Bellicum PHARMACEUTICALS

A Randomized Phase II/III Study of αβ T Cell-Depleted, Related, Haploidentical Hematopoietic Stem Cell Transplant (Haplo-HSCT) Plus Rivogenlecleucel vs. Haplo-HSCT Plus Post-Transplant Cyclophosphamide (PTCy) in Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Protocol Number:	**BPX501-301A**
Trial Sponsor:	**Bellicum Pharmaceuticals, Inc.** 2130 W. Holcombe Blvd, Suite 800 Houston, TX 77030
ClinicalTrials.Gov/	**NCT03699475**
Version Number:	**3.0**
Date:	**05 Mar 2019**

Confidentiality Statement

Investigator's Agreement

I have read this protocol and agree to comply with all provisions set forth in this protocol, including all statements regarding confidentiality, and to complete the study within the time designated.

I assume responsibility for the conduct of this study at my study site. I will ensure that I have sufficient resources allocated to this project such that the safety of my patients is protected at all times and that I complete my obligations to the sponsor according to the agreed timelines. I will delegate responsibilities only to those who are qualified by education, training, and experience. I will ensure the integrity of the data generated by my team and that all team members are familiar with the study protocol and the study medication.

I agree that I will grant access to the applicable records, my staff allocated to the conduct of this protocol and my facilities for the purposes of monitoring, auditing and any required inspections associated with the conduct of this clinical trial.

I agree to comply with the ICH Guideline on Good Clinical Practice, applicable EMA regulations and applicable FDA guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

Confidential information contained in the protocol document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____ _____

Signature Date

_____

Printed Name
Principal Investigator

SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Protocol Title:

A Randomized Phase II/III Study of αβ T Cell-Depleted, Related, Haploidentical Hematopoietic Stem Cell Transplant (Haplo-HSCT) Plus Rivogenlecleucel vs. Haplo-HSCT Plus Post-Transplant Cyclophosphamide (PTCy) in Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Sponsor Approval

I have reviewed and approved the protocol and confirm that the protocol follows GCP.

Signature: [redacted] Date: [redacted]

PROTOCOL SYNOPSIS

Title:	**A Randomized Phase II/III Study of αβ T Cell-Depleted, Related, Haploidentical Hematopoietic Stem Cell Transplant (Haplo-HSCT) Plus Rivogenlecleucel vs. Haplo-HSCT Plus Post-Transplant Cyclophosphamide (PTCy) in Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)**
Protocol Number:	BPX501-301A
Version Number:	3.0
Investigational Product(s):	Rivogenlecleucel (BPX-501) Rimiducid (AP1903)
Phase:	II/III
Indication(s):	Acute Myeloid Leukemia Myelodysplastic Syndromes
Sponsor:	Bellicum Pharmaceuticals, Inc.

Objectives:

Phase II

The primary objectives for the phase II portion of the study are as follows:

- To determine the maximum allowable dose/schedule of rivogenlecleucel and the recommended Phase III dose of rivogenlecleucel
- To assess the activity of rimiducid in subjects who develop GVHD post rivogenlecleucel administration

Phase III

Efficacy Objectives:

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of haplo-HSCT and rivogenlecleucel compared with haplo-HSCT and PTCy in subjects with AML and MDS as measured by overall survival (OS)

The secondary efficacy objectives for this study are as follows:

- To evaluate relapse-free survival (RFS)
- To evaluate graft-versus-host disease-free, relapse-free survival (GRFS)
- To evaluate non-relapse mortality (NRM)
- To evaluate time to resolution of GVHD after administration of rimiducid

Safety Objectives:

The safety objectives for this study are as follows:

- To evaluate the safety of haplo-HSCT and rivogenlecleucel compared with haplo-HSCT and PTCy in subjects with AML and MDS, focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE, v5.0), Grade $\geq$ 3 adverse events

Patient Reported Outcome Objectives:

The patient reported outcome (PRO) objectives for this study are as follows:

- To compare quality of life following haplo-HSCT and rivogenlecleucel compared with haplo-

HSCT and PTCy in subjects with AML and MDS, as measured by MD Anderson Symptom Inventory (MDASI), Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT), and 36-Item Short Form Health Survey (SF-36)

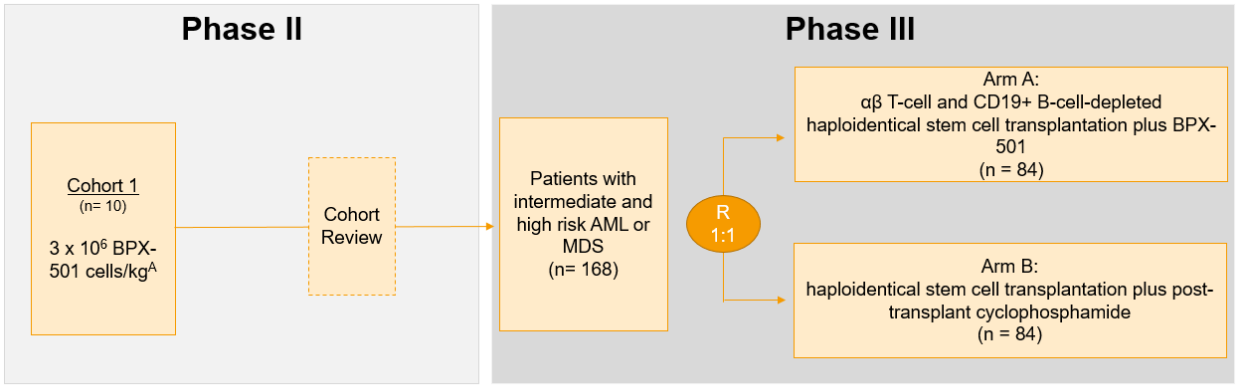
Study Design:

This is a two-part study, consisting of a single-arm Phase II and a randomized Phase III portion. Phase II is an open-label, multicenter study to assess safety and determine the MAD of rivogenlecleucel in subjects with AML or MDS. A total of approximately 10 subjects will be enrolled and dosed in Cohort 1 to confirm the MAD of 3 x 10^6 BPX-501 cells/kg, based on evaluation of dose-limiting toxicities. Based on prespecified DLT criteria and dose modification rules, a second cohort (Cohort 2) may be opened at a lower dose level to enroll an additional 10 subjects, if needed.

Following completion of Phase II and the Safety Cohort meeting, in the Phase III portion, 168 subjects will be enrolled and randomized 1:1 to receive either αβ T cell and CD19+ B cell-depleted haploidentical stem cell transplantation plus rivogenlecleucel (Arm A) or haploidentical stem cell transplantation plus post-transplant cyclophosphamide (Arm B). Randomization will be stratified according to the following factors:

- Age (< 60 and ≥60)
- Disease (AML vs. MDS)
- Conditioning regimen

Overall Study Design



[A] If dose level 1 exceeds the MTD, alternative dose levels (dose level -1: 1 x 10^6 BPX-501 cells/kg) will be explored

Number of Subjects:

Approximately 10 subjects (but up to 20 subjects) will be dosed in Phase II. Approximately 168 subjects will be randomized from approximately 40 centers and randomly assigned in 1:1 ratio to receive either haplo-HSCT and rivogenlecleucel (Arm A) or haplo-HSCT and PTCy (Arm B).

Study Duration:

The enrollment period for Phase II is anticipated to be 3-4 months.

The enrollment period for Phase III is anticipated to be 21 months. Patients will be followed until the time of death, study discontinuation, or the time of the primary analysis for OS, whichever occurs first. The primary analysis for OS is expected to occur approximately 42 months after the first patient is randomized, or, given 18 months of accrual, approximately 24 months after the last patient is randomized.

Study Population:

The target study population consists of subjects with AML or MDS who meet all of the following inclusion criteria and none of the exclusion criteria:

Subject Inclusion Criteria:

1. Signed informed consent
2. Meets institutional criteria to undergo allogeneic HSCT
3. Age 12-70 y/o
4. Diagnosis of AML or MDS as defined below:
    a. AML with intermediate to adverse risk as defined by ELN genetic risk stratification (Dohner 2017)
        i. AML in first complete remission (CR1) with high-risk features defined as > 1 cycle of induction therapy required to achieve remission, OR preceding MDS or myeloproliferative disease
            1. Adverse cytogenetics as defined below:
                a. t(6;9)(p23;q34.1); DEK-NUP214
                b. t(v;11q23.3); KMT2A rearranged
                c. t(9;22)(q34.1;q11.2); BCR-ABL1
                d. inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
                e. -5 or del(5q); -7; -17/abn(17p)
                f. Complex karyotype, monosomal karyotype
                g. Wild-type NPM1 and FLT3-ITD^{high}
                h. Mutated RUNX1
                i. Mutated ASXL
                j. Mutated TP53
        ii. AML in CR1 with $\underline{\geq}$ 1 of the following intermediate-risk features:
            1. mutated NPM1 and FLT3-ITD high
            2. wild-type NPM1 without FLT3-ITD or with FLT3-ITD low (without adverse-risk genetic lesions)
            3. t(9;11)(p21.3;q23.3) MLLT3-KMT2A
            4. Cytogenetic abnormalities not classified as favorable or adverse
    b. AML in second or subsequent complete remission
    c. AML with myelodysplasia-related changes (AML-MRC) in first or subsequent complete remission.
    d. Therapy-related AML in first or subsequent complete remission
    e. De novo AML in first complete remission with intermediate or adverse genetic abnormalities
    f. De novo AML in second or subsequent complete remission
    g. MDS
        i. High or very high-risk by IPSS-R classification
        ii. Intermediate risk or higher having failed a hypomethylating agent
5. Lack of suitable conventional donor (i.e., HLA 10/10 related or unrelated donor)
6. At least a 5/10 genotypic identical haplotype match measured by HLA typing at high resolution (allele level) for the HLA-A, -B, -C, -DRBl, and -DQB1 loci

7. The donor and recipient must be identical for at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1
8. Patients with adequate organ function as measured by:
    a. Cardiac: Left ventricular ejection fraction ≥ 40%
    b. Pulmonary: DLCO (corrected for hemoglobin) ≥ 40% and FEV1 ≥ 50%
    c. Hepatic: total bilirubin ≤ 2x the upper limit of normal and ALT and AST ≤ 3x the upper limit of normal.
    d. Renal: estimated creatinine clearance ≥ 50 mL/min/based on the Cockcroft-Gault formula
9. Eastern Cooperative Oncology Group (ECOG) performance status: 0-2

Subject Exclusion Criteria:

1. HLA 10/10 allele matched (HLA-A, -B, -C, -DRBl, and -DQB1) related donor or unrelated donor
    a. An HLA 10/10 allele-matched unrelated donor may be considered eligible for the study if the Study PI determines a haploidentical donor is the best available donor option for the patient due to other considerations (e.g., graft acquisition time)
2. Autologous hematopoietic stem cell transplant ≤ 3 months before enrollment
3. Prior allogeneic transplantation
4. Active CNS involvement by malignant cells (less than 2 months from conditioning)
5. Current uncontrolled clinically active bacterial, viral or fungal infection
6. Positive HIV serology or viral RNA
7. Pregnancy (positive serum or urine βHCG) or breastfeeding
8. Fertile men or women unwilling to use effective forms of birth control or abstinence for a year after transplantation
9. Radiographic or histologic evidence of, or known history of cirrhosis
10. Overlapping MDS and myeloproliferative neoplasms (MPN) disease
11. Patients with acute promyelocytic leukemia (APL)
12. Known hypersensitivity to dimethyl sulfoxide (DMSO)

Donor Inclusion Criteria:

1. Related donors include biological parents, siblings, or children, half-siblings or grandchildren
2. Age 18-75 y/o
3. Sufficiently healthy to undergo mobilization for peripheral blood stem cell harvest by institutional guidelines
4. Should be at least a full haplotype matched donor (e.g., at least a 5/10 match at HLA-A, -B, -C, -DRB1, and -DQB1); other selection criteria may include gender, age, CMV status and body weight of donor and presence of anti-donor HLA antibodies
5. Donor must be examined and have specific tests performed according to existing institutional guidelines and meet institutional guidelines for candidacy as a donor
6. Donor must have been informed of the investigational nature of rivogenlecleucel and the manufacturing process and have signed an informed consent form to undergo apheresis
7. Donor must have adequate peripheral venous catheter access for leukapheresis or must agree to placement of a central catheter

Donor Exclusion Criteria:

1. Evidence of active infection (including urinary tract infection, upper respiratory tract infection, etc.) or viral hepatitis exposure (on screening), unless only HBs Ab+ and HBV DNA negative

2. Positive HIV serology or viral RNA
3. Medical or physical reason why makes the donor unlikely to tolerate or cooperate with growth factor therapy and apheresis
4. Factors that place the donor at increased risk for complications from apheresis or G-CSF therapy (e.g., autoimmune disease, sickle cell trait, symptomatic coronary artery disease requiring therapy, previous thrombotic events)
5. Pregnancy (positive serum or urine βHCG) or breastfeeding

Investigational Products:

Rivogenlecleucel (formerly BPX-501) is a T cell product consisting of human T cells obtained from donor leukapheresis and gene modified to include the iCasp9 safety gene. The product is provided as a combined CD3+ and CD19+ frozen T cell suspension in a formulation containing DMSO for IV administration.

Rivogenlecleucel will be administered as a single IV infusion on Day +14 after haplo-HSCT (window ± 4 days). The dose for Phase II will be 3 x 10^6 BPX-501 cells/kg, and if this is determined to be the MAD, this will also be the dose pursued in Phase III.

All subjects should receive premedications per institutional standards (e.g., acetaminophen plus an antihistamine) for cellular therapy products, for prevention of infusion-related/ hypersensitivity reactions.

In subjects who receive rivogenlecleucel and develop GVHD and/or neurotoxicity, rimiducid is available to activate the iCasp9 safety gene and induce apoptosis of the gene modified cells. Rimiducid is a lipid-permeable compound available for IV infusion and requires dilution prior to administration. Subjects who receive rimiducid and achieve clinical benefit may receive up to a total of 3 doses. Due to the risk of infusion-related reactions, subjects should receive premedication with acetaminophen, diphenhydramine, ranitidine, and other supportive care therapy per institutional standards for potential anaphylaxis.

Study Assessments:

Efficacy Assessments:

Disease response will be assessed according to CIBMTR criteria for AML and MDS. An independent Data Monitoring Committee (iDMC) will be put in place to support independent analyses of trial efficacy and safety data.

Safety Assessments:

Adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities (type, frequency, and severity) will be collected. Adverse events of special interest (AESIs) will include Grade III-IV encephalopathy or neurologic events, Grade III-IV infections, Grade III-IV graft-versus-host disease, and graft failure; the list of AESIs may be updated during the course of the study based on observed safety signals.

Replication-competent retrovirus (RCR) and viral copy number (VCN) will be performed at specified timepoints during the study.

Other Assessments:

The following assessments will be performed at specified timepoints.

Pharmacokinetic Assessments: Limited PK parameters (for rimiducid) will be estimated using non-compartmental analysis

Pharmacodynamics/Biomarkers: Biomarker assessments will include, but are not limited to, flow cytometry analysis of naïve and memory T cell populations, thymic function, T cell repertoire and T cell function.

Statistical Methods:

Phase II:

The incidence, type, and severity of DLTs and the incidence and severity of AEs will be summarized.

The incidence of acute GVHD (Grade II-IV and Grade III-IV) and chronic GVHD will be summarized, including the time of onset for each.

The incidence of aGVHD and the outcome of treatment with rimiducid will be summarized.

Phase III:

The primary efficacy endpoint is OS, defined as the time from randomization to death due to any cause. Subjects will be followed until the time of death, study discontinuation, whichever occurs first. Subjects still on study at the time of primary analysis will be censored at the date they were last known to be alive. The primary analysis for OS is expected to occur approximately 42 months after the first patient is randomized, or, given 18 months of accrual, approximately 24 months after the last patient is randomized.

LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplant
AML	Acute Myeloid Leukemia
aGVHD	Acute Graft Versus Host Disease
BMT	Bone Marrow Transplant
cGVHD	Chronic Graft Versus Host Disease
CMV	Cytomegalovirus
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTL	Cytotoxic T Lymphocytes
EC	Ethics Committee
eCRF	Electronic Case Report Form
DLT	Dose Limiting Toxicity
EBV	Epstein-Barr Virus
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FKBP	Human FK-506-Binding Protein
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GRFS	Graft-Versus-Host Disease & Relapse-Free Survival
GVHD	Graft-Versus-Host Disease
GVL	Graft-Versus-Leukemia
HSCT	Hematopoietic Stem Cell Transplant
HSV	Herpes Simplex Virus
IB	Investigator's Brochure

IBC	Institutional Biosafety Committee
iCasp9/iC9	Inducible Caspase 9
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
iDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INR	Internationalized Normalized Ratio
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion Related Reaction
ITT	Intent to Treat
IV	Intravenous
LP	Lumbar Puncture
LPLV	Last Patient Last Visit
MAD	Maximum Allowable Dose
MDS	Myelodysplastic Syndrome
MMSE	Mini Mental Status Exam
MNC	Mononuclear Cell
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NRM	Non-Relapse Mortality
PBMC	Peripheral Blood Mononuclear Cell
PBSC	Peripheral Blood Stem Cells
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient Reported Outcome
PTCy	Post-Transplant Cyclophosphamide
PTLD	Post-Transplant Lymphoproliferative Disorder
RBC	Red Blood Cell

RCR	Replication Competent Retrovirus
RFS	Relapse-Free Survival
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
OS	Overall Survival
TBI	Total Body Irradiation
TCR	T Cell Receptor
VCN	Vector Copy Number

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1. INTRODUCTION

1.1 Allogeneic Stem Cell Transplant for AML and MDS

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder resulting from accumulation of abnormal immature cells in the bone marrow, which interfere with normal hematopoiesis and subsequently leads to fatal infection, bleeding, or organ infiltration (Estey 2006). The myelodysplastic syndromes (MDS) encompass a series of hematologic conditions characterized by chronic cytopenias and abnormal cellular maturation, which may in turn predisposes the patient towards progression to AML, often refractory to treatment (Scott 2010). Together, AML and MDS are the most common myeloid malignancies in adults, affecting predominantly an older population.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the best curative option for patients with refractory/relapsed AML or high-risk MDS. The combination of high-dose conditioning chemotherapy/radiation, followed by donor peripheral blood or marrow stem cell products, including mature and immature immune cells, can induce an immune response that helps to destroy any remaining leukemia cells, known as the "graft-versus-leukemia" (GVL) effect. Available clinical data have established that the T cells contained within the donor graft exert this GVL effect. Also, targeted αβ T cell depletion may limit graft-versus-host disease (GVHD) (Locatelli 2017, Bertaina 2014) while maintaining the GVL effect and potentially decreasing opportunistic infections. The combined benefit of targeted αβ T cell depletion and T cells to induce GVL is hypothesized to be instrumental in long term efficacy of patients treated with allo-HSCT.

1.2 Modified Donor T Cells After Allo-HSCT

Despite this potential therapeutic benefit of GVL and decrease in opportunistic infections, the utilization of a “T cell add back” standard approach is limited in clinical practice due to the potential for GVHD. Graft-versus-host disease can result in devastating effects on the patient and is challenging to treat. T cell depletion strategies have reduced GVHD rates (Bertaina 2014); however, such approaches may be associated with reduced GVL and potential for increased opportunistic infections due to delayed immune reconstitution. A treatment approach of selective depletion of αβ T cells and CD19+ B cells, coupled with an infusion of polyclonal T cells with a broad T cell repertoire (BPX-501 T cells) with an inducible Caspase-9 safety switch may lead to low rates of GVHD and more rapid immune reconstitution.

1.3 Rivogenlecleucel Investigational Drug Product

Rivogenlecleucel (formerly BPX-501) is an investigational product in clinical development to allow for improved immune reconstitution, possible protection from infections, and a reduction in malignancy relapse.

Rivogenlecleucel consists of human T cells which are obtained from normal donor leukapheresis, ex vivo culture-expanded to high purity, gene-modified with BPZ-1001 (SFG.iCasp9.2A.ΔCD19 retroviral vector containing the iCasp9 safety gene, as well as truncated

CD19 selectable marker), and then selected to ensure a high percentage of T cells carrying the safety gene. The final product is formulated, cryopreserved, shipped to the clinical site, thawed and infused into the patient. Rivogenlecleucel is intended to aid in engraftment, promote immune reconstitution, potentially aid in graft versus leukemia (GVL) effect and can be removed from the body upon infusion of the dimerizing agent, rimiducid.

1.3.1 iCasp9 Safety Switch

Unmodified donor T cell infusion is potentially an effective strategy for conferring anti-viral and anti-tumor immunity following allogeneic stem cell transplantation (Di Stasi 2011). However, the administration of greater than 10^5 cells/kg unmodified donor T cells to recipients of haploidentical stem cell transplantation has been associated with increased incidence of GVHD. It has been previously demonstrated that administration of up to 10^7 cells/kg of CD25+ allodepleted donor T cells after haploidentical transplantation for hematological malignancies could be administered safely and that the addition of these T cells was effective in controlling viral disease (Amrolia 2006). However, mortality due to disease relapse remained high, presumably due to the estimated frequency of tumor-reactive precursors being 1 to 2 logs lower than the frequency of virus-reactive precursors. The use of higher numbers of allodepleted T cells containing an inducible caspase 9 safety gene to treat the potential increase in GVHD was then evaluated. The caspase-recruiting domain of the human caspase 9 was modified with a drug binding domain, permitting T cell elimination after administration of a chemical dimerization drug, rimiducid. Administration of rimiducid dimerizes and activates caspase 9 which activates downstream caspases, leading to apoptosis potentially within minutes to hours (Di Stasi 2011; Tey 2007).

The gammaretrovirus, SFG.iCaspase9.2ADeltaCD19 (BPZ-1001), consists of inducible caspase 9 (iCasp9) linked, via a 2A-like sequence, to truncated human CD19 (DeltaCD19). The iCasp9 genetic modification, unlike the HSV-TK based safety gene, is human-derived and therefore likely to be less immunogenic. Moreover, pre-clinical and clinical studies show that killing occurs with much greater rapidity (within 3 hours) than with HSV-TK. Further advantages of the iCasp9 system are that killing induced by the dimerizer drug is primarily restricted to activated/proliferating cells, thus targeting alloreactive T cells active in GVHD but sparing anti-viral donor T cells and potentially anti-tumor specific T cells. Additionally, administration of the commonly used drug, ganciclovir, is not precluded which is a limitation of the HSV thymidine kinase depletion strategies.

1.3.2 Rivogenlecleucel and GVHD Treatment Rationale

The goal of graft engineering is to enable alternative transplants such as haploidentical-related HSCT to be performed as safely as matched unrelated donor transplants. Anasetti and colleagues published data from the BMT CTN 0201 randomized study of matched unrelated donor bone marrow (BM) vs. peripheral blood (PB) in hematopoietic cell transplantation for hematologic malignancies. Results from the primary analysis after 2 years of follow up showed similar survival, disease-free survival and treatment-related mortality between the graft types. There

were higher rates of graft failure with BM (9% v. 3%; p=0.002) and a higher rate of chronic GVHD with PB (53% v 41%; p=0.01) (Anasetti 2012).

Lee and colleagues later published 5-year results from this study, specifically looking at GVHD quality of life measures. Their results showed that at 5 years, patient reported outcomes (PROs) were all significantly better for BM patients (as measured by Functional Assessment of Cancer Therapies – Bone Marrow Transplant (FACT-BMT) Trial Outcome Index (TOI), Mental Health Inventory (MHI) psychological well-being, and cGVHD symptoms scale scores) (Lee 2015).

1.4 Clinical Activity of Rivogenlecleucel +/- Rimiducid

1.4.1 CASPALLO TRIAL

In a Phase I study, ten subjects between the ages of 3 and 17 years who had undergone stem cell transplantation for relapsed acute leukemia were treated with the genetically modified T cells. The cells were detected in peripheral blood from all ten subjects and increased in number over time, despite their constitutive transgene expression. A single dose of the dimerizing drug, rimiducid, given to the subjects in whom GVHD developed, eliminated more than 90% of the modified T cells within 30 minutes after administration and a further log reduction within 24 hours. Moreover, acute GVHD of the skin in all three subjects treated with rimiducid, and of the liver disease in one, completely resolved after 24 hours (Di Stasi 2011).

The residual iCasp9 gene-modified T cell population expanded over the next 4-14 days and continued to help repopulate the subjects' immune systems. The transduced cells were further shown to contain the virus and fungal-peptide specific precursor cells which had not caused further GVHD. When examined ex vivo, these non-alloreactive iCasp9 T cells remained susceptible to apoptosis following exposure to the dimerizer rimiducid. The authors concluded that a single dose of dimerizer drug could eliminate the subpopulation of T cells causing GVHD but could spare viral-specific CTLs.

The iCasp9 gene is most highly expressed in activated and proliferating T cells, such as those causing GVHD. If cells are not activated, due to lack of viral stimulation, for example, expression of the transgene is lower and in a minority of these cells, iCasp9 levels are insufficient to induce apoptosis after single rimiducid dose exposure, allowing subsequent re-expansion (Berger 2004). This hypothesis was supported by the CASPALLO clinical data showing activation-dependent induction of iCasp9 in gene-modified T lymphocytes and enhanced susceptibility to dimerizer drug in activated versus resting T cells.

1.4.2 Rimiducid

Rimiducid is a member of a new class of lipid-permeable compounds termed activating, or dimerizer, drugs that act by inducing clustering of engineered proteins inside cells. Rimiducid-inducible activation of the iCasp9 protein is achieved by expressing a chimeric protein (iCasp9), fused to a drug-binding domain derived from human FK506-binding protein (FKBP). This chimeric protein is quiescent inside cells until the administration of rimiducid, which cross-links the FKBP domains of two of these iCasp9 proteins, initiating iCasp9 signaling. This signaling induces apoptosis of the gene-modified cells.

1.4.3 DOTTI Trial

In a follow-up to the CASPALLO trial, an investigator-sponsored Phase I study (DOTTI) was performed to assess the safety and efficacy of iCasp9 T cells not depleted of an alloreactive component. Twelve subjects who underwent haplo-HSCT (median age, 10 years; range, 2-50 years) were infused with non-allodepleted iCasp9 T cells. Four subjects developed Grade I & II acute GVHD and received a single dose of rimiducid eliminating 85-95% of circulating iCasp9 T cells within 30 minutes of rimiducid infusion, with no recurrence of GVHD within 90 days. There were no immediate or delayed adverse events reported associated with the rimiducid infusion.

Following activation and expansion in vivo, adoptively transferred T cells can produce proinflammatory cytokines and induce other cells, including monocytes, to release additional proinflammatory mediators causing life-threatening cytokine release syndrome (CRS). Although severe CRS is an uncommon manifestation of T cell engraftment after HSCT, one subject in this trial developed signs and symptoms compatible with GVHD and CRS. Administration of rimiducid improved clinical symptoms and decreased proinflammatory cytokines including IL-6. (Zhou 2015).

1.5 Ongoing Sponsored Clinical Studies

Currently, there are multiple ongoing clinical trials sponsored by Bellicum investigating rivogenlecleucel and rimiducid in different populations, including adult and pediatric subjects. For additional information on these trials, please refer to the rivogenlecleucel and rimiducid Investigator's Brochures.

2. STUDY PURPOSE AND RATIONALE

2.1 Rationale for Patient Population

Approximately 50% of patients who could potentially benefit from HSCT do not have an HLA-identical sibling or an HLA-identical unrelated donor. This percentage is even higher among patients belonging to non-Caucasian populations, as unrelated donor registries contain relatively fewer donors from these populations (~20%) vs. Caucasian populations (~80%) (CIBMTR Transplant Summary Report, 2012-2016). Development of an alternative stem cell source for patients facing these challenges could expand opportunities for stem cell transplant and is hypothesized to improve patient outcomes.

2.2 Rationale for Study Treatment

2.2.1 Rationale for Post-Transplant Cyclophosphamide Dose

Cyclophosphamide is an alkylating agent used for the treatment of multiple malignant diseases. The administration of high-dose post-transplantation cyclophosphamide (PTCy) has shown positive results in the reduction of GVHD.

Recent studies have shown that high-dose cyclophosphamide given early after HSCT does not compromise engraftment and can decrease the risk of chronic GVHD. In studies of HLA haploidentical BMT with reduced-intensity conditioning, PTCy was given at 50 mg/kg on days 3 and 4 or only on day 3 followed by tacrolimus and mycophenolate mofetil (MMF) (O'Donnell 2002; Luznik 2008; Luznik 2012). The cumulative incidences of grades II-IV GVHD and grades III-IV aGVHD were 34% and 6%, respectively; the incidence of extensive chronic GVHD was 25% after a single dose of cyclophosphamide and only 5% after 2 doses of PTCy (Luznik 2008).

In a prospective phase 2 study, high-dose cyclophosphamide was given as single agent prophylaxis on days 3 and 4 after HLA-matched related or unrelated BMT with busulfan/cyclophosphamide conditioning. The day 100 cumulative incidences of grades II-IV aGVHD and grades III-IV aGVHD were 43% and 10%, respectively (Luznik 2010). In a follow-up study, PTCy was given on days 3 and 4 after HLA-matched related or unrelated BMT with busulfan/fludarabine conditioning. The cumulative incidences of grades II-IV aGVHD, grades III-IV aGVHD, and chronic GVHD were 51%, 15%, and 14%, respectively. Taken together, these results show that the cumulative incidences of GVHD is consistent when PTCy is given as the sole GVHD prophylaxis after HLA-matched related or unrelated BMT (Kanakry 2014).

2.2.2 Rationale for Starting Dose of Rivogenlecleucel

The first dose level explored in this trial will be rivogenlecleucel 3 x 10^6 cells/kg. This dose level was initially explored in the CASPALLO study in pediatric subjects (n= 2) and further evaluated in adults in BP-001, a Phase I/II dose escalation trial study evaluating safety and feasibility of rivogenlecleucel after partially mismatched, related, T cell depleted HSCT. In this trial, four dose levels were explored in the dose escalation stage (1 x 10^5, 2 x 10^5, 5 x 10^5, and 3 x 10^6 BPX-501 T cells/kg), and 3 x 10^6 BPX-501 cells/kg was determined to be the MAD. Preliminary analysis of the 19 subjects treated at this dose level suggests that the toxicity is relatively mild with one case of Grade III acute GVHD.

In BP-001, subjects received GVHD prophylaxis with an abbreviated course of tacrolimus (60 days post-HSCT). In this study, the Phase II portion will help to establish the MAD of BPX-501 in subjects who do not receive GVHD prophylaxis other than T cell depletion.

2.2.3 Rationale for Starting Dose of Rimiducid

The utility of employing rimiducid in the elimination of transduced lymphocytes under the control of iCasp9 has been evaluated in many models including a murine model implanted with Raji tumor cells [Bellicum Study #BEL-R&D-RP-0069]. Here, eight-week-old female, immune-deficient mice (NOD.CgPrkdcscid Il2rgtm1Wjl/SzJ; NSG) were engrafted with 5x10^5 Raji tumor cells re-suspended in 100 µL of PBS. After 2 days, mice were injected IV with 1x107 firefly luciferase-enhanced green fluorescent protein (ffLuc-eGFP) labeled CD19-CIDeCAR-T cells. To evaluate the functionality of the safety gene, mice bearing Raji tumor cells, and receiving CAR-T cells (transduced with the F36V-FKBP receptor) labeled with the eGFP-FFluc gene, were treated with rimiducid (intraperitoneal dosing) over a wide range of doses (5, 0.5, 0.05, 0.005, 0.0005, or 0.00005 mg/kg). Rimiducid treatment was initiated when the T cell bioluminescent signal was exponentially increasing and/or after mice lost 15% of body weight, indicating active expansion

of the transgenic cells. Circulating transfected CAR-T cells were rapidly eliminated, as evidenced by diminished luminescence (BLI), following a single administration of rimiducid with maximal effects noted at doses of 0.5 and 5 mg/kg. An evaluation of the disposition of rimiducid in the NSG mouse has established similar exposures, regarding both Cmax and AUC, following the parenteral administration of equivalent doses in humans (Iuliucci 2001).

Therefore, maximal responses to rimiducid are likely to occur in the range of 0.5 to 5.0 mg/kg. Furthermore, in previous clinical studies conducted in both adult and pediatric subjects, an intravenous dose of 0.4 mg/kg efficiently eliminated alloreactive BPX-501 cells (Di Stasi 2011; Zhou 2015).

2.3 Rationale for PK Evaluation

The pharmacokinetics of rimiducid have been evaluated in 28 normal healthy volunteers in a Phase 1 single ascending dose study. Rimiducid exhibited linear pharmacokinetics across all doses from 0.01 to 1.0 mg/kg. Dose-adjusted Cmax was approximately 1200 ng/mL, while clearance remained constant across all doses at 5.5 to 7.5 ng/ml/kg. To date, a comprehensive evaluation of the disposition of rimiducid in patients has not been conducted. Therefore, this study will serve as an important source for the initial evaluation of rimiducid PK in adult subjects with AML.

2.4 Rationale for Biomarker Evaluation

The effect of rivogenlecleucel on immune reconstitution, thymic function, and T cell repertoire has not been formally assessed in this patient population particularly in direct comparison to patients receiving PTCy for GVHD prophylaxis. Assessment of the relative contribution of rivogenlecleucel to the T cell repertoire in the post-transplant period and the role of rivogenlecleucel in response to a tumor or opportunistic infection will inform a more thorough understanding of the mechanism of action of rivogenlecleucel.

2.5 Justification of Endpoints

The primary objective of the Phase II portion of the study will be to establish the safety and maximum tolerated dose (MTD) of rivogenlecleucel in patients with AML/MDS undergoing αβ T cell and CD19+ B cell depleted haplo-HSCT. This will be determined by the incidence and severity of all adverse events (AEs), including dose-limiting toxicities (DLTs).

The primary objective of the Phase portion of the study will be to confirm the safety and efficacy of rivogenlecleucel in the sample population of patients. This will be determined by overall survival (OS) as assessed by an independent Data Monitoring Committee (iDMC). Key secondary endpoints of the Phase III portion of this study are the rate of graft-versus-host disease (GVHD), relapse-free survival (RFS), and non-relapse mortality (NRM). Treatment response will be assessed according to the Center for International Blood & Marrow Transplant Research (CIBMTR) response criteria for AML and MDS.

3. OBJECTIVES/ENDPOINTS

The objectives and corresponding endpoints for the study are presented in Table 1.

Table 1: Study Objectives and Endpoints

Objective	Endpoints
Phase II	
Primary	
• Determine the maximum allowable dose/schedule of rivogenlecleucel • Assess the activity of rimiducid in subjects developing GVHD post rivogenlecleucel administration • Determine the recommended Phase III dose of rivogenlecleucel	• Incidence of DLTs • Incidence and severity of adverse events (AEs) • Assess the rate of GVHD in subjects at the established rivogenlecleucel maximum allowable dose (MAD)
Phase III	
Primary	
• Evaluate overall survival (OS)	• OS, as defined as the time from randomization until death from any cause
Secondary	
• Evaluate supportive measures of activity of rivogenlecleucel on relapse-free survival (RFS), graft-versus-host disease-free, relapse-free survival (GRFS), and non-relapse mortality (NRM)	• RFS, defined as the time from randomization to relapse or death from any cause, whichever comes first, in subjects in remission • GRFS, defined as the time from randomization to the occurrence of Grade III-IV acute GVHD; chronic GVHD requiring systemic immunosuppression; disease relapse or death; whichever comes first • NRM, defined as time from randomization to death without relapse/disease progression
• Evaluate efficacy of rimiducid in resolving GVHD after rivogenlecleucel	• Time to resolution of GVHD after administration of rimiducid
• Assess patient-reported outcomes (PROs) and quality of life measures	• FACT-BMT total score (change from baseline) • SF-36 total score (change from baseline) • MDASI total score (change from baseline)

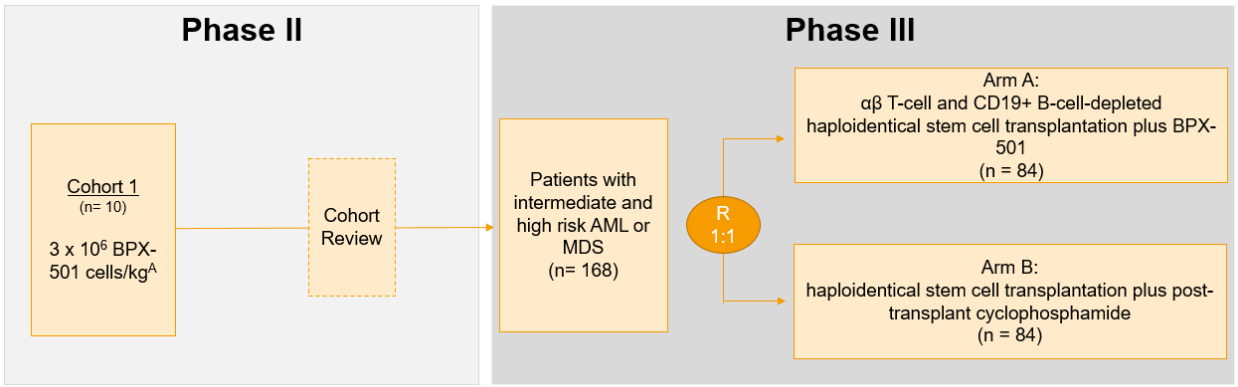
4. STUDY DESIGN AND INVESTIGATIONAL PLAN

This is an open-label, multicenter, randomized Phase II/III study to evaluate the efficacy of αβ T cell and CD19+ B cell-depleted, related haploidentical hematopoietic stem cell transplantation (haplo-HSCT) plus rivogenlecleucel vs. haplo-HSCT followed by post-transplant cyclophosphamide (PTCy) in subjects with AML or MDS.

4.1 Overall Study Design

This study will consist of two parts – a single-arm Phase II portion (to establish MAD, safety and preliminary activity) and a randomized Phase III portion (to assess safety and efficacy). The overall study design is described schematically in Figure 1.

Figure 1: Overall Study Design

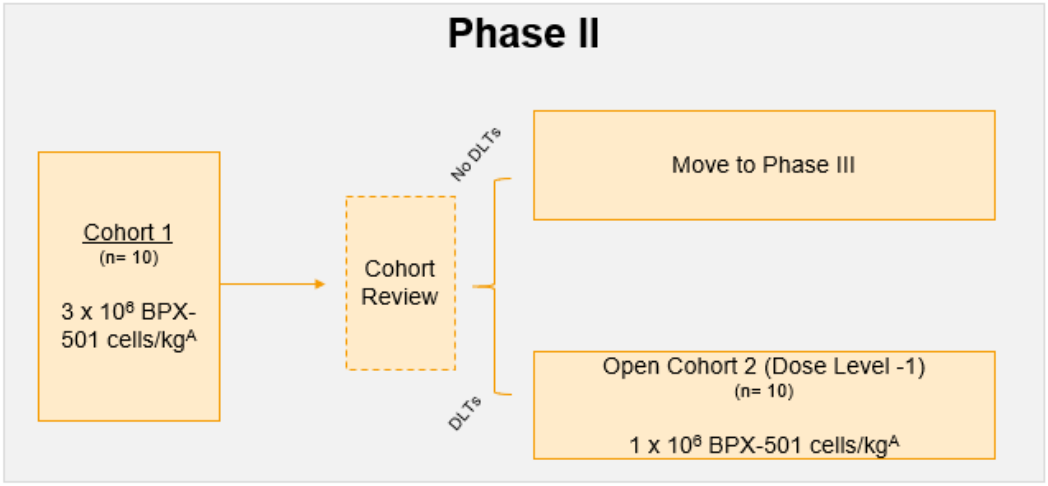


A If dose level 1 exceeds the MTD, alternative dose levels (dose level -1: 1 x 10^6 BPX-501 cells/kg) will be explored

4.2 Phase II Study Design

This is an open-label, multicenter, Phase II study to assess safety and to determine the MAD of rivogenlecleucel in subjects with AML or MDS. A total of approximately 10 subjects will be enrolled and dosed in Cohort 1 to confirm the MAD of 3 x 10^6 BPX-501 cells/kg (Figure 2).

Figure 2: Phase II Design



A If dose level 1 exceeds the MTD, alternative dose levels (dose level -1: 1 x 10^6 BPX-501 cells/kg) will be explored

Following a conditioning regimen (Section 6.1.3), subjects will undergo αβ T cell and CD19+ B cell-depleted HSCT on Day 0 followed by an infusion of rivogenlecleucel 3 x 10^6 cells/kg on Day +14 (with a window of ± 4 days). These subjects will be evaluated for prespecified dose limiting toxicities (DLTs) within a 100-day DLT window (Section 4.2.1).

Safety will be monitored by assessing adverse events including but not limited to rate of infection, and changes in physical exam and laboratory studies.

Subjects participating in the Phase II portion of the study will continue on study and followed for safety leading up to roll-over in the Long-term Follow-up Study (Section 7.8).

4.2.1 Dose-Limiting Toxicities

The dose limiting toxicities detailed in this section will apply only to subjects enrolled in Phase II of the trial. Subjects enrolled outside of Phase II (i.e., Phase III) will undergo comprehensive safety assessments.

All subjects who experience a DLT during the DLT assessment window of 100 days (HSCT to Study Day 100) will be considered evaluable for safety evaluation decisions.

Subjects who withdraw from study treatment (rivogenlecleucel; rimiducid) for any reason other than a DLT during this assessment window will not be considered evaluable for DLTs and will be replaced.

4.2.1.1 DLT Criteria

A DLT is defined as one of the following toxicities occurring during the DLT assessment window that is considered by the investigator to be related to study treatment. If an adverse event is clearly due to progressive disease and unrelated to study treatment, these adverse events will not be considered DLTs. Investigators are encouraged to perform additional testing to determine the underlying etiology and most appropriate attribution.

Any of the following adverse events that occur within the DLT window will be considered a DLT:

- Grade III or IV acute GVHD attributable to rivogenlecleucel and non-responsive to $\geq$ 1 dose of rimiducid treatment (plus standard doses (at least 1 mg/kg) of methylprednisone or dose equivalent of other corticosteroids, and/or calcineurin inhibitor) within 14 days
- Grade 3-4 neurologic events attributable to rivogenlecleucel
- Death due to any cause other than underlying disease
- Any CTCAE Grade 3-5 adverse events related to rivogenlecleucel (including allergic reactions, infusion reactions, and any other related adverse reactions whether expected or unexpected).

4.2.1.1 Dose Modification Rules & Changes in Dose Following Dose-Limiting Toxicity

Dose modification in Phase II will occur in accordance with the following rules:

- Up to 10 subjects will be initially enrolled and dosed in Phase II (Cohort 1)
- If $\geq$ 3 of the 10 subjects enrolled experience a DLT attributable to rivogenlecleucel, an alternative dose/schedule will be evaluated and a second cohort will be opened (i.e., Cohort 2, Dose Level -1)
- If < 3 of the 10 subjects enrolled experience a DLT attributable to rivogenlecleucel, this dose level will be assessed as the MAD and the recommended dose level for Phase III.

In the event of unacceptable toxicity, the Sponsor, in consultation with the Study Investigators, may decide to explore alternative dose/schedules. The regimen for additional dose levels will be adjusted and will depend on the safety and tolerability observed in Dose Level 1. Table 2 describes adjustments that could possibly be made.

Table 2: Alternative Dose Exploration if MAD is Exceeded in Cohort 1

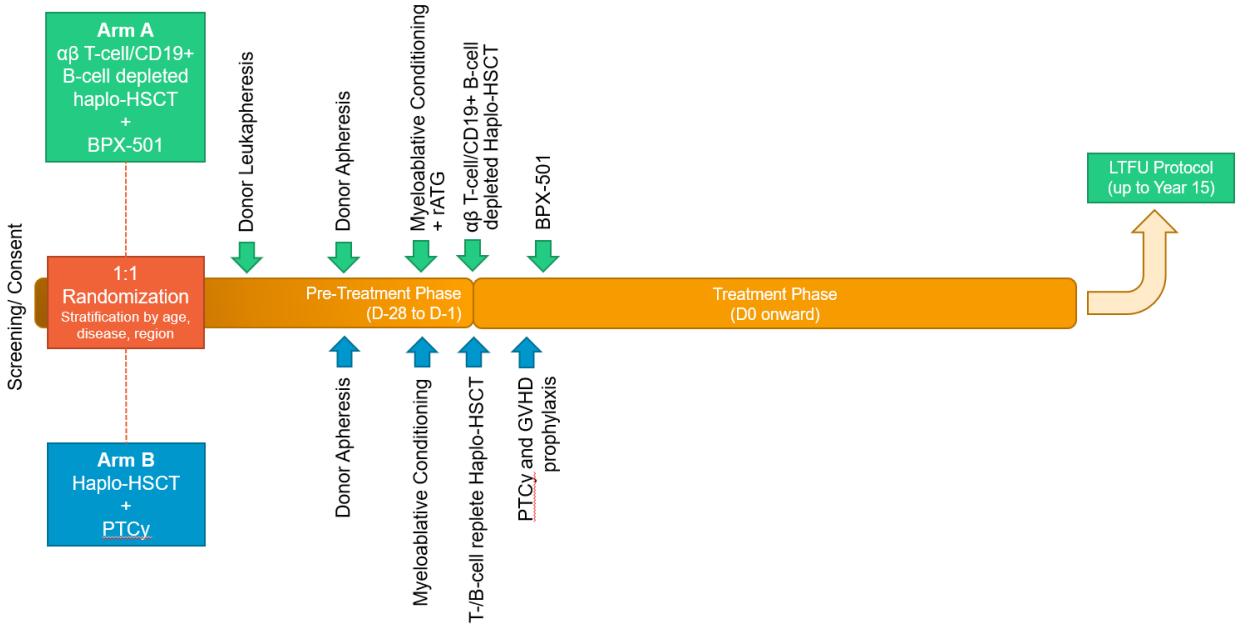
Cohort 1 Tolerability	Safety Outcome	Further Steps
< 3 DLTs	Determined safe and tolerable by DLT criteria	None; MAD established
3 or more DLTs	DLTs observed or Sponsor/Primary Investigator determined safety concerns	Open Cohort 2: Enroll/dose approximately 10 subjects at Dose Level -1 of rivogenlecleucel 1 x 10^6 cells/kg

4.3 Phase III Study Design

Following completion of Phase II and the Safety Cohort meeting, 168 subjects will be enrolled and randomized to one of two treatment arms (see Figure 3).

- Arm A: αβ T cell and CD19+ B cell-depleted haploidentical stem cell transplantation plus rivogenlecleucel
- Arm B: haploidentical stem cell transplantation plus post-transplant cyclophosphamide

Figure 3: Phase III Study Schema



Enrollment will follow a randomized 1:1 design including stratification factors (Section 5.5.2).

Subjects will undergo conditioning chemotherapy and infusion of stem cells (either T/B cell depleted or not). Subjects in Arm A will receive an αβTCR/CD19+ depleted haploidentical stem cell transplant and rivogenlecleucel on Day +14 (±4 days) post-transplant (see Section 6.1). Subjects in Arm B will receive a T cell replete haploidentical HSCT followed by cyclophosphamide 50 mg/kg on Days +3 and +4 post-transplant (see Section 6.2). Subjects who develop GVHD will receive standard GVHD therapy with corticosteroids and/or additional agents per institutional standard of care, and rimiducid (Arm A) to inactivate rivogenlecleucel.

Safety will be monitored by assessing adverse events, including but not limited to the rate of Grade 3/4 infection and changes in physical exam and laboratory studies.

4.4 OUTCOME MEASURES

4.4.1 Safety Outcome Measures

The safety and tolerability of rivogenlecleucel +/- rimiducid will be assessed in the following ways:

- Incidence, type, and severity of DLTs (Phase II only)
- Incidence, type, nature, and severity of adverse events (graded according to NCI CTCAE 5.0 criteria)
- Changes in vital signs, physical findings, and clinical laboratory test results, as appropriate
- Incidence of adverse events of special interest (Section 9.2.3).

4.4.2 Efficacy Outcome Measures

The efficacy outcomes measures will be assessed as indicated in the following sections. Malignant efficacy response criteria (i.e., disease progression) will be determined by the investigator with use of the following response criteria. An independent Data Monitoring Committee (iDMC) will be put in place to support independent analyses of trial efficacy and safety data (Section 4.5.2).

4.4.2.1 Definitions of Response for AML

The Center for International Blood and Marrow Transplant Research criteria for AML will be used to categorize responses (https://www.cibmtr.org/manuals/fim/1/en/topic/aml-response-criteria).

Complete Remission (CR)

Hematologic complete remission is defined as meeting all the following response criteria for at least four weeks.

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Neutrophils ≥ 1,000/µL

- Platelets ≥ 100,000/μL
- Transfusion independent

In some cases, there may not be a four-week interval between completion of therapy and the pre-transplant disease assessment. In this case, CR should still be reported as the patient disease status at transplant since it represents the "best assessment" before HSCT. This is an exception to the criteria that CR be durable beyond four weeks; the pre-transplant disease status should not be changed based on early relapse or disease assessment post-transplant.

Recipients with persistent cytogenetic or molecular abnormalities who meet the above CR criteria will be included for evaluation of hematologic CR.

Recipients meeting the above CR criteria regardless of how many courses of therapy were required to achieve CR will be included for evaluation of hematologic CR.

The number of this complete remission can be determined by using the following guidelines:

- 1st CR: no prior relapse
- 2nd CR: one prior relapse
- 3rd or higher: two or more prior relapses

Complete Remission with Incomplete Hematologic Recovery (CRi)

Hematologic complete remission with incomplete hematologic recovery is defined as meeting all of the following response criteria for at least four weeks:

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Transfusion independent (Please note, if the physician documents transfusion dependence related to treatment and not the patient's underlying AML, CRi can be reported)

Primary Induction Failure (PIF)

PIF will be defined in patients who received treatment for AML but **never achieved CR or CRi at any time**. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in CR or CRi.

Relapse (REL)

Relapse is defined as the recurrence of disease after CR, meeting one or more of the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- Extramedullary disease
- Disease presence determined by a physician upon clinical assessment

The number assigned to this relapse can be determined by using the following guidelines:

- 1st relapse: one prior CR

- 2nd relapse: two prior CRs
- 3rd or higher: three or more CRs

Partial response (PR) will not be included when determining the number of relapses. Recipients who achieve a PR to treatment should be classified as either PIF or relapse; PR in AML is generally of short duration and is unlikely to predict clinical benefit.

4.4.2.2 Definitions of Response for MDS

The Center for International Blood and Marrow Transplant Research criteria for MDS will be used to categorize responses (https://www.cibmtr.org/manuals/fim/1/en/topic/mds-mpn-response-criteria; Savona 2015).

Complete Remission (CR)

Requires all of the following to be maintained for a minimum of four weeks:
Bone marrow evaluation:

- < 5% myeloblasts with normal maturation of all cell lines

Peripheral blood evaluation:

- Hemoglobin ≥ 11 g/dL untransfused without erythropoietic support
- ANC ≥ 1000/mm^3 without myeloid growth factor support
- Platelets ≥ 100,000/mm^3 without thrombopoietic support
- 0% blasts in blood

In some cases, there may not be a four-week interval between completion of therapy and the pre-transplant disease assessment. In this case, CR should still be reported as the status at transplant since it represents the "best assessment" prior to HSCT. This is an exception to the criteria that CR be durable beyond four weeks; the pre-transplant disease status should not be changed based on early relapse or disease assessment post-transplant.

Hematologic Improvement (HI)

Requires one measurement of the following maintained for at least eight weeks without ongoing cytotoxic therapy:

Hematologic improvement – erythropoietic (HI-E):

- Hemoglobin increase of ≥ 1.5 g/dL untransfused, or
- For RBC transfusions performed for hemoglobin ≤ 9.0: reduction in RBC units transfused in 8 weeks by ≥ 4 units compared to the number of units transfused in the 8 weeks prior to treatment

Hematologic improvement – platelets (HI-P):

- For pre-treatment platelet count of > 20×10^9, platelet absolute increase of ≥ 30×10^9
- For pre-treatment platelet count of < 20×10^9, absolute platelet increase of ≥ 20×10^9 and ≥ 100% increase from pre-treatment level

Hematologic improvement – neutrophils (HI-N):

- Neutrophil count increase of ≥ 100% from pre-treatment level and an absolute increase of ≥ 500/mm^3

No Response (NR)/Stable Disease (SD)

Does not meet the criteria for at least HI, but no evidence of disease progression to AML.

Progression from Hematologic Improvement (Prog from HI)

Requires at least one of the following in the absence of another explanation (e.g., infection, bleeding, ongoing chemotherapy, etc.):

- ≥ 50% reduction from maximum response levels in granulocytes or platelets
- Reduction in hemoglobin by ≥ 1.5 g/dL
- Transfusion dependence

Note: declining donor chimerism does not meet the criteria for progression. If the above criteria for progression have been met, but a hematologic improvement was not previously achieved, report "No Response (NR) / Stable Disease (SD)".

Relapse from Complete Remission (Rel from CR)

Requires at least one of the following:

- Return to pre-treatment bone marrow blast percentage
- Decrease of ≥ 50% from maximum response levels in granulocytes or platelets
- Transfusion dependence or hemoglobin level ≥ 1.5 g/dL lower than prior to therapy

Note: declining donor chimerism does not meet the criteria for relapse.

Progression to AML

≥ 20% blasts in the blood or bone marrow

4.4.3 Pharmacokinetic Outcome Measures

Plasma concentrations of rimiducid will be determined in each subject administered rimiducid, and limited pharmacokinetic parameters will be estimated using non-compartmental analysis.

Tmax and the exposure parameters Cmax and AUC_{tlast} will be estimated for each subject where:

- **Cmax** is the maximum observed concentration
- **Tmax** is the time to maximum observed concentration
- **AUC_{tlast}** is the area under the concentration-time curve from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations

Due to the limited number of plasma samples collected, the terminal half-life will not be calculated. Systemic clearance (CLs) will be calculated as: CLs = Doseiv / AUC_{tlast}. Estimated pharmacokinetic parameters will be obtained using commercial software such as Phoenix WinNonlin (Certara USA, Inc., Version 6.2 or higher) or another suitable 21 CFR Part 11 compliant software.

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP) or alternative document. Pharmacokinetic analysis will use actual times as recorded on the CRF. Other data handling procedures will be detailed in the SAP.

4.4.4 Exploratory Biomarker Assessments

Recovery of naïve and memory T cell populations, measured by flow cytometry, may be assessed to evaluate immune reconstitution. The thymic function may be assessed by the measurement of T cell receptor excision circles. T cell repertoire may be assessed by flow cytometry or T cell receptor sequencing. Additional *in vitro* T cell function assays may be conducted to assess the response to a tumor or viral antigens as appropriate and contingent upon the availability of sufficient samples.

4.5 Study Oversight

4.5.1 Cohort Review Committee

Following treatment completion of the ten subjects in Cohort 1 of the Phase II portion of this study, safety and tolerability will be assessed by evaluation of DLTs within the prespecified 100-day DLT window, counting 100 days from the time that the last subject is enrolled and receives haplo-HSCT. If data suggest that a second cohort should be opened at a lower dose level based on evaluation of DLTs (Section 4.2.1), then another cohort review meeting will be scheduled after subjects in Cohort 2 complete the 100-day DLT assessment window.

Subject safety will be evaluated by a Cohort Review Committee, which will include representatives from various functional areas from the Sponsor, as well as principal investigators from sites participating in Phase II. Roles, responsibilities, and further details regarding the Cohort Review Committee are detailed in a separate Charter.

4.5.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be put in place to support periodic review of efficacy and safety data for the Phase III portion of this study. Reviews by the iDMC will be conducted according to a charter written and approved prior to initiation of the Phase III portion of the study. Members of the iDMC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities.

The iDMC will meet approximately every 6 months and subsequently at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile. In addition, either the Sponsor or the iDMC can request ad hoc iDMC meetings at any time that potential safety concerns arise.

An interim analysis of efficacy data will be conducted and further reviewed by the iDMC when approximately 55 (50%) of the OS events required for the primary efficacy analysis have occurred (Section 10.6).

Further details about the definition, role, and responsibility of the iDMC are reflected in the iDMC Charter and remain separate from this protocol.

4.6 End of Study

The end of study will occur after the last patient, last visit (LPLV) occurs and enough events have been observed in order to meet the primary endpoint (Section 10.5.2.1). LPLV is expected to occur approximately 36 months after the last subject is enrolled. After enough events have occurred and it is determined that the study may be closed, subjects will enter a long-term follow-up study for gene monitoring (Section 7.8).

5. STUDY POPULATION

5.1 Patient Eligibility: Inclusion Criteria

Subjects must meet all the following criteria to be enrolled into this study:

1. Signed informed consent
2. Meets institutional criteria to undergo allogeneic HSCT
3. Age 12-70 y/o
4. Diagnosis of AML or MDS as defined below:
    a. AML with intermediate to adverse risk as defined by ELN genetic risk stratification (Dohner 2017)
        i. AML in first complete remission (CR1) with high-risk features defined as > 1 cycle of induction therapy required to achieve remission, OR preceding MDS or myeloproliferative disease
            1. Adverse cytogenetics as defined below:
                a. t(6;9)(p23;q34.1); DEK-NUP214
                b. t(v;11q23.3); KMT2A rearranged
                c. t(9;22)(q34.1;q11.2); BCR-ABL1
                d. inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
                e. -5 or del(5q); -7; -17/abn(17p)
                f. Complex karyotype, monosomal karyotype
                g. Wild-type NPM1 and FLT3-ITD^{high}
                h. Mutated RUNX1
                i. Mutated ASXL
                j. Mutated TP53
        ii. AML in CR1 with ≥ 1 of the following intermediate-risk features:
            1. Mutated NPM1 and FLT3-ITD high
            2. Wild-type NPM1 without FLT3-ITD or with FLT3-ITD low (without adverse-risk genetic lesions)
            3. t(9;11)(p21.3;q23.3) MLLT3-KMT2A
            4. Cytogenetic abnormalities not classified as favorable or adverse
    b. AML in second or subsequent complete remission
    c. AML with myelodysplasia-related changes (AML-MRC) in first or subsequent complete remission.
    d. Therapy-related AML in first or subsequent complete remission

   e. De novo AML in first complete remission with intermediate or adverse genetic abnormalities
   f. De novo AML in second or subsequent complete remission
   g. MDS
      i. High or very high-risk by IPSS-R classification
      ii. Intermediate risk or higher having failed a hypomethylating agent
5. Lack of suitable conventional donor (i.e., HLA 10/10 related or unrelated donor)
6. At least a 5/10 genotypic identical haplotype match measured by HLA typing at high resolution (allele level) for the HLA-A, -B, -C, -DRBl, and -DQB1 loci
7. The donor and recipient must be identical for at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1
8. Patients with adequate organ function as measured by:
   a. Cardiac: Left ventricular ejection fraction $\geq$ 40%
   b. Pulmonary: DLCO (corrected for hemoglobin) $\geq$ 40% and FEV1 $\geq$ 50%
   c. Hepatic: total bilirubin $\leq$ 2x the upper limit of normal and ALT and AST $\leq$ 3x the upper limit of normal.
   d. Renal: estimated creatinine clearance $\geq$ 50 mL/min/based on the Cockcroft-Gault formula
9. Eastern Cooperative Oncology Group (ECOG) performance status: 0-2

5.2 Patient Eligibility: Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. HLA 10/10 allele matched (HLA-A, -B, -C, -DRBl, and -DQB1) related donor or unrelated donor
   a. An HLA 10/10 allele-matched unrelated donor may be considered eligible for the study if the Study PI determines a haploidentical donor is the best available donor option for the patient due to other considerations (e.g., graft acquisition time)
2. Autologous hematopoietic stem cell transplant $\leq$ 3 months before enrollment
3. Prior allogeneic transplantation
4. Active CNS involvement by malignant cells (less than 2 months from conditioning)
5. Current uncontrolled clinically active bacterial, viral or fungal infection
6. Positive HIV serology or viral RNA
7. Pregnancy (positive serum or urine βHCG) or breastfeeding
8. Fertile men or women unwilling to use effective forms of birth control or abstinence for a year after transplantation
9. Radiographic or histologic evidence of, or known history of cirrhosis
10. Overlapping MDS and myeloproliferative neoplasms (MPN) disease
11. Patients with acute promyelocytic leukemia (APL)
12. Known hypersensitivity to dimethyl sulfoxide (DMSO)

5.3 Donor Eligibility: Inclusion Criteria

A donor must meet all the following criteria to be considered eligible and assessments must be completed before leukapheresis.

1. Related donors include biological parents, siblings, or children, half-siblings or grandchildren
2. Age 18-75 y/o
3. Sufficiently healthy to undergo mobilization for peripheral blood stem cell harvest by institutional guidelines
4. Should be at least a full haplotype matched donor (e.g., at least a 5/10 match at HLA-A, -B, -C, -DRB1, and -DQB1); other selection criteria may include gender, age, cytomegalovirus (CMV) status, body weight of donor, and presence of anti-donor HLA antibodies
5. Donor must be examined and have specific tests performed according to existing institutional guidelines and meet institutional guidelines for candidacy as a donor
6. Donor must have been informed of the investigational nature of rivogenlecleucel and the manufacturing process and have signed an informed consent form to undergo apheresis
7. Donor must have adequate peripheral venous catheter access for leukapheresis or must agree to placement of a central catheter

5.4 Donor Eligibility: Exclusion Criteria

If the donor meets any of the following criteria, they will not be considered eligible. All assessments must be completed before leukapheresis.

1. Evidence of active infection (including urinary tract infection, upper respiratory tract infection, etc.) or viral hepatitis exposure (on screening), unless only HBs Ab+ and HBV DNA negative
2. Positive HIV serology or viral RNA
3. Medical or physical reason why makes the donor unlikely to tolerate or cooperate with growth factor therapy and apheresis
4. Factors that place the donor at increased risk for complications from apheresis or G-CSF therapy (e.g., autoimmune disease, sickle cell trait, symptomatic coronary artery disease requiring therapy, previous thrombotic events)
5. Pregnancy (positive serum or urine βHCG) or breastfeeding

5.5 Method of Treatment Assignment

This is a two-part (Phase II and Phase III) clinical trial. The Phase III part of this study will be unblinded and enrolled in a randomized fashion.

5.5.1 Phase II

Before initiating screening, the study site should confirm with the Sponsor or designee that slots remain in the planned cohort for enrollment. The Sponsor or designee will communicate to the sites impending closure of screening for a cohort.

Upon completion of all screening evaluations, the site eligibility packet will be forwarded to the Sponsor for approval.

5.5.2 Phase III

This is an open-label, randomized phase of the trial.

Randomization will be handled in a 1:1 fashion and stratified on the following factors:

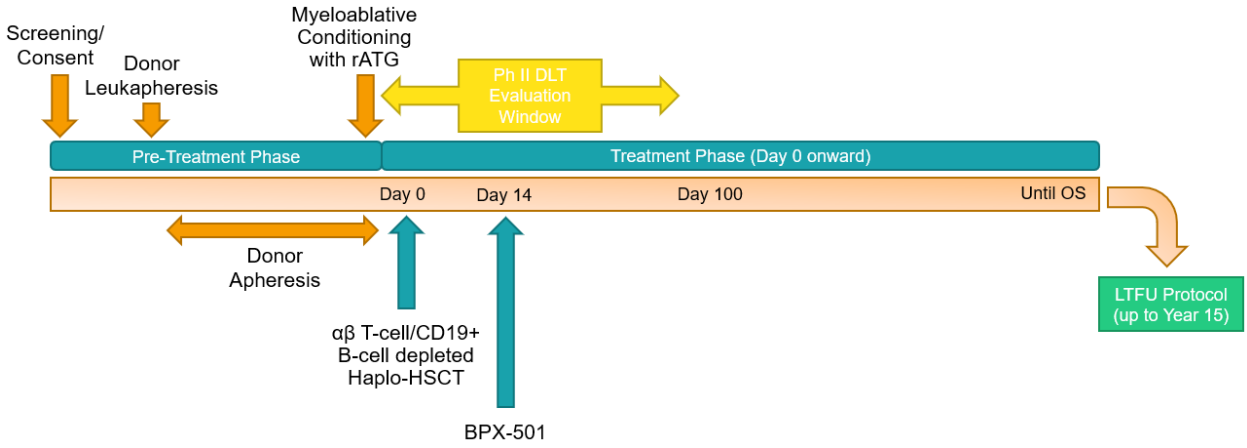
- Age (< 60 and ≥60)
- Disease (AML vs. MDS)
- Conditioning regimen

6. STUDY TREATMENT

6.1 Phase II and Phase III Arm A: αβ T Cell/CD19+ B Cell Depleted Haplo-HSCT Plus Rivogenlecleucel

Subjects in Phase II and in Phase III Arm A will receive an αβTCR and CD19+ B cell depleted haploidentical stem cell transplant on Day 0 with administration of rivogenlecleucel on Day +14 (± 4 days) (Figure 4).

Figure 4: Study Schema for Subjects Receiving Rivogenlecleucel



6.1.1 Donor Leukapheresis and Rivogenlecleucel Manufacturing

For subjects receiving rivogenlecleucel, a standard stem cell leukapheresis for obtaining T cells is performed on the donor prior to starting G-CSF mobilization for stem cell collection; two separate apheresis sessions must occur. Detailed information can be found in the Apheresis & Cell Therapy Manual.

Non-mobilized leukapheresis should occur as soon as possible after donor consent to allow for sufficient time for manufacturing of rivogenlecleucel; at latest, leukapheresis should occur at least 15 days prior to stem cell transplant (Day 0). Time from leukapheresis to arrival of rivogenlecleucel at the site takes approximately 28 days.

The leukapheresed T cells will be shipped overnight in validated shipping units with refrigerated gel packs to the Sponsor's centralized GMP manufacturing facility for processing and gene modification as outlined in the Apheresis & Cell Therapy Manual. If $< 2 \times 10^9$ MNC are collected, then the apheresis results must be discussed with the Medical Monitor and an additional apheresis may be required. Inadequate number of T cells for manufacturing of rivogenlecleucel will result in subjects not receiving rivogenlecleucel treatment; however, the subject will be followed up for 2 years to collect safety data.

6.1.2 Stem Cell Mobilization of Donor

Following screening, and non-mobilized leukapheresis for obtaining T cells, the donor will receive mobilization therapy with G-CSF (or equivalent) administration per institutional protocol for mobilization of peripheral blood stem cells. The mobilization phase starts on the first day of administration of G-CSF and continues until the final day of the stem cell apheresis collection.

6.1.2.1 Donor Apheresis

Donor stem cell apheresis will be performed on a continuous flow cell separator according to institutional standards. The stem cell apheresis typically commences on the morning of the fifth day of G-CSF treatment; a second collection may follow on the sixth day if the target CD34+ cell count is not met. The volume of blood processed per stem cell apheresis session should be approximately three to four times total blood volume as tolerated by the donor. A unique identification and labeling system shall be used to track the stem cell apheresis product from collection to infusion according to AABB and FACT guidelines.

Depletion of TCRαβ cells and CD19+ B cells from the donor hematopoietic stem cell apheresis product will be performed according to procedures given in the Miltenyi CliniMACS ® platform instrument Users Operating Manual and institutional Standard Operating Procedures (SOPs) in place at the study sites. The total nucleated count, CD34+ count, αβ CD3+ T cell count, and CD19+ B cell count, as well as other graft characteristics, will be assessed pre- and post-selection and recorded.

If the target CD34+ cell count from the TCRαβ T cells and CD19+ B depleted product is not met, then a CD34+ cell selection on additional apheresis can be performed according to procedures given in the CliniMACS® Users Operating Manual and institutional Standard Operating Procedures (SOPs) in place at the study sites.

A maximum of three successive daily apheresis sessions may be performed. The target in the combined allografts shall be ≥ 5 million CD34+ cells/kg recipient total body weight. **If there are less than a total of 5 million CD34+ cells/kg recipient weight in the combined allografts, the investigator should immediately contact the Medical Monitor.** If there are fewer than 2.5

million CD34+cells/kg recipient weight in the combined allografts, the subject shall be discontinued from the study and will receive another type of stem cell transplant.

A residual CD3+ TCRαβ+ cell count of > 2 x 10^5 cells/kg recipient total body weight will result in an exclusion criterion and the subject will not receive rivogenlecleucel after infusion of the selected allograft. However, the subject will be followed up to 2 years after transplant.

The selected apheresis product(s) will be stored per institutional procedures prior to infusion.

6.1.3 Preparative (Conditioning) Regimen

The transplant preparative (conditioning) regimen will utilize one of the recommended regimens below and should be administered per institutional standards, including dose adjustments.

It is recommended that dosing of conditioning chemotherapy for obese individuals should follow the recommendations provided in Bubalo 2014.

Selection of the conditioning regimen will be based on the discretion of the investigator.

Option #1: Flu/Bu/Cy (fludarabine, busulfan, and cyclophosphamide) (Solomon 2012)

For fludarabine, busulfan and cyclophosphamide dosing and monitoring guidelines, please refer to the local prescribing information. Seizure prophylaxis should be administered per institutional guidelines while on busulfan.

	Day									
	-10	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**
rATG	X	X	X							
Bu				X	X	X	X			
Flu					X	X	X	X	X	
Cy								X	X	

- **Fludarabine:** 25 mg/m^2/daily IV on Days -6 to -2
- **Busulfan:** 110 mg/m^2/daily IV on days -7 to -4
- **Cyclophosphamide:** 14.5 mg/kg/daily IV on Day -3 and -2

Option #2: Flu/Mel/TBI (fludarabine, melphalan, and total body irradiation) (Karduss-Urueta 2016; Mino 2018)

For fludarabine and melphalan dosing and monitoring guidelines, please refer to the local prescribing information.

	Day									
	-10	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**
rATG	X	X	X							
Mel				X						
Flu					X	X	X	X		
TBI									(X)	(X)

- **Melphalan:** 140 mg/m^2/day IV on Day -7

- **Fludarabine:** 40 mg/m^2/day on Days -6 to -3 (total dose of 160 mg/m^2)
- **TBI:** 200 cGy on Day -2 or -1 (total dose of 200 cGy)

As determined by the treating physician, subject age > 50 years or those with significant comorbidities may receive a lower dose of melphalan at 100 mg/m^2.

6.1.3.1 Rabbit Anti-thymocyte Globulin (Thymoglobulin)

Subjects receiving rivogenlecleucel should receive rabbit anti-thymocyte globulin (rATG) for prevention of graft failure (Locatelli 2017; Lang 2018). Administration of rATG should be completed by Day -7. Dosing should be as follows, with premedications and supportive care per standard institutional guidelines:

- **Thymoglobulin®**: 1-1.125 mg/kg/d starting Day -10 for 3 days

6.1.4 HSCT Infusion

The infusion of the TCR αβ T cell / CD19+ B cell depleted product will be administered on Day 0 for subjects in the rivogenlecleucel treatment arm.

6.1.5 Rivogenlecleucel

Rivogenlecleucel is a T cell product composed of donor T cells that have been ex vivo culture-expanded to high purity, gene-modified with BPZ-1001 (SFG.iCasp9.2A.ΔCD19 retroviral vector containing the iCasp9 safety gene and truncated CD19 selectable marker), and then selected to ensure a high percentage of T cells carrying the safety gene. The drug product is provided as a combined CD3+ and CD19+ frozen T cell suspension in a formulation containing DMSO for IV administration. Additional details of product formulation, packaging, labeling, tracking, accountability, preparation, administration, disposal, and destruction are provided in the Apheresis & Cell Therapy Manual.

6.1.5.1 Dose and Schedule

Rivogenlecleucel will be administered as an IV infusion at the target dose level of 3 x 10^6 cells/kg for all subjects enrolled in Cohort 1 of the Phase II portion of this study. Weight at Screening will be used to determine the total rivogenlecleucel cell dose. Rivogenlecleucel should be administered on Day 14 after HSCT (± 4 days).

Depending on results of the Cohort Review Meeting and evaluation of safety (i.e., DLTs) in Phase II, subjects will either receive rivogenlecleucel 3 x 10^6 cells/kg during Phase III, or a second cohort with treatment at a lower dose level will be opened in Phase II and this MAD will be pursued in Phase III.

6.1.5.2 Premedications

All subjects should receive premedications per institutional standards (e.g., acetaminophen plus an antihistamine) for cellular therapy products, for prevention of infusion-related/ hypersensitivity reactions.

6.1.5.3 Preparation and Administration

Refer to the Apheresis and Cell Therapy Manual for detailed instructions on rivogenlecleucel administration. Briefly, rivogenlecleucel should be thawed, diluted immediately, and infused within 90 minutes using either central or peripheral venous access devices. The start and stop time of the infusion will be recorded.

Record vital signs prior to rivogenlecleucel infusion, at 15 (± 5), 30 (± 5), and 120 (± 15) minutes after start of the infusion.

6.1.6 Rimiducid

Rimiducid may be given to subjects who receive rivogenlecleucel and develop GVHD (acute and/or chronic) and/or neurotoxicity, based on guidelines detailed in Sections 8.2, 8.3, and 8.4.

Subjects who experience disease progression/relapse and move on to receive subsequent anticancer therapy are not eligible to receive rimiducid.

Rimiducid drug substance is dissolved in Solutol® HS15 (also known as Kolliphor® HS15) and therefore has the potential to induce an infusion or hypersensitivity reaction. To minimize or mitigate infusion-related toxicity, subjects should receive premedication with acetaminophen, diphenhydramine, ranitidine, and other supportive care therapy per institutional standards for potential anaphylaxis.

Rimiducid is administered at a dose of 0.4 mg/kg, with a maximum dose of 40 mg. Prior to administration, rimiducid should be diluted in normal saline to a volume that supports infusion over 2 hours, as described in the Pharmacy Manual.

Rimiducid may be administered using either central or peripheral venous access devices. The start and stop time for the infusion will be recorded.

Record vital signs prior to rimiducid infusion, at 15 and 30 (± 5), 60 (± 10), 120 and 240 (± 15) minutes after start of the infusion.

For reach rimiducid administration, blood/tissue samples should be collected. Refer to Appendix D for details of sample collection.

6.1.7 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for this study will be provided by the Sponsor. This includes rivogenlecleucel and rimiducid.

The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation, as

determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

The Sponsor must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.2 Phase III Arm B: Haplo-HSCT Plus Post-Transplant Cyclophosphamide (PTCy)

Subjects in Arm B (Phase III) will receive a T and B cell replete, standard haploidentical stem cell transplant with administration of post-transplant cyclophosphamide and standard GVHD prophylaxis with tacrolimus and mycophenolate mofetil, as described in Sections 6.2.4 and 6.2.5 below.

6.2.1 Stem Cell Mobilization of Donor

The donor will receive mobilization therapy with G-CSF (or equivalent) administration per institutional protocol for mobilization of peripheral blood stem cells. The mobilization phase starts on the first day of administration of G-CSF and continues until the final day of the stem cell apheresis collection.

6.2.1.1 Donor Apheresis

Donor stem cell apheresis will be performed on a continuous flow cell separator according to institutional standards. The stem cell apheresis typically commences on the morning of the fifth day of G-CSF treatment; a second collection may follow on the sixth day if the target CD34+ cell count is not met. The volume of blood processed per stem cell apheresis session should be approximately three to four times total blood volume as tolerated by the donor. A unique identification and labeling system shall be used to track the stem cell apheresis product from collection to infusion according to AABB and FACT guidelines.

A maximum of three successive daily apheresis sessions may be performed. The target in the combined allografts shall be ≥ 5 million CD34+ cells/kg recipient total body weight. **If there are less than a total of 5 million CD34+ cells/kg recipient weight in the combined allografts, the investigator should immediately contact the Medical Monitor.** If there are fewer than 2.5 million CD34+cells/kg recipient weight in the combined allografts, the subject shall be discontinued from the study and will receive another type of stem cell transplant.

The selected apheresis product(s) will be stored per institutional procedures prior to infusion.

6.2.2 Preparative (Conditioning) Regimen (Arm B)

The transplant preparative (conditioning) regimen will utilize one of the recommended regimens below and should be administered per institutional standards, including dose adjustments.

It is recommended that dosing of conditioning chemotherapy for obese individuals should follow the recommendations provided in Bubalo 2014.

Selection of the conditioning regimen will be based on the discretion of the investigator.

Option #1: Flu/Bu/Cy (fludarabine, busulfan, and cyclophosphamide) (Solomon 2012)

For fludarabine, busulfan and cyclophosphamide dosing and monitoring guidelines, please refer to the local prescribing information. Seizure prophylaxis should be administered per institutional guidelines while on busulfan.

	Day									
	-10	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**
Bu				X	X	X	X			
Flu					X	X	X	X	X	
Cy								X	X	

- **Fludarabine:** 25 mg/m^2/daily IV on Days -6 to -2
- **Busulfan:** 110 mg/m^2/daily IV on days -7 to -4
- **Cyclophosphamide:** 14.5 mg/kg/daily IV on Day -3 and -2

Option #2: Flu/Mel/TBI (fludarabine, melphalan, and total body irradiation) (Karduss-Urueta 2016; Mino 2018)

For fludarabine and melphalan dosing and monitoring guidelines, please refer to the local prescribing information.

	Day									
	-10	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**
Mel				X						
Flu					X	X	X	X		
TBI									(X)	(X)

- **Melphalan:** 140 mg/m^2/day IV on Day -7
- **Fludarabine:** 40 mg/m^2/day on Days -6 to -3 (total dose of 160 mg/m^2)
- **TBI:** 200 cGy on Day -2 or -1 (total dose of 200 cGy)

As determined by the treating physician, subject age > 50 years or those with significant comorbidities may receive a lower dose of melphalan at 100 mg/m^2.

6.2.3 HSCT Infusion

Subjects in Arm B will receive a standard haploidentical HSCT (T/B cell replete) on Day 0. Infusion of the PBSC product should follow institutional standards.

6.2.4 Post-Transplant Cyclophosphamide (PTCy) Administration

Cyclophosphamide will be administered at a dose of 50 mg/kg per day intravenously on days 3 and 4 after transplant for subjects in Arm B. Dosing & administration and supportive measures (e.g., IV fluids, mesna) should be per institutional standard of care.

6.2.5 GVHD Prophylaxis

GVHD prophylaxis will only be administered to subjects enrolled in Phase III, Arm B.

PTCy should be administered as detailed in Section 6.2.4. Tacrolimus and mycophenolate mofetil (MMF) will be administered to subjects for GVHD prophylaxis, as detailed below:

- Tacrolimus will be administered from day +5 through day +180. Dosing should follow local prescribing information and institutional guidelines (e.g., 1 mg intravenously daily, adjusted to achieve a therapeutic level of 5-15 ng/mL and then converted to oral form until discontinuation)
- MMF will be administered from day +5 through day +35. Dosing should follow local prescribing information and institutional guidelines (e.g., 15 mg/kg by mouth three times daily)

6.3 Supportive Care

All subjects should receive the following:

- Transfusion support per standard institutional practice
- Anti-infective prophylaxis against herpes viruses, cytomegalovirus, Pneumocystis jirovecii, bacterial, and fungal infections according to standard institutional practices
- Routine CMV antigenemia/viral load testing by hybrid capture or PCR based methods per institutional guidelines (with preemptive ganciclovir or valganciclovir therapy in subjects who develop a positive assay, as per institutional guidelines); CMV testing is recommended weekly through Day 100 post-transplant. Additional timelines are reflected in the Schedule of Assessments (Appendices A, B, and C).
- Monitoring and prevention of EBV reactivation and EBV lymphoproliferative disease (PTLD), with consideration for using rituximab preemptively
- Supportive care (growth factors (e.g., G-CSF), antiemetics, allopurinol, menstrual suppression, prophylactic antibiotics, empiric antibiotics, transfusions of blood products, hyperalimentation, etc.) as indicated.

It is recommended that rituximab will be administrated at a dosage of 200 mg/m2 or per institutional guidelines on Day -1 to prevent the occurrence of EBV-related post-transplant lymphoproliferative disease (PTLD).

It is recommended that filgrastim (or equivalent) be administered to reduce the time to neutrophil recovery after HSCT. Dosing & administration of filgrastim should be per institutional guidelines.

6.4 Concomitant Medications

Concomitant medications include any prescription medication or over-the-counter preparations used by a subject between the screening evaluation and the End of Study visit.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

All treatments such as transfusions and critical medications, defined as below, shall be collected in the EDC database:

- Drugs given in conditioning regimens
- Most recent chemotherapy regimen and use of granulocyte-colony stimulating factor (G-CSF or equivalent)
- Prophylaxis and/or treatment for GVHD
- Prophylaxis and/or treatment for infectious complications
- Treatment in association with SAEs or AEs of special interest, such as febrile neutropenia and anaphylaxis

6.4.1 Permitted Therapies

Permitted therapies include all therapy not listed under prohibited therapy.

In the event of infusion related reactions (IRR), the subject should be treated per institutional guidelines. Treatment may include diphenhydramine, acetaminophen, ranitidine or other H2 blockers, and systemic corticosteroid.

6.4.2 Prohibited Therapies

Other investigational agents may not be administered while on study except as clinically indicated for GVHD non-responsive to frontline standard of care and rimiducid (for subjects receiving rivogenlecleucel), or infections not responding to standard treatment. In the event treatment is administered for any of these events, it should be appropriately documented in the clinical database.

Subjects should remain on study despite receiving another investigational agent for refractory GVHD/infections.

7. STUDY ASSESSMENTS & PROCEDURES

The schedule of assessments is provided in the Appendices: Appendix A, Appendix B, and Appendix C. Subjects will be closely monitored for safety and tolerability throughout the duration of the study. All assessments must be performed and documented for each subject.

Subjects should be assessed for toxicity prior to each dose and during all study assessment visits.

If the timing of the protocol-mandates study visit coincides with a holiday and/or weekend that precludes the visit, the study visit should be scheduled on the nearest following feasible date with subsequent visits rescheduled accordingly.

7.1 Informed Consent

The informed consent will be obtained per institutional practices before study screening is initiated for both subject and donor.

7.2 Screening

The standard screening process begins when the subject signs the IRB/IEC-approved informed

consent form for participation in the study, and continues through the protocol-specified visit window.

Standard pretransplant work-up for the donor and subject performed prior to formally entering the Screening period is acceptable for fulfilling Screening assessments, as long as these are done within a reasonable time frame (as deemed by the Investigator). If there are questions with the timing of assessments, then discussion with the Medical Monitor is warranted.

Refer to the Schedule of Assessments (Appendices A, B and C) for the required Screening evaluations.

7.2.1 Infectious Diseases Screening

Refer to Table 3 for a list of required pretransplant pathogen-specific testing in the donor and recipient (subject).

Table 3: Pretransplant Infectious Diseases Screening

	Donor	Recipient
CMV IgG	✓	✓
Hepatitis B (HBsAg, anti-HBsAg, anti-HBc) +/- viral load	✓	✓
Hepatitis C (IgM, IgG)	✓	✓
Hepatitis C viral load*	✓	
VZV IgG	✓	✓
HSV IgG	✓	✓
EBV (VCA IgG)	✓	✓
HIV-1, -2 antibodies	✓	✓
HIV-1 viral load	✓	
HTLV-1, -2 antibodies	✓	✓
RPR or VDRL or a *Treponema pallidum* antibody test	✓	✓
West Nile virus antibodies	✓	
Toxoplasma gondii IgG	✓	✓
Screening for TB		✓

* In addition to serologic testing for hepatitis C, all HSCT candidates should undergo a careful history and physical examination for risk factors, signs, and symptoms of hepatitis C, as well as serum alanine aminotransferase (ALT) testing. Hepatitis C viral load testing should be performed in all HSCT donors as well as in HCT candidates at increased risk for hepatitis C infection, including those who have received a transfusion with blood not tested for hepatitis C (e.g., before 1992 in developed countries), history of IV or inhaled drug use, tattoos, or unexplained elevation of serum ALT. Viral load testing should also be performed in HSCT candidates with positive hepatitis C serologic testing.

Adapted from:
Wingard JR. Evaluation for infection before hematopoietic cell transplantation. Thorner AR, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on February 5, 2019.)

US Food and Drug Administration. Testing HCT/P donors: Specific requirements. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm151757.htm (Accessed on February 5, 2019).

7.3 Study Assessments

Visit windows for weekly visits are +/- 3 days until Day 100, unless otherwise specified. Visit windows after Day 100 will be +/-14 days, through the first year. Visit windows between Month 12 to Month 24 will be +/- 21 days. After Month 24, visit windows are +/- 28 days.

Refer to Appendices A, B and C for the Schedule of Assessments for the donor and recipient. The study schedule is divided into three portions: Pre-treatment Phase, Treatment Phase (Day 0 to Day +100), and Treatment Phase (> Day +100 to End of Study).

The Pre-treatment Phase refers to the time of screening/subject enrollment (and randomization for Phase III), from Days -42 to -1.

The first Treatment Phase encompasses haplo-HSCT on Day 0 through Day +100, including rivogenlecleucel administration for Phase II and Phase III Arm A subjects. For Phase II, the Treatment period coincides with the DLT evaluation window.

The second Treatment Phase continues from > Day +100 through the End of Study, or at the time that subject experiences an event (i.e., death), whichever occurs later. This Treatment Phase includes follow-up visits for evaluation of safety and disease status at indicated times. The End of Study (EOS) visit will take place after death or withdrawal of consent, and subsequently subjects still alive will be encouraged to participate in the LTFU study (Section 7.8). For subjects who withdraw from the study early, the EOS visit should be completed at the time of study withdrawal.

Beyond Month 24, subjects should continue to be followed every 6 months (or more frequently as clinically indicated, at the discretion of the investigator). Evaluations should be performed as per institutional standard of care, including laboratory assessments.

7.3.1 Laboratory Monitoring

Laboratory monitoring should be performed according to standard institutional practice for HSCT patients. In general, blood counts with differentials should be performed at least 3 times per week after transplant until the neutrophil count reaches 0.5 x 10^9/L. Thereafter, at least 2 times per week until the neutrophil count is > 1.0 x 10^9/L and platelets > 100 x 10^9/L. Subsequently, blood counts and differentials should be performed approximately every 2 weeks until + 100 days. Samples for biochemistry, related to the routine monitoring of hepatic and renal function, will be taken pre-transplant and thereafter at least 3 times weekly until engraftment and subsequently checked twice a week until + 100 days.

7.3.2 Surveillance Cultures and Microbiological Monitoring

Microbiological investigations will be according to standard institutional practice for the determination of an infectious organism in a subject undergoing HSCT. These will include regular surveillance cultures (inclusive of oral flora), blood cultures and viral screening. All infections, either presumed or proven and treated, should be documented, and treated according to standard of care.

7.3.3 Disease Evaluations

Disease evaluations will be conducted at timepoints listed in the Schedule of Assessments (Appendix A, B and C) using the response criteria detailed in Section 4.4.2. Response will be assessed by the investigator and by the iDMC based on physical examinations, laboratory results, bone marrow (BM) examinations, and other findings as clinically relevant, using CIBMTR response criteria for AML and MDS.

All subjects should be evaluated according to institutional standard of care until relapse. If disease recurs, a bone marrow aspirate and biopsy should be performed. For disease evaluation, a BM aspirate is required and BM biopsy in addition is preferred. If aspirate is unattainable (i.e., dry tap), a BM biopsy is required. BM aspirate and biopsy should be sent to the Central Laboratory for confirmation.

7.3.4 Minimal Residual Disease Evaluations

Minimal residual disease (MRD) status should be assessed at various timepoints during the study (including at baseline) to evaluate for depth of response, as performed by the site per institutional standard practice on peripheral blood and/or BM samples.

7.3.5 Exploratory Biomarker Sample Collection

Immune Reconstitution samples will be collected from all subjects, throughout the study period.

For subjects in Phase II and Phase III Arm A, the iCasp T cell tracking samples will be collected at routine timepoints throughout the study from subjects receiving rivogenlecleucel. Assessment of immune reconstitution, thymic function, T cell repertoire and T cell function will be carried out as appropriate and depending on recovery of sufficient cell number after sample processing.

Refer to the Schedule of Assessments and Appendix D for timepoints of sample collection. Further details and instructions for sample collection are in the Laboratory Manual.

7.3.6 Gene Therapy Monitoring Plan

Per FDA guidelines, before HSCT and for 5-years post-stem cell transplant, subjects will be evaluated with a physical exam and blood testing for vector copy number (VCN) and replication competent retrovirus (RCR). VCN will be tested every six months. After 5 years, blood samples will be drawn annually for another 10 years (total of 15-year follow-up), if vector is detected.

Blood drawn for RCR testing will be analyzed pre-HSCT and at 3, 6, and 12 months after treatment, and annually for up to fifteen years. If all post-treatment PCR assays are negative for RCR during the first year, yearly samples are archived. If the testing is positive at one of those time points, additional samples will be drawn and analyzed throughout the 15-year follow-up period.

Refer to the Schedule of Assessments for details of sample collection.

7.4 Assessments to be Performed upon Disease Progression or Relapse

The evaluations listed in the Schedule of Assessments for progressive disease or relapse (Appendix A, Table A-16; Appendix B, Table B-19) should be performed as soon as possible after disease progression/relapse is suspected. These subjects should continue to be followed for survival status and subsequent anticancer therapy (Section 7.5).

7.5 Survival Follow-up and Subsequent Anticancer Therapy

After disease progression or relapse, subjects will be contacted to assess survival status approximately every 12 weeks until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever comes first. Along with survival, subsequent anticancer therapy information will also be collected. Prior to the primary analysis or study closure, subjects whose survival status is unknown may be assessed again for survival follow-up.

If a subject withdraws from the study and does not consent to continued follow-up of associated clinical outcome information, the investigator may consult public records, such as those establishing survival status.

7.6 Subject Discontinuation

The subject has the right to withdraw from the study at any time under the current version of the Declaration of Helsinki and other regulations that may be applicable. Such withdrawal will be without prejudice to his or her future medical treatment at the institution and by the physician.

Other reasons that result in any subject discontinuing from the study may include the following:

- Unable/ineligible to undergo planned HSCT
- Withdrawal of consent by the subject or non-compliance of the subject with the protocol, defined as refusal or inability to adhere to the study schedule
- At the request of the Investigator or Sponsor for administrative or other reasons
- Loss to follow-up
- Death

If a subject withdraws from the study, the Investigator should make reasonable effort to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the appropriate case report forms.

Subjects that cannot be contacted and who do not have a known reason for discontinuation will be classified as "lost to follow-up" concerning the reason for discontinuation. The Investigator's study staff should make three documented attempts to contact the subject by telephone. If the subject cannot be reached by telephone, the Investigator's staff should attempt to contact the subject by certified mail or a similar alternative method, where appropriate.

Even after a subject withdraws from study, they may still be asked to participate in the Long-term Follow-up Study and undergo gene therapy monitoring as per FDA guidelines.

7.7 Study Discontinuation

The Sponsor has the right to terminate this study at any time for various reasons.

The Sponsor has the right to close a study site at any time. Reasons for closing a site may include, but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with the ICH guidelines for GCP
- No study activity (i.e., all subjects have completed treatment and all obligations have been fulfilled)

7.8 Long-term Follow-up (LTFU) Study (Phase II and Phase III Arm A)

Patients will be followed until the time of death, study discontinuation, or the time of the primary analysis for OS, whichever occurs first. The primary analysis for OS is expected to occur approximately 42 months after the first patient is randomized, or, given 18 months of accrual, approximately 24 months after the last patient is randomized. Patients still on study at the time of primary analysis will be consented to agree to a LTFU study as part of a commitment to assessing long-term safety and efficacy of rivogenlecleucel.

The LTFU study may include subjects from all active and future clinical trials exploring rivogenlecleucel. All subjects treated with rivogenlecleucel who either complete the primary follow-up period specified in this protocol or who prematurely withdraw after at least one dose of rivogenlecleucel will be asked to enroll in the LTFU protocol at the end-of-study visit or at the time of withdrawal, respectively. A separate informed consent form will be provided for the LTFU protocol. Subjects who do not consent to participate in the LTFU protocol or who are lost to follow-up will be followed for survival through public record.

8. POTENTIAL RISKS AND MANAGEMENT OF TREATMENT TOXICITIES

A summary of management of potential treatment toxicity is provided below. A complete discussion of potential risks associated with rivogenlecleucel and rimiducid are available in the current version of the Investigator's Brochures.

8.1 Risks Associated with Rivogenlecleucel

Rivogenlecleucel consists of human T cells which are obtained from normal donor leukapheresis, ex-vivo culture-expanded to high purity, gene-modified with BPZ-1001 (SFG.iCasp9.2A.ΔCD19 retroviral vector containing the iCasp9 safety gene, as well as truncated CD19 selectable marker), and then selected to ensure a high percentage of T cells carrying the safety gene.

Rivogenlecleucel is intended to aid in engraftment, promote immune reconstitution, potentially aid in graft versus leukemia (GVL) effect and is largely removed from the body upon infusion of

the dimerizing agent, rimiducid. Considering this mechanism of action, it is hypothesized that administration of rivogenlecleucel can increase the risk of GVHD (acute or chronic). Preliminary results from 100 pediatric subjects with high-risk acute leukemias (acute lymphoblastic leukemia and acute myeloid leukemia) with follow up ≥ 180 days demonstrate that 21.9% of subjects experienced acute GVHD (11.5% Grade II-IV; 3.1% Grade III-IV). Of the 37 subjects who developed GVHD, rimiducid was used in 11 of these subjects. A best overall response of CR or PR was seen in 73% of these subjects (Locatelli 2018). Despite the associated risk of GVHD, these data suggest that BPX-501 does not show an increased risk over standard of care and in subjects who develop GVHD and receive rimiducid, the majority achieved responses of CR or PR.

Toxicities associated or possibly associated with rivogenlecleucel should be managed according to standard medical practice. Additional tests should be used to determine a possible etiology.

8.2 Acute GVHD

For guidance on the treatment of aGVHD please refer to Table 4.

For patients in Arm A, if aGVHD develops before rivogenlecleucel administration, the infusion should be held and the event followed until resolution. If the event completely resolves and the subject is on less than or equal to 0.5 mg/kg methylprednisone (or equivalent) within 28 days from onset of an event, rivogenlecleucel can be administered.

Refer to Appendix F for the grading scale for aGVHD, and Appendix H for GVHD response criteria.

Table 4: Guidelines for Management of Acute GVHD

Event	Management
aGVHD, Grade 1	• Consider skin biopsy to establish the diagnosis • Initial treatment with topical corticosteroids per institutional standard of care for Grade 1 skin aGVHD. Guidelines for topical corticosteroid treatment include the following or per institutional guidelines. The use of fractionated corticosteroid administration is also allowed: o Face, axillae, and groin: lower potency steroids (hydrocortisone 1-2.5%, desonide 0.05%) o From the neck down: mid-strength steroids (e.g., triamcinolone 0.1% cream or ointment) • If no response to topical steroids or worsening in stage or grade of skin aGVHD after 48 hours, subjects may receive systemic corticosteroids per institutional guidelines **For patients in Arm A:** • If no response to systemic steroids or worsening in stage or grade of skin aGVHD after 48 hours, subjects may then receive rimiducid: o Rimiducid Dose: 0.4 mg/kg (max dose 40 mg) IV o If there is evidence of clinical improvement (e.g., partial response) but not complete resolution after the first dose of

	rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours o Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration o For new or recurrent Grade 1 aGVHD episodes, rimiducid may be considered for repeat administration with the above guidelines if the investigator considered rimiducid to offer a clinical benefit with prior episodes • If no response to systemic steroids or rimiducid, the investigator should consider other medications per institutional guidelines (e.g., calcineurin inhibitors, sirolimus, mycophenolate) • Peripheral blood and/or tissue and plasma (PK) samples should be collected in the event of administration of systemic corticosteroids or rimiducid for aGVHD as detailed in Appendix D.
aGVHD, Grades 2, 3 and 4	• Consider tissue (e.g., skin, gut, liver) biopsy to establish the diagnosis • Systemic corticosteroids when used should be administered as methylprednisolone 2 mg/kg/day IV in a single dose; or a dose equivalent of prednisone or dexamethasone (Martin 1990); fractionated dosing of steroids is also permitted • Consideration by the investigator for other medications per institutional guidelines (e.g., calcineurin inhibitors, sirolimus, mycophenolate) **For patients in Arm A:** • If no response to steroids or other aGVHD medications after 48 hours, subjects may then receive rimiducid: o Rimiducid Dose: 0.4 mg/kg (max dose 40 mg) IV o If there is evidence of clinical improvement (e.g., partial response) but not complete resolution after the first dose of rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours o Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration o For new or recurrent Grade 2 through 4 aGVHD episodes, Rimiducid may be considered for repeat administration with the above guidelines if the investigator considered rimiducid to offer a clinical benefit with prior episodes • Peripheral blood and/or tissue and plasma (PK) samples should be collected in the event of administration of systemic corticosteroids or rimiducid for GvHD as detailed in Appendix D.

8.3 Chronic GVHD

For guidance on the treatment of cGVHD please refer to Table 5.

At each evaluation, complete the Chronic GVHD Activity Assessment-Clinician and Chronic GVHD Activity Assessment-Patient Self Report (Appendix G and Appendix I). Refer to Appendix H for GVHD response criteria.

Table 5: Guidelines for Management of Chronic GVHD

Event	Management

cGVHD - Mild	• Consider tissue biopsy to establish the diagnosis
	• Treatment for mild cGVHD should be per institutional guidelines
	
	For patients in Arm A:
	• If no response to steroids/systemic therapies occurs within 7 days, or there is a worsening in cGVHD, subjects may then receive rimiducid:
	  ○ Rimiducid Dose: 0.4 mg/kg (max dose 40 mg) IV
	  ○ If there is evidence of clinical improvement (e.g., partial response) but not complete resolution after the first dose of rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours
	  ○ Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration
	  ○ For new or recurrent cGVHD episodes, rimiducid may be considered for repeat administration with the above guidelines if the investigator considered rimiducid to offer a clinical benefit with prior episodes
	• Peripheral blood and/or tissue and plasma (PK) samples should be collected in the event of administration of systemic corticosteroids or rimiducid for GvHD as detailed in Appendix D.

cGVHD – Moderate to Severe	• Consider tissue biopsy to establish the diagnosis • Initial treatment with IV steroids or other systemic treatments (e.g., calcineurin inhibitors) per institutional standard of care for extensive cGVHD should be instituted • Management of steroid-refractory cGVHD should follow institutional guidelines (Arm B subjects) • Patients with chronic GVHD receiving a prolonged course of systemic steroids should receive adequate infections prophylaxis for encapsulated bacterial infections, PCP, and VZV, per institutional standard of care **For patients in Arm A:** • If no response steroids/systemic therapies occur within 7 days, or there is a worsening in cGVHD, subjects may then receive rimiducid ○ Rimiducid Dose: 0.4 mg/kg (max dose 40 mg) IV

	○ If there is evidence of clinical improvement (e.g., partial response) but not complete resolution after the first dose of rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours ○ Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration ○ For new or recurrent cGVHD episodes, Rimiducid may be considered for repeat administration with the above guidelines if the investigator considered Rimiducid to offer a clinical benefit with prior episodes • Peripheral blood and/or tissue and plasma (PK) samples should be collected in the event of administration of systemic corticosteroids or rimiducid for GvHD as detailed in Appendix D.

8.4 Neurotoxicity

There is a potential risk of neurotoxicity in patients undergoing HSCT, and in those receiving rivogenlecleucel. BPX-501 cells have been documented to enter the central nervous system. This finding is of unknown significance.

Neurologic complications occur in approximately 6.4-19.2% of patients after allogeneic hematopoietic stem cell transplantation (Dowling 2017; Syed 2016; Uckan 2005). They are the cause of death in 10-15% of children undergoing allogeneic HSCT (Uckan 2005). Children who develop encephalopathy have a poor prognosis, with a minority experiencing partial or complete neurologic recovery. The etiologies of these complications are diverse and include infection, posterior reversible encephalopathy syndrome (PRES), metabolic encephalopathy, medications, GVHD, hemorrhage, multi-organ dysfunction, and inflammatory conditions. Risk factors for these complications include acute GVHD, thrombocytopenia, delayed platelet engraftment, primary underlying disease, and age (Dowling 2017; Syed 2016; Uckan 2005; Grauer 2010). CNS toxicity may occur at different rates among different donor sources, with a higher incidence in matched unrelated or haploidentical donors compared with matched related donors (de Brabander 2000).

Careful attention should be paid to the onset of Grade 2 or higher level of depressed consciousness, encephalopathy, hypersomnia, lethargy, leukoencephalopathy, meningismus, myelitis, reversible posterior leukoencephalopathy syndrome (PRES), seizure, or somnolence.

Diagnostic evaluation should include assessment of focal versus the generalized type of symptoms. Generalized findings may include seizures, metabolic encephalopathy, or infection, while focal findings raise suspicion for mass lesions, hemorrhage, stroke, or spinal cord abnormalities.

Guidelines monitoring of neurotoxicity are provided in Table 6. Subjects should undergo a daily neurologic examination and mini-mental status examination (MMSE) (Folstein 1975) or modified mini mental status examination (pediatric population; Ouvrier 1993) while inpatient

during the hematopoietic stem cell transplant. Daily neurologic examinations should be performed during any readmissions after allogeneic HSCT.

In subjects receiving rivogenlecleucel, neurologic evaluation should be performed as stated above, and should occur both before and after the infusion of rivogenlecleucel. A neurologic examination should be performed as part of all routine clinical follow-up examinations during each outpatient visit while subjects are being treated on rivogenlecleucel clinical trials.

In the event of the development of Grade 2 or higher nervous system disorders or mental status changes, refer to Table 7 below for evaluation and management guidelines.

In cases where a lumbar puncture (LP) is potentially warranted to evaluate the cerebrospinal fluid (CSF) to aid in the differential diagnosis of clinical neurological changes, procedures and precautions should be taken to rule out contraindications for performing an LP, consistent with consensus guidelines for performing LPs in subjects with neurological diseases (Table 8; Engelborghs 2017).

If a diagnostic LP is performed, attempts should be made to minimize side effects such as infections, pain, and post-LP headaches, including, but not limited to: a) use of 25G atraumatic type needles, b) performing 4 or fewer attempts, c) passive CSF collection instead of active CSF withdrawal using a syringe, d) collection of less than 30 mL of CSF, and e) lateral recumbent position (Table 8; Engelborghs 2017).

Table 6: Monitoring for Neurologic Complications

Timing	Neurologic examination	Mini-mental status examination
In all subjects		
Baseline (before conditioning and HSCT)	✓	✓
Daily while inpatient	✓	✓
Change in mental status or presence of CNS dysfunction (e.g., reduced consciousness, delirium)	✓	✓
In subjects who receive rivogenlecleucel (in addition to evaluations above)		
Before rivogenlecleucel infusion	✓	✓
Routine outpatient clinic visits or emergency room visits	✓	✓

Table 7: Guidelines for Management of Neurotoxicity

Event	Management*
Grade ≥ 2 (Focal)[1]	• Consider neurology consultation and performing EEG • Perform daily neurological and mini-mental status examinations during hospitalizations to evaluate for resolution/worsening of symptoms

	• Perform CNS imaging (MRI or contrast-enhanced CT)
	• Consider CSF evaluation for the presence of cell counts (and differential), glucose, protein, and gram-stain for bacteria.
	  ○ CSF evaluations for other infectious etiologies (e.g., herpes viruses, JC virus, fungal, West Nile virus and toxoplasma)
	  ○ CSF samples should be sent to the Sponsor for research use to evaluate for the presence of BPX-501 cells
	• Consider empiric use of anticonvulsants if a seizure is expected
	  ○ Special consideration should be considered for conditioning agents (e.g., Busulfan) or prophylactic GVHD medications (e.g., calcineurin inhibitors) as an etiology and institutional guidelines should be instituted for possible treatments (e.g., prophylactic GVHD medication changes or treatment with seizure medications)
	• Start management of stroke/ischemia per institutional guidelines if suspected
	• Administration of antiviral or anti-fungal therapy as per institutional standard of care should be considered if infectious etiology is suspected (tailored for lab data results)
	• A brain biopsy should be considered if other diagnostic tests are unrevealing as to an etiology
	
	For patients in Arm A:
	• Rimiducid 0.4 mg/kg (max dose 40 mg) may be administered if CNS infection is ruled out and there is no improvement after 48 hours of high-dose corticosteroids (e.g., methylprednisone 500 mg IV every 12 hours x 2 days for adults)
	• Rimiducid may be administered in conjunction with corticosteroids and anti-infective agents
	• Samples for PK analysis of rimiducid for research use should be collected before and after rimiducid, including samples of the CSF for PK analysis if the subject's condition allows (see Appendix D for sample collection details)
	• If there is evidence of improvement (e.g., partial response) but not complete resolution after the first dose of rimiducid, then rimiducid can be repeated every 48 hours for up to 3 doses
	• Please notify the medical monitor at Bellicum before the administration of rimiducid for neurotoxicity

Grade ≥ 2 (Generalized)[2]	• Perform routine institutional care for subjects with altered mental status/obtundation (e.g., continuous vital sign monitoring, oxygen, suction, airway protection measurements and consideration of the need for mechanical ventilation, ICU admission) • Neurology consult and EEG evaluation • CBC analysis and peripheral blood smear evaluation to evaluate for thrombotic microangiopathy (TTP/HUS) • Evaluation for electrolyte and acid-base etiologies • Evaluation of liver dysfunction and evidence of hyperammonemia/veno-occlusive disease (VOD)

	• Perform daily neurological and mini-mental status examinations during hospitalizations to evaluate for resolution/worsening of symptoms
	• Perform CNS imaging (MRI or contrast-enhanced CT)
	• Perform CSF evaluation for the presence of cell counts (and differential), glucose, protein and gram stain for bacteria.
	  o CSF evaluations for other infectious etiologies (e.g., herpes viruses, JC virus, fungal, West Nile virus and toxoplasma)
	• Consider empiric use of anticonvulsants if a seizure is expected
	  o Special consideration should be considered for conditioning agents (e.g., Busulfan) or prophylactic GVHD medications (e.g., calcineurin inhibitors) as an etiology and institutional guidelines should be instituted for possible treatments (e.g., prophylactic GVHD medication changes or treatment with seizure medications)
	• Consideration of high-dose corticosteroid treatment (e.g., methylprednisone 500 mg IV every 12 hours x 2 days for adults) if no evidence of CNS/systemic infection
	• Consideration of empiric antiviral or anti-fungal therapy as per institutional standard of care should be considered if infectious etiology is suspected (tailored for lab data results)
	• A brain biopsy should be considered if other diagnostic tests are unrevealing as to an etiology
	
	For patients in Arm A:
	• Rimiducid 0.4 mg/kg (max dose 40 mg) may be administered if CNS infection is ruled out and there is no improvement after 48 hours of high-dose corticosteroids (e.g., methylprednisone 500 mg IV every 12 hours x 2 days for adults)
	• Rimiducid may be administered in conjunction with corticosteroids and anti-infective agents. Samples for PK analysis of rimiducid for research use should be collected before and after rimiducid, including samples of the CSF for PK analysis if the subject's condition allows (see Appendix D for sample collection details).
	• If there is evidence of improvement (e.g., partial response) but not complete resolution after the first dose of rimiducid, then rimiducid can be given every 48 hours for 3 doses
	• Please notify the medical monitor at Bellicum before the administration of rimiducid for neurotoxicity

* All grading corresponding to NCI CTCAE v5.0: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 1. Includes but not limited to cranial nerve abnormalities, brachial plexopathy, ischemia, nystagmus, pyramidal tract syndrome, radiculitis, focal seizure, stroke, transient ischemic attack 2. Includes but not limited to aphonia, ataxia, cognitive disturbance, depressed level of consciousness, dysarthria, dysphasia, encephalopathy, headache, hypersomnia, lethargy, memory impairment, meningismus, seizures, somnolence, tremor, visual disturbances	

Table 8: Recommended Procedures to Rule-out Contraindications for LP and Procedures to Minimize Risks

Recommended Procedures*	Risk Factors
Rule out LP contraindication 1. Brain imaging before LP in case of: a. an intracranial lesion with mass effect b. abnormal intracranial pressure c. tonsillar herniation is suspected d. recent seizures e. impaired consciousness f. papilledema 2. Check platelet and coagulation status (platelet > 40 X 10^9/L; INR <1.5) 3. Check medications before LP	Coagulopathy Uncorrected bleeding diathesis Anti-coagulant medication
Patient-related risk factors: 1. Determine risk profile and inform subject before and during LP procedure	
Procedures to Minimize Risk 1. 25G atraumatic needle; small needle/atraumatic needle 2. < 4 LP attempts 3. Passive withdrawal 4. Lateral recumbent position 5. Collections up to 30 mL	Post-LP Headache, back pain, post-LP complaints

*Table modified from Engelborghs 2017.

8.5 Risks Associated with Rimiducid

Rimiducid is a member of a new class of lipid-permeable divalent compounds, termed activating (or dimerizer) drugs that act by inducing clustering of engineered proteins inside cells. Rimiducid is an investigational new drug to be administered to subjects after the administration of cells carrying engineered proteins that activate signaling in cells. Rimiducid activity is based on the principle of intracellular signaling mechanisms that can be regulated by specific protein-protein interactions. By selecting protein interactions that produce a desired cellular response and engineering those proteins to interact only in the presence of a small molecule drug such as rimiducid, it is possible to bring complex biological processes under direct pharmacologic control.

Rimiducid was tested in normal, healthy people at doses 2.5-fold greater than those used in the clinical trials using gene modified cells. The only side effect noted was facial flushing (redness) in one person. Although not observed in subjects to date, rimiducid was associated with non-clinically significant modest elevations of hepatic transaminases, bilirubin and alkaline phosphatase in the acute and/or subacute non-human primate studies (Covance 6843-121; Charles River WIL-372501). It is possible that other side effects may occur (Iuliucci 2001).

Rimiducid is formulated in 25% Kolliphor HS 15, a non-ionic surfactant. Prior to administration, rimiducid is diluted in normal saline, which may lead to the formation of micro-micelles. Micelles of polyethoxylated pharmaceutical surfactants, such as Kolliphor, are known to activate complement, leading to anaphylactoid-like reactions or pseudoallergy. Such responses may be the result of the activation of mast cell and subsequent degranulation (Szebeni 2001).

Therefore, Bellicum recommends that subjects are pre-medicated using standard procedures for the prevention of infusion reactions prior to administration of rimiducid. Such pre-treatment regimens would typically be administered thirty minutes to one hour prior to the infusion of rimiducid.

Considering rimiducid's mechanism of action, it is hypothesized to have relatively mild toxicity profile. As of 18 October 2018, results from completed and ongoing studies with rivogenlecleucel show that there have been 32 subjects treated with rimiducid. Currently, no SUSARs related to rimiducid have been reported under this program.

For further details regarding clinical safety and a more comprehensive list of observed adverse events, please refer to the rimiducid IB.

8.5.1 Management of Patients Who Experience Rimiducid-Specific Adverse Events

Toxicities associated or possibly associated with rimiducid should be managed according to standard medical practice. Additional tests should be used to determine a possible etiology.

Due to the minimal number of AEs reported, no formalized AE treatment guidelines exist for rimiducid. In the event of IRR, it is recommended to treat the subject per institutional guidelines. For all adverse events thought to be causally related to rimiducid, it is recommended to contact the study Medical Monitor.

8.6 Risks Associated with Cyclophosphamide

Please refer to the local prescribing information for the complete toxicity profile of cyclophosphamide.

9. SAFETY REPORTING AND EVALUATION

9.1 Safety Plan

The safety plan for subjects in this study is based on the available clinical experience with rivogenlecleucel and rimiducid. The anticipated important safety risks for the study treatment is detailed within Section 8. This section is considered a highlight and does not include exhaustive safety and toxicity information on the study treatment(s). Please refer to the individual study treatment IB for a complete summary of safety information.

9.2 Safety Parameters & Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and other variables;

measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Sponsor or its designee is responsible for reporting relevant SAEs to the FDA other, applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

9.2.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period
- Pre-existing medical conditions judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
- Abnormal laboratory values or tests that induce clinical signs or symptoms that are considered clinically significant

9.2.2 Serious Adverse Event

The definition of an SAE is any AE that is any of the following:

- Fatal (i.e., the AE causes or leads to death)
- Life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

The investigator is responsible for ensuring that AEs and SAEs are recorded on the CRF and reported to the Sponsor in accordance with protocol instructions.

9.2.3 Protocol-Defined Events of Special Interest/Non-Serious Expedited Adverse Events

The following events are considered Adverse Events of Special Interest (AESI) and will need to be reported to the Sponsor expeditiously on the CRF and SAE form, irrespective of regulatory seriousness criteria.

- Grade III-IV encephalopathy or neurologic events
- Grade III-IV acute graft-versus-host disease
- Severe chronic graft-versus-host disease

9.3 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.4 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each subject contact. All AEs and SAEs, whether reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the Adverse Event CRF or eCRF or Serious Event CRF.

For each AE and SAE recorded on the applicable CRF or SAE Form, the investigator will make an assessment of seriousness, severity and causality.

The AE grading (severity) scale (Table 9) found in the NCI CTCAE v5.0 will be used for AE reporting: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE.

Table 9: Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description[a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required

3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

The investigator's assessment of causality for individual AE reports is part of the study documentation process and is based on the Investigator's clinical judgment. In addition to the "Related" or "Not Related" Investigator causality assessment (Table 10) for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

To ensure consistency of causality assessments, investigators should apply the following general guidelines for the assessment of causality:

Table 10: Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
Related	There is a reasonable possibility that the investigational product caused the event.
Not Related	There is no reasonable possibility the event was attributed to the investigational product.

9.5 Recording Adverse Events on the CRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF. Avoid colloquialisms and abbreviations. Only one medical concept should be recorded in the event field on the Adverse Event CRF.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms and are considered clinically significant. Grades 1-4 hematologic toxicity is anticipated during the first 100 days after stem cell transplantation and so will not be considered as an adverse event or reported as a SAE.

Readmission to the hospital after stem cell transplantation is anticipated as a result of a number of transplant-associated side effects such as, but not limited to, the following:

- Recurrence of the leukemia or cancer
- Febrile neutropenia
- Bleeding from thrombocytopenia
- Acute or chronic GVHD

If in the opinion of the investigator, these re-hospitalizations are transplant-associated side effects, these events should be reported in the eCRF as AEs (not SAEs) for this study as they are not unexpected after the stem cell transplant.

9.5.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF or SAE Form rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs/SAEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF or SAE Form.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF or SAE Form. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF or SAE Form.

9.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event CRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event CRF or eCRF.

9.5.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF and SAE Form (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF or eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded

as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF or eCRF, unless their severity, seriousness, or etiology changes.

9.5.5 Deaths

All deaths that occur during the protocol-specified AE reporting period (Section 9.6), regardless of attribution, will be recorded on a CRF and expeditiously reported to the Sponsor.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the CRF or eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the CRF or eCRF.

If the death is attributed to the original diagnosis, record "XXX (i.e., AML or MDS) Progression" as the SAE term on the CRF or eCRF.

9.5.6 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical History CRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF or SAE Form, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

9.5.7 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

9.5.8 Pregnancy

The investigator should report to the sponsor or designee all instances in female subjects or partners of male subjects within 24 hours of their knowledge of the pregnancy using the Pregnancy Form. In addition, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be

reported using the SAE Report Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

- If a female subject becomes pregnant while receiving investigational therapy or within 120 days after the last dose of investigational product, a Pregnancy Report CRF should be completed, printed, and faxed to the Sponsor or its designee within 24 hours of learning of the pregnancy
- Abortion, whether therapeutic or spontaneous, should always be classified as serious, recorded on a CRF, and expeditiously reported to the Sponsor
- Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the investigational product should be recorded and reported as an SAE
- The Pregnancy Form should be completed and sent to the Sponsor as described in Section 9.6.4

9.6 Guidance for Capturing and Reporting Adverse Events

9.6.1 Adverse Event Reporting Period

After informed consent, but prior to haplo-HSCT on Day 0, only SAEs caused by a protocol-mandated intervention (i.e., outside of institutional standard protocol) will be collected.

Table 11 details the guidance for Adverse Event Reporting after the Treatment Phase has initiated.

Table 11: Adverse Event Reporting Guidelines

AE type	Timepoint	Rivogenlecleucel	Rimiducid
Adverse Events	≤ 30 days post dose	√	√
Serious Adverse Events	≤ 180 days post dose	√	√
Serious Adverse Events Related to Study Treatment	181 days – 24 months post dose	√	√
Pregnancy of Subject or Partner	No less than 12 months following the last dose of myeloablative therapy	√	√

All AEs (except GVHD) will be collected for 30 days following each infusion of rivogenlecleucel or rimiducid. SAEs regardless of attribution will be collected until 180-days post rivogenlecleucel infusion and/or rimiducid. After this period, investigators should report only SAEs that are felt to be related to the study treatment (rivogenlecleucel and/or rimiducid).

9.6.1.1 GVHD Adverse Event Reporting

All occurrences of GVHD will be reported as Adverse Events (or SAEs), regardless of their start date in relation to rivogenlecleucel (if applicable). GVHD events will also be followed until resolution and not limited to the standard AE/SAE reporting period.

9.6.2 Procedures for Eliciting and Recording Adverse Events

Instructions and clarifications for the eliciting and recording of Adverse Events are in Section 9.6.2 of this protocol.

9.6.3 Expedited Reporting Requirements for Serious Adverse Events or Protocol Defined Events of Special Interest

Any life-threatening or fatal SAE that is attributed by the investigators to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on a SAE Report Form within 24 hours.

Medical Monitor Contact Information:

[redacted]

9.6.4 Reporting Requirements for All SAEs and Pregnancy Reports

Investigators will submit reports of SAEs and pregnancy, to the Sponsor within 24 hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within 24 hours on an SAE Report Form or Pregnancy Report Form and submit electronically. Relevant follow-up information should be submitted to Sponsor or its designee as soon as it becomes available and/or upon request.

[redacted]

9.6.5 Reporting SAEs to the IRB or Ethics Committee

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the required Ethics Committees or IRBs.

9.6.6 Type and Duration of Follow-Up of Patients after Adverse Events

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the subject is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event CRF or eCRF and in the subject's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report). Within 24 hours of receipt of new follow-up information, the Investigator must update the SAE report and submit any supporting documentation to the sponsor or designee.

9.6.7 Post-Study Adverse Events

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a subject has discontinued or terminated study participation if the event is deemed to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that participated in this study. The investigator should report these events to Sponsor via the study CRF or eCRF. If the study CRF of eCRF system is no longer available, the investigator should report the event directly to Sponsor via phone or email.

10. STATISTICAL AND ANALYSIS PLAN

10.1 General Statistical Approach

Analyses will be conducted on databases which are locked or frozen for data extract.

Unless otherwise indicated, data from all investigative sites will be combined in the statistical analysis. Data will be summarized for each of the performance outcomes assessed. Continuous endpoints will be summarized using the number of observations, mean, median, minimum and maximum values. Categorical endpoints will be summarized using the number of observations and percentages. Time-to-event assessments will be summarized using Kaplan-Meier and Nelson-Aalen estimation procedures, as appropriate. Statistical tests will be two-sided with a type-1 error rate of 5% or one-sided with a type-1 error rate of 2.5%. All confidence intervals will be presented at a 95% confidence level.

Baseline demographics, clinical characteristics, and relevant medical history will be summarized for each treatment group.

All outcome analyses will be based on the time from randomization to the first occurrence of the outcome. For each time-to-event endpoint, a Kaplan-Meier plot with the number of subjects at risk at specific time points for each treatment group will be presented.

The significance level for all statistical tests is 5%. The inferential statistics and tests of hypotheses comparing the two treatment arms will be presented in more details in a separate formal statistical analysis plan (SAP) document.

The primary analysis for the Phase III portion is planned to be conducted 24 months after the last subject has been randomized. Adverse events will be coded using the most recent MedDRA version available at the time of analysis. Concomitant medications will be coded using the most recent version of the World Health Organization (WHO) Drug.

10.2 Study Design and Randomization

This study consists of 2 parts:

Phase II (safety and preliminary activity assessment of rivogenlecleucel treatment); and

Phase III (randomized safety and efficacy assessment). The Phase III is a 1:1 ratio randomization to two arms to evaluate the efficacy of αβ T cell and CD19+ B cell depleted, related haploidentical hematopoietic stem cell transplantation (haplo-HSCT) plus rivogenlecleucel (Arm A) vs. haplo-HSCT followed by post-transplant cyclophosphamide (PTCy) (Arm B) in subjects with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Randomization will be stratified as detailed in Section 5.5.2. Each eligible subject will be randomized to one of the treatment arms by the Randomization and Trial Supply Management (RTSM) system and will be assigned a unique subject identification number.

10.3 Sample Size Determination

Total Subject Enrollment: Phase II Sample + Phase III Sample = 10 + 168 = 178 subjects.

The phase III sample size of subjects for the study is based on the primary endpoint of overall survival (OS) from the time of randomization.

10.3.1 Phase II

The sample size for Phase II (10 subjects) was not based on formal statistical power calculations but rather estimation considerations. It is assumed from clinical experience that 10 subjects enrolled would be sufficient to provide clinical precision to detect minimum Grade 3-4 acute GVHD of at least 30% associated with the selected rivogenlecleucel dose to allow adjustment of the dosing of rivogenlecleucel if necessary for the subsequent Phase III of the study.

Confidence Level	Sample Size (N)	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0.950	10	0.423	0.150	0.035	0.459	0.527
0.950	20	0.308	0.150	0.052	0.360	0.401
0.950	30	0.253	0.150	0.063	0.316	0.337

10.3.2 Phase III

A total sample size of 168 (split equally between the two groups), or 110 deaths, achieves 90% power to detect a hazard rate of 0.537 when the proportions surviving in the rivogenlecleucel treatment group is 0.458 and in the Comparator group is 0.234 at 42 months (or 0.80 and 0.66 at 12 months, respectively), at a significance level (alpha) of 0.025 using a one-sided log-rank test.

These results assume that two sequential looks are made using the O'Brien-Fleming spending function to determine the test boundaries and that the survival times are exponential with respect to OS (Chow et al. 2003, Lan and DeMets 1983, O'Brien and Fleming 1979). The nominal significance level at Look 1 is 0.001525 (upper boundary = 2.9626) and at Look 2 (final) is 0.024501 (upper boundary = 1.9686).

A potential sample size adjustment is planned to occur at approximately 50% (55 deaths) of the statistical information, with respect to OS (Look 1). At this occasion, the conditional power (the probability of rejecting a false null hypothesis at the end of the study given the data that have emerged so far) will be calculated, from which an increase in sample size might be made (Pocock 1977; Reboussin 1992; Jennison and Turnbull 2000; Proschan 2006). These calculations will be made by the iDMC at the interim review. The only information that will be conveyed is what the increase in sample size will be or if the sample size will remain the same. There will be no attempt of conducting any hypotheses testing at the time of this interim analysis.

10.4. Populations for Analyses

10.4.1 Phase II

For purposes of analysis, the following populations are defined for the Phase II portion of the study:

- **Safety Evaluable Population (SEP)** – The safety evaluable population will include all subjects enrolled into Phase II who receive rivogenlecleucel.
- **DLT-Evaluable Population** – The DLT-evaluable population will include all subjects enrolled into Phase II who receive rivogenlecleucel and complete the DLT observation window.

10.4.2 Phase III

For purposes of analysis, the following populations are defined for the study:

- **Intent-to-treat Population (ITT)** – The ITT population will include all subjects randomized to receive either treatment. The primary and secondary efficacy outcomes analyses will be based on the ITT population for the study.
- **Safety Evaluable Population (SEP)** – The safety evaluable population will include all subjects who were randomized and who underwent hematopoietic stem cell transplantation. Comparative safety analyses may also be conducted restricting to subjects who were randomized and went on to successfully receive rivogenlecleucel.

- **Rimiducid-evaluable Population (RP)** – The rimiducid population will include all subjects who received rimiducid while on study.

Additional analysis populations may be defined on the availability of data, e.g., samples used for pharmacokinetic or biomarker testing. These populations will be specified in the statistical analysis plan.

10.5 Statistical Analyses

A separate, formal statistical analysis plan (SAP) will be developed and finalized before database lock and will provide details on planned statistical analyses including any inferential statistics and hypothesis testing. Sensitivity analyses intended to characterize the robustness of the safety and efficacy results will also be specified in the SAP. This section provides only a summary of the endpoints and the general planned statistical analyses.

10.5.1 Phase II Analysis

10.5.1.1 Maximum Allowable Dose Determination

The maximum allowable dose is defined as the highest dose of rivogenlecleucel that did not cause dose-limiting toxicities (as specified in Section 4.2.1) in three or more subjects. The rate of DLT-qualified events at the dose(s) explored in the cohort(s) will be summarized.

The MAD established in Phase II will be the recommended dose in Phase III.

10.5.1.2 Assessment of the Rate of GVHD

The incidence of acute GVHD (Grade II-IV and Grade III-IV) and chronic GVHD will be summarized, including the time of onset for each.

10.5.1.3 Outcome Assessment of Rimiducid Treatment for Patients Receiving Rivogenlecleucel

The incidence of aGVHD and the outcome of treatment with rimiducid (Recovered: Yes/No) will be summarized. A resolution will be defined as complete response or improvement of at least one grade of acute GVHD in subjects receiving 1-3 doses of rimiducid. The results will be reviewed to inform the recommendation to begin the Phase III portion of the study.

10.5.2 Phase III Analysis

10.5.2.1 Primary Efficacy Analysis

The primary endpoint is overall survival (OS), defined as the time from randomization to death due to any cause. Subjects will be followed until the time of death, study discontinuation, whichever occurs first. Subjects still on study at the time of primary analysis will be censored at the date they were last known to be alive. The primary analysis for OS is expected to occur approximately 42 months after the first patient is randomized, or, given 18 months of accrual, approximately 24 months after the last patient is randomized. Patients still on study at the time of primary analysis will be consented to agree to a LTFU study as part of a commitment to assessing long-term safety and efficacy of BPX-501.

The primary analysis will be performed using the Cox proportional hazards model (Cox 1972). The Cox regression model will be used to estimate the hazard ratio and 2-sided 95% confidence interval (CI), with the p-value estimated using the log-rank test statistic. Kaplan-Meier plots with numbers of subjects at risk at specific time points will be presented for each treatment group.

10.5.2.2 Secondary Efficacy Analyses

The following secondary endpoints will be evaluated in the study. A Type I error control plan for testing secondary and exploratory endpoints of interest will be provided in a separate SAP. Unless otherwise stated, the Cox regression model will be used to estimate the hazard ratio and the 2-sided 95% CI. Kaplan-Meier or Nelson-Aalen plots with numbers of subjects at risk at specific time points will be presented for each treatment group, as appropriate.

10.5.2.2.1 Relapse-Free Survival (RFS)

Relapse-free survival is defined as the time from randomization to relapse or death from any cause, whichever occurs first.

10.5.2.2.2 GVHD-Free, Relapse-Free Survival (GRFS)

GRFS is defined as the time from randomization to the occurrence of Grade 3-4 acute GVHD, chronic GVHD requiring systemic treatment, disease relapse, or death due to any cause, whichever occurs first.

For AML, relapse is defined as the recurrence of disease after having achieved a CR, following CIBMTR criteria.

For MDS, relapse is defined as a worsening in response after HSCT compared with the disease status prior to the preparative regimen, following CIBMTR criteria. For example, a subject transplanted in HI who has Progression from HI post-HSCT would have this event considered a relapse.

10.5.2.2.3 Non-Relapse Mortality (NRM)

Non-relapse mortality is defined as time from randomization to death without relapse/recurrence. Only deaths without prior evidence of relapse or recurrence will be considered events, and all other deaths will be censored.

10.5.2.2.4 Time to Resolution of GVHD After Administration of Rimiducid

Resolution of GVHD after administration of rimiducid is defined as the time from administration of the first dose of rimiducid to complete response in subjects receiving 1-3 doses of rimiducid.

10.5.2.3 Other Secondary Endpoints

10.5.2.3.1 Patient Reported Outcome (PRO)

The quality of life will be assessed according to self-assessed Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT), 36-Item Short Form Health Survey (SF-36), and the MD Anderson Symptom Inventory (MDASI). The percent change from baseline will be summarized by each treatment arm.

10.5.3. Safety Analyses (Toxicities)

10.5.3.1. Adverse Events (AEs)

The primary safety for this study is mortality. Adverse events (AE) occurring during the study will be collected and graded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE). The incidence, severity, and relationship to study intervention for each treatment arm by MedDRA System Organ Class (SOC) and the preferred term will be summarized. Adverse events leading to premature discontinuation from the study and serious adverse events grades ≥ grade 3 will be summarized separately by treatment arm.

10.5.3.2 Other Safety Analyses (Toxicities)

Other safety summaries will include: (i) Clinical Safety Laboratory Assessments that will be collected and graded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE); (ii) Physical Examinations assessed at different visit time points; and (iii) Vital Signs. Statistical analysis methods and summaries will be described in greater details in the statistical analysis plan to be finalized before the database lock.

10.5.4 Other Analyses

Any PK and biomarker exploratory analyses considered to be necessary for this study will be described in the statistical analysis plan finalized before database lock.

10.6 Interim Analyses

A total sample size of 168 (split equally between the two groups), or 110 deaths, achieves 90% power to detect a hazard rate of 0.537 when the proportions surviving in the BPX-501 treatment group is 0.458 and in the Comparator group is 0.234 at 42 months (or 0.80 and 0.66 at 12 months, respectively), at a significance level (alpha) of 0.025 using a one-sided log-rank test. This analysis is expected to occur approximately 42 months after the first patient is randomized, or, given 18 months of accrual, approximately 24 months after the last patient is randomized.

These results assume that 2 sequential looks are made using the O'Brien-Fleming spending function to determine the test boundaries and that the survival times are exponential OS (Chow 2003; Lan and DeMets 1983; O'Brien and Fleming 1979). The nominal significance level at Look 1 is 0.001525 (upper boundary = 2.9626) and at Look 2 (final) is 0.024501 (upper boundary = 1.9686).

A potential sample size adjustment is planned to occur at approximately 50% (55 deaths) of the statistical information, concerning OS (Look 1). At this occasion, the conditional power (the probability of rejecting a false null hypothesis at the end of the study given the data that have emerged so far) will be calculated, from which an increase in sample size might be made (Pocock 1977; Reboussin 1992; Jennison and Turnbull 2000; Proschan 2006). These calculations will be made by the iDMC at the interim review. The only information that will be conveyed is what the increase in sample size will be or if the sample size will remain the same. There will be no attempt of making any hypotheses testing of any kind at this occasion.

The Sponsor reserves the right to potentially conduct up to one additional interim analysis over the duration of the trial. The decision to conduct this previously unplanned interim analysis may be based off of accumulating information reflective of strong deviations from study planning assumptions, emerging safety signals or other sources of independent information. In this case, a protocol amendment will be submitted, and the iDMC charter and the Type I error control plan set forth in the SAP will both be updated.

11. DATA QUALITY AND MONITORING REQUIREMENTS

11.1 Case Report Forms

Electronic data capture (EDC) will be used. Therefore, patient data from source documents will be entered directly into the clinical database at the Investigator Sites using electronic Case Report Forms (eCRFs). The PI is responsible for assuring that source documentation is appropriately maintained, and that data entered into the eCRF are complete and accurate, and that entries and updates are performed promptly.

Bellicum personnel (or designees) will review the data entered by investigational staff for completeness and accuracy. If potential discrepancies are discovered, electronic data queries stating the nature of the potential discrepancy and requesting clarification will be sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

At the end of the study, the investigator will receive patient CRFs for his or her site in a readable format on a compact disc that must be kept with the study records.

11.2 Study Monitoring

Qualified individuals designated by Bellicum will monitor all aspects of the study according to the protocol/amendment(s), ICH/GCP and standard operating procedures for compliance with applicable government regulations. In accordance with regulations and guidelines, the PI agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to all of the Investigator's source documentation, including but not limited to original medical records of the study subjects, test and procedure results, Investigator and study staff notes, etc. in order to verify the accuracy of the data recorded in the CRF, and, if requested, agrees to assist the monitors. The PI and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by Bellicum or its designees. The review of the subjects' medical records will be performed in a manner to ensure that confidentiality is adequately maintained.

Members of the Bellicum Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The PI will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies may also conduct an audit of the study. If informed of such an inspection, the PI should notify Bellicum immediately. The PI will ensure that the auditors have access to the clinical supplies, study site facilities, source documentation, and all study files. All

inspections and audits will be carried out considering data protection as well as patient confidentiality to the extent that local, state, and federal laws apply.

11.3 Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in place of original hardcopy records), the electronic record can serve as the source document if the system has been validated under FDA requirements on computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

12. ETHICAL CONSIDERATIONS

12.1 Compliance with Laws and Regulations

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC) (as amended).

12.2 Informed Consent

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or their designee must review and approve any proposed deviations from the Sponsor’s sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before submission to the Institutional Review Board (IRB) or Ethics Committee (EC). The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Forms must be signed and dated by the subject or the subject’s legally authorized representative before his or her participation in the study. The case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Informed Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the subject to

participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes. Subjects must be re-consented to the most current version of the Informed Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Informed Consent Forms, the case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained using the updated/revised Informed Consent Forms for continued participation in the study.

A copy of each signed Informed Consent Form must be provided to the subject or the subject's legally authorized representative. All signed and dated Informed Consent Forms must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Informed Consent Form may also include subject authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for subject authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

12.3 Institutional Review Board or Ethics Committee

It is the responsibility of the Investigator to ensure that the appropriate IRB or IEC has reviewed and approved this protocol prior to initiating the study. The IRB/IEC must also review and approve the investigative site's informed consent form (ICF), other written information provided to the subject, and all subject materials that may be used.

If the protocol, Investigator's Brochure, or ICF are amended during the study, per local regulations the Investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. In addition, IRB/IEC approval of the amended documents must be obtained before implementation and before new subjects are consented to participate in the study using the amended version of the ICF.

12.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. Subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the subject or unless permitted or required by law.

Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Sponsor's monitors/representatives and collaborators, and the IRB for each study site, if appropriate.

12.5 Future Use of Stored Specimens

Samples of blood and/or tissue collected during this study may be stored for future research at Bellicum Pharmaceuticals, Inc. in subjects who provide consent.

13. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

13.1 Investigator Responsibilities

The Investigator is responsible for ensuring that all study site personnel, including sub-investigators and other responsible study staff members, conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP, including the archiving of essential documents.

The Investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50 and 21 CFR, Part 56.

The Investigator, sub-investigators, and key study staff as listed on FDA Form 1572 will comply with 21 CFR, Part 54, providing documentation of any financial conflict of interest. This documentation must be provided prior to the Investigator's (and any sub-investigators') participation in the study. The Investigator and sub-investigator(s) agree to notify the Sponsor of any change in reportable interests during the study and for 1 year following study close-out at the Investigator's site.

If necessary to amend either the protocol or the study ICF, the Investigator will be responsible for ensuring that the IRB/EC reviews and approves the amended documents, and that subjects are informed of applicable changes, and updates in a timely manner

The Investigator will sign and return to the Sponsor the "Protocol Signature Page" of the original protocol and any protocol amendment, provide current medical licenses, curriculum vitae, and FDA Form 1572 "Statement of Investigator." All forms must be updated as applicable throughout the study.

13.2 Study Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the subject data, which includes an audit trail containing a complete record of all changes to data.

13.3 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP of the guideline require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, or data on eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor for transfer of any records to another party or moving them to another location.

13.4 Site Audits and Regulatory Inspections

Representatives of regulatory authorities, the Sponsor, or IRB/IEC may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator will notify the Sponsor immediately. The Investigator will provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13.5 Protocol Deviations

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on subject safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

13.6 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. The Investigator shall promptly update this information if any relevant changes occur during the study or for 1 year following completion of the study.

13.7 Quality Control and Quality Assurance

The Sponsor or its designee will perform quality control and quality assurance checks of all clinical studies that it sponsors. Before the enrollment of any subject in this study, Sponsor personnel will review and provide training as needed to the Investigator, sub-investigators, and study site personnel regarding the following: protocol, IB, CRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. Site visits will be performed by the Sponsor or its designee periodically throughout the study. During these visits, information recorded on the CRFs will be verified against source documents, and requests for clarification or correction may be made. The CRFs will be reviewed for safety information,

completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. Requests for clarification or correction will be sent to Investigators via data queries.

13.8 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsors will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

14. REFERENCES

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Appendix A: Arm A – Schedule of Assessments

Table A-12: Pre-treatment Period

	Study Period		
	Screening	**Conditioning**	
Day	-42 to -1	-10 to -1	
Visit window (Days)			**Notes**
Procedure			
Informed Consent	X		
Eligibility Criteria Assessment	X		
Demography	X		
Medical History	X		
ECOG Performance Status	X	X	Assess within 7 days of conditioning.
Concomitant Medications	X	X	Only concomitant medications of interest may be recorded.
Adverse Events	X	X	Record AEs/SAEs related to protocol-mandated procedures during Pre-treatment.
Height & weight	X		Weight at screening will be used to determine total BPX-501/CD34+ cell dose.
Physical Examination	X	X	Should include a routine neurological exam with evaluation of the cranial nerves, motor and sensory skills, coordination, and balance.
Vital Signs	X	X	Vital signs include blood pressure, heart rate, respiratory rate, and temperature.
ECG	X		May be performed up to 8 weeks before Screening.
Echocardiogram/ MUGA	X		Left Ventricular Ejection Fraction (LVEF) to be determined by MUGA or echocardiogram; may be performed up to 8 weeks before Screening.
Pulmonary Function Test (PFT)	X		Pulmonary function testing should include diffusing capacity of the lungs for carbon monoxide (DLCO) and FEV1; may be performed up to 8 weeks before Screening.
Chest X-Ray	X		
Pregnancy Test	X		Serum or urine β-HCG required for females of child bearing potential only.
HLA typing	X		HLA-A, -B, -C, -DRBI performed at high resolution. Screening for anti-HLA donor-specific antibodies should be included.
Hematology	X	X	WBC with differential, RBC, Hgb, HCT, platelet count (quantitative), and ALC.

	Study Period		
	Screening	Conditioning	
Day	-42 to -1	-10 to -1	
Visit window (Days)			**Notes**
Procedure			
Serum Chemistries	X	X	Glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT, AST, magnesium, phosphate, bicarbonate, lactate dehydrogenase (LDH), uric acid, triglycerides.
Coagulation	X		Prothrombin time /activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, and D-dimer; should be performed prior to any biopsy procedures.
Infectious Diseases Screening	X		Refer to Section 7.2.1, Table 4, for details of tests to be performed.
Quantitative Immunoglobulins	X		
iCasp T Cell Tracking	X		
RCR	X		Must be collected prior to start of conditioning.
Bone Marrow & Disease Evaluation	X		Disease evaluation, including bone marrow aspirate/biopsy, MRD status, and cytogenetics and analysis of peripheral blood must be performed in all subjects; assessments must occur within 30 days from initiation of conditioning.
Patient Reported Outcomes (FACT-BMT, SF-36, MDASI)	X		Required in Phase III only.

ALC = absolute lymphocyte count; CMV = cytomegalovirus; Hct = hematocrit; Hgb = hemoglobin; HSV = herpes simplex virus; RBC = red blood cell; VZV = varicella zoster virus; WBC = white blood cell.

*Hepatitis C viral load testing should be performed in all subjects at increased risk for hepatitis C infection, including those who have received a transfusion with blood not tested for hepatitis C (e.g., before 1992 in developed countries), history of IV or inhaled drug use, tattoos, or unexplained elevation of serum ALT. If subject has positive HCV serologic test, viral load testing should be performed.

Table A-13: Treatment Period (Day 0 up to Day +100)

	Study Period									
	Haplo-HSCT		**BPX-501**							
Day	0	7	14	19	26	33	40	68	100	
Month						1		2	3	
Visit window (Days)			± 4	± 3	± 3	± 3	± 3	± 3	± 3	**Notes**
Procedure										
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	Physical Exams are required as listed in the schedule of assessment. Additional physical examinations should be conducted based on the discretion of the investigator.
Vital Signs	X	X	X	X	X	X	X	X	X	For rivogenlecleucel infusion, vitals should be obtained within 1 hour prior to start of infusion and at 15 (+/- 5), 30 (+/- 5), and 120 (+/- 15) minutes after start of infusion.
Neurotoxicity Monitoring	X	X	X	X	X	X	X	X	X	Clinical neurological exam + MMSE (or modified MMSE)
Hematology	X	X	X	X	X	X	X	X	X	Blood counts with differentials should be performed at least 3 times per week after transplant until ANC > 0.5 x 10^9/L for 3 days after nadir reached. Thereafter, CBC at least 2 times per week until the neutrophil count is > 1.0 x 10^9/L and platelets > 100 x 10^9/L.
Serum Chemistries	X	X	X	X	X	X	X	X	X	Prior to start of conditioning, serum creatinine is used to calculate the creatinine clearance using the Cockcroft-Gault method.
Coagulation	X	X	X	X						Prothrombin time /activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, and D-dimer; Coagulation tests should be performed prior to any biopsy procedures.
Viral Monitoring		Weekly until Day +100								Weekly blood monitoring for EBV, HHV6, adenovirus, and CMV is recommended for at least 6 months after last dose of

	Study Period									
	Haplo-HSCT		**BPX-501**							
Day	0	7	14	19	26	33	40	68	100	
Month						1		2	3	
Visit window (Days)			± 4	± 3	± 3	± 3	± 3	± 3	± 3	**Notes**
Procedure										
										rATG or when ALC > 300 cells/mm^3, whichever is later. Additional viral monitoring may be performed at the discretion of the treating physician.
Haplo-HSCT	X									Patients who receive rivogenlecleucel will receive a TCR αβ/B cell-depleted haplo-HSCT.
Bone Marrow & Disease Evaluation						X			X	Disease assessment including bone marrow evaluation should occur on Day +30 and every 3 months for the first year (e.g., Day +100, Month 6, Month 9, and Month 12), then every six months for the 2nd year, and annually thereafter. Additional evaluations may be performed at the discretion of the investigator.
MRD Evaluation	See Notes									MRD evaluation should be assessed based on institutional standard practice as part of disease evaluation post-HSCT.
Immune Reconstitution					X	X	X	X	X	The basic clinical flow panel includes CD3+ cells, α/β CD3+ cells, γ/δ CD3+ cells, CD4+ cells, CD8+ cells, NK cells, and B cells. After BPX-501 infusion, the flow panel will include CD3+/CD19+ cells, CD3+/CD19+/CD4+ cells, and CD3+/CD19+/CD8+ cells. Any sample remaining after flow cytometry analysis will be processed to PBMCs and frozen for further analysis of T cell phenotype and function.
Chimerism						X			X	Donor/host chimerism analyses shall be performed according to standard institutional practice. The same method shall be used for the same patient. Additional tests may be performed as needed.

	Study Period									
	Haplo-HSCT		**BPX-501**							
Day	0	7	14	19	26	33	40	68	100	
Month						1		2	3	
Visit window (Days)			± 4	± 3	± 3	± 3	± 3	± 3	± 3	**Notes**
Procedure										
Quantitative Immunoglobulins								X	X	
GVHD Assessment		X	X	X	X	X	X	X	X	GVHD assessment will occur at all study visits and should be performed according to standard institutional guidelines. Subjects should receive daily GVHD assessments for 7 days after the initiation of the first rimiducid infusion and then resume the GVHD assessments per the schedule in the protocol.
Patient Reported Outcomes (FACT-BMT, SF-36, MDASI)	X	X	X	X	X	X	X	X	X	Required in Phase III only.
BPX-501 infusion			X							Rivogenlecleucel will be administered on Day 14 (window ±4 days).
iCasp T Cell Tracking			See Notes							Immediately prior to BPX-501 infusion, weekly for 1 month, then biweekly through Day 100. If corticosteroids are administered for treatment of GVHD and/or neurotoxicity, additional samples should be collected. Refer to Appendix D for specific timepoints of sample collection.
RCR									X	
Rimiducid PK/PD samples			See Appendix D							If rimiducid is administered, refer to Appendix D for specific timepoints of sample collection.

Table A-14: Treatment Period (> Day 100 to End of Study)

	Study Period										Relapse	EOS	
Day	120	150	180	270	365								
Month	4	5	6	9	12	15	18	21	24	>24*			
Visit window (Days)	±14	±14	±14	±14	±14	±21	±21	±21	±21	±28		±14	**Notes**
Procedure													
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	Physical Exams are required as listed in the schedule of assessments. Additional physical examinations should be conducted based on the discretion of the investigator.
Vital Signs	X	X	X	X	X	X	X	X	X	X		X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistries	X	X	X	X	X	X	X	X	X	X		X	
Bone Marrow & Disease Evaluation			X	X	X		X		X	X	X		Disease assessment including bone marrow evaluation should occur every 3 months for the first year (e.g., Month 6, Month 9, and Month 12), then every six months for the 2nd year, and annually thereafter. Additional evaluations may be performed at the discretion of the investigator.
MRD Evaluation	See Notes									See Notes	X		MRD evaluation should be assessed based on institutional standard practice as part of disease evaluation post-HSCT.
Immune Reconstitution			X		X		X		X				The basic clinical flow panel includes CD3+ cells, α/β CD3+ cells, γ/δ CD3+ cells, CD4+ cells, CD8+ cells, NK cells, and B cells. After BPX-501 infusion, the flow panel will include CD3+/CD19+ cells, CD3+/CD19+/CD4+ cells, and CD3+/CD19+/CD8+ cells. Any sample remaining after flow cytometry analysis will be processed to PBMCs and frozen for further analysis of T cell phenotype and function.

	Study Period										Relapse	EOS	
Day	120	150	180	270	365								
Month	4	5	6	9	12	15	18	21	24	>24*			
Visit window (Days)	±14	±14	±14	±14	±14	±21	±21	±21	±21	±28		±14	**Notes**
Procedure													
Chimerism					X						X		Donor/host chimerism analyses shall be performed according to standard institutional practice. The same method shall be used for the same patient. Additional tests may be performed as needed.
Quantitative Immunoglobulins			X		X		X						
GVHD Assessment	X	X	X	X	X	X	X	X	X	X	X	X	GVHD assessment will occur at all study visits and should be performed according to standard institutional guidelines. Subjects should receive daily GVHD assessments for 7 days after the initiation of the first rimiducid infusion and then resume the GVHD assessments per the schedule in the protocol.
Patient Reported Outcomes (FACT-BMT, SF-36, MDASI)	X	X	X	X	X	X	X	X	X	X	X	X	Required in Phase III only.
Survival and Subsequent Anticancer Therapy											X	X	
iCasp T Cell Tracking	Monthly through 1 year						X		X				Monthly through 1 year, then at Month 18 and Month 24. If corticosteroids are administered for treatment of GVHD and/or neurotoxicity, additional samples should be collected. Refer to Appendix D for specific timepoints of sample collection.
RCR/VCN			X		X		X		X	X			RCR and VCN are tested on the same sample. VCN is tested every 6 months through year 5 then every year through year 10, if vector is detected. RCR is tested at Screening, month 3, 6, 12, then annually through year 15.

	Study Period										Relapse	EOS	
Day	120	150	180	270	365								
Month	4	5	6	9	12	15	18	21	24	>24*			
Visit window (Days)	±14	±14	±14	±14	±14	±21	±21	±21	±21	±28		±14	**Notes**
Procedure													
Rimiducid PK/PD samples	See Appendix D												If rimiducid is administered, refer to Appendix D: Research Laboratory Tests for Subjects Receiving BPX-501 for specific timepoints of sample collection.

* After Month 24, evaluations should be performed every 6 months, or more frequently, at the discretion of the treating physician.

Appendix B: Arm B – Schedule of Assessments

Table B-15: Pre-treatment Period

	Study Period		
	Screening	**Conditioning**	
Day	-42 to -1	-10 to -1	
Visit window (Days)			**Notes**
Procedure			
Informed Consent	X		
Eligibility Criteria Assessment	X		
Demography	X		
Medical History	X		
ECOG Performance Status	X	X	Assess within 7 days of conditioning.
Concomitant Medications	X	X	
Adverse Events	X	X	Record AEs/SAEs related to protocol-mandated procedures during Pre-treatment.
Height & weight	X		Weight at screening will be used to determine total CD34+ cell dose.
Physical Examination	X	X	Should include a routine neurological exam with evaluation of the cranial nerves, motor and sensory skills, coordination, and balance.
Vital Signs	X	X	Vital signs include blood pressure, heart rate, respiratory rate, and temperature.
ECG	X		May be performed up to 8 weeks before Screening.
Echocardiogram/ MUGA	X		Left Ventricular Ejection Fraction (LVEF) to be determined by MUGA or echocardiogram; may be performed up to 8 weeks before Screening.
Pulmonary Function Test (PFT)	X		Pulmonary function testing should include diffusing capacity of the lungs for carbon monoxide (DLCO) and FEV1; may be performed up to 8 weeks before Screening.
Chest X-Ray	X		
Pregnancy Test	X		Serum or urine β-HCG required for females of child bearing potential only.
HLA typing	X		HLA-A, -B, -C, -DRBI performed at high resolution. Screening for anti-HLA donor-specific antibodies should be included.
Hematology	X	X	WBC with differential, RBC, Hgb, HCT, platelet count (quantitative), and ALC.

	Study Period		
	Screening	**Conditioning**	
Day	-42 to -1	-10 to -1	
Visit window (Days)			**Notes**
Procedure			
Serum Chemistries	X	X	Glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT, AST, magnesium, phosphate, bicarbonate, lactate dehydrogenase (LDH), uric acid, triglycerides.
Coagulation	X		Prothrombin time /activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, and D-dimer; should be performed prior to any biopsy procedures.
Infectious Diseases Screening	X		Refer to Section 7.2.1, Table 4, for details of tests to be performed.
Quantitative Immunoglobulins	X		
Bone Marrow & Disease Evaluation	X		Disease evaluation, including bone marrow aspirate/biopsy, MRD status, and cytogenetics and analysis of peripheral blood must be performed in all subjects; assessments must occur within 30 days from initiation of conditioning.
Patient Reported Outcomes (FACT-BMT, SF-36, MDASI)	X		Required in Phase III only.

ALC = absolute lymphocyte count; CMV = cytomegalovirus; Hct = hematocrit; Hgb = hemoglobin; HSV = herpes simplex virus; RBC = red blood cell; VZV = varicella zoster virus; WBC = white blood cell.

*Hepatitis C viral load testing should be performed in all subjects at increased risk for hepatitis C infection, including those who have received a transfusion with blood not tested for hepatitis C (e.g., before 1992 in developed countries), history of IV or inhaled drug use, tattoos, or unexplained elevation of serum ALT. If subject has positive HCV serologic test, viral load testing should be performed.

Table B-16: Treatment Period (Day 0 up to Day +100)

	Study Period										
	Haplo-HSCT	**PTCy**									
Day	0	3-4	7	14	19	26	33	40	68	100	
Month							1		2	3	
Visit window (Days)		± 1			± 3	± 3	± 3	± 3	± 3	± 3	**Notes**
Procedure											
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	Physical Exams are required as listed in the schedule of assessment. Additional physical examinations should be conducted based on the discretion of the investigator.
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Neurotoxicity Monitoring	X	X	X	X	X	X	X	X	X	X	Clinical neurological exam + MMSE (or modified MMSE).
Hematology	X	X	X	X	X	X	X	X	X	X	Blood counts with differentials should be performed at least 3 times per week after transplant until ANC > 0.5 x 10^9/L for 3 days after nadir reached. Thereafter, CBC at least 2 times per week until the neutrophil count is > 1.0 x 10^9/L and platelets > 100 x 10^9/L.
Serum Chemistries	X	X	X	X	X	X	X	X	X	X	Prior to start of conditioning, serum creatinine is used to calculate the creatinine clearance using the Cockcroft-Gault method.
Coagulation	X	X	X	X	X	X	X	X	X	X	Prothrombin time /activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, and D-dimer; coagulation tests should be performed prior to any biopsy procedures.
Viral Monitoring			Weekly until Day +100								Weekly blood monitoring for EBV, HHV6, adenovirus, and CMV is recommended until ALC > 300 cells/mm^3. Additional viral monitoring may be performed at the discretion of the treating physician.

	Study Period										
	Haplo-HSCT	**PTCy**									
Day	0	3-4	7	14	19	26	33	40	68	100	
Month							1		2	3	
Visit window (Days)		± 1			± 3	± 3	± 3	± 3	± 3	± 3	**Notes**
Procedure											
Haplo-HSCT	X										
Post-transplant Cyclophosphamide		X									Cyclophosphamide will be administered to patients on Days 3 and 4.
Bone Marrow & Disease Evaluation							X			X	Disease assessment including bone marrow evaluation should occur on Day +30 and every 3 months for the first year (e.g., Day +100, Month 6, Month 9, and Month 12), then every six months for the 2nd year, and annually thereafter. Additional evaluations may be performed at the discretion of the investigator.
MRD Evaluation	See Notes										MRD evaluation should be assessed based on institutional standard practice as part of disease evaluation post-HSCT.
Immune Reconstitution						X	X	X	X	X	The basic clinical flow panel includes CD3+ cells, α/β CD3+ cells, γ/δ CD3+ cells, CD4+ cells, CD8+ cells, NK cells, and B cells. Any sample remaining after flow cytometry analysis will be processed to PBMCs and frozen for further analysis of T cell phenotype and function.
Chimerism							X			X	Donor/host chimerism analyses shall be performed according to standard institutional practice. The same method shall be used for the same patient. Additional tests may be performed as needed.
Quantitative Immunoglobulins									X	X	
GVHD Assessment		X	X	X	X	X	X	X	X	X	GVHD assessment will occur at all study visits and should be performed according to standard institutional guidelines.

	Study Period										
	Haplo-HSCT	**PTCy**									
Day	0	3-4	7	14	19	26	33	40	68	100	
Month							1		2	3	
Visit window (Days)		± 1			± 3	± 3	± 3	± 3	± 3	± 3	**Notes**
Procedure											
Patient Reported Outcomes (FACT-BMT, SF-36, MDASI)	X	X	X	X	X	X	X	X	X	X	Required in Phase III only.

Table B-17: Treatment Period (> Day 100 to End of Study)

	Study Period										Relapse	EOS	
Day	120	150	180	270	365								
Month	4	5	6	9	12	15	18	21	24	>24*			
Visit window (Days)	±14	±14	±14	±14	±14	±21	±21	±21	±21	±28		±14	**Notes**
Procedure													
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	Physical Exams are required as listed in the schedule of assessments. Additional physical examinations should be conducted based on the discretion of the investigator.
Vital Signs	X	X	X	X	X	X	X	X	X	X		X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistries	X	X	X	X	X	X	X	X	X	X		X	
Bone Marrow & Disease Evaluation			X	X	X		X		X	X	X		Disease assessment including bone marrow evaluation should occur every 3 months for the first year (e.g., Month 6, Month 9, and Month 12), then every six months for the 2nd year, and annually thereafter. Additional evaluations may be performed at the discretion of the investigator.
MRD Evaluation	See Notes									See Notes	X		MRD evaluation should be assessed based on institutional standard practice as part of disease evaluation post-HSCT.
Immune Reconstitution			X		X		X		X				The basic clinical flow panel includes CD3+ cells, α/β CD3+ cells, γ/δ CD3+ cells, CD4+ cells, CD8+ cells, NK cells, and B cells. Any sample remaining after flow cytometry analysis will be processed to PBMCs and frozen for further analysis of T cell phenotype and function.
Chimerism					X						X		Donor/host chimerism analyses shall be performed according to standard institutional practice. The same

	Study Period										Relapse	EOS	
Day	120	150	180	270	365								
Month	4	5	6	9	12	15	18	21	24	>24*			
Visit window (Days)	±14	±14	±14	±14	±14	±21	±21	±21	±21	±28		±14	**Notes**
Procedure													
													method shall be used for the same patient. Additional tests may be performed as needed.
Quantitative Immunoglobulins			X		X		X						
GVHD Assessment	X	X	X	X	X	X	X	X	X	X	X	X	GVHD assessment will occur at all study visits and should be performed according to standard institutional guidelines.
Patient Reported Outcomes (FACT-BMT, SF-36, MDASI)	X	X	X	X	X	X	X	X	X	X	X	X	Required in Phase III only.
Survival and Subsequent Anticancer Therapy											X	X	

Appendix C: Donor – Schedule of Assessments

Table C-18: Donor Assessments

	Study Period				
	Screening	**Leukapheresis (Arm A Only)**	**Mobilization**	**Apheresis**	
Day	-42 to -1	Prior to -15			
Visit window (Days)					**Notes**
Procedure					
Informed Consent	X				
Eligibility Criteria Assessment	X				
HLA typing	X				HLA-A, -B, -C, -DRBI performed at high resolution.
Demography	X				
Medical History	X				
Pregnancy Test	X				Serum or urine β-HCG required for females of child bearing potential only.
Infectious Diseases Screening	X				Refer to Section 7.2.1, Table 4, for details of tests to be performed.
Vital Signs		X	X		
T cell collection		X			For subjects receiving rivogenlecleucel, donor will undergo two separate apheresis sessions. Non-mobilized leukapheresis for collection of donor T cells should occur by Day -21, but no later than Day -15 to allow enough time for manufacturing. The T cells are shipped to Sponsor's centralized GMP manufacturing facility (see Section 6.1.1).
Mobilization			X		The donor will receive mobilization therapy with G-CSF administration per institutional protocol for mobilization of peripheral blood stem cells. For subjects receiving rivogenlecleucel, donor mobilization should start after successful leukapheresis (T cell collection).
Allograft collection				X	For subjects receiving rivogenlecleucel, donor stem cells will be TCRαβ/CD19+ B cell depleted. Subjects not receiving rivogenlecleucel (Phase III, Arm B) will receive a standard T/B cell replete haploidentical transplant.

* Hepatitis C viral load testing should be performed in all donors at increased risk for hepatitis C infection, including those who have received a transfusion with blood not tested for hepatitis C (e.g., before 1992 in developed countries), history of IV or inhaled drug use, tattoos, or unexplained elevation of serum ALT.

Appendix D: Research Laboratory Tests for Subjects Receiving Rivogenlecleucel

Sample Collection	Timing
HAMA	Screening, Day 100
RCR/VCN	RCR and VCN are tested on the same sample. VCN is tested every 6 months (i.e., Month 6, 12, 18, etc.) through year 5 then every year through year 10, if vector is detected. RCR is tested at Screening, Month 3 (Day 100), 6, 12, then annually through year 15.
Immune reconstitution (clinical flow)	The basic clinical flow panel includes CD3+ cells, α/β CD3+ cells, γ/δ CD3+ cells, CD4+ cells, CD8+ cells, NK cells, and B cells. After BPX-501 infusion, the flow panel will include CD3+/CD19+ cells, CD3+/CD19+/CD4+ cells, and CD3+/CD19+/CD8+ cells. Any sample remaining after flow cytometry analysis will be processed to PBMCs and frozen for further analysis of T cell phenotype and function. Timepoints of collection: Screening, Day 26, 33, 40, 68, 100
iCasp T cell tracking	Peripheral blood and/or tissue should be sent to the Sponsor or designee for research purposes to evaluate for BPX-501 cells (CD3+CD19+) at the following times: • Immediately prior to BPX-501 infusion, weekly for 1 month, biweekly through day 100, monthly through 1 year, then at month 18 & month 24. If corticosteroids are administered for treatment of GVHD and/or neurotoxicity, additional samples should be collected at the following times: • Prior to administration of systemic corticosteroids doses (e.g., methylprednisone), at 4 and 24-hours post-systemic corticosteroid initiation, and at 7, 14, 21, and 28 days post systemic corticosteroid initiation. If cerebrospinal fluid (CSF) can be safely obtained prior to the initiation of high-dose corticosteroids, CSF should be sent to the Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+). Clinical staff are to adhere, as closely as practical, to the indicated sample collection timepoints; however, actual collection date and times are to be recorded, and samples collected outside of the specified times are not considered protocol deviations.
Rimiducid PD	For *each* rimiducid administration blood samples should be collected to characterize the pharmacodynamic response of BPX-501 cells: • Within 4 hours prior to rimiducid dose(s), • 30 minutes after initiation of infusion; and • At 2 (≤ 5 minutes prior to infusion termination), 4, 6, 8, 12, 24 and 48 hours after initiation of infusion. Additionally: • Samples should be collected for analysis at 7, 14, 21, and 28 days after the final dose of rimiducid.

	• If additional doses of rimiducid are given beyond 28 days after the end of rimiducid administration(s) then this time course restarts and sample collections should be made following the schedule above. Clinical staff are to adhere, as closely as practical, to the indicated sample collection timepoints; however, actual collection date and times are to be recorded, and samples collected outside of the specified times are not considered protocol deviations. Except samples collected at 2 hours (≤ 5 minutes prior to rimiducid infusion termination) which must be collected within the specified time frame due to the rapid distribution of rimiducid. NOTE: All samples are to be collected contralateral to the site of rimiducid or corticosteroid administration.
Rimiducid Plasma (PK) samples	Plasma should be sent to the Sponsor designee for research purposes to evaluate rimiducid concentrations for each dose of rimiducid at the following times: • For *each* rimiducid administration plasma samples should be collected within 4 hours prior to rimiducid dose(s), 30 minutes after initiation of infusion; and at 2 (≤ 5 minutes prior to infusion termination), 4, 6, 8, 12, 24 hours after initiation of infusion. Clinical staff are to adhere, as closely as practical, to the indicated sample collection timepoints; however, actual collection date and times are to be recorded, and samples collected outside of the specified times are not considered protocol deviations. Except samples collected at 2 hours (≤ 5 minutes prior to rimiducid infusion termination) which must be collected within the specified time frame due to the rapid distribution of rimiducid. NOTE: All samples are to be collected contralateral to the site of rimiducid or corticosteroid administration.
Rimiducid CSF samples	• If a sample of CSF can be safely obtained after initiation of corticosteroids and/or rimiducid for the treatment of neurotoxicity, CSF should be sent to the Sponsor designee for research use such as evaluation of BXP-501 cells (CD3+CD19+), rimiducid, or other analyses . The actual date and time of CSF sample collections should be recorded.

Appendix E: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale and Conversion from Karnofsky Scale

ECOG Status	ECOG Grade	Karnofsky Grade	Karnosfky Status
Fully active, able to carry on all pre-disease performance without restriction	0	100	Normal, no complaints
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	1	90	Able to carry on normal activities. Minor signs or symptoms of disease
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	1	80	Normal activity with effort
Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	2	70	Care for self. Unable to carry on normal activity or to do active work
Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	2	60	Requires occasional assistance, but able to care for most of his needs
Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	3	50	Requires considerable assistance and frequent medical care
Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	3	40	Disabled. Requires special care and assistance
Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	4	30	Severely disabled. Hospitalization indicated though death not imminent
Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	4	20	Very sick. Hospitalization necessary. Active supportive treatment necessary
Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	4	10	Moribund
Dead	5	0	Dead

Adapted from Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5,649-655.

Appendix F: Acute GVHD Grading Scale

GVHD Target Organ Staging

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

Reference:
Harris AC, et al. BBMT 2016; 22:4

Appendix G: Chronic GVHD Activity Assessment – Clinician

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth

Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
			Total score for all mucosal changes					

Gastrointestinal-Esophageal
- Dysphagia OR Odynophagia

0= no esophageal symptoms
1=Occasional dysphagia or odynophagia with solid food or pills during the past week
2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week
3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week

Gastrointestinal-Upper GI
- Early satiety OR
- Anorexia OR
- Nausea & Vomiting

0= no symptoms
1=mild, occasional symptoms, with little reduction in oral intake during the past week
2=moderate, intermittent symptoms, with some reduction in oral intake during the past week
3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week

Gastrointestinal-Lower GI
- Diarrhea

0= no loose or liquid stools during the past week
1= occasional loose or liquid stools, on some days during the past week
*2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion*
*3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L / ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky or Lansky / Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ 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 of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

Shoulder

❑ Not done

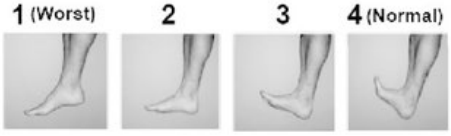
Elbow

❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Appendix H: GVHD Response Criteria

Adapted from:
Lee SJ, et al. Biol Blood Marrow Transplant 2015;21(6):984-999.
Martin PJ, et al. Biol Blood Marrow Transplant 2009;15:777-784.

Complete response (CR) is defined as complete resolution of GVHD manifestation in all organs, without need for secondary GVHD therapy.

Partial response (PR) is defined as improvement in GVHD stage in all initially affected organs, without resolution in all organs, worsening in any other GVHD target organ or need for secondary GVHD therapy.

Progression of GVHD (PD) is defined as worsening GVHD in at least 1 organ with or without improvement in any other organ.

No response (NR) is defined as the same severity of GVHD in any organ or death, or the addition of secondary GVHD and required therapy with increased steroids or additional GVHD therapy were also considered to have no response.

For acute GVHD, **very good partial response (VGPR)** is defined as:

- Skin
  - No rash, or residual erythematous rash involving <25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count)
- Liver
  - Total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment
- Gut
  - Tolerating food or enteral feeding
  - Predominantly formed stools
  - No overt gastrointestinal bleeding or abdominal cramping
  - No more than occasional nausea or vomiting

Appendix I: Chronic GVHD Activity Assessment – Patient Self Report

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Appendix J: Response Determination for Chronic GVHD Based on Clinician Assessment

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.