

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

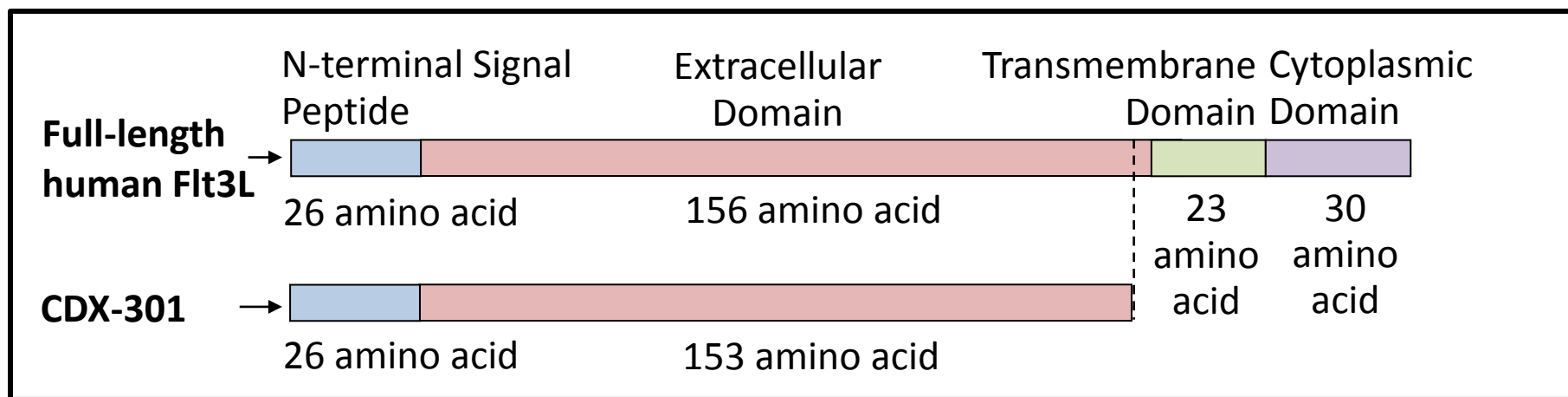
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on behalf of

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CDX-301 (rhuFlt3L)

- CDX-301 is the soluble recombinant human protein form of Fms-like tyrosine kinase-3 ligand (Flt3L)
 - Formerly developed by Immunex (now Amgen) as “Mobista”
 - Program licensed and development reinitiated by Celldex
- Flt3 receptor (CD135): Expressed on hematopoietic stem cells, early progenitor cells, immature thymocytes, and steady state dendritic cells
- Flt3L uniquely binds CD135 and induces proliferation, differentiation and mobilization of CD135-bearing cells in the bone marrow, peripheral blood, and lymphoid organs.



FLT3L Promotes Proliferation and Expansion of Hematopoietic Cells

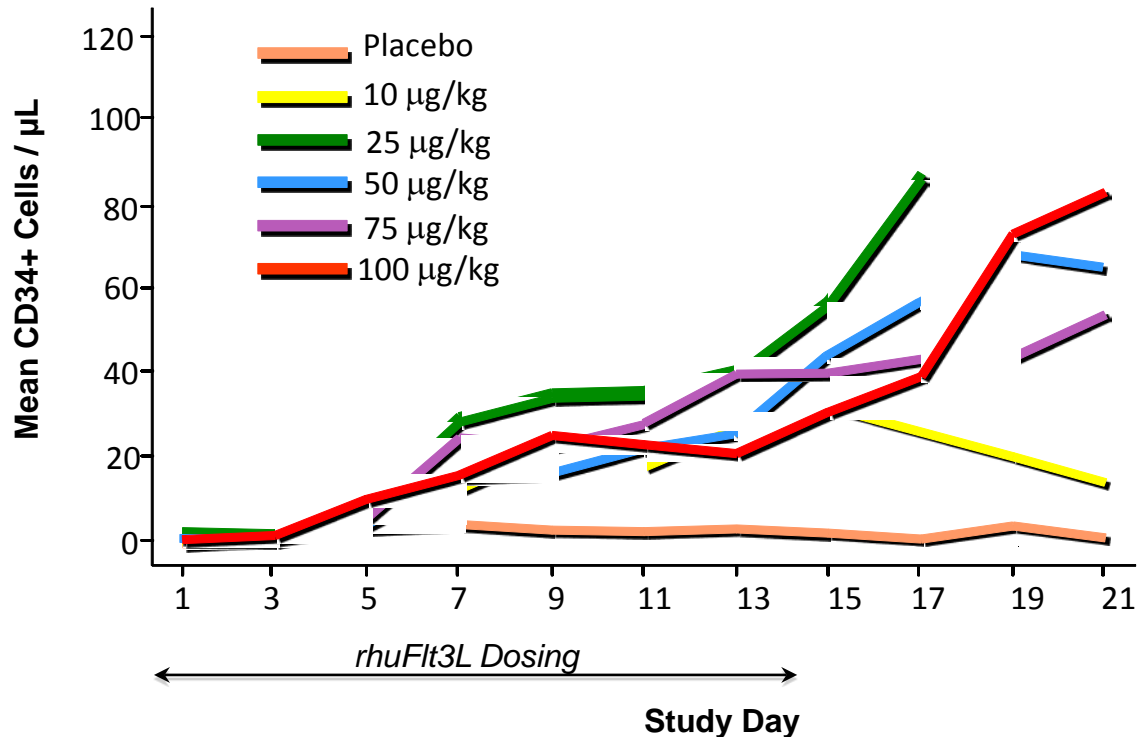
- Induces proliferation/expansion of hematopoietic stem/progenitor cells from BM, Spleen, PB and CB. Effect is markedly augmented in combination with other growth factors (Brasel 1996; De Felice 1998; Wodnar-Filipowicz 2003)
- Key regulator of DC proliferation, inducing marked increases in both myeloid and plasmacytoid DCs (Maraskovsky 1996)
- Enhances immune reconstitution in T cell depleted animals (Fry 2004)
- Mediates protective effects from acute GVHD in rodent transplant model (Teshima 2002)
- Regulates Treg and NK cell homeostasis via effects on DCs (Darrasse-Jeze 2009; Swee 2009; Guimond 2010)
- Mediates radioprotection following total body irradiation (Gratwohl 1998)

Prior Clinical Experience

- >500 individuals treated, including ~150 healthy subjects and 380 oncology patients
- Studied as monotherapy (cancer immunotherapy/vaccine adjuvant) and in combination with GM-CSF or G-CSF (PBSC mobilization)
- 1 and 14 day dosing regimen (with repeat cycles q 28 days in Phase 2 oncology studies)
- Generally well-tolerated
 - In healthy subjects, 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 in 207 tested subjects.

Prior Clinical Experience

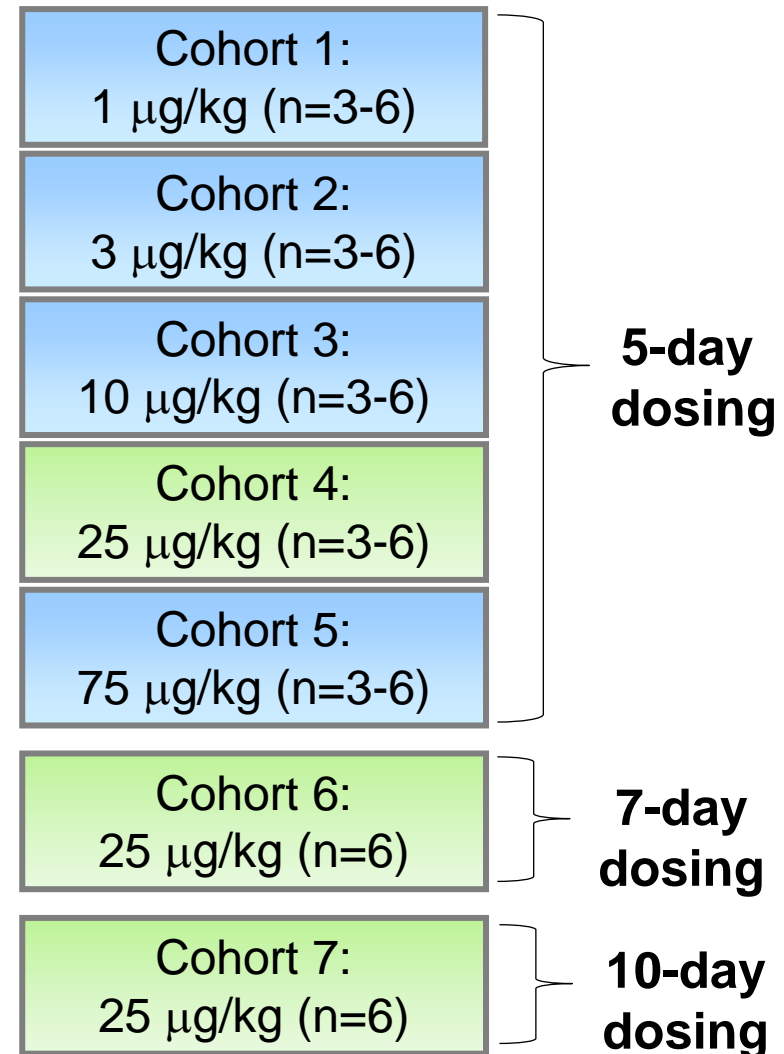
- rhuFlt3L effectively mobilized large numbers of CD34+ stem cells into peripheral blood, and markedly increased the number of myeloid and plasmacytoid dendritic cells in the circulation.
 - Doses above 25 $\mu\text{g}/\text{kg}$ did not increase expansion (14 day regimen)



CDX-301: Phase 1 Study Design

- Open label, dose escalation study in healthy subjects, conducted at Rockefeller University
- Objectives:
 - Investigate mobilization using various doses/schedules
 - Broaden the biological characterization of Flt3L in humans
 - Safety and tolerability
 - Pharmacokinetic profile
 - Immunogenicity
- Design:
 - CDX-301 given by daily subcutaneous injection during an in-patient treatment period
 - Post-treatment safety follow-up for at least 28 days

Treatment Cohorts



Enrolled Subjects

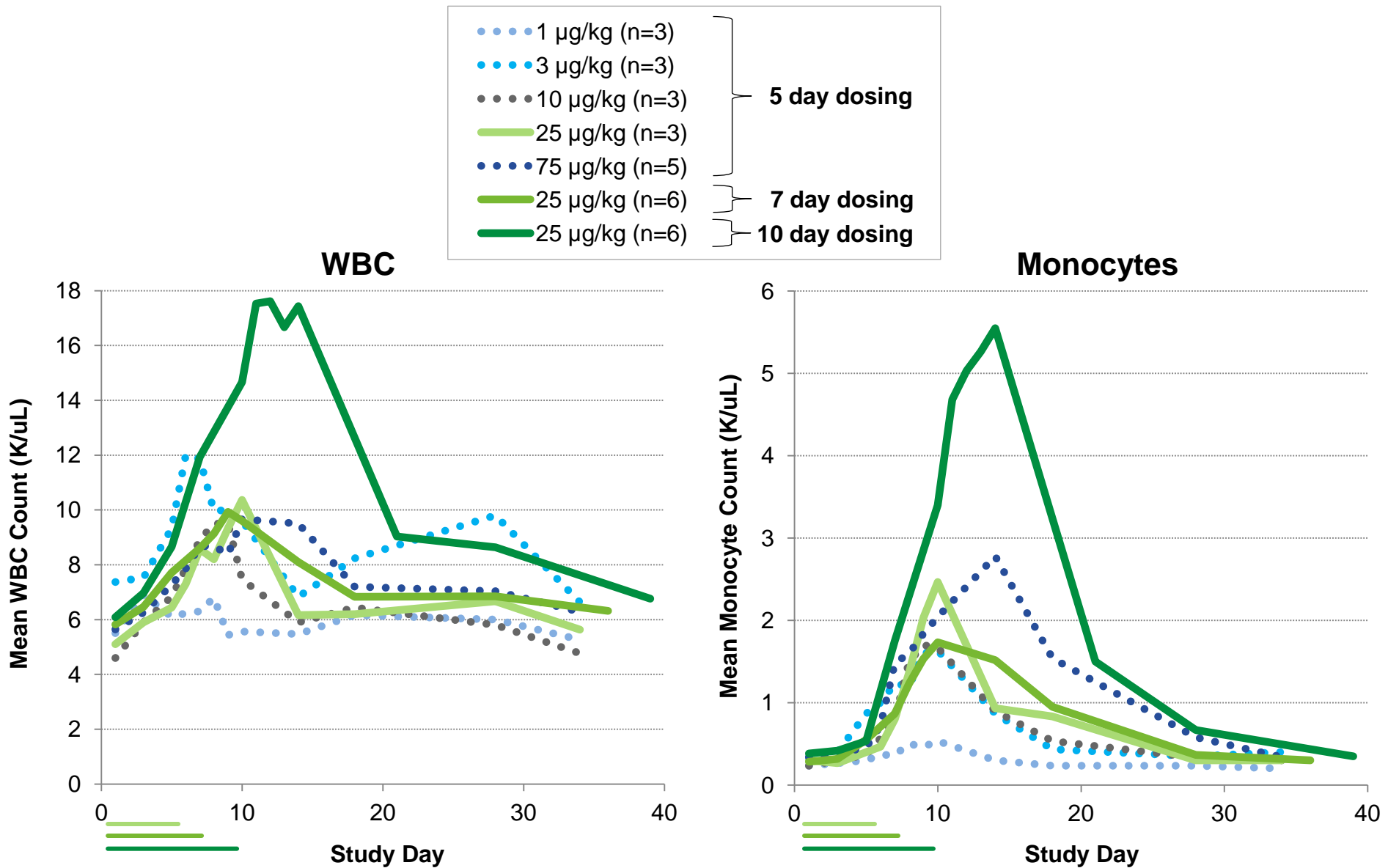
- The study is complete with 30 subjects enrolled.
- All enrolled subjects completed the expected duration of dosing and safety follow-up.

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/Unknown	7 (23%)

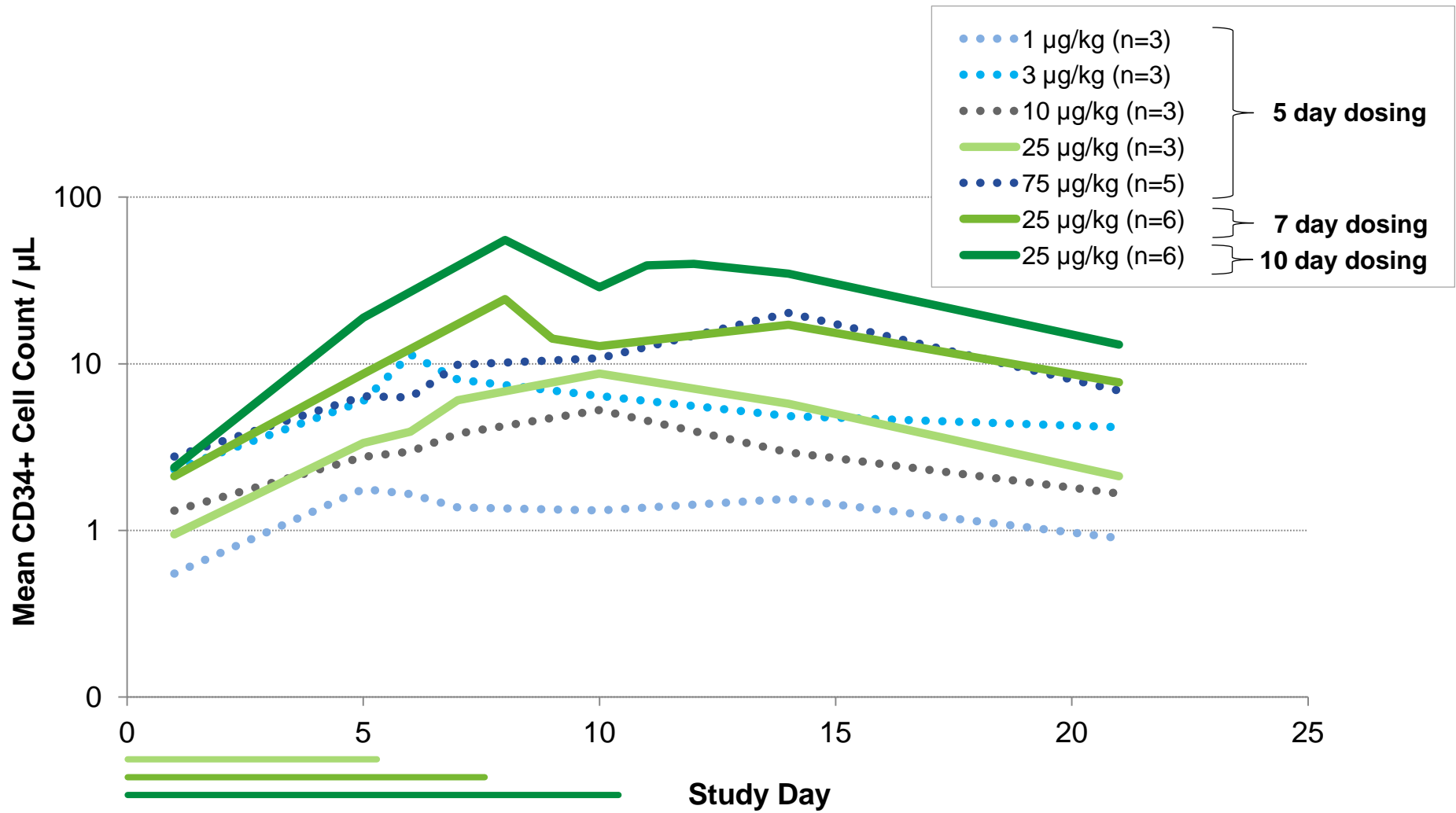
CDX-301 Tolerability

- One subject in Cohort 5 (75 µg/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
 - Attribution to CDX-301 is unclear; considered Dose-Limiting Toxicity (DLT) due to temporal relationship to dosing
 - The cohort was expanded to a total of six subjects, and the study was completed with no additional infections or DLT
- Infrequent treatment-related toxicity
 - Transient Grade 1 lymphadenopathy in six subjects (all treated at 25 µg/kg or 75 µg/kg)
 - Single cases of diarrhea, injection site erythema, folliculitis and dry mouth (all Grade 1)
- No anti-CDX-301 antibodies were detected in any subjects through end of study follow-up.

CDX-301 Increases WBC and Monocyte Count in Peripheral Blood

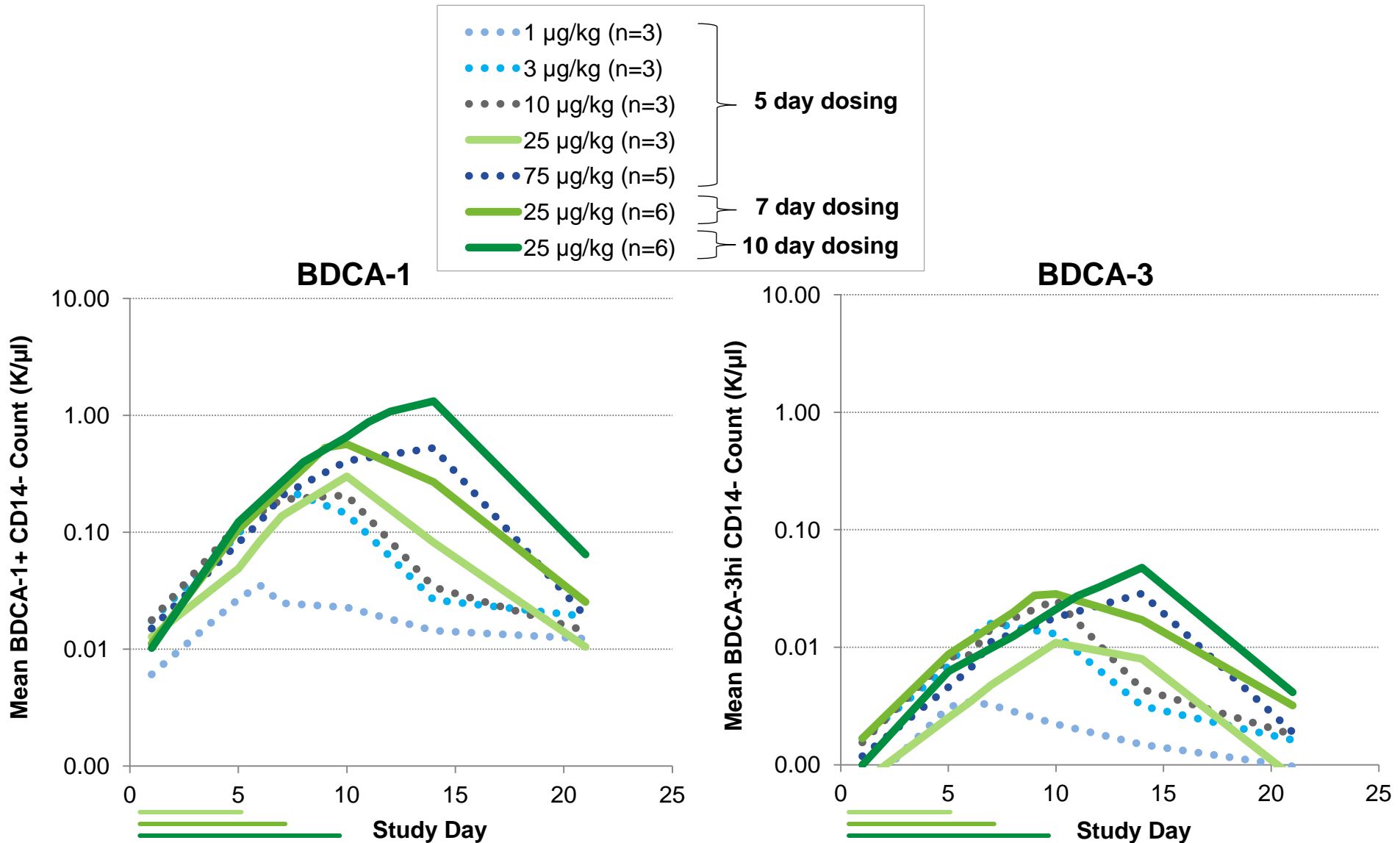


CDX-301 Increases CD34⁺ Cells in Peripheral Blood

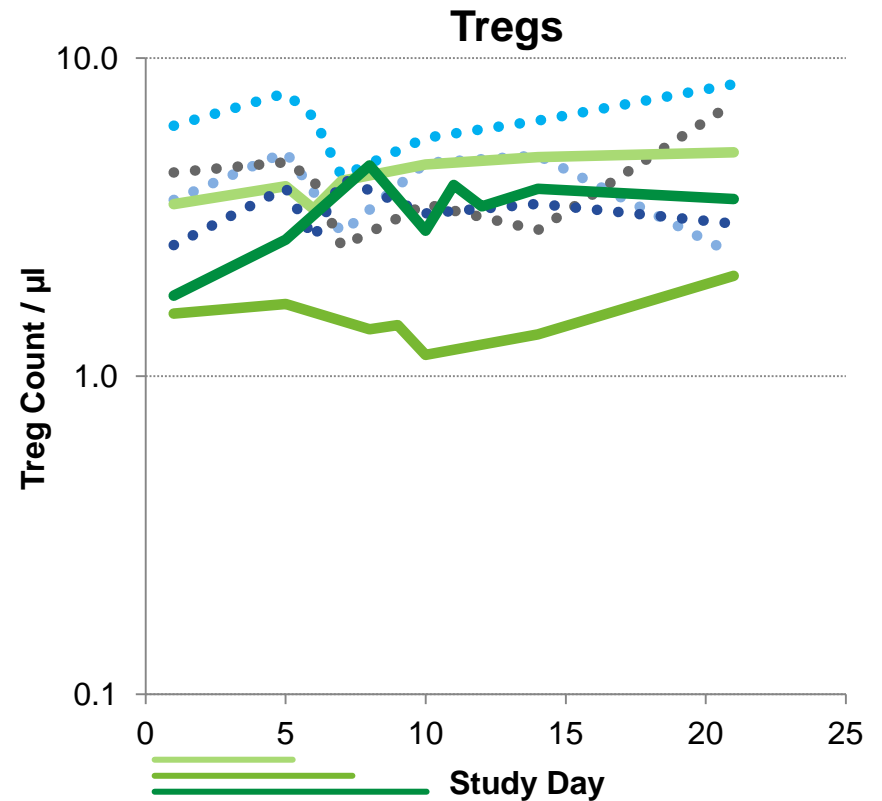
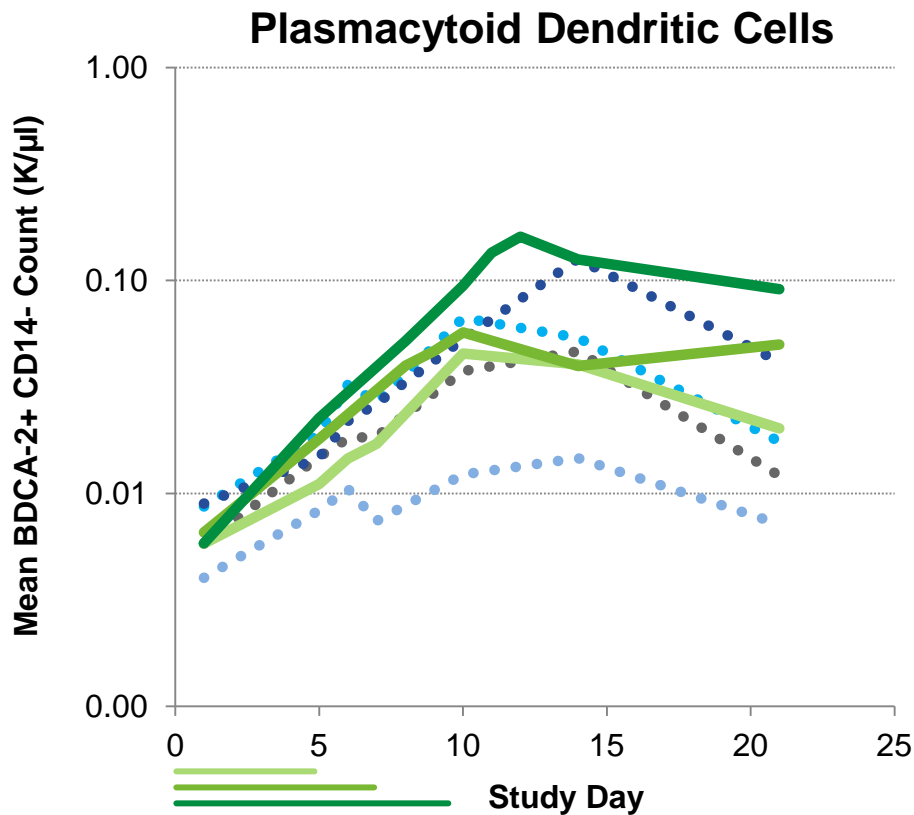
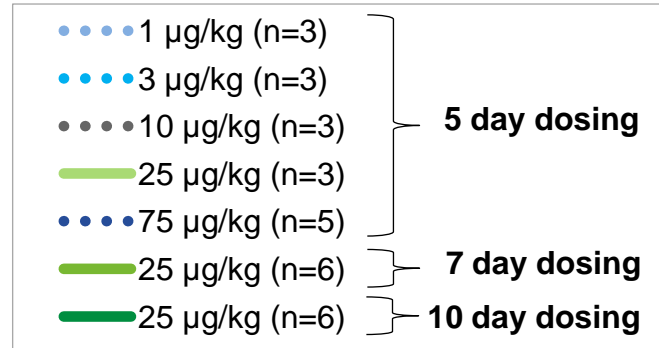


Flow cytometry methods: PBMCs were purified and stored frozen until they could be analyzed together. Subset analysis was carried out using cocktails of labeled antibodies to surface markers and isotype controls to define positive staining.

CDX-301 Increases Myeloid Dendritic Cells in Peripheral Blood



Affect of CDX-301 on Plasmacytoid Dendritic Cells and Tregs in Peripheral Blood



Conclusions

- This phase 1 study provided data consistent with the previous clinical experience showing that rhuFlt3L is well-tolerated and can safely and effectively mobilize CD34+ hematopoietic stem cells and dendritic cells as a single agent in normal subjects.
- A five day dosing regimen showed significant mobilization of hematopoietic stem cells into peripheral blood.
- These data support evaluation of CDX-301 in donor marrow mobilization for allogeneic transplant, including combination with plerixafor.
 - Preclinical data support marked increase in PBSC populations when plerixafor is given in combination with CDX-301 (personal communication from Dr. Steven Devine, OSU)
 - A clinical study is in preparation
- Preclinical data suggest rhuFlt3L may improve engraftment and reduce GVHD, supporting evaluation of multiple endpoints and use in recipients

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