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Official Title:

Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, with Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation

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CLINICAL STUDY PROTOCOL

Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, with Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation

Investigational Product: Posoleucel (ALVR105)
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IND: 27955
EudraCT: 2021-003450-22

Sponsor:
AlloVir
1100 Winter Street
Waltham, MA 02451
United States
Telephone: +1-617-433-2605
Fax: +1-339-204-9528

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Amendment 3: 21 September 2023
Amendment 4: 30 November 2023

SIGNATURE PAGE

STUDY TITLE:

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

[redacted]
AlloVir

[redacted]
AlloVir

[redacted]
AlloVir

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 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

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1 SYNOPSIS

TITLE: Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, with Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation

PROTOCOL NUMBER: P-105-303

INVESTIGATIONAL PRODUCT: Posoleucel (ALVR105)

PHASE: 3

RATIONALE:

During the period of immune recovery after allogeneic hematopoietic cell transplant (allo-HCT), viral infections and reactivations, including those with adenovirus (AdV), are an important cause of morbidity and mortality. One out of 3 children and approximately 6% of adults are reported to have an AdV infection within 6 months post allo-HCT (Sedláček 2019). Progression to AdV disease is associated with significant morbidity and mortality rates of up to 50% in this population (Zecca 2019). Preliminary safety and efficacy data of posoleucel for the treatment of opportunistic viral infections common to immunocompromised allo-HCT patients, including AdV, were recently generated from a Phase 2 proof-of-concept study (Tzannou 2017).

This Phase 3, multicenter, randomized, double-blind, placebo-controlled study will assess the safety and efficacy of posoleucel for the treatment of AdV infection in pediatric and adult allo-HCT recipients receiving standard of care (SoC).

OBJECTIVES AND ENDPOINTS:

Objectives	Endpoints
Primary Efficacy	
• To compare the percent of participants who have clearance of AdV viremia at Day 29 in participants receiving posoleucel and SoC to that in participants receiving placebo and SoC.	• Proportion of participants with undetectable viremia (less than lower limit of quantitation [LLOQ]) at Day 29.
Primary Safety	
• To determine the safety and tolerability of posoleucel by analyzing the incidence and severity of treatment-emergent adverse events (TEAEs), including individual AEs of special interest (AESIs).	• Incidence and severity of TEAEs, including individual AESIs, during the study.

Key Secondary Efficacy	
• To determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses during the study.	• Proportion of participants with disease progression or non-relapse mortality[1] during the study. Progression is defined as: ○ progression from viremia to target organ disease (for participants without target organ disease at screening), or ○ progression of target organ disease (for participants with target organ disease at screening).
Other Secondary Efficacy	
• To evaluate the effect of posoleucel on AdV viremia over a 28-day period.	• Proportion of participants with undetectable viremia (less than LLOQ) at Day 29 in participants: ○ without AdV disease at screening. ○ with AdV disease at screening. • Time-averaged area under the concentration-time curve (AAUC) for plasma AdV viremia (log_{10} copies/mL AdV DNA) as assayed by quantitative polymerase chain reaction (qPCR) through Day 29 for all participants. • AAUC for plasma AdV viremia (log_{10} copies/mL AdV DNA) as assayed by qPCR through Day 29 for participants with no target organ disease at screening.
• To determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses by Day 29.	• Proportion of participants with disease progression or non-relapse mortality[1] by Day 29. Progression is defined as: ○ progression from viremia to target organ disease (for participants without target organ disease at screening), or ○ progression of target organ disease (for participants with target organ disease at screening).
• To determine the percentage of participants who achieve AdV viremia <400 copies/mL AdV DNA.	• Proportion of participants who achieve AdV viremia <400 copies/mL AdV DNA at Day 29.
• To assess the effect of posoleucel on time to clearance of AdV viremia.	• Time to undetectable AdV viremia (less than LLOQ).

• To evaluate the proportion of participants who have recurrence of viremia (≥10,000 copies/mL AdV DNA) and/or target organ disease during the study (among participants who had clearance of AdV viremia).	• Proportion of participants with AdV disease recurrence during the study among participants who had clearance of AdV viremia (prior to any cross-over).
• To evaluate the proportion of participants who are target organ disease-free at Day 29 and at the end of the study.	• Proportion of participants who are target organ disease-free at Day 29 and at the end of the study.
Exploratory Efficacy and Safety	
• To assess length of hospital stay, days spent in the intensive care unit (ICU), hospital re-admission, the need for mechanical ventilation, and the need for supplemental oxygen.	• Number of days in the hospital (for any reason including, but not limited to, AdV) during the study. • Number of days in the hospital due to AdV-related infection. • Number of hospitalizations/re-hospitalizations for any reason during the study. • Number of days spent in the ICU during the study. • Proportion of participants who need mechanical ventilator support, and number of days ventilator support is required during the study. • Proportion of participants who require supplemental oxygen to maintain SpO_2 >90%, and number of days supplemental oxygen is required during the study.
• To evaluate the persistence of posoleucel cells.	• Persistence of posoleucel cells.
• To determine the viral re-activation and disease occurrence due to BK virus (BKV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), or John Cunningham virus (JCV).	• Proportion of participants who develop viremia and/or clinical disease (per Investigator assessment) by Day 29 (due to BKV, CMV, HHV-6, EBV, and/or JCV) for those participants without viremia at randomization. • Proportion of participants with resolution of viremia by Day 29 (due to BKV, CMV, HHV-6, EBV, and/or JCV) for those participants with viremia at randomization.

• To evaluate non-relapse and all-cause mortality.	• Non-relapse mortality[1] at Week 24. • All-cause mortality at Week 24. • Death due to AdV disease.
• To determine the percent of participants who have clearance of AdV in a) stool, and b) nasopharyngeal swab at Day 29.	• Proportion of participants with undetectable AdV viral load (less than LLOQ) in a) stool, and b) nasopharyngeal swab at Day 29.
• To assess the effect of posoleucel on time to resolution of AdV in stool.	• Time to undetectable AdV viral load (less than LLOQ) in stool.
• To determine the percent of participants with a decrease in AdV viremia of at least 2 $\log_{10}$ copies/mL AdV DNA from randomization at Day 29.	• Proportion of participants with a decrease in AdV viremia of at least 2 $\log_{10}$ copies/mL AdV DNA from randomization at Day 29.
• To explore the correlation between magnitude of AdV viremia and progression or non-relapse mortality[1].	• Comparison of AdV viral load versus progression/non-relapse mortality[1].
• To explore the correlation between clearance of AdV viremia and progression or non-relapse mortality[1].	• Comparison of the rates of progression/non-relapse mortality[1] in those participants who demonstrate AdV viremia clearance versus those who do not.
• To assess the age-appropriate impact on quality of life.	• Change in the European Quality of Life 5 dimensions (EQ-5D) at Day 29 and Week 24.

1. Non-relapse mortality is defined as death without relapse/recurrence post allo-HCT.

Abbreviations: AAUC = time-averaged area under the concentration-time curve; AdV = adenovirus; AEs = adverse events; AESIs = adverse events of special interest; allo-HCT = allogeneic hematopoietic stem cell transplant; BKV = BK virus; CMV = cytomegalovirus; CRS = cytokine release syndrome; EQ-5D = European Quality of Life 5 dimension; GVHD = graft versus host disease; HHV-6 = human herpesvirus 6; JCV = John Cunningham virus; LLOQ = lower limit of quantitation; qPCR = quantitative polymerase chain reaction; SoC = standard of care.

POPULATION:

Inclusion Criteria

Patients must meet all of the following criteria in order to be eligible for enrollment into the study. Screening laboratory criteria can be confirmed using local or central laboratories.

1. Male or female of any age.
2. Has undergone allogeneic (including umbilical cord) cell transplantation ≥21 days prior to dosing and has demonstrated engraftment with an absolute neutrophil count >500/mm^3, AND has one of the following:
    a. AdV viremia DNA ≥10,000 copies/mL at screening, OR
    b. Two consecutive and rising AdV viremia DNA results of ≥1,000 copies/mL at screening, AND
        i. has absolute lymphocyte count <180/mm^3, OR
        ii. has received T cell depletion, OR
        iii. had a cord blood transplant.
3. Males and females of childbearing potential who engage in heterosexual intercourse must agree to use contraception as detailed in Appendix 5 of this protocol and refrain from donating sperm or eggs for at least 90 days after treatment completion.
4. Willing and able to provide signed informed consent.
5. Has an HLA type matching with at least 1 suitably matched and available posoleucel VST line for infusion.

Exclusion Criteria

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

1. Grade 3 or higher acute GVHD (see Appendix 6 for information on acute GVHD grading and severity).
2. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone dose >0.5 mg/kg/day or equivalent). Patients actively undergoing corticosteroid tapering during Screening may randomize and dose once they have reached ≤ 1.0 mg/kg/day with Medical Monitor approval, with the expectation that the corticosteroid taper will continue.
3. Has either of the following laboratory parameters at screening:
    a. Aspartate aminotransferase and alanine aminotransferase serum levels ≥5 times the upper limit of normal (ULN), OR
    b. Direct bilirubin serum levels ≥3 times the ULN.

    Exception: Patients with elevations of these laboratory parameters may be included if these elevations are attributed to AdV hepatitis and are not considered attributable to other etiologies.

4. Relapse of primary malignancy, or any other active malignancy, except for non-melanoma skin cancer. Malignancies that are slow growing and/or stable may be allowed with Medical Monitor approval.

5. Grade 4 diarrhea (ie, life-threatening consequences with urgent intervention indicated) regardless of attribution ongoing or within 7 days prior to randomization.

6. Uncontrolled viral (other than AdV), bacterial, or fungal infection(s) leading to hemodynamic instability or radiologic or laboratory evidence attributable to worsening disease.

7. Requirement for fraction of inspired oxygen (FiO_2) >0.5 (ie, 50%) to maintain arterial oxygen saturation >90% (via pulse oximetry) or need for mechanical ventilation, except for planned procedures or surgeries with Medical Monitor approval. For guidance on estimating fraction of inspired oxygen, see Appendix 9.

8. Prior therapy with anti-thymocyte globulin, alemtuzumab (Campath®), or other immunosuppressive T cell monoclonal antibodies within 28 days prior to dosing.

9. Prior donor lymphocyte infusion or CD34+ stem cell infusion within 21 days prior to dosing.

10. Use of vasopressors within 7 days prior to randomization.

11. Use of any investigational antiviral agent, including brincidofovir, within 7 days prior to randomization. Maribavir and letermovir for CMV will be allowed.

12. Pregnant or lactating female unwilling to discontinue nursing prior to randomization.

13. Any condition that, in the opinion of the Investigator, would compromise the safety of the patient, would prevent full participation in this study, or would interfere with the evaluation of any study endpoints.

14. History of severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) allergy to any component of posoleucel (including human serum albumin and dimethyl sulfoxide) or history of severe (CTCAE Grade ≥3) prior reactions to blood product transfusions.

15. Positive for SARS-CoV-2 virus at screening.
    Exception: Patients who test positive for SARS-CoV-2 at screening and who have a recent prior positive test may be enrolled if they have no clinical or radiological manifestations of COVID-19 and if the Investigator and Medical Monitor concur on their enrollment.

STUDY DESIGN AND DURATION:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of posoleucel as compared to placebo for the treatment of AdV infection in pediatric and adult recipients of HCT with AdV infections receiving SoC.

Approximately 82 eligible patients may be randomized [redacted] to receive [redacted] sequential infusions of posoleucel or placebo (separated by [redacted]). Randomization will be stratified [redacted]

[redacted]

The presence or absence of adenovirus target organ disease at screening will be determined initially by the Investigator (using the criteria in Appendix 8) and reviewed subsequently by the Adjudication Committee for analysis purposes.

The Primary Study Period is 4 weeks (28 days) for evaluation of efficacy, including the primary endpoint, plus 20 weeks for safety follow-up, for a total study duration of 24 weeks. For participants who cross-over, the Cross-Over Period is 4 weeks (28 days), plus 20 weeks for safety follow-up. Participants who experience recurrence and receive an additional dose will have safety follow-up for 20 weeks after the final dose.

At Day 29, all participants will be assessed for the primary endpoint, virologic response.

Option for Cross-Over

Participants who progress to active target organ disease or whose existing target organ disease progresses (assessed by the Investigator and Sponsor Medical Monitor and based on the criteria in Appendix 8) between Day 29 and Week 10 will be considered to have experienced progression and will have the option to be crossed over to the alternate treatment arm. Participants can cross over before Day 29 only if they progress with target organ disease as adjudicated by the Adjudication Committee. For potential cases of premature cross-over (ie, prior to Day 29), participants will be expected to have received both infusions of study treatment before evaluation by the Adjudication Committee. Cross-over participants will receive the alternate treatment to which they were originally randomized, posoleucel or placebo [redacted] infusions separated by [redacted]), but study treatment will remain blinded. Participants must meet the following eligibility criteria to cross-over: participant must not have evidence of acute GVHD Grade 3 or higher (Exclusion Criterion 1), must not be receiving ongoing therapy with high-dose systemic corticosteroids >0.5 mg/kg/day prednisone or equivalent unless approved by Medical Monitor (Exclusion Criterion 2), and must not have experienced a severe infusion-related reaction (Grade ≥3) with the prior doses of study treatment (posoleucel or placebo).

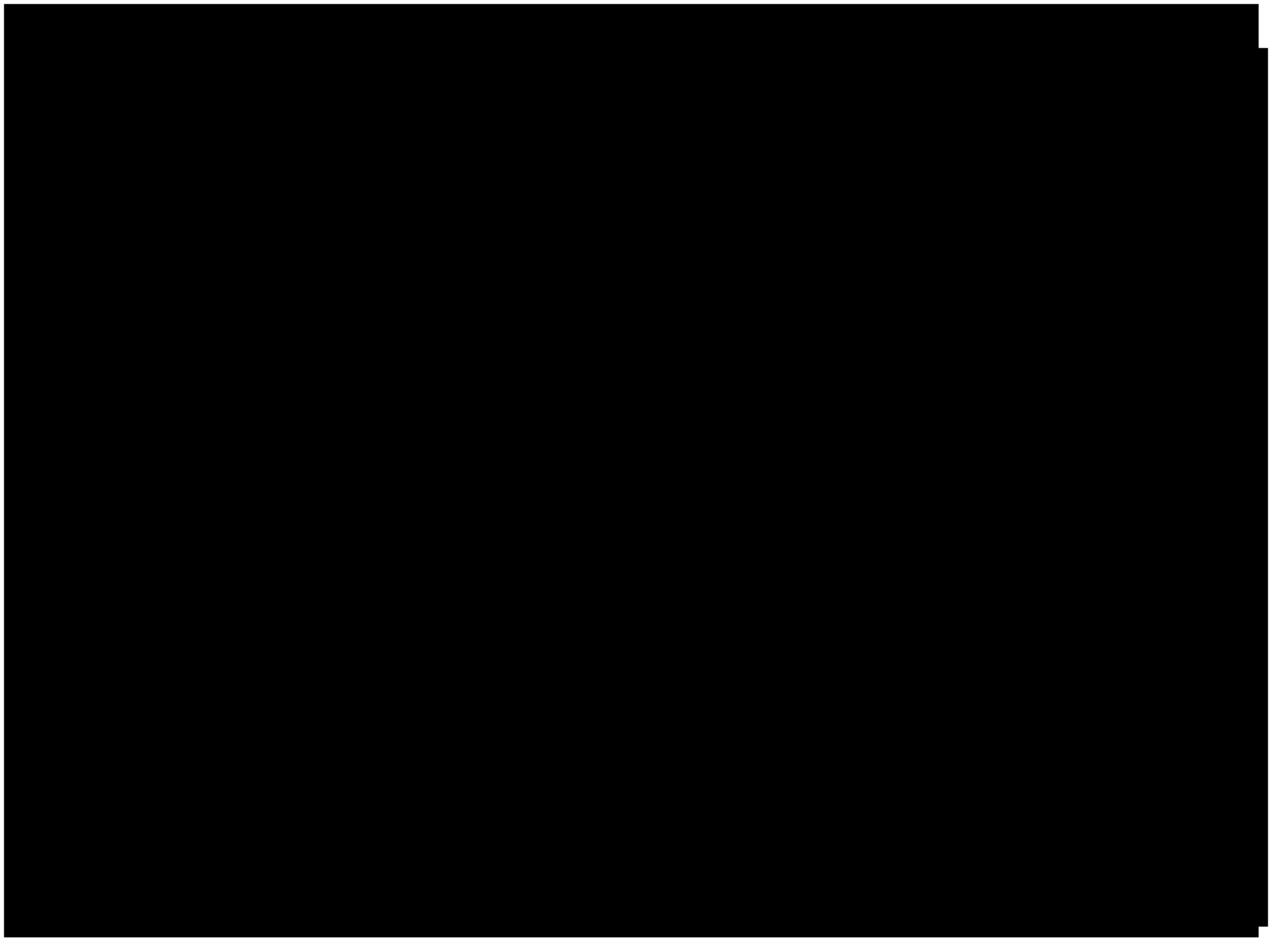
If the participant receives any antiviral drugs in violation of the protocol during the study, that participant will be included in the primary analysis, but will not be eligible for cross-over. Follow-up will be continued for safety and persistence of the virus specific T cells (VSTs).

Participants must meet all of the cross-over eligibility criteria by Week 10 of the Primary Study Period to enter the Cross-Over Period. A new baseline (Day 1' of the Cross-Over Period) will be established at the time of the first cross-over infusion. At Day 29' of the Cross-Over Period, participants will be assessed for clinical and virologic response. The participants will then have 20 weeks of safety follow-up, for a total duration of 24 weeks for the Cross-Over Period. The maximum study duration for participants who cross over is 34 weeks, including up to 10 weeks in the Primary Study Period and 24 weeks in the Cross-Over Period.

Participants who cross over are not eligible to receive treatment for recurrence (described below).

Recurrence

Participants who demonstrate viral clearance by Day 29 of the Primary Study Period but later exhibit a clinically significant recurrence of AdV viremia (ie, ≥10,000 copies/mL AdV DNA at the central laboratory) and/or progression of or to active organ disease, will be eligible for an additional dose of the last received therapy (posoleucel or placebo) for recurrence prior to 20 weeks. These participants will continue to have safety follow-up for an additional 20 weeks after administration of the additional dose. The visit in which the participant receives the additional dose for recurrence should mimic the assessments performed on Day 15. Participants who receive an additional dose for recurrence will be monitored using the schedule as specified in the Primary Study Period schedule of events starting at the Week 5 visit, which should occur 1 week after infusion of the additional dose. This applies even if the participant completed any of these visits prior to receiving the additional dose.



A participant is considered to have completed the study if he/she has completed the Week 24 visit of the Primary Study Period (for participants who do not cross over) or the Week 24' visit of the Cross-Over Period (for participants who cross over). Participants who have a recurrence and receive a third dose are considered to have completed the study once they have completed their 20 Week safety follow up following their third study dose.

The end of the study is defined as completion of the final visit for the final participant.

Oversight Committees

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor participant safety and evaluate prespecified interim analyses for futility and sample size re-estimation (SSRE).

An independent and blinded Adjudication Committee will adjudicate progression from AdV viremia to target organ disease and progression of AdV target organ disease during the study.

Assessment Overview

Viral load of AdV will be measured at the central laboratory at each visit from blood and stool samples and at Day -21 to -1 and Day 29 from nasopharyngeal swab. Blood specimens collected should be analyzed by the central laboratory for screening purposes, however, local laboratory results available up to 5 days prior to and/or during screening will be acceptable to determine eligibility. For the inclusion criterion requiring two consecutive and rising AdV viremia results exceeding 1,000 copies/mL, the two consecutive viremia results used to determine eligibility must have been assayed at the same laboratory, preferably the central laboratory however, local lab results are also acceptable (with Medical Monitor approval). This process is expected to expedite the randomization and dosing of participants whose clinical status may rapidly deteriorate. A central laboratory blood sample must be collected prior to dosing on Day 1. All study analyses will continue to be performed using viral load data from the central laboratory.

Participants will be followed weekly for viremia and viral load in the stool while symptomatic. For participants who require intubation and/or undergo bronchoscopy with bronchoalveolar lavage (BAL), a sample of BAL fluid should, when possible, be obtained for AdV viral load determination at the central laboratory. For participants who develop symptoms and/or signs of possible AdV-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 AdV viral load determination should, when possible, be sent to the central laboratory. In all cases, BAL and CSF samples required for routine clinical care of the patient take precedence over these study-related evaluations.

The presence or absence of abnormalities consistent with lower respiratory tract infection on chest X-ray and/or CT scan as assessed by the local radiologist should be documented at screening (obtained no more than 10 days prior to dosing) and at Day 29 (±3 days). If no routine clinical radiological imaging of the chest is available at either of these timepoints, a chest X-ray should be obtained (chest CT scan is not a study-mandated procedure; however, the results of chest CT scan[s] performed as part of a participant's standard clinical care may be used for the purposes of the study). For those participants who cross over, chest imaging as described above should be documented within 7 days prior to Day 1' of the Cross-Over Period and at Day 29' (±3 days) of the Cross-Over Period. If the Day 29 imaging from the Primary Study Period falls within the 7-day window prior to cross over, this imaging need not be repeated prior to the participant entering the Cross-Over Period (ie, the Day 29 imaging will serve as the baseline imaging for the Cross-Over Period). All chest X-rays and/or CT scans will also be submitted for central reading, which will be used for analysis purposes.

For evaluation of potential renal, urinary tract, and pancreatic manifestations of AdV infection, a urinalysis (dipstick and microscopy) will be obtained at the local laboratory at Day 1 and Day

29, and serum amylase and lipase levels will be included in the clinical chemistry evaluations at the central laboratory.

Blood samples will be obtained from all participants for the measurement of posoleucel cell persistence through Week 24.

Repeat or unscheduled samples may be taken based on symptoms, for safety reasons, or for technical issues with the samples.

Safety assessments will include adverse event (AE) monitoring, clinical laboratory assessments, physical examinations, vital sign measurements, and 12-lead electrocardiograms (ECGs). Additional safety assessments may be performed throughout the duration of the study if clinically indicated.

AEs of special interest (AESIs) include the following:

- Acute or chronic GVHD
- CRS
- Infusion-related reactions (IRRs)
- Graft failure and rejection

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Posoleucel will be frozen in a cryopreservation medium containing [redacted]

Posoleucel will be supplied in [redacted] cryovials at a concentration of [redacted]

Placebo is a [redacted]. Upon thaw, under normal light conditions without magnification, both posoleucel and placebo are clear straw-colored liquids.

Posoleucel is to be administered at a fixed cell dose based on weight, as [redacted] sequential infusions separated by [redacted]

Dose # (Study Day)	**Criteria**
Dose 1 (Study Day 1/ Study Day 1')	Dose levels for all infusions will be as follows: • [redacted] • [redacted]

Dose 2 (Study [redacted])	All participants will receive a 2nd dose based on response after the 1st dose: • If AdV viral load decrease from baseline is ≥0.5 $\log_{10}$ copies/mL AdV DNA at Days 8 or 11/Days 8' or 11', the participant will receive a second dose with the same VST line or placebo lot as the first dose, • If AdV viral load decrease from baseline is <0.5 $\log_{10}$ copies/mL AdV DNA at Days 8 or 11/Days 8' or 11', the participant will receive a second dose with a new VST line from a different donor or placebo from a different lot.

For participants who receive an additional dose for recurrence, the additional dose will be from the same VST line or placebo lot and include the same number of cells as the second dose. An additional dose for recurrence can only be administered after Day 29 of the Primary Study Period (the primary endpoint), but prior to 20 weeks. Participants who receive an additional dose for recurrence are not eligible for subsequent cross-over, and participants who have previously entered the Cross-Over Period are not eligible for a subsequent additional dose.

Participants who have experienced new onset of GVHD, worsening of GVHD, or a Grade ≥3 IRR will be excluded from redosing with additional doses of blinded study treatment. Reference Section 8.1 for Discontinuation of Study Treatment for details.

STATISTICAL ANALYSES:

In order to control the overall type 1 error rate, a sequential approach will be used to analyze the primary and key secondary efficacy endpoints, with undetectable viremia (less than LLOQ) at Day 29 of the Primary Study Period as the primary efficacy endpoint, followed by progression from viremia to target organ disease (for participants without target organ disease at screening), progression of target organ disease (for participants with target organ disease at screening), or non-relapse mortality during the study as the key secondary efficacy endpoint.

Summary statistics will be presented by treatment group for the Primary Study Period and by cross-over group (Posoleucel/Placebo or Placebo/Posoleucel) based on the treatments received for the Cross-Over Period.

Analysis Populations

Intent-to-Treat (ITT) Population

The ITT Population will include all randomized participants. Participants will be analyzed according to the randomized study treatment.

Modified Intent-to-Treat (mITT) Population

The mITT Population will include all randomized participants who receive at least one dose of posoleucel or placebo. All efficacy endpoints will be analyzed based on the mITT Population, and these analyses will be considered the primary analyses of efficacy. Participants will be analyzed according to the randomized study treatment.

Per Protocol Population

The Per Protocol (PP) Population will include all ITT participants who receive any amount of posoleucel or placebo and who do not have any major protocol deviations deemed potentially to impact efficacy or its evaluation, as defined in the statistical analysis plan (SAP). All efficacy endpoints will also be analyzed based on the PP Population, and these analyses will be considered secondary analyses of efficacy. Participants will be analyzed according to the randomized study treatment.

Safety Population

The Safety Population will include all participants who receive any amount of posoleucel or placebo and have at least 1 post-treatment safety assessment. All safety analyses will be based on the Safety Population, and participants will be analyzed according to the actual study treatment received.

Efficacy

All efficacy endpoints will be analyzed and formally compared between randomized treatment groups using statistical tests based on data from the Primary Study Period. In addition, for purposes of complete reporting, results for these endpoints will be reported, if appropriate, for data from the Cross-Over Period by treatment received in the Cross-Over Period, but no formal comparisons or statistical tests will be made.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint, undetectable viremia (less than LLOQ) at Day 29 of the Primary Study Period, will be summarized by treatment group using the count and percentage, together with an exact (Clopper-Pearson) 95% confidence interval for the true percentage.

The null hypothesis is that the true percentage for posoleucel plus SoC is less than or equal to the true percentage for placebo plus SoC, and the alternative hypothesis is that it is greater. This endpoint will be analyzed using logistic regression. The model will include a term for treatment and the following covariates: level of viremia at Baseline (≥10,000 copies/mL or <10,000 copies/mL AdV DNA), age (≥12 years or <12 years), and absolute lymphocyte count at Baseline. The null hypothesis will be tested using a one-sided test of the effect of treatment at the 0.025 significance level.

Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy endpoint will be tested sequentially after the primary endpoint reaches statistical significance. The key secondary efficacy endpoint, progression from viremia to target organ disease (for participants without target organ disease at screening), progression of target organ disease (for participants with target organ disease at screening), or non-relapse mortality during the study, will be analyzed in the same manner as the primary efficacy endpoint.

For AdV viral endpoints at Day 29 or Week 4 visit, a 14-day window will be applied to the Day 29 visit. The last observed plasma AdV DNA result through Day 29 + 14 days (up to 43 days post first infusion) will be used for the analysis. Participants who cross over on or before Day 29 will be treated as failure.

Other Secondary Efficacy Endpoint Analyses

Following the key secondary analysis, progression from viremia to target organ disease and progression of target organ disease will be analyzed as separate subgroups in a step-down manner. If any participants cross over prior to Day 29, they will be considered as having had progression, because the necessary condition for cross-over is that the participant progressed to active target organ disease (for participants without target organ disease at screening) or experienced progression of target organ disease (for participants with target organ disease at screening).

The AAUC for plasma AdV viremia (log_{10} copies/mL AdV DNA), as assayed by qPCR, through Day 29 of the Primary Study Period will be summarized by treatment group using descriptive statistics (number of non-missing observations, mean, median, standard deviation, minimum, and maximum). The null hypothesis for this endpoint is that the true mean for posoleucel is greater than or equal to the true mean for placebo, and the alternative hypothesis is that it is less. The null hypothesis will be tested using a one-sided, two-sample t-test with a 0.025 significance level.

The following secondary efficacy endpoints will each be analyzed in the same manner as the primary efficacy endpoint: achieving AdV viremia <400 copies/mL AdV DNA at Day 29 of the Primary Study Period and AdV disease recurrence during the study among participants who had clearance of AdV viremia (prior to any cross-over).

If there are any cross-over participants who, prior to cross-over, had clearance of AdV viremia, these participants will be considered failures (ie, had recurrence) for the AdV disease recurrence during the study endpoint.

The Kaplan-Meier estimated median time to resolution of AdV viremia will be presented for each treatment group, together with the 95% confidence interval for the true median. The number and percentage of censored and uncensored participants will be presented by treatment group. The null hypothesis for this endpoint is that the true distributions of time to resolution of AdV viremia are equal for posoleucel and placebo, and the alternative hypothesis is that the true distributions are different, with the time to resolution of AdV viremia being less for posoleucel. The null hypothesis will be tested using a one-sided log-rank test with a 0.025 significance level.

Cross-Over Analyses

Undetectable viremia (less than LLOQ) at Day 29' of the Cross-Over Period will be summarized by cross-over group using counts and percentages, together with exact (Clopper-Pearson) 95% confidence intervals for the true percentages. Achieving AdV viremia <400 copies/mL AdV DNA at Day 29' of the Cross-Over Period and AdV disease recurrence during the 24-week Cross-Over Period among participants who had clearance of AdV viremia (after cross-over) will be analyzed in the same way.

The AAUC for plasma AdV viremia (log_{10} copies/mL AdV DNA), as assayed by qPCR, through Week 24' of the Cross-Over Period will be summarized by cross-over group using descriptive statistics.

The Kaplan-Meier estimated median time to resolution of AdV viremia will be presented for each cross-over group, together with the 95% confidence interval for the true median. Cross-over participants who do not achieve resolution of AdV viremia will be censored as of their last

study visit. The number and percentage of censored and uncensored participants will be presented by cross-over group.

Progression from viremia to target organ disease (for participants without target organ disease at screening, progression of target organ disease (for participants with target organ disease at screening), or non-relapse mortality during the 24-week Cross-Over Period will not be analyzed, because all cross-over participants must have already progressed to target organ disease prior to being crossed over.

Analysis of Safety

Safety will be analyzed and compared between treatment received based on data from the Primary Study Period. In addition, for purposes of complete reporting, safety will be reported for data from the Cross-Over Period by treatment received in the Cross-Over Period, but no comparisons will be made between the two treatments.

The primary safety endpoint is the incidence and severity of TEAEs, including individual AESIs, during the study. The safety profile will be further assessed based on changes in clinical laboratory assessments, vital signs, ECGs, and physical examinations. All safety analyses will be based on the Safety Population.

Safety analyses in general will be descriptive and will be presented by study period (Primary Study Period or Cross-Over Period) and treatment group or cross-over group in a tabular format. Categorical endpoints will be summarized using number and percentage of participants within each category. Continuous endpoints will be summarized descriptively with summary statistics (number of non-missing observations, mean, standard deviation, median, minimum, and maximum).

The number and percentage of participants with TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term for each treatment group/cross-over group. This will be done overall, by severity, and by relationship to treatment. Adverse events leading to discontinuation of the study, SAEs, and AESIs will be summarized by treatment group.

The incidence and severity of acute GVHD during the study, the incidence and severity of chronic GVHD during the study, the incidence and severity of CRS during the study, and the incidence and severity of any AESIs during the study will each be summarized by treatment group for the Primary Study Period and by cross-over group for the Cross-Over Period using counts and percentages.

SAMPLE SIZE DETERMINATION:

The required sample size is 82 participants based on the below specifications that have received at least 1 dose of posoleucel or PBO.

The sample size was determined based on the following specifications:

1. Superiority study comparing posoleucel plus SoC to placebo plus SoC
2. Primary endpoint is success or failure based on clearance of ADV viremia at Day 29 visit of the Primary Study Period
3. Allocation (posoleucel:placebo) is 1:1
4. Chi-square test
5. Two-sided alpha = 0.05
6. True success rate (defined as clearance of virus) for posoleucel = 0.55
7. True success rate (defined as clearance of virus) for placebo = 0.25
8. Power = 80%

A SSRE and futility analysis will be performed after approximately 40 participants have completed Day 29 of the Primary Study Period. Details of the SSRE and futility analysis will be provided in the SSRE Plan prior to conducting the interim analyses.

SITES: Approximately 50 clinical sites in the United States, Canada, and Europe.

SPONSOR:

AlloVir
1100 Winter Street
Waltham, MA 02451
United States
Telephone: +1-617-433-2605
Facsimile: +1-339-204-9528

2 SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities for Primary Study Period

Study Week (Primary Study Period)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (Primary Study Period)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days) Study Procedures	NA	NA	±2	±2	±3	±3	±3	±5	±5	±28	±28	±42	NA
Informed consent/assent	X												
I/E criteria	X	X											
Demographics and medical history [2]	X												
HLA match for cell line selection	X												
Randomization	X												
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 PCR virus assessment (nasal/ nasopharyngeal swab)	X												
FSH test [3]	X												
Pregnancy test [4]	X	X			X					X	X	X	X
Study treatment administration [5]		X			X								
Infusion site evaluation [6]		X			X								
Post-infusion monitoring [7]		X			X								
COA (EQ-5D) [8]		X					X			X		X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospital information [9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [10, 11]	X	X	X	X	X		X					X	X
Height and weight [12]	X	X										X	X
Vital signs including SpO_2 [11, 13]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [14]	X	X			X								
Chest X-ray and/or CT scan [15]	X						X						
Urinalysis [16]	X	X					X					X	X
Hematology and clinical chemistry [16]	X	X	X	X			X		X	X	X	X	X
Coagulation (PT, INR, and PTT)		X					X						

Study Week (Primary Study Period)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (Primary Study Period)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	NA	NA	±2	±2	±3	±3	±3	±5	±5	±28	±28	±42	NA
Study Procedures													
[16]													
Adenovirus viral load in blood and stool with viral DNA extraction and storage [16, 17]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adenovirus viral load in urine [16, 18]		X											
BKV, CMV, JCV, EBV, and HHV-6 viral load in blood [16, 19]	X	X			X		X		X	X	X	X	X
Adenovirus viral load in nasopharyngeal swab	X						X						
Adenovirus viral load in BAL fluid and/or CSF [16, 20]		X											
Bank PBMCs for VST persistence and plasma for cytokine evaluation [16, 21]		X			X		X		X	X	X	X	X
Acute GVHD evaluation [22]	X	X	X		X		X				X	X	X
Chronic GVHD evaluation [22]											X	X	X

Note: Participants may return to the clinical site more frequently as determined by their clinical condition at the discretion of the Investigator and in collaboration with the Medical Monitor.

1. An Early Termination Visit should be performed for any participant who discontinues the study early.
2. Medical history will include diagnosis of underlying disease requiring HCT, underlying disease state at the time of AdV diagnosis, type of donor and cell source of the transplant received, date of HCT, conditioning regimen, CMV serostatus, presence of GVHD, pulmonary function tests, and smoking status.
3. 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.
4. A serum pregnancy test will be performed at screening for females of childbearing potential. A serum or urine pregnancy test will be repeated prior to dosing on Day 1 for females of childbearing potential, only if the pregnancy test performed at screening was not completed within 48 hours prior to study treatment administration. A serum or urine pregnancy test will be performed within 48 hours prior to each additional study treatment administration (if applicable) and at the Week 10, Week 16, Week 24, and ET visits for females of childbearing potential. A negative pregnancy test result is required prior to dosing.
5. Participants randomized to the posoleucel group will receive posoleucel cells as an infusion. Participants randomized to the placebo group will receive an IV infusion of [redacted] All infusions will be administered IV over approximately [redacted] as a slow push. Participants will receive a second dose of blinded study treatment approximately [redacted] following the first dose.
6. Includes pain, tenderness, erythema, swelling, and induration. On infusion days, performed pre-dose and at 1 hour post-dose.
7. Participants will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs will be measured at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. Participants must also remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
8. EQ-5D may be performed up to 24 hours prior to study treatment administration.

9. Includes information on hospital admission and discharge, ICU transfer, oxygen supplementation, and ventilation.
10. A complete physical examination will be performed at screening. Abbreviated physical examinations will be performed at all subsequent visits.
11. On days when study treatment is administered, perform vital signs and physical examination before study treatment administration.
12. Height should be collected at screening only. Weight at screening should be used for all doses.
13. Vital signs include body temperature, heart rate, respiratory rate, SpO_2, and systolic and diastolic blood pressure. Vital signs will be collected after the participant has rested for at least 5 minutes in the supine position.
14. Performed within 1 hour after study treatment administration on [redacted]
15. All participants will have screening imaging performed within 10 days prior to dosing and analyzed locally as long as the imaging can be transmitted to the central reader. Images (chest X-ray and/or CT scan) obtained as part of a participant's standard clinical care may be used for the purposes of the study. If standard clinical imaging is not performed at these time-points, a chest X-ray should be performed for the purposes of the study.
16. Sample must be obtained prior to infusion of study treatment.
17. Diagnosis of AdV by blood and stool samples will be determined by the central laboratory. Samples will be stored for potential future genotypic or viral load analysis. Blood specimens collected locally within 5 days of screening will be acceptable to initiate screening activities; a central laboratory blood sample result should be available prior to dosing. Participants may be randomized and dosed (with Medical Monitor approval) based on local laboratory AdV viremia results if the central laboratory result(s) is not available at the time of intended dosing. Participants will be followed weekly for viremia and viral load in the stool while symptomatic. The screening, Day 1, and Day 29 collections of stool for AdV viral load should be collected in all participants, irrespective of GI symptoms. For all other timepoints, these samples are required to be collected if the patient has symptoms (eg, diarrhea). If the patient does not have symptoms at these visits, stool viral load should be collected if feasible.
18. While not a routine evaluation in this study, any participants who manifest clinical signs and/or symptoms of AdV hemorrhagic cystitis should have a urine sample sent to the central laboratory for determination of AdV urine viral load. For this subset of participants, AdV urine viral loads should be measured weekly at the central laboratory until resolution of hemorrhagic cystitis.
19. Blood for BKV, CMV, JCV, EBV, and HHV-6 viral load should be collected prior to study treatment administration.
20. For participants who require intubation and/or undergo bronchoscopy with BAL, a sample of BAL fluid should, when possible, be obtained for AdV viral load determination at the central laboratory. For participants who develop symptoms and/or signs of possible AdV-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 AdV viral load determination should, when possible, be sent to the central laboratory.
21. At each time point indicated, blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Genomic DNA will be extracted from the PBMC fraction. The genomic DNA from PBMC will be cryopreserved for potential future evaluation of VST persistence. The plasma fraction will be cryopreserved for potential future evaluation of cytokines and/or other humoral markers of inflammation/immune function. On Day 1 and Day 15, the sample should be collected pre-dose.
22. If any participant develops GVHD, that participant 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.

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; CBC = complete blood count; CIBMTR = Center for International Blood and Marrow Transplant Research; CMV = cytomegalovirus; COA = clinical outcome assessment; COVID-19 = coronavirus disease 2019; CSF = cerebrospinal fluid; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D = European Quality of Life 5 dimension; ET = Early Termination; FSH = follicle-stimulating hormone; GVHD = graft versus host disease; HCT = hematopoietic cell transplant; HLA = human leukocyte antigen; ICU = intensive care unit; I/E = inclusion and exclusion; IV = intravenous(ly); LFT = liver function test; MAGIC = Mount Sinai Acute GVHD International Consortium; NA = not applicable; PBMC = peripheral blood mononuclear cell; qPCR = quantitative polymerase chain reaction; SpO_2 = peripheral capillary oxygen saturation; VST = virus-specific T cell.

Table 2. Schedule of Activities for Cross-Over Period (Participants with AdV Target Organ Disease by Week 10 of the Primary Study Period)

Study Week (Cross-Over Period)	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (Cross-Over Period)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	NA	NA	±2	±2	±3	±3	±3	±5	±5	±28	±28	±42	NA
Study Procedures													
Cross-over I/E criteria [3]	X												
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [4]	X	X			X					X	X	X	X
Study treatment administration [5]		X			X								
Infusion site evaluation [6]		X			X								
Post-infusion monitoring [7]		X			X								
COA (EQ-5D) [8]		X					X			X		X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospital information [9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [10, 11]	X	X	X	X	X		X					X	X
Weight [12]	X	X										X	X
Vital signs including SpO_2 [11, 13]	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG [14]	X	X			X								
Chest X-ray and/or CT scan [15]	X						X						
Urinalysis [16]	X	X					X					X	X
Hematology and clinical chemistry [16]	X	X	X	X			X		X	X	X	X	X
Coagulation (PT, INR, and PTT) [16]		X					X						
Adenovirus viral load in blood and stool with viral DNA extraction and storage [16, 17]	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Week (Cross-Over Period)	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (Cross-Over Period)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	NA	NA	±2	±2	±3	±3	±3	±5	±5	±28	±28	±42	NA
Study Procedures													
Adenovirus viral load in urine [16, 18]		X											
BKV, CMV, JCV, EBV, and HHV-6 viral load in blood [16, 19]	X	X			X		X		X	X	X	X	X
Adenovirus viral load in nasopharyngeal swab [16]		X					X						
Adenovirus viral load in BAL fluid and/or CSF [16, 20]		X											
Bank PBMCs for VST persistence and plasma for cytokine evaluation [16, 21]		X			X		X		X	X	X	X	X
Acute GVHD evaluation [22]	X	X	X		X		X				X	X	X
Chronic GVHD evaluation [22]											X	X	X

Note: Participants may return to the clinical site more frequently as determined by their clinical condition at the discretion of the Investigator and in collaboration with the Medical Monitor.

1. If any of these evaluations have been completed within 10 days as part of the Primary Study Period, they do not have to be repeated.
2. An Early Termination Visit should be performed for any participant who discontinues the study early.
3. Participant must not have evidence of acute GVHD grade 3 or higher (Exclusion Criterion 1), must not be receiving ongoing therapy with high-dose systemic corticosteroids >0.5 mg/kg/day or equivalent unless approved by Medical Monitor (Exclusion Criterion 2), and must not have experienced a severe infusion-related reaction (Grade ≥3) with the prior doses of study treatment (posoleucel or placebo).
4. A serum pregnancy test will be performed at cross-over for females of childbearing potential. A serum or urine pregnancy test will be repeated prior to dosing on Day 1' for females of childbearing potential, only if the pregnancy test performed at cross-over was not completed within 48 hours prior to study treatment administration. A serum or urine pregnancy test will be performed within 48 hours prior to each additional study treatment administration (if applicable) and at the Week 10', Week 16', Week 24', and ET visits for females of childbearing potential. A negative pregnancy test result is required prior to dosing.
5. Participants who cross over to the posoleucel group will receive posoleucel cells as an infusion. Participants who cross over to the placebo group will receive an IV infusion of [redacted] All infusions will be administered IV over approximately [redacted] as a slow push. Participants will receive a second dose of blinded study treatment approximately [redacted] following the first dose.
6. Includes pain, tenderness, erythema, swelling, and induration. On infusion days, performed predose and at 1 hour postdose.
7. Participants will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs will be measured at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. Participants must also remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.

8. EQ-5D may be performed up to 24 hours prior to study treatment administration.
9. Includes information on hospital admission and discharge, ICU transfer, oxygen supplementation, and ventilation.
10. A complete physical examination will be performed at cross-over unless one has been completed within the past 3 days. Abbreviated physical examinations will be performed at all subsequent visits.
11. On days when study treatment is administered, perform vital signs and physical examination before study treatment administration.
12. Weight at cross-over should be used for all doses.
13. Vital signs include body temperature, heart rate, respiratory rate, SpO_2, and systolic and diastolic blood pressure. Vital signs will be collected after the participant has rested for at least 5 minutes in the supine position.
14. Performed within 1 hour after study treatment administration on [redacted]
15. All participants will have imaging performed and analyzed locally as long as the imaging can be transmitted to the central reader. Images (chest X-ray and/or CT scan) obtained as part of a participant's standard clinical care may be used for the purposes of the study. If standard clinical imaging is not performed at these time-points, a chest X-ray should be performed for the purposes of the study. For those participants who cross over, chest imaging should be documented within 7 days prior to Day 1' of the Cross-Over Period, and at Day 29' (±3 days) of the Cross-Over Period.
16. Sample must be obtained prior to infusion of study treatment.
17. Diagnosis of AdV by blood and stool samples will be determined by the central laboratory. Samples will be stored for potential future genotypic or viral load analysis. Participants will be followed weekly for viremia and viral load in the stool while symptomatic. The Day 1' and Day 29' collections of stool for AdV viral load should be collected in all participants, irrespective of GI symptoms. For all other timepoints, these samples are required to be collected if the patient has symptoms (eg, diarrhea). If the patient does not have symptoms at these visits, stool viral load should be collected if feasible.
18. While not a routine evaluation in this study, any participants who manifest clinical signs and/or symptoms of AdV hemorrhagic cystitis should have a urine sample sent to the central laboratory for determination of AdV urine viral load. For this subset of participants, AdV urine viral loads should be measured weekly at the central laboratory until resolution of hemorrhagic cystitis.
19. Blood for BKV, CMV, JCV, EBV, and HHV-6 viral load should be collected prior to study treatment administration.
20. For participants who require intubation and/or undergo bronchoscopy with BAL, a sample of BAL fluid should, when possible, be obtained for AdV viral load determination at the central laboratory. For participants who develop symptoms and/or signs of possible AdV-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 AdV viral load determination should, when possible, be sent to the central laboratory.
21. At each time point indicated, blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Genomic DNA will be extracted from the PBMC fraction. The genomic DNA from PBMC will be cryopreserved for potential future evaluation of VST persistence. The plasma fraction will be cryopreserved for potential future evaluation of cytokines and/or other humoral markers of inflammation/immune function. On Day 1' and Day 15', the sample should be collected pre-dose.
22. If any participant develops GVHD, that participant 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.

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; CBC = complete blood count; CIBMTR = Center for International Blood and Marrow Transplant Research; CMV = cytomegalovirus; COA = clinical outcome assessment; COVID-19 = coronavirus disease 2019; CSF = cerebrospinal fluid; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D = EuroQol – 5 Dimension; ET = Early Termination; GVHD = graft versus host disease; HCT = hematopoietic cell transplant; HLA = human leukocyte antigen; ICU = intensive care unit; I/E = inclusion and exclusion; IV = intravenous(ly); LFT = liver function test; MAGIC = Mount Sinai Acute GVHD International Consortium; NA = not applicable; PBMC = peripheral blood mononuclear cell; qPCR = quantitative polymerase chain reaction; SpO_2 = peripheral capillary oxygen saturation; VST = virus-specific T cell.

3 INTRODUCTION

AlloVir is developing posoleucel, a novel multivirus-specific cellular therapy, to treat and/or prevent a number of serious, virus-associated causes of morbidity and mortality after allogeneic hematopoietic stem cell transplant (allo-HCT), including those caused by infection or reactivation with BK virus (BKV; and the related polyomavirus JC virus [JCV]), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and adenovirus (AdV).

3.1 Study Rationale

Preliminary safety and efficacy data of posoleucel for the treatment of opportunistic viral infections common to immunocompromised allo-HCT patients, including AdV, were recently generated from a Phase 2 proof-of-concept study (CHARMS).

This Phase 3 clinical study will assess the safety and efficacy of posoleucel (as compared to placebo) for the treatment of AdV infection in pediatric and adult patients receiving standard of care following allo-HCT.

3.2 Background

Adenoviruses are a class of double-stranded DNA viruses, with over 50 immunologically distinct types that can infect humans. Adenoviruses are associated with a wide range of illnesses, from respiratory illnesses, such as the common cold and bronchitis, to illnesses impacting other organ systems. While AdV infections are generally controlled by T-cell immunity in immunocompetent individuals, infection more frequently progresses to end-organ involvement and disseminated disease in individuals who are immunocompromised.

During the period of immune recovery after allo-HCT, viral infections and reactivations, including those with AdV, are an important cause of morbidity and mortality.

One out of 3 children is reported to have an AdV infection within 6 months post allo-HCT (Sedláček 2019). Approximately 6% of adults have been reported to have an AdV infection within 6 months post allo-HCT, with a higher incidence in younger adults compared to older adults (Sedláček 2019). Progression to AdV disease is associated with significant morbidity and mortality rates of up to 50% (Zecca 2019).

There are no approved antiviral agents for AdV available in the United States (US), Canada, or Europe. Cidofovir or brincidofovir are often administered preemptively as treatment for AdV infection, although neither are approved for this indication. The optimum doses of cidofovir and brincidofovir have not been established, and treatment is associated with various toxicities. Brincidofovir is currently in development, but clinical data are limited and brincidofovir has not been approved for indications other than treatment of smallpox in the US (June 2021).

Since recovery of virus-specific T cells (VSTs) after hematopoietic cell transplantation (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 peripheral blood mononuclear cells (PBMCs) procured from healthy pre-screened (for

infectious agents and disease risk factors as mandated by Food and Drug Administration (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 human leukocyte antigen (HLA)-matched "off-the-shelf" product.

Posoleucel is a VST product that is specific for 5 viruses (AdV, BKV, CMV, EBV, and HHV-6). Since posoleucel is only partially matched with the recipient and donor cells, posoleucel cells are intended to circulate only until the patient regains immunocompetence following HCT engraftment and immune system repopulation. Therefore, posoleucel is 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.

A detailed description of the in vitro testing of posoleucel and available clinical data are provided in Sections 5 and 6, respectively, of the Investigator's Brochure (IB).

3.3 Benefit/Risk Assessment

Known and potential benefits and risks associated with participation in this study are summarized below.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of posoleucel may be found in the Investigator's Brochure.

3.3.1 Potential Benefits

A serious unmet medical need exists for patients experiencing AdV infection following allo-HCT. There are no FDA-, Health Canada-, 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 are associated with significant adverse effects. The CHARMS study and other related clinical studies strongly suggest that posoleucel 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 posoleucel efficacy in multiple opportunistic viral infections in allo-HCT patients, and its safety profile has the potential to be significantly better than that of standard, and inadequately effective, antiviral therapy.

3.3.2 Potential Risks

The main potential risks of administration are inflammation at sites of disease or graft versus host disease (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 in doses of ≥1 mg/kg/day. Therefore, if participants develop severe inflammatory reactions thought to be attributable to posoleucel, a therapeutic option is to administer methylprednisolone (1 to 2 mg/kg/day). In patients who develop skin rash or skin GVHD, excellent responses have been seen with administration of topical steroids.

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

All participants enrolled in the study (including children) are expected to have venous access catheters in place for both infusion and blood sampling relating to the treatment of their underlying disease and associated HCT procedures. Since study-related collection of blood samples and infusion of study treatment (posoleucel or placebo) will utilize catheters already in place for routine clinical care, there is minimal incremental risk posed by these study-related procedures. A detailed breakdown of the timepoints and blood volumes to be collected during the course of this study is provided in the Laboratory Manual. Since this study will enroll both adult and pediatric participants, there are different sampling schemes (and associated volumes) based on the participant's 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 wherever possible, and in some cases (eg, pediatric participants weighing <20 kg) collection of blood samples at certain timepoints has been eliminated entirely. This has been done in a manner that is expected to maintain the scientific integrity of the study while minimizing the risks to participants.

4 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy	
• To compare the percent of participants who have clearance of AdV viremia at Day 29 in participants receiving posoleucel and SoC to that in participants receiving placebo and SoC.	• Proportion of participants with undetectable viremia (less than lower limit of quantitation [LLOQ]) at Day 29.
Primary Safety	
• To determine the safety and tolerability of posoleucel by analyzing the incidence and severity of treatment-emergent adverse events (TEAEs), including individual Aes of special interest (AESIs).	• Incidence and severity of TEAEs, including individual AESIs, during the study.
Key Secondary Efficacy	
• To determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses during the study.	• Proportion of participants with disease progression or non-relapse mortality[1] during the study. Progression is defined as: ○ progression from viremia to target organ disease (for participants without target organ disease at screening), or ○ progression of target organ disease (for participants with target organ disease at screening).
Other Secondary Efficacy	
• To evaluate the effect of posoleucel on AdV viremia over a 28-day period.	• Proportion of participants with undetectable viremia (less than LLOQ) at Day 29 in participants: ○ without AdV disease at screening. ○ with AdV disease at screening. • Time-averaged area under the concentration-time curve (AAUC) for plasma AdV viremia (log_{10} copies/mL AdV DNA) as assayed by quantitative polymerase chain reaction (qPCR) through Day 29 for all participants. • AAUC for plasma AdV viremia (log_{10} copies/mL AdV DNA) as assayed by qPCR through Day 29 for participants with no target organ disease at screening.

• To determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses by Day 29.	• Proportion of participants with disease progression or non-relapse mortality[1] by Day 29. Progression is defined as: ○ progression from viremia to target organ disease (for participants without target organ disease at screening), or ○ progression of target organ disease (for participants with target organ disease at screening).
• To determine the percentage of participants who achieve AdV viremia <400 copies/mL AdV DNA.	• Proportion of participants who achieve AdV viremia <400 copies/mL AdV DNA at Day 29.
• To assess the effect of posoleucel on time to clearance of AdV viremia.	• Time to undetectable AdV viremia (less than LLOQ).
• To evaluate the proportion of participants who have recurrence of viremia (≥10,000 copies/mL AdV DNA) and/or target organ disease during the study (among participants who had clearance of AdV viremia).	• Proportion of participants with AdV disease recurrence during the study among participants who had clearance of AdV viremia (prior to any cross-over).
• To evaluate the proportion of participants who are target organ disease-free at Day 29 and at the end of the study.	• Proportion of participants who are target organ disease-free at Day 29 and at the end of the study.
Exploratory Efficacy and Safety	
• To assess length of hospital stay, days spent in the intensive care unit (ICU), hospital re-admission, the need for mechanical ventilation, and the need for supplemental oxygen.	• Number of days in the hospital (for any reason including, but not limited to, AdV) during the study. • Number of days in the hospital due to AdV-related infection. • Number of hospitalizations/re-hospitalizations for any reason during the study. • Number of days spent in the ICU during the study. • Proportion of participants who need mechanical ventilator support, and number of days ventilator support is required during the study. • Proportion of participants who require supplemental oxygen to maintain SpO_2 >90%, and number of days supplemental oxygen is required during the study.

• To evaluate the persistence of posoleucel cells.	• Persistence of posoleucel cells.
• To determine the viral re-activation and disease occurrence due to BK virus (BKV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), or John Cunningham virus (JCV).	• Proportion of participants who develop viremia and/or clinical disease (per Investigator assessment) by Day 29 (due to BKV, CMV, HHV-6, EBV, and/or JCV) for those participants without viremia at randomization. • Proportion of participants with resolution of viremia by Day 29 (due to BKV, CMV, HHV-6, EBV, and/or JCV) for those participants with viremia at randomization.
• To evaluate non-relapse and all-cause mortality.	• Non-relapse mortality[1] at Week 24. • All-cause mortality at Week 24. • Death due to AdV disease.
• To determine the percent of participants who have clearance of AdV in a) stool, and b) nasopharyngeal swab at Day 29.	• Proportion of participants with undetectable AdV viral load (less than LLOQ) in a) stool, and b) nasopharyngeal swab at Day 29.
• To assess the effect of posoleucel on time to resolution of AdV in stool.	• Time to undetectable AdV viral load (less than LLOQ) in stool.
• To determine the percent of participants with a decrease in AdV viremia of at least 2 $\log_{10}$ copies/mL AdV DNA from randomization at Day 29.	• Proportion of participants with a decrease in AdV viremia of at least 2 $\log_{10}$ copies/mL AdV DNA from randomization at Day 29.
• To explore the correlation between magnitude of AdV viremia and progression or non-relapse mortality[1].	• Comparison of AdV viral load versus progression/non-relapse mortality[1].
• To explore the correlation between clearance of AdV viremia and progression or non-relapse mortality[1].	• Comparison of the rates of progression/non-relapse mortality[1] in those participants who demonstrate AdV viremia clearance versus those who do not.
• To assess the age-appropriate impact on quality of life	• Change in the European Quality of Life 5 dimensions (EQ-5D) at Day 29 and Week 24.

1. Non-relapse mortality is defined as death without relapse/recurrence post allo-HCT.

Abbreviations: AAUC = time-averaged area under the concentration-time curve; AdV = adenovirus; Aes = adverse events; AESIs = adverse events of special interest; allo-HCT = allogeneic hematopoietic stem cell transplant; BKV = BK virus; CMV = cytomegalovirus; CRS = cytokine release syndrome; EQ-5D = European Quality of Life 5 dimension; GVHD = graft versus host disease; HHV-6 = human herpesvirus 6; JCV = John Cunningham virus; LLOQ = lower limit of quantitation; qPCR = quantitative polymerase chain reaction; SoC = standard of care.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of posoleucel as compared to placebo for the treatment of AdV infection in pediatric and adult recipients of HCT with AdV infections receiving SoC.

Approximately 82 participants at approximately 50 clinical sites in the US, Europe, and Canada who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled into the study and randomized [redacted] to receive posoleucel or placebo. Randomization will be stratified [redacted] It is expected that no more than 30% of participants, but at least 10% of participants, will be ≥18 years of age.

Enrollment of participants <1 year of age will occur once preliminary safety data are available from 5 participants ≥1 and ≤6 years of age. On 16May2023, the DSMB reviewed data from 6 participants aged 1-6 years that have completed through D29 and recommended opening enrollment to patients <1 year of age. An additional meeting will be held once 6 patients <1 year old have been enrolled and completed through D29 of the study.

Posoleucel is to be administered at a fixed cell dose based on weight, as [redacted] sequential infusions separated by [redacted] (see Section 7.1).

The Primary Study Period is 4 weeks (28 days) for evaluation of efficacy, including the primary endpoint, plus 20 weeks for safety follow-up, for a total study duration of 24 weeks. For participants who cross over, the Cross-Over Period is 4 weeks (28 days), plus 20 weeks for safety follow-up. Participants who experience recurrence and receive an additional dose will have safety follow-up for 20 weeks after the additional dose of study treatment.

At Day 29, all participants will be assessed for the primary endpoint, virologic response.

Option for Cross-Over

Participants who progress to active target organ disease or whose existing target organ disease progresses (assessed by the Investigator and Sponsor Medical Monitor and based on the criteria in Appendix 8) between Day 29 and Week 10 will be considered to have experienced progression and will have the option to be crossed over to the alternate treatment arm. Participants can cross over before Day 29 only if they progress as adjudicated by the Adjudication Committee. For potential cases of premature cross-over (ie, prior to Day 29), participants will be expected to have received both infusions of study treatment before evaluation by the Adjudication Committee. Cross-over participants will receive the alternate treatment to which they were originally randomized, posoleucel or placebo ([redacted] sequential infusions separated by [redacted] but study treatment will remain blinded. Participants must meet the following eligibility criteria to cross-over: participant must not have evidence of acute GVHD Grade 3 or higher (Exclusion Criterion 1), must not be receiving ongoing therapy with high-dose systemic corticosteroids >0.5 mg/kg/day prednisone or equivalent unless approved by Medical Monitor (Exclusion Criterion 2) and must not have experienced a severe infusion-related reaction (Grade ≥3) with the prior doses of study treatment (posoleucel or placebo).

If the participant receives any antiviral drugs in violation of the protocol during the study, that participant will be included in the primary analysis, but will not be eligible for cross-over. Follow-up will be continued for safety and persistence of the virus-specific T cells (VSTs).

Participants must meet all of the cross-over eligibility criteria by Week 10 of the Primary Study Period to enter the Cross-Over Period. A new baseline (Day 1' of the Cross-Over Period) will be established at the time of the first cross-over infusion. At Day 29' of the Cross-Over Period, participants will be assessed for clinical and virologic response. The participants will then have 20 weeks of safety follow-up, for a total duration of 24 weeks for the Cross-Over Period. The maximum study duration for participants who cross over is 34 weeks, including up to 10 weeks in the Primary Study Period and 24 weeks in the Cross-Over Period.

Participants who cross over are not eligible to receive treatment for recurrence (described below).

Recurrence

Participants who demonstrate viral clearance by Day 29 of the Primary Study Period but later exhibit a clinically significant recurrence of AdV viremia (ie, ≥10,000 copies/mL AdV DNA at the central laboratory) and/or progression of or to active organ disease, will be eligible for an additional dose of the last received therapy (posoleucel or placebo) for recurrence prior to 20 weeks. These participants will continue to have safety follow-up for an additional 20 weeks after administration of the additional dose. The visit in which the participant receives the additional dose for recurrence should mimic the assessments performed on [redacted] Participants who receive an additional dose for recurrence will be monitored using the schedule as specified in the Primary Study Period schedule of events starting at the Week 5 visit, which should occur 1 week after infusion of the additional dose. This applies even if the participant completed any of these visits prior to receiving the additional dose.

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

Figure 1. Summary of Study Design

Oversight Committees

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor participant safety and evaluate prespecified interim analyses for futility and sample size re-estimation.

An independent and blinded Adjudication Committee will adjudicate progression from AdV viremia to target organ disease and progression of AdV target organ disease during the study.

Clinical Sites

The Sponsor will ensure that sites selected for participation in this study adhere to the relevant safety standards of the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee of the International Society for Cell and Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) (JACIE).

5.2 Participant and Study Completion

Approximately 115 participants will be screened to achieve 82 randomly assigned to study treatment and dosed to obtain an estimated total of 41 participants per treatment group evaluable for the primary endpoint.

5.3 End of Study Definition

A participant is considered to have completed the study if he/she has completed the Week 24 visit of the Primary Study Period (for participants who do not cross over) or the Week 24' visit of the Cross-Over Period (for participants who cross over).

The end of the study is defined as completion of the final visit for the final participant.

All participants in this study will be approached for enrollment in a long-term registry study.

5.4 Scientific Rationale for Study Design

Patients of all ages are eligible for enrollment in this clinical study. The inclusion of pediatric patients in this study is justified for the following reasons: 1) one out of 3 children develop an AdV infection within 6 months of allo-HCT (Sedláček 2019); 2) progression to AdV disease is associated with significant morbidity and mortality rates of up to 50% in pediatric allo-HCT recipients (Zecca 2019); 3) there are no approved, efficacious antiviral therapies for the treatment of AdV infection; and 4) in the Phase 2 CHARMS study, 17 of 58 patients enrolled (29%) were <18 years of age, with the youngest age of 2 years old (Tzannou 2017). This previous clinical pediatric experience with posoleucel supports the inclusion of patients <18 years of age in this study.

The use of placebo in this clinical study is justified for the following reasons: 1) since the natural history of AdV infection in the allo-HCT population is variable and not readily predictable, a randomized controlled trial with placebo allows for an unbiased evaluation of the efficacy and safety of posoleucel, and 2) 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 AdV infection.

The cross-over design is justified for the following reasons: 1) allows a larger sample size of participants treated with posoleucel without increasing the number of enrolled participants; and 2) allowing participants to cross over ensures that blinding can be maintained until the study is complete.

For a variety of viral diseases, the amount and kinetics of virus levels in blood or plasma has been widely accepted as a surrogate for clinical events (eg, human immunodeficiency virus, hepatitis B virus, hepatitis C virus). In most cases, the goal of conventional small molecule antiviral therapy is suppression of viral replication to undetectable levels. In the recent US FDA Guidance Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease (May 2020), the use of CMV viremia as a validated surrogate endpoint in clinical trials is discussed. There is also evidence to suggest that adenoviremia also serves as a suitable surrogate endpoint to evaluate the antiviral activity of a cell-based immunotherapeutic anti-AdV agent.

The body of published data supports the concept that virological suppression translates into clinical benefit. This view is also robustly expressed in AdV consensus treatment guidelines such as those of ECIL-4 (Matthes-Martin 2012) and EBMT (Hiwarkar 2018), recommending pre-emptive therapy, which is based on a recognition of the surrogacy of viremia.

Since there are no approved antiviral therapies for the treatment of AdV, the kinetics of therapeutic viremia resolution are not established. Data from the CHARMS study, in which patients with persistent and/or recurrent viral infections were treated with posoleucel provide an indication of viral load kinetics that have informed the selection of the Day 29 post-treatment

timepoint for the evaluation of the primary efficacy outcome in the current study. In the CHARMS study, there were 13 participants with informative AdV viremia data; 9 of these participants demonstrated declines in viremia after administration of posoleucel. In all cases, these viremia responses were apparent by 4 weeks (ie, 28 days) of treatment with posoleucel. Accordingly, the evaluation at Day 29 (ie, 28 days after the initial infusion of posoleucel/placebo) has been selected for the primary efficacy outcome in the current study.

It is generally accepted that the magnitude and duration of AdV viremia contribute to the development of clinically relevant infections (Sedlacek 2019), and that the overall AdV viral burden (extent of viremia over time) is predictive of all-cause mortality in pediatric HCT recipients with AdV viremia (Zecca 2019). The levels of AdV viremia required for inclusion in this study have been selected because these are thresholds that place patients at risk for development of disseminated AdV disease and increased mortality (Hiwarkar 2018, Mynarek 2014) and are less likely to be associated with spontaneous resolution. Importantly, AdV unlike CMV or EBV, is a lytic virus so risk of recurrent infections once the virus has cleared is considered to be low. Nonetheless, to assess durability of response longer term data on viremia as well as signs and symptoms will be captured.

The durability of response in viremia will be evaluated after the Day 29 timepoint throughout the remainder of the study. This will be accomplished at the protocol-specified evaluations (including viral load determinations at the central laboratory) at Weeks 5, 6, 10, 16, and 24, and will be addressed specifically by the following two secondary efficacy endpoints: a) To determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses during the study, and b) To evaluate the proportion of participants who have recurrence of viremia (≥10,000 copies/mL AdV DNA) and/or target organ disease during the study (among participants who had clearance of AdV viremia).

5.5 Justification for Dose

Posoleucel is to be administered at a fixed cell dose based on weight. Fixed, weight-based doses were selected based on data from previous clinical studies in which posoleucel was well tolerated, safe, and effective.

The dose of posoleucel 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 [redacted] per infusion. A retrospective analysis of actual doses administered in the CHARMS study demonstrated that, on average, patients who weighed [redacted]

The VST line chosen for the second infusion of posoleucel may come from a different donor than the first infusion, depending on the AdV viral load following the first dose of posoleucel (see Section 7.1 for details). Providing posoleucel cells from a different donor in participants with a higher viral load after the first dose will increase the repertoire of T cells provided, which may increase the likelihood of responding to posoleucel treatment.

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be eligible for enrollment into the study. Screening laboratory criteria can be confirmed using local or central laboratories.

1. Male or female of any age.
2. Has undergone allogeneic (including umbilical cord) cell transplantation ≥21 days prior to dosing and has demonstrated engraftment with an absolute neutrophil count >500/mm^3, AND has one of the following:
    a. AdV viremia DNA ≥10,000 copies/mL at screening, OR
    b. Two consecutive and rising AdV viremia DNA results of ≥1,000 copies/mL at screening, AND
        i. has absolute lymphocyte count <180/mm^3, OR
        ii. has received T cell depletion, OR
        iii. had a cord blood transplant.
3. Males and females of childbearing potential who engage in heterosexual intercourse must agree to use contraception as detailed in Appendix 5 of this protocol and refrain from donating sperm or eggs for at least 90 days after treatment completion.
4. Willing and able to provide signed informed consent.
5. Has an HLA type matching with at least 1 suitably matched and available posoleucel VST line for infusion.

6.2 Exclusion Criteria

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

1. Grade 3 or higher acute GVHD (see Appendix 6 for information on acute GVHD grading and severity).
2. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone dose >0.5 mg/kg/day or equivalent). Patients actively undergoing corticosteroid tapering during Screening may randomize and dose once they have reached ≤ 1.0 mg/kg/day with Medical Monitor approval, with the expectation that the corticosteroid taper will continue.
3. Has either of the following laboratory parameters at screening:
    a. Aspartate aminotransferase and alanine aminotransferase serum levels ≥5 times the upper limit of normal (ULN), OR
    b. Direct bilirubin serum levels ≥3 times the ULN.

Exception: Patients with elevations of these laboratory parameters may be included if these elevations are attributed to AdV hepatitis and are not considered attributable to other etiologies.

4. Relapse of primary malignancy, or any other active malignancy, except for non-melanoma skin cancer. Malignancies that are slow growing and/or stable may be allowed with Medical Monitor approval.
5. Grade 4 diarrhea (ie, life-threatening consequences with urgent intervention indicated) regardless of attribution ongoing or within 7 days prior to randomization.
6. Uncontrolled viral (other than AdV), bacterial, or fungal infection(s) leading to hemodynamic instability or radiologic or laboratory evidence attributable to worsening disease.
7. Requirement for fraction of inspired oxygen (FiO_2) >0.5 (ie, 50%) to maintain arterial oxygen saturation >90% (via pulse oximetry) or need for mechanical ventilation, except for planned procedures or surgeries with Medical Monitor approval. For guidance on estimating fraction of inspired oxygen, see Appendix 9.
8. Prior therapy with anti-thymocyte globulin, alemtuzumab (Campath®), or other immunosuppressive T cell monoclonal antibodies within 28 days prior to dosing.
9. Prior donor lymphocyte infusion or CD34+ stem cell infusion within 21 days prior to dosing.
10. Use of vasopressors within 7 days prior to randomization.
11. Use of any investigational antiviral agent, including brincidofovir, within 7 days prior to randomization. Maribavir and letermovir for CMV will be allowed.
12. Pregnant or lactating female unwilling to discontinue nursing prior to randomization.
13. Any condition that, in the opinion of the Investigator, would compromise the safety of the patient, would prevent full participation in this study, or would interfere with the evaluation of any study endpoints.
14. History of severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) allergy to any component of posoleucel (including human serum albumin and dimethyl sulfoxide) or history of severe (CTCAE Grade ≥3) prior reactions to blood product transfusions.
15. Positive for SARS-CoV-2 virus at screening. Exception: Patients who test positive for SARS-CoV-2 at screening and who have a recent prior positive test may be enrolled if they have no clinical or radiological manifestations of COVID-19 and if the Investigator and Medical Monitor concur on their enrollment.

6.3 Lifestyle Restrictions

There are no lifestyle restrictions for participants in this study.

6.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not randomized into the clinical study. 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, and any serious adverse events (SAEs).

Rescreening may be permitted following discussion with the Sponsor.

7 TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1 Treatments Administered

Participants in the study will receive posoleucel or placebo. Posoleucel is a third-party, donor-derived, "off-the-shelf," VST product with specificity for BKV, AdV, CMV, EBV, and HHV-6 (with additional cross-reactive specificity for JCV) that is cryopreserved and ready for immediate use.

Study Treatment Name:	Posoleucel	Placebo
Dosage formulation:	Posoleucel will be frozen in a cryopreservation medium containing [redacted]	Cryopreservation medium containing [redacted]
Unit dose strength(s)/Dosage level(s):	[redacted] Participants who weigh <40 kg will receive [redacted] posoleucel cells ([redacted] while participants who weigh ≥40 kg will receive [redacted] cells [redacted]	0 cells/mL in a volume of approximately 2.5 mL Participants who weigh <40 kg will receive a volume equivalent to [redacted] posoleucel cells [redacted] while participants who weigh ≥40 kg will receive a volume equivalent to [redacted] cells ([redacted]

Study Treatment Name:	Posoleucel	Placebo
	For the second dose (Day 12-18/Day 12'-18'): • If AdV viral load decrease from baseline is ≥0.5 log $_{10}$ copies/mL AdV DNA at Days 8 or 11 (Days 8' or 11'), the participant will receive a second dose with the same VST line as the first dose. • If AdV viral load decrease from baseline is <0.5 log $_{10}$ copies/mL AdV DNA at Days 8 or 11 (Days 8' or 11'), the participant will receive a second dose with a new VST line from a different donor.	For the second dose (Day 12-18/Day 12'-18'): • If AdV viral load decrease from baseline is ≥0.5 log $_{10}$ copies/mL AdV DNA at Days 8 or 11 (Days 8' or 11'), the participant will receive a second dose with the same placebo lot as the first dose. • If AdV viral load decrease from baseline is <0.5 log $_{10}$copies/mL AdV DNA at Days 8 or 11 (Days 8' or 11'), the participant will receive a second dose with placebo from a different lot.
	Participants will receive the same dose for both infusions (first and second doses) of each study period.	Participants will receive the same dose for both infusions (first and second doses) of each study period.
Route of Administration	IV (via central or peripheral line) over approximately [redacted] as a slow push	
Dosing instructions:	Premedication is not required, except for participants with a prior history of reaction to blood products who may receive premedication with 0.25 to 0.5 mg/kg (maximum dose of 25 mg) diphenhydramine (IV or oral) (or a similar antihistamine preferred by the clinical site), and/or 5 to 10 mg/kg (maximum dose of 650 mg) acetaminophen (IV or oral) prior to study treatment administration. If alternative doses of diphenhydramine and/or acetaminophen are routinely used for the premedication of infusion reactions at the clinical site, then these doses may be used. Premedication with corticosteroids is prohibited. Refer to the Cell Therapy Manual for instructions regarding thawing and preparation of IP	
Packaging and Labeling	Study treatment will be provided in 6.0 mL cryovials. Each cryovial will be labeled as required per country requirement.	
Manufacturer	AlloVir	AlloVir

Posoleucel cell lines will be selected for each participant based on an [redacted]

The appropriate drug product (ie, the VST lines for infusion) for administration will be selected using a software program (CytoMatch), [redacted]

For participants whose AdV viral load as determined by the Central Laboratory has decreased ≥0.5 $\log_{10}$ copies/mL AdV DNA between Day 1 and Day 8 or 11, the second dose will be from the same VST line/placebo lot as the first dose. When possible, the Day 11 value should be used to make this determination; however, if a Day 11 value is not available, the Day 8 value can be used. For participants whose AdV viral load has decreased <0.5 $\log_{10}$ copies/mL AdV DNA between Day 1 and Day 8 or 11, the second dose will be with a new VST line from a different donor or placebo from a different lot. When possible, the Day 11 value should be used to make this determination; however, if a Day 11 value is not available, the Day 8 value can be used. In that case, the VST line chosen for the participant's second infusion will be the VST line with the next-best match according to the CytoMatch hierarchy as described above and will come from a different donor than the first VST line infused, while maintaining a threshold of at least 2 HLA allele matches between the VST line and the virus-infected recipient. The choice of second dose for participants who enter the Cross-Over Period will use the same criteria (with AdV viral load assessment on Day 11' [or Day '8, if Day 11' value is not available] to support the second dose on Day 15').

In the unlikely event that a suitable VST line for the second infusion cannot be identified in the bank, a second dose of the first VST line infused will be substituted for the participant's second infusion.

For participants who receive an additional dose for recurrence, the additional dose will be from the same VST line or placebo lot and include the same number of cells as the second dose. An additional dose for recurrence can only be administered after Day 29 of the Primary Study Period (the primary endpoint), but prior to 20 weeks. Participants who receive an additional dose for recurrence are not eligible for subsequent cross-over, and participants who have previously entered the Cross-Over Period are not eligible for a subsequent additional dose.

Once the lots of drug product have been selected, the treating physician will review and approve documentation that accompanies the drug product shipment prior to dose administration.

Randomization of patients to posoleucel versus placebo will occur only after VST line matching and selection has been confirmed (to satisfy inclusion criteria).

7.1.1 Study Drug Administration

For complete instructions on study drug administration, including the thawing of the product, please refer to the Cell Therapy Manual.

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.
- Participants must remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion.
- Vital signs will be monitored at the end of infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion.

All findings must be recorded in the electronic case report form (eCRF).

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 7.7.1 for additional information.

If a participant experiences an infusion reaction, then 0.25 to 0.5 mg/kg (maximum dose of 25 mg) diphenhydramine (IV or oral) and/or 5 to 10 mg/kg (maximum dose of 650 mg) acetaminophen (IV or oral) may be administered as treatment (even if received as premedication). If diphenhydramine is not available or is not routinely used at the clinical site, an alternative antihistamine may be used instead. If alternative doses of diphenhydramine and/or acetaminophen are routinely used for the treatment of infusion reactions at the clinical site, then these doses may be used. In the case of suboptimal control of an infusion reaction or the need to use corticosteroids for treatment of an infusion reaction, doses of ≤0.5mg/kg/day of prednisone or equivalent should be considered first.

7.2 Dose Modification

No dose modifications are permitted. Reference Section 8.1 for Discontinuation of Study Treatment Criteria.

7.3 Method of Treatment Assignment

Participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to the study prior to Day 1 of the Primary Study Period. Participants [redacted]

7.4 Blinding

The Sponsor designee (eg, interactive response technology [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 AE 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 patient's identification, the reason for breaking the blind, and the date and time for breaking the blind.

7.5 Preparation/Handling/Storage/Accountability

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

All material containing posoleucel (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 VST line to the third-party PBMC donor from whom it originated. These records will be maintained for 30 years after expiry for each VST line.

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

7.6 Treatment Compliance

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

7.7 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines and/or GVHD prophylaxis) that the participant has received within 30 days before screening, is receiving at the time of enrollment, or receives during the study must be recorded. The patient's conditioning regimen for most recent HCT should also be recorded, even if it is outside of the 30 day window. All concomitant therapy outlined above will be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Fluids, electrolytes, vitamins and supplements, mouth care, and laxatives, as well as "as needed" medications, do not need to be recorded during screening unless they are used to treat an AE. "As needed" medications can be reported as 1 item without detailing the components. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1 Permitted Concomitant Therapy

Participants in both treatment arms will continue to receive SoC per their Treating Physician. Any medications, therapies, or procedures performed as SoC will be documented in the appropriate eCRF.

Clinically available (non-investigational) antiviral agents (eg, acyclovir, ganciclovir, foscarnet, maribavir, letermovir) and the use of intravenous immunoglobulin are permitted during the study. For this study, the use of maribavir and letermovir to treat CMV infections will be considered non-investigational, regardless of the regional regulatory approval status.

Cidofovir is not currently approved for the treatment of AdV infection in any regions conducting this trial. Given the unknown efficacy of cidofovir against adenovirus infection and known toxicity (e.g. nephrotoxicity) associated with its use, it is recommended that patients do not initiate or continue the use of cidofovir at the time of enrollment into the study. Cidofovir may be initiated or stopped at any time based on investigator judgment during the study. The dose and regimen of cidofovir is not restricted but must be documented in the EDC as a concomitant medication if used.

7.7.2 Excluded Concomitant Therapy

All participants may receive available supportive therapy with approved treatments.

The use of investigational antiviral agents is prohibited. Whereas brincidofovir (Tembexa®) is approved in the US for the treatment of human smallpox disease (and is specifically not indicated for the treatment of any other diseases), it is considered an investigational antiviral agent for this study and is therefore prohibited.

T cell ablative therapies, such as ATG, alemtuzumab (Campath®), or other immunosuppressive T cell-targeted monoclonal antibodies, are prohibited within 28 days prior to dosing and during the course of the study.

Whereas it is recognized that investigators and treating physicians will as part of their standard of care, where feasible, reduce immunosuppression in their patients with AdV infection, there are no specific guidelines on how this should be achieved. It should be noted in this context that ongoing therapy with high-dose systemic corticosteroids (eg, > 0.5 mg/kg/day prednisone equivalents) may impact the efficacy of posoleucel and is prohibited during the course of the study unless medically indicated.

Prior donor lymphocyte infusions (DLI) or CD34+ stem cell infusion within 21 days prior to dosing is exclusionary (Exclusion Criterion 9).

Any participants who receive any hematopoietic stem cell products after randomization will be discontinued from study treatment but will continue to be followed in the study.

7.8 Treatment after the End of the Study

Participants will not receive study treatment (posoleucel or placebo) after completion of the study.

8 DISCONTINUATION/WITHDRAWAL CRITERIA

8.1 Discontinuation of Study Treatment

Participants will be discontinued from study treatment if any of the following criteria are met:

- Development of Grade 3 or higher acute GVHD or a Grade 3 to 4 non-hematologic adverse event between the first and any subsequent dose of posoleucel or placebo that is considered related to study treatment. 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 participation in the study ends.
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk.
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued dosing of study treatment is not in the best interest of the participant.
- Pregnancy.
- Requirement for prohibited concomitant medication.
- Participant (or parent or legal guardian) chooses not to receive any further doses of study treatment.

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

8.2 Withdrawal from the Study

Participation in this clinical study may 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.
- Participant failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the Sponsor or the regulatory authority.

If a participant withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete an Early Termination Visit (see the SoA in Section 2). The reason for participant withdrawal must be documented in the eCRF.

Withdrawn participants will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is based on weight and detailed in the Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

9.1.1 Viral Load Detection Using Quantitative Polymerase Chain Reaction

Samples will be collected for viral load detection as shown in the SoA (Section 2) and Appendix 3.

Viral load of AdV in blood, stool, and nasopharyngeal samples will be measured by qPCR, performed by the central laboratory during the study. Blood and stool samples will be stored for potential future virus genotypic or viral load analysis.

During Screening, blood specimens may be collected locally in addition to a central laboratory sample. Local laboratory results available up to 5 days prior to or during screening may be used to initiate screening activities and support eligibility determination. For the inclusion criterion requiring two consecutive and rising AdV viremia results exceeding 1,000 copies/mL, the two consecutive viremia results used to determine eligibility must have been assayed at the same laboratory, preferably the central laboratory. Participants may be randomized and dosed (with Medical Monitor approval) based on local laboratory AdV viremia results. This process is expected to expedite the randomization and dosing of participants whose clinical status may rapidly deteriorate.

All study analyses will continue to be performed using viral load data from the central laboratory.

While not a routine evaluation in this study, any participants who manifest clinical signs and/or symptoms of AdV hemorrhagic cystitis should have a urine sample sent to the central laboratory

for determination of AdV urine viral load. For this subset of participants, AdV urine viral loads should be measured weekly at the central laboratory until resolution of hemorrhagic cystitis.

For participants who require intubation and/or undergo bronchoscopy with bronchoalveolar lavage (BAL), a sample of BAL fluid should, when possible, be obtained for AdV viral load determination at the central laboratory. For participants who develop symptoms and/or signs of possible AdV-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 AdV viral load determination should, when possible, be sent to the central laboratory. In all cases, BAL and CSF samples required for routine clinical care of the patient take precedence over these study-related evaluations.

Infections with BKV, CMV, JCV, EBV, and HHV-6 contribute to significant morbidity and mortality in allo-HCT recipients, and posoleucel also targets these 5 viruses. Therefore, viral load of BKV, CMV, JCV, EBV, and HHV-6 will also be assessed in this study by qPCR from blood samples.

9.1.2 Target Organ Disease

Participants with any one of the following manifestations will be adjudicated by the Adjudication Committee for target organ disease:

- Clinically significant AdV viremia
- AdV pneumonia
- AdV hepatitis
- AdV enterocolitis
- AdV pancreatitis
- AdV hemorrhagic cystitis
- AdV nephritis
- AdV encephalitis/myelitis
- AdV retinitis/ocular disease
- AdV carditis
- Death due to AdV disease

These manifestations are defined in Appendix 8.

Participants with BKV, CMV, JCV, EBV, and/or HHV-6 infection, which are also targeted by posoleucel, should be similarly assessed for progression of infection to target organ disease or worsening of target organ disease by the investigator. These manifestations will not be adjudicated by the committee.

9.1.3 Radiological Imaging

The presence or absence of abnormalities consistent with lower respiratory tract infection on chest X-ray and/or CT scan as assessed by the local radiologist should be documented at

screening (obtained no more than 10 days prior to dosing) and at Day 29 (±3 days). If no routine clinical radiological imaging of the chest is available at either of these timepoints, a chest X-ray should be obtained (chest CT scan is not a study-mandated procedure; however, the results of chest CT scan[s] performed as part of a participant's standard clinical care may be used for the purposes of the study. For those participants who cross over, chest imaging as described above should be documented within 7 days prior to Day 1' of the Cross-Over Period and at Day 29' (±3 days) of the Cross-Over Period. If the Day 29 imaging from the Primary Study Period falls within the 7-day window prior to cross over, this imaging need not be repeated prior to the participant entering the Cross-Over Period (ie, the Day 29 imaging will serve as the baseline imaging for the Cross-Over Period). All chest X-rays and/or CT scans will also be submitted for central reading, which will be used for analysis purposes.

9.1.4 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. The 5-level EQ-5D (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 patient 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 Youth (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 patient'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."

9.2 Adverse Events

The definitions of an adverse event (AE) and an SAE can be found in Appendix 4.

All AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (see Section 8.1).

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the Week 24 visit (or Week 24' visit for participants who cross over) at the time points specified in the SoA (Section 2).

Medical occurrences that begin before obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of awareness.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

9.2.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory Reporting Requirements

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

9.2.4.1 Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life threatening- as soon as possible to the applicable regulatory and competent authorities in the US

and elsewhere, 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 applicable regulatory and competent authorities concerned, and the Central Ethics Committee concerned 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.

9.2.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 90 days after the last dose of study treatment.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of the female participant or female partner of a male participant after obtaining the necessary signed informed consents.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The female participant or pregnant female partner of a male participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the female participant or pregnant female partner of a male participant and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 9.2.4. While the Investigator is not obligated to actively seek this information in former study female participants or pregnant female partners of male participants, he or she may learn of an SAE through spontaneous reporting.
- Female participants who become pregnant will be discontinued from the study treatment (see Section 1).

9.2.6 Adverse Events of Special Interest

Adverse events of special interest include acute and chronic GVHD (new onset or worsening of existing GVHD), graft failure and rejection, CRS, and infusion-related AEs. Grading criteria for GVHD and CRS can be found in Appendix 6 and Appendix 7, respectively.

9.2.6.1 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 investigational product 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 the Special Situations Report Form and faxed/emailed to [redacted] (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]
Telephone (within US): [redacted]
Telephone (outside US): [redacted]
Fax: [redacted]
Email: [redacted]

9.3 Safety Assessments

Safety will be assessed by TEAEs (defined in Appendix 4), clinical laboratory evaluations and urinalysis, physical examination, vital signs, ECGs, chest x-ray and/or CT scan, monitoring for GVHD and CRS, and pregnancy testing.

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.3.1 Clinical Laboratory Evaluations

Blood for clinical chemistry and hematology will be obtained as indicated in Section 2 and sent to the central laboratory for evaluation. See Appendix 3 for a complete list of analytes and the Laboratory Manual for blood draw volumes and timepoints based on the participant's weight. Screening laboratory criteria can be confirmed using local or central laboratories.

Urine will be obtained as indicated in Section 2 and sent to each site's clinical laboratory per institutional guidelines for complete urinalysis. See Appendix 3 for a complete list of analytes.

A serum pregnancy test will be performed at screening for all female participants of childbearing potential. A serum or urine pregnancy test will be repeated prior to dosing on Day 1 for females of childbearing potential, only if the pregnancy test performed at screening was not completed within 48 hours prior to study treatment administration. A serum or urine pregnancy test will be performed prior to each additional study treatment administration (if applicable) and at the Week 10 (Week 10'), Week 16 (Week 16'), Week 24 (Week 24'), and ET visits for female participants who are of childbearing potential. See Section 2 and Appendix 3.

9.3.2 Vital Signs

Vital sign measurements will include body temperature, heart rate, respiratory rate, SpO_2, and systolic and diastolic blood pressure, and will be measured after resting for at least 5 minutes in the supine position as indicated in Section 2.

9.3.3 Electrocardiograms

Standard 12-lead ECGs will be performed as indicated in the SoA (Section 2).

9.3.4 Physical Examinations

Physical examinations will be performed, and height and weight will be collected as indicated in the SoA (Section 2). The complete physical examination will be performed by either the Investigator or a Sub-Investigator who is a physician. New abnormal physical examination findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.3.5 Graft Versus Host Disease

Acute and chronic GVHD will be assessed as indicated in Section 2. If any participant develops GVHD, that participant may receive standard GVHD treatment at the discretion of the Investigator.

9.3.5.1 Acute Graft Versus Host Disease

Staging and grading of acute GVHD will be reported using Mount Sinai Acute GVHD International Consortium (MAGIC) 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 6.

9.3.5.2 Chronic Graft Versus Host Disease

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 6.

9.3.6 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 7.

9.3.7 Post-Infusion Monitoring

Post-infusion monitoring will be performed as indicated in Section 2. 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, 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. Participants must also remain on continuous pulse oximetry for a minimum of 30 minutes after the end of the infusion. These monitoring durations are minimum requirements; Investigators should remain vigilant for any changes from pre-infusion baseline in vital signs or clinical condition, and participants should remain at the clinical site and be monitored for longer than these minimum times if abnormalities persist.

9.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6 Genetics

Genetics are not evaluated in this study.

9.7 Biomarkers

Biomarkers are not evaluated in this study.

9.8 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected include:

- Number of hospitalizations
- Duration of hospitalization (total days, including duration by wards [eg, ICU])
- Need for mechanical ventilator support and duration of mechanical ventilator support (total days)
- Need for supplemental oxygen to maintain SpO_2 >90% and duration of supplemental oxygen (total days)

9.9 Other Assessments and Procedures

9.9.1 Informed Consent

Participants or their legally authorized representative must be consented per the informed consent process outlined in Appendix 2.

9.9.2 Demographics

Demographic information, including age, gender, race, and ethnicity, will be obtained if allowed per country-specific regulations.

9.9.3 Inclusion and Exclusion Criteria

All inclusion (Section 6.1) and exclusion (Section 0) criteria will be reviewed by the Investigator or designee to ensure the participant is eligible for study participation.

9.9.4 Medical History

Medical history will include diagnosis of underlying disease requiring HCT, underlying disease state at the time of AdV diagnosis, type of donor and cell source of the transplant received, date of HCT, conditioning regimen, CMV serostatus, presence of GVHD, pulmonary function tests, and smoking status.

9.9.5 SARS-CoV-2 Virus Assessment

A mid-turbinate nasal swab will be taken to test for SARS-CoV-2 virus by PCR.

9.9.6 Randomization

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a [redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The required sample size is 82 participants based on the below specifications that have received at least 1 dose of posoleucel or PBO.

The sample size was determined based on the following specifications:

1. Superiority study comparing posoleucel plus SoC to placebo plus SoC
2. Primary endpoint is success or failure based on clearance of ADV viremia at Day 29 of the Primary Study Period
3. Allocation (posoleucel:placebo) is [redacted]
4. Chi-square test
5. Two-sided alpha = 0.05
6. True success rate (defined as clearance of virus) for posoleucel = 0.55
7. True success rate (defined as clearance of virus) for placebo = 0.25
8. Power = 80%

A SSRE and futility analysis will be performed after approximately 40 participants have completed Day 29 of the Primary Study Period. Details of the SSRE and futility analysis will be provided in the SSRE Plan prior to conducting the interim analyses.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat (ITT)	All randomized participants. Participants will be analyzed according to the randomized study treatment.
Modified ITT	All randomized participants who receive at least one dose of posoleucel or placebo. All efficacy endpoints will be analyzed based on the mITT Population and these analyses will be considered the primary analyses of efficacy. Participants will be analyzed according to the randomized study treatment.
Per Protocol (PP)	All ITT participants who receive any amount of posoleucel or placebo and who do not have any major protocol deviations deemed potentially to impact efficacy or its evaluation, as defined in the SAP. All efficacy endpoints will also be analyzed based on the PP Population, and these analyses will be considered secondary analyses of efficacy. Participants will be analyzed according to the randomized study treatment.
Safety	All participants who receive any amount of posoleucel or placebo and have at least 1 post-treatment safety assessment. All safety analyses will be based on the Safety Population. Participants will be analyzed according to the actual study treatment received.

10.3 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe in detail the planned statistical analyses and the procedures for handling missing data. This section is a summary of the planned statistical analyses. A separate SSRE Plan will be developed and finalized before conducting the interim analysis.

Summary statistics will be presented by treatment group for the Primary Study Period and by cross-over group (Posoleucel/Placebo or Placebo/Posoleucel) based on the treatments received for the Cross-Over Period. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, 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.

10.3.1 Efficacy Analyses

All efficacy endpoints will be analyzed and formally compared between randomized treatment groups using statistical tests based on data from the Primary Study Period. In addition, for purposes of complete reporting, results for these endpoints will be reported, if appropriate, for data from the Cross-Over Period by treatment received in the Cross-Over Period, but no formal comparisons or statistical tests will be made.

The primary and key secondary efficacy endpoints will be analyzed under the estimand framework. The estimand attributes will be described in detail in the SAP.

In order to control the overall type 1 error rate, a sequential approach will be used to analyze the primary and key secondary efficacy endpoints, with undetectable viremia (less than LLOQ) at Day 29 of the Primary Study Period as the primary efficacy endpoint, followed by progression from viremia to target organ disease (for participants without target organ disease at screening), progression of target organ disease (for participants with target organ disease at screening), or non-relapse mortality during the study as the key secondary efficacy endpoint.

For AdV viral endpoints at Day 29 or Week 4 visit, a 14-day window will be applied to the Day 29 visit. The last observed plasma AdV DNA result through Day 29 + 14 days (up to 43 days post first infusion) will be used for the analysis. Participants who cross over on or before Day 29 will be treated as failure.

All efficacy endpoints will be analyzed based on the mITT Population, and these analyses will be considered the primary analyses of efficacy. The primary and key secondary efficacy endpoints will also be analyzed based on the ITT and PP Population to assess the robustness of the primary analysis results.

10.3.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint, undetectable viremia (less than LLOQ) at Day 29 of the Primary Study Period, will be summarized by treatment group using the count and percentage, together with an exact (Clopper-Pearson) 95% confidence interval for the true percentage.

The null hypothesis is that the true percentage for posoleucel plus SoC is less than or equal to the true percentage for placebo plus SoC, and the alternative hypothesis is that it is greater. This endpoint will be analyzed using logistic regression. The model will include a term for treatment and the following covariates: level of viremia at Baseline (≥10,000 copies/mL or <10,000

copies/mL AdV DNA), age (≥12 years or <12 years) and absolute lymphocyte count at Baseline. The null hypothesis will be tested using a one-sided test of the effect of treatment at the 0.025 significance level. Missing data imputation will be described in the SAP.

10.3.1.2 Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy endpoint will be tested sequentially after the primary endpoint reaches statistical significance. The key secondary efficacy endpoint, progression from viremia to target organ disease (for participants without target organ disease at screening), progression of target organ disease (for participants with target organ disease at screening), or non-relapse mortality during the study, will be analyzed in the same manner as the primary efficacy endpoint.

10.3.1.3 Other Secondary Efficacy Endpoint Analyses

Following the key secondary analysis, progression from viremia to target organ disease and progression of target organ disease will be analyzed as separate subgroups in a step-down manner. If any participants cross over prior to Day 29, they will be considered as having had progression, because the necessary condition for cross-over is that the participant progressed to active target organ disease (for participants without target organ disease at screening) or experienced progression of target organ disease (for participants with target organ disease at screening).

The AAUC for plasma AdV viremia (log_{10} copies/mL AdV DNA), as assayed by qPCR, through Day 29 of the Primary Study Period will be summarized by treatment group using descriptive statistics (number of non-missing observations, mean, median, standard deviation, minimum, and maximum). The null hypothesis for this endpoint is that the true mean for posoleucel is greater than or equal to the true mean for placebo, and the alternative hypothesis is that it is less. The null hypothesis will be tested using a one-sided, two-sample t-test with a 0.025 significance level.

The following secondary efficacy endpoints will each be analyzed in the same manner as the primary efficacy endpoint: achieving AdV viremia <400 copies/mL AdV DNA at Day 29 of the Primary Study Period and AdV disease recurrence during the study among participants who had clearance of AdV viremia (prior to any cross-over).

The Kaplan-Meier estimated median time to resolution of AdV viremia will be presented for each treatment group, together with the 95% confidence interval for the true median. The number and percentage of censored and uncensored participants will be presented by treatment group. The null hypothesis for this endpoint is that the true distributions of time to resolution of AdV viremia are equal for posoleucel and placebo, and the alternative hypothesis is that the true distributions are different, with the time to resolution of AdV viremia being less for posoleucel. The null hypothesis will be tested using a one-sided log-rank test with a 0.025 significance level.

10.3.1.4 Cross-Over Analyses

Undetectable viremia (less than LLOQ) at Day 29' of the Cross-Over Period will be summarized by cross-over group using counts and percentages, together with exact (Clopper-Pearson) 95% confidence intervals for the true percentages. Achieving AdV viremia <400 copies/mL AdV DNA at Day 29' of the Cross-Over Period and AdV disease recurrence during the 24-week Cross-Over Period among participants who had clearance of AdV viremia (after cross-over) will be analyzed in the same way.

The AAUC for plasma AdV viremia (log_{10} copies/mL AdV DNA), as assayed by qPCR, through Week 24' of the Cross-Over Period will be summarized by cross-over group using descriptive statistics.

The Kaplan-Meier estimated median time to resolution of AdV viremia will be presented for each cross-over group, together with the 95% confidence interval for the true median. Cross-over participants who do not achieve resolution of AdV viremia will be censored as of their last study visit. The number and percentage of censored and uncensored participants will be presented by cross-over group.

Progression from viremia to target organ disease (for participants without target organ disease at screening, progression of target organ disease (for participants with target organ disease at screening), or non-relapse mortality during the 24-week Cross-Over Period will not be analyzed, because all cross-over participants must have already progressed to target organ disease prior to being crossed over.

10.3.2 Analysis of Safety

Safety will be analyzed and compared between treatment received based on data from the Primary Study Period. In addition, for purposes of complete reporting, safety will be reported for data from the Cross-Over Period by treatment received in the Cross-Over Period, but no comparisons will be made between the two treatments.

The primary safety endpoint is the incidence and severity of TEAEs, including individual AESIs, during the study. The safety profile will be further assessed based on changes in clinical laboratory assessments, vital signs, ECGs, and physical examinations. All safety analyses will be based on the Safety Population.

Safety analyses in general will be descriptive and will be presented by study period (Primary Study Period or Cross-Over Period) and treatment group or cross-over group in a tabular format. Categorical endpoints will be summarized using number and percentage of participants within each category. Continuous endpoints will be summarized descriptively with summary statistics (number of non-missing observations, mean, standard deviation, median, minimum, and maximum).

A TEAE is defined as an adverse event with a start date and time on or after the administration of investigational product or placebo or that worsened in severity after administration of investigational product or placebo through the end of the study. For AEs with a missing start date, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study treatment. The number and percentage of participants with TEAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term for each treatment group/cross-over group. This will be done overall, by severity, and by relationship to treatment. Adverse events leading to discontinuation of the study, SAEs, and AESIs will be summarized by treatment group. By-participant listings will also be provided for any deaths, SAEs, AESIs, and adverse events leading to discontinuation of study drug.

The incidence and severity of acute GVHD during the study, the incidence and severity of chronic GVHD during the study, the incidence and severity of CRS during the study, and the incidence and severity of any treatment-emergent AESIs during the study will each be

summarized by treatment group for the Primary Study Period and by cross-over group for the Cross-Over Period using counts and percentages.

Clinical laboratory data will be summarized by laboratory test, visit, and treatment group using descriptive statistics. The changes from baseline to each post-baseline visit will also be summarized.

Vital signs data will be summarized by visit and treatment group for each vital sign using descriptive statistics. The changes from baseline to each post-baseline visit will also be summarized.

ECG data will be summarized by visit and treatment group for each quantitative ECG parameter using descriptive statistics. The changes from baseline to each post-baseline visit will also be summarized.

Abnormal physical examination findings will be presented in a by-participant data listing.

10.3.1 Interim Analyses

A sample size re-estimation (SSRE) and a futility analysis will be performed after approximately 40 participants have completed Day 29 of the Primary Study Period. The SSRE will be based on the conditional power (CP), ie, the conditional probability of rejecting the null hypothesis, using the method of Mehta and Pocock (2010) for a CP of 80%. For the futility analysis, a CP cutoff of 10% will be applied. The interim analyses (SSRE and futility analysis) will both be conducted in a manner so as to minimize the risk of operational bias. It will be done under the auspices of the independent DSMB overseeing the study. The analyses will be performed by an independent statistician. The unblinded data generated and discussed by the DSMB for the interim analyses will be kept confidential. In particular, the information will not be accessible to the investigators and site staff, the Sponsor's team and medical monitor, and CRO blinded team members, or the Adjudication Committee.

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12 APPENDICES

APPENDIX 1: ABBREVIATIONS

Abbreviation	Definition
AAUC	time-averaged area under the concentration-time curve
AdV	Adenovirus
AE	adverse event
AESI	adverse event of special interest
allo-HCT	allogeneic hematopoietic stem cell transplant
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
BAL	bronchoalveolar lavage
BKV	BK virus
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CP	conditional power
CR	complete response
CRA	Clinical Research Associate
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTA	Clinical Trial Authorisation
DNA	deoxyribonucleic acid
DRE	disease-related event
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D	European Quality of Life 5 dimensions
EQ-5D-5L	5-level European Quality of Life 5 dimensions
EQ-5D-Y	European Quality of Life 5 dimensions Youth
EQ VAS	European Quality of Life Visual Analog Scale
ET	Early Termination

Abbreviation	Definition
FDA	Food and Drug Administration
FEV1	forced expiratory volume in the first second
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	graft versus host disease
HCT	hematopoietic stem cell transplant
HHV-6	human herpesvirus 6
HLA	human leukocyte antigen
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
I/E	inclusion and exclusion
IEC	Independent Ethics Committee
IRB	Institutional Review Committee
IRR	infusion-related reaction
IRT	interactive response technology
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
JCV	John Cunningham virus
LFT	liver function test
LLOQ	lower limit of quantitation
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NR	no response
PBMC	peripheral blood mononuclear cell
PP	Per Protocol
PR	partial response
qPCR	quantitative polymerase chain reaction
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SoC	standard of care
SpO_2	peripheral capillary oxygen saturation

Abbreviation	Definition
SSRE	sample size re-estimation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VST	virus-specific T cell
WBC	white blood cell
WOCBP	woman/women of childbearing potential

APPENDIX 2: STUDY GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

Ethical Conduct of the Study

This study will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and all applicable laws and regulations.

Institutional Review Board/Independent Ethics Committee

Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. 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 patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

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

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.

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 patient 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 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 Clinical Research Associate (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.

Protocol Amendments

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

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.

Informed Consent Process

Informed Consent

Prior to conducting any study-related activities, written informed consent to participate in the study must be provided by the patient, or a parent or legal guardian must provide written informed consent and the potential pediatric patient must provide assent in a manner approved by the IRB/IEC and local regulations. In some jurisdictions, legally effective informed consent must be obtained from all legal guardians for minor patients.

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 prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

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

Subject Card

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

Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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.

Committees Structure

Independent DSMB and Adjudication Committees will be convened for this study to routinely monitor patient safety and evaluate prespecified interim analyses for futility and sample size re-estimation.

Data and Safety Monitoring Board

The DSMB will receive summary reports of all unexpected SAEs at least monthly. A DSMB charter, detailing all aspects of the DSMB's composition, scope of review, and procedures will be provided separately. 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.

Adjudication Committee

The Adjudication Committee will be independent, and all members will remain blinded to the randomized treatment arm. The Adjudication Committee will adjudicate adenovirus target organ disease at Day 29 (Appendix 8). More details are provided in a separate Adjudication Committee charter.

Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments. Each Investigator is obligated to keep data pertaining to the study confidential.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

Data Quality Assurance

Data Handling

Data will be recorded at the sites on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the electronic data capture (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.

Computer Systems

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

Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name 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.

Medical Information Coding

For medical information, the following thesauri will be used:

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

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.

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 participating patients (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.

Source Documents

Records of patients, 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.

Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. 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 GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

Insurance and Indemnity

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

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 Ethics opinion have been received.

APPENDIX 3: CLINICAL LABORATORY TESTS

The tests detailed in Table 3 will be performed by the central laboratory, except for urinalysis and urine pregnancy tests, which will be performed by the local laboratory. All samples that are collected on a dosing day must be collected prior to dosing. Patients may be enrolled and dosed using local lab results if the central results are not available at the time of dosing. Central lab assessments are still required as outlined in Table 3, even when local lab results are used for randomization and dosing.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 and Section 6.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 3. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (Central Laboratory)	Platelets	WBC Count with Differential [1]: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils		
	RBC count			
	Hemoglobin			
	Hematocrit			
Coagulation (Central Laboratory)	PT	INR	PTT	
Clinical Chemistry (Central Laboratory)	BUN	Potassium	AST	Total and direct bilirubin
	Creatinine	Sodium	ALT	Total protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Chloride
	Lactate dehydrogenase	Uric acid	Albumin	Bicarbonate
	Creatine kinase	Gamma-glutamyl transferase	Inorganic phosphorus	Lipase
	Amylase			
Urinalysis (Local Laboratory)	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick			

	• Microscopy [2] • AdV viral load [3]		
Viral Load in Blood (Central Laboratory)	AdV [4]	BKV	CMV
	EBV	HHV-6	JCV
Viral Load in Stool (Central Laboratory)	AdV		
Viral Load from Nasopharyngeal Swab (Central Laboratory)	AdV		
Viral Load from BAL (Central Laboratory) [5]	AdV		
Viral Load from CSF (Central Laboratory) [6]	AdV		
Other Laboratory Assessments	• SARS-CoV-2 PCR virus assessment (mid-turbinate nasal swab) • FSH [7] • Serum pregnancy test [8] • Urine pregnancy test [8] • PBMCs and plasma [9]		

1. Manual microscopic review of peripheral blood smears is performed only if WBC count and/or differential values are out of reference range.
2. Urine microscopy is always performed (cannot be replaced with a dipstick analysis).
3. While not a routine evaluation in this study, any participants who manifest clinical signs and/or symptoms of AdV hemorrhagic cystitis should have a urine sample sent to the central laboratory for determination of AdV viral load. For this subset of participants, AdV urine viral loads should be measured weekly at the central laboratory until resolution of hemorrhagic cystitis.
4. Since AdV infections may progress rapidly, participants may be randomized and dosed (with Medical Monitor approval) based on local laboratory AdV viremia results if the central laboratory screening viremia result is not yet available at the time of intended dosing.
5. For participants who require intubation and/or undergo bronchoscopy with BAL, the BAL fluid will be obtained for AdV viral load determination at the central laboratory.
6. For participants who develop symptoms and/or signs of possible AdV-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 AdV viral load determination should, when possible, be sent to the central laboratory.
7. 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.
8. For female participants of childbearing potential only. A serum (human chorionic gonadotropin) pregnancy test will be performed at screening. Serum or urine pregnancy testing will be performed at other time points as indicated in Section 2.
9. At each time point indicated in Section 2, blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Genomic DNA will be extracted from the PBMC fraction.

The genomic 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).

AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; BKV = BK virus; BUN = blood urea nitrogen; CMV = cytomegalovirus; CSF = cerebrospinal fluid; EBV = Epstein-Barr virus; FSH = follicle-stimulating hormone; HHV-6 = human herpesvirus 6; JCV = John Cunningham virus; PBMC = peripheral blood mononuclear cell; RBC = red blood cell; WBC = white blood cell.

Investigators must document their review of each laboratory safety report.

Study blood sampling volumes and sampling schedule by body weight are described in the Laboratory Manual.

APPENDIX 4: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is defined as any serious AE that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: • Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Definition of AESIs

AESIs include:
• Acute or chronic GVHD • Cytokine release syndrome • Infusion-related reactions • Graft failure and rejection

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to [redacted] in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by [redacted] In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to [redacted]
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Assessment of Intensity

The severity of all AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those AE 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 AE

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to [redacted] However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [redacted]
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [redacted] to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide [redacted] with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to [redacted] within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to [redacted] via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to [redacted] will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone.
- Contacts for SAE reporting can be found in Section 9.2.6.1.

Initial Reports

- All SAEs occurring from signing informed consent until study participation is complete or until resolution, whichever is sooner, must be reported to [redacted] within 24 hours of the knowledge of the occurrence. After study participation is complete, any SAE that the Investigator considers related to study treatment must be reported to [redacted] or the Sponsor/designee.
- To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, [redacted] personnel will be notified electronically by the EDC system and will retrieve the form.

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 awareness 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, patient discharge summary or autopsy reports) to [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined below.

SAE Reporting to [redacted] via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to [redacted]

- If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] or fax/email the completed paper SAE form to [redacted] (contact information listed in Section 9.2.6.1) 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.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Section 9.2.6.1.

APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated within inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause)

Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - oral - intravaginal - transdermal - injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] - oral - injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[e]

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
e. Male condom and female condom should not be used together (due to risk of failure from friction).

APPENDIX 6: 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).

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 patients with acute GVHD. 2009. https://www.cibmtr.org/Meetings/Materials/GVHDworkshop/pages/index.aspx. Accessed 13 May 2019.

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

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).
FEV1 = forced expiratory volume in the first second; 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 7: CYTOKINE RELEASE SYNDROME SCALE

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 principle factor leading to the outcome.
a. Fever is defined as temperature ≥38.0°C not attributable to any other cause. In patients 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 patient 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 8: TARGET DISEASE ENDPOINT DEFINITIONS

These definitions may be modified by the Adjudication Committee, and updated versions will be recorded in the Adjudication Committee Charter.

ADENOVIRUS DISEASE AND DISEASE PROGRESSION DEFINITIONS

1. The CAC will classify the diagnosis of target organ disease – those classified as "proven" or "probable" by the committee will be considered to represent presence of target organ disease for the purpose of study endpoints.
2. Since AdV viremia (DNAemia) is a requirement for study entry, the definition for AdV viremia/DNAemia indicated below will be applied by the CAC only to those participants who clear the AdV viremia/DNAemia present at study initiation, but who the subsequently develop a recurrence. This definition will not be applied to those participants who fail to clear their AdV viremia/DNAemia.
3. For other entities of potential AdV infection not defined below, the infection cases submitted by the Investigator will be reviewed and adjudicated by the CAC.

	DEFINITION	PROGRESSION
Adenovirus Viremia/DNAemia Recurrence		
Recurrence of adenovirus viremia/DNAemia definition does not imply "target organ disease" for the purposes of determining eligibility for crossover as defined in the protocol.	Participants who clear their baseline AdV viremia/DNAemia, defined as 2 consecutive plasma AdV DNA <32 copies/mL, may be evaluated for recurrence of AdV viremia. AdV viremia/DNAemia, is defined below: • A single central laboratory PCR result of plasma AdV viral load >10,000 copies/mL **OR** • Two consecutive, central laboratory PCR results of plasma AdV viral load >1,000 copies/mL and rising. Rising AdV viral load is defined as ≥0.5 log10 copies/mL increase from the first result.	
Adenovirus End Organ Diseases		
	DEFINITION	**PROGRESSION**
Adenovirus pneumonia	• Suggestive signs or symptoms (cough, dyspnea, tachypnea, hypoxia) AND • CT scan or X-ray with infiltrates suggestive of viral pneumonia (and not a dense lobar consolidation suggestive of bacterial pneumonia or nodule(s) suggestive of fungal pneumonia) **AND** • AdV identified in BAL, nasopharyngeal swab, sputum, or lung biopsy by PCR, culture, or antigen via IHC methods. **OR** • If no respiratory specimen results are available, then AdV viremia/DNAemia (defined above) may be considered. Available alternative etiology assessment results (e.g. bacterial, fungal, or other viral culture results) will be provided to the CAC.	• Worsening of clinical signs/symptoms (cough, dyspnea, tachypnea, hypoxia) without alternative attribution (e.g., bacterial pneumonia) **OR** • Escalation of respiratory support: o No supplemental oxygen at baseline o Requirement for supplemental oxygen o Requirement for intubation

Adenovirus hepatitis	• AdV identified via hepatic biopsy via antigen/IHC, or culture **OR** • AdV viremia/DNAemia (defined above) **AND** • Evidence of new or worsening transaminitis, defined as meeting the below criteria or if already met, then an increase by at least 100 IU/mL: o ALT >5xULN o AST >5xULN Available alternative etiology assessment results, both infectious (e.g. hepatitis viral tests) and non-infectious (e.g. drug-induced-liver injury, GvHD) will be provided to the CAC.	• Deteriorating liver function without alternative attribution: o Progression of transaminases o AST/ALT increase by >2-3X from <u>baseline</u> for progression of hepatitis o Decreasing AST/ALT with increasing bili and worsening synthetic function (>30% from baseline) – for burnt-out hepatitis o Progression of hyperbilirubinemia ▪ >30% increase in dBili from baseline o Worsening of hepatic synthetic activity (e.g., PTT, pre-albumin, ammonia/lactate other) ▪ >30% worsening from baseline o Development of clinical signs of hepatic decompensation
Adenovirus enterocolitis	• AdV detected on bowel biopsy via antigen/IHC and/or culture/PCR **AND** • **Both** of the following: o Suggestive signs or symptoms (e.g., diarrhea, abdominal pain, ileus, vomiting, GI bleeding) **AND** o Endoscopic evidence of lesions (macroscopic or microscopic) not attributed to GVHD (or other non-ADV effect) OR cytopathic adenoviral effect identified on biopsy **OR** • At least two suggestive signs or symptoms: diarrhea, abdominal pain, ileus, vomiting, GI bleeding **AND** • AdV isolated from the stool by culture or PCR Available alternative etiology assessment results (e.g., bacterial, viral, amebic, GVHD) will be provided to the CAC.	• Worsening clinical signs or symptoms (better/worse/same) without alternative attribution: o diarrhea o abdominal pain o ileus, vomiting o GI hemorrhage **AND** • AdV in stool persistently positive (qualitative) Available alternative etiology assessment results (e.g. GI GVHD) will be provided to the CAC.
Adenovirus pancreatitis	• AdV identified by pancreatic biopsy or ERCP brushings/washings via antigen/IHC or culture **AND** • At least two clinical and imaging findings such as: o Suggestive signs or symptoms (abdominal pain, GI symptoms) o Amylase or lipase >5xULN o Imaging (e.g., CT scan) findings suggesting pancreatitis	• Progression of clinical and/or imaging findings such as: o Suggestive signs or symptoms (abdominal pain, GI symptoms) o Amylase or lipase o Worsening systemic disease (DIC, sepsis, hemodynamic instability) o Imaging (eg, CT scan) findings suggesting progressive pancreatitis

Adenovirus hemorrhagic cystitis	• Clinical symptoms of cystitis, including dysuria, lower abdominal pain, and/or other bladder-associated pain or spasms **AND** • Grade ≥2 hematuria (per Bedi scale) **AND** • Documented AdV viruria Available alternative etiology assessment results (e.g. BK virus) will be provided to the CAC.	• Worsening disease based on ≥1 grade increase in Bedi scale o E.g., Macroscopic hematuria to clots (Gr 2 to 3) ; or clots to renal insufficiency (Gr 3 to 4) • Requirement for surgical intervention (e.g., nephrostomy tubes, cystectomy, arterial embolization) • Persistent AdV viruria
Adenovirus nephritis	• Suggestive signs or symptoms of nephritis (impaired renal function, proteinuria, microscopic hematuria, hypertension, flank pain) **OR** • Enlarged kidney on imaging **OR** • Renal obstruction **AND** • One of the following: o AdV identified via renal biopsy via antigen/IHC or culture **OR** o AdV viruria **OR** o If both AdV viruria and renal biopsy results are not available, then AdV viremia/DNAemia (defined above) may be considered. Available alternative etiology assessment results (e.g. BK virus, JC virus, bacterial and drug-induced) will be provided to the CAC.	• Worsening of clinical signs/symptoms: o Impaired renal function o Proteinuria o Microscopic hematuria o Hypertension o Flank pain
Adenovirus encephalitis/myelitis	• At least one of the following signs/symptoms of encephalitis: o Abnormal CSF o Focal CNS deficit o Cognitive impairment o Visual symptoms o Seizure o Evidence of compatible lesions by CT scan or MRI **AND** • AdV identified in CSF via antigen/IHC, culture, PCR, or histopath from brain biopsy **OR** (if not possible to perform a lumbar puncture): • At least two of the following signs/symptoms of encephalitis: o Focal CNS deficit o Cognitive impairment o Visual symptoms o Seizure o Evidence of lesions by CT scan or MRI	• Worsening signs/symptoms of encephalitis: o Worsening CSF findings o Increase in number/severity of focal CNS deficits o Worsening cognitive impairment o Worsening visual symptoms o New onset seizure, or worsening of existing seizures

	AND • AdV viremia/DNAemia (defined above) Available alternative etiology assessment results (e.g. JC virus, bacterial, amebic infections and stroke/infarct/CSF leak) will be provided to the CAC.	
Adenovirus retinitis/ocular disease	• Ophthalmologic exam demonstrating findings consistent with retinitis/ocular disease (e.g., retinitis, keratitis, keratoconjunctivitis sicca, iridocyclitis, retinopathy, visual field defects, papilledema, diplopia) and other possible causes (e.g., HIV, CMV, fungal, mycobacterial, bacterial infection, and/or neurologic etiology) not considered more likely as the only cause **AND** • Detection of AdV by PCR from the aqueous or conjunctiva	• Clinical assessment (by ophthalmologist) of progressive ocular disease
Adenovirus carditis	• Specimen from cardiac source (e.g., cardiac tissue biopsy, pericardial fluid) positive for AdV plus evidence of carditis, myocarditis, or pericarditis (e.g., ECHO findings or drained fluid reveals evidence of inflammation) WITHOUT microbiologic evidence of another infectious pathogen or evidence of concurrent GVHD at any site that could explain the presentation.	• Worsening heart failure/ejection fraction on Echocardiography **OR** • New requirement for ECMO
Death attributable to AdV disease	• Proven: Autopsy with histopathologic evidence for human adenovirus presence associated with tissue destruction regardless of other etiologies for death. • Probable: Previously met criteria for probable or proven adenovirus-related disease within the preceding 8 weeks without resolution of symptoms consistent with adenovirus-associated disease and without other clear etiology for death and with no autopsy available	• Not applicable

APPENDIX 9: ESTIMATING FRACTION OF INSPIRED OXYGEN

Method	O_2 Flow (L/min)	Estimated FiO_2 (%)
Nasal cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

Source: https://www.intensive.org/epic2/Documents/Estimation%20of%20PO2%20and%20FiO2.pdf; accessed 16 December 2021

Summary:

- Nasal cannula oxygen at standard flow rates is acceptable (even at 6 L/min, FiO_2 is expected to be <50%).
- Standard face mask oxygen is acceptable at flow rates <7 L/min.
- Face mask with reservoir is not acceptable since FiO_2 is expected to exceed 50% at all flow rates.
- Nasopharyngeal catheters at flow rates <5 L/min are acceptable.

APPENDIX 10: AMENDMENT CHANGES AND RATIONALE

Amendment history is provided below.

Protocol Version	Date	Patient Enrollment
Original, Version 1	20 August 2021	Yes
Amendment 1, Version 2.0	17 December 2021	None
Amendment 2, Version 3.0	23 August 2022	Yes
Amendment 3, Version 4.0	15 September 2023	Not Used
Amendment 3, Version 4.0	21 September 2023	Yes
Amendment 4, Version 5.0	30 November 2023	None

Amendment 4 Rationale

Major Revisions include:

- **Addition of Interim analysis (sample size re-estimation and futility analysis)**

  Rationale: AlloVir has decided to add back in the interim analysis for a sample size re-estimation and futility analysis that were originally planned to address the lack of adequate published data on the natural history of AdV infection in a similar patient population as those enrolled into the AdV Ph3 study. The SSRE/futility assessment will provide an opportunity to increase the sample size and the study power to detect a treatment response based on the interim data.

- **Changes in Sample Size Determination**

  Rationale: The assumptions in sample size determination were updated to be more conservative. The method of the sample size calculation is changed to a Chi-square test because the sample size is sufficient to use this method and it is consistent with the test used for logistic regression model of the primary analysis. Patients who drop out will be included in the analysis, therefore, the dropout rate is not considered in the calculation.

- **Changes in Primary Analysis**

  Rationale: Based on published data absolute lymphocyte count is believed to be a strong predictor of clinical outcome, therefore it has been included as a covariate in the model for post-randomization adjustment.

Amendment 3 Rationale

There is a significant unmet medical need for an AdV treatment option in immunocompromised allo-HCT patients. The population of allo-HCT patients that develop clinically significant AdV infection, as defined by the AdV viral load eligibility criteria, post allo-HCT is limited. However, those that do reactivate or develop de novo AdV infection can rapidly progress to severe disease leading to an increase rate of mortality. Given the limited population of allo-HCT that develop

clinically significant AdV infection, enrollment into this trial is approximately 2-3 patients per month.

The purpose of this amendment was to broaden eligibility criteria and modify study conduct to support acceleration of enrollment. Additional changes were made to correct errors and to provide additional clarity and consistency.

Major Revisions include:

- **Revised Eligibility Criteria**

  Revised Inclusion Criteria #1 to allow enrollment of patients <1 year of age.

  Rationale: DSMB has reviewed the safety data for patients between 1 and <6 years old and approved enrollment of patients under 1.

  Revised Exclusion Criteria # 2 to allow patients actively undergoing corticosteroid tapering to prednisone equivalent dose of 0.5 mg/kg/day to be dosed once they have reached ≤ 1 mg/kg/day with Medical Monitor approval, with the expectation that the corticosteroid taper will continue.

  Rationale: AdV infections in immunocompromised HCT recipients can progress rapidly. Post allo-HCT, patients may be on high dose systemic steroids for prophylaxis of GvHD which would take time to taper down to 0.5 mg/kg/day. There is new literature support for minimal impact of VST function with steroids at typical clinical doses (Al-Akioui-Sanz 2023). Modifying this criterion would provide patients earlier access to study treatment while they continue to taper steroids and minimize risk to efficacy response for dose 2.

  Revised Exclusion Criteria #4 to broaden the treatment population to patients with active malignancies that are slow growing and/or stable disease.

  Rationale: The intent was to exclude patients with unstable active malignancies that could potentially confound safety in this patient population. However, active malignancies that are stable on treatment or slow growing are not likely to confound the safety results collected during the 20-week safety follow up period. This change would not impact safety or efficacy for patients enrolled in the study.

- **Concomitant Medications:**

  Revised medication restriction for cidofovir use to allow sites to use cidofovir at any time during the study

  Rationale: Cidofovir is not approved for the treatment of AdV infection and has been shown to be associated with an increased risk of nephrotoxicity. The antiviral activity of cidofovir and long-term efficacy has not been well studied and is felt to be poor in immunocompromised post allo-HCT patients. However, clinicians often administer cidofovir to patients with AdV infection because there are no available approved treatment options. The modified cidofovir usage language will provide clinical sites the ability to maintain their standard practice for initiation and stopping of cidofovir. Given the limited data to support efficacious use of cidofovir for AdV infection this change would support a real-world evaluation of current standard of care.

- **Analysis updates:**

Removal of the Interim Analysis

Rationale: The interim analysis that included an SSRE and futility assessment was removed. The study will continue enrollment per the current sample size as planned without an SSRE or futility given the slow rate of enrollment of this rare patient population.

Change from ITT to mITT

Rationale: The time from randomization to study treatment infusion is typically delayed by ~5 days due to operational feasibility of shipping HLA matched VST or placebo to the study center and scheduling of treatment administration. This delay has led to a larger than expected number of patients that have randomized and not been treated. Given the smaller sample size in this rare patient population study, an ITT analysis that includes randomized but not treated patients has the potential to obscure the biological effects of VST versus placebo for the primary endpoint. Excluding randomized patients who did not receive at least 1 infusion of study treatment (ie. modified ITT analysis) is not expected to introduce bias by performing the primary analysis on a post-randomization population. The reason patients were randomized and not treated was not influenced by treatment assignment as the study is blinded. The primary reasons for patient not to receive treatment are withdraw of consent from study or new data becoming available after randomization and prior to treatment that can lead to removal of the patient from the study, including clearance of AdV viremia. Excluding these patients will lead to a more informative analysis focused only on patients that received at least 1 dose of study treatment.

The mITT analysis would better represent the treatment response in real-world clinical practice in which patients that clear AdV viremia or decide against treatment would not receive VSTs. The primary efficacy endpoints will also be analyzed based on the ITT Population to assess the robustness of the primary analysis results.

Added analysis window for primary and secondary AdV viral load endpoints

Rationale: The rationale for selection of Day 29 for the primary and secondary AdV viral load endpoints were based on the results from the Phase 2 CHARMS study, reference Section 5.4 above. The two AdV assays used in CHARMS had a higher lower limit of quantitation (LLOQ) of 172 and 190 copies/mL as compared to the assay used in this Phase 3 study with an LLOQ of 32 copies/mL. Review of blinded data in patients with declining AdV viremia showed a delay in reaching <LLOQ beyond Day 29 in some patients. This window would allow the last observed result to be used for primary endpoint analysis when applying this more sensitive assay.

- **Other changes:**

Modification of criteria for cell line assignment for the second dose (primary study period or cross-over)

Rationale:

The current dose 2 criterion is based on an AdV viral load cutoff of 10,000 copies/mL to determine if a patient should switch to a second cell line (or placebo). The intent of a cell line switch criteria is to provide patients who have little to no response to Dose 1, as determined by their AdV viral load on Study Day 8 or Day 11, access to a second cell line (or placebo). The second cell line may provide the patient with different HLA matches increasing their chance of a treatment response.

However, the current criteria do not consider the patient's baseline AdV viral load. Upon review of blinded data, patients with high baseline AdV viral loads demonstrate a significant decline of over 0.5 $\log_{10}$ copies/mL by Day 8 were switching cell lines (or placebo) at Dose 2 based on the current switch criteria. Given the initial cell line assigned to each patient is the best HLA matched cell line or placebo that is available, patients demonstrating a treatment response should maintain their current cell line.

This change will consider a patient's baseline AdV viral load when determining treatment response and allow patients that demonstrate a significant treatment response as defined by AdV viral load decline ≥0.5 $\log_{10}$ copies/mL the ability to stay on the initial cell line assigned.

Section 7.2 Dose Modification

Modified text and deleted GVHD text referencing treatment discontinuation section.

Rationale: Text was modified to clarify no dose modifications were allowed in the study. Additional GVHD text was deleted, and the appropriate protocol section referenced for clarity.

Updated CAC Definitions to reflect the changes as agreed upon by the committee members and finalized in the CAC Charter v2.0 17May2023

Amendment 2 Rationale

This amendment was made to address issues relating to study conduct that arose from investigators and study site personnel after study initiation. Additional changes were made to correct errors and to provide additional clarity and consistency.

Major Revisions include:

- **Revised the order and timing of Study Objectives and Endpoints**

  The order of the secondary objectives, relating to the progression to/of target organ disease, were switched, as indicated below, to make the assessment "during the study" the key secondary objective, and to make assessment "by Day 29" an other secondary assessment. (Sections 1, 4, 10.3.1, and 10.3.1.2).

  Change to the timing of the key secondary objective of "to determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses" and its associated endpoint from "by Day 29" to "during the study" (Sections 1, 4, 10.3.1, and 10.3.1.2).

Changed the timing of the other secondary objective of "to determine the percent of participants who develop target organ AdV disease (eg, lower tract respiratory disease documented radiographically, AdV-associated hemorrhagic cystitis, severe hepatitis) or whose target organ disease progresses" and its associated endpoint from "during the study" to "by Day 29" (Sections 1 and 4).

Rationale: An assessment of disease progression over the entire duration of the study has been considered to be more clinically important than an assessment of disease progression over the first 29 days of the study. As before, both of these objectives will be captured as secondary, the only change is in the ordering of the key secondary objective.

Moved the secondary endpoints of proportion of participants with undetectable viremia (less than LLOQ) at Day 29 in participants without and with AdV disease at screening from key secondary endpoints to other secondary endpoints (Sections 1 and 4).

Rationale: These secondary endpoints are not related to the key secondary endpoint and should be included in the other secondary endpoints. Their previous placement under key secondary endpoint was a typographical error.

- **Revised Eligibility Criteria**

  Updated from Inclusion Criterion #2 to remove the requirement that participants had to have an absolute neutrophil count > 500/mm3 at screening and instead allowed absolute neutrophil count > 500/mm3 at any time post allogeneic cell transplantation and by screening (Sections 1 and 6.1).

  Rationale: Adenovirus infection itself may cause neutropenia in an otherwise engrafted HCT recipient, and in these cases, treating the adenovirus infection may be beneficial.

  Added "had a cord blood transplant" to Inclusion Criterion 2b.
  Rationale: Cord blood transplant are considered an independent high-risk criterion for progression of AdV infection (Feghoul, 2015; doi: 10.1016/j.cmi.2015.03.011) (Sections 1 and 6.1).

  Updated the timing of allogeneic cell transplantation in Inclusion Criterion #2 from ≥21 days prior to randomization to ≥21 days prior to dosing (Sections 1 and 6.1).

  Updated the exclusion on prior therapy with anti-thymocyte globulin, alemtuzumab (Campath®), or other immunosuppressive T cell monoclonal antibodies (Exclusion Criterion 8) to within 28 days prior to dosing (Sections 1 and 6.2).

  Updated the exclusion on prior donor lymphocyte infusion or CD34+ stem cell infusion (Exclusion Criterion 9) to within 21 days prior to dosing (Sections 1 and 6.2).

  Rationale: Dosing is a more appropriate milestone for inclusion/exclusion for the above criteria

  Updated Exclusion Criterion 11 and related text to allow the use of maribavir for CMV (Sections 1, 6.2, and 7.7.1).
  Rationale: Maribavir has recently been approved in some, but not all regulatory jurisdictions for the treatment of CMV infections and is therefore no longer considered to be an investigational antiviral agent. It is not considered to have anti-AdV activity.

  Updated Exclusion Criterion 12 to exclude pregnant females (Sections 1 and 6.2).

Updated Exclusion Criterion 14 and related text to provide more clarification on allergies to posoleucel or blood transfusion products that would preclude study participation (Sections 1, 5.1, and 6.2).

Updated Exclusion Criterion 15 to provide an exception for patients with no clinical or radiological manifestations of COVID-19 if the Investigator and Sponsor Medical Monitor concur on their enrollment (Sections 1 and 6.2).
Rationale: As the COVID-19 pandemic has evolved, investigators at clinical sites are reporting that they are treating HCT recipients who have persistently positive SARS-CoV-2 laboratory tests, but who do not appear to have clinically-significant disease attributable to SARS-CoV-2. In select cases, these patients may be eligible to participate in this study, and the exclusion criterion has been updated to reflect this.

- **Added flexibility in blood specimen testing to allow blood specimen results from local laboratory results to be used for confirmation of eligibility and dosing if AdV viral load results from the central laboratory are not available (Sections 1, 2, and 9.1.1).**

  Simplified blood specimen collection and testing by allowing sites to initiate screening activities based off specimens collected locally within 3 days of screening

  Added language to allow participants to be randomized and dosed (with Sponsor Medical Monitor approval) based on local laboratory AdV viremia results if the central laboratory screening viremia result is not yet available at the time of intended dosing

  Rationale: AdV infections in HCT recipients may progress rapidly. In order to prevent delays in randomization or dosing of otherwise eligible patients that may be caused solely by delays in obtaining AdV viral load results from the central laboratory, patients may enter the study based on local laboratory viral load data. In all cases, as before, all assessments of efficacy relating to AdV viral load values will use values from the central laboratory.

- **Expanded the screening window**

  Screening window expanded from 10 days to 21 days (Day -21 to Day -1) (Section 2).

  Rationale: This change was made based on feedback from clinical sites that indicated operational challenges in completing all screening procedures within the narrow 10 day window.

- **Added clarifying information regarding premature Crossover**

  Added text to clarify that participants with premature cross-over (ie, prior to Day 29) will be expected to have received both infusions of study treatment before evaluation by the Adjudication Committee (Section 5.1).

  Rationale: Added at the request of the Adjudication Committee who will be adjudicating the eligibility of these participants for crossover.

- **Added DSMB review and recommendation of preliminary safety data from 5 participants ≥1 and ≤6 years of age prior to enrolling participants under age 1**

Rationale: Removed the requirement for a protocol amendment prior to enrolling pts <1yr to reduce the operational burden for the sites. In place of a protocol amendment to support this change, the safety data from patients in the 1 – 6 year old age range will be reviewed by the DSMB before opening the study to participants <1 year of age. Once this decision to proceed has been made by the DSMB, it will be communicated to clinical sites, IRBs/ERCs, and regulatory agencies as appropriate.

- **Statistical Updates**

  Updated text to indicate that there will not be a separate SAP for the interim analysis, and that the study SAP will be finalized prior to the interim analysis (Sections 10.1 and 10.3).

  Rationale: Separate documents for these analyses are no longer considered to be necessary, and all the information will be consolidated into a single SAP document that will be finalized prior to any interim analysis.

  Added a sentence to indicate that the primary and key secondary efficacy endpoints will be analyzed under the estimand framework (Section 10.3.1).

  Removed details on missing data imputation and, instead, referred to the SAP for this information (Section 10.3.1.1).

  Added language to clarify that the key secondary efficacy endpoint will be tested sequentially after the primary endpoint reaches statistical significance (Sections 1 and 10.3.1.2).

  Deleted the Other Analyses section (formerly Section 10.3.3), as these will be detailed in the SAP.

  Updated language regarding the interim analysis to indicate that there will not be a separate SAP for the interim analysis and clarified language regarding the roles of the independent statistician and the DSMB and on maintaining the blind (Section 10.3.3).

- **Added language regarding premedication with an antihistamine**

  Text was added to allow premedication with an antihistamine similar to diphenhydramine that is preferred by the study site, and to allow diphenhydramine/acetaminophen doses that are routinely used at these sites to be used for participants with a prior history of reaction to blood products (Sections 7.1 and 7.1.1).

  Rationale: Some clinical sites routinely use antihistamines other than diphenhydramine for this purpose. In some cases, clinical sites routinely use standard doses for these pre-medications that are slightly different than the doses indicated in the protocol.

- **Streamlined study drug administration and dosing instructions**

  IP preparation and infusion procedure description has been removed from the protocol, and referral to the Cell Therapy Manual has been added. (Section 7.1)

  Rationale: Investigational product management is more extensively described in the Cell Therapy Manual.

- **Updated text to clarify that no subsequent infusion of blinded study treatment should occur in participants who develop new onset GVHD (Grade >2) or worsening of GVHD (Section 7.2).**

- **Added Clarifying information regarding Target Disease Endpoint Definitions**

  Added AdV carditis as a manifestation that will be adjudicated by the Adjudication Committee for target organ disease (Section 9.1.2 and Appendix 8).

  Updated the target disease endpoint definitions and added text to indicate that the definitions may be modified by the Adjudication Committee and updated version will be recorded in the Adjudication Committee charter (Appendix 8).

  Rationale: Carditis was added as a manifestation after an initial meeting with the Adjudication Committee. The added text relating to clinically significant viremia is intended to provide clarification that the definition is intended to apply to those participants whose clinically-significant viremia at study entry resolves, but who subsequently develop a recurrence of AdV infection, which will need to be adjudicated using the criteria in Appendix 8

Miscellaneous revisions to reflect administrative changes, correct typographical errors, correct inconsistencies within other study documents and addition of clarifying information

- Updated the sponsor's address and contact information (Title Page, Section 1).
- Added clarifying information regarding "recurrence dose" timing and assessments
- Added United States Adopted Name and International Nonproprietary Name, posoleucel, in lieu of ALVR105
- Added clarification that AEs to be captured for the primary safety endpoint are those that are treatment-emergent (Sections 1, 4, and 10.3.2).
- Minor changes involving grammar, wordsmithing, inconsistencies, and punctuation, as well as other minor editorial changes to improve clarity were made throughout the document

Amendment 1 Rationale

This amendment was made in response to regulatory agency feedback. Additional changes were made to correct errors and to provide additional clarity.

Major revisions include:

- Labeled safety objectives and endpoints as primary (Sections 1 and 4).
- Added a requirement for participants who receive a third dose for recurrence to undergo safety follow-up for 20 weeks after the third dose of study treatment (Sections 1 and 5.1).
- Added a statement that participating sites will adhere to the relevant safety standards of FACT and JACIE (Section 5.1).
- Added a statement that participants will be approached for enrollment in a long-term registry study (Section 5.3).
- Provided additional guidance on permitted and prohibited medications and the recording of concomitant medications (Section 7.7).

- Updated text such that any participant who develops irreversible, life-threatening, Grade 3 to 4 acute GVHD or a Grade 3 to 4 non-hematologic adverse event between the first and any subsequent dose of posoleucel or placebo that is considered related to study treatment administration should discontinue study treatment (Section 8.1).
- Added the Intent-to-Treat Population; all efficacy endpoints will be analyzed based on the Intent-to-Treat Population, and these analyses will be considered the primary analyses of efficacy (Sections 1, 10.2, and 10.3.1).
- Deleted the Modified Intent-to-Treat Population (Sections 1, 10.2, and 10.3.1).
- Updated the planned analysis of the primary efficacy endpoint to be analyzed based on logistic regression instead of Fisher's exact test. The model will include a term for treatment and, in order to take the randomization stratification variables into account, the following covariates: level of viremia (≥10,000 copies/mL or <10,000 copies/mL AdV DNA) and age (≥12 years or <12 years) (Sections 1 and 10.3.1.1).
- Provided justification for analysis of the primary efficacy endpoint at Day 29 and for durability of response assessments (Section 5.4).
- Added weekly AdV viral load detection in urine for patients with clinical signs and/or symptoms of AdV hemorrhagic cystitis until resolution of hemorrhagic cystitis (Sections 2 and 9.1.1, and Appendix 3).
- Added assessment of coagulation parameters (PT, INR, and PTT) at Days 1 and 29 of the Primary Study Period and Days 1' and 29' of the Cross-Over Period (Section 2 and Appendix 3).
- Provided additional clarification on timing of pregnancy testing relative to study treatment administration on Day 15 and added pregnancy testing to the Week 10 (Week 10'), Week 16 (Week 16'), Week 24 (Week 24'), and ET visits (Sections 2 and 9.3.1; Appendix 3).
- Updated the timing of the first visit of the Cross-Over Period from Week -6' to -1' (Day -42' to -1') to Week -2' to -1' (Day -10' to -1') (Section 2).
- Provided clarification that any evaluations required at the Day -10' to -1' visit of the Cross-Over Period do not have to be repeated if completed within 10 days as part of the Primary Study Period (Section 2).
- Removed the assessment of adenovirus viral load in nasopharyngeal swab from the Day -10' to -1' visit of the Cross-Over Period (Section 2).
- Added an assessment of aGVHD at Day 1 (Day 1') (Section 2).
- Updated language for stool collection to clarify that Screening, Day 1 (Day 1') and Day 29 (Day 29') collection is required for all patients, but collection at other timepoints is required only if the participant has symptoms; however, collection at these other timepoints should be collected in all participants if feasible (Section 2).
- Provided clarity on timing of radiological imaging during the Cross-Over Period (Sections 1, 2, and 9.1.3).

- Provided details on interim analyses and timing of finalizing both the interim analysis SAP and the main SAP relative to conducting interim analyses (Sections 1, 10.3, 10.3.3, and 10.3.4).
- Added additional guidance on post-infusion monitoring (Section 9.3.7).
- Added a statement that all protocol amendments will be submitted to regulatory authorities and ethics committees/IRBs as appropriate (Appendix 2).
- Added a statement that in some jurisdictions, legally effective informed consent must be obtained from all legal guardians for minor patients (Appendix 2).
- Provided guidance on estimating fraction of inspired oxygen (Sections 1 and 6.2; Appendix 9).

Signature Page for P-105-303 Adenovirus Protocol v5.0 30Nov2023
VV-CLIN-000353 v1.0

Approval Task	[redacted] 18:14:43 GMT+0000
Approval Task	[redacted] 0:00 GMT+0000
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