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A Phase 2, Open-label Study to Evaluate the Safety and Hematopoietic Stem Cell Mobilization of TG-0054 (burixafor) Alone or in Combination with G-CSF in Patients with Multiple Myeloma, Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma

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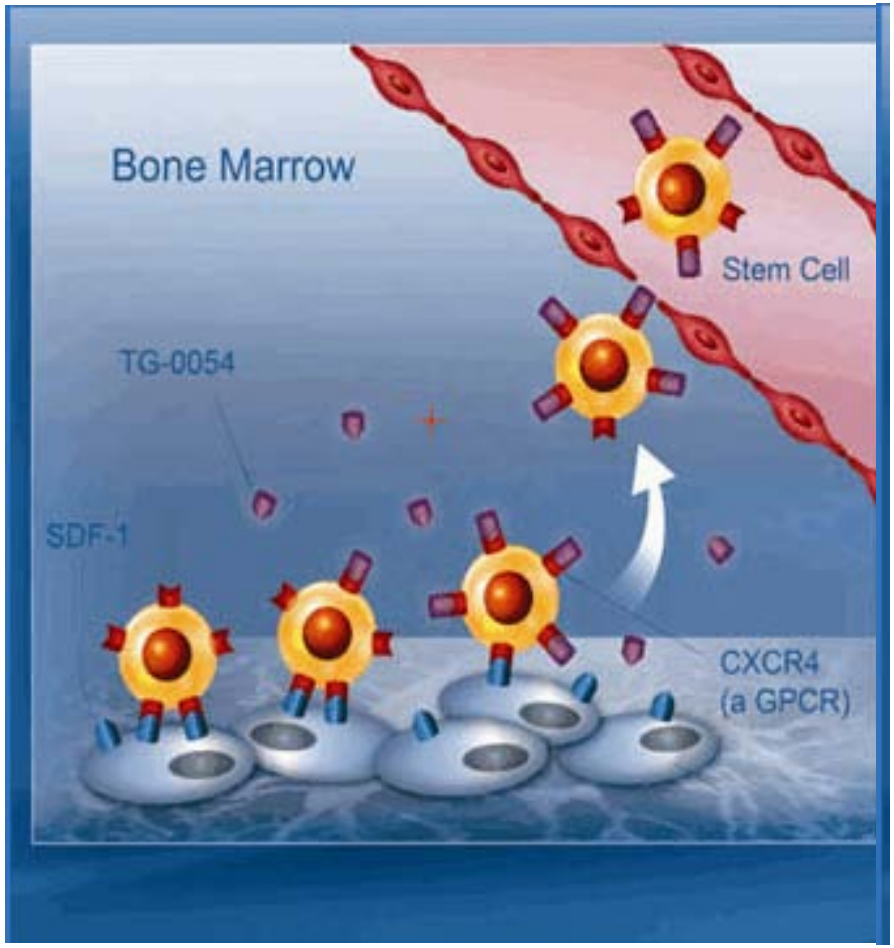
TG-0054 (Burixafor)

- Burixafor is a potent antagonist of CXCR4 and blocks the interaction between the cell surface receptor CXCR4 and its only ligand SDF-1
- The blockage of the interaction causes rapid mobilization of stem cells from bone marrow into peripheral blood



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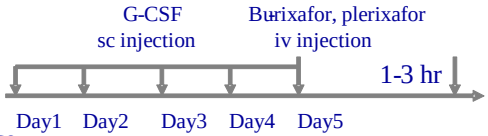
Synergistic Stem Cell Mobilization Activities with G-CSF

- Additive or synergistic effects in mobilizing HSCs were observed when burixafor was combined with G-CSF



BALB/c mice
8- wks old

Cell number of:
- Total WBCs
- CXCR4+ cells
- CD34+ cells

Compound	Fold increase		
	WBC	CXCR4	CD34
G-CSF (100 ug/kg/day)	10.3	7.9	14.8
Plerixafor (3.6 mg/kg)[a]	2.4	6.5	2.7
G-CSF+Plerixafor	11.0	19.3[b]	20.3[b]
Burixafor (5mg/kg)	3.2	5.0	2.9
G-CSF+Burixafor (5mg/kg)	15.4[b]	16.9[b]	15.4[a]
Burixafor (50mg/kg)	8.2	24.0	12.9
G-CSF+Burixafor (50mg/kg)	23.0[b]	29.0[b]	37.1[b]

**Tolerant dose of plerixafor via IV administration is 3.6 mg/kg a: additive b: synergistic*

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Non-Clinical Pharmacology

	Radioligand-binding assay		Eu-GTP binding assay		Calcium mobilization assay	Chemotaxis
	CXCR4	CXCR3	CXCR4	CXCR3	CXCR4 (μM)	CXCR4 (μM)
Burixafor	0.01	> 30	0.006	> 10	0.059	0.043
Plerixafor	0.5	> 30	0.041	> 10	0.146	0.302

- Burixafor is a potent CXCR4 antagonist and shows good selectivity against other human chemokine receptors
- In *in vitro* studies with major human liver microsomal cytochrome P450s, burixafor did not inhibit the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes.
- Burixafor was tested against 68 selected targets of lead profile screening at 100 uM. No significant off-target activities were observed.

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Stem Cell Mobilization by Burixafor

Comparison of *in vivo* Activities of Burixafor vs. Plerixafor Administered Intravenously to Mice

	Minimal effective dose	Fold increase at 1 mg/Kg			Max. fold increase (at tolerant dose)		
		WBC	CXCR4+	CD34+	WBC	CXCR4+	CD34+
Plerixafor	1.0	1.9	4.8	2.1	3.3	8.0	4.8
Burixafor	1.0	2.9	3.4	5.8	6.6	28.7	14.5

The IV MTD of burixafor–HBr salt in mice is 50 mg/kg.
The IV MTD of plerixafor –HCl salt in mice is 3.6 mg/kg

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Phase I Study in Healthy Volunteers

Study Results

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Phase I Study Overview

- **Study Design**
  - Randomized, Double-Blind, Placebo-Controlled, Sequential Ascending Single IV Dose
- **Objectives**
  - Safety and tolerability; Maximum tolerated dose (MTD)
  - PK and PD (Circulating $CD34^+$, $CD133^+$, and WBC cells counts)
- **Dosage**
  - Placebo, 0.10, 0.14, 0.28, 0.56, 1.12, 2.24, 3.14, and 4.40 mg/kg
- **Number of Subjects**
  - 64 subjects in 8 cohorts (8 subjects in each cohort)
  - Active : Placebo = 6:2 in each cohort
- **Study Center -** Parexel Clinical Pharmacology Research Unit, Baltimore, MD, USA

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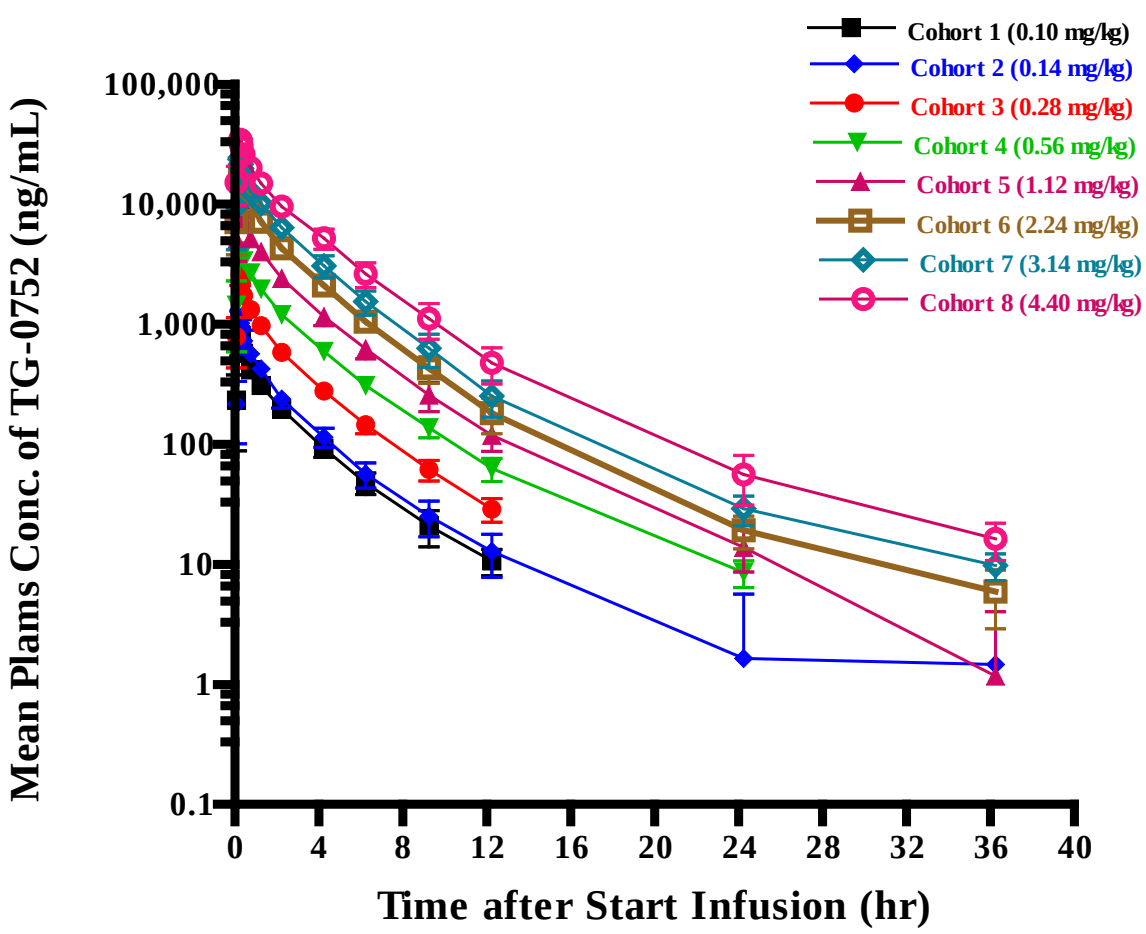
Ph I: PK Parameters



Mean plasma concentrations(ng/mL) of burixafor in log-linear scale vs. time

- Median T_{max}
  15 to 18 mins
- Mean $t_{1/2}$
  2.53 to 5.17 hrs
- C_{max} and AUC increased with dose.

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Ph I Study: Safety Summary

- Good tolerability was observed up to 4.40 mg/kg; All subjects completed the study procedures.
- All Adverse Events (AEs) were mild in severity and recovered spontaneously.
- The most commonly reported AEs were abdominal pain, diarrhea, dizziness, nausea and sweating.
- No significant abnormalities in physical examinations, vital signs, pulse oximetry, ECG, cardiac telemetry, and safety laboratory panel.

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Ph I Study: PD Results

Circulating CD34⁺ cell counts at peak time

Cell Type (Units)	Mean Cell Numbers	Burixafor Dose Level (mg/kg)							
		0.10	0.14	0.28	0.56	1.12	2.24	3.14	4.40
CD34⁺ (cells/μL)	Mean (±SD)	9.1 (±2.5)	10.0 (±3.0)	12.7 (±3.3)	12.7 (±7.7)	27.1 (±9.3)	35.9 (±27.3)	32.5 (±27.7)	29.2 (±12.9)

- **Circulating CD34⁺ Counts:**
  - Dose-dependent increase from baseline between 0.10 and 3.14 mg/kg.
  - Plateau over 2.24 to 3.14 mg/kg
  - Optimal CD34⁺ cell mobilization: 1.12 to 4.40 mg/kg ($p>0.05$), circulating CD34⁺ counts > 20 cells/μL
  - At peak time, burixafor caused a 3 - 14 fold increase in circulating CD34⁺ cells from baseline over the dose range

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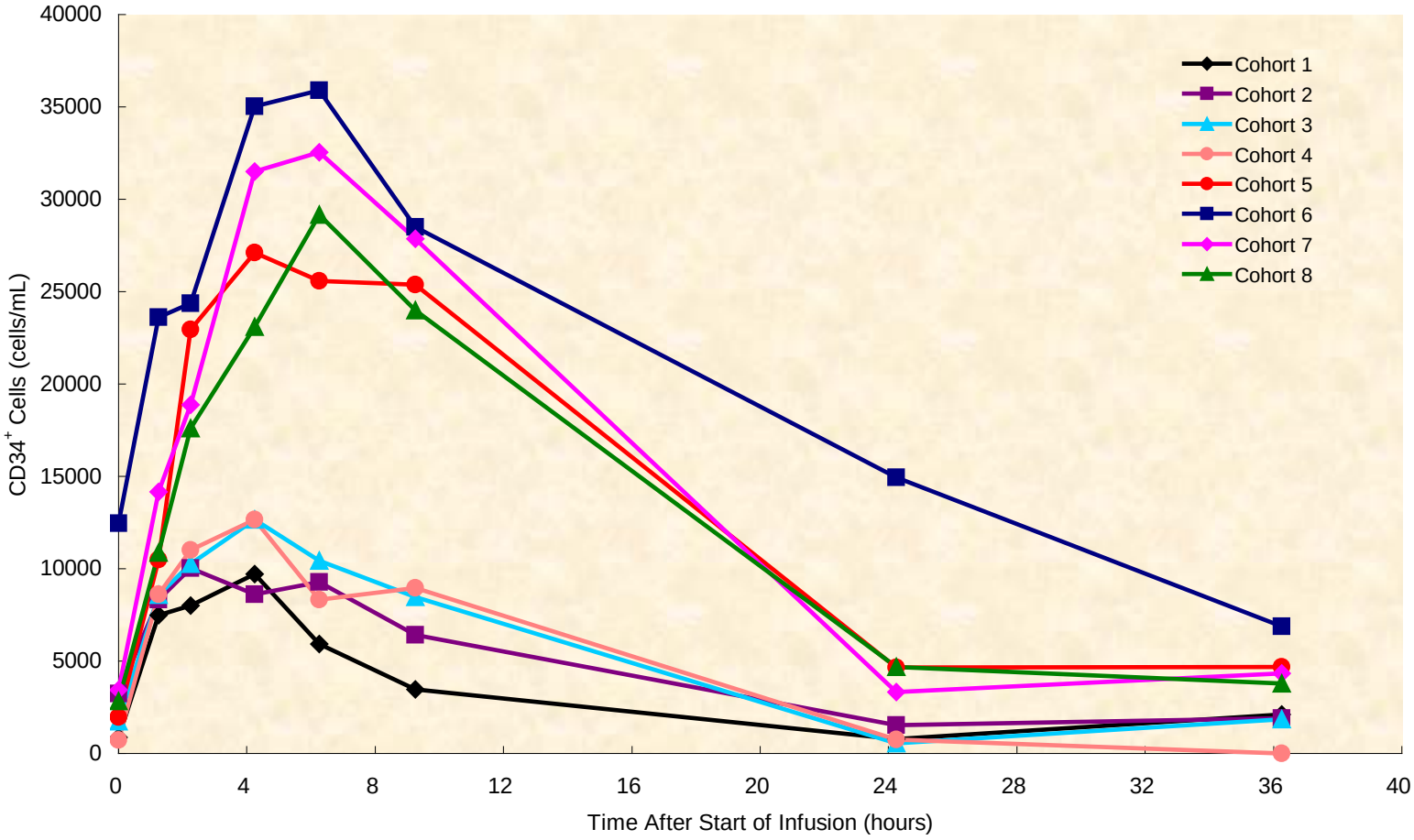
Mean Circulating CD34$^+$ Cells After Burixafor Administration



CD34$^+$ cells peaked at 4-6 hours and returned to baseline at 24 hours post dosing

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Circulating $CD133^+$ and WBC Cell Counts

Cell Type (Units)	Mean Cell Numbers	Burixafor Dose Level (mg/kg)							
		0.10	0.14	0.28	0.56	1.12	2.24	3.14	4.40
$CD133^+$ (cells/µL)	Mean (±SD)	7.5 (±5.9)	8.5 (±5.1)	8.4 (±4.8)	10.4 (±9.2)	25.6 (±10.9)	24.6 (±9.4)	26.9 (±19.9)	23.5 (±9.5)
WBC (cells/µL)	Mean (±SD)	10467 (±2594)	10367 (±2953)	12750 (±3358)	12850 (±2574)	19383 (±4290)	19650 (±6292)	19417 (±3973)	19283 (±3797)

- **Circulating $CD133^+$ and WBC Counts:**
  - Both $CD133^+$ and WBC counts increased after burixafor administration. The trend is similar to that observed for $CD34^+$
  - Plateau over 1.12 to 3.14 mg/kg
  - No AEs were deemed to be associated with WBC increases.

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Phase 1 Study Overall Conclusions

- Burixafor administered as a single IV dose in healthy subjects was well tolerated at doses up to 4.40 mg/kg.
- Due to parasympathetic symptoms observed (grade 1), 4.40 mg/kg was deemed to be the MTD
- PK parameters showed dose proportionality over the dose range studied.
- $CD34^+$, $CD133^+$ cells and WBC count generally increased with increase in burixafor dose from 0.10 to 3.14 mg/kg; at peak time, burixafor caused a 3 - 14 fold increase in circulating $CD34^+$ cells from baseline.

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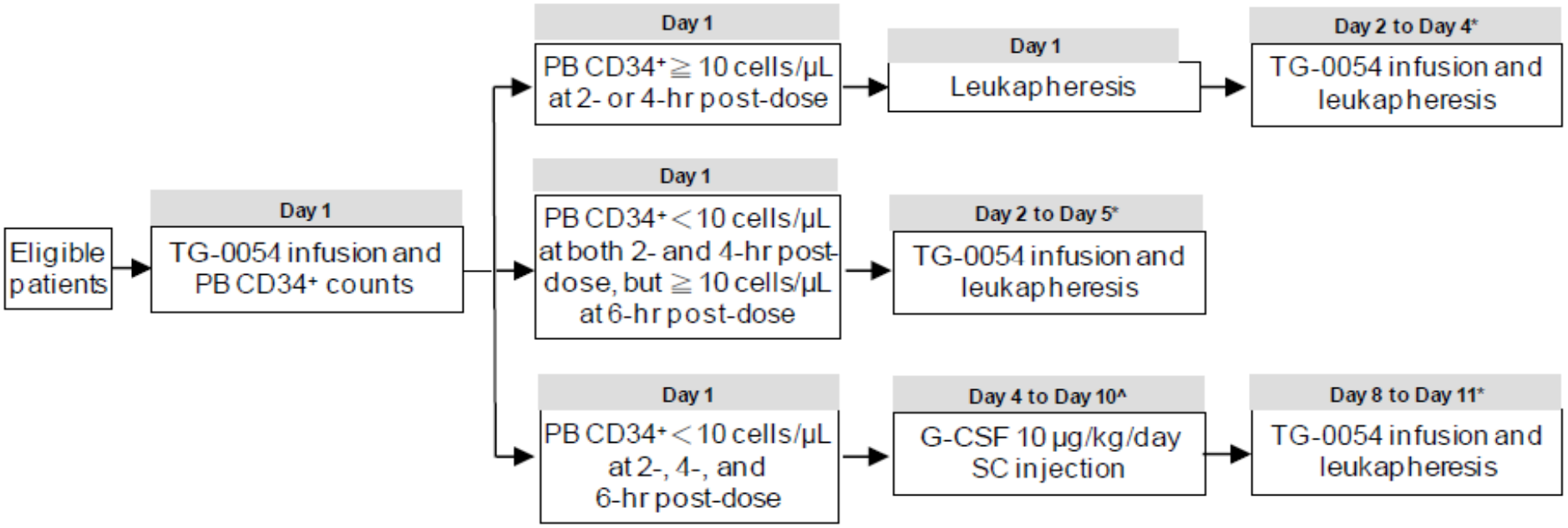
Phase 2 Study

- 12 patients (1 HD, 7 MM, and 4 NHL) were given single agent, intravenous burixafor over 15 minutes on day 1 of collection
- Peripheral blood CD34 counts were assessed at 2 hours, 4 hours and 6 hours after study drug administration
- If the CD34 count was ≥ 10/ul , stem cell collection was initiated
- If CD34 count never reached 10/ul by 6 hours, G-CSF was started on day minus 4 before collection and patient was given G-CSF and burixafor additionally on each day of collection

Schema for Study TG-0054-03



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Inclusion Criteria

- Patients diagnosed with multiple myeloma, non-Hodgkin's lymphoma or Hodgkin's lymphoma needing autologous stem cell transplantation
- Last chemo > 4 weeks prior to 1st dose of burixafor
- WBC count ≥ 3.0 x 10^9/L and platelet count ≥ 100k x 10^9 cells/L
- Patient ages 18-70
- ECOG 0-1
- AST and ALT < 2 x ULN
- Cr < 2.2

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Exclusion Criteria

- Prior pelvic irradiation
- Greater than 6 cycles of Revlimid
- Prior stem cell transplantation
- History of other malignancies (except for basal cell carcinomas)
- Uncontrolled cardiac, pulmonary or infectious disease
- History of retinal proliferative disease
- Known HIV disease
- Investigational drug within 1 month of study entry

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Primary Study objective

- To determine the total number of hematopoietic stem cells (HSCs) collected within four leukapheresis sessions after TG-0054 (3.14 mg/kg) alone or in combination with G-CSF mobilization in patients with multiple myeloma (MM), non-Hodgkin lymphoma (NHL) or Hodgkin disease (HD)

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Secondary Objectives

- To determine the average number of leukapheresis sessions required to collect 2.5 x106 CD34+ cells/kg
- To evaluate the safety of TG-0054 in patients with MM, NHL or HD
- To evaluate engraftment
- To evaluate the pharmacodynamics (PD) of TG-0054 by determining circulating CD34+ cell counts in peripheral blood

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Demographics

- 7 myeloma, 4 non-Hodgkin's lymphoma (NHL) and 1 Hodgkin's lymphoma (HL)
- 5/7 myeloma patients had received 6 cycles of lenalidomide
- 4 NHL patients and 1 HL patient had received 2 lines of prior therapy including 2 cycles of DICE salvage chemotherapy

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Results

- Seven patients (1 HD, 6 MM) were successfully mobilized with TG0054-03 as a single agent achieving a cumulative dose of CD34 of **4.0 -10.4 x10^6** /kg over 1- 4 leukapheresis sessions

- Five patients (4 NHL,1 MM) required the addition of G-CSF after failing to achieve a peripheral blood CD34 count ≥ 10 on day 1 after burixafor infusion

Tiagen Mobilization and CD34+ Dose

Patient	CD34+ 10^6/kg	Number of Leukaphereses
1	4.211	4
2	5.207	4
3	3.037	4
4*	21.03	2
5*	2.235	3
6	6.45	4
7	4.068	4
8*	3.253	4
9*	5.005	2
10*	7.641	1
11	9.421	4
12	10.423	4

* Indicates combination mobilization with G-CSF

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Cells infused

- Within 5 weeks of the last apheresis, the patients underwent high-dose chemotherapy and transplantation using the collected autologous CD34+ cells

- The minimum number of CD34+ cells for transplantation was 2×10^6 cells/kg (actual body weight)

- Actual (mean CD34 infusion was 3.76×10^6 cells/kg (range 2.3-6.2)

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Engraftment Data

Subject #	# of collections	Days to neutrophil engraftment success	Days to platelet engraftment success
001 A-M	4	11	21
002 H-S	4	12	23
003 E-M	4	11	22
004 A-M	2	13	16
005 M-A	3	14	27
006 J-H	4	12	17
007 B-V	4	12	23
008 T-J	4	12	37*
009 M-N	2	11	18
010 G-O	1	12	36*
011 S-B	4	12	22
012 M-B	4	11	17

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Engraftment Results

- Median days to WBC engraftment were 12
- Median days to platelets of 50k were 22
- All patients have now been followed for 6 months or more and have been noted to have stable engraftment

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Adverse Events

- No grade 3-4 toxicity was seen in any of the patients
- The 2 most common AE's reported were loose stools and worsening of peripheral neuropathy (myeloma patients) in 4 patients each
- Single patients reported abdominal cramping, nausea, nasal congestion, cough and joint pain

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Conclusions

- Burixafor was well tolerated in patients undergoing stem cell collection
- 7 patients mobilized stem cells with single agent burixafor (including 5 myeloma patients who had received 6 cycles of lenalidomide
- All 12 patients engrafted promptly after receiving conditioning regimens (BEAM for the lymphoma patients and melphalan 200 for the myeloma patients) followed by a stem cell infusion of at least 2.3 x106 CD34+ cells/kg
- A second phase of the protocol will assess the number of leukaphereses required to mobilize adequate numbers of stem cells using combination burixafor/G-CSF