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

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CLINICAL STUDY PROTOCOL

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

Investigational Product: Posoleucel (PSL, ALVR105; formerly ALVR-105, Viralym-M)

Protocol Number: AVM-003-HC

IND Number: 15092

EudraCT Number: 2020-000722-26

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Amendment 4: 23 February 2022

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by AlloVir, Inc. (AlloVir) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to AlloVir and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by AlloVir, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

PROTOCOL NUMBER: AVM-003-HC

IND NUMBER: 15092

EUDRACT NUMBER: 2020-000722-26

INVESTIGATIONAL PRODUCT: Posoleucel (PSL, ALVR105; formerly ALVR-105, Viralym-M)

PHASE: 3

OBJECTIVES:

The primary objective is to compare the time to resolution of macroscopic hematuria in recipients of posoleucel (PSL) to that in recipients of placebo.

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 and severity 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 all target viruses over the 24-week study period (only for participants with detectable viremia at baseline).
- To assess average daily bladder pain (11-point numeric rating scale [NRS]) over the 6-week period from randomization.

POPULATION:

Inclusion Criteria

Participants must meet all of the following criteria in order to be eligible to participate in the study:

1. Male or female of any age, but enrollment of participants <1 year of age at the time of informed consent will occur only once preliminary safety data are available from 5 participants ≥1 and <6 years of age. See Section 3.3 for details.

2. Had an allogeneic hematopoietic cell transplant (HCT) performed ≥21 days and ≤1 year prior to randomization.
3. Myeloid engraftment confirmed, defined as an absolute neutrophil count ≥500/mm^3 for 3 consecutive laboratory values obtained on different days, and platelet count >10,000/mm^3 at the time of randomization. Platelet transfusions are permitted.
4. Diagnosed with HC based on meeting all of the following criteria:
    a. Clinical signs and/or symptoms of cystitis, such as dysuria, urinary frequency, urinary urgency, lower abdominal pain or tenderness, and/or bladder pain, tenderness, or spasms.
    b. Bedi Grade ≥3 hematuria, defined as macroscopic hematuria with visible clots.
    c. Viruria with ≥1 target virus (ie, BK virus [BKV], adenovirus [AdV], cytomegalovirus [CMV], human herpesvirus 6 [HHV-6], JC virus [JCV], and/or Epstein-Barr virus [EBV]). Randomization of participant may be based on viruria data obtained from either the local or central laboratory.
5. At least 1 identified, suitably matched PSL cell line for infusion is available.
6. Willing and able to provide written informed consent to participate in the study, or a parent or legal guardian is willing and able to provide written informed consent and the potential pediatric patient is able to provide assent in a manner approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and local regulations.
7. Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must agree to use contraception during the study and for a minimum of 90 days after study treatment as detailed in Appendix H; participants must also refrain from donating sperm or eggs during the study and for at least 90 days after treatment completion.
8. Has a negative serum pregnancy test for female participants of childbearing potential.

Exclusion Criteria

Participants who meet any of the following criteria will be excluded from participation in the study:

1. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone dose >0.5 mg/kg/day or equivalent).
2. Therapy with antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies ≤28 days before randomization.
3. Evidence of active Grade >2 acute GVHD (see Appendix E for acute GVHD grading).
4. Uncontrolled or progressive bacterial or fungal infections (ie, evidence of bacteremia, fungemia, dissemination, and/or organ-specific infection not well controlled by present therapies).
5. Uncontrolled or progressive viral infections (ie, evidence of viremia, dissemination, and/or organ-specific infection not well controlled by present therapies) not targeted by PSL.
6. Uncontrolled or progressive EBV-associated post-transplant lymphoproliferative disorder.

7. Known or presumed pneumonia secondary to any organism that is not considered to be well-controlled by antimicrobial therapy (ie, clinically stable for ≥7 days on a stable antimicrobial regimen).
8. Donor lymphocyte infusion performed ≤21 days before randomization.
9. Hemodynamic or respiratory instability defined as either of the following:
    a. Requirement for continuous infusions of inotropes or vasopressors for blood pressure support.
    b. Requirement for endotracheal intubation or mechanical ventilation.
10. Hemoglobin <7 g/dL despite red blood cell (RBC) transfusions.
11. Clinically significant coagulopathy that, based upon the assessment of the Investigator, could result in an increased risk of active bleeding not attributed to hemorrhagic cystitis.
12. Ongoing use of systemic anticoagulant drugs or antiplatelet drugs.
13. Evidence of active hepatic sinusoidal obstruction syndrome.
14. Liver dysfunction, defined as liver transaminases (ie, aspartate aminotransferase or alanine aminotransferase) >5 × upper limit of normal (ULN) or direct bilirubin >3 × ULN unless the participant has a chronic and stable diagnosis that accounts for the abnormality(ies) and eligibility is approved by the AlloVir Medical Monitor.
15. Requiring renal replacement therapy ≤7 days prior to randomization.
16. Evidence of encephalopathy.
17. Relapse of primary malignancy.
18. Receipt of other investigational antiviral treatments (eg, brincidofovir) ≤7 days prior to randomization.
19. Pregnant, lactating, or planning to become pregnant.
20. History of severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) allergy to any component of PSL (including human serum albumin and dimethyl sulfoxide) or history of severe (CTCAE Grade ≥3) prior reactions to blood product transfusions.
21. Any condition that, in the opinion of the Investigator, would compromise the safety of the participant, prevent study participation, or interfere with the evaluation of study endpoints.

STUDY DESIGN AND DURATION:

This is a Phase 3, multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of PSL compared to placebo for the treatment of participants with virus-associated HC following allogeneic 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). A supplementary analysis will 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 (ITT Population).

Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a [redacted] ratio to receive [redacted] sequential infusions of PSL 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) that [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 assessments 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 for each participant 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 (Day 43)**
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. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, 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. In all cases, CSF samples required for routine clinical care of the participant take precedence over these study-related evaluations.

Safety assessments, including 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 (ie, relative to baseline GVHD at the time of randomization) at the proposed time of infusion of the second dose.

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

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

Following consent, study site staff will review the age-appropriate COAs with the participant (or parent or other caregiver, as appropriate).

An independent Data and Safety Monitoring Board will be convened for this study to routinely monitor participant safety and evaluate prespecified interim analyses to stop the study early for futility or success.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Participants randomized to the PSL arm will receive [redacted] separate infusions of partially HLA -matched PSL cells (each administered via central or peripheral intravenous [IV] infusion over approximately [redacted] minutes as a slow push).

The placebo arm will receive [redacted] separate IV infusions of cryopreservation media (without cells).

The second infusion (PSL or placebo) will occur approximately [redacted] (±3) days after the first infusion. Administering the second infusion as early as feasible within this window is encouraged. Participants who weigh <40 kg at the time of screening will receive [redacted] PSL cells

(or placebo), while participants who weigh ≥40 kg at the time of screening will receive [redacted] PSL cells (or placebo).

EFFICACY VARIABLES:

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 ≥2 days apart without continuous bladder irrigation or nephrostomy tubes. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, 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 score. 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). Time to resolution will be calculated starting from the date of randomization. The second urine assessment is required to establish resolution, but for the calculation of time to resolution, the date of the first of these two visual urine assessments without macroscopic hematuria (by the Hemostick® visual scale for outpatients; by the Bedi scale for inpatients) will be used. 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, such as cystectomy, bladder vessel embolization, cauterization, application of fibrin "glue" preparations, 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 these supportive measures.

For participants undergoing continuous bladder irrigation, the primary endpoint (ie, time to resolution of macroscopic hematuria) will be measured once participants discontinue bladder irrigation. Bedi grading will not be performed on days on which the participant is receiving continuous bladder irrigation. Discontinuation of bladder irrigation will be based upon the participant's clinical condition and the treating physician's medical judgement.

All attempts should be made to minimize procedures or manipulations prior to urine collection to ensure that specimens are not contaminated due to trauma.

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 48 to 72 hours after the date of recurrence observed by the Investigator. Recurrence is defined as 2 consecutive Bedi grades ≥2 (macroscopic hematuria). 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.

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" (ie, scores of 3 or below on the Bladder Pain/Interstitial Cystitis Symptom Diary [BPIC SD], 0 to 10 NRS capturing participants' worst daily pain among adolescents ≥12 years of age and adults and a parallel assessment for children 3 to 11 years of age as a score that does not exceed 2 on the Wong-Baker FACES® Pain Rating Scale), without use of prescription pain medications or the use of supportive bladder care.

This endpoint will not be assessed in participants <3 years of age.

Other Secondary Efficacy Endpoints

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 all target viruses (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over the 24-week study period (only for participants with detectable viremia at baseline). 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 detection of the assays used.
- Average daily bladder pain (including lower abdominal pain, bladder-related pressure, and/or spasm pain or dysuria) over the initial 6 weeks following randomization.

SAFETY VARIABLES:

The safety endpoints include the following:

- Incidence and severity of acute GVHD (secondary endpoint)
- Incidence and severity of chronic GVHD (exploratory endpoint)
- Incidence and severity of CRS (secondary endpoint)

Safety assessments will also include adverse events, vital signs, 12-lead electrocardiograms (ECGs), physical examination findings, and clinical laboratory assessments.

STATISTICAL ANALYSES:

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.

The ITT Population will include all randomized participants regardless of whether the participant actually receives PSL or placebo. Participants will be analyzed according to the randomized study treatment.

The BK ITT Population will include participants in the ITT Population who have BKV identified as the cause of their HC. The primary efficacy analysis will be based on the BK ITT Population. A supplementary efficacy analysis will be based on the ITT Population.

The Modified ITT (mITT) Population will include all randomized participants who receive any amount of PSL or placebo.

The BK mITT Population will include participants in the mITT Population who have BKV identified as the cause of their HC. A supplementary efficacy analysis will be based on the BK mITT Population.

The BK Per-Protocol (PP) Population will include all participants in the BK mITT Population who do not have any major protocol violations deemed to impact the results, as defined in the Statistical Analysis Plan (SAP).

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.

The primary efficacy 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; 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, including for the purpose of assessing for resolution.

The objective is to demonstrate the superiority of PSL therapy to placebo with respect to the time to resolution of macroscopic hematuria.

The primary efficacy analysis will be conducted after all participants have completed 24 weeks of follow up or have discontinued early 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 based on the stratification factors at randomization. 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 0.0147 (reduced from 0.025 due to inclusion of an interim analysis based on Pocock method).

If the result of the analysis 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 then be conducted of this same endpoint based on the overall ITT Population.

If the result of this analysis is also statistically significant, a formal hypothesis test will be conducted of the key secondary endpoint of time to resolution of bladder pain based on the BK ITT Population in a manner analogous to that for the primary efficacy endpoint. If the result of this analysis is statistically significant, a formal hypothesis test of this same endpoint will be conducted based on the overall ITT Population.

If the results of the analyses of the key secondary efficacy endpoint are statistically significant for both the BK ITT and overall ITT Populations, a formal hypothesis test will be conducted 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. If the result of the analysis based on the BK ITT Population

is statistically significant, a formal hypothesis test of this same endpoint will be conducted based on the overall ITT population.

Other continuous and categorical efficacy endpoints (including secondary and exploratory endpoints not selected for hierarchical testing above) will be summarized descriptively by treatment groups using the mITT Population.

Time-to-event endpoints will be summarized using Kaplan-Meier estimates. In addition, the hazard ratio along with the 95% confidence intervals for the true hazard ratio will be calculated using a Cox proportional hazards model with treatment, stratification factors at randomization, and other potentially confounding factors.

There will be no adjustment for multiplicity in the analyses of other efficacy endpoints.

The safety profile will be based on treatment-emergent adverse events and changes in vital signs, physical examinations, clinical laboratory assessments, and ECGs. All safety analyses will be based on the Safety Population.

The incidence and severity of acute GVHD, chronic GVHD, and CRS and the corresponding exact binomial confidence intervals with 95% confidence level will be presented by treatment group.

Interim analyses will be conducted by an independent unblinded statistician and reviewed by the independent DSMB. These analyses will be based on primary efficacy endpoint data for the first 60 participants randomized in the BK ITT Population. The interim analyses will be for purposes of both potentially stopping early for success and for futility. Stopping for success will be based on the method of Pocock. If the study is not stopped based on the interim analyses, then accrual to the study will continue until there are 105 participants in the BK ITT Population. The futility stopping in this study is considered non-binding.

SAMPLE SIZE DETERMINATION:

Approximately 125 participants will be randomized at approximately 90 clinical sites 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 based on the method of Pocock; control of the overall Type I error rate at the one-sided 0.025 level; 10% 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 83.8% power.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AdV	Adenovirus
AESI	Adverse event of special interest
BKV	BK virus
BPIC SD	Bladder Pain/Interstitial Cystitis Symptom Diary
CAR	Chimeric antigen receptor
CFR	Code of Federal Regulations
CGIC	Caregiver Global Impression of Change
CGIS	Caregiver Global Impression of Severity
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CR	Complete response
CRA	Clinical Research Associate
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CTA	Clinical trial authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELIspot	Enzyme-linked immunospot
ePRO	Electronic patient-reported outcome
EQ VAS	EQ visual analog scale
EQ-5D	EuroQol 5 Dimensions
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQ-5D-Y	EuroQol 5 Dimensions for Younger Patients
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft versus host disease
HC	Hemorrhagic cystitis
HCP	Health Care Provider
HCT	Hematopoietic cell transplant
HHV-6	Human herpesvirus 6
HLA	Human leukocyte antigen

Abbreviation	Definition
HPF	High power field
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICPI	Interstitial Cystitis Problem Index
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
JCV	JC virus
mITT	Modified Intent-to-Treat
MTD	Maximum tolerated dose
NRS	Numeric rating scale
PBMC	Peripheral blood mononuclear cell
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PP	Per-Protocol
PR	Partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
PSL	Posoleucel
PTLD	Post-transplant lymphoproliferative disease
PVSS	Pharmacovigilance and Safety Services
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SRG	Safety Reporting Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
U/A	Urinalysis
ULN	Upper limit of normal
USA	Unites States of America
VST	Virus-specific T cell
v/v	Volume per volume
WOCBP	Women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Viral Infection Following Allogeneic Hematopoietic Cell Transplant

During the period of immune recovery after allogeneic hematopoietic cell transplant (HCT), viral infections, which are normally controlled by T cell immunity, are an important cause of morbidity and mortality. Viral infections may affect any organ in the body and in HCT can often be serious or, depending on the virus, fatal. Amongst patients with viral infection status post-HCT, one of the most common serious manifestations is hemorrhagic cystitis (HC). The most common cause of severe viral-induced HC is BK virus (BKV), but HC has also been associated, albeit with a lower incidence, with viral infections from adenovirus (AdV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), and JC virus (JCV).[1,2,3,4] The risk for infection is dictated by a number of factors, including the degree of immunosuppression and the immune status of the donor. Reactivation of latent viruses such as BKV and CMV, or infection with a new virus such as AdV, has become increasingly prominent. In a recent study of infections following haplo-identical allogeneic HCT, 72% of patients experienced at least 1 severe viral infection.[5] Fifteen percent of patients developed CMV infection despite prophylaxis and 19% developed BKV-associated HC. One out of 3 children is reported to have an AdV infection within 6 months post-allogeneic HCT.[6] Progression to AdV disease is associated with significant morbidity and mortality rates of up to 50%.[7] Similarly, in patients receiving either cord blood or T cell-depleted transplants, viral infections were frequent and the most common cause of death in both groups. Even among T cell replete transplants using the post-cyclophosphamide protocol, the incidence of viral infections was reported to be 70%, with BKV and CMV being the most frequent and the most clinically threatening etiologies.[8]

The primary clinical manifestation of BKV infection following allogeneic HCT is severe HC, which manifests as gross hematuria and is defined by lower urinary tract symptoms that typically include severe, often debilitating, bladder pain (marked by use of pain medications, often requiring continuous narcotic infusions); bladder pressure; urinary frequency; urinary urgency; nocturia; and the presence of pronounced blood clots in urine that may lead to urinary retention and patient distress.[9,10] A retrospective study demonstrated that among 2477 patients undergoing their first allogeneic HCT over an 8-year period, of whom 98% were transplanted for cancer, 629 patients (25%) developed BKV-associated HC.[11] Moreover, BKV infection was associated with the development of kidney failure as well as increased overall mortality.

Additionally, antiviral pharmacologic agents are only partially effective against many of the target viruses; their use is costly and may be associated with significant toxicities and the emergence of drug-resistant mutant viruses. As delays in the recovery of endogenous virus-specific T cells (VSTs) are clearly associated with viral reactivation and disease in these patients, cellular immunotherapy to restore viral-specific immunity has been investigated as a potential therapeutic option.

1.2 Adoptive Immunotherapy for Viral Infections Following Allogeneic Hematopoietic Cell Transplant

The first virus to be targeted using an adoptive T cell transfer approach was CMV.[12] This was followed by numerous studies with not only CMV-directed T cell products (eg, ex vivo expanded polyclonal lines, interferon [IFN] γ-captured cells, and multimer-selected products)[13,14,15,16,17,18,19] but also T cell products directed toward other viruses, including Epstein-Barr virus (EBV) and

AdV. These clinically implemented immunotherapeutic strategies are considered safe and are associated with clinical benefit.[20,21,22,23,24,25,26,27,28]

1.2.1 Hematopoietic Cell Donor-Derived Virus-Specific T Cells

Adoptive transfer of HCT donor-derived VSTs (ie, VSTs expanded or selected from a transplant donor) has been successfully used to prevent and treat viral infections[29], including AdV and CMV infections as well as drug-refractory EBV-positive lymphomas, that complicate allogeneic HCT.[30]

Previous studies utilized an adoptive immunotherapeutic approach to prevent/treat BKV, AdV, CMV, HHV-6, and EBV-associated infections post-HCT using a multivirus-directed T cell product prepared using peripheral blood mononuclear cells (PBMCs) from a stem cell donor.[31,32] To generate VSTs that recognized all 5 viruses, stem cell donor PBMCs were exposed to overlapping peptide libraries spanning immunogenic antigens derived from each virus, followed by an expansion phase using media supplemented with interleukin (IL)-4 and IL-7.[31,32] When these donor-derived VSTs were administered to 21 corresponding allogeneic HCT recipients at doses ranging from 0.5×10^7 to 2×10^7 cells/m^2, the infused cells expanded in vivo and produced clinical responses without adverse events.[25]

In summary, this study demonstrated that T cell lines having specificity for up to 5 viruses (including BKV, which had never been previously targeted using this therapeutic modality) could be generated from stem cell donors, and treatment with these VSTs was well tolerated and associated with clinical improvement. However, despite the successful use of various stem cell donor-derived VSTs over more than 20 years, there are significant limitations to this approach, making it unsuitable for a potential commercial product.

1.2.2 Third-Party Virus-Specific T Cells

An alternative to preparing stem cell donor-derived VSTs for individual patients is to bank partially human leukocyte antigen (HLA)-matched allogeneic VSTs, obtained from healthy pre-immune third-party donors (not the stem cell donor) with demonstrated immunity to virus(es) that could be available as an "off-the-shelf" product for immediate use. This approach theoretically overcomes some of the limitations of HCT donor-derived VSTs. Specifically, patients do not have to wait for the cell line to be produced, and taking the multivirus approach (ie, deriving cell lines by antigenically stimulating against peptides from multiple viruses of interest) results in a ready-for-use pluripotent cell line specific for multiple viruses of interest. A potential concern with this approach is that the mismatched product may not persist long enough in vivo to control the viral infection, because the recipient may generate an immune response to the non-shared transplantation antigens. Despite this theoretical concern, several studies have demonstrated that third-party VSTs are associated with clinical benefit, including AdV, CMV, and EBV infections.[33,34,35,36]

1.3 Posoleucel

AlloVir, Inc. (AlloVir) is developing posoleucel (PSL, ALVR105; formerly ALVR-105, Viralym-M) for the treatment of virus-associated HC. Posoleucel is a biological product consisting of PSL cells (third-party, multivirus-specific T cells with specificity for BKV, AdV, CMV, HHV-6, JCV, and EBV) in cryopreservation media comprised of [redacted]. Posoleucel cells are generated from PBMCs collected from eligible third-party donors by exposing the PBMCs to peptides spanning

immunogenic antigens from BKV (large T and VP1), AdV (hexon and penton), CMV (IE1 and pp65), HHV-6 (U11, U14, and U90), and EBV (LMP2, EBNA1, and BZLF1). Specificity for JCV is achieved by the substantial homology between the BK and JC human polyomaviruses: at the viral genome level, their deoxyribonucleic acid (DNA) sequences are 72% identical and at the amino acid level, large T and VP1 are >85% homologous.[37] Published preclinical[38,39] and clinical[40] data provide evidence for cross-reactive recognition and antiviral activity of JCV by BK-specific T cells. The PSL cell lines are subsequently characterized for viral specificity by IFNγ enzyme-linked immunospot (ELIspot) assay. Posoleucel is cryopreserved for use as an "off-the-shelf" product.

For additional information on PSL, refer to the current Investigator's Brochure (IB).

1.3.1 Overview of Nonclinical Studies with Posoleucel

Consistent with regulatory guidance, AlloVir proceeded to clinical studies following completion of in vitro studies. No nonclinical animal pharmacology, pharmacokinetic, or toxicology studies of PSL have been conducted or are planned. For additional information related to nonclinical studies with PSL, see the current IB.

1.3.2 Overview of Clinical Studies with Other Virus-Specific T Cells

1.3.2.1 Results of an Initial Phase 1 Study with Viralym-C

Initially, AlloVir completed a Phase 1 study to assess the safety and efficacy of Viralym-C, a third-party, CMV-specific T cell product, in pediatric and adult allogeneic HCT recipients with refractory CMV infections.[41] Similar to PSL, Viralym-C is generated from PBMCs after expansion in the presence of overlapping viral peptides and cytokines. Unlike PSL, Viralym-C is only directed against a single virus, CMV. Although Viralym-C is a single-VST product, the results of this study support the safety and efficacy of AlloVir's VST products when used in a clinical setting. Briefly, a bank of 8 Viralym-C lines were generated from 8 carefully selected, healthy, seropositive, transplant donor-eligible volunteers who were predicted to provide a suitably matched cell line for at least 95% of potential patients. Ten participants were treated with Viralym-C: each participant received a single intravenous (IV) infusion of 2×10^7 partially HLA-matched VSTs/m^2 with the option to receive a second infusion after 4 weeks and additional infusions at biweekly intervals thereafter. Of the 10 treated participants, 8 participants received a single infusion and 2 participants required 2 infusions for sustained benefit. There were no immediate infusion-related toxicities and there were no cases of de novo or recurrent graft versus host disease (GVHD). Based on viral load (measured by quantitative polymerase chain reaction) and/or resolution of signs and/or symptoms, Viralym-C appeared to control CMV infections in all participants with 8 complete responses (CRs) and 2 partial responses (PRs) achieved within 4 weeks of infusion. One participant with CMV retinitis had complete resolution of disease following Viralym-C infusion.

1.3.2.2 Results of the ARMS Study with Donor-Derived Multivirus-Specific T Cells

In order to broaden the range of viral infections targeted by VSTs, AlloVir developed donor-derived multivirus-specific T cells with specificity for BKV, AdV, CMV, HHV-6, and EBV. An initial open-label Phase 1/2 study was conducted to assess the safety and toxicity of the multivirus-specific T cells in participants at risk of developing BKV, AdV, CMV, HHV-6, or EBV infections after allogeneic HCT.[25] The first stage of the study was a Phase 1 dose-escalation study

to evaluate the safety of 3 dose levels and to determine the maximum tolerated dose (MTD) level. Upon the completion of Phase 1, additional participants were to be accrued at the MTD level to evaluate a clinically relevant endpoint for antiviral activity in Phase 2.

Participants received [redacted] donor-derived multivirus cytotoxic T lymphocytes [redacted] in a single infusion in the Phase 1 dose-escalation stage of the study, and [redacted] multivirus CTLs [redacted] for the fixed-dose Phase 2 efficacy component (actual number of cells infused ranged [redacted] per participant). Participants who had a PR or received therapy post-infusion that could ablate the infused T cells were eligible to receive up to 2 additional doses 28 days after the first dose. Participants were followed for toxicity for 30 days, GVHD for 6 weeks, and antiviral responses for 3 months; long-term follow-up continued for 12 months following the final CTL infusion.

A total of 21 participants were enrolled, and all 21 participants completed the study. All doses were well tolerated. There were no adverse events experienced by participants enrolled in the study that were considered treatment-related. Three participants developed Stage 2 skin GVHD (Grade 1 overall) and 1 participant developed Stage 3 skin GVHD (Grade 2 overall) in the 6-week initial follow-up period; all of these reactions responded to topical steroids.

1.3.2.3 The CHARMS Study with Third Party-Derived Multivirus-Specific T Cells, Posoleucel

To investigate the safety and clinical efficacy of PSL, a multivirus-specific T cell product reactive with BKV, AdV, CMV, HHV-6, and EBV generated from third-party, healthy, eligible donors, a Phase 2 clinical study was conducted in recipients of allogeneic HCT with drug-refractory infections with ≥1 of the 5 viruses targeted by PSL.[42] (For additional information on PSL, refer to the current IB.)

1.3.3 Summary

The available data, including data from the Phase 2 CHARMS study, confirm the feasibility and safety of PSL administered as an "off-the-shelf" product to treat drug-refractory virus-associated disease. Infusion of the cells was well tolerated, including in participants who received multiple infusions. The infused cells expanded in vivo and were associated with meaningful clinical improvement in participants suffering from refractory BKV, AdV, CMV, HHV-6, and EBV reactivation and virus-associated disease.

In the Phase 2 CHARMS study with PSL, approximately 25% of participants received more than 1 cell infusion using a similar cell dose per infusion as will be used in this study.[42] These additional infusions were administered when participants did not respond adequately to their initial cell infusions and were not associated with a safety or tolerability profile that was different than that associated with single infusions. In the current study, only severely affected HC participants (Grades 3 and 4) who are expected to benefit from the planned 2 sequential infusions will be enrolled. Given the multi-viral coverage of PSL, the 2 infusions are also expected to provide enhanced prophylaxis against those target viruses that may be inactive at the time of infusion, but to which the participants remain susceptible as their immune systems reconstitute following HCT.

For additional information related to clinical studies with PSL, see the current IB.

1.4 Rationale

In healthy individuals, T cell immunity defends against viruses. In allogeneic HCT recipients, the use of potent immunosuppressive regimens (and subsequent associated immune compromise) leaves patients susceptible to severe viral infections. Viral infections are major causes of mortality and morbidity after HCT and, in general, have become the primary etiology for transplant-related mortality.

There are no FDA-approved therapies for BKV infection or BKV-associated HC. Current standard of care is supportive, including diuresis and continuous bladder irrigation to mitigate urinary obstruction, antispasmodics and narcotics to alleviate suffering, hyperbaric oxygen, nephrostomies, and/or dialysis for acute renal failure. In some cases, a cystectomy has been required to control life-threatening hemorrhage caused by BKV-associated HC. The most frequently used antiviral drug for disease treatment is cidofovir. However, cidofovir is associated with nephrotoxicity and, in the absence of prospective, randomized, controlled clinical studies, its efficacy for the treatment of BKV-associated HC remains uncertain.

Since recovery of VSTs after HCT results in resolution of viral infections, adoptive immunotherapy to decrease the time to immune reconstitution is an attractive alternative to current standard of care. AlloVir's approach is to restore T cell immunity by the administration of ex vivo expanded, non-genetically modified VSTs to control viral infections and eliminate symptoms for the period until the transplant patient's own immune system is restored. To achieve this goal, AlloVir has manufactured VSTs from PBMCs procured from healthy pre-screened (for infectious agents and disease risk factors as mandated by FDA Title 21 of the Code of Federal Regulations [CFR] Part 1271, subpart C) seropositive third-party donors, which are cryopreserved and available as a partially HLA-matched "off-the-shelf" product. Posoleucel is specific for 5 viruses (BKV, AdV, CMV, HHV-6, and EBV). Additional antiviral specificity for JCV is anticipated due to the substantial homology between the BK and JC human polyomaviruses; published preclinical and clinical data provide evidence for cross-reactive recognition and antiviral activity of JCV by BK-specific T cells.[40] Since PSL is only partially matched with the recipient and donor cells, PSL cells are intended to circulate only until the patient regains immunocompetence following HCT engraftment and immune system repopulation. Therefore, PSL cells are designed to be used as an "immunologic bridge therapy" that provides an immunocompromised patient with T cell immunity until the patient engrafts and can mount an endogenous immune response.

To date, clinical studies of PSL conducted in >50 allogeneic HCT participants with refractory infections have demonstrated preliminary clinical safety and efficacy (>90% positive clinical response [either PR or CR]) using these cryopreserved third-party T cells.

1.5 Risk/Benefit

1.5.1 Potential Risks

Posoleucel primarily targets cells infected with BKV (and/or JCV), AdV, CMV, HHV-6, and/or EBV. The main risks of administration are inflammation at sites of disease and GVHD due to cross reactivity with alloantigens. Adverse events attributable to VST administration may potentially occur in a small percentage of the treated population. These can include both hematologic and non-hematologic effects, as reported in the CHARMS study.

Studies of donor-derived VSTs suggest that VSTs do not persist in patients who receive methylprednisolone at doses of ≥1 mg/kg/day. Therefore, if participants develop severe inflammatory reactions due to PSL a therapeutic option is to administer methylprednisolone (1 to 2 mg/kg/day). Skin rashes or skin GVHD can be treated with topical steroids.

As with other biological therapies delivered by IV infusion, possible side effects of PSL infusion include allergic reaction (anaphylaxis), decreased oxygenation, nausea/vomiting, arrhythmia, and hypertension.

Most participants (including children) are expected to have venous access catheters in place for their underlying disease and HCT procedures. Since study-related collection of blood samples and infusion of PSL or placebo will utilize these catheters, there is minimal incremental risk posed by these study-related procedures. The time points and blood volumes to be collected during this study are provided in Appendix C. Since this study will enroll both adult and pediatric participants, there are different sampling schemes (and associated volumes) based on body weight.

In order to minimize the volume of blood collected during the study, especially for pediatric participants, the blood volume of individual samples has been reduced to the maximum extent feasible, and in some cases (eg, pediatric participants weighing <20 kg) collection of blood samples at certain time points has been eliminated entirely (see Appendix C). This has been done to maintain the scientific integrity of the study while minimizing risks to participants.

For the collection of other study-related material from participants, there are no invasive procedures that are required for the study conduct beyond those procedures being used for the routine clinical care of these participants. For example, participants with indwelling urinary catheters will have urine samples drawn off the catheter, but the decision to place and maintain the catheter should be driven by the clinical needs of the participant as determined by the treating physician, and not by study requirements. Similarly, procedures such as viral load assessment on stool or cerebrospinal fluid (CSF) specimens will only be undertaken when the clinical course of the participant necessitates an evaluation of stool (eg, participant develops diarrhea), or of CSF (eg, participant develops neurological signs and symptoms necessitating the collection and evaluation of CSF for clinical management purposes as determined by the participant's treating physician).

For more details regarding potential risks with PSL treatment, see the current IB.

1.5.2 Potential Benefits

A serious unmet medical need exists for patients experiencing viral infections and diseases such as BKV-associated HC following allogeneic HCT. There are no FDA- or European Medicines Agency-approved antiviral therapies in this clinical context, and the antivirals that are employed are narrow in their antiviral spectrum, largely ineffective, and associated with significant adverse effects. The CHARMS study and other related clinical studies suggest that PSL is a safe and effective broad-spectrum approach to treat commonly observed, severe virus-associated disease after HCT. The results of these studies provide preliminary evidence of PSL efficacy in multiple opportunistic viral infections in allogeneic HCT patients, and its safety profile has the potential to be significantly better than that of standard, and inadequately effective, antiviral therapy.

1.5.3 COVID-19 Risk Mitigation

The trial is due to be initiated during the ongoing coronavirus disease 2019 (COVID-19) pandemic. The Sponsor has reviewed guidance from regulatory authorities and reports from the literature while planning trial start-up and conduct.[43,44,45,46] The Sponsor will communicate with study sites before study initiation and during the conduct of the study concerning the potential impact of COVID-19 on study-related procedures and overall conduct. The Sponsor will continue to monitor COVID-19 activity in the geographic areas and institutions where the trial will be conducted and conduct an ongoing risk assessment throughout the trial. The risk assessment will be documented on an ongoing basis in the Sponsor's trial master file. If necessary, the Sponsor will implement and document mitigation strategies to ensure participant safety while enabling sites to generate reliable data and maintain integrity of the trial and trial data. As an example, if it is necessary to conduct some study visits virtually or via home health visits, the Sponsor will document the changes made, communicate recommendations about such changes in a timely fashion to minimize or prevent disruptions to the trial, and support study sites in implementing these changes.

The Sponsor has conducted a specific risk assessment for concomitant use of a COVID-19 vaccine with PSL.[46] The Sponsor does not expect any interactions between PSL and a COVID-19 vaccine, but COVID-19 vaccination should be deferred for at least 28 days following the second dose of study treatment (PSL or placebo) when feasible to minimize confounding due to the possible overlap of adverse effects. Patients with overlapping treatment of PSL and a COVID-19 vaccine within 28 days of one another will be kept on-study and monitored as usual for safety, as defined in Section 8.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to compare the time to resolution of macroscopic hematuria in recipients of PSL to that in recipients of placebo.

2.2 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 HC) over the 24-week study period.
- To assess the incidence and severity of acute GVHD and cytokine release syndrome (CRS) over the 24-week study period.
- To assess time to resolution of viremia for all target viruses over the 24-week study period (only for participants with detectable viremia at baseline).
- To assess average daily bladder pain (11-point numeric rating scale [NRS]) over the 6-week period from randomization.

2.3 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 therapy for HC, including IV hydration, continuous bladder irrigation, and/or nephrostomy tube placement.
- Incidence and time to resolution of HC-associated signs and symptoms other than bladder pain.
- Incidence and time to recurrence of HC-associated signs and symptoms, including bladder pain, bladder pressure, spasms, urinary frequency, urinary urgency, nocturia, dysuria, and/or the presence of blood clots in urine.
- 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 detection of the assay used.
- Resolution of macroscopic hematuria as assessed at Weeks 2, 4, 6, 8, and 12 after randomization.
- Level of pain as assessed at Weeks 2, 4, 6, 8, and 12 after randomization.

- Time to resolution of non-BK target viral infections (ie, associated signs, symptoms, and presence/absence of viral load in blood and/or urine for AdV, CMV, HHV-6, JCV, and/or EBV) present at the time of randomization. Peripheral blood and, where relevant, urine (ie, evidence of virus in the urine at baseline), will be monitored for AdV, CMV, HHV-6, JCV, and/or EBV viral load.
- Incidence of target viral reinfections (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) as defined by new onset viremia or viruria and the presence of associated symptoms relative to baseline.
- Length of use of IV narcotic medication(s) for control of lower abdominal/bladder pain.
- Length of use of any pain medication(s) (IV, oral, or both), including antispasmodics used for pain, for control of lower abdominal/bladder pain.
- Length of use of immunosuppressive agents, by specific agent used (including dose and changes in dose).
- Number of hospitalizations/re-hospitalizations for any reason.
- Cumulative incidence and severity of chronic GVHD.
- Incidence and duration of use of other antiviral therapies (eg, ganciclovir, valganciclovir, foscarnet).
- 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 change and severity.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 3, multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of PSL compared to placebo for the treatment of participants with virus-associated HC following allogeneic 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). A supplementary analysis will 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 (ITT Population). Further detail is provided in Section 9.2.1.1 and will be described in the Statistical Analysis Plan (SAP).

Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a [redacted] ratio to receive [redacted] sequential infusions of PSL 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. Administering the [redacted] infusion as early as 11 days after the first infusion is encouraged if feasible. Participants who weigh <40 kg at the time of screening will receive [redacted] (or placebo), while participants who weigh ≥40 kg at the time of screening will [redacted] (or placebo). Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance upon administration. All infusions will be administered IV (via peripheral or central line) over approximately [redacted] minutes as a slow push.

To support the primary objective, all randomized participants will undergo regular visual assessments of freshly collected urine samples by Bedi grading[47] with 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 (GI) 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 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. In all cases, CSF samples required for routine clinical care of the participant take precedence over these study-related evaluations.

Safety assessments, including 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 (ie, relative to baseline GVHD at the time of randomization) at the proposed time of infusion of the second dose.

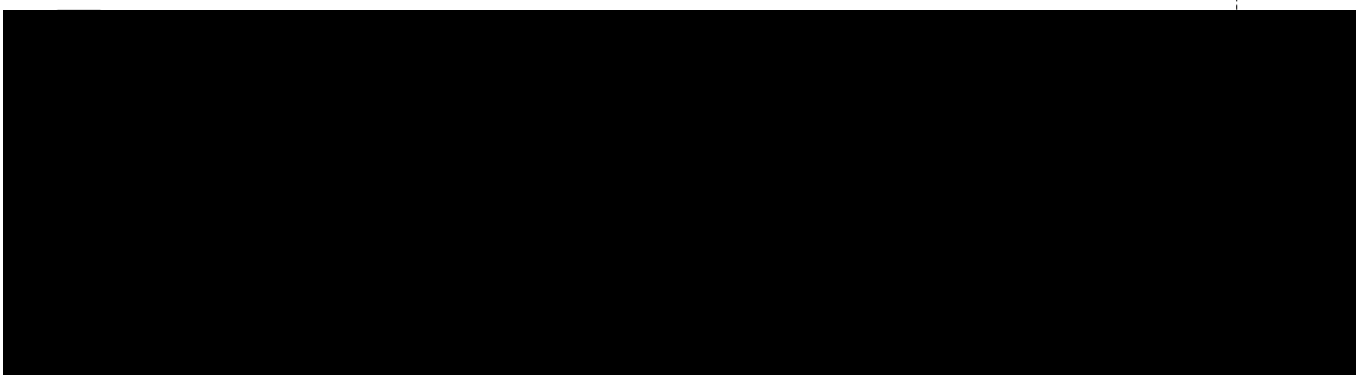
The following data will be recorded in the electronic case report form (eCRF): blood group/type, primary malignancy or underlying disease, prior therapy for malignancy, conditioning regimen for HCT, HCT donor blood type and CMV serostatus, type of HCT, and date of engraftment.

Treatment with supportive therapies, other intravesicular agents for the control of bleeding (including, but not limited to, aminocaproic acid), antispasmodics, treatment for pain control (including opioids), and blood product transfusion support are permitted. Definitive therapies to stop bladder bleeding, such as cystectomy, bladder vessel embolization, cauterization, application of fibrin "glue" preparations, or formalin instillation are permitted but will be considered treatment failures for the primary endpoint of time to resolution of macroscopic hematuria. Analgesic use will be collected daily on a medication log for inpatients (to be collected by study staff) and a pain medication log within the electronic patient-reported outcome (ePRO) system for outpatients (to be reported by participants). Clinically available (ie, not investigational) antiviral agents prescribed for other infections, such as foscarnet and ganciclovir to treat CMV, are allowed (data on their use will be collected along with other concomitant medications).

Participants will continue to be followed on the study for 24 weeks after the participant's first infusion with study treatment. The overall enrollment period will be approximately 15 months.

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

Figure 1. Summary of Study Design



3.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor participant safety and evaluate prespecified interim analyses to determine whether to stop the study early for futility or success. The DSMB will receive summary reports of all serious adverse events (SAEs) and adverse events of special interest (AESI; see Section 8.1.4) 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 composition, scope of review, and procedures will be described in a separate document. In addition, the DSMB will review safety data at the following times: 1) after 9 to 15 participants have been randomized and then again at routine intervals; 2) after five children ≥1 and <6 years of age have been randomized; and 3) at additional ad hoc meeting(s) if determined necessary by the Sponsor or DSMB Chair. The DSMB will review the pre-specified interim analysis to determine whether to stop the study early for futility or success (described in Section 9.2.3). 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.

3.3 Justification for the Study Design

The use of placebo in this clinical study is justified for the following reasons:

- Since the natural history of virus-associated HC in the HCT population is variable and not readily predictable, a placebo control group is required to provide an objective, contemporaneous assessment of the therapeutic effects and adverse event profile of PSL
- The use of an active control group in the study is not feasible since there are no approved, efficacious antiviral therapies for the treatment of virus-associated HC.

Male or female participants of any age will be included in this study, but enrollment of participants <1 year of age will occur only once preliminary safety data are available from 5 participants ≥1 and <6 years of age. The DSMB will review 4-week data from 5 participants ≥1 and <6 years of age once available and make a recommendation as to whether to proceed with enrolling participants <1 year of age.

The inclusion of pediatric participants in this study is justified for the following reasons:

- Virus-associated HC is a well-described complication of HCT in both adult and pediatric patients;[48,49,50]
- Children with HC after HCT are considered to fall into a high-risk category due to their associated high mortality and significant genitourinary morbidity;[51]
- There are no approved, efficacious antiviral therapies for the treatment of virus-associated HC; and
- In the Phase 2 CHARMS study, 17 of 58 participants enrolled (29%) were <18 years of age, with the youngest 2 years of age. This previous clinical pediatric experience with PSL supports the inclusion of participants <18 years of age in this study.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Participants must meet all of the following criteria in order to be eligible to participate in the study:

1. Male or female of any age, but enrollment of participants <1 year of age at the time of informed consent will occur only once preliminary safety data are available from 5 participants ≥1 and <6 years of age. See Section 3.3 for details.
2. Had an allogeneic HCT performed ≥21 days and ≤1 year prior to randomization.
3. Myeloid engraftment confirmed, defined as an absolute neutrophil count ≥500/mm^3 for 3 consecutive laboratory values obtained on different days, and platelet count >10,000/mm^3 at the time of randomization. Platelet transfusions are permitted.
4. Diagnosed with HC based on meeting all of the following criteria:
    a. Clinical signs and/or symptoms of cystitis, such as dysuria, urinary frequency, urinary urgency, lower abdominal pain or tenderness, and/or bladder pain, tenderness, or spasms.
    b. Bedi Grade ≥3 hematuria, defined as macroscopic hematuria with visible clots.
    c. Viruria with ≥1 target virus (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV). Randomization of participant may be based on viruria data obtained from either the local or central laboratory.
5. At least 1 identified, suitably matched PSL cell line for infusion is available.
6. Willing and able to provide written informed consent to participate in the study, or a parent or legal guardian is willing and able to provide written informed consent and the potential pediatric participant is able to provide assent in a manner approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and local regulations.
7. Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must agree to use contraception during the study and for a minimum of 90 days after study treatment as detailed in Appendix H; participants must also refrain from donating sperm or eggs during the study and for at least 90 days after treatment completion.
8. Has a negative serum pregnancy test for female participants of childbearing potential.

4.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from participation in the study:

1. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone dose >0.5 mg/kg/day or equivalent).
2. Therapy with antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies ≤28 days before randomization.
3. Evidence of active Grade >2 acute GVHD (see Appendix E for acute GVHD grading).

4. Uncontrolled or progressive bacterial or fungal infections (ie, evidence of bacteremia, fungemia, dissemination, and/or organ-specific infection not well controlled by present therapies).
5. Uncontrolled or progressive viral infections (ie, evidence of viremia, dissemination, and/or organ-specific infection not well controlled by present therapies) not targeted by PSL.
6. Uncontrolled or progressive EBV-associated post-transplant lymphoproliferative disorder.
7. Known or presumed pneumonia secondary to any organism that is not considered to be well-controlled by antimicrobial therapy (ie, clinically stable for ≥7 days on a stable antimicrobial regimen).
8. Donor lymphocyte infusion performed ≤21 days before randomization.
9. Hemodynamic or respiratory instability defined as either of the following:
    a. Requirement for continuous infusions of inotropes or vasopressors for blood pressure support.
    b. Requirement for endotracheal intubation or mechanical ventilation.
10. Hemoglobin <7 g/dL despite RBC transfusions.
11. Clinically significant coagulopathy that, based upon the assessment of the Investigator, could result in an increased risk of active bleeding not attributed to hemorrhagic cystitis.
12. Ongoing use of systemic anticoagulant drugs or antiplatelet drugs.
13. Evidence of active hepatic sinusoidal obstruction syndrome.
14. Liver dysfunction, defined as liver transaminases (ie, aspartate aminotransferase or alanine aminotransferase) >5 × upper limit of normal (ULN) or direct bilirubin >3 × ULN unless the participant has a chronic and stable diagnosis that accounts for the abnormality(ies) and eligibility is approved by the AlloVir Medical Monitor.
15. Requiring renal replacement therapy ≤7 days prior to randomization.
16. Evidence of encephalopathy.
17. Relapse of primary malignancy.
18. Receipt of other investigational antiviral treatments (eg, brincidofovir) ≤7 days prior to randomization.
19. Pregnant, lactating, or planning to become pregnant.
20. History of severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) allergy to any component of PSL (including human serum albumin and dimethyl sulfoxide) or history of severe (CTCAE Grade ≥3) prior reactions to blood product transfusions.

21. Any condition that, in the opinion of the Investigator, would compromise the safety of the participant, prevent study participation, or interfere with the evaluation of study endpoints.

4.3 Withdrawal Criteria

4.3.1 Withdrawal From the Study

Participation in this clinical study will be discontinued for any of the following reasons:

- The participant (or parent or legal guardian) withdraws consent.
- The participant (or parent or legal guardian) requests discontinuation from the study for any reason.
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk by remaining in the study.
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the participant.
- Participant failure to comply with protocol requirements or study-related procedures making them unsuitable for continuation in the opinion of the Investigator.
- Termination of the study by the Sponsor or the regulatory authority.

If a participant withdraws prematurely from the study due to any of the above criteria or any other reason, study staff should make every effort to complete an Early Termination Visit. The assessments for the Early Termination Visit are the same as those described for the Week 24 (Day 168) Visit. The reason for participant withdrawal must be documented in the eCRF.

In the case of participants lost to follow-up, attempts to contact the participant must be made and documented in the participant's medical records.

Withdrawn participants will not be replaced.

4.3.2 Discontinuation of Study Treatment

The following do not fulfill any of the criteria for withdrawal from the study but do make the participant ineligible to receive any additional infusions of study treatment:

- Development of irreversible, life-threatening, Grade 3 to 4 acute GVHD or a Grade 3 to 4 non-hematologic adverse event between the first and second doses of PSL or placebo that is

considered related to study treatment administration. If this occurs, the participant's toxicities will be followed until resolution or until the participant's participation in the study ends.

- Receipt of any other hematopoietic stem cell product.
- Receipt of therapy for relapse of the participant's primary malignancy.
- Occurrence of Grade 3 or 4 CRS that persists beyond 72 hours. If this occurs, the participant's toxicities will be followed until resolution or until the participant's participation in the study ends.
- Pregnancy.

If any of the above criteria are met, every effort should be made to keep the participant in the study and continue follow-up.

4.4 Pre-Screening

Participants may complete an optional Pre-Screening Visit to evaluate urine viral loads (for BKV, AdV, CMV, HHV-6, JCV, and EBV) to allow sites to send samples to the central laboratory to expedite eligibility confirmation. The optional Pre-Screening Visit may be conducted up to 14 days prior to randomization (at the Baseline Visit). A separate Pre-Screening consent form is available for this purpose.

4.5 Screen Failures

Screen failures are defined as participants who have signed the Informed Consent Form (ICF) to participate in the clinical study but are not randomized into the clinical study. Participants who have signed only the Pre-Screening Consent Form will not be considered screened for the purpose of defining screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, documentation of HLA typing, and any SAEs.

Individuals who do not initially meet criteria for participation in this clinical study (screen failure) may be rescreened once after discussion with the Medical Monitor.

5 STUDY AND SITE CLOSURE

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

6 STUDY TREATMENTS

6.1 Treatment Groups

This is a Phase 3, multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of PSL compared to placebo for the treatment of participants with virus-associated HC following allogeneic HCT. Participants who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a [redacted] ratio to receive [redacted] sequential infusions of PSL or placebo. [redacted]. Administering the [redacted] as early as feasible within this window is encouraged. Based on body weight at the time of screening, participants who weigh <40 kg will receive [redacted] or placebo), while participants who weigh ≥40 kg will receive [redacted] (or placebo).

6.2 Rationale for Dosing

Study treatment is to be administered at a fixed dose based on weight, as [redacted] sequential infusions of PSL cells or placebo. The fixed, weight-based doses were selected based on data from previous clinical studies in which PSL was well tolerated, safe, and effective.

The dose of PSL per infusion ([redacted] is designed to mimic the VST dose administered in the CHARMS study. In the CHARMS study, the protocol-specified VST cell dose was $2\times10^7/m^2$ per infusion. A retrospective analysis of actual doses administered in the CHARMS study demonstrated that, on average, participants who weighed <40 kg received [redacted] cells per infusion (n = 9) while those who weighed ≥40 kg received [redacted] cells per infusion (n = 45).

In order to increase the repertoire of T cells potentially to be provided to each participant, the cell lines chosen for the first and second infusions of PSL may come from different donors (see Section 6.5.1 for details).

For additional information related to previous clinical studies with PSL, see the current IB.

6.3 Randomization and Blinding

Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to the study per the Schedule of Procedures. Participants will be randomized in a [redacted] ratio to receive [redacted] sequential infusions of PSL or placebo, with the first dose administered on Day 0. Randomization assignments will be performed by the Interactive Response Technology (IRT) system. Randomization will be stratified by [redacted]

6.4 Breaking the Blind

The Sponsor designee (ie, IRT vendor) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind integrity is properly maintained. Care should be exercised to ensure that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in Suspected Unexpected Serious Adverse Reaction [SUSAR] reporting).

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.

Unblinding should only occur in the event of an emergency or adverse event for which it is necessary to know the study treatment to determine an appropriate course of therapy. If the participant's study treatment must be unblinded, the Investigator or qualified designee should contact IRT for the study treatment information. The IRT documentation indicating the blind break at the site must be retained with the participant's source documentation in such a way as to avoid unblinding the treatment assignment to other site or Sponsor-blinded personnel.

If possible, the Investigator should attempt to contact the Medical Monitor prior to unblinding in order to get additional information about the study treatment. If not possible, the Investigator should notify the Medical Monitor as soon as possible of the unblinding without disclosing the treatment assignment of the unblinded participant. The Investigator must document the participant's identification, the reason for breaking the blind, and the date and time for breaking the blind.

6.5 Drug Supplies

6.5.1 Selection of Study Drug for the First and Second Dose and Formulation Packaging

Posoleucel is a third-party, donor-derived, "off-the-shelf," VST product with specificity for BKV, AdV, CMV, HHV-6, and EBV (with additional cross-reactive specificity for JCV) that is cryopreserved and ready for immediate use. For more information, see the current IB.

Posoleucel will be checked for cell concentration, viability, identity, phenotype, potency, endotoxin, mycoplasma, and sterility. The final product will be cryopreserved for future use as an "off-the-shelf" VST product.

Posoleucel cell lines will be selected for each participant based on [redacted]. The HLA alleles used for evaluation of matching are HLA-A, HLA-B, HLA-DR, and, if available, HLA-DQ.

The appropriate PSL cell line(s) will be selected using a software program (CytoMatch™), [redacted]

The selection of PSL cell line for the first infusion will be that with the highest match identified by the CytoMatch system. The PSL cell line or placebo lot for the second infusion will be selected based on the following:

- For participants who have demonstrated an initial clinical response, defined by a reduction of ≥1 grade on the Bedi scale 11 (+3) days after the first infusion, the same PSL cell line (or placebo lot) as initially administered will be infused for the participant's [redacted] If there is more than one Bedi score within the window, the assessment closest to the scheduled second infusion should be used.
- For participants who have not demonstrated an initial clinical response, the next-best match according to the CytoMatch hierarchy will be used as long as there are [redacted] If a suitable cell line for the [redacted] cannot be identified from available inventory, a [redacted] of the initial cell line administered or placebo from the same lot as the first dose will be administered.

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 (ie, relative to baseline GVHD at the time of randomization) at the proposed time of infusion of the second dose.

Posoleucel will be supplied as a dispersion for infusion, in 6 mL-capacity closed vials at a concentration of [redacted].

Posoleucel will be frozen in cryopreservation media containing [redacted]

Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance when administered.

6.5.2 Study Drug Preparation, Dispensing, and Administration

Posoleucel and placebo will be supplied in cryovials, which are to be transported from liquid nitrogen storage at the clinical site to the cell-thawing and preparation location in a liquid nitrogen Dewar or other suitable container. Details of the cell thawing, preparation for dosing, and administration to the participant will be provided to clinical sites in a separate Cell Therapy Manual.

Cryovials of PSL and placebo will be removed from liquid nitrogen storage and thawed, and the contents transferred to a syringe prior to infusion as described in detail in the Cell Therapy Manual. Study treatment is to be infused into the participant within 30 minutes of thawing (from completion of thaw to completion of infusion). If the location of the participant is remote from the clinical site's cell storage facility, the thawing of the cryovials and preparation of infusion syringes should be conducted in an appropriate location for cell preparation that is sufficiently close to the participant to ensure that no more than 30 minutes elapse between the completion of thawing and infusion.

Premedication is not required, except for participants with a prior history of reaction to blood products who may receive premedication with diphenhydramine 0.25 to 0.5 mg/kg IV or orally (maximum dose of 25 mg) or a similar antihistamine preferred by the study site and/or acetaminophen (paracetamol) 5 to 10 mg/kg IV or orally (maximum dose of 1000 mg) prior to study treatment administration. Premedication with high-dose systemic corticosteroids (ie, prednisone dose >0.5 mg/kg/day or equivalent) is prohibited.

All infusions of PSL or placebo will be administered IV (via central or peripheral line) over approximately [redacted] minutes as a slow push.

Participants will be monitored according to institutional standards for the administration of blood products and, at a minimum, according to the following requirements:

- Participants in an outpatient setting must remain in the clinic for ≥1 hour after the end of the infusion.
- Vital signs and pulse oximetry will be monitored at baseline and also after the final flush has been administered according to Appendix A.

All findings must be recorded in the eCRF.

If a participant experiences an infusion reaction, then diphenhydramine 0.25 to 0.5 mg/kg IV or orally (maximum dose of 25 mg) or a similar antihistamine preferred by the study site may be administered as treatment (even if received as premedication). Acetaminophen (paracetamol) 5 to 10 mg/kg IV or orally (maximum dose of 1000 mg) may also be given if it was not given as premedication or if 6 hours has elapsed since the prior dose. In the case of suboptimal control of an infusion reaction or the need to use corticosteroids for treatment of an infusion reaction, doses of ≤0.5 mg/kg/day of prednisone or equivalent should be considered first.

Participants will receive supportive care for acute or chronic toxicity, including blood components, antibiotics, or other interventions as appropriate per local treatment guidelines. See Section 6.6.2 for additional information.

Further details concerning study treatment receipt, storage, and administration will be provided to clinical sites in a separate Cell Therapy Manual.

6.5.3 Treatment Compliance

Posoleucel or placebo will be administered only IV and only under the direct supervision of clinical study personnel at the site.

6.5.4 Storage and Accountability

Posoleucel or placebo is stored in the vapor phase of liquid nitrogen in a continuously monitored storage freezer.

All material containing PSL or placebo will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

Posoleucel and placebo accountability are the responsibility of the Principal Investigator and Sponsor. However, this responsibility may be delegated to a suitably qualified Investigator who has had appropriate study-specific training that has been documented. The Sponsor will maintain records that will allow anonymous traceability of each PSL cell line to the third-party PBMC donor from whom it originated. These records will be maintained for 30 years after expiry for each PSL cell line.

Detailed records will be maintained to allow for accurate accountability of PSL and placebo as per applicable Sponsor and clinical site procedures. For further details and specifications, see the Cell Therapy Manual.

6.6 Prior and Concomitant Medications

6.6.1 Prohibited Medications

All participants may receive therapy for HC with cidofovir (IV or through intravesical instillation), fluoroquinolones (eg, ciprofloxacin), or leflunomide, provided that these agents are initiated prior to randomization. Initiation of these agents for the treatment of HC during the first 6 weeks is prohibited. These agents should not be discontinued during the first 6 weeks after randomization unless needed to manage toxicity. Dose changes should not be made during the first 6 weeks unless needed for renal dose adjustment.

Use of cidofovir during the first 6 weeks of the study for the treatment of non-HC-associated AdV or another non-HC viral infection is permitted, but should be discussed with the Medical Monitor.

Receipt of other investigational antiviral treatments (eg, brincidofovir) ≤7 days prior to randomization and throughout the duration of the study is prohibited.

T cell ablative therapies, such as antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies, are prohibited during the study. Use of corticosteroids ≥0.5 mg/kg/day prednisone (or equivalent) should not be administered during the study unless clinically required.

COVID-19 vaccination should be avoided for at least 28 days following the second infusion of study treatment (PSL or placebo) when feasible to minimize confounding due to the possible overlap of adverse effects (see Section 1.5.3).

6.6.2 Supportive Care

Supportive care measures such as the following are permitted:

- Use of intravesicular agents for the control of bleeding
- Analgesics, including opioids/ates (data will be collected daily)
- IV hydration
- Continuous bladder irrigation
- Antispasmodics
- Transfusion of RBCs
- Transfusion of platelets
- Transfusion of fresh frozen plasma
- Nephrostomy tube placement

All supportive care measures must be documented in the participant study records and the eCRF.

6.6.3 Documentation of Prior and Concomitant Medication Use

Medications used within 30 days before screening will be recorded. However, the following medications used within 30 days before screening do not need to be recorded:

- Fluids

- Electrolytes
- Vitamins
- Supplements
- Mouth care
- Laxatives
- "As needed" medications other than pain medications, which need to be collected

At screening, all concomitant medications and concurrent therapies, including the ones listed above, will be documented as indicated in Appendix A. Dose, route, unit frequency of administration, indication for administration, and dates of medication will also be captured in source documents and on the appropriate eCRF.

7 EFFICACY ASSESSMENTS

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[47] 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; Grade 1 hematuria requires confirmation of resolution by urinalysis results of ≤100 RBCs/high power field (HPF). If a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, including for the purpose of assessing for resolution. Details of the macroscopic hematuria assessment are provided in Section 7.1.

The key secondary endpoint is the time to resolution of bladder pain as measured by age-appropriate COAs. Resolution of bladder pain is defined as participants achieving a score on the relevant COA that does not exceed "mild pain" without use of prescription pain medications or the use of supportive bladder care.

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.

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 all target viruses (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) over the 24-week study period (only for participants with detectable viremia at baseline). 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 detection of the assays used.
- Average daily bladder pain (including lower abdominal pain, bladder-related pressure, and/or spasm pain or dysuria) over the initial 6 weeks following randomization.

The exploratory efficacy endpoints include the following:

- Cumulative days and time to discontinuation of supportive therapy for HC, including IV hydration, continuous bladder irrigation, and/or nephrostomy tube placement.
- Incidence and time to resolution of HC-associated signs and symptoms other than bladder pain.
- Incidence and time to recurrence of HC-associated signs and symptoms, including bladder pain, bladder pressure, spasms, urinary frequency, urinary urgency, nocturia, dysuria, and/or the presence of blood clots in urine.

- 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 detection of the assay used.
- Resolution of macroscopic hematuria as assessed at Weeks 2, 4, 6, 8, and 12 after randomization.
- Level of pain as assessed at Weeks 2, 4, 6, 8, and 12 after randomization.
- Time to resolution of non-BK target viral infections (ie, associated signs, symptoms, and presence/absence of viral load in blood and/or urine for AdV, CMV, HHV-6, JCV, and/or EBV) present at the time of randomization. Peripheral blood and, where relevant, urine (ie, evidence of virus in the urine at baseline), will be monitored for AdV, CMV, HHV-6, JCV, and/or EBV viral load.
- Incidence of target viral reinfections (ie, BKV, AdV, CMV, HHV-6, JCV, and/or EBV) as defined by new onset viremia or viruria and the presence of associated symptoms relative to baseline.
- Length of use of IV narcotic medication(s) for control of lower abdominal/bladder pain.
- Length of use of any pain medication(s) (IV, oral, or both), including antispasmodics used for pain, for control of lower abdominal/bladder pain.
- Length of use of immunosuppressive agents, by specific agent used (including dose and changes in dose).
- Number of hospitalizations/re-hospitalizations for any reason.
- Cumulative incidence and severity of chronic GVHD.
- Incidence and duration of use of any other antiviral therapies (eg, ganciclovir, valganciclovir, foscarnet) 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 change and severity.

7.1 Macroscopic Hematuria Assessment

7.1.1 Overview

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[47] 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. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, including for the purpose of assessing for resolution. An 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 score. The same urine sample should be used for the HCP's urine visual assessment and the urinalysis. All visual urine assessments with urinalyses should be performed on freshly collected urine specimens; urine should ideally be collected in the morning, but do not collect the first void of the day. For details regarding urine collection procedures, refer to the urine collection instructions appropriate for the participant's age and site of care.

Although two urine assessments (each including a Bedi assessment with urinalysis) are required to establish resolution of macroscopic hematuria, time to resolution will be calculated from the date of randomization to the date of the first visual urine assessment without macroscopic hematuria (by the Hemostick® visual scale for outpatients; by the Bedi scale for inpatients).

The schedule for visual assessments of the urine and urinalysis is discussed below and summarized in Appendix A.

7.1.2 Hematuria Grading Using the Bedi Criteria

The determination of the Bedi grade is primarily a clinical assessment (ie, visual urine assessment), but additional data are also required as outlined in the Bedi criteria and in Figure 2 below. Urinalysis includes an evaluation for blood and should reflex to microscopy if positive.

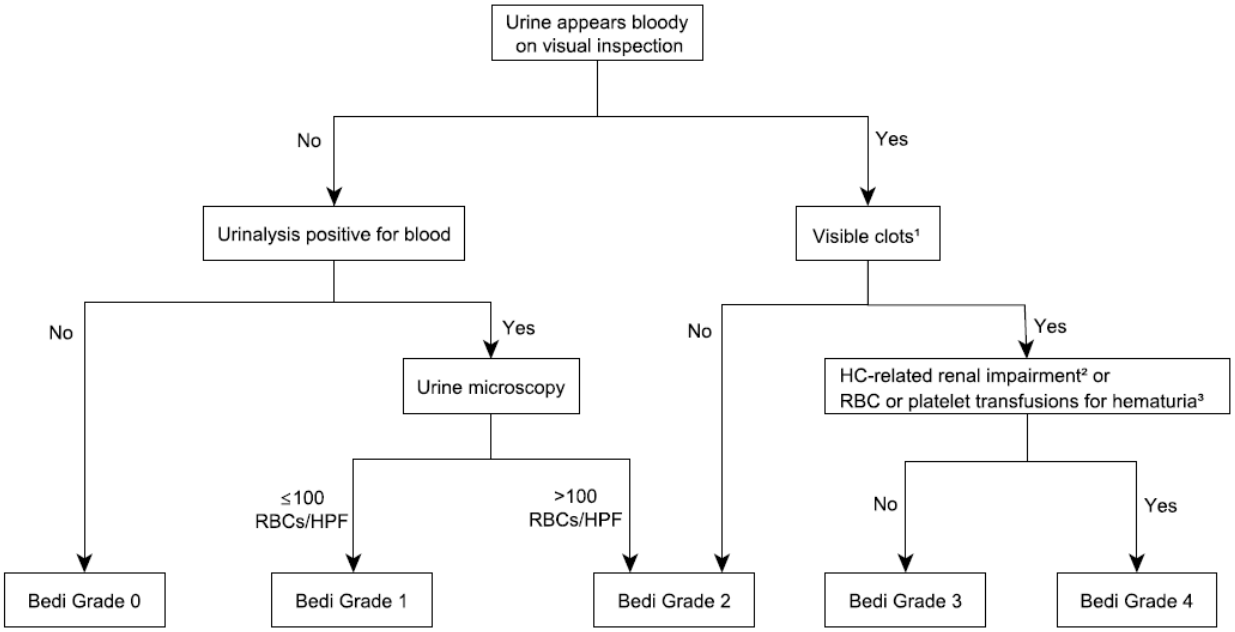
Hematuria grade is adapted from the Bedi criteria[47]:

- Grade 0: No hematuria; urine appears clear or yellow (ie, non-bloody) on visual assessment; urinalysis is negative for blood. Urine microscopy is not required if urinalysis is negative for blood.
- Grade 1: Microscopic hematuria; urine appears clear on visual assessment, but urinalysis is positive for blood and urine microscopy shows ≤100 RBCs/HPF.
- Grade 2:
  - Macroscopic hematuria but no clots on visual assessment; the absence of clots must be confirmed by an HCP.

    OR
  - Microscopic hematuria; urine appears clear on visual assessment, but urinalysis is positive for blood and urine microscopy shows >100 RBCs/HPF.
- Grade 3: Macroscopic hematuria with evidence of visible clots; clots are defined as gelatinous or semi-solid masses of blood in urine, and presence must be confirmed by an HCP.
- Grade 4: Same as Grade 3 with HC-associated renal impairment (new onset elevation of creatinine to ≥1.5 × ULN and considered by the Investigator to be HC-related) or transfusion requirements secondary to hematuria (packed RBCs and/or platelets). On the rare occasion where participants have macroscopic hematuria but no clots (eg, in the setting of low platelets) and have an HC-related transfusion requirement, the Bedi grade should be assessed as Grade 4.

A schema for determining the Bedi grade is displayed in Figure 2.

Figure 2. Schema for Determining the Bedi Grade from Urine Visual Assessment, Laboratory Data, and Clinical Evaluation



The same urine sample should be used for the HCP's urine visual assessment and the urinalysis. Bedi grading should not be performed on days on which the participant is receiving continuous bladder irrigation or has nephrostomy tubes. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, including for the purpose of assessing for resolution.

1. If a participant has visible clots in the urine, the Bedi grade is ≥3 even if the urine does not appear bloody (ie, if the liquid component is yellow or clear).
2. HC-related renal impairment is defined as a new elevation of creatinine to ≥1.5 × ULN that is considered by the investigator to be HC-related (ie, from urinary obstruction due to clots).
3. If a participant is requiring packed RBC or platelet transfusions for hematuria, the Bedi Grade is a 4 even if no clots are present.

HC: hemorrhagic cystitis; RBC: red blood cell; HPF: high-powered field; HCP: healthcare provider; ULN: upper limit of normal.

7.1.3 Hemostick® Visual Scale for Outpatients

The Hemostick is a printed visual scale with 6 color fields that standardizes the characterization of macroscopic hematuria severity.[52] The numbering of the Hemostick scale does not map directly to the Bedi grade. The Hemostick will be used as a monitoring tool for outpatients. A Hemostick score of 0 or 1 will trigger two hematuria visual assessments with Bedi grading by an HCP on the study team, each with an accompanying urinalysis; these assessments will be used to confirm resolution of macroscopic hematuria. Similarly, following resolution of macroscopic hematuria, Hemostick assessments will be used for outpatients to monitor for potential relapse. Participants, caregivers, and home health providers (if needed) will be trained to use and interpret the Hemostick in the outpatient setting via an instruction manual. For an image of the Hemostick visual scale, please visit https://hemostick.com/engelska/picture.

7.1.4 Timing of Urine Visual Assessments with Urinalyses

All randomized participants will undergo regular visual assessments 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 for each participant 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 2. Each time that a participant undergoes a urine visual assessment for Bedi grading, the same sample should be sent for urinalysis.

Table 2. 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 (Day 43)
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. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, including for the purpose of assessing for resolution.
Abbreviations: HCP = healthcare provider; U/A = urinalysis

If participants develop a recurrence of hematuria, refer to Section 7.1.9 for guidance.

7.1.5 Urine Visual Assessment to Confirm Resolution of Macroscopic Hematuria

Resolution of macroscopic hematuria is defined as resolution to Grade 0 or 1 on the Bedi scale[47] on 2 consecutive visual urine assessments ≥2 days apart without continuous bladder irrigation or nephrostomy tubes; Grade 1 hematuria 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, including for the purpose of assessing for resolution.

For inpatients, if absence of macroscopic hematuria is confirmed using the Bedi scale with urinalysis, the resolution date will be considered the date of the first of these 2 consecutive visual urine assessments.

For outpatients, the earliest date of visual assessment without macroscopic hematuria (Hemostick value of 0 or 1) will trigger 2 laboratory urinalysis assessments ≥2 days apart to confirm the resolution of macroscopic hematuria. If absence of macroscopic hematuria is confirmed on

urinalysis (≤100 RBCs/HPF), the resolution date will be considered the first date of visual assessment without macroscopic hematuria using the Hemostick.

7.1.6 Urinalysis for Quantitation of Red Blood Cells

Each time that a participant undergoes a Bedi assessment, a urinalysis should also be sent. During assessments for possible resolution of hematuria, urinalysis will be required to distinguish between Bedi Grade 1 and Bedi Grade 2.

For RBC quantitation on urinalysis, some local clinical laboratories have an upper limit of RBC quantitation below 100 RBCs/HPF (eg, >25 RBCs/HPF, >50 RBCs/HPF). In these cases, if the urine is not grossly bloody on visual assessment, urine samples will be sent to the central laboratory for urine microscopy.

7.1.7 Pharmacologic Agents or Foods that May Cause Urine Discoloration

If at any time during the study there is concern that a participant's urine may be (or may become) discolored by a pharmacological agent (eg, phenazopyridine/pyridium) or by a dietary component (eg, beets), urinalysis should be performed to differentiate between macroscopic hematuria and urine discoloration.

7.1.8 Handling of Participants Receiving Definitive Therapies to Stop Bladder Bleeding, Continuous Bladder Irrigation, or Nephrostomy Tubes

Definitive therapies to stop bladder bleeding, such as cystectomy, bladder vessel embolization, cauterization, application of fibrin "glue" preparations, or formalin instillation are permitted but will be considered treatment failures for the primary endpoint of time to resolution of macroscopic hematuria. Participants receiving continuous bladder irrigation or nephrostomy tubes should be evaluated daily by the Investigator for the ability to discontinue these supportive measures.

For participants receiving continuous bladder irrigation or who have nephrostomy tubes, the primary endpoint (ie, time to resolution of macroscopic hematuria) will be measured once participants discontinue these modalities. Bedi grading will not be performed on days on which the participant is receiving continuous bladder irrigation or has nephrostomy tubes. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, including for the purpose of assessing for resolution. Discontinuation of bladder irrigation and nephrostomy tubes will be based upon the participant's clinical condition and the treating physician's medical judgement.

All attempts should be made to minimize urinary tract procedures or manipulations prior to urine collection to ensure that specimens are not contaminated due to trauma.

7.1.9 Assessments in Participants with Recurrence of Hematuria

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 DNA for potential genotyping. A second Bedi assessment with urinalysis will be repeated 48 to 72 hours after the date of recurrence observed by the Investigator. Recurrence is defined as 2 consecutive Bedi grades ≥2 (macroscopic hematuria). Participants with recurrence will then undergo visual assessment of urine and urinalysis as

indicated in Table 2 for those with unresolved hematuria and according to the participant's treatment location and time on study. Following resolution of recurrent hematuria, follow Table 2 for those with resolved hematuria.

7.2 Clinical Outcome Assessments

Age-appropriate COAs will be administered as indicated in Appendix B. Following consent, study site staff will review the age-appropriate COAs with the participant (or parent or other caregiver, as appropriate), using best practices demonstrated during the Site Initiation Visit and/or the Investigator Meeting.

Participants (or parents or other caregivers) will be asked to enter information about the severity of pain on a hand-held device daily. If the COAs are not accessible on a hand-held device, paper versions of the questionnaires may be used. For participants for whom a COA is not available in an approved, validated translation, that COA will not be administered. The participant's age at the time of informed consent/assent will determine which of the age-appropriate versions of the relevant COAs are administered.

Use of the following COAs is anticipated for the measurement of bladder pain and analgesic use:

- BPIC SD worst pain item (participants ≥12 years of age) – see Section 7.2.1
- BPIC SD average pain item (participants ≥12 years of age) – see Section 7.2.1
- Wong-Baker FACES Pain Rating Scale (participants 3 to 11 years of age) – see Section 7.2.2
- PROMIS Parent Proxy Pain Behavior Short Form (8a) (participants <3 years of age) – see Section 7.2.3
- Use of pain medications (participants of all ages) – see Section 7.2.4

The following COAs will be administered to measure additional signs and symptoms of HC and urinary frequency:

- BPIC SD items 8 and 9 (participants ≥12 years of age) – see Section 7.2.1
  - Urinary urgency (In the past 24 hours, how often did you have to rush to get to the bathroom to urinate?)
  - Constant need to urinate (In the past 24 hours, did you have a constant need to urinate?)
- Interstitial Cystitis Symptoms Index (ICSI) items 2 and 3 (participants ≥12 years of age) – see Section 7.2.5
  - Urinary frequency (During the past 7 days, have you had to urinate less than 2 hours after you finished urinating?)
  - Nocturia (During the past 7 days, how often did you most typically get up at night to urinate?)

The following COAs will be administered to measure overall quality of life (see Section 7.2.7):

- EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire (participants ≥12 years of age)
- EuroQol 5 Dimensions for Younger Patients (EQ-5D-Y) questionnaire (participants 8 to 11 years of age)

- EQ-5D-Y Proxy Version 1 questionnaire (participants ≤7 years of age)

The following age-appropriate Global Impression Scales will also be administered (see Section 7.2.6):

- Patient Global Impression of Severity (PGIS)
- Patient Global Impression of Change (PGIC)
- Caregiver Global Impression of Severity (CGIS)
- Caregiver Global Impression of Change (CGIC)

7.2.1 Selected Items from the Bladder Pain/Interstitial Cystitis Symptom Diary

The BPIC Symptom Diary[53] is a self-reported instrument designed to assess symptoms of bladder pain/interstitial cystitis on a daily basis. The adapted version that will be used in this study is comprised of 2 bladder pain NRSs (average and worst pain), and other urinary symptoms (2 items). The two items assess urinary urgency (In the past 24 hours, how often did you have to rush to get to the bathroom to urinate?) and the constant need to urinate (In the past 24 hours, did you have a constant need to urinate?).

This assessment will be administered to participants ≥12 years of age at baseline, then daily through Week 6, followed by weekly to Week 24.

7.2.2 Wong-Baker FACES Pain Rating Scale

The Wong-Baker FACES Pain Rating Scale[54] is a self-reported measure designed to assess acute pain in young children. Children are instructed to select from 6 line-drawn faces to demonstrate "how they feel inside" from "no hurt" to "hurts worst." Pictorial scales facilitate completion by children as they do not use sophisticated wording or abstract numerical values.[54] The FACES pain scale is widely used and has demonstrated acceptable measurement properties. The tool is appropriate for use in children ages 3 years and older.[54]

This assessment will be administered to children from 3 to 11 years of age at baseline, then daily through Week 6, followed by weekly to Week 24.

7.2.3 PROMIS Parent Proxy Pain Behavior Short Form (8a)

The PROMIS is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being. These tools can be used as primary or secondary endpoints in clinical studies of the effectiveness of treatment and can be used across a wide variety of chronic diseases and conditions and in the general population.

Pain behaviors, such as verbal complaints of pain and suffering, non-language sounds, facial expressions, body posturing and gesturing, and limitations in activities, demonstrate to others that an individual is experiencing pain. The PROMIS Parent Proxy Pain Behavior item bank contains 39 items specific to pain behaviors. From this item bank, a short form (8a) was developed specific to caregiver reports and consists of 8 pain behaviors assessed across a 6-point scale from "had no pain" to "almost always."[55]

This assessment will be administered to caregivers of children <3 years of age and will be performed at baseline, then daily through Week 6, followed by weekly to Week 24.

7.2.4 Pain Medication Log

A pain medication log will be kept for all participants. While participants are hospitalized, the log will be completed by study staff. While participants are not hospitalized, they (or their parents or other caregivers) will enter their medication information into the log. Pain medications and antispasmodics will be collected in the log.

These assessments will be administered at baseline and then daily through Week 6 followed by weekly to Week 24.

7.2.5 Urinary Frequency and Nocturia Items from the Interstitial Cystitis Symptoms Index

The ICSI and Interstitial Cystitis Problem Index (ICPI) are 2 brief, self-reported assessments designed to be utilized together to assess lower urinary tract symptoms and problems in participants with interstitial cystitis.[56] These measures are widely used and well established with acceptable measurement properties. In this study, only items 2 and 3 from the ICSI will be administered. These items assess urinary frequency (During the past 7 days, have you had to urinate less than 2 hours after you finished urinating?) and nocturia (During the past 7 days, how often did you most typically get up at night to urinate?). The ICPI will not be administered.

This item will be administered to participants ≥12 years of age at baseline, weekly through Week 6, and then at Weeks 8, 12, 16, and 24. It has been adapted to capture symptoms over the preceding 7 days, rather than over the preceding month. In the event that the participant has an indwelling urinary catheter (including a 3-way catheter for continuous bladder irrigation), for the duration of catheterization this item will not be administered.

7.2.6 Age-Appropriate Global Impression Scales

The PGIC and CGIC scales consist of 1 question each to be completed by either the participant or the caregiver, respectively, to assess the overall change in HC symptoms. The PGIS and CGIS consist of 1 question each to be completed by either the participant or the caregiver, respectively, to assess overall severity of symptoms.

Age-appropriate versions of the PGIC will be administered to those 8 to 11 years of age, and ≥12 years of age. Age-appropriate versions of the PGIS will be administered to those 3 to 7 years of age, 8 to 11 years of age, and ≥12 years of age. The CGIC will be administered to caregivers of children <8 years of age. The CGIS will be administered to children <3 years of age.

The PGIS and CGIS will be administered at baseline, daily through Week 6, and then weekly to Week 24. The PGIC and CGIC will be administered starting on the day of the first infusion, daily through Week 6, and then weekly to Week 24.

7.2.7 EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1

The EQ-5D is a group of instruments that was developed to assess patient-reported health-related quality of life.[57] The EQ-5D-5L includes the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the EQ-5D-5L, each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The participant is asked to indicate his or her health state by checking the box next to the most

appropriate statement in each of the 5 dimensions. The versions used in children have 3 responses to each question instead of 5.

In this study, the EQ-5D-5L will be used for individuals ≥12 years of age, the EQ-5D-Y for children 8 to 11 years of age, and the EQ-5D-Y Proxy Version 1 for children ≤7 years of age. Data for children <4 years of age will also be collected using the EQ-5D-Y Proxy Version 1, but these results will be analyzed separately from the results for children 4 to 7 years of age.

The EQ-5D-5L, the EQ-5D-Y, and the EQ-5D-Y Proxy Version 1 include the EQ VAS. The EQ VAS records the participant's self-rated health on a vertical visual analog scale, where the endpoints are labeled "The best health you can imagine" and "The worst health you can imagine."

These assessments will be administered at baseline, weekly through Week 6, and then at Weeks 8, 12, 16, and 24.

7.2.8 Planned Exit Interview

Approximately 35 participants at selected sites in countries where English is the primary language may provide additional informed consent to participate in a single participant interview. The interview may be conducted via telephone and will take place approximately 10 days following the Week 24/Early Termination visit and following participant discharge from the hospital (if applicable).

Participant interviews will be conducted over the telephone by highly trained interviewer(s) from Research Triangle Institute Health Solutions, Research Triangle Park, NC 27709, USA utilizing a semi-structured interview guide developed in collaboration with AlloVir.

The participant interview is designed to examine the experience of HC from the perspective of participants and caregivers of pediatric participants, including perceptions of symptom severity and variability, symptom burden, and disease-related impacts, as well as experiences during this clinical study. Participants will also be asked to provide their thoughts about the magnitude of meaningful changes on selected COAs utilized in the study. The participant interview will take approximately 60 minutes. Any adverse event(s) mentioned by a participant or caregiver during the interview will be captured by the interviewer and communicated to the site within the same business day to enable site staff to follow up and report as per protocol requirements.

A detailed description of the participant interview and all related procedures is provided in the Patient Interview Procedures Guide that will be provided separately to the sites.

7.3 Resolution of Viral Infections

In participants with concomitant viral infections at the time of treatment, peripheral blood and, where relevant, urine, will be monitored for BKV, AdV, CMV, HHV-6, JCV, and/or EBV viral load (Appendix A). Resolution of viral infection will be defined as a return to normal range as defined by the assay used and complete resolution of clinical signs and symptoms as determined by the Investigator.

Samples for viral sequence/genotype will be collected on all participants as indicated in Appendix A.

8 SAFETY ASSESSMENTS

The safety endpoints for this study include the following:

- Incidence and severity of acute GVHD (secondary endpoint) (for the acute GVHD grading scale, see Appendix E)
- Incidence and severity of chronic GVHD (exploratory endpoint) (for the chronic GVHD grading scale, see Appendix E)
- Incidence and severity of CRS (secondary endpoint) (for the CRS grading scale, see Appendix F)

Safety will be evaluated throughout the duration of the study as indicated in Appendix A.

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from informed consent until study participation is complete or until resolution, whichever is sooner. For participants who screen fail, only SAEs will be collected (see Section 4.5 for details). Participants should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at informed consent, Investigators should make an assessment for adverse events at each visit and record each event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at informed consent should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline increase in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, electrocardiogram [ECG]) findings that are detected during the study or are present at randomization and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined

to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

The relevant AE, abnormality, or SAE should be followed to the point of resolution or until the event is considered stable, clinical insignificant, or asymptomatic.

If the home health provider identifies or records any new or updated signs or symptoms, the Investigator should be notified immediately.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out. Section 8.1.3 provides further guidance on assessing the causal relationship between an adverse event and the medicinal product.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For PSL, the reference safety information is included in the safety review in Section 7 of the IB currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity

The severity of all adverse events will be graded according to CTCAE version 5.0. For those adverse event terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to the adverse event

Causality Assessment

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (possibly, probably, or certain to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.

- Concomitant drug-

  The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Serious adverse events will be reviewed by the Sponsor Medical Monitor, in consultation and with the global safety physician and further queries issued, if necessary. If there is a disagreement between the Investigator and the Sponsor's Medical Monitor regarding the designation of an event as serious (in line with the appropriate protocol definition), and/or regarding the plausibility of causality of an adverse event, the case will be referred to the DSMB for adjudication. Relevant information will be provided to the DSMB in parallel with the reports prepared for the next planned

data review meeting for evaluation at that meeting. Until the DSMB issues its response, the Investigator's designation will be respected.

8.1.4 Adverse Events of Special Interest

The Investigator will monitor each participant for clinical and laboratory evidence for pre-defined AESI throughout participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an adverse event form, which must be submitted within 24 hours of awareness of the event.

For this study, AESI include the following:

- Acute and chronic GVHD (new onset or worsening of existing GVHD) (for the acute and chronic GVHD grading scales, see Appendix E).
- Graft failure and rejection.
- CRS (for the CRS grading scale, see Appendix F).
- Infusion-related adverse events.

During the study, additional AESI may be identified by the Sponsor.

Adverse events of special interest must be recorded in the eCRF.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.

  Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations.

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

Note: Events of progression of a participant's underlying cancer, as well as events clearly related to the progression of a participant's cancer (signs/symptoms of progression), should not be reported as an SAE unless the outcome is fatal during the study. If the event has a fatal outcome during that timeframe, the event of Progression of "Type of Cancer" must be recorded as an SAE with CTCAE Grade 5 (fatal) outcome indicated. Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as an SAE.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

8.3.1 Initial Reports

All SAEs occurring from informed consent until study participation is complete or until resolution, whichever is sooner, must be reported to [redacted] (PVSS) and Safety Reporting Group (SRG) within 24 hours of the knowledge of the occurrence. After study participation is complete, any SAE that the Investigator considers related to study drug must be reported to [redacted] and SRG or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the Medpace ClinTrak electronic data capture (EDC) system for the study. When the form is completed, [redacted] and SRG personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] and SRG at [redacted] or call the phone number listed below, and fax/email the completed paper SAE form to [redacted] and SRG (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

8.3.2 Follow-Up Reports

The Investigator must continue to follow the participant until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the participant dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, participant discharge summary or autopsy reports) to [redacted] and SRG via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a participant becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to [redacted] and SRG within 24 hours of knowledge of the event. [redacted] and SRG will then provide the Investigator/site the Pregnancy Form for completion. The Investigator/site must complete this form and fax/email it back to [redacted] and SRG.

If the female partner of a male participant becomes pregnant while the participant is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify [redacted] and SRG as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Follow-up Form should be completed and faxed/emailed to [redacted] and SRG. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities in all the Member States concerned, and the Central Ethics Committee as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to the investigational medicinal product.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the participant has taken additional dose(s) or the Investigator has reason to suspect that the participant has taken additional dose(s).

- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, participant, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of participants missing doses of study treatment (PSL or placebo) are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situations Report Form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on using the SAE form and faxed/emailed to [redacted] and SRG (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situations Report Form should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: [redacted] (PVSS) and Safety Reporting Group (SRG):
Telephone (within US): [redacted]
Telephone (outside US): [redacted]
Fax: [redacted]
Email: [redacted]

8.7 Clinical Laboratory Evaluations

Central or local laboratory results including those obtained as standard of care may be used to determine eligibility. Blood samples from Day 0 (pre-infusion baseline) and onward must be collected for analysis at the central laboratory as indicated in Appendix A. See Appendix D for a complete list of analytes and Appendix C for blood draw volumes and time points based on the participant's weight.

Urine will be obtained as indicated in Appendix A and sent to each site's clinical laboratory per institutional guidelines for urinalysis. See Appendix D for a complete list of analytes. For RBC quantitation on urinalysis, some local clinical laboratories have an upper limit of RBC quantitation below 100 RBCs/HPF (eg, >25 RBCs/HPF, >50 RBCs/HPF). In these cases, if the urine is not grossly bloody on visual assessment, urine samples will be sent to the central laboratory for urine microscopy.

A serum pregnancy test will be performed at screening for all participants of childbearing potential. A urine or serum pregnancy test must be performed <24 hours before each infusion and at the end of study visit for participants of childbearing potential. A negative result must be confirmed prior

to administration of each infusion. These tests may be performed at the local laboratory. See Appendix A.

Samples for testing of viral DNA and of short sequences of T-cell receptor DNA to evaluate for virus-specific T-cell persistence may be retained for up to 10 years.

8.8 Vital Signs

Vital sign measurements will include body temperature, blood pressure, heart rate, and respiration rate. Following the infusions of study treatment on Day 0 and Day 14 (±3 days), vital signs will be monitored after the final flush has been administered (or within 5 minutes thereof), and at 15, 30, 45, and 60 minutes (±5 minutes of each of these time points) after the final flush. At every other study visit, they will be measured after resting for 5 minutes as indicated in Appendix A.

8.9 Electrocardiograms

Standard 12-lead ECGs will be performed as indicated in Appendix A. On Day 0 and Day 14, the ECG should be performed within 1 hour after study treatment administration. A post-infusion ECG should be completed for all infusions of study treatment.

8.10 Physical Examinations

Physical examinations will be performed and height and weight will be collected as indicated in Appendix A. The complete physical examination will be performed by the Investigator or another qualified member of the study team. New abnormal physical examination findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

If home health visits are necessary, a body system assessment may be substituted in place of a complete physical examination.

8.11 Graft Versus Host Disease

Acute and chronic GVHD will be assessed as indicated in Appendix A. If any participant develops GVHD, that participant may receive standard GVHD treatment at the discretion of the Investigator.

8.11.1 Acute Graft Versus Host Disease

Grading of acute GVHD will be reported according to CTCAE version 5.0. In addition, staging and grading of acute GVHD will be reported using Mount Sinai Acute GVHD International Consortium guidelines. Response to treatment will be assessed as per Center for International Blood and Marrow Transplant Research (CIBMTR) modifications to the CIBMTR response index as described in Appendix E.[59,60]

8.11.2 Chronic Graft Versus Host Disease

Grading of chronic GVHD will be reported according to CTCAE version 5.0. In addition, manifestations of chronic GVHD and response to treatment will be assessed as per National Institutes of Health consensus guidelines for chronic GVHD as described in Appendix E.[61,62]

8.12 Cytokine Release Syndrome

Manifestations of CRS will be assessed as per the American Society for Transplantation and Cellular Therapy consensus grading for CRS and neurologic toxicity associated with immune effector cells as described in Appendix F. Recommendations for monitoring for and management of CRS are provided in Appendix G.

Posoleucel VSTs do not express a chimeric antigen receptor (CAR) and are not genetically modified. They therefore do not contain the engineered chimeric costimulatory moieties that may predispose to non-physiologic stimulation. Thus, the risk of CRS following administration of these VSTs is expected to be low.

A CRS-like syndrome following administration of VSTs has been reported only rarely (in two patients with bulky EBV-associated lymphoma/post-transplant lymphoproliferative disease [PTLD])[63,64] and has not been reported in other patients receiving VSTs.[65] In PTLD, a rare condition, there is both an overwhelming viral burden and an uncontrolled proliferation of virus-transformed cells. It thus differs significantly from virus-associated HC. In order to avoid the potential for the development of CRS-like symptoms associated with bulky EBV-associated lymphoma, participants with uncontrolled or progressive EBV-associated PTLD are excluded from this study (Exclusion criterion #6).

8.13 Post-Infusion Monitoring

Post-infusion monitoring will be performed as indicated in Appendix A. Participants will be monitored closely and must remain in the clinic for a minimum of 1 hour after the end of the infusion. Vital signs (including body temperature, heart rate, respiration rate, and blood pressure) and pulse oximetry will be measured at the end of the infusion (or within 5 minutes of completion), and at 15, 30, 45, and 60 minutes (±5 minutes of each of these time points) after the end of the infusion.

9 STATISTICAL ANALYSES

9.1 Analysis Populations

9.1.1 Intent-to-Treat Population

The ITT Population will include all randomized participants regardless of whether the participant actually receives PSL or placebo. Participants will be analyzed according to their randomized study treatment.

9.1.2 BK Intent-to-Treat Population

The BK ITT Population will include participants in the ITT Population who have BKV identified as the cause of their HC. The primary efficacy analysis will be based on the BK ITT Population. A supplementary efficacy analysis will be based on the ITT Population.

9.1.3 Modified Intent-to-Treat Population

The mITT Population will include all randomized participants who receive any amount of PSL or placebo.

9.1.4 BK Modified Intent-to-Treat Population

The BK mITT Population will include participants in the mITT Population who have BKV identified as the cause of their HC. A supplementary efficacy analysis will be based on the BK mITT Population.

9.1.5 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 violations deemed to impact the results, as defined in the SAP.

9.1.6 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.

9.2 Statistical Methods

An SAP will be finalized before the interim analysis occurs. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report.

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.

A gatekeeping strategy will be used to control the overall Type I error for analyses of the primary efficacy endpoint, the key secondary endpoint, and the first additional secondary efficacy endpoint.

9.2.1 Analysis of Efficacy

9.2.1.1 Primary Efficacy Endpoint Analysis

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[47] on 2 consecutive urine assessments ≥2 days apart without continuous bladder irrigation or nephrostomy tubes; 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, including for the purpose of assessing for resolution.

The objective is to demonstrate the superiority of PSL therapy to placebo with respect to the time to resolution of macroscopic hematuria.

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 based on the stratification factors at randomization. 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 0.0147 (reduced from 0.025 due to inclusion of an interim analysis based on Pocock method). A supplementary efficacy analysis based on the overall ITT Population will also be conducted. Time to resolution will be calculated from the time of randomization to the date of the first resolution of macroscopic hematuria (see Section 7.1). Participants not observed to achieve resolution will be considered censored at their last follow-up for the primary endpoint. Definitive therapies to stop bladder bleeding, such as cystectomy, bladder vessel embolization, cauterization, application of fibrin "glue" preparations, or formalin instillation are permitted but will be considered treatment failures for the primary endpoint of time to resolution of macroscopic hematuria and will be censored at 24 weeks. The detailed censoring rules will be specified in the SAP.

A supportive analysis of the primary efficacy endpoint will also be conducted, using a Cox proportional hazards model in order to account for additional potential confounders of the treatment effect. The Cox model will include fixed effect terms for randomized treatment assignment, the randomization stratification factors, concomitant antiviral use, and concomitant systemic corticosteroid use.

In addition, analysis of the primary efficacy endpoint will also be performed based on the BK mITT and BK PP Populations as sensitivity analyses. Subgroup analyses will be conducted to compare responses in participants with BKV viruria $<10^7$ copies/mL to those with BK viruria $\geq 10^7$ copies/mL, and to evaluate responses in participants who receive concomitant antiviral therapies to those who do not receive these therapies during the study.

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 0.025 significance level, rather than the Pocock-adjusted 0.0147 significance level used for the primary analysis based on the BK ITT Population. A sensitivity analysis will also be conducted based on the overall mITT Population.

9.2.1.2 Key Secondary Efficacy Analysis

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 Section 7) without use of prescription pain medications or supportive bladder care.

If the result of the analyses of the primary efficacy endpoint (ie, time to resolution of macroscopic hematuria) 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, except that a 0.025 significance level will be used. Additional analyses of the time to resolution of bladder pain will also be performed based on the BK mITT and BK PP Populations as sensitivity analyses.

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 will be conducted based on the mITT Population.

9.2.1.3 Other Efficacy Analysis

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. This secondary endpoint will be tested at the one-sided 0.025 alpha level. Sensitivity analyses will be performed based on the BK mITT and BK PP Populations.

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. A sensitivity analysis will be conducted using the mITT Population.

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 groups 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. In addition, the hazard ratio along with the 95% confidence intervals for the true hazard ratio will be calculated using a Cox proportional hazards model with treatment, stratification factors at randomization, and other potentially confounding factors.

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

9.2.2 Analysis of Safety

The safety profile will be based on treatment-emergent adverse events (TEAEs) and changes in vital signs, physical examinations, clinical laboratory assessments, and ECGs. All safety analyses will be based on the Safety Population.

Safety analyses in general will be descriptive and will be presented by phase and 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).

A TEAE is defined as an adverse event with onset after the start of study treatment (PSL or placebo). The number and percentage of participants with TEAEs will be tabulated by MedDRA System Organ Class and Preferred Term for each treatment group and by severity and relationship to treatment. Adverse events leading to discontinuation of the study and SAEs will be summarized by treatment group. By-participant listings will also be provided for any deaths, SAEs, and adverse events leading to discontinuation of the study.

The key safety endpoint for this study is the incidence and severity of acute GVHD. The incidence and severity of acute GVHD, chronic GVHD, and CRS, and the corresponding exact binomial confidence intervals with 95% confidence level will be presented by treatment group.

Descriptive statistics will be provided for clinical laboratory data, vital sign data, and ECG parameters, presented as both actual values and changes from baseline over time. Abnormal physical examination findings will be presented in a by-participant data listing.

9.2.3 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 60 participants randomized in the BK ITT Population. The interim analysis will be for purposes of potentially stopping early for success and 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.

9.2.3.1 Interim Analysis for Stopping Early for Success

The interim analysis for stopping early for success will be performed based on the primary efficacy endpoint using the method of Pocock. At the interim analysis, if the one-sided p-value from the stratified log-rank test comparing treatment to control is less than 0.0147 (overall alpha = 0.025 adjusted for the interim analysis), the study will be stopped early for success. If the study is stopped early for success based on the primary efficacy endpoint, the key secondary efficacy endpoints and the first other secondary efficacy endpoint will be tested sequentially as described above using a one-sided 0.025 alpha level.

9.2.3.2 Interim Analysis for Futility

The interim analysis for futility will also 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 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

conducted at the one-sided 0.0147 level. 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. 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.

9.2.4 Sample Size Determination

Approximately 125 participants will be randomized at approximately 90 clinical sites 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 based on the method of Pocock; control of the overall Type I error rate at the one-sided 0.025 level; 10% 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 83.8% power.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the sites on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system while the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the CFR (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of participants, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last participant in the study or when the Sponsor receives the last laboratory result, whichever comes last.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

11.2.1 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of participants. The study will only be conducted at sites where IRB approval has been obtained. The protocol, IB, ICF/assent form, advertisements (if applicable), written information given to the participants, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of participants in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs/assent forms, advertisements to be used for participant recruitment, and any other written information regarding this study to be provided to a participant or participant's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.2.2 Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (ie, Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

Prior to conducting any study-related activities, written informed consent to participate in the study must be provided by the participant, or a parent or legal guardian must provide written informed consent and the potential pediatric participant must provide assent in a manner approved by the IRB/IEC and local regulations.

The ICF (and assent form, if applicable) and any changes to the ICF/assent form made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory, and legal requirements.

The Investigator must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the participant has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each participant, or the participant's parent/legal guardian and assent from

the potential pediatric participant, before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF/assent form must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF/assent form will be given to the participant and his/her parent/legal guardian when applicable.

Note that there is a separate consent form for participants in the optional Pre-Screening Visit (see Section 4.4).

11.4 Subject Card

Upon enrollment in the study, the participant will receive a subject card to be carried at all times. The subject card will state that the participant is in a clinical research study, type of treatment, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/EC, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any participant in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent/assent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Participants or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Participant medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participants (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs/assent forms, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH Guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal and/or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor will take out patient liability insurance for all participants who give their consent to the clinical study. This coverage is designed in the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study will be submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorisation (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable IRB/IEC opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by the Sponsor or designee. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for participant safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

12.2 Home Health Visits

Home health visits may be available as an optional service that permits an appropriately trained and delegated HCP to conduct study procedures in the patient's home (or other convenient location). Home health visits may be conducted as agreed with the Sponsor.

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APPENDIX A: SCHEDULE OF PROCEDURES

Study Visit/Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±28**	**±28**
Study Procedures											
Pre-screening informed consent/assent	X										
Informed consent/assent [4]		X									
I/E criteria	X	X									
Demographics [5]		X									
Medical history		X									
Prior and concomitant medications [6]		→									
Adverse events [7]		→									
Complete physical examination [8]		X		X	X	X	X	X	X	X	X
Height and weight [9]		X	X		X						X
Vital signs and pulse oximetry [10]			X	X	X	X	X	X	X	X	X
Clinical outcome assessments [11]		→				See Appendix B					
Documentation of HLA typing [5,12]		X									
Hematology [13]		X [14]	X	X	X	X	X	X	X	X	X
Clinical chemistry [15]		X [14]	X	X	X	X	X	X	X	X	X
Viral loads in urine [15]	X	X [14]	X	X	X	X	X	X	X	X	X
Viral loads in blood [13, 15]			X	X	X	X	X	X	X	X	X
Pregnancy test [16]		X	X		X						X
FSH [17]		X									

Study Visit/Week	Pre-[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±28**	**±28**
Study Procedures											
Visual assessment of urine by Bedi grading with urinalysis		X	Inpatients: At baseline, then 3 × per week [18] through the end of Week 6 (Day 42) or until resolution, then 1 × per week Outpatients: At baseline, then 1 × per week [18] through the end of Week 6 (Day 42)							**Starting Week 7 (Day 43):** Inpatients: 2 × per week [18] ≥2 days apart until resolution, then 1 × per week Outpatients: 1 × per week until resolution, then at study visits	
Visual assessment of urine by Hemostick (outpatients only)			At baseline, then daily through the end of Week 6 (Day 42) or resolution (whichever occurs earlier), then 1 × per week							**Starting Week 7 (Day 43):** 2 × per week ≥2 days apart until resolution, then 1 × per week	
Collection of PBMCs for banking of human genetic DNA and plasma [13, 19]			X	X	X	X	X		X	X	X
Acute GVHD evaluation [20]		X	X	X	X		X		X	X	X
Chronic GVHD evaluation [20]			X							X	X
Randomization [21]			X								
Distribution of subject cards			X								
Study treatment administration [22]			X		X						
Post-infusion monitoring [23]			X		X						
12-Lead ECG		X	X [24]		X [24]						X

Note: Study visits should occur at the study site. If this is not possible, home health visits may be performed as agreed with the Sponsor.

1. Participants may complete an optional Pre-Screening Visit that will be conducted from 14 days prior to the randomization visit to the day of the randomization visit. A separate Pre-Screening consent form is available for this purpose.
2. All screening and baseline assessments must be performed prior to study treatment administration.
3. The Day 0 samples to be sent to the central laboratory must be collected <24 hours prior to study treatment administration. Screening assessments may also be considered baseline assessments if they were done <24 hours prior to study treatment administration.
4. Prior to conducting any study-related activities, written informed consent/assent to participate in the study must be provided by the participant and/or participant's legal guardian. The Pre-Screening ICF is separate from the ICF that is signed at the Screening Visit for study participation.
5. Data will be collected from all participants who consent to participate.
6. Analgesic use will be collected daily on a medication log for inpatients and pain medication log within the ePRO system for outpatients.
7. See Section 8.1 for details on adverse event reporting.
8. If necessary, home health visits may substitute a body system assessment in place of a complete physical examination.
9. Height will be measured at screening only. Weight will be assessed at the screening, baseline, Week 2, and Week 24 visits.
10. Includes body temperature, blood pressure, heart rate, and respiration rate and will be measured after resting for 5 minutes. Pulse oximetry to be collected only on Day 0 and Week 2 study visits prior to study treatment administration.
11. Participants must be trained on the clinical outcome assessments (see Appendix B) at the Screening Visit. Adherence to the required clinical outcome assessments should be reviewed with the participant at each study visit.
12. The HLA types of the participant and HCT donor(s) will be obtained from the medical record.
13. For blood sampling volumes and sampling schedule by body weight, please refer to Appendix C.
14. Central or local laboratory results including those obtained as standard of care may be used to determine eligibility.
15. DNA for viral sequencing/genotyping will be extracted from the blood and urine samples collected for viral load determination. In the event of viral recurrence, viral sequence/genotype at baseline will be compared with that at the time of recurrence. Viral DNA isolated from blood and urine samples will be stored for potential future sequencing/genotyping. Target viruses are BKV, AdV, CMV, HHV-6, JCV, and EBV.
16. A serum pregnancy test will be performed at screening for all participants of childbearing potential. A urine or serum pregnancy test must be performed <24 hours before each infusion and at the end of study visit for participants of childbearing potential. A negative result must be confirmed prior to administration of each infusion. These tests may be performed at the local laboratory.
17. FSH will be tested for women of nonchildbearing potential who are postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.
18. The Bedi assessment with urinalysis may be performed more frequently (as unscheduled visits) if needed to evaluate for resolution of macroscopic hematuria.
19. Blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Human genetic DNA will be extracted from the PBMC fraction. This will be stored for potential future evaluation of VST persistence by T-cell receptor sequencing. The plasma fraction will be stored for potential future evaluation of cytokines and/or other humoral markers of inflammation/immune function.
20. If any participant develops GVHD, they may receive standard GVHD treatment at the discretion of the Investigator. Staging and grading of acute GVHD will be reported using MAGIC guidelines. Response to treatment will be assessed as per CIBMTR modifications to the CIBMTR response index. Manifestations of chronic GVHD and response to treatment will be assessed as per National Institutes of Health consensus guidelines for chronic GVHD.
21. Randomization will occur after all eligibility criteria are met, after all screening procedures are complete, and prior to study treatment administration.
22. All participants will receive [redacted] infusions of either PSL or placebo separated by [redacted]. Administering the [redacted] as early as feasible within this window is encouraged. Based on body weight at screening, participants <40 kg will receive [redacted] or placebo, participants ≥40 kg will receive [redacted] or placebo. As GVHD is a theoretical safety concern, the incidence and severity of GVHD will be monitored during the study. No participants will receive a [redacted] infusion (PSL or placebo) if they develop worsening GVHD (ie, relative to baseline GVHD) at the proposed time for infusion of the [redacted].

23. Participants will be monitored closely and must remain in the clinic for ≥1 hour after the end of study treatment administration. Vital signs, including body temperature, blood pressure, heart rate, and respiration rate, as well as pulse oximetry will be measured within 5 minutes after the final flush has been administered, and at 15, 30, 45, and 60 minutes (±5 minutes of each of these time points) after the final flush.
24. The ECG is to be performed ≤1 hour after study treatment administration.

AdV = adenovirus; BKV = BK virus; CIBMTR = Center for International Blood and Marrow Transplant Research; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; ePRO = electronic patient-reported outcome; ET = Early Termination; FSH = follicle-stimulating hormone; GVHD = graft versus host disease; HCT = hematopoietic cell transplant; HHV-6 = human herpesvirus 6; HLA = human leukocyte antigen; I/E = inclusion and exclusion; JCV = JC virus; LFT = liver function test; MAGIC = Mount Sinai Acute GVHD International Consortium; NA = not applicable; PBMC = peripheral blood mononuclear cell; VST = virus-specific T cell.

APPENDIX B: CLINICAL OUTCOME ASSESSMENTS BY AGE GROUP

Study Week		**Baseline**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)		**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Assessment	**Age Ranges (Years) [2]**								
Children <3 years									
Visual assessment of urine by Hemostick (outpatients only)		At baseline, then daily through the end of Week 6 (Day 42) or resolution (whichever occurs earlier), then 1 × per week							**Starting Week 7 (Day 43):** 2 × per week ≥2 days apart until resolution, then 1 × per week
PROMIS® Parent Proxy Pain Behavior Short Form		X	Daily						Weekly to Week 24
Pain medication log		X	Outpatient: daily by participant/caregiver Inpatient: daily by study staff						Outpatient: weekly by participant/caregiver Inpatient: weekly by study staff
CGIS (severity of HC)		X	Daily						Weekly to Week 24
CGIC (change in HC)		X	Daily						Weekly to Week 24
EQ-5D-Y Proxy Version 1	[3]	X	Weekly						Weeks 8, 12, 16, and 24
Children 3 to 11 years									
Visual assessment of urine by Hemostick (outpatients only)		At baseline, then daily through the end of Week 6 (Day 42) or resolution (whichever occurs earlier), then 1 × per week							**Starting Week 7 (Day 43):** 2 × per week ≥2 days apart until resolution, then 1 × per week
Wong-Baker FACES pain scale		X	Daily						Weekly to Week 24
Pain medication log		X	Outpatient: collected daily by participant/caregiver Inpatient: collected daily by study staff						Outpatient: collected weekly by participant/caregiver Inpatient: collected weekly

Study Week		**Baseline**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)		**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
									by study staff
PGIS (severity of HC)	[4]	X	Daily						Weekly to Week 24
CGIC/PGIC (change in HC)	3 to 7 (CGIC); 8 to 11 (PGIC) [4]	X	Daily						Weekly to Week 24
EQ-5D-Y Proxy Version 1	3 to 7 [3]	X	Weekly						Weeks 8, 12, 16, and 24
EQ-5D-Y	8 to 11	X	Weekly						Weeks 8, 12, 16, and 24
Adolescents ≥12 years and adults									
Visual assessment of urine by Hemostick (outpatients only)		At baseline, then daily through the end of Week 6 (Day 42) or resolution (whichever occurs earlier), then 1 × per week							**Starting Week 7 (Day 43):** 2 × per week ≥2 days apart until resolution, then 1 × per week
Selected BPIC SD items		X	Daily						Weekly to Week 24
Pain medication log		X	Outpatient: daily by participant/caregiver Inpatient: daily by study staff						Outpatient: weekly by participant/caregiver Inpatient: weekly by study staff
Selected ICSI items		X	Weekly						Weeks 8, 12, 16, and 24
PGIS (severity of HC) [4]		X	Daily						Weekly to Week 24
PGIC (change in HC) [4]		X	Daily						Weekly to Week 24
EQ-5D-5L		X	Weekly						Weeks 8, 12, 16, and 24

Note: For participants for whom a COA is not available in an approved, validated translation, that COA will not be administered.

1. The Day 0 assessments must be performed within 24 hours prior to study treatment administration.
2. The age category selected for these assessments will be based upon the age of the participant at the time of informed consent/assent.
3. The EQ-5D-Y Proxy Version 1 is recommended for children 4 to 7 years of age. Data for children <4 years of age will also be collected using the EQ-5D-Y Proxy Version 1, but these results will be analyzed separately from the results for children 4 to 7 years of age.
4. Age-appropriate versions of the PGIS will be administered to those 3 to 7 years of age, 8 to 11 years of age, and ≥12 years of age. Age-appropriate versions of the PGIC will be administered to those 8 to 11 years of age and ≥12 years of age. The CGIC will be administered to caregivers of children <8 years of age. The CGIS will be administered to children <3 years of age.

BPIC SD = Bladder Pain/Interstitial Cystitis Symptom Diary; CGIC = Caregiver Global Impression of Change; CGIS = Caregiver Global Impression of Severity; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; EQ-5D-Y = EuroQol 5 Dimensions for Younger Patients; ET = Early Termination; HC = hemorrhagic cystitis; ICSI = Interstitial Cystitis Symptoms Index; NA = not applicable; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System.

APPENDIX C: BLOOD VOLUME TABLE AND SAMPLING SCHEDULE

Study blood sampling volumes and sampling schedule by body weight are described in the tables below.

Blood Volume (mL) Drawn for Study Assessments: Adult and Pediatric Participants ≥40 kg

Study Week	Baseline	Week 1	Week 2	Week 3	Week 4	Total, First 4 Weeks	Week 5	Week 6	Total, First 8 Weeks	Week 12	Week 24	Total, 24 weeks
Study Day	**0**	**7**	**14**	**21**	**28**	**NA**	**35**	**42**	**NA**	**84**	**168**	**NA**
Visit Window (Days)	**NA**	**±2**	**±3**	**±2**	**±3**	**NA**	**±3**	**±3**	**NA**	**±28**	**±28**	**NA**
Assessment												
Hematology	3	3	3	3	3	15	3	3	21	3	3	27
Clinical chemistry	7	7	7	7	7	35	7	7	49	7	7	63
Viral load (plasma)	24	24	24	24	24	120	24	24	168	24	24	216
EBV viral load (PBMC)	8	8	8	8	8	40	8	8	56	8	8	72
Banked PBMC DNA	8	8	8	8	8	40	0	8	48	8	8	64
Totals	**50**	**50**	**50**	**50**	**50**	**250**	**42**	**50**	**342**	**50**	**50**	**442**

DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; NA = not applicable: PBMC = peripheral blood mononuclear cell.

Blood Volume (mL) Drawn for Study Assessments: Pediatric Participants ≥30 kg to <40 kg

Study Week	Baseline	Week 1	Week 2	Week 3	Week 4	Total, First 4 Weeks	Week 5	Week 6	Total, First 8 Weeks	Week 12	Week 24	Total, 24 weeks
Study Day	**0**	**7**	**14**	**21**	**28**	**NA**	**35**	**42**	**NA**	**84**	**168**	**NA**
Visit Window (Days)	**NA**	**±2**	**±3**	**±2**	**±3**	**NA**	**±3**	**±3**	**NA**	**±28**	**±28**	**NA**
Assessment												
Hematology	2	2	2	2	2	10	2	2	14	2	2	18
Clinical chemistry	4	4	4	4	4	20	4	4	28	4	4	36
Viral load (plasma)	12	12	12	12	12	60	12	12	84	12	12	108
EBV viral load (PBMC)	8	8	8	8	8	40	8	8	56	8	8	72
Banked PBMC DNA	8	8	8	8	8	40	0	8	48	8	8	64
Totals	**34**	**34**	**34**	**34**	**34**	**170**	**26**	**34**	**230**	**34**	**34**	**298**

DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; NA = not applicable; PBMC = peripheral blood mononuclear cell.

Blood Volume (mL) Drawn for Study Assessments: Pediatric Participants ≥20 kg to <30 kg

Study Week	Baseline	Week 1	Week 2	Week 3	Week 4	Total, First 4 Weeks	Week 5	Week 6	Total, First 8 Weeks	Week 12	Week 24	Total, 24 weeks
Study Day	**0**	**7**	**14**	**21**	**28**	**NA**	**35**	**42**	**NA**	**84**	**168**	**NA**
Visit Window (Days)	**NA**	**±2**	**±3**	**±2**	**±3**	**NA**	**±3**	**±3**	**NA**	**±28**	**±28**	**NA**
Assessment												
Hematology	2	2	2	2	2	10	2	2	14	2	2	18
Clinical chemistry	4	4	4	4	4	20	4	4	28	4	4	36
Viral load (plasma)	12	12	12	12	12	60	0	12	72	12	12	96
EBV viral load (PBMC)	8	0	8	0	8	24	0	8	32	8	8	48
Banked PBMC DNA	8	8	8	8	8	40	0	8	48	8	8	64
Totals	**34**	**26**	**34**	**26**	**34**	**154**	**6**	**34**	**194**	**34**	**34**	**262**

DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; NA = not applicable; PBMC = peripheral blood mononuclear cell.

Blood Volume (mL) Drawn for Study Assessments: Pediatric Participants ≥10 kg to <20 kg

Study Week	Baseline	Week 1	Week 2	Week 3	Week 4	Total, First 4 Weeks	Week 5	Week 6	Total, First 8 Weeks	Week 12	Week 24	Total, 24 weeks
Study Day	**0**	**7**	**14**	**21**	**28**	**NA**	**35**	**42**	**NA**	**84**	**168**	**NA**
Visit Window (Days)	**NA**	**±2**	**±3**	**±2**	**±3**	**NA**	**±3**	**±3**	**NA**	**±28**	**±28**	**NA**
Assessment												
Hematology	2	2	2	2	2	10	2	2	14	2	2	18
Clinical chemistry	4	4	4	4	4	20	4	4	28	4	4	36
Viral load (plasma)	8	0	8	0	8	24	0	8	32	8	8	48
EBV viral load (PBMC)	4	0	0	0	0	4	0	0	4	0	4	8
Banked PBMC DNA	4	0	4	0	4	12	0	4	16	4	4	24
Totals	**22**	**6**	**18**	**6**	**18**	**70**	**6**	**18**	**94**	**18**	**22**	**134**

DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; NA = not applicable; PBMC = peripheral blood mononuclear cell.

Blood Volume (mL) Drawn for Study Assessments: Pediatric Participants <10 kg

Study Week	Baseline	Week 1	Week 2	Week 3	Week 4	Total, First 4 Weeks	Week 5	Week 6	Total, First 8 Weeks	Week 12	Week 24	Total, 24 weeks
Study Day	**0**	**7**	**14**	**21**	**28**	**NA**	**35**	**42**	**NA**	**84**	**168**	**NA**
Visit Window (Days)	**NA**	**±2**	**±3**	**±2**	**±3**	**NA**	**±3**	**±3**	**NA**	**±28**	**±28**	**NA**
Assessment												
Hematology	2	2	2	0	2	8	0	2	10	2	2	14
Clinical chemistry	2.5	2.5	2.5	0	2.5	10	0	2.5	12.5	2.5	2.5	17.5
Viral load (plasma)	8	0	4	0	4	16	0	8	24	8	8	40
Banked PBMC DNA	2	0	2	0	0	4	0	2	6	2	2	10
Totals	**14.5**	**4.5**	**10.5**	**0**	**8.5**	**38**	**0**	**14.5**	**52.5**	**14.5**	**14.5**	**81.5**

DNA = deoxyribonucleic acid; NA = not applicable; PBMC = peripheral blood mononuclear cell.

Blood Sampling Notes:

1. Starting with Baseline assessments, blood samples are to be sent to the central laboratory for analysis. In order to ensure that the volumes collected are within the guidelines for maximum blood volumes, the volumes collected vary by the weight of the participant. Additionally, in order to minimize blood volumes collected, blood samples sent to the local laboratory as part of standard of care should be used for eligibility purposes (ie, Screening assessments) whenever possible.
2. Plasma viral load assays:
    a. The following viruses will be assayed: BK virus (BKV), adenovirus (AdV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), and JC virus (JCV).
    b. Viral deoxyribonucleic acid (DNA) isolated from these samples will be stored for potential future sequencing/genotyping.
    c. Pediatric sample volumes are reduced relative to the full volume required in adults. As a consequence, repeat/confirmatory assays using these samples may not be performed in the event of an unanticipated assay failure in the laboratory.
    d. If the volume of plasma available in the laboratory for viral load assay is limited, the viral load assays will be prioritized as follows (highest priority to lowest priority): BKV, AdV, CMV, HHV-6, JCV. In some instances, an individualized prioritization may be required and will be communicated to the central laboratory by the Sponsor.
3. Peripheral blood mononuclear cell (PBMC) Epstein-Barr virus (EBV) viral load assay:
    a. EBV viral load in blood will be assayed in PBMC and not in plasma.
4. Banked PBMC DNA:
    a. Blood collected in cell preparation tubes will be processed to generate PBMC and plasma fractions.
    b. The PBMC fraction will be used to process human genetic DNA which will be cryopreserved for potential future evaluation of virus-specific T cell persistence by DNA sequencing (PBMC fraction).
    c. The plasma fraction will be cryopreserved for potential future evaluation of cytokines and/or other humoral markers of inflammation/immune function.
5. For pediatric participants, blood sampling requirements for the study have been minimized by reducing the volume per sample collected, and by omitting collection at certain time points.

APPENDIX D: CLINICAL LABORATORY ANALYTES

Clinical Chemistry Panel [1]

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatine kinase	Creatinine [2, 3]
Cystatin C [3]	Direct bilirubin
Glucose	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	

1. Central or local laboratory results including those obtained as standard of care may be used to determine eligibility. Blood samples from Day 0 (pre-infusion baseline) and onward must be collected for analysis at the central laboratory.
2. For determination of study eligibility: creatinine clearance using the Cockcroft-Gault equation for adult participants, eGFR using the Schwartz equation for pediatric participants.
3. For the exploratory objective evaluating renal function over the 24-week study period, eGFR will be estimated using creatinine and cystatin C alone and in combination.

eGFR = estimated glomerular filtration rate.

Sources: Laskin BL, Denburg MR, Furth SL, et al. The natural history of BK polyomavirus and the host immune response after stem cell transplantation. *Clin Infect Dis*. 2019;pii:ciz1194. doi: 10.1093/cid/ciz1194. [Epub ahead of print] (see Reference 46); and Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012 Jul 5;367(1):20-9.

Hematology (Central Laboratory)

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Viral Load in Blood and Urine (Central Laboratory)

Adenovirus	BK virus
Cytomegalovirus	Epstein-Barr virus
Human herpesvirus 6	JC virus

Note: When viral load determination is performed in the laboratory, residual viral DNA will be stored for potential viral sequencing and genotyping in the event of recurrent infection.

Note: Viral load determination at screening may be performed at a local or central laboratory for the purpose of determining eligibility. Blood and urine from Day 0 (pre-infusion baseline) and onward must be collected for viral load analysis at the central laboratory. Additional post-infusion samples may be collected, as clinically indicated.

DNA = deoxyribonucleic acid.

Urinalysis

Blood (if positive, reflex to microscopy)	Leukocyte esterase

Stool Specimen (Central Laboratory)

Adenovirus	Cytomegalovirus

Note: If a stool specimen is clinically indicated, stool samples will also be sent to the central laboratory for research purposes.

Cerebrospinal Fluid Sample (Central Laboratory)

Cytomegalovirus	Human herpesvirus 6
JC virus	

Note: If a cerebrospinal fluid sample is clinically indicated, samples will also be sent to the central laboratory for research purposes. Cerebrospinal fluid samples required for clinical care of the participant take precedence over these research-related evaluations.

Other Laboratory Assessments

Serum pregnancy test [1]	Urine pregnancy test [1]
Follicle-stimulating hormone [2]	Peripheral blood mononuclear cells (PBMCs) and plasma [3]

1. For participants of childbearing potential only. A serum (human chorionic gonadotropin) pregnancy test will be performed at screening. A urine or serum pregnancy test must be performed <24 hours before each infusion and at the end of study visit for participants of childbearing potential. A negative result must be confirmed prior to administration of each infusion. These tests may be performed at the local laboratory.
2. Follicle-stimulating hormone will be tested at screening for women of nonchildbearing potential who are postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.
3. At each time point indicated in Appendix A, blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Human genetic DNA will be extracted from the PBMC fraction. The DNA from PBMC and plasma fractions will be cryopreserved for potential future evaluation of virus-specific T cell persistence (PBMC fraction) and for future evaluation of cytokines and/or other humoral markers of inflammation/immune function (plasma fraction).

DNA = deoxyribonucleic acid; PBMC = peripheral blood mononuclear cell.

APPENDIX E: GRAFT VERSUS HOST DISEASE SCALES

MAGIC Criteria for Staging and Grading of Acute Graft Versus Host Disease

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (Stool Output/Day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day. Child: <10 mL/kg per day or <4 episodes/day.
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day. Child: 10-19.9 mL/kg per day or 4-6 episodes/day.
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	-	Adult: 1000-1500 mL/day or 5-7 episodes/day. Child: 20-30 mL/kg per day or 7-10 episodes/day.
3	Maculopapular rash >50% BSA	6.1-15 mg/dL	-	Adult: >1500 mL/day or >7 episodes/day. Child: >30 mL/kg per day or >10 episodes/day.
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL	-	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Note: Overall clinical grade (based on most severe target organ involvement):

Grade 0: No Stage 1 to 4 of any organ.

Grade I: Stage 1 to 2 skin without liver, upper GI, or lower GI involvement.

Grade II: Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI.

Grade III: Stage 2 to 3 liver and/or Stage 2 to 3 lower GI, with Stage 0 to 3 skin and/or Stage 0 to 1 upper GI.

Grade IV: Stage 4 skin, liver, or lower GI involvement, with Stage 0 to 1 upper GI.

BSA = body surface area; GI = gastrointestinal; GVHD = graft versus host disease.

Source: Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10.

Response Definitions for Acute Graft Versus Host Disease

Response Term	Definition
CR	Complete resolution of all signs and symptoms of GVHD in all organs without intervening salvage therapies.
PR	Improvement of 1 stage in 1 or more organs involved by GVHD without progression in others.
Mixed response	Improvement in at least 1 involved organ with progression or newly developed GVHD in 1 or more organs.
Progression	Worsening in 1 or more organs by 1 or more stage without improvement in any involved organ.
NR	No improvement or deterioration in any organ within 14 days of therapy initiation.

CR = complete response; GVHD = graft versus host disease; NR = no response; PR = partial response.

Source: Center for International Blood & Marrow Transplant Research (CIBMTR). Clinical trial endpoints for participants with acute GVHD. May 2009.
https://www.cibmtr.org/Meetings/Materials/GVHDworkshop/GvHD%20Workshop%20Library/08_Alousi_FDAaGVHDwrkshp_May09.pdf. Accessed 09 Nov 2020.

National Institutes of Health Global Severity of Chronic Graft Versus Host Disease

Mild Chronic GVHD	Moderate Chronic GVHD	Severe Chronic GVHD
1 or 2 organs involved with no more than score 1 plus lung score 0	3 or more organs involved with no more than score 1 or at least 1 organ (not lung) with a score of 2 or lung score 1	At least 1 organ with a score of 3 or lung score of 2 or 3

Note: Key points:

In skin: higher of the 2 scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity.

If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.

If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes), the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

GVHD = graft versus host disease.

Source: Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host-Disease: I. The 2014 Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant*. 2015;21:389-401.e1.

National Institutes of Health Response Determinations for Chronic Graft Versus Host Disease

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

%FEV1 = percent predicted forced expiratory volume in the first second; ALT = alanine aminotransferase; GI = gastrointestinal; NIH = National Institutes of Health; PFT = pulmonary function test; P-ROM = photographic range of motion; ULN = upper limit of normal.

Source: Lee ST, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21(6):984-999.

APPENDIX F: CYTOKINE RELEASE SYNDROME SCALE

For participants who have a presumptive diagnosis of cytokine release syndrome (CRS) based on the clinical judgement of the Investigator, the CRS should be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for CRS shown in the table below rather than by CTCAE. The ASTCT consensus grading was developed for chimeric antigen receptor (CAR)-T cell therapies in which sustained engagement between CAR-T cells and targeted malignant cells is expected, leading to substantial rates of CRS. By contrast, CRS remains only a theoretical concern for virus-specific T cells.

CRS is defined as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end organ dysfunction. (For additional details, see Appendix G below.)

Symptoms of Cytokine Release Syndrome by Grade

Grade **CRS Parameter**	**1**	**2**	**3**	**4**
Fever [a]	≥38.0°C	≥38.0°C	≥38.0°C	≥38.0°C
With				
Hypotension	None	Not requiring vasopressors.	Requiring vasopressors with or without vasopressin.	Requiring multiple vasopressors (excluding vasopressin).
And/or [b]				
Hypoxia	None	Requiring low-flow nasal cannula (oxygen delivered at ≤6 L/minute) or blow-by.	Requiring high-flow nasal cannula (oxygen delivered at >6 L/minute), facemask, nonrebreather mask, or Venturi mask.	Requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation).

Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

Note: Grade 5 CRS is defined as death due to CRS in which another cause is not the principal factor leading to the outcome.

a. Fever is defined as temperature ≥38.0°C not attributable to any other cause. In participants who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.

Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

APPENDIX G: MONITORING FOR AND MANAGEMENT OF CYTOKINE RELEASE SYNDROME

The following recommendations have been adapted from recommendations for patients receiving chimeric antigen receptor (CAR)-T cells who develop cytokine release syndrome (CRS).[1] CRS is common following CAR-T cell therapy, but remains a theoretical concern following infusion of virus-specific T cells (VSTs). No cases of CRS were observed in 58 participants in the phase 2 CHARMS study of VSTs for viral infections following allogeneic hematopoietic cell transplant (HCT).[2] Nevertheless, Investigators should remain vigilant for the signs and symptoms of CRS, particularly during the first four weeks following VST infusion, and should be prepared to treat participants immediately for CRS should it develop. Investigators should also counsel participants to seek immediate medical attention if they develop concerning clinical findings. At the first sign of CRS, immediately evaluate the participant for hospitalization and institute treatment as outlined below or according to treatment protocols in use at the study site. CRS typically begins within 1 to 14 days (median 2 to 3 days) after CAR-T cell therapy.[3]

It is also important to note that the common symptoms of CRS are not unique to CRS and clinicians must be cautious and exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress, such as an overwhelming infection.[4]

Treatment of Cytokine Release Syndrome

CRS Grade	CRS Severity	Management
1	Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
2	CRS requiring mild intervention (≥1 of the following): • High fever • Hypoxia • Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
3 to 4	CRS requiring moderate to aggressive intervention (≥1 of the following): • Hemodynamic instability despite intravenous (IV) fluids and vasopressor support • Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation • Rapid clinical deterioration	Administer high-dose and/or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. Administer tocilizumab: • Patient weight <30 kg: 12 mg/kg IV over 1 hour • Patient weight ≥30 kg: 8 mg/kg IV over 1 hour (maximum dose 800 mg) If there is no clinical improvement, repeat tocilizumab after a minimum interval of 8 hours. If there is no response to a second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS. Limit to a maximum total of 4 doses of tocilizumab. If there is no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or if there is worsening at any time, administer methylprednisolone 2 mg/kg IV as an initial dose, then 2 mg/kg IV per day until vasopressors and high-flow oxygen are no longer needed, then taper.

CRS = cytokine release syndrome; IV = intravenous.

References:

1. KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion, prescribing information. https://www.novartis.us/sites/www.novartis.us/files/kymriah.pdf. Accessed on 09 Nov 2020.
2. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2017;35(31):3547-3557.
3. Porter DL and Maloney DG. Cytokine release syndrome (CRS). Post TW, ed. UpToDate. Waltham, MA. Updated 06 Apr 2020. https://www.uptodate.com/contents/cytokine-release-syndrome-crs. Accessed on 09 Nov 2020.
4. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

APPENDIX H: CONTRACEPTIVE REQUIREMENTS

Effective methods of contraception for use in this study are:

a. Intrauterine device.

b. Stable dose of hormonal birth control, such as those listed below, for at least 3 months prior to enrollment.

- Hormonal contraceptive tablets.
- Injectable hormonal contraceptives.
- Implanted hormonal contraceptives.
- Cutaneous contraceptive patches.
- Intravaginal hormonal contraceptive rings.

c. At least 1 barrier method. Effective barrier methods for use in this study are:

- Male or female condom.
- Diaphragm.

A female is considered to be of "childbearing potential" if she has experienced menarche and is not permanently sterile or postmenopausal (postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause and with a serum follicle-stimulating hormone test result in the postmenopausal range). Surgically sterile females (eg, status post-hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) may enter the study with historical documentation of the surgical procedure and a negative pregnancy test at study entry. If a female participant has a male partner who has had surgery to prevent pregnancy (vasectomy), that will be considered evidence of effective contraception for the purpose of this study, provided: a) that the male partner is the sole sexual partner of the participant, and b) historical documentation of the procedure is provided.

In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy for the entire duration of the study and for 90 days after the last dose of study treatment. Abstinence (celibacy) should only be used as a contraceptive method if it is in line with the participant's usual and preferred lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method of contraception. If at any point a previously celibate participant chooses to become heterosexually active during the time period for use of contraceptive measures specified above, he/she is responsible for initiating effective contraceptive measures as defined above.

Signature Page for AVM-003-HC Protocol v5.0 23Feb2022
VV-CLIN-000106 v3.0

Approval Task	[redacted] 23-Feb-2022 20:43:43 GMT+0000

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VV-CLIN-000106 v3.0