A Phase II Study Evaluating the Safety and Efficacy of BL-8040 for the Mobilization of Donor Hematopoietic Stem Cells and Allogeneic Transplantation in Patients with Advanced Hematological Malignancies

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI	*Signature*	*Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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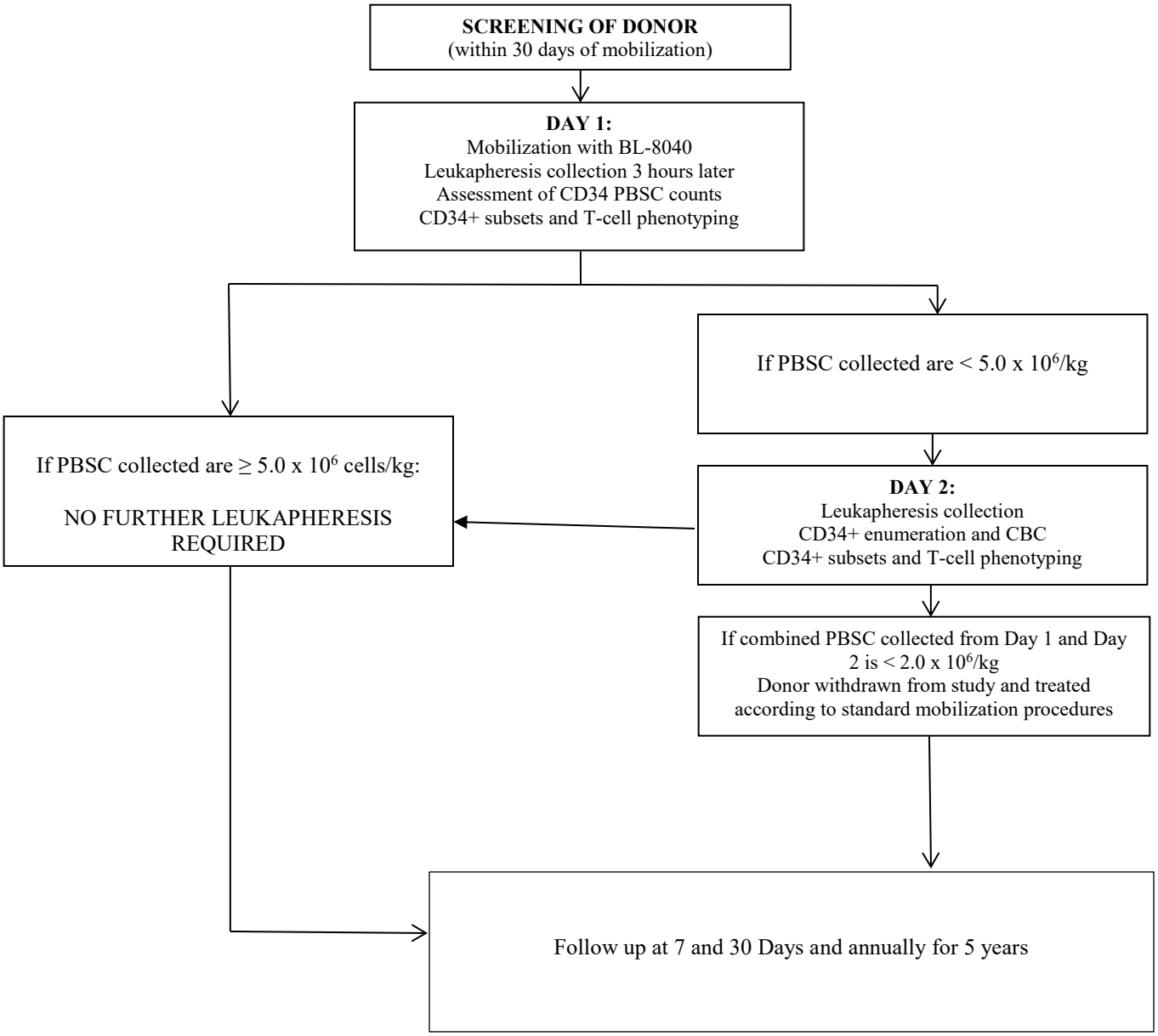
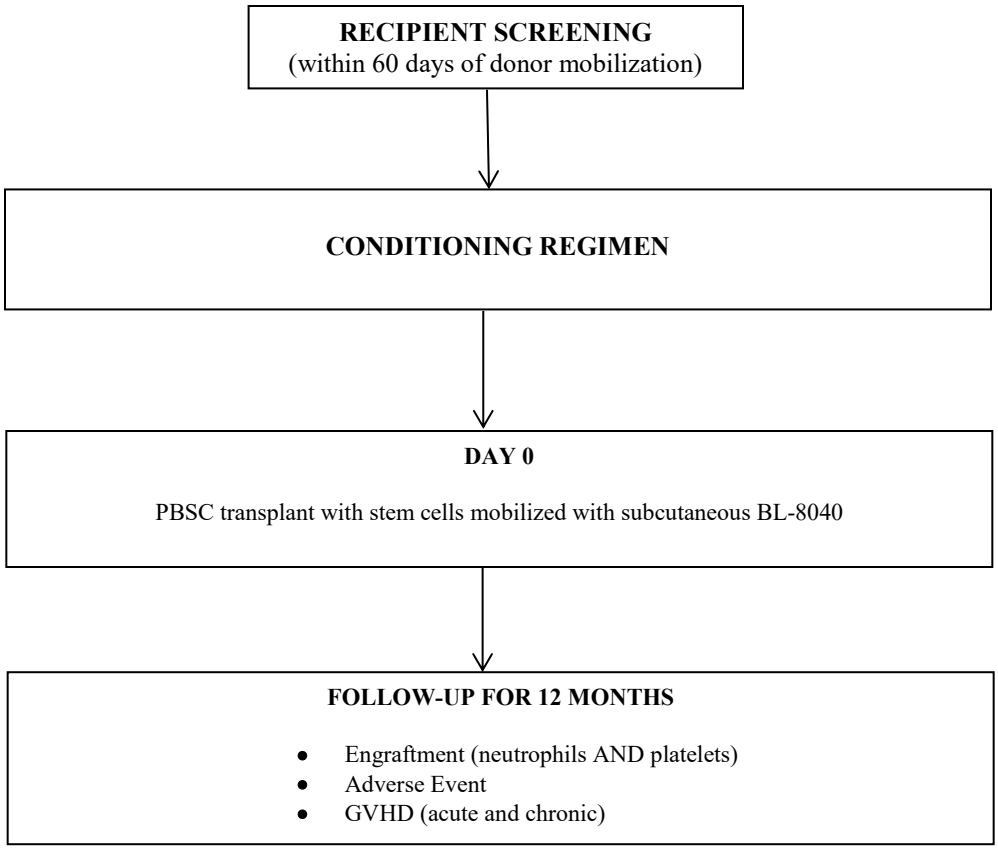
DONOR SCHEMA



RECIPIENT SCHEMA



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1.0 BACKGROUND AND RATIONALE

1.1 Background

Patients with advanced hematologic malignancies are incurable with conventional chemotherapy and often require allogeneic hematopoietic cell transplantation (HCT). The principal goals of HCT are to allow engraftment and development of a donor-derived immune system that can effectively produce an immunologic attack against the recipient's tumor cells resulting in a graft-versus-leukemia effect. Early pilot studies demonstrated that granulocyte colony-stimulating factor (G-CSF) based mobilization is a relatively safe and effective alternative to bone marrow harvesting for collection of hematopoietic stem cells (HSC) prior to allografting[1-4]. Multiple randomized trials have since demonstrated an advantage of G-CSF mobilized peripheral blood stem cells (PBSC) compared to bone marrow (BM) for HCT. PBSCs are associated with more rapid hematopoietic engraftment, similar rates of acute graft versus host disease (GVHD), and higher rates of chronic GVHD[5-10]. Based on these findings, use of PBSC in HCT is now standard practice at many transplant centers.

CD34+ stem cell content in mobilized peripheral blood product is considered the most important parameter of graft quality, and is recognized as a predictor of hematopoietic engraftment after stem cell transplantation. Infusion of more than 2.0 x 10^6 cells/kg recipient body weight (BW) $CD34^+$ cells is associated with rapid and durable engraftment of recipients[12-15]. Although the optimal CD34+ cell dose is unknown, a target of 5 x 10^6 $CD34^+$ cells/kg actual recipient weight and a minimum a threshold of 2 x 10^6 $CD34^+$cells/kg is used at many transplant centers[11]. The focus of current research in stem cell mobilization and collection is to optimize the number of stem cells collected by improving mobilization regimens and increasing the efficiency of apheresis collection by reducing the number of apheresis procedures needed to meet the stem cell dose requirement for HCT[16].

Previous studies have demonstrated a highly significant correlation between the CD34+ concentration in peripheral blood and the potential to collect an adequate amount of CD34+ cells within one or up to three leukapheresis procedures[17-18]. Many groups have suggested that a peak level of 20/μL $CD34^+$ cells should be considered as the threshold[19]. The quality of the apheresis product such as the number of CD34+ cells in the graft and the presence of immune competent cells may also impact post-transplantation outcomes. Ultimately, the efficiency of stem cell mobilization is determined by the number of apheresis procedures needed and the success of transplantation[20-21].

1.1.1 Donors Mobilized with G-CSF

G-CSF is the most frequently used single agent for stem cell mobilization in the allogeneic setting. G-CSF mobilizes stem cells from the bone marrow into the peripheral blood primarily by down-regulation of CXCL12 production by marrow stromal cells. While it is relatively safe, G-CSF requires 4-5 days of administration prior to collection which may be inconvenient for donors and cause absence from work during the mobilization process. In a retrospective study performed using data from the International Bone Marrow Transplant Registry (IBMTR) and European Bone Marrow Transplant (EBMT) Group, 60% of donors required more than one leukapheresis procedure to collect the target number of CD34+ cells, and 15% required three or more[9]. Surprisingly, approximately 20% of donors required placement of a central venous catheter (CVC) and the overall rate of serious complications associated with G-CSF mobilized peripheral blood donation was 1.1%, higher in comparison to the 0.5% rate observed following bone marrow donation.

Although no long-term sequelae have been confirmed with short-term use of G-CSF, there can be associated morbidity including significant bone pain and rarely splenic rupture[9]. Furthermore, a small percentage of healthy donors have a poor mobilization response to G-CSF resulting in the need for additional apheresis collections or repeat mobilization cycles to collect an adequate PBSC dose[23]. These challenges have prompted the evaluation of novel agents for stem cell mobilization with the capacity to rapidly mobilize HSCs while providing a better tolerated drug administration and cell collection regimen.

Plerixafor (AMD3100), an inhibitor of CXCR4, has demonstrated the ability to rapidly mobilize stem cells out of the BM and into the peripheral circulation in healthy donors and cancer patients previously treated with chemotherapeutic agents[24-27]. Interestingly, compared to G-CSF mobilized cells, a higher proportion of plerixafor-mobilized CD34+ cells were in G_1 phase of the cell cycle and gene expression profiling indicated that these cells were of a more primitive type than those mobilized by G-CSF[28]. Animal models showed that plerixafor-mobilized HSCs have a higher frequency of repopulating activity, suggesting an intrinsic difference in the engrafting capacity of the mobilized CD34+ cells[28-29]. Additionally, there is evidence that plerixafor-mobilized grafts have different characteristics compared to grafts obtained with G-CSF[11]. A phase II study of 25 patients receiving PBSC from HLA-identical sibling donors mobilized with a single dose of plerixafor observed a higher content of T-CD3+ and T-CD4+ cells in plerixafor-mobilized grafts compared to historical controls mobilized with G-CSF[30]. Immune reconstitution was prompt despite lower numbers of CD34+ cells and engraftment kinetics and rates of GVHD were not significantly different to historical controls. The differences in graft composition between various mobilizing agents may ultimately influence engraftment, immune recovery, anti-tumor activity, and patient outcomes.

1.1.2 Critical Role of CXCR4 and CXCL12 Interaction in Stem Cell Mobilization

The interaction between CXC chemokine receptor (CXCR4) and its ligand, stromal derived factor-1 (CXCL12), plays a crucial role in hematopoietic cell chemotaxis and adhesion to the BM stromal cells[31-34]. CXCR4 is a member of a large family of seven transmembrane domain receptors coupled to heterotrimeric G_1 proteins that is expressed on CD34+ cells. Binding with its only known ligand CXCL12 (also known as SDF1), expressed on the surface of bone marrow stromal cells, results in activation of multiple signal transduction pathways ultimately triggering chemotaxis[22]. Experiments with neutralizing antibodies directed against CXCR4 or CXCL12 showed that uncoupling the CXCL12/CXCR4 signaling is a crucial step in G-CSF-mediated HSC mobilization[33]. Targeted disruption of either molecule is lethal in mice, resulting in failure of HSC migration from liver to bone marrow, defects in B-lymphopoiesis, and cerebellar dysgenesis[35-37]. Efficient mobilization of murine stem and progenitor cells is observed following injection of adenovirus expressing CXCL12 or after injection of methionine-CXCL12, both resulting in a gradient of CXCL12 from BM to PB[38]. Treatment of mice and primates with sulfated polysaccharides (e.g. fucoidan) results in a rapid increase in circulating CXCL12 and subsequent stem cell mobilization[39]. These preclinical studies confirm the importance of CXCR4 and CXCL12 interaction in stem cell mobilization and targeted disruption of CXCL12/CXCR4 interactions is an effective strategy for mobilization of HSCs[40].

1.2 Study Agent: BL-8040

1.2.1 Mechanism of Action

BL-8040 (developed by BioLineRx Ltd., formerly developed by Biokine Therapeutics and known as BKT140) is a novel selective inhibitor of the CXCR4 chemokine receptor. BL-8040 is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring. It binds and inhibits the CXCR4 chemokine receptor with high affinity (IC_{50} 4.42 nM) and has been shown to be a specific antagonist of CXCR4 both *in vitro* and *in vivo* studies and to have a slow dissociation rate from the receptor.

1.2.2 Pre-clinical Studies of Safety and Toxicology

Pre-clinical pharmacology, safety pharmacology, and toxicology studies have been conducted by BioLineRx to provide nonclinical safety and efficacy support for subsequent clinical trials with BL-8040 in adult patients with hematological malignancies. Special attention was paid to comparison of exposure in the safety studies with the highest systemic exposures reached in humans. The mean human C_{max} and AUC following administration of the highest dose (0.9mg/kg; equivalent to 0.73 mg/kg free base peptide on dry basis) in the clinical study BKTSC001, were found to be 820 ng/ml and 791 ng*h/mL, respectively. The mean human C_{max} and AUC following administration of the highest dose (1.0 mg/kg free base peptide on dry basis) in the clinical study BL-8040.02, were found to be 1090 ng/ml and 1740 ng*h/mL, respectively. These findings were used to compare plasma drug exposures between animal studies and human experience.

Studies have been conducted both in rats and dogs evaluating the single dose toxicity and repeated dose toxicity of BL-8040. Acute toxicity was considered to be low in both rats and dogs following single dose administration. Toxicokinetic evaluation of BL-8040 single dose administration was examined following dose levels in dogs and a maximum tolerated dose (MTD) could not be defined despite pharmacokinetic data which showed that the exposures at 18 mg/kg were > 20 times and > 2 times higher than the exposures reached following administration of the highest dose (0.9 mg/kg; equivalent to 0.73 mg/kg free base peptide on dry basis) in the clinical study BKTSC001. Repeated dose toxicity studies in rats and dogs showed no histopathological organ changes and no target organ toxicity could be identified at exposures (AUC) several times (12.5-fold in dogs and 13.5-fold in rats) higher than the exposure in humans following a single dose of 0.9 mg/kg (0.73 mg/kg free base peptide on dry basis) in study BKTSC001 and higher (6.3-fold in dogs and 6.7-fold in rats) following administration of 1 mg/kg (free base peptide on dry basis) in clinical study BL-8040.02. Similar clinical symptoms were observed in rats and dogs from the first day of dosing and consisted of transient erythema and peripheral edema. In dogs, the reactions were noticed from a few minutes up to approximately 2 hours following SC injection. BL-8040 seemed to be better tolerated with repeated doses over time as the magnitude of the systemic reactions was less pronounced with time and not aggravated with increasing dose. Symptoms occurred at exposure levels similar to those observed following administration of the highest dose (1 mg/kg) in clinical study BL-8040.02, a dose reported to be well tolerated.

Side effects of BL-8040 in the general toxicology studies in rats and dogs included anaphylactoid-type reactions, such as transient erythema and peripheral edema. Both *in-vitro* and *in-vivo* studies indicate that BL-8040 partially activates mobilized immune cells.

In response to BL-8040, known markers of immune cell activation on granulocytes were altered including an increase of cell surface expression of C11b, reduction of cell surface expression of CD62L, as well as secretion of MMP9 (a factor involved in increased motility of granulocytes). BL-8040 did not have any effect on the release of pro-inflammatory mediators, including the cytokines TNF-α, IL-1α, IFN-γ, or ROS and NOS enzymes, in either *in-vivo* or *in-vitro* studies. Likewise, BL-8040 did not have any effect on mast cell degranulation in an *in-vitro* study. Taken together, these findings suggest that the transient reactions observed are related to the pharmacological action of BL-8040 and to the activation of immune cells rather than an effect on the release of pro-inflammatory mediators.

1.2.3 Pre-clinical Studies of Efficacy

Cell line studies demonstrated BL-8040 has high affinity for CXCR4. One study evaluated BL-8040 in a homologous displacement competitive binding assay with radio-labeled ^{125}I-CXCL12 to CHO cells overexpressing CXCR4[41]. The IC_{50} of BL-8040 binding to CHO-CXCR4 cells was 2.5 nM. An additional study further proved that BL-8040 inhibited CXCL12-mediated migration of human Jurkat cells and mouse splenocytes in a dose-dependent manner in vitro (IC_{50} = 0.65 and 0.54 nM, respectively)[42]. The antagonist property of BL-8040 on CXCR4 was also functionally tested *in vitro*, using migration properties of cells overexpressing CXCR4, towards the CXCL12 chemokine gradient. The IC_{50} in these experiments was found to be of the same order of magnitude as in the competitive displacement method (0.54-4.42 nM).

The efficacy of BL-8040 on mobilization of normal and hematopoietic stem cells was demonstrated by *in-vivo* studies in mice, where dose-dependent mobilization of WBCs to the peripheral blood was observed as a result of a single injection of BL-8040[42]. The effect was seen in mice at a dose range of 2.5 – 15 mg/kg, equivalent to 0.2 – 1.25 mg/kg, respectively, in humans. Stem cells mobilized by BL-8040 maintained 90% of transplanted mice for longer than 6 months and were capable of producing long-term rescue in lethally irradiated secondary transplanted mice, indicating that BL-8040 treatment yielded viable and healthy stem cells.

1.2.4 Clinical Trial Experience with BL-8040

To date, two clinical studies (BKTSC001 and BL-8040.02) have been conducted with BL-8040 to assess stem cell mobilization, and both have been completed. BKTSC001 (NCT01010880) was a non-randomized, open-label, single administration, dose escalation study, where BL-8040 was administered to multiple myeloma (MM) patients undergoing treatment with chemo-mobilization and G-CSF. Eligible subjects received a 10-day mobilization regimen in an ambulatory setting according to standard MM mobilization treatment protocol consisting of cyclophosphamide (3-4 g/m2), antiemetic drugs (e.g. Zofran) and 2-mercaptoethane sulfonate sodium (MESNA, prophylactic treatment for hemorrhagic cystitis) on Day 0. On Day 5 until the end of stem cell collection, granulocyte colony-stimulating factor (G-CSF) was self-administered subcutaneously (in the evenings) at 5 µg/kg per day. On Day 10, subjects received one SC injection of BL-8040 in the morning and G-CSF 12 hours later in the afternoon. Stem cell collection (apheresis) was performed at a WBC count over 1,000 cells per 1 µL. A total of 18 subjects were enrolled in this study. BL-8040 was administered as a single SC injection to four subjects per dose group. Administration of BL-8040 was associated with a favorable safety profile, with no apparent trend toward risk with a specific dose. No clinically consistent or cumulative

abnormalities were observed for the safety parameters evaluated, including AE incidence, laboratory safety values, vital signs, ECG parameters or physical examinations, as well as Karnofsky status. Single dose administration of BL-8040 caused rapid mobilization of WBC and CD34+ stem cells in a dose-dependent manner. Fewer apheresis were required as BL-8040 dose increased. In the highest dosage group of 0.9 mg/kg, all subjects had only one apheresis, with a mean of 20.9 x 10^6 CD34+ cells/kg collected (range: 11.5 – 26.1 million cells/kg).

BL-8040.02 (NCT02073019) was a Phase I, two-part study exploring the safety, tolerability, pharmacodynamic and pharmacokinetic effect of ascending doses of BL-8040 in healthy subjects designed to support development of BL-8040 as a single agent treatment for hematopoietic stem cell mobilization for autologous and/or allogeneic transplantation.

Part 1 (Dose Escalation) was a randomized, double-blind, placebo controlled study exploring the safety, tolerability, pharmacodynamic (PD) and pharmacokinetic (PK) profile of BL-8040. CD34+ cell mobilization was measured in healthy subjects following administration of up to two doses of BL-8040 (QD on 2 consecutive days). Each cohort in Part 1 consisted of 8 subjects; 6 subjects in each cohort were randomly allocated to receive BL-8040 (doses 0.5, 0.75 and 1 mg/kg) and 2 subjects randomly allocated to receive placebo. Part 2 involved a single cohort of 8 subjects, who have received BL-8040 at the selected optimal dose level of 1.0 mg/kg. A total of 26 subjects have been exposed to study drug and 6 to placebo. Administration of BL-8040 was associated with a favorable safety profile, with no apparent trend toward risk with a specific dose. Administration of BL-8040 caused rapid mobilization of WBC and CD34+ stem cells in a dose-dependent manner. In Part 1 of the study, at the highest dose tested of 1mg/kg, the mean WBC count rapidly and significantly rose to its peak after 4-8 hrs; from baseline levels of 5.8 (±0.97) x 10^9/L to 31.4 (± 4.3) x 10^9/L at 4 hrs, to 33.4 (± 6.5) x 10^9/L at 8 hrs. WBC count remained high at 23 hrs post the first injection, 24.8 (± 5.7). In Part 2 of the study all 8 subjects received a single dose of 1 mg/kg and approximately 3.5 hrs later underwent standard volume (18L target volume) apheresis. At 3.5 hours after a single dose of BL-8040, the WBC count rose to a median of 32 x 10^3/μL (range; 29 – 39 x 10^3) and the CD34+ cell count to 43/μL (range; 27-84/μL). The number of CD34+ reached its peak after 24 hrs and started to decline slowly after 48 hrs. Single BL-8040 administration resulted in robust collection of CD34+ cells in a single apheresis session. The median CD34+ collected was 11.89 x10^6/kg (range; 5.09 - 15.23 x 10^6/Kg). These results suggest a potential second collection of CD34+ cells after 24hrs if needed without the need for second injection of BL-8040.

In addition to the studies in stem cell mobilization, BioLineRx is currently investigating the safety and efficacy of multiple (7 consecutive administration days) escalating doses of BL-8040 in combination with Ara-C (Cytarabine) in adult subjects with relapsed/refractory acute myeloid leukemia (AML) in a Phase IIa, open-label, multicenter clinical study, BL-8040.01 (NCT01838395).

1.2.5 BL-8040 Related Adverse Events

In general the most common AEs seen in all studies conducted with BL-8040 to date are injection site reactions (including pain, erythema, pruritus and inflammation) and systemic reactions: hives, pruritus (not at the injection site), flushing, chills, rash and urticaria. Other isolated AEs reported among others were paresthesia, musculoskeletal pain, headache, constipation, tingling and elevation of liver function tests.

BKTSC001

In this study BL-8040 was associated with a favorable safety profile, with no apparent trend toward risk with a specific dose. No clinically consistent or cumulative abnormalities were observed for the safety parameters evaluated, including AE incidence, laboratory safety values, vital signs or ECG parameters, among other.

All related TEAEs (13/131) were in the higher dose groups (0.3 and 0.9 mg/kg). Approximately half of them were under the SOC "General Disorder and Administration Site Condition". Ten out of 132 events were considered mild in intensity and 23.1% moderate in intensity (3/133). The Investigator did not consider any of the severe events as related to the study drug.

There were six SAEs reported throughout the study, affecting 4/18 subjects (22.2%); one subject in the 0.006 mg/kg dose group, two subjects in the 0.1 mg/kg dose group and one subject in the 0.3 mg/kg group. Two concurrent SAEs in a single 0.3 mg/kg subject (chest pain and dyspnea) were considered by the Investigator as possibly treatment related. These events were assessed as unrelated by the sponsor's Medical Safety Officer since: (i) they recurred upon later treatment with G-CSF only, (ii) the events were similar to those anticipated with administration of G-CSF, and (iii) AEs were reported 30 hrs post injection, long after the drug was eliminated according to the PK profile (BL-8040 t1/2 is 0.5 hr, see Table 5-1). An additional SAE of hypokalemia occurred following BL-8040 administration and was determined to be unrelated by the Investigator. Upon review of the CRF, the Sponsor's Medical Safety Officer assessed the hypokalemia as severe in intensity and possibly related to the BL-8040. Three other SAEs (two cases of neutropenic fever and one case of sepsis) occurred prior to study drug administration and were anticipated side effects of chemotherapeutic agents applied in conditioning for cell therapy and therefore determined unrelated to BL-8040.

There were very few laboratory abnormalities determined to have been clinically significant, and fewer still post-dosing or associated with an AE. Only one laboratory result (hypokalemia) was considered to be possibly related to BL-8040 by the Sponsor's Medical Safety officer. Blood glucose and LDH tended to slightly increase post-administration, but were not associated with notable negative effects. Physical examination and vital sign parameters were normal or stable in nearly all subjects following BL-8040 administration.

BL-8040.01

To date five dosing cohorts have been completed, in which BL-8040 doses of 0.5 - 1.5 mg/kg were investigated. A total of 22 subjects were exposed to doses escalating according to the protocol's escalation scheme. Only one grade 3 related serious adverse event (SAEs) of Sweet syndrome was reported and assessed as possibly related to BL-8040. The event was reported at the dose level 1.5 mg/kg. It is known that Sweet syndrome occurs in patients with AML, and this particular patient subsequently showed progressive disease. According to the protocol three more patients were recruited for a total of 6 patients. An independent Data Monitoring Committee reviewed the safety data of all cohorts and considered BL-8040 safe and well tolerated at doses up to 1.5 mg/kg. The DMC approved the initiation of the dose expansion part of the study using this dose level.

The 22 subjects dosed to date, reported 348 adverse events (AEs), among which 70% (242 events) of the AEs were assessed as unlikely or unrelated to the study drug. Within the

events assessed as possible, probably or definitely related to BL-8040 (30%), 36% (38) were grade 1, 53% (56) were grade 2, 9% (10) were grade 3 (1 thrombocytopenia, 1 headache, and SAE of Sweet Syndrome, 5 injection site reactions and 2 systemic reactions) and 1% (1) were grade 4 (a case of neutropenia). Injection site reactions and systemic reactions were found to be the most common adverse events reported. During this study in order to mitigate the systemic reactions, pre-treatment with intravenous steroids and anti-histamines was implemented in some patients according to the investigator's judgment. In addition, a new method of reconstitution was developed to enable dilution of BL-8040; and rotation of the site of injection at each dosing was recommended with intent to minimize injection site reactions.

Thirteen out of 22 subjects reported 22 serious adverse events (SAEs), only one was assessed as possible related and was already described above. To date, the maximum tolerated dose (MTD) was not reached when treating AML patients with seven consecutive days of 1.5 mg/kg BL-8040.

BL-8040.02

No Serious Adverse Events were reported in all dose levels. All the AEs but three were mild or moderate, severe AEs included: transient syncope (resolved in one min), two events of asthenia (resolved within 15 - 30 min). Most common BL-8040 related AEs included injections site (IS) reactions characterized by pain, edema and erythema; transient and mild systemic reactions (rash, chills, pruritus, urticaria, hot flashes/flushing, hives, hypotension, chest pain, nausea). All resolved spontaneously within 30 - 120 minutes. Additional less frequent AE's included asthenia, peripheral swelling, paresthesia, hyperhidrosis, tachycardia, edema peripheral, dizziness, headache and pallor. Pre-medication with steroids and anti-histamines was effective in reducing the frequency and magnitude of the systemic reactions.

1.2.6 Rationale for Dosing and Regimen

The dose of 1 mg/kg SC injection was chosen based on the safety and efficacy data from the BKTSC001, BL-8040.02, and the ongoing BL-8040.01 studies. In general, BL-8040 was observed to be associated with a favorable safety profile with the most common AEs being injection site irritation, flushing, and itching, and systemic reactions that were successfully managed with premedication.

In the 1 mg/kg dosage group of the BL-8040.02 healthy volunteers study, all 8 subjects receiving BL-8040 single agent treatment required only one apheresis to collect a mean of 11.89 x 10^6 CD34+ cells/kg. In the 0.9 mg/kg dosage group of the BKTSC001 study, all 4 subjects required only one apheresis to collect a mean of 20.9 x 10^6 CD34+ cells/kg after treatment with G-CSF in combination with a single BL-8040 administration.

Overall, the 1mg/kg dose selected to be used in this study was found to be safe in all studies to date and highly efficacious for SC mobilization and collection in the healthy volunteer study.

1.3 Study Rationale

Current protocols use G-CSF to mobilize hematopoietic progenitor cells from matched sibling and volunteer unrelated donors. Unfortunately, this process requires four to six days of G-CSF injection

and can be associated with side effects, most notably bone pain and rarely splenic rupture[9]. BL-8040 is associated with few side effects, is given as a single SC injection, and collection of cells occurs on the same day as BL-8040 administration. This study will evaluate the safety and efficacy of this novel agent for hematopoietic progenitor cell mobilization and allogeneic transplantation based on the following hypotheses:

1. Healthy HLA-matched donors receiving one injection of BL-8040 will mobilize sufficient CD34+ cells (at least 2.0 x 10^6 CD34+ cells/kg recipient weight) following no more than two leukapheresis collections to support a hematopoietic cell transplant.

2. The hematopoietic cells mobilized by SC BL-8040 will be functional and will result in prompt and durable hematopoietic engraftment following transplantation into HLA-identical siblings with advanced hematological malignancies using various non-myeloablative and myeloablative conditioning regimens and regimens for routine GVHD prophylaxis.

3. If these hypotheses 1 and 2 are confirmed after an interim safety analysis of the data, then the study will continue and include recruitment of haploidentical donors.

1.4 Correlative Studies Rationale and Summary

The ability of BL-8040 to mobilize normal hematopoietic progenitor cells will be examined via peripheral blood samples collected prior to the administration of BL-8040 (pre-treatment baseline assessment), at 0.5 and 1 hour post BL-8040 administration, at 3 hours (immediately before apheresis) post BL-8040 administration, immediately post-completion of apheresis, and 24 hours post BL-8040 administration (Section 8.2). Peripheral blood samples will be analyzed by CBC and flow cytometry to enumerate the CD34+ cells and lymphocytes that are mobilized over time on Day 1.

Because the composition of CD34+ cell subsets, mesenchymal stem cells, NK cells, and T cell subsets may influence recipient outcomes in terms of engraftment, anti-tumor activity, graft versus host disease, morbidity, and mortality, these subsets will be analyzed from samples taken prior to administration of BL-8040 (pre-treatment baseline assessment), at 3 hours (before the beginning of the apheresis), immediately post-completion of apheresis, from the mobilized product, and 24 hours post BL-8040 administration (Section 8.3.1).

If a second leukapheresis is required, peripheral blood samples for CBC and enumeration of CD34+ cells will also be collected immediately prior to the second leukapheresis (approximately 24 hours after BL-8040 injection) and immediately post-completion of apheresis (Section 8.2).

The results of these studies will be used to design further therapeutic trials.

2.0 OBJECTIVES

2.1 Primary Objective

To assess the efficacy of a single injection of BL-8040 to mobilize ≥ 2 x 10^6 $CD34^+$ cells/kg of recipient weight after no more than two leukapheresis collections from healthy donors.

2.2 Secondary Objectives

1. To assess the safety (see Section 2.4 for definition) and tolerability of BL-8040 in healthy donors.
2. To assess the kinetics of neutrophil and platelet recovery post-transplant in patients undergoing allogeneic stem cell transplant.
3. To determine the incidence of primary and secondary graft failure up to one year after transplantation of hematopoietic cells mobilized with BL-8040.
4. To determine the incidence of grade 2-4 acute graft versus host disease (GvHD) in patients who have undergone transplantation of hematopoietic cells mobilized with BL-8040.
5. To determine the incidence of chronic GvHD at 1 year in patients who have undergone transplantation of hematopoietic cells mobilized with BL-8040.
6. To determine the proportion of subjects who collect 5 x 10^6 CD34+ cells/kg of recipient weight in a single leukapheresis and in 2 leukapheresis sessions
7. To determine the incidence of CMV reactivation after transplantation of hematopoietic cells mobilized with BL-8040 in CMV seropositive recipients
8. To determine the incidence of treatment-related mortality and disease relapse/progression after transplantation of hematopoietic cells mobilized with BL-8040
9. To determine the probability of event free and overall survival after transplantation of hematopoietic cells mobilized with BL-8040
10. To determine the change in peripheral blood CD34+ cells concentration from baseline throughout Day 1 and Day 2 (if a second leukapheresis is required)
11. To assess the pharmacokinetic profile of BL-8040.

2.3 Exploratory Objectives

1. To measure alterations in CXCR4 expression and receptor occupancy in the peripheral blood of healthy donors following treatment with BL-8040.
2. To determine the kinetics of mobilization of CD34+ cells and characterize CD34+ subsets mobilized by BL-8040.
3. To characterize the cellular composition of the HSPC graft including T-cell subpopulations in peripheral blood and in the stem cell product.

2.4 Safety Endpoints

1. To assess the number of recipients with primary graft failure
2. To assess the incidence of acute and chronic graft versus host disease in recipients
3. To assess the time to neutrophil engraftment and time to platelet engraftment in recipients
4. Long term safety of the donors after treatment with BL-8040

3.0 PATIENT SELECTION

3.1 Donor Eligibility Criteria

3.1.1 Donor Inclusion Criteria

1. Age 18 to 70 years of age.
2. ECOG performance status of 0 or 1.
3. PART 1: Donor must be a 5/6 or 6/6 HLA-matched sibling willing to donate PBSC for

transplant.
PART 2: Donor must be a 5/6 or 6/6 HLA-matched sibling or ≥3/6 HLA haploidentical donor willing to donate PBSC for transplant. Haploidentical donors will be allowed to participate upon investigator decision and based on the data reached from 5/6 or 6/6 HLA matched transplant done during Part 1 of the study.

4. Adequate organ function defined by:
   a. serum creatinine within normal limits or a minimum creatinine clearance (CrCl) value of ≥ 60 ml/min calculated using the Modification of Diet in Renal Disease (MDRD) Study equation (Appendix 3)
   b. AST, ALT and total bilirubin ≤ 2x institutional upper limit of normal.
5. Women of childbearing potential and men must agree to use adequate contraception with two different forms, including one barrier method, during participation in the study and for 2 weeks following dosing with BL-8040. Abstinence is acceptable if this is the established and preferred contraception for the subject.
6. Female subjects must have a negative urine or serum pregnancy test within 10 days prior to taking study medication if of childbearing potential or must be of non-childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as:
   a. ≥ 45 years of age and has not had menses for > 2 years
   b. Amenorrheic for > 2 years without a hysterectomy and oophorectomy and a FSH value in the postmenopausal range upon pretrial (screening) evaluation
   c. Post-hysterectomy, oophorectomy, or tubal ligation.
7. Able and willing to comply with the requirements of the protocol.
8. Able to understand and willing to sign an IRB-approved written informed consent document.

3.1.2 Donor Exclusion Criteria

1. Received any investigational agent within 30 days and/or 5 half-lives (of the other investigational agent), whichever is longer, of receiving BL-8040.
2. Active HIV or hepatitis B or C infection
3. Pregnant or breastfeeding.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
5. Known allergy or hypersensitivity to any of the test compounds, materials, or contraindication to test products.
6. Any malignancies in the 2 years prior to baseline, excluding: basal cell carcinoma, in situ malignancy, low-risk prostate cancer, cervix cancer after curative therapy.
7. A comorbid condition which, in the view of the investigators, renders the subject at high risk from treatment complications.

3.2 Recipient Eligibility Criteria

3.2.1 Recipient Inclusion Criteria

1. Age 18 to 75 years
2. ECOG performance status of 0-2 (inclusive)
3. One of the following diagnoses:

a. Acute myelogenous leukemia (AML) in 1st or subsequent remission
b. Acute lymphoblastic leukemia (ALL) in 1st or subsequent remission
c. Chronic myelogenous leukemia (CML) in chronic or accelerated phase
d. Non-Hodgkin lymphoma (NHL) or Hodgkin's disease (HD) in 2nd or greater complete remission, partial remission
e. Chronic lymphocytic leukemia (CLL)
f. Multiple myeloma (MM)
g. Myelodysplastic syndrome (MDS)
h. Myeloproliferative neoplasm (MPN) excluding primary or secondary myelofibrosis

4. Adequate organ function defined by:
   a. a creatinine clearance (CrCl) value of ≥ 60 ml/min by MDRD study equation
   b. AST, ALT and a total bilirubin ≤ 2x institutional upper limit of normal.
5. Adequate cardiac function with a left ventricular ejection fraction ≥ 40%.
6. Adequate pulmonary function defined as NO severe or symptomatic restrictive or obstructive lung disease, and formal pulmonary function testing showing an FEV1 ≥50% of predicted and a DLCO ≥ 40% of predicted, corrected for hemoglobin.
8. Female subjects must have a negative urine or serum pregnancy test if of childbearing potential or be of non-childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as:
   a. ≥ 45 years of age and has not had menses for > 2 years
   b. Amenorrheic for > 2 years without a hysterectomy and oophorectomy and a FSH value in the postmenopausal range upon pretrial (screening) evaluation
   c. Post-hysterectomy, oophorectomy, or tubal ligation.
9. Able to understand and willing to sign an IRB-approved written informed consent document.

3.2.2 Recipient Exclusion Criteria

1. Recipient must not have received any investigational drug within 30 days of starting conditioning treatment.
2. Pregnant or breastfeeding.
3. Active HIV or hepatitis B or C infection.
4. Any medical condition which, in the opinion of the clinical investigator, would interfere with the evaluation of the patient. Subjects with a clinically significant or unstable medical or surgical condition or any other condition that cannot be well-controlled by the allowed medications permitted in the study protocol that would preclude safe and complete study participation, as determined by medical history, physical examinations, ECG, laboratory tests, or chest-X-ray and according to the investigator's judgment.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Donors and recipients must not start any protocol intervention prior to the signature of informed consent

and registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Signature of Informed Consent
2. Confirmation of patient eligibility by Washington University
3. Registration of patient in the Siteman Cancer Center OnCore database
4. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Current approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

4.4 Evaluation of Donor and Recipient

Recipients will be evaluated for eligibility prior to donor study enrollment, including reviewing and signing the informed consent document and confirming all eligibility criteria (except donor stem cell collection). Following preliminary confirmation of recipient eligibility, donors will be

consented and checked for eligibility. At the time a donor has been cleared for study entry (i.e., upon completion of the donor's eligibility process), a study identification number will be assigned to both the donor and the recipient. This process constitutes formal study entry.

Should the donor be treated per protocol (mobilization and leukapheresis) only to have the recipient fail eligibility prior to transplantation (due to declining performance status, unacceptable lab results, or other reasons), the donor will be followed per protocol but the donor/recipient pair will be replaced for study evaluation.

5.0 TREATMENT PLAN

5.1 Protocol Summary

This is a phase II open label study to assess the efficacy and safety of the CXCR4 inhibitor BL-8040 in allogeneic transplants. An initial cohort of 10 donor/recipient pairs will be enrolled in Part 1 of the study consisting only of recipients with advanced hematological malignancies and their HLA-identical (5/6 or 6/6 HLA antigen matched) sibling donors. If there are no safety concerns regarding graft failure/rejection after the interim safety review of these 10 Part 1 pairs, then Part 2 of the study will open which will permit enrollment of recipients with either matched sibling or haploidentical donors. During the study, we are aiming to collect $\geq 5.0 \times 10^6$ CD34+ cells/kg actual recipient weight with a minimum of 2.0×10^6 CD34+ cells/kg actual recipient weight in up to two apheresis sessions. The primary study endpoint is efficacy, defined as the ability to mobilize $\geq 2.0 \times 10^6$ CD34+ cells/kg actual recipient weight.

All aspects of the hematopoietic cell transplant for this study including donor selection, graft processing and characterization, and infusion of hematopoietic cells are to be performed in accordance with the standards established by FACT, The Foundation for the Accreditation of Cellular Therapy, cGMP and GTP guidelines relating to human tissue intended for transplantation (21 CFR parts 1270 & 1271) and general biologic products standards (21 CFR part 610).

5.2 Screening Period Assessments

The following assessments should be done at screening; unless otherwise specified, all of these assessments can be done or completed until baseline. The screening period will be up to 30 days for the donor. Recipient screening will be done according to institutional standards.

Donors:

- Signature of informed consent
- Collection of medical history, demographics
- Collection of concomitant medications
- Physical examination
- Vital signs: temperature, blood pressure, pulse, and respiratory rate
- ECOG assessment
- HLA typing
- Blood for CBC
- Blood for CMP
- Urine pregnancy test for women of childbearing potential to be done within 72 hours of dosing (if urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required)

- Serology for hepatitis B and C and HIV
- ECG
- Review of inclusion/exclusion criteria

Recipients:
- Signature of informed consent
- Collection of medical history, demographics
- Collection of concomitant medications
- Physical examination
- ECOG assessment
- HLA typing
- Blood for CBC
- Blood for CMP and LDH
- Urine pregnancy test for women of childbearing potential, to be done within 72 hours of the start of conditioning (if urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required)
- Serology for hepatitis B and C and HIV
- Confirmation of adequate cardiac function, i.e. LVEF ≥40% by Echo, MUGA, or similar
- Pulmonary function test
- Review of inclusion/exclusion criteria

5.3 Pre-Dose Assessments

Pre-dose assessments are to be done on the day of BL-8040 injection, ***before*** the injection.

Donors:
- Vital signs: temperature, blood pressure, pulse, and respiratory rate
- Blood for PK
- Blood for CBC
- FACS for CD34+ cells and lymphocytes, and CD34+ subset analysis and T-cell phenotyping

Recipients:
- Pre-transplant assessment according to institutional guidelines

5.4 Mobilization of Allogeneic Stem Cell Donor

Donors will be mobilized as outpatients with subcutaneous (SC) BL-8040 in the morning (Day 1) followed by leukapheresis approximately 180 minutes (up to 270 minutes) after the injection per institutional protocol. If the donor does not reach the collection goal for mobilization ($\geq 5.0 \times 10^6$ CD34+ cells/kg), a second leukapheresis will be performed on Day 2 (24 hours ± 2 hours from the BL-8040 injection) in an effort to reach a total of $\geq 5 \times 10^6$ cells/kg and at least 2×10^6 cells/kg from the combined collections. Donors who cannot mobilize $\geq 2 \times 10^6$ cells/kg after two apheresis section will be considered mobilization failures (See Section 5.4.4 for information regarding mobilization failure).

5.4.1 BL-8040 Administration

In part 1, BL-8040 will be administered at a dose of 1 mg/kg SC injection on Day 1.

In part 2, BL-8040 will be administered at a dose of 1.25 mg/kg SC injection on Day 1.

The following procedures will be performed after injection of BL-8040 on Day 1:

- Temperature, blood pressure, pulse, and respiratory rate will measured at 1, 2, 3-4, 6, and 8 hours ± 15 min following the end of the BL-8040 injection.
- Approximately 3 hours following injection of BL-8040 (between 180 minutes and 270 minutes is acceptable), begin leukapheresis procedure to process a minimum of three blood volumes according to institutional guidelines
- At various times pre- and post-injection (see Sections 8.1-8.3), obtain venous samples for PK, CBC, and cytometric flow analysis (enumeration of CD34+ cells and lymphocytes, Section 8.2) and CD34+ subset analysis and T-cell phenotyping (Section 8.3). At the completion of leukapheresis, a sample from the leukapheresis product (no more than 10% of product) will be obtained for CBC and flow cytometric analysis (CD34+ subset and T cell phenotype analysis, Section 8.3.2). Cryopreservation of leukapheresis product will be performed according to institutional guidelines.

If a Day 2 leukapheresis is needed, the following procedures will be performed:

- Temperature, blood pressure, pulse, and respiratory rate will be measured immediately before and following the leukapheresis procedure.
- Cryopreservation of leukapheresis product will be performed according to institutional guidelines.
- Venous samples for CBC and enumeration of CD34+ cells will be collected at specific time points (Section 8.2).

5.4.2 Premedication before BL-8040 Injection

Premedication or treatment for local and systemic reaction will be allowed as per Investigator discretion.

- Pre-treatment of subjects prior to BL-8040 injection is allowed with the following concomitant medications: promethazine, hydroxyzine, diphenhydramine, acetaminophen, and steroids.
- Other drugs may also be given as premedication at the Investigator's discretion.
- Clinically appropriate measures in case of BL-8040 related local injection site reactions (e.g., corticosteroids, anti-histamines, local treatments, etc.) may be taken.
- Additional medications/therapies to manage treatment-emergent conditions will be allowed at the discretion of the Investigator in consultation with the Manufacturer, in advance when possible.

5.4.3 Leukapheresis

Donors will undergo no less than three blood volumes leukapheresis (LP) starting approximately 180 minutes (up to 270 minutes) after injection of BL-8040 per institutional protocol. When possible, pheresis will be performed using the same model of pheresis machine in order to maintain consistency. At the end of the leukapheresis, the collected graft will be analyzed by standard flow cytometry for CD34+ cell content. The goal for hematopoietic stem and progenitor cell collection will be $\geq 5.0 \times 10^6$ $CD34^+$ cells/kg actual recipient weight with a minimum of 2.0×10^6 $CD34^+$ cells/kg actual recipient weight.

If the first leukapheresis product contains $\geq 5.0 \times 10^6$ $CD34^+$ cells/kg actual recipient

weight, the mobilization with BL-8040 will be considered completed and successful. If the first leukapheresis product contains < 5.0 x 10^6 $CD34^+$ cells/kg actual recipient weight, a second leukapheresis will be performed approximately 24 hours after the injection of BL-8040 (i.e. Day 2). If the sum of the grafts collected after two days is ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight, the mobilization with BL-8040 will be considered completed and successful.

If a donor fails to mobilize a graft containing at least 2.0 x 10^6 CD34+ cells/kg actual recipient weight after two leukapheresis procedures, mobilization will be considered unsuccessful. These donors will proceed with G-CSF mobilization per standard institution guidelines and will be followed for safety purposes for a period of five years after receiving BL-8040 (Refer to Section 5.4.5).

For the transplant purposes, up to 5.0 x 10^6 $CD34^+$ cells/kg actual recipient weight will be cryopreserved in DMSO per Institutional guidelines and infused in the recipient. Any additional cells will be aliquotted and cryopreserved for future donor cellular infusions to the recipient per Institutional guidelines.

5.4.4 Mobilization Failure with BL-8040

Donors are required to undergo a minimum of three blood volumes apheresis/day for up to two days (i.e. two leukapheresis procedures) to be considered evaluable for the primary endpoint. If the donor fails to collect ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight due to the inability to undergo a minimum of three blood volumes apheresis/day, the donor will be removed from the protocol and the donor/recipient couple will be replaced. The donor will still be followed for safety purposes according to the protocol (Section 5.2.4).

If the donor is able to undergo a minimum of three blood volumes apheresis/day, but the sum of the two leukapheresis products is < 2.0 x 10^6 CD34+ cells/kg actual recipient weight, treatment will be considered unsuccessful (mobilization failure). In this case, the donor will be removed from protocol and will be mobilized with G-CSF according to the standard institutional procedures. The donor/recipient couple will not be replaced, but followed for safety purposes according to the protocol (Sections 5.4.5 and 5.5.5). If the patient is unable to obtain sufficient cells for transplant from the G-CSF mobilization, the BL-8040 product may be pooled with the G-CSF mobilized product for transplant. Recipient outcomes will be collected and described but will not considered part of the primary analysis.

5.4.5 Donor Follow-Up

Donors will be closely monitored during treatment and mobilization with BL-8040 for adverse events for 5 years post-administration of BL-8040. AEs and concomitant medications will be obtained at the 30 day follow-up visit/phone call. New AEs reported during this period and those that are still open will be followed until resolution or stabilization. Adverse events will be graded according to the NCI CTCAE version 4.03. Hypocalcemia documented during the leukapheresis procedure is a known transient side effect and will not require additional follow-up unless determined to be clinically indicated by the treating physician. The donor will have a CBC with differential count drawn at 7 days and 30 days post-completion of BL-8040 administration. If the donor's CBC has clinically significant changes from baseline in the opinion of the treating physician at 30 days post-administration of BL-8040, the donor will continue to have CBCs drawn monthly

until resolution. Telephone contact will be made by the research study coordinator annually for 5 years. Long term donor follow up will be performed in accordance to the consensus statement from the Worldwide Network for Blood and Marrow Transplantation and limited to three items: survival, onset of malignancies and onset of autoimmune diseases. In the case of a positive reply, the level of evidence should be indicated, that is if the diagnosis was confirmed by medical data.[43] See Section 7.1 for donor follow-up schedule of events.

5.5 Treatment of the Recipient

Once it is determined that an allograft of ≥ 2.0 x 10^6/kg has been obtained following BL-8040 injection, the recipients may start their transplant conditioning regimen. On the day of transplantation (Day 0), the previously cryopreserved allograft will be thawed and infused into the recipient (refer to Section 5.5.3).

5.5.1 Administration of Conditioning Regimen

Once it is determined that a sufficient allograft has been obtained following BL-8040 injection, the recipients will undergo myeloablative or reduced intensity conditioning chemotherapy as per institutional guidelines. Conditioning chemotherapy and/or radiation regimens permitted in this study are:

- Fludarabine and busulfan
- Fludarabine and cyclophosphamide +/- TBI
- Fludarabine and melphalan
- Busulfan and cyclophosphamide
- Cyclophosphamide and TBI

Additional regimens may be allowed with approval of the Primary Investigator.

5.5.2 GVHD Prophylaxis

GVHD prophylaxis will be administered to all patients per institutional guidelines.

5.5.3 Stem Cell Transplantation

All or part of the leukapheresis product will be infused into the recipient per institutional guidelines. The day of the infusion will be considered Day 0; if the infusion occurs over multiple days, the final day of infusion will be considered Day 0.

On the day of transplantation (Day 0), the cryopreserved allograft will be thawed and up to 5.0 x 10^6 $CD34^+$ cells/kg (but not less than 2.0 x 10^6 $CD34^+$ cells/kg) actual recipient weight will be infused into the recipient.

5.5.4 General Concomitant Medication and Supportive Care Guidelines

Concomitant medications and supportive care measures, such as growth factors, will be administered at the discretion of the treating physician.

If the recipient requires a donor lymphocyte infusion (DLI) as determined by the treating physician, data will be collected on the number of cells infused and all grade 3-5 AEs (see Section 11.1.7 for exceptions) will be recorded from Day 0 to Day 30 post DLI.

5.5.5 Recipient Follow-Up

Recipients will be closely monitored for serious adverse events (see Section 11.1.7 for exceptions), neutrophil and platelet recovery, and GVHD. These will be recorded in medical records and transcribed into case report forms. Serious adverse events will be graded according to the NCI CTCAE version 4.03 and all grade 3-5 nonhematologic AEs will be collected from start of conditioning through Day 100 or until relapse or start of subsequent treatment for their hematologic malignancy, whichever comes first.

See Section 7.2 for recipient follow-up schedule of events. All recipients will be followed post-transplant regardless of relapse, subsequent treatment, etc.

5.5.6 Failure to Engraft

If any recipient receiving the BL-8040 mobilized allograft does not have evidence of absolute neutrophil count (ANC) of at least 500/μL by Day +28 following transplantation, the donor will be contacted to begin G-CSF mobilization immediately and the recipient will be treated according to standard institutional policies for engraftment failure. The recipient will still be monitored for safety per protocol.

5.6 Evaluation of Toxicity, Response, and Study Endpoints

5.6.1 Donor and Recipient Toxicity Evaluations

All donors who receive BL-8040 are evaluable for toxicity (including CBC recovery).

All recipients who receive any hematopoietic cells mobilized with BL-8040 are evaluable for toxicity, hematopoietic recovery, GVHD and disease relapse.

5.6.2 Donor and Recipient Response Evaluations

Donors are required to undergo a minimum of 3 blood volumes of apheresis / day and up to two apheresis (depends on the number of cells collected) to be evaluable for efficacy.

Recipients who receive hematopoietic cells mobilized with BL-8040 only will be evaluable for engraftment.

5.6.3 Evaluation of Donor/Recipient Pairs for Study Endpoints

If a donor fails to collect $\geq 2.0 \times 10^6$ CD34+ cells/kg actual recipient weight despite undergoing at least 3 blood volumes of apheresis/day for 2 days, the donor will be considered evaluable, but will be considered a mobilization failure that will count towards the primary analysis (see Section 13.1.1).

If a donor collects $\geq 2.0 \times 10^6$ CD34+ cells/kg actual recipient weight and the recipient fails eligibility prior to transplantation (due to declining performance status, unacceptable lab results, or other reasons), the donor will be followed for safety per protocol, but the donor/recipient pair will not be considered evaluable and will be replaced.

5.7 General Concomitant Medication and Supportive Care Guidelines

Concomitant medications and supportive care measures will be given at the discretion of the treating physician whenever medically necessary.

5.8 Women of Childbearing Potential

Women of childbearing potential (women with regular menses, amenorrhea, irregular cycles, using a contraceptive method that precludes withdrawal bleeding, or who have had a tubal ligation) are required to have a negative pregnancy test within 10 days prior to the first dose of BL-8040 (donor) or prior to start of conditioning (recipient).

Non-childbearing potential is defined as (by other than medical reasons):

- ≥ 45 years of age and has not had menses for greater than 2 years.
- Amenorrheic for > 2 years without a hysterectomy and oophorectomy and an FSH value in the postmenopausal range upon pretrial (screening) evaluation.
- Post-hysterectomy, oophorectomy, or tubal ligation.

Donors or recipients (female or male along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 2 weeks following the dose of BL-8040 (donor) or 2 weeks following the stem cell transplant (recipient).

If a donor or recipient is suspected to be pregnant, BL-8040 administration to the donor and/or stem cell transplant to the recipient should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the recipient or donor is not pregnant, the donor may resume dosing and the recipient may receive the transplant.

If a female donor or recipient or female partner of a male donor or recipient becomes pregnant during treatment or within 1 month after the dose of BL-8040 (donor) or the stem cell transplant (recipient), the investigator must be notified in order to facilitate outcome follow-up.

5.9 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the donor and/or recipient's health and/or the donor and/or recipient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Donor and /or recipient may be removed from the protocol treatment or study for any of the following reasons:

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the primary investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up

- Patient request, i.e. withdrawal of consent
- Study termination by the Sponsor, Investigator or regulatory agency

6.0 DOSE MODIFICATIONS

Dose modifications for BL-8040 are **not** permitted.

7.0 STUDY CALENDARS

7.1 Donor

	Screening[1]	Day 1							Day 2		Day 7 (± 3d)	Day 30 (± 7d)	1 Yr (± 30d)	2 Yr (± 30d)	3 Yr (± 30d)	4 Yr (± 30d)	5 Yr (± 30d)
		Pre-dose	0.5h post	1h post	2h post	3-4h post (prior to LP)	6h post	8h post (end of LP)	24h post (prior to LP)	30h post (end of LP)							
Labs/Procedures																	
Physical exam	X																
CBC	X	X				X		X	X	X[3]	X	X[4]					
CMP	X																
CMV IgG	X																
Pregnancy test	X[5]																
HLA typing	X																
ECG	X																
Vital signs	X	X		X	X	X	X	X	X	X[3]							
Correlative Studies																	
PK monitoring		X	X	X		X		X	X								
CD34 enumeration		X	X	X		X		X	X	X[3]							
Lymphocyte subsets		X	X			X		X	X	X[3]							
T-cell phenotyping		X				X			X								
CD34+ subset analysis		X				X			X								

1: Screening assessments should occur within 30 days prior to registration
2: On leukapheresis product
3: Only if leukapheresis is required on Day 2
4: If CBC has not returned to baseline, continue checking monthly CBCs until hematologic recovery is observed.5: No more than 10 days prior to dose.

7.2 Recipient

The timing of screening assessments will match institutional standards.

	Screening	Day 1-21	Day 30 (± 5d)	Day 60 (± 5d)	Day 100 (± 14d)	Day 180 (± 14d)	Day 270 (± 14d)	Day 365 (± 14d)	Year 2 (± 28d)	Year 3 (± 28d)
Physical Exam	X	X[1]	X	X	X	X	X	X		
CBC	X	X[1]	X	X	X	X	X	X		
BMP / CMP & LDH	X	X[3]	X	X	X	X	X	X		
CMV IgG[4]	X	X[4]	X	X	X	X	X	X		
Pregnancy test	X									
HLA Typing	X									
Lymphocyte Subset-13+CD25+			X		X	X		X		
Disease Restaging			X		X	X		X		
Chimerism Analysis			X		X	X		X		
Acute GVHD Assessment		X[2]	X	X	X	X	X	X		
Chronic GVHD Assessment					X	X	X	X		
Survival and relapse/progression								X	X[5]	X[5]

1: To occur daily until engraftment
2: To occur weekly starting at the time of neutrophil engraftment.
3: BMP daily, with CMP and LDH to be performed at least twice weekly until engraftment
4: CMV IgG performed at screening and CMV PCR post transplant per institutional standard
5: May be a telephone call in lieu of a clinic visit

8.0 CORRELATIVE STUDIES

8.1 Pharmacokinetics and PK Monitoring

Non-compartmental PK parameters for BL-8040 (see below) will be derived from the individual concentration obtained at each of the PK time-points. Additional PK parameters may be derived if considered necessary:

- C_{max} - maximum BL-8040 plasma concentration
- T_{max} - time to reach the maximum BL-8040 plasma concentration
- AUC_{0-t} - Area under the BL-8040 plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post dosing, calculated by linear up-logarithmic down trapezoidal summation
- $AUC_{0-\infty}$ - Area under the BL-8040 plasma concentration-time curve extrapolated to infinity, calculated as: $AUC_{0-\infty} = AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration
- λ_z - elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve
- $t_{1/2}$ - terminal elimination half-life, defined as $0.693/\lambda_z$

At the following time points on Day 1, approximately 4 mL of peripheral blood will be collected in EDTA tube(s) for pharmacokinetic analysis:

- Prior to SC injection of BL-8040
- 0.5 hours after administration of BL-8040
- 1 hour after the administration of BL-8040
- 3 hours after the administration of BL-8040 (just prior to leukapheresis)
- 8 hours post-completion of drug injection (immediately after leukapheresis)
- 24 hours after administration of BL-8040

Ship PKs to:

Shedeka Marriott
Washington University School of Medicine
660 South Euclid Avenue, CB 8615
St. Louis, MO 63110

8.2 Enumeration of CD34+ Cells and Lymphocytes and CBC Analysis after BL-8040 Administration

At the following time points on Day 1, approximately 3 mL of peripheral blood will be collected in EDTA tube(s) for enumeration of CD34+ cells and lymphocytes. The latter is ordered as an "allogeneic transplant flow cytometry panel +CD25" measuring CD2, CD3, CD4, CD8, CD19, CD20, CD25, and CD56 and is performed at the local study center hematology laboratory or a Sponsor designated central laboratory.

<u>Day 1 Enumeration of CD34+ cells and lymphocytes (3 mL blood, EDTA) and CBC (EDTA)</u>

- Prior to SC injection of BL-8040
- 0.5 hours (+/- 15 min) after administration of BL-8040 (CD34+ only)
- 1 hour (+/- 30 min) after administration of BL-8040 (CD34+ only)
- 3hours (+/- 1 hour) after the administration of BL-8040 and just prior to leukapheresis

- 8 hours (+/- 2 hours) post-completion of drug injection (immediately after leukapheresis)
- 24 hours (+/- 2 hours) after administration of BL-8040

If a second leukapheresis is required (Day 2), approximately 3 mL of peripheral blood will be collected in EDTA tube(s) for enumeration of CD34+ cells and lymphocytes and CBC at 24h (prior to leukapheresis) and 30h (end of leukapheresis) post BL-8040 injection.

The actual time of the sample must be documented.

The used tubes and color codes and required procedures may change during the study. In this case, the Manufacturer will provide separate description on the required collection methods.

8.3 CD34+ Subset Analysis and T-cell Phenotyping Evaluations after BL-8040 Administration

8.3.1 Peripheral Blood Samples

At the following time points on Day 1, approximately 16 mL of peripheral blood will be collected in EDTA tubes for CD34+ subset analysis and T-cell phenotyping.

Day 1 CD34+ subset analysis (8 mL blood, EDTA) and T-cell phenotyping (8 mL blood, Na Hep)

- Prior to SC injection of BL-8040
- 3-4 hours after the administration of BL-8040 (prior to leukapheresis)
- 24 hours (+/- 2 hours) after administration of BL-8040

If a second leukapheresis is required (Day 2), approximately 16 mL of peripheral blood will be collected in EDTA tube(s) for CD34+ subset analysis and T-cell phenotyping at 24 h (prior to leukapheresis) post BL-8040 injection.

The actual time of the sample must be documented.

8.3.2 Sampling of Leukapheresis Product

In addition to the peripheral blood samples collected, on Day 1, 10 to 15 mL of the final leukapheresis product (no greater than 10% of volume of the entire leukapheresis product) will be collected and sent to the laboratory of Dr. DiPersio on cold pack (See Section 8.6).

8.4 Handling of Specimens

All samples will be labeled with patient initials, study number, date and time of collection.

8.5 Site Performing CD34+, Lymphocyte, CBC Analysis and T-Cell Phenotyping

Samples will be analyzed at the Washington University study center hematology laboratory as appropriate.

8.6 Samples to Be Sent to Dr. DiPersio's Laboratory at Washington University

The samples for CD34+ subset analysis and T-cell phenotyping will be sent **on the same day on cold pack** to the laboratory of Dr. DiPersio on the 6th floor of the Southwest Tower for analysis. Shipping address is:

DiPersio Lab c/o Leah Gehrs / Mike Rettig
Washington University Medical School
4940 Parkview Place
626P Southwest Tower
St. Louis, MO 63110-1025

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section. Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

9.1 Donor Submission Schedule

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Donor On-Study Form Donor Medical and Surgical History Form Donor CBC Form	At baseline
Donor Study Drug Dosing	After dose of BL-8040
Donor Leukapheresis Log Donor CBC Form (multiple time points)	Day 1 Day 2 (if required)
Donor Correlative Log (multiple time points)	Day 1 Day 2
Donor Follow-Up Form Donor CBC Form	Day 7 Day 30 Year 1 Year 2 Year 3 Year 4 Year 5
Adverse Events	Continuous from baseline through safety follow-up visit
MedWatch Form	See Section 10.0 for reporting requirements
Concomitant Medications	Continuous from baseline through leukapheresis

9.2 Recipient Submission Schedule

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Recipient On-Study Form Recipient Medical and Surgical History Form	At baseline
Recipient Conditioning Form	Completion of conditioning
Recipient Transplant Form	After engraftment (or Day 30)
Recipient Disease Response Form	Day 30 Day 100 Day 180 Day 365
Recipient Acute GVHD Assessment Form	Week 3 Day 30 Day 60 Day 100 Day 180 Day 270 Day 365
Recipient Chronic GVHD Assessment Form	Day 100 Day 180 Day 270 Day 365
Recipient CBC Form	Baseline Day 0 Day 30 Day 60 Day 100 Day 180 Day 270 Day 365
Recipient CMV Reactivation	Any time CMV testing occurs (will be performed as per institutional standard)
Recipient Relapse / Progression Form	Time of relapse / progression
Recipient Survival Form	Day 365 Year 2 Year 3
Adverse Events	Continuous from start of conditioning through day 100
MedWatch Form	See Section 10.0 for reporting requirements

10.0 SAFETY, PHARMACOVIGILANCE, AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 10.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 10.4. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

BioLineRX requires that all SAEs be reported as outlined in Section 10.5.

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is defined in ICH E6 as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in subject's withdrawal by the Investigator
- Is associated with an SAE
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance
  A new condition or the worsening of a pre-existing condition will be considered an AE.
  AEs do not include the following:
- Medical/surgical procedures are not AEs (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if the procedure was not planned at the Screening visit.
- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Disease progression.

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, should be recorded individually on an AE CRF page with the following information: the specific event or condition, the dates of occurrence, duration, severity, relationship to study medication, action taken to study drug, outcome, and whether considered non-serious or serious.

Once the subject has signed the informed consent form (ICF), AEs will be recorded up to and including 30 days after the last dose of the treatment drug for donors. AEs from time of consent to immediately prior to receiving BL-8040 will be captured as baseline events. The severity of the AE will be assessed by the investigating physician in accordance with the definitions below. A Serious AE must fulfill the requirements listed in Section 10.1.2.

In addition, any AEs at least possibly related to study drug that occurs up to 5 years after the BL-8040 dose (donor) should be recorded.

For recipients, Grade 3-5 nonhematologic AEs will be recorded from the start of the conditioning regimen until Day +100 post transplant.

AE severity (Table 1) will be recorded and graded according to NCI-CTCAE (v 4.03).

Table 111: Severity of Adverse Events According to CTCAE (Version 4.03)

Grade	Description
0	No AE or within normal limits
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semi-colon indicates 'or' within the description of the grade.

The following definitions should be used for toxicities/AEs that are not defined in the CTCAE:

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity, no medical intervention is required;
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest;
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy;
- Life-threatening (Grade 4): The subject is at immediate risk of death.
  The Investigator will document his/her opinion of the relationship of the AE to treatment with the study drug, using the criteria outlined in Table 2.

The possible outcomes of the AEs are classified as follows:

- Recovered: The subject has fully recovered from the AE with no residual effects observable
- Recovered with sequelae: The subject has recovered from the AE with residual effects observable
- Ongoing: AE is not recovered
- Fatal
- Unknown

All AEs, serious and not serious, will be recorded on the AE Case Report Form, and if relevant, the Concomitant Medications Record in the CRF will be updated. The Investigator will assess severity and relationship to study drug (See **Table 1** and **Table 2** respectively). Particular attention should be made to ensure no discrepancies between the AE and the SAE form (i.e. outcome, severity, relationship must be consistent).

Treatment-emergent AEs (TEAEs) are defined as AEs observed after 1st dose of study drug.

Table 222: Relationship of Adverse Event to Treatment

Relationship	Criteria
Unrelated	The patient did not receive the study medication. OR The temporal sequence of the AE onset relative to administration of the study medication is not reasonable. OR There is another obvious cause of the AE.
Unlikely	There is evidence of exposure to the study medication. However, it does not follow a reasonable temporal sequence from administration of drug. It does not follow a known response pattern to the suspected drug. It does not re-appear or worsen upon re-challenge. There is another more likely cause of the AE.
Possible	There is evidence of exposure to the study medication. The temporal sequence of the AE onset relative to the administration of the study medication is reasonable. The AE could have been due to another equally likely cause.
Probable	There is evidence of exposure to the study medication. The temporal sequence of the AE onset relative to administration of the study medication is reasonable. The AE is more likely explained by the study medication than by another cause. A direct cause and effect relationship between the suspected drug and the adverse event is likely. It disappears or decreases upon cessation of drug administration or reduction in dose.
Related	There is evidence of exposure to the study medication. The temporal sequence of the AE onset relative to administration of the study medication is reasonable. The AE is more likely explained by the study medication than by another cause. The AE shows a pattern consistent with previous knowledge of the study medication. A direct cause and effect relationship between the suspected drug and the adverse event has been demonstrated. It disappears or decreases upon cessation of drug administration or reduction in dose.

10.1.2 Serious Adverse Events (SAEs)

An SAE is any AE occurring at any dose that suggests a significant hazard or side effect, regardless of the Investigator's opinion on the relationship to the investigational medicinal product and which results in, but may not be limited to, any of the following outcomes:

- Death (regardless of the cause)
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care

facility)
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Significant Medical event

A **life-threatening** adverse drug experience is any AE that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition (pre-Baseline) that did not worsen while on study and optional hospitalizations not associated with a clinical AE (e.g. elective cosmetic surgery) are not considered SAEs.

Significant medical events are those that may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; such an AE will normally be considered serious by this criterion.

10.1.3 Suspected Unexpected Serious Adverse Events (SUSARs)

A serious adverse event which is assessed as related and is unexpected will be considered as SUSAR and should be reported in an expedited manner (see Sections 10.8 and 10.9).

Definitions:
- Unexpected: a case in which in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; is not expected to be present
- Relationship: related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.1.4 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, study protocol, or determinations of the IRB.

10.1.5 Serious Noncompliance

Definition: noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

10.1.6 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation. No exceptions to the eligibility criteria (Section 3.0) will be considered.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

10.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any Barnes Jewish Hospital (BJH) or Saint Louis Children's Hospital (SLCH) institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

10.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

10.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report any unanticipated problem to the FDA as

follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 10.1.2) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 10.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

Secondary sites must submit a completed MedWatch form to the Washington University PI and research coordinator within **4 calendar days** (for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences). The Washington University PI will be responsible for submitting all MedWatch forms from secondary sites to the FDA within the timeframes specified above.

10.5 Notification of Serious Adverse Events to BioLineRx

Initial notification of SAEs
An initial SAE report form must be completed and sent by fax/email to the BioLineRx Medical Monitor within 24 hours of the Investigator's knowledge of the event. Any fatal or life-threatening event should be reported immediately, by phone, fax or email.

Medical Monitor
Dr. Abi Vainstein-Haras
Mobile +972 54 4709208
Email: safety8040@biolinerx.com
Fax: + 972-8-642-9137

The initial SAE report will be followed within 24 hours by a completed SAE report including a sufficiently detailed narrative, as well as copies of hospital case reports, results of applicable diagnostic tests, laboratory results, biopsy results, autopsy reports and other documents when requested and applicable.

Minimum criteria for a valid initial SAE case:
For regulatory purposes, initial SAE reports should be submitted to BioLineRx immediately and should include:

- Protocol identification
- A suspected investigational medicinal product,
- An identifiable subject (e.g. study subject code number),

- An AE with the Investigator's assessment of seriousness and relationship to any the study drugs,
- An identifiable reporting source i.e. Investigator contact details.

Follow-up of SAEs

A Follow-up SAE Report Form must be completed by the site (marked as "Follow-up report") and sent to the Medical Monitor within a reasonable timeframe (an SAE Follow-up report is required whether or not there is any additional information to the initial report).

The contact information for Follow-up SAE reporting is the same as for initial SAE reports (see above Section).

10.6 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

10.7 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

10.8 Timeframe for Reporting Required Events

Adverse events will be collected on donors from first dose of study treatment (Day 1) through the Day +30 visit. Adverse events will be collected on recipients from the start of conditioning through the Day +100 visit.

Unexpected CTCAE grade 4 or 5 nonhematologic AEs experienced by transplant recipients must be reported within 24 hours of knowledge of the event. Unexpected CTCAE grade 3 nonhematologic AEs must be reported within 3 business days of knowledge of the events.

Expected AEs will be reported using NCI's CTCAE Version 4.03 at regular intervals as defined in Section 9.0.

11.0 PHARMACEUTICAL INFORMATION

Refer to Section 1.2

12.0 MEASUREMENT OF EFFECT

12.1 Definition of Primary Efficacy Endpoint

12.1.1 Adequate Allograft

For the purposes of this study, an adequate allograft is defined as a graft that contains ≥ $2.0x10^6$ CD34+ cells/kg actual recipient weight collected in no more than two leukapheresis sessions using BL-8040 as the sole mobilizing agent

12.2 Definition of Secondary Endpoints

12.2.1 Neutrophil Engraftment

Time to neutrophil engraftment is measured by determining the first of 3 consecutive measurements of neutrophil count ≥ 500/μL following conditioning regimen induced nadir.

12.2.2 Platelet Engraftment

Time to platelet engraftment is measured by determining the first of 3 consecutive measurements of platelet count ≥ 20,000/μL without platelet transfusion support for 7 days.

12.2.3 Graft Failure / Graft Rejection

Graft failure/rejection will be defined as an ANC < 500 /μL after Day 28 post-HCT and bone marrow biopsy with < 5% cellularity in the absence of evidence of disease.

12.2.4 CMV Reactivation

CMV reactivation will be defined as a positive test for CMV viremia as determined by an antigenemia assay or quantitative PCR that results in the administration of antiviral treatment directed against CMV.

12.2.5 Relapse or Disease Progression

Disease relapse occurs in recipients who entered transplant in CR. Progression occurs in recipients with existent disease at transplant who meet criteria for progressive disease post-transplant. A recipient will be considered relapsed when there is a recurrence of the original malignant disease after transplantation. Date of relapse/progression is defined as the date at which the first observation of hematologic, radiographic, or cytogenetic changes which signify progression/relapse is made.

12.2.6 Event Free Survival

An event is defined as either graft failure (Section 12.2.3), disease relapse as evidenced by

hematologic, radiographic, or cytogenetic changes, or death. The event free survival is the time from Day 0 to occurrence of the first event.

12.2.7 Overall Survival

The time from Day 0 to death.

12.3 Definition of Safety Endpoints

12.3.1 Acute GVHD

Acute GVHD rate and severity for the first year after PBSC infusion will be assessed based on the Minnesota-Center for International Blood and Marrow Transplant Research (CIBMTR) GVHD grading system (Appendix 1)[44, 45, 46]. All grades of severity of acute GVHD will be collected.

12.3.2 Chronic GVHD

Chronic GVHD rate and severity for the first 365 days after PBSC infusion will be assessed based on the NIH criteria (Appendix 2).

12.3.3 Treatment Related Mortality

Death that results from a transplant procedure related complication (e.g. infection, organ failure, hemorrhage, GVHD) rather than from relapse of the underlying disease or an unrelated cause.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early

stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study Principal Investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 10.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

In addition, the study may be monitored by BioLineRx or a designee. On-site monitoring of all study records including source documentation may be performed to ensure accuracy and completeness of case report forms.

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:
- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 STATISTICAL CONSIDERATIONS

15.1 Primary Analysis

15.1.1 Primary Analysis Set

The full analysis set (FAS) will consist of all donors having received a dose of BL-8040. The FAS will be the primary analysis set for all efficacy and safety analyses.

15.1.2 Primary Efficacy Analysis and Sample Size Calculation

We predict that approximately 90% of donors will collect ≥ 2.0 x 10^6 CD34+ cells/kg within two apheresis sessions. The power analysis was performed assuming type 1 error (alpha) = 0.025, one sided non-inferiority test (0.7 reference (inferiority), true response rate of 0.9, inferiority margin = 0.001)[47]. To achieve 0.9 power, a total of 24 evaluable subjects will be enrolled.

15.1.3 Accrual

Approximately 1 – 3 donor/recipient pairs per month.

15.1.4 Stopping Rules

14.1.4.1 Stopping Rule for Continuation of Study Enrollment

As a stopping rule to ensure that the rate of graft failure does not exceed 5%, there are three planned interim looks and no more than 1 graft failure can be observed in the first 5 patients, no more than 2 in the first 10 patients, and no more than 2 in the first 15 patients. If the number of graft failures exceeds the specified numbers, no further patients will be enrolled on study. The stopping rule was determined using Pocock boundary[48].

14.1.4.2 Stopping Rule for Enrollment of Haploidentical Donor/Recipient Pairs

We will first enroll 10 patients with matched sibling donors. If no instances of graft failure are observed among the initial 10 sibling/recipient pairs enrolled, we will then enroll patients with **either** matched sibling **or** haploidentical donors. If one graft failure is observed among the initial 10 subjects, then the study will **not** enroll haploidentical donor/recipient pairs.

15.2 Secondary Efficacy and Safety Analyses

15.2.1 Safety Analysis

AEs (all, grade (for recipients), severity (for donors), relatedness to study drug, serious AEs, and AEs leading to deaths) recorded during the study will be summarized and listed.

Laboratory values will be summarized and categorized based on their normality status. Individual data listing will also be provided.

Data from vital signs and physical examinations will be listed and summarized.

15.2.2 Kinetics of Neutrophil and Platelet Engraftment

Summary of number of recipients with neutrophil engraftment by Day +28 along with 95% confidence intervals and listings will be provided. Kaplan-Meier models will be used to estimate median time to neutrophil engraftment including 95% confidence intervals. Time to neutrophil engraftment is measured by determining the first 3 consecutive measurements of neutrophil count ≥ 500/μL following conditioning regimen induced nadir.

Summary of number of recipients with platelet engraftment along with 95% confidence intervals and listings will be provided. Kaplan-Meier models will be used to estimate median time to platelet engraftment including 95% confidence intervals. Time to platelet engraftment is measured by determining the first of 3 consecutive measurements of platelet count ≥ 20,000/uL without platelet transfusion support for 7 days.

15.2.3 Acute and Chronic GVHD

Summary of number of recipients with acute GVHD and chronic GVHD along with 95% confidence intervals and listings will be provided. If there is sufficient number of recipients with events additional Kaplan-Meier models will be used to estimate median times to acute GVHD, chronic GVHD, relapse, disease progression, and death of any cause with 95% confidence intervals.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the

participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

17.0 REFERENCES

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APPENDIX 1: MINNESOTA-CIBMTR STAGING AND GRADING FOR ACUTE GVHD

Acute GVHD Staging

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin (% BSA)	No rash	< 25%	25%-50%	> 50%	Generalized erythroderma with bullae
Gut (diarrhea, mL/day)	< 500	> 500	> 1000	> 1500	Severe abdominal pain +/- ileus
Upper GI		Persistent, severe nausea			
Liver (bilirubin, mg/dL)	≤ 2	2.1-3	3.1-6	6.1-15	> 15

BSA = body surface area; GI = gastrointestinal.

Acute GVHD Grading, MN-CIBMTR Criteria

Grade	Skin	Liver	Lower GI	Upper GI
Minnesota				
I	1-2	0	0	0
II	3	1	1	1
III	-	2-4	2-3	-
IV	4	-	4	-
CIBMTR				
A	1	0	0	0
B	2	1-2	1-2	1
C	3	3	3	-
D	4	4	4	-

APPENDIX 2: Chronic GVHD Assessment

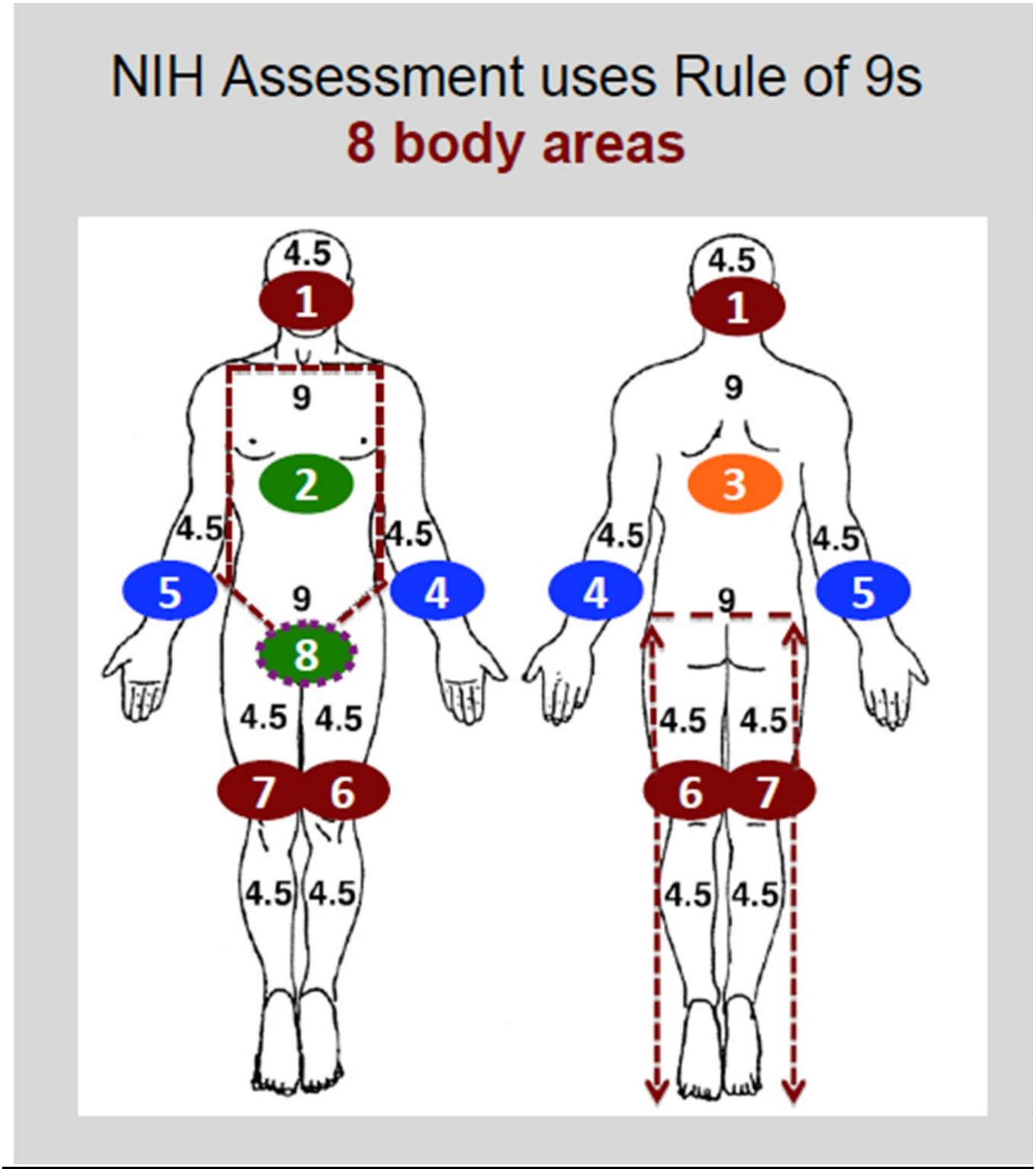
Date of Assessment: _____

SKIN (Patient History and Exam)
Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
Skin Score	No Symptoms	< 18% BSA with disease signs but **NO** sclerotic features	19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch	>50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus

NIH item that scores maximum severity based on:
- → Percent body surface area involved by erythema ***OR***
- → Degree of sclerotic features ***OR***
- → Impaired mobility ***OR***
- → Ulceration ***OR***
- → Severe pruritus

Maculopapular rash	☐	Erythroderma	☐
Lichen planus-like features	☐	Poikiloderma	☐
Papulosquamous lesions or ichthyosis	☐	Sclerotic features	☐
Hyperpigmentation	☐	Pruritus	☐
Hypopigmentation	☐	Hair Involvement	☐
Keratosis pilaris	☐	Nail Involvement	☐
Erythema	☐	% BSA involved: _____	☐



***% BSA Reference**

cGVHD signs and symptoms seen with NAILS, SCALP, BODY HAIR

Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

Check all that apply:

Distinctive (seen in Chronic GVHD, but insufficient alone to establish diagnosis of Chronic GVHD)

Dystrophy ☐
Longitudinal ridging, splitting, or brittle features ☐
Onycholysis ☐
Pterygium unguis ☐
Nail loss (usually symmetic; affects most nails) ☐
New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) ☐
Scaling, papulosquamous lesions ☐

Other features/common (seen with both Acute and Chronic GVHD)

Thinning scalp hair, typically patchy, course or dull (not explained by endocrine or other causes) ☐
Premature gray hair ☐

Please describe:
Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD

_____
_____
_____

cGVHD signs and symptoms seen with MOUTH

Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
Oral Score	No Symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs with partial limitation of oral intake	Severe symptoms with disease signs on examination with major limitation of oral intake

Oral Exam
Check all that apply:

Diagnostic (sufficient to establish Chronic GVHD)

Lichen-type features ☐
Hyperkeratotic plaques ☐
Restriction of mouth opening from sclerosis ☐

Distinctive (seen in Chronic GVHD, but insufficient alone to establish diagnosis of Chronic GVHD)

Xerostomia ☐
Mucocele ☐
Muscosal atrophy ☐
Pseudomembranes ☐
Ulcers ☐

Other features/common (seen with both Acute and Chronic GVHD)

Gingivitis ☐
Mucositis ☐
Erythema ☐
Pain ☐

Please describe:
Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD

_____
_____
_____

cGVHD signs and symptoms seen with EYES

Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
Eye Score	No Symptoms	Mild dry eye symptoms not affecting ADL (requiring eye drops <3x per day) OR asymptomatic signs of keratoconjunctivitis sicca	Moderate dry eye symptoms partially affecting ADL (requiring eye drops >3x per day or punctal plugs) without vision impairment	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision cause by keratoconjunctivitis sicca

Nuances for a patient using drops < 3 x per day:

- But wearing a Boston Scleral lens → Score 3
- But had punctal plugs placed 7 days → Score 2
- But had plugs placed a month ago →Score 1

Check all that apply:

Distinctive (seen in Chronic GVHD, but insufficient alone to establish diagnosis of Chronic GVHD)

New onset dry, gritty, or painful eyes ☐
Cicatricial conjunctivitis ☐
Keratoconjunctivitis sicca ☐
Confluent areas of punctate keratopathy ☐

Other features/common (seen with both Acute and Chronic GVHD)

Photophobia ☐
Periorbital hyperpigmentation ☐
Blepharitis (erythema of the eyelids with edema) ☐

Please describe:
Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD

_____
_____
_____

cGVHD signs and symptoms seen with GI TRACT

Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
GI Tract Score	No Symptoms	Symptoms such as dysphagia, anorexia, nausea, abdominal pain or diarrhea without significant weight loss (<5%)	Symptoms with mild to moderate weight loss (5-15%)	Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs OR esophageal dilation

Check all that apply:

Diagnostic (sufficient to establish Chronic GVHD)

Esophageal web ☐

Strictures or stenosis in the upper to mid third of the esophagus ☐

Other features/common (seen with both Acute and Chronic GVHD)

Exocrine – pancreatic insufficiency ☐

Anorexia ☐

Nausea ☐

Vomiting ☐

Diarrhea ☐

Weight loss ☐

Failure to thrive (infants and children) ☐

Please describe:

Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD

_____

_____

_____

cGVHD signs and symptoms seen with LIVER

Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

Liver Score	0	1	2	3
	Normal LFT	Elevated Bilirubin, AP, AST or ALT <2x ULN	Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	Bilirubin or enzymes >5 x ULN

Check all that apply:

Other features/common (seen with both Acute and Chronic GVHD)

Total Bilirubin, alkaline phosphatase
>2x upper limit of normal ☐
ALT or AST > 2 x upper limit of normal ☐

Please describe:
Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD

_____
_____
_____

cGVHD signs and symptoms seen with LUNGS
Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
Lung Score	No Symptoms FEV1 > 80% **OR** LFS = 2	Mild symptoms (shortness of breath after climbing 1 flight of steps) FEV1 60-79% **OR** LFS 3-5	Moderate symptoms (shortness of breath after walking on flat ground) FEV1 40-59% **OR** LFS 6-9	Severe symptoms (shortness at rest requiring O_2) FEV1 ≥39% **OR** LFS 10-12

FEV1:_____ Not done☐ NA☐
DLCO: _____ Not done☐ NA☐
LFS: _____ Not done☐ NA☐

Check all that apply:

Diagnostic (sufficient to establish Chronic GVHD)
Bronchiolitis obliterans diagnosed with lung biopsy ☐

Distinctive (seen in Chronic GVHD, but insufficient alone to establish diagnosis of Chronic GVHD)
Bronchiolitis obliterans diagnosed with PFTs and radiology ☐

Other features/common (seen with both Acute and Chronic GVHD)
Bronchiolitis obliterans with organizing pneumonia (BOOP) ☐

Please describe:
Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD
_____
_____
_____

cGVHD signs and symptoms seen with MUSCLE, FASCIA, JOINTS
Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
Muscles, Fascia & Joints Score	No Symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation to ADL	Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirt, dress self etc.)

Check all that apply:

Diagnostic (sufficient to establish Chronic GVHD)

Fasciitis ☐
Joint stiffness or contracture secondary to sclerosis ☐

Distinctive (seen in Chronic GVHD, but insufficient alone to establish diagnosis of Chronic GVHD)
Myositis or polymyositis ☐

Other features/common (seen with both Acute and Chronic GVHD)
Edema ☐
Muscle cramps ☐
Arthralgia or arthritis ☐

Please describe:
Patient timeline, extent of finding, duration/rapidity of onset, relationship to immunosuppression and likely attributability to GVHD

_____
_____
_____

cGVHD signs and symptoms seen with GENITALIA

Score 0 ☐ Score 1 ☐ Score 2 ☐ Score 3 ☐

	0	1	2	3
Genitalia Score	No Symptoms	Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	Symptomatic with moderate signs on exam **AND** with mild dyspareunia **OR** with discomfort with gynecologic exam	Symptomatic **WITH** advanced sign (stricture, labial, agglutination, or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Check all that apply:

Diagnostic (sufficient to establish Chronic GVHD)

Lichen planus-like features ☐

Vaginal scarring or stenosis ☐

Distinctive (seen in Chronic GVHD, but insufficient alone to establish diagnosis of Chronic GVHD)

Erosion ☐

Fissures ☐

Ulcers ☐

Other Indicators	None	Mild	Moderate	Severe	Not Assessed
Ascites (serositis)					
Myasthenia Gravis					
Polymyositis					
Platelets less than 100,000/ul					
Pericardial effusion					
Nephrotic syndrome					
Cardiomyopathy					
Cardiac conduction defects					
Progressive onset					
Pleural Effusion(s)					
Peripheral Neuropathy					
Eosinophilia >500ul					
Coronary artery					

Other, specify:_____

Does the patient have chronic GVHD? Yes ☐ No ☐
If yes, specify Severity: Mild ☐ Moderate ☐ Severe ☐

NIH CGVHD Global Severity Category reflects overall disability

SEVERITY	ORGAN SCORE	NO. OF ORGANS
Mild	**All 1 (0 for Lung)**	**1-2**
Moderate	**All 1 (0 for Lung)**	**3 or more**
	At least one 2 (1 for Lung)	**1-2**
Severe	**At least one 3 (2 for Lung)**	**1 or more**

Were there additional exams performed? Yes ☐ No ☐
If yes, check all that apply:

Procedure	Date	Result
☐Biopsy		
☐CT Scan		
☐MRI		
☐Photo		
☐Schirmer Eye Test		
☐ PFT		
☐ LFT		
☐Ultrasound/Echocardiogram		
☐X-Ray		
☐Other: _____		

Signature: _____ Date: _____

Appendix 3: MDRD Study Equation

$eGFR = 175 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times 0.742$ [if female] $\times$ 1.210 [if Black]

where eGFR is estimated glomerular filtration rate (in mL/min/1.73 m^2)
S_{Cr} is standardized serum creatinine (in mg/dL)
and age is in years

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