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The Anti-KIT Antibody, CDX-0159, Reduces Mast Cell Numbers and Circulating Tryptase and Improves Disease Control in Patients with Chronic Inducible Urticaria (CIndU)

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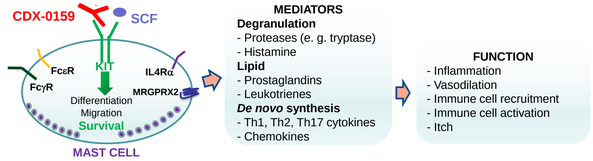
BACKGROUND

- 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).
- The activation of KIT receptors by stem cell factor (SCF) is essential for differentiation, proliferation and survival of MCs.
- CDX-0159 is a monoclonal anti-KIT antibody that is engineered to selectively inhibit SCF-dependent KIT activation.
- In healthy volunteers, CDX-0159 induced a profound dose-dependent reduction in circulating tryptase, a biomarker of MC burden, and was overall well-tolerated[1].
- A single 3 mg/kg IV dose demonstrated a 95% complete response (negative provocation testing) in CIndU patients and was generally well tolerated, with marked improvement in urticaria control and QoL as presented previously[2,3].
- Data presented here show the effect of CDX-0159 on urticaria control and CDX-0159 pharmacodynamics (PD), and pharmacokinetics (PK).



MEDIATORS
Degranulation
- Proteases (e. g. tryptase)
- Histamine

Lipid
- Prostaglandins
- Leukotrienes

***De novo* synthesis**
- Th1, Th2, Th17 cytokines
- Chemokines

FUNCTION
- Inflammation
- Vasodilation
- Immune cell recruitment
- Immune cell activation
- Itch

STUDY DESIGN AND METHODS

CDX0159-03 is an ongoing open-label, Phase 1b trial in patients with CIndU (including ColdU and SD) refractory to antihistamine treatment, who receive a single IV infusion of CDX-0159 at 3 mg/kg with a 12-week follow-up.

- Primary objective is to evaluate safety/tolerability of CDX-0159 (adverse events and clinical lab tests).
- Secondary objectives include evaluating the effect of CDX-0159 on clinical effect and serum tryptase.
- Study assessments included adverse events, clinical laboratory testing, provocation testing. (TempTest [ColdU] and FricTest [SD]), Urticaria Control Test with 7-day recall (UCT7; range 0-16), circulating tryptase and SCF, cutaneous MC numbers, and PK.

STUDY STATUS

- 21 ColdU and SD patients received study drug and are included in the safety analysis.
- 20: ColdU (n=10) and SD (n=10) patients received a full dose of study drug, have completed the 12-week observation period and are included in UCT7, provocation tests, PK, PD and MC data presented herein.
- Study results are presented as Mean ± SEM where applicable

DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

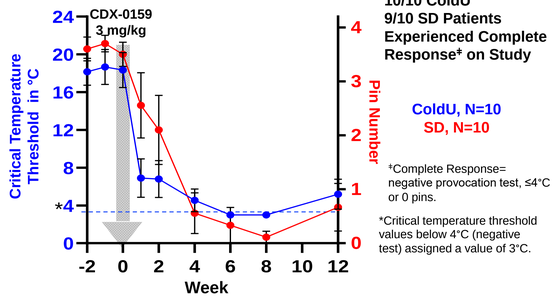
		ColdU (N=11)	SD (N=10)	All (N=21)
Age median (range) years		43 (27- 65)	39 (25- 56)	41 (25 - 65)
Gender Female, n (%)		6 (54.5%)	4 (40.0%)	10 (47.6%)
Race	White, n (%)	10 (90.9%)	10 (100%)	20 (95.2%)
	Asian, n (%)	1 (9.1%)	0 (0%)	1 (4.8%)
Ethnicity	Hispanic or Latino	1 (9.1%)	0 (0%)	1 (4.8%)
Weight median (range) kg		77.0 (61.0 – 93.0)	85.7 (57.0 – 122.0)	81.5 (57.0 – 122.0)
Disease Duration	< 5 yr, n (%)	5 (45.5%)	4 (40%)	9 (42.9%)
	≥ 5 yr, n (%)	6 (54.5%)	6 (60%)	12 (57.1%)
History of Angioedema		6 (54.5%)	0	6 (28.6%)
Prior Medication H1 Antihistamines		11 (100%)	10 (100%)	21 (100%)
Biologics (omalizumab)		1 (9%)	2 (20%)	3 (14.3%)
Provocation Threshold Mean (range)		18.9 (5-27) °C	3.5 (2-4) Pins	
UCT7 Mean (range)		7.6 (2-13)	5.1 (0-10)	6.4 (0-13)
Tryptase median (range) ng/mL		3.8 (2.4-5.5)	4.6 (1.3-8.6)	4.2 (1.3-8.6)

[1] Maurer et. al. Allergy. 2020; 75(S109):280
[2]Terhorst-Molawi et al. Allergy. 2021;76(S110):651
[3]Howro et. al, presented at EADV 2021

RESULTS

A Single 3 mg/kg Dose of CDX-0159 Results in a Rapid and Durable Clinical Response and Improves Urticaria Control

Rapid and Durable Improvement in Provocation Tests with a 95% Complete Response



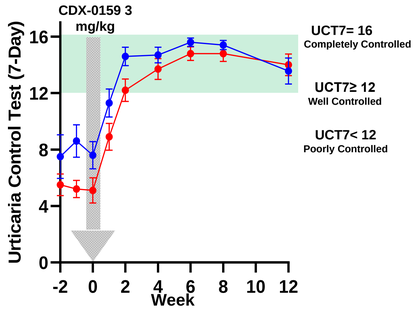
10/10 ColdU
9/10 SD Patients Experienced Complete Response* on Study

ColdU, N=10
SD, N=10

*Complete Response= negative provocation test, ≤4°C or 0 pins.

*Critical temperature threshold values below 4°C (negative test) assigned a value of 3°C.

Sustained Improvement in Urticaria Control



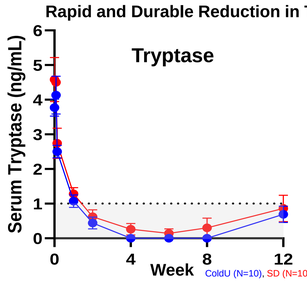
UCT7= 16
Completely Controlled

UCT7≥ 12
Well Controlled

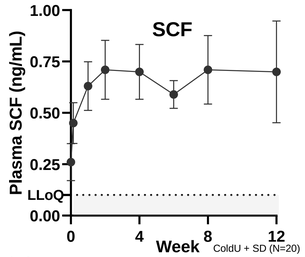
UCT7< 12
Poorly Controlled

Kinetics of Tissue KIT inhibition Mirrors Urticaria Control

Rapid and Durable Reduction in Tryptase and Increase in SCF

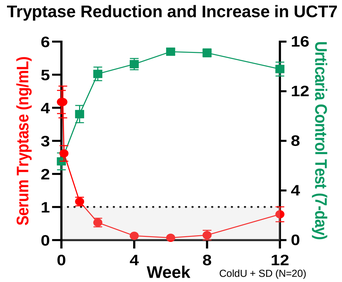


ColdU (N=10), SD (N=10);
Tryptase values below lower limit of quantitation (1 ng/mL) normalized to 0



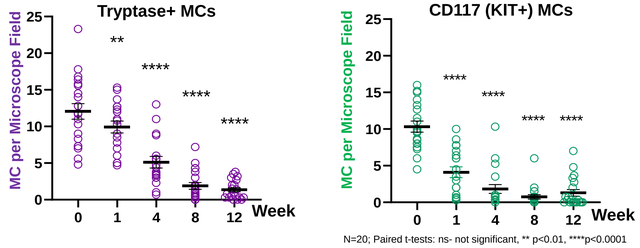
ColdU + SD (N=20)

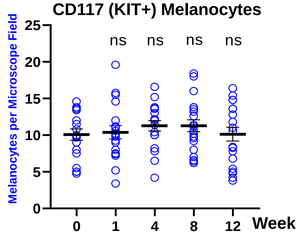
Tryptase Reduction and Increase in UCT7



ColdU + SD (N=20)

CDX-0159 Treatment Reduces Skin Mast Cells But Not Melanocytes

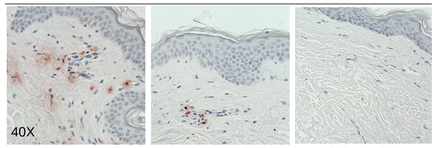




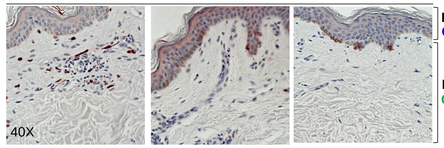
N=20; Paired t-tests: ns- not significant, ** p<0.01, ****p<0.0001

- CDX-0159 administration depletes skin mast cells as assessed independently by tryptase and CD117 (KIT) IHC.
- By contrast, CDX-0159 does not alter the number of CD117+ skin melanocytes.

Tryptase IHC



CD117 IHC



Epidermis
CD117+ melanocytes

Dermis
CD117+ mast cells

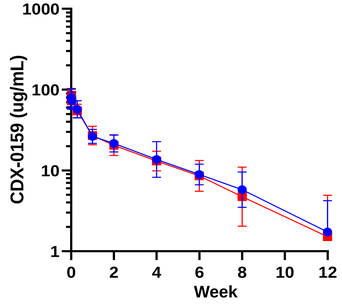
Representative IHC photomicrographs from one patient are shown.

CDX-0159 SAFETY

- CDX-0159 was generally well tolerated in patients with CIndU (ColdU and SD).
- The most common AEs were hair color changes (16/21 [76%]), infusion reactions (9/21 [43%]), and taste disorders (8/21 [38%]). Most AEs were mild.
- Hair color changes improved upon longer observation period.
- Infusion reactions were mostly mild, generally manifested as hives and itching and resolved spontaneously. A single severe infusion reaction occurred that was not attributed to MC activation.
- Taste disorders were selective and transient.
- Hematology parameters generally remained within the normal ranges. Mild, transient, and asymptomatic decreases in hemoglobin and WBC parameters were noted.

CDX-0159 PHARMACOKINETICS

CDX-0159 Serum Concentrations



ColdU (N=10), SD (N=10); Geometric mean ± geoSD

Noncompartmental Parameters

	Mean	Std Dev
$T_{1/2}$ (Days)	20.1	7.1
C_{max} (µg/mL)	88	18.7
AUC_{INF} (day*µg/mL)	1247	373
CL (mL/day/kg)	2.6	0.9
V_z (mL/kg)	69.5	7.0

ColdU + SD (N=20)

Summary and Discussion

- In patients with CIndU refractory to antihistamines, a single dose of CDX-0159 (3 mg/kg) resulted in rapid, profound, and durable responses as determined by provocation testing in 100% of patients with 95% achieving complete response, with marked improvement in urticaria control and QoL as previously reported[2,3].
- A rapid and sustained improvement in the UCT7 score mirrors reduction in tryptase and an increase in SCF.
- A marked (89%) and sustained reduction in skin mast cells is noted when assessed independently by tryptase or CD117 (KIT+) IHC and is consistent with reduction in circulating tryptase.
- The differential effect of CDX-0159 on mast cells vs. melanocyte numbers is consistent with the known distinct role of KIT in each cell type.
- Pharmacokinetics were typical for an IgG1 mAb, similar between urticaria patients and healthy volunteers[1] and circulating drug was detectable over the 12-week follow-up period.
- CDX-0159 was generally well tolerated. There was no evidence of clinically significant decreases in hematology parameters. Hair color changes and taste disorders are consistent with KIT inhibition and are expected to be fully reversible.
- CDX-0159 has significant potential as a therapy for CIndU and other mast cell-related diseases.

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