Poster #541

Briquilimab Potently Inhibits Stem Cell Factor (SCF)/c-Kit Signaling and Induces Mast Cell Apoptosis

Song Eun Lee*, Hind Bouzid, Cheryl Kwan, Ajay Sharma, Andrea Romo, Iris Zhan, Mang Yu, Hye-Sook Kwon, Wendy W. Pang

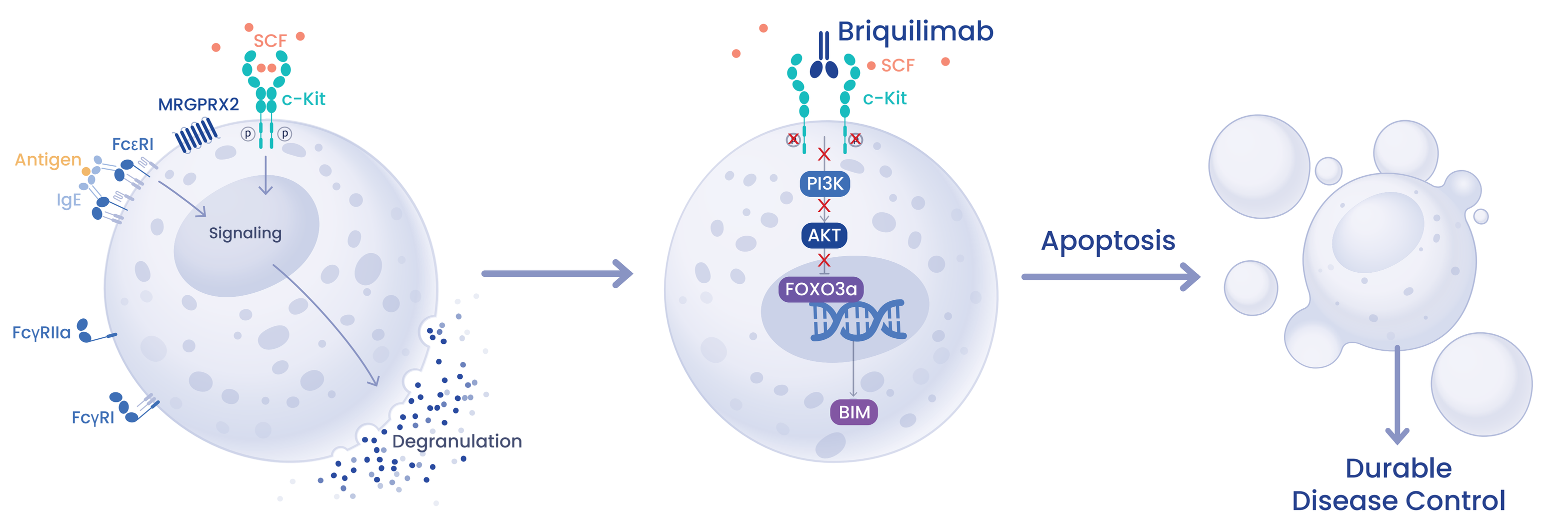
Jasper Therapeutics, Inc., Redwood City, CA USA

*Presenting Author

Introduction

- The activation and survival of mast cells (MCs) rely on SCF/c-Kit signaling.
- Briquilimab is a humanized aglycosylated monoclonal antibody (mAb) that binds to the SCF ligand-binding domain of c-Kit and blocks SCF binding to c-Kit, thereby inhibiting SCF/c-Kit signaling, leading to MC apoptosis.

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



Methods

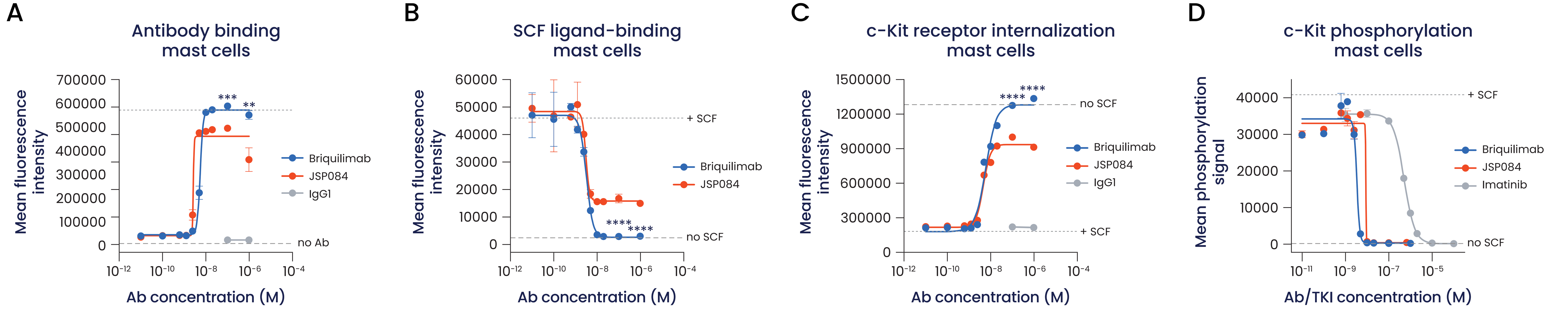
- Briquilimab's effects on MC survival/apoptosis signaling were evaluated in primary human MCs (CD34⁻FcεRI⁺c-Kit⁺) differentiated from mobilized peripheral blood CD34⁺ cells.
- Briquilimab was compared to a tool compound mAb that inhibits c-Kit dimerization (JSP084) and the small molecule multi-tyrosine kinase inhibitor, imatinib.

Conclusions

- Briquilimab's potent inhibition of SCF/c-Kit signaling and rapid induction of MC apoptosis may provide a promising novel treatment option 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).

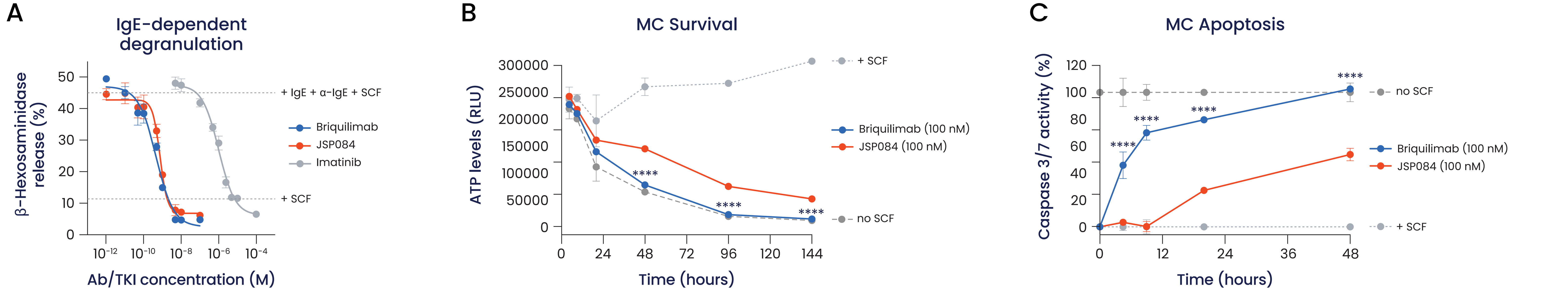
Results

Figure 2. Briquilimab potently and nearly completely inhibits SCF/c-Kit signaling in primary human MCs.



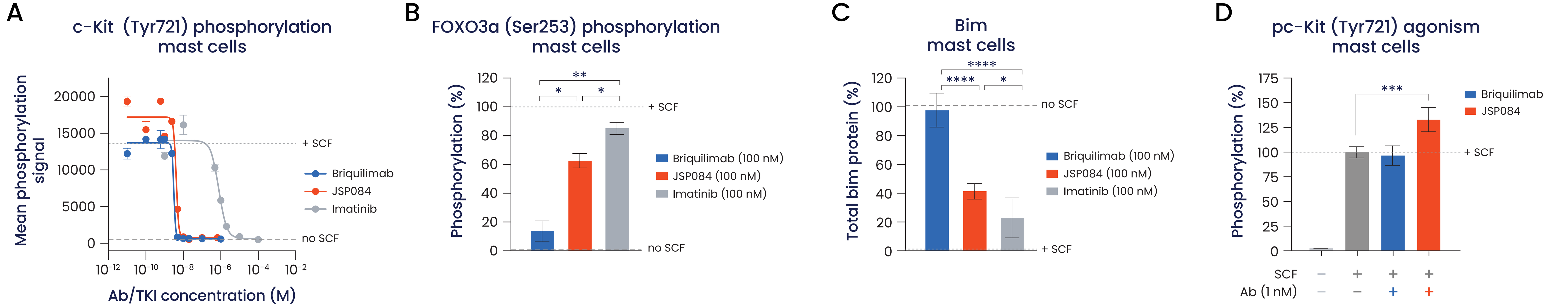
(**A**) *Briquilimab binds to more c-Kit than JSP084 in primary human MCs. Even at the highest concentrations evaluated, JSP084 binding to c-Kit does not fully reach the level of briquilimab (19.9% less than briquilimab).* (**B**) *Briquilimab nearly completely blocks SCF ligand-binding to c-Kit on MCs (98.4% blockade) while JSP084 only partially blocks SCF ligand-binding in MCs (69.5% blockade).* (**C**) *SCF-mediated c-Kit receptor internalization is more potently and completely inhibited by briquilimab than by JSP084 in MCs (38.4% less inhibition by JSP084).* (**D**) *Briquilimab inhibits SCF-dependent c-Kit phosphorylation at tyrosine residues more potently (IC_{50} = 3.4 nM) than JSP084 (IC_{50} = 8.8 nM, **P = .0018) and imatinib (IC_{50} = 507.1 nM, ***P = .0002) in MCs. All data are representative of n = 3-5 independent experiments and are shown as the mean ± SD. Asterisks on Figure 2A-C indicate statistically significant differences between briquilimab and JSP084 data at 100 nM and 1 µM concentrations, as determined by 2-way ANOVA. Significance levels are indicated as *P < .05; **P < .01; ***P < .001; ****P < .0001.*

Figure 3. Briquilimab potently inhibits MC degranulation and survival, and rapidly induces MC apoptosis.



(**A**) *Briquilimab more potently inhibits IgE/FcεR-dependent MC degranulation (IC_{50} = 331 pM) than JSP084 (IC_{50} = 615 pM, *P = .0484) and Imatinib (IC_{50} = 902 nM, **P = .00014), as measured by β-hexosaminidase release.* (**B**) *Briquilimab inhibits MC survival more potently than JSP084, as measured by ATP levels as an indicator of cell viability, which shows a decrease over time in the absence of SCF or presence of briquilimab and JSP084 together with SCF at 100 ng/ml.* (**C**) *Briquilimab more rapidly and potently induces MC apoptosis compared to JSP084 as measured by Caspase-3/7 activity, which increases over time upon addition of briquilimab and JSP084 despite the presence of SCF. All data are representative of n = 3-5 independent experiments and are shown as the mean ± SD. Asterisks on Figure 3B-C indicate statistically significant differences between briquilimab and JSP084 data at 100 nM and 1 µM concentrations, with significance levels indicated as **P < .01; ***P < .001; ****P < .0001, not as determined by 2-way ANOVA.*

Figure 4. Briquilimab induces MC apoptosis by inhibiting SCF/c-Kit/PI3K/Akt pathway without agonistic effect.



(**A**) *C-Kit phosphorylation at tyrosine residue 721 (Tyr721) is more potently inhibited by briquilimab (IC_{50} = 3.1 nM) compared to JSP084 (IC_{50} = 4.2 nM, *P = .0451) and imatinib (IC_{50} = 797.9 nM, **P = .0076).* (**B**) *Phosphorylation of FOXO3a, a target downstream transcription factor of SCF/c-Kit/PI3/Akt signaling, at serine residue 253 (Ser253) is more potently inhibited by briquilimab (86.3% inhibition) than JSP084 (37.3% inhibition) and Imatinib (11.8% inhibition) at 100 nM concentration.* (**C**) *Briquilimab more potently and nearly completely induces accumulation of pro-apoptotic protein Bim levels (97.6% of the total Bim level observed in the no SCF control) than JSP084 and imatinib (41.5% and 23.1% of the total Bim level observed in the no SCF control, respectively).* (**D**) *At lower concentrations of 1 nM or below, JSP084 appears to be agonistic for c-Kit phosphorylation at Tyr721 in primary human MCs. All data are representative of n = 3-5 independent experiments and are shown as the mean ± SD. Significant differences between groups were determined by a two-tailed Student's t-test, with significance levels indicated as *P < .05; **P < .01; ***P < .001; ****P < .0001.*

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.