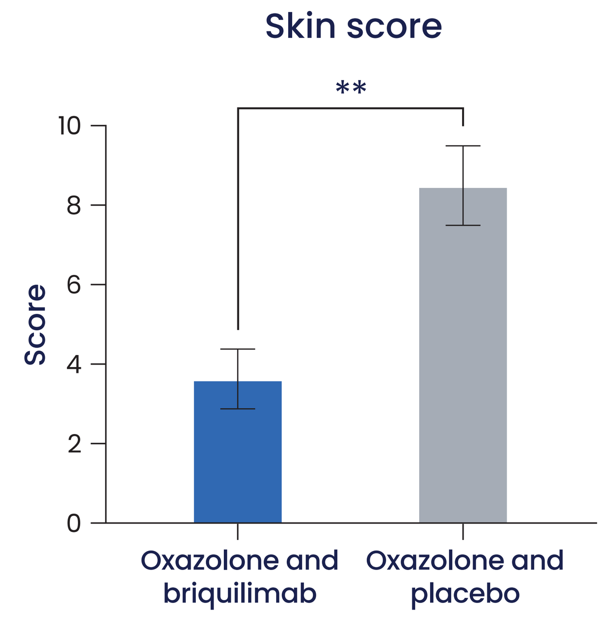
- Endpoint evaluations on day 10 included assessments of skin condition, dermal MC density, and inflammatory leukocyte infiltration (**Figure 2**).
- Skin condition was assessed by a trained observer using the following metrics: redness, bleeding, eruption, and scaling.
- Each metric was scored on a scale from 0 (none) to 3 (severe), and the scores were summed for each animal within experimental groups (briquilimab vs. placebo).
- Dorsal skin from each animal was collected, fixed in 10% formalin, embedded in paraffin, sectioned, and stained with toluidine blue for MCs and hematoxylin and eosin (H&E) for inflammatory leukocytes, respectively.
- The densities of MCs and inflammatory leukocytes were determined by imaging the sections and dividing cell counts within the field of view by the exposed area.
- Statistical comparisons between experimental groups for skin condition scores and leukocyte densities were performed using Welch's t-test.
- Comparison of MC densities were conducted using one-way ANOVA followed by Dunnett's test to account for the multiple comparisons.

Conclusions & Takeaways

- Mast cells play a critical role in the pathogenesis of hapten-induced dermatitis, including oxazolone-induced dermatitis.
- A single dose of briquilimab effectively depletes MCs in h/mCD117 mice that are healthy and that have epicutaneous oxazolone-induced dermatitis.
- Briquilimab's MC-depleting activity provides significant protection against the development of oxazolone-induced dermatitis in h/mCD117 mice.
- Briquilimab shows strong potential as a therapeutic agent for hapten-induced dermatitis by effectively targeting MCs.

Results

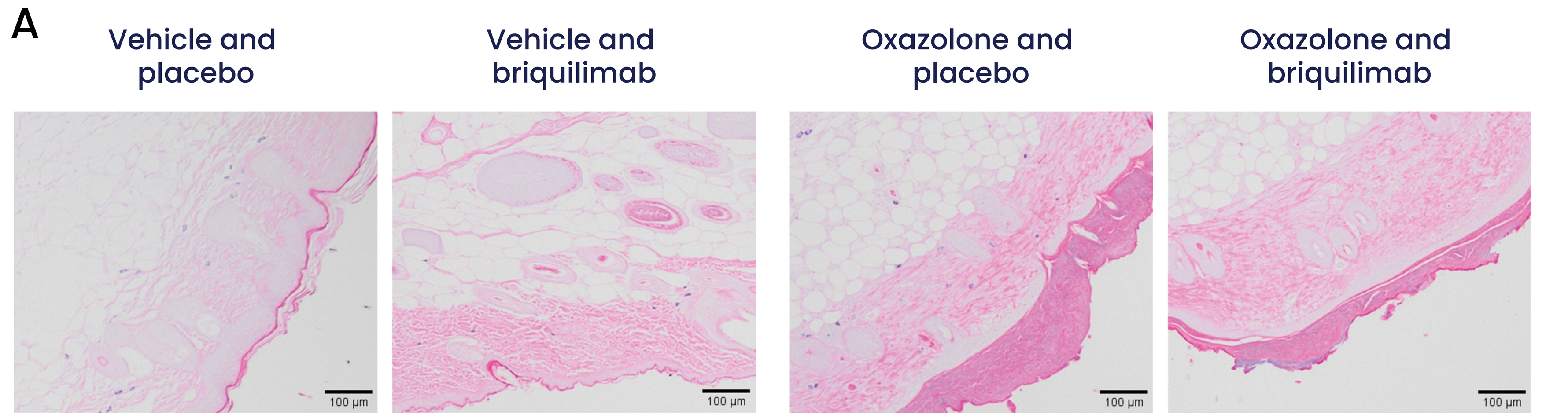
Figure 3. Effect of briquilimab treatment on skin condition in the oxazolone-induced dermatitis model in h/mCD117 mice.



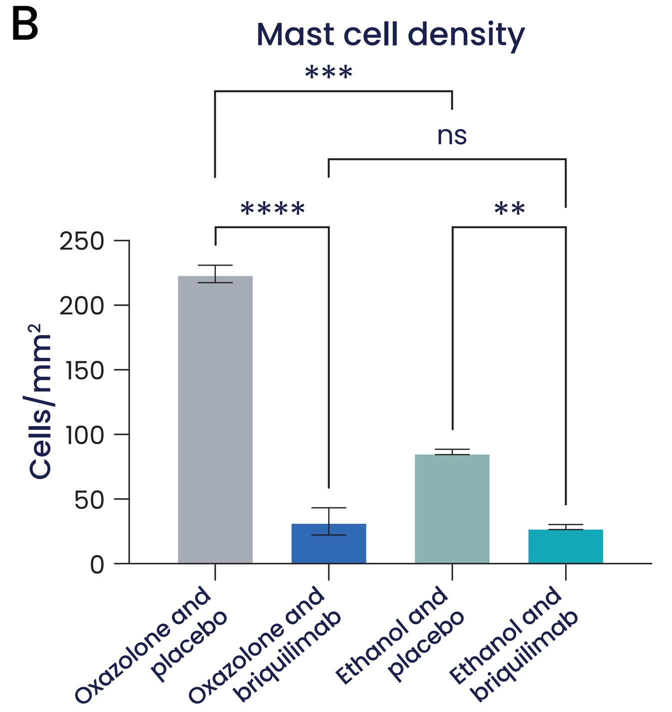
*Skin condition was assessed one day after the final e.c. application of oxazolone, with scores assigned for redness, bleeding, eruption, and scaling on a scale of 0 (none) to 3 (severe). ** P < 0.01 between the indicated groups; n = 3–4 per group.*

- Following *e.c.* exposure to oxazolone, briquilimab-treated mice exhibited significantly healthier skin, as indicated by markedly lower clinical scores (3.6 ± 0.8) compared to the placebo-treated group, which displayed more severe skin condition (clinical scores 8.5 ± 1.0, $P < 0.05$ vs. briquilimab-treated group, **Figure 3**)

Figure 4. Effect of briquilimab treatment on dermal mast cell counts in the oxazolone-induced dermatitis model in h/mCD117 mice.



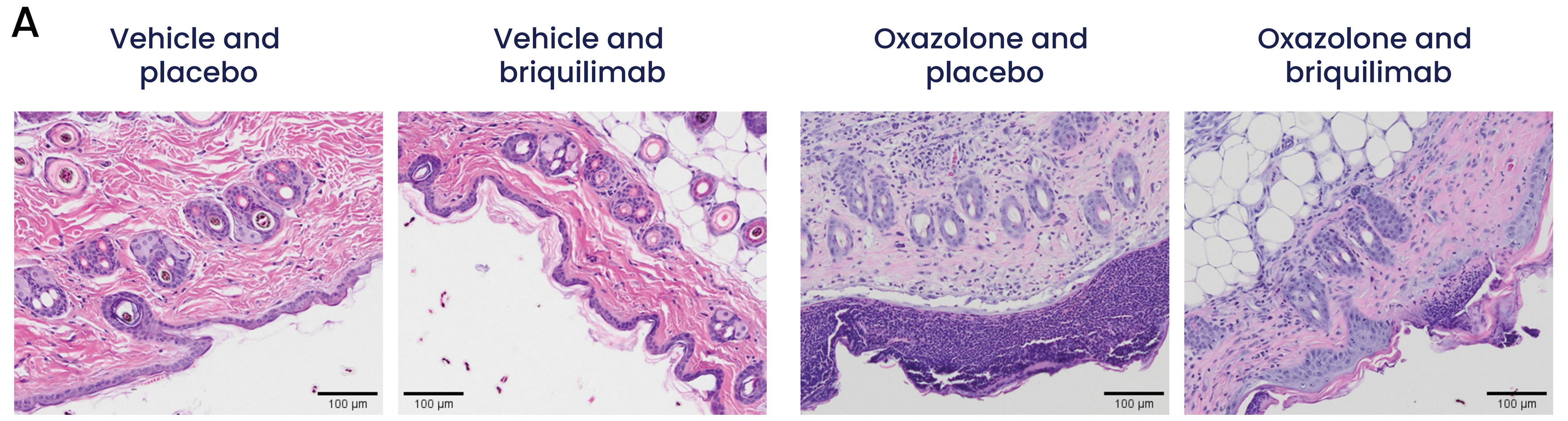
*(**A**) Representative images of toluidine blue-stained, formalin-fixed, paraffin-embedded tissue sections demonstrating dermal mast cells in the back skin one day after the final e.c. application of oxazolone or vehicle (ethanol). Scale bar = 100 um.*



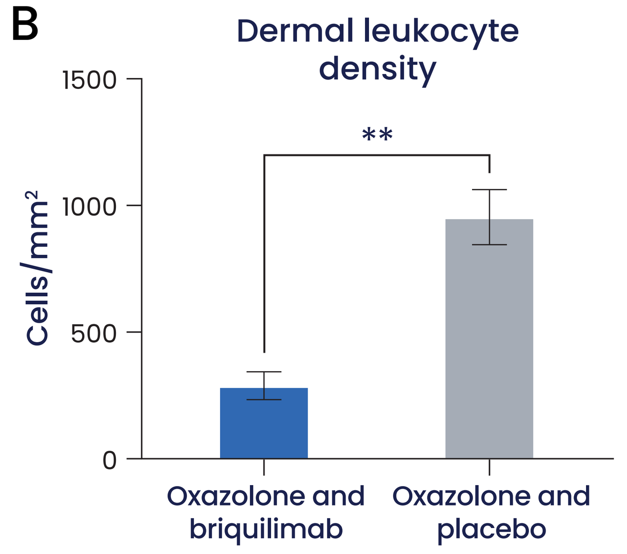
*(**B**) Quantification of dermal mast cell densities from toluidine blue-stained tissue sections. ns, not significant; **, ***, or **** P < 0.01, 0.005, or 0.001 between the indicated groups; n = 2–4 per group.*

- In control mice that received epicutaneous ethanol, briquilimab treatment significantly reduced dermal MC counts compared to the placebo treatment (28.3 ± 2.1 vs. 86.4 ± 2.2 cells/mm²; $P < 0.01$, **Figure 4**).
- Placebo-treated dermatitis models exhibited significantly elevated dermal MC counts compared to the ethanol vehicle mice that received placebo ($2.2 \pm 0.2 \times 10^2$ vs. 86.4 ± 2.2 cells/mm², $P < 0.005$).
- However, briquilimab-treated dermatitis models showed a significantly reduced dermal MC count (32.8 ± 10.6 cells/mm²) compared to placebo-treated dermatitis models ($P < 0.001$, **Figure 4**).

Figure 5. Effect of briquilimab treatment on dermal leukocyte infiltration in the oxazolone-induced dermatitis model in h/mCD117 mice.



*(**A**) Representative images of H&E-stained, formalin-fixed, paraffin-embedded tissue sections showing histological features and dermal leukocytes in the back skin one day after the final e.c. application of oxazolone or vehicle (ethanol). Scale bar = 100 um.*



*(**B**) Quantification of dermal leukocyte densities from H&E-stained tissue sections. ** P < 0.01 between the indicated groups; n = 3–4 per group.*

- Briquilimab treatment significantly reduced dermal leukocyte infiltration in the dorsal skin of oxazolone-induced dermatitis models, with leukocyte densities of $2.2 \pm 0.2 \times 10^2$ cells/mm², compared to substantially higher densities in the placebo-treated group ($9.5 \pm 1.1 \times 10^2$ cells/mm², **Figure 5**).
- This reduction highlights the potent anti-inflammatory effect of briquilimab and was statistically significant ($P < 0.01$).

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