Abstract ID: 79998

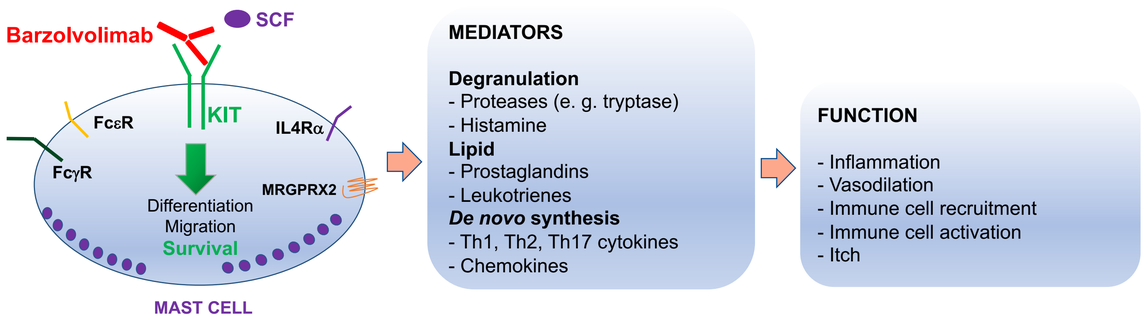
Barzolvolimab-induced Response and Mast Cell Suppression are Durable and Linked

Dorothea Terhorst-Molawi[1], Eva Grekowitz[1], Lea Kiefer[1], Martin Metz[1], Sophia Neisinger[1], Melba Munoz-Roldan[1], Diego Alvarado[2], Kunal Merchant[2], Deena Maurer[2], Linda Malenchek[2], Elizabeth Crowley[2], Margo Heath-Chiozzi[2], Marcus Maurer[1]

[1]Institute for Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [2]Celldex Therapeutics, Hampton, NJ, USA. Study Identifiers: CDX0159-03; EUDRACT2020-002792-35; NCT04548869

BACKGROUND

- Chronic inducible urticaria is a mast cell (MC)-driven disease characterized by itch and wheals triggered by cold in cold urticaria (ColdU), or skin scratching in symptomatic dermographism (SD).[1]
- Barzolvolimab is a monoclonal anti-KIT antibody that is engineered to selectively inhibit SCF-dependent KIT activation, which is essential for several MC functions, including their survival.[2]
- A single 3 mg/kg IV dose in antihistamine refractory ColdU and SD patients was generally well tolerated and demonstrated a 95% complete response (negative provocation testing), 100% well controlled urticaria by Urticaria Control Test (UCT), and profound reduction in serum tryptase and skin MCs during the 12 week follow-up period.[3]
- Here we present the results of optional longer term follow-up out to 36 weeks in a subset of these patients.



STUDY DESIGN AND METHODS

This is an ongoing open-label, Phase 1b trial in patients with CIndU (ColdU, SD, and cholinergic urticaria) refractory to antihistamine treatment, who receive a single IV infusion of CDX-0159 at 3 mg/kg or 1.5 mg/kg with a 12-week follow-up.

- Protocol was amended to collect optional clinical activity and pharmacodynamic data through 36 weeks post dose administration.
- Assessments included provocation testing: ColdU with TempTest® (CR=no whealing at 4°C) and SD using FricTest® (CR=no whealing), UCT, serum tryptase levels, and cutaneous MC numbers.

STUDY STATUS

- Of 21 ColdU and SD patients treated with a single 3 mg/kg dose of barzolvolimab, 14 consented to the optional long term follow-up evaluation (6 ColdU, 8 SD). Data were collected at one or more timepoints beyond week 12 through week 36.
- All drug related adverse events noted during the study were resolved during the long term follow-up period.

DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

		All (N=21)	LTFU (N=14)
Age median (range) years		41 (25 - 65)	44 (25 - 65)
Gender Female, n (%)		10 (48%)	6 (42.9%)
Race	White, n (%)	20 (95%)	14 (100%)
	Asian, n (%)	1 (5%)	0 (0%)
Ethnicity	Hispanic or Latino	1 (5%)	1 (7.1%)
Weight median (range) kg		81.5 (57.0 - 122.0)	85.5 (57.0 - 122.0)
Disease Duration	< 5 yr, n (%)	9 (43%)	7 (50%)
	≥ 5 yr, n (%)	12 (57%)	7 (50%)
History of Angioedema		6 (29%)	3 (21%)
Prior Medication	H1 Antihistamines	21 (100%)	14 (100%)
	Biologics (omalizumab)	3 (14%)	2 (14%)
Provocation Threshold mean (range)		ColdU (n=11), SD (n=10)	ColdU (n=6), SD (n=8)
CTT		18.9 (5-27) °C	18.4 (15-23) °C
Number of Pins		3.5 (2-4) Pins	3.4 (2-4) Pins
UCT median (range)		5 (0-13)	6 (2-13)
Tryptase median (range) ng/mL		4.2 (1.3-8.6)	4.2 (1.3-5.7)

References

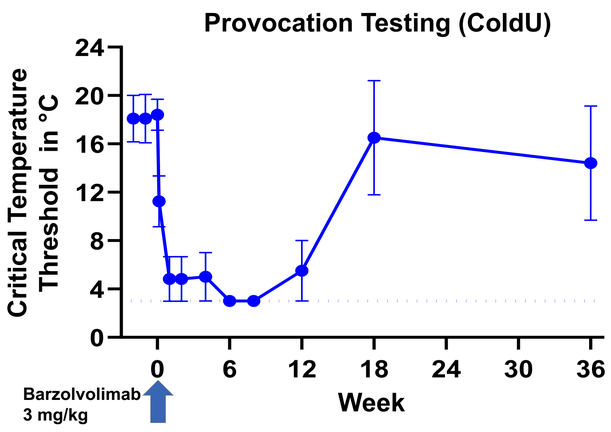
[1] Maurer et al. JACIP. 2018 Jul-Aug;6(4):1119-1130

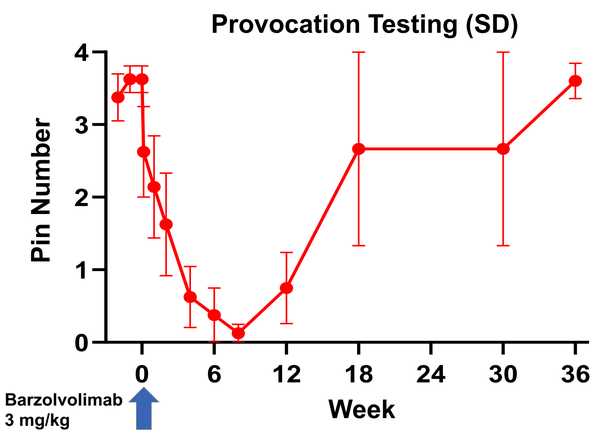
[2] Alvarado et al. Allergy. 2022. 2022 Aug;77(8):2393-2403

[3] Terhorst-Molawi et al. Allergy. 2022. In press.

RESULTS

A Single Dose of Barzolvolimab Induces Rapid and Durable Clinical Response and Improves Urticaria Control with Sustained Results for 12-36 Weeks



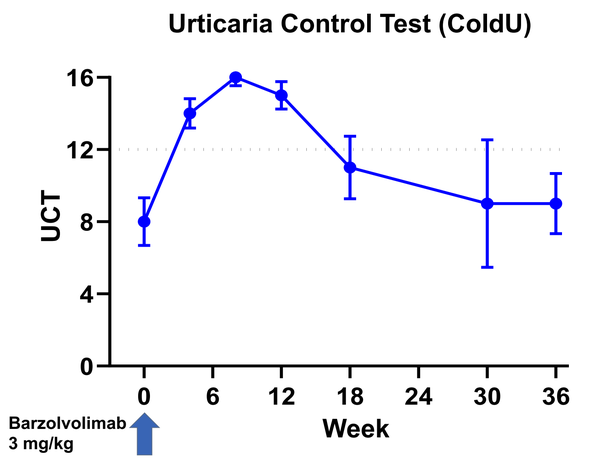


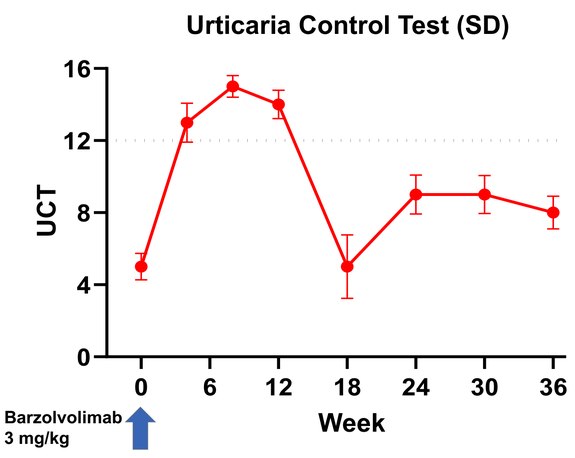
- Critical temperature threshold values below 4°C (negative test) assigned a value of 3°C.
- Visit timepoints with only 1 patient were excluded

% Patients with Complete Response

Week	0	12	36
		ColdU	
CR (%)	0 (0)	5/6 (83)	2/5 (40)
		SD	
CR (%)	0 (0)	5/8 (63)	0/5 (0)

Complete Response (CR) = negative provocation test, ≤4°C or 0 pins



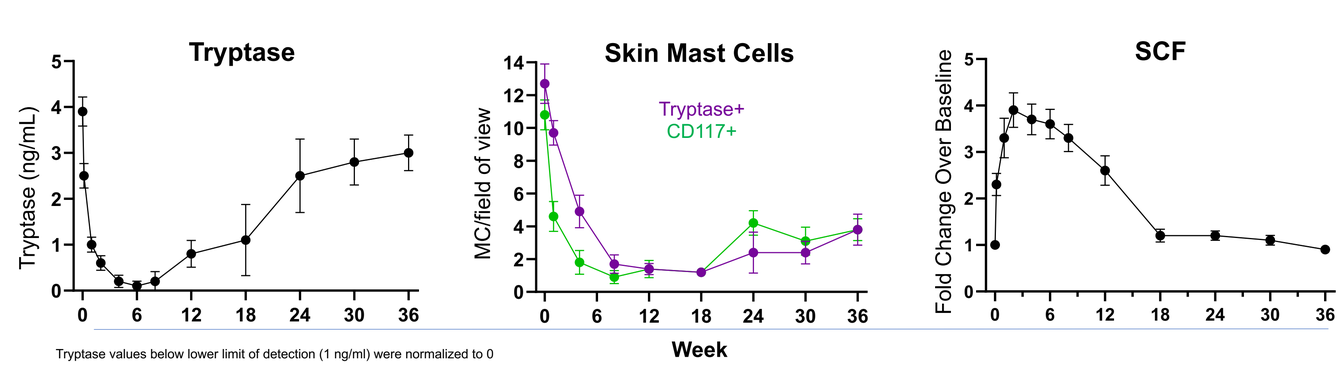


% Patients with Well Controlled Urticaria

Week	0	12	36
		ColdU	
UCT≥ 12 (%)	1/6 (17)	5/6 (83)	3/6 (50)
		SD	
UCT≥ 12 (%)	0 (0)	6/8 (75)	1/8 (13)

UCT≥ 12 = Well controlled urticaria

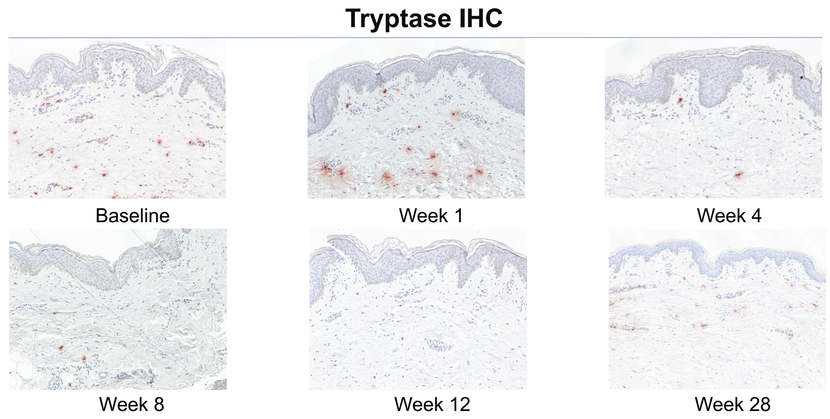
Recovery Kinetics of Tryptase, Skin MCs and SCF



Tryptase values below lower limit of detection (1 ng/ml) were normalized to 0

- Tryptase levels return to pretreatment levels during follow-up, while mast cells continue to recover
- Tissue KIT signaling, as approximated by SCF levels, is rapidly inhibited and fully reactivated at ~18 weeks after dosing

Representative Micrographs of MC reduction and recovery



SUMMARY AND DISCUSSION

- In patients with CIndU refractory to antihistamines, a single dose of barzolvolimab (3 mg/kg) resulted in rapid, profound, and durable responses to provocation testing, well-controlled symptoms by UCT, sustained tryptase suppression, and profound MC reduction within the 12 week follow-up period.
- Longer term follow-up data in 14 patients showed most patients had return of symptoms / loss of urticaria control between 12 and 36 weeks. Two patients remained provocation negative at 36 weeks, and four had well controlled disease (UCT ≥ 12) 36 week post dosing.
- Serum tryptase exhibits a similar rate of recovery as clinical symptoms, while skin MCs return at a slower rate.
- All drug related adverse events noted during the study resolved during the long term follow-up period.
- A phase 2 study in CIndU (ColdU and SD) is ongoing (NCT05405660)