410 Safety and Clinical Activity of Multiple Doses of Barzolvolimab, an anti-KIT Antibody, in Patients with Chronic Spontaneous Urticaria

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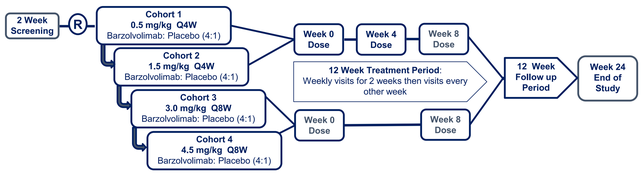
BACKGROUND

- Mast cells (MCs) are key effector cells of chronic urticaria which require activation of their KIT receptors by stem cell factor (SCF) for differentiation, tissue recruitment, and survival.
- 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.
- Single dose studies have shown that barzolvolimab is generally well tolerated and has significant clinical activity in antihistamine refractory chronic inducible urticaria (CINDU), including biologic refractory, with profound suppression of circulating tryptase and depletion of skin MCs.[1, 2]
- Here we report safety and clinical activity data of a Phase 1 multiple-ascending dose trial of barzolvolimab in antihistamine refractory chronic spontaneous urticaria (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 antihistamines; prior treatment with biologics permitted with washout. Patients were followed for 12 weeks post-treatment period or until resumption of symptoms.
- 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), PK and serum tryptase.
- All data were analyzed by treatment group (placebo patients pooled) for patients who received at least one dose of study treatment. Data cut 29NOV2022
- Complete data are included for all patients in dose levels through 3 mg/kg through 24 weeks. All available data for the 4.5 mg/kg and placebo doses are presented for adverse events. Figures for the 4.5 mg/kg dose include all data through Week 20 with data available for 6 of 9 patients at that timepoint as of the data cut-off. Figures for the placebo dose only include data through Week 20 as most placebo patients had resumption of symptoms ahead of Week 24.
- Two patients did not receive all doses of study treatment (4.5 mg/kg [1], placebo [1]).

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)	Barzolvolimab 4.5 mg/kg Q8W (N= 9)	All Barzolvolimab (N= 35)	Pooled Placebo (N= 10)
Age years		43.8 (21 - 73)	53.3 (29 - 75)	49.4 (26 - 65)	51.1 (29 - 68)	49.3 (21 - 75)	49.8 (18 - 70)
Gender	Female, n (%)	6 (67)	7 (88)	6 (67)	9 (100)	28 (80)	7 (70)
Race n (%)	White	6 (67)	7 (88)	9 (100)	7 (78)	29 (83)	7 (70)
	African American	3 (33)	1 (13)	0 (0)	1 (11)	5 (14)	3 (30)
	Other	0 (0)	0 (0)	0 (0)	1 (11)	1 (3)	0 (0)
BMI kg/m^2		31.1 (26.0 - 36.0)	37.8 (28.6 - 58.9)	29.4 (22.3 - 36.9)	27.1 (21.5 - 34.4)	31.2 (21.5 - 58.9)	31.8 (16.4 - 55.2)
CSU Duration years		7.5 (0.6 - 41.1)	17.1 (2.6 - 61.3)	4.8 (0.6 - 21.3)	10.4 (1.0 - 35.4)	9.7 (0.6 - 61.3)	5.6 (1.4 - 13.1)
Prior Angioedema n (%)		5 (56)	5 (63)	5 (56)	6 (67)	21 (60)	5 (50)
Prior Omalizumab* n (%)		4 (44)	3 (38)	4 (44)	2 (22)	13 (37)	6 (60)
UAS7		31.1 (20.0 - 39.0)	29.4 (20.0 - 40.6)	29.4 (16.3 - 42.0)	27.8 (17.5 - 38.0)	29.4 (16.3 - 42.0)	35.8 (19.0 - 42.0)
ISS7		15.7 (11.0 - 21.0)	15.5 (12.0 - 21.0)	14.6 (1.2 - 21.0)	15.4 (10.5 -19.0)	15.3 (1.2 - 21.0)	19.3 (12.0 - 21.0)
HSS7		15.4 (8.0 - 21.0)	14.0 (8.0 - 21.0)	14.8 (8.0 - 21.0)	12.4 (7.0 -19.0)	14.1 (7.0 - 21.0)	16.5 (7.0 - 21.0)
UCT		1.7 (0 - 4)	2.4 (1- 8)	3.1 (0 - 7)	4.7 (1 -12)	3.0 (0 - 12)	3.4 (0 - 11)
Tryptase ng/mL		5.0 (2.0 - 10.3)	6.3 (2.8 - 15.1)	8.6 (3.3 - 28.8)	5.5 (2.3 - 10.2)	6.2 (2.0 - 28.8)	5.3 (3.2 - 7.5)
Total IgE (kU/L)		80 (2 - 239)	161 (13 - 328)	337 (4 - 1371)	88 (2 - 307)	165 (2 - 1371)	161 (5 - 409)

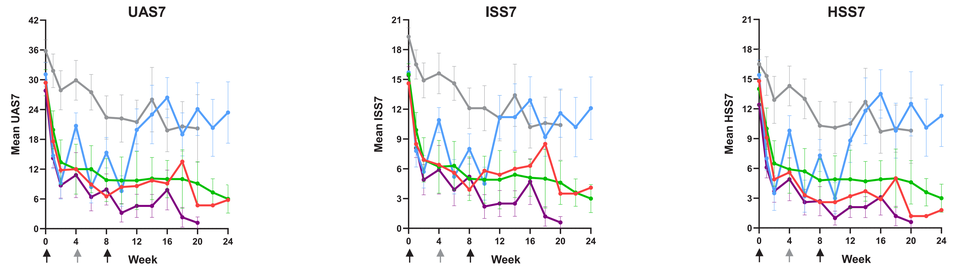
Mean (range) is presented unless otherwise indicated, *The majority had inadequate response to omalizumab.

References

1. Alvarado D et al, Allergy. 2022;77(8):2393-2403. doi:10.1111/all.15262
2. Terhorst-Molawi, et al, *Allergy*. Allergy. 2022 Nov 16. doi: 10.1111/all.15585. Epub ahead of print

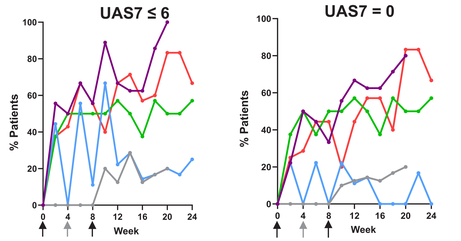
RESULTS

Barzolvolimab Drives Rapid and Durable Symptom Improvement in Antihistamine Refractory CSU Patients



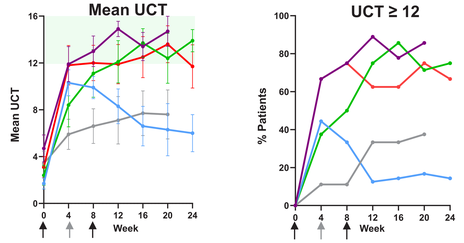
- Sustained activity with barzolvolimab doses ≥ 1.5 mg/kg with similar improvement in hives and itch.

Barzolvolimab Resulted in Durable Responses by UAS7 at Doses ≥ 1.5 mg/kg



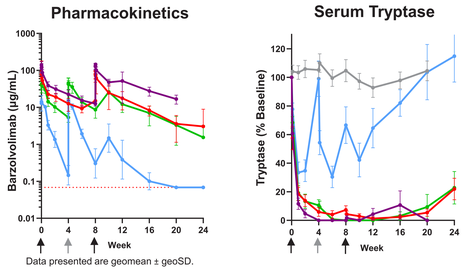
- 56% of patients treated with doses ≥ 1.5 mg/kg achieved complete response at week 12 and 68% at week 20 with additional follow up ongoing for patients treated with 4.5 mg/kg.

Greater Urticaria Disease Control (UCT ≥ 12) with Barzolvolimab Doses ≥ 1.5 mg/kg



UCT =16: Complete control
UCT ≥12: Well controlled disease

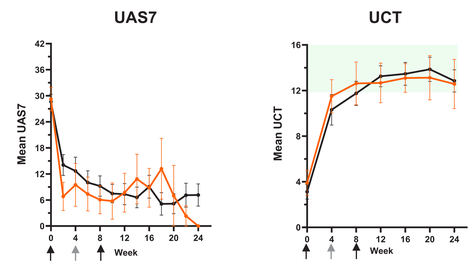
Prolonged Barzolvolimab Exposure and Tryptase Suppression Achieved at Doses ≥ 1.5 mg/kg



Data presented are geomean ± geoSD.

- Sustained barzolvolimab exposure noted for doses ≥ 1.5 mg/kg which supports prolonged tryptase inhibition and CSU symptom control.
- The kinetics of tryptase suppression parallel symptom improvement.
- Treatment-emergent ADA observed in 51% of patients receiving study drug, without apparent impact on exposure.

Robust Clinical Activity Observed in Both Omalizumab Experienced and Naïve Patients



- Combined data from saturating doses (1.5, 3 and 4.5 mg/kg), as determined by PK and tryptase analysis, are shown.
- Patients with omalizumab refractory disease had similar results.

LEGEND

0.5 mg/kg Q4W · 1.5 mg/kg Q4W · 3.0 mg/kg Q8W · 4.5 mg/kg Q8W · Placebo · Dosing for all treatment groups · Dosing for the Q4W treatment groups only · - Data presented are mean ± S.E.

Lower limit of quantitation · - Tryptase values below lower limit of detection normalized to 0

Multiple IV Doses of Barzolvolimab Were Well Tolerated in CSU Patients

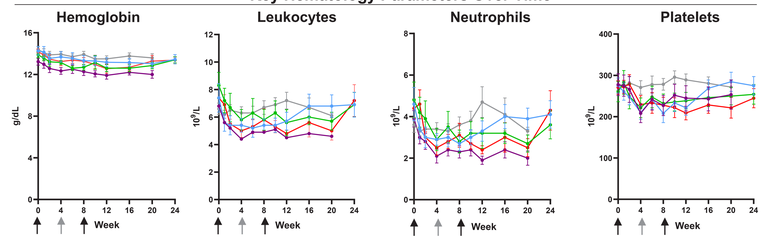
- The most common AEs occurring in ≥ 10% barzolvolimab treated patients include hair color changes, COVID-19, headache, neutropenia, and urinary tract infections.
- Most AEs were mild or moderate in severity and resolved while on study; one patient who received 1.5 mg/kg experienced a SAE of salmonella colitis, which was considered unrelated to the study treatment.
- Hematology parameters generally remained within the normal range. Generally transient, asymptomatic decreases in neutrophils were reported as AEs for five 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)	Barzolvolimab 4.5 mg/kg Q8W (N= 9)	All Barzolvolimab (N= 35)	Pooled Placebo (N= 10)
Any AE	8 (89)	7 (88)	9 (100)	6 (67)	30 (86)	5 (50)
Hair Color Changes	0 (0)	1 (13)	3 (33)	4 (44)	8 (23)	0 (0)
COVID-19	0 (0)	1 (13)	2 (22)	2 (22)	5 (14)	0 (0)
Headache	2 (22)	0 (0)	2 (22)	1(11)	5 (14)	1 (10)
Neutropenia	2 (22)	2 (25)	1 (11)	0 (0)	5 (14)	0 (0)
Urinary Tract Infection*	1 (11)	2 (25)	2 (22)	0 (0)	5 (14)	0 (0)

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

Key Hematology Parameters Over Time



SUMMARY AND DISCUSSION

- Multiple IV doses of barzolvolimab up to 4.5 mg/kg resulted in extended exposure at doses ≥ 1.5 mg/kg and were well tolerated.
  - Overall safety profile through 24 weeks of observation was similar to data observed in single dose studies.
  - Changes in hematologic parameters showed no pattern of further decreases with multiple doses.
- Barzolvolimab resulted in rapid and marked response in antihistamine refractory patients with moderate to severe CSU.
  - Durable clinical response was observed with doses ≥ 1.5 mg/kg, achieved through sustained exposure and tryptase reduction reflecting MC depletion.
    - At week 12, greater than 50% of patients achieved completely-controlled urticaria activity (UAS7 = 0) and well-controlled urticaria (UCT ≥ 12) with prolonged symptom control for up to 24 weeks.
- Patients had similar symptom improvement irrespective of prior omalizumab use.
  - Findings consistent with predicted role of MCs in driving both IgE- and non-IgE mediated disease.
- The magnitude and durability of symptom control and observed safety profile support the ongoing Phase 2 studies of barzolvolimab in CSU and CINDU.

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