STATISTICAL ANALYSIS PLAN
PHASE II

DATE OF PLAN:

8 May 2019

BASED ON:

Protocol BP-004 Version 10.0, 2 April 2018 (Italy); Version 7.0, 2 April 2018 (United Kingdom); Protocol BP-404 Version 3.0, January 2019 (Italy follow-up study)

STUDY DRUGS:

BPX-501 – Donor T cells genetically modified with BPZ-1001 retroviral vector containing the iC9 suicide gene

Rimiducid (AP1903) (Dimerizer drug)

PROTOCOL NUMBERS:

BP-004, BP-404 (Italy follow-up study)

BP-004 STUDY 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:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
aGvHD	Acute Graft Versus Host Disease
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
AML	Acute Myeloid Leukemia
cGvHD	Chronic Graft Versus Host Disease
CNS	Clinical Network Services
CRF	Case Report Forms
CRO	Contract Research Organization
CSR	Clinical Study Report
DFS	Disease-Free Survival
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EFS	Event-Free Survival
GCP	Good Clinical Practice
GvHD	Graft-Versus-Host Disease
Haplo-HSCT	HLA-haplo-identical Hematopoietic Stem Cell Transplantation
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IV	Intravenous
LFS	Leukemia-Free Survival
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRM	Non-Relapse Mortality
PB-HSCT	Peripheral Blood Hematopoietic Stem Cell Transplantation
PBMC	Peripheral Blood Mononuclear Cell
PBSC	Peripheral Blood Stem Cell
RFS	Relapse-Free Survival

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TRM	Transplant-Related Mortality
WHO	World Health Organization

2. INTRODUCTION

Over the last 4 decades, allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched donor has been increasingly used to treat patients affected by life-threatening malignant or non-malignant disorders. 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 graft-vs-tumor (GvT) effects and immune cell reconstitution, in the context of increased immune genetic disparity between patient and donor, the T cells are also responsible for the occurrence of adverse T-cell mediated events such as graft-versus-host disease (GvHD), a severe, sometimes fatal, immune complication, which also impairs patient's immune reconstitution.

Haploidentical HSCT (typically derived from a parent or sibling) is an alternative donor option for pediatric AML patients; however, clinical outcomes have typically been limited due to graft failure, poor immune reconstitution, infection, and relapse with T-cell depletion approaches; or GVHD, relapse and transplant-related mortality (TRM) with unmanipulated grafts followed by post-transplant cyclophosphamide (Shaw PJ, Blood 2010; Ho VT, Blood 2001).

Treatment with the adjuvant polycolonal BPX-501 T cell product containing an inducible 'safety switch', in combination with a haploidentical HSCT, has the potential to address this high unmet medical need in children with high-risk malignancies or life-threatening non-malignant disorders that do not have a matched related or matched unrelated stem cell donor available.

The BPX-501 T cell product is intended to aid in engraftment, promote immune reconstitution, and potentially aid in graft-vs-leukemia (GVL) effect. In addition, the BPX-501 T cell product contains an inducible caspase-9 (iC9) safety switch, mediated by the infusion of the dimerizing agent rimiducid, that can be used to deplete alloreactive T-cells in the event of uncontrolled GvHD or other potential T-cell mediated adverse events that can occur with T-replete HSCT products (e.g., neurotoxicity). Rimiducid is an inert, lipid-permeable compound that rapidly induces dimerization and activation of the iC9 suicide gene via a drug-binding domain derived from human FK506-binding protein (FKBP), inducing apoptosis of the gene modified T cells.

This Statistical Analysis Plan (SAP) is based on the BP-004 study protocol and is intended to provide the statistical methods and summaries for the analysis of the data arising from the clinical trial (Protocol BP-004, Italy Version 10.0, 2 April 2018; United Kingdom Version 7.0,c 2 April 2018). Once completing the initial 180-day follow-up period, subjects enrolled into the Italian version of the BP-004 protocol were enrolled into a follow-up protocol, BP-404. Analyses presenting data beyond Day 180 in this SAP may therefore pull data from all three protocol sources (Italy and United Kindom BP-004; Italy BP-404). The analysis approaches and methods outlined in this document, if different from the respective protocols, will supersede those specified in the protocol.

3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

3.1. Study Objective(s)

Primary Objective:

- To determine whether infusion of the BPX-501 T cell product can enhance immune reconstitution in patients with malignant and non-malignant haematological disorders, with the potential for reducing the severity and duration of severe acute GvHD, thereby improving overall survival.

Secondary Objective:

- To evaluate the treatment of GvHD by infusion of the dimerizer drug (AP1903/rimiducid), activating the suicide gene iC9, in those subjects who present with GvHD who progress on, or do not respond to, standard of care treatment.

3.2. Study Endpoint(s)

Endpoints will be further defined in subsequent sections. Unless otherwise specified, time-to-event endpoints will be calculated from the date of HSC infusion. If a patient received more than one HSCT, the time of the last HSC infusion immediately preceding infusion with BPX-501 will be the transplant date.

Primary Endpoint:
Event-Free Survival (EFS) at 180 days. Events are defined as the first occurrence of either transplant-related mortality (TRM) for non-malignant patients or non-relapse mortality (NRM) for malignant patients, severe GvHD (Grade 2-4 acute organ GvHD or extensive/moderate-severe chronic GVHD), and life-threatening infections (Grade 4).

NB: In the BPX-501 protocols, the terminology 'extensive' chronic GvHD was used. For the purposes of the primary analysis and for the rest of this SAP, extensive chronic GvHD will be defined as moderate or severe chronic GvHD. 'Overall' chronic GvHD or chronic GvHD without a qualifier will be interpreted as mild, moderate or severe chronic GvHD.

The following secondary endpoints are in the BP-004 protocols, although additional endpoints and analyses are described below in subsequent sections of this document.

Secondary Endpoints:

(i) Transplant-Related Mortality (TRM) in patients with non-malignant diagnoses or Non-Relapse Mortality (NRM) in patients with malignant diagnoses at 100 and 180 days
(ii) Cumulative incidence and severity of acute GvHD (any Grade 2-4 or Grade 3-4) as well as overall and moderate-severe chronic GvHD at 180 days.
(iii) Time to resolution of acute GvHD after administration of rimiducid
(iv) Immune reconstitution as determined by T cell subsets up through 180 days
    a. Absolute CD3 count
    b. Absolute CD4 count

c. Absolute CD8 count

(v) Time-to-immune reconstitution defined by CD3 count > 500 cells/uL; CD4 count > 200 cells/uL; CD8 count of 200 cells/uL

(vi) Disease-Free/chronic GvHD Survival (DFGS) defined as the first of either disease recurrence, death from any cause, or chronic GVHD

(vii) Disease status within the following disease indications at 180 days:

a. Primary immune disorders as determined by CD3 T cell count ≥ 500 cells/uL and normal levels of IgA and IgM
b. Haemoglobinopathies as determined by incidence of RBC transfusion independence for 8 consecutive weeks and untransfused haemoglobin of ≥ 8.5 g/dL
c. Fanconi Anemia as determined by RBC ≥ 3,000,000 cells/uL, neutrophil count ≥1500 cells/uL and platelet count ≥ 150,000
d. Relapse Free Survival (RFS) in subjects with leukemia

Safety Endpoints:

Safety assessments and summaries will include reported AEs and SAEs; protocol-specified hematology; and clinical chemistry.

4. STUDY DESIGN

This phase II study is a multi-center single-arm extension study following completion of a phase I dose escalation study, where subjects were treated in a 3+3 dose escalation design.

As stated in the protocol, this study enrolled 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. Patients will have access to a partially matched family donor who will provide PBMCs for creating the BPX-501 modified T cells as well as the HSCT.

Up to 175 pediatric patients were to be enrolled in this phase II extension trial at the dose of $1x10^6$ cells/kg regardless of disease classification (malignant or non-malignant). The study follow-up for each patient will be at least 180 days.

After completing the study, eligible subjects will be enrolled in a gene therapy follow-up study for a total of 15 years. Given the various protocols referenced in this document, additional follow-up beyond 180 days is within scope of this SAP and longer-term results may be presented for supportive purposes.

4.1. Definition of Study Drugs

The study drugs are:

- BPX-501: *Donor T cells genetically modified with BPZ-1001 retroviral vector containing the iC9 suicide gene*, and
- Rimiducid (AP1903): *Dimerizer drug used in case of a patient developing GvHD*

The BPX-501 T cell infusion is administered 14 days (+/-4 days) after completion of the stem cell allograft infusion. Under certain protocol versions, subjects may have been administered BPX-501 within 21 days (+/- 14 days) after completion of the stem cell allograft infusion. Subjects with uncontrolled Grade I or II skin-only, Grade II (non-skin), III, or IV acute GvHD were eligible to receive a up to three doses of rimiducid at 0.4 mg/kg as a 2-hour intravenous (I.V.) infusion. Chronic GvHD, under conditions specified by protocol, will be treated with an infusion of rimiducid in individuals who have not previously received an infusion of rimiducid.

4.2. Sample Size Considerations

This study was originally designed as a 3+3 Phase 1 dose escalation study of BPX-501, with sample size considerations based on estimating a maximum tolerated dose (MTD) and assessing preliminary safety. The study was later expanded to enroll up to 175 subjects having various diseases considered amenable to treatment with BPX-501. Power considerations were later based on the use of a non-inferiority analysis comparing patients treated with BPX-501 in the BP-004 study to the cohort of subjects enrolled at largely overlapping study centers in the C-004 and CP-004 studies who received a matched unrelated donor (MUD) transplant (with two additional sites Italian brought on under C-004). A non-inferiority margin of 10% was pre-specified.

Sample size considerations were updated pending reporting of interim results (Algeri et al, ASH 2018). Assuming a sample size of 100 efficacy-evaluable subjects and a baseline EFS rate at day

180 of 88% in subjects receiving a MUD transplant, and assuming a sample size of 160 efficacy-evaluable subjects and an EFS rate at day 180 of 91% in subjects receiving BPX-501, this study has approximately 91% power to claim non-inferiority of BPX-501 relative to a MUD transplant based on a test of difference of proportions. Assuming a sample size of 70 efficacy-evaluable subjects receiving a MUD transplant, and assuming a sample size of 140 efficacy-evaluable subjects receiving BPX-501, this study has approximately 84% power to claim non-inferiority of BPX-501 relative to a MUD transplant based on a test of difference of proportions. Power calculations were performed using PASS software and checked using the gsDesign package in R.

4.3. Randomization

This a single arm study and randomization is not applicable.

4.4. Clinical Assessments

Clinical and laboratory assessments were conducted at screening and on days 0, 14, 30, 60, 100 and 180. Patients received TCR αβ T cell and CD19+ B cell depleted HSC on day 0. Unless otherwise protocol-specified, patients received the BPX-501 infusion on day 14+/- 4 days.

Clinical assessment, laboratory investigations, radiological investigations, and microbiological investigations will be conducted as per protocol schedule of assessments Table 1. Adverse events will be followed throughout the study period. In this study protocol, the scheduled study follow-up for each patient defined as 180 days. Further details of the schedule of assessments recorded on the electronic Case Report Form (eCRF) at each visit are provided in Table 1.

A full description of the study design, including inclusion/exclusion criteria, is provided in the study protocol.

5. PLANNED ANALYSES

5.1. Interim Analyses

Outside of safety monitoring, no formal interim analyses were planned for this study.

5.2. Final Analysis

The primary analysis will be conducted after the last patient enrolled has completed 180 days of follow-up and the source-verified data can be extracted from the clinical study database. A final analysis will be performed after the last subject under the UK version of the protocol has completed at least 2 years of follow-up.

6. STATISTICAL METHODS AND DATA HANDLING

6.1. Analysis Populations

The following analysis populations are defined for the study:

(i) Enrolled Population (EP) – Defined as all patients who signed informed consent, were assessed for inclusion/exclusion criteria during the screening period, and who were considered eligible for enrollment and post-enrollment follow-up. This population will be used to present overall study disposition data and for summarizing the total number of patients screened and considered eligible for the study.

(ii) HSCT Safety Population (HSP) – Defined as all patients in the enrolled population (EP) who received Hematopoietic Stem Cell Transplantation (HSCT). Only SAEs were reported in subjects prior to receiving to BPX-501. The HSP therefore represents the analysis population for certain analyses of SAEs as well as disposition and outcomes in subjects who did not go on to receive BPX-501 for any reason.

(iii) BPX-501 Safety Population (BSP) – Defined as all patients who received HSCT and went on to receive any dose of BPX-501. Unless otherwise specified, this will be the default primary safety analysis population.

(iv) Intent-to-treat Population (ITT) – Given that this is a single-arm study, a "Full Analysis Set" (FAS) population is proposed to serve as the ITT population from which to provide estimates of treatment effects in subjects receiving BPX-501. The FAS/ITT population includes all patients treated with HSCT who received BPX-501 at the dose of $1x10^6$ cells/kg.

(v) Per Protocol Populations (PP) – Defined as all patients in the ITT/FAS analysis population who were infused with BPX-501 at the dose of at least $1x10^6$ cells/kg within a dosing around Day 14 (+/- 4 days) or Day 21 (+/- 14 days) after HSCT. The primary and key secondary efficacy analyses may be repeated on the PP populations as a means of characterizing the robustness of any outcome results.

(vi) Rimiducid Population (RP) – Defined as all patients who received at least one dose of rimiducid for the treatment of acute or chronic GvHD.

(vii) Rimiducid Pharmacokinetics Population (RPK) – Defined as all patients who received at least one dose of rimiducid for the treatment of acute or chronic GvHD and have a plasma sample to measure rimiducid concentrations over time.

6.2. Statistical and Analytical Methods

6.2.1. General Statistical Approach Summaries

Data will be summarized with respect to each of the performance outcomes assessed, pooled across all the investigative sites and, in many cases, stratified by type of disorder (malignant or non-malignant). Continuous endpoints will be summarized using the number of observations, mean, median, standard deviation or interquartile range, and minimum and maximum values. Categorical endpoints will be summarized using the number of observations and percentages. Time-to-event assessments will be summarized using either Kaplan-Meier or Nelson-Aalen statistical techniques, as appropriate, with display of parameter estimates at pre-defined timepoints along with the number of censored observations. Unless otherwise stated, confidence intervals will be constructed at the 95% confidence level. Any potential statistical tests will be two-sided, with type 1 error rate of 5%. *P*-values will be rounded to three decimal places, with *p*-values less than 0.001 will be reported as <0.001, and *p*-values greater than 0.999 will be reported as >0.999.

Data listings will be sorted by treatment, dose, site identification number, subject identification number and visit.

The primary analysis is planned to be conducted after the last patient enrolled has either completed 180 days of follow-up on study or withdraws from the study prior to 180 days. Unless otherwise stated, statistical analysis will be performed using SAS statistical software (Version 9.4, unless otherwise noted). Adverse events were coded using MedDRA version 18.0. Concomitant medications were coded using World Health Organization (WHO) coding standards and the WHO 2015 drug dictionary. For key adverse events and concomitant medications, any coding changes between the versions used for analyses and more recent versions will be highlighted.

For rimiducid plasma concentration data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number of observations. Data listings will be provided for all subjects up to the point last evaluable sample collection. Any subjects excluded from the relevant population will be highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used

6.2.2. Missing Data and Handling of Dropouts

Unless otherwise specified, missing data will not be imputed for efficacy variables. For subjects who withdrew from the study prior to study completion, all data attained up to the point of discontinuation will be listed and included in data summaries. Patients will be censored at the time of their last documented study visit prior to or at the time of study withdrawal.

The term missing date refers to a completely missing date or to a partial date where month, day or year are missing. Unless otherwise stated, the handling of partial missingness of dates will impute using midpoint values. That is, missing days will be imputed as the 15th of the month and

missing months will be imputed as July 1st, unless a more suitable value can be imputed based on study or treatment start and end dates.

If an adverse event (AE) resolution date is completely missing, the duration (ongoing/resolved status) will be checked before imputing a date, noting when the AE started in relation to study treatments. If the ongoing flag is missing, then it is assumed that the AE is still present (i.e., do not impute a date).

Adverse event relationship missing: If the relationship for an adverse event is not recorded, it will be reported as missing in the presentation of listings and summaries of incidence results. Assessments of relatedness to AP1903/rimiducid should only apply for AEs which occur on or after the date of first rimiducid dose.

Adverse event severity missing: If the severity of an adverse event is missing, the severity will be assumed to be missing when summarizing data. Missing information will be reported as missing in the subject listings.

Non-study medication (concomitant medications, steroids) start and stop dates missing: If the start and/or stop dates of non-study medication use are incomplete or missing, the use will be assumed to be concomitant, unless the incomplete date information clearly indicates that the use stopped prior to the on-study-date. Missing or incomplete information will be reported as missing/incomplete in the subject listings.

For pharmacology and pharmacokinetic data, the following rules will be applied if there are values that are below the limit of quantitation (BLQ) or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
  - If there are less than three values in the data series, only the min, max, and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
  - If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min, and max will be presented as zero.
  - If the value of the arithmetic mean or median is below the assay LLOQ, it will be presented as zero.

6.2.3. Baseline Definition

For this study, the patient begins study treatment on the day of hematopoietic stem cell transplantation (HSCT) defined as Day 0 in the protocol and study Day 1 for analysis. It is noted that the study schedule from the protocol refers to the reference date as Day 0. For reporting purposes, CDISC standards will be used, referring to the first day as Day 1.

If a patient received multiple HSCTs, the date of HSCT which occurred immediately before administration of BPX-501 will be considered study Day 1.

For all endpoints requiring a baseline reference, e.g., comparison with a post-baseline value, the baseline value will be the last non-missing result prior to HSCT.

6.2.4. Pooling Investigative Sites

The primary analysis will use data pooled across all investigative sites.

6.2.5. Examination of Subgroups

Subgroup analyses are intended for exploratory purposes to characterize the robustness of the primary and key secondary endpoints. Primary analysis subgroups include type of disease (malignant or non-malignant), and, potentially further subgroup analyses within these two major disease groups (e.g., ALL, AML, PID, hemoglobinopathies, etc.), highlighted below.

6.3. Subject Characteristics

Subject data will be displayed in subject listings and summarized in the appropriate analysis populations defined above.

6.3.1. Subject Disposition

Subject disposition will be presented for the appropriate analysis populations defined above. The following categories will be displayed in descriptive statistics summary tables:

- Subjects enrolled
- Subjects in the HSCT Safety Population (HSP)
- Subjects in the BPX-501 Safety Population (BSP)
- Subjects in the ITT (FAS) Population
- Subjects completed study (180-day follow-up)
- Subjects discontinued from the study early and reason of discontinuation.

6.3.2. Protocol Deviations

Protocol deviations will be identified as major or minor through data reviews by the Sponsor prior to database lock. Descriptive statistics will be summarized for subjects with major protocol deviations with respect to the relevant analysis population. The summary may be grouped into different categories of major violations such as:

- Violation of inclusion/exclusion criteria
- Non-compliance with study procedures
- Inappropriate intake of prohibited concomitant medications
- Missing essential study visit assessments

- Lost to follow-up
- Administrative decision of investigator or sponsor

Multiple deviations can occur in the same subject and thus a subject may be counted in more than one deviation category.

Major and minor protocol deviations will be presented in a subject data listing for all enrolled population, sorted by site.

6.3.3. Demographics and Background Baseline Characteristics

To further characterize the patient population at baseline, the following demographic and background characteristics will be summarized for the relevant analysis populations, stratified by type of disorder (malignant or non-malignant): demographics (age at enrollment, sex, and ethnicity), type of disease, prior HSCT (number of HSCT, type of HSCT), HLA typing, donor characteristics (age, ethnicity, relationship), conditioning regimen, and performance status (Lansky/Karnofsky score).

Demographic data will be presented in a listings and tables for the relevant analysis populations.

6.3.4. Treatment Exposure

Study treatment data including dose level of BPX-501 and rimiducid dosing (AP1903) information will be presented by type of disorder (malignant or non-malignant) and presented as patient data listings for the appropriate safety and ITT (FAS) populations.

Days on study will be calculated using the HSCT date as the reference date. The days on study for the date of interest will be calculated as (date of interest – date of HSCT + 1) for dates later than HSCT. For dates earlier than HSCT, the days on study will be calculated as (date of interest – date of HSCT).

Data listings will present study days in addition to assessment dates. Study day 1 is defined in section 6.2.3. For efficacy and safety endpoints the same rule for study day will apply.

6.3.5. Physical Examination

Physical examination of each subject's major body systems: general appearance, head/eyes/ears/nose/throat, neck, lungs, heart, abdomen, genitourinary, extremities, neurological, skin, and lymphatics and other. Results (normal, abnormal and clinically significant abnormal and not clinically significant) at screening visit will be tabulated for each body system with the number and percentage of subjects. The number and percentage of subjects in new or worsened conditions reported will be tabulated in the follow-up visits.
Physical examination results will be presented in a subject data listing, including the description of abnormalities observed by study visit.

Additional physical examination assessments are based on Karnofsky/Lansky performance status. The score for Karnofsky/Lansky performance status will be provided as patient listings by study visit.

6.3.6. Medical History

Pre-existing medical conditions are recorded in the medical history eCRF. Descriptive statistics including the number and percentage of subjects will be displayed for each medical condition.

Medical history data will be presented in patient listings for the safety populations.

6.3.7. Prior and Concomitant Medications

Following protocol specification and the schedule of assessments, concomitant medications are medications after BPX-501 infusion. Concomitant medication statistical summaries will include medications taken on or after the start date of BPX-501infusion as well as medications that started prior to start date of BPX-501 infusion and continued after BPX-501 infusion. The following algorithm will be used to define prior and concomitant information:

- Prior medications: Any medications which started and ended before the date of BPX-501 infusion. If the start date of the medication is incomplete or missing, it will be treated as a prior medication.
- Concomitant medications: Any medications which start on or after the date of BPX-501 infusion as well as medications that started prior to date of BPX-501 infusion and continued after BPX-501 infusion.

All prior and concomitant medications recorded on the CRF will be mapped to standardized terms using the World Health Organization Drug Dictionary (WHO DD) coding system. The Anatomical–Therapeutic–Chemical (ATC) classification level 2 and preferred term will be used to summarize the data overall and by disease type (malignant and non-malignant) A subject having the same medication more than once will be counted only once in the incidence table for that medication. For each ATC classification and preferred term, the number and percentage of subjects will be displayed. Separate prior and concomitant medication summary tables will be presented in the BPX safety population (BSP).

Additional subgroup concomitant medications tables will be summarized by usage context that may include: conditioning treatment, GvHD treatment, prophylaxis or infection treatment, and SAE treatment.

Prior and concomitant medications will be presented in a data listing with dose, units, frequency, route of administration, indication, start and end dates, and reason in the broader HSCT safety population (HSP).

6.4. Efficacy Analysis

The analysis of primary and secondary endpoints will be based on the ITT (FAS) population as the primary analysis population. Any supportive sensitivity analyses may be assessed on the PP population or other subgroup defined below. Final decisions on different exploratory subgroups will be determined prior to the time of primary analysis.

6.4.1. Primary Efficacy Analysis

The primary efficacy endpoint is Event-Free Survival (EFS) up to 180 days using the ITT (FAS) population. Events corresponding to EFS outcome include

- Transplant-Related Mortality (TRM) for non-malignant patients or Non-Relapse Mortality (NRM) for malignant patients, defined as the time from transplant until death without evidence of recurrence or relapse,
- Severe GvHD, defined as any case of grade 3-4 acute GvHD regardless of organ involvement, any case of grade 2 acute GvHD with visceral (non-skin-only) organ involvement, or any case of moderate-severe chronic GvHD, and
- Life-threatening infections (Grade 4).

For patients with multiple events, the event that occurs first and the corresponding time will be used for the EFS. Subsequent EFS-qualifying events will be provided in a listing in order to describe longer-term outcomes observed in patients with a primary EFS event. Patients who do not experience an EFS-qualifying event will be censored on the last day of observation. EFS will be calculated from the date of HSCT transplant defined above.

Kaplan-Meier techniques will be used to estimate EFS at day 180. When estimable, additional summary statistics will include the median, minimum, maximum, the 25th and 75th percentiles of EFS along with the number of events and censored observations. Kaplan-Meier plots with descriptive summary statistics will be presented along with the number of patients at risk at various time points.

An additional sensitivity analysis of EFS may be performed using an expanded definition of EFS-qualifying events to include patients with skin-only grade 2 acute GvHD.

6.4.2. Secondary Efficacy Analyses

(i) Transplant-Related Mortality (TRM) for Non-Malignant patients or Non-Relapse Mortality (NRM) for Malignant patients at 100 and 180 days

This analysis is intended to characterize the contribution of Time-to-Transplant-Related Mortality (TRM) or Non-Relapse Mortality (NRM) to the composite EFS endpoint. TRM/NRM will be estimated using a Nelson-Aalen cumulative incidence function at days 100 and 180. An event for this endpoint is death without evidence of disease recurrence. Recurrence of disease or relapse will be considered a competing event. Cumulative incidence plots with descriptive summary statistics including incidence and 95% confidence intervals will be presented. If there is sufficient data, the analysis may be repeated by type of disease (malignant or non-malignant).

(ii) Cumulative Incidence and Severity of grade 2-4 acute organ GvHD and moderate - severe chronic GvHD at 180 days

This analysis is intended to characterize the contribution of acute or chronic GvHD to the composite EFS endpoint. Severity of acute and chronic GvHD will be summarized and further in the analysis of safety data. Cumulative incidence of GvHD at day 180 will be estimated from time of transplant using a Nelson-Aalen cumulative incidence function and treating death prior to GvHD as a competing risk.

Cumulative incidence plots with descriptive summary statistics including incidence and 95% confidence intervals will be presented. If there is sufficient data, the analysis will be repeated for each type of disorder (malignant or non-malignant) stratification.

Depending on the number of events, additional GvHD severity subgroups to be analysed include acute grade 1-4 GvHD, grade 2-4 GvHD including skin-only presentation, grade 3-4 GvHD, mild-severe chronic GvHD, and, severe chronic GvHD. The same statistical methods and summary statistics described above will be applied to these analyses.

(iii) Time to Resolution of Acute or Chronic GvHD After Administration of Rimiducid (including Response to Rimiducid)

The resolution of acute GvHD (aGvHD) or chronic GvHD (cGvHD) after administration of rimiducid will be based on the response grading of the GvHD criteria provided in the protocol. The event for this endpoint is any patient who achieved a best overall response (BOR, i.e., either a Complete Response (CR) or Partial Response (PR)) based on aGvHD grading. Only patients experiencing aGVHD who received rimiducid (AP1903) infusion for treatment will be considered for this endpoint. Best overall resolution of aGVHD is defined from the date of AP1903 infusion. The percentage of patients with acute or chronic GvHD, the number of doses of rimiducid, and the best overall response to rimiducid within 7 and 30 days will be presented in listings and summarized. Concomitant medication usage in subjects with acute or chronic GvHD and, further, among those subjects who went on to receive rimiducid, will also be summarized.

Additional analysis and summary statistics will be conducted for resolution of chronic GvHD after administration of rimiducid as well as any case of GvHD (acute or chronic).

(iv) Immune reconstitution as determined by T cell subset counts at day 180

a. Median and range of CD3 counts at 30, 60, 100 and 180 days
b. Median and range of CD4 counts at 30, 60, 100 and 180 days
c. Median and range of CD8 counts at 30, 60, 100 and 180 days

Quantitative assessment of each immune T-cell counts will be performed at various visit time points after transplant as captured in clinical database up to day 180 of follow-up. Analysis and statistical summaries will be performed separately for each T cell subtype assessed. The pattern of each immune reconstitution lab counts will be summarized using graphical summaries and descriptive statistic summary tables including mean (standard deviation), median, and range (minimum, maximum) across the time points assessed. Plots of mean and median cell counts representing measurements over time will be generated to visualize general patterns over time of immune reconstitution.

Additional cell types and analytes for quantitative immunophenotyping include the absolute and relative numbers of CD3+CD19+ T cells (containing iC9), as well as the number of B cells, NK cells, and levels of IgA, IgM and IgG. In order to describe the pharmacodynamic effects of BPX-501 via proliferation of CD3+CD19+ cells, values post-rimiducid may be excluded. A separate analysis will examine CD3+CD19+ levels using the most recent samples available before and after treatment with rimiducid.

(v) Time to immune reconstitution defined by CD3 count > 500 cells/uL; CD4 > 200 cells/uL or CD8 count of 200 cells/uL

Time to immune reconstitution will be based on CD3, CD4 or CD8 counts for the defined thresholds above. Events are defined from the time of transplant to the time at which the threshold is achieved, with death considered as competing event. A patient not achieving the threshold T cell count will be censored on the last recorded visit day.

Time to immune reconstitution will be estimated using a Nelson-Aalen cumulative incidence function for each T cell subtype. Parameters estimates will be summarized for all subjects and by disease type (malignant or non-malignant). When estimable, additional summary statistics will include the median, minimum, maximum, the 25th and 75th percentiles of immune reconstitution, along with the number of events and censored observations. A cumulative incidence plot with descriptive summary statistics will be presented along with the number of patients at risk at various time points.

(vi) Disease-Free/chronic GvHD-Free survival at 180 days

The disease-free/chronic GvHD-free survival endpoint at 180 days will be assessed on the ITT (FAS) population. Events corresponding to disease-free/chronic GvHD-free survival outcomes include chronic GvHD, disease relapse for malignant subjects, disease recurrence for non-malignant subjects, or death by any cause. For patients with multiple events, the event that occurs first and the corresponding time will be used. Patients who do not experience an event will be censored on the last recorded visit day. Each patient outcome duration will be calculated from the date of transplant.

Kaplan-Meier techniques will be used to estimate disease-free/chronic GvHD-free survival at day 180. When estimable, additional summary statistics will include the median, minimum, maximum, the 25th and 75th percentiles along with the number of events and censored observations. Kaplan-Meier plots with descriptive summary statistics will be presented along with the number of patients at risk at various time points.

(vii) Disease status for the following diseases at 180 days:

a. Primary immune disorders as determined by CD3 T cell count ≥ 500 cells/ul and normal levels of IgA and IgM at 180 days

b. Haemoglobinopathies as determined by incidence of RBC transfusion independence (TI) and untransfused haemoglobin of ≥ 8.5 g/dL at 180 days

   Transfusion Independence (TI) is defined as not having received packed red blood cell transfusions for the previous 8 weeks.

c. Fanconi Anemia as determined by RBC ≥ 3,000,000 cells/ul, neutrophil count ≥ 1500 cells/ul and platelet count ≥ 150,000 at 180 days

d. Leukemia as determined by relapse-free-survival (RFS) at 180 days

For a)-d) above, cumulative incidence or survival will be assessed within the patient subpopulation defined as having those diseases at baseline. Cumulative incidence events for a.)-c.) are defined from the time of transplant until the event criteria described is achieved. Competing risks for a.)-c.) include any non-recurrence mortality. Events for RFS are defined as time to relapse or death from any cause.

Cumulative incidence for a.)-c.) will be estimated using a Nelson-Aalen cumulative incidence function for each disease subtype. When estimable, additional summary statistics will include the median, minimum, maximum, the 25th and 75th percentiles of immune reconstitution, along with the number of events and censored observations. A cumulative incidence plot with descriptive summary statistics will be presented along with the number of patients at risk various time points.

Kaplan-Meier techniques will be used to estimate RFS in subjects with leukemia. When estimable, additional summary statistics will include the median, minimum, maximum, the 25th and 75th percentiles along with the number of events and censored observations. Kaplan-Meier plots with descriptive summary statistics will be presented along with the number of patients at risk at various time points.

6.4.3. Other Efficacy Analyses:

(i) Time to Relapse in Subjects with Leukemia

Cumulative incidence of acute leukemia relapse will be estimated from time of transplant using a Nelson-Aalen cumulative incidence function and treating death prior to relapse as a competing risk. Cumulative incidence plots with descriptive summary statistics including incidence and 95% confidence intervals will be presented.

(ii) Time to Neutrophil Engraftment

Events for neutrophil engraftment is defined as the first of three consecutive measurements of an ANC ≥ 500/μL following the conditioning regimen induced nadir, starting from Day 0 (day of transplant). A patient that does not achieve the count of ANC ≥ 500/μL will be censored at the last assessment date.

Time to neutrophil engraftment will be estimated using a Nelson-Aalen cumulative incidence function. Death will be considered a competing event. Cumulative incidence plots with descriptive summary statistics including median engraftment time and 95% confidence intervals will be presented.

(iii) Time to Platelet Engraftment

Events for platelet engraftment is defined as the first of three consecutive measurements of platelet count ≥ 20,000/μL without platelet transfusion support for seven days. A patient that does not achieve the threshold platelet count of ≥ 20,000/μL as required will be censored at the last assessment date.

Time to platelet engraftment will be estimated using a Nelson-Aalen cumulative incidence function. Death will be considered a competing event. Cumulative incidence plots with descriptive summary statistics including median engraftment time and 95% confidence intervals will be presented.

(iv) Analysis of Primary and Secondary Graft Failure

Primary graft failure is defined as failure to achieve an absolute ANC ≥ 500 cells/μL by Day 30. The proportion of patients experiencing primary graft failure in the first 30 days will be summarized and reported with a 95% confidence interval.

Secondary graft failure is defined as initial neutrophil engraftment followed by a subsequent decline in neutrophil counts to < 500 cells/uL which is unresponsive to growth factor therapy. Sustained neutropenia, i.e., neutrophil counts to < 500 cells/uL, observed for greater than 30 days from the administration of growth factors will be summarized.

(v) Infectious Complications

Infectious complications are defined as clinically significant viral reactivations, viral infections requiring antiviral treatment, bacterial and fungal infections requiring the use of non-prophylactic antibiotics and antifungals, and rehospitalizations due to viral infection. Each of these occurrences will be summarized in tables and listings.

6.5. Safety Endpoints

Data for adverse events (AEs), serious adverse events (SAEs), clinical laboratory parameters, vital signs, and physical examinations will be presented in subject listings, including assessments of abnormality and clinical significance, where applicable. Summaries will be prepared for key variables (detailed below) by study visit (where applicable) for all patients as well as by malignant/non-malignant disease status. No inferential statistical testing will be performed for safety variables.

Unless otherwise specified, safety analyses will be conducted primarily within the BPX-501 safety population. Additional safety listings will be provided focusing (i) on the subjects enrolled into the initial dose escalation portion of the study, and on the subjects enrolled into the study but who either (ii) did not receive HSCT, or who (iii) received HSCT but did not receive BPX-501. Only SAEs were collected prior to administration of BPX-501.

For the purposes of analysis, treatment-emergent adverse events will be defined as those AEs with onset or worsening date occurring on or after the date of infusion with BPX-501.

6.5.1. Adverse Events

Each verbatim adverse event (AE) term recorded during the study will be mapped to a system organ class and preferred term using MedDRA Dictionary version 18.0.

Study treatment-related adverse events will be defined as the adverse events for which the investigator indicates the relationship to study drug as possible, probable, or definite. Relatedness of AEs for patients treated with rimiducid will be assessed among those patients from the date of first dose of AP1903.

All summaries of AEs will present the number and percent of subjects reported events by system organ class and preferred term. If a subject has multiple occurrences of an AE, the subject will be counted only once for the respective AE category at the SOC or preferred term level.

At a minimum, the following AE tables will be summarized by SOC and preferred term:

- Number and percentage of patients with any AE
- Number and percentage of patients with AEs by maximum severity
- Number and percentage of patients with G3 or higher AEs
- Number and percentage of patients with serious AEs (SAEs)
- Number and percentage of patients with AEs leading to death

Summaries will be presented for all subjects as well as by type of disorder (e.g. malignant or non-malignant). If any of the proposed tables has very limited occurrence, only patient listings may be provided.

At a minimum, the following patient listings will be provided:

- All AEs
- All SAEs
- All AEs leading to death

Specific listings and tables for GvHD, infections, and neurological events will be provided. Neurological events will be categorized relative to basket of preferred terms curated against MedDRA version 21.0. Key coding differences between this list and the MedDRA version used for broader AE coding will be highlighted.

6.5.2. Laboratory Data

Individual clinical laboratory results (hematology and chemistry) will be presented in data listings.

Frequency tabulations of the number of normal and abnormal (low and high) records will also be summarized in shift tables showing the number and percentage of subjects with lab values in each classification at each post-baseline visit relative to baseline classification frequencies.

Listings of individual laboratory data, indicating any clinically significant or values out of the normal range will be produced.

6.5.3. Vital Signs

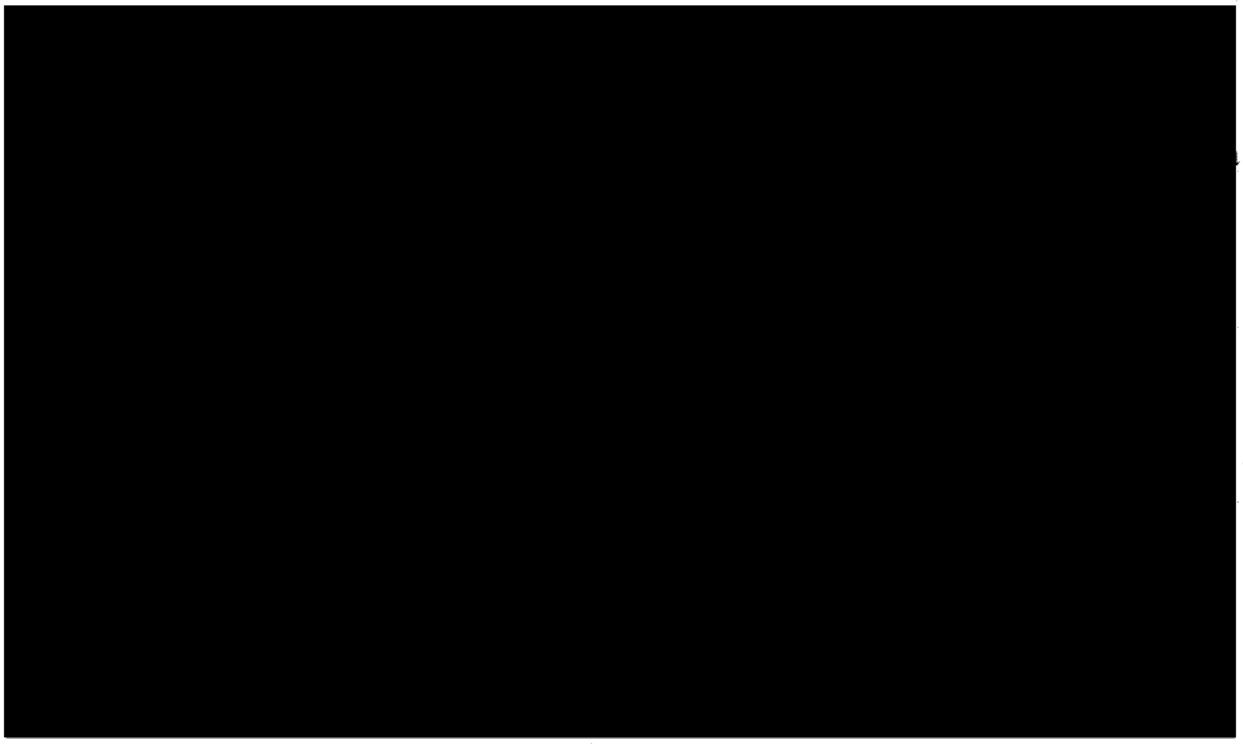
Vital signs are recorded at baseline and at different visits post-baseline. All individual vital signs results (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature) will be presented in data listings. Visit-wise observed vital signs parameter values and changes from baseline will be summarized by study visit using descriptive statistics. Vital signs following HSCT infusion, BPX-501 infusion and AP1903 administration will be included.

6.6. Changes to Statistical Analysis Methods Planned in the Protocol

No major changes have been identified in this SAP when comparing to the protocol. Analysis populations have been further clarified. Cut-offs for certain analytes, e.g, T cell subsets relating to immune reconstitution, may have been changed in order to harmonize across BPX-501 protocols

Prior versions of the protocol had referred to measuring progression-free survival or leukemia-free survival in subjects with leukemia. As BP-004 subjects were transplanted while in remission, and for consistency with other BPX-501 protocols, this endpoint has been appropriately renamed and corrected to relapse-free survival.

In several instances, the protocol mentioned that certain exploratory analyses will be summarized by BPX-501 dose, CD34+ cell dose in the allograft, γδT cell dose in the allograft, αβT cell dose in the allograft, ATG dosing, and conditioning regimen, among other parameters. Based on data availability or suitability, subgroup analyses and/or analyses accounting for each of these variables may not be provided for all such endpoints.



7. ATTACHMENTS

7.1. Table of Contents for Data Display Specifications

Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation.

Minor modifications may be necessary to the planned design of tables, listings and figures to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP, e.g., change in the population used, change from statistical methods or assumptions listed, transformation of data type, exclusion of planned analysis, or additional unplanned analyses will be documented, with justification, in the CSR.

7.1.1. Planned Data Outputs

The following outputs are intended to be produced for the study (NB: Numbering is indicative only and may be updated based on CSR requirements):

Tables:

14.1.1.1	Number of Subjects by Analysis Population and Disposition
14.1.1.2	Summary of Study Analysis Populations
14.1.1.3	Major Protocol Deviations and Violations
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14.1.2.2	Baseline Primary Disease Type, Conditioning and Treatment History
14.1.2.3	Donor Demographics, Relationships and HLA Typing
14.1.4.1	Prior Medications Use
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14.1.5	Study Treatment Exposure
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14.2.1.2	Kaplan-Meier Parameter Estimates of Event-Free Survival: Sensitivity Analysis for Any Grade 2-4 Acute GvHD
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14.2.1.5	Kaplan-Meier Parameter Estimates of Event-Free Survival: Sensitivity Analysis for Dose in Subjects with Malignant Disease
14.2.2	Cumulative Incidence Function Parameters Time to Transplant-Related or Non-Relapse Mortality
14.2.3.1	Cumulative Incidence Function Parameters Time to Acute GvHD Grades 2-4

14.2.3.1.1	Cumulative Incidence Function Parameters Time to Acute GvHD: Grade 2 Organ, Grades 3-4
14.2.3.2	Cumulative Incidence Function Parameters Time to Acute GvHD Grades 3-4
14.2.3.3	Cumulative Incidence Function Parameters Time to Severe Chronic GvHD
14.2.3.3.1	Cumulative Incidence Function Parameters Time to Moderate or Severe Chronic GvHD
14.2.3.4	Cumulative Incidence Function Parameters Time to Chronic GvHD Mild-Severe
14.2.4.1	Kaplan-Meier Parameter Estimates of Time to Resolution of Acute GvHD After Rimiducid Administration
14.2.4.2	Kaplan-Meier Parameter Estimates of Time to Resolution of Chronic GvHD After Rimiducid Administration
14.2.4.3	Kaplan-Meier Parameter Estimates of Time to Resolution of GvHD (Acute or Chronic) After Rimiducid Administration
14.2.4.4	Best Overall Clinical Response to Rimiducid in Subjects with Acute or Chronic GvHD
14.2.4.5	GvHD Types and Grades
14.2.5	Immune Reconstitution
14.2.6	Cumulative Incidence Function Parameters of Time to Immune Reconstitution of CD3, CD4, and CD8 T-cell Counts
14.2.7	Kaplan-Meier Parameter Estimates of Time to Disease-Free/Chronic-GvHD-Free Survival
14.2.8.1-3	Cumulative Incidence Function Parameters of Time to Recovery of Primary Immune Disorders as Determined by CD3 T Cell Count >500 cells/uL, and Normal Levels of IgA and IgM
14.2.8.2	Cumulative Incidence Function Parameter Estimates of Time to Recovery of Haemoglobinopathies as Determined by Incidence of RBC Transfusion Independence and Haemoglobin of >8.5 g/dL
14.2.8.3-3	Cumulative Incidence Function Parameter Estimates of Time to Recovery of Fanconi Anemia as Determined by RBC > 3,000,000 cells/uL, Neutrophil Count > 1500 cells/uL, and Platelet Count >150,000
14.2.8.4	Kaplan-Meier Parameter Estimates of Relapse-Free Survival in Subjects with Leukemia
14.2.8.5	Cumulative Incidence of Relapse in Subjects with Acute Leukemia
14.2.9	Cumulative Incidence Function Parameter Estimates of Time to Neutrophil Engraftment
14.2.10	Cumulative Incidence Function Parameter Estimates of Time to Platelet Engraftment
14.2.11	Graft Failures

14.2.12.1	Time to Any Grade Infection
14.2.12.2	Time to Grade 3 or Higher Infection
14.2.13.1	Kaplan-Meier Parameter Estimates of Overall Survival
14.2.13.2	Kaplan-Meier Parameter Estimates of Disease-Free Survival in Subjects with Non-Malignant Disease
14.2.13.3	Sensitivity Analysis: Kaplan-Meier Parameter Estimates of Disease-Free Survival, by Dosing Window
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14.3.1.4.2	Treatment-Emergent Adverse Events Occurring After AP1903 Administration, by System Organ Class, Preferred Term, and Maximum Severity
14.3.1.5.1	Treatment-Emergent Infection Adverse Events Regardless of Relationship to Study Treatment, by Preferred Term and Maximum Severity
14.3.1.5.2	Treatment-Emergent Infection Adverse Events Regardless of Relationship to Study Treatment, by Preferred Term and Maximum Severity
14.3.1.5.3	Treatment-Emergent Adverse Events Grades 3-5 Regardless of Relationship to Study Treatment, by System Organ Class, Preferred Term and Maximum Severity
14.3.1.5.4	Treatment-Emergent Neurotoxicity Adverse Events Regardless of Relationship to Study Treatment, by Preferred Term and Dose of BPX-501
14.3.2.1	Serious Treatment-Emergent Adverse Events Regardless of Relationship to Study Treatment by System Organ Class, Preferred Term, and Dose of BPX-501
14.3.2.2	Serious Treatment-Emergent Adverse Events Occurring After AP1903 Administration, by System Organ Class, Preferred Term, and Dose of BPX-501
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14.2.8.2	Cumulative Incidence Function Parameter Estimates of Time to Recovery of Haemoglobinopathies as Determined by Incidence of RBC Transfusion Independence and Haemoglobin of >8.5 g/dL
14.2.8.3.1	Cumulative Incidence Function Parameter Estimates of Time to Recovery of Fanconi Anemia as Determined by RBC > 3,000,000 cells/uL, RBC Transfusion Independence and Haemoglobin of >8.5 g/dL
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14.2.8.5	Cumulative Incidence of Relapse in Subjects with Acute Leukemia
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14.2.13.6	Sensitivity Analysis: Kaplan-Meier Parameter Estimates of Relapse-Free Survival, in Subjects Dosed at 1 x10^6 Cells/kg or Above
14.2.13.7	Sensitivity Analysis: Kaplan-Meier Parameter Estimates of Relapse-Free Survival, by Dosing Window in Subjects Dosed at 1 x10^6 Cells/kg or Above

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16.2.6.9	Types and Severity of Infectious Complications by Time
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16.2.7.2.3	Adverse Events in Subjects Treated with BPX-501 During Phase I Dose Escalation, Including Dose-Limiting Toxicities
16.2.7.3.1	Adverse Events Leading to Interruption or Discontinuation of Therapy or Permanent Discontinuation of Study Medication (BPX-501/AP1903)
16.2.7.3.2	Adverse Events Related to BPX-501
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16.2.7.3.3.2	Adverse Events Related to AP1903 (Rimiducid)
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16.2.8.1.2	Subject Abnormal Hematology Results and NCI CTCAE Grades
16.2.8.2.1	Subject Chemistry Results and NCI CTCAE Grades
16.2.8.2.2	Subject Abnormal Chemistry Results and NCI CTCAE Severity Grades
16.2.8.3	Vital Signs
16.2.8.4	Physical Examination, Karnofsky/Lansky Performance Status and WHO Score
16.2.8.5	ECG Results and Findings

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