Initial Results from BEACON, a Phase 1b/2a Dose Escalation Study of the anti-c-Kit Briquilimab Antibody in Adults with Chronic Spontaneous Urticaria

Thomas Casale[1], Edwin Tucker[2], Jinwei Yuan[2], Daniel Adelman[2], David Ku[2], Annette Marcantonio[2], Patricia Carlos[2], Sophia R. Majeed[2], Wendy W, Pang[2], Martin Metz[3]

1. Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL, USA
2. Jasper Therapeutics, Redwood City, CA, USA
3. Institute of Allergology, Charité-Universitätsmedizin Berlin, Germany

Conflict of Interest Statement

Dr. Tom Casale has received honoraria as a speaker and/or advisor for Genentech, Sanofi, Novartis, Regeneron, Celldex, Jasper Therapeutics, Eli Lilly, and FARE, and has received research grants from Novartis, Genentech, Sanofi, Regeneron, Escient, Leo, Alakos, DBV, Jasper Therapeutics and Celldex.

Background

- Chronic spontaneous urticaria (CSU) is a mast-cell driven, recurring inflammatory skin condition lasting ≥ 6 weeks, with itchy wheals (hives), angioedema, or both.

- c-Kit receptor signaling, driven by stem cell factor (SCF), is an important regulator of mast cell survival, making it a potential therapeutic target for CSU.

- Briquilimab is a humanized, aglycosylated, anti-c-Kit antibody that directly blocks the SCF binding site on c-Kit, leading to c-Kit/ SCF signal inhibition and mast cell apoptosis.

- We report the preliminary results from the Phase 1b/2a randomized, double blind, placebo-controlled multiple ascending dose clinical study of subcutaneous briquilimab in participants with moderate to severe CSU who are symptomatic despite H1 antihistamines and omalizumab.

Phase 1b/2a BEACON Study in Chronic Spontaneous Urticaria

Randomized, double-blind, placebo-controlled, multiple ascending dose study (NCT 06162728)

Screening/Eligibility
- CSU diagnosis ≥ 6 mos.
- UAS7 ≥ 16
- 18+ years
- H1-antihistamine-failed
- Inadequate response to omalizumab**

Study Operations
- **US Lead:** Tom Casale, MD
- **EU Lead:** Martin Metz, MD
- ~30 sites in the US & EU

Key Assessments
- **Disease Scores:** UAS7, UCT
- **Safety:** TEAEs, SAEs
- **Pharmacokinetics**
- **Mast Cell Depletion & Recovery:** Serum Tryptase, Skin Biopsies

	Dose	Patients (Randomization)	Schedule
Open Label (n=6)	10mg	n=3+3	Weeks 0, 4, 12, 20
	40mg	n=3+3	
Double-Blind Placebo-Controlled (n=71)	80mg	n=8 (3:1)	Q8W
	120mg	n=6 (2:1)	Q8W
		n=6 (2:1)	Q12W
	180mg	n=10 (3:1)	Q8W
		n=9 (3:1)	Q12W
	240mg	n=4* (3:1)	Single Dose
	240mg → 180mg**	n=8** (3:1)	Q8W
	240mg**	n=8** (3:1)	Q8W
	360mg	n=8* (3:1)	Single Dose

Note: *Expanding 240 mg and 360 mg SD cohorts to 8 participants each; **Enrolling omalizumab-naïve participants with CSU.

Briquilimab is an investigative drug and is not approved for any indication.

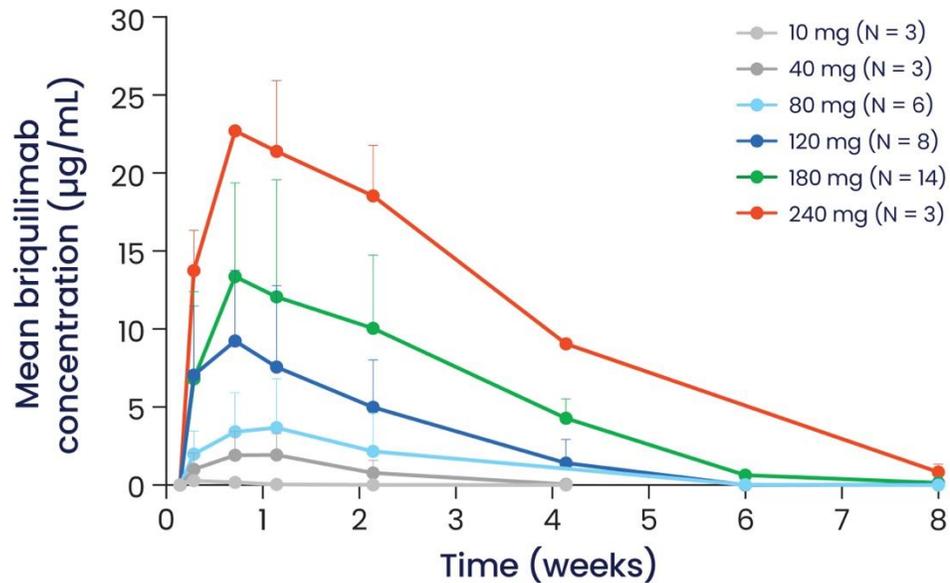# Baseline Demographics and Disease Characteristics

	Pooled Briquilimab (N=37)	Pooled placebo (N=12)
Age (years), median (range)	41 (18-82)	39 (26-60)
Female Sex, n (%)	24 (65%)	10 (83%)
BMI, median (range)	28 (22-50)	27 (24-42)
UAS7 (0-42), mean (SD)	27.3 (8.2)	28.6 (9.4)
UCT (0-16), mean (SD)	3.8 (2.3)	3.7 (3.6)
Serum tryptase (ng/mL), mean (SD)	6.7 (3.4)	8.1 (4.7)

- All participants were refractory or intolerant to omalizumab, representing a CSU population of highest unmet medical need.

Briquilimab Demonstrates Rapid T_{max} and High C_{max} and Rapid, Dose-dependent Reductions in Serum Tryptase
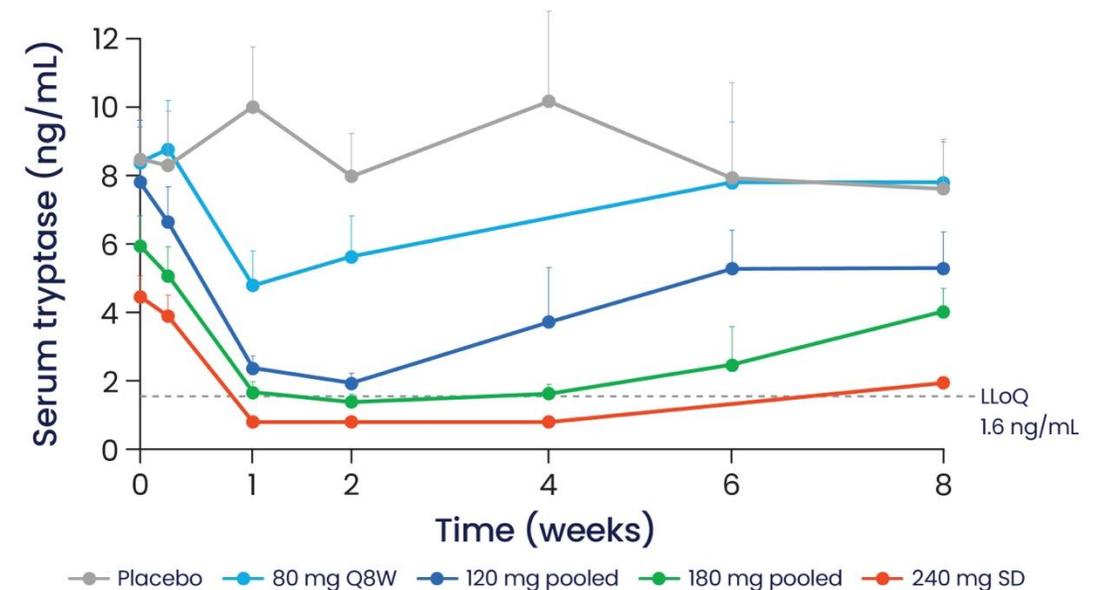
Consistent with Early Onset of Clinical Responses in CSU Patients

Briquilimab serum concentration over time in CSU patients following subcutaneous (SC) administration

Legend:
- 10 mg (N = 3)
- 40 mg (N = 3)
- 80 mg (N = 6)
- 120 mg (N = 8)
- 180 mg (N = 14)
- 240 mg (N = 3)

Serum Tryptase over time in CSU patients

LLoQ 1.6 ng/mL

Legend:
- Placebo
- 80 mg Q8W
- 120 mg pooled
- 180 mg pooled
- 240 mg SD

Note: *All values below LLOQ (1.6 ng/ml) are represented as 50% of LLOQ (0.8 ng/ml); Data cut-off 31 Jan 2025

- 240 mg briquilimab SC T_{max} is 4-7 days with a half-life of approximately 9 days

- Reduction below LLOQ in all 240 mg participants and in 57% of 180 mg participants by Week 2

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Primary Efficacy Analysis of 80, 120 and 180 mg Q8W Cohorts
75% WC disease observed at 12 weeks – 4 weeks post second dose

Week 12	80 mg Q8W (N=6)	120 mg Q8W (N=4)	180 mg Q8W (N=7)	Pooled placebo (N=12)[1]
Mean (SE) UAS7 at Week 12	21.7 (7.2)	2.7 (2.7)	9.9 (4.8)	19.5 (4.0)
Mean (SE) UAS7 change from baseline at Week 12	-9.3 (5.8)	-27.2 (3.9)	-15.1 (4.7)	-9.2 (3.6)
Complete response (CR) rate[2,3]	17%	50%	43%	8%
Well controlled rate[3]	33%	75%	43%	8%

1. 50% of participants in the pooled placebo group utilized rescue medications, including steroids during the study.
2. Median time to first dose CR <3 weeks (pooled 120mg, 180mg)
3. Last observation carried forward (LOCF) method was applied for missing data.

Primary Efficacy Analysis of 120 and 180 mg Q12W Cohorts

## 75% WC disease observed at 16 weeks - 4 weeks post second dose

Week 16	120 mg Q12W (N=4)	180 mg Q12W (N=7)	Pooled placebo (N=12)[1]
Mean (SE) UAS7 at Week 16	0.5 (0.5)	7.2 (4.9)	15.6 (4.5)
Mean (SE) UAS7 change from baseline at Week 16	-29.8 (6.9)	-21.7 (6.5)	-13 (3.2)
Complete response (CR) rate[2,3]	50%	57%	17%
Well controlled rate[3]	75%	57%	33%

1. 50% of participants in the pooled placebo group utilized rescue medications, including steroids during the study.
2. Median time to first dose CR <3 weeks (pooled 120mg, 180mg)
3. Last observation carried forward (LOCF) method was applied for missing data
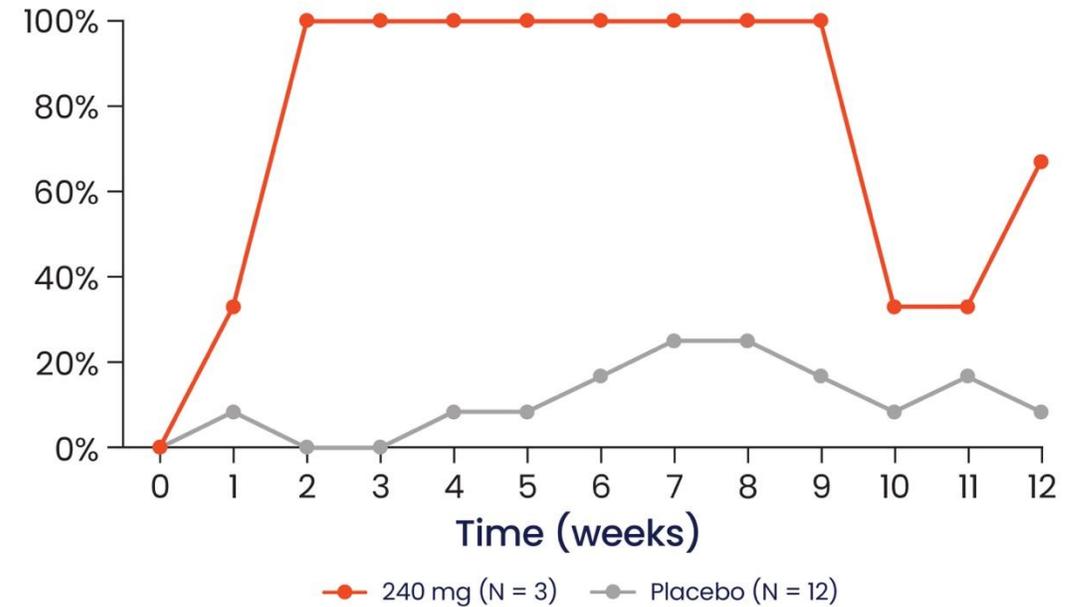
Primary Efficacy Analysis of 240mg Single Dose Cohort
Mean baseline UAS7=26.6; Mean week 2 UAS7=0

Complete response
Weeks 1-12 (UAS7 = 0)
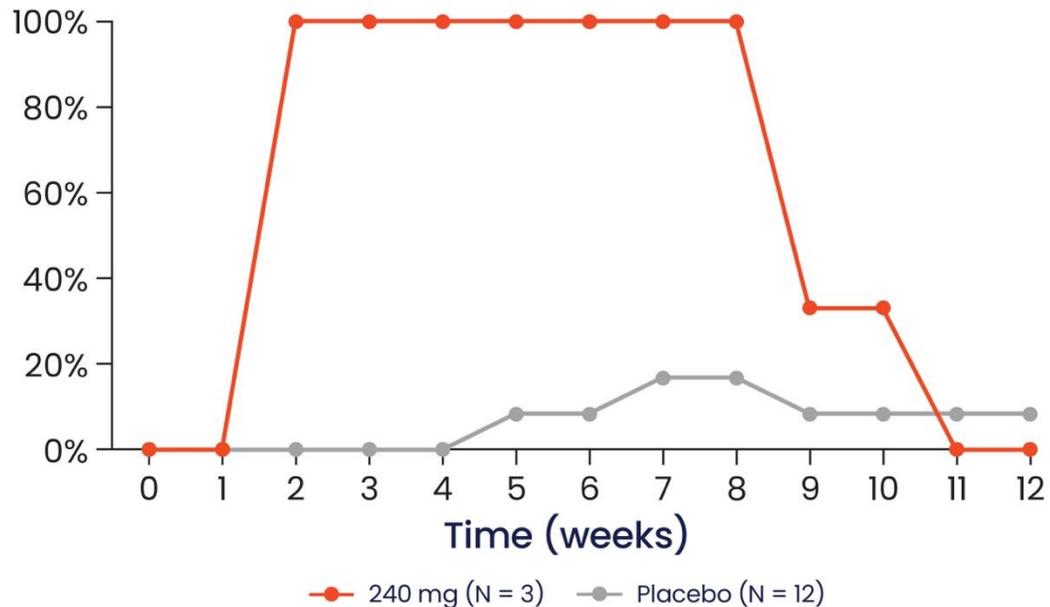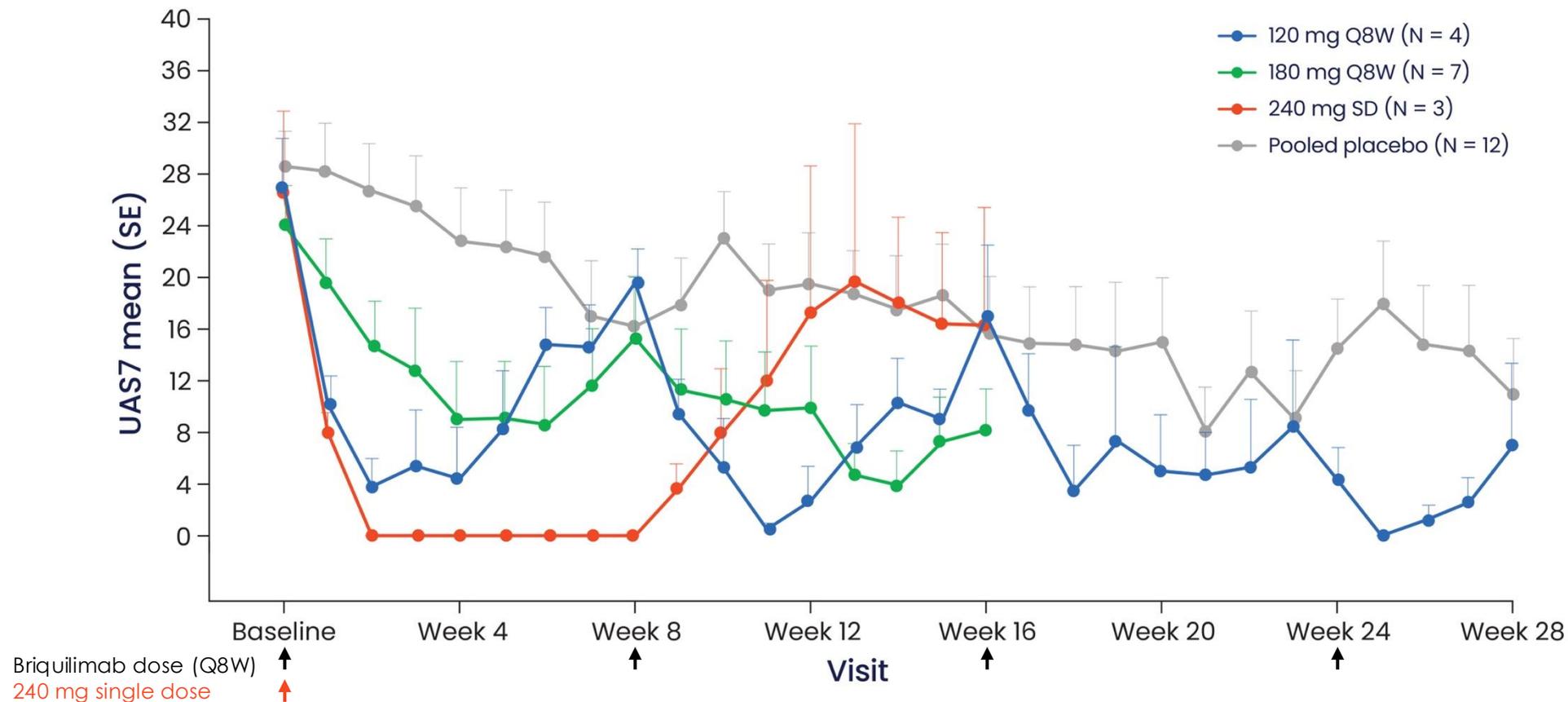
Well controlled
Weeks 1-12 (UAS7 $\leq$ 6)

Note: Data cut-off 31 Jan 2025

Dose Dependent UAS7 Reductions Observed Over 28-Week Treatment Period

Deeper UAS7 reductions observed in subsequent doses

Note: 1. 50% of participants in the pooled placebo group utilized rescue medications, including steroids during the study; Data cut-off 31 Jan 2025.

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Briquilimab Demonstrated a Favorable Safety Profile

28-week exposure for 10 mg – 180 mg doses as of 31Jan25

Number of participants with:	Pooled briquilimab N=37 (n, %)	Pooled placebo N=12 (n, %)
Any DLT	0 (0)	0 (0)
Any TEAE	27 (73.0)	8 (66.7)
Any treatment-related serious TEAE	1 (2.7)[1]	0 (0)
Any hypersensitivity	1 (2.7)[1]	0 (0)
Any TEAE leading to discontinuation of IP	1 (2.7)[1]	0 (0)
Any anaphylaxis	0 (0)	0 (0)
Adverse event ≥ Grade 3	1 (2.7)[2]	1 (8.3)[3]

Note: Most commonly reported AEs (≥5 participants): nasopharyngitis, fatigue, hair color change, taste changes; **1.** Single participant, 180 mg Q8W, CoFAR grade 2 hypersensitivity reaction; **2.** Single participant, 180 mg Q12W, CTCAE grade 3 AE: neutropenia, unrelated - prior history of idiopathic neutropenia, thrombocytopenia; **3.** Single participant, placebo, CTCAE grade 3 bronchitis

Safety Observations Possibly Related to c-Kit Blockade were Infrequent and Generally Limited to Grade 1 Events

Majority resolved during repeat dosing and none resulted in discontinuations or dose delays

Adverse event	Pooled briquilimab N = 37 (n, %)	Pooled placebo N = 12 (n, %)	CTCAE Grade / comments
Hair color changes	4 (10.8)	1 (8.3)	• All reported as Grade 1. • 2 cases reported to be resolved/resolving on treatment. • 1 at 80 mg, 1 at 120 mg, 2 at 180 mg and 0 at 240 mg.
Skin discoloration	0 (0)	1 (8.3)	• No skin discoloration observed with patient exposure up to 28 weeks.
Taste change/ Hypogeusia	6 (16.2)	0 (0.0)	• All mild, Grade 1 occurring on first dose, 2 recurrences (resolved). • Taste reductions: bitter, salt, umami. • Resolved in 5 participants: Median time to resolution of 31 days. • 1 at 80 mg, 1 at 120 mg, 1 at 180 mg and 3 at 240 mg.
Neutropenia / Neutrophil count decreased	5 (13.5)	1 (8.3)	• All resolved while on therapy prior to subsequent dose. • Grade 3 neutropenia in a single participant with prior history of idiopathic neutropenia and thrombocytopenia, resolved on therapy. • Grade 1 neutropenia/neutrophil count decrease in 5 participants, all resolved on therapy. • No associated fevers or infections. • 0 at 80 mg, 2 at 120 mg, 2 at 180 mg and 1 at 240 mg.

Note: Data cut-off 31Jan2025.

Neutrophil Counts Generally Remained Stable, with Predictable Reduction Which Subsequently Resolved

No discontinuations or dose delays due to reductions in neutrophil counts
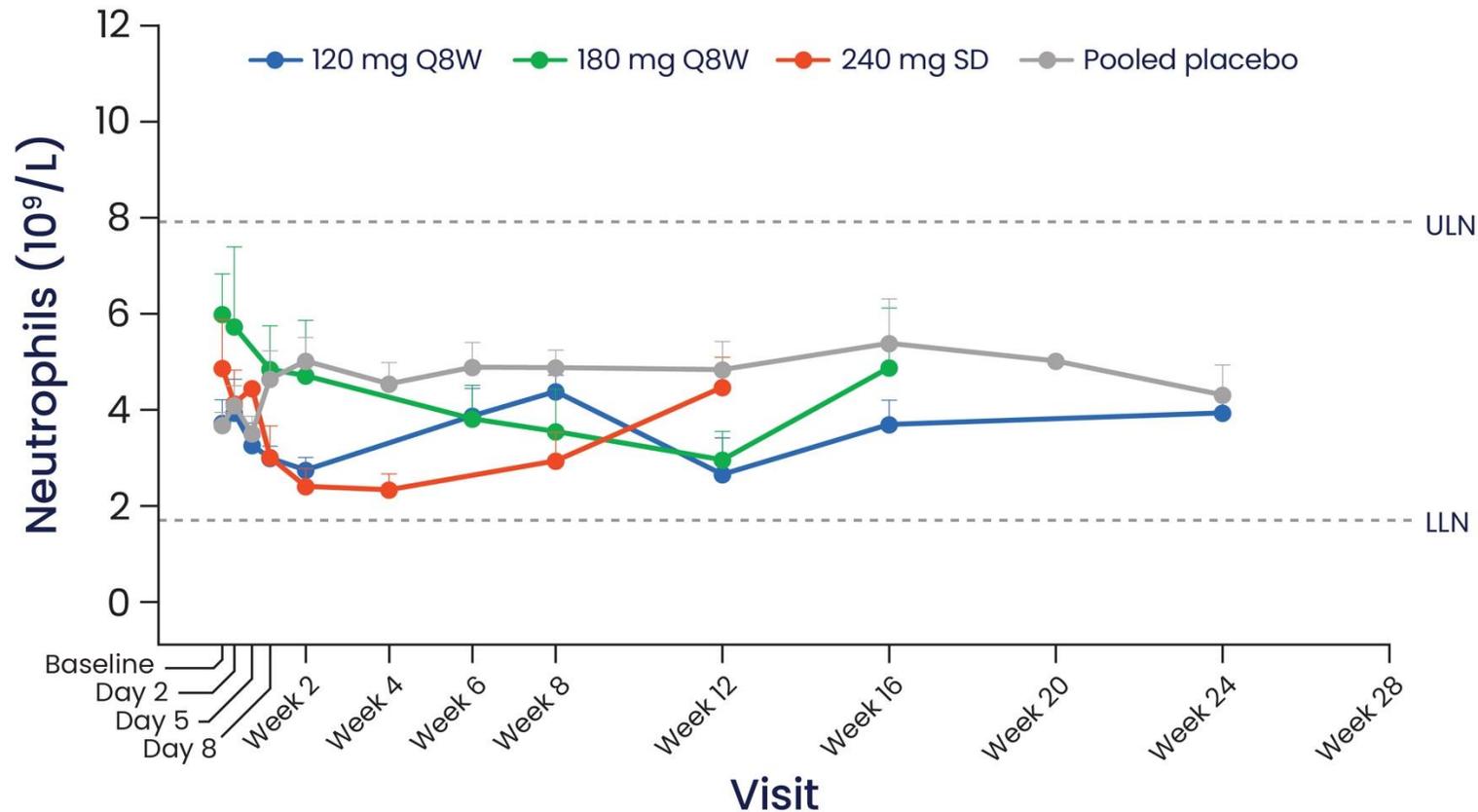
Note: ULN = upper limit of normal; LLN = lower limit of normal; Data cut-off 31Jan2025; Source – Figure 14.3.4.1.

Conclusions

- Subcutaneous briquilimab demonstrated an early T_{max} consistent with rapid onset of clinical response
  - Rapid decline in UAS7 as early as Week 1
  - Median time to first dose CR < 3 weeks (pooled 120 mg, 180 mg cohorts)

- Dose dependent durability observed in complete responses and well-controlled disease
  - High CR rate observed, durable to 8 weeks, following single 240 mg dose

- Briquilimab was well tolerated and demonstrated a favorable safety profile
  - Predictable clearance may allow for restoration of signaling on other c-Kit-expressing cells

- Dose optimization, based on PK/PD variables, may enhance efficacy and mitigate potential safety events

- Mast cell depletion, occurring after briquilimab administration, appears to be a promising therapeutic approach for mast cell mediated diseases, including CSU

- The data support advancing into a late-stage clinical development program for CSU

Acknowledgements

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Our thanks to **AAAAI** for providing the scientific venue to share this important clinical data.

Our thanks to **Jasper Therapeutics** and their staff for supporting this important development program for **briquilimab.**

Thank You.