Protocol Number: P-105-303

Official Title:

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

NCT Number: NCT05179057

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STATISTICAL ANALYSIS PLAN

Protocol Title:	*Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, with Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation*
Protocol Number:	P-105-303
Protocol Version/Date:	Amendment 4, 30 November 2023
Investigational Product:	Posoleucel (ALVR105)
Sponsor:	AlloVir 1100 Winter Street Waltham, MA 02451 United States
SAP Version/Date:	V1.0/12 January 2024

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SIGNATURE PAGE

Protocol Title:	Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, with Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation
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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature

[redacted]
AlloVir, LLC

[redacted]
AlloVir, LLC

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AdV	Adenovirus
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GVHD	Graft Versus Host Disease
HCT	Hematopoietic Cell Transplant
HHV-6	Human Herpesvirus 6
HLA	Human Leukocyte Antigen
JCV	JC Virus
LFT	Liver Function Test
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
OL	Open Label
PBMC	Peripheral Blood Mononuclear Cell
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
WHO	World Health Organization

1 INTRODUCTION

This document details the analysis plan for the study entitled "Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, with Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation". It is based on Protocol P-105-303 Amendment 4 dated 30 November 2023 and describes the proposed efficacy and safety analyses. Since the study is terminated due to futility, only the primary efficacy endpoint and selected safety endpoints will be analyzed.

The Statistical Analysis Plan (SAP) will be finalized prior to interim database lock. After the database lock, any deviation from the SAP will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary efficacy objective of this trial is to compare the percentage of participants who have clearance of Adenovirus (AdV) viremia at Day 29 in participants receiving posoleucel and standard of care (SoC) to that in participants receiving placebo and SoC.

The primary safety objective is to determine the safety and tolerability of posoleucel cells by analyzing the incidence and severity of treatment-emergent adverse events (TEAEs), including individual AEs of special interest (AESIs).

2.2 Study Design

2.2.1 Overview

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

Approximately 80 participants may be randomized [redacted] to receive [redacted] infusions of posoleucel or placebo [redacted]). Randomization will be stratified [redacted]
It is expected that no more than 30% of participants, but at least 10% of participants, will be [redacted] Enrollment of participants <1 year of age will occur once preliminary safety data are available from 5 participants ≥1 and ≤6 years of age. The Data Safety Monitoring Board (DSMB) will review data through Day 29 from these 5 participants once available and make a recommendation. A formal memo will be provided to ethics committees and sites once the DSMB approves enrollment of participants <1 year of age.

The Primary Study Period is 4 weeks (28 days) for evaluation of efficacy, including the primary endpoint, plus 20 weeks for safety follow-up, for a total study duration of 24 weeks. For participants who cross over, the Cross-Over Period is 4 weeks (28 days), plus 20 weeks for safety

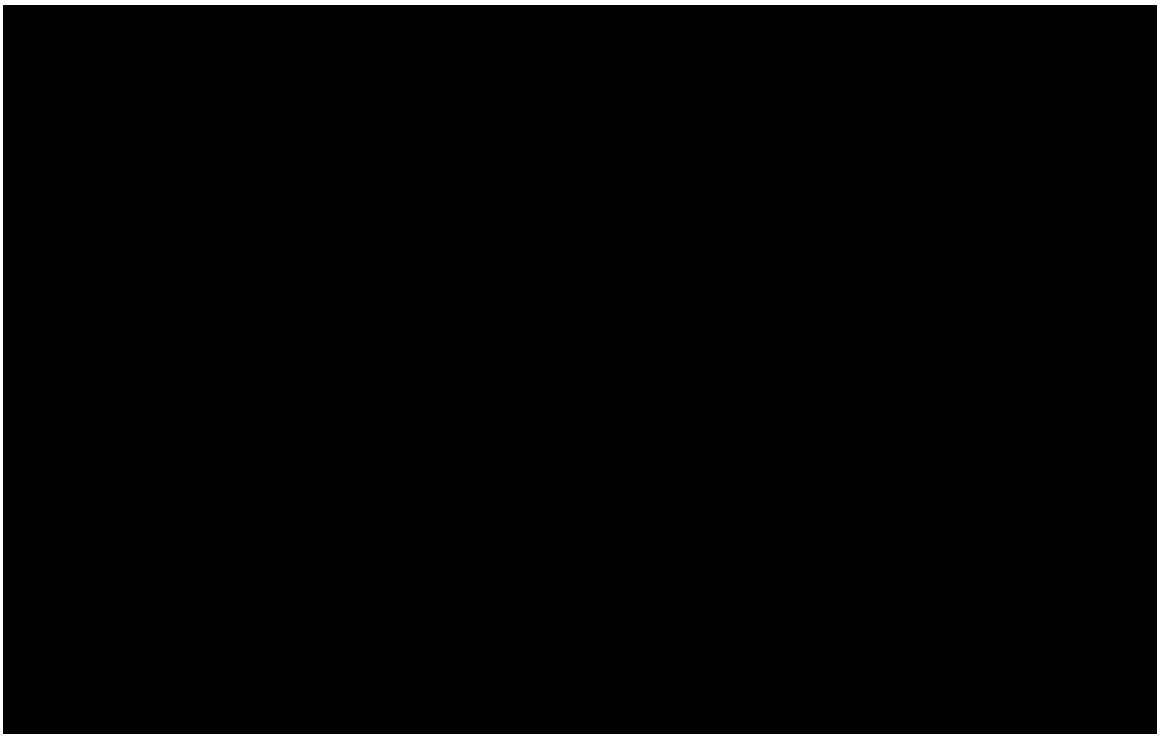
follow-up. Participants who experience recurrence and receive an additional dose will have safety follow-up for 20 weeks after the final dose.

Participants who progress to active target organ disease or whose existing target organ disease progresses (as assessed by the Investigator and Sponsor Medical Monitor and based on the criteria in Appendix 8 of the protocol) between Day 29 and Week 10 will be considered to have experienced progression and will have the option to be crossed over to the alternate treatment arm. Participants can cross over before Day 29 only if they progress with target organ disease as adjudicated by the Adjudication Committee. Cross-over participants will receive the alternate treatment to which they were originally randomized, posoleucel or placebo [redacted] sequential infusions separated by [redacted] ± 3 days), but study treatment will remain blinded.

Participants who demonstrate viral clearance by Day 29 of the Primary Study Period but later exhibit a clinically significant recurrence of AdV viremia (i.e., ≥10,000 copies/mL AdV DNA at the central laboratory) and/or progression of or to active organ disease, will be eligible for an additional dose of the last received therapy (posoleucel or placebo) for recurrence prior to 20 weeks. These participants will continue to have safety follow-up for an additional 20 weeks after administration of the additional dose.

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

Figure 1. Summary of Study Design



2.2.2 Method of Treatment Assignment

Participants who meet all the inclusion criteria and none of the exclusion criteria will be randomized to the study prior to Day 1 of the Primary Study Period. Participants will be randomized [redacted] to receive [redacted] infusions of posoleucel or placebo. Randomization will be stratified [redacted]

2.2.3 Blinding

The Sponsor designee (e.g., interactive response technology [IRT] vendor) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind integrity is properly maintained. Care should be exercised to ensure that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (e.g., staff involved in suspected unexpected serious adverse reaction (SUSAR) reporting).

An unblinded statistician will be assigned to the DSMB. This statistician will not be involved in any aspects of study conduct outside of the DSMB, and their role will be defined in the DSMB charter.

Unblinding should only occur in the event of an emergency or adverse event (AE) for which it is necessary to know the study treatment to determine an appropriate course of therapy. If the participant's study treatment must be unblinded, the Investigator or qualified designee should contact IRT for the study treatment information. The IRT documentation indicating the blind break at the site must be retained with the participant's source documentation in such a way as to avoid unblinding the treatment assignment to other site or Sponsor blinded personnel.

If possible, the Investigator should attempt to contact the Medical Monitor prior to unblinding in order to get additional information about the study treatment. If not possible, the Investigator should notify the Medical Monitor as soon as possible of the unblinding without disclosing the treatment assignment of the unblinded participant. The Investigator must document the participant's identification, the reason for breaking the blind, and the date and time for breaking the blind.

2.2.4 Sample Size Determination

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

The sample size was determined based on the following specifications:

1. Superiority study comparing posoleucel plus SoC to placebo plus SoC
2. Primary endpoint is success or failure based on clearance of AdV viremia at Day 29 visit of the Primary Study Period
3. Allocation (posoleucel:placebo) is[redacted]
4. Chi-square test
5. Two-sided alpha = 0.05
6. True success rate (defined as clearance of virus) for posoleucel = 0.50
7. True success rate (defined as clearance of virus) for placebo = 0.25
8. Power = 80%

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

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants with undetectable viremia (less than lower limit of quantitation [LLOQ]) at Day 29.

2.3.2 Safety Endpoints

The safety endpoint is the incidence and severity of TEAEs, including adverse events of special interest (AESIs), during the study.

The clinical laboratory evaluations (hematology, chemistry, and urinalysis) will also be summarized.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or higher.

Data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using the frequency count and the percentage of participants in each category. For continuous data, the minimum and the maximum will use the same decimal place accuracy as the raw data. The mean, median, and standard deviation will use one more decimal place than the raw data. For categorical data, percentages will be reported to one decimal place.

Summary statistics will be presented by randomized or actual treatment group for the Primary Study Period. The key efficacy and selected safety endpoints will be summarized for the Primary Study Period.

No hypothesis tests will be performed.

3.1.1 Study Day

Study day will be calculated from the date of first dose of study drug, as actual visit date – first dose date for dates before the first dose date and +1 for dates on or after the first dose date. The day of the first dose of study drug will be Day 1, and the day immediately before and after Day 1 will be Day -1 and Day 2.

For participants who crossed over, the first dosing date of the Cross-Over Period will be Day 1' for that period. Study day of the Cross-Over Period will be calculated as actual visit date in the Cross-Over Period – Cross-Over Period Day 1' + 1.

3.1.2 Analysis Visits

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, all scheduled, unscheduled, and early termination visits will be assigned to analysis visits according to the analysis windows (Appendix 1) based on study days. If there is more than 1 assessment in an analysis window, the assessment closest to the target day will be used in the analysis. If there are 2 assessments in a window equidistant from the target day, the later assessment will be used in the analysis.

3.1.3 Definition of Baseline

Baseline is defined as the last non-missing measurement prior to the first dose of study treatment. This can be on Day 1 as long as the measurement is taken prior to the first dose.

3.1.4 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 and safety, unless otherwise specified. The missing data handling for the primary efficacy endpoints is discussed in Section 3.4.

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, 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.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population will include all randomized participants and will be used for listings.

3.2.2 Modified Intent-to-Treat (mITT) Population

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

3.2.3 Safety Population

The Safety Population will include all participants who receive any amount of posoleucel or placebo. All safety analyses will be based on the Safety Population. Participants will be analyzed according to the actual study treatment received. All safety analyses will be based on the Safety Population.

3.3 Participant Data and Study Conduct

3.3.1 Participant Disposition

Participant disposition information will be summarized using the Enrolled Population (all participants who sign the informed consent form). The numbers and percentages of participants who were screened, screen failure along with the reasons of screen failure, randomized, randomized and not dosed, dosed, completed study drug, discontinued study drug early along with the reasons for early discontinuation of study drug, entered Cross-Over, completed the study, and discontinued the study early along with the reasons for early discontinuation of study. The study and study drug disposition will be summarized for the Primary Study Period and the Cross-Over Period. The numbers and percentages of recurrence participants will be summarized. The number of participants who received any study treatment will be summarized by the number of infusions.

By-participant listings will also be provided for participant disposition.

3.3.2 Demographic and Baseline Characteristics

Demographic (age and age subgroups [e.g. 0 to <2y; 2-<6y; 6 to <12y; 12 to <18; <65, >=65, sex, race, and ethnicity), baseline characteristics (height, weight, BMI), and randomization stratification factors will be summarized with descriptive statistics or counts and percentages of participants as appropriate for mITT Population.

The following disease characteristics will also be summarized using frequencies and percentages or descriptive statistics:

- Baseline Weight (kg) (overall, Age >/≤ 18 years)
- Baseline Height (cm) (overall, Age >/≤ 18 years)
- Baseline BMI (kg/m²) (overall, Age >/≤ 18 years)
- Baseline Target Organ Disease Diagnosis, n (%)
- Screening AdV Viremia, n (%)
- Baseline AdV Viremia, n (%)
- Baseline Viremia, n (%)
- Use of Cidofovir at Baseline, n (%)
- Hematopoietic Cell Transplantation Donor Type, n (%)
- Time (Days) from Hematopoietic Cell Transplantation at Screening
- Type of Conditioning Regimen, n (%)
- Reduced intensity conditioning regimen
- Any aGVHD at Screening, n (%)
- Any cGVHD at Screening, n (%)
- Donor Recipient HLA Match, n (%)

3.3.3 Prior and Concomitant Medications/Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary. All medications taken prior to the first dose of study treatment will be considered as prior medications. The medications taken prior to the first dose of study treatment and were ongoing or started on or after the first dose of study treatment will be considered as concomitant medications.

The numbers and percentages of participants taking prior and concomitant medications by ATC class and preferred term will be summarized based on the Safety Population.

3.4 Efficacy Analyses

Only the primary efficacy endpoint will be summarized for the primary treatment period based on the mITT Population.

For AdV viral endpoints at Day 29 or Week 4 visit, a +14-day window will be applied to the Day 29 visit. The last observed plasma AdV DNA result through Day 29 + 14 days (up to 43 days post first infusion) will be used for the analysis for all the participants including those who crossover from PSL to placebo. For participants who crossover from placebo to PSL, the pre-dose cross-over Day 1 viral load may be used. Participants who cross over on or before Day 29 will be treated as failure.

3.4.1 Primary Efficacy Endpoint Analysis

3.4.2 Primary Analysis of Primary Efficacy Endpoint

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

This endpoint will be analyzed using logistic regression. The model will include a term for treatment and the following covariates: level of viremia at Baseline (≥10,000 copies/mL or <10,000 copies/mL AdV DNA), age (≥12 years or <12 years) and absolute lymphocyte count at Baseline. For participants who discontinued treatment but remain on the study, data collected after treatment discontinuation will be included in the analysis. If a participant doesn't have plasma AdV DNA result in the Day 29 through Day 43 window but has undetectable viremia before Day 29 and after Day 43, it will be imputed as success for the primary endpoint. The deaths related to adenovirus infection on or before Day 29 will be imputed as failure.

Subgroup analyses of the primary endpoint will be performed for both of the randomization stratification variables: (1) level of viremia: ≥10,000 copies/mL and <10,000 copies/mL AdV DNA and (2) age: ≥12 years or <12 years.

3.5 Safety Analyses

Safety will be analyzed and compared between treatments received based on data from the Primary Study Period. No formal comparisons will be made between these groups.

All safety analyses will be based on the Safety Population.

Categorical endpoints will be summarized using the number and percentage of participants within each category. Continuous endpoints will be summarized descriptively with summary statistics (number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum).

3.5.1 Adverse Events (AEs)

All AEs will be coded to system organ class and preferred term using MedDRA. A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date and time on or after the administration of investigational product or placebo or that worsened in severity after administration of investigational product or placebo through the end of the study.

An overall summary of AEs will be provided with the number and percentage of participants who experienced at least one (1) AE or TEAE in the following categories:

- Any TEAEs
- Any TEAEs by severity
- Any treatment-related TEAEs
- Any treatment-related TEAEs by severity
- Any treatment-emergent AESI (TEAESIs)
- Any treatment-emergent serious AEs (TESAEs)
- Any treatment-related TESAEs
- Any TEAEs leading to discontinuation of study treatment
- Any TEAEs leading to discontinuation of study, and
- Any AEs leading to death

The numbers and percentages of participants will also be presented by system organ class (SOC) and preferred term (PT) for each of the TEAE categories in the summary. Participants with multiple AEs will be counted only once per SOC and PT.

Listings will be presented specifically for any AEs, SAEs, AESIs, and AEs leading to discontinuation of study treatment and study.

3.5.2 AEs of Special Interest

The AESIs will be reviewed by the DSMB as per the DSMB Charter. Criteria for acute and chronic GVHD and CRS can be found in Protocol Appendix 6 and 7, respectively.

The number and percentage of participants who had the treatment-emergent AESIs will be summarized by treatment group for the Primary Study Period and by cross-over treatment group for the Cross-Over Period:

- Severity and incidence of acute GVHD
- Severity and incidence of chronic GVHD
- Severity and incidence of CRS (ASTCT Score)
- Severity and incidence of infusion-related AEs
- Severity and incidence of graft failure and rejection

3.5.3 Clinical Laboratory Tests

Clinical laboratory data (hematology, clinical chemistry, and routine urinalysis) from the Primary Study Period will be summarized by laboratory test, visit, and treatment group using descriptive statistics. The changes from baseline to each post-baseline visit will also be summarized.

Listings will be presented for selected laboratory data and the test values outside the normal range will be flagged.

3.6 Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor participant safety. The DSMB will receive summary reports of all unexpected SAEs at least monthly. A DSMB charter, detailing all aspects of the DSMB's composition, scope of review, and procedures will be provided separately. An unblinded statistician will be assigned to the DSMB. This statistician will not be involved in any aspects of study conduct outside of the DSMB, and their role will be defined in the DSMB charter.

3.7 Interim Analysis

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

Appendix 1 Analysis Visit Windows

Table 1 Analysis Visit Windows for Adenovirus Viral Load Data

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1		≤1
Week 1	8	2	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	57
Week 10	71	58	92
Week 16	113	93	141
Week 24	169	>141	

Table 2. Analysis Visit Windows for Other Viral Load and Clinical Lab

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1		≤1
Week 1	8	2	11
Week 2	15	12	22
Week 4	29	23	36
Week 6	43	37	57
Week 10	71	58	92
Week 16	113	93	141
Week 24	169	>141	

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