Poster #690

Briquilimab, an Anti-Human CD117 (c-Kit) Antibody, Treats Low-Calcemic Vitamin D3 Analog MC903-Induced Dermatitis in Mouse Model Expressing Chimeric Human/Mouse CD117

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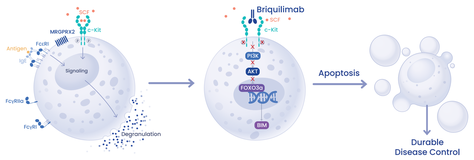
Introduction

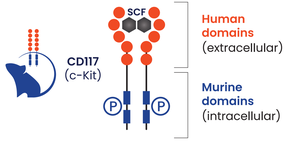
- Briquilimab is a humanized, aglycosylated, c-Kit (CD117) monoclonal antibody that blocks the SCF/c-Kit interaction, disrupting the critical signal for mast cell (MC) survival and inducing apoptosis.

Figure 1. Briquilimab mechanism of action.



- A single dose of briquilimab was previously shown to treat epicutaneous house dust mite and Staphylococcal enterotoxin B (HDM/SEB)-induced features of dermatitis in h/mCD117 mice, which express a chimeric extracellular human and intracellular mouse c-Kit (**Figure 2**), through MC depletion.

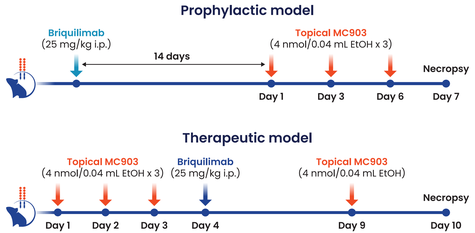
Figure 2. Chimeric CD117 (c-Kit) expressing human extracellular and mouse intracellular domains.



- MC903, a vitamin D3 analog, represents a distinct class of molecules compared to allergens, characterized by its ability to disrupt epidermal barrier function and trigger robust immune responses through keratinocyte activation and cytokine production, particularly thymic stromal lymphopoietin (TSLP).
- MC903-induced dermatitis murine models are used to replicate key features of dermatitis, with TSLP playing a pivotal role in initiating and amplifying the inflammatory cascade by activating dendritic cells and promoting T-cell differentiation.
- MCs further contribute to the inflammatory process by enhancing immune cell recruitment, amplifying cytokine signaling, and driving tissue damage.
- In the present study, we utilized MC903-induced dermatitis models in h/mCD117 mice to establish a robust preclinical framework for evaluating briquilimab treatment for dermatitis.

Methods

Figure 3. Schema of Prophylactic and Therapeutic models.



Prophylactic Model

- In h/mCD117 mice, dermatitis features were induced through epicutaneous (e.c.) application with 4 nmol MC903 in 0.04 mL ethanol to the back skin on days 1, 3, and 6.
- Fourteen days prior to the first MC903 application, the mice received an intraperitoneal (*i.p.*) dose of either 25 mg/kg briquilimab or saline (placebo).
- A separate control group received e.c. application of vehicle ethanol instead of MC903 on days 1, 3, and 6 and received an *i.p.* dose of either 25 mg/kg briquilimab or saline (placebo) 14 days prior to the first e.c. application of vehicle ethanol.
- Endpoint evaluations on day 7 included assessments of skin condition, dermal MC density, and inflammatory leukocyte infiltration (**Figure 3**, upper panel).

Therapeutic Model

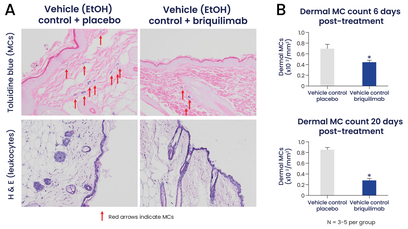
- In h/mCD117 mice, dermatitis features were induced through e.c. application with 4 nmol MC903 in 0.04 mL ethanol to the back skin on days 1, 2, and 3.
- On day 4, the mice received an *i.p.* dose of either 25 mg/kg briquilimab or saline (placebo).
- A separate control group received e.c. application of vehicle ethanol instead of MC903 on days 1, 2, and 3 and received an *i.p.* dose of 25 mg/kg briquilimab or placebo on day 4.
- On day 9, all groups received an additional e.c. application of MC903 or ethanol. Endpoint evaluations on day 10 included assessments of skin condition, dermal MC density, and inflammatory leukocyte infiltration (**Figure 3**, lower panel).

Endpoint Evaluations

- 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 the experimental groups (briquilimab vs. placebo).
- Dorsal skin specimens from each animal were 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 calculated by imaging the sections and dividing cell counts within the field of view by the exposed area.
- Statistical comparisons between the placebo and briquilimab-treated groups for skin condition scores and leukocyte densities were performed using Welch's t-test. MC density comparisons were analyzed using one-way ANOVA followed by Tukey's HSD test to account for multiple comparisons.

Results

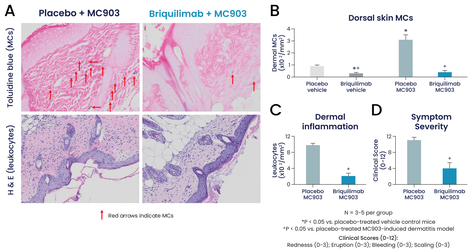
Figure 4. Briquilimab-mediated depletion of dermal mast cells.



- A single dose of briquilimab in control mice reduced dermal MCs by 36% at 6 days ($P < 0.05$ versus placebo-treated control mice).
- A single dose of briquilimab in control mice reduced dermal MCs by 67% at 20 days ($P < 0.05$ versus placebo-treated control mice).
- Representative images of toluidine blue-stained (upper panels) and H&E-stained (lower panels), formalin-fixed, paraffin-embedded tissue sections showing dermal MCs and histological features, respectively, in back skin 20 day after briquilimab or placebo treatment (**Figure 4A**).
- Quantification of dermal MC densities in toluidine blue-stained tissue sections at 6 days and 20 days following briquilimab or placebo treatment. * $P < 0.05$ briquilimab vs. placebo-treated vehicle control mice (**Figure 4B**).

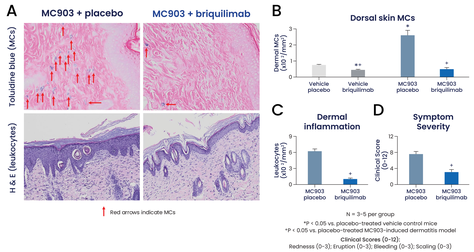
Results (cont.)

Figure 5. Prophylactic effect of briquilimab treatment on the MC903-induced dermatitis model in h/mCD117 mice.



- A single dose of briquilimab reduced dermal MCs by 67% at 20 days in vehicle control mice (no dermatitis).
- Dermatitis mouse models prophylactically treated with briquilimab exhibited significantly healthier skin, with reduced dermal MC and leukocyte densities compared to placebo-treated dermatitis mouse models.
- Representative images of toluidine blue-stained (upper panels) and H&E-stained (lower panels), formalin-fixed, paraffin-embedded tissue sections showing dermal MCs and leukocytes, respectively, in back skin 20 days after briquilimab or placebo treatment. Red arrows indicate mast cells (**Figure 5A**).
- Dermal mast cells densities in toluidine blue-stained tissue sections are shown in **Figure 5B** and dermal leukocyte densities in H&E-stained tissue sections are shown in **Figure 5C**.
- Skin condition was assessed one day after the final e.c. MC903 application, with scores assigned for redness, bleeding, eruption, and scaling on a scale of 0 (none) to 3 (severe) (**Figure 5D**).

Figure 6. Therapeutic effect of briquilimab treatment on MC903-induced dermatitis model in h/mCD117 mice.



- A single dose of briquilimab reduced dermal MCs by 36% at 6 days in vehicle control mice (no dermatitis).
- Dermatitis mouse models therapeutically treated with briquilimab exhibited significantly healthier skin, with reduced dermal MC and leukocytes densities compared to placebo-treated dermatitis model.
- Representative images of toluidine blue-stained (upper panels) and H&E-stained (lower panels), formalin-fixed, paraffin-embedded tissue sections showing dermal mast cells and leukocytes, respectively, in the back skin 6 day after briquilimab or placebo treatment. Red arrows indicate mast cells (**Figure 6A**).
- Dermal MC densities in toluidine blue-stained tissue sections are shown in **Figure 6B**, and dermal leukocyte densities in H&E-stained tissue sections are shown in **Figure 6C**.
- Skin condition was assessed one day after the final e.c. MC903 application, with scores assigned for redness, bleeding, eruption, and scaling on a scale of 0 (none) to 3 (severe) (**Figure 6D**).

Conclusions & Takeaways

- MCs play a critical role in the pathogenesis of MC903-induced skin conditions, which develop independently of specific allergen exposure.
- A single dose of briquilimab effectively depletes MCs in healthy mice as well as in dermatitis models induced by epicutaneous MC903 in h/mCD117 mice.
- Briquilimab-mediated MC depletion significantly contributes to both prophylactic and therapeutic effects in MC903-induced dermatitis models in h/mCD117 mice.
- Briquilimab shows potential as a therapeutic agent for targeting MCs in complex skin conditions driven by allergen-independent mechanisms, including TSLP-driven Th2-mediated dermal inflammation.

Acknowledgments

Stephen J. Galli and Judith Shizuru, Stanford University; Edwin Tucker, Daniel Adelman, Patricia Carlos, Ryan Taylor, Dheepika Weerasinghe, Hye-Sook Kwon, Kavitha Arulprakasam, and Anne Le, Jasper Therapeutics, Inc.

This poster was presented at the 2025 American Academy of Allergy, Asthma, and Immunology Conference, Feb 28 - Mar 3, San Diego, CA. Funding for this study was sponsored by Jasper Therapeutics, Inc.