Protocol Number: P-106-001

Official Title:

Phase 1/2, Double-Blind, Placebo-Controlled, Dose Escalation and Expansion Study of ALVR106 in Addition to Standard of Care for the Treatment of High-Risk Patients with Respiratory Viral Infections After Hematopoietic Cell or Solid Organ Transplant

NCT Number: NCT04933968

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CLINICAL STUDY PROTOCOL

Phase 1/2, Double-Blind, Placebo-Controlled, Dose Escalation and Expansion Study of ALVR106 in Addition to Standard of Care for the Treatment of High-Risk Patients with Respiratory Viral Infections After Hematopoietic Cell or Solid Organ Transplant

Investigational Product: ALVR106

Protocol Number: P-106-001

Sponsor:

AlloVir

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Version Number: 5.0

Date: 19 May 2022

INVESTIGATOR AGREEMENT

By signing below I agree that:

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

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

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: Phase 1/2, Double-Blind, Placebo-Controlled, Dose Escalation and Expansion Study of ALVR106 in Addition to Standard of Care for the Treatment of High-Risk Patients with Respiratory Viral Infections After Hematopoietic Cell or Solid Organ Transplant

PROTOCOL NUMBER: P-106-001

IND NUMBER: 19723

INVESTIGATIONAL PRODUCT: ALVR106

PHASE: 1/2

OBJECTIVES:

Part A (Dose Escalation)

The primary objective of Part A is to determine the safety and tolerability of ascending doses of ALVR106 when administered to high-risk adult patients with upper respiratory tract infections (URTIs) caused by respiratory syncytial virus (RSV), influenza virus (IFV), human metapneumovirus (hMPV), and/or parainfluenza virus (PIV) following HCT or SOT.

The secondary objectives of Part A are the following:

- To identify the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of ALVR106 in patients with URTIs
- To characterize the individual patient antiviral response as measured by change in viral load from nasal swab specimens from baseline through Day 28 following the patient's first ALVR106 infusion

Part B (Recommended Phase 2 Dose Cohort Expansion)

The primary objective of Part B is to determine the antiviral activity of the RP2D of ALVR106, as compared to placebo, when administered to high-risk adult patients with URTIs caused by RSV, IFV, hMPV, and/or PIV following HCT or SOT.

The secondary objectives of Part B are the following:

- To determine the safety and tolerability of the RP2D of ALVR106 when administered to high-risk adult patients with URTIs caused by RSV, IFV, hMPV, and/or PIV following HCT or SOT
- To characterize the individual patient antiviral response as measured by the percent reduction in viral load from nasal swab specimens and a reduction in clinical signs and symptoms from baseline through Day 28, Day 60, Day 90, and Month 6 following the patient's first ALVR106 infusion

Reference Protocol Section 2 for additional study objectives.

POPULATION:

Key Inclusion Criteria

- Aged 17 to 75 years at screening.
- Undergone hematopoietic cell transplantation (HCT) ≥21 days or solid organ transplantation (SOT) ≥28 days prior to study treatment administration
- Detection of at least 1 target virus of interest (ie, RSV, IFV, hMPV, and/or PIV) in the respiratory tract
- Diagnosis of respiratory tract infection, defined by new onset of symptoms

Key Exclusion Criteria

- Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day) within 7 days prior to screening
- Prior therapy with abatacept or belatacept, within 3 months of screening; or antithymocyte globulin (ATG), alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies within 28 days of study treatment administration
- Infection with coronavirus disease 2019 (COVID-19) within 28 days prior to study treatment administration
- For HCT patients, evidence of Grade >2 acute graft versus host disease (aGVHD); and for SOT patients, any history or evidence of aGVHD at Screening
- Significant hypoxemia (ie, oxygen saturation <90% while breathing ambient air at rest)
- Requirement for continuous infusions of inotropes or vasopressors for blood pressure support
- Systolic blood pressure <90 mmHg, except for patients with normal resting SBP <90 mmHg confirmed by investigator
- Requirement for mechanical ventilation or noninvasive ventilation
- Resting respiratory rate ≥30 breaths/min
- Evidence of encephalopathy or confusion
- For HCT or non-lung SOT recipients, chest X-ray and/or CT scan with multifocal consolidation or diffuse alveolar consolidation. For lung transplant recipients, any new abnormalities on a chest X-ray and/or CT scan, other than patchy atelectasis, hyperinflation, and/or bronchial wall thickening, caused by LRTI.

Reference Protocol Section 4 for detailed inclusion and exclusion criteria.

STUDY DESIGN AND DURATION:

This is a Phase 1/2, double-blind, placebo-controlled, dose escalation and expansion study to assess the safety and dose selection of ALVR106 in addition to standard of care for the treatment of high-risk patients with respiratory tract infections (RTIs) and clinical manifestations caused by RSV, IFV, hMPV, and/or PIV following HCT or SOT. This study will be conducted in 2 parts:

- Part A: Dose Escalation
- Part B: Recommended Phase 2 Dose Cohort Expansion

Throughout the study, all patients may receive standard of care as determined by the Investigator (or designee). Reference Protocol Section 5.7 for additional information on concomitant medications.

The specific ALVR106 drug product for infusion selected for each participant will be determined by an electronic software system (CytoMatch™) based on [redacted]. Reference the JUDI Manual for additional details.

An independent Safety Review Committee (SRC) will be convened for this study to routinely monitor safety in a blinded fashion, unless the SRC makes a specific request for individual patient unblinding. Further details can be found in the SRC Charter.

Part A (Dose Escalation)

Part A will include up to 4 cohorts, with 4 high-risk adult patients per cohort (potentially expanding to 8 patients per cohort), randomized in a [redacted] ratio to ALVR106 or placebo in a -double-blind fashion. Patients in each cohort will receive an infusion of ALVR106 cells or placebo on Day 1 and will return to the clinical site for assessment on Days 3, 7, 10, and 14 or more frequently as determined by the patient's clinical condition at the discretion of the Investigator and in collaboration with the Medical Monitor.

Patients who have not fully recovered should receive a second dose of blinded study treatment approximately 14 days following the first dose (reference DOSAGE FORMS AND ROUTE OF ADMINISTRATION below or Protocol Section 5.6.3 for additional administration information).

Follow-up visits will occur at Day 28 (Week 4), Day 60 (Week 8), Day 180 (Month 6), and Day 365 (Month 12) following the patient's first study treatment infusion. All patients will follow the same schedule of follow-up visits, including any patients who receive a partial infusion (less than the recommended dose for the patient).

The planned doses for Cohorts 1 through 4 are presented below. Intra-patient dose escalation is not permitted. Reference Protocol Section 5.1 for Table on weight range dose to be administered.

Planned Doses for Cohorts 1 Through 4

Dose Cohort	ALVR106 Dose Level
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]

In the event of toxicity at a planned dose, the doses may be de-escalated, based on recommendations from the SRC, to an interpolated intermediate dose from the planned cohorts as presented below.

Intermediate Doses

Dose Cohort	ALVR106 Dose Level
Toxicity adjusted dose between Dose Cohort 1 and 2	[redacted])
Toxicity adjusted dose between Dose Cohort 2 and 3	[redacted]

For each dosing cohort in Part A, the SRC will review the safety and available efficacy data after the first two patients have completed at least 7 days of safety monitoring following the initial dose. No additional patients will be dosed until that review is completed. Once review of the first two patients is complete (and the SRC has endorsed continuation of the study) the study enrollment of the remaining patients in the cohort will continue.

At least one week after the last patient's first dose in each cohort, the SRC will convene to assess blinded safety data from the current cohort and, if applicable, previous cohorts. This will allow for a consolidated safety review, with patients within the cohort averaging at least 14 days post the last dose.

Dose escalation will proceed to identify the maximum tolerated dose (MTD) within the planned dose range and a recommended Phase 2 dose (RP2D) that may be the MTD or a lower dose within the tested dose range.

Based on routine safety reviews, the SRC may recommend escalating the dose as planned, recommend an intermediate dose, recommend expansion of the current cohort, recommend stopping dose escalation (Part A), or stop the study. In the event of cohort expansion, up to 4 additional patients may be enrolled and randomized in a [redacted] ratio to ALVR106 or placebo. In addition, the SRC will make a recommendation for the RP2D and starting enrollment of Part B. The Sponsor will determine the final RP2D based on SRC recommendation and after review of all available relevant safety and available efficacy data through at least Day 28 following the first ALVR106 or placebo infusion. Reference the SRC Charter for additional information.

Part B (Recommended Phase 2 Dose Cohort Expansion)

Following the determination of the RP2D in Part A, based on review of relevant safety and efficacy data, approximately 45 high-risk adult patients with URTIs will be randomized in a [redacted] ratio to ALVR106 or placebo in a double-blind fashion.

Patients in the ALVR106 group will receive an infusion of the RP2D as determined in Part A. Patients will receive an infusion of ALVR106 cells or placebo on Day 1 and will return to the clinical site for assessment on Days 3, 7, 10, and 14.

Patients who have not fully recovered should receive a second dose of blinded study treatment approximately [redacted] following the first dose (reference DOSAGE FORMS AND ROUTE OF ADMINISTRATION below or Protocol Section 5.6.3 for additional administration information).

Additional follow-up visits will occur at Day 28 (Week 4), Day 60 (Week 8), Day 90 (Month 3), Day 180 (Month 6), and Day 365 (Month 12). All patients will follow the same schedule of follow-up visits, including any patients who receive a partial infusion (less than the recommended dose for the patient).

The SRC will continue to routinely monitor safety in the expansion cohort. Further details can be found in the SRC Charter.

During the study, the severity of adverse events will be graded by the Investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All hospitalizations, intensive care unit (ICU) admissions and SAEs will be reported and will be assessed as to whether they were caused by the RTI.

Changes in patient reported respiratory status will be captured in the patient reported respiratory clinical symptoms form (reference Appendix D) and not as adverse events. A new diagnosis of lower respiratory tract infection (LRTI) will be captured as an AE. Any respiratory events that meet SAE criteria will be captured as both AEs and SAEs. Respiratory status with imaging will be assessed by the investigator and graded using the Radiation Therapy Oncology Group Lung Toxicity Scale presented below.

Radiation Therapy Oncology Group Lung Toxicity Scale

Organ Tissue	0	Grade 1	Grade 2	Grade 3	Grade 4
Lung	**None**	**Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances**	**Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances**	**Severe symptomatic fibrosis or pneumonitis Dense radiographic changes**	**Severe respiratory insufficiency/ Continuous oxygen/ Assisted ventilation**

Dose-Limiting Toxicity

DLTs are defined as treatment-related Grade ≥3 SAEs and/or Grade ≥3 adverse event of special interest (AESI) that emerge or worsen during the study. Treatment-related AE are those that occur after the administration of study drug and cannot be reasonably attributed to the patient's underlying disease, other medical condition, or concomitant medications.

For this study, AESI include the following as reported by the Investigator:

- New (HCT and SOT patients) or worsening (HCT patients) of acute or chronic GVHD
- Graft failure or rejection
- Cytokine release syndrome (for the CRS grading scale, see Appendix C)
- Infusion related reactions (IRRs)
- New or worsening interstitial pneumonitis as reported by the Investigator from review of radiologic findings
- Progressive dyspnea

Focusing on AESI will provide further assurance that emergent safety issues are identified promptly. The AESI for this study, noted above, were selected based on the need to identify potential worsening in the underlying disease being targeted, as well as theoretical complications

of virus-specific T cells (VSTs).

Stopping Rules

Stopping rules in Parts A and B are defined as:

- A patient with a DLT that is a Grade ≥3 SAE or considered a Grade ≥3 AESI that emerges or worsens during the study period following the patient's initial dose and cannot be reasonably attributed to the patient's underlying disease, other medical condition, or concomitant medications. The study enrollment would pause to allow time for a safety review by the SRC.

Focusing on AESI will provide further assurance that emergent safety issues are identified promptly. The AESI for this study, noted above, were selected based on the need to identify potential worsening in the underlying disease being targeted, as well as theoretical complications of virus-specific T cells (VSTs).

The SRC will consist of an external chair and two additional independent experts in the field, at least one of the members will be a transplant physician and at least one member will be an infectious disease expert.

The SRC will meet at least every 2 weeks to review emerging safety data and will conduct both open and closed meetings. Should any safety issues require review by the SRC, an emergency meeting will be scheduled within 72 hours. Should a death occur in the study that is considered to be definitely or probably related to the study product by the Investigator, the SRC will meet on an urgent basis, within 72 hours, to review the data available and make an assessment. Further dosing will be stopped until the SRC makes an assessment.

The SRC will also convene following any Grade 4 or 5 SAE, irrespective of relatedness, or a Grade ≥3 SAE that may possibly, probably, or definitely be related to study treatment.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

For detailed instructions on ALVR106 or matching placebo administration reference the Cell Therapy Manual. For additional dose administration information reference Protocol Section 5.1.

All eligible participants will be randomized to receive:

ALVR106 cells or matching placebo administered IV over approximately [redacted] minutes as a slow push on Day 1 and [redacted] if applicable.

Administration of the [redacted] dose will be based on [redacted] visit assessments, as follows:

- Patients who have demonstrated an initial objective clinical response, and a decrease in viral load defined by at least 50% reduction of viral load in nasal swab, will receive a [redacted] with the first cell line (or second dose of placebo) as initially administered, if available.
- Patients who have not demonstrated either clinical improvement or decrease in viral load in nasal swab following the first dose will receive a new partially HLA-matched drug product from a different donor or placebo, if available. If another partially HLA-matched drug product is not available, they will receive the same initial partially HLA-matched drug product or placebo.

- Patients who have fully recovered will not receive a second dose. Full recovery is defined as undetectable viral load in nasal swab by qPCR post first study treatment infusion, absence of respiratory symptoms, and, as applicable, normalization of imaging.
- Patients who have experienced new onset of systemic GVHD (HCT and SOT patients), a Grade ≥3 worsening of GVHD (HCT patients) or Grade ≥3 infusion related reaction will not receive a second dose.

Premedication can be administered to any participant at the investigator's discretion but is not required, except for patients with a prior history of reaction to blood products (reference Section 5.7.2 for premedication options).

EFFICACY VARIABLES:

Primary Efficacy Endpoint

The primary efficacy endpoints include the following:

- The reduction in viral load from nasal swab specimens from pre-dose through Day 28. Time-weighted average change from baseline to Day 28 in $\log_{10}$ viral load will be measured by qPCR (based on the central laboratory) for Part A.
- Proportion of patients with ≥50% reduction in viral load from nasal swab specimens and improvement in clinical signs and symptoms through Day 28 following the patient's first ALVR106 infusion for Part B.

Reference Protocol Section 6.1 for efficacy endpoints.

SAFETY VARIABLES:

The safety endpoints include the incidence of the following AESI as reported by the Investigator:

- New (HCT and SOT patients) or worsening (HCT patients) of acute or chronic GVHD
- Graft failure or rejection
- Cytokine release syndrome (for the CRS grading scale, see Appendix C)
- Infusion related reactions (IRRs)
- New or worsening interstitial pneumonitis as reported by the Investigator from review of radiologic findings
- Progressive dyspnea

Safety assessments also include treatment-emergent adverse events (TEAEs); infusion site reactions; clinical laboratory assessments; changes in corticosteroid dosage; and abnormalities in vital signs or physical examination findings (including heart and lung auscultation, skin, and ears/nose/throat). Treatment-emergent is defined as adverse events from the first dose of study drug to the last dose of study drug plus 12 weeks.

Reference Protocol Section 7.1 for safety endpoints.

STATISTICAL ANALYSES:

A Statistical Analysis Plan (SAP) will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the Clinical Study Report.

Data from Part A and Part B of the study will be summarized and analyzed separately. All the safety and efficacy endpoints will be summarized using descriptive statistics by treatment group.

Categorical data will generally be summarized with counts and percentages of patients. Continuous data will generally be summarized with descriptive statistics, including the number of non-missing values, mean, median, standard deviation, minimum, and maximum.

Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term and further by severity (according to the NCI CTCAE v5.0) and relationship to study treatment. The incidence of AESI and the corresponding 95% exact binomial confidence intervals will be presented by treatment group. Descriptive statistics will be provided for relevant laboratory and vital sign data.

The SRC will review the cumulative safety and available efficacy data from each previous cohorts to recommend dose level and regimen for the subsequent cohorts.

SAMPLE SIZE DETERMINATION:

No formal sample size determination was performed due to the exploratory nature of this study. The sample size has been set for an initial assessment of the safety and antiviral activity of ALVR106.

For the Part A dose escalation portion of the study, approximately 16 to 32 patients will be randomized. The actual number of patients randomized will depend on the safety profile for each cohort and when the MTD is reached.

For Part B, the RP2D cohort expansion, a total of approximately 45 patients will be randomized.

SITES: Approximately 45 sites

SPONSOR:

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SCHEDULE OF PROCEDURES – PART A

Schedule of Procedures – Part A (Dose Escalation)

Study Week/Month	Weeks -[redacted]	[redacted]			[redacted]		[redacted]	[redacted]	[redacted]	[redacted]]
Study Day	-[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	NA	NA	±2	±2	±2	±3	±5	±5	±28	±28
Study Procedures										
Informed consent/assent	X									
I/E criteria	X	X [1]								
Demographics and medical history [2]	X									
HLA match and/or typing for drug product selection	X									
Randomization [3]		X								
Prior and concomitant medications	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X
Hospital information [4]	X	X	X	X	X	X	X	X	X	X
Physical examination [5]	X	X	X	X	X	X	X			
Height and weight [7]	X	X								
Vital signs including SpO2 [8]	X	X	X	X	X	X	X			
12-lead ECG	X									
Chest X-ray and/or CT scan [9]	X				X		X			
Clinical laboratories (CBC with differential, chemistry, LFTs [10])	X	X				X	X			
Urinalysis	X	X					X			
RSV, IFV, hMPV, and PIV viral load measured [11]	X	X	X	X	X		X	X	X	

Study Week/Month	Weeks [redacted]	[redacted]			[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Study Day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	NA	NA	±2	±2	±2	±3	±5	±5	±28	±28
Study Procedures										
Blood sample for viremia assessment (stored for possible analysis)	X	X		X		X	X	X	X	
SARS-CoV-2 assessment	X									
Pregnancy test [12]	X	X				X			X	
Donor-specific antibody sample (SOT only)		X						X		
Bank PBMCs for virus-specific immunity and plasma for cytokine evaluation [13]		X				X	X	X	X	
Patient (or caretaker)-reported respiratory clinical signs/symptoms [14]	X	X	X	X	X	X	X			
Investigator assessment of respiratory status and, if applicable, may include assessment of spirometry [15]	X	X	X	X	X	X	X		X [15]	X [15]
Acute GVHD evaluation [16]	X	X	X	X	X	X	X			
Chronic GVHD evaluation [16]		X					X	X	X	X
Study treatment administration [17]		X				X				
Infusion site evaluation [18]		X	X	X	X	X	X			
Post-infusion monitoring [19]		X				X				
Health Status (Survival)										X

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

1. Patient eligibility must be reconfirmed prior to study treatment administration. See Section 4.3.
2. Medical history will include diagnosis of underlying disease requiring transplant, underlying disease state at the time of RTI diagnosis, type of donor and cell source of the HCT received (HCT participants only), type of SOT, date of transplant, conditioning regimen, CMV serostatus, presence of GVHD, and smoking status.
3. Randomization will occur after all screening procedures are complete and prior to study treatment administration.

4. Includes information on hospital admission and discharge, ICU transfer, oxygen supplementation, and mechanical or noninvasive ventilation.
5. A complete physical examination will be performed at screening and Baseline/Day 1. Abbreviated physical examinations will be performed at all subsequent visits.
6. On Day 1, all assessments should be performed before dosing, except treatment administration, infusion site evaluation and post-infusion monitoring
7. Height should be collected at screening only. The patient's screening weight will be used to calculate the 1st and 2nd doses and the dose will remain the same for both infusions.
8. Vital signs include body temperature, heart rate, respiratory rate, SpO2, and systolic and diastolic blood pressure. Vital signs will be collected after the patient has rested for at least 5 minutes in the supine position.
9. All patients will have screening imaging performed and analyzed locally as long as the imaging can be transmitted to the central reader. Imaging will be repeated at Days 10 and 28 for all patients, and as needed in cases of suspected progression to LRTI. Patient management will be based on the local reading, but the final analysis of radiologic progression will be based on the central reader's assessment.
10. LFTs will include alkaline phosphatase, total and direct bilirubin, AST, and ALT.
11. Confirmation of RTI associated with the 4 target viruses will be done through a nasal swab. Local laboratory results obtained within 3 days of Screening or during the screening period will be acceptable for eligibility determination. However, a central nasal swab sample must be collected and submitted to the central laboratory prior to dosing. Nasal swabs for Screening and Baseline should also be analyzed for SARS-CoV-2. All eligible participants will have a nasal swab collected at Baseline and post-treatment visits and sent to Central Laboratory for analysis. Samples will be stored for potential future viral genotypic or viral load analysis.
12. A serum pregnancy test will be performed at screening for females of childbearing potential. A serum or urine pregnancy test will be repeated prior to dosing on Day 1 and Day 14 for females of childbearing potential, only if the pregnancy test performed at screening was not completed within 48 hours prior to study treatment administration. These tests may be performed at the local laboratory.
13. Day 1 blood will be collected predose. Blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Plasma should be aliquoted into two samples and frozen for potential future evaluation. PBMC should be aliquoted into at least 2 aliquots or at $5x10^6$ cells/vial.
14. The patient will complete the electronic respiratory clinical signs questionnaire (see Appendix D)
15. The Investigator will assess patient's respiratory status and complete the Respiratory Tract Infection Status eCRF in EDC at each visit through Week 4 post-initial infusion for all patients. For lung transplant recipients, the Investigator will complete additional assessments at Month 6 and 12 post-initial infusion. For lung transplant recipients, if required by the investigator to support assessment of respiratory status, a spirometry assessment may be completed by the patient at Baseline, Week 4, Months 6 and 12. Spirometry should be collected in line with local standard clinical practice. Reference P-106-001 eCRF Completion Guidelines for additional information.
16. If any patient develops GVHD, that patient may receive standard GVHD treatment at the discretion of the Investigator. Staging and grading of acute GVHD will be reported using MAGIC guidelines; for HCT patients, response to treatment will be assessed as per CIBMTR modifications to the CIBMTR response index. For HCT patients, manifestations of chronic GVHD and response to treatment will be assessed as per National Institutes of Health consensus guidelines for chronic GVHD.
17. Patients randomized to the ALVR106 group will receive ALVR106 cells or placebo as an infusion (administered IV over approximately [redacted] minutes as a slow push). Based on treatment response on Day [redacted] patients may receive a [redacted] dose of blinded study treatment approximately [redacted] following the first dose.
18. Includes pain, tenderness, erythema, swelling, and induration. On infusion days, performed pre-dose and at 1 hour post-dose.
19. Patients will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs and pulse oximetry will be measured at the end of the infusion (+/- 5 minutes), and at 15 minutes (+/- 5 minutes), 30 minutes (+/- 10 minutes), 45 minutes (+/- 15 minutes), and 60 minutes (+/- 15 minutes) after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
20. Patients who discontinue the study before the Month 12 visit should complete all assessments in the Month 12/Early Termination visit either in clinic or virtually via phone or telemedicine. At a minimum a follow-up should occur within 2 weeks of the last study dose.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CIBMTR = Center for International Blood and Marrow Transplant Research; CMV = cytomegalovirus; COA = clinical outcome assessment; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = Early Termination;; GVHD = graft versus host disease; HCT = hematopoietic cell transplant; HLA = human leukocyte antigen; hMPV = human metapneumovirus; ICU = intensive care unit; I/E = inclusion and exclusion; IV = intravenous(ly); LFT = liver function test; LRTI = lower respiratory tract infection; MAGIC = Mount Sinai Acute GVHD International Consortium; NA = not applicable; PBMC = peripheral blood mononuclear cell; PIV = parainfluenza virus;; qPCR = quantitative polymerase chain reaction; RSV = respiratory syncytial virus; RTI = respiratory tract infection; SOT=Solid Organ Transplant; SpO2 = peripheral capillary oxygen saturation; URTI = upper respiratory tract infection; VC = vital capacity; VST = virus-specific T cell.

SCHEDULE OF PROCEDURES – PART B

Schedule of Procedures – Part B (RP2D Cohort Expansion)

Study Week/Month	Weeks -2 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day	-10 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit Window (Days)	NA	NA	±2	±2	±2	±3	±5	±5	±28	±28	±28
Study Procedures											
Informed consent/assent	X										
I/E criteria	X	X [1]									
Demographics and medical history [2]	X										
HLA match and/or typing for drug product selection	X										
Randomization [3]		X									
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Hospital information [4]	X	X	X	X	X	X	X	X	X	X	X
Physical examination [5]	X	X	X	X	X	X	X	X	X	X	
Height and weight [7]	X	X								X	
Vital signs including SpO2 [8]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X										
Chest X-ray and/or CT scan [9]	X				X		X				
Clinical laboratories (CBC with differential, chemistry, LFTs [10])	X	X				X	X	X		X	
Urinalysis	X	X					X			X	

Study Week/Month	[redacted]										
Study Day	[redacted]										
Visit Window (Days)	NA	NA	±2	±2	±2	±3	±5	±5	±28	±28	±28
Study Procedures											
RSV, IFV, hMPV, and PIV viral load measured [11]	X	X	X	X	X		X	X	X	X	
Blood sample for viremia assessment (stored for possible analysis)	X	X		X		X	X	X		X	
SARS-CoV-2 assessment	X										
Pregnancy test [12]	X	X				X				X	
Donor specific antibody sample (SOT only)		X							X		
Bank PBMCs for virus-specific immunity and plasma for cytokine evaluation [13]		X				X	X	X	X	X	
Patient (or caretaker)-reported respiratory clinical signs/symptoms [14]	X	X	X	X	X	X	X				
Investigator assessment of respiratory status and, if applicable, may include assessment of spirometry [15]	X	X	X	X	X	X	X			X [15]	X [15]
Acute GVHD evaluation [16]	X	X	X	X	X	X	X				
Chronic GVHD evaluation [16]		X					X	X		X	X
Study treatment administration [17]		X				X					
Infusion site evaluation [18]		X	X	X	X	X	X				
Post-infusion monitoring [19]		X				X					
Health Status (Survival)											X

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

1. Patient eligibility must be reconfirmed prior to study treatment administration. See Section 4.3.
2. Medical history will include diagnosis of underlying disease requiring transplant, underlying disease state at the time of RTI diagnosis, type of donor and cell source of the HCT received (HCT participants only), type of SOT, date of transplant, conditioning regimen, CMV serostatus, presence of GVHD, and smoking status.
3. Randomization will occur after all screening procedures are complete and prior to study treatment administration.
4. Includes information on hospital admission and discharge, ICU transfer, oxygen supplementation, and ventilation.
5. A complete physical examination will be performed at screening and Baseline/Day 1. Abbreviated physical examinations will be performed at all subsequent visits.
6. On Day 1, all assessments should be performed before dosing, except treatment administration, infusion site evaluation and post-infusion monitoring
7. Height should be collected at Screening only. The patient's screening weight will be used to calculate the 1st and 2nd doses and the dose will remain the same for both infusions.
8. Vital signs include body temperature, heart rate, respiratory rate, SpO2, and systolic and diastolic blood pressure. Vital signs will be collected after the patient has rested for at least 5 minutes in the supine position.
9. All patients will have screening imaging performed and analyzed locally as long as the imaging can be transmitted to the central reader. Imaging will be repeated at Days 10 and 28 for all patients, and as needed in cases of suspected progression to LRTI. Patient management will be based on the local reading, but the final analysis of radiologic progression will be based on the central reader's assessment.
10. LFTs will include alkaline phosphatase, total and direct bilirubin, AST, and ALT.
11. Confirmation of RTI associated with the 4 target viruses will be done through a nasal swab. Local laboratory results obtained within 3 days of Screening or during the screening period will be acceptable for eligibility determination. However, a central nasal swab sample must be collected and submitted to the central laboratory prior to dosing. Nasal swabs for Screening and Baseline should also be analyzed for SARS-CoV-2. All eligible participants will have a nasal swab collected at Baseline and post-treatment visits and sent to Central Laboratory for analysis. Samples will be stored for potential future viral genotypic or viral load analysis.
12. A serum pregnancy test will be performed at screening for females of childbearing potential. A serum or urine pregnancy test will be repeated prior to dosing on Day 1 and Day 14 for females of childbearing potential, only if the pregnancy test performed at screening was not completed within 48 hours prior to study treatment administration. These tests may be performed at the local laboratory
13. Day 1 blood will be collected predose. Blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. Plasma should be aliquoted into two samples and frozen for potential future evaluation. PBMC should be aliquoted into at least 2 aliquots or at $5x10^6$ cells/vial.
14. The patient will complete the electronic respiratory clinical signs questionnaire (see Appendix D).
15. The Investigator will assess patient's respiratory status and complete the Respiratory Tract Infection Status eCRF in EDC at each visit through Week 4 post-initial infusion for all patients. For lung transplant recipients, the Investigator will complete additional assessments at Month 6 and 12 post-initial infusion. For lung transplant recipients, if required by the investigator to support assessment of respiratory status, a spirometry assessment may be completed by the patient at Baseline, Week 4, Months 6 and 12. Spirometry should be collected in line with local standard clinical practice. Reference P-106-001 eCRF Completion Guidelines for additional information.
16. If any patient develops GVHD, that patient may receive standard GVHD treatment at the discretion of the Investigator. Staging and grading of acute GVHD will be reported using MAGIC guidelines; for HCT patients, response to treatment will be assessed as per CIBMTR modifications to the CIBMTR response index. For HCT patients, manifestations of chronic GVHD and response to treatment will be assessed as per National Institutes of Health consensus guidelines for chronic GVHD.
17. Patients randomized to the ALVR106 group will receive ALVR106 cells or placebo as an infusion (administered IV over approximately[redacted] minutes as a slow push). Based on treatment response on Day[redacted] patients may receive a[redacted] dose of blinded study treatment approximately[redacted] following the first dose.
18. Includes pain, tenderness, erythema, swelling, and induration. On infusion days, performed pre-dose and at 1 hour post-dose.
19. Patients will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs and pulse oximetry will be measured at the end of the infusion (+/- 5 minutes), and at 15 minutes (+/- 5 minutes), 30 minutes (+/- 10 minutes), 45 minutes (+/- 15 minutes), and 60 minutes (+/- 15 minutes) after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
20. Patients who discontinue the study before the Month 12 visit should complete all assessments in the Month 12/Early Termination visit either in clinic or virtually via phone or telemedicine. At a minimum a follow-up should occur within 2 weeks of the last study dose.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CIBMTR = Center for International Blood and Marrow Transplant Research; CMV = cytomegalovirus; COA = clinical outcome assessment; CT = computed tomography; ECG = electrocardiogram; ET = Early Termination; GVHD = graft versus host disease; HCT = hematopoietic cell transplant; HLA = human leukocyte antigen; hMPV = human metapneumovirus; ICU = intensive care unit; I/E = inclusion and exclusion; IV = intravenous(ly); LFT = liver function test; LRTI = lower respiratory tract infection; MAGIC = Mount Sinai Acute GVHD International Consortium; NA = not applicable;

PBMC = peripheral blood mononuclear cell; PIV = parainfluenza virus; qPCR = quantitative polymerase chain reaction; RP2D = recommended Phase 2 dose; RSV = respiratory syncytial virus; SOT=Solid Organ Transplant; SpO2 = peripheral capillary oxygen saturation; URTI = upper respiratory tract infection; VC = vital capacity; VST = virus-specific T cell.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AdV	Adenovirus
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BKV	BK virus
CAR	Chimeric antigen receptor
CARV	Community-acquired respiratory virus
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CRS	Cytokine release syndrome
CT	Computed tomography
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
DLI	Donor lymphocyte infusion
DLT	Dose-limiting toxicity
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GVHD	Graft versus host disease
HCT	Hematopoietic cell transplant
HHV-6	Human herpes virus-6
HLA	Human leukocyte antigen
hMPV	Human metapneumovirus
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IFV	Influenza virus
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Definition
IV	Intravenous(ly)
LRTI	Lower respiratory tract infection
mITT	Modified Intent-to-Treat
MTD	Maximum tolerated dose
NCI	National Cancer Institute
PBMC	Peripheral blood mononuclear cell
PIV	Parainfluenza virus
qPCR	Quantitative polymerase chain reaction
RP2D	Recommended Phase 2 dose
RSV	Respiratory syncytial virus
RTI	Respiratory tract infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sCRS	Severe cytokine release syndrome
SRC	Safety Review Committee
SOT	Solid Organ Transplant
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
VAS	Visual analog scale
VC	Vital capacity
VST	Virus-specific T cell

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Viral Infection Following Transplant

Respiratory infections are among the most common types of tissue-invasive infections in immunocompromised patients (eg, hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT)). Community-acquired viruses such as respiratory syncytial virus (RSV), influenza (IFV), parainfluenza virus (PIV), and human metapneumovirus (hMPV) are global leading causes of morbidity and mortality during the period prior to immune recovery after HCT or in the setting of potent immunosuppressive regimens following HCT or SOT.

Young children, the elderly, and patients with compromised immune systems are particularly at risk. Respiratory tract infections (RTIs) affect up to 40% of allogeneic HCT and up to 21% SOT recipients, with symptoms ranging from mild to severe.[1,2,3] While initial symptoms of these viruses in transplant patients may be limited to the upper respiratory tract and include rhinorrhea, cough, and/or fever, approximately 50% of cases progress to the lower respiratory tract,[4] leading to more severe conditions such as pneumonia, bronchiolitis, and specific to lung transplant recipients, bronchiolitis obliterans syndrome (BOS) or chronic lung allograft dysfunction (CLAD).[4] Mortality rates in HCT recipients due to these conditions are as high as 23% to 50%.[1] In SOT, especially lung transplant recipients, mortality rates due to these conditions are as high as 20%.[5]

Currently, there are no approved vaccines or antiviral drugs for hMPV or PIV. For IFV, treatment with antiviral agents such as neuraminidase inhibitors is available, however, immunocompromised patients are at greater risk for developing infection with drug resistant IFV. While prophylactic IFV vaccines are available annually, they are not recommended for HCT and SOT patients until at least 3-6 months following transplant.[6,7] For RSV, aerosolized ribavirin has been approved by the FDA for the treatment of RSV, but it is costly and difficult to administer.

In healthy individuals, T cell immunity defends against RSV, IFV, PIV, and hMPV. In HCT and SOT recipients, the use of potent immunosuppressive regimens leaves patients susceptible to severe viral infections. There is a significant unmet need for treatment options that can address these common community-acquired respiratory infections in immunocompromised transplant patients. Cellular immunotherapy to restore viral-specific immunity has been investigated as a potential therapeutic option in immunocompromised patients' post-transplant.

1.2 Adoptive Immunotherapy for Viral Infections Following Hematopoietic Cell Transplant

The first virus to be targeted using an adoptive T cell transfer approach was cytomegalovirus (CMV).[8] This was followed by numerous studies with not only CMV-directed T cell products (eg, ex vivo expanded polyclonal lines, interferon γ-captured cells, and multimer-selected products),[9,10,11,12,13,14,15] but also T cell products directed toward other viruses, including Epstein-Barr virus (EBV) and adenovirus (AdV). These clinically implemented immunotherapeutic strategies are considered safe and are associated with clinical benefit.[16,17,18,19,20,21,22,23,24]

Adoptive transfer of HCT donor-derived VSTs (ie, VSTs expanded or selected from a transplant donor) has been successfully used to prevent and treat viral infections,[25] including CMV and AdV infections, as well as drug-refractory EBV-positive lymphomas, that complicate HCT.[26] However, despite the successful use of various stem cell donor-derived VSTs over more than 20 years, there

are significant limitations to this approach, making it unsuitable for a potential commercial product.

An alternative to preparing stem cell donor-derived VSTs for individual patients is to bank partially human leukocyte antigen (HLA)-matched allogeneic VSTs, obtained from healthy third-party donors (not the stem cell donor) with demonstrated immunity to virus(es), that could be available as an "off-the-shelf" product for immediate use. This approach theoretically overcomes some of the limitations of HCT donor-derived VSTs. Specifically, patients do not have to wait for the drug product to be produced, and, taking the multivirus approach (ie, deriving drug products by antigenically stimulating against peptides from multiple viruses of interest), results in a ready-for-use drug product specific for multiple viruses of interest. A potential concern with this approach is that the mismatched product may not persist long enough in vivo to control the viral infection, because the recipient may generate an immune response to the non-shared transplantation antigens. Despite this theoretical concern, several studies have demonstrated that third-party VSTs are associated with clinical benefit.[27,28,29,30]

1.3 Adoptive Immunotherapy for Viral Infections Following Solid Organ Transplant

Adoptive transfer of donor-derived VSTs (ie, VSTs expanded or selected from a transplant donor) has been successfully used to treat EBV-associated post-transplant lymphoproliferative disease (PTLD) in SOT recipients. Haque T et al.[31] conducted a phase 2 multicenter clinical trial aimed to test the safety and efficacy of banked allogeneic EBV-specific VSTs used on a best HLA-match basis to treat PTLD. Thirty-three PTLD patients who had failed on conventional therapy were enrolled. Transplant types were as follows: stem cell, 2; heart, 2; kidney, 13; liver, 10; liver and small bowel, 3; lung, 2; heart and lung, 1. The response rate (complete or partial) in 33 patients was 64% at 5 weeks and 52% at 6 months. Fourteen patients achieved a complete remission, 3 showed a partial response, and 16 had no response at 6 months (5 died before completing treatment). The response rate in this poor prognosis patient group were encouraging. No adverse effects of VST infusions were observed; the infusions were well tolerated with no evidence of acute infusion reactions. No adverse effect on the transplanted organ or evidence of VST-host disease was observed. Their results demonstrated that allogeneic VSTs for the treatment of PTLD in SOT recipients was safe and well tolerated.

1.4 ALVR106

ALVR106 is a novel, allogeneic, off-the-shelf, multi-virus specific T cell (VST) therapy for the treatment of respiratory infection caused by RSV, IFV, PIV, and hMPV. ALVR106 is a polyclonal (CD4+ and CD8+) VST product containing cells that are reactive against 4 viruses (RSV, IFV, PIV, and hMPV). Virus specific T cells are generated by exposing peripheral blood mononuclear cells (PBMCs) to peptide mixtures (pepmixes) and cytokines [redacted], in culture medium followed by ex vivo expansion. [redacted]

A bank of VSTs from eligible third-party healthy, pre-screened (for infectious agents and disease risk factors as mandated by Food and Drug Administration [FDA] 21 Code of Federal Regulations [CFR] part 1271, subpart C) donors that have prior exposure to the 4 target viruses

(RSV, IFV, PIV, and hMPV) were generated. These donors were carefully chosen to reflect and accommodate the HLA diversity of the allogeneic HCT population to be enrolled in this study. ALVR106 is cryopreserved for use as a partially HLA-matched "off the shelf" product.

Please reference the Investigator Brochure (IB) for additional information on ALVR106 including:

- Nonclinical Studies

1.4.1 Overview of Nonclinical Studies

AlloVir previously demonstrated that the adoptive transfer of in vitro expanded VSTs can be safely administered to treat infections associated with EBV, CMV, BK virus (BKV), human herpesvirus-6 (HHV-6), and AdV in allogeneic HCT recipients (ALVR105, IND 015092). To determine whether a similar strategy could be applied to treat community-acquired respiratory viruses (CARVs), AlloVir conducted the following studies: 1) explored the cellular immune response directed against RSV, IFV, PIV, and hMPV; 2) assessed the feasibility of expanding T cells reactive against immunodominant antigens within each of the target viruses; 3) performed in vitro characterization studies to assess the effector and safety profile of such cells; and 4) sought evidence that T cell immunity played a protective role by examining the endogenous immune response in allogeneic HCT *recipients* with active infections.

See the Investigator's Brochure for further information regarding the nonclinical studies conducted with ALVR106.

1.5 Overview of Clinical Experience with Similar VST Platforms to ALVR106

No clinical data with ALVR106 is currently available. This study is the first study evaluating ALVR106 in humans.

The use of virus-specific T cells developed using the same platform as ALVR106 has been in the clinic for the treatment of viral infections in immunocompromised patients including HCT and SOT recipients. The below preliminary clinical data offers some guidance on what we would anticipate the safety of ALVR106 to be in HCT and SOT patient populations for the treatment of respiratory viral infection associated with 1 or more of the target viruses.

1.5.1 ALVR109: VST in the Treatment of COVID-19 Lower Respiratory Tract Infection

ALVR109, is an allogeneic, VST targeting SARS-CoV-2 virus. ALVR109 [redacted] cells [redacted] has been administered to 12 immunocompromised patients with lower respiratory tract infection (LRTI) associated with COVID-19 infection.[32] Of the 12 patients, 4 patients were enrolled in a Phase 1 study (IND # 23426) and 8 patients were administered ALVR109 as compassionate use under emergency INDs. Preliminary data was available in 9 LRTI participants (4 Phase 1 patients and 5 compassionate use patients) that had received at least 1 infusion with at least 28 days of follow up post-initial infusion. Of the 9 patients the mean age was 60 y old and 5 were male. The risk factors included: 6 post-transplant patients (1 heart transplant, 2 lung transplants, and 3 bone marrow transplants), 2 patients were >65y old with comorbidities, and 1 patient was pre-transplant with diffuse large B cell lymphoma (DLBCL). A

majority of patients (n=8) had received and failed treatment with remdesivir and corticosteroids, and 6 were receiving supplemental oxygen, with one of these patients being on a ventilator at the time of first ALVR109 infusion. Of the 9 LRTI patients, all showed clinical improvement post-ALVR109 infusion with 8 of 9 achieving suppression of SARS-CoV-2. No patients experienced a treatment-related adverse event. One post-BMT patient experienced cytokine release syndrome (CRS) on Day 13 post infusion but was considered by the investigator to be related to COVID-19 disease progression and not ALVR109. Three LRTI patients died during follow up for reasons related to underlying disease: 1 post-BMT patient showed initial signs of viral decline and clinical improvement before worsening with progression of COVID-19 on Day 26, and ultimately died; 1 patient with DLBCL died due to the cancer, and 1 lung transplant patient died of organ failure. Autopsy of the lung transplant patient showed no evidence of SARS-CoV-2 infection by lung in-situ hybridization (ISH). Overall, the preliminary safety profile has demonstrated VST are generally safe and well tolerated in immunocompromised patients with lower respiratory tract infection and support further evaluation of VSTs for treatment of respiratory tract infection.

1.5.2 Posoleucel (ALVR105): VST in the Treatment of Viral Infection in HCT Patients

To investigate the safety and clinical efficacy of posoleucel, a multivirus-specific T cell product reactive for BKV, AdV, HHV-6, EBV, and CMV generated from third-party, healthy, eligible donors, a Phase 2 clinical study was conducted in recipients of allogeneic HCT with drug-refractory infections with ≥1 of the 6 viruses targeted by posoleucel (patients infected with JCV were also eligible) (Tzannou, 2017). In this open-label study, patients received a single IV infusion of [redacted] HLA-matched posoleucel cells[redacted], with the option to receive a second infusion [redacted] and additional infusions [redacted] thereafter. Therapy with standard antiviral medications could be continued at the discretion of the treating physician.

Of the 82 patients screened for participation in this study, two (2.4%) could not be enrolled due to inability to provide an appropriately HLA-matched posoleucel drug product. A total of 58 patients with persistent and/or refractory virus infections following allogeneic HCT were infused with posoleucel drug products matched at 1 to 6 HLA antigens (the first 38 patients to complete the study are reported in Tzannou et al, 2017). Thirty (n=30) participants were male and 28 (n=28) were female. Participant ages ranged from 2 to 73 years with a mean age of 32.7 years.

Thirty-nine participants (67.2%) each received 1 infusion of posoleucel, 15 (25.9%) received 2 infusions (including one participant who was enrolled twice, each for a different viral infection), and 4 (6.8%) received 3 infusions. All infusions were administered in full. Of the 58 participants who received at least 1 infusion of posoleucel, 46 participants had a single target virus identified at study entry for their initial infusion of posoleucel (including the one participant who was enrolled twice in the study, each time for a single target virus), 11 participants had two, and one participant had three target viruses identified concomitantly at the time of initial infusion of posoleucel. Of the 70 target virus infections confirmed at study entry, 27 (38.6%) infections were BKV, 12 (17.1%) were AdV, 4 (5.7%) were HHV6, 2 (2.9%) were EBV, 1 (1.4%) was JCV, and 24 (34.3%) infections were CMV.

Infusion with posoleucel was generally well tolerated, with an adverse event profile reflective of the underlying clinical status of a patient population that had undergone allogeneic HCT that was subsequently complicated by infection/reactivation by one or more of the viruses targeted by posoleucel (AdV, BKV, CMV, EBV, and HHV6), and/or JCV. None of the patients developed cytokine release syndrome (CRS). Thirteen of 58 (22%) participants were documented with acute GVHD within 42 days of their last VST infusion; the majority of these were mild and resolved, and 1 of these (1.7% of all 58 participants) developed acute GVHD Grade III, the only participant with an acute GVHD severity exceeding Grade II, a primary safety endpoint. Seven of the 36 (19%) participants with chronic GVHD assessments recorded were diagnosed with chronic GVHD at 3, 6, and/or 12 months after infusion of posoleucel. These rates are consistent with the expected published incidence of acute and chronic GVHD in this patient population.[33]

The antiviral efficacy of posoleucel was demonstrated by the high proportion of participants with persistent and/or refractory viral infections that achieved a clinical antiviral response to posoleucel infusion. Of the 46 participants with a single target virus at study entry, 45 (97.8%) were reported to have either a partial response, PR (37/45, 82.2%) or complete response, CR (8/45, 17.8%) at the 6-week assessment after their initial infusion of posoleucel. Of the 12 participants with more than 1 target virus identified concomitantly at study entry, 10 (83.3%) were reported to have either a PR or CR for all evaluable target viruses at the 6-week assessment after their initial infusion of posoleucel. Taken together, 55 of all 58 participants (94.8%) experienced a PR or CR by the 6-week assessment after their initial infusion of posoleucel.

Overall, this study supports the feasible, safe, and effective use of posoleucel, a partially HLA-matched, allogeneic, banked VST cell product for the treatment of clinically important viral infections in the hematopoietic cell transplant recipient population.

1.5.3 Posoleucel: VSTs in the Treatment of Viral Infection in SOT Patients

This ongoing Phase 2 randomized, placebo-controlled, proof-of-concept study evaluating the safety, tolerability and effectiveness of posoleucel (ALVR105) to treat BK viremia in kidney transplant recipients. The study consists of 3 blinded treatment arms:

- [redacted]
- [redacted]
- [redacted]

Blinded preliminary safety data review from this ongoing study was available in 37 participants that have been randomized and received at least 1 infusion with a median follow up of 41 days. There have been 12 adverse events considered treatment related by the investigator: headache

(n=6), chills (n=3), nausea (n=2), and dizziness (n=1); all were Grade 1 (mild) in severity. There have been no SAEs, deaths, or early treatment discontinuations reported. No AE of special interest (e.g. cytokine release syndrome (CRS), infusion related reactions (IRR) or acute/chronic GvHD) have been reported and no adverse effect on the transplanted organ or evidence of VST versus host disease has been observed to date. The safety profile to date is consistent with other published studies that have demonstrated VST are safe and well tolerated in SOT patients.

Overall, the preliminary safety data in this Phase 2 study which demonstrates the lack of VST versus host disease, acute GVHD, and CRS, to date, supports the safe use of VSTs to target viral infection in a transplanted organ and in SOT patients in general.

1.6 Rationale

Community acquired respiratory viruses are a significant cause of morbidity and mortality among immunocompromised transplant (e.g. HCT and SOT) recipients. Effective therapies are available only for IFV, and also to some extent for RSV infection, but no options exist for hMPV or PIV. Even with the current IFV options, immunocompromised patients are at increased risk of developing drug resistant IFV infections due to the increase in viral replication and shedding that occurs in the absence of an immune response. Preventive measures are also lacking, as vaccination is only available against IFV at this time. Given the severe implications respiratory viral infections have on the immunocompromised population, development of new treatment options is needed.

In healthy individuals, T cell immunity defends against RSV, IFV, PIV, and hMPV. In HCT and SOT recipients, the delay in immune reconstitution post HCT and the use of potent immunosuppressive regimens to prevent GvHD or organ rejection leaves patients susceptible to severe viral infections. Co-infections in the context of immunocompromised HCT or SOT recipients can occur and there exists a significant unmet need for new cellular therapy to address these infections.[34]

AlloVir's approach is to restore T cell immunity by the administration of ex vivo expanded, non-genetically modified VSTs that may control viral infections and alleviate/eliminate symptoms until the transplant patient's innate immunity is restored. To achieve this goal, AlloVir will use VSTs manufactured from PBMCs procured from healthy, pre-screened (for infectious agents and disease risk factors as mandated by FDA 21 CFR part 1271, subpart C) donors that have had prior exposure to the 4 target viruses (RSV, IFV, PIV, and hMPV). These VSTs will be available as a partially HLA-matched "off the shelf" product.

The aim of this two-part study is to evaluate the safety and tolerability of ascending doses of ALVR106 in combination with the current standard of care for the treatment of RTI in immunocompromised patients (Part A) and the antiviral activity of a selected ALVR106 dose in an expansion cohort (Part B). This study will enroll both HCT and SOT immunocompromised patient populations. Treatment response to ALVR106 in HCT and SOT immunocompromised patients with RTI is not anticipated to be impacted by the type of transplant a patient had undergone prior to enrollment. Preclinical data has demonstrated that ALVR106 consists of CD4+ and CD8+ memory T cells targeting the 4 respiratory viruses. Stimulation of ALVR106 in the presence of antigen would lead to a virus specific immune response and not a generalized immune response, lowering the risk of off-target effects in transplant patients, including risks of organ rejection, graft versus host disease, and cytokine release syndrome. Current data in VSTs (Section 1.5, posoleucel

and ALVR109) would support the use of ALVR106 VSTs in immunocompromised patients after HCT or SOT for treatment of RTI.

1.7 Risk/Benefit

1.7.1 Potential Risks

ALVR106 specifically targets cells infected with RSV, IFV, PIV, and/or hMPV. The main potential risks of administration are enhanced inflammation at sites of viral infection and graft versus host disease (GVHD) due to cross reactivity with alloantigens in HCT recipients. Adverse events attributable to VST administration may potentially occur in a small percentage of the treated population. These can include both hematologic and non-hematologic effects, as reported in the CHARMS clinical study, in which ALVR105 (a multivirus-specific T cell product reactive for BKV, AdV, HHV-6, EBV, and CMV) was administered to allogeneic HCT recipients with drug-refractory infections with ≥1 of the 5 target viruses.[35]

The risk that adoptively transferred partially HLA-matched ALVR106 will cause Grade 2 or higher acute GVHD has been demonstrated to be low, according to data from previous studies with third party multivirus-specific T cells. If any patient develops GVHD, that patient will receive standard GVHD treatment at the discretion of the Investigator. The risk that adoptively transferred VST can cause VST versus host disease in SOT patients is low as the VST will target only target virus infected cells. As stated above, there have been no cases of GVHD in 37 kidney transplant patients with BK viremia administered up to 8 doses of posoleucel (ALVR105).

Studies of donor-derived VSTs suggest that VSTs do not persist in patients who receive methylprednisolone in doses of ≥1 mg/kg. Therefore, if patients develop severe inflammatory reactions thought to be attributable to ALVR106, a therapeutic option is to administer methylprednisolone (1 to 2 mg/kg). In patients who develop skin rash or skin GVHD, excellent responses have been seen with administration of topical steroids.

Cytokine release syndrome (CRS) is the most common serious complication arising from infusion of chimeric antigen receptor (CAR) T cells; however, the infused T cells in this study do not express a CAR and are not genetically modified. Thus, the risk of CRS is low. However, case reports of CRS with VSTs have been reported in the setting of bulky EBV disease.[23] Therefore, CRS remains a theoretical possibility, at least in patients who are infected with EBV and have expansive disease. To ensure that any potential cases of CRS are discovered in a timely manner, CRS has been included as an AE of special interest. Patients will be closely monitored for signs or symptoms of CRS, which include constitutional symptoms (fever, rigors, headache, malaise, fatigue, nausea, vomiting, and arthralgia), vascular (hypotension), cardiac (arrhythmia), respiratory compromise, renal (kidney failure and uremia), and laboratory (including coagulopathy and a hemophagocytic lymphohistiocytosis-like syndrome). The development of CRS of any grade will necessitate urgent medical assessment and immediate notification of the Medical Monitor.

Multiple reports have established that IL-6 is a key cytokine involved in severe cytokine release syndrome (sCRS). Infusion of tocilizumab (an IL-6R monoclonal antibody) has rapidly eradicated symptoms of sCRS. The established dose of tocilizumab for treatment of CRS is 8 mg/kg intravenously (IV) infused over 1 hour for children and adults (maximum single dose of 800 mg). A lower dose can be administered at the discretion of the physicians caring for the patient. Doses can be repeated if symptoms are not improved within 12 to 24 hours.

Possible side effects of infusion include allergic reaction (anaphylaxis), decreased oxygenation, nausea/vomiting, arrhythmia, and hypertension.

1.7.2 Potential Benefits

A serious unmet medical need exists for immunocompromised patients experiencing viral infections following HCT or SOT. Community acquired respiratory viral infections involving IFV, RSV, PIV, and hMPV have been attributed to mortality caused by progression to lower respiratory tract infection (LRTI) such as pneumonia and bronchiolitis in immunocompromised HCT and SOT patients, and specific to lung transplant recipients, bronchiolitis obliterans syndrome (BOS) or chronic lung allograft dysfunction (CLAD).[4,36,37] With changes in transplant practices, their severity is increasing and the timeframe when patients are subjected to potentially fatal infections has expanded. Mortality from these infections can be as high as 23% to 50% for HCT patients with pneumonitis. In SOT, especially lung transplant recipients, mortality rates due to progression to LRTI are as high as 20%.[38] ALVR106 has the potential to address such a serious unmet medical need.

The nonclinical data have shown that it is feasible to generate a single preparation of polyclonal multi-respiratory VSTs with specificities directed to IFV, RSV, PIV, and hMPV in clinically relevant numbers using Good Manufacturing Practice compliant methodologies. These results support the clinical importance of T cell immunity in mediating protective antiviral effects against CARVs and demonstrate the feasibility of utilizing a broad-spectrum immunotherapeutic in immunocompromised patients with uncontrolled infections. Such a broad-spectrum immunotherapeutic may provide an important treatment benefit to immunocompromised individuals suffering from respiratory infections.

2 STUDY OBJECTIVES

2.1 Part A (Dose Escalation)

2.1.1 Primary Objective

The primary objective of Part A is to determine the safety and tolerability of ascending doses of ALVR106 when administered to high-risk adult patients with upper respiratory tract infections (URTIs) caused by RSV, IFV, hMPV, and/or PIV following HCT or SOT.

2.1.2 Secondary Objectives

The secondary objectives of Part A are the following:

- To identify the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of ALVR106 in patients with URTIs
- To characterize the individual patient antiviral response as measured by change in viral load from nasal swab specimens from baseline through Day 28 following the patient's first ALVR106 infusion

2.1.3 Exploratory Objectives

The exploratory objectives of Part A are the following:

- To characterize the individual patient antiviral response as measured by change in viral load from nasal swab specimens from baseline through Day 60 following the patient's first ALVR106 infusion
- To describe the individual patient antiviral response as measured by the percent change in viremia from baseline through Day 28 and Day 60 following the patient's first ALVR106 infusion
- To assess the effect of ALVR106 on time to resolution of viremia.
- To assess the effect of ALVR106 on target viral reinfection.
- To determine improvement and resolution of clinical symptoms of URTI following the patient's first ALVR106 infusion
- To determine the proportion of patients with progression from URTI to LRTI or worsening LRTI as defined by new onset LRTI symptoms (eg, shortness of breath, fever, fatigue, coughing, chest discomfort, production of mucus, coarse crackles) and either a sustained oxygen saturation <90% while breathing ambient air at rest, or new findings on chest X-rays and/or CT scans suggestive of progressive lung involvement.
- To describe overall and LRTI-related mortality in adult patients treated with ALVR106
- To determine the duration of oxygen dependency, defined as the inability to maintain an oxygen saturation ≥90% in the absence of supplemental oxygen, in adult patients treated with ALVR106
- To determine viral genotypic changes from baseline associated with single and/or multiple infusions of ALVR106, when applicable

- To assess the effect of ALVR106 for resolution, improvement, stability, or progression of LRTI as measured by imaging

2.2 Part B (Recommended Phase 2 Dose Cohort Expansion)

2.2.1 Primary Objective

The primary objective of Part B is to determine the antiviral activity of the RP2D of ALVR106, as compared to placebo, when administered to high-risk adult patients with URTIs caused by RSV, IFV, hMPV, and/or PIV following HCT or SOT.

2.2.2 Secondary Objectives

The secondary objectives of Part B are the following:

- To determine the safety and tolerability of the RP2D of ALVR106 when administered to high-risk adult patients with URTIs caused by RSV, IFV, hMPV, and/or PIV following HCT or SOT
- To characterize the individual patient antiviral response as measured by the percent reduction in viral load from nasal swab specimens and a reduction in clinical signs and symptoms from baseline through Day 28, Day 60, Day 90, and Month 6 following the patient's first ALVR106 infusion

2.2.3 Exploratory Objectives

The exploratory objectives of Part B are the following:

- To characterize the individual patient antiviral response as measured by the percent change in viremia from baseline through Day 28, Day 60, and Month 6 following the patient's first ALVR106 infusion
- To assess the effect of ALVR106 on time to resolution of viremia.
- To assess the effect of ALVR106 on target viral reinfection.
- To determine viral genotypic changes from baseline associated with single and/or multiple infusions of ALVR106, when applicable
- To determine improvement and resolution of clinical symptoms of URTI following the patient's first ALVR106 infusion
- To determine the proportion of patients with progression from URTI to LRTI or worsening LRTI as defined by new onset LRTI symptoms (eg, shortness of breath, fever, fatigue, coughing, chest discomfort, production of mucus, coarse crackles) and either a sustained oxygen saturation <90% while breathing ambient air at rest, or new findings on chest X-rays and/or CT scans suggestive of progressive lung involvement.
- To describe overall and LRTI-related mortality in adult patients treated with ALVR106
- To assess long-term safety of ALVR106 through Day 365

- To determine the duration of oxygen dependency, defined as the inability to maintain an oxygen saturation ≥90% in the absence of supplemental oxygen, in adult patients treated with ALVR106
- To assess the effect of ALVR106 for resolution, improvement, stability, or progression to LRTI as measured by imaging

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 1/2, double-blind, placebo-controlled, dose escalation and expansion study to assess the safety and dose selection of ALVR106 in addition to standard of care for the treatment of high-risk patients with RTIs and clinical manifestations caused by RSV, IFV, hMPV, and/or PIV following transplant. This study will be conducted in 2 parts:

- Part A (Dose Escalation)
- Part B (RP2D Cohort Expansion)

Throughout the study, all patients may receive standard of care as determined by the Investigator (or designee). Reference Protocol Section 5.7 for additional information on concomitant medications.

The specific ALVR106 drug product for infusion selected for each participant will be determined by an electronic software system (CytoMatch™) based on the [redacted]

Reference the JUDI Manual for additional details.

During the study, the severity of adverse events will be graded by the Investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All hospitalizations, intensive care unit (ICU) admissions and SAEs will be reported and will be assessed as to whether caused by the RTI.

Changes in patient reported respiratory status will be captured in the patient reported respiratory clinical symptoms form (reference Appendix D) and not as adverse events. A new diagnosis of lower respiratory tract infection (LRTI) will be captured as an AE. Any respiratory events which meet SAE criteria will be captured as both an AE and SAEs. Respiratory status with imaging will be assessed by the investigator and graded using the Radiation Therapy Oncology Group Lung Toxicity Scale presented in Table 2.

Table 1. Radiation Therapy Oncology Group Lung Toxicity Scale

Organ Tissue	0	Grade 1	Grade 2	Grade 3	Grade 4
Lung	**None**	**Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances**	**Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances**	**Severe symptomatic fibrosis or pneumonitis Dense radiographic changes**	**Severe respiratory insufficiency/ Continuous oxygen/ Assisted ventilation**

An independent Safety Review Committee (SRC) will be convened for this study to routinely monitor safety in a blinded fashion, unless the SRC makes a specific request for individual patient unblinding. Further details can be found in the SRC Charter.

Figure 1 provides a summary of the study design.

Figure 1. Summary of Study Design

3.1.1 Part A (Dose Escalation)

Part A will include up to 4 cohorts, with 4 high-risk adult patients per cohort (potentially expanding to 8 patients per cohort), randomized in a [redacted] ratio to ALVR106 or placebo in a double-blind fashion. Patients in each cohort will receive an infusion of ALVR106 cells or placebo on Day 1 and will return to the clinical site for assessment on Days 3, 7, 10, and 14 or more frequently as determined by the patient's clinical condition at the discretion of the Investigator and in collaboration with the Medical Monitor.

Administration of the [redacted] dose will be based on [redacted] visit assessments (reference Sections 5.1 and 5.6.3 for additional information on dose administration).

Follow-up visits will occur at Day 28 (Week 4), Day 60 (Week 8), Day 180 (Month 6), and Day 365 (Month 12) following the patient's first study treatment infusion. All patients will follow the same schedule of follow-up visits, including any patients who receive a partial infusion (less than the recommended dose for the patient).

The planned doses for Cohorts 1 through 4 are presented in Table 2. Intra-patient dose escalation is not permitted.

Table 2. Planned Doses for Cohorts 1 Through 4

Dose Cohort	ALVR106 Dose Level
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]

In the event of toxicity at a planned dose, the doses may be de-escalated, based on recommendations from the SRC, to an interpolated intermediate dose from the planned cohorts as presented below.

Intermediate Doses

Dose Cohort	ALVR106 Dose Level
Toxicity adjusted dose between Dose Cohort 1 and 2	[redacted]
Toxicity adjusted dose between Dose Cohort 2 and 3	[redacted]

For each dosing cohort in Part A, the SRC will review the safety and available efficacy data after the first two patients have completed at least 7 days of safety monitoring following the initial dose. No additional patients will be dosed until that review is completed. Once review of the first two patients is complete (and the SRC has endorsed continuation of the study) the study enrollment of the remaining patients in the cohort will continue.

At least one week after the last patient's first dose in each cohort, the SRC will convene to assess blinded safety data from the current cohort and, if applicable, previous cohorts. This will allow for a consolidated safety review, with patients within the cohort averaging at least 14 days post the last dose.

Dose escalation will proceed to identify the maximum tolerated dose (MTD) within the planned dose range and a recommended Phase 2 dose (RP2D) that may be the MTD or a lower dose within the tested dose range.

Based on routine safety reviews, the SRC may recommend escalating the dose as planned, recommend an intermediate dose, recommend expansion of the current cohort, recommend stopping dose escalation (Part A), or stop the study. In the event of cohort expansion, up to 4 additional patients may be enrolled and randomized in a [redacted] ratio to ALVR106 or placebo. In addition, the SRC will make a recommendation for the RP2D and starting enrollment of Part B. The Sponsor will determine the final RP2D based on SRC recommendation and after review of all available relevant safety data through at least Day 28 following the first ALVR106 or placebo infusion. Reference the SRC Charter for additional information.

3.1.2 Part B (Recommended Phase 2 Dose Cohort Expansion)

Following the determination of the RP2D in Part A, based on review of safety and efficacy data, approximately 45 high-risk adult patients with URTIs will be randomized in a [redacted] ratio to ALVR106 or placebo in a double-blind fashion.

Patients in the ALVR106 group will receive an infusion of the RP2D as determined in Part A. Patients will receive an infusion of ALVR106 cells or placebo on Day 1 and will return to the clinical site for assessment on Days 3, 7, 10, and 14.

Administration of the [redacted] visit assessments (reference Section 5.6.3 for additional information on dose administration).

Additional follow-up visits will occur at Day 28 (Week 4), Day 60 (Week 8), Day 90 (Month 3) Part B only, Day 180 (Month 6), and Day 365 (Month 12). All patients will follow the same schedule of follow-up visits, including any patients who receive a partial infusion (less than the recommended dose for the patient).

The SRC will continue to routinely monitor safety in the expansion cohort. Further details can be found in the SRC Charter.

3.2 Dose-Limiting Toxicity

DLTs are defined as treatment-related Grade ≥3 SAEs and/or Grade ≥3 adverse event of special interest (AESI) that emerge or worsen during the study. Treatment-related AEs are those that cannot be reasonably attributed to the patient's underlying disease, other medical condition, or concomitant medications.

The AESI for this study are included in Section 7.2.4.

3.3 Stopping Rules

Stopping rules for Parts A and B are defined as

A patient with a DLT which is a Grade ≥3 SAE or a Grade ≥3 AESI that emerges or worsens during the study period following the patient's initial dose and cannot be reasonably attributed to the patient's underlying disease, other medical condition, or concomitant medications. The study enrollment would pause to allow time for a safety review by the SRC.

Focusing on AESI will provide further assurance that emergent safety issues are identified promptly. The AESI for this study were selected based on the need to identify potential worsening in the underlying disease being targeted, as well as theoretical complications of VSTs.

The AESI for this study are included in Section 7.2.4.

The SRC will consist of an independent Chairperson and two additional independent experts in the field, at least one of the members will be a transplant physician and at least one member will be an infectious disease expert. In addition, an unblinded statistician (responsible for generating and submitting unblinded data of individual adverse events to the SRC upon request) will also be members of the SRC.

The SRC will meet at least every 2 weeks to review emerging safety data and will conduct both open and closed meetings. Should any safety issues require review by the SRC, an emergency

meeting will be scheduled within 72 hours. Should a death occur in the study that is considered to be definitely or probably related to the study product by the Investigator, the SRC will meet on an urgent basis, within 72 hours, to review the data available and make an assessment. Further dosing will be stopped until the SRC makes an assessment.

The SRC will also convene following any Grade 4 or 5 SAE, irrespective of relatedness, or a Grade ≥3 SAE that may possibly, probably, or definitely be related to study treatment.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Willing and able to provide written informed consent to participate in the study.
2. Aged 17 to 75 years at screening.
3. Undergone hematopoietic cell (HCT) or solid organ (SOT) transplantation.
    a. HCT must have been performed ≥21 days prior to study treatment administration and demonstrated engraftment with an absolute neutrophil count >500/μL.
    b. SOT includes kidney, liver, heart, lung, pancreas, and/or intestines must have been performed ≥28 days prior to study treatment administration. Other SOT that requires immunosuppression to prevent organ rejection may be allowed with medical monitor approval.
4. Detection of at least 1 target virus of interest (ie, RSV, IFV, hMPV, and/or PIV) in the respiratory tract obtained by nasal swab. For Screening, a local laboratory result obtained ≤3 days before or during the screening period will be acceptable for eligibility determination in place of a central laboratory result. However, a baseline central nasal swab sample must be collected and submitted to the central laboratory prior to dosing on Day 1 for all eligible patients.
5. Has at least 1 suitably matched ALVR106 drug product for infusion available. HLA Class I and II typing can be obtained during Screening.

    Note: If an ALVR106 drug product is not available, demographic data and HLA type will be collected.
6. Diagnosis of respiratory tract infection, defined as new onset of at least 1 of the following respiratory symptoms prior to screening: nasal congestion, runny nose, cough, or sore throat, or worsening of 1 of these chronic respiratory symptoms (associated with a previously existing diagnosis, eg, chronic rhinorrhea, seasonal allergies, or chronic lung disease). Sign(s) or symptom(s) of respiratory tract infection must be present at the time of initial study drug administration on Day 1.
7. Immunocompromised HCT or SOT patients considered by the investigator to be at high risk of viral respiratory disease progression. High risk may be determined based on the HCT transplant type (e.g. haploidentical donor, unrelated donor, undergone cord blood HCT, or ex vivo HCT graft manipulation), delay in immune reconstitution in HCT patients (e.g. lymphocyte count <180/mm^3 or CD4 T cell count <50/mm^3), time from transplant (e.g. <100 days from transplant), and/or immunosuppressive regimens required post-transplant.
8. A negative serum pregnancy test for female patients of childbearing potential.
9. Female patients of childbearing potential and male patients with female partners must agree to use an effective contraceptive method during the study and for a minimum of 90 days after study treatment.

Note: A female is considered to be of "childbearing potential" if she has experienced menarche and is not permanently sterile or postmenopausal (postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause).

Note: In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention), defined as a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; however, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

4.2 Exclusion Criteria

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

1. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day) within 7 days prior to screening.
2. Prior therapy with abatacept or belatacept, within 3 months prior to screening; or antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies within 28 days prior to study treatment administration.
3. Infection with novel coronavirus disease 2019 (COVID-19) defined as positive antigen or detectable PCR result within 28 days prior to study treatment administration
4. Significant hypoxemia (ie, oxygen saturation <90% while breathing ambient air at rest)
5. Requirement for continuous infusions of inotropes or vasopressors for blood pressure support
6. Systolic Blood Pressure <90 mmHg, except for patients with normal resting SBP <90 mmHg confirmed by investigator
7. Requirement for mechanical ventilation or noninvasive ventilation
8. Resting respiratory rate ≥30 breaths/min
9. Evidence of encephalopathy or confusion
10. For HCT or non-lung SOT, chest X-ray and/or CT scan with multifocal consolidation or diffuse alveolar consolidation. For lung transplant recipients, any new abnormalities on a chest X-ray and/or CT scan, other than patchy atelectasis, hyperinflation, and/or bronchial wall thickening[39], caused by LRTI. Images obtained within 3 days of screening will be acceptable to determine eligibility. All chest X-rays and/or CT scans will also be submitted for central reading, which will be used for analysis purposes.
11. For HCT patients, evidence of Grade >2 acute GVHD; and for SOT patients, any history or evidence of GVHD (see Appendix B).
12. For SOT patients, ABO incompatible or complement-dependent lymphocytotoxic crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion)
13. Presence of uncontrolled or progressive bacterial or fungal infections (ie, evidence of bacteremia, fungemia, disseminated, and/or organ-specific infection not well controlled by present therapies).

14. Presence of progressive, uncontrolled viral infections not targeted by ALVR106 with evidence of end organ disease.
15. Known or presumed non-viral pneumonia or sinusitis secondary to any organism.
16. Known history or current (suspected) diagnosis of CRS associated with the administration of peptides, proteins, and/or antibodies.
17. Receipt of any investigational agents, including antiviral treatment (not ALVR106 or placebo) targeting RSV, IFV, PIV, and/or hMPV, from 28 days or 5 half-lives (whichever is longer) prior to study treatment administration, unless approved by Medical Monitor.
18. Donor lymphocyte infusion or other T cell therapies performed <21 days prior to study treatment administration.
19. 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.
20. Renal dysfunction, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or require ongoing dialysis and/or renal replacement therapy at screening
21. Relapse of primary malignancy other than minimal residual disease.
22. Pregnant, breastfeeding, or planning to become pregnant during the study.
23. Significant underlying lung disease that confounds the assessment of the URTI or LRTI episode or any condition that, in the opinion of the Investigator, would prevent full participation in this study or would interfere with the evaluation of any study endpoints.

4.3 Eligibility Confirmation

Patients may receive up to 2 doses of study treatment. On Day 1, prior to dosing, the following eligibility criteria must be assessed. Patients who meet any of the following criteria on Day 1 will be excluded from participation in the study:

1. No sign(s) or symptom(s) of respiratory tract infection present at the time of initial study drug administration.
2. Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day).
3. For HCT patients, evidence of Grade >2 acute GVHD; and for SOT patients, evidence of any GVHD (see Appendix B)
4. Receipt of any investigational agents, including antiviral treatment (not ALVR106 or placebo) targeting RSV, IFV, PIV, and/or hMPV, not approved by Medical Monitor

Prior to administration of the second dose, the following criteria must be assessed by the Investigator:

1. Last available viral load result from nasal swab specimens analyzed at central lab
2. Clinical status, specifically respiratory symptoms
3. Last available imaging
4. Evidence of GVHD and grade

If needed, Investigator should contact the Medical Monitor to discuss patient's status.

4.4 Withdrawal Criteria

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 study treatment 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 receive additional study treatment
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued receipt of study treatment is not in the best interest of the patient
- Pregnancy
- Requirement of 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 a patient discontinues from the study early, before the Month 12 visit, due to the above criteria or any other reason, the patient should return to complete all assessments in the Month 12/early termination visit. If patient is not able to return to the site to complete the early termination visit, all efforts will be made to gather available information via a phone call.

The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

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

Withdrawn patients due to AE will not be replaced.

4.5 Screen Failures

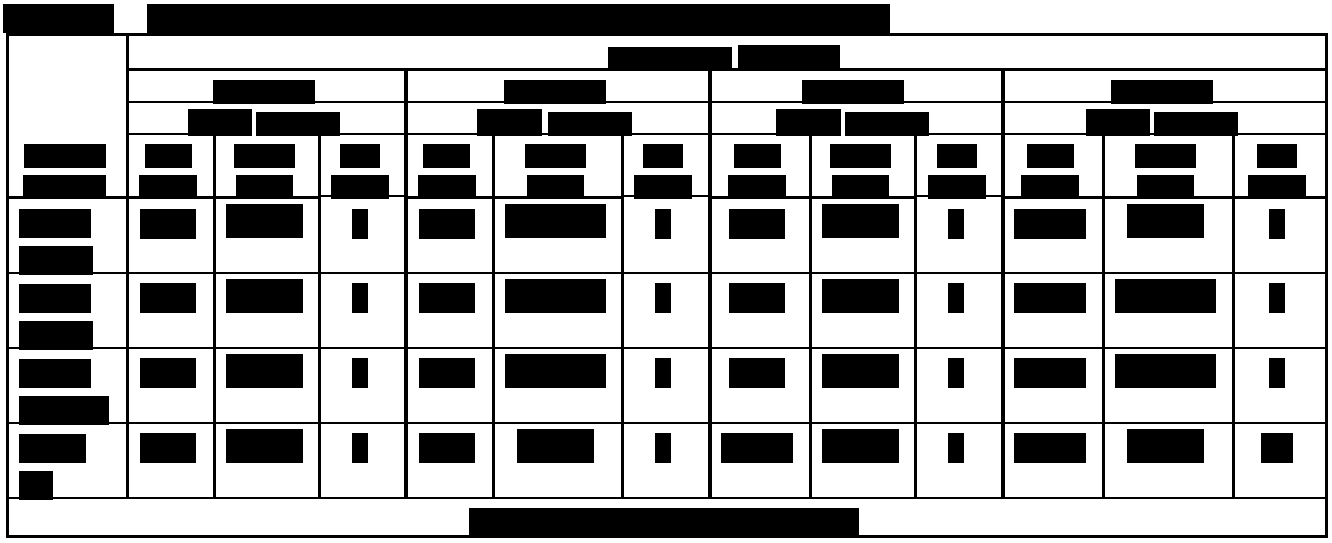
Screen failures are defined as participants who consent to participate in the clinical study but are not randomized into the clinical study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5 STUDY TREATMENTS

5.1 Treatment Groups

For Part A, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled and randomized in a 3:1 ratio to ALVR106 or placebo in a double-blind fashion. In a similar fashion, patients in Part B will be enrolled and randomized in a 2:1 ratio. The planned doses for Part A (dose escalation) are listed in Table 2. For Part B, ALVR106 will be administered at the RP2D as determined in Part A. The dosage in this study will be on a bracket-based per kg basis, as per Table 3.

All patients will receive an infusion of ALVR106 cells or placebo on Day 1 and may receive additional infusions of blinded study treatment as detailed in Section 5.6.3.



In the event of toxicity at a planned dose, the doses may be de-escalated, based on recommendations from the SRC, to an interpolated intermediate dose from the planned cohorts as presented below.

5.2 Cohort Progression and Dose Escalation

For each dosing cohort in Part A, the SRC will review the safety and available efficacy data after the first two patient have completed at least 7 days of safety monitoring following the initial dose. No additional patients will be dosed until that review is completed. Once review of the first two patients is complete (and the SRC has endorsed continuation of the study) the enrollment of the remaining patients in the cohort will continue.

At least one week after the last patient's first dose in each cohort, the SRC will convene to assess blinded safety data from the current cohort and, if applicable, previous cohorts. This will allow for a consolidated safety review, with patients within the cohort averaging at least 14 days post the last dose.

The SRC may recommend escalating the dose as planned, recommend an intermediate dose, recommend expansion of the current cohort, recommend stopping dose escalation, or recommend stopping the study. In the event of cohort expansion, up to 4 additional patients may be enrolled and randomized in a [redacted] ratio to ALVR106 or placebo. Further details can be found in the SRC Charter.

Dose escalation will proceed to identify the MTD within the planned dose range and, for Part A, an RP2D that may be the MTD or a lower dose within the tested dose range.

5.3 Rationale for Dosing

The starting dose was chosen based on 1) previous human experience using adoptively-transferred donor-derived T cells[18,19,20,23] and third-party–derived VSTs and 2) clinical precedent established using donor leukocyte infusions in the haploidentical stem cell transplant setting.

Patients will receive no more than [redacted] doses in total. Patients that demonstrated improvement following the first dose but not resolution will receive the [redacted]. [redacted] dose for patients that did not demonstrate improvement following the first dose. Data collected in real-time will be analyzed to monitor safety of ascending doses cumulatively. Should there be untoward effects of any of the doses, subsequent doses would not be administered to that patient. This is a first-in-man study, so the rationale for this dosing schema is derived from prior experience with other VSTs.

5.4 Randomization and Blinding

For Part A, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled and randomized in a [redacted] ratio to ALVR106 or placebo in a double-blind fashion. In a similar fashion, patients in Part B will be enrolled and randomized in a [redacted] ratio. Randomization assignments will be performed by the Interactive Response Technology (IRT) system.

The Sponsor designee (ie, IRT vendor) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind integrity is properly maintained. Care should be exercised to ensure that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in SAE reporting). Randomization information will be concealed from the Investigators and the

patients until the end of the study, with the exception of an emergency situation involving a patient who requires unblinding of the treatment assignment.

5.5 Breaking the Blind at Investigational Sites

Unblinding should only occur in the event of an emergency or adverse event for which it is necessary to know the study treatment to determine an appropriate course of therapy. If possible, the Investigator should attempt to contact the site monitor or the Medical Monitor prior to unblinding in order to obtain additional information about the study treatment. If not possible, the Investigator should notify the site monitor or Medical Monitor as soon as possible of the unblinding without disclosing the treatment assignment of the unblinded patient.

If the patient's study treatment must be unblinded, the Investigator or qualified designee should contact IRT for the study treatment information. The IRT documentation indicating the blind break at the site must be retained with the patient's source documentation in such a way as to avoid unblinding the treatment assignment to other site- or Sponsor-blinded personnel. The Investigator must document the patient's identification, reason for breaking the blind, and the date and time of breaking the blind.

5.6 Drug Supplies

5.6.1 Formulation and Packaging

ALVR106 is a third-party, donor-derived, "off-the-shelf" VST product with specificity for RSV, IFV, PIV, and hMPV. ALVR106 drug products will be checked for identity, phenotype, and sterility. The final product will be cryopreserved and ready for immediate use.

ALVR106 drug product is cryopreserved under controlled rate conditions in cryovials and stored in the vapor phase of liquid nitrogen. Drug product vials will be [redacted].

Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance to ALVR106. Cryopreservation media contains [redacted]

5.6.2 Study Treatment Preparation and Dispensing

ALVR106 (or placebo) will be supplied in a cryovial which is to be transported from vapor phase liquid nitrogen storage at the Current Good Manufacturing Practice BioStorage facility to the site of infusion location in a liquid nitrogen dewar or other suitable container. No additional preparation is required.

5.6.3 Study Treatment Administration

The specific ALVR106 drug product for infusion selected for each participant will be determined by an electronic software system (CytoMatch™) based on the [redacted]
Reference the JUDI Manual for additional details.

For detailed instructions on ALVR106 or matching placebo administration reference the Cell Therapy Manual and Section 5.1 above for Part A, weight range-based dose to be administered.

All eligible participants will be randomized to receive:

ALVR106 cells or matching placebo administered IV over approximately [redacted] minutes as a slow push on [redacted] if applicable.

Administration of the [redacted] visit assessments, as follows:

- Patients who have demonstrated an initial objective clinical response, and a decrease in viral load defined by at least 50% reduction of viral load in nasal swab, [redacted], if available.
- Patients who have not demonstrated either clinical improvement or decrease in viral load in nasal swab following the first dose will receive [redacted]. If another partially HLA-matched drug product is not available, they will receive the same initial partially HLA-matched drug product or placebo.
- Patients who have fully recovered will not receive [redacted] Full recovery is defined as undetectable viral load in nasal swab by qPCR post first study treatment infusion, absence of respiratory symptoms, and, as applicable, normalization of imaging.
- Patients who have experienced new onset of systemic GVHD (HCT and SOT patients), a Grade ≥3 worsening of GVHD (HCT patients) or Grade ≥3 infusion related reaction will not receive [redacted]

Premedication can be administered to any participant at the investigators discretion but is not required, except for patients with a prior history of reaction to blood products (reference Section 5.7.2 for premedication options).

Post-infusion monitoring will be performed as indicated in Section 7.14.

5.6.4 Treatment Compliance

ALVR106 (or placebo) will be administered IV and under the supervision of clinical study personnel at the site.

5.6.5 Storage and Accountability

ALVR106 will be stored in the vapor phase of liquid nitrogen in a continuously monitored storage freezer.

All material containing ALVR106 will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

ALVR106 accountability is the responsibility of the Principal Investigator and Sponsor. However, this responsibility may be delegated to a suitably qualified Investigator.

Detailed records will be maintained to allow for accurate accountability of ALVR106. For further details and specifications, see the Study Investigational Medicinal Product Manual.

5.7 Prior and Concomitant Medications and/or Procedures

5.7.1 Excluded Medications and/or Procedures

The following medications and/or procedures are prohibited as specified below or from Screening, and through study Week 24:

- Ongoing therapy with high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day) from 7 days prior to screening
- Prior therapy with abatacept or belatacept, from 3 months prior to screening; or antithymocyte globulin, alemtuzumab (Campath-1H), or other immunosuppressive T cell-targeted monoclonal antibodies from 28 days prior to study treatment administration
- Receipt of any investigational agents, including antiviral treatment (not ALVR106 or placebo) targeting RSV, IFV, PIV, and/or hMPV, from 28 days or 5 half-lives (whichever is longer) prior to study treatment administration, unless approved by Medical Monitor.
- Donor lymphocyte infusion or other T cell therapies performed <21 days prior to study treatment administration
- Mechanical ventilation of any type within 1 month or noninvasive ventilation during screening prior to the administration of ALVR106
- Ongoing dialysis and/or requirement for renal replacement therapy at screening

5.7.2 Permitted Medications and/or Procedures

The following medications and/or procedures are permitted:

- Throughout the study, all patients may receive standard of care as determined by the Investigator (or designee). This may include antivirals targeting RSV (eg, oral, IV, or inhaled ribavirin), IFV (eg, oseltamivir, zanamivir, peramivir, baloxavir), hMPV, and/or PIV, as well as other viruses; polyclonal IV immunoglobulin; antibiotics; or antifungals; in addition to standard of care treatment for the patient's underlying disease (eg, immunosuppressants), which should be kept as stable as possible during the study. However, as noted in the exclusion criteria, the dose of systemic corticosteroids may not exceed a prednisone equivalent dose of 0.5 mg/kg/day.
- If respiratory exacerbation not related to bacterial or fungal infections and requiring systemic corticosteroids is observed, then high-dose systemic corticosteroids (ie, prednisone equivalent dose >0.5 mg/kg/day) may be initiated at the Investigator's discretion. If acute GVHD Grade 3 or 4 is observed, a standard protocol will be followed per the site (see Appendix B). If CRS is observed, a standard protocol will be followed per the site (see Appendix C).
- Premedication can be administered to any participant at the investigators discretion but is not required, except for patients with a prior history of reaction to blood products who will receive premedication with 0.25 to 0.5 mg/kg (maximum dose of 25 mg) diphenhydramine (IV or oral), 5 to 10 mg/kg (maximum dose of 650 mg) acetaminophen (IV or oral), and/or Dipyrone 0.5 to 1.0 g (IV) where approved (e.g. Brazil), prior to study treatment administration. Dipyrone, a nonsteroidal anti-inflammatory drug, should be used with caution in renally impaired patients. The use of corticosteroids as premedication is prohibited.

- Female patients of childbearing potential and male patients with female partners must agree to use an effective contraceptive method during the study and for a minimum of 90 days after study treatment. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention), defined as a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; however, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.7.3 Documentation of Prior and Concomitant Medication Use

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

- Fluids
- Electrolytes
- Vitamins
- Supplements
- Mouth care
- Laxatives
- "As needed" medications

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

6 EFFICACY ASSESSMENTS

6.1 Efficacy Endpoints

The primary efficacy endpoints include the following:

- The reduction in viral load from nasal swab specimens from pre-dose through Day 28. Time-weighted average change from baseline to Day 28 in $\log_{10}$ viral load will be measured by qPCR (based on the central laboratory) for Part A.
- Proportion of patients with ≥50% reduction in viral load from nasal swab specimens and improvement in clinical signs and symptoms by least 1 grade for clinical signs and symptoms abnormal at baseline through Day 28 following the patient's first ALVR106 infusion for Part B.

The secondary efficacy endpoints include the following:

- The reduction in viral load from nasal swab specimens (measured by qPCR) from baseline to Day 60, Day 90 (Part B only), and Month 6 (based on the central laboratory).

The exploratory efficacy Endpoints include the following:

- Percentage of patients needing oxygen supplementation or ventilation throughout the study.
- Number of days with oxygen supplementation.
- Length of hospital stay for RTI defined as time between the first dose of study treatment and discharge for patients initially hospitalized for RTI at inclusion.
- Change from baseline in viral load area under the curve will be measured by qPCR (based on the central laboratory).
- Time to resolution of viral load from nasal swab specimens for all target viruses (ie, RSV, IFV, hMPV, and/or PIV) over the 6-month study period.
- Persistence of infused VSTs.
- Incidence of target viral reinfections (ie, RSV, IFV, hMPV, and/or PIV).
- Time to resolution of viremia for all target viruses (ie, RSV, IFV, hMPV, and/or PIV) over the 6-month study period (only for patients with detectable viremia at baseline). Resolution of viremia will be defined by the lower limits of detection of the assays used.
- Incidence of use of any other antiviral therapies targeting ALVR106 viruses during the study.
- Proportion of patients with progression from URTI to LRTI or worsening LRTI as defined by new onset LRTI symptoms (eg, shortness of breath, fever, fatigue, coughing, chest discomfort, production of mucus, coarse crackles) and either a sustained oxygen saturation <90% while breathing ambient air at rest, or new findings on chest X-rays and/or CT scans suggestive of progressive lung involvement.
- Proportion of patients with resolution, improvement, stability, or progression of LRTI as measured by imaging.
- Overall survival, defined as time to death (from any cause) from the first dose of study treatment.

- LRTI-related mortality, defined as time to LRTI-related death from the first dose of study treatment.
- Incidence of relapse or progression of the primary malignancy.

6.2 Viral Load Assessment

Reference the laboratory manual for detailed instructions on nasal swab sample collection.

Viral load from nasal swab specimens (measured by qPCR and analyzed in a central laboratory) will be assessed as indicated in the Schedule of Procedures. Central tests will be performed from baseline through the end of study. A nasal swab of both nostrils will be performed and sent to the central laboratory for analysis.

Blood samples for assessment of viremia will be collected as indicated in the Schedule of Procedures and stored for possible analysis.

An aliquot of the blood and nasal swab turbinate will be stored for possible viral genotypic or viral load analysis.

6.3 Imaging

All patients will have screening imaging performed and analyzed locally as long as the imaging can be transmitted to the central reader. For Parts A and B, imaging will be repeated as needed in cases of suspected progression to LRTI. Patient management will be based on the local reading, but the final analysis of radiologic progression will be based on the central reader's assessment. For Parts A and B imaging will be repeated at Days 10 and 28 for all patients, and as needed if clinically indicated. The central reader will compare subsequent imaging to the screening measurement to assess resolution, improvement, stability, or progression. Additional details will be provided in the study manual. Imaging performed to assess the RTI at non-protocol required visits will also be collected and sent to the central reader.

Chest X-rays and/or CT scans will be performed as indicated in the Schedule of Procedures.

6.4 Reconstitution of Antiviral Immunity

Patient plasma and PBMCs will be tested for virus-specific activity by functional studies including enzyme-linked immunospot assay with appropriate viral -specific peptide mixtures and available HLA -restricted epitope peptides, intracellular cytokine staining, cytokine profiling, and/or other assays as they become available for immune profiling purposes.

Persistence of infused T cells will be tested using deep sequencing and additional tests to track the T cell receptor v-beta repertoire in the patient peripheral blood prior to and post-infusion. Sequencing will be limited to evaluation of the persistence of VSTs and not any other genetic evaluations.

Patient plasma and PBMCs will be collected as indicated in the Schedule of Procedures.

6.5 Respiratory Clinical Signs/Symptoms

The evolution of respiratory clinical signs/symptoms will be as assessed by the Investigator (or designee) and the patient (or caretaker) (see Appendix D) as indicated in the Schedule of

Procedures. Reference P-106-001 eCRF Completion Guidelines for additional information on both the investigator's assessment and patient reported respiratory assessment.

For lung transplant recipients, if required by the investigator to support assessment of respiratory status, a spirometry assessment may be completed by the patient at Baseline, Week 4, Months 6 and 12. Spirometry should be collected in line with local standard clinical practice.

Additionally, oxygen use and duration and outcome of hospitalization for LRTI will be captured.

7 SAFETY ASSESSMENTS

7.1 Safety Endpoints

Safety endpoints will include review of adverse events (AEs); adverse events of special interest (AESI), clinical laboratory abnormalities; changes in corticosteroid dosage; abnormalities in vital signs or physical examination findings (including heart and lung auscultation, skin, and ears/nose/throat). The AESI as reported by the Investigator include:

- New (HCT and SOT patients) or worsening (HCT patients) of acute or chronic GVHD
- Graft failure or rejection
- Cytokine release syndrome (for the CRS grading scale, see Appendix C)
- Infusion related reactions (IRRs)
- New or worsening interstitial pneumonitis as reported by the Investigator from review of radiologic findings
- Progressive dyspnea

On treatment data will be analyzed separately and include treatment-emergent safety data from the first dose of study drug to the last dose of study drug plus 12 weeks.

7.2 Adverse Events

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

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent. Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment.

Wherever possible, a specific medical diagnosis rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if a medical diagnosis is not initially known the Investigator should record the sign or symptom as separate adverse event on the eCRF. Additionally, the underlying condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study or is a result of a study procedure. In this case, it should be reported as an adverse event.

All respiratory symptoms will be captured on a Respiratory Status CRF and not as adverse events. A new diagnosis of lower respiratory tract infection (LRTI) will be captured as an AE. Any

respiratory events which meet SAE criteria will be captured as both an AE and SAEs. All hospitalizations, ICU admissions and SAEs will be reported and will be assessed as to whether caused by the RTI.

Clinically significant abnormal laboratory or other examination (eg, electrocardiogram [ECG]) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

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

7.2.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

7.2.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

7.2.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event and will also categorize each adverse event as to its potential relationship to study treatment using the categories of related or not related.

Assessment of Severity

The severity of all adverse events, except for changes in respiratory status and imaging, which will be graded using the Radiation Therapy Oncology Group Lung Toxicity Scale (Table 1), should be graded according to the CTCAE version 5.0. For those adverse event terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to the adverse event

Causality Assessment

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

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

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

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

The following factors should also be considered:

- The temporal sequence from study treatment administration-

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

- Underlying, concomitant, intercurrent diseases-

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

- Concomitant drug-

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

- Known response pattern for this class of study treatment-

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

- Exposure to physical and/or mental stresses-

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

- The pharmacology and pharmacokinetics of the study treatment (as applicable)-

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

7.2.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence of pre-defined AESI throughout the patient's participation in this study.

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

For this study, AESI include the following as reported by the Investigator:

- New (HCT and SOT patients) or worsening (HCT patients) of acute or chronic GVHD
- Graft failure and rejection
- Cytokine release syndrome (for the CRS grading scale, see Appendix C).
- Infusion related reactions (IRRs). Signs and symptoms of an IRR may include the following: headache, fever, facial flushing, pruritis, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, urticaria and somnolence
- New or worsening interstitial pneumonitis as reported by the Investigator from review of signs and symptoms, and radiologic findings
- Progressive dyspnea

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

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

7.3 Serious Adverse Events

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

- Death.
- A life-threatening adverse event.

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

- Requires hospitalization or prolongation of existing hospitalizations, or prolonged admission to emergency room.

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

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

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

7.4 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until study participation is complete must be reported to [redacted]) within 24 hours of the knowledge of the occurrence. Once the study is completed, if the Investigator becomes aware of a new event occurring in a study participant that is thought to be causally related, or follow up to an event that was previously reported, the event should be reported to [redacted].

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send via email at [redacted] within 24 hours of awareness. [redacted] -7.7 When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided 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 Medpace Clinical Safety and/or [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.5 Pregnancy Reporting

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. 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.

7.6 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (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 investigational medicinal product.

7.7 Special Situation Reports

Special Situation Reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with ALVR106.

- **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 not 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 error.
- 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 Situation Report form and faxed/emailed to [redacted] (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situation Reports should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available 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.

Fax: [redacted]
[redacted] reporting line – USA:

• Email: [redacted]

• Fax: [redacted]

7.8 Clinical Laboratory Evaluations

Nasal swabs for viral load testing will be obtained as indicated in the Schedule of Procedures and sent to the central laboratory.

Blood for clinical chemistry and hematology will be obtained as indicated in the Schedule of Procedures and sent to the central laboratory. See Appendix A for a complete list of analytes.

Urine will be obtained as indicated in the Schedule of Procedures and sent to the central laboratory. See Appendix A for a complete list of analytes.

A serum or urine pregnancy test will be performed for females of childbearing potential as indicated in the Schedule of Procedures and sent to the central or local laboratory.

Blood for PBMC and plasma collection for exploratory assays will be obtained as indicated in the Schedule of Procedures and sent to the central laboratory.

7.9 Vital Signs

Vital sign measurements will include body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure and will be collected after resting for at least 5 minutes in the supine position as indicated in the Schedule of Procedures.

7.10 Electrocardiograms

Standard 12-lead ECGs will be performed as indicated in the Schedule of Procedures.

7.11 Physical Examinations

A complete physical examination will be performed at screening. Abbreviated physical exams will be performed at all subsequent visits.

The complete physical examination will include:

- General appearance
- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic

Abbreviated physical examinations will include a review of the respiratory and cardiovascular systems; skin and ears, nose, and throat; and a symptom-directed exam of all other systems. Physical examinations will be performed as indicated in Schedule of Procedures.

If an abnormality noted on physical examination is considered by the Investigator to be clinically significant, then the abnormality will be recorded as part of the patient's medical history if occurring prior to start of study treatment administration and as an adverse event if occurring after study treatment administration, where the finding represents a change from baseline. Any worsening of a baseline medical condition during the study should be recorded as an adverse event.

7.12 Graft Versus Host Disease

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

7.12.1 Acute Graft Versus Host Disease

Staging and grading of acute GVHD will be reported using Mount Sinai Acute GVHD International Consortium guidelines (MAGIC) in Appendix B. For HCT patients, response to

treatment will be assessed as per Center for International Blood and Marrow Transplant Research (CIBMTR) modifications to the CIBMTR response index as described in Appendix B.[40, 41]

7.12.2 Chronic Graft Versus Host Disease (HCT Only)

In HCT patients manifestations of chronic GVHD and response to treatment will be assessed as per National Institutes of Health Global Severity consensus guidelines for chronic GVHD as described in Appendix B.[42,43]

7.13 Infusion Site Evaluation

Infusion site evaluation (includes pain, tenderness, erythema, swelling, and induration) will be performed as indicated in the Schedule of Procedures. On infusion days, injection site evaluation will be performed pre-dose and at 1 hour post-dose.

7.14 Post-Infusion Monitoring

Post-infusion monitoring will be performed as indicated in the Schedule of Procedures. Patients will be monitored closely and must remain in the clinic for ≥1 hour after the end of each infusion. Vital signs and pulse oximetry will be measured at the end of the infusion (+/- 5 minutes), and at 15 minutes (+/- 5 minutes), 30 minutes (+/- 10 minutes), 45 minutes (+/- 15 minutes), and 60 minutes (+/- 15 minutes) after the end of the infusion. Data will be recorded on the eCRF. Post-infusion monitoring should be completed for all infusions of study treatment.

8 STATISTICAL CONSIDERATION

This section provides the key details of the statistical analyses to be performed using data captured according to this protocol. A complete Statistical Analysis Plan (SAP) describing all planned analyses will be finalized prior to database lock.

8.1 Analysis Populations

8.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all randomized patients regardless of whether the patient receives ALVR106 or placebo. The ITT population will be used for listings.

8.1.2 Safety Population

The Safety Population will include all randomized patients who receive any amount of ALVR106 or placebo. All safety and efficacy analyses will be based on the Safety Population.

8.2 Statistical Methods

Data from Part A, and Part B of the study will be summarized and analyzed separately.

Within each Part, placebo patients will be pooled. Pooling of the placebo patients between the cohorts provides a control group to better evaluate both safety and efficacy in this patient population, for which very little natural history exists. This will allow an informed decision on dose and safety.

8.2.1 Analysis of Efficacy Endpoints

The efficacy endpoints are described in Section 6.1. All the efficacy analyses will be performed using descriptive statistics by treatment group based on the Analysis Population.

Categorical data will generally be summarized with counts and percentages of patients. Continuous data will generally be summarized with descriptive statistics, including the number of non-missing values, mean, median, standard deviation, minimum, and maximum. For time-to-event variables, the Kaplan-Meier method will be used to estimate the median time (days) and its 95% confidence interval.

8.2.2 Analysis of Safety Endpoints

The safety endpoints are described in Section 7.1. All the safety data will be summarized by treatment group based on the Safety Population.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. A TEAE is defined as an adverse event with a start date and time on or after the first dose of study treatment to the last dose of study drug plus 12 weeks. Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term and further by severity (according to the NCI CTCAE v5.0) and relationship to study treatment. Summaries will include all TEAEs, TEAEs by relationship, TEAEs by severity, serious TEAEs, TEAEs leading to study drug discontinuation. The incidence of AESI and the corresponding 95% exact binomial confidence intervals will be presented by treatment group. All AEs and DLTs will be listed by patient.

Descriptive statistics will be provided for relevant laboratory and vital sign data. Abnormal laboratory results will be graded according to NCI CTCAE v5.0, if applicable, except changes in respiratory status and imaging which will be graded using the Radiation Therapy Oncology Group lung toxicity scale (Table 1). A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline grade according to NCI CTCAE, may be provided for selected clinical laboratory tests.

8.2.3 Interim Analysis

The SRC will review the cumulative safety and available efficacy data from each previous cohorts to recommend dose level and regimen for the subsequent cohorts.

8.2.4 Safety Review Committee

An independent SRC will be convened for this study to routinely monitor safety. The SRC will consist of an external chair and two additional independent experts in the field, at least one of the members will be a transplant physician and at least one member will be an infectious disease expert. The SRC will regularly review emerging safety data and will conduct both open and closed meetings. Should any safety issues require review by the SRC, an emergency meeting will be scheduled within 72 hours. Further dosing will be stopped until the SRC makes an assessment.

Based on routine safety reviews, the SRC may recommend escalating the dose as planned, recommend an intermediate dose, recommend expansion of the current cohort, recommend stopping dose escalation (Part A), or stop the study.

In addition, the SRC will make a recommendation for the RP2D and starting enrollment of Part B. The Sponsor will determine the final RP2D based on SRC recommendation and after review of all available relevant safety and efficacy data through at least Day 28 following the first ALVR106 or placebo infusion.

Reference the SRC Charter for additional information.

8.2.5 Sample Size Determination

No formal sample size determination was performed due to the exploratory nature of this study. The sample size has been set for an initial assessment of the safety and antiviral activity of ALVR106.

For the Part A dose escalation portions of the study, approximately 16 to 32 patients will be randomized. The actual number of patients randomized will depend on the safety profile for each cohort and when the MTD is reached.

For Part B RP2D cohort expansion portion of the study, a total of approximately 45 patients will be randomized.

9 DATA MANAGEMENT AND RECORD KEEPING

9.1 Data Management

9.1.1 Data Handling

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

9.1.2 Computer Systems

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

9.1.3 Data Entry

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

9.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

9.1.5 Data Validation

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

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

9.2 Record Keeping

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

9.3 End of Study

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

10 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

10.1 Ethical Conduct of the Study

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

10.2 Institutional Review Board/Independent Ethics Committee

10.2.1 Institutional Review Board

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

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

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

10.2.2 Independent Ethics Committee

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

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

10.3 Informed Consent

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

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient (or a parent or legal guardian) before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the patient (or a parent or legal guardian).

10.4 Study Monitoring Requirements

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

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

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

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

10.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB 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.

10.6 Retention of Records

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

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

10.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal 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.

10.8 Financial Disclosure

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

10.9 Insurance and Indemnity

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

10.10 Legal Aspects

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

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

11 STUDY ADMINISTRATIVE INFORMATION

11.1 Protocol Amendments

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

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APPENDIX A: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Direct bilirubin
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

Hematology

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.

Urinalysis

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

Microscopy (Microscopy is always performed (cannot be replaced with a dipstick analysis).

Pregnancy Tests (Female patients of childbearing potential only)

Serum
Urine human chorionic gonadotropin

Viral Load (Measured by nasal swab)

Human metapneumovirus	Influenza
Parainfluenza virus	Respiratory syncytial virus
SARS-CoV-2	

Blood Sample for Viremia Assessment and Donor specific antibody (Stored for possible analysis). Bank PBMCs for virus-specific immunity and ALVR106 persistence, and plasma for cytokine evaluation (Stored for possible analysis)

APPENDIX B: GRAFT VERSUS HOST DISEASE SCALES

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

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

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No Stage 1 to 4 of any organ.
Grade 1: Stage 1 to 2 skin without liver, upper GI, or lower GI involvement.
Grade 2: Stage 3 rash and/or Stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI.
Grade 3: 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 4: 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.

Response Definitions for Acute Graft Versus Host Disease

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

CR = complete response; GVHD = graft versus host disease; NR = no response; PR = partial response.
Source: Center for International Blood & Marrow Transplant Research (CIBMTR). Clinical trial endpoints for patients with acute GVHD. 2009. https://www.cibmtr.org/Meetings/Materials/GVHDworkshop/pages/index.aspx. Accessed 06 July 2020.

For HCT only:

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(3):389-401.e1.

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

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

%FEV1 = percent predicted forced expiratory volume in the first second; ALT = alanine aminotransferase; GI = gastrointestinal; NIH = National Institutes of Health; PFT = pulmonary function test; P-ROM = photographic range of motion; ULN = upper limit of normal.
Source: Lee ST, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21(6):984-999.

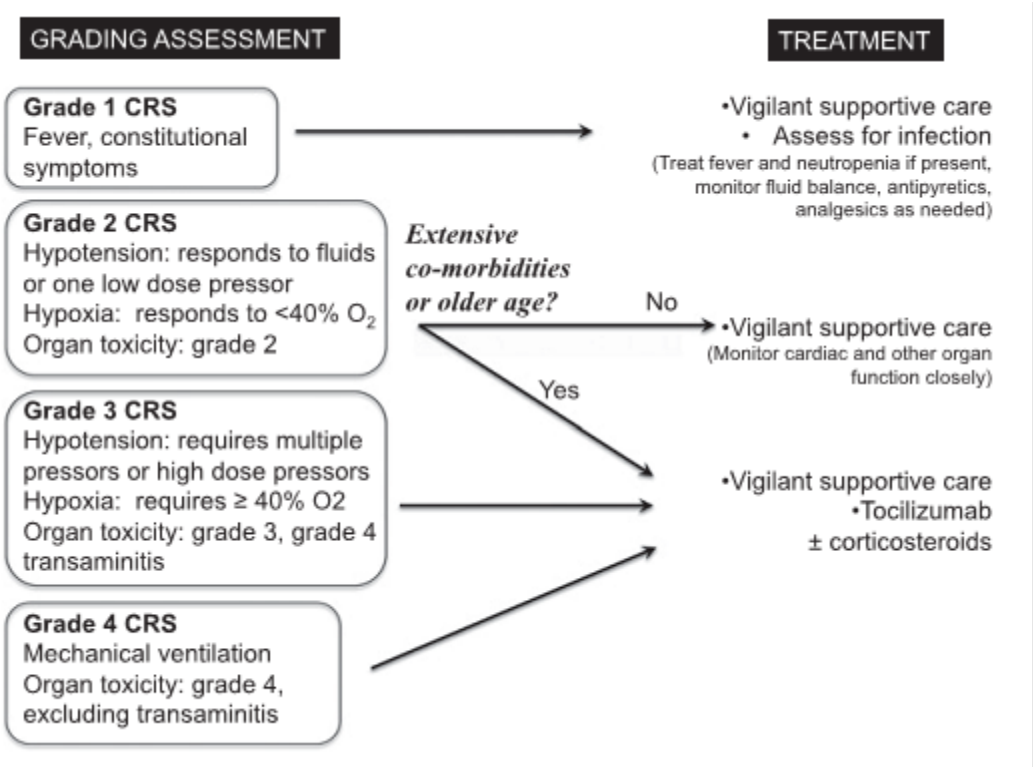
APPENDIX C: CYTOKINE RELEASE SYNDROME GRADING SCALE AND MANAGEMENT

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

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

a. Fever is defined as temperature ≥38.0°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
b. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

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



CRS = cytokine release syndrome; O_2 = oxygen.
Source: Adapted from Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

APPENDIX D: PATIENT-REPORTED ASSESSMENT OF RESPIRATORY CLINICAL SYMPTOMS

This assessment tool consists of four questions related to your *respiratory (breathing) symptoms*. Every time you are asked to evaluate your symptoms of cough, breathlessness (difficulty breathing, shortness of breath), wheezing, and sputum (phlegm, mixture of saliva and mucous) production by scoring them from 0 to 3 based on the following definition:

0	1	2	3
(none)	(mild)	(moderate)	(severe)
	discomfort noticed but no disruption of normal daily activity	discomfort sufficient to reduce or affect normal daily activity	discomfort with inability to perform normal daily activities

In the last 24 hours:

Date:	**Visit:**		**Time:**
Respiratory Symptoms			
Please mark only one "X" in the cell underneath the response.			
1. Cough: How severe was your cough?			
0 (none)	1 (mild)	2 (moderate)	3 (severe)
2. Breathlessness: How severe was your breathlessness?			
0 (none)	1 (mild)	2 (moderate)	3 (severe)
3. Wheezing: How severe was your wheezing?			
0 (none)	1 (mild)	2 (moderate)	3 (severe)
4. Sputum production: How severe was your sputum production?			
0 (none)	1 (mild)	2 (moderate)	3 (severe)
5. Fever: What was your highest body temperature?			
0 (normal body temperature)	1 (mild)	2 (moderate)	3 (severe)
<99°F	>100°F	>101°F	>103°F

SUMMARY OF CHANGES

Please refer to the attached Summary of Changes document entitled:

Summary of Changes:
Protocol Number P-106-001
Amendment Number 3 (Version 4.0) to
Amendment Number 4 (Version 5.0)

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VV-CLIN-000112 v3.0

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