CDX-0159, an anti-KIT monoclonal antibody, demonstrates dose-dependent reductions in plasma Tryptase and a favorable safety profile in a Phase 1a healthy volunteer study

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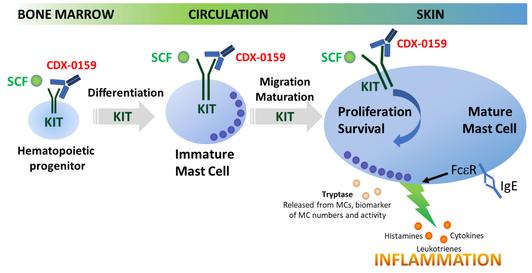
BACKGROUND

- Mast cells (MCs) underlie the etiology of many allergic and chronic inflammatory diseases, such as chronic urticaria
  - Systemic MC burden is proportional to plasma Tryptase, a protease secreted specifically by MCs
- Activation of the KIT receptor tyrosine kinase by Stem Cell Factor (SCF) is required for the differentiation, chemotaxis, maturation and survival of MCs
- KIT-specific inhibitors have the potential to ablate systemic MC activity and benefit patients with MC disorders
- CDX-0159 is a humanized anti-KIT IgG1 monoclonal antibody (mAb) that:
  - Selectively inhibits SCF-dependent KIT activation and *in vitro* MC degranulation with picomolar affinity
  - Is devoid of effector function and agonist activity
  - Has been engineered for enhanced serum half-life for more infrequent dosing
  - Is 100-1000-fold more potent than KIT-targeting small molecules



STUDY DESIGN

- Cohorts of healthy volunteers (HV) received escalating single doses of CDX-0159 or placebo (3:1) in a blinded fashion and were followed for 42 days thereafter
- **Primary Objectives:**
  - Safety and tolerability
- **Secondary Objectives**
  - Pharmacokinetics, Pharmacodynamics (Tryptase and SCF) and Immunogenicity
- 32 subjects dosed in one center (Altasciences, Overland Park, KS)
- All subjects completed the study (Day 43)

Cohort	CDX-0159 Dose Level	Number of Subjects: CDX-0159	Number of Subjects: Placebo*
1	0.3 mg/kg	6	2
2	1 mg/kg	6	2
3	3 mg/kg	6	2
4	9 mg/kg	6	2
Total		24	8

* Placebo-dosed volunteers were pooled for analysis

RESULTS

Demographics

	CDX-0159 0.3 mg/kg (n=6)	CDX-0159 1 mg/kg (n=6)	CDX-0159 3 mg/kg (n=6)	CDX-0159 9 mg/kg (n=6)	CDX-0159 Total (n=24)	Placebo (n=8)
Age (median, range, years)	29.5 (24 - 55)	27.5 (26 - 44)	39.5 (23 - 55)	25.5 (20 - 53)	29.0 (20 - 55)	33.5 (24 - 51)
Gender						
Female, N (%)	2 (33%)	4 (67%)	3 (50%)	3 (50%)	12 (50%)	4 (50%)
Male, N (%)	4 (67%)	2 (33%)	3 (50%)	3 (50%)	12 (50%)	4 (50%)
Race						
White, N (%)	2 (33%)	3 (50%)	6 (100%)	1 (17%)	12 (50%)	1 (12%)
Black/African American, N (%)	4 (67%)	3 (50%)	0 (0%)	5 (83%)	12 (50%)	7 (88%)
Ethnicity						
Not Hispanic or Latino	6 (100%)	6 (100%)	6 (100%)	6 (100%)	24 (100%)	8 (100%)
Weight (median, range, kg)	79.0 (60.5 – 89.9)	76.8 (55.1 – 95.4)	74.3 (57.4 - 94.1)	68.7 (59.7 – 85.8)	76.0 (55.1 – 95.4)	71.6 (62.0 - 84.7)
Baseline Tryptase Levels (median, range, ng/mL)	3.9 (2-21.2)	2.3 (1.8-3.8)	3.8 (1.7-8.4)	3.4 (1.9-4.7)	3.4 (1.7-21.2)	3.1 (1.9-6.7)

CDX-0159 Demonstrates a Favorable Safety Profile

- CDX-0159 was well tolerated at all dose levels
- 13 (54%) subjects treated with CDX-0159 experienced grade 1 (mild) infusion-related reactions
  - Symptoms of hives and/or erythema with some itching
  - Reactions spontaneously resolved without intervention during infusion or up to 180 minutes after completion of infusion
  - Not clearly dose dependent
- Mild and asymptomatic decreases in hematologic parameters (white blood cells, neutrophils) appeared to occur more frequently in subjects treated with CDX-0159 than placebo
- No notable differences observed in chemistry analytes or RBC, platelets or hematocrit

Treatment Emergent Adverse Events Occurring in 3 or More Subjects

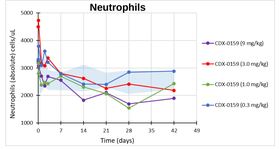
	CDX-0159 0.3 mg/kg (n=6)	CDX-0159 1 mg/kg (n=6)	CDX-0159 3 mg/kg (n=6)	CDX-0159 9 mg/kg (n=6)	CDX-0159 Total (n=24)	Placebo (n=8)
Any Event	2 (33%)	5 (83%)	6 (100%)	6 (100%)	19 (79%)	5 (63%)
Infusion related reaction	2 (33%)	5 (83%)	5 (83%)	1 (17%)	13 (54%)	0 (0%)
WBC count decreased	0 (0%)	0 (0%)	0 (0%)	4 (67%)	4 (17%)	1 (13%)
Neutrophil count decreased	0 (0%)	0 (0%)	0 (0%)	4 (67%)	4 (17%)	1 (13%)
Sensation of Foreign Body in the Throat	0 (0%)	0 (0%)	0 (0%)	3 (50%)	3 (13%)	0 (0%)

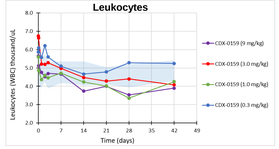
Hematology Laboratory Data

Change from Baseline to Post-Baseline Minimum, mean (SD)

	CDX-0159 0.3 mg/kg (n=6)	CDX-0159 1 mg/kg (n=6)	CDX-0159 3 mg/kg (n=6)	CDX-0159 9 mg/kg (n=6)	CDX-0159 Total (n=24)	Placebo (n=8)
Leukocytes (WBC, 10^9/L)	-1.7 (1.2)	-2.3 (0.8)	-3.0 (0.9)	-2.5 (0.7)	-2.4 (1.0)	-1.4 (1.3)
Erythrocyte Count (RBC, 10^{12}/L)	-0.4 (0.3)	-0.5 (0.3)	-0.6 (0.2)	-0.8 (0.3)	-0.6 (0.3)	-0.4 (0.2)
Hematocrit (%)	-3.0 (2.0)	-3.9 (2.1)	-4.0 (1.9)	-6.4 (2.8)	-4.3 (2.5)	-3.3 (2.0)
Platelets (10^9/L)	-40.2 (24.7)	-67.2 (40.1)	-67.3 (40.7)	-54.5 (30.4)	-57.3 (34.2)	-45.2 (38.9)
Neutrophils (10^9/L)	-1.3 (1.1)	-1.8 (1.0)	-2.7 (0.8)	-1.9 (0.7)	-1.9 (1.0)	-1.0 (1.1)

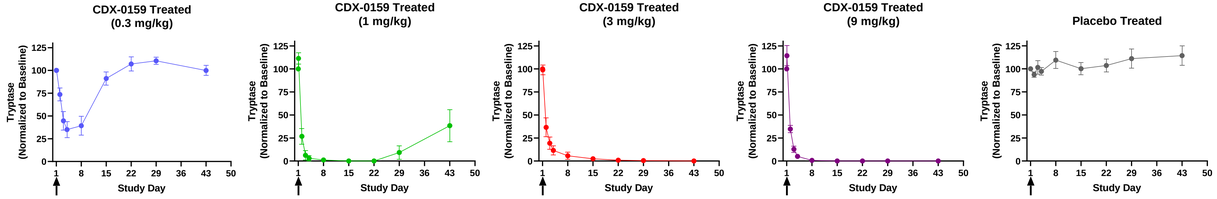
Hematology (cohort means and placebo 95% confidence interval)





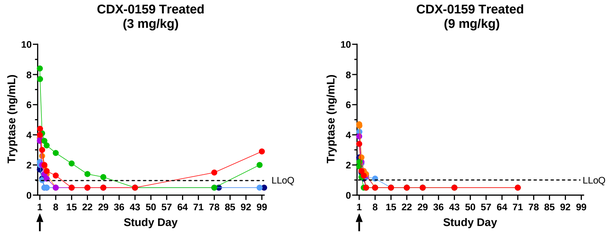
CDX-0159 Suppresses Plasma Tryptase and Increases SCF in a Dose-Dependent Manner

Dose-dependent Tryptase Inhibition to Day 43



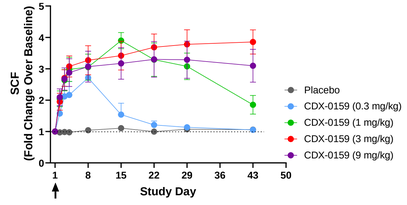
- Tryptase is a protease released specifically by MCs, and its plasma level is proportional to systemic MC load
- A single dose of CDX-0159 suppressed plasma Tryptase levels in a dose-dependent manner, indicative of systemic MC suppression
  - Baseline-normalized cohort means +/- S.E.M. are shown

Sustained Tryptase Suppression



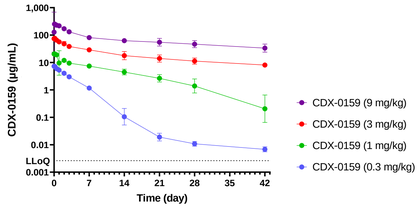
- Durable Tryptase suppression observed at 3 and 9 mg/kg doses to > day 71
  - Reduction below 1 ng/mL (LLoQ) observed in 3/4 volunteers at day 71-78 and 2/4 volunteers at days 98-99 at 3 mg/kg
  - Reduction below LLoQ in all (4/4) volunteers at day 71 at 9 mg/kg
  - Additional Tryptase analysis to day ~130 for cohorts 3 and 4 is planned

CDX-0159 Increases Plasma SCF Levels



- Dose dependent increases in plasma SCF consistent with allosteric blockade of SCF to KIT by CDX-0159
  - Cohort means +/- S.E.Ms reported

Pharmacokinetics and Immunogenicity



Dose	Half-life (days)	Cmax (µg/mL)	AUCINF (day*µg/mL)	Cl (mL/day/kg)
0.3 mg/kg (N=6)	15.1 (2.3)	7.6 (0.6)	28.2 (3.5)	10.8 (1.4)
1 mg/kg (N=6)	6.2 (2.4)	21.8 (2.5)	175.9 (37.8)	5.9 (1.2)
3 mg/kg (N=4*)	22.9 (3.9)	76.2 (12.7)	1085.7 (133.9)	2.8 (0.3)
9 mg/kg (N=6)	32.3 (10.1)	275.0 (28.4)	4563.6 (1193.1)	2.1 (0.6)

* *PK data from 2 volunteers excluded*

- Long serum half life and decreased clearance consistent with engineered Fc mutations that enhance FcRN binding
- No evidence of anti-drug antibodies

CONCLUSIONS

- Phase 1a healthy volunteer study with CDX-0159 demonstrated a favorable safety profile and profound Tryptase suppression, indicative of systemic MC ablation
  - Most common adverse events were mild infusion-related reactions, and mild and asymptomatic decreases in neutrophil and WBC count were observed
  - Profound reduction in plasma Tryptase was observed for > 2 months at single 3 and 9 mg/kg CDX-0159 doses
  - Dose dependent increases in plasma SCF mirror decreases in Tryptase and are consistent with allosteric blockade of SCF to KIT
- Long serum half-life and non-immunogenic profile support a more flexible dosing schedule
  - Enhanced PK profile and durable Tryptase suppression at low doses support re-formulation for sub-cutaneous administration
- Data support multiple dosing in patients with MC-driven disorders
- Phase 1b studies in chronic inducible urticaria (CINDU) and chronic spontaneous urticaria (CSU) are planned for 2H 2020

Presented by Dr. Marcus Maurer at the 2020 EAACI Conference