Effects of Multiple Dose Treatment with an Anti-KIT Antibody, CDX-0159, in Chronic Spontaneous Urticaria

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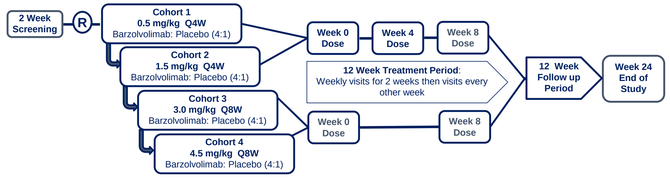
BACKGROUND

- Mast cells (MCs) are key effector cells of chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU)
- MCs require activation of their KIT receptors by stem cell factor (SCF) for survival, proliferation, and differentiation
- Circulating tryptase, a protease secreted specifically by MCs, is a biomarker that correlates with MC burden
- Barzolvolimab (CDX-0159) is a monoclonal anti-KIT antibody that selectively inhibits SCF-dependent KIT activation
- A single IV dose of barzolvolimab up to 9 mg/kg was generally well tolerated and demonstrated a profound suppression of circulating tryptase in adult healthy volunteers[1]
- A single 3 mg/kg IV dose of barzolvolimab demonstrated significant clinical response in patients with antihistamine-refractory CIndU, which mirrored decreases in circulating tryptase and skin mast cells[2]
- We report interim results from the first multiple dose study of barzolvolimab in CSU patients

STUDY DESIGN AND METHODS



- This is a randomized, double-blind, placebo-controlled, multiple ascending dose study in adults with moderate-to-severe chronic CSU (weekly urticaria activity score [UAS7] ≥ 16) refractory to H1 antihistamine therapy; prior treatment with biologics including omalizumab was permitted with washout
- Primary endpoint is safety profile; secondary endpoints include changes from baseline in UAS7, weekly hives severity score (HSS7), weekly itch severity score (ISS7), urticaria control test (UCT), and serum tryptase
- All data were analyzed based on safety population, which includes all patients who received at least one dose of study treatment, and by treatment group with placebo patients pooled; diary data were analyzed based on observed data

STUDY STATUS

- Study is ongoing; data cut as of 23May2022, unblinded by dose group only (individual patient data remains blinded)
- Cohorts 1 and 2 are complete; 7 of 12 patients in Cohort 3 completed Week 12, Cohort 4 enrollment is ongoing
- Adverse events through data cutoff and hematology data through week 12 are presented; clinical and tryptase data are presented through week 12 for 0.5 mg/kg and 1.5 mg/kg, and through week 8 for 3 mg/kg

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristics		Barzolvolimab 0.5 mg/kg Q4W (N= 9)	Barzolvolimab 1.5 mg/kg Q4W (N= 8)	Barzolvolimab 3.0 mg/kg Q8W (N= 9)	All Barzolvolimab (N= 26)	Pooled Placebo (N= 8)
Age years		43.8 (21.0 - 73.0)	53.3 (29.0 - 75.0)	49.4 (26.0 - 65.0)	48.7 (21.0 - 75.0)	47.4 (18.0 - 70.0)
Gender	Female, n (%)	6 (67)	7 (88)	6 (67)	19 (73)	5 (63)
Race	White, n (%)	6 (67)	7 (87.5)	9 (100)	22 (85)	6 (75)
	African American n (%)	3 (33)	1 (12.5)	0 (0)	4 (15)	2 (25)
BMI kg/m^2		31.1 (26.0 - 36.0)	37.8 (28.6 - 58.9)	29.4 (22.3 - 36.9)	32.6 (22.3 - 58.9)	32.1 (16.4 - 55.2)
CSU Duration years		7.5 (0.6 - 41.1)	17.1 (2.6 - 61.3)	5.3 (0.6 - 21.3)	9.8 (0.6 - 61.3)	6.0 (1.4 - 13.1)
History of Angioedema n (%)		5 (56)	5 (63)	5 (56)	15 (58)	4 (50)
Prior Omalizumab* n (%)		4 (44)	3 (38)	4 (44)	11 (42)	5 (63)
UAS7		31.1 (20.0 - 39.0)	29.4 (20.0 - 40.6)	29.4 (16.3 - 42.0)	30.0 (16.3 - 42.0)	36.6 (19.0 - 42.0)
HSS7		15.4 (8.0 - 21.0)	14.0 (8.0 - 21.0)	14.8 (8.0 - 21.0)	14.7 (8.0 - 21.0)	17.5 (7.0 - 21.0)
ISS7		15.7 (11.0 - 21.0)	15.5 (12.0 - 21.0)	14.6 (1.2 - 21.0)	15.2 (1.2 - 21.0)	19.1 (12.0 - 21.0)
UCT		1.7 (0.0 - 4.0)	2.4 (1.0 - 8.0)	3.1 (0.0 - 7.0)	2.4 (0.0 - 8.0)	3.4 (0.0 - 11.0)
Tryptase ng/mL		5.1 (2.0 - 10.3)	6.4 (2.8 - 15.1)	8.6 (3.3 - 28.8)	5.4 (2.0 - 28.8)	6.1 (3.6 - 7.7)

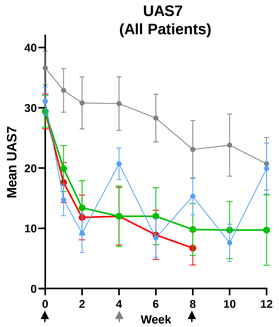
Mean (range) is presented unless otherwise indicated, *The majority had inadequate response to omalizumab

References

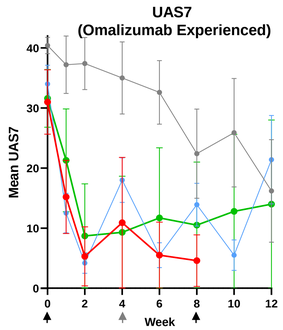
1. Alvarado D et al, Allergy. 2022;00:1–11;
2. Terhorst-Molawi D et al, J Allergy Clin Immunol. 2022; 149(2) Suppl. AB178

RESULTS

Barzolvolimab Drives Rapid Symptom Improvement in Anti-histamine Refractory, Including Omalizumab Experienced CSU Patients

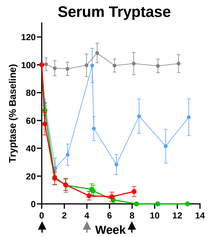


Rapid onset and dose-dependent symptom improvement with barzolvolimab



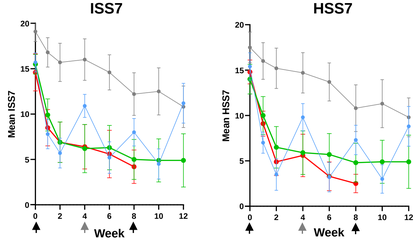
Similar pattern of symptom improvement in omalizumab-experienced patients

Kinetics of Tryptase Suppression Parallels Symptom Improvement



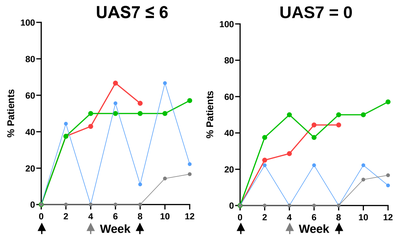
More profound tryptase suppression with higher doses

Rapid Improvement in Itch and Hives



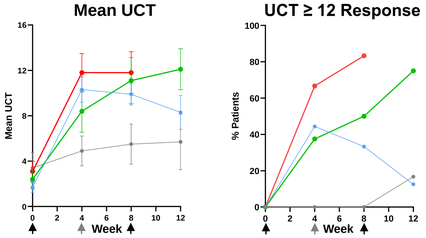
Higher doses achieved more sustained itch and hive improvement

Higher Doses of Barzolvolimab Resulted in More Durable Responses by UAS7



57% of patients treated with 1.5 mg/kg achieved complete response (UAS7=0) at week 12 and 44% of patients treated with 3 mg/kg achieved complete response at week 8 with additional follow up ongoing

Greater Urticaria Disease Control (UCT ≥ 12) with Higher Doses of Barzolvolimab



LEGEND

0.5 mg/kg Q4W · 1.5 mg/kg Q4W · 3.0 mg/kg Q8W · Placebo

- Data presented are mean ± S.E.
- Tryptase values below lower limit of detection normalized to 0

Dosing for all treatment groups

Dosing for the Q4W treatment groups only

Multiple IV Doses of Barzolvolimab Were Well Tolerated in CSU Patients

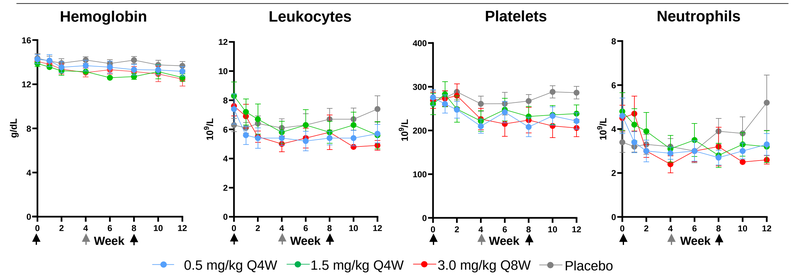
- The most common AEs occurring in ≥ 10% barzolvolimab treated patients include urinary tract infections, headache, neutropenia, and back pain
- Most AEs were mild or moderate in severity and resolved while on study, with none leading to treatment discontinuation; One patient who received 1.5 mg/kg experienced a SAE of salmonella colitis, which was considered unrelated to the study treatment
- Hematology parameters generally remained within the normal range. Generally transient, asymptomatic, mild decreases in neutrophils were reported as AEs for four patients. Changes in key hematology parameters were similar to those observed in previously reported single dose studies, with no pattern of further decreases with multiple doses.

Adverse Events Reported in ≥ 10% Barzolvolimab Treated Patients

	Barzolvolimab 0.5 mg/kg Q4W (N= 9)	Barzolvolimab 1.5 mg/kg Q4W (N= 8)	Barzolvolimab 3.0 mg/kg Q8W (N= 9)	All Barzolvolimab (N= 26)	Pooled Placebo (N= 8)
All AEs	8 (89)	7 (88)	6 (67)	21 (81)	6 (75)
Urinary Tract Infection*	1 (11)	2 (25)	2 (22)	5 (19)	1 (13)
Headache	2 (22)	0 (0)	2 (22)	4 (15)	1 (13)
Neutropenia	2 (22)	2 (25)	0 (0)	4 (15)	0 (0)
Back pain	0 (0)	1 (13)	2 (22)	3 (12)	0 (0)

*Includes preferred terms: urinary tract infection, cystitis, and bacteriuria

Key Hematology Parameters Over Time



SUMMARY AND DISCUSSION

- Multiple IV doses of barzolvolimab for up to 12 weeks were well tolerated. Changes in hematologic parameters were consistent with observations in single dose studies; with no pattern of further decreases with multiple doses
- Barzolvolimab results in rapid, marked and durable response in patients with moderate to severe CSU refractory to anti-histamines, including patients with prior omalizumab treatment
  - All three doses of barzolvolimab markedly improved urticaria symptoms and disease control
  - Rapid onset as early as 1 week after the first dose
  - The two higher dose groups showed greater and more sustained clinical activity than the lowest dose group
  - Tryptase suppression, indicative of mast cell depletion, paralleled symptom improvement, demonstrating the impact of mast cell depletion on CSU disease activity
- Patients with prior omalizumab therapy had similar symptom improvement as their respective overall groups
  - This is consistent with the distinct mechanism of barzolvolimab in depleting mast cells thereby addressing both the IgE- and non-IgE-mediated pathways in CSU pathogenesis
- The favorable safety profile and promising clinical activity in this early study supports further Phase 2 clinical studies in broad CSU patient populations including those with prior biologic therapy