A Phase 1 Trial of the Hematopoietic Growth Factor CDX-301 (rhuFlt3L) in Healthy Volunteers

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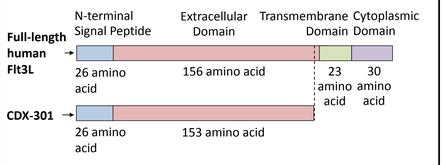
CDX-301: BACKGROUND

- Flt3 receptor (CD135) is expressed on hematopoietic stem cells (HSC), early progenitor cells, immature thymocytes, and steady state dendritic cells
- Fms-like tyrosine kinase-3 ligand (Flt3L) uniquely binds CD135 and induces the proliferation, differentiation and mobilization of CD135-bearing cells in the bone marrow, peripheral blood, and lymphoid organs.

CDX-301 is the Soluble Recombinant Human Protein Form of the Hematopoietic Cytokine, Flt3L



Prior Clinical Experience

Safety and biologic activity of recombinant human Flt3L (rhuFlt3L) were originally demonstrated in clinical studies conducted by Immunex utilizing a 14 day dosing regimen.

- Over 500 individuals treated, including ~150 healthy volunteers and 380 oncology patients.
- Studied as monotherapy for cancer immunotherapy and cancer vaccine adjuvant and in combination with GM-CSF or G-CSF for peripheral blood stem cell (PBSC) mobilization.
- Effectively mobilized large numbers of CD34+ stem cells into peripheral blood, and markedly increased the number of myeloid and plasmacytoid dendritic cells in the circulation.
- Generally well-tolerated
  - In healthy volunteers, Grade 2 events were limited to injection site reactions/pain.
  - The expected pharmacologic effects of rhuFlt3L (increased WBC and monocytes) were observed.
  - No neutralizing anti-rhuFlt3L antibodies were seen in 207 tested patients.

CDX-301 is composed of the identical amino acid sequence and has comparable biologic activity as the Immunex product.

STUDY DESIGN

- Phase 1 open label, dose escalation study in healthy volunteers
- Objectives:
  - Safety and tolerability
  - Pharmacokinetic profile
  - Immunogenicity
  - Extend biological characterization of rhFLT3L in humans
- Design:
  - Sequential cohorts enrolled after 21-day observation for dose-limiting toxicity (DLT) and immunogenicity
  - CDX-301 given by daily subcutaneous injection during an in-patient treatment period
  - Post-treatment safety follow-up for at least 28 days

Planned Treatment Cohorts

Cohort 1: 1 μg/kg (n=3-6)	5-day dosing
Cohort 2: 3 μg/kg (n=3-6)	
Cohort 3: 10 μg/kg (n=3-6)	
Cohort 4: 25 μg/kg (n=3-6)	
Cohort 5: 75 μg/kg (n=3-6)	
Cohort 6: 25 μg/kg (n=6)	7-day dosing
Cohort 7: 25 μg/kg (n=6)	10-day dosing

ENROLLED SUBJECTS

- The study is complete with 30 subjects enrolled.
- All enrolled volunteers completed the expected duration of dosing and safety follow-up.

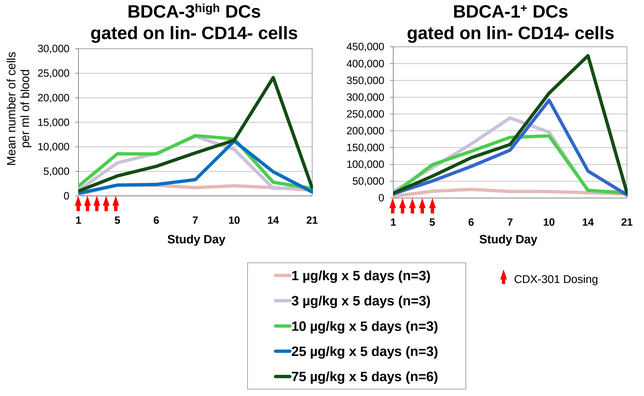
Demographic Characteristics (n=30)	
Age, years [Median (range)]	34 (19-54)
Male [n (%)]	20 (67%)
Race [n (%)]	
Black /African American	12 (40%)
White	10 (33%)
Asian	1 (3%)
Other	7 (23%)

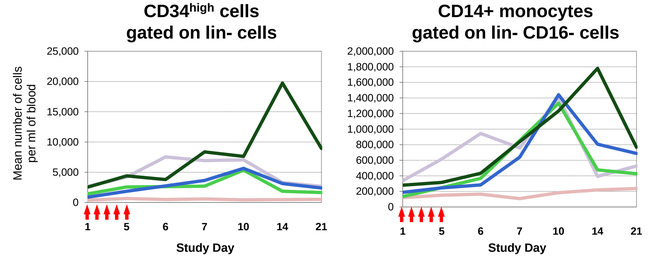
SAFETY

- One possible DLT (temporal association with dosing)
  - A volunteer in Cohort 5 (75 mg/kg) with a remote history of community acquired pneumonia developed community acquired pneumonia on study day 12; the event responded rapidly to antibiotic treatment and fully recovered within 2 weeks
  - The cohort was expanded to a total of six volunteers, and the study was completed through Cohort 7 with no additional infections or DLT
- Infrequent treatment-related toxicity
  - Transient Grade 1 lymphadenopathy in five volunteers (Cohorts 4, 5 and 7)
  - Grade 1 diarrhea in two volunteers (Cohorts 5 and 7)
- No anti-CDX-301 antibodies were detected in any volunteers through end of study follow-up.

FLOW CYTOMETRY

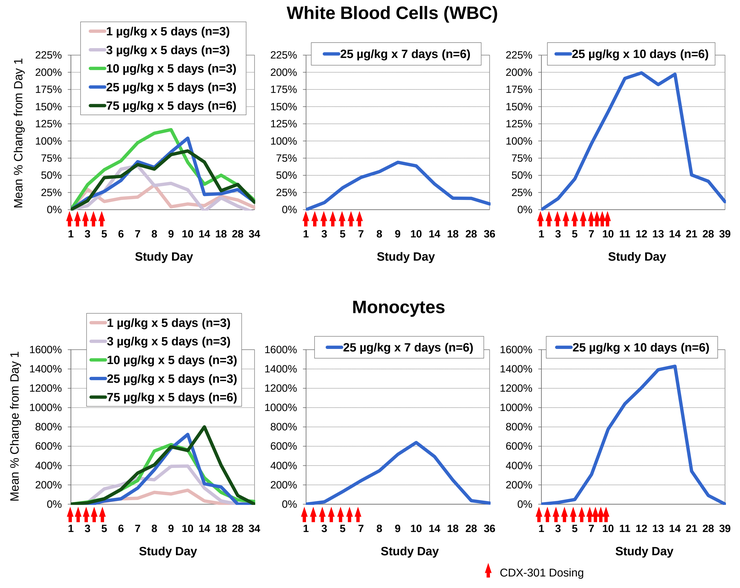
- Preliminary peripheral blood flow cytometry results are available for the first five cohorts (5 day dosing).
- No consistent changes observed in $CD3^+$T cells, $CD20^+$ B cells, or $CD335^+$ NK cells.
- Marked increase in $CD14^+$ monocytes, $CD34^+$ stem cells, type 1 myeloid DCs ($BDCA\text{-}1^+$) and type 2 myeloid DCs ($BDCA\text{-}3^+$) observed.
- Greatest effect observed at the 75 mg/kg dose level, with peak effects occurring at 10-14 days.





PBMCs were purified and stored frozen until they could be analyzed together. Subset analysis was carried out using cocktails of labeled antibodies to surface markers and isotype controls to define positive staining.

HEMATOLOGIC CELL POPULATIONS



CONCLUSIONS

- Data from this current Phase 1 trial are consistent with previous studies showing that rhFlt3L is well-tolerated and can safely and effectively mobilize hematopoietic cell populations.
- The short term dosing regimen (5 days) showed significant mobilization of dendritic cells (DCs) and stem cells, with the highest levels achieved with the maximum dose of 75 μg/kg/day.
- The longer dosing regimen of 7 and 10 days significantly enhanced the expansion of circulating WBC and monocytes compared to 5 days regimen. Comprehensive analysis on the expansion of stem cells, DCs, and other specific cell populations are pending.
- Investigation of varying dose and duration of treatment with rhFlt3L has not been reported previously and will be valuable for assessing the appropriate regimen for future studies of CDX-301 in allogeneic hematopoietic stem cell transplantation (HSCT) and immunotherapy.

Conflict of interest disclosures: Renee Riggs, Jennifer Green, Michael Yellin, MD, Thomas A. Davis, MD, and Tibor Keler, PhD are employees and have equity ownership in Celldex Therapeutics, Inc.