A Study Evaluating BPX-501 T cells and AP1903 for Prevention of GVHD after HLA-Haploidentical, Related, T Cell-Depleted Hematopoietic Cell Transplantation for Non-Malignant Diseases.

BP-003

Protocol Number	**BP-003**
Combination Product	**Rivogenlecleucel (BPX-501)** – Donor T cells genetically modified with BPZ-1001 retroviral vector containing the iCasp safety switch gene **Rimiducid (AP1903) (Dimerizer drug)**
Investigators and Institution:	**Laurie Burroughs , MD, PI** *Fred Hutchinson Cancer Research Center*
Trial Sponsor:	**Bellicum Pharmaceuticals, Inc.** 3730 Kirby Drive, Suite 1200, Houston, Texas 77098
Version Number and Date:	Version 3.0 22 February 2021
ClinicalTrials.gov number	NCT02231710

Investigator's Agreement

I have read the Investigator's Brochure and the attached protocol and agree to comply with all provisions set forth in protocol number BP-003.

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

I agree to ensure that Financial Disclosure Statements will be completed by:

- myself (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

I agree that these statements will be completed before study initiation, during the study if there are changes, and after the study is completed.

This document contains information confidential to Bellicum Pharmaceuticals, Inc. and it must not be disclosed to anyone other than recipient study staff and members of the Institutional Review Board (IRB). I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Bellicum Pharmaceuticals, Inc.

Signature _____ Date _____

Printed Name _____

Principal Investigator

Protocol Agreement

Protocol Title:
A Study Evaluating BPX-501 T cells and AP1903 for Prevention of GVHD after HLA-Haploidentical, Related, T Cell-Depleted Hematopoietic Cell Transplantation for Non-Malignant Diseases.

Sponsor Approval

I (we) agree to comply with applicable FDA regulations and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

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PROTOCOL SYNOPSIS

A Study Evaluating BPX-501 T cells and AP1903 for Prevention of GVHD after HLA-Haploidentical, Related, T Cell-Depleted Hematopoietic Cell Transplantation for Non-Malignant Diseases. **BP-003**	
Study Design	This is a single arm dose finding study evaluating the safety and efficacy of a BPX 501 infusion (T cells genetically modified with the iCasp9 safety switch) of $3x10^6$ to $1x10^7$ cells/kg recipient body weight followed by an rimiducid (AP1903) infusion on day 7 after a partially mismatched, related, T cell-depleted hematopoietic cell transplantation (HCT) in patients with non-malignant diseases. The purpose of this clinical trial is to determine the dose of BPX 501 T cell infusion with subsequent planned infusion of rimiducid (AP1903) which can facilitate engraftment and prevent the occurrence of GVHD.
Number of Patients	20 Patients
Number of Sites	Up to 10 Clinical Sites
Study Length	Accrual targeted 24 months; main study conduct 2 years post transplantation (and a total of 15 years gene therapy long-term follow-up after last BPX-501 treatment)
Investigational Products	1. **BPX-501** – Single administration of BPX 501 T cells ($3x10^6$ to $1x10^7$ BPX-501 T cells/Kg), given per intravenous infusion. 2. **Rimiducid (AP1903,Dimerizer drug)** of 0.4mg/kg administered per intravenous infusion

Patient Eligibility **Inclusion Criteria**	1. Patient must meet eligibility criteria for allogeneic transplantation 2. Males or females 3. Age < 55 years old and > 4 months 4. Diagnosis of a nonmalignant disorder considered treatable by HCT. **i. Primary Immune Deficiency Disorders** a. Severe Combined Immune Deficiency (SCID) b. Combined Immune Deficiency (CID) c. Congenital T-cell Defect/Deficiency d. Common Variable Immune Deficiency (CVID) e. Chronic Granulomatous Disease f. IPEX (Immune deficiency, polyendocrinopathy, enteropathy, X-linked) or IPEX-like g. Wiskott-Aldrich Syndrome h. CD40 Ligand Deficiency i. Leukocyte Adhesion Deficiency j. DOCK 8 Deficiency k. IL-10 Deficiency/IL-10 Receptor Deficiency l. GATA 2 deficiency m. X-linked lymphoproliferative disease (XLP) n. Cartilage Hair Hypoplasia o. Other primary immune deficiency deemed eligible for HCT by the Non-Malignant Board **ii. Hemophagocytosis Lymphohistiocytosis (HLH) or other hemophagocytic disorders** **iii. Inherited Marrow Failure Disorders** a. Shwachman Diamond Syndrome b. Diamond Blackfan Anemia c. Dyskeratosis Congenita d. Fanconi Anemia e. Congenital Neutropenia

f. Other inherited marrow failure disorder deemed eligible for HCT by the Non-Malignant Board

iv. Hemoglobinopathies

a. Sickle Cell Disease

b. Thalassemia

c. Other hemoglobinopathies deemed eligible for HCT by the Non-Malignant Board

v. Metabolic Disorders

a. Mucopolysaccharidosis

b. Sphingolipidoses

c. Other Metabolic disorder deemed eligible for HCT by the Non-Malignant Board

5. Lack of suitable conventional donor (i.e. 10/10 related or unrelated donor) or the presence of advanced disease not permitting time to identify an unrelated donor
6. HLA typing will be performed at high resolution (allele level) for the HLA-A, -B, Cw, DRBl, and DQB1 loci.
   a. A minimum match of 5/10 is required.
   b. The donor and recipient must be identical, as determined by high resolution typing, in at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and DQB1.
7. If capable of reproduction, patient must agree to use contraception or abstinence to prevent pregnancy during the first year of enrollment and treatment.
8. Informed consent signed by patient (if ≥18 years old) or parent/guardian (if <18 years old).
9. Fanconi anemia patients ONLY

   i. Patients must meet one of the following criteria to be eligible for this study:

   a. Any patient with Fanconi anemia and bone marrow failure involving 2 of the following 3 lineages: granulocyte count $<0.5 \times 10^9$/L, platelet count $<20 \times 10^9$/L, or hemoglobin <8 g/dL.

	b. Any patient with Fanconi anemia who requires red blood cell or platelet transfusions because of marrow failure c. Any patient with Fanconi anemia who has a life-threatening bone marrow failure involving a single hematopoietic lineage.

Patient Eligibility **Exclusion Criteria**	Patients are excluded from enrollment if one or more of the following criteria are present: 1. Serious organ dysfunction, defined as: a. Cardiac: Left ventricular ejection fraction <35% or left ventricular shortening fraction <26%. b. Hepatic: Bilirubin >2.5 mg/dL or any AST, ALT, or alkaline phosphatase >5 times the upper limit of normal (ULN) for age unless discussed and approved by gastroenterology. c. Renal: Serum creatinine > 2x ULN or a measured or calculated as Glomerular Filtration Rate < 40 ml/min/1.73m^2. d. Pulmonary: DLCO (diffusion capacity) <50% predicted. If the patient is too young to perform pulmonary function tests (PFTs), then oxygen saturation <92% on room air. 2. Pregnant or breast-feeding. 3. Evidence of HIV infection or known HIV positive serology, antigen or PCR. 4. Bovine product allergy. 5. Patients with an active infectious disease requiring deferral of conditioning; as recommended by an Infectious Disease specialist. 6. Patients with Fanconi anemia with AML/MDS.
Donor Eligibility **Inclusion Criteria**	Eligible donors include biological parents, siblings, children, or half-siblings, etc. Matching will be determined by class I and class II DNA typing. 1. Males or females 2. Donor age $\geq$ 18 and $\leq$ 60 years. 3. The donor should be sufficiently healthy not to be at increased risk from the mobilization procedure. 4. The donor and patient must be genetically HLA-haploidentical, based on high-resolution typing at HLA-A, -B, -C, -DRB1, and –DQB1. If more than one HLA-haploidentical donor is available and of equivalent health, then preference will be given to the least HLA-incompatible donor. 5. Donors must meet the selection criteria as defined by the Foundation for the Accreditation of Cell Therapy (FACT) and will be screened per the FDA and American Association of Blood Banks (AABB) guidelines.

	6. The donor must have been informed of the investigational nature of BPX 501 and have signed an informed consent form that they will undergo an additional pheresis procedure. 7. Capable of undergoing a minimum of two separate leukapheresis procedures. The donor must have adequate veins for collection or agree to placement of a central venous catheter. If more than one HLA-haploidentical donor is available, preference will be given to a donor who does not require placement of an apheresis catheter.
Donor Eligibility Exclusion Criteria	1. Presence of a mismatch at an HLA-locus for which the patient is homozygous (e.g., patient is homozygous HLA- A01:01, and the donor is heterozygous at the same locus, such as HLA-A01:01, -A02:01. 2. Presence in the patient plasma of antibody to donor HLA, including donor HLA-DP (i.e., patient has a positive anti-donor HLA antibody). 3. Evidence of active infection. 4. Evidence of any infection capable of being transmitted by blood transfusion, including HIV I/II, HTLV I/II, Hepatitis A, Hepatitis B, Hepatitis C, West Nile Virus, or Chagas. Exceptions include EBV, CMV, and history of exposure to hepatitis B vaccine (defined by positive hepatitis B surface (HBs) antibody and negative HBV DNA). 5. Medical or psychological factors which increase the risk for complications from leukapheresis or G-CSF treatment, including but not limited to autoimmune disease, sickle cell trait, coronary artery disease, schizophrenia. 6. Pregnant (positive serum or urine HCG) or breast feeding at the time of G-CSF mobilization.

Objectives	**Primary Objectives** 1. To determine the safety (as defined by non-responsive Grade III-IV GVHD to rimiducid) of HCT with HLA-haploidentical CD34+ selected peripheral blood stem cell (PBSC) grafts and BPX 501 T cells followed by scheduled rimiducid infusion on Day 7. 2. To determine the engraftment rate (defined as >50% donor CD3 chimerism) on day 28 after HCT with HLA-haploidentical CD34+ selected PBSC grafts per dose cohort of BPX 501 T cells followed by rimiducid infusion on Day 7. **Secondary Objectives:** 1. To determine the incidence and severity of acute Grade 2-4 GVHD after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducidinfusion on Day 7. 2. To determine the incidence and severity of chronic GVHD after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7. 3. To measure immune reconstitution after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7 4. To determine the risk for severe infection during the first 180 days after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7 5. Measure disease–specific outcomes 6. Incidence of graft rejection as measured by CD3 chimerism <5% at Day 28 7. Time to resolution of acute GVHD after administration of rimiducid treatment infusion 8. Time to resolution of chronic GVHD after administration of rimiducid treatment infusion 9. Rates of > grade 3 toxicities according to the modified NIH CTCAE criteria version 4.0

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
aGvHD	Acute Graft Versus Host Disease
BMT	Bone Marrow Transplantation
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
cGvHD	Chronic Graft Versus Host Disease
CIHSCTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CRF	Case Report Forms
CRO	Contract Research Organization
CSP	Cyclosporine
CTL	Cytotoxic T Lymphocytes
CTN	Clinical Trials Network
CY	Cyclophosphamide
DLT	Dose Limiting Toxicity
EBV	Epstein Barr Virus
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EKG	Electrocardiogram
FDA	Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
G-CSF	Granulocyte-Colony Stimulating Factor
GvHD	Graft Versus Host Disease
HCT	Hematopoietic Cell Transplantation
HIPAA	(US) Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSCT	Haploidentical Stem Cell Transplant
HSV	Herpes Simplex Virus
HVG	Host versus Graft Disease

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IV	Intravenous
LN2	Liquid Nitrogen
LPDs	Lymphoproliferative Diseases
LTFU	Long Term Follow-up
LVEF	Left Ventricular Ejection
MACS	Magnetically Activated Cell Sorting
MHC	Major Histocompatibility Complex
MTD	Maximum Tolerated Dose
MUGA	Multi-Gated Acquisition Scan
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NK	Natural Killer
NR	No Response
PBMC	Peripheral Blood Mononuclear Cell
PBSC	Peripheral Blood Stem Cell
PD	Progressive Disease
PR	Partial Response
RCR	Replication Competent Retrovirus
SAE	Serious Adverse Event
SDV	Source Data Verification
TBI	Total Body Irradiation
TCR	T-Cell Receptor
TNC	Total Nuclear Cell
TRM	Transplant-Related Mortality

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1 BACKGROUND

1.1 INHERITED HEMATOLOGIC DISORDERS (NON-MALIGNANT DISEASE)

There are 5 major "groups" of non-malignant inherited diseases: 1) Primary immune deficiency disorders, 2) Inherited marrow failure disorders, 3) Metabolic disorders, 4) Hemoglobinopathies, and 5) Hemophagocytic disorders. In general, patients with non-malignant inherited diseases are born with an underlying genetic defect that leads to a deficiency in production of normal cells or cellular proteins. Hematopoietic cell transplantation (HCT) is effective in the treatment of a variety of non-malignant disorders, by restoring normal cells or cellular proteins to the deficient host. For example, HCT corrects the underlying T cell and platelet defect in patients with Wiskott Aldrich syndrome, a primary immune deficiency disorder. Transplantation has been used to provide normal RBCs to patients with hemoglobinopathies such as patients with sickle cell disease. Patients with Hurler's syndrome, also known as mucopolysaccharidosis type I (MPS I), lack or have insufficient levels of the enzyme α-L-iduronidase which is corrected by HCT.

1.2 HAPLOIDENTICAL TRANSPLANTATION FOR NON MALIGNANT DISEASE

As discussed above, allogeneic HCT is a potentially curative therapy for a variety of life-threatening nonmalignant diseases. Around half of patients who could benefit from HCT do not have an HLA-identical sibling or an HLA-matched unrelated donor. This proportion is even higher among patients belonging to racial or ethnic minorities, since unrelated donor registries contain fewer individuals belonging to these minorities. For these patients, it also may be difficult to find umbilical cord blood units of suitable size and HLA-match, and the use of two cord blood units together confers a high risk for graft-vs-host disease (GVHD), an undesirable complication for patients with nonmalignant diseases. In addition, if graft rejection were to occur, it is not possible to go back to the same cord blood donor. Development of an alternative stem cell source for patients lacking an HLA-identical sibling or unrelated donor could expand the availability of this procedure.

One potentially attractive alternative source of stem cells is a HLA-haploidentical relative. There are at least two advantages of HLA-haploidentical relatives as compared to unrelated donors. First, since all biological parents and children and half of siblings share one HLA haplotype, there is a high likelihood of identifying an eligible donor. Second, donors can be identified promptly, whereas the time from initiation of search to identification of an unrelated donor takes a median of 49 days.

The primary barrier to HLA-haploidentical HCT is the occurrence of life-threatening GVHD, which is unavoidable unless the graft is depleted of T cells, either through T cell depletion or $CD34^+$ cell selection. The Perugia group has pioneered the use of the CliniMACS device to T cell deplete G-CSF mobilized HLA-haploidentical allografts, resulting in a 4-5 log CD3+ depletion and a median $CD3^+$ dose of $2x10^4$/kg. Their studies show that transplantation of $CD34^+$ selected HLA-haploidentical peripheral blood stem cell (PBSC) grafts without pharmacological GVHD prophylaxis is associated with an incidence of acute GVHD of less than 10%. Similar results are reported by Handgretinger et al in pediatric patients. Immunophenotyping studies find that NK

cells are the first lymphoid subset to emerge, usually within 2 to 3 weeks after HCT, followed by B cells (3-6 months) and T cells (3-12 months). CD8+ T cells typically reconstitute the T cell compartment first, and most recipients of $CD34^+$ selected HLA-haploidentical PBSC grafts have a deficiency in CD4+ cells, with an inverted CD4+ to CD8+ ratio, for up to 2 years. The delay in reconstitution of CD4+ cells and impairment in TCR diversity likely are the reasons that recipients of T cell depleted HCT are at risk for opportunistic infections for months to years after HCT. Specifically, reactivation of viruses such as CMV and adenovirus, and EBV-associated lymphoproliferative disorders (EBV-LPD), are observed to a greater degree after T cell depleted HCT.

In addition to delayed T cell reconstitution, T-cell depletion is associated with a heightened risk of graft rejection. The Perugia group has overcome this problem by delivery of highly immunoablative conditioning including high-dose total body irradiation (TBI), thiotepa, and fludarabine and high doses of CD34+ cells and immunosuppressive agents [Aversa 2011, 2008]. However, high-dose conditioning is not inconsequential, causing damage to non-hematopoietic organs, particularly the liver and lungs, and high risk for infection. These risks may be unacceptable for patients with non-malignant diseases, since myeloablative conditioning is not required for cure of the disease. In addition, many patients with nonmalignant diseases are not eligible for myeloablative conditioning regimens due to significant underlying infections or other comorbidities.

1.3 REDUCED INTENSITY CONDITIONING FOR HLA-HAPLOIDENTICAL HCT

A central concept that emerged from canine models of nonmyeloablative conditioning was that allogeneic cells induced bidirectional activation and proliferation of host versus graft (HVG) and graft versus host (GVH) alloreactive-T cells. Storb and colleagues showed that intensive post-grafting immune suppression with MMF/CSP controlled both donor and recipient alloreactive T cells [Storb 1997]. This fundamental observation allowed the intensity of the conditioning regimen to be reduced, resulting in development of a nonmyeloablative regimen consisting of fludarabine (FLU; 90 mg/m^2) and 2 Gy TBI followed by HLA-matched related or unrelated grafts [Niederwieser 2003, Maris 2003]. However, post-HCT MMF/CSP was not sufficient to prevent rejection or GVHD after HCT of T-replete HLA-mismatched grafts. The Hopkins group established that intensification of post-HCT immune suppression with CY after nonmyeloablative HLA-haploidentical HCT could overcome graft rejection and prevent severe GVHD, presumably by elimination of activated donor and recipient T cells. A key finding was that activated T-cells were more susceptible to CY compared to resting T-cells, therefore this approach differed from traditional in vivo T cell depletion (e.g., ATG or Campath) and potentially spared non-alloreactive T cells that could reconstitute immunity to viral or tumor antigens. Pilot studies conducted jointly at the FHCRC and Johns Hopkins demonstrated that this approach could establish stable HLA-haploidentical grafts in adult patients with hematologic malignancies, with low TRM and low incidence of GVHD [Kasamon 2010]. However, the rate of relapse was higher than desired . Since relapse is not a factor determining outcome of patients with nonmalignant diseases, researchers at the FHCRC studied this approach in 4 patients to date (FHCRC Protocol 2032). Patients were conditioned with low-dose CY, fludarabine, and 2 Gy TBI, and post grafting immunosuppression

consisted of CY [50 mg/kg, day +3 (n=3) and +4 (n=1)], MMF and tacrolimus beginning on day +4 (n=3) or +5 (n=1). All 4 patients engrafted, 3 survive >5.8, 4.9 and 3.3 years after HCT and the d]Day 100 TRM is 0% to date. However, among the 3 patients given a single dose of post-HCT CY, grade II-IV GVHD and chronic extensive GVHD developed in all, and one died of GVHD-associated infections. The first patient given 2 doses of post-HCT CY developed delayed acute grade III and chronic extensive GVHD (Burroughs, unpublished). Researchers at the FHCRC have studied a similar approach for patients with Fanconi anemia, who have a genetic sensitivity to the alkylating agent CY. In this case, no pre-HCT CY was given and post-HCT CY was limited to 25 mg/kg on days +3 and +4. Of 3 patients treated thus far, engraftment was 100%, however severe acute or chronic GVHD developed in 2 (Thakar and Kiem, personal communication to L. Burroughs).

Together these studies show feasibility of establishing donor chimerism in patients given T-replete HLA-haploidentical marrow grafts using nonmyeloablative conditioning; however the incidence of both acute and chronic GVHD appears to be unacceptably high when post-HCT CY is used as a strategy to eliminate “alloreactive” donor T cells.

1.4 BPX 501: T CELLS MODIFIED WITH THE ICASP SAFETY SWITCH

1.4.1 iCasp9 Safety Switch

Unmodified donor T cell infusion is potentially an effective strategy for conferring anti-viral and anti-tumor immunity following allogeneic HCT. However, the administration of greater than 10^5/kg unmodified donor T cells to recipients of haploidentical HCT has been associated with an increased incidence of GVHD. Brenner et al demonstrated that administration of up to 10^6/kg of CD25+ allodepleted donor T cells after haploidentical HCT 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 fact that the estimated frequency of tumor-reactive precursors is 1 to 2 logs lower than the frequency of virus- reactive precursors. The group then evaluated the use of higher numbers of allodepleted T cells containing an inducible Caspase 9 safety switch in order to treat the potential increase in GVHD. 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 - AP1903. Administration of AP1903 dimerizes and activates caspase 9 downstream, leading to apoptosis potentially within minutes to hours [Tey 2007, DiStasi 2011].

The vector, SFG.iCaspase9.2A.DeltaCD19, consists of inducible caspase 9 (iCasp9) linked, via a 2A-like sequence, to truncated human CD19 (DeltaCD19). The iCasp genetic modification, unlike the HSV-TK based suicide 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 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 donor 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.

1.4.2 Caspallo TRIAL

In a recently published clinical report [DiStasi et al 2011], allodepleted haploidentical T cells co-expressing iCasp9 and a surface-selectable marker gene (Delta CD19) were demonstrated to persist and expand in vivo, and repopulate the patients with virus specific T cells. Two patients infused with 10^6 T cells/kg and a third receiving $3x10^6$ T cells/Kg received a single dose (0.4mg/Kg) of AP1903 upon developing Grade I/II GVHD. In all three patients, there was a greater than 90% reduction in PCR signal and a greater than 90% reduction in CD19+ (i.e. transduced) T cells within 30 minutes of drug administration, and a further log reduction within 24 hours. Moreover, acute GVHD of the skin in all three patients, and of the liver disease in one patient, completely resolved after 24 hr. The residual iCasp9 gene modified T cell population then expanded over the next 4-14 days and continued to help repopulate the patients' immune system. The transduced cells were further shown to contain virus and fungal-peptide specific precursor cells but 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 AP1903. 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. Where cells are non-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 dose exposure, allowing subsequent re-expansion. This hypothesis was supported by the clinical data showing activation-dependent induction of iCasp9 in T lymphocytes and enhanced susceptibility to dimerizer drug in activated versus resting T cells.

1.5 RATIONALE FOR BPX 501 T CELL ADDBACK TO HLA-HAPLOIDENTICAL CD34$^+$ SELECTED PBSC HCT

As discussed previously, current strategies for establishing T-cell depleted HLA-haploidentical grafts rely on high-dose conditioning, which is associated with toxicity and delayed immune reconstitution. The major hurdle to developing a successful reduced-intensity regimen for HLA-haploidentical grafts is overcoming the bidirectional T-cell mediated alloreactions, which form primary and opposing barriers of host versus graft (HVG) and GVHD. HVG reactions are significantly greater in the setting of HLA-mismatching, therefore a counterbalancing, donor T-cell mediated, graft-versus-host (GVH) reaction must be maintained in order to reduce conditioning intensity. Recent studies of T-replete HLA-haploidentical HCT using the nonmyeloablative conditioning regimen of FLU, low dose CY and 2 GY TBI followed by post-HCT CY as a means to deplete T cells post-HCT have shown successful engraftment without significant transplant related toxicities and mortality. In addition, our studies in patients with malignant and nonmalignant diseases have shown: 1) alloreactive donor T cells are required for 3-6 days following HCT in order to establish engraftment after nonmyeloablative conditioning, and 2) purging of alloreactive T cells in vivo reduces the risk for life-threatening GVHD and spares non-alloreactive T cell immunity. However, the incidences of acute and chronic GVHD remain unacceptably high for patients with nonmalignant diseases who do not require a GVL effect.

The recent report by Brenner et al [DiStasi 2011] supports the following concepts:

1) Donor T cells can be expanded ex vivo and transduced with a safety switch, *iCasp9*.
2) Gene-modified alloreactive T cells express inducible caspase 9, rendering them susceptible to the dimerizing agent AP1903.
3) Infusion of *iCasp9* modified T cells does not appear to be associated with severe adverse reactions.
4) Subsequent infusion of AP1903 reverses clinical signs of acute GVHD, suggesting it destroys alloreactive donor T cells.
5) Inactive (i.e, non-alloreactive) donor T cells, are generally sparing from the action of AP1903.

These observations were acquired in a clinical trial using *iCasp9* gene-modified donor T cells as donor lymphocyte infusion (DLI). These findings suggest the opportunity for using *iCasp9* modified T cells to facilitate engraftment of HLA-haploidentical $CD34^+$ selected grafts, with a strategy of pre-emptive "suicide" of alloreactive T cells so as to prevent GVHD, yet allow eventual reconstitution of non-alloreactive T cell immunity.

1.6 RATIONALE FOR PLANNED AP1903 INFUSION ON DAY 7 AFTER HLA-HAPLOIDENTICAL $CD34^+$ SELECTED PBSC HCT WITH BPX 501 T CELL ADDBACK

The purpose of this clinical study is to determine whether the CaspaCIDe infusion can facilitate engraftment and enhance immune reconstitution of HLA-haploidentical $CD34^+$ selected PBSC grafts following nonmyeloablative conditioning with Fludarabine (FLU), Cyclophosphamide (CY), and 2 Gy TBI. The current study design is based on results of our previous studies of post-HCT CY. The backbone conditioning regimen of FLU/CY/TBI is the same as used in studies of post-HCT CY. Essentially, instead of using CY to preemptively deplete alloreactive T cells, we will trigger apoptosis in the alloreactive T cells by infusion of AP1903. As noted above, the iCasp9 gene is preferentially expressed in activated cells compared to resting T cells, therefore apoptosis will be triggered in the alloreactive cells, sparing viral specific T cells.

The dose of BPX 501 (1.0×10^7 CD3+ cells/kg) has been chosen to simulate the "T-replete graft" necessary to assure engraftment and similar to that given in studies of post-HCT CY. Since GVHD is not desired, we propose a strategy of pre-emptive elimination of alloreactive T cells. In this strategy, the safety switch will be activated on day +7 after HCT so as to eliminate activated, presumably alloreactive T cells, but not other T cells important for immune reconstitution. BPX 501 addback will allow us to test whether graft rejection can be overcome in the nonmyeloablative HLA-haploidentical setting through the use of higher T cell doses (genetically modified T cells) with the ability to eliminate GVHD through activation of the safety switch with the dimerizer, AP1903. This study is important since it may improve the safety of HLA-haploidentical HCT through the abrogation of GVHD a major and long-standing complication of allogeneic HCT.

2.0 STUDY DESIGN

This is a single arm study evaluating the safety and efficacy of a BPX 501 infusion (T cells genetically modified with the iCasp9 safety switch) followed by rimiducid infusion on Day 7 after partially mismatched, related, T cell-depleted HCT in patients with non-malignant diseases. The purpose of this clinical trial is to determine whether the BPX 501 T cell infusion can facilitate engraftment and the infusion of rimiducid can prevent the occurrence of GVHD.

2.1 PLANNED ACCRUAL

20 patients

2.2 NUMBER OF CENTERS

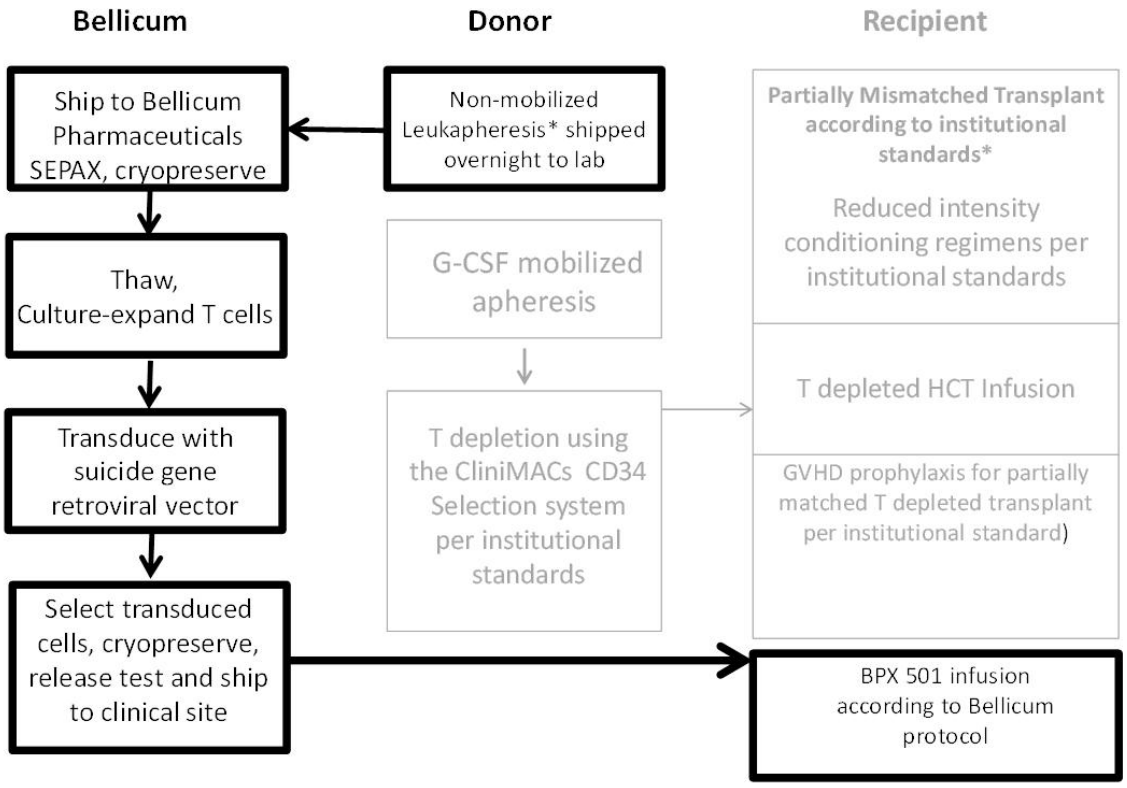
Up to 10 centers

2.3 ESTIMATED STUDY DURATION

Accrual targeted 24 months; main study conduct 2 years post HCT (and a total of 15 years gene therapy long-term follow-up)

2.4 CLINICAL SCHEMA

Figure 1: Clinical Flow Diagram



Partially Mismatched T depleted HSCT per standard institutional protocols in grey
Experimental BPX 501 T cell infusion in bold

2.5 STUDY OBJECTIVES

2.5.1 Primary Objectives

1. To determine the safety (as defined by non-responsive Grade III-IV GVHD to rimiducid) of HCT with HLA-haploidentical CD34+ selected peripheral blood stem cell (PBSC) grafts and BPX 501 T cells followed by scheduled rimiducid infusion on Day 7.
2. To determine the engraftment rate (defined as >50% donor CD3 chimerism) on day 28 after HCT with HLA-haploidentical CD34+ selected PBSC grafts per dose cohort of BPX 501 T cells followed by rimiducid infusion on Day 7.

2.5.2 Secondary Objectives

1. To determine the incidence and severity of acute Grade 2-4 GVHD after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7.
2. To determine the incidence and severity of chronic GVHD after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7.
3. To measure immune reconstitution after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7
4. To determine the risk for severe infection during the first 200 days after HCT with HLA-haploidentical CD34+ selected PBSC grafts and BPX 501 T cells followed by rimiducid infusion on Day 7
5. Measure disease–specific outcomes
6. Incidence of graft rejection as measured by CD3 donor chimerism <5% at Day 28
7. Time to resolution of acute GVHD after administration of rimiducid treatment infusion
8. Time to resolution of chronic GVHD after administration of rimiducid treatment infusion
9. Rates of > grade 3 toxicities according to the modified NIH CTCAE criteria version 4.0

2.6 PATIENT INCLUSION CRITERIA

1. Patient must meet eligibility criteria for allogeneic HCT
2. Lack of suitable conventional donor (10/10 allele matched related or unrelated donor) or presence of rapidly progressive disease not permitting time to identify an unrelated donor
3. Males or females
4. Age < 55 years old and >4 months.
5. Diagnosis of a nonmalignant disorder considered treatable by HCT.

i. Primary Immune Deficiency Disorders

a) Severe Combined Immune Deficiency (SCID)

b) Combined Immune Deficiency (CID)

c) Congenital T-cell Defect/Deficiency

d) Common Variable Immune Deficiency (CVID)

e) Chronic Granulomatous Disease

f) IPEX (Immune deficiency, polyendocrinopathy, enteropathy, X-linked) or IPEX-like

g) Wiskott-Aldrich Syndrome

h) CD40 Ligand Deficiency

i) Leukocyte Adhesion Deficiency

j) DOCK 8 Deficiency

k) IL-10 Deficiency/IL-10 Receptor Deficiency

l) GATA 2 deficiency

m) X-linked lymphoproliferative disease (XLP)

n) Cartilage Hair Hypoplasia

o) Other primary immune deficiency deemed eligible for HCT by the Non-Malignant Board

ii. Hemophagocytic Lymphohistiocytosis (HLH) or other Hemophagocytic disorders

iii. Inherited Marrow Failure Disorders

a) Shwachman Diamond Syndrome

b) Diamond Blackfan Anemia

c) Dyskeratosis Congenita

d) Fanconi Anemia

e) Congenital Neutropenia

f) Other inherited marrow failure disorder deemed eligible for HCT by the Non-Malignant Board

iv. Hemoglobinopathies

a) Sickle Cell Disease
b) Thalassemia
c) Other hemoglobinopathies deemed eligible for HCT by the Non-Malignant Board

v. Metabolic Disorders

a) Mucopolysaccharidosis

b) Sphingolipidoses

c) Other metabolic diseases deemed eligible for HCT by the Non-Malignant Board

6. Lack of suitable conventional donor (i.e. 10/10 related or unrelated donor) or the presence of advanced disease not permitting time to identify an unrelated donor
7. HLA typing will be performed at high resolution (allele level) for the HLA-A, -B, Cw, DRBl, and DQB1 loci.
   i. A minimum match of 5/10 is required.
   ii. The donor and recipient must be identical, as determined by high resolution typing, in at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA- DRB1, and DQB1.
8. If capable of reproduction, patient must agree to use contraception or abstinence to prevent pregnancy during the first year of enrollment and treatment.
9. Informed consent signed by patient (if ≥18 years old) or parent/guardian (if <18 years old).
10. Fanconi anemia patients ONLY

    i) Patients must meet one of the following criteria to be eligible for this study:

    a) Any patient with Fanconi anemia and bone marrow failure involving 2 of the following 3 lineages: granulocyte count <0.5 x 109/L, platelet count <20 x 109/L, or hemoglobin <8 g/dL.

    b) Any patient with Fanconi anemia who requires red blood cell or platelet transfusions because of marrow failure

    c) Any patient with Fanconi anemia who has a life-threatening bone marrow failure involving a single hematopoietic lineage.

2.7 PATIENT EXCLUSION CRITERIA

Patients are excluded from enrollment if one or more of the following criteria are present:

1. Serious organ dysfunction, defined as:
    a) Cardiac: Left ventricular ejection fraction <35% or left ventricular shortening fraction <26%.
    b) Hepatic: Bilirubin >2.5 mg/dL or any AST, ALT, or alkaline phosphatase >5 times the upper limit of normal (ULN) for age unless discussed and approved by gastroenterology.
    c) Renal: Serum creatinine > 2x ULN or a measured or calculated Glomerular Filtration Rate < 40 ml/min/1.73m^2.
    d) Pulmonary: DLCO (diffusion capacity) <50% predicted. If too young to perform pulmonary function tests (PFTs), then oxygen saturation <92% on room air.
2. Pregnant or breast-feeding.
3. Evidence of HIV infection or known HIV positive serology, antigen or PCR.
4. Bovine product allergy.
5. Patients with an active infectious disease requiring deferral of conditioning; as recommended by an Infectious Disease specialist.
6. Patients with Fanconi anemia with AML/MDS.

2.8 DONOR SELECTION

2.8.1 Donor Inclusion Criteria

Eligible donors include biological parents, siblings, children, or half-siblings, etc. Matching will be determined by class I and class II DNA typing.

1. Males or females
2. Donor age $\geq$ 18 and $\leq$ 60 years.
3. The donor should be sufficiently healthy not to be at increased risk from the mobilization procedure.
4. The donor and patient must be at least 5/10 genetically HLA-haploidentical, based on high-resolution typing at HLA-A, -B, -C, -DRB1, and –DQB1. If more than one HLA-haploidentical donor is available and of equivalent health, then preference will be given to the least HLA-incompatible donor.
5. Donors must meet the selection criteria as defined by the Foundation for the Accreditation of Cell Therapy (FACT) and will be screened per the FDA and American Association of Blood Banks (AABB) guidelines.

6. The donor must have been informed of the investigational nature of BPX 501 and have signed an informed consent form that they will undergo an additional pheresis procedure.

7. Capable of undergoing a minimum of two separate leukapheresis procedures. The donor must have adequate veins for collection or agree to placement of a central venous catheter. If more than one HLA-haploidentical donor is available, preference will be given to a donor who does not require placement of an apheresis catheter.

2.8.2 Donor Exclusion Criteria

1. Presence of a mismatch at a HLA-locus for which the patient is homozygous (e.g., patient is homozygous HLA- A01:01, and the donor is heterozygous at the same locus, such as HLA-A01:01, -A02:01.
2. Presence in the patient plasma of antibody to donor HLA, including donor HLA-DP (i.e., patient has a positive anti-donor HLA antibody).
3. Evidence of active infection.
4. Evidence of any infection capable of being transmitted by blood transfusion, including HIV I/II, HTLV I/II, Hepatitis A, Hepatitis B, Hepatitis C, West Nile Virus, or Chagas. Exceptions include EBV, CMV, and history of exposure to hepatitis B vaccine (defined by positive HBs antibody and negative HBV DNA).
5. Medical or psychological factors which increase the risk for complications from leukapheresis or G-CSF treatment, including but not limited to autoimmune disease, coronary artery disease, schizophrenia.
6. Pregnancy (positive serum or urine HCG) or breast feeding at the time of G-CSF mobilization.

3 CLINICAL TRIAL SCHEDULE

3.1 INFORMED CONSENT OF PATIENT AND DONOR

Patients will be referred for consideration of an HLA-haploidentical PBSC HCT. Both patient and donor will be completely evaluated. The protocol will be discussed thoroughly with patient, donor and family, and all known risks to the patient and donor will be described. The procedure and alternative forms of therapy will be presented as objectively as possible and the risks and hazards of the procedure explained to the patient or, in the case of minors, to the patient's responsible family members. Consent will be obtained using forms approved by the institution’s Institutional Review Board.

3.2 GENERATION OF BPX 501 ICASP9 T CELLS

3.2.1 Leukapheresis of Donor

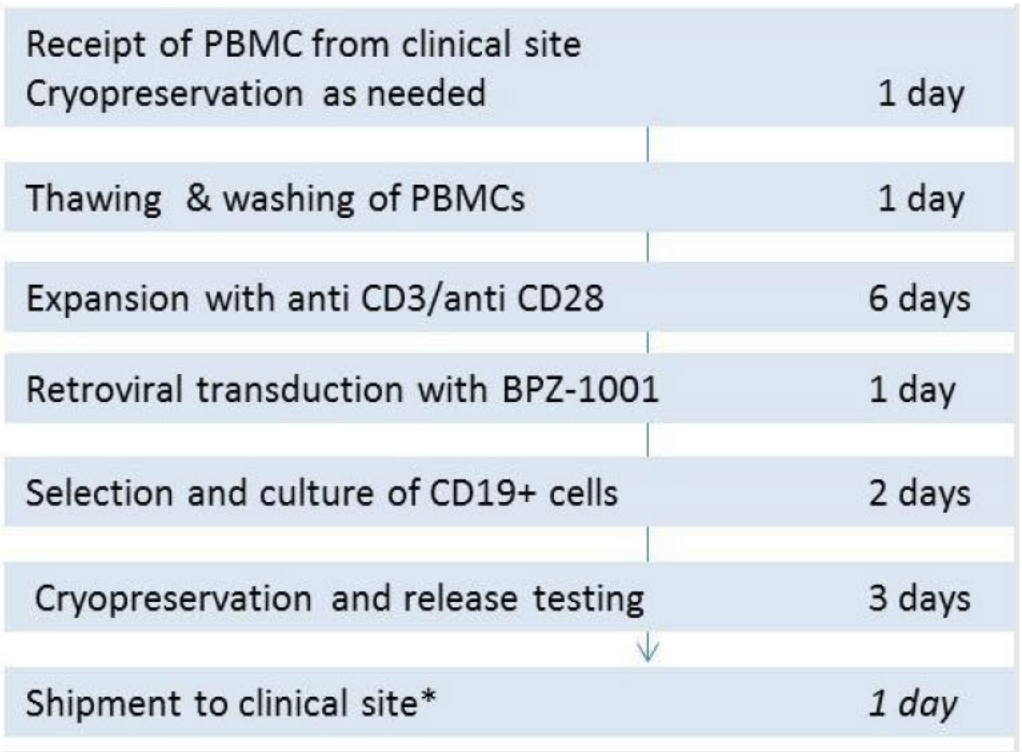
A standard stem cell leukapheresis is performed on the donor prior to starting G-CSF mobilization for stem cell collection. The leukapheresis collection will either be shipped overnight in E48 validated refrigerated shippers with refrigerated gel packs or mononuclear cells will be isolated from the PBMC collection per institutional SOPs and cryopreserved in DNase and a standardized formulation (BioLife Solutions CryoStor CS10) in 3-4 aliquots, depending on yield. Aliquots will be

shipped to Bellicum Pharmaceutical laboratories for processing and gene modification as outlined in the procedures manual. If <1 X 10^9 MNC are collected, then the apheresis results **must be discussed with the Medical Monitor** and a second apheresis may be required. Inadequate number of T cells for manufacturing of the BPX-501 product will result in discontinuation of the patient. A blood sample for donor blood borne pathogen testing will also be obtained and shipped for analysis if indicated.

3.2.2 BPX 501 Manufacture

3.2.2.1 Processing Schema

Figure 2: BPX 501 Process



3.2.2.2 BPX 501 Manufacturing process

The starting material for BPX-501 production is a donor derived PBMC collection from which the mononuclear cells have been previously selected and cryopreserved in DNase; and a standardized formulation (BioLife Solutions CryoStor CS10). The leukapheresis product is shipped to Bellicum's centralized GMP manufacturing facility. Alternatively, the PBMC collection may be ficolled, cryopreserved and shipped to Bellicum via dry shipper (CryoPort).

After verification of the acceptability of the starting material, the leukapheresis is placed on the SEPAX device for mononuclear separation, and subsequent cryopreservation. At the initiation of

manufacturing, an aliquot is transferred to the manufacturing cleanroom and rapidly thawed. The cells are washed and treated with CD3+/CD28+ antibodies and placed into culture media so that the T-cells will proliferate until achieving a target cell number for transduction. The expanded T cells are transduced with BPZ-1001 retroviral construct. Post-transduction, the cells are selected for CD19+ surface marker and the enriched T cell population is allowed to proliferate further in order to reach the target dose of CD3+/CD19+ cells. The cells are formulated with the cryopreservation media (CryoStor CS10) and cryopreserved. The final BPX-501 product is stored cryopreserved in the LN2 vapor phase until release testing is complete. The BPX-501 product and potentially any remaining PBMC aliquots will be shipped in the LN2 vapor phase in validated cryoshippers (Cryoport).

3.3 HAPLOIDENTICAL RELATED T DEPLETED HCT PER INSTITUTIONAL STANDARDS

3.3.1 Mobilization of Donor

Following screening, and leukapheresis, the donor will receive mobilization therapy with subcutaneous G-CSF 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 collections.

3.3.2 Stem Cell Apheresis

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 and a second collection may follow on the sixth day. 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.

3.3.3 T Cell Depletion using the Miltenyi CD34+ CliniMACs

CD34+ cell selection will be performed according to procedures given in the CliniMacs Users Operating Manual and institutional Standard Operating Procedures (SOPs) in place at the study sites. The total nucleated count, CD34+ count and the CD3+ T cell count will be assessed pre and post selection and recorded.

If there are less than 10 million CD34+ cells/kg recipient weight after the processing of 2 aphereses, then the investigator should immediately contact the Medical Monitor.

The selected CD34+ cells will be stored per institutional procedures prior to infusion.

3.3.4 Conditioning Prior to HCT

A reduced intensity conditioning regimen will be used. Patients will be assigned to one of the following regimens based on disease and rejection risk.

A. Regimen A: Patients with primary immune deficiency disorders and inherited marrow failure disorders (except Fanconi Anemia): Fludarabine, Cyclophosphamide, and 200cGy total body irradiation.

a) Fludarabine (FLU): Fludarabine will be administered intravenously at a dose of 30 mg/m^2/day IV over 60 minutes for five consecutive days (day -6, -5, -4, -3, and -2) for a total dose of 150 mg/m^2.
b) Cyclophosphamide (CY): CY will be given at a dose of 25 mg/kg IV daily on days -6 and -5 for a total dose of 50 mg/kg. Mesna will be given per institutional standard practice.
c) Total Body Irradiation (TBI): TBI will be given on day -1 at a dose of 200 cGy, delivered according to institutional standard operating procedures.

B. Regimen B: Patients with Sickle Cell Disease and Inherited Metabolic Disorders: Due to higher risk of graft rejection in patients with sickle cell disease and inherited metabolic disorders a slightly more intense regimen will be used. Specifically, patients will receive Fludarabine, Cyclophosphamide, and 4 Gy TBI.

a. Fludarabine (FLU): Fludarabine will be administered intravenously at a dose of 30 mg/m^2/day IV over 60 minutes for five consecutive days (day -6, -5, -4, -3, and -2) for a total dose of 150 mg/m^2.
b. Cyclophosphamide (CY): CY will be given at a dose of 25 mg/kg IV daily on days -6 and -5 for a total dose of 50 mg/kg. Mesna will be given per institutional standard practice.
c. Total Body Irradiation (TBI): TBI will be given on day -1 at a dose of 400 cGy (200 cGy twice daily), delivered according to institutional standard operating procedures.

C. Regimen for Fanconi Anemia: Due to an inherent increased risk of transplant related toxicity and mortality a slightly less intense regimen will be used for patients with Fanconi anemia. Specifically, patients will receive fludarabine and 2 Gy TBI (NO cyclophosphamide pre HCT),

a. Fludarabine (FLU): Fludarabine will be administered intravenously at a dose of 30 mg/m^2/day IV over 60 minutes for five consecutive days (day -6, -5, -4, -3, and -2) for a total dose of 150 mg/m^2.
b. Total Body Irradiation (TBI): TBI will be given on day -1 at a dose of 200 cGy, delivered according to institutional standard operating procedures.

The chemotherapeutic agents and TBI administration practices in the conditioning regimens will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above.

Bladder prophylaxis, supportive care, including fluids and anti-emetics on the day of TBI will be administered according to institutional protocols.

PLAN OF TREATMENT/CONDITIONING REGIMENS A, B and C:

	Regimen A: Patients with primary immune deficiency disorders and inherited marrow failure disorders (except Fanconi Anemia): Fludarabine, Cyclophosphamide, and 200cGy total body irradiation.
Day	**Drug(s)**
-6	Fludarabine 30 mg/m^2/day IV Cyclophosphamide 25 mg/kg IV
-5	Fludarabine 30 mg/m^2/day IV Cyclophosphamide 25 mg/kg IV
-4	Fludarabine 30 mg/m^2/day IV
-3	Fludarabine 30 mg/m^2/day IV Start Cyclosporine
-2	Fludarabine 30 mg/m^2/day IV
-1	TBI 200 cGy X1
0	PBSC infusion
+1	BPX 501 Infusion 6 hours after end of infusion start MMF

	Regimen B: Patients with Sickle Cell Disease and Inherited Metabolic Disorders: Due to higher risk of graft rejection in patients with sickle cell disease and inherited metabolic disorders a slightly more intense regimen will be used. Specifically, patients will receive Fludarabine, Cyclophosphamide, and 4 Gy TBI.
Day	**Drug(s)**
-6	Fludarabine 30 mg/m^2/day IV Cyclophosphamide 25 mg/kg IV
-5	Fludarabine 30 mg/m^2/day IV Cyclophosphamide 25 mg/kg IV
-4	Fludarabine 30 mg/m^2/day IV
-3	Fludarabine 30 mg/m^2/day IV Start Cyclosporine
-2	Fludarabine 30 mg/m^2/day IV
-1	TBI 200 cGy X 2
0	PBSC infusion
+1	BPX 501 Infusion 6 hours after end of infusion start MMF

	Regimen C for Fanconi Anemia: Due to an inherent increased risk of transplant related toxicity and mortality a slightly less intense regimen will be used for patients with Fanconi anemia. Specifically, patients will receive fludarabine and 2 Gy TBI (NO cyclophosphamide pre HCT)
Day	**Drug(s)**
-6	Fludarabine 30 mg/m^2/day IV
-5	Fludarabine 30 mg/m^2/day IV
-4	Fludarabine 30 mg/m^2/day IV
-3	Fludarabine 30 mg/m^2/day IV Start Cyclosporine
-2	Fludarabine 30 mg/m^2/day IV
-1	TBI 200 cGy X 1
0	PBSC infusion
+1	BPX 501 Infusion 6 hours after end of infusion start MMF

3.3.5 Infusion of the HLA-Haploidentical CD34+ Selected PBSC graft

Infusion of the HLA-haploidentical CD34+ selected PBSC graft will be performed per institutional protocol on Day 0 of the study. Vital signs blood pressure, heart rate, and respiratory will be monitored per institutional standard practice with a recording at least 30 minutes before and 1 hour after starting infusion.

Maximum dose of CD34+ stem cells/kg is $30X10^6$/kg. **If dose of CD34+ stem cells is less than $10X10^6$/kg recipient body weight call the Bellicum medical monitor**. The medical monitor in consultation with the Principle Investigator will determine whether to infuse part or all of the CD34-negative fraction along with the CD34+-selected PBSC graft.

3.3.6 BPX-501 Infusion

BPX-501 infusion of $3X10^6$ to $1X10^7$ cells/kg recipient body weight as per the dosing schedule in approximately 15ml will be thawed and infused as outlined in the Procedures Manual.

The BPX-501 infusion should be administered within 24 hours after the infusion of the HLA-haploidentical CD34+ selected PBSC graft is complete. **Any delay after 24 hours should be discussed with and approved by the Bellicum medical monitor.** The BPX-501 infusion will be thawed in a 37 °C water bath, diluted with 50ml Plasmalyte, as instructed in the Study Procedures Manual and administered over 30 minutes. The patient will be pretreated with Benadryl and

Tylenol (or equivalent drugs per pharmacy standards) per institutional standards for cryopreserved cells. Vital signs blood pressure, heart rate, and respiratory within 1 hour prior to starting infusion and at 15, 30, 120 and 240 minutes post-infusion.

Delayed infusion of BPX-501 cells: Patients who receive a CD3+ T cell dose >2 x 10^5/kg should not be given the BPX-501 cells within the first 24 hours after infusion of the CD34+ selected PBSC graft. The BPX-501 cells may be reserved for infusion between days +7 to +10, provided post-transplant cyclophosphamide is given for GVHD prophylaxis on days +3 and +4 (refer to section 3.4.3). Delayed infusion of BPX-501 cells must be approved by the medical monitor. Patients who receive delayed infusion of BPX-501 cells should not receive scheduled rimiducid infusion on day +7.

3.4 POST-HCT GVHD PROPHYLAXIS / IMMUNESUPPRESSION

Post-HCT immune suppression will consist of Cyclosporine and Mycophenolate Mofetil

3.4.1. Cyclosporine (CSP):

Cyclosporine is given IV starting day -3 and administered, monitored and adjusted per institutional standards. The initial dose for patient's ≥6 years old will be 2.0 mg/kg/dose every 12 hours. The initial dose for patients <6 years old will be 2.0 mg/kg every 8 hours. Patients ≥ 12 years old may start CSP orally at 5.0 mg/kg orally every 12 hours. IV CSP may be transitioned to oral CSP after day +7 if clinically tolerated. CSP should be maintained until day +180. The CSP taper will commence on day 180, providing there is no ongoing GVHD. The taper should be at a rate of roughly 5% per week. CSP will be dosed based on actual or adjusted body weight per institutional standard practice.

CSP Dose adjustments:

a. CSP, whole blood "trough" levels (i.e., just prior to the next dose) will be evaluated on day 0 and twice weekly post-transplant until the initiation of the taper and adjusted if necessary to maintain blood levels that target the upper end of the therapeutic range during the first 28 days (See Table below).

b. Further CSP determinations should be performed on a weekly or twice-weekly basis until CSP taper is initiated unless high levels are detected (see below table), or toxicity is suspected in which case more frequent monitoring will be performed as clinically indicated.

c. After day 28, targeted therapeutic levels of CSP will drop to standard range (see table below) until day 180. CSP levels are not required upon initiation of taper unless clinically indicated.

d. Dose reductions should only be made if CSP toxicity is present or levels exceed the upper limits of target by 20%, depending on the method (see below table). Dose reductions for high levels without toxicity should be conservative, e.g. 25%, to avoid inadequate immunosuppression.

e. If there is nausea and vomiting at any time during CSP treatment the drug should be given intraveneously at the dose that was used to obtain a therapeutic level. ORAL to IV conversion: Oral CSP dose divided by 2.5 = IV dose.

	CSP Level to Target Using LC-MS/MS Method	**CSP Level to Target Using Immunoassay Method**
Day "0" – Day +28 **Whole blood "trough" (just prior to next dose)**	400 ng/ml	500 ng/ml (upper end therapeutic range for this method)
After Day +28	120-360 ng/ml	150 - 450 ng/ml
Levels exceeding upper limits of target by >20% • **With or without CSP toxicity** • **Decrease in GFR ≥50%** • **Increase in creatinine 2x baseline due to CSP**	25% dose reduction	25% dose reduction

f. Drugs that may affect CSP levels are:

Decrease CSP levels	**Increase CSP levels**	
Phenytoin	Erythromycin	Caspofungin
Phenobarbital	Ketoconazole	Azithromycin
Carbamazepine	Azetazolamide	Diltiazem
Primidone	Fluconazole*	Clarithromycin
Rifampicin	Colchicine	Verapamil
Nafcillin	Itraconazole*	Doxycycline
Octreotide	Fluoroquinolones	Nicardipine
Sulfonamides	Voriconazole	Nifedipine
Trimethoprim	Imipenem	Alcohol
Metoclopramide		
*Discontinuation of fluconazole or itraconazole may lower CSP levels, and if used for antifungal prophylaxis, then changes in these drugs should be avoided during the first 2 months posttransplant.		

3.4.2 Mycophenolate mofetil (MMF):

MMF will be given at a dose of 15 mg/kg every 8 hours IV or oral (45 mg/kg/day) starting 6 hours after the gene modified T cell (BPX 501) infusion is complete. MMF will continue at a dose of 15 mg/kg every 8 hours until day 35. After day 35, MMF will be given at a dose of 15 mg/kg every 12 hours provided there is no evidence of GVHD or poor donor engraftment (see below for definition). MMF will continue at a dose of 15 mg/kg every 12 hours through day 90 followed by a taper of approximately 10% per week if there is no evidence of GVHD. Patients can be transitioned from IV to oral once they are able to take oral medications. MMF will be dosed based on actual or adjusted body weight per institutional standard practice.

Guidelines for mycophenolate mofetil dose adjustment and monitoring:

a. **Maintaining MMF:** Markedly low (<40%) donor T cell chimerism after HCT may indicate impending graft rejection. MMF should be continued at full dose or, if the MMF taper has been initiated, reinstitution of full dose MMF should occur. If MMF has been discontinued, MMF should be reinitiated at full dose.

Guidelines for MMF dose adjustment due to drug toxicity:

a. If in the clinical judgment of the attending physician the observed toxicity is related to MMF administration, a dose adjustment may occur. The discontinuation of MMF at any point should be discussed with the Study PI and should be documented in the permanent medical record and all Case Report Forms (CRF).

b. **Gastrointestinal toxicity.** Severe gastrointestinal toxicities such as gastrointestinal hemorrhage have been very rare after nonmyeloablative HCT. In the event of gastrointestinal toxicity that requires medical intervention including medication for control of persistent vomiting or diarrhea that is considered to be due to MMF after day 28, a 20% dose reduction will be made or the drug may be given IV. If severe refractory diarrhea or overt gastrointestinal bleeding occurs, MMF may be temporarily stopped. The MMF should be restarted at 20% reduced dose when the underlying toxicity subsides.

c. **Neutropenia.** Based on previous experience in patients after nonmyeloablative HCT, dose adjustments are likely to occur because of hematopoietic adverse effects, in particular neutropenia. A thorough evaluation of neutropenia should occur including peripheral blood chimerism studies, marrow aspiration and review of marrow suppressive medications. If all other potential causes of marrow toxicity are ruled out, dose adjustments will only be made for severe, prolonged neutropenia (ANC <500 for 5 days or more) that persists after day +21 post-transplant. Dose reductions should be conservative (20%). After day +21, the use of G-CSF will be permitted for severe neutropenia. For severe hematologic toxicity related to MMF (neutropenia > 5 days refractory to G-CSF), MMF may

be temporarily stopped. The MMF should be restarted at 20% reduced dose when the underlying toxicity subsides."

3.4.3 GVHD prophylaxis contingency plan for patients who receive a CD3 T cell dose >2 x 105/kg

Patients who receive a CD3 T cell dose >2 x 10^5/kg will be at higher risk for developing GVHD from the unmodified donor T cells. Therefore, these patients should receive post-transplant cyclophosphamide for GVHD prophylaxis.

At notification of a CD3 T cell dose >2 x 10^5/kg, the following changes to the treatment plan should be made:

- No BPX-501 cells within 24 hours of the PBSC graft. (Refer to section 3.3.6 for information about potential delayed infusion of BPX-501 cells.)
- Cyclosporine should be discontinued,
- MMF should either not be started or be discontinued.
- Rimiducid should not be given on day +7.
- Contingency GVHD prophylaxis should be given as outlined below

Contingency GVHD prophylaxis for patients who receive CD3 dose >2 x 10^5/kg

Day + 3 and +4: Cyclophosphamide 50 mg/kg should be given through the central line on days +3 and +4 (total cyclophosphamide dose of 100 mg/kg). Dose calculation and administration of cyclophosphamide will be according to institutional standard practice. Bladder prophylaxis with Mesna should be given per institutional standard practice.

Day +5: Cyclosporine should be resumed on day +5, as described in section 3.4.1. Refer to section 3.4.1 for guidelines for cyclosporine dose adjustment, taper, and monitoring.

Day +5: MMF 15 mg/kg every 8 hours should be started on day +5, as described in section 3.4.2. Refer to section 3.4.2 for guidelines for MMF dose adjustment, taper, and monitoring.

3.5 SUPPORTIVE CARE

Patients should receive supportive care (growth factors, anti-emetics, menstrual suppression, prophylactic/empiric antibiotics, transfusions of blood products, hyperalimentation, etc.) as indicated per institutional standards for allogeneic HCT.

3.6 SCHEDULED RIMIDUCID (AP1903) INFUSION

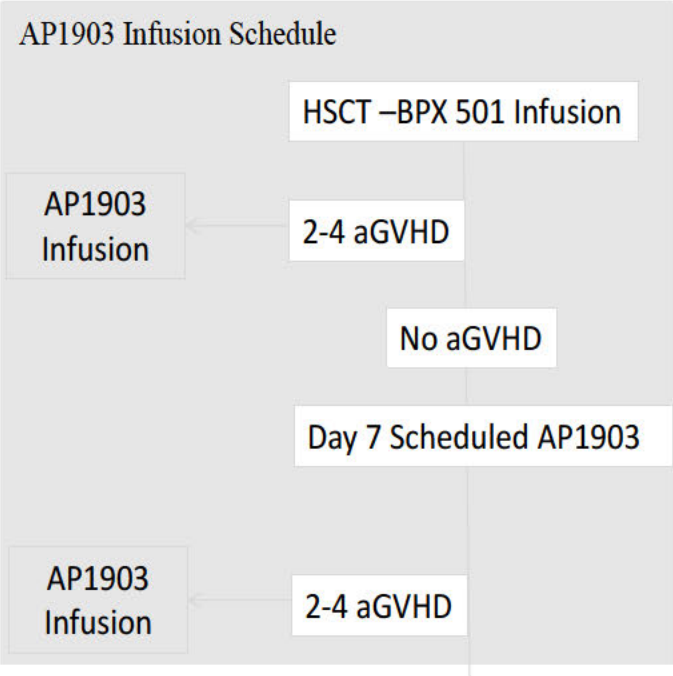
Scheduled rimiducid will be infused 7 days (+/- 1 day) following BPX501 infusion. The rimiducid infusion is given intravenously over 2-4 hours at a dose of 0.4 mg/kg. Pre-medications, including Tylenol and Benadryl dosed per SPM, will be given to prevent potential infusional reactions. Vital signs will be monitored and research blood samples will be taken according to Table 1 to analyze the effects of the dimerizer drug on circulating gene modified T cells.

Table 1 – For Each Rimiducid Dose: Vital Sign Monitoring and Research Blood Samples

Rimiducid Monitoring	
Vital Signs	• Recorded within 1 hour prior to start of rimiducid Infusion and at 15, 30, 60, 120 and 240 minutes after the start of the infusion

Rimiducid Research Blood Draws (at least 30 cc in adults and 2cc/kg in pediatric patients up to 15 kg as feasible based on patient weight)	
iCasp Blood Draw	• Within 4 hours prior to the initiation of rimiducid infusion • 3-4 hours after the initiation of infusion of each does of rimiducid • 24 hours (±2 hours) after the initiation of infusion of each dose of rimiducid

3.7 GVHD TREATMENT



3.7.1 Rimiducid (AP1903) Treatment of acute GVHD

Rimiducid (AP1903) for treatment of GVHD may be infused at any time based on the diagnosis of GVHD. If patients develop acute GVHD before or after the scheduled rimiducid infusion, they should be evaluated by the clinician at the first signs and symptoms of acute GVHD (see Acute GVHD grading scales Appendix C) for grading, possible biopsy and potential initiation of treatment with rimiducid.
Any patient developing acute GVHD Grade 2-4 prior to the Day 7 scheduled rimiducid infusion should be treated according to standard institutional protocols, including topical steroids and/or systemic steroid treatment and receive an rimiducid infusion at a dose of 0.4 mg/kg IV over 2-4 hours. Premedication, including Tylenol and Benadryl (or their equivalents based on standard institutional pharmacy guidelines) should be given prior to the start of the rimiducid infusion. The Day 7 scheduled infusion will then proceed at the investigator's discretion based on the patient's clinical status.

For Grades 2, 3, and 4, corticosteroids (0.5-2 mg/kg/day) should be administered. Consideration by the investigator for other medications per institutional guidelines (eg, calcineurin inhibitors, sirolimus, mycophenolate). If no response to steroids and/or other aGVHD medications after 48 hours, patients may then receive rimiducid (children: 0.4 mg/kg to a maximum of 40 mg IV; adults: 40 mg IV). Acetaminophen and diphenhydramine, or other standard institutional pretreatment/prophylaxis, are required prior to the infusion of rimiducid. 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.

3.7.2 Rimiducid (AP1903) Treatment of chronic GVHD

Initial treatment with topical or IV steroids, or other systemic treatments (eg, calcineurin inhibitors), per institutional standard of care for mild cGVHD should be instituted. Guidelines for topical corticosteroid treatment for mild disease include the following. Face, axillae, and groin: lower potency steroids (hydrocortisone 1-2.5%, desonide 0.05%) and from the neck down: mid-strength steroids (e.g., triamcinolone 0.1% cream or ointment).

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). If no response to steroids/systemic therapies occurs within 7 days, or there is a worsening in cGVHD, patients may then receive rimiducid:

Children: 0.4 mg/kg to a maximum of 40 mg IV

Adults: 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 clinical benefit with prior episodes.

3.7.3 Other investigational agents

Other investigational agents may not be administered from the time of HCT through day 180 except for the treatment of non-responsive GVHD or infections not responding to standard treatment. Additional investigational agents will need Medical Monitor approval.

3.7.4 Gene therapy monitoring plan

Long-term follow-up beyond 24 months will follow FDA and EMA guidelines (Table 2). Before HSCT, and for up to 5-years post stem cell transplant, patients will be evaluated with a physical exam and blood testing for vector copy number (VCN) and replication competent retrovirus (RCR). After 5 years, blood samples will be drawn annually until 15 years after the last BPX-501 administration). Bellicum will inform the site if sample collection can stop for any patient (criteria for this include all post-treatment PCR assays negative for RCR during the first year, and vector no longer present in 2 consecutive results).

Table 2 Gene Therapy Monitoring Schedule

Time point of collection	Evaluation	Blood
Pre-infusion	√	√
3 months	√	√
6 months	√	√
1 year	√	√
18, 24, 30, 36, 42, 48, 54, 60 months	√	√*
Annually from 6 years to 15 years after the last BPX-501 administration.	√	√*

** Bellicum will inform the site if sample collection can stop for any patient (criteria for this include all post-treatment PCR assays negative for RCR during the first year, and vector no longer present in 2 consecutive results).*

4. PRODUCT PACKAGING, LABELING, STORAGE AND SHIPPING

4.1 BPX-501 PRODUCT PACKAGING, LABELING AND STORAGE

Packaging and Formulation

BPX-501 T cells are cryopreserved in 10-15mL freezing medium (Cryostor CS10, BioLife) and are stored frozen in cryostorage bags in the vapor phase of liquid nitrogen.

Labeling

The product label (directly applied to the primary container) includes the patient specific lot number, cryopreservation date, T cell dose, storage conditions, sponsor, and product name. All products manufactured under the IND are also labeled with: "Caution: New Drug-Limited by Federal Law to Investigational Use" per 21 CFR 312.6.

Shipping and Storage

Cryopreserved BPX-501 will be shipped in liquid nitrogen vapor phase to clinical sites in a validated shipping container. The receiving cell processing laboratory will store the product in vapor phase of LN2 until time of infusion. At that time, the product will be thawed at 37°C ± 2°C per Bellicum instructions for infusion to the recipient.

4.2 RIMIDUCID (AP1903) DIMERIZER DRUG PACKAGING, LABELING AND STORAGE

Packaging and Formulation

The rimiducid for Injection is packaged in 10 mL Type 1 clear glass serum vials. [redacted] Each vial is stoppered with a Teflon© coated serum stopper and a yellow flip-off seal.

Labeling

The primary product label (applied directly to the vial) will contain all information for regional use, following the requirements of each competent authority and applicable national and international regulations as described in the pharmacy manual.

Storage

The Rimiducid for Injection vials must be stored at 2-8°C (41°F ± 5°F) in a limited access, qualified and monitored refrigerator, preferably without light.

Preparation for Treatment

For use, the rimiducid will be diluted prior to administration. The rimiducid is administered via IV infusion at the target dose diluted in normal saline with volume as appropriate for weight of patient to be administered over 2 hours, using a DEHP-free saline bag and solution set.

5 STUDY TREATMENT

The study treatment will only continue after the patient (and/or guardian) and the donor have signed the informed consent.

The Schedule of Assessments is outlined in Appendix A.

5.1 INFORMED CONSENT

All potential patients (or guardian) are required to personally sign and date an IRB approved Informed Consent Form before beginning any study screening.

5.2 VISIT WINDOWS

Visit windows for Weekly visits are ± 3 days. Visit windows for Monthly visits are ± 7 days.

5.3 SCREENING

Screening refers to the period prior to conditioning. Assessments other than donor identification should be made within 6 weeks as clinically indicated prior to day of conditioning.

Assessment	Description
1. History and Physical exam	• Vital Signs: Blood pressure, pulse rate, respiratory rate and temperature, oxygen saturation on room air • Height & Weight • Concurrent diseases and therapies, • Date of initial diagnosis • Transfusion history • Females post puberty: pregnancy history, date of last sexual intercourse
2. Karnofsky/Lansky Scale	• See Appendix I
3. CBC w/differential, platelet count	• Complete blood count (CBC) • Differential • Reticulocyte if clinically indicated • Quantitative platelets.
4. Serum chemistries	• Electrolytes (Na, K, Chloride, Bicarbonate, Calcium, Magnesium, Phosphorus • Glucose • BUN • Creatinine • ALT, AST, Alkaline phosphatase, total bilirubin, direct bilirubin, LDH • Albumin.
5. Quantitative Immunoglobulins	IgG, IgA, and IgM

6. Fasting cholesterol and triglycerides	*As clinically indicated*
7. Infectious Disease screening	See Table 3
8. EKG/LVEF or LVSF	
9. Corrected DLCO, FEV1 and FEV2 or 0_2 saturation	
10. Renal Ultrasound	*If clinically indicated* It is recommended that all patients with Dyskeratosis Congenita and Shwachman Diamond Syndrome have a renal ultrasound pre HCT.
11. Bone marrow biopsy/aspirate	*If clinically indicated*
12. CT scan of the chest abdomen and pelvis	*If clinically indicated*
13. Chest x-ray	*If clinically indicated*
14. Serum Pregnancy (females who have gone through puberty only)	
15. ABO/Rh typing, direct coombs	
16. HLA typing	
17. As a pre-transplant reference for subsequent determination of donor chimerism 10 cc of heparinized peripheral blood from the patient (and the donor) will be drawn*.	
18. Disease staging	Appendix B
19. iCasp baseline sample	Any time after consent through Day 0
20. Concomitant Medications	Or on day 0
21. Baseline Sample for RCR	Any time after consent through Day 0
22. Baseline Sample for HAMA	Any time after consent through Day 0

Pre Transplant Viral Testing	All 2615 Patients	Patients with Antibody Deficiencies or on IVIG	If Clinically Indicated
Hepatitis Screen	X		
CMV Serology	X		
VZV Serology	X		
HSV Serology	X		
Toxoplasma Serology	X		
Anti HIV Serology	X		
Hepatitis B PCR		X	
Hepatitis C PCR		X	
HIV PCR		X	
CMV PCR	X*		
EBV PCR	X*		X*
Adenovirus PCR	X*		X*
VZV PCR			X
HSV PCR			X
Toxoplasma PCR			X
23. Immune Reconstitution Research studies:	Any time after consent through Day 0		
24. Neurological Exam	• Standard neurological exam and MMSE/mMMSE		

Table 3: Screening Table for Infectious Disease.

*Approximately 1 month prior to conditioning

5.4 ENROLLMENT

Patients may be enrolled following screening if all eligibility criteria are met.

5.5 DONOR CONSENT AND STEM CELL COLLECTION

Assessment	Description
1. Donor Consent	• Donor Informed Consent

	• Donor Inclusion/Exclusion.
2. Leukapheresis – non mobilized peripheral blood	• Leukapheresis product shipped to Bellicum
3. Mobilization	• Donor treatment with subcutaneous G-CSF
4. Stem Cell Apheresis	• Graft analysis CD34+ and T cell counts.

5.6 PATIENT CONDITIONING

Assessment	Description
1. Conditioning Regimen	Determine A, B or C.

5.7 DAY 0 – T DEPLETED HCT AND BPX-501 INFUSION

Assessment	Description
1. Vital signs blood pressure, heart rate, and respiratory rate, per institutional standard - pre, during, and after infusion of CD34+ stem cells	• Blood pressure • Pulse rate • Respiratory rate • Temperature
2. Vital signs blood pressure, heart rate, and respiratory rate within 1 hour prior to starting infusion and at 15, 30, 120 and 240 minutes after starting infusion of BPX-501	• Blood pressure • Pulse rate • Respiratory rate • Temperature
3. CBC w/differential, platelets prior to stem cell infusion	• Complete blood count (CBC)
4. Adverse Events	
5. Concomitant Medications and Transfusions	

5.8 DAYS 0 – DAY 28

5.8.1 Day 0 to Day 28

Assessment	Description
1. Modified H&P/vital signs	Days 7, 14, 21, 28
2. GvHD assessment Grading Scales (Appendix C & D)	Daily until Day 28 prior to discharge then 2x/week
3. CBC w/differential	Daily until ANC > 500 for 3 days, then 2X per week
4. Quantitative platelet count	Daily until Platelet count is >20,000 (non-transfused) then 2X per week
5. EBV,CMV, and Adeno PCR	*Weekly through day 100*
6. Serum chemistries *Days 14 and 28 only*	• Electrolytes • Calcium • Magnesium • Phosphorus • Glucose • Albumin • ALT and AST • Bilirubin (total and direct) • Alkaline phosphatase • LDHBUN • Creatinine
7. iCasp9 Research Sample	Day 28 only
8.Chimerism CD33, CD3, CD19 and CD56	Day 28 only
9. Adverse Events	Daily until discharge and then 2x/week
10. Concomitant Medications and Transfusions	Daily until discharge and then 2x/week

11. Neurological Exam	• Standard neurological exam and MMSE/mMMSE

5.8.2 Day 7

Rimiducid (AP1903) Infusion

Assessment	Description
1. Vital signs blood pressure, heart rate, and respiratory rate. See Table 1 For Each Rimiducid Dose: Vital Sign Monitoring and Research Blood Samples.	• Blood pressure • Pulse rate • Respiratory rate • Temperature
2. iCasp9 Research Sample	See Table 1

5.9 WEEKS 5 TO 12

Assessment	Description
1. Modified history / Physical exam / GvHD assessment, weights	Grading Scales (Appendix C & D)
2. CBC w/differential	Complete blood count (CBC)
3. platelet count	quantitative platelets
4. EBV,CMV, and Adeno PCR	*Weekly through day 100*
5. Serum chemistries *weeks 8 and 12 only*	• Electrolytes • Calcium • Magnesium • Phosphorus • Glucose • albumin • ALT and AST • Bilirubin (total and direct) • Alkaline phosphatase • LDH • BUN

	• Creatinine
6. iCasp9 Research Sample	Weeks, 8, and 12
7. RCR sample	Week 12 only
8. immunophenotyping (CD3, CD4, CD8, B cell, NK cell)	Week 12 only
9.Chimerism: CD33, CD3, CD19 and CD56	Weeks 8, 12
10. Quantitative Immunoglobulins	IgG, IgA, and IgM (week 12 only)
11. Adverse Events	weekly
12. Concomitant Medications and Transfusions	weekly
13.Neurological Exam	• Standard neurological exam and MMSE/mMMSE

5.10 MONTHS 6, 9, 12, 18 AND 24

Assessment	Description
1. Modified History & Physical exam / GvHD assessment, weights	Grading Scales (Appendix C & D)
2. CBC w/differential	Complete blood count (CBC)
3. platelet count	Differential quantitative platelets
4. Serum chemistries *(months 6, 12, 24)*	• Electrolytes • Calcium • Magnesium • Phosphorus • Glucose

	• ALT and AST • Bilirubin • Alkaline phosphatase • LDH • Glucose • BUN • Albumin • Creatinine
5. iCasp9 Research Sample	*Months 6, 12, 24*
6. Disease staging	Month 12; Appendix B
7. immunophenotyping (CD3, CD4, CD8, B cell, NK cell)	*Months 6, 12, 24*
8. RCR (6 12, 18 and 24 months only)	
9. Chimerism CD33, CD3, CD19 and CD56	Months 6, 12, 24
10. Quantitative Immunoglobulins	IgG, IgA, and IgM (months 12, 24 only)
11. Adverse Events	Safety Reporting Criteria (Appendix F) All AEs for 30 days starting after BPX-501 infusion or rimiducid infusion(s).GVHD will be reported as Adverse Events (or SAEs) and followed until resolution. • All SAEs regardless of attribution for 180 days post BPX-501 infusion. • After 180 days only SAEs relating to study treatment
12. Concomitant Medications and Transfusions	
13.Neurological Exam	• Standard neurological exam and MMSE/mMMSE

5.11 MONTHS 30, 36, 42, 48, 54, AND 60

Assessment	Description
1. Modified History and Physical exam	
2.Adverse Events	All AEs for 30 days starting after BPX-501 infusion or rimiducid infusion(s).GVHD will be reported as Adverse Events (or SAEs) and followed until resolution. • All SAEs regardless of attribution for 180 days post BPX-501 infusion. • After 180 days only SAEs relating to study treatment
3. Blood Sample for Vector and RCR	
4 Neurological Exam	• Standard neurological exam and MMSE/mMMSE

5.12 YEARS 6 THROUGH 15

Assessment	Description
1. Blood Sample for Vector and RCR	
2.Adverse Events	All AEs for 30 days starting after BPX-501 infusion or rimiducid infusion(s).GVHD will be reported as Adverse Events (or SAEs) and followed until resolution. • All SAEs regardless of attribution for 180 days post BPX-501 infusion. • After 180 days only SAEs relating to study treatment

5.13 MONITORING FOR DISEASE SPECIFIC OUTCOMES

Baseline testing will occur pre-transplant and follow up testing will occur at 12 weeks post-transplant and yearly as per appendix B.

5.14 ADDITIONAL MONITORING FOR RIMIDUCID (AP1903)

In patients who develop GVHD and receive rimiducid, blood samples will be obtained to monitor the effects of rimiducid on transgene persistence Vital signs and research blood draws are required. See Table 1 For Each rimiducid Dose: Vital Sign Monitoring and Research Blood Samples.

5.15 DISCONTINUATION CRITERIA

Patients and/or parent(s) or legal guardian(s) are free to discontinue participation or withdraw consent from the study at any time, for any reason, and without prejudice to further treatment. They may withdraw consent to future treatment with rimiducid, or from continuing participation in the study and LTFU. Patients discontinuing from the main study visits (for example due to difficulty attending visits) may stay on study, enter LTFU and remain eligible for rimiducid if needed.

Where possible patients who have been treated with BPX-501 will be encouraged to remain on-study and complete appropriate follow-up assessments. Patients treated with any BPX-501 who discontinue, or who are unable to continue to participate in the assessments during the main 24-month study conduct should still participate in LTFU. Where possible patients should complete the 6 month, 12 month and 18 month assessments prior to LTFU.

If an adverse event (AE) is the reason the patient's treatment is being discontinued by the investigator or the reason that a patient chooses to discontinue treatment, then that adverse event must be documented as the reason for treatment discontinuation.

Patients who withdraw from the study will receive treatment as deemed appropriate by their treating physician.

A patient's participation in the study also may be discontinued at any time at the discretion of the investigator. The following may be justifiable reasons for the investigator to remove a patient from the study:

The patient was erroneously included in the study

The patient has developed an exclusion criterion or concurrent disease after having been considered eligible for the trial but before the start of the preparative regimen

The patient receives other investigational product(s) during the study

The patient experiences an adverse event (AE) that is considered intolerable by the patient or the investigator

Data of patients withdrawn from the study will be collected, stored and, whenever indicated, analyzed. These patients will be monitored in terms of outcome with regard to survival and, in case of malignancies, risk of recurrence.

If a patient is withdrawn 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. Data of patients withdrawn from the study will be evaluated, as detailed in the fully executed original consent signed by the patient/parent/guardian upon study entry, unless otherwise indicated. Where possible, these patients will be monitored in terms of outcome for survival and risk of recurrence. The patient/parent/guardian will be informed that follow-up testing or end of study procedures may be required to ensure patient safety is properly maintained.

Patients who have disease relapse or progression should continue to be followed on study to assess survival status and participate in long-term gene therapy monitoring, as appropriate.

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

6 TRIAL DESIGN AND STOPPING RULES

6.1 ESCALATION/DE-ESCALATION TRIAL DESIGN

The target enrollment is up to 20 patients. The primary efficacy endpoint is engraftment, defined as >50% donor CD3 chimerism. The primary safety endpoint is resistant severe (grade 3-4) acute GVHD after treatment with rimiducid.

The starting dose of $5x10^6$ BPX-501 cells/kg has been chosen based on an estimated one-half log lower T cell dose than that found in a bone marrow graft. The proposed dose should have engraftment rates of $\geq$ 4/5 patients. Based on the published study (DiStasi) for early GvHD treatment intervention with rimiducid after BPX-501 administration in HLA-haploidentical HCT in the DLI setting, 4/4 patients were successfully treated with rimiducid and the predicted incidence of severe acute GVHD (grade 3-4) is hypothesized to be 1/5 patients.

The overall dose finding design could be viewed as the inverse of a traditional MTD study, namely, higher dose limiting toxicity of non-engraftment is expected with doses which are too low, rather than too high a dose. The trial design is an escalation/de-escalation trial design with planned enrollment of 5 patients /BPX501 dose/Regimen (group) based on the expected engraftment rates ($\geq$ 4/5 engraftment) and based on historical data at the FHCRC (see schema diagram below).

We propose three BPX501 T cell doses to be evaluated in the trial in order to evaluate the safe and potentially efficacious dose in enabling engraftment in the non-myeloablative setting in transplantation of non-malignant diseases:

i. 5×10^6/kg BPX 501 T cells (starting dose)

ii. 1×10^7/kg BPX 501 T cells (escalation)

iii. 3×10^6/kg BPX 501 T cells (de-escalation)

The multiple inherited disease indications are essentially stratified over 3 conditioning regimens (Conditioning Regimen A, B, or C), and each conditioning regimen will be treated as an independent group with respect to dose finding. Patient treatment will be staggered between BPX501 dose cohorts within a group (conditioning regimen), and within a cohort, with a patient not being treated until the prior patient in a given cohort/group has completed 30 days post-

transplant, thereby allowing analysis of engraftment and chimerism (as outlined in the secondary endpoints).

1 Five patients will be treated at the starting dose. If 1of 5 experience non-engraftment then an additional 5 patients will be enrolled at this dose. If no further patients fail to engraft, or an additional 1 patient fails to engraft (total 2 or fewer of 10 patients), then an additional 5 patients will be enrolled at the starting dose.

2 If 2 of the first 5 or 3 of the first10 experience non-engraftment at 5 X 10^6/kg BPX501 T cells then the higher dose level will be triggered, and subsequent patients will receive 1 X 10^7/kg BPX501 T cells.

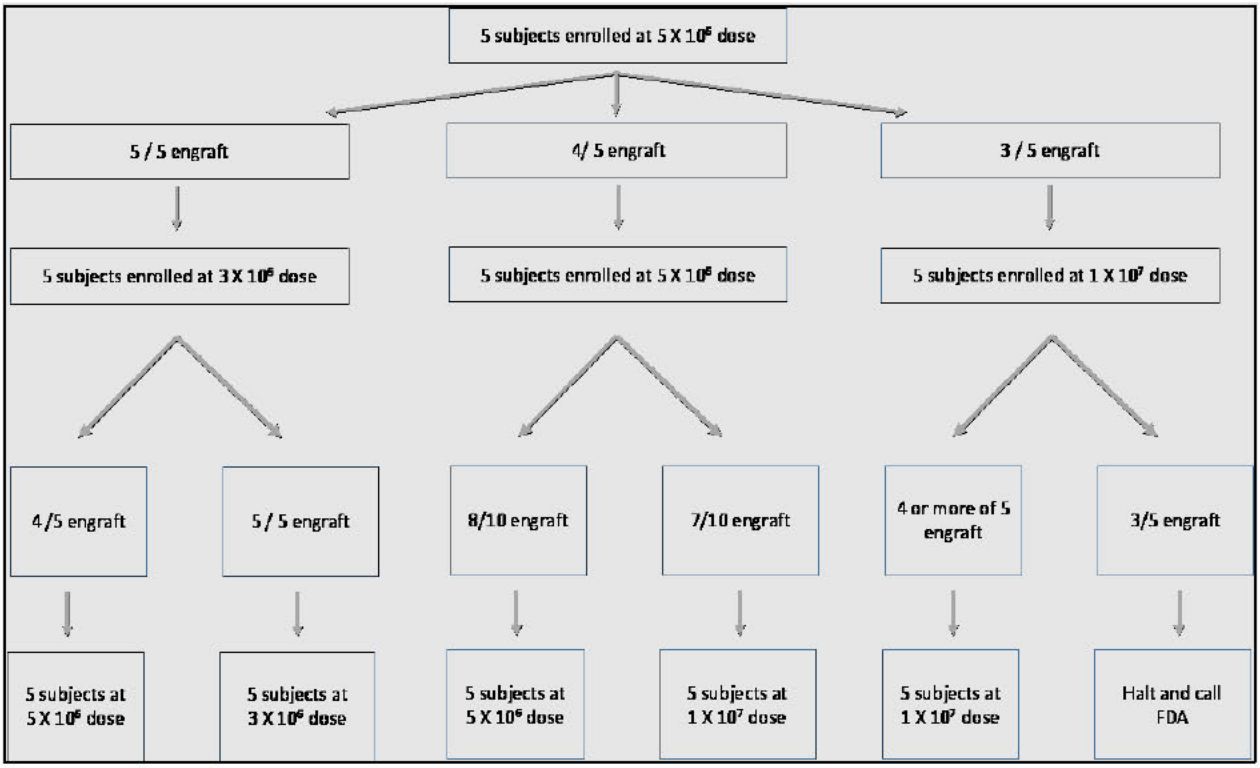
3 If 5 of 5 patients engraft at 5 X 10^6/kg BPX501 T cells, then the following 5 patients will be enrolled at the lower dose of 3 X 10^6/kg BPX501 T cells. If 5 of 5 engraft at 3 X 10^6/kg BPX501 T cells then an additional 5 patients will be enrolled at the 3 X 10^6/kg BPX501 T cell dose. However, if 1 of the additional 5 patients fail to engraft at 3 X 10^6/kg BPX501 T cell dose then the remaining cohort will be enrolled at 5 X 10^6/kg BPX501 T cell dose and will follow the rules #1 and #2 above, not to exceed 15 total treated patients.

4 If 2 of 5 patients do not engraft at 1 X 10^7/kg BPX501 T cell dose, then the study will be halted and plans discussed with the investigators and FDA. If 1 or fewer of 5 patients do not engraft at 1 X 10^7/kg BPX501 T cell dose, then 5 more patients will be enrolled at the dose of 1 X 10^7/kg BPX501 T cells. If 1 of these additional patients does not engraft, then the study will be halted and discussed with the investigators and FDA.

The corresponding data on incidence of GVHD will be analyzed in the context of the engraftment data in order to determine the ideal dose. We expect that 5 patients per dose change would yield at least 10 informative patients for dose finding.

Patients with a residual CD3+ T cell count of >2 X 10^5/kg recipient weight in the CD34+ stem cell infusion will be considered non-evaluable for purposes of dose adjustment and analysis of primary endpoints. Patients who receive delayed infusion of BPX-501 cells will remain on study as an exploratory group and monitored for safety. The stopping rule for death in the first 30 days will remain in effect for this group; the stopping rules for GVHD before day 7 and graft failure cannot be applied.

Dosing Schema



6.2 STOPPING RULES

Stopping rules will be applied separately to the 3 conditioning regimens (Regimen A, B, and C).

Hyper acute GVHD before day 7 in first patient – trial will be halted and discussed with FDA and investigators

Death in first 30 days post-transplant, regardless of specific treatment attribution - trial will be halted and discussed with FDA and investigators

Graft failure in 2 of 5 patients at the highest proposed dose

If 2 patients in any BPX501 dose cohort experience the following dose limiting toxicities, no further patients will be enrolled into that BPX501 dose cohort until discussion with the FDA and

investigators.

- Grade III or IV acute GvHD non-responsive to rimiducid infusions
- Grade 3 or 4 reactions related to infusion;
- Grade 3 or 4 non-hematologic and noninfectious adverse events, occurring within 30 days after infusion

The Sponsor has the right to pause enrollment at any time.

6.3 STATISTICS

Descriptive statistics will be utilized to summarize engraftment rates, GvHD incidence, clinical and biologic response and other measures of safety and toxicity for the whole population as well as analysis stratified by disease and conditioning regimen.

6.3.1 Analysis of Graft Failure

Primary graft failure is defined as failure to achieve an absolute ANC > 500 cells/µL by Day +30. Secondary graft failure is defined as initial neutrophil engraftment followed by subsequent decline in neutrophil counts < 500 cells/µL, unresponsive to growth factor therapy and not explained by marrow suppressive medications or infections.

The cumulative incidence of graft failure estimates will be analyzed by BPX-501 dose, CD34+ cell dose in the allograft, and disease.

6.3.2 Analysis of Acute and Chronic GvHD

The time and severity of aGvHD are graded according to the Modified Keystone Grading Scale (Appendix C). The time and severity of chronic GvHD are graded according to NIH Consensus Criteria (Appendix D).

6.3.2.1 Analysis of Acute GvHD

The initial incidence of aGvHD Grades 2-4 by days 100, 180 and 1 year will be determined and analyzed by conditioning regimen, BPX-501 dose, rimiducid treatment and degree of HLA match.

The response rates of aGvHD Grades 1-4 to standard treatment will be determined, as well as the number of Grades 1-4 demonstrating non-improvement or progression on standard treatment.

The rate of Grades 2-4 aGvHD in patients receiving rimiducidtreatment will be determined at days 100, 180 and 1 year and analyzed by the number of rimiducid infusions and time to resolution of GvHD after last rimiducid infusion.

The initial incidence of severe aGvHD Grades 3-4 by days 100, 180 and 1 year will be determined and analyzed by conditioning regimen, BPX-501 dose, degree of HLA match and age. The response rates of severe aGvHD Grades 3-4 in patients receiving rimiducid treatment will be determined at days 100, 180 and 1 year and analyzed by the number of rimiducid infusions and time to resolution of GvHD after last rimiducid infusion.

6.3.2.2 Analysis of Chronic GvHD

The incidence of chronic GvHD according to the new NIH scoring system at 3 months, 6 months 1 and 2 years will be determined for and analyzed by conditioning regimen, T cell dose, disease status, degree of HLA match and age. The response rates of cGvHD in patients receiving rimiducid treatment will be determined at 3 months, 6 months 1 and 2 years and analyzed by the number of rimiducid infusions and time to resolution of chronic GvHD after last rimiducid infusion.

6.3.3 Transplant-Related Mortality

The cumulative incidence of TRM will be determined at 6 months, one year and 2 years for all patients transplanted and analyzed by BPX-501 dose, and age.

6.3.4 Immune Reconstitution

We will analyze several parameters measuring immune reconstitution resulting from iCasp9-transduced T cells. Descriptive summaries of these parameters in the overall patient group and by dose group as well as by time of measurement will be presented. Growth curves representing measurements over time within a patient will be generated to visualize general patterns of immune reconstitution. The proportion of iCasp9 positive cells will also be summarized at each time point.

6.4 DATA QUALITY ASSURANCE

Sponsor will supply eCRFs for this study. A CRO will be responsible for data management of this trial, including quality checking of the data. In the event of discrepant data, the CRO will send requests for data clarification to the sites for resolution.

Sponsor will perform oversight of the data management of this trial, including approval of the CRO's data management and data quality plans. eCRFs and correction documentation will be indexed and imaged. System backups for data stored at Sponsor and records retention for the study data will be consistent with Sponsor's standard procedures.

The investigator agrees to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports (ICH E6, section 4.9.1) this responsibility may be delegated by the investigator to a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator provided such authorization is documented.

Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained (ICH E6, section 4.9.2).

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes and corrections. Any changes required on paper source documents or paper CRF should be lined through, ~~example,~~ such that the original entry is clear to read and then the change should be initialed and dated by the person making the change. In the

case of electronic records or other data capture, changes should be made in a way that allows the capture of an audit trail with similar intent to the example given for the paper document. The investigator should retain records of the changes and corrections ICH E6, section 4.9.3).

eCRFS are to be completed using the selected EDC system. Sites will receive training and a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

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.

7 ASSESSMENT OF SAFETY

7.1 SAFETY PARAMETERS AND DEFINITIONS

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

Bellicum 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.

7.2 ADVERSE EVENT

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

This includes the following:

1. AEs not previously observed in the patient that emerge during the protocol specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period
2. 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
3. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms and are considered clinically significant

An event which is part of the natural course of the disease under study (i.e., disease progression, death due to disease progression) should still be recorded as an AE or serious AE as applicable considering the signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy.

For events not associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE or SAE as applicable.

7.3 SERIOUS ADVERSE EVENT

An SAE is any AE that is any of the following:

1. Fatal (i.e., the AE actually causes or leads to death)
2. Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
3. Requires or prolongs inpatient hospitalization
4. Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
5. A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
6. Considered a significant medical event by the investigator (e.g., may jeopardize the patient 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 patient or event outcome or action criteria usually associated with events that pose a threat to a patient'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 or eCRF.

Per ICH E6 Guideline for Good Clinical Practice 4.11 Safety Reporting, all serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting.

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 7.3 and 7.4) are recorded on the CRF or eCRF and reported to the Sponsor in accordance with protocol instructions.

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

The following events are considered of Special Interest and will need to be reported to the Sponsor expeditiously (see Section 7.5 for reporting instructions), irrespective of regulatory seriousness criteria.

- Grade III-V encephalopathy or neurologic events

7.4 ADVERSE EVENT REPORTING PERIOD

The reporting periods for AEs and SAEs are described in Table 4. After informed consent, but prior to initiation of BPX-501 infusion, only SAEs caused by a protocol-mandated intervention (i.e. outside of institutional standard protocol) will be collected.

All AEs will be collected for 30-Days following each infusion of BPX-501 or rimiducid. SAEs regardless of attribution will be collected until 180 Days post BPX-501 infusion. After this period, investigators should report only SAEs that are felt to be related to the study treatment. After 24 months post-transplant patients will be monitored for delayed adverse events for a period of 15 years (see Section 3.7.4).

Table 4 Adverse Event Reporting Guidelines

Event Type	Reporting Period	Additional Requirements
SAEs (screening)	Date of informed consent signature to prior to BPX-501 infusion.	• Report new SAE only if related to a protocol-mandated intervention.
GvHD	All cases of GvHD should be reported regardless of onset date and should not be limited to the below AE/SAE reporting period	Not applicable
AEs (post-IMP)	• From the date of BPX-501 infusion until 30 days after administration regardless of causality assessment. • From the date of rimiducid infusion until 30 days after administration regardless of causality assessment.	• Report new AEs for up to 15 years if assessed as related to the investigational products BPX-501 and/or rimiducid.
SAEs (post-IMP) including Adverse Events of Special Interest (AESI)	• From the date of BPX-501 infusion until 180 days after administration regardless of causality assessment. • From the date of rimiducid infusion until 30 days after administration regardless of causality assessment.	• Report new SAEs for up to 15 years if assessed as related to the investigational products BPX-501 and/or rimiducid. • Report diagnosis of any new secondary malignancy regardless of relationship to investigational product for up to 15 years.
Pregnancy of patients or partner	• 12 months after administration of BPX-501 or rimiducid, whichever occurs later.	• Report diagnosis of any congenital anomaly in offspring from a study participant or partner for up to 15 years.

7.4.1 GVHD Adverse Event Reporting

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

7.5 PROCEDURES FOR ELICITING AND RECORDING ADVERSE EVENTS

Instructions and clarifications for the eliciting and recording of Adverse Events are located in Appendix F of this protocol.

7.6 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

7.6.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal SAE that is attributed by the investigator to the investigational product will be telephoned and emailed / faxed to the Medical Monitor immediately, followed by submission of written case details on a CRF within 24 hours.

7.6.2 Reporting Requirements for All SAEs

All SAEs must be reported to Bellicum within 24 hours of learning of the event using the Bellicum SAE Report Form. SAE details must also be entered in the eCRF.

For initial SAE reports, investigators should record all case details that can be gathered within the reporting timeframe (24 hours) on the Bellicum SAE Report Form and submit the report to [redacted] SAE information should also be entered into the eCRF as soon as possible. Follow-up information should be collected on the eCRF and reported to Bellicum or its designee using the Bellicum SAE Report Form as soon as it becomes available and/or upon request.

If local laws require that the site submit all SAEs then the local law will supersede the protocol requirements

7.6.3 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 patient 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 patient'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).

7.6.4 Post-Study Adverse Events

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt 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 patient that participated in this study. The investigator should report these events to Bellicum on the study CRF or eCRF. If the study CRF of eCRF system is no longer available, the investigator should report the event directly to Bellicum via phone or email.

Special Reporting Requirements for Neurotoxicity

BPX-501 cells have been documented to enter the CNS. As the significance of this finding is unknown, all CNS events with apparent encephalitis of ≥ Grade 3 severity must be reported to Bellicum within the 24 hours (SAE reporting timelines).

Refer to Appendix H for guidelines pertaining to monitoring and management of neurotoxicity.

Record all case details that can be gathered within the reporting timeframe (24 hours) on the Bellicum SAE Report Form and submit the report to [redacted] SAE information should also be entered into the eCRF as soon as possible. Follow-up information should be collected on the eCRF and reported to Bellicum or its designee using the Bellicum SAE Report Form as soon as it becomes available and/or upon request.

Guidelines for medical management of neurotoxicity are provided in Appendix H.

8 REGULATORY AND ETHICAL OBLIGATIONS

8.1. INVESTIGATOR REQUIREMENTS AND STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Bellicum:

- U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator
    - The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all sub-investigators
- Complete financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572
- Federal wide Assurance number or IRB.
- Written documentation of IRB approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB approved Informed Consent Form
    - Bellicum or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Bellicum-approved central laboratory), as well as current references ranges for all laboratory tests
- Institutional Biosafety Committee approval of the protocol
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator

- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable) , IRB approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Approval by the NIH Recombinant DNA Review Committee

8.2 STUDY COMPLETION

The following data and materials are required by Bellicum before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the main study conduct
- All laboratory certifications for laboratories performing the analysis (if other than Bellicum-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- CRFs or eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and sub-investigator, U.S. FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s)[if applicable]
- Updated financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

8.3 INFORMED CONSENT FORM

- Bellicum's Sample Informed Consent Form will be provided to each site. Bellicum or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB approved Consent Forms must be provided to Bellicum for regulatory purposes.

- The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.
- All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.
- The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.
- For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB approved Informed Consent Form must be provided to Bellicum for regulatory purposes.
- If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (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.

8.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB. Investigators are also responsible for promptly informing the IRB of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB all unanticipated problems involving risk to human patients. Some IRBs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Bellicum. Investigators are responsible for ensuring that such reports are

reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB and archived in the site's Study File.

8.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Bellicum representative to inspect study data, patients' medical records, and CRFs or eCRFs. The Principal Investigator will permit Bellicum's monitors/representatives or its designees and collaborators, the U.S. FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

8.5.1 Case Report Forms

eCRFs will be completed per the data management system. Sites will receive training and a manual for appropriate CRF or eCRF completion.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and signed and dated by the investigator.

8.5.2 Source Data Documentation

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered onto the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the CRFs or eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB review. The investigational site must also allow inspection by applicable regulatory authorities.

8.5.3 Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to 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.

8.5.4 Study Medication Accountability

All study drug required for completion of this study will be provided by Bellicum. 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 Bellicum 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.

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

8.6 DISCLOSURE OF DATA

Patient 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 patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient'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, Bellicum monitors/representatives and collaborators, and the IRB for each study site, if appropriate.

8.7 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, or printouts of the 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 Bellicum. Written notification should be provided to Bellicum for transfer of any records to another party or moving them to another location.

9 REFERENCES

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10 APPENDICES

APPENDIX A: SCHEDULE OF ASSESSMENTS

A1: Screening Assessments

Activity	Screening[1]
History, Physical exam, height and weight[2]	**X**
Vital Signs[3]	**X**
CBC w/differential, platelet count (reticulocyte, if indicated)	**X**
Disease staging (Appendix B)	**X**
Serum chemistries[4]	**X**
Quantitative Immunoglobulins (IgG, IgA, and IgM)	**X**
Infectious Disease titers[5]	**X**
EKG/LVEF or LVSF[6]	**X**
DLCO, FEV1 and FEV2 or 0_2 saturation	**X**
Renal Ultrasound, if clinically indicated	**X**
Bone marrow biopsy[7]/aspirate, if clinically indicated	**X**
CT scan of the chest, abdomen and pelvis, if clinically indicated	**X**
Chest x-ray, if clinically indicated	**X**
Serum Pregnancy (females past puberty only)	**X**
ABO/Rh typing direct coombs	**X**
HLA typing	**X**
10 cc of heparinized peripheral blood to determine subsequent chimerism (patient and donor)	**X**
Blood sample for iCasp tracking - research	**X**
Concomitant Medications	**X**
Blood Sample for RCR	Any time after consent through Day 0
Blood Sample for HAMA	Any time after consent through Day 0
Immune Reconstitution Research Studies	Any time after consent through Day 0

[1]Screening refers to the period prior to conditioning. Assessments, other than donor identification, should be made within 6 weeks prior to day of conditioning.

[2]History and height are required only at Screening.

[3]Vital signs: blood pressure, pulse rate, respiratory rate, temperature and oxygen saturation on room air.

[4]Serum chemistries panel: electrolytes, glucose, BUN, ALT, AST, creatinine, bilirubin (total and direct), alkaline phosphatase, LDH, albumin. Include fasting cholesterol and triglycerides if clinically indicated. Electrolytes to include; sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphorus..

[5]Infectious disease titers: Cytomegalovirus (CMV), antibody test, hepatitis panel (Hepatitis B including HBsAg, HBcAb (IgM and IgG); Hepatitis C Ab), HIV including HIV Ag, HIV 1+2 Ab, HTLV I/II Ab, herpes simples virus (HSV), varicella zoster virus VZV) and Toxoplasma serology. For patients with an underlying B cell deficiency or defect or those that have received IVIG within 3 months of HCT the following PCR studies are required: Hepatitis B PCR, Hepatitis C PCR, HIV PCR, CMV PCR, EBV PCR; Adenovirus PCR, VZV, and HSV PCR, as clinically indicated.

[6]To be determined by MUGA or echocardiogram.

[7]For pathology and cytogenetics, flow cytometry, and molecular studies. Sample to be provided to Bellicum.

Appendix A2: Schedule of Assessments to be Collected for Data Capture

	Day	Days	Week Post-Transplant*								Month Post-Transplant*					Months Post-Transplant	Year Post-Transplant
Activity	**0**	**1-28**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**6**	**9**	**12**	**18**	**24**	**30, 36, 42, 48, 54, 60**	**6-15**
Modified History, Physical exam[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[2]	X[3]		X	X	X	X	X	X	X	X	X	X	X	X	X		
CBC w/differential[4], platelet count[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistries[6]		X				X				X	X		X		X		
EBV and CMV[7]			X	X	X	X	X	X	X	X							
Chimerism[8]		X				X				X	X		X		X		
Quantitative Immunoglobulins										X			X		X		
Immunophenotyping										X	X		X		X		
GvHD assessments[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Rimiducid (AP1903) Infusion	Vital signs and research blood draws are required. See Table 1 For Each rimiducid Dose: Vital Sign Monitoring and Research Blood Samples																
Blood sample for iCasp tracking - research		Day 28				X				X	X		X		X		
Blood sample for RCR										X	X		X	X	X	X	X
Blood sample for HAMA							X										
Neurological Exam[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease staging													X				
Adverse Events[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications and Transfusions[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Schedule of Activities Notes:

*Visit windows for weekly visits are ± 3 days. Visit windows for Monthly visits are ± 7 days.

[1]Days 7, 14, 21, 28 only

[2]Vital signs (blood pressure, heart rate, respiratory rate and temperature.

[3]Vital Signs 30 minutes prior to starting infusion and at 30, minutes after starting infusion of CD34+ stem cells AND within 1 hour prior to starting infusion and at 15, 30, 120 and 240 minutes of starting of BPX-501 infusion.

[4]Clinical collection daily until ANC > 500 for 3 days, then 2x/week. [5] Clinical collection daily until quantitative platelet count is > 20,000 (non-transfused) then 2x/week

[6]Serum chemistries (Day 14 and 28 only) including Electrolytes, calcium, magnesium, phosphorus, glucose, albumin, ALT/AST, bilirubin (total and direct(, alkaline phosphatase, LDH, BUN, and creatinine. [7] Days 7, 14, 21, 28 [8]CD33, CD3, CD19,and CD56 Day 28 only.

[9] Clinical collection daily until Day 28 prior to discharge then 2x/week. [10] See Appendix G

[11] All AEs will be collected for 30 days following each infusion of BPX-501 or rimiducid (AP1903). GvHD will be reported as Adverse Events (or SAEs) and followed until resolution. SAEs regardless of attribution will be collected until 180 days post BPX-501 infusion. After this period, investigators should report only SAEs related to the study treatment.

APPENDIX B: DISEASE OUTCOME MEASURES TABLE

Disease-Specific Studies – as feasible
Timing of studies: Studies should be obtained pre-transplant and on specified post-HCT timelines

1. **Sickle Cell Disease**: All patients with Sickle Cell Disease will require a % hemoglobin S pre HCT and around day +84 and then at 1 year following HCT. In addition, % hemoglobin S should be checked if there is falling donor chimerism and concern of inadequate disease response.
2. **Bone Marrow Failure Syndromes**: All bone marrow failure syndromes should have appropriate genetic testing pre HCT.
3. **Dyskeratosis Congenita** - Telomere length analysis and appropriate genetic studies
4. **Shwachman Diamond Syndrome** - Appropriate genetic studies
5. **Diamond Blackfan Anemia** - Appropriate genetic studies
6. **Fanconi Anemia** – Appropriate genetic studies
7. **Immunodeficiency Diseases:** Lymphocyte phenotype (subsets), Lymphocyte function as clinically indicated, Quantitative Immunoglobulins and Immunology Consult. In addition, the following immunodeficiency disease specific studies should be considered.
    a) **Chronic granulomatous disease -**Genetic analysis of cytosolic components of NADPH oxidase system (pre-transplant only if not already completed). Neutrophil oxidative burst should be evaluated pre-transplant if not already completed and around day 80 and 1 year following transplantation or as clinically indicated.
    b) **Leukocyte adhesion defect -**Flow cytometry analysis of CD18 expression pre-transplant if not already completed and around day 80 and 1 year following transplantation or as clinically indicated.
    c) **Wiskott-Aldrich syndrome -** Gene sequence (pre-transplant only if not already completed); Flow cytometry for determination of WASP expression pre-transplant if not already completed and around day 80 and 1 year following transplantation or as clinically indicated.and
    d) **IPEX:** - Flow cytometry for expression of FOXP3 pre-transplant if note already completed and around day 80 and 1 year following transplantation or as clinically indicated.
    e) **CD40 Ligand Deficiency** - Flow cytometry for expression of CD40 Ligand pre-transplant if not already completed and around day 80 and 1 year following transplantation or as clinically indicated.

f) **Hemophagocytosis Lymphohistiocytosis (HLH) –** Appropriate genetic studies (pre-transplant only if not completed). NK function analysis pre transplant if not already completed and around day 80 and 1 year following transplantation or as clinically indicated.

8. **Mucopolysaccharidosis -** Disease specific enzyme level.
   - **a)** Marrow, skin, liver, and/or gut biopsy as indicated according to disease for determination of storage material
   - **b)** Lumbar puncture for storage material determination, as indicated
   - **c)** MRI of head, as indicated.

9. Sphingolipidoses
   - **a)** Nerve conduction studies.
   - **b)** MRI of head.

9 Osteopetrosis
   - **a)** Send bone biopsy to pathology for assessment of disease.
   - **b)** Head MRI

APPENDIX C: ACUTE GVHD GRADING SCALE

Table C.1 Modified Keystone Grading Schema

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Generalized erythroderma plus bullae and desquamation
Gut	Adult: < 500 ml/day diarrhea	Adult: 500-1000 ml/day diarrhea or nausea, anorexia or vomiting with biopsy confirmation	Adult: 1001-1500 ml/day diarrhea	Adult: >1500 ml/day	Severe abdominal pain +/- ileus, frank blood or melena
	Child <10ml/kg/day	Child 10-19.9ml/kg/day	Child 20-30ml/kg/day	Child >30ml/kg/day	
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl

Table C.2 Grading of Acute GvHD

	Skin	Liver	Gut	Upper GI
0	None and	None and	None and	None
I	Stage 1-2 and	None and	None	None
IIA	Stage 3 and/or	Stage 1 and/or	Stage 1 and/or	Stage 1
IIIA,B	Stage 4 and/or	Stage 2-4 and/or	Stage 2-4 and/or	N/A
IVA,C	Stage 4 and/or	Stage 2-4 and/or	Stage 2-4	N/A

A. Grade II-IV GVHD with only single organ involvement should be biopsy confirmed
B. Non-fatal GVHD
C. Fatal GVHD

APPENDIX D: CHRONIC GVHD GRADING SCALE

NIH Consensus Grading Chronic GvHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

Appendix D NIH Consensus Grading Chronic GvHD (cont)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS† **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
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.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

APPENDIX E: GVHD RESPONSE CRITERIA

Complete response (CR) is defined as a CIHSCTR score of 0 for the GvHD grading in all evaluable organs. For a response to be scored as CR at Day 56 or later, the participant must still be in CR on that day and have had no intervening additional therapy for an earlier progression, PR or NR.

Partial response (PR) is defined as improvement in one or more organs involved with GvHD symptoms without progression in others. For a response to be scored as PR at Day 28 or later, the participant must still be in PR on that day and have had no intervening additional therapy for an earlier progression, PR or no response (NR).

Mixed response (MR) is defined as improvement in one or more organs with deterioration in another organ manifesting symptoms of GvHD or development of symptoms of GvHD in a new organ.

Progression of GvHD (PD) is defined as deterioration in at least one organ without any improvement in others.

No response (NR) is defined as absence of any improvement or progression as defined. Patients receiving secondary therapy (including need to re-escalate steroid dose to > 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) will be classified as non-responders.

APPENDIX F: SAFETY REPORTING CRITERIA

Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient 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?"

Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient'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 eCRF, the investigator will make an assessment of seriousness (see Section 7.3 for seriousness criteria), severity and causality.

The adapted AE grading (severity) scale found in the NCI CTCAE v4.03 will be used for AE reporting.

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

Adapted from
COMMON TOXICITY CRITERIA (CTC)
Version 4.0

Grade			
Adverse Event	**3**	**4**	**5**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Disseminated intravascular coagulation	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Febrile neutropenia	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Hemolysis	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Hemolytic uremic syndrome	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Grade			
Adverse Event	**3**	**4**	**5**
CARDIAC DISORDERS			
Atrial fibrillation	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Atrial flutter	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Atrioventricular block complete	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death

Constrictive pericarditis	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Left ventricular systolic dysfunction	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Myocardial infarction	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Myocarditis	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Pericardial effusion	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Pericardial tamponade	-	Life-threatening consequences; urgent intervention indicated	Death
Ventricular arrhythmia	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death

Grade			
Adverse Event	**3**	**4**	**5**
GASTROINTESTICAL DISORDERS			
Ascites	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Diarrhea	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Duodenal ulcer	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric ulcer	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Gastritis	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Lower gastrointestinal hemorrhage	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Mucositis oral	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Oral hemorrhage	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pancreatitis	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death

Typhlitis	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
		Grade	
Adverse Event	**3**	**4**	**5**
GENERAL DISORDERS AND ADMINISTARTION SITE CONDITIONS			
Multi-organ failure	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
		Grade	
Adverse Event	**3**	**4**	**5**
HEPATOBILIARY DISORDERS			
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
		Grade	
Adverse Event	**3**	**4**	**5**
IMMUNE SYSTEM DISORDERS			
Allergic reaction	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Immune system disorders - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Grade			
Adverse Event	**3**	**4**	**5**
INFECTIONS AND INFESTATIONS			
Enterocolitis infectious	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Infections and infestations - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
INVESTIGATIONS			
Alanine aminotransferase increased	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate aminotransferase increased	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Blood bilirubin increased	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Carbon monoxide diffusing capacity decreased	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g. , >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Cardiac troponin I increased	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Cardiac troponin T increased	Levels consistent with myocardial infarction as defined by the manufacturer	-	-

Creatinine increased	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Weight gain	>=20% from baseline	-	-
		Grade	
Adverse Event	**3**	**4**	**5**
METABOLISM AND NUTRITIONAL DISORDERS			
Hypercalcemia	Corrected serum calcium of >12.5 - 13.5 mg/dL;>3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hypertriglyceridemia	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Tumor lysis syndrome	Present	Life-threatening consequences; urgent intervention indicated	Death
		Grade	
Adverse Event	**3**	**4**	**5**
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INC CYSTS AND POLYPS)			
Treatment related secondary malignancy	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
		Grade	
Adverse Event	**3**	**4**	**5**
NERVOUS SYSTEM DISORDERS			
Dysarthria	Severe impairment of articulation or slurred speech	-	-
Intracranial hemorrhage	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Ischemia cerebrovascular	-	-	-

Leukoencephalopathy	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Syncope	Fainting; orthostatic collapse	-	-
Nervous system disorders - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
RENAL AND URINARY DISORDERS			
Chronic kidney disease	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Renal and urinary disorders - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			

Grade			
Adverse Event	**3**	**4**	**5**
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS			
Adult respiratory distress syndrome	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Apnea	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Bronchopulmonary hemorrhage	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Hypoxia	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Pleural effusion	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Pneumonitis	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Pulmonary edema	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Respiratory failure	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death

Grade			
Adverse Event	**3**	**4**	**5**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Erythema multiforme	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
VASCULAR DISORDERS			
Capillary leak syndrome	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypotension	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Thromboembolic event	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Vasculitis	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death

Table F.1 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. Regardless of the "Yes" or "No" causality assessment 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 F.2 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?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Recording Adverse Events on the CRF or eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF or eCRF. Avoid colloquialisms and abbreviations.

Only one medical concept should be recorded in the event field on the Adverse Event CRF or eCRF.

a. Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF or eCRF 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 or eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Adverse Events Occurring Secondary to Other Events

In general, AEs 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 eCRF.

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 eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF or eCRF.

c. Persistent or Recurrent Adverse Events

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

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

d. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF or eCRF (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 5x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF or eCRF.

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.

e. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 7.4), regardless of attribution, will be recorded on a CRF or eCRF 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 “Disease Progression” (*listing specific disease*) as the SAE term on the CRF or eCRF.

f. 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 and Surgical 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, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

g. 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

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 patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

If a female patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of investigational product, Bellicum should be notified within 24 hours of learning of the pregnancy, but this is not reported as an AE or SAE

APPENDIX G: CHIMERISM ANALYSIS

Samples from FHCRC should be sent to Clinical Immunogenetics Lab (206-667-7700; SCCA G7-200) for a DNA-based assay that compares the profile of amplified fragment length polymorphisms (ampFLP) of the patient and donor.

Sample should consist of 20cc (or 2cc/kg for patients <10kg) peripheral blood in heparinized green top and 3cc red top tube (no additive)

Other institutions may use VNTR analysis (sex- matched transplants) or sex chromosome analysis

APPENDIX H: GUIDELINES FOR MONITORING & MANAGEMENT OF NEUROTOXICITY

Neurologic complications occur in approximately 6.4-19.2% (Dowling 2017, Syed 2016, Uckan 2005) of patients after allogeneic hematopoietic stem cell transplantation. 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). CNS toxicity may occur at different rates among different donor sources (matched unrelated or haploidentical donors have a higher rate than matched related donors) (de Brabander 2000).

Particular 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 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 (Syed 2016, Uckan 2005).

Guidelines monitoring of neurotoxicity are provided in Table F.1. Patients should undergo a daily neurologic examination and mini-mental status examination (MMSE) (Folstein 1975) or modified mini mental status examination (pediatric population) while inpatient during the hematopoietic stem cell transplant, both before and after infusion of BPX-501. Daily neurologic examinations should also be performed during any readmissions after allogeneic HSCT. A neurologic examination should be performed as part of all routine clinical follow-up examinations during each outpatient visit while patients are being treated on BPX-501 clinical trials.

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

In cases where a lumbar punctures (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 (Table H.3), consistent with consensus guidelines for performing LPs in patients with neurological diseases (Engelborghs2017).

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 less 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 (see Table H.3; Engelborghs 2017).

Table H.1. Monitoring of Patients for Neurological Complications

Timing	Neurologic examination	MMSE
Inpatient prior to BPX-501 infusion	√	√
Daily while inpatient after BPX-501 infusion	√	√
Routine outpatient clinic visits or emergency room visits	√	√
Change in mental status or presence of CNS dysfunction (e.g., reduced consciousness, delirium)	√	√

Table H.2 Management Guideline for 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 neurotoxicity symptoms • Perform CNS imaging (MRI and/or contrast enhanced CT) • Consider CSF evaluation for presence of cell counts (and differential), glucose, protein and gram-stain for bacteria. (see Table H.3) ○ 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 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 (eg, prophylactic GVHD medication changes and/or treatment with seizure medications) • Start management of stroke/ischemia per institutional guidelines if suspected • Administration of antiviral and/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. • Rimiducid may be administered if CNS infection ruled out and no improvement after 48 hours of high-dose corticosteroids (e.g. methylprednisolone 500 mg IV every 12 hours x 2 days for adults or 30 mg/kg/day IV x 2 days in children) 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 CNS for PK analysis if the patient's condition allows. If there is evidence 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 prior to the administration of rimiducid for neurotoxicity (see Table H.3). • Peripheral blood should be sent to the Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+) at the following times: ○ Prior to administration of systemic corticosteroid doses (e.g, methylprednisolone), at 4 and 24 hours post-systemic corticosteroid doses, and at 7, 14, 21 and 28 days post-systemic corticosteroid doses ○ Within 4 hrs prior to rimiducid dose(s), 30 minutes after initiation of infusion; and at 2, 4, 6, 8, and 24 hours post-rimiducid doses, and at 7, 14, 21, and 28 days after the final dose of rimiducid (if more than one dose is administered) • If cerebrospinal fluid (CSF) can be safely obtained, CSF should be sent to the Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+) prior to initiation of high-dose corticosteroids or rimiducid. 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 for research use to evaluate for BXP-501 cells (CD3+CD19 +) (see Table H.3)

Grade ≥ 2 (Generalized)[2]	• Perform routine institutional care for patients with altered mental status/obtundation (eg, continuous vital sign monitoring, oxygen, suction, airway protection measurements and consideration of 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 for 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 and/or contrast enhanced CT)
	• Perform CSF evaluation for presence of cell counts (and differential), glucose, protein and gram stain for bacteria. (see Table H.3)
	  ○ CSF evaluations for other infectious etiologies (eg, 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 seizure is expected
	  ○ Special consideration should be considered for conditioning agents (eg, Busulfan) or prophylactic GVHD medications (eg, calcineurin inhibitors) as an etiology and institutional guidelines should be instituted for possible treatments (eg, prophylactic GVHD medication changes and/or treatment with seizure medications)
	• Consideration of high-dose corticosteroid treatment (e.g. methylprednisolone 500 mg IV every 12 hours x 2 days for adults or 30 mg/kg/day IV x 2 days in children) if no evidence of CNS/systemic infection
	• Consideration of empiric antiviral and/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.
	• Rimiducid may be administered if CNS infection ruled out and no improvement after 48 hours of high-dose corticosteroids (e.g. methylprednisolone 500 mg IV every 12 hours x 2 days for adults or 30 mg/kg/day x 2 days in children) 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 CNS for PK analysis if the patient's condition allows. If there is evidence 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 prior to the administration of rimiducid for neurotoxicity (see Table H.3). • Peripheral blood should be sent to the Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+) at the following times: o Prior to administration of systemic corticosteroid doses (e.g, methylprednisolone), at 4 and 24 hours post-systemic corticosteroid doses, and at 7, 14, 21, and 28 days post-systemic corticosteroid doses o Within 4 hrs prior to rimiducid dose(s), 30 minutes after initiation of infusion; and at 2, 4, 6, 8, 12, and 24 hours post-rimiducid doses, and at 7, 14, 21, and 28 days after the final dose of rimiducid (if more than one dose is administered) • If cerebrospinal fluid (CSF) can be safely obtained, CSF should be sent to the Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+) prior to initiation of high-dose corticosteroids or rimiducid. 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 for research use to evaluate for BPX-501 cells (CD3+CD19+) (see Table H.3)

* All grading corresponding to NCI CTCAE v4.03:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

a. Includes but not limited to cranial nerve abnormalities, brachial plexopathy, ischemia, nystagmus, pyramidal tract syndrome, radiculitis, focal seizure, stroke, transient ischemic attack
b. 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 H.3 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 diathesisAnti-coagulant medication
Patient-related risk factors: 1. Determine risk profile and inform patient 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 1. Collections up to 30 mL	Post-LP Headache, back pain, post-LP complaints,

*Table H.3. modified from Engelborghs 2017

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APPENDIX I: KARNOFSKY/LANSKY PERFORMANCE SCALE

KARNOFSKY (>16 years of age)		LANSKY (< 16 years of age)	
100	Normal, no complaints, no signs of disease	100	Fully active
90	capable of normal activity, few symptoms or signs of disease	90	Minor restriction in physically strenuous play
80	normal activity with some difficulty, some symptoms or signs	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	caring for self, not capable of normal activity or work	70	Both greater restriction of and less time spent in active play
60	requiring some help, can take care of most personal requirements	60	Ambulatory up to 50% of the time, limited active play with assistance/supervision
50	requires help often, requires frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	disabled, requires special care and help	40	Able to initiate quiet activities
30	severely disabled, hospital admission indicated but no risk of death	30	Needs considerable assistance for quiet activity
20	very ill, urgently requiring admission, requires supportive measures or treatment	20	Limited to very passive activity initiated by others (e.g. TV)
10	moribund, rapidly progressive fatal disease processes	10	Completely disabled, not even passive play