Briquilimab Demonstrates Rapid, Clinically Meaningful Disease-Control in Adults with Chronic Spontaneous Urticaria (CSU): Updated Results from a Phase 1b/2a Study

Abstract #100281

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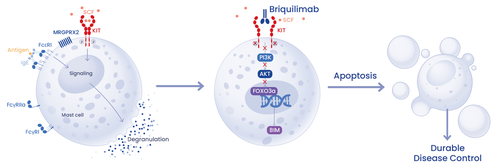
Background

- Chronic Spontaneous Urticaria (CSU) is a recurring inflammatory skin condition lasting ≥6 weeks, with itchy wheals (hives), angioedema, or both driven by aberrant activation and degranulation of mast cells in cutaneous tissues
- KIT receptor signaling driven by stem cell factor (SCF), is an important regulator of mast cell survival, making it a potential therapeutic target for CU
- Briquilimab, a humanized, aglycosylated, anti-KIT monoclonal antibody, directly blocks the SCF binding site on KIT, leading to inhibition of SCF/KIT signaling and mast cell apoptosis
- Briquilimab (subcutaneous) was evaluated for safety, tolerability, and efficacy in a Phase 1b/2a randomized, double blind, placebo-controlled multiple ascending dose clinical study (BEACON, NCT06162728) in participants with moderate to severe CSU who were symptomatic despite H1 antihistamines and omalizumab
- The Urticaria Control Test (UCT) is a participant-reported outcome (PRO) tool used to assess disease control in participants with CSU. We present efficacy and safety data including results of UCT scores captured electronically during the study

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



Methods

Phase 1b/2a BEACON Study Design

Screening/eligibility

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

Key assessments

- *Disease scores:* UAS7, UCT
- *Safety:* TEAEs, SAEs
- Pharmacokinetics
- *Mast cell depletion & recovery:* serum tryptase, skin biopsies

Study operations

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

Table 1. Dosing regimen for cohorts.

	Dose	Participants (randomization)	Schedule
Open label (n = 6)	10 mg 40 mg	n = 3+3 n = 3+3	Weeks 0, 4, 12, 20
Double-blind placebo-controlled (n = 67)	80 mg	n = 8 (3:1)	Q8W
	120 mg	n = 6 (2:1)	Q8W
		n = 6 (2:1)	Q12W
	180 mg	n = 10 (3:1)	Q8W
		n = 9 (3:1)	Q12W
	240 mg	n = 4* (3:1)	Single dose
	240 mg → 180 mg**	n = 8** (3:1)	Q8W
	240 mg**	n = 8** (3:1)	Q8W
	360 mg	n = 8* (3:1)	Single dose

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

Results

Table 2. 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)
ISS7 (0-21), mean (SD)	14.1 (3.8)	14.6 (4.7)
HSS7 (0-21), mean (SD)	13.2 (5.2)	14.0 (5.4)
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)

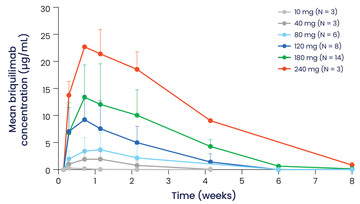
Note: Data presented for 49 participants from BEACON; Data cutoff Jan 31, 2025.

Results

Primary Efficacy Analysis

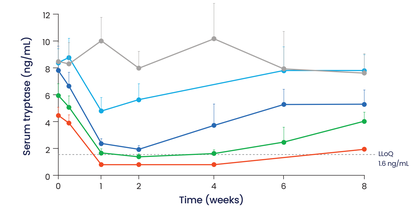
- Briquilimab demonstrated rapid Tmax and high Cmax along with rapid, dose-dependent reductions in serum tryptase consistent with early onset of clinical responses in CSU participants (Fig. 2A and 2B)

Figure 2A. Briquilimab serum concentration over time in CSU participants following subcutaneous (SC) administration.



- Briquilimab at 240 mg SC had a T_{max} of 4 - 7 days with a half-life of approximately 9 days

Figure 2B. Serum tryptase over time in CSU participants.



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.

- Reductions in serum tryptase were below LLOQ in 100% of 240 mg cohort and in 57% of 180 mg cohort by week 2

Table 3. Primary efficacy analysis of 80, 120 and 180 mg Q8W cohorts

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	21.7 (7.2)	2.7 (2.7)	9.9 (4.8)	19.5 (4.0)
Mean (SE) UAS7 change from baseline	-9.3 (5.8)	-27.2 (3.9)	-15.1 (4.7)	-9.2 (3.6)
Mean (SE) ISS7 change from baseline	-4.8 (2.7)	-13.3 (0.9)	-8.1 (2.4)	-4.8 (1.8)
Mean (SE) HSS7 change from baseline	-4.5 (3.1)	-13.8 (3.1)	-7.0 (2.4)	-4.4 (1.9)
Complete response (CR) rate[2,3]	17%	50%	43%	8%
Well controlled rate[3] (UAS7 ≤6)	33%	75%	43%	8%

Note: [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.

- 75% of participants in 120 mg Q8W4 briquilimab cohort had well controlled disease at 12 weeks – 4 weeks post second dose
- Resolution of hives and itch was consistent with briquilimab-mediated mast cell depletion

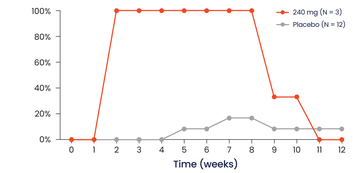
Table 4. Primary efficacy analysis of 120 and 180 mg Q12W cohorts.

Week 16	120 mg Q12W (N = 4)	180 mg Q12W (N = 7)	Pooled placebo (N = 12)[1]
Mean (SE) UAS7	0.5 (0.5)	7.2 (4.9)	15.6 (4.5)
Mean (SE) UAS7 change from baseline	-29.8 (6.9)	-21.7 (6.5)	-13 (3.2)
Mean (SE) ISS7 change from baseline	-14.2 (3.6)	-11.3 (3.1)	-6.8 (1.6)
Mean (SE) HSS7 change from baseline	-15.5 (3.3)	-10.4 (3.4)	-6.2 (1.8)
Complete response (CR) rate[2,3]	50%	57%	17%
Well controlled rate[3] (UAS7 ≤6)	75%	57%	33%

Note: [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 120 mg, 180 mg); [3]Last observation carried forward (LOCF) method was applied for missing data.

- 75% of participants in the 120 mg Q12W briquilimab cohort had well controlled disease at 16 weeks - 4 weeks post second dose
- Resolution of hives and itch was consistent with briquilimab-mediated mast cell depletion

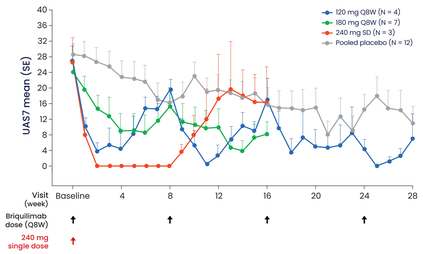
Figure 3. Primary efficacy analysis of 240 mg single dose cohort.



Note: Data cut-off 31 Jan 2025.

- In the 240 mg single dose cohort, mean baseline UAS7 = 26.6; mean week 2 UAS7 = 0 demonstrating a complete response
- During Weeks 1-12, the UAS7 = 0

Figure 4. Dose dependent UAS7 reductions observed over 28-week treatment period.



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

- Deeper UAS7 reductions observed in subsequent doses
- Two participants in the 180 mg Q8W with typical PK and significant tryptase reductions did not have any change in UAS7 score

Figure 5. UCT scores for 120 mg, 180 mg Q8W, and 240 mg SD cohorts over 12 weeks.

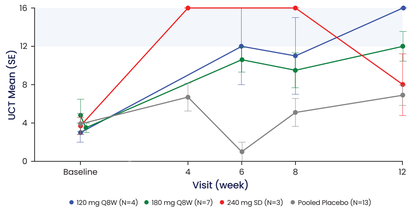
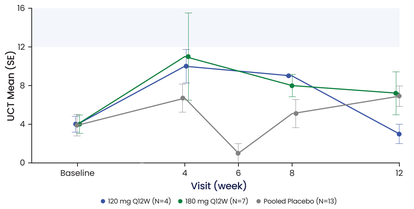


Figure 6. UCT scores for 120 mg and 180 mg Q12W cohorts over 12 weeks.



- Improvements in UCT scores occurred by Week 4 for participants on briquilimab for all cohorts

Summary of Adverse Events

Table 5. Briquilimab demonstrated a favorable safety profile.

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 anaphylaxis	0 (0)	0 (0)
Any TEAE leading to discontinuation of IP	1 (2.7)[1]	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 profile during 28-week exposure for 10 mg – 180 mg doses, as of 31Jan25

Table 6. Safety observations possibly related to KIT blockade were infrequent and generally limited to Grade 1 events.

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 participant 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

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

Conclusions

- Subcutaneous briquilimab demonstrated an early T_{max} consistent with rapid onset of clinical response
  - Rapid decline in serum tryptase and UAS7 as early as Week 1
  - Increase in UCT indicating disease control as early as Week 4
- 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
  - No dose-limiting toxicities were observed
  - Predictable clearance may allow for restoration of signaling on other 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

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