Protocol Number: P-105-202

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

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STATISTICAL ANALYSIS PLAN

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Protocol Number:	P-105-202
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Investigational Product:	Posoleucel (ALVR105, Viralym-M)
Sponsor:	AlloVir 1100 Winter Street Waltham, MA 02451 United States
SAP Version/Date:	V1.0/22 June 2023 (Phase 3)

SIGNATURE PAGE

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

[redacted]
AlloVir, Inc

[redacted]
AlloVir, Inc

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AUC	Area Under the Curve
AdV	Adenovirus
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BKV	BK Virus
CAC	Clinical Adjudication Committee
CMV	Cytomegalovirus
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D	European Quality of Life 5 Dimensions
FCS	Fully Conditional Specification
FSH	Follicle-Stimulating Hormone
GVHD	Graft-Versus-Host Disease
HCT	Hematopoietic Cell Transplant
HHV-6	Human Herpesvirus 6
HLA	Human Leukocyte Antigen
IRT	Interactive Response Technology
IVRS/IWRS	Interactive Voice/Web Response System
JCV	John Cunningham virus
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PBMC	Peripheral Blood Mononuclear Cell
SAE	Serious Adverse Event
SD	Standard Deviation
SoC	Standard of Care
SSRE	Sample Size Re-estimation
TEAE	Treatment Emergent Adverse Event
VST	Virus-Specific T cell
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This document details the analysis plan for the study entitled "Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ALVR105 (Viralym-M) Compared to Placebo for the Prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV Infection and/or Disease, in High-Risk Patients After Allogeneic Hematopoietic Cell Transplant". It describes the proposed efficacy and safety analyses, focusing on the Phase 3 portion of the study.

Posoleucel (ALVR105, formerly known as Viralym-M and ALVR-105) is a cellular therapy consisting of third-party, multivirus-specific T cells with specificity for adenovirus [AdV], BK virus [BKV], cytomegalovirus [CMV], Epstein-Barr virus [EBV], human herpesvirus 6 [HHV- 6], and John Cunningham virus [JCV], in cryopreservation medium.

This is a Phase 2/3 study to evaluate the efficacy and safety of posoleucel for the prevention of clinically significant AdV, BKV, CMV, EBV, HHV-6, and JCV infections and/or disease in patients at high risk for these viruses following allogeneic HCT. In healthy, immunocompetent individuals, T cell immunity plays a central role in controlling viruses. In HCT recipients, the use of potent immunosuppressive regimens (and subsequent associated immunocompromise) leaves patients at high risk of severe viral infections. In approximately 90% of allogeneic HCT patients, the suppressed immune system allows viruses that were previously in a latent, quiescent state to reactivate and more than 60% of allogeneic HCT patients experience a reactivation of more than one virus, including BKV, CMV, AdV, EBV, and HHV-61. Viral infections result in devastating morbidities and have become leading etiologies for transplant-related mortality. There is no approved anti-viral agent that can prevent such potentially fatal multi-virus infection(s) as a single therapy. Some off-label use of antiviral agents is associated with significant toxicities (notably myelosuppression and renal toxicity which might impede their use) and the emergence of drug-resistant viruses.

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

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

2 STUDY OBJECTIVES

The primary efficacy objective of this trial is to compare the efficacy of posoleucel to placebo by the number of new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 14.

The key secondary efficacy objective is to compare the efficacy of posoleucel to placebo by the number of new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 26.

The other secondary efficacy objective is as follows:

- To compare the efficacy of posoleucel to placebo by new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 due to each individual virus as determined by an independent, blinded CAC through Week 14 and Week 26, and by investigator reported assessment.

The exploratory efficacy objectives are as follows:

- To determine the incidence and number of re-hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26
- To assess patient-reported quality of life (QoL) through Week 26
- To compare the efficacy of posoleucel to placebo in the proportion of patients with undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the lower limit of quantification [LLOQ]) at Week 14 and 26
- To determine hospital length of stay (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection or disease through Week 26
- To evaluate persistence of posoleucel cells
- To compare the efficacy of posoleucel to placebo in mean area under the curve (AUC) viral load for AdV, BKV, CMV, EBV, HHV-6, or JCV each through Week 14 and Week 26

The safety objective is to characterize the safety and tolerability of posoleucel when administered to patients at high-risk for AdV, BKV, CMV, EBV, HHV-6, or JCV following allogeneic HCT.

3 STUDY DESIGN

3.1 Overview

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

There are 2 parts to the study, an open label Phase 2 cohort and the primary Phase 3 randomized study cohort. The subject of this SAP is the Phase 3 placebo-controlled portion of the study. The first 26 patients (open label cohort) received posoleucel for 14 weeks of open-label dosing, and an assessment and optimization of study processes was performed. The Phase 2 portion of this study will be summarized in a separate CSR and statistical analysis plan.

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

A review by the Data Safety Monitoring Board (DSMB) was performed when 26 patients in the open label cohort completed 30 days of treatment. At this time, an assessment of benefit, risk, and process was undertaken, and it was determined that the Phase 3 portion should proceed. Following this DSMB review, patients began enrollment in the Phase 3 study cohort. Approximately 302 patients in the Phase

3 study cohort will be randomized to posoleucel or placebo at a [redacted] ratio. Open label patients completed their participation in the open label arm.

In order to best facilitate comparable baseline characteristics in the active and placebo arms of the Phase 3 study, randomization is stratified for the following criteria: [redacted]

The schedule of activities for this study is presented in protocol Section 1.3 (Tables 1, 2, and 3).

3.2 Method of Assigning Subjects to Treatment

Patients who meet all of the inclusion criteria and none of the exclusion criteria are randomized to the study. Randomization is performed using an Interactive Voice/Web Response System (IVRS/IWRS). Randomization will be stratified for the following criteria:

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

[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

If there are discrepancies in stratification factor values between the Interactive Response Technology (IRT) and the Electronic Data Capture (EDC) clinical database, the baseline values recorded in the clinical database will be used for analyses. To derive the letermovir use at randomization, the start date of the medication should be before or on the same date of the randomization with either the stop date of the medication being on or after the randomization date or with 'ongoing' status.

3.3 Blinding

The CRO has a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind integrity is properly maintained. Care will be exercised to ensure that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (e.g., staff involved in Suspected Unexpected Serious Adverse Reaction [SUSAR] reporting).

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.

3.4 Determination of Sample Size

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

cohort. An increase in sample size may result following the sample size re-estimation, which is to be conducted when approximately 40% of the patients have reached Week 14.

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

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

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

The results of the sample size calculations are presented in Table 1.

Table 1 Required Sample Sizes

Treatment	Mean	Standard Deviation	Sample Size		
			Posoleucel	Placebo	Total
Placebo	0.450	0.669			
Posoleucel	0.225	0.524	[redacted]	[redacted]	302

4 EFFICACY AND SAFETY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the number of new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 14.

4.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is the number of new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded CAC through Week 26.

Additional secondary efficacy endpoints include:

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

4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

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

The persistence of posoleucel will not be analyzed in this SAP but reported separately.

4.4 Safety Endpoints

The safety endpoints are as follows:

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

5 STATISTICAL CONSIDERATIONS

5.1 General Methodology

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. Unless otherwise stated, 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 treatment group. The primary analyses will be based on the Phase 3 portion of the study. All two-sided hypothesis tests will be performed at the 0.05 significance level, and all one-sided hypothesis tests will be performed at the 0.025 significance level.

5.1.1 Study Day

Study day will be calculated from the date of first dose of study drug (ie. actual visit date minus 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, respectively.

5.1.2 Analysis Visits

Not all 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.

5.1.3 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.

5.2 Adjustments for Covariates

The primary efficacy endpoint will be analyzed using Analysis of Variance (ANCOVA) with a term for study treatment and the following covariates: letermovir use at randomization, age (continuous variable), and the underlying allogeneic transplant risk of viral infections. The key secondary endpoint, number of new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV through Week 26, will be analyzed in the same manner as the primary efficacy endpoint. The additional secondary efficacy endpoint, new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 from each individual virus through Week 14 and Week 26, as determined by the investigators and by an independent, blinded CAC (5 endpoints each at Week 14 and Week 26), will be analyzed

using logistic regression with a term for study treatment and the same covariates as used for the analysis of the primary efficacy endpoint. As a sensitivity analysis for the primary efficacy endpoint, the letermovir use at Baseline may be adjusted in the ANCOVA model if it is very different from the letermovir use at randomization.

5.3 Handling of Dropouts and Missing Data

If there are missing data due to intercurrent events or early termination from study for the primary efficacy endpoint or the key secondary efficacy endpoint, multiple imputation methods (Rubin, 1987) will be used to impute the missing data. The overall imputation will be based on distinct Cox proportional hazards (PH) analyses for each of the six types of viral infection for each of the two arms separately (i.e., 12 distinct Cox PH models overall). These models will be fit on patients with complete data. For patients with missing data, each model will be used to estimate the probability that the patient will have an infection of the given type between the time they were lost to follow-up (t) and Week 14 based on the Cox PH model for that treatment and type of infection, and assuming that the patient did not have the particular infection by time t. For each iteration of the multiple imputation, these probabilities of infection will be used to impute the missing value for each viral infection for each patient, and these imputed values will be summed together with the observed occurrences up through time t to obtain the value of the endpoint for the patient for the given iteration. Additional details of the imputation approach are described in Section 8 (Efficacy Analyses).

5.4 Interim Analyses and Data Monitoring

A formal interim futility analysis and a sample size re-estimation (SSRE) based on the primary efficacy endpoint will be conducted after the first 121 subjects have completed Week 14 or discontinued prior to Week 14, which is 40% of the planned sample size of 302 subjects. The SSRE will be conducted in a manner so as to minimize the risk of operational bias. Information concerning the specific results of the SSRE will be kept confidential. In particular, the information will be kept from the investigators and site staff, sponsor clinical operations team, and the CAC. The sample size may be increased to approximately 125 additional (a total of 425) patients dosed, and only the decision to increase the sample size, if such a decision were to be made, will be communicated. Details of the SSRE will be provided in a separate SSRE plan.

The decision to stop for futility is based on the conditional probability that the study will be successful at the time of final analysis, assuming the current trend observed at the interim. If, at the interim analysis, the conditional probability of study success with 302 mITT Population falls below 10%, the study may stop early for futility. Enrollment and patient follow-up will then be discontinued, and the final analyses will be conducted. The futility stopping in this study is considered non-binding.

5.5 Multicenter Study

This is a multicenter global study.

5.6 Multiple Comparisons / Multiplicity

In order to control the overall type 1 error rate, a fixed sequential approach will be used to analyze the primary and key secondary efficacy endpoints in the order presented in Section 4. Multiplicity will not be taken into account in the analysis of the additional secondary efficacy endpoint or the exploratory efficacy endpoints.

5.7 Examination of Subgroups

Subgroup analyses of the primary and key secondary efficacy endpoints may be performed. The following subgroups will be considered:

- Age groups: <12/≥12, < 18/≥18, and <65/≥65
- High risk vs standard risk as randomized
- Letermovir use at randomization
- Letermovir use at Baseline
- Sex
- Race
- Presence of viremia prior to Day 1 dosing (Yes/No)
- Presence of viremia with 0, 1 vs 2+ viruses prior to Day 1 dosing
- Presence of acute GVHD at Day 1 (Yes/No)
- Presence of acute GVHD at during the study (Grade 0/I vs Grade II/III/IV)
- Number of days from HCT to Day 1 dosing (<median vs ≥median)
- Subjects developing clinically significant infections within 21 days from Day 1 dosing
- Subjects receiving post-transplant cyclophosphamide (pre-dose) (Yes/No)
- Subjects by myeloablative conditioning (myeloablative, reduced intensity, and non-myeloablative)
- Subjects taking oral/IV steroids (highest dose) during study (≤/>1 mg/kg and ≤/>0.5 mg/kg)
- Subjects who have relapsed, experienced graft failure, or required additional chemotherapy for underlying disease during study (Yes/No)
- Subjects taking any prophylactic antiviral for CMV (Letermovir, valganciclovir, acyclovir, ppx rituximab) at Day 1
- Subjects who are CMV D+ or R+ at Day 1
- HLA matches (< or ≥ median)
- Class of HLA matches between the patient, the donor and posoleucel (Class I/II/both)
- Region: North America, Europe, Asia Pacific

6 ANALYSIS POPULATIONS

6.1 Enrolled Population

The Enrolled Population will include all participants who sign the informed consent form.

6.2 Modified Intent-to-Treat (mITT) Population

The mITT Population will include all randomized patients who receive at least one dose of posoleucel or placebo. All efficacy endpoints will be analyzed based on the mITT Population. Patients will be analyzed according to their randomized study treatment. These analyses will be considered the primary analyses of efficacy.

6.3 Safety Population

The Safety Population will include all patients who receive at least one dose of posoleucel or placebo. All safety analyses will be based on the Safety Population. Patients will be analyzed according to the treatment actually received.

7 PATIENT DATA AND STUDY CONDUCT

7.1 Patient Disposition

The number of screened patients and the number of screen failures will be presented. The number of randomized participants and the number and the number of randomized participants who are in the mITT Population (i.e., receive at least one dose of posoleucel or placebo), and the Safety Population; who completed the study; who discontinued from the study early; who completed the study drug; and who discontinued from the study drug and their reason for discontinuation, will be summarized by treatment group. The number of patients who received a Week 52 follow-up call will also be summarized as available.

7.2 Protocol Deviations

The numbers and percentages of patients with major protocol deviations by deviation category will be summarized on the Safety Population. All protocol deviations will be determined prior to database lock and listed by patient.

7.3 Demographic and Baseline Characteristics

Descriptive statistics will be presented by treatment group for continuous demographic and baseline characteristic variables (age, weight, and height); frequencies and percentages will be presented for the categorical demographic and baseline characteristic variables (sex, race, and ethnicity). Continuous variables will be analyzed using a two-sided, two-sample t-test to test for a difference in means between treatment groups. Categorical variables will be analyzed using a two-sided, Fisher's Exact Test to test for a difference in proportions between treatment groups.

The following data will each be summarized by treatment group using frequencies and percentages: reason for transplant by disease category (eg lymphoma vs leukemia, vs primary immunodeficiency etc), type of hematopoietic cell transplant by donor type (MUD vs MMUD vs haplo vs cord etc), receipt of T cell depletion by source (ATG vs alemtuzumab vs ex vivo), use of post-transplant cyclophosphamide,, stem cell source (peripheral blood vs bone marrow vs cord), level of conditioning (myeloablative, reduced intensity, and non-myeloablative), HLA alleles from the study patient, the allogeneic HCT donor(s), and the VST donor(s) as well as the number of shared alleles among these individuals, pre-conditioning therapy received, CMV serostatus at baseline of donor and recipient, woman of childbearing potential, letermovir use, and presence of baseline viremia (based on central lab). Whether the patient has a matched unrelated donor and whether the patient received ATG, alemtuzumab, or ex vivo T cell depletion therapy will also be summarized by treatment group.

These results will be based on the mITT Population. A by-patient listing will be provided.

7.4 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The numbers and percentages of patients with medical history by system organ class and preferred term will be summarized for the mITT Population.

A by-patient listing of medical history will be provided.

7.5 Prior and Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug 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 patients taking prior and concomitant medications by ATC class and preferred term will be summarized based on the mITT Population. A by-patient listing will be provided for prior and concomitant medications.

7.6 Study Drug Exposure and Compliance

Study drug administration data will be summarized, for the Safety Population, by treatment group using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

The length of exposure to study drug will be calculated as the number of days from the first dose of study drug to the last dose of study drug plus 14 days, regardless of if the patient missed one or more doses of study drug. Length of exposure will be summarized using descriptive statistics for the safety population. A by-patient listing will be provided for study drug exposure.

The frequencies and percentages of patients will be summarized by the number of doses and treatment group for the Safety Population.

Overall compliance will be calculated as:

*(Sum of total vials administrated)/ (total vials planned)*100*

The number and percentage of patients will be summarized for the Safety Population for the following categories: 0- <70% and ≥70%.

8 EFFICACY ANALYSES

All efficacy endpoints will be analyzed and formally compared between randomized treatment groups using statistical tests based on data for the Phase 3 study cohort. Analyses based on the mITT Population will be considered primary.

8.1 Primary Efficacy Endpoint Analysis

8.1.1 Definition of Estimand

For the primary efficacy objective of comparing the efficacy of posoleucel to placebo by the number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV as determined by an independent, blinded Clinical Adjudication Committee (CAC) through Week 14, the estimand is defined as follows:

Treatment condition: (1) posoleucel or (2) placebo each administered as [redacted] sequential infusions ([redacted] ± 3 days) at a dose of [redacted] (< 40 kg) in [redacted] solution or [redacted] (≥ 40 kg) cells in [redacted] solution or equivalent volume of placebo.

Target patient population: Pediatric and adult patients at high risk for clinically significant adenovirus (AdV), BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and John Cunningham virus (JCV) infections and/or disease following allogeneic hematopoietic cell transplant (HCT).

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

Population-level summary: Mean number of clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6 or JCV through Week 14.

Intercurrent events and strategies: Intercurrent events include assigned treatment discontinuation, other anti-viral treatment received for target virus infection and/or disease, and death. These require different strategies, which are described in the table below. The imputation will be applied to a virus that an event has not developed prior to the intercurrent events occurring.

The following anti-viral treatments will be considered for the corresponding target virus(es) indicated in the labels: cidofovir (CMV), ganciclovir (CMV), valganciclovir (CMV), rituximab (EBV), maribavir (CMV), foscarnet (CMV), and tabelecleucel (EBV). Imputation will be applied for any use of cidofovir, rituximab, and tabelecleucel, and for at least 2-day use of other drugs taken at or after Baseline but not for prophylactic use. Data will be inputted starting from the first day of the use.

Table 2 Intercurrent Event Strategies for the Primary Analysis of the Primary Efficacy Endpoint

Intercurrent Event	Strategy
Assigned treatment discontinuation prior to Week 14	Treatment policy strategy: Primary efficacy endpoint data collected after treatment discontinuation will be included in the analysis.
Other anti-viral treatment for target virus infection and/or disease received prior to Week 14	Hypothetical strategy: The primary efficacy endpoint will be considered missing and will be imputed for a target virus that the treatment is indicated in the label.
Death prior to Week 14	Hypothetical strategy: The primary efficacy endpoint will be considered missing and will be imputed.

8.1.2 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the number of clinically significant infections and/or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6 or JCV as determined by an independent, blinded CAC through Week 14.

The statistical hypotheses are as follows:

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

Clinically significant infections/episodes will be considered as a failure of prevention, thus, in calculating the value of this endpoint for a patient, each virus will be counted at most once, even if there are multiple infections/episodes for a given virus. If patients have a clinically significant infection at baseline, infection with that virus will not be counted as an event in the primary endpoint. Primary endpoint is counted as study Day 1 through study Day 105 (Day 98 visit (+7 day window).

This endpoint will be analyzed based on patients in the mITT population in the Phase 3 portion of the study. It will be summarized by treatment group using both descriptive statistics and frequency counts and percentages, together with a 95% confidence interval for the true mean based on the t distribution. The difference in means (placebo – posoleucel) will also be presented, together with a 95% confidence interval for the true difference in means based on the t distribution. The endpoint will be analyzed using Analysis of Covariance (ANCOVA) with a term for the randomized treatment group and the following covariates: letermovir use at randomization, age (continuous variable) and the underlying allogeneic transplant risk of viral infections. The null hypothesis will be tested using a one-sided test of the effect of treatment at the 0.025 significance level.

If there are any missing data for this endpoint, multiple imputation methods will be used to impute the missing data. The imputation will be based on 12 distinct Cox proportional hazards analyses corresponding to each of the six types of viral infection for each of the two treatment arms. The models will be fit on patients with complete data and will include the same covariates (except treatment) as in the primary analysis of the primary efficacy endpoint.

Patients with missing data will be handled in one of two ways: (1) For patients with missing data and no known infection, each of the six models will be used to estimate the conditional probability that the patient would have had an infection of the given type between the time they were lost to follow-up (t) and Week 14, assuming that the patient did not have the particular infection by time t; (2) Patients with at least one type of viral infection prior to time t will only have probabilities calculated for the types of viral infection that were not observed prior to time t (i.e., known outcomes will be used).

Subjects with missing data for an infection type will have their outcome for that infection type imputed as infected (1) or not infected (0) with the probability of infection equal to the conditional probability calculated from the relevant model for that infection type and treatment arm. For each iteration, these imputed values will be summed together with the observed occurrences across infection types to obtain the value of the endpoint for each patient for that iteration. Each iteration will then contain complete

data for all subjects and will be analyzed independently as described above. This imputation approach will be repeated for N=50 iterations. The resulting mean and standard error (SE) for each imputation will then be combined across all imputations to obtain pooled estimates. The pooled mean and SE will form the basis for the statistical comparisons of the relevant endpoints.

Tipping point analysis will be performed as a sensitivity analysis to assess the robustness of the analysis results for the primary endpoint (Yuan, 2014). A set of shift parameters that adjust the imputed values will be examined. The shift parameter that alters the study conclusion for the hypothesis testing under the missing at random assumption will be reported as the tipping point and provided. The tipping point analysis will be conducted by iteratively assigning plausible outcomes to missing values for subjects in different treatment group independently until the conclusion is reversed (eg, analyses are no longer statistically significant).

8.2 Secondary Efficacy Endpoints Analyses

The secondary efficacy endpoints will be analyzed based on the mITT Population. The definition of clinically significant infections shall be the same for relevant secondary efficacy endpoint analyses as in the primary efficacy endpoint analysis. The same estimand framework will be applied to the secondary efficacy endpoints.

The key secondary efficacy endpoint is:

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

Additional secondary efficacy endpoints include:

- Number of new onset clinically significant infections and/or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 as determined by the investigators through Week 14 and Week 26 and 5 endpoints from each individual virus at Week 14 and Week 26.

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

Summary tables will be presented by treatment group for the Phase 3 study cohort.

The key secondary endpoint, number of clinically significant infections and/or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, HHV-6, or JCV through Week 26, will be analyzed in the same manner as the primary endpoint, including the potential use of multiple imputation to handle any missing data, for the Phase 3 study cohort of patients.

The additional secondary efficacy endpoints listed in Section 4 will be summarized by treatment group using frequency counts and percentages, together with an exact (Clopper-Pearson) 95% confidence interval for the true percentage. The difference in percentages between the two treatments (placebo – posoleucel), together with a 95% Wald confidence interval for the true difference, will be presented. The null hypothesis for these endpoints is that the true proportion for posoleucel patients is greater than or equal to the true proportion for placebo patients, and the alternative hypothesis is that the true

proportion for posoleucel patients is less than the true proportion for placebo patients. These endpoints will be analyzed using logistic regression. The model will include a term for treatment and the following covariates: letermovir use at randomization, age (continuous variable), and the underlying allogeneic transplant risk of viral infections. The null hypothesis will be tested using a one-sided test of the effect of treatment at the 0.025 significance level. If there are any missing data, multiple imputation methods will be used to impute the missing data. Missing data will be imputed using the same method as used for the primary efficacy endpoint for each virus. The data will then be analyzed using the normal approximation test for the difference in two proportions.

8.3 Exploratory Efficacy Endpoints Analyses

The exploratory efficacy endpoints will be analyzed based on patients in the Phase 3 study cohort. Summary tables will be presented by treatment group for this cohort.

The following exploratory endpoints will be summarized by treatment group using descriptive statistics:

- The number of new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection and/or disease through Week 26.
- Change from baseline in QoL assessments, EQ-5D-5L, EQ-5D-Y, and EQ-5D-Y Proxy Version 1, through Week 26
- Number of hospital days related to clinically significant AdV, BKV, CMV, EBV, HHV-6, or JCV infection and/or disease through Week 26

The following exploratory efficacy endpoints will be summarized by treatment group using frequencies and percentages:

- Proportion of patients with new hospitalizations (following initial hospital discharge) for AdV, BKV, CMV, EBV, HHV-6, or JCV infection and/or disease through Week 26
- Undetectable AdV, BKV, CMV, EBV, HHV-6, or JCV viremia (defined as below the LLOQ) at Week 14 and Week 26
- Mean viral load for AdV, BKV, CMV, EBV, HHV-6, or JCV for each individual virus through Week 14 and Week 26, obtained as AUC/number of days (6 endpoints each at Week 14 and Week 26)

Time to first clinically significant infection will be calculated for any virus and for each virus as starting at the first dose date and ending at the first clinically significant infection of any virus and each virus. Patients who discontinued from the study early or deceased before they are observed to have any infection will be censored at the last assessment date for this endpoint. The time-to-event endpoint will be summarized using the Kaplan-Meier method. The number of patients with events and number of patients censored and reason of censoring will be presented along with estimate for the median time (days) and its 95% CI. Time-to-event will be presented using Kaplan-Meier plots. A Cox proportional hazards (PH) analysis will be performed including treatment and the following covariates: letermovir use at randomization, age (continuous variable) and the underlying allogeneic transplant risk of viral infections.

9 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

An additional secondary efficacy objective is added: to compare the efficacy of posoleucel to placebo by new onset clinically significant infections or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 as determined by investigator reported assessment.

The corresponding secondary efficacy endpoints are added: number of new onset clinically significant infections and/or episodes of end-organ disease per patient due to AdV, BKV, CMV, EBV, or HHV-6 as determined by the investigators through Week 14 and Week 26 and 5 endpoints from each individual virus at Week 14 and Week 26. These endpoints will be based on the investigators' assessment.

10 SAFETY ANALYSES

Safety endpoints include:

- Severity and incidence of acute GVHD
- Severity and incidence of chronic GVHD
- Severity and incidence of CRS
- Severity and incidence of graft failure
- Severity and incidence of clinically significant cytopenias
- Severity and incidence of renal dysfunction
- Effect on measures of engraftment
- Overall and non-relapse-related mortality
- Physical examination, clinical laboratory, and imaging results

All safety data will be summarized by treatment arm using the Safety Population. Categorical endpoints will be summarized using the number and percentage of patients within each category. Continuous endpoints will be summarized using descriptive statistics.

10.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only treatment emergent AEs will be summarized. A treatment emergent adverse event (TEAE) is defined as an AE with onset or worsening on or after the first dose of study treatment through Week 26. For AEs with a missing start date, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study treatment.

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

- Any TEAEs
- Any TEAEs by severity
- Any treatment-related TEAEs
- Any treatment-emergent AESI (TEAESIs)
- Any treatment-related 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
- Any TEAEs leading to death

TEAEs will be summarized at both the subject- and event-levels using counts and percentages by System Organ Class and Preferred Term. Event-level TEAEs will be further summarized by severity (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] and by causality with study treatment. Subject-level summaries will include each subject at most once for each PT, SOC, and overall. Severity tables will count the number of events at each relationship/severity grade assessed for that PT/SOC and overall. The incidence of SAEs will be similarly summarized. By-patient listings will also be provided for any deaths, SAEs, AESIs, and adverse events leading to discontinuation of study drug.

Subgroup analysis may be performed for any TEAEs by sex, race, ethnicity, and stratification factors, and for the severity and incidence of GVHD by HLA type and the number of HLA matching.

10.2 AEs of Special Interest

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

Adverse events of special interest (AESI) include acute and chronic GVHD, CRS, infusion-related AEs, and graft failure. Criteria for acute and chronic GVHD and CRS can be found in Protocol Appendix 5 and 6, respectively. The number and percentage of patients who had the AESIs will be summarized:

- Severity and incidence of acute GVHD
- Severity and incidence of chronic GVHD
- Severity and incidence of CRS
- Severity and incidence of infusion-related AEs
- Severity and incidence of graft failure

Subgroup analyses may be conducted for the severity and incidence of acute GVHD, including by HLA class and the number of HLA matches.

10.3 Clinical Laboratory Tests

Laboratory assessments comprise safety laboratory tests (hematology, clinical chemistry and routine urinalysis), pregnancy test and other screening tests.

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

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

The number and percentage of participants with the following potentially clinically significant abnormal liver function tests will be summarized:

- Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN), ≥5xULN, ≥10xULN, and ≥20xULN
- Aspartate aminotransferase (AST) ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- Hy's Law cases: ALT or AST ≥3xULN, total bilirubin ≥2xULN, and alkaline phosphatase (ALP) <2xULN.

A listing with any post-baseline potentially clinically significant abnormal liver function tests will be presented.

10.4 Vital Signs

Descriptive statistics will be provided for vital signs (including blood pressures, pulse rate, respiratory rate, oximetry, and body temperature), body weights, and BMIs by visit. Changes from baseline will also be summarized.

All vital sign data will be listed by patient.

10.5 Electrocardiograms

Electrocardiogram (ECG) is only measured at the screening visit and will be listed by patient.

10.6 Physical Examinations

Abnormal physical examination findings will be presented in a by-participant data listing.

11 DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will be convened for this study to routinely monitor patient safety and evaluate pre-specified interim analyses for sample size re-estimation or futility to stop the study early. The DSMB will receive summary reports of all SAEs including unexpected SAEs. A DSMB charter, details all aspects of the DSMB's composition, scope of review, and procedures. 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.

12 REFERENCES

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc, 1987

Yuan Y. Sensitivity Analysis in Multiple Imputation for Missing Data. 2014

APPENDIX 1 - ANALYSIS VISIT WINDOWS

Table 1: Analysis Visit Windows for Quality of Life Data

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1		≤1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	92
Week 14	99	93	120
Week 20	141	121	162
Week 26	183	>162	

Table 2: Analysis Visit Windows for 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	50
Week 8	57	51	64
Week 10	71	65	78
Week 12	85	79	92
Week 14	99	93	120
Week 20	141	121	162
Week 26	183	>162	

Table 3: Analysis Visit Windows for Clinical Labs and Vital Sign Data

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1		≤1
Week 2	15	2	22
Week 4	29	23	36
Week 6	43	37	50
Week 8	57	51	64
Week 10	71	65	78
Week 12	85	79	92
Week 14	99	93	120
Week 20	141	121	162
Week 26	183	>162	

Table 4: Analysis Visit Windows for Physical Exam Data

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1		≤1

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 2	15	2	22
Week 4	29	23	36
Week 6	43	37	50
Week 8	57	51	64
Week 10	71	65	78
Week 12	85	79	92
Week 14	99	>92	

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