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TO THE EDITOR:

Hematopoietic stem cell mobilization for allogeneic stem cell transplantation by motixafortide, a novel CXCR4 inhibitor

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Granulocyte colony-stimulating factor (G-CSF) is the most common agent used for mobilizing peripheral blood (PB) hematopoietic stem and progenitor cells (HSPCs) for allogeneic hematopoietic cell transplantation (allo-HCT). However, G-CSF mobilization often requires multiple leukapheresis procedures (LPs) and injections.^{1,2} G-CSF is also associated with bone pain, rare but life-threatening splenic rupture, and vaso-occlusive complications in patients with sickle-cell disease.^{1,3-5}

CXCR4 and SDF-1/CXCL12 interactions are crucial for HSPC retention within the bone marrow niche.⁶⁻⁸ Plerixafor (AMD3100), is a low-affinity (K_i: 652 nM), short-acting CXCR4 inhibitor (CXCR4i) previously shown to mobilize PB HSPCs for HCT.⁹⁻¹¹ In these studies, up to 34% of allogeneic donors (allo-donors) mobilized with single-agent plerixafor failed to collect $>2 \times 10^6$ CD34⁺ cells per kg with 1 injection and 1 LP; whereas 10% required ≥ 3 injections, ≥ 3 LPs, and G-CSF rescue.¹¹⁻¹⁴ Therefore, development of rapid and reliable HSPC mobilization regimens remains an unmet need.

Motixafortide (BL-8040) is a novel 14-residue, cyclic, synthetic peptide CXCR4i with high affinity (K_i 0.32 nM) and slow receptor dissociation rate, previously shown to induce rapid (onset, 0.5-2 hours) and sustained (duration, >48 hours) HSPC mobilization.¹⁵ To our knowledge, the authors report the first trial evaluating motixafortide mobilization of allo-donors for HCT.

A multicenter, open-label, single-arm, 2-part, phase 2 study (NCT02639559) was conducted with institutional review board approval and written informed consent from all participants. Donors were aged between 18 and 70 years, with an Eastern Cooperative Oncology Group performance status from 0 to 1. Recipients were aged between 18 and 75 years, with an Eastern Cooperative Oncology Group performance status from 0 to 2, undergoing allo-HCT for hematologic malignancy (Table 1). Part-1 included HLA-identical (5/6 or 6/6 HLA-matched) sibling donors. Part-2 included HLA-matched sibling or haploidentical donors. Motixafortide was administered via subcutaneous injection at 1.0 mg/kg in part-1 and 1.25 mg/kg in part-2. The rationale for motixafortide dosing strategy in this study was based on data from 3 prior clinical trials (NCT01010880, NCT02073019, and NCT01838395), in which motixafortide alone or in combination with other mobilizing agents (chemotherapy \pm G-CSF) was administered at doses of 0.5 or 1.5 mg/kg in healthy volunteers, patients with multiple myeloma, and patients with acute myeloid leukemia with an acceptable toxicity profile and a dose-dependent increase in CD34⁺ cell mobilization at the 1.0 and 1.25 mg/kg dose range. The primary end point was efficacy of 1 motixafortide injection to mobilize $\geq 2 \times 10^6$ CD34⁺ cells per kg (recipient weight) in ≤ 2 LPs. First LP (≥ 3 blood volumes) began from 180 to 270 minutes after motixafortide administration. Second LP (if needed) began 24 hours after motixafortide administration. If $\geq 2.0 \times 10^6$ CD34⁺ cells per kg were collected within 2 LPs, mobilization was complete (supplemental Figure 1). Myeloablative and reduced

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All information regarding renewable materials and data sets are available on request from the corresponding author, Geoffrey L. Uy (guy@wustl.edu).

The full-text version of this article contains a data supplement.

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Table 1. Patient characteristics at baseline

Donors (n = 25)	
Age, median in y (range)	55 (20-69)
Sex, male, n (%)	18 (72)
HLA-match, n (%)	
Matched sibling	18 (72)
Haploidentical	7 (28)
Recipients (n = 25)	
Age, median in y (%)	58 (26-71)
Sex, male, n (%)	15 (60)
Disease, n (%)	
AML	16 (64)
ALL	4 (16)
MDS	3 (12)
MPN	1 (4)
Hodgkin lymphoma	1 (4)
Conditioning regimen, n (%)	
Fludarabine + busulfan 2 (RIC) or busulfan 4 (MAC)	11 (50)
Fludarabine/cytosin/TBI	7 (32)
Busulfan/cytosin	3 (14)
cytosin/TBI	1 (5)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; RIC, reduced intensity conditioning; TBI, total body irradiation.

intensity conditioning regimens were permitted. Graft-versus-host disease (GVHD) prophylaxis and supportive care were per investigator discretion. Adverse events (AEs) were graded per National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03, with all grades from 3 to 5 nonhematologic AEs collected from conditioning until day 100, relapse, or subsequent treatment. Neutrophil or platelet engraftment was defined per Center for International Blood and Marrow Transplant Research criteria. GVHD was graded per consensus criteria. The cumulative incidence of nonrelapse mortality and relapse were analyzed as competing risks. Correlative studies including pharmacokinetic analyses, CD34⁺ enumeration and T-cell immunophenotyping were performed per the protocol (supplemental Protocol). Multicolor fluorescence-activated cell sorting was performed as previously described^{11,16,17} (supplemental Table 1).

Twenty-five donor-recipient pairs were enrolled (n = 24 donors evaluable for primary end point; n = 22 recipients with completed allo-HCT). Median donor age was 55 years (range, 20-69 years), with 18 HLA-matched siblings and 7 haploidentical donors. Median recipient age was 58 years (range, 26-71 years; Table 1). In part-1, 13 evaluable allo-donors received motixafortide (1.0 mg/kg), with 11 of 13 (85%) collecting $\geq 2 \times 10^6$ CD34⁺ cells per kg in ≤ 2 LPs (median, 5.18×10^6) and 8 of 11 (73%) doing so in 1 LP (median, 2.32×10^6 ; Figure 1A; supplemental Table 2). In part-2, 11 allo-donors received motixafortide (1.25 mg/kg), with 11 of 11 (100%) collecting $\geq 2 \times 10^6$ CD34⁺ cells per kg in ≤ 2 LPs (median, 6.07×10^6) and 8 of 11 (73%) doing so in 1 LP (median, 3.28×10^6) (Figure 1B). Motixafortide was well tolerated.

Twenty-five of 25 donors reported at least 1 AE, with the most common nonhematologic AEs being transient grade 1 injection site reactions (20/25), including pain, erythema, and hives. Clinically significant cytopenias in donors were not observed at 7 or 30 days after collection; with no serious AEs, long-term treatment-related AEs, or treatment-related deaths observed.

PB CD34⁺ cell counts from 24 participants (n = 14, 1.0 mg/kg; n = 10, 1.25 mg/kg) reached maximal levels at ~24 hours after motixafortide administration (supplemental Figure 2). The increase in absolute PB CD34⁺ cell counts was similar: average (\pm standard deviation) of 26.9 ± 13.1 cells per μL with motixafortide 1.0 mg/kg and 25.4 ± 13.8 cells per μL with motixafortide 1.25 mg/kg.

Twenty-two patients underwent allo-HCT with motixafortide-mobilized PB HSPCs. Median time-to-neutrophil engraftment was 13 days (range, 11-26 days). Time-to-neutrophil engraftment was prolonged in haploidentical transplants compared with that in matched-sibling donor transplants (median, 20 vs 13 days; $P = .02$). Median time-to-platelet engraftment was 18 days (range, 15-41 days).

Based on Minnesota grading criteria, cumulative incidence of grade 2 or 4 acute GVHD (aGVHD) at 180 days after HCT was 32% (7 of 22). Cumulative incidence of chronic GVHD (cGVHD) at 2 years was 60%, with a moderate cGVHD rate of 39% (7 of 18) and 1 case of severe cGVHD. Cumulative incidence of relapse or progression was 22.2% (95% confidence interval, 0.079-0.52) at 1 year and 27.3% (95% confidence interval, 0.107-0.470) at 2 years. Median overall survival was not reached, with 71% overall survival at 1 year.

CXCR4 expression on CD34⁺ HSPCs from the day 1 apheresis product were assessed using 2 antibodies to CD184 (CXCR4), clone 12G5, which competes with motixafortide for CXCR4 binding, and clone 1D9, which does not compete with motixafortide for CXCR4 binding.^{18,19} Significantly reduced 12G5 binding to HSPCs mobilized with motixafortide was observed while 1D9 remained detectable, consistent with extended CXCR4 occupancy and CXCR4 surface expression by motixafortide (Figure 1C). Immunophenotyping via multicolor fluorescence-activated cell sorting of CD34⁺ HSPCs from the day 1 apheresis product demonstrated 3 distinct HSPC populations, including (i) hematopoietic stem cells and common myeloid progenitors (HSCs/CMPs), defined by CD34⁺CD45RA⁻CD123^{lo} comprising 47.9% of CD34⁺ HSPCs; (ii) granulocytic myeloid progenitors and common lymphoid progenitors, defined by CD34⁺CD45RA⁺CD123^{lo} comprising 26.7% of CD34⁺ HSPCs; and (iii) lineage-committed plasmacytoid dendritic cell precursors (pre-pDCs), defined by CD34⁺CD45RA⁺CD123⁺ comprising 23.1% of CD34⁺ HSPCs (Figure 1D). Motixafortide induced pan-mobilization of all major myeloid and lymphoid subsets in PB, with maximum relative changes in pDCs, B cells, basophils, myeloid DCs, CD8 T cells, and classical monocytes (Figure 1E; subsets defined in supplemental Table 3). In general, magnitude of mobilization of each subset correlated with baseline CXCR4 expression level (Figure 1F; $R^2 = 0.4$; $P = .02$). Although CD4 and CD8 T-cell subsets were pan-mobilized, motixafortide preferentially mobilized naïve and central memory CD8 T cells (Figure 1G; subsets defined in supplemental Table 4). Naïve CD8 and CD4 T cells expressed the greatest amount of baseline CXCR4 (Figure 1H).

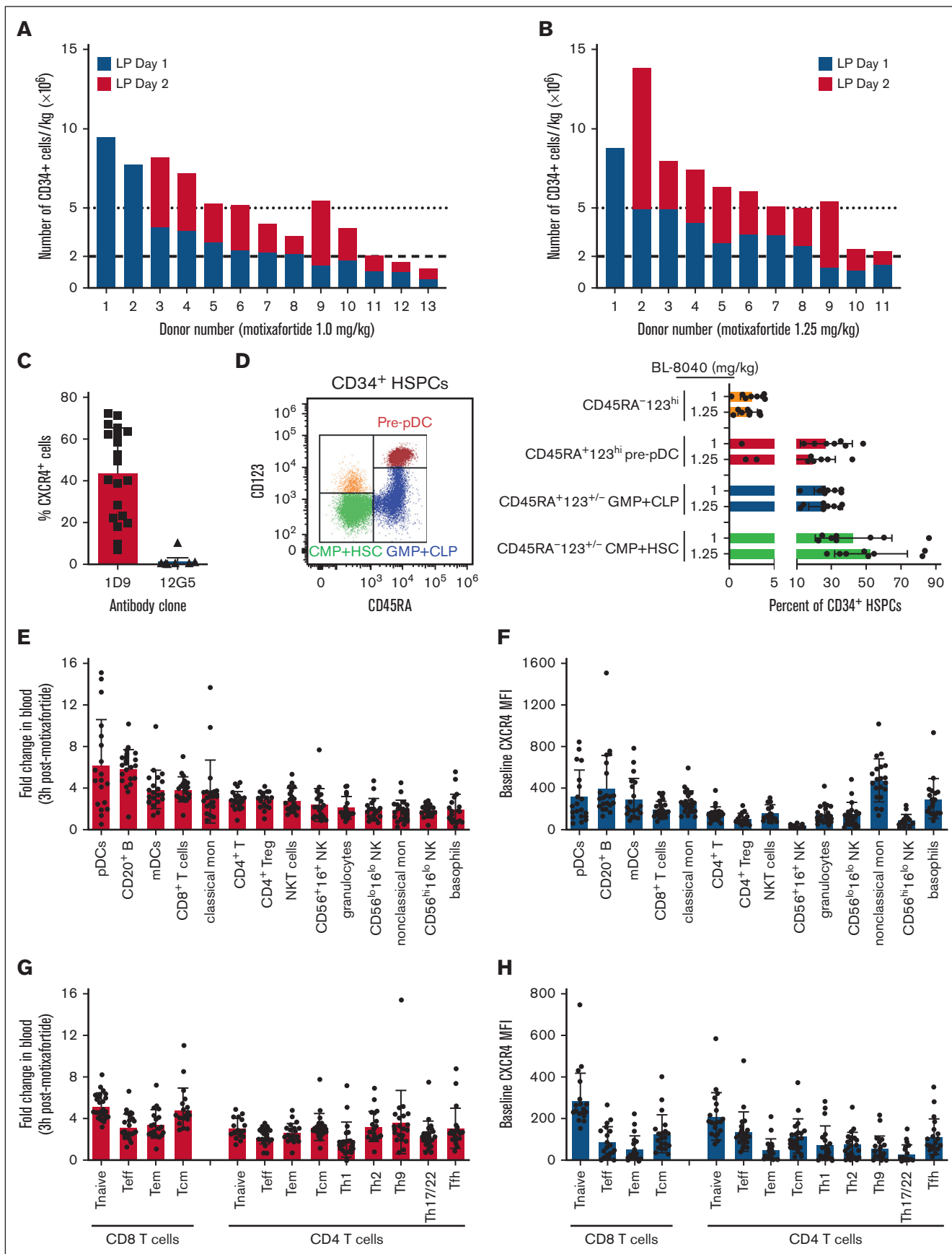


Figure 1.

In this study, a single injection of motixafortide resulted in a 22 of 24 (92%) allo-donors collecting $\geq 2.0 \times 10^6$ CD34⁺ cells per kg within 2 LPs, including 11 of 11 (100%) receiving motixafortide at 1.25 mg/kg. In comparison, 10 of 29 (34%) of plerixafor-mobilized donors required ≥ 2 plerixafor injections and ≥ 2 LPs (goal, $\geq 2 \times 10^6$ CD34⁺ per kg), with 3 of 29 (10%) requiring G-CSF rescue after 2 LPs.¹¹ However, multiple G-CSF injections (≥ 5) and LPs may yield higher total HSPCs than a single injection of motixafortide or plerixafor.¹⁴ HSPC immunophenotyping in this study revealed CXCR4 inhibition with motixafortide mobilized a large population of multipotent HSCs and a distinct population of pre-pDCs, a pattern similarly observed in prior studies with plerixafor when compared with G-CSF-mobilized allografts.¹¹ In addition, recent data with extended immunophenotyping of CD34⁺ HSPCs demonstrated that long-acting CXCR4 inhibition with motixafortide + G-CSF, as compared with plerixafor + G-CSF, resulted in the mobilization of a significantly higher number of combined HSCs, multipotent progenitors, and CMPs.²⁰⁻²² Interestingly, gene expression profiling via single-cell RNA-sequencing also revealed that motixafortide-mobilized CD34⁺ HSPCs may be more transcriptionally primitive with enhanced repopulating activity versus G-CSF and with uniquely upregulated gene expression profiles associated with enhanced self-renewal, quiescence, and regeneration versus both plerixafor and G-CSF.²⁰⁻²² Assessment of immune cell subsets mobilized with motixafortide in the allo-graft demonstrated a pattern similar to that previously observed with CXCR4 inhibition with plerixafor, in which increases in lymphocyte subsets were observed relative to G-CSF mobilization (supplemental Table 5).¹² Extended T-cell immunophenotyping in PB also demonstrated motixafortide induced pan-mobilization of CD4 and CD8 T cells, with preferential mobilization of naïve and central memory CD8 T cells. Of clinical relevance, specific T-cell immunoreceptor with Ig and ITIM domains (TIGIT) positive T-cell subsets have been associated with impaired graft-versus-leukemia and increased risk of relapse after allo-HCT, whereas increased effector memory and central memory T cells along with decreased naïve T cells are associated with lower GVHD risk.^{23,24} In this study, the observed GVHD rates of 32% grade 2 or 4 aGVHD and 60% cumulative cGVHD at 2 years appear comparable with that of historical controls reported in the literature using alternative mobilization regimens.¹¹⁻¹³ In studies evaluating plerixafor as a single-agent mobilizing regimen in allo-donors, rates of grade 2 or 4 aGVHD ranged from 18% to 53%; whereas the cumulative rates of cGVHD at 1 year of follow-up ranged from 33% to 52%.¹¹⁻¹³ Similarly, a previously performed analysis using an institutional cohort of patients undergoing allo-HCT with G-CSF-mobilized CD34⁺ cells treated with similar conditioning, and GVHD prophylaxis from 2009 to 2011 demonstrated GVHD rates of 68% grade 2 or 4 aGVHD and 28% cumulative cGVHD at 100-days after allo-HCT.¹¹ However, these patient populations were heterogeneous with regard to disease type, donor type, conditioning regimen, and GVHD prophylaxis, thus

limiting definitive conclusions regarding post-allo-HCT outcomes on the basis of these studies alone. Rather, these findings highlight the potential effectiveness of single-agent motixafortide as a rapid mobilizing agent for allo-donors while raising important questions regarding how specific HSPC and T-cell subsets mobilized for allo-HCT by different mobilization regimens may affect post-HCT immune reconstitution, graft-versus-leukemia, and GVHD. As HSPC mobilization regimens are developed, future studies systematically comparing HSPC and T-cell graft characteristics with relevant clinical outcomes are needed.

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Conflict-of-interest disclosure: Z.D.C. received research funding from BioLineRx and holds advisory committee membership at BioLineRx. A.V.-H., E.S., and I.G.-K. are employed at BioLineRx. J.F.D. holds equity stock/ownership at Magenta Therapeutics, WUGEN; receives consulting fees from Incyte and RiverVest Venture Partners; holds a board or advisory committee membership at Cellworks Group, RiverVest Venture Partners, and Magenta; receives research funding from Amphivena Therapeutics, Neolimmune Tech, MacroGenics, Incyte, BioLineRx, and WUGEN; receives speaking fees from Incyte; and holds patents in WUGEN. The remaining authors declare no competing financial interests.

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Figure 1. Total HSPC yields, with extended CD34⁺ HSPC and T-cell immunophenotyping. (A) Total CD34⁺ HSPC yields in HLA-matched sibling donors mobilized with 1 injection of motixafortide (1.0 mg/kg) and up to 2 LPs. (B) Total CD34⁺ HSPC yields in HLA-matched sibling donors or haploidentical donors mobilized with 1 injection of motixafortide (1.25 mg/kg) and up to 2 LPs. (C) Inhibition of anti-CXCR4 monoclonal antibody clone 12G5 binding to motixafortide-mobilized CD34⁺ HSPCs. CXCR4 expression on CD34⁺ HSPCs obtained from the day 1 apheresis product was determined via flow cytometry, using anti-CXCR4 clones 12G5 and 1D9. (D) Extended HSPC immunophenotyping of CD34⁺ purified cells from apheresis product mobilized with motixafortide with relative proportions of HSC/CMPs, granulocytic myeloid progenitors and common lymphoid progenitors, and pre-pDCs. (E,G) Pan-mobilization of myeloid and lymphoid subsets by using motixafortide. The PB concentration of each subset was calculated before and 3 hours after BL-804 treatment (before initiation of LP) and relative change calculated. (F,H) The expression of CXCR4 on each subset at baseline was determined via flow cytometry, using anti-CXCR4 clone 12G5.

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