Bellicum PHARMACEUTICALS

Phase II extension study of CaspaCIDe T cells (BPX-501) from an HLA-partially matched family donor after negative selection of TCR αβ+T cells in pediatric patients affected by hematological disorders

Protocol Number:	**BP-004**
Combination Product:	**BPX-501** – Donor T cells genetically modified with BPZ-1001 retroviral vector containing the iCasp suicide gene **AP1903 (Rimiducid) (Dimerizer drug)**
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ClinicalTrials.Gov / EudraCT Number:	**NCT02065869 / 2014-000584-41**
Version Number:	**11.0 Italy**
Date:	**29 October 2018**

Investigator's Agreement

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

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

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

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

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

_____ _____

Signature Date

_____

Printed Name

Investigator

SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Protocol Title:

Phase II extension study of CaspaCIDe T cells (BPX-501) from an HLA-partially matched family donor after negative selection of TCR αβ+T cells in pediatric patients affected by hematological disorders

Sponsor Approval

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

Signature: [redacted] Date: 5 December 2018

Sponsor Title: Vice President
Sponsor: Bellicum Pharmaceuticals Inc.

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SYNOPSIS

Background

Over the last 4 decades, allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched donor, either related or unrelated, has been increasingly used to treat patients affected by several malignant or non-malignant disorders. However, only 25% of patients who need or could benefit from an allograft have an HLA-identical sibling and fewer than 60% of remaining patients can be matched with suitable HLA-compatible, unrelated donors (Rocha 2008). In the absence of an HLA-matched donor, alternative donor/sources of hematopoietic stem cells such as HLA-haploidentical relatives are being increasingly used. While mature donor T cells present in the graft facilitate T-cell reconstitution, in the context of increased immune genetic disparity between patient and donor, the T cells are also responsible for the occurrence of graft-versus-host disease (GVHD), a severe, sometimes fatal, immune complication, which also impairs patient's immune reconstitution.

Strategies to prevent GVHD after HLA-haploidentical allo-HSCT based on either pharmacological immunosuppression or T-cell depletion of the graft have been developed. The physical elimination of T cells from the graft has been shown to be highly effective to prevent both acute and chronic GVHD. However, with T-cell depletion of the graft, the patient does not receive the adoptive transfer of donor-derived memory T lymphocytes, which are mainly responsible for protection from severe infections during the state of profound immune deficiency that usually lasts for at least 4-6 months after transplantation. Overall, HLA-haploidentical allo-HSCT is associated with a higher incidence of graft rejection, and both viral and fungal infections, resulting in high transplantation-related mortality (TRM).

Recent data has shown that not only adaptive immunity, but also innate immunity, such as natural killer (NK) cells, influence the patient's outcome (Locatelli 2013). Therefore, transplantation of mobilized peripheral blood stem cells (PBSCs) selectively depleted of TCR αβ T-lymphocytes offers potential advantages over the use of positively selected CD34+ hematopoietic stem cells because of the presence of other ancillary non-stem cells, including NK and TCRγδ T cells.

Clinical Outcomes after TCR αβ T Cell and CD19+ Cell Depletion

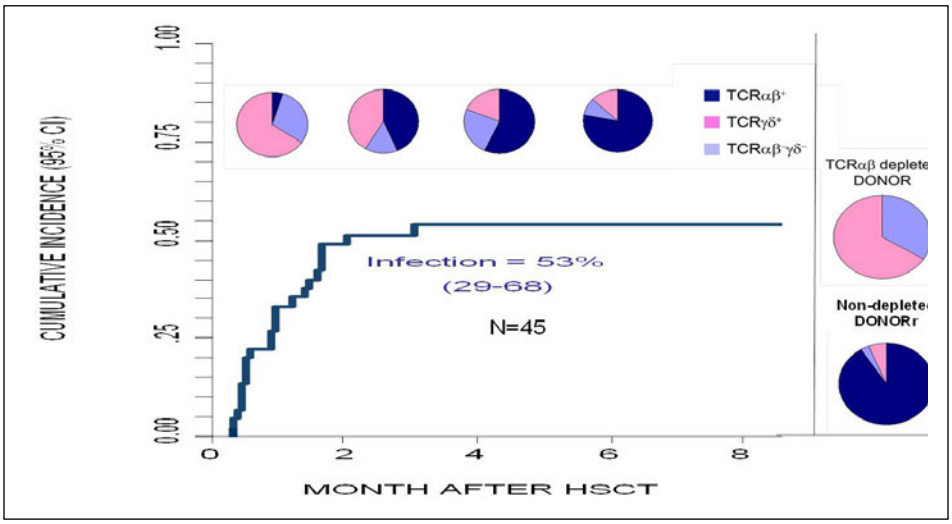
Locatelli and colleagues started the program of T-cell depleted haplo-HSCT using the negative selection of αβTCR T-cells in November 2010. The study is officially registered at the clinicaltrials.gov website as NCT01810120. More than 100 patients with either hematological malignancies or with non-malignant disorders received transplants depleted of αβTCR T cells. The data collected to date demonstrates that

depletion of αβTCR+ and CD19+ cells led to an approximate 4.1-log and 3.1-log depletion of αβ TCR T cells and B cells, respectively. The residual T-cell content was below the previously published safe threshold (i.e. $1x10^5$/kg recipient body weight) for HLA-haploidentical HSCT. Patients did not receive any post-transplant immune suppression.

The outcome of children with acute leukemia given αβ TCR T-cell and B-cell depleted haplo-HSCT demonstrated a transplant-related mortality of less than 10% and a 20% risk of malignant disease recurrence (Locatelli 2012; Bertaina 2014). There has been no reported acute GvHD with either gastrointestinal or liver involvement, and skin-only Grade I-II GvHD was observed in approximately 30% of patients, without chronic GvHD.

Despite the positive patient outcome results in terms of leukemia-free survival (75%), reconstitution of adaptive immunity was still sub-optimal. Until 2 months after transplantation, the proportion of circulating αβTCR+ mature T cells is lower than that of γδ TCR+ immature T-cells. The delayed immune reconstitution resulted in a high probability of serious infections, and the cumulative incidence of CMV, adenovirus or aspergillus infections approached 50% (Figure 1).

Figure 1: Correlation Between T Cell Subset Distribution and Likelihood of Viral and Fungal Infections



Immune reconstitution remains a challenge since T cell engraftment and expansion can take up to 180 days; therefore, the addition of mature T cells which exhibit a broad repertoire of T cell immunity against viral antigens, and potentially against cancer antigens, might provide a clinical benefit. However, the potential occurrence of acute graft-versus-host disease (aGVHD) is an expected side effect due to these mature T cells. The use of a suicide gene switch which would trigger the initiation of the apoptosis (programmed cell death) of the alloreactive T cells by the infusion of dimerizer drug (rimiducid) would represent a potential means for restoring early immunity with a built in "safety switch" against GvHD side effects.

Study Rationale

This is a Phase II extension study evaluating the safety and feasibility of BPX-501 T cells infused after partially matched, related, T cell-depleted HSCT in pediatric patients. The purpose of this clinical trial is to determine whether BPX-501 infusion can enhance immune reconstitution in those patients with hematologic disorders, with the potential for reducing the severity and duration of severe acute GvHD, thereby improving overall survival. The trial will also evaluate the treatment of GvHD by the infusion of dimerizer drug (Rimiducid/AP1903) in those subjects who present with GvHD who do not respond to standard of care treatment.

Study Type

Interventional Study

Study Design

Allocation: Non-Randomized

Endpoint Classification: Efficacy/ Safety

Intervention Model: Single Group Assignment

Masking: Open Label

Primary Purpose: Treatment

Estimated Enrollment: up to 175 evaluable patients treated with BPX-501

Phase I Dose Escalation Summary

Nine subjects were treated according to a 3+3 dose escalation design. Cohorts 1-3 subjects received 0.2 x10^6 BPX-501 T cells/kg, 0.5 x 10^6 BPX-501 T cells/kg, and 1 x 10^6 BPX-501 T cells/kg, respectively. No DLTs were observed and the study then continued at the highest tested dose, namely 1 x 10^6 BPX-501 T cells/kg. No related AEs or SAEs were reported. All 9 subjects showed evidence of BPX-501 T cells. Subjects experienced Grade II skin-only GvHD which resolved without treatment with rimiducid. These preliminary results support further dose escalation in the malignant disease indications in the attempt to further the Graft versus Leukemia effect (GvL) in these high-risk patients.

Therefore, subjects with malignant diseases were evaluated at two higher dose levels: 2x10^6 or 4x10^6 cells/kg. No DLTs have been noted at either 2x10^6 or 4x10^6 cells/kg doses, so a true MTD was not determined. The Phase II extension study will evaluate the 1x10^6 BPX-501 T cells/kg dose for both malignant and non-malignant diseases.

Phase II Primary End-Points

Event-Free-Survival at 180 days (events include TRM (or NRM for malignant patients), severe GvHD (acute Grade 2-4 organ or extensive chronic GvHD) and life threatening infections (Grade 4).

Phase II Secondary End-Points

1. TRM (non-malignant) or NRM (malignant) at 100 and 180 days
2. Cumulative incidence and severity of acute (grade 2-4) and chronic GvHD at 180 days;
3. Time to resolution of acute or chronic GvHD after administration of rimiducid
4. Immune reconstitution as determined by T cell subsets at day 180
    a. Absolute CD3 count

b. Absolute CD4 count

c. Absolute CD8 count

5. Time to immune reconstitution
6. Disease Free/cGvHD survival at 180 days
7. Disease status of each specific disease indication at 180 days:
   a. Primary immune disorders as determined by CD3 T cell count >500 cells/ul and lower normal levels of IgA and IgM at 180 days
   b. Haemoglobinopathies as determined by incidence of RBC transfusion dependence and untransfused haemoglobin of >8.5 g/dL at 180 days
   c. Fanconi Anemia as determined by RBC >3,000,000 cells/ul, neutrophil count determined by 1500 cells/ul and >150,000 platelet counts at 180 days
   d. Leukemia as determined by PFS at 180 days

ELIGIBILITY

Subject Inclusion Criteria

1. Age $\leq$ 18 years and $\geq$ 1 month (< 1 month upon approval by Sponsor)
2. Life expectancy > 10 weeks
3. Patients deemed clinically eligible for allogeneic stem cell transplantation.
4. Patients may have failed a prior allograft
5. Patients with life-threatening acute leukemia (high-risk ALL in 1st CR, ALL in 2nd CR, high-risk AML in 1st CR, AML in 2nd CR) or myelodysplastic syndromes. Morphological CR must be documented and minimal residual disease measurement before transplantation is recommended.
6. Non-malignant disorders deemed curable by allogeneic transplantation:
   a. Primary immune deficiencies,
   b. Severe aplastic anemia not responding to immune suppressive therapy,
   c. Osteopetrosis
   d. Selected cases of erythroid disorders, such as β0 β0 thalassemia major, sickle cell disease, Diamond-Blackfan anemia
   e. Congenital/hereditary cytopenia, including Fanconi Anemia before any clonal malignant evolution (MDS, AML).

Note: Subjects will be eligible if they meet either item 5 OR item 6.

7. Lack of suitable conventional donor (HLA identical sibling or HLA phenotypically identical relative or 10/10 unrelated donor evaluated using high resolution molecular typing) or presence of rapidly progressive disease not permitting time to identify an unrelated donor
8. A minimum genotypic identical match of 5/10 is required.
9. The donor and recipient must be identical, as determined by high resolution typing, on at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA- DRB1 and HLA-DQB1.
10. Lansky/Karnofsky score > 50
11. Signed informed consent by the patient or the patient's parent or guardian for patients who are minors

Subject Exclusion Criteria

1. Greater than active Grade II acute GvHD or chronic extensive GvHD due to a previous allograft at the time of screening
2. Patient receiving an immunosuppressive treatment for GvHD treatment due to a previous allograft at the time of screening
3. Dysfunction of liver (ALT/AST > 5 times normal value, or bilirubin > 3 times normal value), or of renal function (creatinine clearance <30ml/min/1.73m^2)
4. Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or left ventricular ejection fraction < 40%)
5. Current uncontrolled clinically active infectious disease (including positive HIV serology or viral RNA)
6. Serious concurrent uncontrolled medical disorder
7. Pregnant or breast feeding female patient
8. Lack of parents'/guardian's informed consent for children who are minors.

Donor Inclusion Criteria

1. Eligible donors include 5/10 HLA identical relative, including but not limited to biological parents, siblings, or half-siblings. Matching will be determined by class I and class II DNA typing. The donor of the BPX-501 T cells must be the HSCT donor.

2. Donor age must be ≥ 18 and ≤ 65 years.
3. The donor should be sufficiently healthy not to be at increased risk from the mobilization procedure.
4. Should more than one "equally" MHC compatible donor be identified, other selection criteria may include natural killer cell (NK) alloreactivity, NK cell KIR-Haplotype, B-content for B-haplotype donors, size of the NK alloreactive subset, gender, age, CMV status, health status and body weight of donor. The physician treating the subject will make the final decision.
5. Donors must meet the selection criteria as defined by the European Directive 2006/17/CE) and according to the FACT-JACIE International Standards and local regulations for donor selection.
6. The donor must have been informed of the investigational nature of the BPX-501 product and have signed an informed consent form that they will undergo a second apheresis procedure. Donor must have adequate peripheral venous access for leukapheresis or must agree to placement of a central venous catheter.
7. The collection of donor T cells to be transduced with the suicide gene will be performed before the mobilization procedure with G-CSF in order to avoid any potential negative influence of this cytokine on function of genetically modified T cells.
8. Signed informed consent

Donor Exclusion Criteria

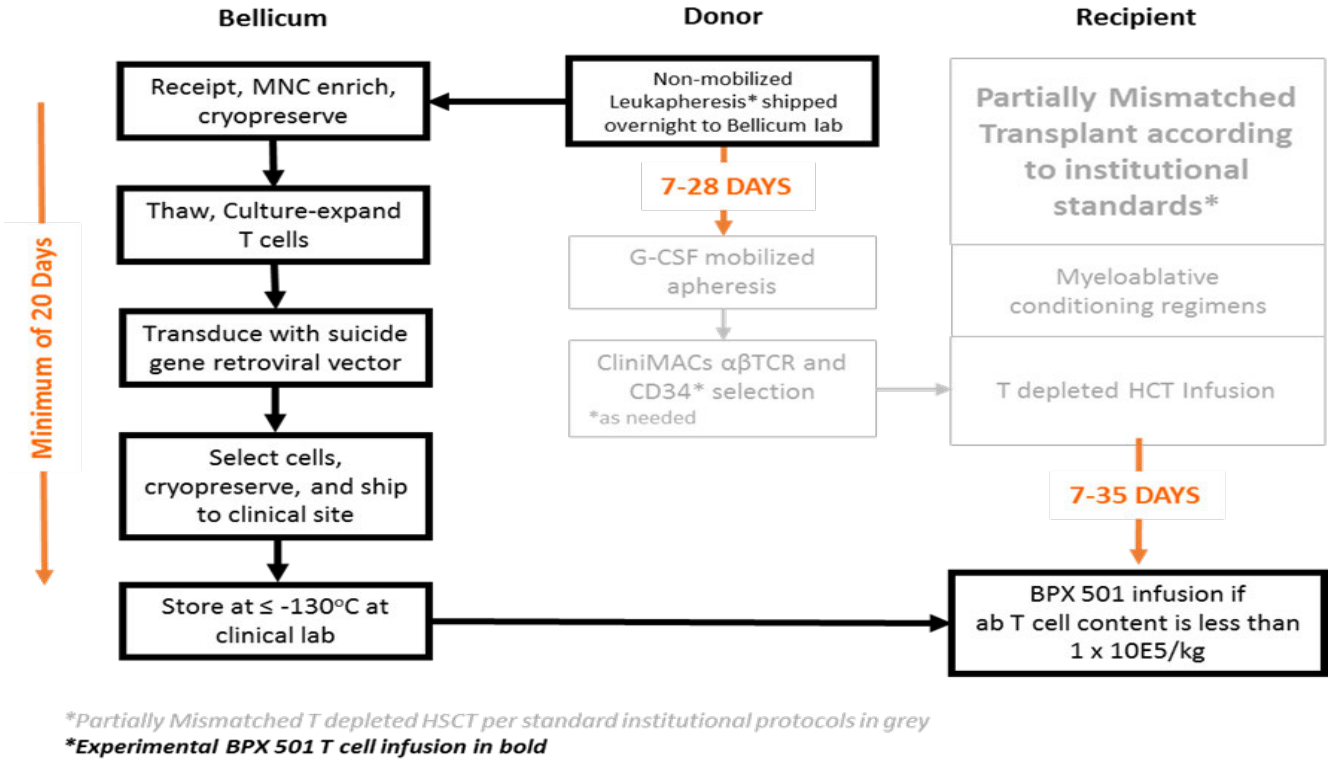
1. Evidence of active infection (including urinary tract infection, or upper respiratory tract infection) or viral hepatitis exposure (on screening), unless HBs Ab+ and HBV DNA negative.
2. Factors which place the donor at increased risk for complications from leukapheresis or mobilization therapy (e.g., autoimmune disease, symptomatic sickle cell trait, symptomatic coronary artery disease requiring therapy, previous thrombotic events).
3. Pregnancy at the time of normal leukapheresis for the T cells and at the time of the mobilization for the stem cell allograft collection.
4. Breastfeeding at the time of mobilization

Trial Design

This is a Phase II extension, multi-center, open label study. The trial will be completed at the $1x10^6$ cells/kg dose for both malignant and non-malignant patients. In the event that the target dose cannot be manufactured, the subject will receive any available cells.

The study will evaluate event-free survival for all evaluable patients at 180 days (6 months) after transplantation (active period). There will be an efficacy and safety analysis at the end of the 180-day active period with active long term follow-up for up to 2 years on a follow-on protocol (BP-404), with gene therapy safety follow-up for a total of 15 years.

Clinical Schema



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

The diagram above describes the steps and timing of manufacture and infusion of BPX-501 T cells following the TCR αβ depleted HSCT.

Acute GVHD treatment

There is the potential for patients to experience both acute and chronic graft vs. host disease (aGVHD and cGVHD) due to their allogeneic transplantation for their underlying disease (primary immunodeficiency or malignancy). The BPX-501 T cells are intended to: aid in engraftment, promote immune reconstitution, enhance allogeneic graft-vs-leukemia (GvL) effects in malignant recipients, and

can be eliminated upon infusion of rimiducid (AP1903) for potential mitigation of allo-reactive side effects.

Acute GvHD grading should be conducted in accordance with the Modified Keystone Staging Schema (Appendix B) Refer to guidelines for management of aGvHD provided in (Appendix B) .

When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours and 7 days after the start of each rimiducid infusion, and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

Chronic GvHD Treatment

Chronic GvHD (cGvHD) typically occurs 100 days or later after HSCT. Chronic GvHD can often present with a sicca-like syndrome with thickened skin, lichen planus, papules, cholestatic jaundice, scleroderma-like skin, eye and GI lesions. Chronic GvHD patients can also develop obstructive pulmonary disease symptoms.

Chronic GvHD is typically classified into mild (i.e., localized skin involvement, with/or without liver dysfunction) or moderate to severe (i.e., generalized skin involvement or localized skin and/or hepatic dysfunction, plus liver histology showing hepatitis/necrosis/cirrhosis, eye involvement, salivary gland involvement, or effects on other organs). Moderate to severe cGvHD usually involves more than one organ with an organ severity score of moderate or greater (or mild or greater for lungs). Management guidelines for cGvHD are shown in Appendix C.

Response should be assessed per Appendix C. Three general categories of overall response are used in clinical trials: complete response (CR), partial response (PR), and lack of response (unchanged, mixed response, progression). Complete response is defined as resolution of all manifestations in each organ or site, and PR is defined as improvement in at least 1 organ or site without progression in any other organ or site. The 2014 NIH Consensus Working Group recommends that skin, mouth, liver, upper and lower

GI, esophagus, lung, eye, and joint/fascia be considered in evaluating overall response. Genital tract and other manifestations are not included due to lack of validated response measures.

Partial response in a specific organ requires an improvement of 1 or more points on a 4 to 7-point scale or an improvement of 2 or more points on a 10 to 12-point scale. The overall category of PR requires the absence of progression in any organ.

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Table 1: COMPLETE SCHEDULE OF ASSESSMENTS (LABORATORY AND CLINICAL)

Time - Days (+/-7)	-10 to -1 [1]	0	14±4	30	44	60	74	88	100 (+/-10)	180(+/-10)
Screening Tests; Scans	X									X
BM & Disease Evaluation [2]	X			X					X	X
Chimerism [3]				X					X	X
Hematology; Chemistry	X	X		X	X	X	X	X	X	X
Immune Reconstitution (iCasp) [4]	X			X		X			X	X
IgG, IgA, IgM	X			X		X			X	X
Bellicum Research Samples[11]	X	**BPX-501 T cell Post-Dose Levels** Research samples for assessment of BPX-501 cells (CD3+CD19+) will be collected at baseline (-10 days to -1 day), immediately prior to BPX-501 infusion, 7 days post-BPX-501 infusion, weekly for one month after BPX-501 infusion (± 4 days), every 2 weeks ± 4 days to 100-days post BPX-501 infusion, monthly ± 14 days for until 1 year post BPX-501 infusion, every 6 months ± 1 month for 24 months post BPX-501 infusion. **Post-systemic corticosteroid administration:** Research samples (peripheral blood and/or tissue) for assessment of BPX-501 cells (CD3+CD19+) will be collected prior to administration of systemic corticosteroids doses (e.g. methylprednisolone), at 4 and 24 hours post-systemic corticosteroid initiation, and at 7, 14, 21, and 28 days post-systemic corticosteroid initiation.								
HAMA	X								X	
RCR	X								X	X
BPX-501 Infusion			X							
Neurological Exam[5]	X	X	X	X	X	X	X	X	X	X
Modified History & Physical	X			X		X			X	
Vital Signs [6]	X	X	X	X		X			X	X
Viral Monitoring [7]	X	X	X	X		X			X	X
GvHD Assessment [8]				X	X	X	X	X	X	X
Concomitant Medication [9]			X	X	X	X	X	X	X	X
Adverse Event			X	X	X	X	X	X	X	X
Rimiducid Infusion [10]	Vital signs are recorded prior to rimiducid, and 15, 30, 60, 120 and 240 minutes (± 5 minutes) after start of infusion. When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. These additional samples (at									

	least 0.3 mL) will be drawn at 48 hours and 7 days (after each rimiducid dose), then at 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

1 Screening activities shall occur after consenting. Screening refers to the period prior to conditioning. Historical assessments can be used to determine eligibility if performed within 42 days prior to the day of conditioning, except vital signs, complete blood count (CBC) with differential and platelet count (PLT), performance score, and serum chemistry panel which should be within 1 week prior to the day conditioning begins. HLA testing can be within 6 months prior to the day conditioning begins. Visit windows up to Day 60 are ± 3 days. Visit windows for from Day 100 to Day 180 are ± 7 days.

2 Bone marrow evaluation is for subjects with hematological malignancies or non-malignant disorders such as congenital/hereditary cytopenia, including Fanconi Anemia and severe aplastic anemia. Disease evaluations for hematological malignancies such as acute leukemia and MDS include a bone marrow aspirate and biopsy. Cytogenetics, molecular, or other institutional assessment to determine Minimal Residual Disease (MRD) can be recorded at Baseline. Bone marrow aspirate for pathology and cytogenetics will be performed at Day 30, Day 100 and Day 180. Additional assessment can be performed if clinically indicated.

3 Donor/host chimerism analyses shall be performed according to standard practice in the hospital. The same method shall be used for the same subject.

4 The immune reconstitution flow panel includes CD3+ cells, alpha/beta CD3+ cells, gamma/delta CD3+ cells, CD4+ cells, CD8+ cells, NK cells and B cells, CD45RA, CD45RO, CD62L and CCR7. After BPX-501 infusion, the flow panel will expand to include CD3+/CD19+ cells, CD3+/CD19+/CD4+ cells and CD3+/CD19+/CD8+ cells. Baseline samples shall be collected within 10 days prior to Day 0. See Appendix H. Data from flow panel will be used to assess immune reconstitution. Samples should be analyzed locally whenever possible.

5 For clinical assessment and management of neurotoxicity refer to Appendix K.

6 Vital signs include blood pressure, heart rate, respiratory rate and temperature. Before, during and after infusion of CD34+ stem cells and BPX-501 T cells, vital signs shall be collected 1 hour prior to starting infusion and at 15, 30 and 120 minutes after start of infusion.

7 Viral monitoring may include CMV, HHV6, EBV and/or other viral studies as deemed necessary by the treating physician which may be monitored more frequently than the stated timepoints to monitor reactivation and viral status.

8 According to standard practice in the hospital, blood counts and differentials will be performed at least 3 times per week after transplant until the neutrophil count reaches 0.5 x 10^9/L. Thereafter, at least 2 times per week until the neutrophil count is > 1.0 x 10^9/L and platelets > 100 x 10^9/L. GvHD assessments will be performed according to standard practice in the hospital. Subjects will receive GvHD assessment daily for 7 days after the initiation of the first rimiducid infusion and then resume the GvHD assessments per the schedule in the protocol. Refer to Appendix B and Appendix C.

9 Concomitant Medication: The protocol will be conducted during the routine clinical care of the patients. All treatments such as transfusions and critical medications, defined below shall be collected in the EDC database:

- Drugs and radiation treatment in conditioning regimens, including most recent chemotherapy regimen and G-CSF
- Treatment for GvHD
- Prophylaxis and/or treatment for infectious complications
- Treatments in association with SAEs or AEs of special interest such as febrile neutropenia and anaphylaxis

Standard supportive care treatments, non-prescription medications/OTCs, NSAIDs, laxatives/stool softeners, vitamins, and herbal supplements will not be collected if they are not protocol-mandated.

10 Research blood samples collected in association with rimiducid infusion should be assessed locally(see Appendix H). Refer to Appendix J for the processing of samples for pPK testing. Additional details are provided in the laboratory manual.

11 BPX-501 T cell post-dose levels samples should be sent to Bellicum and the post systemic corticosteroids administration should be analyzed locally, similar to rimiducid sample.

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LIST OF ABBREVIATIONS AND TERMS

ALL	Acute lymphoblastic leukemia
ABW	Adjusted Body Weight
AE	Adverse Event
aGvHD	Acute Graft Versus Host Disease
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
AML	Acute Myeloid leukemia
APC	Antigen presenting cells
BFU-E	Burst-forming units erythroid
BM	Bone marrow
BMT	Bone Marrow Transplantation
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CB	Cord blood
CFU-GM	Colony-forming units granulocytes macrophage
CFU-M	Colony-forming units macrophage
cGvHD	Chronic Graft Versus Host Disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CR	Complete Remission
CRF	Case Report Forms
CRO	Contract Research Organization
CTL	Cytotoxic T Lymphocytes
CTN	Clinical Trials Network
DFS	Disease-free survival
DLT	Dose Limiting Toxicity
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein Barr Virus
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid

EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good clinical practice
G-CSF	Granulocyte-Colony Stimulating Factor
GMP	Good medical practice
GTP	Good Tissue Practice
GvHD	Graft-Versus-Host Disease
GvL	Graft-versus-leukemia
HAMA	Human Anti-Mouse Antibody
Haplo-HSCT	HLA-haplo-identical hematopoietic stem cell transplantation
HCT	Hematopoietic Cell Transplantation
HIPAA	(US) Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
KIR	Killer immunoglobulin-like receptor
LFS	Leukemia-free survival
LN2	Liquid Nitrogen
LPDs	Lymphoproliferative Diseases
LVEF	Left Ventricular Ejection
MACS	Magnetically Activated Cell Sorting
MDS	Myelodysplastic Syndrome
MHC	Major Histocompatibility Complex
MMSE	Mini-Mental Status Examination
mMMSE	Modified Mini Mental Status Examination
MTD	Maximum Tolerated Dose

NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NCR	Natural cytotoxicity receptor
NK	Natural Killer
NKR	Natural killer receptor
NOD	Non-obese diabetic
NR	No Response
NRM	Non-Relapse Mortality
OPBG	Ospedale Pediatrico Bambino Gesù
OS	Overall survival
PAgs	Non-peptide Phosphoantigens
PB-HSCT	Peripheral blood hematopoietic stem cell transplantation
PBMC	Peripheral Blood Mononuclear Cell
PBSC	Peripheral Blood Stem Cell
PK	Pharmacokinetics
PD	Progressive Disease
PR	Partial Response
RCR	Replication Competent Retrovirus
SAE	Serious Adverse Event
SCID	Severe combined immunodeficiency
SDV	Source Data Verification
TBI	Total Body Irradiation
TCR	T-Cell Receptor
TNC	Total Nuclear Cell
TNF	Tumor necrosis factor
TPHA	Treponema pallidum haemagglutination test
TRM	Transplant-Related Mortality
UCBT	Umbilical cord blood transplantation
VNTR	Variable Number of Tandem Repeats
WHO	World Health Organization

1 INTRODUCTION

1.1 Haplo-identical Hematopoietic Stem Cell Transplantation (Haplo-HSCT)

Over the last 4 decades, allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched donor, either related or unrelated, has been increasingly used to treat patients affected by several malignant or non-malignant disorders. Thanks to this procedure, thousands of subjects have been cured of their original disease (Copelan 2006). The total number of allo-HSCT performed in Europe in 2008 was 11,408 (corresponding to an increase of 7%) and 1,426 in Italy according to the 2008 EBMT activity survey. However, only 25% of patients who need or could benefit from an allograft have an HLA-identical sibling and fewer than 60% of remaining patients can be matched with suitable HLA-compatible, unrelated donors (Rocha 2008). Moreover, the median time to locate a suitable unrelated donor is in the order of 3-4 months. In the absence of an HLA-matched donor, alternative donor/sources of hematopoietic stem cells (HSC), such as unrelated umbilical cord blood (UCB) and HLA-haploidentical relatives, are being increasingly used (Gluckman 2006; Locatelli 2009). In particular, the majority of patients have a family member, identical for one HLA haplotype and fully mismatched for the other (i.e. haploidentical), who could immediately serve as HSC donor (Martelli 2002). Thus, HSCT from an HLA-haploidentical relative (haplo-HSCT) offers an immediate transplant treatment for those patients lacking a matched donor or a suitable UCB unit. Mature donor T cells present in the graft facilitate T-cell reconstitution, but are also responsible for the development of graft-versus-host disease (GvHD), a severe, sometimes fatal, immune complication, which also impairs the patient's immune reconstitution.

Strategies to prevent GvHD after HLA-haploidentical allo-HSCT based on either pharmacological immunosuppression or T-cell depletion of the graft have been developed. A milestone in the history of haplo-HSCT was the demonstration that an efficient T-cell depletion of the graft is able to prevent both acute and chronic graft-versus-host disease (GvHD) even when using a related donor differing at the three major HLA loci (Reisner 1983). The benefits of T-cell depleted haplo-HSCT were first demonstrated in children with severe combined immunodeficiency (SCID) and it can now be estimated that hundreds of SCID patients have been transplanted worldwide using an HLA-haploidentical related donor, with a high rate of long-term, partial or complete immune reconstitution (Antoine 2003). However, the infusion of BM cells obtained from an HLA-haploidentical relative has been reported to be associated with a high incidence of graft failure in patients with acute leukemia. Indeed, due to the extensive T-cell depletion of the donor's graft, the balance between

competing host and donor T cells shifted in favor of the unopposed host-versus-graft reaction (Bachar-Lustig 1995; Reisner 1999). The use of "megadoses" of G-CSF-mobilized peripheral blood donor HSC has been shown to overcome the barrier of HLA incompatibility in the donor/recipient pair and to elude the residual anti-donor cytotoxic T-lymphocyte activity of the recipient.

An effective translation of this approach into the clinical setting was first reported in a pilot study performed in adults with acute leukemia by a group in Perugia. In that study, Aversa et al harvested "megadoses" of G-CSF–mobilized peripheral blood HSC, and transplanted them after T-cell-depletion cells using the soybean agglutination and E-rosetting technique, without any subsequent pharmacological GvHD prophylaxis. The engraftment rate was above 90%, with a cumulative incidence of both Grade II-IV acute and chronic GvHD below 10%. Subsequently, the same group has adopted a more standardized method of T-cell depletion based on the positive selection of CD34 cells from peripheral blood by magnetic beads using the CliniMACS (Miltenyi) system. The clinical trials performed using this approach of T-cell depletion have confirmed that sustained engraftment of donor hematopoietic stem cells, without the occurrence of GvHD, can be obtained in the majority of adult patients and that a substantial proportion of them, especially those affected by acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), became long-term survivors. The feasibility and efficacy of haplo-HSCT was reproduced in children with acute leukemia and documented in several pilot studies enrolling a limited number of patients. A larger study was performed by The Acute Leukemia and Pediatric Working Parties of the European Blood and Marrow Transplantation (EBMT) Group which analyzed the outcome of a large cohort of children with acute lymphoblastic leukemia (ALL) given T-cell depleted haplo-HSCT. This study showed that the 5-year leukemia-free survival (LFS) for children transplanted in complete remission was about 30%, indicating that haplo-HSCT is a useful treatment for patients in morphological remission of this disease. Furthermore, this study showed that the stem cell dose infused in haplo-HSCT is crucial, as patients receiving a dose of CD34+ cells greater than $12x10^6$ progenitors/kg have a better clinical outcome (Klingebiel 2010).

More recently, the group at OPBG analyzed the outcome of 72 pediatric patients given a T-cell depleted PB-HSCT for the treatment of ALL (42 cases), AML (21 cases) or MDS (9 cases). Most children with acute leukemia were beyond 1st complete remission. The patients were given $CD34^+$ cells positively selected using the one-step CliniMacs device (Miltenyi Biotech, Germany) with a median number of $CD34^+$ cells infused of $20x10^6$/kg (range 9-41) and no post-transplantation pharmacologic immune suppression. The 5-year estimate of disease-free survival (DFS) for the whole

cohort was 55%; it was 61% in ALL, 33% in AML and 78% in MDS patients ($p<0.01$) (Bernardo 2011).

Thus, in leukemia patients, the combination of a myeloablative conditioning regimens with the infusion of large numbers of highly purified peripheral blood $CD34^+$ cells could guarantee: 1) the successful and sustained engraftment of donor hematopoietic stem cells across the HLA barrier; and 2) a very low incidence of Grade II–IV acute GvHD without the need for any post-transplantation immune suppression.

One disadvantage of this procedure is that the elimination of mature T cells from the graft means that recipients cannot benefit from the adoptive transfer of donor memory T lymphocytes that are primarily responsible for protection from severe infections during the first months after transplantation. Indeed, a state of profound immune deficiency has been documented to last for at least 4-6 months after haplo-HSCT and it translates into an increased risk of TRM, mainly attributable to infectious complications (Aversa 1998; Aversa 2005). Moreover, the absence of the T cell-mediated graft-versus leukemia (GvL) effect has also been thought to render the recipients of a T-cell depleted allograft more susceptible to leukemia relapse.

The clinical results only partly confirmed these expectations and showed that not only adaptive immunity, but also innate immunity plays a crucial role in the outcome of the transplant. Indeed, adult patients transplanted from a donor displaying NK cell alloreactivity were found to have a lower risk of leukemia recurrence, especially if affected by AML and when transplanted in morphological remission (Moretta 2011).

1.2 Potential Role of the Cells Remaining in the Graft

NK cells represent an important component of the innate immunity and are of fundamental importance in limiting or eradicating pathogens during the early phases of a primary infection, (before T and B cells can mount efficient responses). Indeed, NK cells and phagocytes do not require clonal expansion and can enter and defend a tissue almost as soon as it becomes infected.

Other potentially beneficial cells infused with the graft are γδ T lymphocytes. These lymphocytes have been termed non-conventional, innate-like or transitional T cells, owing to several distinguishing features that are shared with innate immune cells (Bendelac 2001; Hayday 2009).

The role of γδ T cells in graft-host interactions is not fully understood, but the available evidence suggests that they do not cause GvHD (Drobyski 1999) and are associated with a potent GvL effect. Indeed, in their study Lamb et al showed that in patients with ALL or AML transplanted from a partially matched TCR αβ T cell depleted graft, those with an increased (≥10%) proportion of γδ T cells in their peripheral blood 60-120 days after the transplantation were free of disease in 90% of the cases at 2.5 years, as compared with a disease-free survival probability of 31% among patients with a lower proportion of circulating γδ T cells (Lamb 1996).

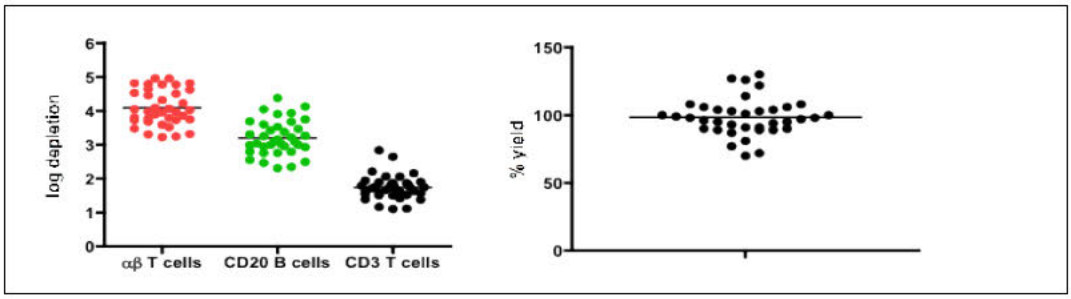
1.3 Clinical Outcomes after αβ TCR T Cell and CD19+ Cell Depletion

Locatelli and colleagues started the program of T-cell depleted haplo-HSCT using the depletion of αβ TCR T cells in November 2010. The study is officially registered at the clinicaltrials.gov website as NCT01810120. More than 100 patients with either hematological malignancies or non-malignant disorders have received transplants depleted of αβ TCR T cells. The data collected to date clearly demonstrates that this method of graft manipulation is reproducible, leading to an approximate 4.1-log and 3.1-log depletion of αβ TCR T cells and B cells, respectively. The residual T-cell content was below the safe threshold (i.e. $1x10^5$/kg recipient body weight) for performing HLA-haploidentical HSCT without any post-transplant immune suppression in all donor depletions performed.

1.4 Selective αβ TCR T Cell and CD19 Depletion

The allogeneic donors were mobilized with G-CSF, and if deemed necessary, plerixafor for 4 days with apheresis on Day 5 (and possibly Day 6). A total of up to $60x10^9$ total nucleated cells from the mobilized leukapheresis product underwent TCRαβ T cell negative selection followed by CD19+ B cell negative selection. The log depletion of $TCR\alpha\beta^+$ is 4.1 (3.23 - 4.97), of $CD20^+$ is 3.1 (2.32 – 4.39) and of $CD3^+$ is 1.7 (1.12 – 2.85), as shown in Figure 2.

Figure 2: Log Depletion and Yield Recovery After αβ TCR T Cell CD19+ Negative Depletion



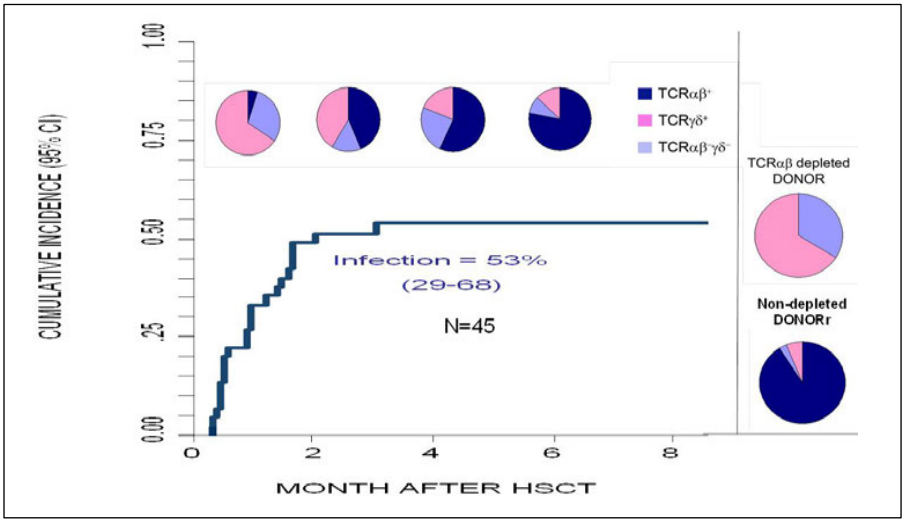
Total median % recovery yield of $CD19^-$ $TCR\alpha\beta^-$ cells in the graft after selection is 98% (70 – 130%). The remaining allograft composition for the reported leukemia patients is listed in Table 1 below.

Table 1: TCR Depleted Graft Composition per kg Recipient Body Weight

Total Nucleated Cell Count	1.1 (0.35-3.27) X 10^9/kg
CD34+ Cells	14.6 (4.8-27.9) X 10^6/kg
CD3+ cells	8 (1-10) X 10^6/kg
NK Cells	31.7 (14-105) X 10^6/kg
Tαβ	4 (1-10) X10^4/kg
Tγδ	7.8 (0.9-14) X 10^6/kg

The outcome of children with acute leukemia given αβ TCR T-cell and B-cell depleted haplo-HSCT demonstrated a transplant-related mortality of less than 10% and a 20% risk of malignant disease recurrence (Locatelli 2012; Bertaina 2014). There has been no reported acute GvHD with either gastrointestinal or liver involvement, and skin-only Grade I-II GvHD was observed in approximately 30% of patients, without chronic GVHD (Bertaina 2015). Despite these positive patient outcome results, reconstitution of adaptive immunity was still sub-optimal. Until 2 months after transplantation, the proportion of circulating αβ T cells is lower than that of γδ cells. The delayed immune reconstitution resulted an increased probability of experiencing serious infections, with the cumulative incidence of CMV, adenovirus or aspergillus infection approaching 50% (Figure 3).

Figure 3: Correlation between T Cell Subset Distribution and Likelihood of Viral and Fungal Infections.



Since immune reconstitution remains a challenge with T cell engraftment taking up to 180 days, the addition of mature T cells which exhibit a broad repertoire of T cell immunity against viral antigens, as well as cancer antigens, might provide a clinical benefit. However, an expected side effect of the presence of T cells is the potential occurrence of aGvHD. The use of a suicide gene switch which would trigger the initiation of the apoptosis (killing) of the alloreactive T cells by the infusion of dimerizer drug (RUMIDUCID/AP1903) would represent the potential means for restoring early immunity with a built in "safety switch" against GvHD side effects.

The delayed reconstitution of CD4+ cells and impaired recovery of T cell receptor (TCR) diversity may predispose recipients of T cell depleted HSCT to opportunistic infections for months to years after transplantation. Several studies demonstrate a higher probability of reactivation of viruses such as CMV and EBV (van Burik 2007), and increased risk for EBV-associated lymphoproliferative disorders (EBV-LPDs) after T cell depleted transplantation (Zutter 1988). Therefore, recipients of T cell depleted allografts often require ongoing surveillance for opportunistic viral pathogens.

1.5 BPX-501: Genetically Modified T Cells With Suicide Safety Switch

1.5.1 iCasp9 Suicide Gene

Unmodified donor T cell infusion is potentially an effective strategy for conferring anti-viral and anti-tumor immunity following allogeneic stem cell transplantation (Di Stasi 2011). However, the administration of greater than 10^5 cells/kg unmodified donor T cells to recipients of haploidentical stem cell transplantation has been associated with increased incidence of GvHD. It has been previously demonstrated that administration of up to 10^7 cells/kg of CD25+ allo-depleted donor T cells after haploidentical transplantation for hematological malignancies could be administered safely and that the addition of these T cells was effective in controlling viral disease (Amrolia 2006). However, mortality due to disease relapse remained high, presumably due to the fact that the estimated frequency of tumor-reactive precursors is 1 to 2 logs lower than the frequency of virus- reactive precursors.

The use of higher numbers of allodepleted T cells containing an inducible caspase 9 suicide gene in order to treat the potential increase in GVHD was then evaluated. The caspase recruiting domain of the human caspase 9 was modified with a drug binding domain, permitting T cell elimination after administration of a chemical dimerization drug, rimiducid. Administration of rimiducid dimerizes and

activates caspase 9 which activates downstream caspases, leading to apoptosis potentially within minutes to hours (Di Stasi 2011; Tey 2007).

The gamma retrovirus, SFG.iCaspase9.2A.DeltaCD19 (BPZ-1001), consists of inducible caspase 9 (iCasp9) linked, via a 2A-like sequence, to truncated human CD19 (DeltaCD19). The iCasp9 genetic modification, unlike the HSV-TK based 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 with HSV-TK. Further advantages of the iCasp9 system are that killing induced by the dimerizer drug is primarily restricted to activated/proliferating cells, thus targeting 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.

1.5.2 Rimiducid Dimerizer Drug

Rimiducid is a member of a new class of lipid-permeable compounds termed activating, or dimerizer, drugs that act by inducing clustering of engineered proteins inside cells. RUMIDUCID- inducible activation of the Caspase 9 suicide gene is achieved by expressing a chimeric protein (iCasp9), fused to a drug-binding domain derived from human FK506-binding protein (FKBP). This chimeric protein is quiescent inside cells until administration of rimiducid, which cross-links the FKBP domains, initiating iCasp9 signaling. This signaling induces apoptosis of the gene modified cells. [redacted]

1.5.3 CASPALLO Trial

In a Phase I study, ten patients between the ages of 3 and 17 years who had undergone stem-cell transplantation for relapsed acute leukemia were treated with the genetically modified T cells. The cells were detected in peripheral blood and increased in number over time, despite their constitutive transgene expression. A single dose of dimerizing drug, rimiducid, given to the patients in whom GvHD developed, eliminated more than 90% of the modified T cells within 30 minutes after administration 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 without any reports of infusion related toxicity. Moreover, acute GvHD of the skin in all three subjects, and of the liver disease in one subject, completely resolved after 24 hr. (Di Stasi 2011). The patients who developed

GvHD received rimiducid. None of the 10 patients developed chronic GVHD. Six of the 10 patients are alive to date, with relapse as the primary cause of death in the other 4 patients (Zhou 2014).

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

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

1.6 Evaluation of Benefits/Risks

The direct benefit for the patient will be to improve his clinical outcome in terms of successful eradication of disease, modulation of GvHD and speed of both hematopoietic and immune recovery.

The benefit for the community will be to potentially improve the clinical outcome of patients receiving a haplo-HSCT for the treatment of hematological disorders in terms of: promoting engraftment, lowering TRM and reducing the risk of disease recurrence, thus rendering the procedure more widely applicable.

The potential risk undertaken in this study is to increase the incidence of GVHD in patients receiving a TCRαβ depleted graft as compared with patients receiving a positive selected CD34+ cells graft from an HLA-partially matched family donor. To decrease this risk, the efficiency of the depletion of TCRαβ+ T cells will be checked before the infusion of the graft.

The benefits of infusing a TCRαβ T cell-depleted graft instead of a positive selected CD34+ cells graft from an HLA-partially matched family donor, would be the potential to decrease the incidence

of bacterial, viral or invasive fungal infection, to promote engraftment and to reduce the risk of recurrence of the disease in case of malignant disorders.

There is a potential risk of neurotoxicity in patients undergoing HSCT and receiving BPX-501 cells. Neurologic complications are not uncommon after allogeneic HSCT and occur in 6-19% of patients depending on the type of transplant, the underlying disease (such as immune deficiency disorders) and prior treatments. They are the cause of death in 10-15% of children undergoing allogeneic HSCT. These events can be a result of agents used in the conditioning regimen, drug related toxicities, infections, or immune-mediated reactions such as GVHD. To date, 7 events of neurotoxicity (3%) in 241 patients treated with BPX-501 after TCR αβ depleted HSCT (pediatric and adult) have been reported. Three had an identified viral infection (CMV or HHV6), one patient had an unidentified infection but responded to anti-viral, anti-fungal and anti-bacterial treatment. One patient had acute disseminated encephalitis (ADEM) as a potential late complication of GVHD. Two cases of encephalitis or encephalopathy were of unknown cause. BPX-501 cells have been documented to enter the central nervous system. Two patients experienced a complete resolution of encephalopathy after treatment with corticosteroids, rimiducid, and anti-infective agents.

Patients will undergo a daily neurologic examination and mini-mental status examination (MMSE) (Folstein 1975) while inpatient and as part of all routine clinical follow-up examinations during each outpatient visit while patients are being treated on BPX-501 clinical trials.

The sponsor assesses the risk-benefit status at this time to be favorable. The potential risks of BPX-501 T cells, including potential immune-mediated events such as GvHD or encephalopathy, at this time do not appear to outweigh the benefits of enhanced immune reconstitution, relapse prevention, or the ability to treat GvHD with rimiducid.

2 OBJECTIVES OF THE STUDY

2.1 Primary Objectives

This is a Phase II extension study evaluating the safety and feasibility of BPX-501 T cells infused after partially matched, related, T cell-depleted HSCT in pediatric patients. The purpose of this clinical trial is to determine whether BPX-501 infusion can enhance immune reconstitution in those patients with hematologic disorders, with the potential for reducing the severity and duration of severe acute GvHD, thereby improving overall survival. The trial will also evaluate the treatment of GVHD

by the infusion of dimerizer drug rimiducid (AP1903), activating the suicide gene, in those subjects who present with GVHD who do not respond to standard of care treatment.

2.1.1 Phase II primary end-points

Event-Free -Survival at 180 days (events include TRM (or NRM for malignant patients), severe GVHD (acute Grade 2-4 organ or extensive chronic GVHD) and life threatening infections (Grade 4).

2.1.2 Phase II secondary end-points

1. TRM (non-malignant) or NRM (malignant) at 100 and 180 days
2. Cumulative incidence and severity of acute (grade 2-4) and chronic GVHD at 180 days;
3. Time to resolution of acute or chronic GvHD after administration of rimiducid
4. Immune reconstitution as determined by T cell subsets at day 180
    a. Absolute CD3 count
    b. Absolute CD4 count
    c. Absolute CD8 count
5. Time to immune reconstitution
6. Disease Free/cGVHD survival at 180 days
7. Disease status of each specific disease indication at 180 days:
    a. Primary immune disorders as determined by CD3 T cell count >500 cells/ul and lower normal levels of IgA and IgM at 180 days
    b. Haemoglobinopathies as determined by incidence of RBC transfusion dependence and untransfused haemoglobin of >8.5 g/dL at 180 days
    c. Fanconi Anemia as determined by RBC >3,000,000 cells/ul, neutrophil count determined by 1500 cells/ul and >150,000 platelet counts at 180 days
    d. Leukemia as determined by PFS at 180 days

3 PATIENT POPULATION AND SELECTION

This study will enroll any infant (1 month -24 months), child (2-11 years) or teenager (12-18 years) with malignant hematological disorders in complete morphological remission or non-malignant hematological disorders eligible for an allogeneic transplantation and lacking either a related or unrelated HLA-matched donor or whose disease status does not allow the extensive wait for an unrelated donor.

- **Estimated Enrollment:** Approximately 175 evaluable patients treated by BPX-501.

3.1 ELIGIBILITY

3.1.1 Subject inclusion criteria

1. Age ≤ 18 years and ≥ 1 month (< 1 month upon approval by Sponsor)
2. Life expectancy > 10 weeks
3. Patients deemed clinically eligible for allogeneic stem cell transplantation.
4. Patients may have failed prior allograft
5. Patients with life-threatening acute leukemia (high-risk ALL in 1st CR, ALL in 2nd CR, high-risk AML in 1st CR, AML in 2nd CR.) or myelodysplastic syndromes. Morphological CR must be documented and minimal residual disease measurement before transplantation is recommended.
6. Non-malignant disorders deemed curable by allogeneic transplantation:
    a. primary immune deficiencies,
    b. severe aplastic anemia not responding to immune suppressive therapy,
    c. osteopetrosis
    d. selected cases of erythroid disorders such as β0 β0 thalassemia major, sickle cell disease, Diamond-Blackfan anemia.
    e. congenital/hereditary cytopenia, including Fanconi Anemia before any clonal malignant evolution (MDS, AML).

Note: Subjects will be eligible if they meet either item 5 OR item 6.

7. Lack of suitable conventional donor (HLA identical sibling or HLA phenotypically identical relative or 10/10 unrelated donor evaluated using high resolution molecular typing) or presence of rapidly progressive disease not permitting time to identify an unrelated donor
8. A minimum genotypic identical match of 5/10 is required.
9. The donor and recipient must be identical, as determined by high resolution typing, on at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA- DRB1 and HLA-DQB1.
10. Lansky/Karnofsky score > 50
11. Signed informed consent by the patient or the patient's parent or guardian for patients who are minors

3.1.2 Subject exclusion criteria

1. Greater than active Grade II acute GvHD or chronic extensive GvHD due to a previous allograft at the time of screening
2. Patient receiving an immunosuppressive treatment for GvHD treatment due to a previous allograft at the time of screening
3. Dysfunction of liver (ALT/AST > 5 times normal value, or bilirubin > 3 times normal value), or of renal function (creatinine clearance <30ml/min/1.73m^2)
4. Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or left ventricular ejection fraction < 40%)
5. Current uncontrolled clinically active infectious disease (including positive HIV serology or viral RNA)
6. Serious concurrent uncontrolled medical disorder
7. Pregnant or breast feeding female patient
8. Lack of parents'/guardian's informed consent for children who are minors.

3.1.3 Donor inclusion criteria

1. Eligible donors include 5/10 HLA identical relative, including but not limited to biological parents, siblings, or half-siblings. Matching will be determined by class I and class II DNA typing. The donor of the BPX-501 T cells must be the HSCT donor.
2. Donor age must be $\geq$ 18 and $\leq$ 65 years.
3. The donor should be sufficiently healthy not to be at increased risk from the mobilization procedure.
4. Should more than one "equally" MHC compatible donor be identified, other selection criteria may include natural killer cell (NK) alloreactivity, NK cell KIR-Haplotype, B-content for B-haplotype donors, size of the NK alloreactive subset, gender, age, CMV status, health status and body weight of donor. The physician treating the subject will make the final decision.

5. Donors must meet the selection criteria as defined by the European Directive 2006/17/CE) and according to the FACT-JACIE International Standards and local regulations for donor selection.
6. The donor must have been informed of the investigational nature of the BPX-501 product and have signed an informed consent form that they will undergo a second apheresis procedure. Donor must have adequate peripheral venous access for leukapheresis or must agree to placement of a central venous catheter.
7. The collection of donor T cells to be transduced with the suicide gene will be performed before the mobilization procedure with G-CSF in order to avoid any potential negative influence of this cytokine on function of genetically modified T cells.
8. Signed informed consent

Donor exclusion criteria

1. Evidence of active infection (including urinary tract infection, or upper respiratory tract infection) or viral hepatitis exposure (on screening), unless HBs Ab+ and HBV DNA negative.
2. Factors which place the donor at increased risk for complications from leukapheresis or mobilization therapy (e.g., autoimmune disease, symptomatic sickle cell trait, symptomatic coronary artery disease requiring therapy, previous thrombotic events).
3. Pregnancy at the time of normal leukapheresis for the T cells and at the time of mobilization for the stem cell allograft collection.
4. Breastfeeding at the time of mobilization

Sponsor will be notified of any AEs (infections, etc.) occurring in the donor between the leukapheresis and stem cell apheresis.

3.2 Patient Discontinuation/Withdrawal 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. Patients who discontinue/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 experiences an adverse event 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.

4 DESIGN AND CONDUCT OF THE STUDY

4.1 Trial Rationale

Previously, Aversa (2008) reported that a dose of $2x10^5$ residual CD3+ cells after T cell depletion of a peripheral blood stem cell graft administered to haploidentical patients resulted in an incidence of Grade II-IV aGvHD of 18%. The occurrence of aGvHD reported by Di Stasi et al after a donor lymphocyte infusion (DLI) of gene modified T cells provides a basis for calculating the initial probability of toxicity. Ten patients who had undergone haploidentical stem-cell transplantation for relapsed acute leukemia were treated with DLI of T cells genetically modified with the iCasp9 suicide gene. Four patients who developed aGvHD (40%) and received a single dose of dimerizing drug, rimiducid, eliminated more than 90% of the modified T cells within 30 minutes after administration and the GvHD resolved in all four patients without recurrence (0% GvHD after rimiducid infusion). The probability of aGvHD in this clinical protocol is dependent on the number of T cells remaining in the T cell depleted stem cell graft, as well as the BPX-501 T cell dose. The onset of aGvHD will depend on interplay between a broad array of host and donor factors, including the presence, phenotype and precise specificity of residual major and minor histocompatibility antigen reactive T cells, and the numbers and functionality of T regulatory cells in the stem cell graft and the infused BPX-501 T cells.

4.2 Trial Design

This is a Phase II extension multi-center, open label study.

Phase I dose escalation summary

Nine subjects were treated according to a 3+3 dose escalation design. Cohorts 1-3 subjects received $0.2x10^6$ BPX-501 T cells/kg, $0.5x10^6$ BPX-501 T cells/kg, and $1x10^6$ BPX-501 T cells/kg, respectively. No DLTs were observed and the study then continued at the highest tested dose, that of $1x10^6$ BPX-501 T cells/kg. No related AEs or SAEs were reported. All 9 subjects showed evidence of BPX-501 T cells. Subjects experienced Grade II skin-only GvHD, which resolved without treatment with rimiducid. These preliminary results support further dose escalation in the malignant disease indications in the attempt to further the Graft versus Leukemia effect (GvL) in these high-risk patients. Therefore, subjects with malignant diseases were evaluated at two higher dose levels: $2x10^6$ or $4x10^6$ cells/kg. No DLTs have been noted at either $2x10^6$ or $4x10^6$ cells/kg doses, so a true MTD was not determined.

Patients in the Phase II extension trial will be enrolled at the at the dose of $1x10^6$ cells/kg dose regardless of disease (malignant or non-malignant) and the study follow-up for each patient will be 180 days. Subjects will be enrolled in a long-term follow-up protocol (BP-404) for up to 2-years post-transplant, with gene therapy follow-up for a total of 15 years.

4.3 Patient Enrollment, Registration and Assignment to Treatment

Informed consent will be obtained from each patient/guardian and donor after the nature of the study is explained and prior to the performance of any study-specific procedures.

Prior to enrollment into the study, a preliminary eligibility determination will be conducted for each patient. The investigator or designee shall complete the Patient Registration Form and submit for initial approval in the EDC system. Following confirmation that all appropriate forms have been completed, Bellicum will approve the subject assignment number in the EDC system. Before the starting of conditioning, the site shall confirm the subject eligibility and complete the subject enrollment.

5 TREATMENTS ADMINISTERED

5.1 Screening

Screening activities shall occur after consenting. Historical assessments can be used to determine eligibility if performed within 42 days prior to the day of conditioning, except vital signs, complete blood count (CBC) with differential and platelet count (PLT), performance score, and serum chemistry panel which should be within 1 week prior to the day conditioning begins.

5.2 Donor Screening Investigation

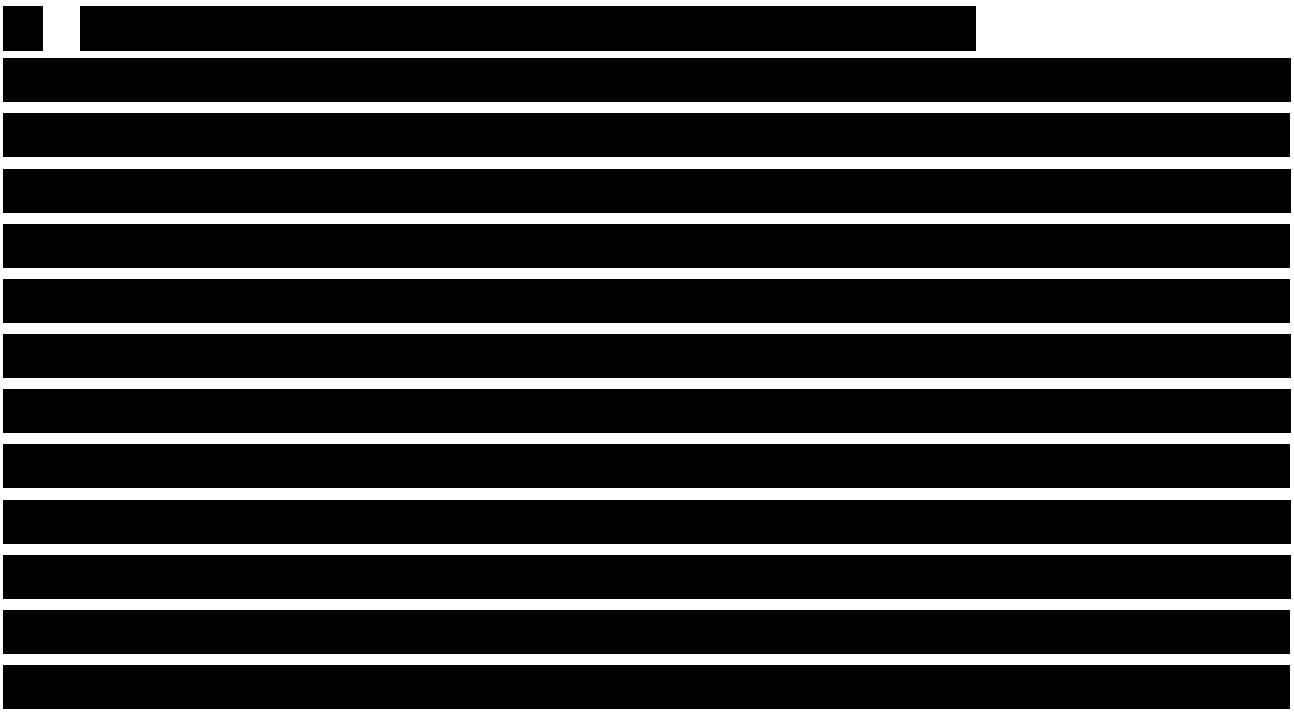
Infectious disease monitoring per the established local regulatory guidelines will be performed, and per local regulations. Any or all of the following tests may be performed as required per donor selection guidelines:

anti-HIV-1; anti-HIV-2; HIV-antigen, anti-HTLV I/II; HBs-antigen; anti-HBc; anti-HCV; CMV status; EBV status; TPHA

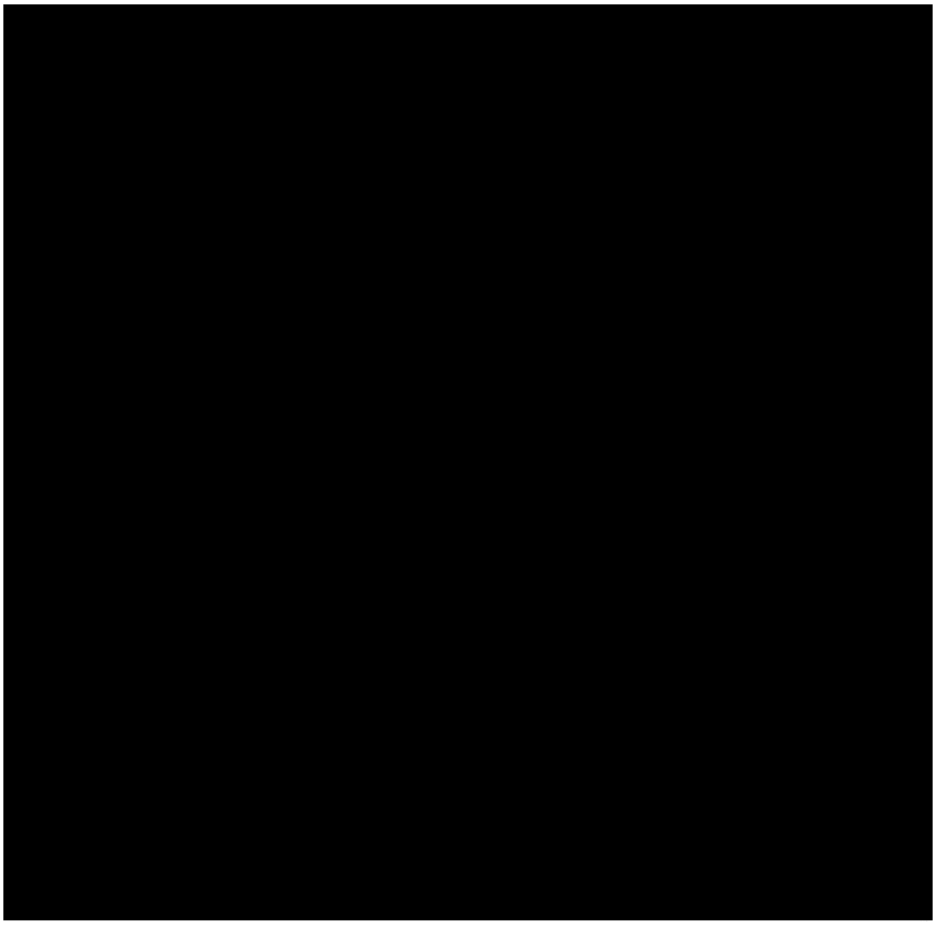
Positive HIV, Hepatitis B and C DNA and TPHA serology are contra-indications to stem cell donation. Positive results will be discussed with the donor. Selected virology screening will be repeated at the time of leukapheresis for the BPX-501 (CaspaCIDe) T cells

5.3 T Cell Apheresis for T Cell Manufacture at Bellicum Pharmaceuticals

Prior to the non-mobilized T cell leukapheresis, the donor will be evaluated per the local guidelines. Leukocyte fraction will be collected using standardized continuous flow centrifugation. The donor will be monitored during apheresis. A standard apheresis procedure of up to approximately 2 blood volumes will be processed per institutional standard procedures. The volume processed and the duration of leukapheresis will be documented and recorded. If less than $5x10^9$ mononuclear cells are collected, the Medical Monitor or Sponsor representative must be consulted immediately.



[redacted]



5.4.1 Packaging and Formulation

BPX-501 T cells are cryopreserved in 10-15 mL freezing medium (Cryostor, BioLife) and are stored frozen in cryostorage bags at or below -130ºC.

5.4.2 Labeling

The product label and insert include the subject ID number, cryopreservation date, lot number, total T cell dose, storage conditions, sponsor, and product name. All products manufactured also labeled with: "For Clinical Trial Use Only". The product will be labeled according to the requirement of each competent authority.

5.4.3 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 at or below -130°C until time of infusion. At that time, the product will be thawed at 37°C ± 2°C per instructions for infusion to the recipient. Depending on the day of shipment timing may be longer than 1 day.

5.5 Rimiducid Dimerizer Drug Packaging, Labeling and Storage

5.5.1 Packaging and Formulation

The rimiducid for Injection is packaged in Type 1 clear glass serum vials. [redacted]

[redacted] Each vial is stoppered with a Teflon©coated serum stopper and flip-off seal.

5.5.2 Labeling

The primary product label (applied directly to the vial) for the rimiducid for Injection will contain at a minimum the following information: product name, rimiducid; the manufacturers' lot number; product concentration, 5 mg/mL; volume of solution available in the vial; total RIMIDUCID contents of the vial. The product will be labeled according to the requirement of each competent authority.

5.5.3 Storage

The rimiducid for injection vials must be stored at 5°C ± 3°C (41°F ± 5°F) in a limited access, qualified refrigerator, preferably without light.

5.5.4 Preparation for Treatment

For use, the rimiducid will be diluted prior to administration. The rimiducid is administered via I.V. infusion at a dose of 0.4mg/kg diluted in normal saline with volume as appropriate for age of patient to be administered over 2 hours, using a DEHP-free saline bag and solution set.

5.6 Donor Peripheral Stem Cells Mobilization

The selected donor will receive recombinant G-CSF (Neupogen®), as per site SOP by daily subcutaneous injection beginning from day –5 from the leukapheresis procedure. For a representative protocol, see Appendix G.

5.7 Stem Cell Apheresis Procedure

The target number of CD34+ stem cells apheresed (i.e. prior to selection) should be ≥ 12-15 x 10^6 /kg recipient weight. This should correspond to at least 8-10 x 10^6 /kg CD34+ cells post-selection to be infused (allowing for up to 40% loss during the selection procedure). The actual numbers achieved will be documented. A maximum of three successive daily apheresis sessions may be performed to facilitate achieving the target dose of $CD34^+$ cells is ≥ 0.04 x10^9/L, the leukapheresis may be performed on Day –1; if not, the donor may receive plerixafor (240 µg/kg) on Day –1 and the leukapheresis targeted to be performed on Day 0 as per institutional procedures. Repeated doses of plerixafor may be given per institutional practices if the targeted number of peripheral CD34+ cells not achieved.

- The ideal number of peripheral CD34+ cells is ≥ 0.04 x10^9/L.
- The minimal number of peripheral CD34+ cells is 0.02 x10^9/L.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.9 Conditioning Regimen

Patients will receive a myeloablative conditioning regimen depending on their underlying disease, age and whether they have undergone previous autologous HSCT. One of the following

recommended conditioning regimens should be used (for details please see Appendix I: Conditioning Regimens) or those per institutional procedures:

- Total Body Irradiation (TBI, 1200 cGy over 6 fractions or 8 fractions) + Thiotepa (TT, 10 mg/kg in 2 divided doses) + Fludarabine (Flu, 160 mg/m^2 over 4 days)
- Total Body Irradiation (TBI, 1200 cGy over 6 fractions or 8 fractions) + Thiotepa (TT, 10 mg/kg in 2 divided doses) + Melphalan (L-PAM, 140 mg/m^2 in single dose).
- Busulfan (0.8-1.2 mg/kg iv 4 times per day for 4 days) + TT (10 mg/kg in 2 divided doses) + Flu (160 mg/m^2 over 4 days)
- Treosulfan* (Treo, 42 gr/m^2 over 3 days) + TT (10 mg/kg in 2 divided doses) + Flu (160 mg/m^2) (* If not available, busulfan can be used per institutional standard)
- Treosulfan* (Treo, 42 gr/m^2) + Flu (160 mg/m^2 over 4 days) (*If not available, busulfan can be used per institutional standard)
- Cyclophosphamide (Cyclo, 1200 mg/m^2 over 4 days) + Flu (160 mg/m^2 over 4 days) $\pm$ low-dose TBI (200 cGy)

Table 2: Recommended Conditioning Regimens per Disease Indication

Conditioning regimen	TBI, TT, Flu	TBI, TT, L-PAM	Bu, TT, Flu	Treo, TT, Flu	Treo, Flu	Cyclo, Flu, +/- low-dose TBI
ALL	√	√	√	√	√	
AML		√	√			
Myelodysplastic syndromes			√	√	√	
Congenital immune deficiencies				√	√	
Severe aplastic anemia						√
Fanconi anemia						√
Osteopetrosis			√	√		
Selected cases of hemoglobinopathies			√	√		

Rabbit anti-thymocyte globulin will be administrated from Day -4 to Day -2 (3 consecutive days) (Appendix F) and rituximab will be administrated at a dosage of 200 mg/m^2 on Day -1. Neovii rabbit

ATG is recommended to be administered at a dose of 12-15 mg/kg over 3 days. Rituximab will be given for preventing the occurrence of EBV-related post-transplant lymphoproliferative disease (PTLD). Seizure prophylaxis will be administered per institutional guidelines while on busulfan.

5.10 Infusion of BPX-501 Cells

The BPX-501 T cell infusion should be administered 14 days (±4 days) after completion of the stem cell allograft infusion. The BPX-501 T cell product will be thawed in a 37 °C water bath, diluted with 50 ml Plasmalyte (or NS), 35 ml initially, then 15 ml to "rinse" the bag, and administered over 30 minutes (or as appropriate for patient weight). The patient will be pretreated with diphenhydramine and acetaminophen or equivalent per institutional standards. All treatments administered will be documented. No additional pharmacological GvHD prophylaxis will be administered after transplantation and during the period of the study.

In the event of primary graft failure, the patient may receive additional conditioning prior to receiving the BPX-501 infusion. In the event of secondary graft failure, after additional immunosuppressive conditioning, an additional lot of BPX-501 may be manufactured from the donor.

5.11 Infusion of Rimiducid

5.11.1 GVHD Treatment

5.11.1.1 Acute GvHD Treatment

There is the potential for patients to experience both acute and chronic graft vs. host disease (aGVHD and cGVHD) due to their allogeneic transplantation for their underlying disease (primary immunodeficiency or malignancy). The BPX-501 T cells are intended to: aid in engraftment, promote immune reconstitution, enhance allogeneic graft-vs-leukemia (GvL) effects in malignant recipients, and can be eliminated upon infusion of rimiducid for potential mitigation of allo-reactive side effects. Acute GvHD grading should be conducted in accordance with the Modified Keystone Grading Schema (Appendix B). Refer to guidelines for management of aGVHD provided in Appendix B: `Acute GvHD Grading Scale by Organ`

Vital signs are recorded prior to rimiducid infusion, at 15, 30, 60, 120 and 240 minutes after start of infusion. When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate

processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours, and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

5.11.1.2 Chronic GvHD Treatment

Chronic GVHD (cGVHD) typically occurs 100 days or later after HSCT. cGvHD can often present with a sicca-like syndrome with thickened skin, lichen planus, papules, cholestatic jaundice, scleroderma-like skin, eye and GI lesions. cGVHD patients can also develop obstructive pulmonary disease symptoms.

cGVHD is typically classified into mild (i.e., localized skin involvement, with/or without liver dysfunction) or moderate to severe (i.e., generalized skin involvement or localized skin and/or hepatic dysfunction, plus liver histology showing hepatitis/necrosis/cirrhosis, eye involvement, salivary gland involvement, or effects on other organs). Moderate to severe cGVHD usually involves more than one organ with an organ severity score of moderate or greater (or mild or greater for lungs). Management guidelines for cGVHD are shown in Appendix C.

Response should be assessed per Appendix C. Three general categories of overall response are used in clinical trials: complete response (CR), partial response (PR), and lack of response (unchanged, mixed response, progression). Complete response is defined as resolution of all manifestations in each organ or site, and PR is defined as improvement in at least 1 organ or site without progression in any other organ or site. The 2014 NIH Consensus Working Group recommends that skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia be considered in evaluating overall response. Genital tract and other manifestations are not included due to lack of validated response measures.

Partial response in a specific organ requires an improvement of 1 or more points on a 4 to 7-point scale or an improvement of 2 or more points on a 10 to 12-point scale. The overall category of PR requires the absence of progression in any organ.

5.11.2 Contraception after Rimiducid Infusion

Subjects with child-bearing potential (defined as age ≥ 13 years) must either commit to true abstinence from heterosexual contact or agree to use and be able to comply with two-physician approved effective contraception methods for 6 months after the last dose of rimiducid.

5.12 Monitoring

5.12.1 Immune Monitoring Phase II Extension

Peripheral blood samples will be assessed to determine immune reconstitution. Phenotypic and functional studies of peripheral blood lymphocytes will be performed when feasible based on body weight and blood cell recovery (Appendix H).

5.12.2 Gene Therapy Monitoring

Per FDA guidelines, before HSCT and for 5-years post stem cell transplant, subjects will be evaluated with a physical exam and blood testing for vector and replication competent retrovirus (RCR) every six months. After 5 years, blood samples will be drawn annually for another 10 years (total of 15-year follow-up) if all post-treatment PCR assays are negative for RCR during the first year, yearly samples will be archived. This will be performed under a separate long-term follow-on protocol.

Table 3: Gene Therapy Monitoring Schedule

Time point of collection	Clinical Evaluation	Blood
Pre-infusion of gene modified cells	X	X
3 months	X	X
6 months	X	X
1 year	X	X
18, 24, 30, 36, 42, 48, 54, 60 months	X	X*
6-15 years	X	X*

** If all post-treatment PCR assays are negative for RCR during the first year, yearly samples will be archived.*

5.13 Management of Experimental Drugs

The investigational T cell product (BPX-501 CaspaCIDe T cells) will be infused on or about Day 14 (±4 days) after stem cell transplant.

Rimiducid will be infused upon the development of GvHD per Section 5.11.

5.14 Concomitant Therapies

The protocol will be conducted during the routine clinical care of the patients. All treatments such as transfusions and critical medications, defined as below shall be collected in the EDC database:

- Drugs and radiation treatment in conditioning regimens, including most recent chemotherapy regimen and G-CSF
- Treatment for GvHD
- Prophylaxis and/or treatment for infectious complications
- Treatments in association with SAEs or AEs of special interest such as febrile neutropenia and anaphylaxis

Standard supportive care treatments, non-prescription medications/OTCs, NSAIDs, laxatives/stool softeners, vitamins, and herbal supplements will not be collected if they are not protocol-mandated. Anti-viral prophylaxis will be administered per standard site procedures (for representative treatment see Appendix G).

Any post-transplantation pharmacological treatment (including steroids, calcineurin inhibitors, Mycophenolate Mofetil (MMF), Methotrexate (MTX), serotherapy) aimed at preventing GvHD will not be allowed unless approved by Medical Monitor/Sponsor.

5.15 Transfusion Requirements

The use of platelet transfusions will be carried out according to standard practice and will be recorded as the number and type of units given.

Red cell transfusion will be given according to standard practice and the number and type of units will be recorded.

All platelets and red cells will be leukocyte depleted and irradiated in accordance with transfusion policy for patients undergoing HSCT.

6 EVALUATION CRITERIA

6.1 Clinical Assessment

2-3 weeks prior to the start of the study a clinical assessment of the patients will be performed with documentation of performance status, height, weight and surface area calculated. Constitutional symptoms will also be documented at this time.

6.2 Laboratory Investigations

Lab tests will be performed according to Appendix G and H. Additional tests will be undertaken as is the standard institutional practice post-transplant (for representative protocols see Appendix G).

6.3 Radiological Investigations

Radiological investigations will be undertaken as is the standard practice prior to transplant.

6.4 Microbiological Investigations

Microbiological investigations and treatment will be undertaken as is the standard institutional practice post-transplant (for representative protocols see Appendix G)

6.5 Definition of Engraftment

For the purpose of evaluation hematopoietic recovery is defined as neutrophils > 0.5 x 10^9/L for 3 consecutive days together with platelet count > 20 x 10^9/L and without platelet support for 7 consecutive days.

Donor/recipient chimerism will be evaluated post-transplant through the analysis of Variable Number of Tandem Repeats (VNTR) polymorphism or other types of chimerism analysis per institutional standard. The same method shall be used for the same subject throughout the post- transplant period.

7 SAFETY REPORTING

7.1 Parameters of safety, assessment of AE and SAE

Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry variables vital signs and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s). The AE grading (severity) scale found in the NCI CTCAE v4.03 will be used for AE reporting. The NCI CTCAE v4.03 can be found:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Bellicum or its designee is responsible for reporting relevant SAEs to the FDA, EU and 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.

Adverse Event

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

This includes the following:

1. AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period
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

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 subject 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 subject'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 subject or may require medical/surgical intervention to prevent one of the outcomes listed above)
7. Suspected transmission of infectious agent via a medicinal product

Readmission to the hospital after stem cell transplantation is expected as a result of a number of transplant-associated adverse effects such as:

- Recurrence of the leukemia or cancer
- Febrile episode, including febrile neutropenia
- Bleeding from thrombocytopenia (low platelets)
- Acute or chronic GvHD

These re-hospitalizations should be reported in the electronic case report form (eCRF) as AEs, not SAEs, for this study as they are expected after the stem cell transplant. However, if local laws require that the site submit all SAEs then the local law will supersede the protocol requirements. Should any of the above expected conditions worsen or develop into serious, life-threatening events which are unexpected or considered study-related, then they must be reported to the sponsor as per SAE reporting guidelines.

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

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

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

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 7.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

Adverse Event Reporting Period

After informed consent, but prior to initiation of BPX-501 infusion, only SAEs will be collected. All AEs (except GvHD) will be collected following infusion of BPX-501 or rimiducid until 180-days post-transplant. SAEs regardless of attribution will be collected during the same timeframe until 180-days post-transplant. From 180 days, AEs and SAEs will be collected on the follow-on protocol BP-404.

GvHD Adverse Event Reporting

All occurrences of GvHD will be reported as Adverse Events (or SAEs) regardless of their start date in relation to BPX-501 infusions. GvHD events will also be followed until resolution and not limited to the standard AE/SAE reporting period.

Expedited Reporting Requirements for Serious Adverse Events

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

Any life-threatening or fatal SAE will be submitted to the sponsor on the Bellicum SAE Report form by email or fax, within 24 hours of the site study team learning of the event. Additionally, the Medical Monitor may also be contacted by phone to discuss event details. It is expected that the Serious Adverse event details are entered in the eCRF. All other SAEs will be reported to Bellicum on the SAE Report form and eCRF within 1 business day of learning of the event.

Special Reporting Requirements for Neurotoxicity

BPX-501 cells have been documented to enter the central nervous system (CNS). As the significance of this finding of 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 K for guidelines pertaining to monitoring and management of neurotoxicity.

Report all Serious Adverse Event Notifications to:

Email for SAE Reporting:	[redacted]
SAE Fax Number:	[redacted]

For Urgent Communication:

Medical Monitor Contact Information:

Medical Monitor/Director	
Email:	[redacted]
SAE Telephone No:	[redacted]

Reporting SAEs to the Ethics Committee and Regulatory Authorities

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

All events qualifying as Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the relevant regulatory authorities, central Ethics Committees and to EudraVigilance by the Sponsor or its representative. SUSARs are required to be reported within 7 calendar days for life threatening events and those resulting in death, or 15 calendar days for all others. These timeframes begin with the first notification of the SUSAR to the Sponsor from the investigator.

Reporting Requirements for All SAEs

Investigators will submit reports of life-threatening or fatal SAEs, to Bellicum within 24 hours of learning of the events. All other SAEs will be reported to Bellicum on the SAE Report form within 1 business day of learning of the event. For initial SAE reports, investigators should record all case details that can be gathered within 24 hours on the Bellicum SAE Report form and submit the report electronically. Relevant follow-up information should be submitted to Bellicum or its designee as soon as it becomes available and/or upon request.

Type and Duration of Follow-Up of Subjects after Adverse Events

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

For some SAEs, the Sponsor or its designee may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Post-Study Adverse Events

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

7.2 End of Study

The study will evaluate event-free survival for all evaluable patients enrolled at 180 days (6 months) after transplantation (active period). Patients will then be followed for long term safety and outcome study for 2-years post-transplant in BP-404, and then for a total of 15 years for gene therapy safety events.

DATA COLLECTION, QUALITY ASSURANCE AND MANAGEMENT

7.3 Recording of Data

Data will be recorded on electronic database and will be entered after validation into a computer system for subsequent tabulation and analyses. The investigator must ensure that each subject's anonymity is maintained. Subjects will be identified by a unique Subject Identification Number. Study related documents should be kept in strict confidence by the investigator in compliance with applicable regulations and ICH GCP Guidelines.

7.4 Data quality Assurance

The Investigators undertake to perform the study in accordance with this Protocol, Good Clinical Practice and the applicable regulatory requirements.

The Investigators are required to ensure compliance with the investigational product schedule, visits schedule and procedures required by the protocol.

The Investigators agree to provide all information requested in the Case Report Form in an accurate and legible manner.

7.5 Data Management

The investigator will fill in eCRF for documentation. All relevant data collected during the study for all of the patients enrolled into the study have to be entered into the database by the responsible investigator or someone authorized by him in a timely manner. The principal investigator (PI) will review all the eCRF's of each patient and confirm the completeness, medical correctness and plausibility of the documented data by his signature on all eCRF pages.

Additions and corrections in the eCRF will be dated and signed by the responsible physician or an authorized person. Reasons must be given for corrections that are not self-explanatory

Bellicum or CRO will ensure that the clinical trial is conducted, recorded, and reported in accordance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

Representatives of Bellicum or the CRO must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. On-site they will review study records and directly compare them with source documents, and discuss the conduct of the study with the investigator, and

verify that the facilities remain acceptable. Source documents are defined as: patient files, letters, and laboratory/histology records.

7.6 Statistical Methods

The material of this section is the basis for the Statistical Analysis Plan of this study. This plan may be revised during the study to accommodate Clinical Trial Protocol Amendments.

7.6.1 Sample Size

175 evaluable patients treated with BPX-501 T cells in the Phase II extension phase will be recruited over a total over a period of 60 months.

7.6.2 Analysis Populations

The analysis population will be stratified by malignant and non-malignant indications. The safety population is proposed to comprise the entire pediatric population.

7.6.3 General Statistical Approach

Descriptive statistics will be utilized to summarize GvHD rates, clinical and biologic response and other measures of safety and toxicity in those subjects who received rimiducid administration as well as for the whole population.

Data per cohort will be presented, stratified according to the type of disorder, e.g. malignant or non-malignant.

All summary tables for quantitative parameters will display mean, standard deviation, median, range (minimum and maximum), and two-sided 95% confidence intervals, as well as number of missing data, where relevant. All summary tables for qualitative parameters will display counts, percentages, two-sided 95% confidence intervals, and, number of missing data, where relevant. Time to event parameters, such as time to immune reconstitution, will be summarized using the Kaplan-Meier (KM) analysis method, including the 25^{th}, 50^{th} (median) and 75^{th}-percentile statistics, and number of censored observations.

7.6.4 Study Patient Description

- Disposition of Patients

- The number of enrolled patients will be summarized by country, center, and dose using counts and percentages.
- The number of patients either completing 180 days follow-up as well as those eligible to be enrolled in the follow-up protocol will be summarized using counts and percentages.

7.6.5 Demographic and Baseline Characteristics

Baseline characteristics will be described using the patient populations and their accompanying donors. Demographics, medical history, qualifying disorder, and other baseline variables will be summarized as appropriate to the type of data. Data analysis will include evaluation of demographic and baseline characteristic data, including at least age, sex, race, ethnicity, type of disease and duration, prior HSCT, conditioning and HLA typing. Donor characteristics including age, ethnicity and relationship will also be summarized.

7.6.6 Infectious complications

Cumulative incidence of infectious complications at 180 days will be analyzed, as defined by cumulative incidence of clinically significant viral reactivations, patients requiring antiviral treatment, rehospitalizations due to viral infection, bacterial and fungal infections and use of non-prophylactic antibiotic and antifungal use at 180 days

7.6.7 Engraftment and GVHD Analysis

Duration of hospitalization for the transplant procedure will be reported

7.6.7.1 Analysis of Time to Neutrophil Engraftment

The time to neutrophil engraftment will be measured by determining the first of three consecutive measurements of an ANC > 500/μL following the conditioning regimen induced nadir, starting from Day 0.

The cumulative incidence of neutrophil engraftment estimates will be analyzed by BPX-501 dose, CD34+ cell dose in the allograft, γδT cell dose in the allograft, αβT cell dose in the allograft, ATG dosing, conditioning regimen and disease status.

7.6.7.2 Analysis of Platelet Engraftment

Time to platelet engraftment will be measured by determining the first of three consecutive measurements of platelet count >20,000/μL without platelet transfusion support for seven days, starting from Day 0. The cumulative incidence of platelet engraftment estimates will be analyzed by BPX-501 dose, CD34+ cell dose in the allograft, γδT cell dose, αβT cell dose in the allograft, ATG dosing, conditioning regimen and disease status.

7.6.7.3 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.

The cumulative incidence of graft failure estimates will be analyzed by BPX-501 dose, CD34+ cell dose in the allograft, γδT cell dose, αβT cell dose in the allograft, ATG dosing, conditioning regimen and disease status.

7.6.7.4 Analysis of Acute and Chronic GvHD

The time and severity of aGvHD are graded according to the Modified Keystone Grading Staging Schema (Appendix B). The time and severity of cGvHD are graded according to NIH Consensus Criteria (Appendix C).

7.6.8 Grade I-IV Acute GvHD:

The initial incidence of aGvHD Grades I-IV by Days 100 and 180 will be determined and will be analyzed by indication (malignant, non-malignant), conditioning regimen, BPX-501 dose, αβ T cell dose in the allograft, ATG dosing and degree of HLA match.

The response rates of aGvHD to standard treatment will be determined, as well the number of patients with aGVHD demonstrating non-improvement or progression on standard treatment. Time to resolution of GvHD will be analyzed in patients receiving rimiducid.

The initial incidence of severe aGvHD Grades III-IV by Days 100 and 180 will be determined and will be analyzed by conditioning regimen, BPX-501 dose, and degree of HLA match. The response rates of severe aGvHD Grades III and IV in patients receiving rimiducid treatment will be determined at Days 100 and 180 and time to resolution of GvHD after rimiducid infusion.

7.6.9 Chronic GvHD:

The initial incidence of severe cGvHD at 6 months will be determined and will be analyzed by conditioning regimen, αβT cell dose, disease status, and degree of HLA match. The response rates of cGvHD in patients receiving rimiducid treatment will be determined at 6 months and analyzed by the number rimiducid infusion and time to resolution of cGvHD after rimiducid infusion.

7.6.10 Analysis of Time to Disease Relapse

To assess the incidence of acute leukemia relapse from the day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to relapse will be considered a competing risk. The risk of relapse estimates at six-months post-transplant will be analyzed by regimen, disease status, GvHD status, and BPX-501 dose.

7.6.11 Transplant-Related Mortality

TRM will be assessed within the first 6 months following transplant. In malignant patients TRM (NRM) is defined as death occurring in a patient who was in complete remission. Relapse will be considered a competing risk. The cumulative incidence of TRM at will be determined at 6 months. The follow-on protocol will determine disease free survival at 1 year and 2 years, followed by safety evaluations for gene therapy for 15 years.

7.6.12 Immune Reconstitution

- CD3+ cell count, CD4+ cell count and CD8+ cell count at day 180, as well as B cells and Immunoglobulin levels at Day 180, additional analysis will include CD45 RA/RO, CD62L and CCR7.
- Descriptive summaries of these parameters in the overall patient group and by dose group as well as by time of measurement will be presented.
- Kinetics 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.

7.6.13 Disease-free/cGvHD free survival at 180 days

Chronic GvHD/Disease free survival will be assessed at 180 days.

7.6.14 Disease status at time of discharge, 100 and 180 days

7.6.14.1 Non-malignant disease patients:

Disease status of each specific disease indication at 180 days:

a. Primary immune disorders as determined by CD3 T cell count >500 cells/ul and lower normal levels of IgA and IgM at 180 days
b. Haemoglobinopathies as determined by incidence of RBC transfusion dependence and haemoglobin of >8.5 g/dL at 180 days
c. Fanconi Anemia as determined by RBC >3,000,000 cells/ul, neutrophil count determined by 1500 cells/ul and >150,000 platelet counts at 180 days

7.6.14.2 Malignant disease patients

Leukemia as determined by PFS at 180 days

7.7 Safety Analysis

Safety analysis will investigate the analysis populations over the time period defined as from the infusion date of the respective treatment to study end date.

7.8 Adverse Events (AEs)

All adverse events recorded during the study will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and be graded according to the NCI CTCAE v4.03 scale (see Appendix C).

AEs will be summarized for the following

Number (%) of patients with any AE,

Number (%) of patients with any SAE,

Number (%) of patients permanently withdrawn from study due to an AE.

All summaries will be presented by treatment group and stratified by type of disorder (e.g. malignant or non-malignant). They will include overall frequency of patients with events as well as frequency of patients with events by primary system organ class and preferred term. A patient will only be counted once within each system organ class and preferred term. For summaries regarding severe or study-drug related AEs, the highest severity or relationship will be considered for each patient per preferred term.

7.9 Deaths and Serious Adverse Events (SAE), AEs Leading to Treatment Discontinuation

SAEs, events leading to death, and AEs leading to treatment discontinuation will be summarized overall as well as by primary system organ class and preferred term.

7.10 Reporting of Deviations to the Protocol

All the deviations to the protocol will be described and justified in a separate form.

8 ETHICAL ISSUES/CONSIDERATIONS

8.1 Institutional and Ethical Review

The study will be conducted according to the ethical principles of the declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/120/EG), Italian Ministry of Health decree of July 15, 1997, FDA and other international regulatory agencies.

8.2 Investigator's Responsibilities

Any investigator or co-investigator who signed this protocol agrees to carry out this research in accordance with the protocol approved by the ethical committee, GCP and regulatory requirements. Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). The PI has the right to prematurely discontinue the study for significant efficacy or safety problems and will notify the co-investigators in writing, as well as the ethics committees and the competent authorities according to law and regulations.

8.2.1 Patient Informed Consent

The patient or parents/legal guardians are to be informed both in writing and verbally by the investigating physician. The patient and his/her parents/guardians must be given ample opportunity to decide whether or not to participate in this study and to ask questions concerning this. It must also be made clear to the patient that he/she can withdraw from the study at any time without giving reasons and that he/she will not be in any way disadvantaged by this. Assent will be documented as required by the IRB or the EC. The informing physician, the patient or guardian must each personally date and sign an informed consent form with a declaration on data privacy. Any informed consent will be part of the investigator’s file and retained with it. The patient will retain a copy of the patient information.

Each patient enrolled in this experimental protocol will not be included in any other trial, including those addressing issues related to supportive care. Other investigational agents may not be administered from the time of HSCT through Day 180 (6 months) except as clinically indicated for any experimental therapy for GvHD non-responsive to rimiducid, infections not responding to standard treatments or disease relapse.

8.2.2 Data Management and Storage

The investigator will organize the storage of the identification codes of the patients for at least 15 years after the end of the study. The files of the patients (medical records) and other original data will be kept for a minimum period of 15 years. Relevant parts of those records specific to support the traceability of BPX-501 from donor to recipient will be retained as applicable by the investigator, manufacturer and Sponsor per local requirement.

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Appendix A: Performance Status Criteria

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

Appendix B: Acute GvHD Grading Scale by Organ

Table B.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	Plus bullae and desquamation
Gut	Adult: < 500 ml/day	Adult: 500-1000 ml/day	Adult: 1001-1500 ml/day	Adult: >1500 ml/day	Severe abdominal pain +/- ileus, frank blood or melena
	Children: < 10 ml/kg/d	Children: 10-15 ml/kg/d	Children: 16-20 ml/kg/d	Children: 21-25 ml/kg/d	Children: ≥26 ml/kg/d
Upper GI		Severe nausea/vomiting			
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl

Reference: From "Graft-vs-host disease" Sullivan, Keith M. Hematopoietic Cell Transplantion Ed: D. Thomsa, K. Blume, S. Forman, Blackwell Sciences; 1999, pages 518-519.

Appendix B: Acute GvHD Grading Scale by Organ (cont.)

Table B.2: Overall Acute GvHD Grading

	Skin	Liver	Gut	Upper GI
0	None and	None and	None and	None
I	Stage 1-2 and	None and	None	None
II	Stage 3 and/or	Stage 1 and/or	Stage 1 and/or	Stage 1
III	None-Stage 3 with	Stage 2-3 or	Stage 2-4	N/A
IV	Stage 4 or	Stage 4	N/A	N/A

Reference:

From "Graft-vs-host disease" Sullivan, Keith M. Hematopoietic Cell Transplantion Ed: D. Thomsa, K. Blume, S. Forman, Blackwell Sciences; 1999, pages 518-519.

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Table B.3 Guidelines for Medical Management of Acute GvHD

Event	Management

aGvHD, Grade 1	• Consider skin biopsy to establish diagnosis
	  o Initial treatment with topical steroids per institutional standard of care for Grade 1 skin aGvHD
	• If no response to topical steroids or worsening in stage or grade of skin aGvHD after 48 hours, patients may receive systemic corticosteroids.
	• If no response to systemic steroids or worsening in stage or grade of skin aGVHD after 48 hours, patients may then receive rimiducid:
	  o Children: 0.4 mg/kg to a maximum of 40 mg IV
	  o Adults: 40 mg IV
	  o If there is evidence of clinical improvement (e.g. partial response) but not complete resolution after the first dose of rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours
	  o Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration
	  o For new or recurrent Grade 1 aGvHD episodes, rimiducid may be considered for repeat administration with the above guidelines if the investigator considered rimiducid to offer clinical benefit with prior episodes
	• If no response to topical steroids or rimiducid, the investigator should consider other medications per institutional guidelines (eg, calcineurin inhibitors, sirolimus, mycophenolate)
	• Peripheral blood should be collected for evaluation of 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 When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours, and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

aGvHD, Grades 2, 3 and 4	• Consider tissue (eg, skin, gut, liver) biopsy to establish diagnosis • 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: o Children: 0.4 mg/kg to a maximum of 40 mg IV o Adults: 40 mg IV o If there is evidence of clinical improvement (e.g. partial response) but not complete resolution after the first dose of rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours o Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration o For new or recurrent Grade 2 through 4 aGvHD episodes, rimiducid may be considered for repeat administration with the above guidelines if the investigator considered rimiducid to offer clinical benefit with prior episodes • Peripheral blood should be collected for evaluation of 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 When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours, and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

Appendix C: 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 C 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:_____

Table C.1: Global scoring of cGvHD

Number of Organs	Mild cGvHD	Moderate cGvHD	Severe cGvHD
1	Score 1	Score 2	Score 3
2	Score 1	Score 2	Score 3
3		Score 1	Score 3
Lung involvement		Score 1	Score 2

Mild cGvHD = 1 or 2 organs involved (except for lung) with maximum score of 1
Moderate cGvHD = lung score of 1 or 3 organs with score of 1 or at least 1 organ with score of 2
Severe cGvHD = lung score of 2 or score of 3 in any organ.

Reference:
Filipovitch AH et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005 Dec;11(12):945-56.

Table C.2 Management of Chronic GvHD (cGvHD)

Event	Management

cGvHD - Mild	• Consider tissue biopsy to establish diagnosis
	  o 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
	• If no response to steroids/systemic therapies occurs within 7 days, or there is a worsening in cGvHD, patients may then receive rimiducid:
	  o Children: 0.4 mg/kg to a maximum of 40 mg IV
	  o Adults: 40 mg IV
	  o If there is evidence of clinical improvement (e.g. partial response) but not complete resolution after the first dose of rimiducid, then rimiducid may be repeated up to a total of 3 doses beginning 48 hours after the first dose, with each dose separated by 48 hours
	  o Daily examination on day 1 and day 2 should be performed after initiating treatment with rimiducid, then weekly for 1 month, every 2 weeks for 100 days, and monthly after 100 days post-rimiducid administration
	  o For new or recurrent 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
	• Peripheral blood should be collected for evaluation of 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
	• When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours, and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.At each evaluation, complete Chronic GvHD Activity Assessment-Clinician and Chronic GvHD Activity Assessment-Patient Self Report

cGvHD – Moderate to Severe	• Consider tissue biopsy to establish diagnosis • Initial treatment with IV steroids or other systemic treatments (eg, calcineurin inhibitors) per institutional standard of care for extensive cGvHD should be instituted • If no response 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 • Peripheral blood should be collected for evaluation of 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 ○ When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours, and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

Table C.3 Response Determination for Chronic GvHD

Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

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

ULN indicates upper limit of normal.

Reference: Lee SJ et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant 2015;21: 984-999.

Appendix D: AE Grading and Toxicity

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

The NCI CTCAE v4.03 can be found:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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 subject's daily activities; no medical intervention and therapy required
2	Moderate (apply event specific- NCI CTCAE grading criteria)	Mild to moderate interference with the subject's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the subject'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 and 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.

Appendix E: Eligibility for Allotransplantation

1. High-risk ALL in 1st CR
2. ALL in 2nd CR
3. High-risk AML in 1st CR
4. AML in 2nd CR
5. Myelodysplastic syndromes

Appendix F: ATG Pharmacokinetics and Dosing

Anti-thymocyte globulin will be administrated from Day -4 to Day -2 (3 consecutive days).

Fresenius rabbit ATG is recommended to be administered at a dose of 4-5 mg/kg/day whereas the approximate equivalent dose of Thymoglobulin to be administered will be 1-1.25 mg/kg/day.

Table F1 below, shows the pharmacokinetics of a dose twice that which is intended in to be used in the study of the rabbit ATG, and demonstrates that by Day 14 the concentration of ATG falls below 100ug/ml.

Similarly, Figure F2 demonstrates that a dose of 10 mg/kg/day over 4 days (twice that suggested for the current protocol) has an active ATG (the fraction binding T cells) half-life of about 7 days.

The proposed administration period for the BPX-501 T cells of Day14 ± 4 days is consistent with approximately 2 half-life reductions in ATG levels regardless of the source of ATG.

Table F1: Median serum levels of ATG in 14 children after receiving dose of 10mg/kg ATG on Days -5, -4 and -3 (Rabbit ATG, Fresenius) *(Locatelli, personal communication)*

Sampling Time	ATG-Fresenius Serum Concentration (All Patients n=14)	
	Median (µg /mL)	IQR (µg /mL)
Follow up		
Day -2	181.7	111.75-261.8
Day -1	168.6	119.65-325.8
Day 0	153.1	104.6-195.8
Day +3	154.6	91.71-187.3
Day +5	103.7	84.6-177.9
Day +7	112.5	96.0-148.8
Day +14	99.1	71.9-136.4
Day +21	93	63.8-134.1
Day +28	75.6	49.7-104.1
Day +42	57.6	30.8-77.2
Day +56	44.5	18.1-46.8

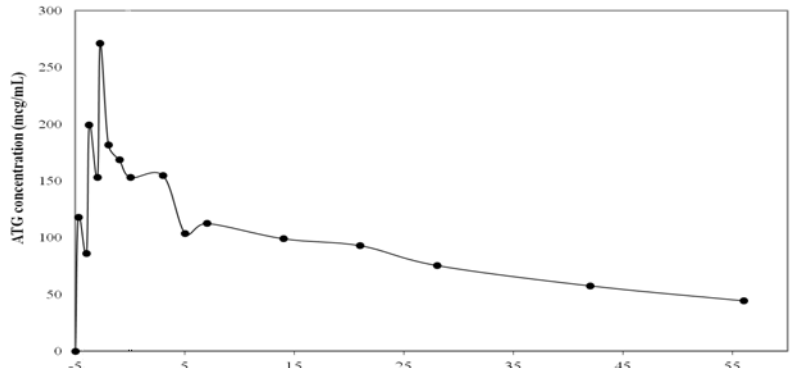
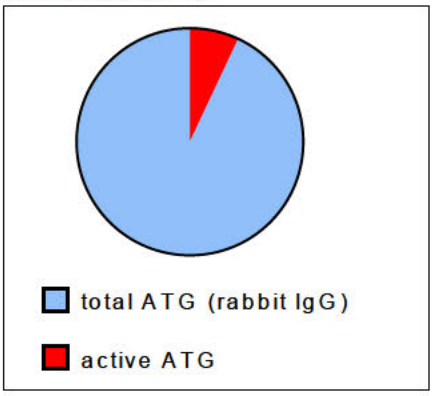


Figure F2 Thymoglobulin: 10 mg/kg Thymoglobulin Divided Over 4 Days (*Locatelli, personal communication)*



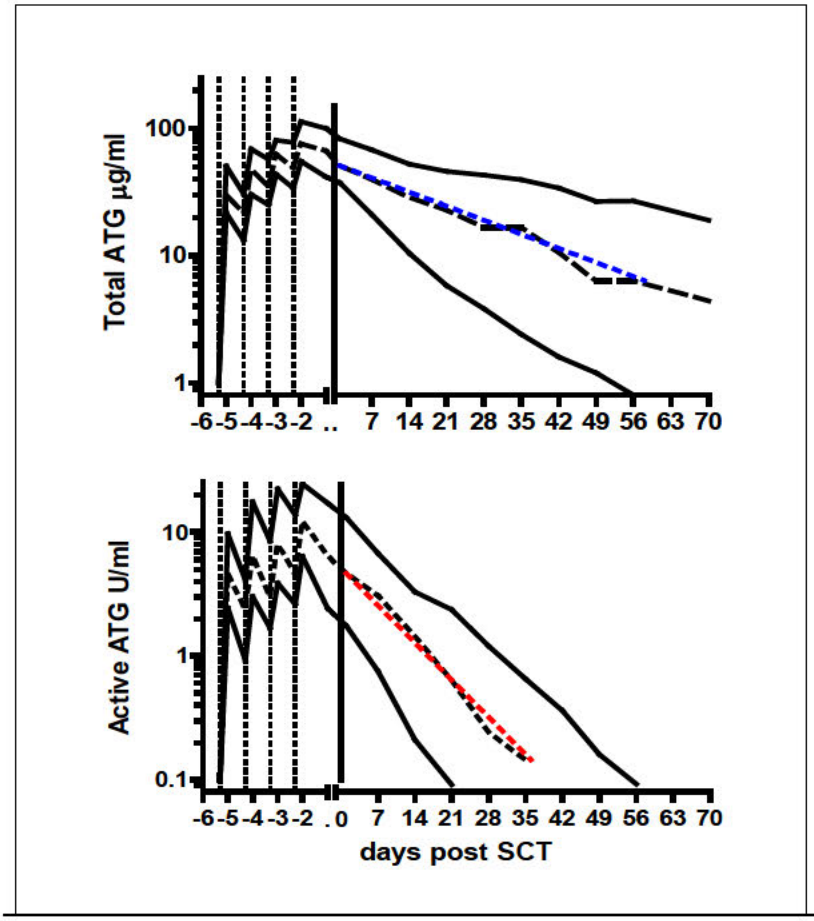
Total ATG

- Max Conc* ATG 80 ug/ml (54-125 ug/ml)
- Half-life from SCT d+1 onwards: ~19 days

Active ATG

- Quantitative FACS: ATG capable of binding to cells
- Max Conc* act ATG 12 U/ml (5-25 U/ml) (* *15 min past last dose)*
- Half-life from SCT d+1 onwards: ~7 days* *15 min past last dose*

Figure F3



Appendix G: Standard Institutional Donor Mobilization, Clinical Concomitant Care, Lab and Microbiological Monitoring

Suggested recommendations based on the Pediatric Hospital (OPBG), Rome standards

The selected donor will receive recombinant G-CSF at a dose of 12-16 µg/kg/d by daily subcutaneous injection beginning from Day –5 from the leukapheresis procedure with twice daily injection to Day –3 and three daily injection being administered from Day –2. On Day –2, CD34+ cells counts will be taken, if the number of CD34+ cells is ≥ 0.04 x10^9/L, the leukapheresis will be performed on Day –1; if not, the donor will receive plerixafor (240 µg/kg) on Day –1 and the leukapheresis will be performed on Day 0.

All patients will receive anti-viral prophylaxis with acyclovir (10 mg/kg/day from Day -2 to Day +180), anti-bacterial prophylaxis and anti-fungal prophylaxis with i.v. liposomal amphotericin-B or mold-active azoles (i.e. voriconazole, posaconazole). Pneumocistis Jirovecii pneumonia prophylaxis will be administered with cotrimoxazole (or aerosol pentamidine in case of allergy/intolerance to cotrimoxazole) from engraftment to 1 year after the allograft.

According to standard practice in the hospital, blood counts and differentials will be performed at least 3 times per week after transplant until the neutrophil count reaches 0.5 x 10^9/L. Thereafter, at least 2 times per week until the neutrophil count is > 1.0 x 10^9/L and platelets > 100 x 10^9/L. Subsequently, blood counts and differentials will be performed approximately every 2 weeks until + 100 days. Samples for biochemistry, related to the routine monitoring of hepatic and renal function, will be taken pre-transplant and thereafter at least 3 times weekly until engraftment and subsequently checked twice a week until + 100 days. Further results from routine outpatient follow-up controls after this time will be documented up to one-year post transplant.

Microbiological investigations will be according to standard procedures for the determination of an infectious organism in a child undergoing HSCT. These will include regular surveillance cultures (inclusive of oral flora), blood cultures and viral screening. All infections, either presumed or proven and treated, will be documented. Anti-microbial therapy and its duration will be documented. Reactivation of human cytomegalovirus (HCMV) infection will be tested at least twice a week till Day +60, using assessment of quantitative DNA in blood. Between Day +60 and 100 patients will be tested at least once a week. Thereafter, children will be tested during scheduled controls in the outpatient unit until 1 year after the allograft. Patients experiencing HCMV reactivation will be pre-emptively treated in the presence of more than 5,000 HCMV DNA copies/mL. Pre-emptive therapy will be based on administration of intravenous ganciclovir (5 mg/kg twice a day), replaced by foscarnet (90 mg/kg twice a day) in case of ganciclovir-induced neutropenia (less than 0.5x10^9 neutrophils/l) or sustained increase of HCMV DNA levels in blood during therapy with ganciclovir. Anti-viral treatment will be stopped in the presence of virus clearance from blood, i.e. after two consecutive negative results. Relapse episodes will be treated similarly.

Determination of quantitative EBV DNA and adenovirus DNA in blood will be performed at least once a week for the first 100 days after the allograft. Children with an Adenovirus viral load in blood greater 100,000 copies/mL confirmed on 2 consecutive samples will be treated with cidofovir (1 mg/kg/dose thrice a week) till viral clearance.

Patients with more than 10,000 copies/mL of EBV DNA in blood will be allowed to receive further doses of rituximab, which will be administered according to the schedule usually employed to prevent/treat EBV-related PTLD.

Galactomannan will be determined twice a week for the first 2 months after transplantation. Children with galactomannan levels greater than the normal values, associated with clinical or radiological signs suspected for an invasive aspergillosis will receive appropriate anti-fungal therapy.

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Appendix H: Laboratory Tests

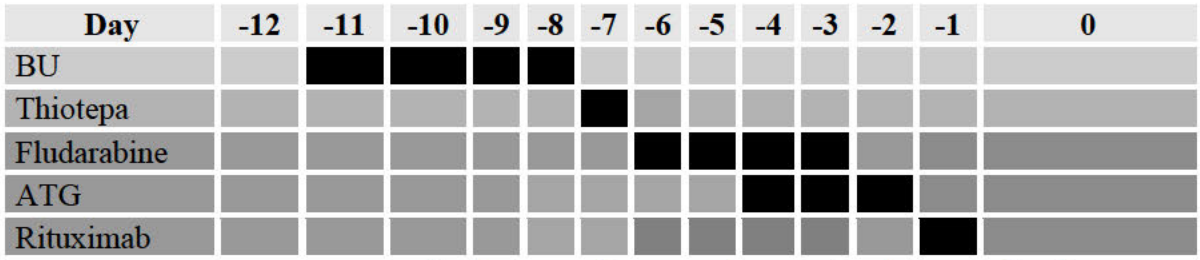
Activity	Timing
BM & Disease Evaluation [1]	Pre-transplant, Days 30±7, 100±10, and 180±10 post-transplant, and thereafter as needed
Chimerism [2]	Days 30±7 and 100±10 post-transplant, and thereafter as needed
Hematology[3]	Pre-transplant, post-transplant according to standard practice in the hospital until engraftment; then, 30±7, 44±7, 60±7, 74±7, 88±7, 100±10, and 100±10 post-transplant.
Serum Chemistry[4]	Pre-transplant, Days 30±7, 60±7, 44±7, 88±7, 100±10, 180±10 post-transplant.
Blood Sample for Immune Reconstitution/iCasp[5]	Pre-transplant, Day 30±7, 60±7, 100±10, and Day 180±10 post-transplant.
IgG	IgG, IgM and IgA levels: Pre-transplant, Day 30±7, Day 60±7, Day 100±10, and Day 180±10 post-transplant.
Bellicum Research Samples[6]	**BPX-501 T cell Post-Dose Levels** Baseline (-10 days to -1 day), immediately prior to BPX-501 infusion, 7 days post-BPX-501 infusion, weekly for one month after BPX-501 infusion (± 4 days), every 2 weeks ± 4 days to 100-days post BPX-501 infusion, monthly ± 14 days for until 1 year post BPX-501 infusion, every 6 months ± 1 month for 24 months post BPX-501 infusion. **Post-systemic corticosteroid administration:** Prior to administration of systemic corticosteroids doses (e.g. methylprednisolone), at 4 and 24 hours post-systemic corticosteroid initiation, and at 7, 14, 21, and 28 days post-systemic corticosteroid initiation.
Blood Sample for HAMA	Pre-transplant and Day 100±10 post-transplant
Blood Sample for RCR	Pre-transplant, Day 100±10d post-transplant, Day 180±10d. Follow-up protocol to monitor for 1 year, then every 6 months for 5 years then yearly for 10 years (15 years total)
Rimiducid Infusion Blood Samples[7]	When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

[1]Bone marrow evaluation is for subjects with hematological malignancies or non-malignant disorders such as congenital/hereditary cytopenia, including Fanconi Anemia and severe aplastic anemia. Disease evaluations for hematological malignancies such as acute leukemia include a bone marrow aspirate and biopsy. Cytogenetics, molecular, or other institutional assessment to determine Minimal Residual Disease (MRD) can be recorded at Baseline. Bone marrow aspirate for pathology and cytogenetics will be performed at Day 30, Day 100 and 180 Days. Additional assessment can be performed if clinically indicated.

[2]Donor/host chimerism analysis shall be performed according to standard practice in the hospital. The same method shall be used for the same subject.
[3]According to standard practice in the hospital, blood counts and differentials will be performed at least 3 times per week after transplant until the neutrophil count reaches 0.5 x 10^9/L. Thereafter, at least 2 times per week until the neutrophil count is > 1.0 x 10^9/L and platelets > 100 x 10^9/L.
[4]Serum chemistry panel: electrolytes, glucose, BUN, ALT, AST, creatinine, bilirubin, alkaline phosphatase, LDH, albumin. Electrolytes include sodium, potassium, chloride, carbon dioxide, calcium, and magnesium.
[5]The immune reconstitution flow panel includes CD3+ cells, alpha/beta CD3+ cells, gamma/delta CD3+ cells, CD4+ cells, CD8+ cells, NK cells and B cells, CD45RA, CD45RO, D62L and CCR7. After BPX-501 infusion, the flow panel will expand to include CD3+/CD19+ cells, CD3+/CD19+/CD4+ cells and CD3+/CD19+/CD8+ cells. Data from flow panel will be used to assess immune reconstitution.
[6] BPX-501 T cell post-dose levels samples should be sent to Bellicum and the post systemic corticosteroids administration should be analyzed locally, similar to rimiducid sample.
[7]At least 20 ml (or as weight permits) will be taken and sent to the Sponsor to analyze the effects of the rimiducid dimerizer drug on circulating gene modified T cells. Refer to Appendix J for the processing of samples for pPK testing.

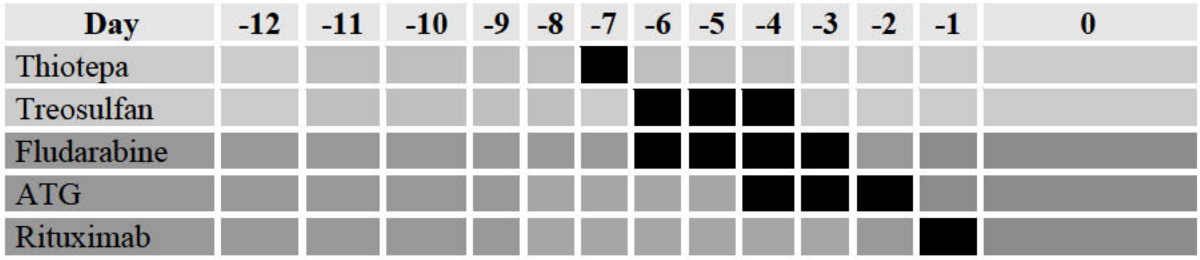
Appendix I: Conditioning Regimens

Busulfan-Thiotepa-Fludarabine



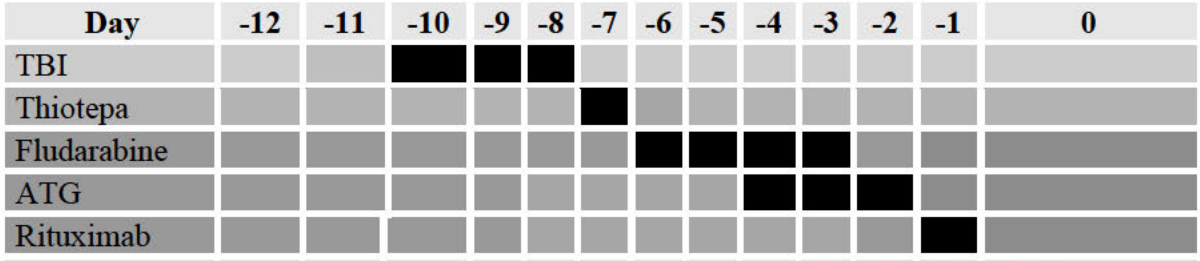
BU	0.8-1.2 mg/kg iv (according to patient BW) 4 times per day for 4 consecutive days (d -11,-10,-9,-8)
Thiotepa	5 mg/kg iv every 12 hours for 2 consecutive doses (d -7)
Fludarabine	40 mg/m^2/day iv for 4 consecutive days (d -6, -5, -4, -3)
ATG*	4 mg/kg/day iv for 3 consecutive days (d -4, -3, -2)
Rituximab	200 mg/ m^2 iv in a single dose (d -1)

Treosulfan**-Thiotepa-Fludarabine



Thiotepa	5 mg/kg iv every 12 hours for 2 consecutive doses (d -7)
Treosulfan	14 gr/ m^2/day iv for 3 consecutive days (d -6, -5, -4)
Fludarabine	40 mg/ m^2/day iv for 4 consecutive days (d -6, -5, -4, -3)
ATG*	4 mg/kg/day iv for 3 consecutive days (d -4, -3, -2)
Rituximab	200 mg/ m^2 iv in a single dose (d -1)

TBI-Thiotepa-Fludarabine



TBI	12 Gy divided in 6 fractions over 3 days (d -10,-9,-8) or in 8 fractions per institutional standard
Thiotepa	5 mg/kg iv every 12 hours for 2 consecutive doses (d -7)
Fludarabine	40 mg/m^2/day iv for 4 consecutive days (d -6, -5, -4, -3)
ATG*	4 mg/kg/day iv for 3 consecutive days (d -4, -3, -2)
Rituximab	200 mg/ m^2 iv in a single dose (d -1)

TBI-Thiotepa-Melphalan

Day	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
TBI													
Thiotepa													
Melphalan													
ATG													
Rituximab													

TBI	12 Gy divided in 6 fractions over 3 days (d -6, -5, -4) or in 8 fractions per institutional standard
Thiotepa	5 mg/kg iv every 12 hours for 2 consecutive doses (d -3)
Melphalan	140 mg/m^2 iv in a single dose (d -2)
ATG*	4 mg/kg/day iv for 3 consecutive days (d -4, -3, -2)
Rituximab	200 mg/ m^2 iv in a single dose (d -1)

Treosulfan**±Thiotepa-Fludarabine

Day	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
Treosulfan													
Fludarabine													
ATG													
Rituximab													

Thiotepa	5 mg/kg iv every 12 hours for 2 consecutive doses (d -7)
Treosulfan	14 gr/ m^2/day iv for 3 consecutive days (d -6, -5, -4)
Fludarabine	40 mg/ m^2/day iv for 4 consecutive days (d -6, -5, -4, -3)
ATG*	4 mg/kg/day iv for 3 consecutive days (d -4, -3, -2)
Rituximab	200 mg/ m^2 iv in a single dose (d -1)

Cyclophosphamide –Fludarabine ± TBI

Day	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
±TBI													
Cy													
Fludarabine													
ATG													
Rituximab													

TBI	200 cGy in a single dose (d -1)
Cyclophosphamide	300 mg/ m^2/day iv for 4 consecutive days (d -6, -5, -4, -3)
Fludarabine	40 mg/ m^2/day iv for 4 consecutive days (d -6, -5, -4, -3)
ATG*	4 mg/kg/day iv for 3 consecutive days (d -4, -3, -2)
Rituximab	200 mg/ m^2 iv in a single dose (d -1)

* Fresenius rabbit ATG is recommended to be administered at a dose of 4-5 mg/kg/day whereas the approximate equivalent dose of thymoglobulin to be administered will be 1-1.25 mg/kg/day.
** Busulfan can substitute for treosulfan per institutional practice.

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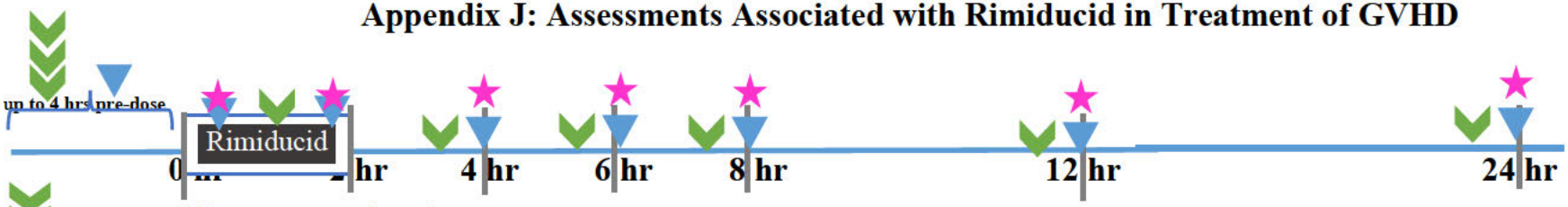
Appendix J: Assessments Associated with Rimiducid in Treatment of GVHD



Triplicate ECG: at pre-dose only.
Taken ~5 min prior to blood draws.

ECG: Should be taken ~5 min prior to blood draws.

Rimiducid PK Sample:
2 hr sample must be taken ≤ 5 min prior to end of rimiducid infusion.

Cellular Kinetics Sample.

Assessments: GVHD Treatment with rimiducid			
Time Point[1]	**BPX-501 Cellular Kinetics (CD3+/ CD19+)**	**Rimiducid PK (plasma)**	**ECG[4]**
Pre-Dose (≤ 4 hr)	✓	✓	✓ (triplicate)
30 minutes	✓	✓	✓
2 hr	✓[2]	✓[2]	✓
4 hr	✓	✓	✓
6 hr	✓	✓	✓
8 hr	✓	✓	✓
12 hr	✓	✓	✓
24 hr	✓	✓	✓
48 hr	✓	N/A	N/A
7 days	✓	N/A	N/A
14 days	✓[3]	N/A	N/A
21 days	✓[3]	N/A	N/A
28 days	✓[3]	N/A	N/A

[1]Rimiducid is infused over 2 hours. The reference point for all time points (0 hr) is the initiation of the rimiducid infusion.
[2]The 2 hr PK must be collected ≤ 5 min prior to the end of the rimiducid infusion.
[3] After the last dose of rimiducid
[4] All ECG should be performed approximately ≤ 5 mins prior to any sample collection if there is a collection at the same time-point.

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Appendix K: 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 K.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. Some pediatric populations (<3 years old) are exempt from completing this examination. 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 or mental status changes, refer to Table K.2 below for evaluation and management guidelines.

Table K.1.: Monitoring of Patients for Neurologic Complications

Timing	Neurologic examination	Mini-mental status examination
Inpatient prior to BPX-501 infusion	✓	✓
Daily Inpatient after BPX-501 infusion	✓	✓
Routine outpatient clinic visits or emergency room visits	✓	✓

Table K.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 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. o CSF evaluations for other infectious etiologies (e.g., herpes viruses, JC virus, fungal, West Nile virus and toxoplasma) o 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 o Special consideration should be considered for conditioning agents (e.g., Busulfan) or prophylactic GvHD medications (e.g., calcineurin inhibitors) as an etiology and institutional guidelines should be instituted for possible treatments (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 (1000 mg/day 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 repeated every 48 hours for up to 3 doses. Please notify the medical monitor at Bellicum prior to the administration of rimiducid for neurotoxicity. • Peripheral blood should be collected for evaluation of 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 When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours, and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

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. o CSF evaluations for other infectious etiologies (eg, herpes viruses, JC virus, fungal, West Nile virus and toxoplasma) o 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 o 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 (1000 mg/day x 3-5 days for adults or 30 mg/kg/day x 2-5 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 (1000 mg/day 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. • Peripheral blood should be collected for evaluation of 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 When possible, considering patient weight, blood samples will be drawn within 4 hours prior to the initiation of rimiducid infusion; 30 mins after initiation of the infusion; at 2 hours (< 5 min prior to end of the rimiducid infusion), 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after the initiation of the infusion. Each sample collected

		out to 24 hours should be split for separate processing. Approximately 0.5 to 1 mL of blood should be processed to plasma and stored at -80 C for later PK analysis of rimiducid. The remaining samples, at least 0.3 mL of blood, should be used for prompt CD3+CD19+ T cell analysis. Additional samples (at least 0.3 mL) will be drawn at 48 hours and 7 days after the start of each rimiducid infusion and 14 days, 21 days, and 28 days after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

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

1. Includes but not limited to cranial nerve abnormalities, brachial plexopathy, ischemia, nystagmus, pyramidal tract syndrome, radiculitis, focal seizure, stroke, transient ischemic attack
2. Includes but not limited to aphonia, ataxia, cognitive disturbance, depressed level of consciousness, dysarthria, dysphasia, encephalopathy, headache, hypersomnia, lethargy, memory impairment, meningismus, seizures, somnolence, tremor, visual disturbances

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