CLINICAL STUDY PROTOCOL

Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Viralym-M (ALVR105) 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: ALVR105 (Viralym-M)

Protocol Number: P-105-202

IND: 15092

EudraCT: N/A

Sponsor:

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FINAL PROTOCOL

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Confidentiality Statement

SIGNATURE PAGE

STUDY TITLE: Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of 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, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
[redacted]	7-APR-202

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol, Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of 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
ALVR105	Viralym-M, ALVR-105
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cell Therapy
BKV	BK virus
CBC	Complete blood count
CFR	Code of Federal Regulations
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
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HC	Hemorrhagic cystitis

Abbreviation	Definition or Term
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
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
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIMP	Non-investigational medicinal product
PBMC	Peripheral blood mononuclear cell
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
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

Abbreviation	Definition or Term
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, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of 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 study to evaluate the efficacy and safety of ALVR105 (also known as Viralym-M and formerly known as ALVR-105) for the prevention of clinically significant adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and JC 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 devastating single and/or 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 (VST) 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 Viralym-M for the prevention and preemptive treatment of AdV, BKV, CMV, EBV, HHV-6, and/or JCV infections represents an unmet medical need.

Objectives and Endpoints:

Objectives	Endpoints
Primary 1. To compare the efficacy of ALVR105 to placebo in the proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection and/or end-organ disease as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 14	1. The proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection (defined as infection and/or end-organ disease as determined by an independent, blinded CAC) through Week 14
Secondary	
1. To compare the efficacy of ALVR105 to placebo in time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia over 14 weeks, in patients at high risk, following allogeneic HCT	1. Time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia over 14 weeks
2. To compare the efficacy of ALVR105 to placebo in area under the curve (AUC) for cumulative viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV over 14 weeks	2. AUC for cumulative viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV over 14 weeks
3. To compare the efficacy of ALVR105 to placebo in incidence of clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease (excludes asymptomatic viremia) through Week 14	3. Proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease (excludes asymptomatic viremia) through Week 14
4. To compare the efficacy of ALVR105 to placebo in the proportion of patients with clearance of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia in allogenic HCT patients with detectable viremia prior to the start of treatment	4. Proportion of patients with clearance of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia by Week 8 in HCT patients with detectable viremia prior to the start of treatment
5. To compare the efficacy of ALVR105 to placebo in the proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection and/or end-organ disease as determined by an independent, blinded CAC through Week 26 (the end of the 12-week safety	5. Proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease and/or end-organ disease as determined by an independent, blinded CAC through Week 26 (the end of the 12-week safety follow-up period)

Objectives	Endpoints
follow-up period)	
6. To compare the efficacy of ALVR105 to placebo in reducing hospitalization in HCT recipients through Week 26 7. To compare the efficacy of ALVR105 to placebo in reducing non-relapse mortality in allogeneic HCT recipients through Week 26 8. To compare the efficacy of ALVR105 to placebo on patient-reported quality of life through Week 26 9. To assess the safety and tolerability of ALVR105 when administered to adult and pediatric patients at high-risk for AdV, BKV, CMV, EBV, HHV-6, and/or JCV following allogeneic HCT	6. Total number of hospital days related to AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection or disease through Week 26 7. Proportion of patients with AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease-related mortality as determined by an independent, blinded CAC through Week 26 8. Quality of life assessments, FACT-BMT, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26 9.1. Incidence of overall non-relapse related mortality AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease related mortality as determined by an independent, blinded CAC 9.2. Severity and incidence of acute GVHD 9.3. Severity and incidence of chronic GVHD 9.4. Severity and incidence of cytokine release syndrome 9.5. Severity and incidence of clinically significant cytopenias 9.6. Severity and incidence of renal dysfunction 9.7. Effect on measures of engraftment

Objectives	Endpoints
Exploratory 1. To assess the development of anti-viral- specific T cells 2. To assess healthcare resource utilization through Week 26	1. Detection of anti- AdV, BKV, CMV, EBV, HHV-6, and/or JCV -specific T cells through Week 26. 2.1. Hospital readmission rate related to AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia/disease through Week 26 2.2. Total days in the ICU through Week 26 2.3. Proportion of patients requiring mechanical ventilation related to AdV, BKV, CMV, EBV, HHV-6 and/or JCV infection or disease through Week 26 2.4. Duration of anti-viral therapy (foscarnet, ganciclovir, cidofovir or other) due to viremia and/or disease through Week 26

For the open-label portion of the study, similar endpoints will be analyzed. Additional details can be found in the Statistical Analysis Plan (SAP).

Overall Design:

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, multiple dosing interval study comparing ALVR105 to placebo for the prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV infections and/or diseases, in high-risk patients after allogeneic HCT.

There are 3 cohorts (Cohort Open Label [OL], Cohort A, and Cohort B). [redacted] he first 25 to 35 patients (Cohort OL) will receive ALVR105 for 30 days of open-label dosing to assess and optimize processes. A review by the Data Safety Monitoring Board (DSMB) will be done when approximately 30 patients have completed 30 days of treatment. At this time an assessment of benefit, risk and process will be done, and study optimization will be considered. [redacted]. Open label patients will continue in the open label arm. [redacted].

Once patients are assigned to ALVR105 or placebo (administration to begin as early as 15 days post-HCT as long as, in the Investigator's judgment, the patient has met the 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).

[redacted]. Cohort OL will also include a 50% cap for letermovir prophylaxis; Sponsor can revisit this limit in Cohort OL based on on-going assessment of feasibility.

[redacted]

Intervention Groups, Key Inclusion Criteria, and Duration:

Male and female patients ≥1 year of age at high risk for viral infection after HCT:

1. Be within 15 and 42 (+7) days of receiving a first allogeneic HCT at the time of treatment assignment and demonstrated engraftment with an absolute neutrophil count >500/μL.
2. <u>High-risk</u>: Patients meeting <u>one or more of the following criteria</u> at the time of treatment assignment:
    - 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
    - Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1
    - Use of umbilical cord blood as stem cell source

- Ex vivo graft manipulation resulting in T cell depletion
- Lymphocyte count <180/mm^3 and/or cluster of differentiation 4 (CD4) T cell count <50/mm^3

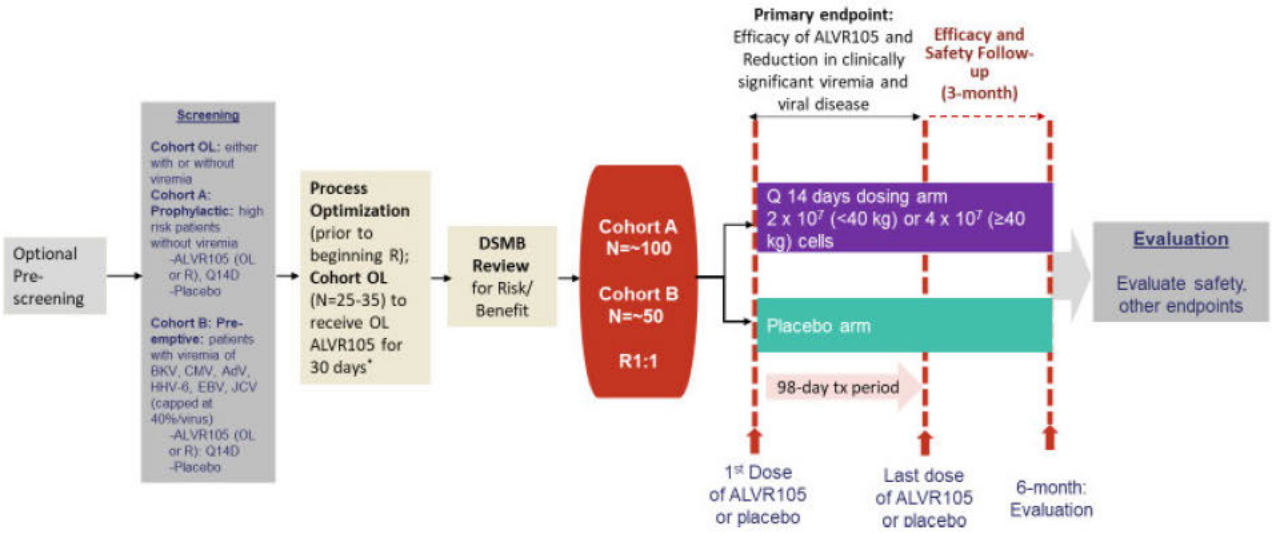
Patients will be tested once a week by the central laboratory during Screening until treatment assignment, using polymerase chain reaction (PCR) assays for each virus. Cohort OL will include patients with and without detectable AdV, BKV, CMV, EBV, HHV-6, and JCV viremia. After Cohort OL, Cohort A will include patients without detectable AdV, BKV, CMV, EBV, HHV-6, and JCV viremia (ie, below the level of quantitation) based on the last viral load assessment available within 7 days prior to randomization, and Cohort B will include patients who are positive with AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia based on the last viral load available within 7 days prior to randomization, as documented by central laboratory test results. Randomization will occur prior to Day 1. Patients who are positive for >3 viruses will not be eligible to participate.

After HCT, eligible patients in Cohort A and Cohort B will receive either ALVR105 ([redacted] for patients <40 kg or [redacted] for patients ≥40 kg, every 14 days) or placebo every 14 days. Patients in Cohort OL will receive ALVR105 ([redacted] for patients <40 kg or [redacted] for patients ≥40 kg, every 14 days for 14 weeks. Treatment with either ALVR105 or placebo will begin between 15 to 42 (+7) days post-HCT and will continue for 14 weeks. The total duration of patient participation is approximately 28 to 32 weeks, including up to 6 weeks for screening, the 14-week treatment period, and 12 weeks of follow-up.

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; EBV = Epstein-Barr virus; HHV-6 = human herpes virus 6; JCV = JC virus; OL = open-label; Q= every; R = randomized/randomization; tx = treatment

*OL Cohort continues through full treatment period after this initial 30 days of treatment.

1.3. Schedules of Activities

Table 1: Schedule of Activities–Pre-screening Period and Screening Period (All Cohorts)

	Pre-screening Visit[a]	**Pre-screening Period[a]**	**Screening Visit[b]**	**Screening Period[b]**
Study Week	NA	Weekly Visits	Up to 6 weeks before Study Drug Administration	Weekly after Screening Visit until Study Drug Administration
Study Day	NA	NA	May be from Day -42 to Study Drug Administration Day	May be from Day -42 to Study Drug Administration Day
Visit Window (Days)	NA	±3	NA	±3
Study Procedures				
Informed consent/assent[c]	X		X	
I/E criteria	X[d]		X	
Demographics			X	
Medical history[d]			X	
Documentation of HLA typing[e]			X	
Prior and concomitant medications including			X	X

	Pre-screening Visit[a]	**Pre-screening Period[a]**	**Screening Visit[b]**	**Screening Period[b]**
Study Week	NA	Weekly Visits	Up to 6 weeks before Study Drug Administration	Weekly after Screening Visit until Study Drug Administration
Study Day	NA	NA	May be from Day -42 to Study Drug Administration Day	May be from Day -42 to Study Drug Administration Day
Visit Window (Days)	NA	±3	NA	±3
conditioning regimen for HCT				
Adverse events[f]			X	X
Complete physical examination			X	
Weight and height[g]			X	
Vital signs[h]			X	
12-lead ECG			X	
Clinical labs[i]			X	
Pregnancy test[j]			X	
Testing for HIV, HCV, HBV[k]			X	

	Pre-screening Visit[a]	Pre-screening Period[a]	Screening Visit[b]	Screening Period[b]
Study Week	NA	Weekly Visits	Up to 6 weeks before Study Drug Administration	Weekly after Screening Visit until Study Drug Administration
Study Day	NA	NA	May be from Day -42 to Study Drug Administration Day	May be from Day -42 to Study Drug Administration Day
Visit Window (Days)	NA	±3	NA	±3
BKV, AdV, CMV, JCV, EBV, and HHV-6 viral load[l]	X	X	X	X[m]

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; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HHV-6 = human herpesvirus 6; HLA = human leukocyte antigen; 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. Please see the Study Manual for more information.

[a] Adult patients and pediatric patients ≥12 years old may participate in an optional pre-screening period that may begin up to 4 weeks prior to administration of conditioning for HCT and continue until there is a decision on whether to screen for the study. Viremia testing during pre-screening will begin after HCT and will continue weekly, if possible. Pre- screening is not required for eligibility.

[b] The Screening Visit could occur any time between the day of HCT and up to 42 (+7) days post-HCT. When this visit occurs during this time period may vary by patient depending upon when the decision is made to participate in the study.

[c] 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 ICF for the pre-screening period is separate from the ICF that is signed at Screening Visit for study participation.

[d] To include CMV sero status of both patient and HCT donor

[e] The HLA type of the patient and their HCT cell donor(s) will be obtained from the medical record.

[f] Adverse events will be monitored and documented from signing of the ICF for study participation until study participation is complete.

[g] Height and weight will be measured at screening. At later assessments during the Treatment Period, only weight will be assessed.

[h] Includes body temperature, blood pressure, heart rate, O2 saturation, and respiration rate and will be measured after resting for 5 minutes.

[i] Clinical laboratory assessments collected as part of standard of care may be used to fulfill these requirements. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin (total and direct), GGT, AST, and ALT. Urinalysis must be performed. Laboratory safety evaluations (hematology, chemistry, and urinalysis) specified in Section 8.4.4 will be performed prior to study therapy initiation. These samples will be sent to the appropriate central laboratory(ies) following the procedure(s) described in the study manual(s).

[j] For female patients, at Screening a β-HCG blood test will be performed. A urine pregnancy test will also be performed at the site prior to study therapy initiation (SoA for Treatment Period, Table 2).

[k] 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.

[l] Viral loads of BKV, AdV, CMV, JCV, and HHV-6 in plasma and of EBV in PCMBs will be measured weekly for adult patients and pediatric patients ≥ 12 years old after allogenic HCT conditioning during pre-screening period and screening period until treatment assignment, if possible. Pediatric patients < 12 years old will have only one blood draw during the Screening visit and will not have weekly blood draws during the screening period. Viral load testing should NOT be done on day of HCT during pre-screening. The results of the repeat analyses from the screening period must be available at the time of treatment assignment, unless the timing of the Screening Visit is 1 week or less before treatment administration. Results of central laboratory testing for viral load will be used for the purpose of determining eligibility/inclusion.

[m] Adult patients and pediatric patients ≥ 12 years old only

Table 2: Schedule of Activities – Treatment -- Period 1 for Patients ≥12 Years of Age (Week 1 to 14, All Cohorts)

		Treatment Period														
Time Period	**Treatment Assignment**	**Study Drug Administration Day**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13**	**Wk 14**
Study Day		**1[a]**	**8**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**	**91**	**98**
Visit Window (Days)		**NA[b]**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±3**
Study Procedures																
Review of I/E criteria		X														
Prior & concomitant medications as well as conditioning regimen for HCT		X		X		X		X		X		X		X		X
Adverse events[c]		X		X		X		X		X		X		X		X
Physical examination [d]		X		X		X		X		X		X		X		X
Weight		X				X				X				X		X
Vital signs[e]		X		X		X		X		X		X		X		X
12-lead ECG[f]		X		X		X		X		X		X		X		X
Clinical labs[g]		X		X		X		X		X		X		X		X
Pregnancy test[h]		X		X		X		X		X		X		X		

		Treatment Period														
Time Period	**Treatment Assignment**	**Study Drug Administration Day**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13**	**Wk 14**
Study Day		**1**[a]	**8**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**	**91**	**98**
Visit Window (Days)		**NA**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±3**
Study Procedures																
BKV, AdV, CMV, JCV, and HHV-6 viral load[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EBV PCMBs[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment[j]	X															
Virus-Specific T Cell Assessment[k]		X				X		X			X			X		X
Study treatment administration[l]		X		X		X		X		X		X		X		
Post infusion monitoring[m]		X		X		X		X		X		X		X		
Infection assessment[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		Treatment Period														
Time Period	**Treatment Assignment**	**Study Drug Administration Day**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13**	**Wk 14**
Study Day		**1**[a]	**8**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**	**91**	**98**
Visit Window (Days)		**NA**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±3**
Study Procedures																
Quality of Life (FACT-BMT, EQ-5D-5L, EQ-5D-Y, EQ-5D-Y Proxy Version 1)[o]		X				X				X				X		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; GGT = gamma-glutamyl transferase; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency 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 may be done via a home health visit as agreed with the Sponsor. Please see the Study Manual for more information.

[a] Unless noted otherwise, Day 1 procedures must be performed within 72 hours prior to study treatment administration.
[b] Dosing day may be up to +7 days with Sponsor approval.
[c] Adverse event monitoring should include the collection of all adverse events through the treatment period in all patients, including those who have discontinued study treatment but are continuing in the study. For patients who have discontinued, only drug-related SAEs and SAEs leading to death will be collected until Week 26.[d] After treatment assignment, a targeted physical exam 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.
[e] Includes body temperature, blood pressure, heart rate, O_2 saturation, and respiration rate and will be measured after resting for 5 minutes. After treatment assignment, vital signs should be performed during and after infusions and if targeted physical examination is performed.
[f] Performed within 1 hour after study treatment administration and at the end of study or early termination visit, which are listed in the SoA for the Short-term Follow-up period (Table 3).
[g] Clinical laboratory assessments collected as part of standard of care may be used to fulfill these requirements. CBC must include differential and LFTs

must include alkaline phosphatase, bilirubin (direct and indirect); GGT, AST, and ALT. Urinalysis must be performed. Laboratory safety evaluations (hematology, chemistry, and urinalysis) 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).

[h] For female patients, 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 treatment assignment and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not be assigned to treatment and should reflex to a β-HCG blood test before screen failing. A urine pregnancy test will be performed prior to each treatment for female patients who are of childbearing potential.

[i] Viral loads of AdV, BKV, CMV, JCV, and HHV-6 in plasma and of EBV in PCMBs 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).

[j] Patients in Cohort OL will be assigned to ALVR105. Patients in Cohorts A and B will be randomized to either ALVR105 or placebo based upon the last viral load assessed and within 7 days of randomization. Treatment assignment will be about 2 to 3 days before Day 1.

[k] Patient peripheral blood mononuclear cells will be assessed for the presence of virus-reactive T cells using enzyme-linked immunospot.

[l] All patients will receive infusions of either ALVR105 or placebo. Patients will receive the same [redacted] dose for patients ≤40 kg or [redacted] dose for patients >40 kg for all infusions of ALVR105, administered at a dose interval of every 14 days (±3 days). Placebo infusions will be administered 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 ALVR105 if they develop new onset GVHD Grade >2 or worsening of GVHD (ie, relative to baseline GVHD at the time of enrollment into the study) at the proposed time for infusion of the next dose, or if they develop CRS Grade >2; if any patient develops GVHD or CRS, the Medical Monitor should be contacted immediately, and the patient treated per standard of care. If discontinued for CRS or GVHD these participants should be followed up to resolution of symptoms. Patients may resume treatment only with consultation and agreement between the Medical Monitor and the Investigator. If possible, IVIG and ALVR105 should not be administered on the same day.

[m] 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, heart rate, O_2 saturation, respiration rate, and blood pressure, will be measured at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. Patients must also remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.

[n] The infection assessment will be performed for all patients who require either treatment for disease or initiation of preemptive therapy during both the primary study period and the follow-up period through Week 26 (Section 8.3). It is very important to ensure that all procedures, as outlined in the SoA, are performed immediately 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 sample for EBV for PCR testing at the central laboratory should be collected. Patients who develop viral infections will continue to be followed in the study and complete all remaining visits through Week 26.

[o] Assessment of quality of life (using FACT-BMT, EQ-5D-5L, EQ-5D-Y, EQ-5D-Y Proxy Version 1questionnaires, as age-appropriate) should be completed prior to any study procedures at this visit.

Table 3: Schedule of Activities – Treatment -- Period 1 for Patients < 12 Years of Age (Week 1 to 14, All Cohorts)

		Treatment Period														
Time Period	**Treatment Assignment**	**Study Drug Administration Day**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13**	**Wk 14**
Study Day		**1**[a]	**8**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**	**91**	**98**
Visit Window (Days)		**NA**[b]	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±3**
Study Procedures																
Review of I/E criteria		X														
Prior & concomitant medications as well as conditioning regimen for HCT		X		X		X		X		X		X		X		X
Adverse events[c]		X		X		X		X		X		X		X		X
Physical examination[d]		X		X		X		X		X		X		X		X
Weight		X				X				X				X		X
Vital signs[e]		X		X		X		X		X		X		X		X
12-lead ECG[f]		X		X		X		X		X		X		X		X
Clinical labs[g]		X		X		X		X		X		X		X		X
Pregnancy test[h]		X		X		X		X		X		X		X		
BKV, CMV, JCV, and HHV-6 viral load[i]		X		X		X		X		X		X		X	X	X

		Treatment Period														
Time Period	**Treatment Assignment**	**Study Drug Administration Day**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 13**	**Wk 14**
Study Day		**1[a]**	**8**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**	**91**	**98**
Visit Window (Days)		**NA[b]**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±5**	**±3**	**±3**
Study Procedures																
EBV PBMCs[i]		X		X		X		X		X		X		X	X	X
AdV viral load		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment[j]	X															
Virus- Specific T Cell Assessment[k]		X				X		X			X			X		X
Study treatment administration[l]		X		X		X		X		X		X		X		
Post infusion monitoring[m]		X		X		X		X		X		X		X		
Infection assessment[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (FACT- BMT, EQ- 5D-5L, EQ-5D-Y, EQ-5D-Y Proxy Version 1)[o]		X				X				X				X		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; GGT = gamma-glutamyl transferase; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency 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 may be done via a home health visit as agreed with the Sponsor. Please see the Study Manual for more information.

[a] Unless noted otherwise, Day 1 procedures must be performed within 72 hours prior to study treatment administration.
[b] Dosing day may be up to +7 days with Sponsor approval.
[c] Adverse event monitoring should include the collection of all adverse events through the treatment period in all patients, including those who have discontinued study treatment but are continuing in the study. For patients who have discontinued, only drug-related SAEs and SAEs leading to death will be collected until Week 26.
[d] After treatment assignment, a targeted physical exam 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.
[e] Includes body temperature, blood pressure, heart rate, O2 saturation, and respiration rate and will be measured after resting for 5 minutes. After treatment assignment, vital signs should be performed during and after infusions and if targeted physical examination is performed.
[f] Performed within 1 hour after study treatment administration and at the end of study or early termination visit, which are listed in the SoA for the Short-term Follow-up period (Table 3).
[g] Clinical laboratory assessments collected as part of standard of care may be used to fulfill these requirements. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin (direct and indirect); GGT, AST, and ALT. Urinalysis must be performed. Laboratory safety evaluations (hematology, chemistry, and urinalysis) 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).
[h] 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 treatment assignment and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not be assigned to treatment and should reflex to a β-HCG blood test before screen failing. A urine pregnancy test will be performed prior to each treatment for female patients who are of childbearing potential.
[i] Viral loads of AdV, BKV, CMV, JCV, and HHV-6 in plasma and of EBV in PCMBs 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).
[j] Patients in Cohort OL will be assigned to ALVR105. Patients in Cohorts A and B will be randomized to either ALVR105 or placebo based upon the last viral load assessed and within 7 days of randomization. Treatment assignment will be about 2 to 3 days before Day 1.
[k] Patient peripheral blood mononuclear cells will be assessed for the presence of virus-reactive T cells using enzyme-linked immunospot.
[l] All patients will receive infusions of either ALVR105 or placebo. Patients will receive the same [redacted] dose for patients ≤40 kg or [redacted] dose for patients >40 kg for all infusions of ALVR105, administered at a dose interval of every 14 days (±3 days). Placebo infusions will be administered 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 ALVR105 if they develop new onset GVHD Grade >2 or worsening of GVHD (ie, relative to baseline GVHD at the time of enrollment into the study) at the proposed time for infusion of the next dose, or if they develop CRS Grade >2; if any patient develops GVHD or CRS, the Medical Monitor should be contacted immediately, and the patient treated per standard of care. If discontinued for CRS or GVHD these participants should be followed up to resolution of symptoms. Patients may resume treatment only with consultation and agreement between the Medical Monitor and the Investigator. If possible, IVIG and ALVR105 should not be administered on the same day.
[m] 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, heart

rate, O2 saturation, respiration rate, and blood pressure, will be measured at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. Patients must also remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.

[n] The infection assessment will be performed for all patients who require either treatment for disease or initiation of preemptive therapy during both the primary study period and the follow-up period through Week 26 (Section 8.3). It is very important to ensure that all procedures, as outlined in the SoA, are performed immediately 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 sample for EBV for PCR testing at the central laboratory should be collected. Patients who develop viral infections will continue to be followed in the study and complete all remaining visits through Week 26.

[o] Assessment of quality of life (using FACT-BMT, EQ-5D-5L, EQ-5D-Y, EQ-5D-Y Proxy Version 1questionnaires, as age-appropriate) should be completed prior to any study procedures at this visit.

Table 4: Schedule of Activities: Short-Term Follow-Up--Period 2, All Ages (Weeks 18 to 26, All Cohorts)

Study Week	**Week 18**	**Week 22**	**Week 26/ET[a]**
Study Day	**126**	**154**	**182**
Visit Window (Days)	**±3**	**±3**	**±3**
Study Procedures			
Prior & concomitant medications	X	X	X
Adverse events[b]	X	X	X
Weight			X
Vital signs	X	X	X
12-lead ECG			X
Clinical Labs			X
BKV, AdV, CMV, JCV, and HHV-6 viral load[c]		X	X
EBV PCMBs[d]		X	
Virus-Specific T Cell assessment[e]	X	X	X
Infection assessment[f]	X	X	X
Quality of Life (FACT-BMT and EQ-5D-5L, EQ-5D-Y, EQ-5D-Y Proxy Version 1)[f]	X	X	X

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BKV = BK virus; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ECG = electrocardiogram; ET = Early Termination Visit; GVHD = graft versus host disease; HHV-6 = human herpesvirus 6; JCV = JC virus; LFT = liver function test; PBMCs = peripheral blood mononuclear cells

Note: Visits may be done via a home health visit as agreed with the Sponsor. Please see the Study Manual for more information.

[a] 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 PCMB sample for EBV for PCR testing at the central laboratory should be collected at this visit.

[b] Adverse event monitoring should include the collection of all adverse events through follow-up in all patients, including those who have discontinued study treatment but are continuing in the study. Positive pregnancy and partner pregnancy information up to 90 days after last study drug administration will be collected.

[c] Viral loads of AdV, BKV, CMV, HHV-6, and JCV in plasma and in PCMBs for EBV will be measured and evaluated at the central lab. Additional post-infusion samples may be collected if 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 completed prior to initiating standard of care therapy (see Section 8.3).

[d] Patient peripheral blood mononuclear cells will be assessed for the presence of virus-reactive T cells using enzyme-linked immunospot.

[e] The infection assessment will be performed for all patients who require either treatment for disease or initiation of preemptive therapy during both the primary study period and the follow-up period through Week 26 (Section 8.3). It is very important to ensure that all procedures, as outlined in the SoA, are performed immediately 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 PCMB sample for EBV for PCR testing at the central laboratory should be collected. After developing an infection, such patients will continue to be followed in the study and complete all remaining visits through Week 26.

[f] Assessment of quality of life (using FACT-BMT, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1questionnaires, as age-appropriate) should be completed prior to any study procedures at this visit.

2. INTRODUCTION

ALVR105 (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], JC virus [JCV], human herpesvirus 6 [HHV- 6], Epstein-Barr virus [EBV], and cytomegalovirus [CMV] in [redacted]

AlloVir is developing ALVR105 (also known as ALVR105, formerly ALVR-105), a novel multivirus-specific cellular therapy, to treat or prevent a number of serious, virus-associated causes of morbidity and mortality after allogeneic 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 study to evaluate the efficacy and safety of ALVR105 for the prevention of clinically significant adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and JC 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 devastating single and/or 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 (VST) 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 ALVR105 for the prevention and preemptive treatment of AdV, BKV, CMV, EBV, HHV-6, and/or JCV infections represents an unmet medical need.

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 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 increased 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 ALVR105

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 ALVR105 have been conducted or are planned. For additional information related to nonclinical studies with ALVR105, 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, ALVR105

To investigate the safety and clinical efficacy of ALVR105, 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 ALVR105 (Tzannou, 2017). In this study, patients received a single IV infusion of 2×10^7 partially HLA-matched ALVR105 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 ALVR105 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) 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, patients with JCV infection will be included in the Phase 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 ALVR105 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 ALVR105 is a safe and effective broad-spectrum therapy to treat commonly observed and severe virus-associated diseases after allogenic HCT. The results of these studies provide preliminary evidence of ALVR105'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

ALVR105 primarily targets cells infected with AdV, BKV (and/or JCV), CMV, EBV, and/or HHV-6. The main 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, as reported in the CHARMS

study.

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 ALVR105, 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 ALVR105 infusion include allergic reactions (anaphylaxis), decreased oxygenation, nausea/vomiting, arrhythmia, and hypotension.

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

In order to minimize the volume of blood collected during the study trial, the blood volume of individual samples has been reduced to the maximum extent feasible wherever possible. This has been performed in a manner that is expected to maintain the scientific integrity of the study and related data, while minimizing the risks to the patients.

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, and/or HHV-6, and JCV) is limited to every other week and blood volume is sufficient for testing only AdV viremia in the other weeks. Pediatric patients also do not participate in pre-screening blood samples. 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. For maximum blood draw volumes, see 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 ALVR105 to placebo in the proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection and/or end-organ disease as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 14	1. The proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection (defined as infection and/or end-organ disease as determined by an independent, blinded CAC) through Week 14
Secondary	
1. To compare the efficacy of ALVR105 to placebo in time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia over 14 weeks, in patients at high risk, following allogeneic HCT	1. Time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia over 14 weeks
2. To compare the efficacy of ALVR105 to placebo in area under the curve (AUC) for cumulative viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV over 14 weeks	2. AUC for cumulative viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV over 14 weeks
3. To compare the efficacy of ALVR105 to placebo in incidence of clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease (excludes asymptomatic viremia) through Week 14	3. Proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease (excludes asymptomatic viremia) through Week 14
4. To compare the efficacy of ALVR105 to placebo in the proportion of patients with clearance of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia in allogeneic HCT patients with detectable viremia prior to the start of treatment	4. Proportion of patients with clearance of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia by Week 8 in HCT patients with detectable viremia prior to the start of treatment
5. To compare the efficacy of ALVR105 to placebo in the proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV	5. Proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease and/or end-organ disease as determined by an

Objectives	Endpoints
infection and/or end-organ disease as determined by an independent, blinded CAC through Week 26 (the end of the 12-week safety follow- up period)	independent, blinded CAC through Week 26 (the end of the 12-week safety follow- up period)
6. To compare the efficacy of ALVR105 to placebo in reducing hospitalization in HCT recipients through Week 26	6. Total number of hospital days related to AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection or disease through Week 26
7. To compare the efficacy of ALVR105 to placebo in reducing non-relapse mortality in allogeneic HCT recipients through Week 26	7. Proportion of patients with AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease-related mortality as determined by an independent, blinded CAC through Week 26
8. To compare the efficacy of ALVR105 to placebo on patient-reported quality of life through Week 26	8. Quality of life assessments, FACT-BMT, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26
9. To assess the safety and tolerability of ALVR105 when administered to adult and pediatric patients at high-risk for AdV, BKV, CMV, EBV, HHV-6, and/or JCV following allogeneic HCT	9.1. Incidence of overall non-relapse related mortality AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease related mortality as determined by an independent, blinded CAC 9.2. Severity and incidence of acute GVHD 9.3. Severity and incidence of chronic GVHD 9.4. Severity and incidence of cytokine release syndrome 9.5. Severity and incidence of clinically significant cytopenias 9.6. Severity and incidence of renal dysfunction 9.7. Effect on measures of engraftment

Objectives	Endpoints
Exploratory 1. To assess the development of antiviral-specific T cells 2. To assess healthcare resource utilization through Week 26	1. Detection of anti- AdV, BKV, CMV, EBV, HHV-6, and/or JCV - specific T cells through Week 26. 2.1. Hospital readmission rate related to AdV, BKV, CMV, EBV, HHV- 6, and/or JCV viremia/disease through Week 26 2.2. Total days in the ICU through Week 26 2.3. Proportion of patients requiring mechanical ventilation related to AdV, BKV, CMV, EBV, HHV-6 and/or JCV infection or disease through Week 26 2.4. Duration of anti-viral therapy (foscarnet, ganciclovir, cidofovir or other) due to viremia and/or disease through Week 26

For the open-label portion of the study, similar endpoints will be analyzed. Additional details can be found in the Statistical Analysis Plan (SAP).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, multiple dosing, trial to investigate ALVR105 administered intravenously, with the first dose between 15 and 42 (+7) days after allogeneic HCT, followed by every 2-week infusions until Week 14, in comparison to matching placebo for the prevention of active replication and clearance of active viremia of AdV, BKV, CMV, EBV, HHV-6, and/or JCV in high-risk patients.

This study is comprised of an optional pre-screening period, a screening period, a treatment period, and a follow-up period. The optional pre-screening period is included to allow for the assessment of viral loads for patients who may potentially be eligible for participation in the study prior to actual screening. The screening period may begin at the time of HCT and may vary in length of up to 6 weeks. The treatment period is 14 weeks, and the follow-up period is approximately 12 weeks. Overall, the total duration patient participation in the study is approximately 28 to 32 weeks (up to 6 weeks for screening, 14 weeks of treatment, and 12 weeks of follow-up). The overall enrollment period is anticipated to be approximately 12 months.

Patients will also receive a telephone call follow-up approximately 52 weeks after their last study visit to assess mortality.

There are 3 cohorts (Cohort Open Label [OL], [redacted] The first 25 to 35 patients (Cohort OL) will receive ALVR105 for 30 days of open-label dosing to assess and optimize processes. A review by the Data Safety Monitoring Board (DSMB) will be done when approximately 30 patients have completed 30 days of treatment. At this time an assessment of benefit, risk, and process will be done, and study optimization will be considered. [redacted] Open label patients will continue in the open label arm. [redacted]

Patients will be tested at the first 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. Patients will then be tested weekly during Screening until treatment assignment. In **Cohort OL**, patients may test positive or negative for AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia. [redacted] ohort OL will also include a 50% cap for letermovir prophylaxis; Sponsor can revisit this limit based on on-going assessment of feasibility. With respect to other

prophylaxis treatments see the inclusion criteria (Section 5.1).

Study therapy (with ALVR105 or placebo) will begin between 15 and 42 (+7) days (inclusive) post- HCT. Administration may begin as early as day 15 post-HCT as long as, in the Investigator's judgment, the patient has met the engraftment criteria. 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 and/or disease of AdV, BKV, CMV, EBV, HHV-6, and/or JCV through Week 14 and with a secondary objective of preventing clinically significant infections and/or diseases of AdV, BKV, CMV, EBV, HHV-6, and/or JCV through Week 26 (~6 months). [redacted]

On the day of treatment assignment (randomization), eligibility for enrollment into the study should be confirmed (including confirmation that HCT has taken place). [redacted]

Once enrolled in the study, patients will have study visits scheduled at weekly intervals 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 and time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia and/or disease; (2) all adverse events through the treatment period in all patients, including those who have discontinued study treatment but are continuing in the study. For patients who have discontinued, only drug-related SAEs and SAEs leading to death will be collected until Week 26.; and (3) quality of life (QoL) measures using validated patient reported outcome tools. During the follow-up period, study visits will occur monthly after Week 14 until Week 26. Patients will also receive a follow-up call one year after the Week 26 visit to assess mortality.

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) when the Investigator intends to initiate either treatment for viral infection or disease, infection assessments should be conducted (Section 8.3). These patients will continue to receive infusions of study drug during the treatment period.

[redacted]

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 HCT recipients. Since recovery of virus-specific T cells after HCT results in resolution of viral infections, adoptive immunotherapy to decrease the time to immune reconstitution is an attractive alternative to current standard of care. ALVR105 cells are intended to circulate only until the patient regains immunocompetence following HCT engraftment and immune system repopulation. Therefore, ALVR105 cells are designed to be an "immunologic bridge therapy" that provides an immunocompromised patient with T cell immunity until the patient engrafts 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 primary endpoint is the prevention of clinically significant viral infections which is the goal of treatment. Secondary efficacy endpoints address the time to onset of viral infection as well as end-organ disease and mortality, all critically relevant outcomes. [redacted]

The broad age range for inclusion in the study (≥1 year of age) 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).

The inclusion of the open-label period is to assess and optimize the related procedures prior to beginning the randomization to treatment assignment.

Repeated doses are required because in the absence of virus, more doses are needed for coverage.

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 ALVR105.
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 for [redacted] the OL Cohort. 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 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 endpoint adjudication committee.

4.3. Justification for Dose

ALVR105 is to be administered at a fixed cell dose. The fixed dose was selected based on data from previous clinical studies in which ALVR105 cells were well tolerated, safe, and effective.

The dose of ALVR105 per infusion ([redacted] for patients <40 kg and [redacted] 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 [redacted]. A retrospective analysis of

actual doses administered in the CHARMS study demonstrated that, on average, patients who weighed ≥40 kg received [redacted] per infusion (n = 45). For patients <40 kg, the dose will be [redacted]

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 (including telephone contact) 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 follow up telephone call at approximately 52 weeks (12 months) after the end of study visit to collect mortality data.

4.4.1. Meals and Dietary Restrictions

This section is not applicable.

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. Be ≥1 year of age at the day of screening.

Type of Participant and Disease Characteristics

[redacted]

For OL Cohort

4. May meet viremia criterion for either Cohort A or Cohort B

For OL Cohort, [redacted]

5. Be within 15 and 42 (+7) days of receiving a first allogeneic HCT at the time of treatment assignment and have demonstrated engraftment with an absolute neutrophil count >500/μL.
6. High-risk: Patients meeting one or more of the following criteria at the time of treatment assignment:
    - 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
    - Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1
    - Use of umbilical cord blood as stem cell source
    - Ex vivo graft manipulation resulting in T cell depletion
    - Lymphocyte count <180/mm^3 and/or cluster of differentiation 4 (CD4) T cell count <50/mm^3

Sex

7. 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 an acceptable contraceptive method 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 highly sensitive serum pregnancy test within 14 days before the first dose of study intervention, see Section 8.4.5.
      - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.4.5.
      - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. 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

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 treatment assignment
2. Has evidence of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia for more than 3 viruses, from a central or local laboratory at any time during Screening prior to treatment assignment
3. Evidence of active Grade >2 acute GVHD (for additional information on acute GVHD grading and severity, see Appendix 5 [Section 10.5] or CRS Appendix 6 [Section 10.6], respectively).
4. 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)
5. Presence of progressive, uncontrolled viral infections with evidence of end organ disease
6. Known history or current (suspected) diagnosis requiring treatment of CRS associated with the administration of peptides, proteins, and/or antibodies
7. Evidence of encephalopathy at screening
8. Relapse of primary malignancy other than minimal residual disease.

Prior/Concomitant Therapy

9. Donor lymphocyte infusion performed within 21 days prior to randomization
10. Received within 7 days prior to treatment assignment any of the following: ganciclovir, valganciclovir, foscarnet, 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)
11. Received any investigational antiviral agent/biologic therapy within 30 days prior to screening or plans to receive during the study any of the following: cidofovir, CMV hyper-immune globulin, or any investigational CMV antiviral agent/biologic therapy.
12. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day) within 7 days prior to screening
13. Prior therapy with antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies within 28 days of treatment assignment
14. Receipt of mechanical ventilation of any type, within 1 month prior to the administration of ALVR105 (unless related to airway control)
15. Undergoing dialysis at any time during the screening period

Prior/Concurrent Clinical Study Experience

16. Received a previous allogeneic HCT (Note: Receipt of a previous autologous HCT is acceptable)
17. Receipt of another investigational antiviral vaccine or treatment during the study or within 28 days prior to treatment assignment or study treatment administration

Diagnostic assessments

18. Aspartate aminotransferase or alanine aminotransferase serum levels >5 × the upper limit of normal (ULN) or direct bilirubin serum levels >2 × the ULN reference per central laboratory.
19. Presence of any progressive, uncontrolled viral infections (ie, evidence of viremia, dissemination, and/or organ-specific infection not well controlled by present therapies) not targeted by ALVR105.

Other Exclusions

20. Pregnant, breastfeeding, or planning to become pregnant during the study
21. 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. Caffeine, Alcohol, and Tobacco

This section is not applicable.

5.3.2. Activity

This section is not applicable.

5.4. Screen Failures

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, eligibility criteria, and any serious adverse events (SAEs).

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

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

ALVR105 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 [redacted] and ready for immediate use. The Control Arm will receive IV infusions of [redacted] (without cells) as placebo.

Arm Name	**Treatment (Cohort A and B and OL)**	[redacted]
Intervention Name	ALVR105	
Type	Drug	
Dosage formulation	Ampule (Cryovial)	
Unit dose strength(s)	[redacted]	
Dosage Level(s)	[redacted] (<40 kg) or [redacted] (≥40 kg) [redacted] dosed Q14D	
Route of Administration	IV slow push [redacted]	
Use	Experimental	
Sourcing	Provided centrally by Sponsor	
Packaging and Labeling	Study Intervention will be provided in cryovials. Each cryovial will be labeled as required per country requirement	
Current/ Former Name(s) or Alias(es)	ALVR105	

6.1.1. Cell Line Selection

ALVR105 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 [redacted]

6.1.2. Study Intervention Administration

At, or close to the time of administration, the product will be thawed at 37°C. As soon as the product has thawed completely, each vial will be wiped with an alcohol swab and the appropriate volume of study treatment will be removed from the vial or vials using a 16-gauge blunt-ended needle and 5 mL syringe. Study treatment is to be infused into the patient within 30 minutes of thawing. If the location of the patient is remote from the clinical site's cell storage facility, the thawing of the cryovials and preparation of infusion syringes should be conducted in an appropriate location for cell preparation that is sufficiently close to the patient to ensure that no more than 30 minutes elapse between the completion of thawing and infusion. See the Cell Handling 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.
- Patients must remain on continuous pulse oximetry for ≥30 minutes after the end of the infusion.
- Vital signs will be monitored at the end of infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion.

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

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 for additional information. If possible, ALVR105 and intravenous immunoglobulin (IVIG) should not be administered on the same day.

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) 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

ALVR105 (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 Handling Manual.

6.2.2. Storage and Accountability

ALVR105 (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 ALVR105 (or placebo) will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

ALVR105 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 ALVR105 cell line to the third-party 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 ALVR105 and placebo as per applicable Sponsor and clinical site procedures. For further details and specifications, see the Cell Handling Manual.

[redacted]

[redacted]

[redacted]

[redacted]

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 ALVR105 (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 ALVR105 (or placebo) after Week 14. 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 ALVR105 greater than any dose over the IRT assigned dose ($2x10^7$ 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

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.

6.8.1. 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 (eg, brincidofovir or anti-BK virus monoclonal antibodies) within 28 days prior to randomization and throughout the duration of the study is prohibited.

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. Analgesic use will be collected on a daily basis. Clinically available (ie, not investigational) antiviral agents prescribed for other infections are allowed. Use of cidofovir or brincidofovir (eg, for the treatment of AdV) must be discussed with the Medical Monitor prior to initiation. All instances of the use of any antiviral agents during the study will be recorded in the eCRF (including the drug name, dose, and

duration of treatment).

T cell ablative therapies, such as antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies, are prohibited during the course of the study. Daily doses of corticosteroids exceeding 0.5 mg/kg prednisone (or equivalent) are prohibited during the course of the study. Should patients require medically a higher dose of steroids, no further study drug will be administered until the steroids are tapered to a dose equivalent of 0.5 mg/kg prednisone (or equivalent) or less.

6.8.2. Restricted Medications and/or Procedures

6.8.2.1. Supportive care

The following supportive care measures are permitted:

- Analgesics
- Narcotics
- IV hydration
- Antispasmodics
- Transfusion of red blood cells (RBCs)
- Transfusion of platelets
- Transfusion of fresh frozen plasma

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

6.8.3. Documentation of Prior and Concomitant Medication Use

All medications, including GVHD prophylaxis, used within 30 days before screening will be recorded. All concomitant medications and concurrent therapies will be documented as indicated in the SoA (Section 1.3). Dose, route, unit frequency of administration, indication for administration, and dates of medication will also be captured in source documents and on the appropriate eCRF.

6.8.4. 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, or a Grade 3 to 4 non-hematologic AE within 4 weeks from last ALVR105 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. Receipt of any other hematopoietic stem cell product.
3. Receipt of therapy for relapse of the patient's primary malignancy.
4. 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.

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

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 exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- 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
- Pregnancy
- Requirement for prohibited concomitant medication
- Patient failure 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, 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 up to Week 26 from the study; however, patients who decide only to discontinue therapy early will continue to complete trial procedures as per protocol. 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 PCMB 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 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. Pre-screening visit (optional)

A pre-screening visit will be completed if possible at least 1 week prior to HCT. A separate ICF for pre-screening will be obtained.

8.1.2. Screening period

Screening of potential eligible patients may begin as soon as the day of HCT and within 42 (+7) days after transplantation. Patients will have plasma samples tested for AdV, BKV, CMV, HHV-6, and JCV viremia and PBMCs for EBV viremia using PCR assays weekly during the screening period. Patients should be tested at the first assessment during Screening by the central laboratory for AdV, BKV, CMV, EBV, HHV-6, and JCV viremia using PCR assays for each virus. Patients

will then be tested weekly during Screening until treatment assignment. For initial screening purposes, results of the assay done at a local laboratory will be acceptable; however, a test by the central lab must be done prior to treatment assignment.

8.1.3. Treatment period

The treatment period is 14 weeks. Study therapy (with ALVR105 or placebo) will begin between 15 and 42 (+7) days (inclusive) post-HCT. 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 (Cohort OL) will be assigned to ALVR105 for 30 days of open-label dosing [redacted].

8.1.4. Follow-up period

The follow-up period is for 12 weeks with monthly visits. A telephone follow-up call will occur approximately 12 months (~52 weeks) after Week 26.

8.2. Efficacy Assessments

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

8.2.1. Definitions and Determination of Viremia

8.2.2. 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 will be measured at times specified in Section 1.3. The results of any repeat analyses from screening must be available at the time of treatment assignment, with the exception of patients screened within 7 days of treatment assignment, who would not have more than 1 analysis. [redacted] dditional 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.

[redacted] Resolution of viral infection will be defined as a return to normal range as defined by the assay used and complete resolution of clinical signs and symptoms as defined in the CAC charter.

Viral load will be quantitated using PCR assays.

8.2.3. 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 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 less than

the lower limit of quantification (LLOQ) and complete resolution of clinical signs and symptoms as determined by the Investigator and the CAC (see Appendix 7, Section 10.7).

8.2.4. Quality of Life

Quality of life will be measured using the FACT-BMT and the age-appropriate version of the EQ-5D at times indicated in Section 1.3. The FACT-BMT was designed to measure the QoL in patients undergoing bone marrow transplantation. It combines the general Functional Assessment of Cancer Therapy (FACT-G), assessing physical well-being, social/family well- being, emotional well-being and functional well-being, with the Bone Marrow Transplantation Sub-scale (BMTS) to measure BMT-specific concerns (McQuellon 1997).

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 (EQ VAS). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the EQ-5D-5L, each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his or her health state by checking the box next to the most appropriate statement in each of the 5 dimensions. The versions used in children have 3 responses to each question instead of 5.

In this study, the EQ-5D-5L will be used for individuals ≥12 years of age, the EQ-5D-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 and prior to any study procedures at the visit.

8.2.5. Virus-specific T Cell Assessment

Patient peripheral blood mononuclear cells will be assessed for the presence of each of the viral-specific virus-reactive T cells using enzyme-linked immunospot. 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 described in Appendix 8, Section 10.8. It is very important to ensure that all procedures, as outlined in the SoA, are performed for infection assessment immediately prior to the initiation of treatment of viral diseases or initiation of preemptive therapy (ie, on the day anti- viral therapy is initiated).

A symptom checklist should be completed in the infection assessment eCRF.

Patients will continue to be 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

Most importantly, a plasma sample for AdV, BKV, CMV, HHV-6, and JCV, and a PBMC sample for EBV for PCR testing at the central laboratory should be collected. Should confirmatory test results from the central laboratory not be available within the timeframe that the Investigator wishes to initiate anti-viral therapy, the Investigator may use a positive local laboratory test result to make the decision. Whenever it is deemed clinically necessary to use a local laboratory, a plasma sample should also be collected and sent to the central laboratory.

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 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, urine, and/or CSF samples should be collected for AdV, BKV, CMV, EBV, HHV-6, and JCV and sent to the central laboratory as feasible (see Appendix 8, Section 10.8.)

When local laboratory test results are used for initiating anti-viral therapy, two plasma (and 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. The local laboratory result must also be reported in such instances.

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 who is a physician. New abnormal physical examination findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

8.4.2. Vital Signs

- Temperature, pulse rate, O2 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 in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

8.4.3. Electrocardiograms

- Single 12-lead electrocardiograms (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 Fredericia's and Bazett's methods) intervals.
- The ECG will be performed within 1 hour after study treatment administration on visits with administration of study therapy.

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.
- 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. Pregnancy Testing

- A serum pregnancy test will be performed at screening for all female patients of childbearing potential. Prior to treatment assignment, a urine pregnancy test will be performed. If the urine pregnancy test result is negative, the patient will be eligible for treatment assignment and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not be assigned to treatment and should reflex to a β-HCG blood test before screen failing. 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.

8.4.6. 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 4 (Section 10.6).

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 signing of informed consent until study participation is complete.
- Medical occurrences that begin before treatment assignment but after obtaining informed consent/assent will be recorded as Medical History/Current Medical Conditions, not as AEs.
- 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. 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 8.5.7), 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 4 (Section 10.6).

8.5.4. 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.

8.5.4.1. Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the 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.

8.5.5. 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.

8.5.6. Cardiovascular and Death Events

This section is not applicable.

8.5.7. Adverse Events of Special Interest

Adverse events of special interest (AESIs) include infusion-related AEs, acute and chronic GVHD, 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.

8.5.7.1. 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: [redacted]

8.6. Pharmacokinetics

- Pharmacokinetic parameters 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

- Hospital length of stay and re-admission rates are assessed in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary statistical hypothesis is that the proportion of patients with clinically significant Adv, BKV, CMV, EBV, HHV-6 and/or JCV infection through Week 14, as determined by an independent, blinded CAC as outlined in Appendix 1 (Section 10.1.5.2), is less for ALVR105 treated subjects than for subjects treated with Placebo.

9.2. Sample Size Determination

[redacted] The open label cohort will not be considered in the primary statistical analysis.

[redacted]

[redacted]

9.3. Analysis Populations

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

Population	Description
Enrolled	All participants who sign the ICF.
Intent to Treat (ITT)	All randomized patients regardless of whether the patient receives ALVR105 or placebo. All efficacy analyses will be based on the ITT Population. Patients will be analyzed according to their randomized study treatment.
Safety	All patients who receive ALVR105 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

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. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Summary statistics will be presented by cohort and treatment group. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized using the frequency count and the percentage of patients in each category. All hypothesis tests will be performed at the 0.05 significance level unless otherwise noted.

For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the median time (days) and the corresponding 95% confidence interval for the true median.

9.4.2. Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The primary efficacy endpoint is the proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6 and/or JCV infection (defined as clinically significant infection and/or end-organ disease as determined by an independent, blinded CAC through Week 14.

This endpoint will be summarized by cohort and treatment group using frequency counts and percentages. [redacted]

[redacted]

9.4.3. Secondary Efficacy Endpoints

The secondary efficacy analysis will be performed on patients in Cohort OL, [redacted]

The secondary efficacy endpoints are:

- Time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia at Week 14
- AUC for cumulative viral load for AdV, BKV, CMV, EBV, HHV-6, and JCV over 14 weeks
- Proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease (excludes asymptomatic viremia) through Week 14
- Proportion of patients with clearance of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia by Week 8 in HCT patients with detectable viremia prior to the start of treatment
- Proportion of patients with clinically significant AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease and/or end-organ disease as determined by an independent, blinded CAC through Week 26 (the end of the 12-week safety follow-up period)
- Total number of hospital days related to AdV, BKV, CMV, EBV, HHV-6, and/or JCV infection or disease through Week 26
- Proportion of patients with AdV, BKV, CMV, EBV, HHV-6, and/or JCV disease-related mortality through Week 26 as determined by an independent, blinded CAC
- Quality of life assessments, FACT-BMT, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26
- Incidence of overall non-relapse related mortality AdV, BKV, CMV, EBV, HHV 6, and/or JCV disease related mortality as determined by an independent, blinded CAC
- Severity and incidence of acute GVHD
- Severity and incidence of chronic GVHD
- Severity and incidence of CRS
- Severity and incidence of clinically significant cytopenias
- Severity and incidence of renal dysfunction
- Effect on measures of engraftment

Summary tables will be presented by cohort, stratum (Stratum1: Letermovir pretreatment and Stratum 2: No Letermovir pretreatment, and Overall) and [redacted] For Cohort OL, results will be presented by stratum and overall, as all patients in Cohort OL receive only ALVR105. Combined summary for patients in Cohort OL [redacted] will also be provided.

Time to onset of each type of infection (AdV, BKV, CMV, EBV, HHV-6, JCV viremia) and overall will be summarized using Kaplan-Meier method for Cohort OL [redacted]

Number of patients with onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia and number of patients censored, and reason of censoring will be presented along with estimate for the median time (days) and its 95% CI.

Time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia will be calculated from the time of randomization until the first date of appearance of any observed viremia. Patients not observed with the onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia will be censored. Patients who discontinued from the study early before the onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia will be censored at the last assessment date for this endpoint. Patients who deceased prior to the onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia will be censored at the last assessment date for this endpoint.

Kaplan-Meier plot for time to onset of AdV, BKV, CMV, EBV, HHV-6, and/or JCV viremia at Week 14 will also be provided for each treatment.

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

No adjustment for the multiplicity of secondary and exploratory endpoints will be made for this Phase 2 trial.

9.4.4. Exploratory Endpoints

The exploratory endpoints are as follows

- Detection of anti-AdV, BKV, CMV, EBV, HHV-6 and/or JCV-specific T cells through Week 26
- Hospitalization readmission rate related to AdV, BKV, CMV, EBV, HHV-6 and/or JCV viremia/disease through Week 26
- Total days in the ICU
- Proportion of patients requiring mechanical ventilation related to AdV, BKV, CMV, EBV, HHV-6 and/or JCV infection or disease through Week 26
- Duration of anti-viral therapy (foscarnet, ganciclovir, cidofovir or other) due to viremia and/or disease through Week 26

The exploratory efficacy analysis will be performed on patients in Cohort OL, [redacted] For Cohort OL, results wil be presented by stratum and overall, as all patients in Cohort OL receive only ALVR105. Combined summary for patients in Cohort OL [redacted] will also be provided.

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 Analysis

All safety data will be summarized by cohort, stratum, [redacted]. For Cohort OL, results will be presented by stratum and overall, as all patients in Cohort OL receive only ALVR105.. 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. 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 summarized.

The incidence of AEs of special interest (AESIs), including acute and chronic GVHD and CRS, and their corresponding exact binomial 95% confidence intervals will be presented.

Descriptive statistics will be provided for continuous clinical laboratory, vital sign, and ECG data for both the raw data and change from baseline. 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, etc., will be summarized by cohort and 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.

9.5. Interim Analyses

A review by the DSMB will be done when approximately 30 patients in the OL Cohort have completed 30 days of treatment. At this time an assessment of benefit, risk, and process will be done, and study optimization will be considered. [redacted]

A sample size re-estimation (SSRE) and futility analyses will be performed.

The planned interim analyses will be described in greater detail in a separate document.

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 ALVR105 or placebo if:

1. They develop irreversible, life-threatening, Grade 3 to 4 acute GVHD within 6 weeks, or a Grade 3 to 4 non-hematologic AE within 4 weeks from last ALVR105 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. Receive any other hematopoietic stem cell product,
3. Receive therapy for relapse of the patient's primary malignancy,
4. Develop Grade 3 or 4 CRS that persists beyond 72 hours.

9.5.1.2. Stopping Criteria for the Study

Treatment assignment will be halted if 3 patients experience SAEs that meet 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, treatment assignment will not resume until there has been a thorough review of all safety data to date and concluded that it is safe for the study to continue.

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 will be done when approximately 30 patients have completed 30 days of treatment and 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: Protocol-Required Safety Laboratory Tests will be performed by the central laboratory.
- Local laboratory results are only required 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 required, 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.
- 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	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Direct bilirubin Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

Hematology (Central Laboratory)

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

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

Viral Load in Blood and Urine (Central Laboratory)

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

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. If the results from the local laboratory are used for determination of eligibility/inclusion, an additional pre-randomization sample for viruria testing must be collected for assay at the central laboratory. 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.

Urinalysis (Local Laboratory)

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

Stool Specimen (Central Laboratory)

Adenovirus	Cytomegalovirus

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

Cerebrospinal Fluid Sample (Central Laboratory) Cytomegalovirus
Human herpesvirus 6 JC virus

If a cerebrospinal fluid sample is clinically indicated, samples will 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.
    - 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**Error! Reference source not found.**):

- 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 treatment assignment 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 CROsafetynotification@CRO.com 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 8.3.4) 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 8.3.7.1.

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 more than 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:

3. 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.

4. Postmenopausal female

   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

      i. 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 more than one FSH measurement

         >40 IU/L or mIU/mL is required.

      ii. 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.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. e. Male condom and female condom should not be used together (due to risk of failure from friction).

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 2×ULN
Lungs	Normal %FEV1 after previous involvement If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	Increase by 10% predicted absolute value of %FEV1 If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	Decrease by 10% predicted absolute value of %FEV1 If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1

Organ	Complete Response	Partial Response	Progression
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

Grade CRS Parameter	1	2	3	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 principle factor leading to the outcome.
1. Fever is defined as temperature ≥38.0°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
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 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.
Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

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.

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10.8. Appendix 8: Endpoint Definitions

Infection and disease definitions for AlloVir prevention trial

- The prevention trial has a primary objective of preventing clinically significant CMV, BKV, EBV, AdV, HHV-6, and/or JCV infection and end-organ disease through Week 14 (~100 days) and a secondary objective of preventing clinically significant CMV, BKV, EBV, AdV, HHV-6, and/or JCV infection and end-organ disease through Week 26 (~6 months).
- The definitions below are intended to assist the Endpoint Adjudication Committee with adjudicating cases of infection and disease, but the committee may also use their judgment to adjudicate cases that are not captured by the definitions below (e.g., rare disease manifestations of the viruses).

Manifestation	Definition
HHV-6	
Clinically significant HHV-6 viremia[1,2]	• HHV-6 plasma viral load >10,000 copies/mL on one occasion or >1,000 on ≥2 occasions separated by at least a week
HHV-6 encephalitis/post-transplant acute limbic encephalitis[3]	• Detection of HHV-6 in the CSF coinciding with acute-onset altered mental status (encephalopathy) or short-term memory loss or seizures **AND** • Other likely infectious or non-infectious causes have been excluded **AND** • ciHHV-6 has been excluded **OR (if lumbar puncture not possible):** • Detection of HHV-6 in the plasma >1,000 copies/mL coinciding with acute-onset altered mental status (encephalopathy) or short-term memory loss or seizures **AND** • MRI findings suggestive of HHV-6 encephalitis such as hyperintensities in the limbic system (abnormalities outside the medial temporal lobes are less common) • Other likely infectious or non-infectious causes have been excluded **AND** • ciHHV-6 has been excluded
Other	• Also consider these manifestations as appropriate: delirium/decreased neurocognitive functioning, acute GVHD, bone marrow suppression, elevated LFTs, idiopathic pulmonary syndrome (in setting of HHV-6 detected from BAL fluid)
BK virus	
Clinically significant BK viremia	• BK virus plasma viral load >100,000 copies/mL or >10,000 copies/mL on ≥2 occasions separated by at least a week
BK virus-associated hemorrhagic cystitis[5]	• Clinical signs and symptoms of cystitis, including dysuria, lower abdominal pain, and/or other bladder-associated pain or spasms **AND** • Grade ≥2 hematuria (per Bedi scale) **AND**

	• BK viruria of >5 log_{10} copies/mL **AND** • No other cause for the HC is apparent
Adenovirus	
Clinically significant adenovirus viremia	• AdV plasma viral load >10,000 copies/mL on a single occasion or >1,000 copies/mL and rising, defined as two consecutive results of >1,000 copies/mL from the central laboratory, with the second result being higher than the first and drawn at least 48 hours after the first sample.
Adenovirus pneumonia[6]	• At least one of the following clinical and/or imaging findings: o Suggestive signs or symptoms (cough, dyspnea, tachypnea, hypoxia) o CT scan or X-ray with infiltrates suggestive of viral pneumonia (and **not** a dense lobar consolidation suggestive of bacterial pneumonia or nodule(s) suggestive of fungal pneumonia) **AND** • AdV identified in BAL, nasopharyngeal swab, sputum, or lung biopsy by PCR, culture, or antigen via IHC methods or clinically significant AdV viremia detected by PCR from plasma (as defined above) **AND** • No bacterial, fungal, or other probable causative agent identified/cultured
Adenovirus hepatitis[6]	• At least one of the following: o Serum bilirubin >5xULN or o ALT >5xULN or o AST >5xULN **AND** • **Either** clinically significant AdV viremia detected by plasma PCR (as defined above) **and** other causative agents (e.g., other viral causes of hepatitis) and causes (eg, drug-induced, GVHD) ruled out **OR** • AdV identified via hepatic biopsy via antigen/IHC, or culture
Adenovirus enterocolitis[6]	• AdV detected on bowel biopsy via antigen/IHC and culture/PCR **AND** • **EITHER both** of the following: o Suggestive signs or symptoms (e.g., diarrhea, abdominal pain, ileus, vomiting, GI hemorrhage) **AND** o Endoscopic evidence of lesions (macroscopic or microscopic) not attributed to GVHD

	OR cytopathic adenoviral effect identified on biopsy **OR** • At least 2 suggestive signs or symptoms: diarrhea, abdominal pain, ileus, vomiting, GI hemorrhage AND • AdV isolated from the stool by culture or PCR **AND** • Other causative agents (e.g., bacterial, viral, amebic) ruled out **AND** endoscopic evidence of lesions (macroscopic or microscopic) not attributed to GVHD (i.e., biopsy-proven)
Adenovirus pancreatitis[6]	• Consistent clinical and imaging findings such as: o Suggestive signs or symptoms (abdominal pain, GI symptoms) o Amylase or lipase >5xULN o Imaging (eg, CT scan) findings suggesting pancreatitis **AND** • AdV identified by pancreatic biopsy or ERCP brushings/washings via antigen/IHC or culture **OR** • AdV detected by plasma PCR **AND** • Other causes (e.g., gallstones, hypertriglyceridemia, parasites, paramyxovirus, other viruses) ruled out
Adenovirus hemorrhagic cystitis	• Clinical signs and symptoms of cystitis, including dysuria, lower abdominal pain, and/or other bladder-associated pain or spasms **AND** • Grade ≥2 hematuria (per Bedi scale) **AND** • AdV viruria of >5 $\log_{10}$ copies/mL **AND** • No other cause for the HC is apparent
Adenovirus nephritis	• At least one of the following: o Suggestive signs or symptoms (impaired renal function, proteinuria, microscopic hematuria, hypertension, dysuria) o Enlarged kidney on imaging o Renal/bladder obstruction **AND** • AdV identified via renal biopsy via antigen/IHC or culture **OR** • AdV detected by urine PCR +/- plasma PCR **and** other causes (e.g., BK virus, JC virus, bacterial and drug-induced) ruled out
Adenovirus encephalitis/myelitis[6]	• At least one of the following signs/symptoms of encephalitis: o Abnormal CSF o Focal CNS deficit o Cognitive impairment o Visual symptoms o Seizure o Evidence of compatible lesions by CT scan or MRI

	AND
	• AdV identified in CSF via antigen/IHC, culture, or PCR
	OR (if not possible to perform a lumbar puncture):
	• At least two of the following signs/symptoms of encephalitis:
	  o Focal CNS deficit
	  o Cognitive impairment
	  o Visual symptoms
	  o Seizure
	  o Evidence of lesions by CT scan or MRI **AND**
	• AdV detected by plasma PCR **AND**
	• Other causes (e.g., JC virus, bacterial, amebic infections and stroke/infarct/CSF leak) ruled out

Adenovirus retinitis/ocular disease[6]	• Ophthalmologic exam demonstrating findings consistent with retinitis/ocular disease (eg, retinitis, keratitis, keratoconjunctivitis sicca, iridocyclitis, retinopathy, visual field defects, papilledema, diplopia) and other possible causes (e.g., HIV, CMV, fungal, mycobacterial, bacterial infection, and/or neurologic etiology) ruled out **AND** • Detection of AdV by PCR from the aqueous or conjunctiva
CMV[7-18]	
Clinically significant CMV viremia	• CMV plasma viremia >500 copies/mL on two consecutive results between 1 and 5 days apart

CMV pneumonia	• At least one of the following clinical and/or imaging findings:
	  o Suggestive signs or symptoms (cough, dyspnea, tachypnea, hypoxia)
	  o CT scan or X-ray with infiltrates suggestive of viral pneumonia **AND**
	• Detection of CMV in BAL or tissue samples (virus isolation, histopathology, immunohistochemical analysis or in situ hybridization)

CMV GI disease	• Signs and/or symptoms of upper and/or lower GI tract involvement (eg, nausea, vomiting, diarrhea) **AND** • Macroscopic findings on endoscopy **AND** • Detection of CMV (by culture, histopathology, immunohistochemical analysis or in situ hybridization) in a GI biopsy specimen **AND** • Other causes (eg, GVHD and AdV) have been excluded
CMV hepatitis	• Increased bilirubin and/or increased enzymes **AND** • No other documented cause of hepatitis **AND**

	• Detection of CMV (by culture, histopathology, immunohistochemical analysis or *in situ* hybridization) in a liver biopsy specimen • Coinfection with other pathogens like hepatitis C virus may be present without excluding the diagnosis of CMV hepatitis
CMV encephalitis[17]	• Suggestive signs and/or symptoms (eg, confusion, lethargy, disorientation, seizures) **AND** • Detection of CMV in a CSF sample (culture or PCR) OR a brain biopsy specimen (culture, histopathology, IHC analysis or *in situ* hybridization)
CMV retinitis[18]	• Decreased visual acuity and blurred vision symptoms. Lesions typical of CMV retinitis (eg, small white lesions with intraretinal hemorrhage and vasculitis of nearby retinal vessels, granular necrotizing lesions, post-infectious scars characterized by geographic areas of chorioretinal atrophy with surrounding hyperpigmentation) must be confirmed by an ophthalmologist.
CMV nephritis	• CMV infection (by culture, immunohistochemical analysis or *in situ* hybridization) **AND** • Histologic features of CMV infection in a renal biopsy specimen (eg, owl's eye intranuclear inclusions, viral particles on electron microscopy) in a patient with renal dysfunction • (Detection of CMV in the urine of a patient with renal dysfunction does **not** fulfill the definition of CMV nephritis.)
EBV	
Clinically significant EBV viremia	• EBV PBMC viral load >10,000 copies/mL on one occasion or >1,000 copies/mL on ≥2 occasions separated by at least a week
PTLD (caused by EBV)[19]	• Suggestive signs and/or symptoms (eg, fever, weight loss, and fatigue; lymphadenopathy with or without compression of surrounding structures; dysfunction of involved organs such as the gastrointestinal tract, lungs, liver, central nervous system, or the allograft) **AND** • Imaging (eg, CT scan) demonstrating enlarged lymph nodes or a focal mass (Note: PET-CT may be helpful in the evaluation, showing PET-avid lesion, potentially guiding decisions on where to direct biopsies) **AND**

	• EBER *in situ* hybridization from tissue biopsy
EBV meningoencephalitis	• Neurologic signs and/or symptoms, such as confusion or focal weakness **AND** • Brain MRI with gadolinium with suggestive findings **AND** • EBV detected by CSF PCR
JC virus	
JC viremia[20]	• N/A (disregard plasma viral load unless there is evidence of clinical disease)
PML (caused by JC virus)	• The presence of clinical manifestations and brain imaging findings consistent with PML and not better explained by other disorders AND JC virus detected by PCR from CSF.[21] Clinical manifestations are diverse but may include behavioral and cognitive abnormalities, motor weakness, gait abnormalities, visual field deficits, speech and language disturbances, incoordination, sensory loss, seizures, headache, and diplopia.[21] Brain MRI typically shows focal or multifocal white matter lesions, generally without mass effect, that do not conform to vascular territories.[22]

HHV-6: human herpes virus 6; ciHHV-6: chromosomally integrated HHV-6; ddPCR: droplet digital polymerase chain reaction; MRI: magnetic resonance imaging; BAL: bronchoalveolar lavage; AdV: adenovirus; HC: hemorrhagic cystitis; IHC: immunohistochemistry; CT: computed tomography; CMV: cytomegalovirus; GVHD: graft versus host disease; ULN: upper limit of normal; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ERCP: endoscopic retrograde cholangiopancreatography; CSF: cerebrospinal fluid; GI: gastrointestinal; CNS: central nervous system; EBV: Epstein-Barr virus; JCV: JC virus; aGVHD: acute GVHD; ECIL: European Conference on Infections in Leukemia; PTLD: post-transplant lymphoproliferative disorder; PET: positron emission tomography; EBER: EBV-encoded RNA; PML: progressive multifocal leukoencephalopathy.

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