Poster #540

Briquilimab, an Anti-c-Kit Antibody, Induces Durable Depletion of Mast Cells (MCs) Across Multiple Tissues in Mice Expressing Chimeric Human/Mouse CD117 (c-Kit)

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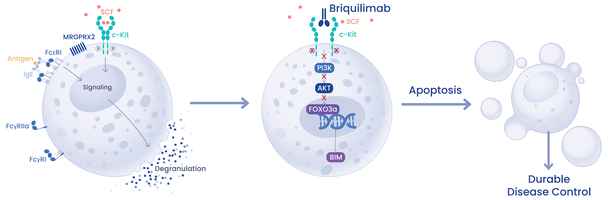
Introduction

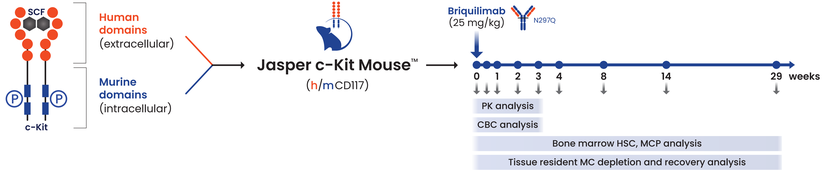
Figure 1. Briquilimab blocks SCF ligand-binding to c-Kit, inhibits SCF/c-Kit signaling, and induces MC apoptosis.

- Mast cells (MCs) are key players in many allergic and inflammatory diseases.
- Mast cell activation and survival relies on SCF/c-Kit signaling.
- Briquilimab, an aglycosylated humanized monoclonal anti-c-Kit antibody, inhibits MC development, function and survival by blocking SCF binding to c-Kit, thereby inhibiting SCF/c-Kit signaling.



Methods

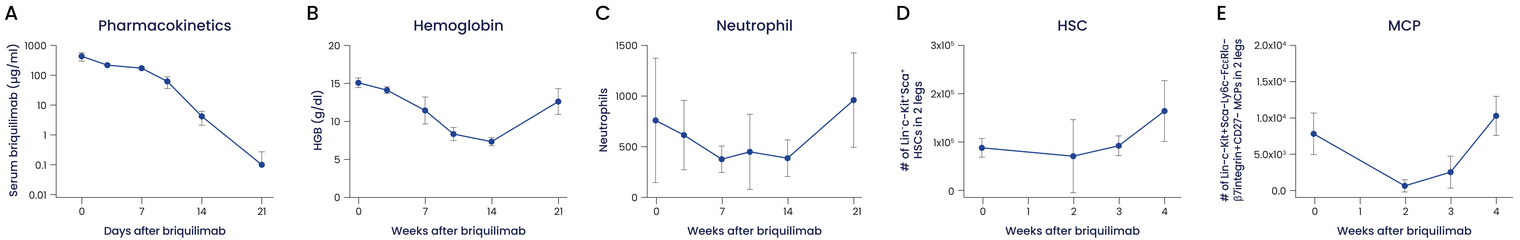
Figure 2. Experimental scheme using Jasper c-Kit Mouse™.



- We evaluated briquilimab's pharmacokinetics (PK) and pharmacodynamics (PD) as well as the kinetics of tissue-resident MC depletion and repopulation in Jasper c-Kit Mouse™ (human/mouse (h/m) CD117) mice, which express chimeric human extracellular/mouse intracellular c-Kit in lieu of wild-type mouse c-Kit (**Figure 2**).
- A single 25 mg/kg briquilimab (equivalent to 2 mg/kg human dose via body-surface area conversion) was intravenously administered into Jasper c-Kit (h/mCD117) mice.
- Pharmacokinetics (PK), complete blood cell (CBC) counts, frequencies of bone marrow (BM) hematopoietic stem cells (HSCs, Lineage$^-$cKit$^+$Sca$^+$) and MC progenitors (MCPs, Lineage$^-$cKit$^+$Sca$^-$Ly6c$^-$FcεRIα$^-$β7integrin$^+$CD27$^-$), and the kinetics of tissue-resident MC depletion and repopulation (by toluidine blue) were evaluated at indicated time points following briquilimab treatment.

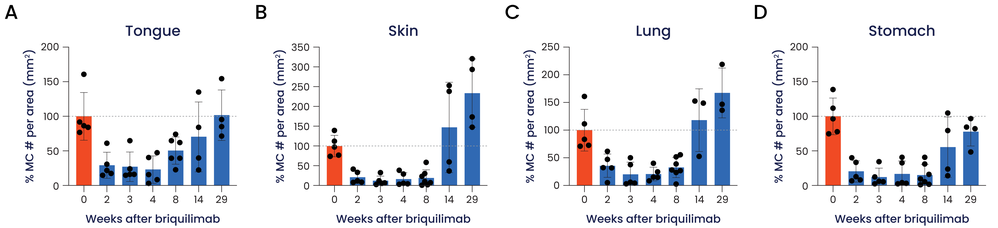
Results

Figure 3. Briquilimab exhibits transient and reversible effects on hematopoietic compartments in Jasper c-Kit Mouse™.



*(**A**) Briquilimab serum concentrations are below the lower limit of quantification (LLOQ, 0.02 µg/ml) by 3-4 weeks after a single IV dose administration at 25 mg/kg. (**B**) Blood hemoglobin and (**C**) neutrophil are transiently decreased and returned to baseline by 3 weeks post-briquilimab. (**D**) No significant decreases in BM HSC numbers are observed whereas (**E**) MCPs are decreased at 2 weeks but returned to baseline by 4 weeks post-briquilimab.*

Figure 4. Briquilimab depletes MCs across multiple tissues with variable MC repopulation kinetics.



*After a single IV dose of briquilimab at 25 mg/kg, significant reductions of MCs (>74%) are observed at 2-4 weeks post-briquilimab across multiple tissues, including (**A**) tongue, (**B**) skin, (**C**) lung and (**D**) stomach. Early evidence of MC repopulation was observed in the tongue starting at 8 weeks, skin, lung and stomach starting at 14 weeks post-briquilimab. At 29 weeks post-briquilimab, tongue, skin and lung MCs had returned to baseline levels in all mice; stomach MCs also had returned to baseline levels in 3 out of 4 mice. N = 3-7 mice per time point were analyzed.*

Conclusions

- Briquilimab's effects on the hematopoietic compartments are transient and reversible by 3-4 weeks post-treatment.
- Briquilimab induces rapid and deep MC depletion across multiple tissues, which appears sustainable up to 8-14 weeks.
- The rate of tissue MC repopulation to basal levels varies across tissues.
- These data suggest that briquilimab can induce rapid, deep, and durable MC depletion across multiple tissues, and offer insights into potential dosing intervals for MC-mediated diseases.
- The optimal biologic dosing, activity and safety of briquilimab are being explored in chronic spontaneous urticaria (CSU, NCT06162728) and chronic inducible urticaria (CIndU, NCT06353971). Briquilimab is also being evaluated in a proof-of-concept Phase 1b/2a allergic asthma challenge study (NCT06592768).

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.