Protocol Number: AVM-003-HC

Official Title: Phase 3 Multicenter, Double-Blind, Placebo-Controlled Trial of Viralym-M (ALVR105) for the Treatment of Patients With Virus-Associated Hemorrhagic Cystitis After Allogeneic Hematopoietic Cell Transplant

NCT Number: NCT04390113

Document Date: 14 Nov 2023

STATISTICAL ANALYSIS PLAN

Protocol Title:	Phase 3 Multicenter, Double-Blind, Placebo-Controlled Trial of Viralym-M (ALVR-105) for the Treatment of Patients with Virus-Associated Hemorrhagic Cystitis After Allogeneic Hematopoietic Cell Transplant
Protocol Number:	AVM-003-HC
[redacted]	[redacted]
Investigational Product:	Posoleucel (PSL, ALVR105; formerly ALVR-105, Viralym-M)
Sponsor:	AlloVir, Inc. 1100 Winter Street Waltham, MA 02451 United States
SAP Version/Date:	V1.0 14 November 2023

CONFIDENTIAL

SIGNATURE PAGE

Protocol Title: Phase 3 Multicenter, Double-Blind, Placebo-Controlled Trial of Viralym-M (ALVR-105) for the Treatment of Patients with Virus-Associated Hemorrhagic Cystitis After Allogeneic Hematopoietic Cell Transplant

Protocol Number: AVM-003-HC

SAP Version/Date: V1.0 14 November 2023

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

[redacted] 14-Nov-2023

Biostatistician
Medpace, Inc.

[redacted] *Reason: Approved*
Date: Nov 14, 2023 15:16 EST 14-Nov-2023

Biostatistician
Medpace, Inc.

[redacted] *Reason: Approved*
Date: Nov 14, 2023 16:33 EST 14-Nov-2023

Senior Medical Director, Medical Department
Medpace, Inc.

Reason: Approved
Date: Nov 14, 2023 20:51 PST 14-Nov-2023

Vice President, Biostatistician
AlloVir, Inc.

[redacted] *Reason: Approved*
Date: Nov 15, 2023 07:09 EST 15-Nov-2023

Senior Director, Clinical Research
AlloVir, Inc.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AdV	Adenovirus
AE	Adverse Event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BKV	BK Virus
BPIC SD	Bladder Pain/Interstitial Cystitis Symptom Diary
CMV	Cytomegalovirus
CRF	Case Report Form
CRS	Cytokine Release Syndrome
COAs	Clinical Outcome Assessments
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
ECG	Electrocardiograms
eGFR	Estimated Glomerular Filtration Rate
GVHD	Graft Versus Host Disease (GVHD)
HC	Hemorrhagic Cystitis
HCT	Hematopoietic Cell Transplant
HHV-6	Human Herpesvirus 6
HLA	Human Leukocyte Antigen
HPF	High Powered Field
ITT	Intent-to-Treat
IP	Investigational Product
IV	Intravenous(ly)
JCV	JC Virus
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
NRS	Numeric Rating Scale
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
PSL	Posoleucel, ALVR105; formerly ALVR-105, Viralym-M
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number AVM-003-HC. The SAP will be finalized prior to the interim analysis for futility. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare the time to resolution of macroscopic hematuria in recipients of posoleucel (PSL, ALVR105; formerly ALVR-105, Viralym-M) to that in recipients of placebo.

2.1.2 Secondary Objectives

The key secondary objective is to compare the time to resolution of bladder pain as measured by clinical outcome assessments (COAs) in recipients of PSL to that in recipients of placebo.

Other secondary objectives include comparisons of the following in recipients of PSL and recipients of placebo:

- To assess number of days in the hospital (for any reason including hemorrhagic cystitis [HC]) over the 24-week study period.
- To assess the incidence of acute graft versus host disease (GVHD) and cytokine release syndrome (CRS) over the 24-week study period.
- To assess time to resolution of viremia for each target virus over the 24-week study period (only for participants with detectable viremia at randomization).
- To assess average daily bladder pain over the 24-week study period.
- To assess time to global impression of hemorrhagic cystitis severity of none or mild.

2.1.3 Exploratory Objectives

The exploratory objectives include comparisons of the following in recipients of PSL and recipients of placebo as measured over the 24-week study period:

- Cumulative days and time to discontinuation of supportive bladder care for HC, specifically continuous bladder irrigation and/or nephrostomy tubes.
- Summary of HC-associated signs and symptoms other than bladder pain.
- Incidence and time to recurrence of HC.
- Incidence and time to recurrence of bladder pain.
- Requiring red blood cell (RBC) and/or platelet transfusions and the number of required RBC and/or platelet transfusions (measured in transfusion units/participant).
- Change in renal function as assessed by estimated glomerular filtration rate (eGFR). For participants requiring dialysis, number of days on dialysis will be captured.

- Time to resolution of BK viruria. Resolution of viruria will be defined by the lower limits of quantitation of the assay used.
- Viremia and viruria with each target virus (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over time.
- Length of use of any pain medication(s) (IV, oral, or other), including antispasmodics anticholinergics, and beta-3-agonists, used for control of lower abdominal/bladder pain.
- Use of immunosuppressive agents, by specific agent during the study.
- Number of hospitalizations, number of intensive care unit (ICU) stays, and number of days of ICU care for any reason.
- Use of antiviral therapies other than cidofovir with potential activity against at least one target virus by specific agent during the study.
- Overall survival, defined as time to death (from any cause) from the time of randomization in days.
- Incidence of relapse or progression of primary malignancy.
- Overall quality of life as measured by EuroQol 5 Dimensions (EQ-5D) questionnaires.
- Global impression of hemorrhagic cystitis change.

2.2 Study Design

2.2.1 Overview

This is a Phase 3, multicenter, double-blind, placebo-controlled trial to assess the efficacy and safety of PSL compared to placebo for the treatment of participants with virus-associated HC following allogeneic hematopoietic cell transplant (HCT).

The study hypothesis is that the administration of PSL to participants with virus-associated HC will demonstrate superiority for the time to resolution of HC (as measured by resolution of macroscopic hematuria) compared to participants treated with placebo. The primary hypothesis will be tested in participants with BKV viruria to demonstrate superiority over placebo in this population (BK Intent-to-Treat [ITT] Population). The analysis will also be conducted in all participants with any virus-associated HC (BKV, AdV, CMV, HHV-6, JCV, and/or EBV) in order to evaluate efficacy in this broader population (overall ITT Population).

Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a [redacted] to receive [redacted] sequential infusions of PSL cells or placebo and will be monitored for resolution of macroscopic hematuria as defined by the primary endpoint. Randomization will be stratified by [redacted].

In the dosing strategy being evaluated in this study, all participants will receive [redacted] infusions of either PSL or placebo separated by [redacted](±3) days.

The specific PSL cell line for infusion will be selected using an electronic-based software system (CytoMatch) [redacted]. Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance to PSL.

All randomized participants will undergo regular visual inspections of freshly collected urine samples for: 1) the presence or absence of visible blood, and 2) the presence or absence of blood clots. The schedule of assessments will be determined by the treatment location (inpatient vs. outpatient), time on study (through the end of Week 6 [Day 42] vs. after Week 6), and status of macroscopic hematuria (unresolved vs. resolved), as shown in Table 1. Each time that a participant undergoes a urine visual assessment for Bedi grading, the same sample should be sent for urinalysis.

Table 1. Timing of Visual Urine Assessments with Urinalysis

Treatment Location	Macroscopic Hematuria [1]	Time on Study	
		Through the End of Week 6 (Day 42)	After Week 6
Inpatient	Unresolved	Bedi assessment with U/A 3 × per week	Bedi assessment with U/A 2 × per week ≥2 days apart
	Resolved	Bedi assessment with U/A 1 × per week	Bedi assessment with U/A 1 × per week
Outpatient	Unresolved	Hemostick daily; Bedi assessment with U/A 1 × per week	Hemostick 2 × per week ≥2 days apart; Bedi assessment with U/A 1× per week
	Resolved	Hemostick 1× per week; Bedi assessment with U/A 1 × per week	Hemostick 1 × per week; Bedi assessment with U/A at Week 12 and 24 study visits

[1] Resolved macroscopic hematuria is defined as resolution to Grade 0 or 1 on the Bedi scale as assessed by an HCP on the study team on 2 consecutive visual urine assessments ≥2 days apart without continuous bladder irrigation or nephrostomy tubes that are uncapped. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed on urine voided through the urethra or a bladder catheter (eg, Foley or suprapubic catheter), including for the purpose of assessing for resolution.
Abbreviations: HCP = healthcare provider; U/A = urinalysis

In support of the key secondary objective, bladder pain will be assessed using age-appropriate COAs.

Participants will also have urine and blood samples sent at prespecified intervals during the study to monitor viral loads of all the viruses targeted by PSL (BKV, AdV, CMV, HHV-6, JCV, and EBV). For participants who develop symptoms and/or signs of possible virus-associated gastrointestinal disease, and whose treating physician determines that laboratory evaluation of stool specimens for diagnostic and/or monitoring reasons is clinically indicated, stool samples for AdV and CMV viral load determination should, when possible, be sent to the central laboratory. Similarly, for participants who develop symptoms and/or signs of possible virus-associated neurological disease, and whose treating physician determines that laboratory evaluation of cerebrospinal fluid (CSF) for diagnostic and/or monitoring reasons is clinically indicated, CSF samples for CMV, HHV-6, and JCV viral load determination should, when possible, be sent to the central laboratory.

Safety assessments including, but not limited to chemistries, complete blood counts with differentials, and physical examinations will be performed. Adverse events will be assessed.

As GVHD is a theoretical safety concern, the incidence and severity of GVHD will be monitored during the study. No participants will be permitted to receive a second infusion of PSL or placebo if they develop worsening of GVHD at the proposed time of infusion of the second dose.

Analgesic use will be collected by the study staff and a pain medication log within the electronic patient-reported outcome (ePRO) system will be completed by outpatients.

Participants will be followed on the study for 24 weeks after the participant's first infusion with study treatment.

An independent Data and Safety Monitoring Board will be convened for this study to routinely monitor participant safety and evaluate a prespecified interim analysis for the purpose of potentially stopping the study early for futility.

A summary of the study design is shown in Figure 1.

Figure 1. Summary of Study Design

R = Randomization (on Day 1)

See section 3.1.1 (Analysis Day) for an explanation of the differences in definitions of day of the first dose and randomization between the SAP and the protocol.

2.2.2 Study Drug

Posoleucel is a third-party, donor-derived, "off-the-shelf," virus-specific T cell (VST) product with specificity for BKV, AdV, CMV, HHV-6, and EBV (with additional cross-reactive specificity for JCV due to the substantial homology between BKV and JCV) that is cryopreserved and available for immediate use. For more information, see the current IB.

2.2.3 Sample Size Determination

Approximately 125 participants will be randomized to achieve 105 participants in the BK ITT Population (the primary efficacy analysis population), assuming 85% of randomized participants will be included in the BK ITT Population. Enrollment in the study will continue until there are 105 participants in the BK ITT Population. Participants will be randomized in a [redacted] ratio to receive PSL or placebo. Assuming the median times to resolution for the placebo arm and the PSL arm are, respectively, 12 weeks and 6 weeks; time to resolution follows an exponential distribution; 24 weeks of follow-up; use of a log-rank test; one interim analysis for futility; Type I error rate at the one-sided 0.025 level; 20% of participants are censored for losses to follow-up

or dropout by 24 weeks; time to censoring follows an exponential distribution and is equivalent in the two arms, the study will have 86.4% power.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary endpoint is the time to resolution of macroscopic hematuria in participants with documented BK viruria. A supplementary analysis will evaluate the time to resolution of macroscopic hematuria in participants with any virus-associated HC. Resolution of macroscopic hematuria is defined as resolution to Grade 0 or 1 on the Bedi scale as assessed by the Investigator on 2 consecutive visual urine assessments with urinalysis ≥2 days apart without continuous bladder irrigation or nephrostomy tubes that are uncapped. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed on urine voided through the urethra or a bladder catheter (eg, Foley or suprapubic catheter), including for the purpose of assessing for resolution.

A healthcare provider (HCP) on the study team (including a home health provider) may perform the visual urine assessment, but it is the Investigator's responsibility to determine the Bedi grade. Grade 0 requires no detectable blood by urinalysis; Grade 1 hematuria requires confirmation of resolution by urinalysis results of ≤100 RBCs/high power field (HPF).

Participants will be followed for the primary endpoint for a maximum of 24 weeks from the date of randomization.

Definitive therapies to stop bladder bleeding, including cystectomy, bladder vessel embolization, cauterization, fulguration, or formalin instillation are permitted, but will be considered treatment failures for the primary endpoint of time to resolution of macroscopic hematuria. Participants with ongoing continuous bladder irrigation should be evaluated daily by the Investigator for the ability to discontinue this supportive measure.

Participants who are receiving continuous bladder irrigation or who have nephrostomy tubes that are uncapped at randomization will be considered to have Bedi Grade 3 hematuria at randomization. For participants undergoing continuous bladder irrigation, the primary endpoint (ie, time to resolution of macroscopic hematuria) will be measured once participants discontinue continuous bladder irrigation. Bedi grading will not be performed on days on which the participant is receiving continuous bladder irrigation. Discontinuation of continuous bladder irrigation will be based upon the participant's clinical condition and the treating physician's medical judgement.

If, following resolution of macroscopic hematuria, recurrence is observed, a Bedi assessment with urinalysis will be obtained and the date of recurrence observed by the Investigator will be recorded. Urine obtained at the time of recurrence will also be sent for BKV, AdV, CMV, HHV-6, JCV, and EBV viral load determination and banking of viral deoxyribonucleic acid for potential genotyping. A second Bedi assessment with urinalysis will be repeated ≥2 days after the date of recurrence observed by the Investigator. Recurrence is defined as 2 consecutive Bedi grades ≥2 with macroscopic hematuria (visibly bloody urine) that are at least 2 days apart. Participants with recurrence will then undergo visual assessment of urine and urinalysis as indicated in Table 1 for those with unresolved hematuria and according to the participant's treatment location and time on study. Following resolution of recurrent hematuria, follow Table 1 for those with resolved hematuria.

2.3.2 Secondary Efficacy Endpoints

The key secondary endpoint is the time to resolution of bladder pain as measured by age-appropriate COAs. Resolution of pain is defined as participants achieving a score on the relevant COA that does not exceed "mild pain," confirmed with 2 consecutive scores, without use of prescription pain medications (not PRN or "as needed") or the use of supportive bladder care, specifically continuous bladder irrigation and nephrostomy tubes.

Mild bladder pain is defined as:

- In participants ≥12 years of age: a score ≤3 on the worst daily pain question from the Bladder Pain/Interstitial Cystitis Symptom Diary (BPIC SD).
- In participants 3 to 11 years of age: a score ≤2 on the Wong-Baker FACES® Pain Rating Scale.

The analysis will include all participants whose pain scores exceed "mild pain" at randomization, or who are receiving prescription pain medications (not PRN or "as needed") or supportive bladder care at randomization. Use of prescription pain medications (not PRN or "as needed") or supportive bladder care will be considered equivalent to pain that exceeds "mild pain." If the pain scores at randomization are missing, the screening pain scores will be used. Otherwise, the participant will not be included in the analysis.

This endpoint will not be assessed in participants <3 years of age as there is no COA that has been validated for this purpose. Instead, data regarding pain behaviors will be collected in this age group using the Patient-Reported Outcomes Measurement Information System® (PROMIS) Parent Proxy Pain Behavior Short Form.

Additional secondary efficacy endpoints include the following:

- Number of days in the hospital (for any reason including, but not limited to, HC) over the 24-week study period.
- Time to resolution of viremia for each target virus (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over the 24-week study period (only for participants with detectable viremia at randomization). Evaluation of this endpoint will be based on viremia quantitation performed at the central laboratory. Resolution of viremia will be defined by the lower limits of quantitation (LLOQ) of the assays used (BKV, AdV, CMV, HHV-6, JCV are measured in the plasma, EBV is measured in peripheral blood mononuclear cells).
- Average daily bladder pain over the 24-week study period, without use of prescription pain medications (not PRN or "as needed") or supportive bladder care.
- Time to global impression of hemorrhagic cystitis severity of none or mild, confirmed with 2 consecutive scores, without use of prescription pain medications (not PRN or "as needed") or supportive bladder care.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Cumulative days and time to discontinuation of supportive bladder care for HC, specifically continuous bladder irrigation and/or nephrostomy tubes.

- Summary of HC-associated signs and symptoms other than bladder pain, including urinary frequency, urinary urgency, constant need to urinate, and nocturia.
- Incidence and time to recurrence of HC, defined as two consecutive Bedi grades ≥2 with macroscopic hematuria (visibly bloody urine) that are at least 2 days apart.
- Incidence and time to recurrence of bladder pain.
- Requiring RBC and/or platelet transfusions and the number of required RBC and/or platelet transfusions (measured in transfusion units/participant).
- Change in renal function as assessed by eGFR. For participants requiring dialysis, number of days on dialysis will be captured.
- Time to resolution of BK viruria. Resolution of viruria will be defined by the lower limits of quantitation of the assay used.
- Viremia and viruria with each target virus (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over time.
- Length of use of any pain medication(s) (IV, oral, or other), including antispasmodics, anticholinergics, and beta-3-agonists, used for control of lower abdominal/bladder pain.
- Use of immunosuppressive agents, by specific agent during the study.
- Number of hospitalizations, number of ICU stays, and number of days of ICU care for any reason.
- Use of antiviral therapies other than cidofovir with potential activity against at least one target virus by specific agent during the study.
- Overall survival, defined as time to death (from any cause) from the time of randomization in days.
- Incidence of relapse or progression of the primary malignancy.
- Overall quality of life as measured by EQ-5D questionnaires.
- Global impression of hemorrhagic cystitis change.

2.3.4 Safety Endpoints

The safety endpoints include the following:

- Incidence and severity of acute GVHD (for the acute GVHD grading scale, see Appendix E of the Protocol)
- Incidence and severity of chronic GVHD (for the chronic GVHD grading scale, see Appendix E of the Protocol)
- Incidence and severity of cytokine release syndrome (CRS) (for the CRS grading scale, see Appendix F of the Protocol)

Safety assessments also include adverse events, vital signs, 12-lead electrocardiograms (ECGs), physical examination findings, and clinical laboratory evaluations (blood chemistry, hematology, and urine).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Day from Randomization

Study day will be calculated from the date of randomization, as analysis day = actual assessment/collection/visit date – randomization date (+1 for dates on or after the randomization date and not for dates before the randomization date). All the efficacy endpoints will be summarized at and post randomization based on the study day from randomization.

3.1.2 Study Day from First Dose

Study day will be calculated from the date of first dose of study drug, as analysis day = actual assessment/collection/visit date – first dose date (+1 for dates on or after the first dose date and not for dates before the first dose date). The day of the first dose of study drug will be Day 1, and the day immediately before and after Day 1 will be Day -1 and Day 2. This is different from the protocol for the scheduled visit day, which defined the day of the first dose and randomization as day 0. All the safety endpoints will be summarized based on the study day from the first dose of study drug.

3.1.3 Analysis Visits

All the visits will be assigned to analysis visits according to the visit windows indicated by analysis windows of this SAP (Appendix A). If two or more visits fall into the same analysis window, the visit closest to the planned visit timepoint will be used. If the distances to the planned visit are equal, the latest one will be used. If multiple assessments occur on the same day, the values will be averaged. For laboratory data, if a retest visit can be identified due to result error (eg, laboratory error or physiologically improbable results) in the original test visit, the retest visit will be used in place of the original test result for that visit.

3.1.4 Definition of Baseline

Baseline is defined as the last non-missing measurement on or prior to Study Day 1.

3.1.5 Strata and Covariates

Randomization will be stratified by [redacted]. If there are discrepancies in stratification factor values between the IRT and the EDC database, the values recorded in the EDC database will be used for all the analyses in this SAP. For deriving cidofovir use within 4 weeks prior to screening or during the screening process, such medication is taken within 4 weeks prior to screening visit through the randomization date.

3.1.6 Summary Statistics

Summary statistics will be presented by treatment group. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized using the frequency count and the percentage of participants in each category as descriptive statistics.

3.1.7 Handling of Missing Data

In general, data will be analyzed and presented as observed and will not be imputed for the analysis of efficacy and safety.

In case the start and end dates for adverse events (AEs) and concomitant medications/procedures are missing or incomplete, the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study treatment or ended prior to the start of study treatment. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment emergent. Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

3.1.8 Handling of Contaminated Data

In general, viral load data from the central laboratory will be used for efficacy analyses If evidence can be provided for the contamination of central lab sample as “questionable integrity” or “questionable sample integrity”, local laboratory viral load data will be used in place of the contaminated central laboratory sample.

3.1.9 Data Collected After End of Study

Data collected after the end of study will not be included in the summary tables but will only be presented in listings.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all randomized participants regardless of whether they are dosed or not. Participants will be analyzed according to the randomized study treatment.

3.2.2 BK Intent-to-Treat Population

The BK ITT Population will include participants in the ITT Population who have BKV detected in the urine. The primary efficacy analysis will be based on the BK ITT Population. In the BK ITT Population definition, BKV identification is determined based on the last available BKV urine viral load test result on or before the randomization date from central laboratory data or if central laboratory data are missing or have “questionable integrity” or “questionable sample integrity,” from local laboratory data.

3.2.3 Modified ITT Population

The modified Intent-to-Treat (mITT) Population will include all randomized participants who receive any dose of study drug.

3.2.4 BK Modified Intent-to-Treat Population

The BK mITT Population will include participants in the BK ITT Population who receive any dose of study drug.

3.2.5 BK Per-Protocol Population

The BK Per-Protocol (PP) Population will include all participants in the BK mITT Population who do not have any major protocol deviations deemed to impact the results. Factors potentially impacting the primary efficacy result may include but are not limited to:

- Participants had major inclusion or exclusion violations
- Participants received the wrong study treatment (ie, did not receive the randomized study treatment assigned by the interactive responsive technology [IRT] system)
- Participants had low study drug compliance (<80%)
- Participants took a restricted concomitant medication
- Participants failed to complete the primary efficacy assessment
- Participants who did not have a Bedi Grade ≥ 2 at randomization

The list of participants to be excluded from the BK PP Population will be finalized before database lock.

3.2.6 Safety Population

The Safety Population will include all participants who receive any amount of PSL or placebo. All safety analyses will be based on the Safety Population. Participants will be analyzed according to the treatment actually received.

3.3 Participant Data and Study Conduct

3.3.1 Participant Disposition

The number and percentages of participants who were screened and failed to meet eligibility criteria at screening will be summarized. The numbers and percentages of participants who were randomized, treated, discontinued early from study drug and study, and completed the study drug and study will be summarized by treatment group and in total based on the ITT population. Reasons for early discontinuation will also be summarized.

The numbers and percentages of participants in each analysis population will be summarized by treatment group and in total based on the ITT population. Reasons for exclusion from each analysis population will also be summarized.

3.3.2 Protocol Deviations

The numbers and percentages of participants with important protocol deviations by deviation category will be summarized by treatment group and in total based on the ITT population. Important protocol deviations related to the COVID-19 pandemic will be summarized by treatment group and listed based on the ITT population.

3.3.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized, but not limited to:

- Age (years) and age group (<12 or ≥12 years; <18 or ≥18 years; <65 or ≥65 years)
- Use of cidofovir within 4 weeks prior to screening or during the screening process
- Sex
- Childbearing potential

- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI group (<30 kg/m^2, ≥30 kg/m^2)
- Primary malignancy/underlying disease for transplant
- Type of transplant
- Participant CMV serostatus
- Blood Type
- Rh Factor
- HLA alleles from the study participant, the allogeneic HCT donor(s), and the VST donor(s) as well as the number of shared alleles among these individuals
- Baseline viral load in plasma (for BKV, AdV, CMV, HHV-6, JCV) or peripheral blood mononuclear cells (PBMCs; for EBV) for all target viruses
- Baseline viral load in urine for all target viruses
- Receipt of donor lymphocyte infusion >21 days prior to randomization

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of participants as appropriate by treatment group and in total for all analysis populations.

3.3.4 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The numbers and percentages of participants with medical history by system organ class and preferred term will be summarized by treatment group and in total based on the safety population.

3.3.5 Prior and Concomitant Medications

Prior and Concomitant medications will be collected starting 30 days before screening and coded to anatomical therapeutic chemical (ATC Level 2) class and preferred term using the WHODrug Dictionary. All medications taken prior to the first dose of study treatment will be considered as prior medications. The medications taken prior to the first dose of study treatment and were ongoing or started on or after the first dose of study treatment will be considered as concomitant medications.

The numbers and percentages of participants taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and in total based on the Safety Population.

3.3.6 Study Drug Exposure and Compliance

The number of doses and total dosing (including but not limited to prepared volume, total volume administered and duration of study drug infusion) will be summarized based on the safety population. The number of patients in the active treatment group who received two doses of the same PSL line versus two different PSL lines will be specified.

The length of exposure to study drug will be calculated as the number of days from the first dose of study drug to the last dose of study drug as:

Date of last dose – date of first dose + 14

Length of exposure will be summarized using descriptive statistics for the safety population.

A by-participant listing will be provided for study drug exposure.

Overall compliance will be calculated as:

*(Sum of total volume administrated)/ (total volume planned)*100*

The number and percentage of participants will be summarized for the safety population for the following categories for overall compliance: 0- <80% and >= 80%.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint

The primary endpoint is the time to resolution of macroscopic hematuria in participants with documented BK viruria. Resolution of macroscopic hematuria is defined as resolution to Grade 0 or 1 on the Bedi scale on 2 consecutive urine assessments ≥2 days apart without continuous bladder irrigation or nephrostomy tubes that are uncapped; Grade 1 requires confirmation of resolution by urinalysis results of ≤100 RBCs/HPF. If a participant has nephrostomy tubes that are capped, Bedi assessments may be performed on urine voided through the urethra or a bladder catheter (eg, Foley or suprapubic catheter), including for the purpose of assessing for resolution.

If the Bedi grade at randomization is missing, then the most recent screening Bedi grade will be used if available. If there are no Bedi grades at either randomization or during screening, the participant will be assumed to be eligible. The primary efficacy analysis will be conducted after all participants have completed 24 weeks of follow up or discontinued from the study. At the primary analysis, the PSL group will be compared to the placebo group in the BK ITT Population using a stratified log-rank test adjusting for stratification factors at randomization (derived based on EDC data). The study will be considered a success if the one-sided p-value from the stratified log rank test comparing treatment to control is less than 0.025. A stratified Cox proportional hazards model will be conducted to produce the hazard ratio of the treatment effect.

Time to resolution will be calculated starting from the date of randomization to the date of the first visual urine assessment without macroscopic hematuria (by the Hemostick® visual scale with score of 0 for outpatients; by the Bedi scale with a Grade 0 or 1 for inpatients) will be used, but 2 consecutive Bedi grades of 0 or 1 are required to establish resolution as noted above. If an outpatient does not have a Hemostick score at the time of resolution, the first of the 2 consecutive Bedi grades of 0 or 1 will be used for determining the time to resolution, which is the same approach being applied to inpatients. For inpatients who resolve on the date of hospital discharge, the Bedi grade scored on the discharge date will be used for determining time to resolution if available; if no Bedi grade is available at the time of discharge, then the Hemostick score will be used.

Participants not observed to achieve resolution will be considered censored at their last study follow up. Definitive therapies to stop bladder bleeding, such as cystectomy, bladder vessel embolization, cauterization, fulguration, or formalin instillation are permitted. If it is given before or on the day of randomization, the participant will be included in the BK ITT analysis assuming a Bedi of 2 or above. If it is given post randomization, it will be considered treatment failure for the primary endpoint of time to resolution of macroscopic hematuria and will be censored at the last follow-up time of any participant. Participants who discontinued early from the study before

achieving resolution will be censored at the time of last follow up. Participants who died or took non-PSL VSTs prior to reaching resolution will be considered treatment failures and censored at the last follow-up time of any participant.

For Bedi assessments where the grade is not evaluable and the participant is receiving continuous bladder irrigation, has nephrostomy tubes that are uncapped, or the urine is visually bloody, macroscopic hematuria is considered unresolved. For all other Bedi assessments where the grade is not evaluable, the grade is considered missing.

The analysis date for a Bedi assessment is the visual assessment date. If there is no visual assessment date, the urine collection date will be used. Otherwise, the visit date will be used. One Bedi assessment will be selected per analysis date. If there are multiple Bedi assessments on the same analysis date, the worst case is selected. If for a visit, there are Bedi assessments with a visual assessment date or urine collection date, assessments with only a visit date will not be selected.

If there are multiple Hemostick scores on the same date, the highest score will be selected.

If the result of the primary efficacy endpoint (ie, time to resolution of macroscopic hematuria) is statistically significant based on the BK ITT Population, a formal hypothesis test will be conducted sequentially of this same endpoint based on the overall ITT Population using a one-sided 0.025 significance level.

A sensitivity analysis of the primary efficacy endpoint will also be conducted for the BK ITT population, using a Cox proportional hazards model in order to account for additional potential confounders of the treatment effect. In addition, supportive analyses of the primary efficacy endpoint will also be performed based on the BK mITT, BK PP and mITT Populations.

Primary efficacy endpoint in the estimand framework is described as follows:

<table>
<tr><td>Statistical category</td><td colspan="3">Estimand:
Treatment: Study Treatment (PSL) or Placebo
Population: Pediatric and adult participants with virus-associated hemorrhagic cystitis following allogeneic HCT
Endpoint (Variable): Time to resolution of macroscopic hematuria in participants with documented BK viruria. Resolution of macroscopic hematuria is defined as resolution to Grade 0 or 1 on the Bedi scale as assessed by the Investigator on 2 consecutive visual urine assessments ≥2 days apart without continuous bladder irrigation or nephrostomy tubes that are uncapped. If a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, for the purpose of assessing for resolution.
Population-level summary: Median time to resolution of macroscopic hematuria.
Intercurrent events (ICE):
1. Use of definitive therapies to stop bladder bleeding
2. Early discontinuation from the study treatment before achieving resolution
3. Death due to any cause before achieving resolution
4. Treatment for hemorrhagic cystitis with non-PSL VSTs before achieving resolution</td></tr>
<tr><td></td><td>Analysis set</td><td>Intercurrent event handling strategy</td><td>Population-level summary (Analysis):</td></tr>
<tr><td>Primary</td><td>BK ITT</td><td>1. Composite strategy: Participants with ICE 1 will be considered treatment failures for the primary endpoint of time to resolution of macroscopic hematuria and will be censored at the last follow-up time of any participant.
2. Treatment policy strategy: Data collected after occurrence of ICE 2 will be used for the primary endpoint.
3. Composite strategy: Participants with ICE 3 will be censored at the last follow-up time of any participant.
4. Composite strategy: Participants with ICE 4 will be considered treatment failures for the primary endpoint of time to resolution of macroscopic hematuria and will be censored at the last follow-up time of any participant.</td><td>Treatment comparison using a stratified log-rank test (by stratification factors at randomization)</td></tr>
<tr><td>Sensitivity Analysis</td><td>BK ITT</td><td>Same as primary</td><td>A stratified Cox model including fixed effect terms for randomized treatment assignment, concomitant antiviral use, and concomitant systemic corticosteroid use.</td></tr>
<tr><td>Supportive 1</td><td>BK mITT</td><td>Same as primary</td><td>Same as primary</td></tr>
<tr><td>Supportive 2</td><td>BK PP</td><td>Same as primary</td><td>Same as primary</td></tr>
<tr><td>Supportive 3</td><td>mITT</td><td>Same as primary</td><td>Same as primary</td></tr>
</table>

Subgroup analyses will be conducted for the BK ITT population to compare the primary endpoint by baseline BKV viruria ($<10^7$ copies/mL vs $\geq 10^7$ copies/mL), demographic characteristics (eg, age group, sex), stratification factors (derived based on EDC data), and use of concomitant antiviral therapies with potential activity against BK virus during the study. Such agents include cidofovir, ciprofloxacin, and leflunomide. The subgroup analysis will also be conducted by the number of HLA matches and class of HLA matches (class I/II/both).

Analysis will be performed excluding participants who did not have a Bedi Grade ≥2 at randomization from the BK ITT and BK mITT.

All the time to event primary efficacy endpoints will be presented using Kaplan-Meier plots. The estimated median time to event with the corresponding 95% confidence intervals will be presented by treatment group.

3.4.2 Key Secondary Efficacy Endpoint

The key secondary endpoint is the time to resolution of bladder pain as measured by age appropriate COAs. Resolution of pain is defined as participants achieving a score on the relevant COA that does not exceed “mild pain” (defined in Protocol Section 7), confirmed with 2 consecutive scores, without use of prescription pain medications (not PRN or “as needed) or supportive bladder care. The relevant COA is the worst daily pain (ie, the participant’s worst bladder pain over the previous 24 hours), which is recorded daily for the first 6 weeks of the study and once weekly thereafter. Intermittent missing scores will be omitted.

The analysis will include all the participants whose pain scores exceed “mild pain” at randomization or who use prescription pain medications (not PRN or “as needed”) or supportive bladder care at randomization, assuming their bladder pain scores exceed mild. If the scores at randomization are missing, a prior pain score will be used if available. Otherwise, the participant will not be included in the analysis.

Time to resolution will be calculated from the date of randomization to the date of the first resolution of bladder pain. Participants not observed to achieve resolution will be considered censored at their last follow up. The pain scores collected while participants use pain medications (not PRN or “as needed”) or supportive bladder care will not be used.

If the result of the analyses of the primary efficacy endpoint is statistically significant based on both the BK ITT and overall ITT Populations, a formal hypothesis test will be conducted sequentially of the time to resolution of bladder pain based on the BK ITT Population in the same manner as described for the primary efficacy analysis of the primary efficacy endpoint, and a one-sided 0.025 significance level will be used. If this result of the analysis of time to resolution of bladder pain based on the BK ITT Population is statistically significant, a formal hypothesis test of this endpoint will then be conducted based on the overall ITT Population using a 0.025 significance level.

A sensitivity analysis of the key secondary efficacy endpoint will also be conducted for the BK ITT population, using a Cox proportional hazards model in order to account for additional potential confounders of the treatment effect. In addition, supportive analyses of the key secondary efficacy endpoint will also be performed based on the BK mITT, BK PP and mITT Populations.

Secondary efficacy endpoint in the estimand framework is described as follows:

<table>
<tr><td rowspan="2">Statistical category</td><td colspan="3">Estimand:
Treatment: Study Treatment (PSL) or Placebo
Population: Pediatric and adult participants with virus-associated hemorrhagic cystitis following allogeneic HCT
Endpoint (Variable): Time to resolution of bladder pain as measured by age appropriate COAs. Resolution of pain is defined as participants achieving a score on the relevant COA that does not exceed “mild pain” (defined in Protocol Section 7), confirmed with 2 consecutive scores, without use of prescription pain medications (not PRN or “as needed”) or supportive bladder care.
Intercurrent events: Include intercurrent events from primary efficacy endpoint and
1. Use of prescription pain medications (not PRN or “as needed”) or supportive bladder care
2. Early discontinuation from the study treatment before achieving resolution
3. Death due to any cause before achieving resolution
4. Missing daily or weekly assessment of bladder pain
5. Treatment for hemorrhagic cystitis with non-PSL VSTs before achieving resolution</td></tr>
<tr><td>Analysis set</td><td>Intercurrent event handling strategy</td><td>Population-level summary (Analysis):</td></tr>
<tr><td>Secondary</td><td>BK ITT</td><td>1. Composite strategy: Data collected while on ICE 1 will not be used for the key secondary endpoint, ie, assuming using ICE 1 is equivalent to pain exceeds “mild pain.”
2. Treatment policy strategy: Data collected after occurrence of ICE 2 will be used for the key secondary endpoint.
3. Composite strategy: Participants with ICE 3 will be censored at the last follow-up time of any participant.
4. Hypothetical strategy: ICE 4 will be omitted and next observed assessment will be used
5. Composite strategy: Participants with ICE 5 will be considered treatment failures for the key secondary endpoint of time to resolution of bladder pain and will be censored at the last follow-up time of any participant.</td><td>As primary but using a one-sided 0.025 significance level.</td></tr>
<tr><td>Supportive 1</td><td>BK mITT</td><td>Same as secondary</td><td>Same as secondary</td></tr>
<tr><td>Supportive 2</td><td>mITT</td><td>Same as secondary</td><td>Same as secondary</td></tr>
</table>

Subgroup analyses may be conducted for the BK ITT population for age appropriate COAs to evaluate responses in participants who took different outcome measurements, similar to the primary efficacy endpoint.

3.4.3 Other Efficacy Endpoints

If the result of the key secondary efficacy analyses based on the BK ITT and overall ITT Populations are both statistically significant, a formal hypothesis test will be conducted sequentially of the first other secondary endpoint, number of days in the hospital, based on the BK ITT Population. The analysis will be performed using a linear regression model with terms for treatment and the stratification factors at randomization (defined based on EDC data). This secondary endpoint will be tested at the one-sided 0.025 alpha level. If the result of the analysis based on the BK ITT Population is statistically significant, a formal hypothesis test of this endpoint will be conducted based on the overall ITT Population using a 0.025 alpha level. Supportive analyses will be conducted using the BK mITT, BK PP, and mITT Populations.

The sequential testing described above will control the overall Type I error for these endpoints at the one-sided 0.025 level.

Other continuous and categorical efficacy endpoints (including secondary and exploratory endpoints not selected for hierarchical testing above) will be summarized descriptively by treatment group using appropriate populations. Categorical endpoints will be summarized using the number and percentage of participants within each category.

Time-to-event endpoints will be summarized using Kaplan-Meier estimates. Treatment comparison using a stratified log-rank test adjusted by stratification factors at randomization (defined based on EDC data) at one-sided significance level 0.025 will be reported as well. In addition, the hazard ratio along with the 95% confidence intervals for the true hazard ratio will be calculated using a stratified Cox proportional hazards model with treatment, and other potentially confounding factors.

There is no adjustment for multiplicity in the analyses of these other efficacy endpoints.

Specifically, the following efficacy endpoints will be analyzed based on BK ITT Population unless mentioned otherwise, and equally at the one-sided 0.025 level.

Time to resolution of viremia for each target virus (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over the 24-week study period (only for participants with detectable viremia at randomization) will be analyzed using Kaplan-Meier estimates, and treatment effect will be compared using stratified log-rank test and hazard ratio with stratified Cox proportional model. Evaluation of this endpoint will be based on viremia quantitation performed at the central laboratory. Resolution of viremia will be defined by the lower limits of quantitation (LLOQ) of the assays used (BKV, AdV, CMV, HHV-6, JCV are measured in the plasma, EBV is measured in peripheral blood mononuclear cells). Only participants who had viremia at randomization for each target virus will be included in the analysis.

Average daily bladder pain (ie, the participant's average bladder pain over the previous 24 hours) will be recorded daily for the first 6 weeks of the study and once weekly thereafter. The average daily bladder pain will be averaged for each week for the first 6 weeks and starting at Week 7, the single average daily pain score will be recorded. The applicable weekly measures will be summarized by treatment group over the 24-week study period. Only pain assessments

without use of prescription pain medications (not PRN or “as needed”) or supportive bladder care will be used.

Time to global impression of hemorrhagic cystitis severity of none or mild, confirmed with 2 consecutive scores, will be analyzed similar to the key secondary endpoint. The analysis will include all the participants who exceed “mild” at randomization. If the scores at randomization are missing, a prior score will be used if available. Otherwise, the participant will not be included in the analysis. Time to resolution will be calculated from the date of randomization to the date of the first time reaching the global impression of hemorrhagic cystitis severity of non or mild, without use of prescription pain medications (not PRN or “as needed”) or supportive bladder care. Participants not observed to achieve the threshold will be considered censored at their last follow up.

Cumulative days of supportive bladder care for HC, specifically continuous bladder irrigation and/or nephrostomy tubes, will be summarized by treatment group. In the analysis, cumulative days of supportive bladder care will include all days of such therapy for the entirety of the trial. Time to discontinuation refers to time from randomization to initial discontinuation of all supportive bladder care in participants who were receiving a supportive bladder care at randomization. Time to discontinuation of supportive bladder care for HC will be analyzed using Kaplan-Meier estimates, and treatment effect will be compared using stratified log-rank test and hazard ratio with stratified Cox proportional model.

HC-associated signs and symptoms other than bladder pain will be descriptively summarized. The signs and symptoms analyzed include urinary frequency, urinary urgency, constant need to urinate, and nocturia.

Incidence and time to recurrence of HC will be analyzed using Kaplan-Meier estimates, and treatment effect will be compared using stratified log-rank test and hazard ratio with stratified Cox proportional model. Only participants who have reached the HC resolution will be included in the analysis. Time to recurrence of HC refers to time from the HC resolution to the time when the initial Bedi grade to evaluate for recurrence demonstrates a Bedi Grade ≥2 with macroscopic hematuria.

Incidence and time to recurrence of bladder pain will be analyzed using the same methods. Only participants who have reached the bladder pain resolution will be included in the analysis. Time to recurrence of bladder pain refers to time from the bladder pain resolution to the time when the initial pain score exceeds “mild pain” without use of prescription pain medications or supportive bladder care.

The number of participants requiring RBC and/or platelet transfusions and the number of required RBC and/or platelet transfusions (measured in transfusion units/participant) will be summarized by treatment group.

Change in renal function as assessed by eGFR and number of days on dialysis for participants requiring dialysis will be summarized by treatment group.

Time to resolution of BK viruria will be analyzed using Kaplan-Meier estimates, and treatment effect will be compared using stratified log-rank test and hazard ratio with stratified Cox proportional model. Resolution of viruria is defined by the lower limits of quantitation of the assay used. Resolution of viruria is defined by the lower limits of quantitation of the assay used. Only the participants who had BK viruria at randomization will be included in the analysis. Time to resolution refers to the time from randomization to the initial resolution of viruria.

The numbers and proportions of patients with viremia and viruria with each target virus (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over time for all the participants as well as for participants who are negative at randomization only.

Length of use of any pain medication(s) (IV, oral, or other), including antispasmodics anticholinergics, and beta-3-agonists, used for control of lower abdominal/bladder pain will be summarized as the total days on any pain medication for each participant.

The use of immunosuppressive agent(s) by specific agent during the study will be summarized by treatment group. The specific dosage information will be listed only.

Number of hospitalizations, number of ICU stays, and number of days of ICU care for any reason will be summarized by treatment group, and reasons will be listed by participant.

Use of antiviral therapies other than cidofovir with potential activity against at least one target virus will be summarized by specific agent during the study. Agents analyzed include foscarnet, ganciclovir, letermovir, maribavir, and valganciclovir. Rd

Overall survival, defined as time to death (from any cause) from the time of randomization in days, will be analyzed as displaying number of participants who died from any cause by week 24 and censored by week 24.

Incidence of relapse or progression of the primary malignancy will also be summarized by treatment group over the 24-week period.

Overall quality of life as measured by appropriate EQ-5D questionnaires will be summarized by treatment for each subdomain over time.

Global impression of change will be summarized by treatment over time.

3.5 Safety Analyses

All safety analyses will be based on the Safety Population. Safety analyses in general will be descriptive and will be presented by treatment group in tabular format. Categorical endpoints will be summarized using the number and percentage of participants within each category. Continuous endpoints will be summarized descriptively with summary statistics (number, mean, standard deviation, standard error, median, first quartile, third quartile, minimum, and maximum).

3.5.1 Adverse Events (AEs)

All AEs will be coded to system organ class and preferred term using MedDRA. Treatment emergent adverse events (TEAEs) are defined as AEs with onset after the start of study treatment (PSL or placebo) through the end of study. Adverse events of special interest (AESI) include , acute graft versus host disease (GVHD), chronic GVHD, graft failure and rejection, cytokine release syndrome (CRS), and infusion-related AEs. These AESI will be reviewed by the DSMB as per the DSMB Charter.

An overall summary of AEs will be produced by treatment group. The numbers and percentages of participants will be provided for the following:

- Any TEAEs
- Any TEAEs by severity
- Any treatment-related TEAEs

- Any treatment-emergent AESIs (TEAESIs)
- Any treatment-related TEAESIs
- Any treatment-emergent serious AEs (TESAEs)
- Any treatment-related TESAEs
- Any TEAEs leading to discontinuation of study treatment
- Any TEAEs leading to discontinuation of study
- Any TEAEs leading to death

All the TEAE categories will be summarized by system organ class (SOC) and preferred term (PT). Participants with multiple AEs will be counted only once per SOC and PT. In addition, the TEAEs will be summarized by PT only. The number and percentage of participants with TEAEs, TESAEs and TEAESIs will be tabulated by PT and by the highest CTCAE Grade. CRS will only be graded by ASTCT grade.

Listings will be presented specifically for any AEs, deaths, SAEs, AESI, and TEAEs leading to discontinuation of study treatment and study.

3.5.2 AEs of Special Interest

The AESIs will be reviewed by the DSMB as per the DSMB Charter. Criteria for acute and chronic GVHD and CRS can be found in Protocol Appendices E, F and G. The number and percentage of participants who had the treatment-emergent AESIs will be summarized by treatment group:

- Severity and incidence of acute GVHD
- Severity and incidence of chronic GVHD
- Severity and incidence of CRS
- Severity and incidence of infusion-related AEs
- Severity and incidence of graft failure and rejection

For GVHD, a separate table will be prepared that summarizes:

- aGVHD by MAGIC overall grade and by stage and organ involvement
- cGVHD by NIH score

Subgroup analyses may be conducted for the severity and incidence of acute GVHD by HLA Class (I, II, and I & II) and the number of HLA matches.

Incidence and severity of AESI and the corresponding exact binomial confidence intervals with 95% confidence level will be presented by treatment group.

3.5.3 Clinical Laboratory Tests

Laboratory assessments comprise safety laboratory tests (hematology, clinical chemistry) and other laboratory tests.

Descriptive statistics will be provided at each scheduled visit for selected clinical laboratory test results (hematology and clinical chemistry, appendix A) and changes from baseline.

A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline value according to the NCI CTCAE grade, will be provided for clinical laboratory tests

(hematology, clinical chemistry). In addition, shift tables reflecting the shift over visits will be presented for selected laboratory tests (hematology, clinical chemistry).

The number and percentage of participants with the following potentially clinically significant abnormal liver function tests will be summarized:

- Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN), ≥5xULN, ≥10xULN, and ≥20xULN
- Aspartate aminotransferase (AST) ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- Potential Hy's Law cases: ALT or AST ≥3xULN, total bilirubin ≥2xULN, and alkaline phosphatase (ALP) <2xULN.

A table listing of participants with any post-baseline potentially clinically significant abnormal liver function tests will be presented.

3.5.4 Vital Signs

Descriptive statistics will be provided for vital signs by treatment group, presented as both actual values and changes from baseline over time. All vital sign data will be listed by participants.

3.5.5 Electrocardiograms

Electrocardiogram (ECG) data will be summarized by visit and treatment group for each quantitative ECG parameter using descriptive statistics. The changes from baseline to each post-baseline visit will also be summarized. All ECG parameters and details of any abnormalities will be listed by participant.

3.5.6 Physical Examinations

All Physical examination findings, including details of any abnormalities will be listed by participant.

3.6 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor safety and evaluate prespecified interim analyses to stop the study early for futility. The DSMB will receive summary reports of all unexpected SAEs and AESI at least monthly. In addition, the DSMB will receive expedited reporting of all individual, unexpected, related SAEs occurring within 14 days of an infusion of study drug, and infusion related AESI of at least Grade 2 severity occurring within 24 hours of an infusion. A DSMB charter, detailing all aspects of the DSMB's scope of review and procedures as well as the frequency of DSMB meetings, will be provided in a separate document. An unblinded statistician will be assigned to the DSMB. This statistician will not be involved in any aspects of study conduct outside of the DSMB, and their role will be defined in the DSMB charter.

3.7 Interim Analysis

An interim analysis will be conducted by an independent unblinded statistician and reviewed by the independent DSMB. This analysis will be based on primary efficacy endpoint data for the first approximately 60 participants randomized in the BK ITT Population. The interim analysis will be performed for the purpose of potentially stopping early for futility. If the study is not

stopped based on the interim analysis, then accrual to the study will continue until there are 105 participants in the BK ITT Population.

The interim analysis for stopping early for futility will be based on the primary efficacy endpoint. The decision to stop for futility is based on the conditional probability that the study will be successful, assuming the current trend observed at the interim, should it continue to the sample size of 105 participants in the BK ITT Population with participants being followed for 24 weeks. The calculation will assume that the final analysis will be a log-rank test with overall alpha = 0.025 (one-sided) adjusted for the interim analysis. If, at the interim analysis, the conditional probability of study success with 105 BK ITT Population participants falls below 5%, the study will stop early for futility (Lachin 2005). Enrollment and participant follow-up will then be discontinued, and the final analyses will be conducted. The futility stopping in this study is considered non-binding.

REFERENCE

Lachin JM. (2005). A review of methods for futility stopping based on conditional power. Stat Med 2005;24 (18):2747-64).

APPENDIX A: ANALYSIS WINDOWS

Table 1.1 Analysis Visit Window for Selected ePRO Endpoints (Daily for First Six Weeks)

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1/Baseline	1		1
Day 2	2	2	2
…	…	…	…
Day 42	42	42	42
Week 7	50	43	49
…	…	…	…
Week 23	162	156	162
Week 24	169	163	

Table 1.2 Analysis Visit Window for Selected ePRO Endpoints (Weekly for First Six Weeks)

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1/Baseline	1		1
Week 1	8	2	8
Week 2	15	9	15
Week 3	22	16	22
Week 4	29	23	29
Week 5	36	30	36
Week 6	43	37	43
Week 7	50	44	50
…	…	…	…
Week 23	162	156	162
Week 24	169	163	

Table 2. Analysis Visit Window for EQ-5D-Y Proxy Version 1, EQ-5D-Y and EQ-5D-5L

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1/Baseline	1		1
Week 1	8	2	8
Week 2	15	9	15
Week 3	22	16	22
Week 4	29	23	29
Week 5	36	30	36
Week 6	43	37	43
Week 8	57	51	57
Week 12	85	79	85
Week 16	113	107	113
Week 24	169	163	

Table 3. Analysis Visit Window for Viral Load (in Blood and Urine), Vital Signs, Pulse Oximetry, Clinical Chemistry and Hematology

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1/Baseline	1		1
Week 1	8	2	11
Week 2	15	12	18
Week 3	22	19	25

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	63
Week 12	85	64	126
Week 24	169	>126	

Table 4. Analysis Visit Window for 12-Lead ECG and Weight

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1/Baseline	1		1
Week 2	15	2	92
Week 24	169	>92	