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Sustained Efficacy and Safety of Barzolvolimab in Chronic Inducible Urticaria

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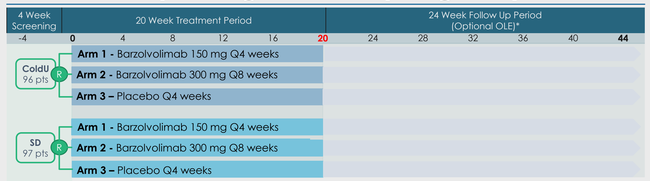
Background

- Chronic inducible urticaria (CIndU) is a mast cell-driven disease characterized by itch and wheals, triggered by cold in cold urticaria (ColdU), or pressure on the skin in symptomatic dermographism (SD).
- Barzolvolimab (CDX-0159), an anti-KIT monoclonal antibody, has demonstrated clinically meaningful improvement in itch and urticarial lesions accompanied by depletion of skin mast cells in chronic urticarias.
- In a Phase 2 study (NCT05405660), barzolvolimab significantly improved complete response rates (negative provocation tests) with a favorable safety profile through 12 weeks of treatment in patients with CIndU inadequately controlled by antihistamines.
- Herein, we report the impact of barzolvolimab treatment versus placebo on urticaria disease control with antihistamine-refractory ColdU or SD over 20 weeks of treatment. Patients with symptom recurrence were eligible to enter the open-label extension (OLE).

Study Design and Key Eligibility



*Optional OLE: Starting at week 24, patients with uncontrolled disease (UCT < 12 and positive provocation test) have the option to enter an open label extension period

Randomized, double-blind, placebo-controlled, dose-finding study

Key Eligibility Criteria:

- Diagnosis of ColdU or SD for more than 3 months
- Recurrent wheals despite stable antihistamine regimen. Prior biologics permitted
- Positive provocation test at screening and randomization

Primary Endpoint:

- % of patients with a negative provocation test at Week 12
- ColdU (TempTest®) & SD (FricTest®)

Secondary Endpoints:

- CTT (Critical Temperature Threshold)
- CFT (Critical Friction Threshold)
- WI-NRSprovo (Worst Intensity of Itch Evoked at Provocation Testing)
- Safety

Exploratory Endpoints:

- UCT (Urticaria Control Test)

Methodology

Provocation Tests

Cold Urticaria (ColdU) TempTest ®

- Critical Temperature Threshold (CTT): Threshold temperature at which wheals are triggered assessed at the 10 minute mark
- Complete Response: negative test at 4 °C
- Partial Response: ≥ 4 °C improvement

Symptomatic Dermographism (SD) FricTest ®

- Critical Friction Threshold (CFT): Threshold pin number (out of 4) at which wheals are triggered assessed at the 10 minute mark
- Complete Response: 0 pins
- Partial Response: ≥ 2 pin improvement

Worst Itch Rating Scale with provocation test (WI-NRSprovo)

- Patients assess their worst itch triggered by the provocation test via a numerical rating scale (NRS) ranging from 0 (no itch) – 10 (worst itch)

Urticaria Control Test (UCT)

- The UCT is comprised of 4 dimensions including physical symptoms, quality of life, treatment and overall disease control, with each dimension rated on a scale of 0-4 and a total score of 0-16
- Well-controlled disease (UCT ≥ 12); Complete disease control (UCT=16)

Analysis

- Analysis was conducted on the mITT populations. A non-responder imputation approach was used for calculating proportions of participants with complete and partial responses. Observed data was used for UCT values. These endpoints demonstrated statistically significant improvements (p values ranged from ≤ 0.0001 to 0.0295) at week 12 and week 20 in the active arms compared to placebo
- Analyses shown reflect mean ± SE values

Demographics and Baseline Characteristics

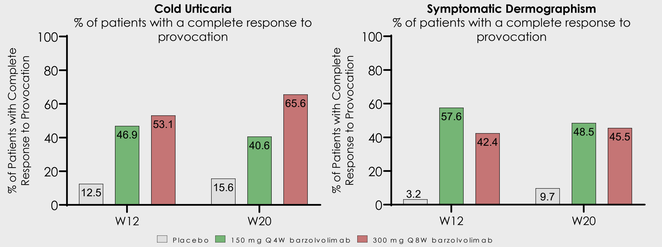
- Well balanced across treatment groups

Baseline characteristics Mean (range)	Cold Urticaria			Symptomatic Dermographism		
	Barzolvolimab 150 mg Q4W (n=32)	Barzolvolimab 300 mg Q8W (n=32)	Placebo (n=32)	Barzolvolimab 150 mg Q4W (n=33)	Barzolvolimab 300 mg Q8W (n=33)	Placebo (n=31)
Age (years)	40 (18-72)	40 (18-64)	41 (20-69)	41 (19-70)	42 (21-70)	42 (18-71)
Gender, Female, n (%)	27 (84)	23 (72)	19 (59)	18 (55)	26 (79)	19 (61)
Race						
White, n (%)	26 (81)	31 (97)	28 (88)	29 (88)	29 (88)	27 (87)
Black, n (%)	4 (13)	1 (3)	2 (6)	3 (9)	2 (6)	1 (3)
Other, n (%)	2 (6)	0 (0)	2 (6)	1 (3)	2 (6)	3 (10)
Weight (kg)	83 (55-124)	82 (49-140)	83 (47-129)	84 (58-121)	85 (55-139)	83 (53-115)
CIndU Duration, yr	7 (0.3-31)	11 (0.3-49)	10 (0.3-34)	7 (0.3-53)	6 (0.3-41)	5 (0.4-23)
Prior angioedema, n (%)	9 (28)	11 (34)	11 (34)	9 (27)	7 (21)	7 (23)
Prior anti-histamine therapy, n (%)	32 (100)	32 (100)	32 (100)	33 (100)	33 (100)	31 (100)
Prior omalizumab therapy, n (%)	2 (6)	1 (3)	1 (3)	1 (3)	2 (6)	2 (7)
CTT (°C)	18.7 (4-38)	20.7 (8-40.5)	18.6 (4-44)	NA	NA	NA
CFT (pins)	NA	NA	NA	3.64 (2-4)	3.58 (2-4)	3.55 (3-4)
WI-NRSprovo	6.28 (0-10)	5.47 (0-10)	5.41 (0-9)	5.73 (1-9)	5.70 (2-9)	5.23 (1-9)
UCT	5.56 (0-12)	4.94 (0-11)	5.78 (0-12)	5.30 (0-11)	5.52 (0-13)	5.26 (0-13)

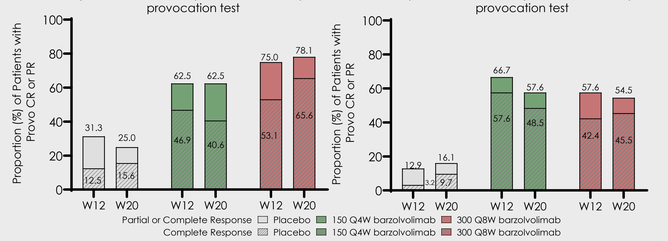
CTT, Critical Temperature Threshold; CFT, Critical Friction Threshold; WI-NRSprovo, Numerical Rating Scale of Worst Itch at the time of provocation testing; UCT, Urticaria Control Test

Results

Clinically Meaningful Improvement in Rates of Complete Responses Through Treatment Period

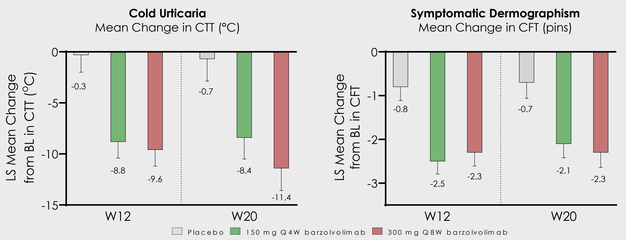


Up to 78% of Patients with ColdU and 58% of Patients with SD Obtained a Partial or Complete Response at Week 20



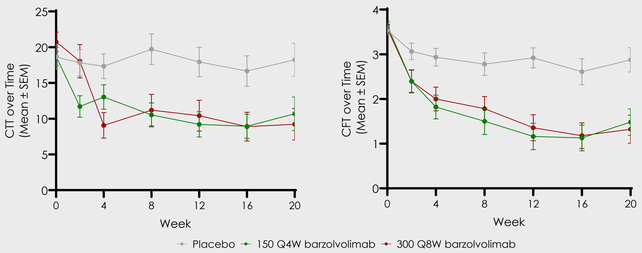
Results

Marked Improvement in Critical Temperature (CTT) and Friction Thresholds (CFT) Throughout Treatment

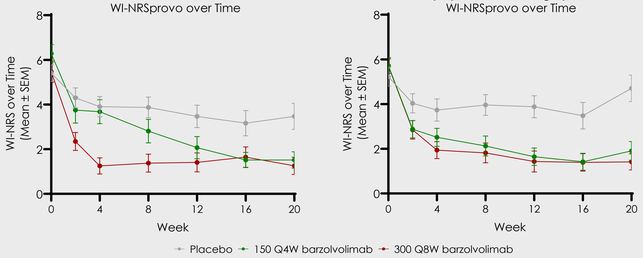


- Week 12 analysis was conducted using a multiple imputation approach; Week 20 analysis was conducted using observed data.

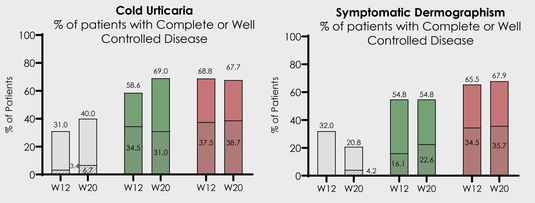
Reduction in Critical Temperature and Friction Thresholds



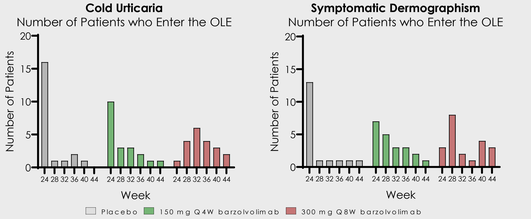
Reduction in Itch at the Time of Provocation Testing (WI-NRSprovo)



Clinically Meaningful Improvement in UCT Throughout Treatment



Placebo Treated Patients Enter OLE at a Faster Rate Compared to Barzolvolimab Treated Patients



- Barzolvolimab-treated patients with a complete response (CR) at EOT enter OLE later than those without a CR at EOT.
  SD: median time to entry (34 weeks with CR vs 28 weeks w/o CR)
  ColdU: median time to entry (34 weeks with CR, 28 weeks w/o CR)

Safety

- Barzolvolimab was well tolerated
- No difference between active treatment (2%) and placebo (3%) groups in rate of discontinuations due to adverse events
- Most adverse events were mild. Adverse events reported by >10% of patients in any treatment group through week 20 were hair color changes (18%) and neutropenia (12%)
- Most common events were mechanism-related (KIT) and expected to be reversible
- No association between infections and neutropenia; neutropenia was transient

Discussion

- First large, randomized, placebo-controlled study to demonstrate clinical benefit in patients with CIndU
- Up to 66% of patients with ColdU and 49% of patients with SD had a complete response at Week 20
- Marked and rapid improvement in provocation thresholds and associated itch
- Barzolvolimab treatment resulted in clinically meaningful improvements in urticaria control, achieving a high rate of well controlled disease: up to 69% of patients with ColdU and 68% of patients with SD
- Barzolvolimab was well tolerated with a safety profile consistent with previous studies
- Phase 3 development initiating soon