The Anti-kit Antibody, CDX-0159, Reduces Disease Activity and Tryptase Levels in Patients with Chronic Inducible Urticaria

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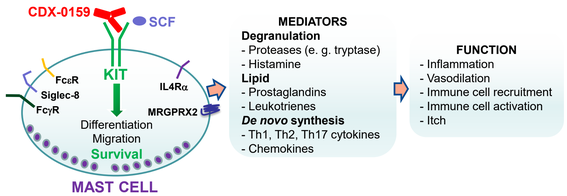
BACKGROUND

- Chronic inducible urticaria (CIndU) is characterized by mast cell (MC)-driven wheals in response to triggers such as cold in cold urticaria (ColdU) or scratching of the skin in symptomatic dermographism (SD).
- MCs require activation of their KIT receptors by stem cell factor for survival, proliferation, and differentiation. MC burden is correlated with circulating tryptase, a protease secreted specifically by MCs.
- CDX-0159 is a monoclonal anti-KIT antibody that is engineered to selectively inhibit SCF-dependent KIT activation.
- CDX-0159 demonstrated a profound dose related reduction of circulating tryptase and was overall well-tolerated in healthy volunteers.
- Patients with CIndU may benefit from treatment with CDX-0159.



STUDY DESIGN AND METHODS

CDX0159-03 is an ongoing open-label, Phase 1b trial in patients with CIndU (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 activity and serum tryptase.
- Activity endpoints include provocation test [TempTest/ColdU; FricTest/SD], physician's global assessment [Phys-GA], and patient's global assessment [Pat-GA] of disease severity.
- Mean ± SE are displayed for provocation tests, biomarkers and hematology.
- Skin MC numbers assessed using non-lesional skin biopsies enumerated by tryptase staining.

STUDY STATUS

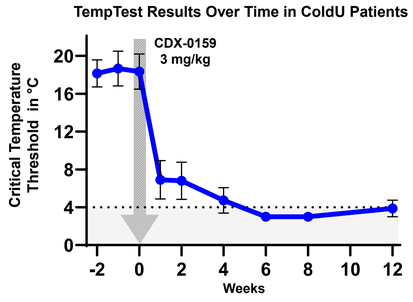
- Study is ongoing; data cut as of 11June2021.
- 20 patients received study drug and are included in the safety analysis.
- 19 patients received full dose and are included in the activity analysis. 14 of 19 patients completed the 12-week observation period; 5 are ongoing.

DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

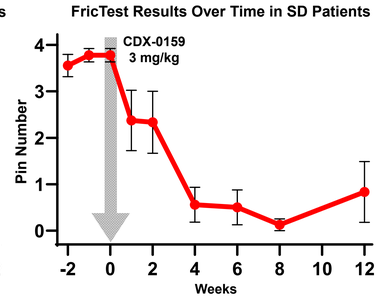
		ColdU (N=11)	SD (N=9)	All (N=20)
Age median (range) years		43 (27- 65)	41 (27- 56)	42 (27 - 65)
Gender Female, n (%)		6 (54.5%)	4 (44.4%)	10 (50%)
Race	White, n (%)	10 (90.9%)	9 (100%)	19 (95%)
	Asian, n (%)	1 (9.1%)	0 (0%)	1 (5%)
Ethnicity	Hispanic or Latino	1 (9.1%)	0 (0%)	1 (5%)
Weight median (range) kg		77.0 (61.0 – 93.0)	88.2 (57.0 – 122.0)	80.0 (57.0 - 122.0)
Disease Duration	< 5 yr, n (%)	6 (54.5%)	4 (44.4%)	10
	≥ 5 yr, n (%)	5 (45.5%)	5 (55.6%)	10
History of Angioedema		6 (54.5%)	0	6 (30%)
Provocation Threshold Mean (range)		18.9 (5.0-27.0) °C	3.8 (3-4) pins	
Phys-GA ≥ 2, n (%)		10 (91%)	9 (100%)	19 (95%)
Pat-GA ≥ 2, n (%)		6 (55%)	8 (89%)	14 (70%)
Prior Medication H1 Antihistamine		11 (100%)	9 (100%)	20 (100%)
	Biologics (omalizumab)	1 (9%)	2 (22%)	3 (15%)
Tryptase median (range) ng/mL		3.6 (2.1-5.5)	4.7 (1.6-8.6)	4.1 (1.6-8.6)

RESULTS

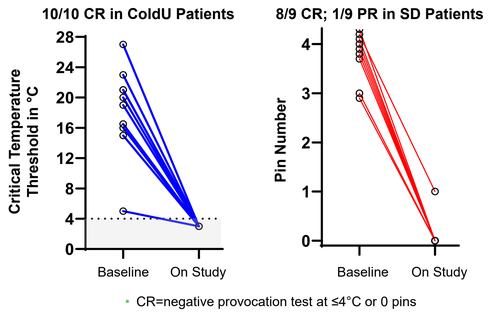
A Single Dose of CDX-0159 Results in a Rapid and Durable Response with 95% Complete Response (CR) Rate in Patients with CIndU



Among completed ColdU patients (n=8), CR was sustained for a median duration of 77+ days



Among completed SD patients (n=6), CR was sustained for a median duration of 57+ days



- CR=negative provocation test at ≤4°C or 0 pins
- PR=improvement by 4°C or ≥2 pins
- Maximum response for each patient is shown

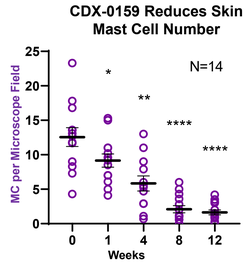
Overall Disease Improvement as Evidenced by Phys-GA and Pat-GA

Phys-GA and Pat-GA assess disease severity using a Likert scale of 0-3, where 0 is none and 3 is severe.

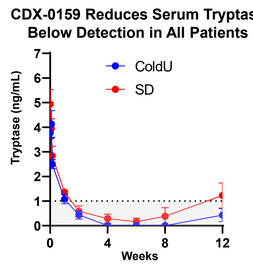
ColdU (CDX-0159 3 mg/kg)								
Weeks	-2 (n=10)	0 (n=10)	1 (n=10)	2 (n=10)	4 (n=9)	6 (n=9)	8 (n=9)	12 (n=8)
Phys-GA Mean (range)	2.3 (2-3)	1.9 (1-3)	0.6 (0-1)	0.6 (0-2)	0.4 (0-1)	0.1 (0-1)	0.2 (0-1)	0.6 (0-2)
Pat-GA Mean (range)	1.7 (0-3)	1.1 (0-2)	0.4 (0-1)	0.3 (0-1)	0.1 (0-1)	0.0	0.1 (0-1)	0.3 (0-2)

SD (CDX-0159 3 mg/kg)								
Weeks	-2 (n=9)	0 (n=9)	1 (n=9)	2 (n=9)	4 (n=9)	6 (n=9)	8 (n=8)	12 (n=6)
Phys-GA Mean (range)	2.4 (2-3)	2.0	1.8 (1-2)	1	0.6 (0-1)	0.4 (0-1)	0.5 (0-1)	0.7 (0-2)
Pat-GA Mean (range)	2.2 (3-9)	2 (1-3)	1.3 (1-2)	1 (0-2)	0.6 (0-2)	0.2 (0-1)	0.3 (0-1)	0.8

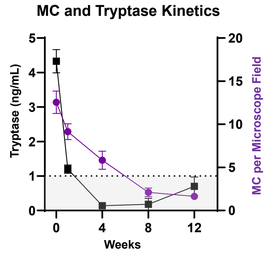
CDX-0159 Treatment Markedly Depletes Skin Mast Cells and Serum Tryptase

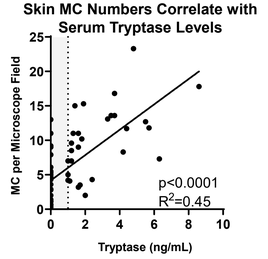


*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

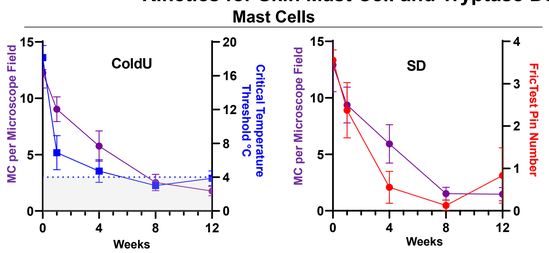


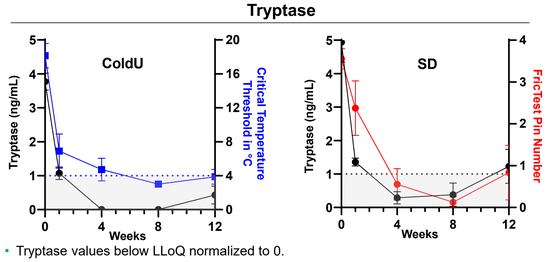
- Tryptase values below assay limit of quantitation (LLoQ = 1 ng/mL) normalized to 0





Kinetics for Skin Mast Cell and Tryptase Depletion Mirror Decreases in Provocation Thresholds

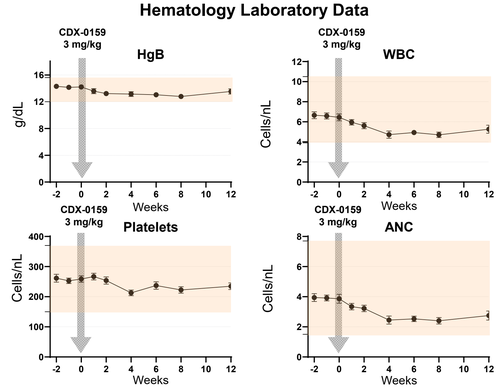




- Tryptase values below LLoQ normalized to 0.
- Critical temperature threshold values below 4°C (negative test) assigned a value of 3°C.

CDX-0159 Demonstrates Favorable Safety and Tolerability

- CDX-0159 was generally well tolerated in patients with CIndU.
- The most common AEs were hair color changes (14/20 [70%]), infusion reactions (9/20 [45%]), and taste disorders (8/20 [40%]). Most AEs were mild.
  - Hair color changes improved upon longer observation period.
  - Infusion reactions, generally manifested as hives and itching, 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.



Shaded area represents the normal range

SUMMARY AND DISCUSSION

- A single dose of CDX-0159 (3 mg/kg) results in a rapid, profound, and durable complete response in patients with CIndU refractory to antihistamines.
  - Complete response was achieved in 95% patients (100% in ColdU and 89% in SD patients) including in patients who had received prior omalizumab and was sustained for a median duration of 77 days in ColdU and 57 days in SD patients who completed the 12 week follow-up period.
  - Improved disease activity assessed by Phys-GA and Pat-GA is consistent with the complete response per the provocation test.
- A single 3 mg/kg CDX-0159 dose resulted in a rapid, marked, and durable depletion of skin MCs and serum tryptase.
  - The kinetics of skin MC and serum tryptase depletion mirror clinical activity.
  - Serum tryptase level is a robust pharmacodynamic biomarker for assessing MC burden and clinical activity in patients with CIndU.
- 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 inhibiting KIT signaling in other cell types and are expected to be fully reversible.
- CDX-0159 demonstrated unprecedented MC depletion with a favorable safety profile, providing significant potential as a therapy for CIndU and opening opportunities for the evaluation of MC involvement across many diseases.