CLINICAL STUDY PROTOCOL

Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Posoleucel (ALVR105, Viralym-M) Compared to Placebo for the Prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV Infection and/or Disease, in High-Risk Patients After Allogeneic Hematopoietic Cell Transplant

Investigational Product: posoleucel (PSL), formerly ALVR105, Viralym-M
Protocol Number: P-105-202

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Sponsor:
AlloVir, Inc.
1100 Winter Street
Waltham, MA 02451 United States
Telephone: 617-433-2605

FINAL PROTOCOL

Amendment 5, Version 6.0, 11 January 2023

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol, *Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of posoleucel (ALVR105, Viralym-M) Compared to Placebo for the Prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV Infection and/or Disease, in High-Risk Patients After Allogeneic Hematopoietic Cell Transplant*. 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 and applicable national or regional regulations and guidelines.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

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LIST OF ABBREVIATIONS

Abbreviation	Definition or Term
AdV	Adenovirus
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cell Therapy
ATG	Anti-thymocyte globulin
BKV	BK virus
CAC	Clinical Adjudication Committee
CAR	Chimeric antigen receptor
CBC	Complete blood count
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination visit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HC	Hemorrhagic cystitis
HCT	Hematopoietic cell transplant
HCV	Hepatitis C virus
HHV-6	Human herpes virus 6
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council on Harmonisation

Abbreviation	Definition or Term
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous, -ly
IVIG	Intravenous immunoglobulin
JCV	JC virus
LLOQ	Lower limit of quantitation
MAGIC	Mount Sinai Acute GVHD International Consortium
mITT	Modified Intent to Treat
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIMP	Non-investigational medicinal product
PBMC	Peripheral blood mononuclear cell
Posoleucel	PSL, formerly AVLR105, Viralym-M
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PVSS	Pharmacovigilance and Safety Services
Q	Every
qPCR	Quantitative polymerase chain reaction
QTL	Quality tolerance limit
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SSRE	Sample size re-estimation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VL	Viral load
VST	Virus-specific T cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of posoleucel (ALVR105, Viralym-M) Compared to Placebo for the Prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV Infection and/or Disease, in High-Risk Patients After Allogeneic Hematopoietic Cell Transplant

Protocol Number: P-105-202

Rationale:
This is a Phase 2/3 study to evaluate the efficacy and safety of posoleucel (formerly known as Viralym-M and ALVR105) for the prevention of clinically significant adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and John Cunningham virus (JCV) infections and/or disease in patients at high risk for these viruses following allogeneic hematopoietic cell transplant (HCT).
In healthy, immunocompetent individuals, T cell immunity plays a central role in defending against viruses. In HCT recipients, the use of potent immunosuppressive regimens (and subsequent associated immunocompromise) leaves patients susceptible to severe viral infections. In approximately 90% of allogeneic HCT patients, the suppressed immune system allows viruses that were previously in a latent, quiescent state to reactivate and more than 60% of allogeneic HCT patients experience a reactivation of more than one virus, including BKV, CMV, AdV, EBV and HHV-6 (Hill 2017). Viral infections result in devastating morbidities and have become leading etiologies for transplant-related mortality. There is no approved anti-viral agent that can prevent such potentially fatal multi-virus infection(s) as a single therapy. Some off-label use of antiviral agents is associated with significant toxicities (notably myelosuppression and renal toxicity which might impede their use) and the emergence of drug-resistant viruses.
As delay in the recovery of endogenous virus-specific T cells (VSTs) is clearly associated with viral reactivation and disease in these patients, cellular immunotherapy to restore viral-specific immunity has been investigated as a potential therapeutic option. The development of posoleucel for the prevention and preemptive treatment of AdV, BKV, CMV, EBV, HHV-6, or JCV infections aims to address this important unmet medical need.
This study is designed to evaluate the capability of posoleucel to prevent serious viral infections in high-risk patients post-HCT.

Objectives and Endpoints:

Objectives	Endpoints
Primary 1. To compare the efficacy of posoleucel to placebo by the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 14	1. The number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 14
Key Secondary 1. To compare the efficacy of posoleucel to placebo by the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 26	1. The number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 26
Secondary 2. To compare the efficacy of posoleucel to placebo by clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 due to each individual virus as determined by an independent, blinded CAC through Week 14 and Week 26	2. Clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6, from each individual virus as determined by an independent, blinded CAC through Week 14 and Week 26 (5 endpoints each at Week 14 and Week 26)
Exploratory 1. To determine the incidence and number of new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26	1.1 Proportion of patients with new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26 1.2 For patients with new hospitalizations, number of new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26
2. To assess patient-reported quality of life (QoL) through Week 26	2 Change from baseline in QoL assessments, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26
3. To compare the efficacy of posoleucel to	

Objectives	Endpoints
placebo in the proportion of patients with undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the lower limit of quantification [LLOQ]) at Week 14 and week 26	3.1 Undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the LLOQ) at Week 14 and Week 26 3.2 Time to event analysis of clinically significant infections
4. To determine hospital length of stay (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26	4 Number of hospital days related to clinically significant AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26
5. To evaluate persistence of posoleucel cells	5 Persistence of posoleucel
6. To compare the efficacy of posoleucel to placebo in mean area under the curve (AUC) viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV each through Week 14 and Week 26	6 Mean viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV for each individual virus through Week 14 and Week 26, obtained as AUC/number of days (6 endpoints each at Week 14 and Week 26)
Safety 1. To characterize the safety and tolerability of posoleucel when administered to patients at high-risk for AdV, BKV, CMV, EBV, HHV-6, or JCV following allogeneic HCT	**Including** 1.1 Severity and incidence of acute GVHD 1.2 Severity and incidence of chronic GVHD 1.3 Severity and incidence of cytokine release syndrome 1.4 Severity and incidence of graft failure 1.5 Severity and incidence of infusion related reactions 1.6 Severity and incidence of clinically significant cytopenias 1.7 Severity and incidence of renal dysfunction 1.8 Overall and non-relapse-related mortality 1.9 Incidence and severity of TEAEs, including AESIs, and clinical laboratory results

Overall Design

This is a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled trial comparing posoleucel to placebo for the prevention of infection or disease due to AdV, BKV, CMV, EBV, HHV-6, or JCV in high-risk adult and pediatric patients after allogeneic HCT.

There are 2 parts to the study, an open label Phase 2 cohort and the primary Phase 3 randomized study cohort. Approximately 327 to 337 eligible allogeneic HCT recipients will be dosed. The first 25 to 35 patients (open label cohort) will receive posoleucel for 14 weeks of open-label dosing and an assessment and optimization of study processes will be performed.

A review by the Data Safety Monitoring Board (DSMB) was conducted when 26 patients in the open label cohort completed 30 days of treatment, and the DSMB confirmed agreement with initiation of Phase 3. Approximately 302 patients in the Phase 3 study cohort will be dosed with posoleucel or placebo at a 1:1 ratio. Open label patients already enrolled will continue in the open label cohort.

Once patients are assigned to posoleucel or placebo, administration can begin as early as 15 days post-HCT as long as the patient has met the clinical engraftment criteria, and no later than 42 (+7) days post-HCT. AdV, BKV, CMV, EBV, HHV-6, and JCV viremia will be monitored as detailed in the Schedule of Activities (SoA). When possible the first dose should be targeted to occur after engraftment and between Day 18 and Day 25 post-HCT.

Patients may receive all standard of care antiviral prophylaxis at their treating institutions including letermovir.

Additionally, an independent, blinded CAC will be established. This CAC will review Phase 3 clinical, virologic, histopathological data, and the Investigator's assessments. The CAC will use the reviewed information for adjudicating all potential cases of clinically significant infection or end-organ disease due to AdV, BKV, CMV, EBV, HHV-6, and JCV, and for attributing, as appropriate, the mortality due to graft failure, relapse of primary disease, related to infection/disease of AdV, BKV, CMV, EBV, HHV-6, and JCV-V, or other causes, as defined in the CAC charter, throughout the trial.

Intervention Groups, Key Inclusion Criteria, and Duration:

Male and female patients of any age at high risk for viral infection after HCT. Enrollment of participants <1 year of age at the time of informed consent will occur only once DSMB reviews preliminary safety data are available from 5 participants ≥1 and ≤6 years of age:

1. Be within 15 and 42 days of receiving a first allogeneic HCT at the time of randomization and demonstrated clinical engraftment, as evidenced by absolute neutrophil count (ANC) $\geq 500/mm^3$.
2. Patients meeting <u>one or more of the following criteria</u> at the time of randomization:
   - Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR
   - Haploidentical donor
   - Matched unrelated donor (Approximately 1/3 of total patients will have received a transplant from a MUD, without T cell depletion)
   - Mismatched unrelated donor
   - Umbilical cord blood as stem cell source
   - Ex vivo graft manipulation resulting in T cell depletion
   - Received T-cell depletion by anti-thymocyte globulin (ATG) or alemtuzumab (Campath-1H)

Patients will be tested by the central laboratory during Screening using polymerase chain reaction (PCR) assays for each virus. The open label cohort and the Phase 3 study cohort will include patients with and without detectable AdV, BKV, CMV, EBV, HHV-6, and JCV viremia. Randomization in the Phase 3 study cohort will occur prior to Day 1 (dosing day).

Between 15 to 42 days post-HCT, patients will begin receiving posoleucel (2×10^7 cells for patients <40 kg or 4×10^7 cells for patients ≥40 kg), every 14 days for 14 weeks (7 study drug administrations and 2-week follow-up after the last administration). For patients on ATG, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies, study therapy will begin at least 21 days from the last dose of anti-T cell antibody. The total duration of patient participation is up to approximately 36 weeks, including up to 10 weeks for screening, the 14-week treatment period, and 12 weeks of follow-up.

Statistical Analysis

Summary statistics will be presented by treatment group. The primary analyses will be based on the Phase 3 portion of the study. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized using the frequency count and the percentage of patients in each category. All two-sided hypothesis tests will be performed at the 0.05 significance level, and all one-sided hypothesis tests will be performed at the 0.025 significance level.

The primary endpoint will be analyzed based on patients in the modified intent-to-treat population in the Phase 3 portion of the study. It will be summarized by treatment group using frequency counts and percentages. It will be analyzed using Analysis of Variance (ANOVA) with terms for study treatment and letermovir prophylaxis, age and the underlying allogeneic transplant risk of viral infections to test the null hypothesis that the mean number of clinically significant AdV, BKV, CMV, EBV, HHV-6 or JCV infections or episodes of end-organ disease per patient in posoleucel treated patients through Week 14 is greater than or equal to the corresponding mean for placebo treated patients versus the alternative hypothesis that the mean number of clinically significant infections per patient is less for posoleucel treated patients.

The key secondary endpoint, number of clinically significant infections or episodes of end-organ disease due to AdV, BKV, CMV, EBV, HHV-6, or JCV per patient through Week 26 will be analyzed in the same manner as the primary endpoint. The analyses of the other efficacy endpoints will be described in the statistical analysis plan (SAP).

All safety data will be summarized by treatment arm using the Safety Population for the Phase 3 study cohort. For open label cohort, results will be presented overall, as all patients in this cohort receive only posoleucel. Categorical endpoints will be summarized using the number and percentage of patients within each category. Continuous endpoints will be summarized descriptively with summary statistics (number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum).

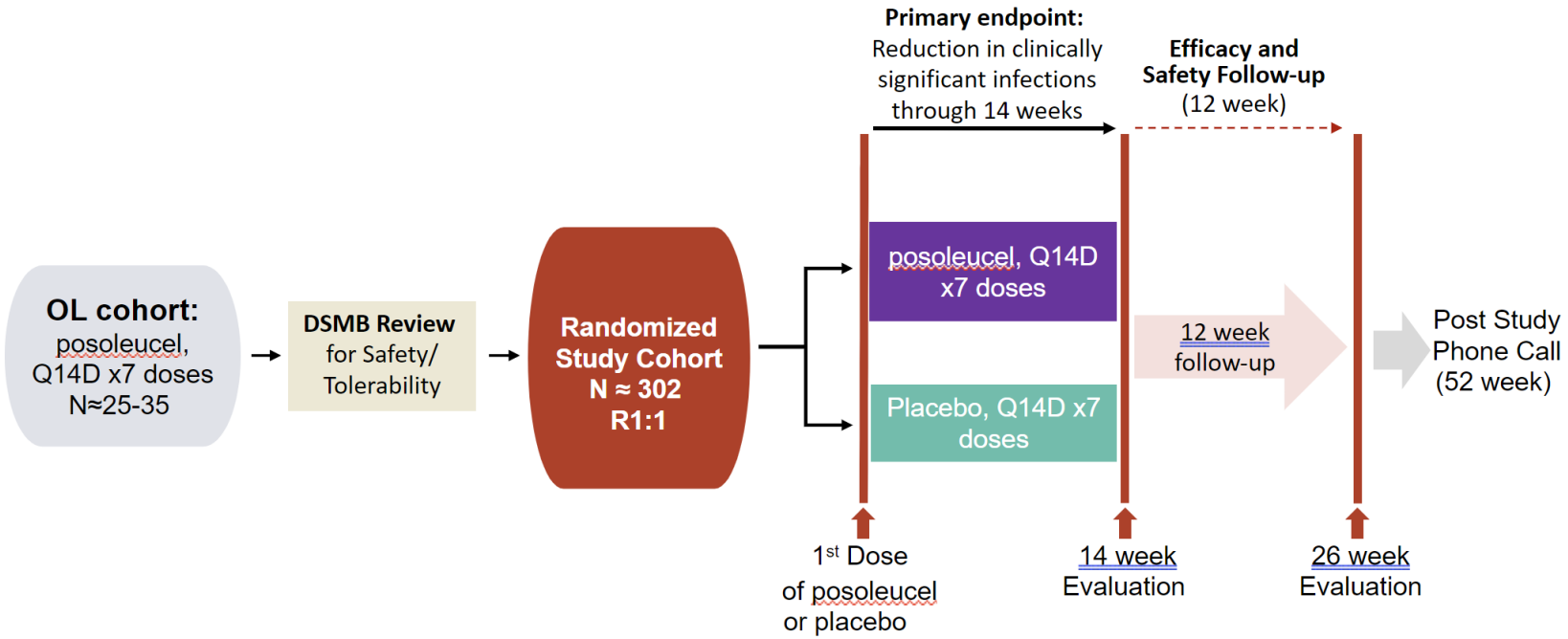
Adverse events will be coded using the Medical Dictionary for Regulatory Activities. A treatment emergent adverse event (TEAE) is defined as an AE with onset or worsening on or after the first dose of study treatment through Week 26. TEAEs will be summarized by System Organ Class and Preferred Term and further by severity (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) and by relationship to study treatment. The incidence of SAEs will be similarly summarized.

The incidence of AEs of special interest (AESIs) and their corresponding exact binomial 95% confidence intervals for the true incidence will be presented by treatment group.

1.2. Schema

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

Figure 1: Study Flow Chart



Abbreviations: AdV = adenovirus; BKV = BK virus; CMV = cytomegalovirus; D = day; DSMB = Data Safety Monitoring Board; OL = open-label; Q = every; R = randomized/randomization

1.3. Schedules of Activities

Table 1: Schedule of Activities–Screening Period

	Screening Period[1]	Screening Visit[1]
Study Day	May be from Day -28 prior to planned date of HCT	May be up to 42 days post HCT
Study Procedures		
Informed consent/assent[2]	X	
I/E criteria		X
Demographics		X
Medical history[3]		X
Documentation of HLA typing[4]		X
Prior and concomitant medications including conditioning regimen for HCT	X	X
Complete physical examination		X
Weight and height[5]		X
Vital signs[6]		X
12-lead ECG		X
Clinical labs[7]		X
Pregnancy test[8]		X
Testing for HIV, HCV, HBV[9]		X
BKV, AdV, CMV, JCV, EBV, and HHV-6 viral load[10]		X

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ; β-HCG = beta human chorionic gonadotropin; BKV = BK virus; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ECG = electrocardiogram; HBV = hepatitis B virus; HCT = hematopoietic stem cell transplant; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HHV-6 = human herpesvirus 6; HLA = human leukocyte antigen; ICF = informed consent form; I/E = inclusion and exclusion; JCV = JC virus; LFT = liver function test; NA = not applicable; PBMCs = peripheral blood mononuclear cells

Note: Visits may be done via a home health visit as agreed with the Sponsor.

1. Informed consent may be obtained as early as 28 days prior to planned HCT, however, Screening Visit procedures must occur after HCT and up to 42 days post-HCT.
2. Prior to conducting any study-related activities, written informed consent/assent to participate in the study must be provided by the patient and/or patient's

guardian. The informed consent form may be signed at any time during the screening period and must be signed to conduct the screening visit.

3. To include CMV sero status of both patient and HCT donor and EBV status for pediatric patients
4. The HLA type of the patient and their HCT cell donor(s) will be obtained from the medical record.
5. Height and weight will be measured at screening.
6. Includes body temperature, blood pressure, heart rate, O_2 saturation, and respiration rate and will be measured after resting for 5 minutes.
7. Clinical laboratory assessments collected locally as part of standard of care may be used to fulfill Screening requirements only. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin (total and direct), AST, and ALT). Urinalysis must be performed at Screening visit only. Patients in diapers or unable to provide urinalysis are exempted from this requirement.
8. For female patients who are of childbearing potential, at Screening a β-HCG blood test will be performed.
9. Serum will be screened for HIV, HBV, and HCV antibodies with reflex nucleic acid testing of plasma. Medical records of previous testing in the last 3-6 months may be used in lieu of collecting samples.
10. Viral loads of AdV, BKV, CMV, JCV, and HHV-6 in plasma and of EBV in PBMCs or plasma will be measured. Viral load testing should NOT be done on day of HCT.

Table 2: Schedule of Activities – Treatment and Follow-up Period for Patients ≥12 Years of Age (Week 1 to 52)

		Treatment Period											Follow-up Period		Post Study
Time Period	**Random-ization[1]**	**Study Drug Administration Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 20**	**Wk 26/ET[16]**	**Wk 52**
Study Day		**1[2]**	**8**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**98**	**140**	**182**	**365**
Visit Window (Days)		**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±10**	**±10**	**±30**
Study Procedures															
Review of I/E criteria and confirmation of eligibility[2]	X	X													
Prior & concomitant medications and HCT conditioning regimen		X		X		X		X	X	X	X	X	X	X	
Adverse events[3]	X	X		X		X		X	X	X	X	X	X	X	
Physical examination[4]		X		X		X		X	X	X	X	X			
Weight		X				X			X		X	X		X	
Vital signs[5,6]		X		X		X		X	X	X	X	X	X	X	
Clinical labs[7]		X		X		X		X	X	X	X	X	X	X	
Pregnancy test[8]		X		X		X		X	X	X	X				
BKV, AdV, CMV, JCV, and HHV-6 viral load[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	
EBV PBMCs or plasma[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization[10]	X														
Virus- Specific T Cell Assessment[11]		X				X		X		X	X	X	X	X	
Study treatment administration[12]		X		X		X		X	X	X	X				
Post infusion monitoring[6]		X		X		X		X	X	X	X				
Infection assessment[13]		Infection assessments occur for patients who require either treatment for viral infection or disease or initiation of preemptive therapy ◄——————————————————————► X													

		Treatment Period											Follow-up Period		Post Study
Time Period	**Random-ization[1]**	**Study Drug Administration Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 20**	**Wk 26/ET[16]**	**Wk 52**
Study Day		**1[2]**	**8**	**14**	**21**	**28**	**35**	**42**	**56**	**70**	**84**	**98**	**140**	**182**	**365**
Visit Window (Days)		**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±10**	**±10**	**±30**
Study Procedures															
Quality of Life (EQ- 5D-5L, EQ-5D-Y, EQ-5D-Y Proxy Version 1)[14]		X				X			X		X	X	X	X	
Post-study follow-up contact[15]															X

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ; β-HCG = beta human chorionic gonadotropin; BKV = BK virus; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ECG = electrocardiogram; ET = Early Termination Visit; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HHV-6 = human herpesvirus 6; I/E = inclusion and exclusion; IVIG = intravenous immunoglobulin; JCV = JC virus; LFT = liver function test; NA = not applicable; PBMC = peripheral blood mononuclear cell; SoA = Schedule of Activities; VST = virus-specific T cell; Wk = week

Note: Visits for weeks where no infusion is scheduled (odd-numbered weeks) may be done as home health visits. Other visits may be done via a home health visit as agreed with the Sponsor.

1. Randomization may occur on the same day as Screening and can occur up to 42 days post HCT.
2. Dosing should be completed as early as possible after patient meets eligibility criteria and may be up to 49 days post HCT with Sponsor approval for dosing after day 42. When possible the first dose should be targeted to occur after engraftment and between Day 18 and Day 25 post-HCT. Unless noted otherwise, Day 1 procedures must be performed within 72 hours prior to study treatment administration. Baseline is Day 1. On Day 1, confirmation of relevant eligibility criteria should occur prior to dosing.
3. Adverse event monitoring should include the collection of all adverse events through Week 26 in all patients.
4. After randomization, a targeted physical examination may be performed. Post-HCT, the skin should be examined, even if the patient has no complaint, for evidence of rash/acute skin GVHD.
5. Includes body temperature, blood pressure, pulse rate, O_2 saturation, and respiratory rate and will be measured after resting for 5 minutes. After randomization, vital signs should be performed during and after infusions and if targeted physical examination is performed.
6. Patients will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs, including body temperature, pulse rate, O_2 saturation, respiratory rate, and blood pressure, will be measured prior to starting infusion, at the end of the infusion, and at 15, 30, and 60 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
7. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin (direct and indirect); AST, and ALT. CD4 and CD8 counts will be collected on Day 1 and Week 14 only. On dosing days, laboratory safety evaluations (hematology, and chemistry) specified in Section 8.4.4 will be performed prior to study drug initiation. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) described in the study manual(s).
8. For female patients of childbearing potential, a urine pregnancy test will be performed at the site prior to study therapy initiation. If the urine pregnancy test result is negative, the patient will be eligible for dosing and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not be dosed and should receive a β-HCG blood test confirming positive result before failing randomization. A urine pregnancy test will be performed

prior to each treatment for female patients who are of childbearing potential.

9. Viral loads of AdV, BKV, CMV, JCV, and HHV-6 in plasma and of EBV in PBMCs or plasma will be measured. Additional post-infusion samples may be collected, as clinically indicated. If patient develops any clinically significant infection of AdV, BKV, CMV, EBV, HHV-6, or JCV at any point during the study periods, infection assessments should be followed prior to initiating standard of care therapy (see Section 8.3). Baseline viral load will be the Day 1 assessment. On dosing days, all laboratory samples should be collected prior to dosing. If patient is seen in the clinic on weeks 7, 9, 11 and 13 attempts should be made to collect viral load samples for central analysis.
10. Patients in the open label cohort will be assigned to posoleucel. Patients in the Phase 3 study cohort will be randomized to either posoleucel or placebo. Randomization will be about 2 to 3 days before Day 1.
11. Patient PBMCs or whole blood will be assessed for the presence of virus-reactive T cells, this analysis will not include whole genome sequencing.
12. All patients will receive infusions of either posoleucel or placebo. Patients will receive the same dose for all posoleucel infusions depending on their weight at screening: 2×10^7 cells dose for patients <40 kg or 4×10^7 cells dose for patients ≥40 kg, administered at a dose interval of every 14 days (±3 days). Placebo infusions will be administered, using the same weight-based dosing as for posoleucel, every other week in order to maintain the blind. As GVHD and CRS are a theoretical safety concern associated with administration of third-party allogeneic T cells, the incidence and severity of GVHD and CRS will be monitored during the study. No patients will be permitted to receive a subsequent infusion of posoleucel if they meet the criteria outlined in Section 7.1. If treatment is discontinued for CRS or GVHD, these patients should continue to be followed in the study. If they are discontinued from the study, they should be followed until the resolution of symptoms. Patients may resume treatment only with consultation and agreement between the Medical Monitor and the Investigator. If possible, IVIG and posoleucel should not be administered on the same day.
13. The infection assessment will be performed for all patients who require either treatment for disease or initiation of preemptive therapy through Week 26 (Section 8.3). It is very important to ensure that all procedures are performed prior to the initiation of treatment of viral diseases or initiation of preemptive therapy (ie, on the day anti-viral therapy is initiated). Most importantly, a plasma sample for AdV, BKV, CMV, HHV-6, and JCV and a PBMC or plasma sample for EBV for PCR testing at the central laboratory should be collected as outlined in Section 8.3.2. Patients who develop viral infections will continue to be followed in the study and complete all remaining visits through Week 26.
14. Assessment of quality of life (using EQ-5D-5L, EQ-5D-Y, or EQ-5D-Y Proxy Version 1 questionnaires, as age-appropriate) should be completed prior to any study procedures.
15. The Early Termination Visit will be performed for all patients who are prematurely discontinued from the study up to Week 26. It is very important to ensure that all procedures are performed in such patients at this visit prior to discontinuing the patient from the trial. Most importantly, a plasma sample for AdV, BKV, CMV, HHV-6, and JCV and a PBMC or plasma sample for EBV for PCR testing at the central laboratory should be collected at this visit.
16. Post-study follow-up contact to assess patient status. Patients enrolled in the United Kingdom will not complete a post study follow-up contact.

Table 3: Schedule of Activities – Treatment and Follow-up Period for Patients < 12 Years of Age (Week 1 to 52)

		Treatment Period								Follow-up Period		Post Study
Time Period	**Random-ization[1]**	**Study Drug Administration Day**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 20**	**Wk 26 /ET[16]**	**Wk 52**
Study Day		**1[2]**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**140**	**182**	**365**
Visit Window (Days)		**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±10**	**±10**	**±30**
Study Procedures												
Review of I/E criteria and confirmation of eligibility[2]	X	X										
Prior & concomitant medications and HCT conditioning regimen		X	X	X	X	X	X	X	X	X	X	
Adverse events[3]	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[4]		X	X	X	X	X	X	X	X			
Weight		X		X		X		X	X		X	
Vital signs[5,6]		X	X	X	X	X	X	X	X	X	X	
Clinical labs[7]		X	X	X	X	X	X	X	X	X	X	
Pregnancy test[8]		X	X	X	X	X	X	X				
BKV, AdV, CMV, JCV, and HHV-6 viral load[9]		X	X	X	X	X	X	X	X	X	X	
EBV PBMCs or plasma[9]		X	X	X	X	X	X	X	X	X	X	
Randomization[10]	X											
Virus- Specific T Cell Assessment[11]		X		X	X		X	X	X	X	X	
Study treatment administration[12]		X	X	X	X	X	X	X				
Post infusion monitoring[6]		X	X	X	X	X	X	X				
Infection assessment[13]		Infection assessments occur for patients who require either treatment for viral infection or disease or initiation of preemptive therapy ←→ X										
Quality of Life (EQ-5D-Y, EQ-5D-Y Proxy Version 1)[14]		X		X		X		X	X	X	X	
Post-study follow-up contact[15]												X

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ; β-HCG = beta human chorionic gonadotropin; BKV = BK virus; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ECG = electrocardiogram; ET = Early Termination Visit; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HHV-6 = human herpesvirus 6; I/E = inclusion and exclusion; IVIG = intravenous immunoglobulin; JCV = JC virus; LFT = liver function test; NA = not applicable; PBMC = peripheral blood mononuclear cell; SoA = Schedule of Activities; VST = virus-specific T cell; Wk = week

Note: Visits for weeks where no infusion is may be done via a home health visit as agreed with the Sponsor.

1. Randomization may occur on the same day as Screening, and can occur up to 42days post HCT.
2. Dosing should be completed as early as possible after patient meets eligibility criteria and may be up to 49 days post HCT with Sponsor approval for dosing after Day 42. When possible the first dose should be targeted to occur after engraftment and between Day 18 and Day 25 post-HCT. Unless noted otherwise, Day 1 procedures must be performed within 72 hours prior to study treatment administration. Baseline will be Day 1. On Day 1, confirmation of relevant eligibility criteria should occur prior to dosing.
3. Adverse event monitoring should include the collection of all adverse events through Week 26 in all patients.
4. After randomization, a targeted physical exam may be performed. Post-HCT, the skin should be examined, even if the patient has no complaint, for evidence of rash/acute skin GVHD.
5. Includes body temperature, blood pressure, pulse rate, O_2 saturation, and respiratory rate and will be measured after resting for 5 minutes. After randomization, vital signs should be performed during and after infusions and if targeted physical examination is performed.
6. Patients will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs, including body temperature, pulse rate, O2 saturation, respiratory rate, and blood pressure, will be measured prior to starting infusion, at the end of the infusion, and at 15, 30, and 60 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
7. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin (direct and indirect); AST, and ALT. CD4 and CD8 counts will be collected on Day 1 and Week 14 only. On dosing days, laboratory safety evaluations (hematology, and chemistry) specified in Section 8.4.4 will be performed prior to study drug initiation. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) described in the study manual(s).
8. For female patients who are of childbearing potential, a urine pregnancy test will be performed at the site prior to study therapy initiation. If the urine pregnancy test result is negative, the patient will be eligible for dosing and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not be dosed and should receive a β-HCG blood test confirming positive result before failing randomization. A urine pregnancy test will be performed prior to each treatment for female patients who are of childbearing potential.
9. Viral loads of AdV, BKV, CMV, JCV, and HHV-6 in plasma and of EBV in PBMCs or plasma will be measured. See the Laboratory Manual for more detailed information on volume of blood draws. Additional post-infusion samples may be collected, as clinically indicated. If patient develops any clinically significant infection of AdV, BKV, CMV, EBV, HHV-6, or JCV at any point during the study periods, infection assessments should be followed prior to initiating standard of care therapy (see Section 8.3). Baseline viral load will be the Day 1 assessment. On dosing days, all lab samples should be collected prior to dosing.
10. Patients in the open label cohort will be assigned to posoleucel. Patients in the Phase 3 study cohort will be randomized to either posoleucel or placebo. Randomization will be about 2 to 3 days before Day 1.
11. Patient PBMCs or whole blood will be assessed for the presence of virus-reactive T cells, this analysis will not include whole genome sequencing.
12. All patients will receive infusions of either posoleucel or placebo. Patients will receive the same dose for all posoleucel infusions depending on their weight at screening: 2 ×X 10^7 cells dose for patients <40 kg or 4 × 10^7 cells dose for patients ≥40 kg, administered at a dose interval of every 14 days (±3 days). Placebo infusions will be administered, using the same weight-based dosing as for posoleucel, every other week in order to maintain the blind. As GVHD and CRS are a theoretical safety concern associated with administration of third-party allogeneic T cells, the incidence and severity of GVHD and CRS will be monitored during the study. No patients will be permitted to receive a subsequent infusion of posoleucel if they meet the criteria outlined in Section 7.1. If treatment is discontinued for CRS or GVHD, these patients should continue to be followed in the study. If they are discontinued from the study, they should be followed until the resolution

of symptoms. Patients may resume treatment only with consultation and agreement between the Medical Monitor and the Investigator. If possible, IVIG and posoleucel should not be administered on the same day.

13. The infection assessment will be performed for all patients who require either treatment for disease or initiation of preemptive therapy through Week 26 (Section 8.3). It is very important to ensure that all procedures are performed prior to the initiation of treatment of viral diseases or initiation of preemptive therapy (ie, on the day anti-viral therapy is initiated). Most importantly, a plasma sample for AdV, BKV, CMV, HHV-6, and JCV and a PBMC or plasma sample for EBV for PCR testing at the central laboratory should be collected as outlined in Section 8.3.2 Patients who develop viral infections will continue to be followed in the study and complete all remaining visits through Week 26.
14. Assessment of quality of life (using EQ-5D-Y or EQ-5D-Y Proxy Version 1 questionnaires, as age-appropriate) should be completed prior to any study procedures.
15. The Early Termination Visit will be performed for all patients who are prematurely discontinued from the study up to Week 26. It is very important to ensure that all procedures are performed in such patients at this visit prior to discontinuing the patient from the trial. Most importantly, a plasma sample for AdV, BKV, CMV, HHV-6, and JCV and a PBMC or plasma sample for EBV for PCR testing at the central laboratory should be collected at this visit.
16. Post-study follow-up contact to assess patient status. Patients enrolled in the United Kingdom, will not complete a post study follow-up contact.

2. INTRODUCTION

Posoleucel (also known as Viralym-M and formerly known as ALVR-105) is a cellular therapy consisting of third-party, multivirus-specific T cells with specificity for adenovirus [AdV], BK virus [BKV], John Cunningham virus [JCV], human herpesvirus 6 [HHV- 6], Epstein-Barr virus [EBV], and cytomegalovirus [CMV] in cryopreservation medium.

AlloVir is developing posoleucel, a novel multivirus-specific cellular therapy, to treat or prevent a number of serious, virus-associated causes of morbidity and mortality after allogeneic hematopoietic cell transplant (HCT), including those caused by infection or reactivation with BKV (and the related polyomavirus JCV), CMV, HHV-6, EBV, and AdV.

2.1. Study Rationale

This is a Phase 2/3 study to evaluate the efficacy and safety of posoleucel for the prevention of clinically significant AdV, BKV, CMV, EBV, HHV-6, and JCV)) infections and/or disease in patients at high risk for these viruses following allogeneic HCT. In healthy, immunocompetent individuals, T cell immunity plays a central role in defending against viruses. In HCT recipients, the use of potent immunosuppressive regimens (and subsequent associated immunocompromise) leaves patients susceptible to severe viral infections. In approximately 90% of allogeneic HCT patients, the suppressed immune system allows viruses that were previously in a latent, quiescent state to reactivate and more than 60% of allogeneic HCT patients experience a reactivation of more than one virus, including BKV, CMV, AdV, EBV, and HHV-6 (Hill 2017). Viral infections result in devastating morbidities and have become leading etiologies for transplant-related mortality. There is no approved anti-viral agent that can prevent such potentially fatal multi-virus infection(s) as a single therapy. Some off-label use of antiviral agents is associated with significant toxicities (notably myelosuppression and renal toxicity which might impede their use) and the emergence of drug-resistant viruses.

As delay in the recovery of endogenous virus-specific T cells (VSTs) is clearly associated with viral reactivation and disease in these patients, cellular immunotherapy to restore viral-specific immunity has been investigated as a potential therapeutic option. The development of posoleucel for the prevention and preemptive treatment of AdV, BKV, CMV, EBV, HHV-6, or JCV infections aims to address this important unmet medical need.

This study is designed to evaluate the capability of posoleucel to prevent serious viral infections in high-risk patients post-HCT.

2.2. Background

During the period of immune recovery after allogeneic HCT, viral infections and reactivations, which are normally controlled by T cell immunity, are an important cause of morbidity and mortality. The risk for infection is dictated by a number of factors, including the degree of immunosuppression and the immune status of the donor. Reactivation of latent viruses such as CMV and BKV, or primary infection with a virus such as AdV, has become increasingly prominent. In a study at a large United States (US) HCT center, in approximately 90% of allogeneic HCT patients, the suppressed immune system allows viruses that were previously in a latent, quiescent state to reactivate and more than 60% of allogeneic HCT patients experience a reactivation of more than one virus, including BKV, CMV, AdV, EBV and HHV-6 (Hill 2017). In another recent study of infections following haploidentical allogeneic HCT, Slade, et al

documented that 72% of patients experienced at least one severe viral infection (Slade 2017). Fifteen percent of patients developed CMV infection despite prophylaxis, and 19% developed BK virus-associated hemorrhagic cystitis. One of 3 children is reported to have an AdV infection within 6 months following allogeneic HCT (Sedláček 2019). Progression to AdV disease is associated with significant morbidity and mortality rates of up to 50% (Zecca 2019). Similarly, Mulanovich and colleagues (2011) reported that, among patients receiving either cord blood or T-cell depleted transplants, viral infections were frequent and the most common cause of death in both groups. Even among T cell-replete transplants using the post-cyclophosphamide protocol, Crocchiolo (2015) reported the incidence of viral infections to be 70%, with CMV and BKV being the most frequent and the most clinically threatening etiologies. The risk of mortality in the first 60 days post-transplant was approximately 18 times greater for patients with a CMV viral load ≥250 IU/mL (Green 2016).

2.2.1. Overview of Nonclinical Studies with *Posoleucel*

Consistent with guidance from the United States Food and Drug Administration (FDA), AlloVir proceeded to clinical studies following completion of in vitro studies. No nonclinical animal pharmacology, pharmacokinetic, or toxicology studies of posoleucel have been conducted or are planned. For additional information related to nonclinical studies with posoleucel, see the Investigator's Brochure.

2.2.2. Overview of Clinical Studies with Virus-Specific T Cells

2.2.2.1. Results of the CHARMS Study with Third Party-Derived Multivirus-Specific T Cells, *Posoleucel*

To investigate the safety and clinical efficacy of posoleucel, a multivirus-specific T cell product reactive for BKV, AdV, HHV-6, EBV, and CMV generated from third-party, healthy, eligible donors, a Phase 1/2a clinical study was conducted in recipients of allogeneic HCT with drug-refractory infections with ≥1 of the 5 viruses targeted by posoleucel (Tzannou, 2017). In this study, patients received a single IV infusion of 2×10^7 partially HLA-matched posoleucel cells/m^2, with the option to receive a second infusion after 4 weeks (actual range 14 days to >6 weeks) and additional infusions at biweekly intervals thereafter. Therapy with standard antiviral medications could be continued at the discretion of the treating physician (Tzannou, 2017).

A total of 58 patients with drug-refractory infections following allogeneic HCT were infused with posoleucel cell lines matched at 1 to 6 HLA antigens; 54 of these patients completed study treatment and the initial 28-day safety follow-up (the first 38 patients to complete the study are reported in Tzannou et al, 2017. Of the 71 total infections treated, 25 (35.2%) infections were BKV, and 24 (33.8%) infections were CMV. Of the 58 patients who were treated (one of whom had 2 courses of treatment), 48 patients were treated for a single virus, 10 patients were treated for 2 viral infections, and 1 patient was treated for infections by 3 different viruses.

All infusions were well tolerated. None of the patients developed cytokine release syndrome (CRS). In the weeks after infusion, 1 patient developed recurrent Grade 3 gastrointestinal (GI) graft versus host disease (GVHD) following rapid systemic corticosteroid taper, and 8 patients developed recurrent (n = 4) or de novo (n = 4) Grade 1 to 2 skin GVHD, which resolved with the administration of topical treatments (n = 7) and reinitiation of systemic corticosteroids after taper (n = 1). Between 3 and 6 months after infusion, 2 patients experienced a flare of upper GI GVHD, which resolved after a brief systemic corticosteroid course.

Fifty-four (93%) of 58 evaluable patients had either a partial or complete clinical or virological response (either PR [defined as >50% reduction in viral load, or >50% improvement of clinical signs and symptoms] or CR [defined as return of the viral load to the normal range and resolution of clinical signs and/or symptoms]); no response was observed in 2 patients with AdV, and 1 each with CMV and HHV-6. Of note, all 23 patients with BKV-associated hemorrhagic cystitis (HC), 2 of 3 patients with CMV colitis, the patient with CMV encephalitis (n = 1), the patients with AdV enteritis (n = 1) and AdV HC (n = 1), and 2 patients with HHV-6 encephalitis had improvement or resolution of symptoms within 6 weeks of treatment. In most responders (CR or PR), a post-infusion increase in the frequency of circulating VSTs was detected.

In addition to patients with post-HCT CMV-, EBV-, AdV-, BKV-, and HHV-6-associated infections, patients with JCV infections were also enrolled in this Phase 1/2 study. This decision was based on the identical nature of BKV and JCV T cell epitopes and on results of previous studies. More recently, it was demonstrated that partially HLA-matched third-party BKV-specific T cells could produce similar results in 3 immunosuppressed patients with progressive multifocal leukoencephalopathy (PML). Post-infusion, 2 patients experienced an alleviation of the clinical signs and imaging features of PML while the third patient had a reduction in JC viral load and stabilization of symptoms (Muftuoglu 2018). Given these promising results in the context of a complete lack of proven antiviral medications effective against JCV and the potentially devastating complications associated with JCV, JCV infection will be included in the Phase 2/3 study.

2.3. Benefit/Risk Assessment

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

2.3.1. Potential Benefits

A serious unmet medical need exists for patients experiencing viral infections and diseases such as AdV, BKV, CMV, EBV, HHV-6, and JCV following allogeneic HCT. Viral diseases post HCT are one of the highest causes of non-relapse morbidity and mortality in the post-transplant period. Despite the emergence of multiple anti-viral therapies, there is a major medical need due to 1) emergent resistance to therapy, 2) toxicity of available anti-virals, and 3) a subset of viruses: AdV, BKV, HHV-6, EBV, and JCV for which there are no approved and/or clearly effective therapies. The CHARMS study and other related clinical studies strongly suggest that posoleucel is a safe and effective broad-spectrum therapy to treat commonly observed and severe virus-associated diseases after allogeneic HCT. The results of these studies provide preliminary evidence of posoleucel's efficacy for multiple opportunistic viral infections in allogeneic HCT recipients, and its safety profile has the potential to be significantly better than that of standard, and inadequately effective, currently available antiviral therapy.

2.3.2. Potential Risks

Posoleucel primarily targets cells infected with AdV, BKV (and/or JCV), CMV, EBV, and/or HHV-6. The main potential risks of administration are inflammation at sites of existing disease or GVHD due to cross-reactivity with the recipient's HLA antigens. Adverse events attributable to virus- specific T cell administration may potentially occur in a small percentage of the treated population. These can include both hematologic and non-hematologic effects.

Studies of donor-derived virus-specific T cells suggest that virus-specific T cells do not persist in

patients who receive methylprednisolone in doses ≥1 mg/kg/day. Therefore, if patients 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 noted with the administration of topical steroids.

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

In order to minimize the volume of blood collected during the study, especially for pediatric patients, the blood volume of individual samples has been reduced to the maximum extent feasible wherever possible. For pediatric patients <12 years of age, collection of blood samples for the evaluation of viral load for all six viruses (AdV, BKV, CMV, EBV, HHV-6, and JCV) is limited to every other week. This reduction in volume of blood collection has been done in a manner that is expected to maintain the scientific integrity of the study while minimizing the risks to patients.

A detailed breakdown of the timepoints and blood volumes to be collected during the study is provided in the Laboratory Manual.

For the collection of other study-related material from the patients, there are no invasive procedures that are required for the study conduct beyond those that are used as part of the routine and standard clinical care of patients undergoing allogeneic HCT.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary 1. To compare the efficacy of posoleucel to placebo by the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 14	1. The number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 14
Key Secondary 1. To compare the efficacy of posoleucel to placebo by the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 26	1. The number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 26
Secondary 2. To compare the efficacy of posoleucel to placebo by clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 due to each individual virus as determined by an independent, blinded CAC through Week 14 and Week 26	2. Clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6, from each individual virus as determined by an independent, blinded CAC through Week 14 and Week 26 (5 endpoints each at Week 14 and Week 26)
Exploratory 1. To determine the incidence and number of new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26 2. To assess patient-reported quality of life (QoL) through Week 26	1.1 Proportion of patients with new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26 1.2 For patients with new hospitalizations, number of new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26 2. Change from baseline in QoL assessments, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26

Objectives	Endpoints
3. To compare the efficacy of posoleucel to placebo in the proportion of patients with undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the lower limit of quantification [LLOQ]) at Week 14 and week 26	3.1. Undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the LLOQ) at Week 14 and Week 26 3.2. Time to event analysis of clinically significant infections
4. To determine hospital length of stay (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26	4. Number of hospital days related to clinically significant AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26
5. To evaluate persistence of posoleucel cells	5 Persistence of posoleucel
6. To compare the efficacy of posoleucel to placebo in mean area under the curve (AUC) viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV each through Week 14 and Week 26	6 Mean viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV for each individual virus through Week 14 and Week 26, obtained as AUC/number of days (6 endpoints each at Week 14 and Week 26)
Safety 1. To characterize the safety and tolerability of posoleucel when administered to patients at high-risk for AdV, BKV, CMV, EBV, HHV-6, or JCV following allogeneic HCT	**Including** 1.1 Severity and incidence of acute GVHD 1.2 Severity and incidence of chronic GVHD 1.3 Severity and incidence of cytokine release syndrome 1.4 Severity and incidence of graft failure 1.5 Severity and incidence of infusion related reactions 1.6 Severity and incidence of clinically significant cytopenias 1.7 Severity and incidence of renal dysfunction 1.8 Overall and non-relapse-related mortality 1.9 Incidence and severity of TEAEs, including AESIs, and clinical laboratory results

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2/3, multi-center, randomized, double-blind, placebo-controlled trial comparing posoleucel to placebo for the prevention of infection or disease due to AdV, BKV, CMV, EBV, HHV-6 or JCV in high-risk adult and pediatric patients after allogeneic HCT.

There are 2 parts to the study, an open label Phase 2 cohort and the primary Phase 3 randomized study cohort. Approximately 327 to 337 eligible allogeneic HCT recipients will be dosed. The first 25 to 35 patients (open label cohort) will receive posoleucel for 14 weeks of open-label dosing and an assessment and optimization of study processes will be performed. Enrollment of participants <1 year of age will occur once preliminary safety data are available from 5 participants ≥1 and ≤6 years of age.

This study is comprised of a screening period, a treatment period, and a follow-up period. The screening period for eligibility may begin at up to 4 weeks (28 days) prior to the estimated time of HCT, although study screening labs can only be obtained after HCT has occurred. The screening period may vary in length of up to 10 weeks. The treatment period is 14 weeks, and the follow-up period is approximately 12 weeks. Overall, the total duration of patient participation in the study is up to approximately 36 weeks (up to 10 weeks for screening, 14-week treatment period, and 12 weeks of follow-up).

Patients will also receive a post-study follow-up contact (eg, telephone call, e-mail) approximately 52 weeks after their first treatment to assess patient status. Patients enrolled in the United Kingdom will not complete a post study follow-up contact.

A review by the Data Safety Monitoring Board (DSMB) was conducted when 26 patients in the open label cohort completed 30 days of treatment, and the DSMB confirmed agreement with initiation of Phase 3. Approximately 302 patients in the Phase 3 study cohort will then be dosed with posoleucel or placebo at a 1:1 ratio. A futility analysis and sample size re-estimation (SSRE) will be conducted, the details of which will be described separately.

In order to best facilitate comparable baseline characteristics in the active and placebo arms of the study, randomization will be stratified for the following criteria: 1) letermovir prophylaxis, 2) age, and 3) the underlying allogeneic transplant risk of viral infections.

Patients will be tested at the first laboratory assessment during Screening by the central laboratory for AdV, BKV, CMV, EBV, HHV-6, and JCV viremia using polymerase chain reaction (PCR) assays for each virus. On the day of randomization, eligibility for enrollment into the study should be confirmed (including confirmation that HCT has taken place).

Patients may receive all standard of care antiviral prophylaxis at their treating institutions. Letermovir prophylaxis begun prior to randomization is thus allowed. With respect to other prophylaxis treatments see the inclusion criteria (Section 5.1).

Study therapy (with posoleucel or placebo) will begin between 15 and 42 (inclusive) post-HCT. Administration should begin as early as possible if the patient has clinically engrafted and should be targeted to occur between Day 18 and Day 25. For patients on anti-thymocyte globulin (ATG), alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies, study therapy will begin at least 21 days from the last dose of anti-T cell antibody. Study therapy will be given at 2-week intervals through Week 14, and the study evaluation will continue through Week 26 (~6 months), with the primary objective of preventing clinically

significant infections or disease of AdV, BKV, CMV, EBV, HHV-6, and/or JCV through Week 14. AdV, BKV, CMV, EBV, HHV-6, and JCV viremia will be monitored as detailed in the Schedule of Activities (SoA, Section 1.3).

Once enrolled in the study, patients will have study visits scheduled weekly for adults and biweekly for children <12 years of age through Week 14. Following completion of the primary study period at Week 14, all patients will remain in the study through Week 26 in order to continue collecting information on (1) incidence of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia, infections, and/or disease, (2) all adverse events through Week 26 in all patients, and (3) quality of life (QoL) measures using validated patient reported outcome tools. During the follow-up period, study visits will occur at Week 20 and Week 26. Patients will also receive a post-study follow-up contact 52 weeks after the start of treatment to assess patient status. Patients enrolled in the United Kingdom will not complete a post study follow-up contact.

For patients who develop any clinically significant infection of AdV, BKV, CMV, EBV, HHV-6, and/or JCV during the primary study period (up to Week 14) or during the follow-up period (after Week 14 and through Week 26) an infection assessment (Section 8.3) should be conducted prior to initiating treatment for viral infection or disease. These patients will continue to receive infusions of study drug during the treatment period.

An independent, blinded CAC will be established to review Phase 3 data. This CAC will review clinical, virologic, and histopathological data as well as the Investigator's assessments. The CAC will use the reviewed information for adjudicating all potential cases of clinically significant infection or end-organ disease due to AdV, BKV, CMV, EBV, HHV-6, and JCV, and for attributing, as appropriate, the mortality due to graft failure, relapse of primary disease, related to infection/disease of CMV, EBV, HHV-6, JCV, BKV, AdV, or other causes, as defined in the CAC charter, throughout the trial.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the SoA (Section 1.3). Details of each procedure are provided in Section 8.

This study will be conducted in conformance with Good Clinical Practices. Stopping rules for the study are detailed in Section 9.5.1.

4.2. Scientific Rationale for Study Design

Viral infections are a major cause of morbidity after allogeneic HCT, and in general have become the primary etiology for transplant-related mortality in HCT recipients. Since recovery of virus-specific T cells after HCT results in resolution of viral infections, typically weeks to months post-transplant, adoptive immunotherapy to decrease the time to immune reconstitution is an attractive alternative to current standard of care. posoleucel partially-matched HLA cells are intended to circulate only until the patient regains immunocompetence following HCT engraftment and immune system repopulation. Therefore, posoleucel cells, when started early post transplant, are designed to be an "immunologic bridge therapy" that provides an immunocompromised patient with T cell immunity until the donor's immune system reconstitutes and can mount an endogenous immune response. The duration of the treatment period is designed to be sufficiently long enough to provide this "bridge" and the follow-up period after study therapy ends is designed to assess the long-term effectiveness of the study therapy.

The overarching goal of the study is to determine if posoleucel can meaningfully prevent

clinically significant viral infection or end-organ disease due to AdV, BKV, CMV, EBV, HHV-6, and JCV.

For this trial it is estimated that 25% of patients will have 1 clinically significant infection due to AdV, BKV, CMV, EBV, HHV-6 or JCV and 10% of patients will have 2 clinically significant infections from two of the different viruses over the course of the study. The estimated incidence of clinically significant viral disease used to derive the sample size estimates is predicated on the assumption that a significant proportion of adults enrolled in this study may receive letermovir for prophylaxis against CMV disease. As such, a conservative estimate of CMV was selected based on the active treatment arm of the high-risk cohort in the letermovir registrational trial (Marty et al, 2018). This CMV estimate was combined with conservative estimates of clinically significant infection due to AdV, BKV, EBV, HHV-6 and JCV and the likelihood that a proportion of patients will have more than one clinically significant viral infection over the course of the study (Hill 2017). An efficacy of 50% for posoleucel in this study is assumed, and this estimate is based on the lowest response rate observed across all six viruses in the CHARMS study where 50% patients treated for refractory HHV-6 had a response. The response rate was at least 75% for all the other viruses in CHARMS, making this a conservative estimate.

The broad age range for inclusion in the study is justified by the age range of patients undergoing allogeneic HCT (Ahmed et al, 2019; Braunlin et al, 2018; D'Souza et al, 2019; Shah et al, 2018; Wais et al, 2018) and by data from CHARMs (Tzannou, 2017). Infants under 1 year of age are being included as they are at high risk of both primary viral infection and potentially viral reactivation and would potentially sustain the same benefits from VSTs as older patients undergoing high-risk HCT.

The inclusion of the open-label period is to assess and optimize the safety and efficacy related procedures prior to beginning the randomized phase of the study.

The biweekly dosing schedule was designed to provide immunologic bridge for patients who may not be actively viremic, but are still at high risk of developing a clinically significant viral reactivation and infection. T cells in the absence of antigenic stimulation may only persist for ~2 weeks, and the use of 7 total doses across 14 weeks provides theoretical immune coverage until the donor immune system reconstitutes.

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

1. A placebo control group is required to provide an objective, contemporaneous assessment of the therapeutic effects and AE profile of posoleucel.
2. Though pharmacologic agents are available for selected clinically problematic viruses, they are not always effective and can result in significant adverse effects. Letermovir is allowed as previously described. Patients who develop clinically significant viral disease will be treated with standard of care therapies as determined by the Investigator. The Investigator should, however, document the new onset or worsening of disease prior to initiation of any additional or new anti-viral therapy and discuss the clinical case with the blinded clinical study Medical Monitor in order to assure appropriate information is captured for the CAC.

4.3. Justification for Dose

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

The dose of posoleucel per infusion (2×10^7cells for patients <40 kg and 4×10^7 cells for

patients ≥40 kg) is designed to mimic the VST dose administered in the CHARMS study. In the CHARMS study, the protocol-specified VST cell dose was $2 \times 10^7/m^2$ per infusion. A retrospective analysis of actual doses administered in the CHARMS study demonstrated that, on average, patients who weighed ≥40 kg received $4.1 \pm 0.5 \times 10^7$ cells per infusion (n = 45) and those who weighed <40 kg received $1.9 \pm 0.6 \times 10^7$ cells per infusion (n=9). For patients <40 kg, the dose will be 2×10^7 cells.

4.4. End of Study Definition

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the Week 26 visit.

Patients will be asked to have a post-study contact (eg, telephone call or email) at approximately 52 weeks (12 months) after the start of treatment to collect patient status. Patients enrolled in the United Kingdom will not complete a post study follow-up contact at week 52.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Any age the day of screening visit. Enrollment of participants <1 year of age at the time of informed consent will occur only once preliminary safety data are available from 5 participants ≥1 and ≤6 years of age.

Type of Participant and Disease Characteristics

2. Has no known or suspected clinically significant disease from AdV, BKV, CMV, EBV, HHV-6, and/or JCV
3. Be within 15 and 42 days of receiving a first allogeneic HCT at the time of randomization and have demonstrated clinical engraftment, as evidenced by absolute neutrophil count (ANC) ≥500/mm^3.
4. Patients meeting one or more of the following criteria at the time of randomization:
   - Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR
   - Haploidentical donor
   - Matched unrelated donor (Approximately 1/3 of total patients will have received a transplant from a MUD, without T cell depletion)
   - Mismatched unrelated donor
   - Umbilical cord blood as stem cell source
   - Ex vivo graft manipulation resulting in T cell depletion
   - Received t-cell depletion by ATG or alemtuzumab (Campath-1H)

Sex

5. Male and/or female
   a. Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 90 days after the last dose of study intervention:

- Refrain from donating sperm PLUS, either**:**
- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1

OR

  - Is a WOCBP and using a highly effective method of contraception as described in Section 10.4.2 during the study intervention period and for at least 90 days after the last dose of study intervention. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative serum pregnancy test within 14 days before the first dose of study intervention, see Section 8.4.7.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.4.7.

Informed Consent and Cell Line Match

6. Willing and able to provide written informed consent as described in Section 10.1.3 to participate in the study, or a parent or legal guardian is willing and able to provide written informed consent and the potential pediatric patient is able to provide assent in a manner approved by the Institutional Review Board (IRB) and local regulations.
7. Has an HLA type matching with at least 1 suitably matched and available posoleucel VST line for infusion.

5.2. Exclusion Criteria

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

Medical Conditions

1. Has a history of AdV, BKV, CMV, EBV, HHV-6, and/or JCV end-organ disease within 6 months prior to randomization
2. Evidence of active Grade >2 acute GVHD [for additional information on acute GVHD grading and severity, see Appendix 5 (Section 10.5)].
3. Presence of non-minor uncontrolled or progressive bacterial or fungal infections (ie, evidence of bacteremia, fungemia, disseminated, and/or organ-specific infection not well controlled by present therapies)
4. Presence of any progressive, uncontrolled viral infections (ie, evidence of viremia (eg HIV, HCV, HBV), dissemination, and/or organ-specific infection not well controlled by present therapies).
5. Known history or current (suspected) diagnosis of Grade ≥3 CRS or ICANS [immune effector cell-associated neurotoxicity syndrome) requiring treatment associated with the administration of peptides, proteins, and/or antibodies, see Appendix 6 (Section 10.6)].
6. Evidence of encephalopathy at randomization
7. Relapse of primary malignancy other than minimal residual disease.

Prior/Concomitant Therapy

8. Donor lymphocyte infusion performed within 21 days prior to randomization
9. Received within 7 days prior to randomization any of the following (or equivalent pediatric dosing):
    - ganciclovir, foscarnet, cidofovir, maribivir, or rituximab at any dose
    - valganciclovir (at doses > 900 mg per day)
    - acyclovir (at doses >3200 mg PO per day or >25 mg/kg IV per day),
    - valacyclovir (at doses >3000 mg PO per day),
    - famciclovir (at doses >1500 mg PO per day)
10. Use of any investigational antiviral agent, including brincidofovir, within 7 days prior to randomization or actively receiving any investigational agent at randomization.
11. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day) within 24 hours prior to dosing
12. ATG, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies within 21 days prior to dosing (patients who have received prior therapy with cyclophosphamide at any time are eligible for study participation)
13. Receipt of mechanical ventilation of any type, within 1 month prior to treatment (unless related to airway control)
14. Undergoing dialysis at randomization

Prior/Concurrent Clinical Study Experience

15. Received a previous allogeneic HCT (Note: Receipt of a previous autologous HCT is acceptable)

Diagnostic Assessments

16. Aspartate aminotransferase or alanine aminotransferase serum levels >5× the upper limit of normal (ULN) or direct bilirubin serum levels >3× the ULN at randomization.

Other Exclusions

17. Pregnant, breastfeeding, or planning to become pregnant during the study.
18. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or would be put at undue risk as judged by the Investigator, such that it is not in the best interest of the patient to participate in this study.

5.3. Lifestyle Restrictions

This section is not applicable.

5.3.1. Meals and Dietary Restrictions

This section is not applicable.

5.3.2. Caffeine, Alcohol, and Tobacco

This section is not applicable.

5.3.3. Activity

This section is not applicable.

5.4. Screen Failures and Participants Randomized But Not Dosed

Screen failures are defined as participants 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, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in consultation with the Medical Monitor.

For participants who consent to participate in the clinical study, are randomized into the clinical study, but do not receive any doses the following information will be obtained: screening and Day 1 visit information (if available), demography, reason for not dosing, eligibility criteria, and any adverse events (including clinically significant infections) experienced after randomization and prior to study discontinuation. These patients should be maintained in the study through Day 49, if possible, to confirm if dosing can proceed.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

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. The Control Arm will receive IV infusions of cryopreservation media (without cells) as placebo.

Arm Name	Treatment (Both Cohorts)	Control (Phase 3 Study Cohort)
Intervention Name	Posoleucel	Placebo
Type	Drug	Drug
Dosage formulation	Ampule (Cryovial)	Ampule (Cryovial)
Unit dose strength(s)	2×10^7 VSTs / 2 mL	0 VSTs / 2 mL
Dosage Level(s)	2×10^7 cells (<40 kg at screening) or 4×10^7 (≥40 kg at first administration) cells dosed Q14D	Placebo, at same weight-based dose levels as posoleucel, dosed Q14D
Route of Administration	IV slow push over 5 minutes	IV slow push over 5 minutes
Use	Experimental	Placebo control
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and Labeling	Study Intervention will be provided in cryovials. Each cryovial will be labeled as required per country requirement	Study Intervention will be provided in cryovials. Each cryovial will be labeled as required per country requirement
Current/ Former Name(s) or Alias(es)	Posoleucel also known as Viralym-M and formerly known as ALVR-105	Not applicable

6.1.1. Cell Line Selection

posoleucel cell lines will be selected for each patient based on an overall HLA match with 2 shared alleles set as a minimum threshold as outlined below. The HLA alleles used for evaluation of matching are HLA-A, HLA-B, HLA-DR, and HLA-DQ. The same cell line should

be used for all infusions.

The appropriate drug product (ie, the cell lines for infusion) for patient administration will be selected using a software program (CytoMatch), which uses a stepwise algorithm to identify the best overall HLA-matched posoleucel drug product lots for each patient. The HLA types of the patient and of their HCT cell donor (obtained from the medical record) will be manually entered into the software and verified before the cell matching algorithm is run. CytoMatch compares each posoleucel drug product lot available in the bank first with the HLA type of the patient, and second with that of the patient's HCT donor, and generates an overall total score that is used to establish a ranking hierarchy of matching cell lines. The top ranked posoleucel drug product lots will be identified by CytoMatch as the cell lines with the highest overall HLA match total. In the event of a tie, the selection process will follow the First in First out method, where cell lines with the earliest manufacture date will be selected. Cell lines with appropriate HLA match or placebo may be substituted depending on treatment assignment for patient, if needed.

6.1.2. Study Intervention Administration

At, or close to the time of administration, the product will be thawed at 37°C. See the Cell Therapy Manual for further information.

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

- Patients in an outpatient setting must remain in the clinic for ≥1 hour after the end of the infusion.
- Vital signs will be monitored prior to starting infusion, at the end of infusion, and at 15, 30, and 60 minutes after the end of the infusion.

All findings must be recorded in the electronic Case Report Form (eCRF).

Patients will receive supportive care for acute or chronic toxicity, including blood components, antibiotics, or other interventions as appropriate per local treatment guidelines. See Section 6.8.2.1 for additional information. If possible, posoleucel and intravenous immunoglobulin (IVIG) should not be administered on the same day to better assess whether any observed AEs are related to study intervention.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) and Sponsor is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Cell Handling Manual.

6.2.1. Study Drug Preparation and Dispensing

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

6.2.2. Storage and Accountability

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

After investigational medicinal product (IMP) accountability and reconciliation procedures have been followed, 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 posoleucel cell line to the third-party peripheral blood mononuclear cell (PBMC) donor from whom it originated. These records will be maintained for 30 years after expiry for each cell 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 Handling Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using IVRS/IWRS	All participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in the SoA.

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to the study. Patients will be randomized in a 1:1 ratio to receive up to 7 doses of posoleucel or placebo. Randomization assignments will be performed by the IWRS. Randomization will be stratified for the following criteria: 1) letermovir prophylaxis, 2) age, and 3) the underlying allogeneic transplant risk of viral infections.

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 will 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).

Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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 patient'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 patient'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 patient. The Investigator must document the patient's identification, the reason for breaking the blind, and the date and time for breaking the blind.

6.4. Study Intervention Compliance

Study patients are dosed at the site. They will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

This section is not applicable.

6.5.1. Retreatment Criteria

No further treatment is planned after the last dose of posoleucel (or placebo) after Week 14. Patients will continue in the study for evaluation of safety, efficacy, and other endpoints after Week 14 for an additional 3 months (through Week 26).

6.6. Continued Access to Study Intervention after the End of the Study

No further treatment will be provided after the last dose of posoleucel (or placebo) after Week 12. However, patients will continue in the study for evaluation of safety, efficacy, and other endpoints for an additional 12 weeks (3 months).

6.7. Treatment of Overdose

For this study, any dose of posoleucel greater than any dose over the IRT assigned dose (2×10^7 cells for patients <40 kg or 4×10^7 cells for patients ≥40 kg) within a 24-hour period (±1 hour) will be considered an overdose.

As there is no antidote, the Sponsor does not recommend specific treatment for an overdose. In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the patient to determine, in consultation with the Medical Monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until the next dosing day.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8. Concomitant Therapy

All patients may receive available supportive therapy with approved treatments.

6.8.1. Antiviral Therapy

Clinically available (ie, not investigational) antiviral agents prescribed for other infections, such as foscarnet and ganciclovir to treat CMV, are allowed. Data on their use will be collected along with other concomitant medications.

Letermovir use is permitted when used in accordance with locally approved product label (e.g., US Prescribing Information, EU Summary of Medicinal Product Characteristics).

Asymptomatic CMV viremia (no signs or symptoms of end organ disease) should be managed as follows:

- Pre-emptive antiviral treatment should be initiated only if CMV viral load is ≥910 IU/mL (1000 copies/mL) and rising on 2 consecutive central lab measurements separated by a minimum of 72 hours
- When possible, low level viremia should be observed for as long as possible prior to initiation of antiviral treatment to allow time for posoleucel to expand and target virus-infected cells

For any questions about a patient's specific clinical situation, contact the ICON or AlloVir medical monitor prior to initiating pre-emptive anti-viral CMV therapy.

6.8.2. Steroid Therapy

Daily doses of steroids >0.5mg/kg prednisone or equivalent should only be used if medically necessary. For corticosteroids exceeding 0.5 mg/kg prednisone (or equivalent), it is recommended to delay dosing until the dose is ≤0.5 mg/kg if still within a particular dose's dosing window. If corticosteroids are unable to be tapered to ≤0.5mg/kg prednisone equivalent within a dose window, the patient can proceed with usual dosing. If possible, the subsequent posoleucel dose after the corticosteroids are tapered to <0.5 mg/kg prednisone equivalent should be given as soon as possible.

6.8.3. Other Concomitant Therapies

Premedication prior to infusion of study treatment is allowed (eg, diphenhydramine or equivalent). Corticosteroids as premedication should be avoided.

Treatment with supportive regimen therapies, other intravesicular agents for the control of bleeding (including, but not limited to, aminocaproic acid), antispasmodics, treatment for pain control (including opioids), and blood product transfusion support are permitted. Clinically available (ie, not investigational) antiviral agents prescribed for other infections are allowed.

All COVID-19 regimens recommended by local health authorities are permitted in the study.

All instances of the use of any concomitant therapies during the study will be recorded in the eCRF (including the drug name, dose, and duration of treatment).

6.8.4. Excluded Medications and/or Procedures

All patients may receive available supportive therapy with approved treatments. Investigators should try to maintain stable treatment to the extent possible.

Receipt of other investigational antiviral treatments including brincidofovir or anti-viral monoclonal antibodies throughout the duration of the study is prohibited.

T cell ablative therapies, such as ATG, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies, are prohibited during dosing.

6.8.5. Restricted Medications and/or Procedures

6.8.5.1. Supportive Care

Supportive care as needed and determined by the Investigator is permitted.

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

6.8.6. Documentation of Prior and Concomitant Medication Use

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

- Fluids
- Electrolytes
- Vitamins
- Supplements
- Mouth care
- Laxatives
- “As needed” medications

At screening, all concomitant medications and concurrent therapies, including the ones listed above, will be documented as indicated in the SoA (Section 1.3). Dose, route, frequency of administration, indication for administration, and dates of medication will also be captured in source documents and on the appropriate eCRF.

6.8.7. Rescue Medication

This section is not applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

The following criteria do not necessitate withdrawal from the study, but do render the patient ineligible to receive any additional infusions of study treatment:

1. Development of irreversible, life-threatening, Grade 3 to 4 acute GVHD within 6 weeks from last study drug dose that is considered related to study treatment administration. If this occurs, the patient's toxicities will be followed until resolution or until the patient's participation in the study ends.
2. Development of Grade 3 to 4 non-hematologic AE within 4 weeks from last study drug dose that is considered related to study treatment administration. If this occurs, the patient's toxicities will be followed until resolution or until the patient's participation in the study ends.
3. Receipt of any other hematopoietic stem cell product from another donor.
4. Receipt of therapy for relapse of the patient's primary malignancy.
5. Occurrence of Grade 3 or 4 CRS that persists beyond 72 hours. If this occurs, the patient's toxicities will be followed until resolution or until the patient's participation in the study ends.
6. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
7. Pregnancy
8. Requirement for prohibited concomitant medication.
9. Patient (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 patient in the study and complete as many protocol required procedures as feasible to continue follow-up, even if treatment is discontinued.

7.1.1. Temporary Discontinuation

Temporary discontinuation will be allowed only if discussed with and approved by the Medical Monitor.

7.1.2. Rechallenge

This section is not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent.
- The patient requests discontinuation from the study for any reason.
- Occurrence of any medical condition or circumstance that in the judgment of both the Investigator and the Medical Monitor exposes the patient to substantial risk and/or does not allow the patient to continue in the study.

- In the judgment of both the Investigator and the Medical Monitor, the patient is repeatedly unable to comply with protocol requirements or study-related procedures.
- Termination of the study by the Sponsor or the regulatory authority.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Patients who are discontinued from the study for any reason will not be replaced. Patients who discontinue the study early after dosing has started, should have the procedures scheduled for the Week 26/ET visit completed at the time of discontinuation from the study. The reason for patient withdrawal must be documented in the eCRF.

7.3. Early Termination

The ET Visit will be performed for all patients who are prematurely discontinued from the study up to Week 26; however, patients who decide only to discontinue therapy early will continue to complete as many trial procedures as feasible per protocol and should receive the post-study Week 52 follow-up contact. Patients enrolled in the United Kingdom will not complete a post study follow-up contact. It is very important to ensure that all procedures, as outlined in the SoA ET visit, are performed in such patients at this visit prior to discontinuing the patient from the trial. Most importantly, a plasma sample for AdV, BKV, CMV, HHV-6, and JCV and a PBMC or plasma sample for EBV for PCR testing at the central laboratory should be collected at this visit.

7.4. 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 or emails 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 in Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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 informed consent form (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.
- Results (eg, Safety/Laboratory/analyte) that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The amount of blood collected from each adult (≥18 years) and pediatric patient over the duration of the study are described in the Laboratory Manual. The maximum amount of blood collected, including any extra assessments that may be required, will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period for adult patients.
- For pediatric patients, blood sampling requirements for the study have been minimized by reducing the volume per sample collected (where possible), and by omitting collection at certain timepoints.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Study Periods

8.1.1. Screening period

Informed consent may be obtained as early as 28 days prior to HCT, however, Screening Visit must occur within 42 days after HCT.

After screening or randomization, if possible, patients should be maintained on study until screening or dosing window closes to avoid failing patients who may be eligible once ongoing events resolve.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in consultation with the Medical Monitor.

Patients should have plasma samples tested at the first assessment during Screening Visit by the central laboratory for AdV, BKV, CMV, HHV-6, and JCV viremia and PBMCs or plasma for EBV viremia, using PCR assays for each virus.

8.1.2. Treatment period

The treatment period is 14 weeks. Study therapy (with posoleucel or placebo) will begin between 15 and 42 (+7) days (inclusive) post-HCT. When possible the first dose should be targeted to occur after engraftment and between Day 18 and Day 25 post-HCT. For patients on ATG, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies study therapy will begin at least 21 days from the last dose of anti-T cell antibody. Study therapy will be given at 2-week intervals through Week 14, and the study evaluation will continue through Week 26 (~6 months). The first 25 to 35 patients (open label cohort) will be assigned to posoleucel for 30 days of open-label dosing prior to DSMB review and beginning randomization of Phase 3 study cohort patients to treatment groups.

8.1.3. Follow-up period

The follow-up period is for 12 weeks with visits at Week 20 and 26.

A post-study contact (eg, telephone call or email) will occur approximately 12 months (~52 weeks) after the start of treatment. Patients enrolled in the United Kingdom will not complete a post study follow-up contact.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. Viral Load

Samples for viral sequence/genotype will be collected on all patients as indicated in Section 1.3. Viral loads of AdV, BKV, CMV, HHV-6, and JCV in plasma and of EBV in PBMCs or plasma will be measured at times specified in Section 1.3. Additional post-infusion samples may be collected, as clinically indicated. If patient develops any clinically significant infection of AdV, BKV, CMV, EBV, HHV-6, and JCV at any point during the study periods, infection assessments (Section 8.3) should be followed prior to initiating standard of care therapy. On dosing days, all laboratory samples should be collected prior to dosing.

Viral load will be quantitated using PCR assays.

8.2.2. Resolution of Viral Infections

In patients who develop viral infections, plasma will be monitored for AdV, BKV, CMV, HHV-6, or JCV viral load and PBMCs or plasma will be monitored for EBV. See Section 1.3. Resolution of viral infection is defined in the CAC Charter. Resolution of viral infection will be defined as asymptomatic with the completion of any antiviral therapy.

8.2.3. Quality of Life

Quality of life will be measured using an age-appropriate version of the EQ-5D at times indicated in Section 1.3.

The EQ-5D is a group of instruments that was developed to assess patient-reported health-related QoL (EuroQol Group 1990). The EQ-5D-5L includes the EQ-5D descriptive system and the EQ visual analog scale (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-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 Visual Analog Scale (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."

Quality of life measures should be completed as indicated in the SoA (See Section 1.3) and prior to any study procedures at the visit.

8.2.4. Virus-specific T Cell Assessment

Patient PBMCs or whole blood will be assessed for the presence of each of the viral-specific virus-reactive T cells. See Section 1.3.

8.3. Infection Assessments

Infection assessments will be performed for all patients who, in the opinion of the Investigator, might meet the criteria for viral infection or disease as described in the Adjudication Manual. It is very important to ensure that all procedures are performed for infection assessment prior to the initiation of treatment of viral diseases or initiation of preemptive therapy (ie, on the day anti-viral therapy is initiated).

Patients who develop infections will continue to be treated and followed in the study and complete all remaining visits through Week 26 as outlined in the SoA.

8.3.1. Confirmatory Plasma Samples for Suspected Infection at Central Laboratory

A plasma sample for AdV, BKV, CMV, HHV-6, and JCV, and a PBMC or plasma sample for EBV for PCR testing at the central laboratory should be collected to confirm suspected infections. Should confirmatory test results from the central laboratory not be available within the timeframe that the Investigator wishes to initiate anti-viral therapy, it is understood that the Investigator may use local laboratory test results to make treatment decisions.

8.3.2. Samples When Initiating Anti-viral Therapy

If antiviral therapy is to be initiated, it is mandatory to send a plasma sample for AdV, BKV, CMV, HHV-6, and JCV and a PBMC or plasma sample for EBV for DNA PCR testing to the central laboratory immediately prior to (ie, on the day of) initiating treatment for AdV, BKV, CMV, EBV, HHV-6, or JCV disease or preemptive therapy in all instances. As clinically indicated, stool (AdV and CMV only), urine, and/or CSF (CMV, HHV-6 and JCV only) samples should be collected for AdV, BKV, CMV, EBV, HHV-6, and JCV and sent to the central laboratory as feasible. Please see Section 6.8.1 for additional guidance on the management of CMV.

When local laboratory test results are used for initiating anti-viral therapy, two plasma (or PBMC

for EBV) samples for PCR testing must be sent to the central laboratory. The first sample must be collected immediately prior to (ie, on the day of) initiating anti-viral therapy. The second sample must be collected 48-72 hours after initiating anti-viral therapy.

Regular central lab viral loads should resume during the usual visit windows after infection is confirmed.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems and skin.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Physical examinations will be performed, and height and weight will be collected as indicated in Section 1.3. The complete physical examination will be overseen by either the Investigator or a Sub-Investigator. New abnormal physical examination findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.
- After randomization, a symptom-directed physical examination may be performed if a patient has any complaints. Post-HCT, the skin should be examined, even if the patient has no complaint, for evidence of rash/acute skin GVHD.

8.4.2. Vital Signs

- Temperature, pulse rate, O_2 saturation, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse O_2 saturation, and respiratory rate.
- Vital signs will be monitored prior to starting the infusion and at several timepoints after each infusion as outlined in Section 6.1.2.

8.4.3. Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (corrected using Fridericia's and Bazett's methods) intervals.

8.4.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- Samples will be sent to the appropriate central laboratory(ies) following the procedure(s) described in the lab manual. On dosing days, all laboratory samples should be collected prior to dosing.

- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.
- Assessment of blood cell counts and renal function will be monitored for anti-viral toxicity.

8.4.5. Graft Versus Host Disease

Acute GVHD status by the MAGIC criteria should be assessed on study Day 1 prior to dosing to establish a baseline. If any patient develops GVHD, that patient may receive standard GVHD treatment at the discretion of the Investigator. All events of GVHD should be assessed by CTCAE (acute and chronic GVHD) and by Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (acute GVHD) or National Institutes of Health scales (chronic GVHD).

8.4.5.1. Acute Graft Versus Host Disease

In addition to the CTCAE grading of severity, staging and grading of acute GVHD will be reported using MAGIC (Table 6). Response to treatment will be assessed as per Center for International Blood and Marrow Transplant Research (CIBMTR) modifications to the CIBMTR response index (Table 7) as described in Appendix 5 (Section 10.5).

8.4.5.2. Chronic Graft Versus Host Disease

In addition to the CTCAE grading of severity, manifestations of chronic GVHD and response to treatment will be assessed as per National Institutes of Health consensus guidelines for chronic GVHD (Table 8 and Table 9) as described in Appendix 5 (Section 10.5).

8.4.6. 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 6 (Section 10.6). Recommendations for monitoring for and management of CRS are provided in Appendix 7 (Section 10.7).

posoleucel VSTs do not express a chimeric antigen receptor (CAR) and are not genetically

modified. They therefore do not contain the engineered chimeric costimulatory moieties that may predispose to non-physiologic stimulation. Thus, the risk of CRS following administration of these VSTs is expected to be low.

8.4.7. Pregnancy Testing

- A serum pregnancy test will be performed at screening for all female patients of childbearing potential. Prior to dosing on Day 1, a urine pregnancy test will be performed. If the urine pregnancy test result is negative, the patient will be eligible for dosing and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not be dosed and should receive a β-HCG blood test confirming a positive result before failing randomization. See Section 1.3.
- A urine pregnancy test will be performed prior to each treatment for female patients who are of childbearing potential. See Section 1.3.

8.4.8. Suicidal Ideation and Behavior Risk Monitoring

This section is not applicable.

8.5. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

- The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3).
- The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3).
- 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 qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs and SAEs will be collected at the time points specified in the SoA (Section 1.3) from randomization until study participation is complete through Week 26.
- Medical occurrences that begin before randomization but after obtaining informed consent/assent will be recorded as Medical History/Current Medical Conditions, not as AEs.
- Treatment emergent adverse events (TEAEs) are AEs with onset or worsening on or after the first dose of study treatment through Week 26.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after

conclusion of the study participation. 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 intervention or study participation, the Investigator must promptly notify the Sponsor.

8.5.2. Method of Detecting AEs and SAEs

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.

8.5.3. Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from randomization until study participation is complete or until resolution, whichever is sooner, must be reported to ICON Pharmacovigilance and Safety Services (PVSS) within 24 hours of awareness of the event. After study participation is complete, any SAE that the Investigator considers related to study drug must be reported to ICON PVSS or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, ICON PVSS personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, the paper SAE form should be completed and sent to ICON PVSS via email at STUDY-PVSS-4690-0000@iconplc.com or via Fax: +1 215 616 3096) 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.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided, until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient 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 ICON PVSS via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.5.4. 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, and AEs of special interest (as defined in Section 8.5.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.5.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.5.5.1. Expedited Reporting

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

All other SUSARs will be reported to the FDA, applicable competent authorities 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.

8.5.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 90 days after the last dose of study intervention.
- 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 [female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner)] pregnancy.
- 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 patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the 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

intervention by the Investigator will be reported to the Sponsor as described in Section 8.5.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.5.7. Cardiovascular and Death Events

This section is not applicable.

8.5.8. Adverse Events of Special Interest

Adverse events of special interest (AESIs) include infusion-related AEs, acute and chronic GVHD, graft failure, and CRS. Criteria for acute and chronic GVHD and CRS can be found in Appendix 5 (Section 10.5) and Appendix 6 (Section 10.6), respectively. Graft failure is considered a severe event and should be graded as Grade 4 (life-threatening) or Grade 5 (fatal) per CTCAE criteria.

8.5.8.1. 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 patient has taken additional dose(s) or the Investigator has reason to suspect that the patient 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, patient, 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 patients 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 Clinical Research Organization (CRO) Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situations Report Form should be reported as adverse events or SAEs as well as

recorded on the AE 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: ICON Safety reporting line – USA:

- Email: STUDY-PVSS-4690-0000@iconplc.com
- Fax: +1 215-616-3096

8.6. Pharmacokinetics

- Pharmacokinetic parameters of posoleucel are not evaluated in this study.

8.7. Genetics and/or Pharmacogenomics

- Genetics are not evaluated in this study.

8.8. Biomarkers

- Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

- Immunogenicity assessments are not evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

- Total number of hospital days related to clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection or disease and re-admission rates related to clinically significant AdV, BKV, CMV, EBV, HHV-6 and/or JCV viremia/disease are assessed in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Research Hypotheses

The primary research hypothesis is that the mean number of clinically significant infections or end-organ disease due to AdV, BKV, CMV, EBV, HHV-6 and/or JCV per patient through Week 14, as determined by an independent, blinded CAC, is less for posoleucel treated patients than for patients treated with placebo.

9.2. Sample Size Determination

A total of approximately 302 patients will be dosed in the Phase 3 study cohort to achieve 90% power, approximately 151 patients in the posoleucel treatment group and approximately 151 patients in the placebo group. This is in addition to the 25 to 35 non-randomized patients to be included in the open label cohort.

The sample sizes for the Phase 3 study cohort were determined based on the following specifications:

1. Two-arm superiority study: posoleucel vs. Placebo
2. Endpoint is the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6 and/or JCV through Week 14, as determined by an independent, blinded CAC
3. Allocation is 1:1 (posoleucel: Placebo)
4. One-sided alpha = 0.025
5. Power =90%
6. True mean (SD) for Placebo as in Table 4 below
7. True mean (SD) for posoleucel as in Table 4 below
8. Use of Satterthwaite unpooled t-test for a difference in means

The mean and SD for Placebo were estimated assuming that 25% of Placebo patients will have one clinically significant infection and a distinct 10% will have two clinically significant infections from different viruses. The remaining Placebo patients were assumed to have no clinically significant infections. The mean and SD for posoleucel were estimated assuming that there would be a 50% reduction in the percentages for Placebo having one and two clinically significant infections.

The results of the sample size calculations are presented in Table 4.

Table 4: Required Sample Sizes

Treatment	Mean	Standard Deviation	Sample Size		
Placebo	0.450	0.669	posoleucel	Placebo	Total
posoleucel	0.225	0.524	151	151	302

Thus, the total required sample size for the Phase 3 cohort to achieve at least 90% power is approximately 302 subjects dosed (151 posoleucel and 151 placebo).

9.3. Analysis Populations

For the purposes of analysis, the following analysis populations are defined:

Population	Description
Modified Intent to Treat (mITT)	Phase 3: All randomized patients who receive at least one dose of posoleucel or placebo. All efficacy analyses will be based on the mITT Population. Patients will be analyzed according to their randomized study treatment. Open Label: All patients who receive at least one dose of posoleucel.
Safety	All patients who receive at least one dose of posoleucel or placebo. All safety analyses will be based on the Safety Population. Patients will be analyzed according to the treatment actually received.

9.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

Summary statistics will be presented by treatment group. The primary analyses will be based on the Phase 3 portion of the study. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized using the frequency count and the percentage of patients in each category. All two-sided hypothesis tests will be performed at the 0.05 significance level, and all one-sided hypothesis tests will be performed at the 0.025 significance level.

Baseline viral load will be the Day 1 assessment of viral load.

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

9.4.2. Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6 or JCV as determined by an independent, blinded CAC through Week 14.

The statistical hypotheses are as follows:

- H_0: Mean number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6 or JCV through Week 14 in the posoleucel arm is greater than or equal to the corresponding mean in the placebo arm.
- H_1: Mean number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6 or JCV through Week 14 in the posoleucel arm is less than the corresponding mean in the placebo arm.

Clinically significant infections/episodes will be considered as a failure of prevention, thus, in calculating the value of this endpoint for a patient, each virus will be counted at most once, even if there are multiple infections/episodes for a given virus.

This endpoint will be analyzed based on patients in the mITT population in the Phase 3 portion of the study. It will be summarized by treatment group using frequency counts and percentages. It will be analyzed using Analysis of Variance (ANOVA) with terms for study treatment and letermovir prophylaxis, age, and the underlying allogeneic transplant risk of viral infections to test the null hypothesis that the mean number of clinically significant AdV, BKV, CMV, EBV, HHV-6 or JCV infections or episodes of end-organ disease per patient in posoleucel treated patients through Week 14, is greater than or equal to the corresponding mean for placebo treated patients versus the alternative hypothesis that the mean number of clinically significant infections per patient is less for posoleucel treated patients.

Methodology for imputation of missing data, and additional sensitivity analyses and subgroup analyses will be described in detail in the SAP.

9.4.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on patients in both cohorts.

The key secondary efficacy endpoint is:

- Number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 26

Additional secondary endpoints are:

- Clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6, from each individual virus as determined by an independent, blinded CAC through Week 14 and Week 26 (5 endpoints each at Week 14 and Week 26)

Summary tables will be presented by treatment group (posoleucel and Placebo) for the Phase 3 study cohort. For the open label cohort, results will be presented overall, as all patients in this cohort receive only posoleucel.

The key secondary endpoint, number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV through Week 26, will be analyzed in the same manner as the primary endpoint. The analyses of the other efficacy endpoints will be described in the statistical analysis plan.

Categorical variables will be summarized using frequency counts and percentages. Continuous variables will be summarized by visit using descriptive statistics.

9.4.4. Exploratory Endpoints

The exploratory endpoints are as follows:

- Proportion of patients with new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26
- For patients with new hospitalizations, number of new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26

- Change from baseline in QoL assessments, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26
- Undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the LLOQ) at Week 14 and Week 26
- Time to event analysis of clinically significant infections
- Number of hospital days related to clinically significant AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease as determined by an independent, blinded CAC through Week 26
- Persistence of posoleucel
- Mean viral load for AdV, BKV, CMV, EBV, HHV-6, or JCV for each individual virus through Week 14 and Week 26, obtained as AUC/number of days (6 endpoints each at Week 14 and Week 26)

The exploratory efficacy endpoints will be analyzed based on patients in the Phase 3 study cohort. Summary tables will be presented by treatment group for this cohort. For the open label cohort, results will be presented overall, as all patients in this cohort receive only posoleucel.

Continuous variable will be summarized by descriptive statistics. Categorical variables will be summarized by frequency count and the percentages by visit and overall.

9.4.5. Safety Endpoints and Analysis

Safety Endpoints include:

- Severity and incidence of acute GVHD
- Severity and incidence of chronic GVHD
- Severity and incidence of CRS
- Severity and incidence of graft failure
- Severity and incidence of infusion related reactions
- Severity and incidence of clinically significant cytopenias
- Severity and incidence of renal dysfunction
- Overall and non-relapse-related mortality
- Incidence and severity of TEAEs, including AESIs and clinical laboratory results

All safety data will be summarized by treatment arm using the Safety Population for the Phase 3 study cohort. For open label cohort, results will be presented overall, as all patients in this cohort receive only posoleucel. Categorical endpoints will be summarized using the number and percentage of patients within each category. Continuous endpoints will be summarized descriptively with summary statistics (number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. A TEAE is defined as an AE with onset or worsening on or after the first dose of study treatment through Week 26. TEAEs will be summarized by System Organ Class and Preferred Term and further by severity (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) and by relationship to study treatment. The incidence of SAEs will be similarly summarized.

The incidence of AEs of special interest (AESIs) and their corresponding exact binomial 95% confidence intervals for the true incidence will be presented by treatment group.

Descriptive statistics will be provided for continuous clinical laboratory, and vital sign. Abnormal laboratory results will be graded according to NCI CTCAE v5.0, if applicable. Shift tables, presenting the 2-way frequency tabulation for baseline and the worst post-baseline value according to the NCI CTCAE grade, will be provided for selected clinical laboratory tests.

9.4.6. Other Analyses

The baseline demographics of participants, such as age and gender, will be summarized by treatment group using frequency counts and percentages for categorical variables and descriptive statistics for continuous variables. Continuous variables will be analyzed using a two- sided, two-sample t-test to test for a difference in means between treatment groups. Categorical variables will be analyzed using a two-sided, Fisher's Exact Test to test for a difference in proportions between treatment groups.

Subgroup analyses may be performed to assess the impact of type of disease, type of transplant, concomitant medications, and other potential groups.

9.5. Interim Analysis

A futility analysis and sample size re-estimation (SSRE) will be conducted, the details of which will be described separately.

The SSRE will be conducted in a manner so as to minimize the risk of operational bias. Information concerning the specific results of the SSRE will be kept confidential. In particular, the information will be kept from the investigators and site staff, patients, sponsor study team, and the CAC. The sample size may be increased up to 375 patients dosed, and any decision to increase the sample size, if such a decision were to be made, will be communicated.

9.5.1. Stopping Criteria

9.5.1.1. Stopping Criteria for Individual Patients

As GVHD and CRS are theoretical safety concerns associated with administration of third-party allogeneic T cells, the incidence and severity of GVHD and CRS will be monitored during the study.

No patients will be permitted to receive subsequent infusions of posoleucel or placebo if they meet criteria outlined in Section 7.1.

9.5.1.2. Stopping Criteria for the Study

Randomization and active dosing in the open label Phase 2 cohort will be halted if 3 patients experience SAEs that meet all the following criteria:

- CTCAE ≥ Grade 3
- Considered related by the Investigator
- Occur during the Treatment Period following the initial dose
- Cannot be reasonably attributed to the patient's underlying disease, other medical condition, or concomitant medications

If this occurs, in the open label Phase 2 cohort, randomization will not resume until the DSMB has completed a thorough review of all safety data to date and concluded that it is safe for the study to continue.

In Phase 3, the DSMB will assess safety on an ongoing basis and will make recommendations on study continuation.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their

legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. Committee Structure

10.1.5.1. Clinical Adjudication Committee

The CAC will determine the definition of AdV, BKV, CMV, EBV, HHV-6, or JCV end organ disease (see CAC charter).

10.1.5.2. Data Safety Monitoring Board

A review by the DSMB was conducted when 26 patients in the open label cohort completed 30 days of treatment, and the DSMB confirmed agreement with initiation of Phase 3. In Phase 3, the DSMB will meet throughout the study as indicated in the DSMB charter (see DSMB charter).

10.1.6. Dissemination of Clinical Study Data

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

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the Study Manual.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Manual.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, legible, complete, original, attributable, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the activation of the first open site in the Interactive Response System (IRS) and will be the study start date.

10.1.9.2. Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory.
- Local laboratory results are only allowed at Screening or due to an adverse event in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is collected, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 5: Protocol-Required Safety Laboratory Tests

Clinical Chemistry Panel (Central Laboratory)

Alanine aminotransferase	Alkaline phosphatase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Creatinine	Creatine kinase
Direct bilirubin	Glucose
Potassium	Sodium
Total bilirubin	Total protein

Hematology (Central Laboratory)

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential[1]	CD4 and CD8 (Baseline and Week 14)

Viral Load in Blood and Urine (Central Laboratory)

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

When viral load determination is performed in the laboratory, residual viral deoxyribonucleic acid (DNA) will be stored for potential viral sequencing and genotyping in the event of recurrent infection.
Viral load determination at screening may be performed at a local or central laboratory for the purpose of determining eligibility/inclusion. These results do not have to be available at the time of randomization or study treatment infusion. Additional post-infusion samples may be collected, as clinically indicated.

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

Urinalysis (Central Laboratory)

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Nitrite pH
Protein	Specific gravity
Urobilinogen	

Stool Specimen (Central Laboratory)

Adenovirus Cytomegalovirus

This is an optional sample, which may be collected centrally if a patient is suspected to have a clinically significant infection. If a stool specimen is clinically indicated, stool samples should also be sent to the central laboratory for research purposes.

Cerebrospinal Fluid Sample (Central Laboratory)

Cytomegalovirus

Human herpesvirus 6

JC virus

This is an optional sample, which may be collected centrally if a patient is suspected to have a clinically significant infection. If a cerebrospinal fluid sample is clinically indicated, samples should also be sent to the central laboratory for research purposes as feasible. Cerebrospinal fluid samples required for clinical care of the patient take precedence over these research-related evaluations.

Other Laboratory Assessments

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

Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) along with confirmatory tests if requested

Virus Specific T-cell Assessment

1. For female patients of childbearing potential only. A serum (β-human chorionic gonadotropin) pregnancy test will be performed at screening. A urine pregnancy test will be performed prior to dosing for female patients who are of childbearing potential.
2. Follicle-stimulating hormone will be tested at screening for women of nonchildbearing potential who are postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.
3. At each time-point indicated in the SoAs (Section 1.3), 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).

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • 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 intervention.

• Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event 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, ECG, 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 intervention 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 intervention 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.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event 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 or significant 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 authorised 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.

o 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.

10.3.3. 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 Sponsor in lieu of completion of the required form. • There may be instances when copies of medical records for certain cases are requested by CRO Clinical Safety. 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 CRO Clinical Safety. • 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 adverse event, not the procedure itself.
Assessment of Intensity
The severity of all adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those adverse event terms not listed in the CTCAE, the following grading system should be used, with the exception of CRS (see Appendix 6, Section 10.6): • 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

Assessment of Causality
• The Investigator is obligated to assess the relationship between study intervention 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 intervention administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure (IB) 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 CRO Clinical Safety. 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 CRO Clinical Safety • The Investigator may change his/her opinion of causality in light of follow-up information and send an 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 CRO Clinical Safety 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 CRO Clinical Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The Investigator will submit any updated SAE data to CRO Clinical Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to CRO Clinical Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to CRO Clinical Safety 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 participant 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 will be provided.

Initial Reports

- All SAEs occurring from randomization until study participation is complete or until resolution, whichever is sooner, must be reported to CRO Clinical Safety within 24 hours of the knowledge of the occurrence. After study participation is complete, any SAE that the Investigator considers related to study drug must be reported to CRO Clinical Safety or the Sponsor/designee.
- To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, CRO Safety personnel will be notified electronically by the EDC system and will retrieve the form.

Follow-Up Reports

- The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.
- Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to CRO Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined below.

SAE Reporting to CRO Clinical Safety via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the CRO Clinical Safety. • If the event meets serious criteria and it is not possible to access the EDC system, send an email to CRO Safety at STUDY-PVSS-4690-0000@iconplc.com, facsimile +1 215 616 3096 or call the CRO SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to CRO (contact information listed in Section 8.5.3) 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 8.5.8.1.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (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, confirmation with one FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.
   - Permanent sterilization methods (for the purpose of this study) include:
     - Documented hysterectomy
     - Documented bilateral salpingectomy
     - Documented bilateral oophorectomy
     - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy
   d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative

medical cause.

- A high follicle stimulating hormone (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, confirmation with one FSH measurement >40 IU/L or mIU/mL is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• 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 participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*)*
Highly Effective Methods 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 – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation – 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 intervention. 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 participant.)*

10.5. Appendix 5: Graft Versus Host Disease

Table 6: 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 34 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 57 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; MAGIC = Mount Sinai Acute GVHD International Consortium.
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.

Table 7: 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.

Table 8: 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.

Table 9: 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 2XULN
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.

10.6. Appendix 6: Cytokine Release Syndrome Scale

For patients who have a presumptive diagnosis of Cytokine Release Syndrome (CRS) based on the clinical judgement of the Investigator, CRS will be graded according to the ASTCT Consensus Grading for CRS (shown in Table 10) rather than by CTCAE. ASTCT characterizes CRS as: "A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction." The ASTCT Consensus Grading was developed for chimeric antigen receptor (CAR)-T cell therapies in which sustained engagement between the CAR-T cells and targeted malignant cells is expected, leading to substantial rates of CRS. By contrast, CRS remains only a theoretical concern for virus-specific T cells. (For additional details, see Appendix 7, Section 10.7 below.)

Table 10: ASTCT Consensus Cytokine Release Syndrome Grading Scale

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [1]	≥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 [2]				
Hypoxia	None	Requiring lowflow nasal cannula (oxygen delivered at ≤6 L/minute) or blowby	Requiring highflow nasal cannula (oxygen delivered at >6 L/minute), facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)

Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
Note: Grade 5 CRS is defined as death due to CRS in which another cause is not the principal factor leading to the outcome.

[1] Fever is defined as temperature ≥38.0oC 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.

[2] 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 39.5oC, 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.

10.7. Appendix 7: Monitoring for and Management of Cytokine Release Syndrome

The following recommendations have been adapted from recommendations for patients receiving chimeric antigen receptor (CAR)-T cells who develop cytokine release syndrome (CRS).[1] CRS is common following CAR-T cell therapy, but remains a theoretical concern following infusion of VSTs. No cases of CRS were observed in 58 patients in the phase 2 CHARMS study of VSTs for viral infections following allogeneic HCT.[2] Nevertheless, investigators should remain vigilant for the signs and symptoms of CRS, particularly during the first four weeks following VST infusion, and should be prepared to treat patients immediately for CRS should it develop. Investigators should also counsel patients to seek immediate medical attention if they develop concerning clinical findings. At the first sign of CRS, immediately evaluate the patient for hospitalization and institute treatment as outlined below or according to treatment protocols in use at the study site. CRS typically begins within 1 to 14 days (median 2 to 3 days) after CAR-T cell therapy.[3] It is also important to note that the common symptoms of CRS are not unique to CRS and clinicians must be cautious and exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress, such as an overwhelming infection.[4]

Treatment of Cytokine Release Syndrome

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

References:

1 KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion, prescribing information. https://www.novartis.us/sites/www.novartis.us/files/kymriah.pdf. Accessed on 09 Nov 2020.

2 Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2017;35(31):3547-3557.

3 Porter DL and Maloney DG. Cytokine release syndrome (CRS). Post TW, ed. UpToDate. Waltham, MA. Updated 06 Apr 2020. https://www.uptodate.com/contents/cytokine-release-syndrome-crs. Accessed on 09 Nov 2020.

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

10.8. Appendix 8: Amendment Changes and Rationale

Several amendments have occurred and a summary of changes and rationale is included below.

Protocol Version	Date	Patient Enrollment
Original, Version 1	13 July 2020	None
Amendment 1, Version 2	27 October 2020	Yes
Amendment 2, Version 3	7 April 2021	Yes
Amendment 3, Version 4	28 July 2021	None
Amendment 4, Version 5	19 October 2021	Yes
Amendment 4, Version 5.1	12 January 2022	Planned, UK Specific Amendment
Amendment 5, Version 6	26 December 2022	Planned

10.8.1. Amendment 1 rationale

This amendment updates and supersedes P-105-202 Original Protocol, dated 13 July 2020, as follows:

Modifications made to the protocol as a part of Amendment 1 and a brief rationale for the change are summarized below.

Major Revisions include:

- Clarification on cell line change language

The original protocol states “A cell line different from the initial infusion will be considered for patients with new or progressing infection; the Investigator may change to a different cell line only with consultation and approval from the Sponsor.” This sentence was deleted in Amendment 1.

Given the size and phase of this protocol, cell line changes will not be approved for participants in this study to ensure clear study results.

- Clarification on retreatment option

The original protocol states “If clinically significant viremia occurs and/or there is new or recurring clinically significant disease during the follow-up period, a patient may be retreated at the discretion of the Investigator in consultation with the Medical Monitor.” This sentence is deleted in Amendment 1.

Given the size and phase of this protocol, retreatment will not be approved for participants in this study to ensure clear study results.

- Update to blood volume table

The original protocol includes blood volumes by weight in sections 2.3.2 and 10.4. Specific blood volume information in the protocol has been deleted and reference is made instead to the Laboratory Manual.

There was an error in the blood volume calculations. They did not include the blood volumes needed for viral load testing as described in the Schedule of Activities and Assessments. The blood volume table was updated in accordance with the full scope of lab tests and included it in the laboratory manual. The laboratory manual will be the official blood sampling schedule document for this study.

- Update to Open Label Cohort Inclusion criteria

A weight criterion of at least 30 kg has been added to the Open Label Cohort in Amendment 1. Updated blood volume tables revealed that blood sampling from the lightest pediatric participants was not within ethical guidelines. Given the critical nature of the viral load sampling for the primary endpoint, robust endpoint, data from participants under 30 kg is unlikely.

- Clarification to unblinding section direction

The original protocol states in section 6.3 "Following unblinding, the Investigator must withdraw the patient from the study."

The text in Amendment 1 now reads, "the Investigator must discontinue the patient from the study drug."

These patients should be followed for safety throughout the full length of the study if possible.

10.8.2. Amendment 2 Rationale

This amendment updates and supersedes P-105-202 Amendment 1, dated 27 October 2020, as follows:

Modifications made to the protocol as a part of Amendment 2 and a brief rationale for the change are summarized below. Viralym-M was changed to posoleucel throughout.

Major Revisions include:

- Extended the window for dosing post-hematopoietic cell transplant (HCT) (Synopsis; Sections 1.3, 4.1, 5.1, 8.1.2, and 8.1.3)

The upper limit of the number of days post-HCT patients can be dosed is given a +7-day window.

- Increased cap on percentage of patients receiving letermovir prophylaxis (Synopsis; Sections 4.1 and 4.2)

The cap on the percentage of patients enrolled in the study who have received letermovir prophylaxis is increased from 30% to 50% in all cohorts.

- Changes to inclusion/exclusion criteria (Synopsis; Section 5.1 and 5.2)

Deleted "Patients between 15 to 28 days cannot have received T cell depleting antibodies (e.g.: anti-thymocyte globulin [ATG] or Campath)" and "Within 90 days after HCT."

Removed the weight limit criterion for the Open Label Cohort.

Added exclusion criterion of receiving donor lymphocyte infusion within 21 days prior to randomization.

For Open Label Cohort, added criterion that these patients may meet the viremia criterion for either Cohort A or Cohort B.

Removed "within 90 days after HCT" from the lymphocyte count and CD4 count inclusion criterion.

- Assessment of viremia prior to randomization (Synopsis; Sections 1.3, 4.1, and 8.2.2)

Clarified the assessment of viremia that will determine which cohort the patient is eligible for

(Cohort A or Cohort B).

- Reduction in plasma samples collected in pediatric patients < 12 years of age (Section 2.3.2)

To reduce the overall blood volume drawn from pediatric patients < 12 years of age, weekly blood draws are only done for adenovirus (AdV); all other viral load samples are done every other week through the treatment period.

- Updates to Schedule of Activities (Section 3.1)

Created separate Schedules of Activities (SoA) for patients who are adults or pediatric patients ≥ 12 years old and for patients who are < 12 years old. The SoA for patients who are < 12 years old reduces the amount of blood volume drawn by collecting samples for testing for all 6 viruses every other weekly visit and collecting for only AdV every weekly visit during the treatment period.

Added additional assessments for persistence of virus specific T cells (VSTs) at Weeks 14 and 26.

- Updated language regarding adverse events assessments (Sections 4.1 and 8.5.1)

Added text to clarify that all adverse events would be collected through the treatment period for all patients, including those who have discontinued study treatment but are continuing in the study. For patients who have discontinued, only drug-related serious adverse events (SAEs) and SAES leading to death will be collected through Week 26.

Adverse events and SAEs will be collected from signing of informed consent rather than from randomization.

- Treatment of Overdose (Section 6.7)

Expanded the description of overdose being greater than dose assigned to include the specific doses for patients < 40 kg and patients ≥ 40 kg.

- Updated Concomitant Therapy and Excluded Medications Sections (Sections 6.8, 6.8.1, and 6.8.2)

Added text to describe in greater detail medications that are permitted and excluded.

Deleted supportive care therapies that are associated primarily with hemorrhagic cystitis as they are not relevant to this study.

- Definitions of clinical viremia, disease, and resolution (Sections 8.2.3 and 10.7)

Added definition of resolution of viral infections (**Section 8.2.3**)

Added an appendix that includes the definitions of viremia and disease for each of the six viruses. This was missing from the original protocol and Amendment 1.

- Infection Assessments (Section 8.3)

Reorganized the infection assessments section and added subsections to clarify the procedures for plasma samples for confirming infection and for those prior to initiating therapy for infection.

- Updated Statistical Analysis Section (Sections 9.4.3, 9.4.4, 9.4.5, 9.5, and 9.5.1)

Added text to provide more detail to statistical analysis description. **(Sections 9.4.3, 9.4.4, and**

9.4.5)

Expanded the explanation of the interim analyses. (**Section 9.5**)

Aligned stopping criteria for individual patients with other AlloVir protocols. (**Section 9.5.1**)

- Updated Laboratory Tests (Section 10.2)

Updated Appendix 2: Clinical Laboratory Tests to be consistent in format with other AlloVir protocols and to be sure that all tests were included.

- Updated Cytokine Release Syndrome Information (Sections 10.6 and 10.7)

Appendix 6, Cytokine Release Syndrome Scale, was updated and a new appendix was added for the monitoring and management of CRS

- Changed references to the study drug from Viralym-M to posoleucel to conform to other company protocols.

10.8.3. Amendment 3 Rationale

This amendment updates and supersedes P-105-202 Amendment 2, dated 7 April 2021. Minor administrative and organizational changes were made for clarifications not affecting content. Major changes are as follows:

- Design of randomized Phase 3 placebo-controlled study (throughout protocol)

Randomized patients are now in one cohort, the Phase 3 study cohort. The open label cohort remains the same. Cohorts A and B were removed.

The study schema was updated to identify the Phase 3 study cohort and to be clearer on the timing of the Open Label cohort. Cohorts A and B were removed.

The inclusion criterion indicates that patients should have no known or suspected clinically significant disease from any of the 6 viruses. Inclusion criteria for viremia levels for Cohorts A and B were removed.

Exclusion criterion #2 regarding having evidence for more than 3 viruses was removed.

Removed optional pre-screening period to assess viral load because it is no longer necessary since patients are not assigned to cohort based on viral load.

A targeted percentage of patients not receiving letermovir is described.

- Objectives updated (Synopsis, Section 3.0., Sections 9.4.2., 9.4.3., 9.4.4., 9.4.5. and throughout where endpoint timing is described)

Edited the primary objective to target the number of clinically significant infections or episodes of end-organ disease rather than proportion of patients as this reflects better the effect of the study treatment on all six viruses.

The secondary endpoints were updated and reordered to reflect the relative clinical importance of the endpoints, following the change in the primary endpoint.

The secondary endpoint of proportion of patients with clearance of viremia for all six viruses was updated to Week 14 instead of Week 8 so that it is assessed 2 weeks after the final dose of posoleucel.

Deleted time to onset objective and endpoint.

Added the secondary endpoint of proportion of AUC for cumulative viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV over 26 weeks.

Added "through Week 26" for secondary endpoint 5 (originally 9.1) because the timing was missing originally.

Hospital readmission rate was elevated to a secondary endpoint and total days of hospitalization was moved to an exploratory endpoint because of the greater importance of reducing hospital readmission rates due to prevention of viral reactivation in this study.

Deleted exploratory endpoint of number of patients requiring ventilation.

Added definition of clearance of viremia to the relevant endpoint (less than the lower limit of quantification) for clarification.

Safety endpoints are now a separate set of objectives/endpoints rather than included in the secondary endpoints.

Added graft failure to safety endpoints as an adverse event of special interest.

Anti-viral specific T-cell monitoring added to Exploratory Objective/Endpoints.

- Synopsis, Section 4.1 Overall Design, Section 9.4.5. Safety Endpoints and Analysis

Engraftment was defined as requiring >500 neutrophils/µL.

- Section 1.3. Schedule of Activities

Removed optional pre-screening period to assess viral load because it is no longer necessary since patients are not assigned to cohort based on viral load. Updated footnotes to reflect Phase 3 design.

Combined the Follow-up Period Schedule of Activities with the Treatment Period Schedule of Activities since there are now only two visits in the follow-up period. Added a column for the 52-week follow-up contact (telephone or email) to assess patient status that is not part of the study period but needed to be reflected in the Schedule of Activities so that the sites will complete the contact.

Made it clearer that the Infection Assessment only occurs for patients requiring either treatment for infection or initiation of preemptive therapy during the study.

Made the window for all visits during the treatment period ±3 days.

In the Schedule of Activities for pediatric patients < 12 years, Week 9 virus-specific T cell assessment was changed to Week 10.

The Schedule of Activities was updated to reduce patient burden in the following ways:

- Updated timing of ECG's to screening and baseline only.
- Combined Week 18 and Week 22 visits into one Week 20 visit during the study follow-up period.
- Visits between infusion visits may now be home visits with blood draws only.
- Removed the FACT-BMT quality of life assessment.
- Eliminated the 45-minute post-infusion vital signs assessment.

- Extended window for visits during the follow-up period (Period 2) from 7 days to 10 days.

- Synopsis, Section 4.1 Overall Design

Phase 3 design is described as discussed above in overall changes throughout protocol.

Patients on antithymocyte globulin, alemtuzumab, or other immunosuppressive T cell-targeted monoclonal antibodies, study therapy will begin between day 28 and 42 (+7) days rather than between 15 and 42 (+7) days.

- Section 4.2 Scientific Rationale for Study Design

Added the rationale for the assumptions behind the calculation of the sample size.

- Section 4.4. End of Study Definition, Section 7.3 Early Termination, Section 8.1.3. Follow-up period

The end of study definition was updated to be clear that the Week 26 visit is the end of study visit. The timing of the post-study telephone call to assess mortality was updated to occur approximately 52 weeks (12 months) after the start of treatment rather than after the last study visit.

- Synopsis, Section 5.1. Inclusion Criteria

Inclusion criterion with respect to viremia/disease indicates that patients should have no known or suspected clinically significant disease from any of the 6 viruses. Inclusion criteria for viremia levels for Cohorts A and B were removed.

Removed the +7 day window to upper limit of time since HCT as it was incorrectly included. The +7 day window applies to starting study treatment not enrollment into the study.

Updated high risk criteria so that having an unrelated donor would qualify as high-risk and that receipt of T-cell depletion or Campath (alemtuzumab) would qualify as high-risk. Removed the lymphocyte count or CD4 T cell count criterion as high-risk.

Prior therapy with antithymocyte globulin or alemtuzumab (Campath-1H) was added to high-risk definition inclusion criterion #4.

Received T-cell depletion or Campath (alemtuzumab) was added to high-risk definition inclusion criterion #4.

Description of contraception in inclusion criterion # 5b was updated to “highly effective” rather than “acceptable.”

- Section 5.2. Exclusion Criteria

Exclusion criterion #2 regarding having evidence for more than 3 viruses was removed.

Cytokine release syndrome was removed from exclusion criterion #2 (originally #3) as it was duplicated in exclusion criterion #5 (originally #6).

Exclusion criterion #4 (originally #5) describes progressive, uncontrolled viral infection as evidence of viremia, dissemination, and/or organ specific infection not well controlled by present therapies.

Exclusion criterion #10 (originally #11) was edited to be consistent with other protocols.

Exclusion criterion #11 (originally #13): Length of time a patient may have received high-dose systemic corticosteroids was updated to within 24 hours prior to treatment so that there is no interference with the performance of the study treatment.

Increased the direct bilirubin serum levels for exclusion to >3 times the upper limit of normal.

Deleted original exclusion criteria #18 and #20 because they were duplicates of exclusion criteria #10 (originally #11) and #4 (originally #5), respectively.

- Section 6.1. Study Intervention(s) Administered

Clarified that the weight for determining dosage level is the weight at first study treatment administration.

- Section 6.1.2. Study Intervention Administration

Text was simplified and more specific information can be found in the Cell Therapy Manual.

Timing of monitoring of vital signs was updated to include prior to starting infusion and the removal of 45 minutes after end of infusion.

- Section 6.8.2.1. Supportive care

Updated text to clarify that all supportive care as needed and determined by the Investigator is permitted.

- Section 7.1. Discontinuation of Study Intervention and Section 7.2. Participant Discontinuation/Withdrawal from the Study

If at all possible, patients who qualify for discontinuing study drug should continue to be followed in the study. Thus, reasons that may have led to patients discontinuing the study but could instead lead to discontinuing study treatment but continuing in the study were moved from Section 7.2. to Section 7.1.

- Section 8.1 Study Periods, Section 8.2.1. Viral Load

The study periods reflect the Phase 3 study design as discussed above in overall changes throughout protocol.

- Section 8.2.2. Resolution of Viral Infections

Resolution of viral infection is defined as asymptomatic with the completion of any antiviral therapy.

- Section 8.2.4. Quality of Life

Removed FACT-BMT as a measure of quality of life.

- Section 8.2.4. Virus-specific T Cell Assessment

Removed enzyme-linked immunospot.

Section 8.3. Infection Assessments

Clarification of when central lab or local lab results should be collected and their use. Symptom checklist was removed.

- Section 8.4.1. Physical Examinations

Clarified the timing and extent of targeted physical examinations.

- Section 8.4.5. Graft Versus Host Disease and Section 8.4.6. Cytokine Release Syndrome

Included these sections for consistency between protocols and to provide additional information regarding the identification and treatment of Graft versus Host Disease and Cytokine Release Syndrome.

- Section 8.5.1. Time Period and Frequency for Collecting AE and SAE Information

Collection of AEs and SAEs will be from randomization instead of signing of informed consent.

Added the definition of treatment emergent adverse events (TEAEs).

- Section 8.5.3. Serious Adverse Event Reporting

Section was included to fully describe the procedures for SAE reporting and to be consistent between protocols.

- Section 8.5.8. Adverse Events of Special Interest

Added graft failure as an adverse event of special interest for consistency across protocols.

- Section 8.10. Medical Resource Utilization and Health Economics

Clarified hospital utilization to be specific to clinically significant infection or disease due to one or more of the 6 viruses.

- Synopsis, Section 9 Statistical Considerations

The statistical analysis section of the synopsis was expanded to provide more information about the statistical plan and Phase 3 design.

The statistical analysis section was edited to address the Phase 3 design, including the sample size calculation and changes to endpoints.

- Section 10.2 Appendix 2 Clinical Laboratory Tests

Urinalysis tests are central laboratory tests rather than local laboratory tests, which was corrected in the appendix.

- Section 10.4.2. Contraceptive Guidance

Removed section of table of describing effective methods that are not considered highly effective as only highly effective contraceptive methods are allowed.

- Section 10.8 Appendix 8: Endpoint Definitions

This appendix was removed as endpoint definitions are included in the CAC Charter and reference is now made to the charter rather than the appendix within the protocol.

- Section 10.8 Amendment Changes and Rationale

Previous amendment changes were moved from the beginning of the protocol to the appendix.

10.8.4. Amendment 4 Rationale

This amendment updates and supersedes P-105-202 Amendment 3, dated 28 July 2021. Minor administrative and organizational changes were made for clarifications not affecting content. Changed treatment assignment throughout to randomization. Major changes were to add stratification factors, revise power and sample size, revise endpoints and remove visits and

laboratories at odd numbered weeks for patients <12 years of age to reduce patient burden. Specific changes include:

- Cover Page

Deleted IND number.

Addition of EudraCT number.

Moved protocol version history to Appendix 8.

- Objectives and endpoints updated (Synopsis Section 1, Section 3.0, Sections 9.4.2, 9.4.3, 9.4.4, 9.4.5, and throughout where endpoints are described)

Clarified that primary and secondary endpoints are per patient.

Edited the secondary objectives and endpoints to include assessment of efficacy for each target virus individually.

Moved secondary endpoints to exploratory endpoint section, including: healthcare utilization, QoL assessments, proportion of patients with undetectable viremia.

Moved secondary endpoint of overall mortality to safety endpoint section.

Added physical examination, clinical laboratory, and imaging results safety endpoint.

- Section 1.1 Synopsis

Clarified number of patients in open label required for DSMB review.

Increased sample size in randomized phase to approximately 302.

Removed letermovir enrollment cap.

Removed absolute neutrophil count and clarified clinical engraftment requirement.

Clarified timing of treatment period start after receipt of ATG, alemtuxumab, or other immunosuppressive T cell-targeted monoclonal antibodies.

Clarified total weeks on study inclusive of screening period as 36 weeks.

Added stratification variables of letermovir usage, age, allogeneic transplant risk of viral infections.

- Section 1.2, Schema

Updated diagram to add new sample size and correct dosing duration bar.

- Section 1.3, Schedule of Assessments

Table 1: Removed collection of adverse events in screening table as collection starts after randomization.

Table 1: Clarified footnote to note EBV viral load could be assessed from PBMCs or plasma.

Table 1: Clarified footnote to remove collection of weekly viral loads during screening.

Table 2: Corrected Week 20 study day from 154 to 140

Table 2: Changed Treatment Assignment to Randomization throughout table and footnotes.

Table 2: Added pregnancy tests at Weeks 14, 20 and 26.

Table 2: Clarified footnote on timing of AE collection for all patients.

Table 2: Removed statement that clinical laboratory assessments collected as part of standard of care may be used

Table 2: Clarified that negative pregnancy test confirms patient eligibility for dosing.

Table 2: Clarified that all samples on dosing days should be collected prior to dosing.

Table 2: Clarified footnote to note EBV viral load could be assessed from PBMCs or plasma.

Table 2: Clarified footnote to note VSTs could be assessed from PBMCs or whole blood.

Table 2: Clarified that only new onset Grade >2 GVHD would preclude additional dosing.

Table 2: Clarified that Week 52 follow-up is for patient status.

Table 3: Removed visits at odd numbered weeks after Day 1 (Week 1, 3, 5, 7, 9, 11 and 13).

Table 3: Corrected Week 20 study day from 154 to 140.

Table 3: Changed Treatment Assignment to Randomization throughout table and footnotes.

Table 3: Clarified footnote on timing of AE collection for all patients.

Table 3: Removed statement that clinical laboratory assessments collected as part of standard of care may be used.

Table 3: Clarified that all samples on dosing days should be collected prior to dosing.

Table 3: Clarified EBV viral load could be assessed from PBMCs or plasma.

Table 3: Clarified VSTs could be assessed from PBMCs or whole blood.

Table 3: Clarified that only new onset Grade >2 GVHD would preclude additional dosing.

Table 3: Clarified that Week 52 follow-up is for patient status.

- Section 2.3.2, Potential Risks

Removed weekly viral load testing for pediatric patients <12 years of age.

- Section 3, Objectives and Endpoints

Updated objectives and endpoints.

- Section 4.1, Overall Design

Clarified number of patients in open label required for DSMB review.

Increased sample size in randomized phase to approximately 302.

Removed statement about duration of enrollment.

Added stratification variables of letermovir usage, age, allogeneic transplant risk viral infections.

Clarified timing of treatment period start after receipt of ATG, alemtuxumab, or other immunosuppressive T cell-targeted monoclonal antibodies.

Removed collection of weekly viral loads during screening.

Removed letermovir enrollment cap.

Removed absolute neutrophil count and clarified clinical engraftment requirement.

Changed weekly visits to biweekly through Week 14 for children <12 years of age.

Clarified timing of AE collection for all patients.

Clarified that infection assessments should be collected prior to initiating therapy for viral infection or disease.

Clarified that Week 52 follow-up is for patient status.

- Section 4.2, Scientific Rationale for Study Design

Removed endpoint language and added study goal.

Updated estimated percent of patients with 2 clinically significant infections.

Clarified rationale for repeated dosing.

- Section 4.3, Justification for Dose

Added CHARMS dose used in patients <40 kg.

- Section 4.4, End of Study Definition

Clarified that Week 52 follow-up is for patient status.

- Section 5.1, Inclusion Criteria

Inclusion 3: Removed absolute neutrophil count and clarified clinical engraftment requirement and changed treatment assignment to randomization.

Inclusion 4: Changed treatment assignment to randomization.

Inclusion 5: Removed requirement to review menstrual or sexual activity history.

Inclusion 7: Added requirement that patients have matching posoleucel cell line.

- Section 5.2, Exclusion Criteria

Exclusion 1: Changed treatment assignment to randomization.

Exclusion 8: Changed treatment assignment to randomization.

Exclusion 9: Changed treatment assignment to randomization.

Exclusion 10: Clarified that active dosing with another investigational agent is not allowed and changed treatment assignment to randomization.

Exclusion 11: Changed timing of dosing with corticosteroids to occur within 24 hours prior to dosing, instead of treatment.

Exclusion 12: Changed timing of dosing with ATG, alemtuxumab, or other immunosuppressive T cell-targeted monoclonal antibodies to occur within 28 days prior to dosing, instead of treatment assignment.

- Section 6.1.1, Cell Line Selection

Clarified “First In First Out” method.

- Section 6.2, Preparation/Handling/Storage/Accountability

Clarified that sponsor is also involved in study treatment accountability.

- Section 6.3, Measures to Minimize Bias: Randomization and Blinding

Added stratification variables of letermovir usage, age, allogeneic transplant risk viral infections.

- Section 6.6, Continued Access to Study Intervention after the End of the Study

Clarified that dosing is complete at Week 12.

- Section 6.8, Concomitant Therapy

Removed daily collection of analgesic use.

Deleted statement on brincidofovir use.

- Section 6.8.1, Excluded Medications and/or Procedures

Clarified that systemic steroids could be used during the study if medically required.

Clarified that ATG, alemtuxumab, or other immunosuppressive T cell-targeted monoclonal antibodies are prohibited during dosing.

- Section 7.1, Discontinuation of Study Intervention

Clarified AE criteria was from last study drug, not posoleucel, as patient could be on placebo.

Clarified that HCT from another donor would render patient ineligible to receive additional doses.

- Section 7.2, Participant discontinuation/Withdrawal from the Study

Removed statement on patient follow-up as it was captured in Section 7.1.

Clarified that follow-up should occur for patients who discontinue early after starting dosing.

- Section 7.3, Early Termination

Clarified EBV could include PBMC or plasma collection.

- Section 8.1.1, Screening period

Clarified EBV could include PBMC or plasma collection.

Removed collection of weekly viral loads during screening.

- Section 8.1.2, Treatment period

Clarified timing of treatment period start after receipt of ATG, alemtuxumab, or other immunosuppressive T cell-targeted monoclonal antibodies.

- Section 8.2,1 Viral load

Clarified EBV could include PBMC or plasma collection.

Changed treatment assignment to randomization.

Clarified that all samples on dosing days should be collected prior to dosing.

- Section 8.2.2, Resolution of Viral Infections

Clarified EBV could include PBMC or plasma collection.

- Section 8.2.4, Virus-specific T Cell Assessment

Clarified VST could include PBMC or whole blood collection.

- Section 8.3, Infection Assessments

Clarified that patients who develop infections will continue to be followed in the study.

- Section 8.3.1, Confirmatory Plasma Samples for Suspected Infection at Central Laboratory

Clarified EBV could include PBMC or plasma collection.

- Section 8.3.2, Samples When Initiating Anti-viral Therapy

Clarified EBV could include PBMC or plasma collection.

- Section 8.4.1, Physical Examinations

Changed treatment assignment to randomization.

- Section 8.4.2, Vital Signs

Clarified that vital signs would be collected prior each infusion.

- Section 8.4.4, Clinical Safety Laboratory Assessments

Clarified that all samples on dosing days should be collected prior to dosing.

- Section 8.4.7, Pregnancy Testing

Changed treatment assignment to randomization.

- Section 8.5.1, Time Period and Frequency for Collecting AE and SAE Information

Changed treatment assignment to randomization.

- Section 8.5.3, Serious Adverse Event Reporting – Procedures for Investigators

Changed treatment assignment to randomization.

- Section 9.1 Research Hypothesis

Clarified that main outcomes are per patient.

- Section 9.2, Sample Size Determination

Updated sample size and power.

- Section 9.4.1 General Considerations

Clarified that summary statistics will not be presented by cohorts.

- Section 9.4.2, Primary Efficacy Endpoint

Updated endpoints.

Clarified how breakthrough infections would be handled in analysis.

Added stratification variables of age, and allogeneic transplant risk viral infections.

Changed model from Kaplan Meier to Cox Proportional Hazards model.

- Section 9.4.3, Secondary Efficacy Endpoint

Updated endpoints.

- Section 9.4.4, Exploratory Endpoints

Updated endpoints.

- Section 9.4.5, Safety Endpoints and Analysis

Updated endpoints.

- Section 9.4.6, Other Analyses

Added potential for subgroup analyses to be conducted.

- Section 9.5, Interim Analysis

Removed DSMB information as it was not relevant.

Clarified that a sample size re-estimation will be completed, but that no formal interim analyses will be performed

- Section 9.5.2, Stopping Criteria for the Study

Changed treatment assignment to randomization.

Clarified that DSMB would need to review safety data prior to resuming randomization.

- Section 10.1.5.2, Data Safety Monitoring Board

Clarified number of patients in open label required for DSMB review.

- Section 10.3.4, Reporting of SAEs

Changed treatment assignment to randomization.

- Section 10.8, Appendix 8, Amendment Rationale and Changes

Added rationale and summary of changes to Amendment 4.

- Last Page

Removed signature page as document is signed in Veeva.

10.8.5. Amendment 4 (UK Specific) Rationale

This amendment updates and supersedes P-105-202 Amendment 4, dated 19 October 2021 in the United Kingdom only. Changes were made to address request from Medicines and Healthcare Products, Regulatory Agency (MHRA). Major change included removal of 52-week follow-up as patients will be offered a long-term registry study.
Specific changes include

- Section 1.2, Schema
- Updated diagram to remove Week 52 follow-up
- Section 1.3, Schedule of Assessments

Updated Table 2 and 3 to remove Week 52 follow-up

- Section 4.1, 4.4, 7.3, 8.1.3, Overall Design, End of Study Definition, Early Termination, Follow-up Period

Removed Week 52 follow-up visit

- Section 6.8, Concomitant Therapy

Clarified that COVID-19 vaccination is acceptable

10.8.6. Amendment 5 Rationale

This amendment updates and supersedes P-105-202 Amendment 4, Version 5, dated 19 October 2021 and Amendment 4 (UK Specific), Version 5.1, dated 12 January 2022.
Modifications made to the protocol as part of Amendment 5 and a brief rationale for the changes are summarized below. Formatting changes were made throughout the document to align with company templates. ALVR105 was changed to posoleucel throughout.
Major Revisions include:

Title Page

- Added new sponsor address and IND number

Section 1.2

- Updated schematic to replace ALVR105 with posoleucel.

Section 1.3

- Clarified local labs are only allowed to fulfill Screening requirements.
- Revised urinalysis timing to collect only at Screening.
- Clarified urinalysis is not required for patients in diapers or unable to provide sample.
- Removed GGT testing which is not being performed.
- Revised "treatment assignment" to randomization for consistency.
- Clarified that adverse events are captured starting at randomization.
- Added additional testing of CD4 and CD8 on Day 1 and Week 14.
- Clarified that certain eligibility criteria should be confirmed prior to dosing on Day 1.
- Removed visits on Weeks 7, 9, 11 and 13 for patients ≥12 years of age.

Sections 1.3 and 6.1

- Clarified that dosing will be based on weight at Screening.

Sections 1.3 and 6.1.2

- Removed requirement for continuous pulse oximetry after the end of infusion to reduce site burden as this is not considered necessary.

Sections 1.3, and 8.4.3

- Removed the requirement for ECG to be completed within 1 hour after study treatment on Day 1 to reduce site burden as this is not necessary.

Sections 1.3 and 8.4.7

- Clarified timing and type of pregnancy tests to be completed. β-HCG blood test is required at Screening and in the event of a positive urine pregnancy test only. For all other visits a urine pregnancy test is acceptable. Pregnancy test is not required at Visits Wk14, 20 and 26.

Sections 1.3, 4.1, 4.4, 7.3, and 8.1.3

- Clarified that patients in the UK will not complete Week 52 follow-up visit.

Synopsis; Sections 3, 9.4.3, 9.4.4, and 9.4.5

- Revised wording of endpoints, added safety and exploratory endpoints to capture planned analysis.

Synopsis; Sections 4.1, 4.2 and 5.1

- Clarified that participants under 1 year of age will be enrolled after safety data is available for participants ages 1 to 6. Infants under 1 year of age are being included as they are at high risk of both primary viral infection and potentially viral reactivation and would potentially sustain the same benefits from VSTs as older patients undergoing high-risk HCT.

Synopsis; Sections 4.1 and 10.1.5.2

- Updated information to capture the completed review of open-label cohort by the DSMB.

Synopsis; Section 4.1

- Clarified that CAC will only review Phase 3 data, not open-label data

Section 4.2

- Added clarification for dosing schedule.

Synopsis; Section 5.1

- Provided clarification in Inclusion Criterion #3, defined clinical engraftment as ANC $\geq 500/mm^3$.

Synopsis; Section 5.1

- Provided clarification in Inclusion Criterion #4, clarified that unrelated donors include both matched and mismatched. Added enrollment cap for matched unrelated donors.

Synopsis, Section 5.2

- Provided clarification in Exclusion Criterion #4, provided examples of viral infections
- Provided clarification in Exclusion Criterion #5, noted that patients who have Grade ≥3 CRS or ICANS (immune effector cell-associated neurotoxicity syndrome) are excluded from study participation.
- Provided clarification in Exclusion Criterion #6, noted that absence of encephalopathy should be confirmed at randomization, not screening.
- Provided clarification in Exclusion Criterion #9, noted additional medications that are not allowed within 7 days prior to randomization and clarified pediatric dosing should be taken into account, if applicable.
- Provided clarification in Exclusion Criterion #12, revised wash-out window for T cell-targeted monoclonal antibodies from 28 to 21 days prior to dosing.
- Provided clarification in Exclusion Criterion #12, noted that patients who have received prior therapy with cyclophosphamide are still eligible for study participation.
- Provided clarification in Exclusion Criterion #16, noted that dialysis status should be confirmed at randomization, not screening

Synopsis, Sections 8.5.1, and 9.4.5

- Clarified definition of TEAE.

Section 5.4

- Added clarification on the procedures and data to be collected on patients who fail screening or randomize but do not dose.

Section 6.1.1

- Added clarification that appropriate HLA matched cell lines may be substituted if needed, eg damaged inventory.

Section 6.1.2

- Removed instructions on time to that study treatment as details are captured in the Cell Therapy Manual.
- Added rationale for not administering posoleucel and IVIG on the same day. Avoiding administration of IVIG on the same day as posoleucel administration will allow for a better assessment of whether observed AEs are related to study intervention.

Section 6.8

- Separated Concomitant Therapy Section into new sections as noted below:
- Section 6.8.1, Provided clarification on antiviral use and guidance for management of CMV infections.
- Section 6.8.2, Provided clarification on steroid use and tapering to resume dosing. Provided flexibility to dose through steroids given the high risk nature of patients on immunosuppression for viral reactivation/infection and the longitudinal nature of this prevention trial.
- Section 6.8.3, Added language stating that all COVID-19 regimens recommended by local health authorities are permitted in the trial.

Section 6.8.4

- Removed language on medications that are allowed during the study, eg steroids.

Section 6.8.6

- Provided instructions on prior medications that do not need to be recorded to minimize collection of unnecessary data.

Section 7.1

- Formatted section to clarify reasons for discontinuations of study treatment. Clarified that if treatment is discontinued as many protocol required procedures as feasible should be completed, to allow flexibility for patients.

Section 7.3

- Clarified that if treatment is discontinued as many protocol required procedures as feasible should be completed, to allow flexibility for patients.

Section 8.1.1

- Clarified that patients in screening should be maintained on study as long as protocol allows to allow verification of eligibility criteria, prior to making a final determination on patient eligibility for dosing.
- Clarified that patients may be re-screened.

Section 8.2.1

- Removed language on viral load testing prior to screening, the language was relevant to a prior protocol version.

Section 8.1.1

- Clarified that screened patients should remain on study through screening window to assess eligibility prior to failing patient.

Section 8.3

- Clarified name of manual where infection definitions are captured.
- Clarified that patients who develop infections can continue to be treated.

Section 8.3.2

- Added note that additional guidance on treatment of CMV is included in Section 6.8.1.
- Clarified handling of viral load testing after an infection is confirmed.

Section 8.4.1

- Removed the requirement for physical exams to be captured only by physicians to allow flexibility for nurse practitioners, physician's assistant or other qualified personnel to complete exams.

Section 8.4.2

- Removed the requirement for vital signs to be measured in a semi-supine position to provide site flexibility in vital sign measurement as per site typical protocols.
- Clarified that O_2 saturation should be captured when vitals are captured.

Section 8.4.5

- Provided clarification on assessments of GVHD. Added language to clarify that all events of GVHD should be assessed by CTCAE (acute and chronic GVHD) and by MAGIC criteria (acute GVHD) or National Institutes of Health Scales (chronic GVHD) and linked directly to those scales within Appendix 5.

Section 8.5.1

- Provided clarification on timing of AE collection.

Section 8.5.8

- Provided clarification on grading of graft failure AESI.

Section 9.2

- Clarified sample size for study is based on dosed not randomized patients. As this is a high risk population, patients may randomize, then become too sick to receive any

study drug. To protect the integrity of the primary analysis, only patients who received any study drug will be included in the primary analysis.

Sections 9.3 and 9.4.2

- Updated the planned analysis populations to remove Enrolled population and align with SAP.

Section 9.4.1

- Clarified analysis framework for primary and secondary endpoints.

Synopsis; Section 9.4.2

- Provided clarification that additional details of the statistical analysis will be included in the SAP.

Sections 9.4.2 and 9.4.3

- Removed imputation methods as these will be described in the SAP.

Sections 9.4.3 and 9.4.4

- Clarified that combined summary of open label and Phase 3 data is not planned.
- Removed visits on Weeks 7, 9, 11 and 13 for patients ≥12 years of age.
- Clarified timing of QoL endpoint.

Sections 9.5

- Provided additional details on planned sample size re-estimation and potential to increase sample size.

Section 9.5.1.2

- Removed individual patient stopping criteria and referenced relevant protocol section.
- Updated stopping criteria for the study. Stopping criteria are stated only for the open label Phase 2 cohort of the study (previously agreed with the DSMB). In Phase 3, study continuation will be assessed by the DSMB.

Section 10.2

- Clarified local labs are only allowed to fulfill Screening requirements or for management of adverse events.
- Clarified chemistry analytes to be completed.
- Added additional laboratory (CD4 and CD8) to be collected on Day 1 and Week 14.
- Clarified that stool and CSF samples are optional central lab samples and can be collected locally only.
- Removed screening sample to measure viruria to ensure document consistency.

Section 10.3.4

- Clarified email and facsimile for submission of SAE reports in the event that EDC system is not available.

Section 10.4.1

- Clarified only a single FSH may be used to confirm postmenopausal state

Section 10.5

- Corrected typo in Table 9

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Approval Task	Heather Tiscia Regulatory Affairs 13-Jan-2023 21:21:18 GMT+0000

Approval Task	Michelle Matzko Medical 13-Jan-2023 21:52:34 GMT+0000

Approval Task	Badrish Patel Pharmacovigilance 14-Jan-2023 11:48:05 GMT+0000

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