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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STATISTICAL ANALYSIS PLAN

Protocol 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 Transplant
Protocol Number:	P-106-001
Protocol Version/Date:	V4.0/25 May 2021
Investigational Product:	ALVR106
Sponsor:	AlloVir Kirby Grove 2925 Richmond Avenue, Suite 1200 Houston, TX 77098 United States
SAP Version/Date:	V1.0/25 February 2022

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SIGNATURE PAGE

Protocol 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 Transplant

Protocol Number: P-106-001

SAP Version/Date: V1.0/25 February 2022

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	Date
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BKV	BK Virus
BPIC SD	Bladder Pain/Interstitial Cystitis Symptom Diary
CDISC	Clinical Data Interchange Standards Consortium
CMV	Cytomegalovirus
CRF	Case Report Form
CRS	Cytokine Release Syndrome
COAs	Clinical Outcome Assessments
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
ECG	Electrocardiograms
eGFR	estimated Glomerular Filtration Rate
EQ-5D	EuroQol – 5 Dimension
FEV1	Forced Expiratory Volume in the First Second
FVC	Forced Vital Capacity
GVHD	graft vs host disease (GVHD)
HC	Hemorrhagic Cystitis
HCT	Hematopoietic Cell Transplant
HHV-6	Human Herpesvirus 6
hMPV	Human Metapneumovirus
HPF	High Power Field
ITT	Intent-to-Treat
IV	Intravenous(ly)
JCV	JC Virus
LRTI	Lower Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute
PD	Pharmacodynamics
PK	Pharmacokinetics
PIV	Parainfluenza Virus
PROMIS-29	Patient-Reported Outcomes Measurement Information System – 29 Profile
PT	Preferred Term
qPCR	Quantitative Polymerase Chain Reaction

Abbreviation	Definition
RBC	Red Blood Cell
RP2D	Recommended Phase 2 Dose
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SRC	Safety Review Committee
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	upper limit of normal
URTI	Upper Respiratory Tract Infection
VC	Vital Capacity
VST	Virus-specific T cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the Phase 1/2 study with protocol number P-106-001. The SAP will be finalized prior to the first patient being randomized.

2 STUDY OVERVIEW

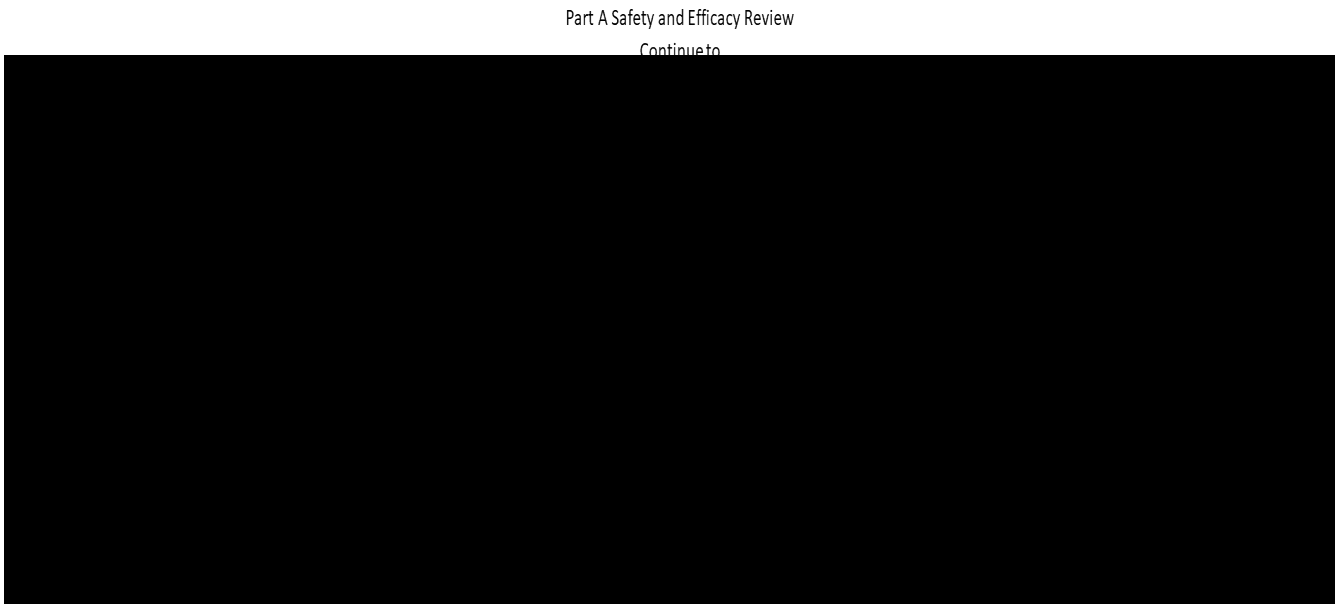
This is a Phase 1/2, double-blind, placebo-controlled, dose escalation and expansion study to assess the safety and dose selection of ALVR106 in addition to standard of care for the treatment of high-risk patients with respiratory tract infections (RTIs) and clinical manifestations caused by RSV, influenza, hMPV, and/or PIV following HCT. This study will be conducted in 2 parts (each part of the study will include unique patients – there will be no crossovers between parts):

- Part A (dose escalation in patients with URTIs at high-risk of progression to LRTIs)
- Part B (RP2D cohort expansion in patients with URTIs at high-risk of progression to LRTIs)

Throughout the study, all patients will receive standard of care as determined by the Investigator (or designee). This may include antivirals targeting RSV (eg, oral, IV, or inhaled ribavirin), influenza (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.

Figure 1 provides a summary of the study design.

Figure 1. Summary of Study Design



Note: Each part of the study will include unique patients – there will be no crossovers between parts.

R = randomized; URTD = upper respiratory tract disease; URTI = upper respiratory tract infection.

2.1 Study Objectives of Part A

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 adult patients with high-risk upper respiratory tract infections (URTIs) caused by respiratory syncytial virus (RSV), influenza, human metapneumovirus (hMPV), and/or parainfluenza virus (PIV) following hematopoietic cell transplant (HCT).

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 in nasal swab 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 in nasal swab 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 lower respiratory tract infection (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 decrease in forced expiratory volume in the first second (FEV1) of >25%, a sustained oxygen saturation <92%, or new findings on chest X-rays and/or computed tomography (CT) scans suggestive of pneumonitis or bronchiolitis obliterans with organizing pneumonia
- 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 ≥92% 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 infusion on overall health and perceived well-being as measured by patient-reported outcomes
- To assess the effect of ALVR106 infusion on lung function as measured by pulmonary function tests (spirometry and diffusing capacity of the lungs for carbon monoxide [DLCO])
- To assess the effect of ALVR106 for resolution, improvement, stability, or progression of LRTI as measured by imaging.

2.2 Study Objectives of Part B

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 adult patients with high-risk URTIs caused by RSV, influenza, hMPV, and/or PIV following HCT.

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 adult patients with high-risk URTIs caused by RSV, influenza, hMPV, and/or PIV following HCT
- To characterize the individual patient antiviral response as measured by the percent reduction in viral load in nasal swab 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
- To determine the proportion of patients with progression from URTI to 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 decrease in FEV1 of >25%, a sustained oxygen saturation <92%, or new findings on chest X-rays and/or CT scans suggestive of pneumonitis or bronchiolitis obliterans with organizing pneumonia

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 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 ≥92% in the absence of supplemental oxygen, in adult patients treated with ALVR106
- To assess the effect of ALVR106 infusion on overall health and perceived well-being as measured by patient-reported outcomes
- To assess the effect of ALVR106 infusion on lung function as measured by pulmonary function tests (spirometry and DLCO)
- To assess the effect of ALVR106 for resolution, improvement, stability, or progression of LRTI as measured by imaging

2.3 Study Design

2.3.1 Study Drug

ALVR106 is a third-party, donor-derived, "off-the-shelf" virus-specific T cell (VST) product with specificity for RSV, influenza, PIV, and hMPV. ALVR106 cell lines 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] final volume at a concentration of [redacted]

2.3.2 Sample Size Determination

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. 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, the operating characteristics when dose levels have monotonically increasing true toxicity rates are provided in Table 1. The simulation demonstrates that the study will need 9.55 patients to 18.24 patients (including placebo patients) to find the right dose level with different scenarios of true toxicity rates. The probability of identifying a MTD is between 97.1% (low toxicity scenario) and 50.1% (high toxicity scenario).

For Part B, assuming the proportions of patients with ≥50% reduction in viral load in nasal swab and patient assessed improvement in clinical signs and symptoms at baseline through Day 28 in ALVR106 group and placebo group will be 74% vs. 30%, 45 patients would provide approximately 90% power to test the treatment effect at a 2-sided significance level of 0.05.

Table 1. Operating Characteristics when Dose Levels Have Monotonically Increasing True Toxicity Rates in Part A

True toxicity rate (dose1, …, dose4)	**(0.05, 0.1, 0.2, 0.3) Low toxicity**	**(0.1, 0.2, 0.3, 0.4)**	**(0.2, 0.3, 0.4, 0.5)**	**(0.3, 0.4, 0.5, 0.6) High toxicity**
Expected number of patients treated at each dose level (without placebo patients)	(3.48, 3.64, 3.71, 2.85)	(3.73, 3.80, 2.77, 1.36)	(4.15, 3.05, 1.47, 0.46)	(4.34, 2.09, 0.64, 0.09)
Expected number of patients treated at each dose level (with placebo group)	(4.64, 4.85, 4.95, 3.8)	(4.97, 5.07, 3.69, 1.81)	(5.53, 4.07 1.96, 0.61)	(5.79, 2.79, 0.85, 0.12)
Mean number of enrolled patients (without placebo patients)	13.68	11.66	9.13	7.16

Mean number of enrolled patients (with placebo group)	18.24	15.55	12.17	9.55
Mean number of observed DLTs at each dose level (without placebo patients)	(0.20, 0.36, 0.69, 0.85)	(0.38, 0.76, 0.79, 0.52)	(0.83, 0.91, 0.56, 0.25)	(1.31, 0.82, 0.31, 0.05)
Mean number of observed DLTs (no Placebo)	2.10	2.45	2.55	2.49
Percentage of each dose recommended as MTD among the 1000 experiments	(9.2, 22.9, 33.3, 31.7)	(26, 32.2, 21.3, 10.2)	(35.8, 22.6, 10.3, 1.4)	(33.4, 12.9, 2.2, 0.2)
Percentage of no recommendation, the first level is too toxic	2.9	10.3	29.9	51.3

2.3.3 Randomization

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. For Part B, enrollment will be capped such that no more than approximately 50% of patients will be <18 years of age.

2.4 Study Endpoints

2.4.1 Primary Efficacy Endpoints

The primary efficacy endpoints include the following:

- The reduction in viral load in nasal swab 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 in nasal swab and improvement in clinical signs and symptoms through Day 28 following the patient's first ALVR106 infusion for Part B.

2.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- The reduction in viral load in nasal swab (measured by qPCR) from baseline to Day 60, Day 90, and Month 6 (based on the central laboratory).
- Proportion of patients with progression to LRTI by Day 10 and Day 28 (Parts A and B). Progression to LRTI will be assessed by the Investigator based on standard of care clinical, radiological, and laboratory assessments and defined by new onset LRTI symptoms (eg, shortness of breath, fever, fatigue, coughing, chest discomfort, production of mucus, coarse crackles) and either a decrease in FEV1 of >25%, a sustained oxygen saturation <92%, or new findings on chest X-rays and/or CT scans

suggestive of pneumonitis or bronchiolitis obliterans with organizing pneumonia. All chest X-rays and/or CT scans will be sent for central reading. Every attempt to document LRTI should be made.

2.4.3 Exploratory Efficacy Endpoints

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 in nasal swab for all target viruses (ie, RSV, influenza, hMPV, and/or PIV) over the 6-month study period.
- Persistence of infused VSTs.
- Incidence of target viral reinfections (ie, RSV, influenza, hMPV, and/or PIV).
- Time to resolution of viremia for all target viruses (ie, RSV, influenza, 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 during the study.
- Change in pulmonary function tests (FEV1, vital capacity [VC], forced vital capacity [FVC], and DLCO).
- 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.
- Change in the EQ-5D (EuroQol – 5 Dimension) and PROMIS-29 (Patient-Reported Outcomes Measurement Information System – 29 profile).
- Incidence of relapse or progression of the primary malignancy.

2.4.4 Safety Endpoints

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

- Acute or chronic GVHD
- Cytokine release syndrome
- Infusion related reactions
- New or worsening interstitial pneumonitis as reported by the Investigator from review of radiologic findings
- Progressive dyspnea (including grunting, increased respiratory rate, and/or wheezing)
- High fever (body temperature >39°C)

Safety assessments also include treatment-emergent adverse events (TEAEs); 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).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Definition of Baseline

Baseline is defined as the last non-missing measurement prior to the first dose of study treatment. Both date and time will be considered in baseline derivation. Measurement from Day 1 prior to study treatment administration will be used. If not available, the last non-missing measurement prior to Day 1 will be used. For baseline, the viral load and radiographic results from the central lab will be utilized.

3.1.2 Summary Statistics

Data from Part A and Part B of the study will be summarized and analyzed separately and by dose cohort. Within each part, placebo data will be pooled. Virology endpoints will be summarized by individual virus.

Summary statistics will be presented by treatment group (ALVR106 and placebo) and dose cohort (Part A,and Part B). 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, IQR, 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.

For key endpoints, only central reading data will be used to perform analysis. For secondary and exploratory endpoints, both central and local reading data will be used to perform analysis.

3.1.3 Handling of Dropouts and Missing Data

In general, data will be analyzed and presented as observed and will not be imputed for the analysis of efficacy.

In case the start and end dates for adverse events and concomitant medications/procedures are missing or incomplete, the missing component(s) will be assumed as the most conservative value possible. For example, Adverse Events (AEs) with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study treatment or ended prior to the start of study treatment. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

Viral load values detectable but below the limit of quantification will be imputed as LOQ/2 copy/mL. Undetectable viral load values will be imputed as the lower limit of detection of the assay minus 1 copy/mL.

3.1.4 Analysis Day and Visit

Analysis Day 1 will be considered as the date of the first dose of study drug. The day immediately before Day 1 will be Day -1. There will be no Day 0. The Analysis Day will be calculated as:

- For days prior to first dose date, Analysis Day = date – first dose date

- For days on/after first dose date, Analysis Day = date – first dose date + 1

Analysis visit is a timing variable to be used for analyses involving visits. Analysis window will be used to determine the analysis visit to which a measurement should be mapped. For this study, the target date and window specified per protocol will be used to map measurements unless no visit was completed within the per protocol specified window.

If a scheduled visit is missing or outside of per protocol window, measurement(s) taken at a visit falling within the statistical analysis window in Table 2 may be used as the measurement for that specific visit. If more than one visit falls into the same statistical analysis visit window, the visit closest to the scheduled visit timepoint (per protocol specified visit and window) will be used. For laboratory data, if a retest visit can be identified due to result error (e.g. laboratory error or physiologically improbable results) in the original test visit, the retest visit will be used in place of the original test result for that visit.

All laboratory results will be reported in the patient listings.

Table 2. Statistical Analysis Visit Windows

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 4	28	15	42
Week 8	60	43	120
Month 6	180	121	270
Month 12/ET	365	271	

3.2 Analysis Populations

3.2.1 Modified ITT (mITT) Population

The modified Intent-to-Treat (mITT) Population will include all randomized patients who receive any amount of ALVR106 or placebo and had confirmed virologic infection of interest at Baseline (detectable nasal viral load). All efficacy analyses will be based on the mITT Population.

3.2.2 Per Protocol Population

The per protocol (PP) Population will include all mITT patients without significant protocol deviations. The Per-Protocol Population will be used to assess robustness of the primary analysis results.

3.2.3 Safety Population

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

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened, randomized, treated, discontinued early from the study, and completed the study will be summarized based on the screened patients. Reasons for screen failure and early discontinuation will also be summarized.

Counts and percentages of patients in each analysis population will be summarized based on the ITT population. Reasons for patient data exclusion from each analysis population will also be summarized.

3.3.2 Protocol Deviations

Counts and percentages of patients with protocol deviations by CSR reportable deviation category will be summarized by treatment group and in total based on the ITT Population. Descriptions and categories of CSR-reportable events are found in the Protocol Deviation Plan.

A final listing of all subjects to be excluded from the analysis populations will be completed prior to unblinding the study database.

3.3.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate for all analysis populations.

Demographic and baseline characteristics will include

- age (years)
- age group (<18 years, >=18 years)
- sex (male, female)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported)
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, Other)
- weight (kg)
- height (cm)
- body mass index (BMI) in kg/m^2
- duration of respiratory tract infection diagnosis (days)
- radiation therapy oncology group lung toxicity grade (Grade 0, Grade 1, Grade 2, Grade 3, Grade 4)
- Recipient CMV serostatus (Positive, Negative, Unknown)
- Donor CMV serostatus (Positive, Negative, Unknown)
- blood type (O, A, B, AB)
- Rh factor (+, -)
- primary malignancy/underlying indication for transplant
- duration of diagnosis of primary malignancy/underlying indication for transplant (years)
- Virus type
- Time from transplant to randomization (days)
- Type of transplant
- Type of conditioning regimen
- Viral load at Baseline
- Neutrophil count at Baseline
- Lymphocyte count at Baseline

- Platelets count at Baseline
- Presence of acute or chronic GVHD at Baseline
- Smoking history (Y/N and mean number of pipes, cigars, cigarette packs per day)
- Respiratory status (Tract infection symptoms, cough, difficulty breathing/shortness of breath, wheezing, sputum production, and fever)
- Number of HLA matches

3.3.4 Medical History

Medical history will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) v 24.0. Counts and percentages of patients with medical history by SOC and PT will be summarized based on the Safety Population.

3.3.5 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and PT using the WHO Drug Dictionary B3, MAR 2021. Medications will be considered prior medications if they stopped prior to the first dose of study treatment and concomitant medications if they were taken on or after the first dose of study treatment (i.e., started prior to the first dose of study treatment and were ongoing or started on or after the first dose of study treatment).

Counts and percentages of patients taking prior and concomitant medications by ATC class and PT will be summarized based on the Safety Population.

3.4 Efficacy Assessment

3.4.1 Primary Efficacy Analysis

The reduction (% change and absolute change) in viral load in log and linear scales in nasal swab from pre-dose through Day 28 will be summarized by treatment group and dose cohort. ALVR106 and placebo groups will be compared using a Wilcoxon signed rank test.

Proportion of patients with ≥50% reduction in viral load in nasal swab and patient assessed improvement in clinical signs and symptoms at baseline through Day 28 will be summarized by treatment group and dose cohort.

The difference in proportions will be presented together with 95% confidence intervals.

Clinical signs and symptoms data assessed by both patient and investigator will be listed for comparison.

Patients whose systemic steroids are increased above the threshold (0.5 mg/kg/day prednisone equivalents) after randomization will be excluded from the primary analysis at Day 28.

3.4.2 Secondary Efficacy Analysis

For Part B, the reduction in viral load in nasal swab (measured by qPCR) from baseline to Day 28 and Day 60, Day 90, and Month 6 will be summarized by treatment group and dose cohort. It may also be summarized by target virus (RSV, influenza, hMPV, and PIV measured by qPCR) if needed. ALVR106 and placebo groups will be compared using a Wilcoxon signed rank test.

For Part A and B, proportion of patients with progression to LRTI based on central lab reading by Day 10 and Day 28 will be tabulated. The difference in proportions will be presented together with 95% confidence intervals. The 95% two-sided confidence interval of the treatment difference will be presented based on Wilson's Score method.

Both central and local radiographs data will be listed for comparison.

3.4.3 Exploratory Efficacy Analysis

Exploratory continuous and categorical efficacy endpoints will be summarized descriptively by treatment group and dose cohort.

Censoring rules for overall survival analysis are summarized in Table 3.

Table 3. Censoring Rules for Overall Survival

Situation	Date of progression or censoring	Outcome
Death reported on or prior to cutoff date	Death date	Event
Withdrew on or prior to cutoff date	Last known alive date	Censored
Known to be alive on or after the cutoff date	Cutoff date	Censored

Following sample data collected for exploratory reasons will be summarized, if data is available.

- Blood sample for viremia assessment
- Banked PBMCs for virus-specific persistence
- Plasma for cytokine evaluation

Days in hospital and ICU will be summarized descriptively by unplanned vs planned hospitalization and if LRTI-related. All ER visits and hospitalization will be listed by patients.

Time to recurrence of infections will be summarized descriptively for all and target infections.

Time from transplant to first infusion will be summarized descriptively.

Administration will be summarized for inpatient or outpatient by visit.

3.4.4 Sub-group Analysis

Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups.

Descriptive statistics of selected efficacy and safety endpoints will be provided within each category of the following variables if data allow:

- Degree of HLA mismatch in VSTs [redacted])
- Number of ALVR106 doses in Part A or B (1 or 2)

3.5 Safety Assessment

The safety profile will be based on TEAEs and changes in vital signs and clinical laboratory assessments. All safety data will be summarized.

3.5.1 Adverse Events (AEs)

Adverse events will be coded using MedDRA v24.0. A TEAE is defined as an adverse event with a start date and time on or after the first dose of study treatment. TEAEs will be summarized by SOC and PT and further by severity (according to the NCI CTCAE v5.0) and relationship to study treatment. The incidence of SAEs will be summarized. TEAEs will be also summarized by PT only.

An overview of AEs will be provided including counts and percentages of patients and AE event counts with the following:

- Any TEAEs (by NCI CTCAE grade and relationship to study treatment)
- Any study treatment related TEAEs (by NCI CTCAE grade)
- Any TEAEs of special interest (by NCI CTCAE grade and relationship to study treatment)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study treatment
- Any AEs leading to death
- Any TEAEs leading to death

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study treatment.

3.5.2 Dose-limiting Toxicity (DLT)

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

All DLTs will be listed and summarized.

3.5.3 AEs of Special Interest

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

- Acute or chronic GVHD
- Cytokine release syndrome (for the CRS grading scale, see Protocol Appendix C)
- Infusion related reactions (IRRs)
- New or worsening interstitial pneumonitis as reported by the Investigator from review of radiologic findings
- Progressive dyspnea (including grunting, increased respiratory rate, and/or wheezing)
- High fever (body temperature >39°C)

The overall and each type of AESIs incidences and the corresponding 95% exact binomial confidence intervals will be presented. AESIs will be summarized by severity (according to the NCI CTCAE v5.0). Descriptive statistics will be provided for duration of AESIs.

3.5.4 Infusion Site Evaluation

Infusion site reaction will be summarized with counts and percentages of patients. The size of Erythema, Swelling, and Induration will be summarized descriptively.

3.5.5 Laboratory Tests and Vital Signs

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 for adverse changes in pulmonary function (FEV1, VC, FVC, and DLCO), which will be graded using the Radiation Therapy Oncology Group lung toxicity scale.

A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline grade according to NCI CTCAE grades, will be provided for selected clinical laboratory tests. The worst post-baseline grade will be derived from all post-baseline visits including scheduled and unscheduled.

3.5.6 Physical Examinations

All physical examination data will be listed by patients.

Pulmonary function test data will be summarized descriptively.

Respiratory tract infection status data will be summarized with counts and percentages of patients.

3.5.7 Electrocardiograms (ECG)

ECG will be assessed at Screening and Day 1 within 1 hour after study treatment administration. All ECG abnormalities and their interpretation will be listed by patients.

3.6 Safety Review Committee

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.

3.7 Interim Analyses

No formal interim analysis is planned for the study. Each part of the study will be reviewed and analyzed separately.

In Part A, analysis will be performed after each cohort completes and a decision on the recommended phase 2 dose for Part B will be made after the MTD is reached in Part A. In Part B, there will be an administrative analysis, with the potential for sample size re-estimation, once approximately half of the patients have been enrolled. The administrative analysis will be performed by an independent unblinded statistician.

4. CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No changes affecting the statistical analysis defined in the protocol are made.

5. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject. Detailed Programming Specifications will be provided in a separate document.