Bellicum

Follow-up of Phase I/II 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-404**
Combination Product:	**BPX-501** – Donor T cells genetically modified with BPZ-1001 retroviral vector containing the iCasp safety gene **Rimiducid (Dimerizer drug)**
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Trial Sponsor:	**Bellicum Pharmaceuticals, Inc.** 2130 W. Holcombe Blvd, Suite 800 Houston, TX 77030
ClinicalTrials.Gov / EudraCT Number:	**2016-003226-16**
Version Number:	**4.0**
Date:	**30 June 2020**

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:

Follow-up of Phase I/II 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: _____ Date: _____
Name: Charity Scripture, MS, PharmD, BCOP
Title: Vice President, Clinical and Medical Affairs
Sponsor: Bellicum Pharmaceuticals Inc.

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1 BACKGROUND

Over the past 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. In particular, the physical elimination of T cells from the graft has been shown to be highly effective to prevent both acute and chronic GVHD (cGVHD). However, with T- cell depletion of the graft, the patient cannot benefit from 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).

US and European gene therapy guidelines require monitoring delayed adverse events in patients who are exposed to gene therapy products for a period of 5-15 years depending on the nature of the product. A potential, but rare, risk of gene therapy using retroviral vectors is the generation of a replication competent retrovirus. This long term follow-up observation period provides a chance to mitigate risks associated with the gene therapy.

2 SYNOPSIS

Study Identifier(s)	BP-404 EudraCT #2016-003226-16
Aim of the Study	This is a Phase I/II study to evaluate the long-term safety of the infusion of BPX-501 gene-modified T cells after mismatched, T cell-depleted allogeneic transplantation and evaluate disease free survival at 1 and 2 years post-transplant
Study Design	Open label, multi-centre, non-randomized, non-controlled long-term safety evaluation Follow-up of all patients enrolled on BP-004 and treated with BPX-501 who are beyond Day 180 and have completed or discontinued the parent study.
Study Population	The patient population is identical to BP-004 as it is the long-term follow-up of those patients. Estimated enrolment up to 175 BP-004 patients.
Main Inclusion Criteria	1. Signed written informed consent by the patient or the patient's guardian for children who are minors 2. Enrolled on BP-004 protocol, received BPX-501 infusion, completed or discontinued from the study, and are beyond Day 180.
Main Exclusion Criteria	1. Lack of parents'/guardian's informed consent for children who are minors 2. Withdrawal from BP-004 study prior to BPX-501 infusion.
Dosage, Treatment Regimen, Route of Administration	No BPX-501 infusions will be administered under this protocol. Rimiducid to be given at 0.4 mg/kg weight (intravenous infusion) only in the setting of uncontrolled GVHD.
Locations (e.g. regions)	Italy, Saudi Arabia.
Primary Endpoint(s) with Time Point(s) of Assessment	Overall Survival and incidence of Disease-Free Survival in both malignant and non-malignant patients at 1 year and 2 years post-transplant. Relapse-Free Survival in malignant patients at 1 year and 2 years post-transplant.
Main Secondary Endpoint(s) with Time(s) of Assessment	Long-term safety for a total of 15 years from BPX-501 administration

Table 1: Schedule of Events (Laboratory and Clinical)

Time - Months (+/-14 Days)	9	12	15	18	21	24	30	36	42	48	54	60	YEARLY	6-15
Overall Survival (OS)		X				X		X		X		X		X
Disease-Free Survival (DFS)		X				X		X		X		X		X
Relapse-Free Survival (RFS)		X				X		X		X		X		X
Hematology; Chemistry	X	X	X	X	X	X								
Immune Reconstitution[1]:	X	X	X	X	X	X								
RCR[4]	X	X	X	X	X	X	X	X	X	X	X	X		X
Modified History & Physical	X	X	X	X	X	X	X	X	X	X	X	X		X
Neurological Exam[5]	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital Signs[2]	X	X	X	X	X	X								
GVHD Assessment[6]	X	X	X	X	X	X								
Concomitant Medication[3]	X	X	X	X	X	X								
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X		X
Bellicum Research Samples	**BPX-501 T cell Assessment** Research samples for assessment of BPX-501 cells (CD3+CD19+) will be collected monthly (± 14 days) 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 and sent to the sponsor prior to administration of systemic corticosteroids doses (e.g. methylprednisolone), at 4-hours (± 30 minutes) and 24-hours (± 1 hour) post-systemic corticosteroid initiation, and at 7-days, 14-days, 21-days, and 28-days (± 24 hours) post-systemic corticosteroid initiation.													
Rimiducid Infusion[7]	**BPX-501 Cellular Kinetics (post-rimiducid)** Within 4 hours (± 30 minutes) prior to initiation of rimiducid infusion, 30 minutes (± 5 minutes), then at 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours (± 30 minutes) after initiation of infusion (of each dose of rimiducid) samples will be collected (and will be split for separate processing). Subsequently at 48 hours (± 1 hour) and 7 days (after initiation of infusion of each dose of rimiducid), and then at 14 days, 21 days, and 28 days (± 24 hours) **after** the final dose of rimiducid (if more than one dose is administered) blood samples will be drawn and evaluated for T cell responses only. **Rimiducid Pharmacokinetics (PK):** As achievable, blood samples will be drawn at the following time-points (in the same series as the split samples above): within 4 hours (± 30 minutes) prior to the initiation of rimiducid infusion; 30 mins (± 5 minutes) 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 (± 30 minutes) after the start of the infusion. (see Appendix F).													

1 Peripheral blood (~12 mL, in green top tubes; as feasible for patient weight) shall be collected for Immune Reconstitution and clinical flow cytometry studies. The basic clinical flow panel includes CD3+ cells, (if achievable, alpha/beta CD3+ cells, gamma/delta CD3+ cells), CD4+ cells, CD8+ cells, Natural Killer cells, B cells, and CD3+/CD19+ cells, CD3+/CD19+/CD4+ cells and CD3+/CD19+/CD8+ cells. Additional flow panels may be included as deemed necessary by the treating physician. IgG, IgM and IgA levels shall be reported.
2 Vital signs include blood pressure, heart rate, respiratory rate and temperature.
3 Concomitant Medication: The protocol will be conducted during the routine clinical care of the patients. All treatments and critical medications, defined below shall be collected in the EDC database:

- Treatment for GVHD
- Prophylaxis and/or treatment for infectious complications
- Treatments in association with serious adverse events (SAE)s

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.
4 Two purple top tubes (heparinized) of whole blood to be collected and frozen and then batch shipped to the Sponsor or designee per instructions in the laboratory manual for collection of the gene therapy monitoring.
5 For clinical assessment and management of neurotoxicity refer to Appendix E.
6 GvHD assessments will be performed according to standard practice in the hospital. Refer to Appendix A and Appendix B.
7 Research blood sample collection for rimiducid infusion to be sent as directed. Refer to Appendix F for collection and processing of samples for pPK testing.

3 LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
aGVHD	Acute Graft Versus Host Disease
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
CFR	Code of Federeal Regulations
cGVHD	Chronic Graft Versus Host Disease
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CTL	Cytotoxic T Lymphocytes
DFS	Disease Free Survival
eCRF	Electronic Case Report Form
DEHP	Bis(2-ethylhexyl) phthalate
EC	Ethics Committee
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FKBP	Human FK-506-binding protein
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft Versus Host Disease
HLA	Human Leukocyte Antigens
HSV	Herpes Simplex Virus
iCasp 9	Inducible Caspase 9
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
LTFU	Long-term Follow Ups
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events

NGHA	Ministry of Naional Guard – Health Affairs
NSAID	Nonsteroidal Anti-inflammatory Drugs
OPBG	Ospedale Pediatrico Bambino Gesù
OTC	Over the Counter
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
pPK	Population PK
RFS	Relapse-Free Survival
RCR	Replication Competent Retrovirus
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Serous Adverse Reaction
TCR	T-Cell Receptor
TK	Thymidine Kinase
TRM	Transplant-Related Mortality
VCN	Vector Copy Number

4 INTRODUCTION

4.1 BPX-501: Genetically Modified T Cells With Safety Switch

4.1.1 iCasp9 Safety Gene

Unmodified donor T cell infusion is potentially an effective strategy for conferring anti-viral and anti-tumor immunity following allo-HSCT (Di Stasi 2011). However, the administration of greater than 10^5 cells/kg unmodified donor T cells to recipients of haploidentical stem cell transplantation has been associated with increased incidence of GVHD. It has been previously demonstrated that administration of up to 10^7 cells/kg of CD25+ allodepleted donor T cells after haploidentical transplantation for hematological malignancies could be administered safely and that the addition of these T cells was effective in controlling viral disease (Amrolia 2006). However, mortality due to disease relapse remained high, presumably due to the 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 safety 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.iCaspase9.2ADeltaCD19 (BPZ-1001), consists of inducible caspase 9 (iCasp9) linked, via a 2A-like sequence, to truncated human CD19 (DeltaCD19). The iCasp9 genetic modification, unlike the Herpes Simplex Virus (HSV)-TK based safety gene, is human derived and therefore likely to be less immunogenic. Moreover, pre-clinical and clinical studies show that killing occurs with much greater rapidity (within 3 hours) than with HSV-TK. Further advantages of the iCasp9 system are that killing induced by the dimerizer drug is primarily restricted to activated/proliferating cells, thus targeting 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.

4.1.2 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.

Rimiducid -inducible activation of the Caspase 9 safety 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. Rimiducid is formulated at [redacted]

4.1.3 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 toxicity. Moreover, acute GVHD of the skin in all three patients, and of the liver disease in one patient, completely resolved after 24 hours. (Di Stasi 2011). The patients who developed GVHD received rimiducid. None of the 10 patients developed cGvHD. 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 patients' 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 the dimerizer rimiducid. The authors concluded that a single dose of dimerizer drug could eliminate the subpopulation of T cells causing GVHD but could spare viral specific cytotoxic T lymphocytes (CTL)s.

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.

4.2 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 HLA-haplo-identical 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 long term risk of gene therapy using a retroviral vector (although considered a rare risk) is the generation of replication competent retrovirus. While the vector has been constructed to minimize the risk of Replication Competent Retrovirus (RCR), which is therefore considered low risk and unlikely, the inclusion of the safety gene switch and potential to administer rimiducid to rapidly clear the product is a clear advantage of therapy.

5 OBJECTIVES OF THE STUDY

5.1 Primary Objective

Overall Survival and incidence of Disease-Free Survival in both malignant and non-malignant patients at 1 and 2 years post-transplant. Relapse-Free Survival in malignant patients at 1 year and 2 years post-transplant.

5.2 Secondary Objectives

1. Long-term survival and safety for a total of 15 years from BPX-501 administration.
2. Assessment of PK (rimiducid) and PD (BPX-501) profiles after treatment with rimiducid for aGVHD.

5.3 Estimated Enrollment

Up to 175 patients who were previously treated on the BP-004 protocol.

5.4 Subject Inclusion Criteria

1. Signed written informed consent by the patient or the patient's guardian for children who are minors.

2. Enrolled on BP-004 protocol, received BPX-501 infusion, completed or discontinued from the study, and are beyond Day +180.

5.5 Subject Exclusion Criteria

1. Lack of parents'/guardian's informed consent for children who are minors
2. Withdrawal from BP-004 study prior to BPX-501 infusion

6 PATIENT POPULATION AND SELECTION

This study will enroll any infant (1 day - 23 months), child (2-11 years) or teenager (12-18 years) with malignant hematological disorders in complete morphological remission or non-malignant hematological disorders who did not have a HLA-matched sibling donor and was enrolled on BP-004 and received BPX-501 infusion. No patients between the age of 0-27 days are likely to be enrolled.

6.1 Patient Discontinuation/Withdrawal Criteria

Patients and/or parent(s) or legal guardian(s) are free to discontinue participation or withdraw consent from the long term follow up study at any time, for any reason, and without prejudice to further treatment.

They may withdraw consent to future treatment with rimiducid, or from continuing participation in the LTFU. Patients with difficulty attending visits may stay on study, attend LTFU visits as they are able and remain eligible for rimiducid if needed.

Where possible patients will be encouraged to remain on-study and complete appropriate follow-up assessments.

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

Patients who 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 long term follow up study.

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 particular regard to survival and, in case of malignancies, risk of recurrence.

If a patient is withdrawn from the study, the investigator should make reasonable effort to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the appropriate case report forms. Data of patients withdrawn from the study will be evaluated, as detailed in the fully executed original consent signed by the patient/parent/guardian upon study entry, unless otherwise indicated. Where possible, these patients will be monitored in terms of outcome for survival and risk of recurrence. The patient/parent/guardian will be informed that follow-up testing or end of study procedures may be required to ensure patient safety is properly maintained.

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

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

7 DESIGN AND CONDUCT OF THE STUDY

7.1 Trial Rationale

This is a long-term follow-up study evaluating the safety of BPX-501 T cells infused after partially matched, related, T cell-depleted HSCT in pediatric patients previously enrolled on the BP-004 protocol who received BPX-501, completed or discontinued from the study and are beyond Day 180. The trial will evaluate the treatment of GvHD by the infusion of dimerizer drug (rimiducid) in those patients who present with cGvHD who progress or do not respond to standard of care treatment.

7.2 Trial Design

The BP-004 Phase I trial design consisted of 3 different escalating doses ($2.5x10^5$, $5x10^5$, $1x10^6$ cells/kg recipient total body weight) in all patient populations and further escalation of 2 doses ($2x10^6$, $4x10^6$ cells/kg recipient total body weight) were evaluated in patients with malignant disease only.

Patients were enrolled at the recommended dose for a maximum of 175 pediatric patients total (for both phases), and the minimum active study follow-up for each patient was 180 days in protocol BP-004.

Patients enrolled on the BP-004 study who received BPX-501 T-cells and are beyond Day 180 will be requested to enroll on this long-term follow up protocol, regardless of whether they completed or discontinued from the parent study BP-004.

The follow-up time for evaluation for overall survival and disease-free survival in patients with malignant disease and patients with non-malignant disease will be 1 and 2-years post-transplant. Relapse-free survival in malignant patients will be evaluated at 1 and 2 years. Long term follow-up for survival and gene therapy safety will be 15 years after BPX-501 treatment.

7.3 Patient Enrollment, Registration and Assignment to Treatment

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

Upon enrollment into the study, the patient will continue with the same number assignment as assigned in BP-004.

7.4 Rimiducid Dimerizer Drug Packaging, Labeling and Storage

7.4.1 Packaging and Formulation

The Rimiducid for Injection is packaged in Type 1 clear glass serum vials (each 3 mL vial contains approximately 2 mL of drug product solution). The contents of each vial is composed [redacted]. Each vial is stoppered with a Teflon© coated serum stopper and a flip-off seal.

7.4.2 Labeling

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

7.4.3 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.

7.4.4 Preparation for Treatment

For use, the rimiducid will be diluted prior to administration. The rimiducid is administered via intravenous (IV) infusion at a dose of 0.4 mg/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.

7.5 Infusion of Rimiducid

7.5.1 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 B.

Response should be assessed per Appendix B. 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 partial response 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.

7.5.2 Contraception after Rimiducid Infusion

Patients 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.

7.6 Monitoring

7.6.1 Rimiducid Response Monitoring

Vital signs are recorded prior to rimiducid infusion, and at 15, 30, 60, 120 and 240 minutes (+/- 5 minutes) after start of infusion. Prior to and after administration of rimiducid, research samples should be collected for BPX-501 T cell tracking and PK testing. Samples for PK testing will be processed differently (Appendix F).

As achievable, and carefully considering patient weight, blood samples should 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 sample, at least 0.3 mL of blood, should analyzed locally for prompt CD3+CD19+ T cell analysis. Additional samples, at least 0.3 mL, should be drawn at 48 hours and 7 days (after initiation of infusion of each dose of rimiducid), and then at 14 days, 21 days and 28 days after the final dose of rimiducid, in the event multiple doses are administered, for evaluation of T cell responses only.

7.6.2 Gene Therapy Monitoring

Long-term follow-up is conducted according to FDA and EMA guidelines Before HSCT and for up to 5-years post stem cell transplant, patients will be evaluated with a physical exam and blood testing testing as outlined below (see Table 2) for vector copy number (VCN) and replication competent retrovirus (RCR) every six months. After 5 years, blood samples will be drawn

annually until 15 years after the last BPX-501 administration. Bellicum will inform the site if sample collection can stop for any patient (criteria for this include all post-treatment PCR assays negative for RCR during the first year, and vector no longer present in 2 consecutive results).

Table 2: Gene Therapy Monitoring Schedule

Collection Time Point	Clinical Evaluation	Blood (8 mL)
1 year	X	X
18, 24, 30, 36, 42, 48, 54, 60 months	X	X*
Annually from 6 years to 15 years after the last BPX-501 administration	X	X*

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

7.7 Management of Experimental Drugs

Rimiducid will be infused upon the development of GVHD (per instructions in Section 7.2).

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

- Treatment for GvHD
- Prophylaxis and/or treatment for infectious complications
- Treatments in association with SAEs

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.

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.

8 TREATMENTS IN ASSOCIATION WITH SAES EVALUATION CRITERIA

8.1 Laboratory Investigations

Lab tests will be performed according to standard institutional procedures. Additional tests will be undertaken as is the standard institutional practice post-transplant.

9 RESPONSE AND TOXICITY EVALUATION

9.1 Parameters of safety, assessment of AE and SAE during the duration of the study

9.1.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs including 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 other applicable regulatory authorities and participating investigators in accordance with International Conference on Harmonization (ICH) guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC) and/or local regulatory requirements.

9.1.2 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product 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.

9.1.3 Serious Adverse Event

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

1. Fatal (i.e., the AE actually causes or leads to death)
2. Life threatening (i.e.,the AE, in the view of the investigator, places the 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

All AEs that meet any of these criteria must be recorded as SAEs, including events that are a normal part of the underlying disease or associated with the general medical management of the patient.

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 SAEs on the electronic Case Report Form (eCRF).

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

9.1.4 Adverse Event Reporting Period

After informed consent, all adverse events will be reported as per Table 3 which details the guidance for AE reporting after study treatment has initiated.

Table 3: Guidance for Adverse Event Reporting

Event Type	Reporting Period	Additional Requirements
GvHD	All cases of GvHD should be reported regardless of onset date and should	Not applicable

	not be limited to the below AE/SAE reporting period	
AEs (post-IMP)	• From the date of BPX-501 infusion until 30 days after administration regardless of causality assessment (including later worsening of events that began during this timeframe). • From the date of rimiducid infusion until 30 days after administration regardless of causality assessment.	• Report new AEs for up to 15 years if assessed as related to the investigational products BPX-501 and/or rimiducid.
SAEs (post-IMP) including Adverse Events of Special Interest*	• From the date of BPX-501 infusion until 180 days after administration regardless of causality assessment (including later worsening of events that began during this timeframe). • From the date of rimiducid infusion until 30 days after administration regardless of causality assessment.	• Report new SAEs for up to 15 years if assessed as related to the investigational products BPX-501 and/or rimiducid. • Report diagnosis of any new secondary malignancy regardless of relationship to investigational product for up to 15 years.
Pregnancy of patients or partner	• 12 months after administration of BPX-501 or rimiducid, whichever occurs later.	• Report diagnosis of any congenital anomaly in offspring from a study participant or partner for up to 15 years.

* Adverse Events of Special Interest are Grade III-V encephalopathy or neurologic events - these should be reported to the Sponsor expeditiously, irrespective of regulatory seriousness criteria.

9.1.5 GVHD Adverse Event Reporting

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

9.2 Expedited Reporting Requirements for Serious Adverse Events

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

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

Sponsor Primary Medical Contact

Contact	Melissa Aldinger
Email	maldinger@bellicum.com
Telephone No.	1-415-656-6341
Contact for SAE Reporting	FAX No.: 617-315-4825/ +34-976 20 44 02 (EU) E-Mail: BellicumSafety@pharmalex.com

Medical Monitor

Medical Monitor	Swati Gupta Karia, MD, PharSafer Associates Ltd, White Hart Meadows, Ripley, Surrey GU23 6ND, UK
Email	swatigupta@pharsafer.com
Telephone No.	Mobile: +44 (0) 7576575575

9.2.2 Reporting SAEs to the IRB or Ethics Committee and Regulatory Authorities

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

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.

9.2.3 Special Reporting Requirements for Neurotoxicity

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

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

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

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

9.2.4 Reporting Requirements for All SAEs

All SAEs must be reported to Bellicum (via Pharmalex) within 24 hours of learning of the event using the Bellicum SAE Report Form.

For initial SAE reports, investigators should record all case details that can be gathered within the reporting timeframe (24 hours) on the Pharmalex SAE Report Form and submit the report to [redacted] Follow-up information should be collected on the Pharmalex SAE Report Form as soon as it becomes available.

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

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

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

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).

9.2.6 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 CRF or eCRF. If the study CRF of eCRF system is no longer available, the investigator should report the event directly to Bellicum via phone or email

9.3 End of Study

The study will evaluate overall survival and disease-free survival for all patients enrolled at 1 and 2 years post-transplant. Patients will be followed for a total of 15 years after BPX-501 treatment for gene therapy safety events. The study will be closed after the completion of the 15 years of follow-up.

10 DATA COLLECTION, QUALITY ASSURANCE AND MANAGEMENT

10.1 Recording of Data

Data will be recorded on an 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. Patients 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 Good Clinical Practice (GCP) Guidelines.

10.2 Data Quality Assurance

The investigators undertake to perform the study in accordance with this protocol, GCP 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.

10.3 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/her in a timely manner. The principal investigator (PI) will review all the eCRFs of each patient and confirm the completeness, medical correctness and plausibility of the documented data by signing on all eCRF pages.

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

Bellicum or the Contract Research Organization (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.

10.4 Statistical Methods

10.4.1 Sample Size Determination

The sample size is identical to BP-004 as it is the long term follow-up of those patients.

10.4.2 General Statistical Approach

Descriptive statistics will be utilized to summarize overall survival, RFS, DFS, GvHD rates, clinical and biologic response and other measures of safety and toxicity in those patients who received rimiducid administration as well as for the whole population. The analysis population will be stratified by malignant and non-malignant indications.

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), as well as number of missing data, where relevant. All summary tables for qualitative parameters will display counts, percentages, and, number of missing data, where relevant.

10.4.3 Study Patient Description

10.4.3.1 Disposition of Patients

The number of enrolled patients will be summarized by country, center, and dose using counts and percentages.

10.4.4 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.

10.4.5 Endpoint Analysis

10.4.5.1 Analysis of Overall Survival

Overall survival, measured as the period of time from the start of the treatment that the patients are still alive at 1 year and 2 years post-transplant will be assessed and reported.

10.4.5.2 Analysis of Graft Failure

Secondary graft failure is defined as initial neutrophil engraftment followed by subsequent decline in neutrophil counts < 500 cells/μL, unresponsive to growth factor therapy.

10.4.5.3 Analysis Chronic GVHD

The time and severity of cGVHD are graded according to NIH Consensus Criteria (Appendix A).

The initial incidence of severe cGVHD at 6 months will be determined for and will be analyzed by conditioning regimen, αβ T 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.

10.4.5.4 Analysis of Time to Disease Relapse

To assess the incidence of acute leukemia relapse from the day of transplant, a cumulative incidence curve will computed along with a 95% confidence interval. Death prior to relapse will be considered a competing risk.

10.4.5.5 Transplant-Related Mortality

The follow-on protocol will determine long-term TRM/Non-Relapse Mortality at 1 year and 2 years, followed by safety evaluations for gene therapy for 15 years.

10.4.5.6 Immune Reconstitution

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. We will also evaluate any indication of differences immune reconstitution across different disease populations.

10.4.6 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.

10.4.6.1 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 National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) v4.03 scale (see Appendix D).

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.

10.4.6.2 Deaths,SAEs, and 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.

10.5 Reporting of Deviations to the Protocol

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

11 ETHICAL ISSUES/CONSIDERATIONS

11.1 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), Saudi Food and Drug Authority, FDA and other international regulatory agencies.

11.2 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.

11.2.1 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.

11.2.2 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.

12 REFERENCES

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Uckan D, et al. Life-threatening neurological complications after bone marrow transplantation. Bone Marrow Transplant 2005, 35:71-76.

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Appendix A: Chronic GVHD Grading Scale and Assessment

Appendix A.1: 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 A.1 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:_____

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.

Appendix A.2: 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.

Appendix A.3: Chronic GvHD Activity Assessment - Clinician

Date: _____ Subject Weight (kg): _____ SUBJECT ID: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible							**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse	
Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
				Total score for all mucosal changes					
Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	0= *no esophageal symptoms* 1=*Occasional dysphagia or odynophagia with solid food or pills during the past week* 2=*Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* 3=*Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*								
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	0= *no symptoms* 1=*mild, occasional symptoms, with little reduction in oral intake during the past week* 2=*moderate, intermittent symptoms, with some reduction in oral intake during the past week* 3=*more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*								
Gastrointestinal-Lower GI • Diarrhea	0= *no loose or liquid stools during the past week* 1= *occasional loose or liquid stools, on some days during the past week* 2=*intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion* 3=*voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion*								
Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1		FVC		Single Breath DLCO (adjusted for hemoglobin)			TLC	RV
Liver Values	Total serum bilirubin mg/dL		ULN mg/dL		ALT U/L	ULN U/L		Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins ☐ 2 min ☐ 6 min				Karnofsky or Lansky	Platelet Count K/uL		TotalWBC K/uL	Eosinophils %
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____ ☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____ ☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____								

Appendix A.3: Chronic GvHD Activity Assessment – Clinician (cont)

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

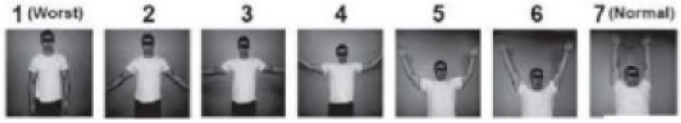
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA*: **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA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

Appendix A.3: Chronic GvHD Activity Assessment – Clinician (cont)

CHRONIC GVHD ACTIVITY ASSESSMENT

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

Shoulder



❑ Not done

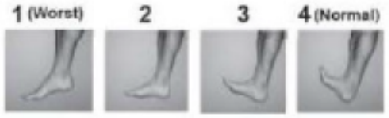
Elbow

❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

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

Appendix A.3: Chronic GvHD Activity Assessment – Clinician (cont)

Today's Date _____ SUBJECT ID _____

CHRONIC GVHD ACTIVITY ASSESSMENT - PATIENT SELF REPORT

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

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

Patient Global Ratings:

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

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

0 1 2 3 4 5 6 7 8 9 10

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

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

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

Appendix B: Management of Chronic GVHD (cGVHD)

Event	Management
cGVHD - Mild	• Consider tissue biopsy to establish diagnosis • Initial treatment with topical or IV steroids, or other systemic treatments (eg, calcineurin inhibitors), per institutional standard of care for mild cGVHD should be instituted. Guidelines for topical corticosteroid treatment include the following (Couriel 2006): o Face, axillae, and groin: lower potency steroids (hydrocortisone 1-2.5%, desonide 0.05%) o From the neck down: mid-strength steroids (e.g., triamcinolone 0.1% cream or ointment) • Systemic corticosteroids when used should be administered as methylprednisolone 2 mg/kg/day IV in a single dose; or a dose equivalent of prednisone or dexamethasone) (Martin 1990; see also corticosteroid conversion table C below). • 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 maxium 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. • If no response to topical steroids or rimiducid, the investigator should consider other medications per institutional guidelines (eg, calcineurin inhibitors, sirolimus, mycophenolate). • Peripheral blood will be used to evaluate 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 (± 30 minutes) post-systemic corticosteroid doses, and at 7, 14, 21 and 28 days (± 24 hours) post-systemic corticosteroid doses o When possible, considering patient weight, blood samples will be drawn within 4 hours (± 30 minutes) prior to the initiation of rimiducid infusion; 30 mins (± 5 minutes) 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 (± 30 minutes) 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 analyzed locallyfor prompt CD3+CD19+ T cell analysis. These additional samples (at least 0.3 mL) will be drawn at 48 hours (± 30 minutes), then at 7 days (after initiation of infusion of each dose of rimiducid), and at 14 days, 21 days, and 28 days (± 24 hours) 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 to topical steroids or rimiducid, the investigator should consider other medications per institutional guidelines (eg, calcineurin inhibitors, sirolimus, mycophenolate). • If no response 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 above guidelines if the investigator considered rimiducid to offer clinical benefit with prior episodes • Peripheral blood will be used to evaluate BPX-501 cells (CD3+CD19+) at the following times: o Prior to administration of systemic corticosteroid doses (e.g, methylprednisolone), at 4 hours and 24 hours (± 30 minutes) post-systemic corticosteroid doses, and at 7, 14, 21 and 28 days (± 24 hours) post-systemic corticosteroid doses o As achievable, considering patient weight, blood samples will be drawn within 4 hours (± 30 minutes) prior to the initiation of rimiducid infusion; 30 mins (± 5 minutes) 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 (± 30 minutes) 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 analyzed locallyfor prompt CD3+CD19+ T cell analysis. These additional samples (at least 0.3 mL) will be drawn at 48 hours (± 30 minutes) and 7 days (± 24 hours) (after initiation of infusion of each dose of rimiducid), and then at 14 days, 21 days, and 28 days (± 24 hours) after the final dose of rimiducid (in the event multiple doses are administered) and evaluated for T cell responses only.

References:

Couriel D, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biology of Blood and Marrow Transplant 2006;12:375-396.

Martin PJ, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. Blood 1990;76:1464-1472.

Appendix C: Corticosteroid Conversion Table

Corticosteroid Conversion Table		
Glucocorticoid	**Approximate equivalent dose (mg)**	**Half-life (hr)**
Short-Acting		
Cortisone	25	8-12
Hydrocortisone	20	8-12
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

1. Dixon JS. Second-line Agents in the Treatment of Rheumatic Diseases. Informa Health Care, 1991. (456).
2. Meikle AW and Tyler FH. Potency and duration of action of glucocorticoids. Am J of Med 1977;63;200.
3. Webb R, Singer M. Oxford Handbook of Critical Care. Oxford ; New York : Oxford University Press, 2005.

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

AE 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/therapy required
2	Moderate (apply eventspecific-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 eventspecific NCI CTCAE grading criteria-)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

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

Appendix E: 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 E.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 E.2 below for evaluation and management guidelines.

In cases where a lumbar punctures (LP) is potentially warranted to evaluate the cerebrospinal fluid (CSF) to aid in the differential diagnosis of clinical neurological changes, procedures and precautions should be taken to rule out contraindications for performing an LP (Table E.3), consistent with consensus guidelines for performing LPs in patients with neurological diseases (Engelborghs 2017).

If a diagnostic LP is performed, attempts should be made to minimize side effects such as infections, pain and post-LP headaches, including, but not limited to: a) use of 25G atraumatic type needles, b) performing 4 or less attempts, c) passive CSF collection instead of active CSF withdrawal using a syringe, d) collection of less than 30 mL of CSF, and e) lateral recumbent position (see Table E.3; Engelborghs 2017).

Table E.1: Monitoring of Patients for Neurologic Complications

Timing	Neurologic examination	Mini-mental status examination
Routine outpatient clinic visits or emergency room visits	✓	✓
Change in mental status or presence of CNS dysfunction (e.g., reduced consciousness, delirium)	✓	✓

Table E.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 evaluated for BPX-501 cells (CD3+CD19+) at the following times: o Prior to administration of systemic corticosteroid doses (e.g, methylprednisolone), at 4 and 24 hours (± 30 minutes) post-systemic corticosteroid doses, and at 7, 14, 21 and 28 days (± 24 hours) post-systemic corticosteroid doses o Within 4 hours (± 30 minutes) prior to initiation of rimiducid infusion, 30 minutes (± 5 minutes) after initiation of infusion, at 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours (± 30 minutes) (split samples). Subsequently at 48 hours (± 30 minutes) , 7 days (after initiation of infusion of each dose of rimiducid), and at 14 days, 21 days, and 28 days (± 24 hours) after the final dose of rimiducid (if more than one dose is administered) blood samples will be drawn. Vital signs are recorded prior to rimiducid, and 15, 30, 60, 120 and 240 minutes (± 5 minutes) after start of infusion. o If cerebrospinal fluid (CSF) can be safely obtained, CSF should be sent to the Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+) prior to initiation of high-dose corticosteroids or rimiducid. If a sample of CSF can be safely obtained after initiation

	of corticosteroids and/or rimiducid for the treatment of neurotoxicity, CSF should be sent to the Sponsor for research use to evaluate for BXP-501 cells (CD3+CD19+) (see Table E.3)
Grade ≥ 2 (Generalized)[2]	• Perform routine institutional care for patients with altered mental status/obtundation (eg, continuous vital sign monitoring, oxygen, suction, airway protection measurements and consideration of need for mechanical ventilation, ICU admission) • Neurology consult and EEG evaluation • CBC analysis and peripheral blood smear evaluation to evaluate for thrombotic microangiopathy (TTP/HUS) • Evaluation for electrolyte and acid-base etiologies • Evaluation for liver dysfunction and evidence of hyperammonemia/veno-occlusive disease (VOD) • Perform daily neurological and mini-mental status examinations during hospitalizations to evaluate for resolution/worsening of symptoms • Perform CNS imaging (MRI and/or contrast enhanced CT) • Perform CSF evaluation for presence of cell counts (and differential), glucose, protein and gram stain for bacteria. 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 will be collected for research purposes to evaluate 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 (± 30 minutes) post-systemic corticosteroid doses, and at 7, 14, 21 and 28 days (± 24 hours) post-systemic corticosteroid doses o Within 4 hours (± 30 minutes) prior to initiation of rimiducid infusion, 30 minutes (± 5 minutes) after initiation of infusion, at 2

	hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours (± 30 minutes) (split samples), and subsequently at 48 hours (± 30 minutes), and 7 days (± 24 hours) (after initiation of infusion of each dose of rimiducid), and at 14 days, 21 days, and 28 days (± 30 minutes) after the final dose of rimiducid (if more than one dose is administered) blood samples will be drawn. Vital signs are recorded prior to rimiducid, and 15, 30, 60, 120 and 240 minutes (± 5 minutes) after start of infusion. • If cerebrospinal fluid (CSF) can be safely obtained, CSF should be sent to Sponsor for research use to evaluate for BPX-501 cells (CD3+CD19+) prior to initiation of high-dose corticosteroids or rimiducid. If a sample of CSF can be safely obtained after initiation of corticosteroids and/or rimiducid for the treatment of neurotoxicity, CSF should be sent to the Sponsor for research use to evaluate for BXP-501 cells (CD3+CD19+) (see Table E.3)

* 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

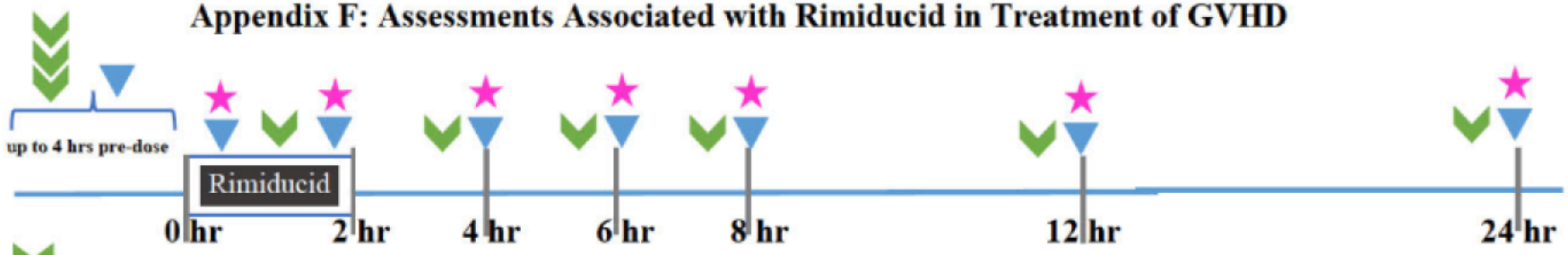
Table E.3: Recommended Procedures to Rule-out Contraindications for LP and Procedures to Minimize Risks*

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

References:

de Brabander C, et al. Increased incidence of neurological complications in patients receiving an allogeneic bone marrow transplantation from alternative donors. J Neurol Neurosurg Psychiatry. 2000,68:36-40.
Dowling MR, et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation: risk factors and impact. Bone Marrow Transplantation 2017;1-8.
Folstein MF, et al. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975:12:189-198.
Mental Status Examination in Primary Care: A Review. American Family Physician. 2009:80: No.8. pp809-814.
Syed FI CNS complications of hematopoietic stem cell transplant. Hematol Oncol Clin N Am 2016, 30:887-898.
Uckan D, Life-threatening neurological complications after bone marrow transplantation. BMT 2005, 35:71-76.

Appendix F: 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.